The Inferior Colliculus

Jeffery A. Winer • Christoph E. Schreiner
Editors

Springer

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With 168 Illustrations

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Cover illustration: A transverse section through the center of the cat inferior colliculus showing its principal subdivisions. See page 20 of the text.

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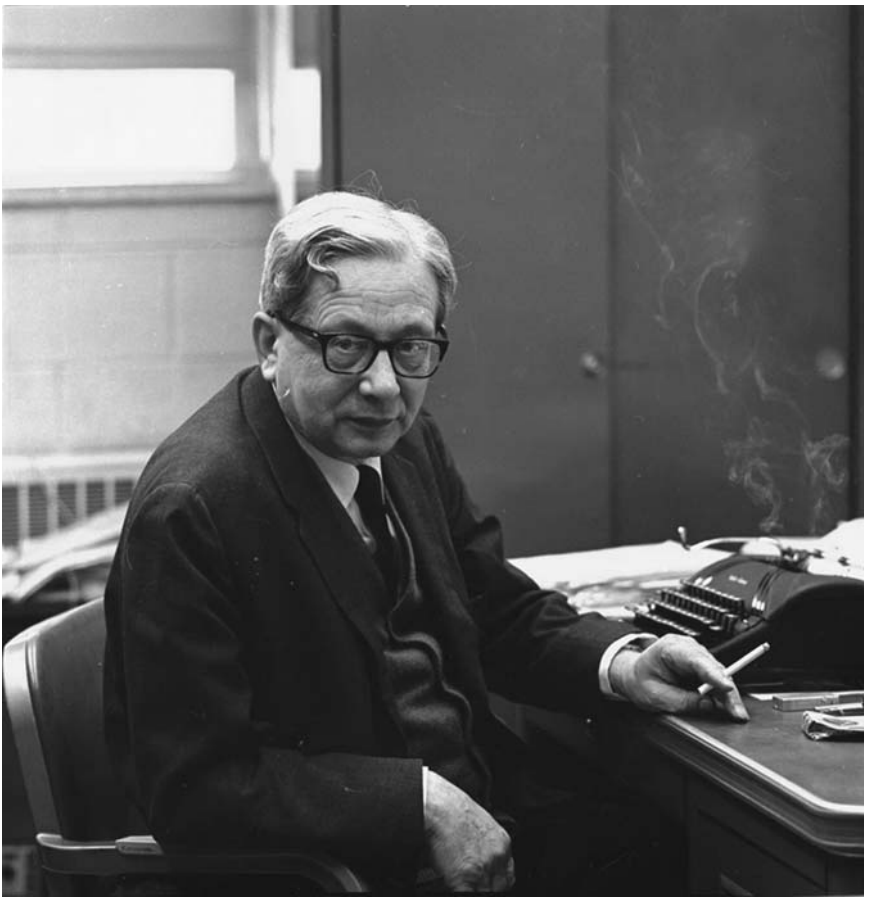

Photograph by courtesy of T. Stewart

Dedicated to the memory of
Jerzy E. Rose (1909–1992)
Scholar, scientist, colleague, mentor, friend

Preface

The purpose of this volume is twofold. First, it offers an in-depth analysis of current approaches and issues in the study of the auditory system. By concentrating on one structure, the inferior colliculus, a focused and coherent treatment of many aspects of auditory neural processing is possible. The position of the inferior colliculus is unique, as its study offers insights into the influence of the peripheral auditory system and at the same time reveals the initial stages of central processing principles. By providing, in the first chapter, an overview of auditory system function and structure, a framework is given that guides the interpretation of operational mechanisms and rules. Second, the book provides a state-of-the-art reference tool for researchers working on the inferior colliculus. The last such treatment appeared in the mid-1980s (Aitkin 1986) and was 246 pages long with 507 citations; since then, more than 1900 articles on the inferior colliculus have been published, and there has been no inclusive summary of facts and ideas about this critical junction in the auditory pathway. In this period, there has been substantial progress on the many facets of inferior colliculus function that constitute the subject matter for this volume. The mere accretion of publications alone would not in itself justify a new volume devoted to the auditory midbrain. The rationale, then, is to summarize recent advances in this discipline from the perspective of some of the many researchers who have engendered this progress. As a case in point, consider the growing body of data on the role of the inferior colliculus in seizure genesis and as a model system for the study of epilepsy (Chapter 21), an area that has grown considerably since 1986 and that has had a significant impact on diverse areas including sensory-to-motor transformations and the possible role of GABAergic neurons in kindling and seizure control. Any consideration of GABAergic neurons, of course, must include their role in local processing as putative interneurons (Oliver et al. 1991) as well as their ascending projection to the medial geniculate body (Winer et al. 1996), the differential, subdivision-specific concentration of GABAergic neurons and axon terminals (Oliver et al. 1994), and the maturation of GABAergic transmission (Yigit et al. 2003); each of these topics is of moment, each crosses interdisciplinary boundaries that can range from development to pathology, and none could have received the appropriate attention in prior synthe-

ses. Because we could not in conscience exclude a particular subject, we attempted to include all that seemed to us to capture best the sense of flux and excitement of current approaches. There remain, of course, many gaps: for example, the subject of synaptic organization has received less attention than might have been expected, and it remains an area that will require further scrutiny if we are to understand how signals arising from the many medullary auditory centers and converging onto the inferior colliculus are transformed locally before they ascend to the auditory thalamus or descend within the brain stem. Likewise, developmental studies are at their earliest stage other than the purely descriptive, and we have little knowledge of how closely the cellular ontogenetic molecules and migratory processes that shape the midbrain follow principles established in the cerebral cortex (Molnár and Blakemore 1995).

Other conceptual approaches that have not been included explicitly are those that can be subsumed under the umbrella of computational neuroscience. There are a few modeling approaches to aspects of temporal coding or binaural processing that were designed to reflect properties specific to the inferior colliculus (e.g., Hewitt and Meddis 1994; Cai et al. 1998; Shackleton et al. 2000; Borisyuk et al. 2002). But it is difficult, and perhaps premature, to assemble a coherent theoretically oriented treatment of inferior colliculus properties, mechanisms, and function.

Where it was possible, we asked that authors propose an agenda for the future in which the salient questions for their discipline are enumerated as an organic part of their exposition. To keep the reference list within manageable limits, we requested that authors cite only the most recent work when this was possible; this strategy acknowledges the historical and intellectual value of Aitkin's (1986) volume.

The conceptual framework for this volume is integrative and reflects a systems perspective. In this context, integrative implies that we sought authors who would collaborate with peers who often held a different perspective, thus producing what we hope are balanced accounts of a given area that are free of parochialism. Where there is only one author, it was our view that the consensus of opinion (or the limited knowledge) in that particular area could be captured by the author we chose. Likewise, chapter length was guided by the literature available and whether the issues at hand were perceived as volatile or matters of settled opinion. The systems viewpoint construes the brain in terms of interacting neural networks whose separate elements contribute to the abstraction of larger entities related to hearing, perception, and binding the disparate streams from independent neural channels into a coherent experience. Perhaps the next volume devoted to the auditory midbrain can realize that goal.

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Chapter 1
The Central Auditory System: A Functional Analysis

JEFFERY A. WINER AND CHRISTOPH E. SCHREINER

1. INTRODUCTION

Auditory neurons must encode and decipher the spectral, spatial, and temporal properties of sound. These processes are a prerequisite to the subsequent extraction of biologically meaningful signals from a noisy environment and to establish perceptual attributes. The goal of this survey is to provide a framework for thinking about how the auditory system performs these tasks. Such a framework seems essential when considering a network of neurons that extends from the external ear to the cochlea and through many synaptic relays before reaching the cerebral cortex (Figs. 1.1A and 1.2). The internal complexity of this system is apparent in each of the nuclei that comprise the auditory pathway: a given nucleus contains thousands of neurons, each connected to and sharing information with nearby neurons as well as many other, remote nuclei. These neurons thus interact with themselves and their neighbors through many neurotransmitters, a host of synaptic mechanisms, and a wide range of membrane channels. These neurochemical and physiologic features endow the various neuronal classes with an enormous range of response repertoires individually as well as the functional capacity to decipher the temporal, amplitopic, and spatial aspects of the auditory signal. In each nucleus, the several kinds of cells each have a particular constellation of response properties that defines them. Some discharge most strongly to sound onset, others respond to noise or frequency-modulated sound, and still others prefer changes in loudness, to name just a few of the many stimulus dimensions that the auditory system routinely extracts, encodes, and represents. Considering the diversity of response types, the possible multiplicity of their connections, and the many levels of interaction between nuclei from the medulla to the cortex, the auditory system presents a formidable challenge to, and an opportunity for, reductionistic thinking.

To confront such a challenge, this system is considered from the perspective of its operating elements, the neurons, and the circuits they form. This viewpoint is useful as the many cells and circuits and the operations they perform have now been characterized in sufficient detail that they can be described in a biological context. This level of discourse is among the first steps toward a mature

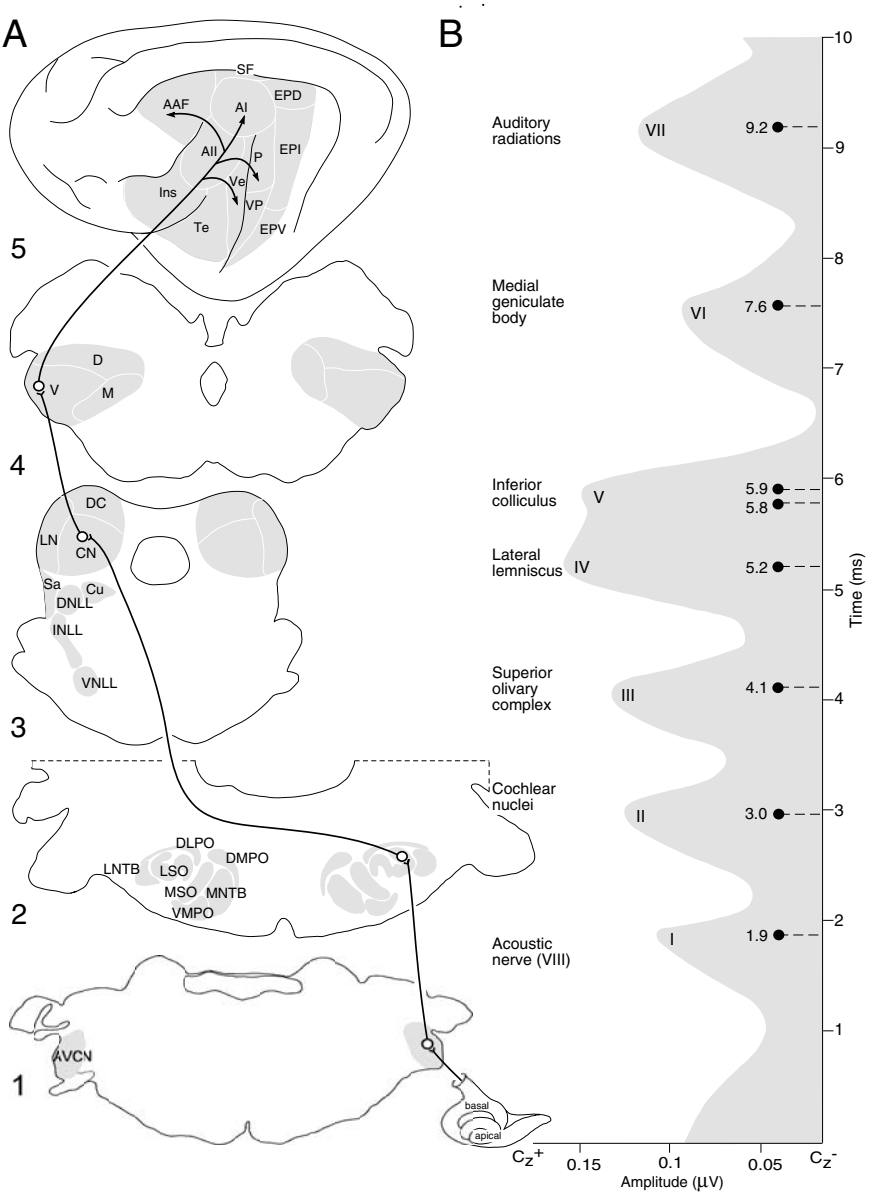

Figure 1.1. Primary components of the central acoustic system **(A)** and level-specific distribution of components of the auditory evoked potential **(B)**. **(A)** The major nuclei of the auditory pathway; for clarity, the cochlea has been omitted (see Fig. 1.2), as has the posteroventral cochlear nucleus (see Fig. 1.3A). *1:* The cochlear nucleus receives its ascending input via the cochlear nerve. Cochlear nucleus axons then decussate (present example) or terminate ipsilaterally (Fig. 1.2: cochlear nuclei). Intrinsic cochlear nucleus connections are not shown, and the totality of cochlear nucleus targets is extensive,

science of hearing, as these elements constrain the performance of the system by defining its permissible operations. This brief introduction concentrates on the central auditory system from the cochlear nucleus to the cerebral cortex; the cochlea is excluded because it merits a separate and extended treatment in its own right and because the issues it entails are beyond the scope of the themes addressed here.

The emphasis is explicitly functional and it treats the auditory pathway as a network of six interrelated parts whose organization will be explored in a neuroanatomical and a neurophysiological context. The parts are:

- Cochlear nucleus: genesis of basic response patterns and emergence of parallel pathways.
- Olivary complex: construction of binaural pathways and establishment of time lines.
- Lateral lemniscal nuclei: emergence of chemically specific nuclei.
- Inferior colliculus: site of brain stem convergence and multisensory integration.
- Medial geniculate body: modulation of auditory information by cortical and limbic systems.
- Auditory cortex: interface of hearing and higher order communication and cognitive networks.

Unless noted otherwise, the cat is the reference species because the literature available is so extensive. Surveys of basic auditory system organization should be consulted for other topics (Brodal 1981; Edelman et al. 1988; Popper and Fay 1992; Webster et al. 1992).

Figure 1.1. *Continued*
involving up to eight nuclei (Fig. 1.7). *2:* Input to the lateral superior olive *(LSO)* is topographic and ends in regular arrays (Feng and Vater 1985) that preserve the tonotopic arrangement in the cochlear nuclei (Fig. 1.3C, D). *3:* The LSO projects to the contralateral central nucleus of the IC; it conserves this topography (Servière et al. 1984) and may selectively target specific aural subregions in the IC (Ross et al. 1988; Brückner and Rübsamen 1995). *4:* The tectothalamic input is bilateral (not shown), with the ipsilateral component dominant (González-Hernández et al. 1991). *5:* The projection to auditory cortex is entirely ipsilateral, and highly divergent, involving several primary fields (Niimi and Matsuoka 1979) and has a specific laminar arrangement (Sousa-Pinto 1973); the latter feature could redirect thalamocortical influences to parts of the ipsilateral corticocortical system (Rouiller et al. 1991) or to the corticofugal network (Prieto and Winer 1999). Although the auditory system is depicted as hierarchical, its operations involve direct descending projections (Fig. 1.18) at almost every level (Aitkin 1986) as well as extensive connections with auditory-related areas of the neocortex (Seltzer and Pandya 1994). **(B)** The brain stem evoked response at seven levels (I to VII) in the auditory system. In humans, the superior olivary complex is in the pons and the cochlear nucleus at the junction of the pons and medulla. The arrival time of each waveform appears on the ordinate, while the abscissa shows their amplitude. For all figures, please refer to the list of abbreviations in the text. [Redrawn and modified from original sources (Chusid 1982; Webster and Garey 1990).]

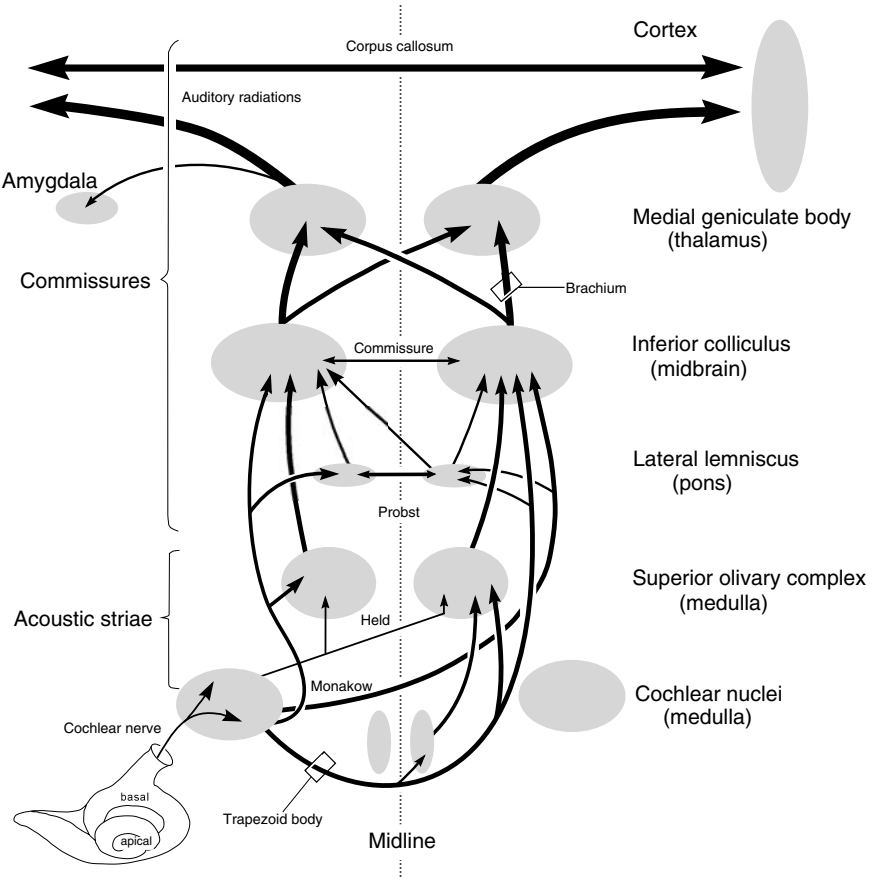

Figure 1.2. Schematic view of the principal ascending connections of the central auditory pathways. Local circuit arrangements and descending connections have been omitted for clarity, as have smaller nuclei such as the interstitial nucleus of the cochlear nerve root (Hutson and Morest 1996). Several important principles are embodied even in this highly schematic picture of connectivity. First, the output of almost every nucleus targets many centers and is highly divergent; this is accomplished either via branching axons from a single projection cell (Friauf and Ostwald 1988) or by different cochlear nucleus cell types targeting separate nuclei (Cant 1982; Thompson 1998). A second principle is connectional convergence: most nuclei receive multiple sources of input, of which the inferior colliculus is among the best examples, with more than 10 different projections to the central nucleus (Roth et al. 1978; Brunso-Bechtold et al. 1981). The acoustic striae are the main output tracts of the cochlear nuclei; their fibers converge ventral and medial to the superior olivary complex as the trapezoid body (Fig. 1.8A), in which many small nuclei are embedded (Brownell 1975). Third, commissural projections are present at most synaptic stations in the auditory system (Aitkin and Phillips 1984a). Not shown are commissural interconnections between the cochlear nuclei (Cant and Gaston 1982); an exception is the medial geniculate body, which has no commissural pathway. Fourth, there is an array of internal circuitry in every nucleus, and a nucleus- and sometimes a

2. The Cochlear Nuclei

In the cochlear nuclei the principles emerge that will dominate the auditory system at subsequent levels of processing (Osen 1988; Rhode and Greenberg 1992). The major themes are that there is (1) an orderly input that preserves the topography of frequency established in the cochlea (Osen 1970); (2) massive divergence of auditory nerve projections creates multiple new and nonequivalent maps from a single cochlear origin (Osen 1972); (3) great variety in structure and function among the specialized postsynaptic neurons that process the output of the auditory nerve (Osen 1969; Cant 1992); (4) an abundant number of inhibitory neurons to constrain, modulate, and refine the primary excitatory input (Adams and Mugnaini 1987); and (5) an array of descending projections from higher order auditory structures that provide feedback (Kane and Conlee 1979). The cochlear nucleus will be considered in slightly more detail because a large literature is available and because the functional principles that govern it are repeated and elaborated at many further levels.

The cochlear nuclei are among the first parts of the central auditory system to have evolved, and they are present in every vertebrate (Baird 1974). In amphibians and reptiles they form a semicircular mass of a few hundred neurons on the lateral edge of the medulla (Gregory 1974), and in carnivores and primates they represent a distinct lobe of highly differentiated cells beside the cochlea and the cerebellum. The auditory nerve is thus among the shortest cranial nerves in most species, and the thick coat of myelin on primary afferent axons and even covering ganglion cell perikarya ensures rapid transmission of acoustic impulses to the medulla. The auditory nerve axons spiral as they traverse the cochlea to reach the brain. They enter the cochlear nucleus rostroventrally, and then divide into descending and ascending branches (Ryugo 1992). This bifurcation redistributes the single sheet of the cochlear sensory epithelium across a volume; because each point (or, more properly, strip) represents a limited range of frequency (Fig. 1.3) and because each frequency is in topographic registration with its neighbors, the cochlear nucleus contains at least two independent maps of the frequency spectrum (Rose et al. 1959) (Fig. 1.4). The volume that corresponds to a frequency is termed isofrequency, and an isofrequency contour may contain several thousand neurons arrayed in flattened sheets and across which the cochlear axons are distributed more or less evenly (Fekete et al. 1984) (Fig. 1.3). This or analogous arrangements in which a distal map

Figure 1.2. *Continued*
species-specific distribution of interneurons and their synapses (Winer and Larue 1996). Fifth, many projections are reciprocal (not shown), especially those between the brain stem nuclei (Conlee and Kane 1982) and those of the thalamus and cortex (Colwell 1975). [Redrawn and modified from original sources: main diagram (Gulick et al. 1989); cochlea (Brödel 1946).]

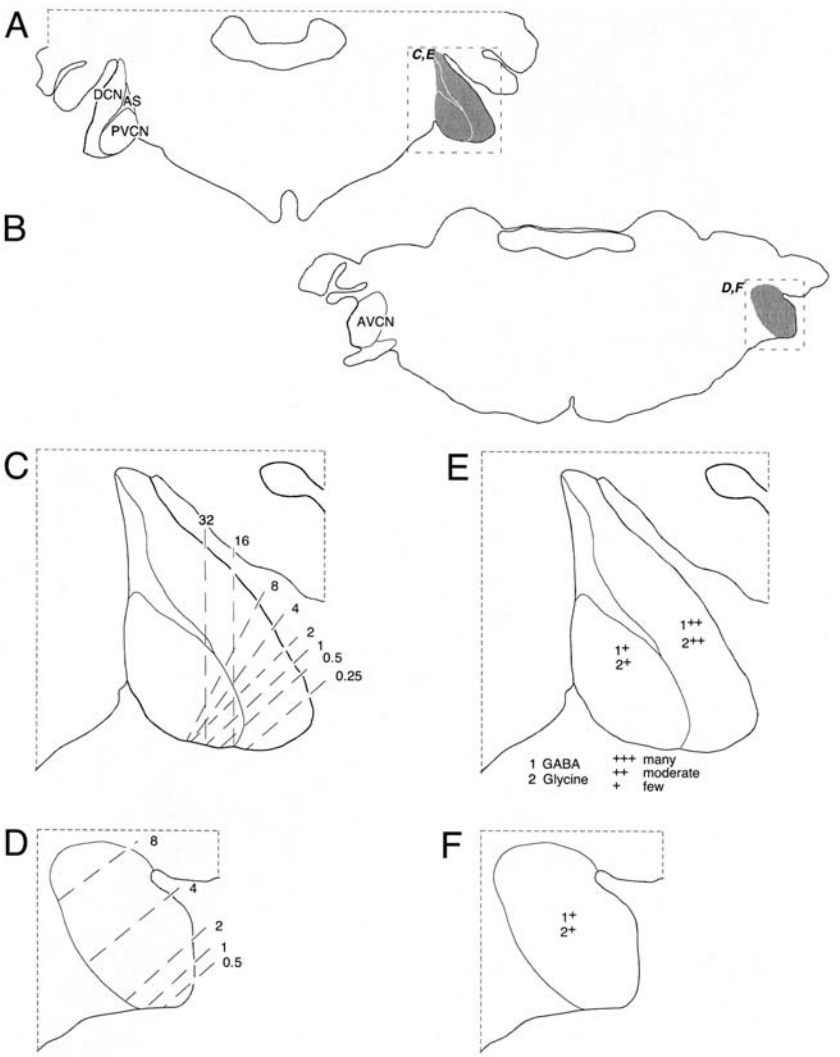

Figure 1.3. Some physiologic and neurochemical aspects of cochlear nucleus organization. **(A, B)** Cochlear nucleus subdivisions (Osen 1969; Brawer et al. 1974). In this and subsequent figures relating to other auditory nuclei, only the principal subdivisions are shown. **(C)** Spatial and nuclear arrangement of characteristic frequency as expressed in isofrequency lines *(dashed)* in the anteroventral and posteroventral cochlear nuclei (*AVCN* and *PVCN*). The systematic representation of frequency reflects the topography of cochlear nerve input (Leake-Jones and Snyder 1982) and it is conserved in both the AVCN and PVCN. Noteworthy features include the large spatial representation of frequencies $<$10 kHz, and the complexity of laminar overlap near nuclear borders and in regions where cochlear nerve axons bifurcate and their complex spatial geometry (Osen 1970) distorts a simple laminar organization; elsewhere in the central auditory system a spatial

of frequency is expanded, contracted, or distorted will be repeated many times between the cochlear nuclei and the cortex.

A constraint on a perfectly uniform distribution of the frequency spectrum is the biological significance of particular subregions: frequencies essential in communication are likely to have an enlarged representation (Suga and Jen 1976), and the degree of this expansion can match that in the cochlea itself (Feng and Vater 1985). This principle recalls the disproportionate sensory and motor neural representation of the primate hand relative to that of the foot (Kaas et al. 1984), or the central (foveal) part of the retina compared to its more peripheral regions (Tusa et al. 1981).

The divergence of the auditory nerve is not simply a bifurcation: it entails a structural reorganization of the postsynaptic neurons as well. The axons of the descending branch terminate in delicate boutons that will make synapses on the dendrites and cell bodies of neurons in the dorsal cochlear nucleus (DCN). These synapses—their number, location, and shape—will profoundly influence the physiologic behavior of the postsynaptic neurons. For example, synapses closest to the axon hillock, which is the electrogenic membrane controlling the discharge behavior of the cell, will have the maximum efficacy (Peters et al. 1991). The divergence of connectivity multiplies the channels of information exiting the cochlear nuclei and which, after reaching a variety of medullary auditory centers, converge on the inferior colliculus (IC). (See Fig. 1.5.)

The potential functional ramifications of the diverging projections from the auditory nerve are magnified by the great variety of morphologic cell classes that is targeted. As a consequence of morphology, convergence, and local circuitry, these cell classes differ functionally in distinct ways including their temporal response pattern, spectral selectivity, and discharge regularity. To highlight differences in their response properties, we next compare two types of cochlear nucleus neurons. Among the most conspicuous of the many types of DCN neu-

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Figure 1.3. *Continued*
compression of higher frequencies occurs (Morest 1965). This distortion is partly an artifact of collapsing a three-dimensional geometry onto two dimensions. [**(C, D)** Redrawn and modified from original sources (Bourk et al. 1981 with permission from Elsevier Science).] **(D)** In the AVCN the expanded volume devoted to low frequencies is even more pronounced than in the dorsal cochlear nucleus *(DCN).* **(E)** The distribution of GABAergic and glycinergic neurons follows specific patterns in the cochlear nucleus. In the DCN, both are concentrated in layers I to III; both neurons and axon terminals are plentiful here and much sparser elsewhere. GABAergic neurons may also colocalize glycine (Osen et al. 1990) and there is evidence for simultaneous corelease of both molecules (Jonas et al. 1998). In this and other nuclei, the vast majority of the other neurons are glutamatergic (Saint Marie 1996) or aspartatergic (Altschuler et al. 1981), as is the cochlear nerve (Wenthold 1985). [**(E, F)** Redrawn and modified from original GABA observations (Adams and Mugnaini 1987); redrawn and modified from original glycine observations (Wenthold et al. 1987).] **(F)** In the AVCN, there are few GABAergic or glycinergic neurons.

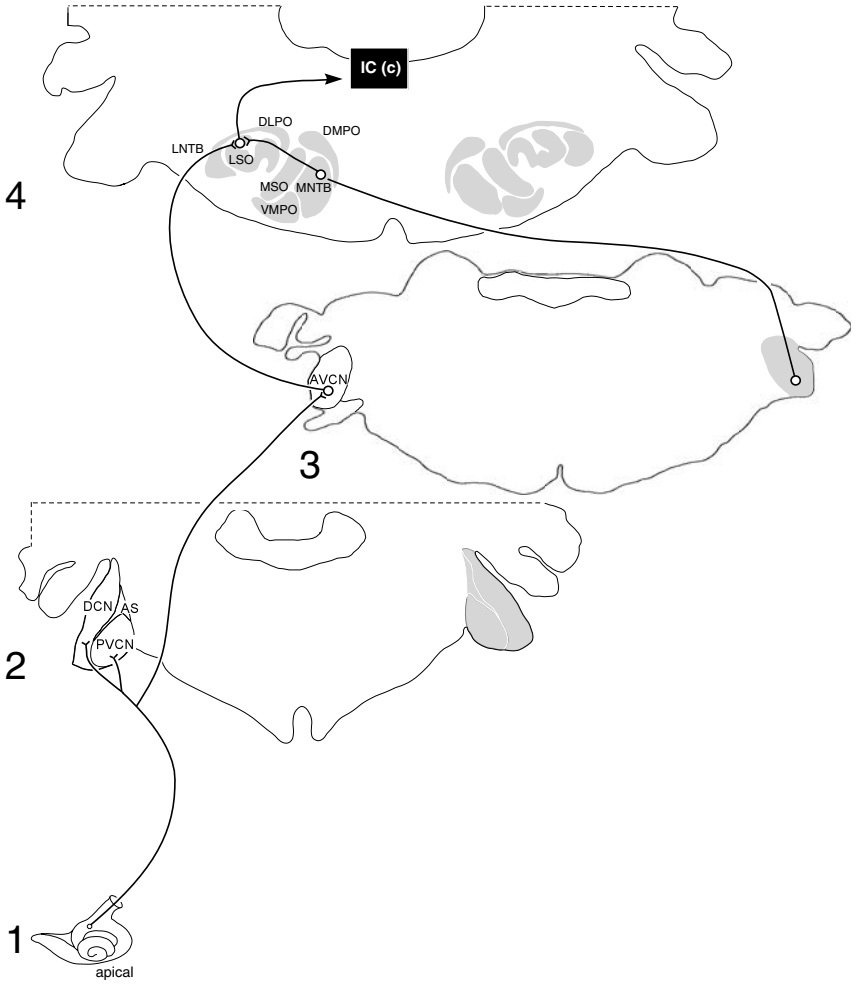

Figure 1.4. Representation of two basic principles of auditory brain stem connectivity—divergence and convergence—and their complementary functional roles. *1, 2:* Spiral ganglion cell axons divide and project to subdivisions of the cochlear nucleus (Lorente de Nó 1933, 1981). This creates independent maps of characteristic frequency (Rose et al. 1959). *3, 4:* Topographically matched projections from each anteroventral cochlear nucleus *(AVCN)* have different targets in the medulla: the ipsilateral projection ends in the lateral superior olive *(LSO)* (Cant and Casseday 1986), while the contralateral AVCN projects to the medial nucleus of the trapezoid body (*MNTB*) (Warr 1966), whose axons converge on the other primary dendritic trunk of the same postsynaptic neuron (Spangler et al. 1985; Vater et al. 1995). This creates binaural receptive fields among superior olivary complex neurons (Tsuchitani and Boudreau 1966; Tsuchitani and Johnson 1991).

rons is the fusiform cell; it has a pyramidal cell body and an extensive dendritic tree (Brawer et al. 1974). These processes act as postsynaptic sites: their thick trunks and slender spines are studded with presynaptic axon terminals, most from the auditory part of the eighth cranial nerve (Cant 1992). A consequence of this pattern of axodendritic organization is that it requires spatiotemporal summation to elicit a postsynaptic response that differs significantly from the rate of spontaneous discharge. A constraint is that the postsynaptic dendritic propagation of all-or-none signals is decremental because the dendritic membrane typically lacks the regenerative channels found in myelinated axons and that permit them to send spike codes over long distances while conserving amplitude or fidelity. Thus, inputs to the most distal dendrites usually have correspondingly less influence than terminals near the axon hillock (Jack et al. 1975), unless they are amplified at dendritic branch points (Stuart et al. 1997). Dendritic input may require a coordinated volley of presynaptic impulses arriving optimally to achieve the spatial and temporal summation necessary to cross the threshold of the postsynaptic neuron. The threshold and the electrotonic properties of the dendrites act as adaptive filters to reduce spontaneous discharges in an auditory environment filled with ambient noise. Many neurons respond best to changes in sound pressure level (dynamic response), while others prefer steady-state (tonic) conditions (Young 1984). These extremes effectively reduce noise yet preserve the ability to respond to static stimuli or to signals with a wide dynamic range.

The physiologic types of cochlear nucleus neurons have been determined using tonal or noise stimuli to generate peristimulus time histograms that provide insight into basic coding properties (Fig. 1.6). This strategy was applied originally in the auditory nerve to classify the responses of cochlear ganglion cell fibers (Kiang et al. 1965), and it has revealed the temporal profile of neuronal responses in many regions (Kiang et al. 1973). The discharge pattern of intracellularly identified fusiform cells in the DCN shows a pauser/buildup pattern (Fig. 1.6D, E). This consists of a delayed discharge after stimulus onset, a burst of spikes concentrated in the first few milliseconds, an abrupt decline to near-zero spikes, and, finally, a subsequent slow growth in spike rate punctuated by briefer reductions; the unit never reestablishes the spike density at onset, and the discharge can persist or even increase long after the poststimulus period (Rhode et al. 1983b).

As viewed in the electron microscope, many of these physiologic attributes have ultrastructural correlates that could support them. Thus, fusiform cells receive synapses indicative of independent excitatory and inhibitory input on their distal dendrites. The excitatory endings (Oliver et al. 1983) are axodendritic synapses of eighth nerve origin and terminals from granule cell parallel fibers, which project in long rows across these dendrites (Fig. 1.7B: pf). Prospective inhibitory input arises from four types of neuron—each with a specific synaptic arrangement on the postsynaptic cell. Stellate, vertical, Golgi, and cartwheel cells each project to fusiform cell dendrites (Berrebi and Mugnaini 1991). Some of these neurons may be glycinergic (Wenthold and Hunter 1990) and others

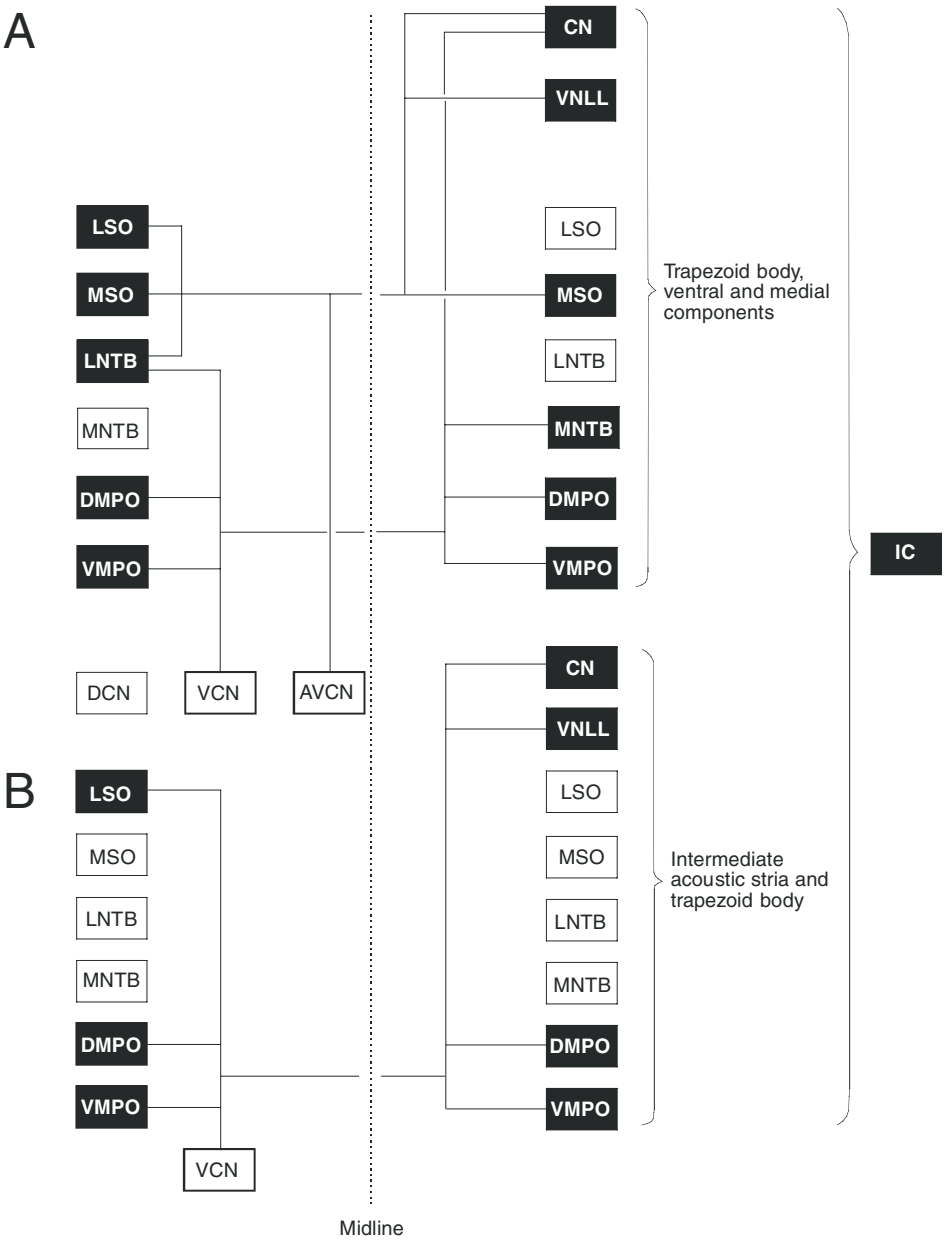

Figure 1.5. Components of the striae of Held and von Monakow and the trapezoid body (Fig. 1.2) shown schematically. Their medullary target nuclei each project to the inferior colliculus. **(A)** Trapezoid body, ventral and medial components. **(B)** Intermediate acoustic stria and trapezoid body. [Redrawn and modified from original sources (Warr 1982; Irvine 1986).] Key for this and subsequent schematics: *open boxes with heavy outlines,* origins of projections; *solid boxes with white lettering,* targets of projection; *lines,* axons; *dotted line,* midline; *brackets,* fiber tracts. Ascending pathways are shown in these diagrams unless indicated otherwise (Fig. 1.18).

γ-aminobutyric acid (GABA)-ergic (Adams and Mugnaini 1987); this suggests cell-specific interactions that mediate the discharge properties and influence the receptive field profile of postsynaptic neurons. Although the exact nature of the dynamic interactions among these convergent inputs on fusiform cells is not known, they could contribute to the periodic fluctuations and gradual decline in rate seen in pauser/buildup units. Overall, then, fusiform cells perform a profound and complex spectral and temporal transformation of the auditory nerve input whose ultimate functional purpose may contribute to several, still largely elusive, central auditory tasks.

In the anteroventral cochlear nucleus (AVCN), the response of a different type of neuron, the bushy cell, can be contrasted with, and complements that of, the DCN fusiform cell. Here, ascending auditory nerve fibers end on bushy cell somata. These neurons differ fundamentally from fusiform cells (Lorente de Nó 1981). Bushy cells have only one or two short dendrites, and their predominant synaptic ending is an auditory nerve axon, the endbulb of Held, which forms a massive cuplike terminal that encloses the perikaryon, with several such endings and with virtually identical tuning curves converging onto a cell (Cant and Morest 1979). Thus, the dendritic arbors of these cells are modest, while the most potent synaptic input from the endbulbs terminates near the axon hillock. The net probability of presynaptic signals evoking a postsynaptic discharge therefore is effectively unity (Rhode et al. 1983a). Moreover, these neurons discharge preferentially to the earliest, onset-related features of the stimulus. The tonotopic representation in the AVCN is unusual: frequencies <5 kHz are mapped selectively and expansively. The electrophysiologic profile of the response is also unique because of the size of the endbulb and the large-amplitude prepotential in the afferent fiber, neither of which is present in the DCN (Bourk et al. 1981). Frequency tuning, rate-intensity function, and discharge regularity of bushy cells closely resemble their auditory nerve inputs. Hence, they perform only a minimal transformation of the input and, rather, ensure a faithful information transmission beneficial for processes in the following stations, such as binaural comparators. The fusiform and bushy cells are just two examples of the wide range of structural/functional patterns represented in the cochlear nucleus, and they embody only some of the nuclear- and cell-specific response patterns (Rhode 1991). More than 20 kinds of neuron have been identified in the cochlear nucleus (Brawer et al. 1974).

The presence of local circuitry within the cochlear nucleus itself further refines signal processing. These circuits may function to reject unwanted signals, amplify weak inputs, provide inhibition that enhances the signal-to-noise ratio (Berrebi and Mugnaini 1991), or serve a disinhibitory role. Because the responses of auditory nerve axons are sharply tuned to specific frequencies with no inhibition, and because stimulation at unfavorable frequencies elicits a negative or no response (Kiang et al. 1965), such circuitry intuitively might not seem necessary. In the cochlear nucleus, however, the convergence of input from many different fibers onto a single neuron could blur the fine spatial and temporal patterns of activity, or help to retune or focus the cell's response area to a particular aspect of the stimulus, such as in monaural echo suppression

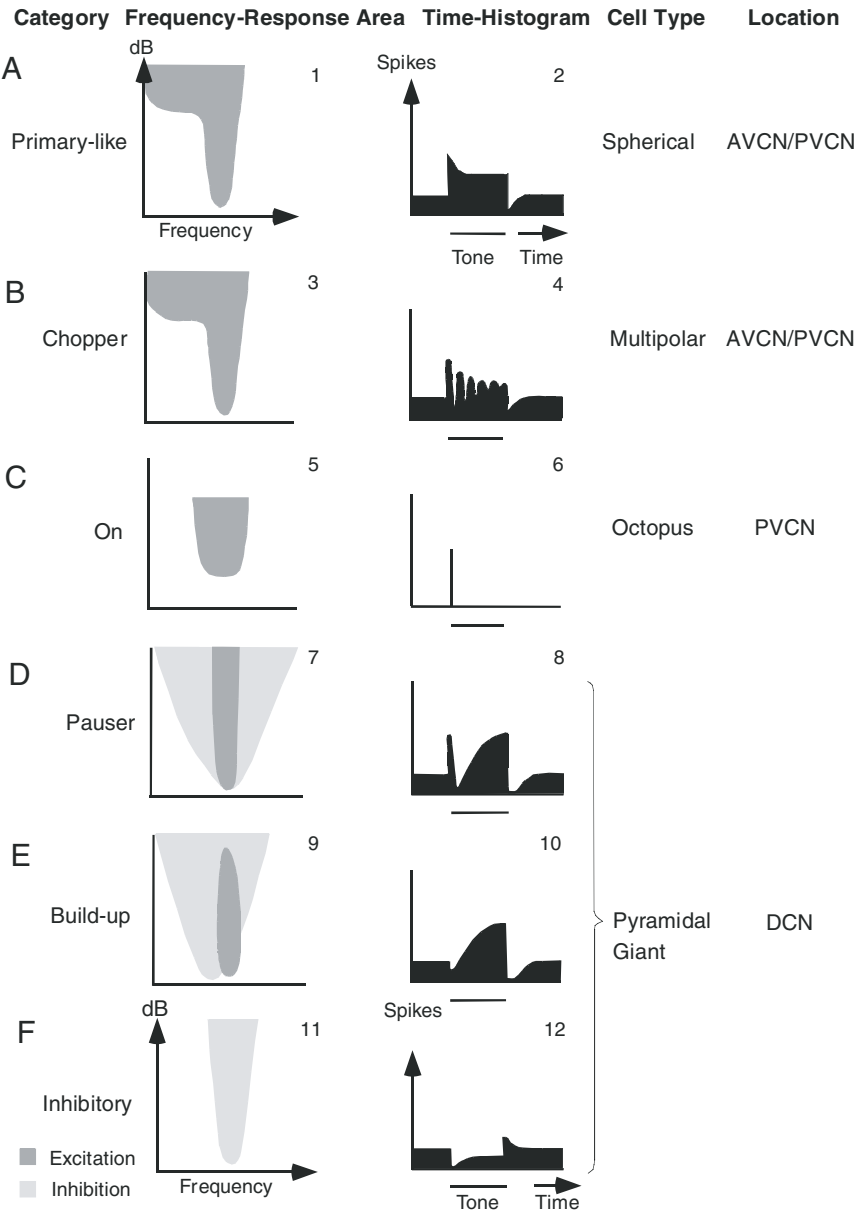

Figure 1.6. A categorical description of cochlear nucleus physiologic response profiles and their correlation with neuronal types. The frequency-response areas *(1, 3 . . . 11)* depict the tuning curve types, while the peristimulus time-histogram *(2, 4 . . . 12)* shows the interplay of intrinsic membrane properties and the excitatory–inhibitory interactions that shape the cell's dynamic response to tones. The inhibitory contribution to the receptive field is also visible in the frequency-response area (**D:** *7,* **E:** *9,* **F:** *11*). Although

(Wickesberg and Oertel 1990). Inhibition can impose unique filter properties on the tuning behavior and modify the neural response profiles. Thus, type II DCN interneurons are sharply tuned, with large excitatory response areas flanked by lateral zones of inhibition, and they have little spontaneous activity (Young and Voigt 1982). Type II cells are thought to have local feedforward projections onto type IV neurons, the fusiform or giant cells. Thus, type IV cells cease firing when the type II units increase their spike rate. The type II discharge creates powerful inhibitory subregions in the tuning curve of the type IV cell; the tight temporal cross correlation in spike discharge indicates that these neurons may be linked monosynaptically. Such circuits could underlie the type IV unit's robust response to broad-band noise and the inhibitory effects of pure tones (Young 1984). This circuit is analogous to one made in the cerebral neocortex by inhibitory interneurons (basket cells) on pyramidal cells (White and Keller 1989; Prieto et al. 1994a) and by similar kinds of IC cells (Oliver et al. 1994). Such circuits may be a common feature in many nuclei for regulating the output of projection neurons and for reorganizing their receptive fields in response to environmental demands (Bjordahl et al. 1998; Kilgard and Merzenich 1998a). It remains to elucidate in equal detail the functional connectivities among the many other cochlear nucleus neuronal populations.

Already in this first nucleus of the auditory pathway, several themes are established that have major consequences in subsequent processing and reflect equivalent mechanisms throughout the auditory system. Many of the different cell types distribute the transformed information to specific proximal targets. Although there is not necessarily a one-to-one relationship between type of projecting neuron and target nucleus or cell type, at least six parallel streams of diversely transformed or modulated auditory information emerge. Each stream embodies a different preprocessing principle that is likely best suited for further, specific central processing tasks. Accordingly, the auditory signal is decomposed not just in terms of its frequency content but also in terms of a variety of other stimulus features that are composed of complex aspects of spectral, temporal, and spatial signal attributes. The particular contributions of most of these concurrent streams originating in the cochlear nucleus to the process of feature extraction, object recognition, and, ultimately, perception remain to be established.

Figure 1.6. *Continued*
a detailed treatment of the individual categories is beyond the scope of this chapter, the range of responses in the primary auditory nuclei suggests that peripheral receptor diversity contributes little to coding, while in the somatic sensory system peripheral receptor diversity plays a major role in the establishment of separate processing streams (Sinclair 1981). A major basis for auditory coding is thus local circuitry, although diversity in hair cell responses (Ashmore 1991) and spiral ganglion cell behavior (Kim and Molnar 1979) and differential projections (Brown and Ledwith 1990) must contribute to this pattern. [Redrawn and modified from the original sources (Evans 1982 with the permission of Cambridge University Press; Webster and Garey 1990).]

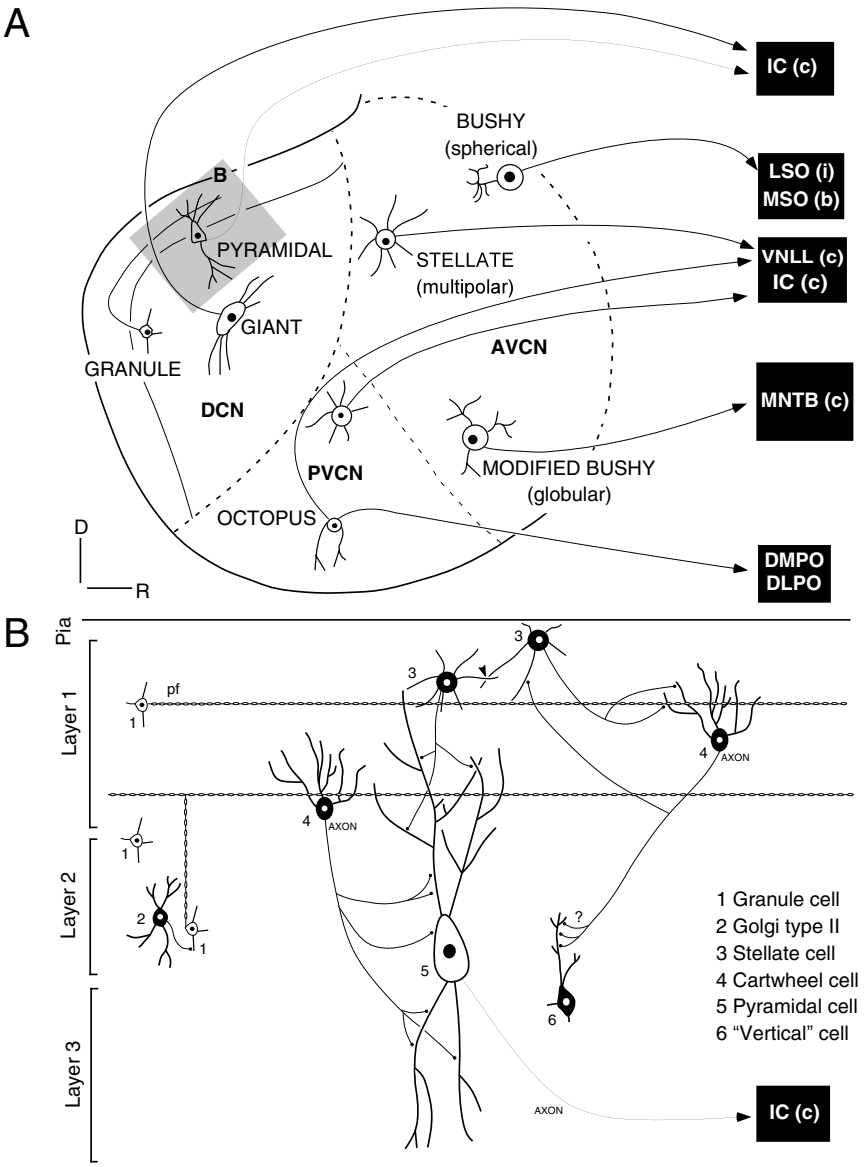

Figure 1.7. Some projections of cochlear nucleus neurons that may contribute to parallel processing in the superior olivary complex, lateral lemniscal nuclei, and inferior colliculus. **(A)** In a parasagittal schematic, cartoons of the principal cochlear nucleus neurons demonstrate that they have diverse ipsi- and contralateral targets. Differences in the temporal coding among these cell types (Fig. 1.6: *2, 4 . . . 12*) suggest that the streams leaving the cochlear nucleus are integrated in higher centers (when they converge) or contribute to parallel pathways (when they diverge) (Warr 1982). [Redrawn and modified from

3. The Olivary Complex

The olivary complex consists of four (humans) to nine (cats) nuclei (Moore and Moore 1971) that have several complementary physiologic roles. Neurons in the LSO integrate the monaural input of the cochlear nuclei to derive intensity-difference sensitive binaural signals, mainly for high frequencies, and to send this information to the lateral lemniscal nuclei (LLN) and the IC (Schwartz 1992). Neurons in the medial superior olive (MSO) encode phase relationships and delay sensitivity from the two ears (Fig. 1.8D), mainly from lower frequencies; these signals are essential for accurate spatial localization (Yin and Chan 1990). Neurons in the medial nucleus of the trapezoid body (MNTB) contribute to the creation of binaural subtypes via their inhibitory input to the LSO (Guinan and Li 1990). The construction and variety of binaural interactions represent a situation in which emergent function can be directly related to a particular neural circuit (Tsuchitani and Johnson 1991). The species-specific variability in the size, shape, and disposition of the olivary nuclei (Schofield and Cant 1991) suggests that ecologic factors (Masterton et al. 1975) might induce structural changes related to evolutionary adaptations in hearing (Papez 1929). All subdivisions have a tonotopic organization (Fig. 1.8B).

The striking precision of connectivity in the central auditory system is exemplified in the ascending projection onto principal cell lateral dendrites in the LSO. In this example, one primary dendrite is postsynaptic to input from the ipsilateral AVCN, whose output cells may be aspartatergic and are likely excitatory (Oliver et al. 1983). The other dendrite is the target of axons from cells in the MNTB (Cant and Casseday 1986), which are glycinergic and probably inhibitory (Bledsoe et al. 1990). The contralateral AVCN provides the excitatory drive to the MNTB. This convergence has important functional consequences, as olivary principal cells integrate ipsilateral (excitatory) and contralateral (inhibitory) input whose chemical signals can facilitate or suppress postsynaptic neurons. This convergence creates the first binaural neurons in the auditory system and their discharge pattern integrates excitation and inhibition.

Figure 1.7. *Continued*
Aitkin (1989).] **(B)** Schematic view of local circuits in layers 1 to 3 of the dorsal cochlear nucleus, showing the main types of neurons and their synaptic relationships. Some connections, for example, between stellate cells *(3),* have not yet been demonstrated. The major relationships shown here in the guinea pig depict cartwheel cells *(4)* projecting to the superficial and deep dendrites of pyramidal cells *(5);* the cartwheel cell input to the vertical cell *(6)* is likewise unconfirmed. Parallel fibers *(pf)* arising from granule cells *(1)* provide excitatory input to the layer 1 inhibitory neurons and to the apical dendrites of pyramidal cells. A '?' indicates a possible projection. Arrowhead, gap junction between stellate cell dendrites. [Redrawn and modified from original sources (Berrebi and Mugnaini 1991).] Neurons in *black* are considered inhibitory (Osen et al. 1990).

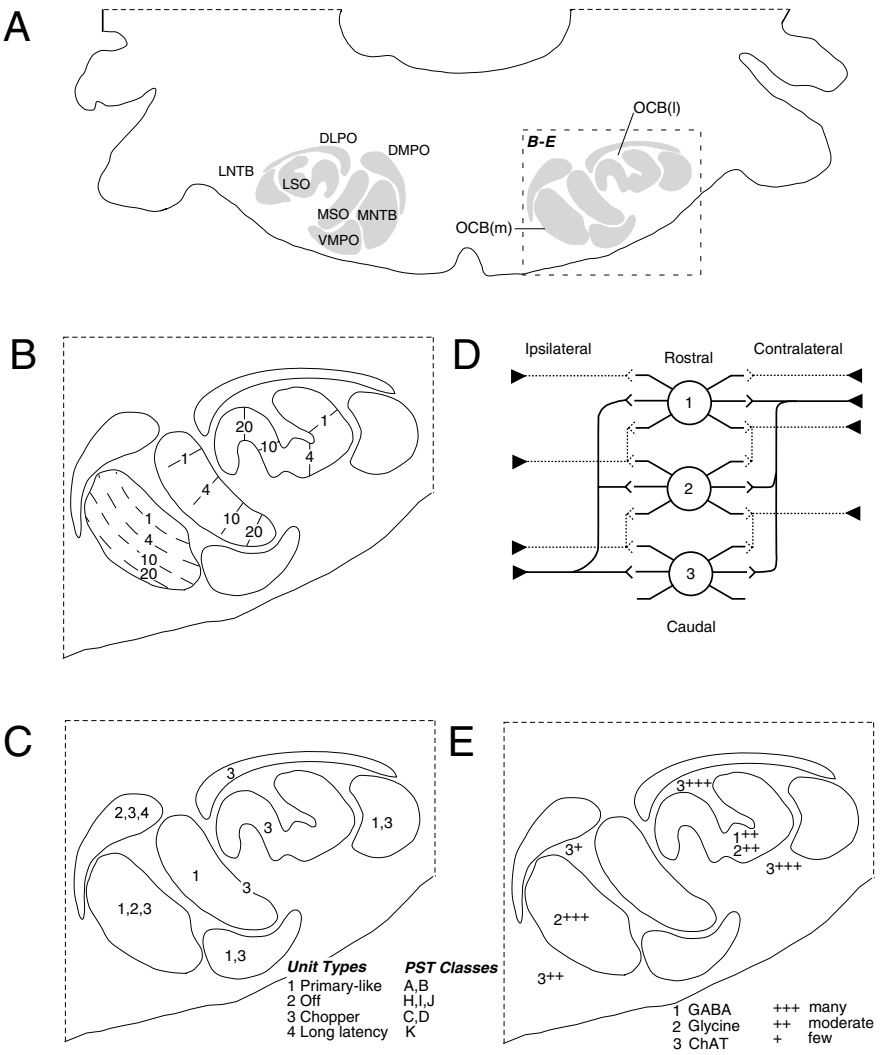

Figure 1.8. Basic organizational features of the superior olivary complex. **(A)** The individual nuclei of the superior olivary complex are well developed in the cat. As these nuclei have species-specific sizes and shapes (Harrison and Feldman 1970; Schofield and Cant 1991), proposals for homologies require careful analysis (Carr and Friedman 1999). **(B)** The principal nuclei each have a tonotopic organization in which frequencies <10 kHz are overrepresented at the expense of neurons with higher characteristic frequencies, a trend most evident in the medial superior olive. [Material in **B, C** redrawn from original source (Guinan et al. 1972b, Taylor and Francis Ltd. http://www.tandf.co.uk/journals).] **(C)** Summary profile of the main response types found in the superior olivary complex. The classification scheme ("Primary-like" . . . "Long latency") integrates the frequency response areas (Fig. 1.6, *left*) and the peristimulus response histograms (Fig. 1.6, *right*), which resemble those derived for neurons in cochlear nucleus sub-

An interesting issue is the existence of the MNTB in humans (Richter et al. 1983). Its absence would be unexpected because human performance in a test for discriminating the minimum audible azimuthal angle in sound localization is superior to that of all rodents and carnivores, and better than that of the porpoise for both noise and clicks (Fay 1988). Perhaps nuclei other than the MNTB have assumed the functions it once may have supported, or humans use other pathways for accurate localization, or the MNTB is undistinguished anatomically. There are certainly massive species differences among medullary nuclei and that undoubtedly have behavioral correlates (Harrison and Irving 1966). A second theme, which is preserved at subsequent levels of synaptic processing, is that two (or more) representations of a sensory attribute are interleaved across the several spatial axes of the LSO. One is related to frequency and has approximately a medial-to-lateral orientation; the other is concerned with aurality and runs roughly dorsoventral or orthogonal to the axis of frequency. It is highly probable that single nuclei do not represent one function only. A third idea that

Figure 1.8. *Continued*
divisions. [Redrawn and modified from original sources (Evans 1982); some material redrawn from other sources (Webster and Garey 1990).] The responses in the superior olivary complex not shown in this key are "Off" (in which stimulus onset suppresses all spontaneous activity, much like "Inhibitory" in Fig. 1.6F) and "Long latency" (in which the stimulus evokes a delayed response). **(D)** Circuit summary of axons in the medial superior olive from the anteroventral cochlear nucleus [Redrawn from original source (Beckius et al. 1999. Copyright by the Society for Neuroscience.).] The original, Jeffress, model is indicated by the *solid lines* (Jeffress 1948). Contralaterally, the shortest axons reach the central and caudal medial superior olive; ipsilaterally, the most caudal part was the target of the short fibers. Some axons *(dashed lines)* had a more restricted pattern of termination. **(E)** A neurochemical profile of the superior olivary complex, showing transmitter specific differences among nuclei. Some nuclei have glycinergic neurons only (medial nucleus of the trapezoid body), and others have both GABAergic and glycinergic cells (lateral superior olive). Projections of specific cell types to the inferior colliculus and elsewhere may be segregated in some cases and convergent in others (Oliver et al. 1997). Even within a nucleus such as the lateral superior olive, the distribution of GABAergic neurons and axon terminals (puncta) can be nonuniform, with gradients of immunoreactivity that are parallel to or cross the tonotopic axis (Winer et al. 1995). Observations on GABA taken from an original source (Adams and Mugnaini 1990). The periolivary cholinergic neurons have a special role in hearing as they are the primary source of the olivocochlear system. These neurons form a heterogeneous group (Vetter and Mugnaini 1992), most of which are dispersed on the margins of the ipsilateral lateral superior olive (about 50%) and medial to the medial superior olive (11%), while the crossed component is situated less in periolivary regions (15%) and medial to the medial superior olive (Liberman and Brown 1986). This system thus has multiple nuclear origins and at least some neurons receive descending input from the inferior colliculus (Vetter et al. 1993). Although the olivocochlear system is numerically small—ranging from 475 (mouse) to 2346 neurons (guinea pig)—it has widespread effects on cochlear processing (Warr 1992).

is reinforced by this convergence is that cell shape can have implications for functional arrangements in some cases. Thus, some principal cells in the LSO have polarized dendritic fields ideal for segregating ipsi- and contralateral afferents. A fourth observation is that neurons with binaural properties will be found at most subsequent levels of the auditory pathway. This implies that the processing at each synaptic station extracts different information from a stimulus; it may serve to explain the otherwise bewildering multiplicity of nuclei, maps, and representations in audition. A fifth issue is developmental, as the accuracy of innervation from the converging inputs must be high, and errors in connectivity low, for optimum performance (Sanes et al. 1990). Finally, the emergence early in the ascending auditory pathway of binaural neurons underscores a fundamental difference between it and the visual system, where the appearance of binocular neurons is deferred until the cerebral cortex (Ferster and LeVay 1978; LeVay et al. 1978).

The LSO has an important redistributive role: it sends axons bilaterally to the IC, with the most lateral, low-frequency (Tsuchitani 1977) projections ending ipsilaterally and the more medial, high-frequency portions terminating contralaterally (Elverland 1978; Glendenning and Masterton 1983). This projection has been characterized as an acoustic chiasm, a decussation like that in the visual and somatic sensory systems (Glendenning et al. 1985) in which a sensory hemifield is represented contralaterally within the brain. The idea of parallel pathways carrying different types of synaptic information is reinforced by the finding that the ipsilateral input has two neurochemical components, one of which is glycinergic and constitutes 41% to 60% of the projection neurons, while the contralateral pathway has only 4% glycinergic cells (Saint Marie et al. 1989). Such neurochemically specialized projections appear to be absent in the cochlear nucleus, excepting a glycinergic projection with a proposed role in monaural echo suppression (Wickesberg and Oertel 1990), and they are absent in the somatic sensory and visual systems.

A further novel feature of the olivary nuclei is the emergence of the olivocochlear efferent pathway. This system arises from fewer than 2000 neurons in the periolivary cell groups, a collection of small nuclei that are the origin of the centrifugal projection to peripheral receptors, principally to the outer hair cells. These primarily cholinergic (Vetter and Mugnaini 1990) centrifugal cells (yet another example of auditory neurochemical specificity) may influence the micromechanical properties of outer hair cells, thereby affecting basilar membrane dynamics and influencing the gain of the inner hair cells (Liberman and Brown 1986; Warr 1992). The olivocochlear system exemplifies the neurochemical and connectional diversity of the olivary complex in particular and the auditory system in general. Again, there are no parallels to the centrifugal pathways in the visual or somatic sensory systems in mammals.

In addition, another descending projection arises in the olivary complex, from the lateral and medial nuclei of the trapezoid body. These neurons project heavily, bilaterally, and topographically onto most parts of the cochlear nucleus (Spangler et al. 1987). This theme of prominent descending projections is pre-

served in the IC and the auditory cortex (and less so in the thalamus), and it is a robust feature in the subcortical auditory system. Such descending connections are absent in visual and somatic sensory systems.

The olivary nuclei, then, are the clearest examples of task-specific structures in the auditory system yet identified. The LSO and the MSO contain prime examples of computational maps, that is, systematic construction and representation of aspects of sound sources that cannot be derived from each ear in isolation but require convergence of different information streams. The mechanisms that lead to these maps, namely the use of coincidence detection and delay lines, also reflect general elements of neuronal processing evident in many other stations and a variety of tasks throughout the auditory system.

4. The Lateral Lemniscal Nuclei

The lateral lemniscus (Gr., *ribbon*) consists of three nuclei (dorsal, intermediate, and ventral) and the axons in which they lie along the lateral surface of the brain stem, near the transition from the pons to the midbrain. The nuclei extend from the rostral pole of the LSO to the ventral tip of the inferior colliculus. Many of their connections and physiologic properties resemble those of collicular neurons (Aitkin et al. 1970); however, certain structural and neurochemical arrangements are unique, such as the virtually pure GABAergic population of the dorsal nucleus (Adams and Mugnaini 1984) and the prominence of glycinergic cells in the ventral nucleus (Winer et al. 1995). These nuclei appear to be present in all mammals studied so far (Schwartz 1992). They have as wide a range in size and shape in different species as any auditory nucleus, from modest in rats (Bajo et al. 1993; Merchán et al. 1994) to well developed in cats (Berman 1968) (Fig. 1.9B: 2) to hypertrophied in some echolocating bats (Pollak and Casseday 1989). They do not represent a mandatory synaptic relay as some projections from the cochlear nuclei (Oliver 1984) or superior olivary complex Glendenning and Masterton 1983) bypass the LLN en route to the IC (Fig. 1.10B: 1). Perhaps the LL nuclei are essential only in some facets of auditory processing. They differ from the IC and more rostral auditory centers in having functional and connectional affiliations that are exclusively auditory. Current thinking suggests that they are part of a brain stem binaural and monaural system parallel to those in the LSO (Irvine 1986) and intimately related to the olivary nuclei and the IC.

A striking feature that sets the LLN apart from many other brain stem nuclei is their neurochemical specificity and heterogeneity. About 85% of dorsal nucleus neurons are GABAergic, only 18% of intermediate nucleus cells are either GABAergic or glycinergic, and >80% of ventral nucleus cells are glycinergic (Saint Marie et al. 1997) (Fig. 1.11D, E). These values should be interpreted with caution as GABAergic neurons may be immunoreactive for glycine, and vice versa; the significance of this colocalization is unknown (Wenthold and Hunter 1990; Winer et al. 1995; Saint Marie et al. 1997). Much the same pattern

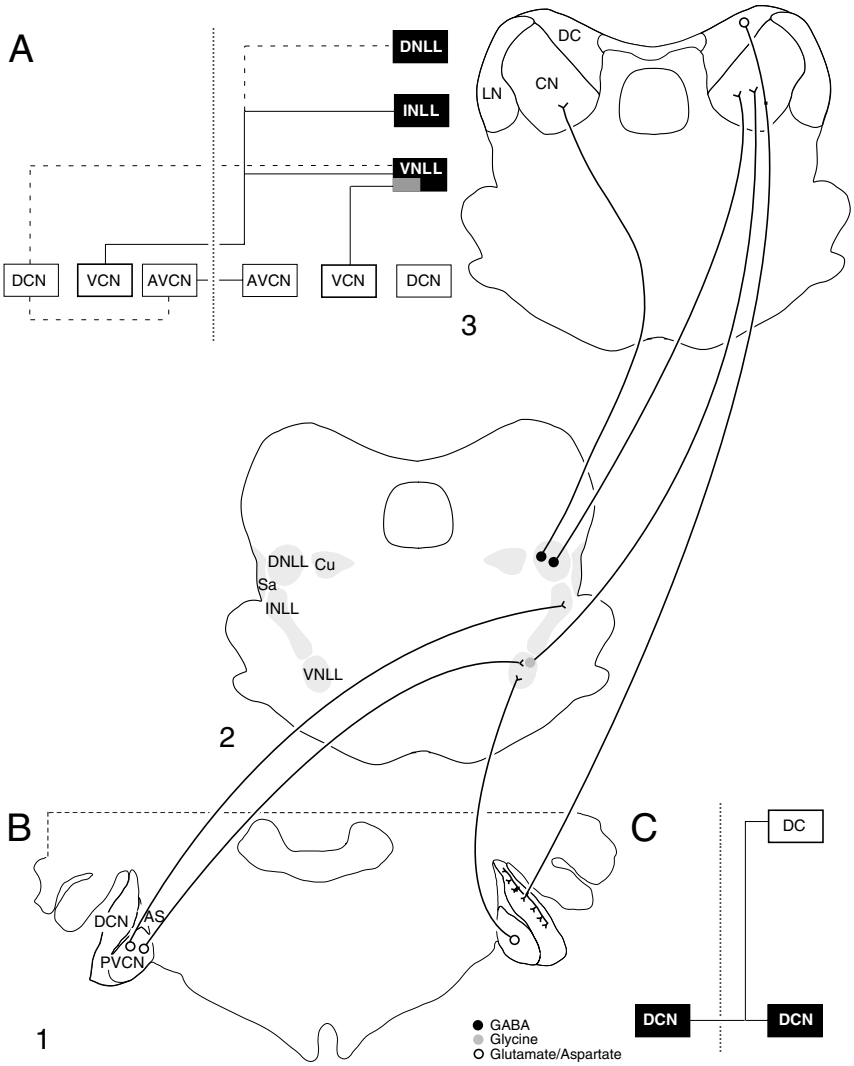

Figure 1.9. Connections between the cochlear nuclei and the lateral lemniscal nuclei, and the nuclei of the lateral lemniscus and the inferior colliculus; descending projections from the inferior colliculus to the cochlear nucleus are also present. **(A)** Each cochlear nucleus subdivision has different targets, and a different strength of projection, to the lateral lemniscal nuclei. The dorsal nucleus of the lateral lemniscus receives stronger input from the superior olivary complex (Fig. 1.10B: *2*) than from the cochlear nuclei. [**A, B** redrawn from the original source (Irvine 1986).] **(B)** The nuclei of the lateral lemniscus share many projections with the inferior colliculus, for example, from the cochlear nucleus (Fig. 1.13B: *3*) and the superior olivary complex (Fig. 1.14B: *2*). It is unknown whether the postsynaptic targets of these projections are also segregated or if they converge onto single neurons (Oliver et al. 1997). *1:* Each posteroventral cochlear nucleus projects to the ventral nucleus of the lateral lemniscus, which then sends fibers

is seen in the mustache bat, with three differences: when both types of immunoreactivity are present, they may be segregated spatially. Second, the intermediate nucleus has clusters of immunoreactive cells associated with physiologic subregions: glycinergic neurons predominate in the presumptive areas of the 30- and 90-kHz components of the bat's echolocation call, while the constant-frequency, 60-kHz territory has many GABAergic neurons (Winer et al. 1995). This suggests a functional dissociation between the dorsal nucleus, which provides binaural inhibition to both ICs (Markovitz and Pollak 1994), and the ventral nucleus, which is part of a monaural system (Fig. 1.11C). Third, neurons in the dorsal and ventral nuclei of the lateral lemniscus show interesting temporal properties with regard to spiking precision (Covey and Casseday 1991), onset, and duration, suggesting modulatory or even instructive roles in the shaping of timing information in their respective targets. Fourth, there is strong evidence for further physiologic subdivisions within the bat LLN as indicated by the spectral tuning, spontaneous activity, and timing of neural discharge in the columnar part of the bat ventral nucleus of the lateral lemniscus. Despite these nuclear and physiologic differences among the LLN, their specific role in hearing remains largely uncertain. Overall, the LLN add further branches of segregated processing streams and additional diversity and complexity to the expression and role of functional stream segregation and information integration.

5. The Inferior Colliculus

The IC (La., *small posterior hill*) is a dome-shaped structure that is among the largest auditory nuclei in the vertebrate brain and it is virtually an obligatory synaptic terminus for ascending input to the medial geniculate body (MGB) (Aitkin and Phillips 1984b). Its size and its many connections suggest that it has critical roles in both the ascending and descending limbs of the auditory system. In reptiles and amphibia, its homologue, the torus semicircularis, is a massive prominence that forms the roof of the caudal midbrain (Foster and Hall 1978). The importance of the IC is accentuated by the relatively reduced size of the homologue of the MGB in frogs (Hall and Feng 1987) and alligators (Pritz 1974a,b).

Figure 1.9. *Continued*
to the central nucleus of the inferior colliculus. *2:* The dorsal nucleus of the lateral lemniscus, which receives input mainly from cochlear nucleus subdivisions outside the posteroventral cochlear nucleus **(A)**, also projects onto the central nucleus. The central nucleus thus receives direct and indirect input from all cochlear nucleus subdivisions. *3:* Besides its integrative role in the ascending auditory system, the inferior colliculus sends descending projections to the cochlear nucleus *(CN).* Thus, the dorsal cortex *(DC)* of the inferior colliculus, which receives only sparse ascending input from the brain stem, projects to the dorsal cochlear nucleus (Weedman and Ryugo 1996a). **(C)** Schematic of tectocochlear projection. [Redrawn from the original source (Conlee and Kane 1982).]

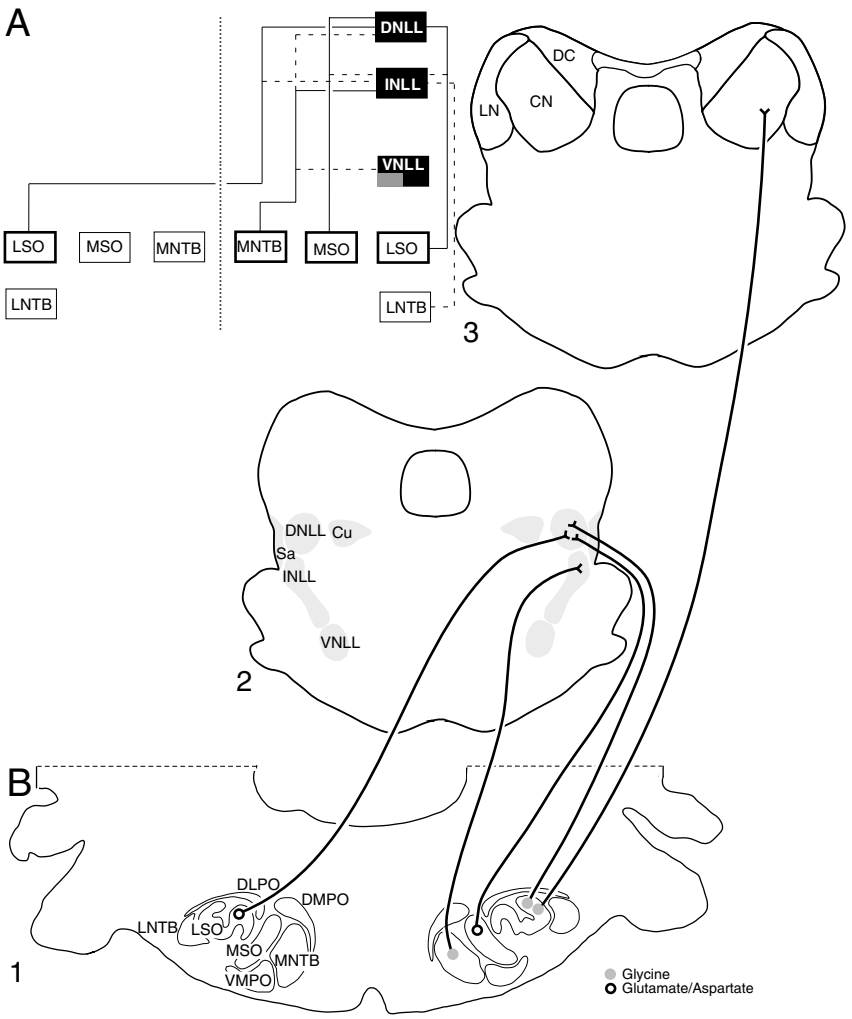

Figure 1.10. Ascending projections from the olivary complex to the lateral lemniscal nuclei and the inferior colliculus. **(A)** Schematic view of connections. Each lateral lemniscal nucleus has both common and unique input from subdivisions of the superior olivary complex. [Redrawn from original source (Irvine 1986).] **(B)** The lateral superior olive *(LSO),* the medial superior olive *(MSO),* and the medial nucleus of the trapezoid body *(MNTB)* each have convergent projections to the dorsal nucleus of the lateral lemniscus. *1:* The input to the dorsal nucleus of the lateral lemniscus is heterogeneous chemically as well: some contralateral projections from the lateral superior olive *(LSO)* may be glutamatergic (Glendenning et al. 1992; Saint Marie 1996); parts of the ipsilateral input are GABAergic *(black cells)* while the neurons in the MNTB are glycinergic (Bledsoe et al. 1990; Spirou and Berrebi 1997). *2:* The MNTB also projects to the intermediate nucleus of the lateral lemniscus. *3:* GABAergic superior olivary complex neurons also end in the central nucleus *(CN)* of the inferior colliculus, reaching it presumably before the parallel GABAergic projection from the dorsal nucleus of the lateral lemniscus.

A second feature is that the IC may have the most diverse connections of any auditory structure. These include input from almost all parts of the cochlear nucleus (Oliver 1984, 1987), from much of the olivary complex (Glendenning et al. 1992), from each of the LLN (Saint Marie et al. 1997), and from every auditory cortical area (Winer et al. 1998). Besides these extrinsic projections, there is a rich array of commissural (Aitkin and Phillips 1984a) and intrinsic projections (Oliver et al. 1991). The IC itself projects to almost all brain stem nuclei that project to it (Huffman and Henson 1990), and it sends axons bilaterally to the auditory thalamus (Andersen et al. 1980). Most of these connections are topographic; perhaps they are related to processes embedded in the tonotopic arrangement of characteristic frequency in the central nucleus.

The IC contains three principal divisions: central nucleus, lateral nucleus, and dorsal cortex (Fig. 1.12A). Each has several nuclei that differ in neuronal structure (Morest and Oliver 1984) and connections (Rockel and Jones 1973a,b) and probably in their ontogenetic sequence (Aitkin and Moore 1975; Aitkin and Reynolds 1975; Binns et al. 1995) and in their functional (Aitkin 1979) roles. The central nucleus is exclusively auditory (Aitkin et al. 1994) and it is essential for normal hearing (Jenkins and Masterton 1982); the lateral nucleus is multisensory (Aitkin et al. 1978) and the target of considerable nonauditory input (Morest and Oliver 1984), the dorsal cortex receives most of its projections from the cerebral cortex (Winer et al. 1998) and its role in hearing is unknown (Oliver and Huerta 1992).

The arrangement of afferent input from brain stem neurons to the central nucleus preserves the topographic relations in the various afferent populations (Figs. 1.13 and 1.14). Thus, low-frequency (lateral) parts of the LSO (Guinan et al. 1972a,b) project to the dorsal part of the central nucleus (Glendenning and Masterton 1983), where low frequencies are represented preferentially (Merzenich and Reid 1974). Here, projections from the most dorsal, low-frequency parts of the dorsal nucleus of the lateral lemniscus (Aitkin et al. 1970) also terminate (Shneiderman et al. 1988) among those from other brain stem nuclei (Oliver et al. 1995). Because there is only one map of the basilar membrane in the central nucleus of the IC (Aitkin 1986), and because input from intrinsic (Oliver et al. 1991), commissural (Hutson et al. 1991), and many other sources (González-Hernández et al. 1996) converges along with brain stem input, perhaps each projection has a considerable topographic precision, or elaborate local inhibitory connections that could suppress the activity of tonotopically inappropriate input. The evidence available favors the first interpretation but does not necessarily exclude the second.

A feature of IC organization that has attracted considerable attention is the structural basis for frequency–specific arrangements, the isofrequency or frequency-band lamina, which contains thousand of neurons with a similar characteristic frequency (Fig. 1.12B). One mechanism for enhancing the precision of ascending axons ending within the inferior colliculus is to restrict spatially the afferent input available to the postsynaptic neuron by adjusting the size and shape of the postsynaptic cell's dendritic domain and that of the associated

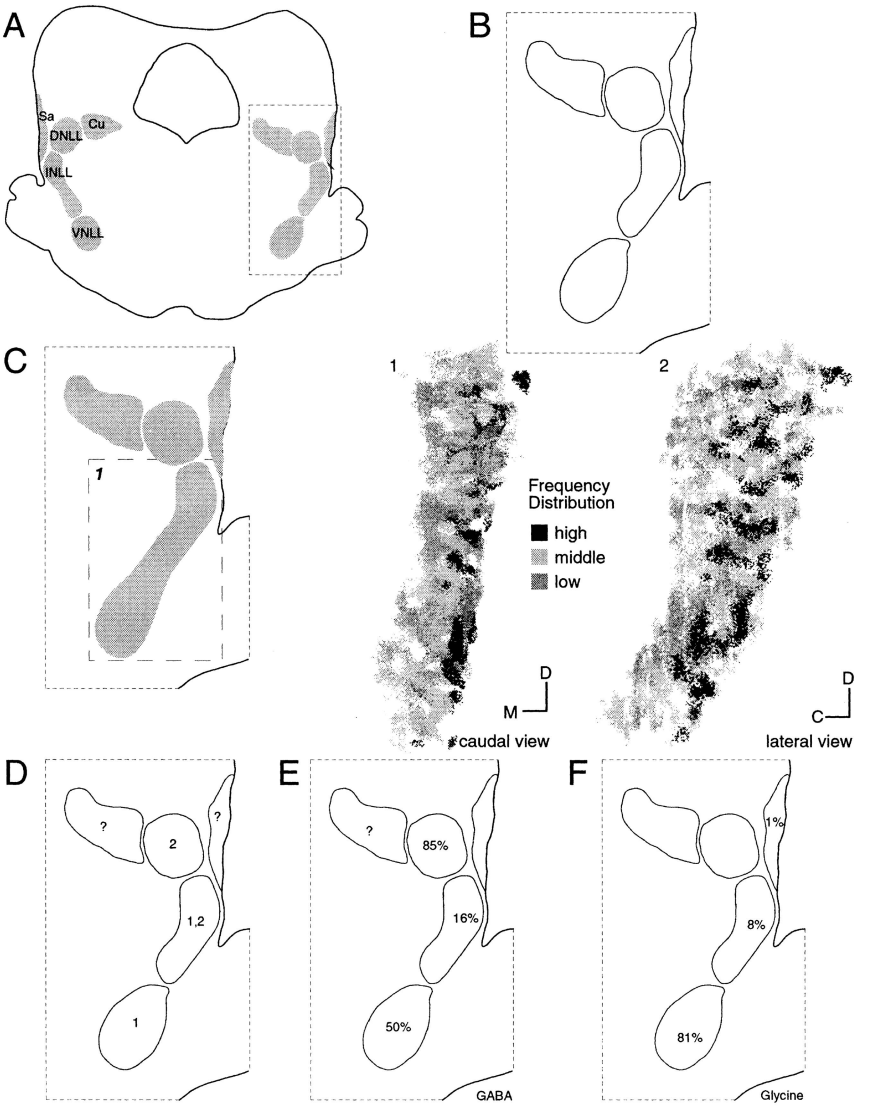

Figure 1.11. The lateral lemniscal nuclei. **(A)** Nuclear subdivisions; the functional status of the cuneiform *(Cu)* and sagulum *(Sa)* nuclei is uncertain, although the latter has widespread connections with the IC, the MGB, and the auditory cortex (Beneyto et al. 1998). [**A, B:** Adapted from published data (Aitkin et al. 1970).] **(B)** Distribution of characteristic frequency in a transverse section of the dorsal nucleus of the lateral lemniscus (Aitkin et al. 1970). **(C)** Mosaic pattern of characteristic frequency within the ventral lateral lemniscal subdivisions is consistent with a complex topographic projection pattern. [Redrawn and modified from the original source (Malmierca et al. 1998)]; color values in original converted to grayscale. The intermediate and ventral nuclei **(B)** are here combined (C: *1*). The periodic distribution of characteristic frequency is noteworthy

afferent axonal plexus. Thus, central nucleus neurons are variable in size, packed densely, and form long rows between which are interposed fascicles of ascending fibers. One of the two main classes of neuron has a disc–shaped dendritic field 200 to 800 μm long and only 50 to 70 μm wide; the long processes are oriented parallel to the axis of the afferent axons. Together, the preterminal afferent fibers and the polarized dendritic arbors of these neurons constitute fibrodendritic laminae that extend through the central nucleus. These resemble the laminated parts of the DCN and the sheetlike dendritic configurations in the MSO and the laminae in the ventral division of the MGB. This arrangement may be a common device for frequency–specific representation and segregation elsewhere in the central auditory system. Laminae are not necessarily uniform physiologically despite their narrow frequency range, as recordings along the primary tonotopic axis reveal systematic, small discontinuities that could correspond to critical bands (Schreiner and Langner 1997), and recordings within laminae reveal systematic shifts of several response properties, including onset latency (Langner et al. 1987) and response threshold (Stiebler and Ehret 1985). A task for future work is to understand more fully the range of computational possibilities within a frequency-band lamina, and the interactions between them. These neural ensembles have much in common with the laminae in the DCN, cell columns in the ventral nucleus of the lateral lemniscus, and frequency-specific columnar regions in auditory cortex. These are analogous to laminae in the lateral geniculate body and the ventrobasal complex (Jones 1985), and to the columnar organization of the sensory neocortex (Mountcastle 1997).

A second variety of central nucleus neuron, the stellate cell, has a spherical dendritic field and radiating processes that cross central nucleus laminae. Other neuronal subtypes vary in size but share features of dendritic architecture. The smallest such neurons have dendritic arbors $<$200 μm wide, and presumably intercept influences from narrower spatial domains than the large disc–shaped neurons, while some stellate cells span territories of approximately 500 μm. Other stellate neurons have dendritic orientations at right angles to the fibrodendritic axis and could integrate afferent input across a wider range of the frequency spectrum (or other possible physiologic axes) than neurons with narrower dendritic domains. Central nucleus subdivisions exist that vary mainly on the basis of local differences in laminar organization and neuronal density.

Figure 1.11. *Continued*
(1, 2). **(D)** Aural classes and their distribution within the lateral lemniscal nuclei. The segregation of response properties on a nuclear basis in the mustache bat suggests that they serve different functional roles (Markovitz and Pollak 1993), that there may be species differences in physiologic properties (Markovitz and Pollak 1994), and at least one nucleus (e.g., dorsal nucleus) has connectional subdivisions (Yang et al. 1996). **(E)** GABAergic neurons have a differential distribution within the lateral lemniscal nuclei and sagulum. [**E, F:** The lateral lemniscal nuclei redrawn from the original source (Saint Marie et al. 1997); for the sagulum (Beneyto et al. 1998).] **(F)** Proportion of glycinergic neurons.

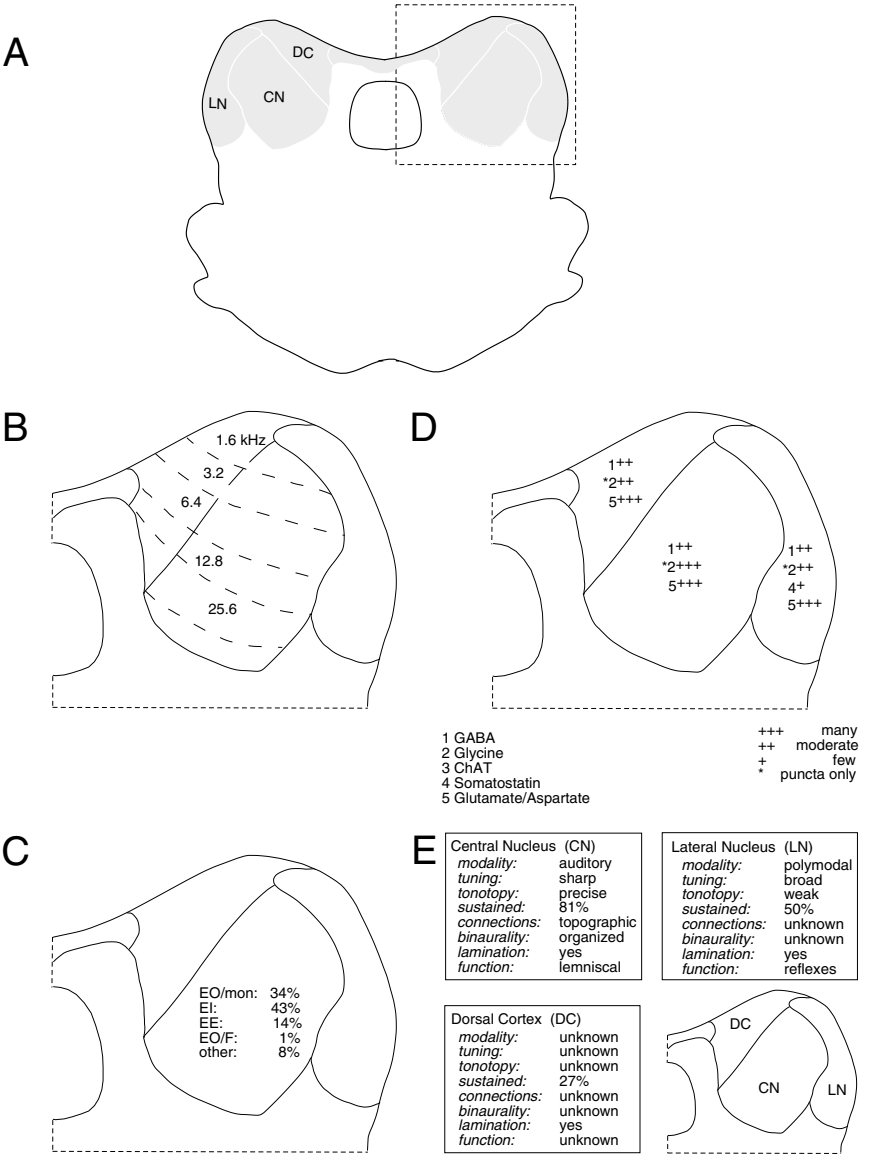

Figure 1.12. Physiologic and neurochemical aspects of IC organization. **(A)** Subdivisions of the IC. **(B)** Presumptive laminae *(dashed lines)* have a characteristic dorsomedial-to-ventrolateral orientation that, in the central nucleus, recapitulates the distribution of characteristic frequency (Rose et al. 1963) and the arrangement of the fibrodendritic laminae (Rockel and Jones 1973a). There is a substantial low-frequency representation; the precise disposition of frequency in the dorsal cortex is uncertain as it has a laminated structure (Morest and Oliver 1984), and the orientation of the cytoarchitectonically defined layers may not be in register with that of the isofrequency laminae. More than one map of characteristic frequency may occur as the discharge properties of dorsal cortex neurons

Intracellular filling studies reveal that the axons of most central nucleus cell types have extensive local branches, thus resembling interneurons elsewhere in the brain, while their collaterals often contribute to tectofugal projections. The local axonal network may run parallel to, or cross, the fibrodendritic laminae. A smaller subset of cells has only local connections within the central nucleus and could function as short axon Golgi type II cells (Oliver et al. 1991).

Although inhibitory neurons can enhance tonotopic organization, the laminated structure of the central nucleus imposes a physical arrangement that does not necessarily require the participation of interneurons in that process. If interneuronal effects are important in tonotopic organization, then their unique contribution cannot be discerned without more intracellular recordings (Nelson and Erulkar 1963; Oliver et al. 1991). This underscores an important difference between the central nucleus of the IC and the anterior part of the AVCN: in the latter, there are few or no GABAergic inhibitory interneurons (Adams and Mugnaini 1987) and the tuning curves of bushy cells are as, or more sharply, tuned than those in the central nucleus (Bourk et al. 1981), a process that would seem to depend on operations of the auditory nerve alone (Kiang et al. 1965). A related point is that there appears to be more than one way to organize topographic input (Kaas 1997).

There is evidence for other forms of organization in the central nucleus besides tonotopy. The representations of monaural inputs seem to vary spatially with regard to onset latency, receptive field bandwidth, and response threshold (Stiebler and Ehret 1985; Langner et al. 1987; Schreiner and Langner 1988). The binaural neurons represent several physiologic subclasses (Irvine 1986). In

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Figure 1.12. *Continued*
differ from those in the central and lateral nuclei (Aitkin et al. 1994). [Redrawn and modified from the original source (Merzenich and Reid 1974 with permission from Elsevier Science).] **(C)** The percentage of aural subtypes in the central nucleus of the IC, showing the dominance of contralateral excitatory-occluded/monaural *(EO/mon)* and excitatory/inhibitory *(EI)* neurons. This is congruent with the notion that there is a spatial segregation of response types within the mustache bat central nucleus (Wenstrup et al. 1986). Whether these patterns are preserved in the MGB is unknown (see Fig. 1.15C). [Adapted and modified from the original source (Irvine 1986).] **(D)** Regional distribution and concentration of prospective neurotransmitters in IC subdivisions. In all subdivisions, glutamatergic neurons are numerous; whether tectothalamic and other projection neurons are glutamatergic requires further experimental study because of the structural role of glutamate/aspartate. Glycinergic axon terminals, but not neurons, are present in each part. [Interpreted from original observations (Oliver et al. 1994) for GABA; for glycine and glutamate/aspartate (Winer, unpublished observations); for somatostatin (Spangler and Morley 1987).] **(E)** Summary of comparisons of physiologic responses in IC subdivisions. The central nucleus is the principal component of the lemniscal pathway; the lateral nucleus integrates auditory and somatic sensory information, and too little is known of the details of dorsal cortex functional organization to reach firm conclusions. [Adapted and modified from the original sources (Aitkin 1986; Aitkin et al. 1994).]

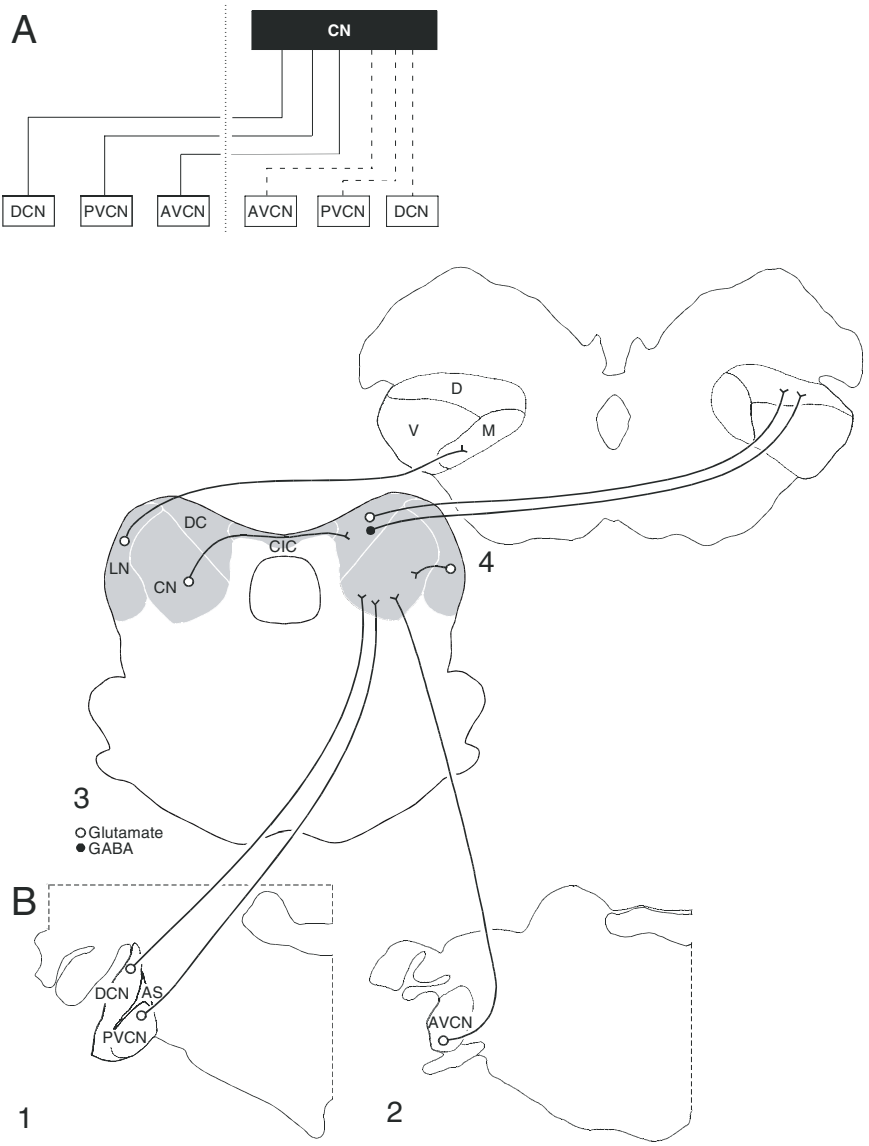

Figure 1.13. Some pathways between the cochlear nucleus, the IC, and the MGB. **(A)** Schematic view of cochlear nucleus projections to the central nucleus. [Adapted and modified from the original source (Irvine 1986).] **(B)** The contralateral input is strongest. The ascending convergence to the IC (Fig. 1.14A) arises from all major parts of the cochlear nucleus. *1:* Dorsal cochlear nucleus *(DCN)* and posteroventral cochlear nucleus *(PVCN)* projections reach the central nucleus. [Interpreted from original sources (Warr 1969; Oliver 1984).] *2:* The anteroventral cochlear nucleus *(AVCN)* projects topographically to the central nucleus laminae. [Adapted from the original source (Oliver 1987).]

the mustache bat, populations of binaural and monaural neurons appear to be segregated regionally within the central nucleus, forming vertical columns 250 μm long with common binaural properties and confined to an isofrequency region (Wenstrup et al. 1985). This suggests that, although central nucleus neurons are ordered across the entire frequency spectrum, other internal representations may also be present.

A new kind of physiologic organization arises in the auditory midbrain that enlarges its functional role and distinguishes it from medullary auditory nuclei. This pertains to the lateral nucleus and the dorsal cortex, structures whose role in inferior collicular processing is not well understood. The lateral nucleus receives input primarily from the medullary dorsal column nuclei and the trigeminal system in the pons (Aitkin et al. 1981), which represent the somatic sensory system for the body and head, respectively. Other projections come from the auditory cortex (Winer et al. 1998); there are no or very few axons from the lateral lemniscus (Rockel and Jones 1973b). What auditory influence it receives may arise principally from intracollicular connections (Aitkin and Phillips 1984a). In any case, the lateral nucleus has no tonotopic map, its neurons respond with long latencies compared to those of central nucleus cells, and they have very broad tuning curves. In the lateral nucleus of guinea pigs, contralateral azimuth position appears to be represented systematically, suggesting a role for this station in sound localization (Binns et al. 1992). Moreover, there is a coarse map of the body surface that overlaps with the auditory representation (Aitkin et al. 1978). A plausible function for the lateral nucleus might be to represent the position of the body with respect to sound sources in extrapersonal space. In the barn owl auditory midbrain (the lateral mesencephalic nucleus), for example, there are independent representations of the basilar membrane and a map of auditory space (Knudsen and Konishi 1978). These maps may be independent in the owl because prey acquisition involves rapid spatial processing and nearly ballistic motor estimates of the precise position of acoustic signals (Konishi 1973a,b). Such computations may be best performed independently by specific nuclei. In the cat, in contrast, the maps may not require the precision and independence that are manifest in the owl, perhaps behaving as combinatorial gates that require independent signals to converge to elicit a response.

Figure 1.13. *Continued*

[*3:* Adapted and modified from the original sources for intrinsic ipsilateral and commissural projections (Aitkin and Phillips 1984a); for tectothalamic connections (Calford and Aitkin 1983).] These circuits link parts of the IC that receive differential degrees of brain stem and cortical input. Some projections are reciprocal (e.g., commissural), others asymmetric (e.g., between the lateral and central nuclei). This could permit cortical access to nuclei that receive indirect cortical input via polysynaptic pathways in the mustache bat (Zhang et al. 1997; Jen et al. 1998). *4:* The dorsal cortex of the IC receives little ascending auditory input (Irvine 1986) and a substantial projection from many areal origins (Fig. 1.18G) of cerebral cortex (Winer et al. 1998). The mustache bat tectothalamic pathway likely includes GABAergic and nonGABAergic projection neurons (Winer et al. 1996).

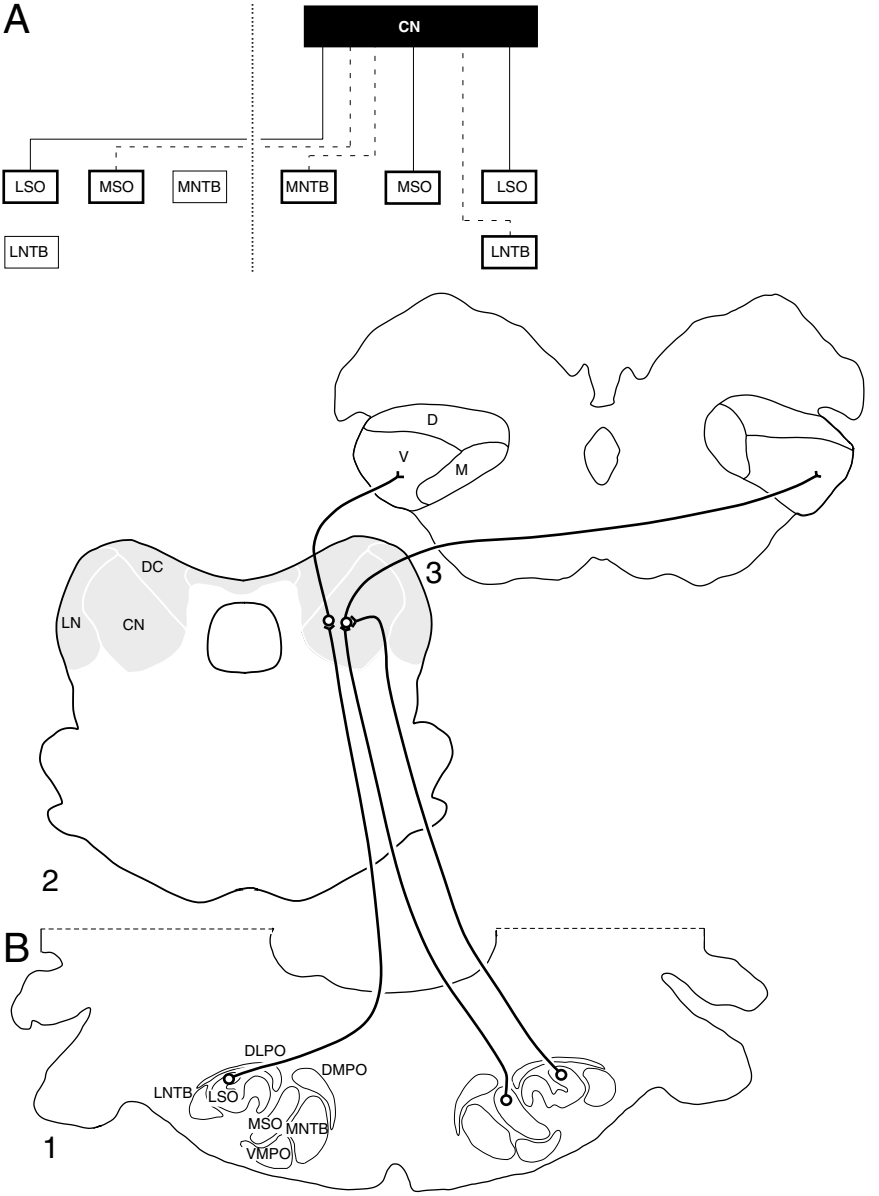

Figure 1.14. Some connections between the olivary complex, the IC, and the MGB. **(A)** Schematic of some ascending input to the central nucleus of the IC; only a few of the many projections are shown. [Adapted and modified from the original source (Irvine 1986).] *1:* It is unknown whether the projections from the lateral superior olive *(LSO)* and medial superior olive *(MSO)* are segregated onto single postsynaptic cells in the central nucleus; connectional studies suggest considerable spatial overlap in their terminal targets (Glendenning and Masterton 1983; Oliver 1987; Shneiderman and Henkel 1987). *2:* The IC projection to the MGB is bilateral from the central nucleus (Andersen et al. 1980; Calford and Aitkin 1983. Copyright by the Society for Neuroscience.). Descending pathways from the central nucleus to the DCN have been omitted (Conlee and Kane 1982).

Broad tuning is not confined to the lateral nucleus and it even occurs among some neurons in the posteroventral cochlear nucleus (PVCN) (Rhode and Greenberg 1992). Moreover, the DCN has a somatic sensory representation (Young et al. 1995). This suggests that even at the earliest stages of central neural processing, broad tuning and noncochlear input are both present, although the dominant functional influence in both cases remains auditory. In the lateral nucleus, however, a new principle emerges: auditory function is only one of many and any laminar organization differs fundamentally from that in the central nucleus (Morest and Oliver 1984; Oliver and Morest 1984). The emerging picture of lateral nucleus function suggests a multisensory integrative role in acoustico-motor behavior.

The dorsal cortex resembles the lateral nucleus as its neurons are tuned broadly, and they strongly prefer vocal stimuli to noise (Aitkin et al. 1994). Although isofrequency laminae seem to be absent, the neurons do form layers (Aitkin 1986), suggesting that further levels of functional organization may be present. The layers appear to have a closer relationship to corticocollicular, commissural, and intrinsic projections than to specific maps (Winer et al. 1998). Thus, auditory projections to the dorsal cortex are limited exclusively to indirect, polysynaptic auditory input from intrinsic and commissural midbrain neurons (Aitkin and Phillips 1984a) and the auditory cortex (Winer et al. 1998). Behavioral data, although limited, suggest that lesions that include the central nucleus lead to deficits in sound localization in the contralateral hemifield (Jenkins and Masterton 1982), while damage to the dorsal cortex affects attention and vigilance more severely than auditory discrimination behavior (Jane et al. 1965). Other dorsal cortex projections terminate in the paralemniscal and perireticular regions medial to the lateral lemniscus in the tegmental midbrain. Stimulation here can elicit a variety of vocalizations in which the cortex may participate (Schuller and Radtke-Schuller 1990). Neurons here have also been implicated in the startle reflex (Aitkin 1986). Substantial cortical input also ends in the nearby central gray, a center concerned with ascending and descending modulation of nociceptive influences and in vocalization related to emotive and visceral aspects of communication (Aitkin 1986; Winer et al. 1998).

A final example illustrates the breadth of functional arrangements that the IC mediates. In genetically epilepsy-prone rats, somatic motor seizures can be induced by acoustic stimulation (Faingold et al. 1989). GABAergic neurons, which are plentiful in the IC (Oliver et al. 1994), may participate in seizure genesis as blocking GABA uptake reduces seizure development (Faingold et al. 1994). This demonstrates the manifold roles of inhibitory neurons and the complex behaviors mediated by the IC and adjoining tegmental and reticular parts of the midbrain, which range from exclusively auditory processing (Aitkin 1986) to possible participation in vocalization (Suga and Yajima 1988) or the startle reflex (Yeomans and Frankland 1996). These properties are specific to the auditory midbrain and emphasize its pivotal role in auditory processing and the breadth of its functional impact.

6. The Medial Geniculate Body

The mammalian thalamus (Gr., *inner chamber*) consists of two oval masses that extend from the midbrain to the forebrain. The thalamus contains different nuclei that have been classified as sensory, motor, association, or intralaminar on the basis of their functions, connections, cell structure, and evolutionary history (Jones 1985). Sensory nuclei represent one modality, such as the MGB for hearing and the lateral geniculate body (LGB) for vision. Motor nuclei receive input from the cerebellum (and other structures) and participate in preparation for movement and ongoing motor behavior. Association nuclei are tied less securely to one modality, their internal maps may not be as fine-grained or as topographic as those of sensory nuclei, and their role is probably integrative. The intralaminar nuclei are conserved phylogenetically, they receive input from several modalities, and project broadly on the cerebral cortex and to subcortical nuclei; they may have a role in mediating shifts in behavioral state, for example, between sleeping and waking. Corresponding thalamic nuclei in different modalities are not necessarily equivalent functionally and there are significant species differences in size and internal circuitry. Thus, destroying one LGB in rodents causes a severe visual defect (Thompson 1969), whereas bilateral destruction of the medial geniculate body does not materially impair sound localization (Kelly and Judge 1985). In contrast, even unilateral damage in cats has serious consequences for auditory localization (Jenkins and Masterton 1982). Such nonequivalence between systems and across species reflects the concentration of thalamic visual function and a broader distribution of auditory function across brain stem nuclei.

The MGB differs from the IC in several ways (Winer 1991). First, its projections are almost entirely ascending and ipsilateral. Second, the inputs target not only auditory cortex but also subcortical limbic forebrain structures such as the amygdala and caudate nucleus; thus, the role of the MGB may be more than only auditory. Third, the MGB has a wide range of species-specific variability: it is relatively small in reptiles and amphibia, even when the midbrain homologue of the IC is well developed, and massive in carnivores. Fourth, MGB internal circuitry, especially the number of Golgi type II/GABAergic neurons, differs across species, suggesting that some forms of processing might be species-specific. Fifth, the strength of corticofugal input to the MGB is far greater than that of the corresponding corticocollicular projection. This implies a tighter coupling between thalamic and cortical oscillatory behavior than between the cortex and the auditory midbrain. Sixth, there are no internal connections linking MGB divisions, which accentuates their independence, while these pathways are plentiful in the IC and cochlear nucleus.

The main sensory nucleus of the MGB is the ventral division (Fig. 1.15), whose bushy tufted principal cells are arranged in fibrodendritic laminae (Morest 1965; Cetas et al. 2001) across which there is a systematic representation of characteristic frequency (Imig and Morel 1984) (Fig. 1.15B). Neurons with diverse response profiles are present, including specific binaural properties (Clarey

et al. 1992). The primary input to the ventral division arises from the central nucleus of the IC (Calford and Aitkin 1983) (Fig. 1.16B: 1, 2) and from the auditory cortex (Diamond et al. 1969; Winer et al. 2001). There are many parallels between the central nucleus of the IC (Aitkin 1986) and the ventral division (Winer 1992), including its laminated cytologic and orderly physiologic organizations. An important difference is the degree of cortical input, which is massive in the thalamus and sparser in the central nucleus (Winer et al. 1998). A second difference relates to intrinsic organization. In the ventral division there are Golgi type II cells whose axons are confined entirely to the thalamus and that are GABAergic (Rouiller et al. 1990), while in the IC many of the GABAergic neurons—especially the largest—project to the MGB (Winer et al. 1996). Perhaps there are no or few interneurons in the IC (Oliver et al. 1994), while all ventral division GABAergic neurons are type II cells as none have projections which leave the thalamus (Huang et al. 1999). The ventral division has a specialized synaptic arrangement, the glomerulus, in which dendrites and axons from Golgi type II cells are presynaptic to bushy tufted cell dendrites and ascending afferents, and this ensemble is surrounded by a glial sheath that isolates it from neighboring influences (Morest 1975). This synaptic pattern does not seem to occur in the IC (Rockel and Jones 1973c). The function of the glomeruli is not known (Morest 1971) but they may be a module for local intrathalamic processing, as they are present in all the corresponding sensory thalamic nuclei in all modalities (Rakic 1975).

Finally, there are species-specific differences in the proportion of GABAergic cells, ranging from $<1\%$ in some bats (Vater et al. 1992) to $>25\%$ in cat (Huang et al. 1999) and monkey (Smith et al. 1987). Such differences are far more marked in the thalamus than in the auditory midbrain (Oliver et al. 1994) or cerebral cortex (Prieto et al. 1994a), where these neurons represent 20% to 25% of the populations. The evolution of thalamic GABAergic circuitry may be relatively recent and system specific, as in other thalamic nuclei there is much more homogeneity with regard to Golgi type II cells (Winer and Larue 1996).

Ventral division response properties have much in common with those in the central nucleus of the IC, the main input source. Consequently, no clear hypothesis has emerged regarding the nature and purpose of functional transformation at this processing stage. One noticeable difference between the central nucleus of the IC and the MGBv is an increased local diversity of response properties, including best frequency (Morel et al. 1987). Similar to the central nucleus, local gradients can be seen for a variety of response properties. Gradients in the rostrocaudal axis include temporal response pattern, the ability to synchronize to repetitive stimuli, responsiveness to broad-band stimuli, and the monotonicity of rate-level functions (Rodrigues-Dagaeff et al. 1989). Binaural response classes also show some differences along the rostrocaudal domain and are characterized by clustering in the dorsoventral domain (Middlebrooks and Zook 1983; Rodrigues-Dagaeff et al. 1989).

The dorsal division receives its primary brain stem input from the dorsal cortex of the IC and from the lateral tegmental area, near the IC (Calford and

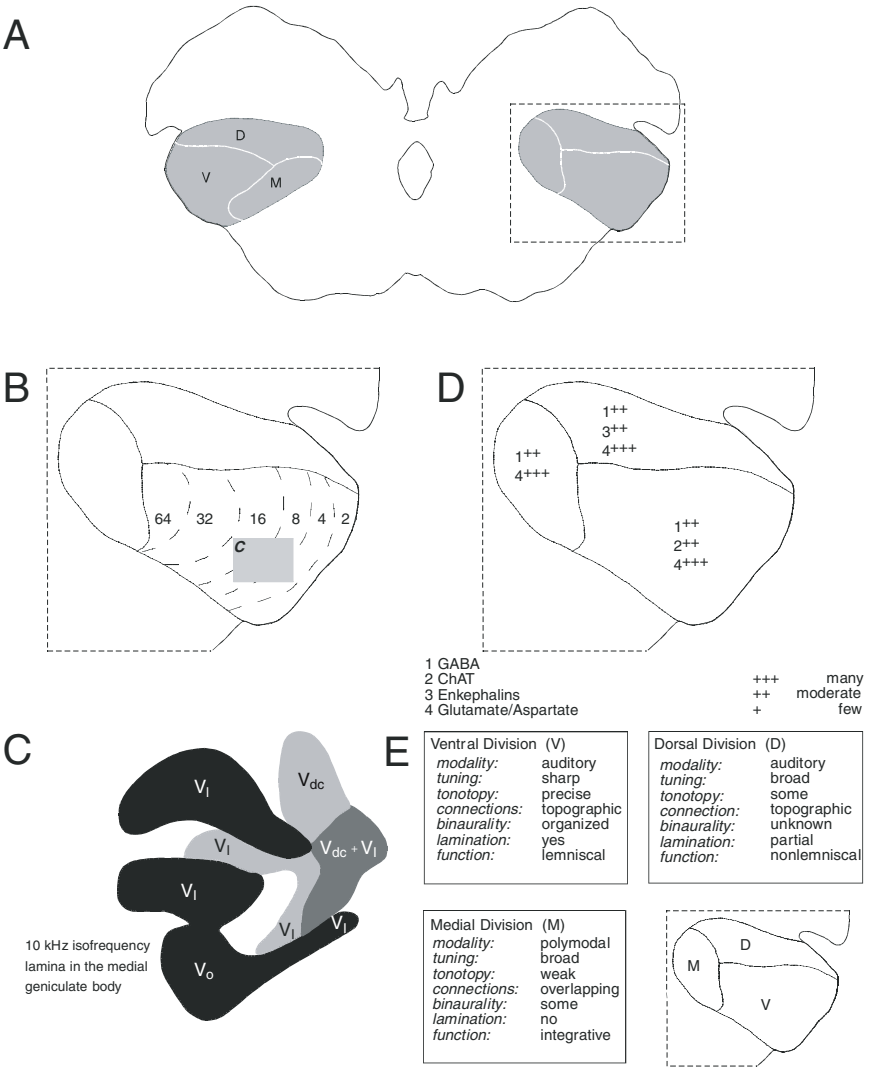

Figure 1.15. Basic features of medial geniculate body organization. **(A)** Subdivisions of the medial geniculate complex include the ventral division, which is present in all mammals and essential for normal hearing, and the dorsal and medial divisions, which are far more variable in size and have roles in auditory integration and polysensory processing, respectively. Not shown are the caudal dorsal and rostral dorsal nuclei or the rostral pole nucleus; the latter may be an extension of the ventral division (Imig and Morel 1985a,b). Some prior accounts considered the ventral and dorsal divisions collectively as the principal division (Rose and Woolsey 1958; Rinvik et al. 1987). **(B)** The schematic organization of unit best frequency in the ventral division (Imig and Morel 1985b) is in good accord with the configuration of anatomical fibrodendritic laminae (Morest 1965). **(C)** Orthogonal to the fibrodendritic laminae and interdigitated with them may be various binaural subregions. [Adapted and modified from the original source

Aitkin 1983). Like the cells in the dorsal cortex of the IC, dorsal division neurons have wide tuning curves, long latencies, and an uncertain tonotopic arrangement. They also have extended, oscillating slow-wave activity whose origins and functions are unknown but that is specific to this division (Aitkin and Dunlop 1968, 1969). Dorsal division projections to auditory cortex differ in two ways from those of the ventral division neurons. First, their targets include many more areas—up to nine—while the ventral division projects to only five areas (Huang and Winer 2000). Second, the cortical targets of the dorsal division are heterogeneous functionally and widely dispersed spatially (Shinonaga et al. 1994), while ventral division projections end in areas with similar auditory properties (Reale and Imig 1980) and which adjoin. Dorsal division function(s) appear independent of those in the tonotopic system; perhaps these nuclei affect attentional processes or global thalamic control of cortical excitability (Winer and Morest 1983). Responsiveness to structured signals, such as vocalizations (Shipley et al. 1988), may be more prominent in the dorsal division than responses to simpler stimuli (Buchwald et al. 1988). Damage to the cortical targets of the dorsal division impairs the perception of temporal patterns (Kelly 1973; Colavita et al. 1974).

The medial division has few of the features described here as characteristic of an auditory nucleus. It has a coarse tonotopic organization (more properly, a gradient) (Rouiller et al. 1989), and its afferent input includes nonauditory sources such as the vestibular system (Blum et al. 1979) as well as fibers from the lateral nucleus of the IC (Calford and Aitkin 1983). The medial division has the widest spectrum of targets in the MGB: it projects to every part of auditory cortex (Niimi and Matsuoka 1979), to nonauditory cortex (Jones and Powell 1973), and to the amygdala (Shinonaga et al. 1994). The thalamoamygdaloid pathway is unique to the auditory system (LeDoux et al. 1985), and it is essential for autonomic learning based on auditory cues (LeDoux et al. 1986). Because medial division neurons can show long-term potentiation (Gerren and Weinberger 1983), they may play a role in higher functions. A final difference with regard to the medial division is that its projections terminate mainly in layers I

Figure 1.15. *Continued*
(Middlebrooks and Zook 1983).] For locus of this arrangement, see **(B)**, box. **(D)** Neurochemical profile of the auditory thalamus. GABAergic neurons represent about 26% of the cells on average, ranging from 33% in the ventral division to 18% in the medial division (Huang et al. 1999). Choline acetyltransferase-positive axon terminals are concentrated in the rat ventral division (Levey et al. 1987). Enkephalinergic neurons are found mainly in the dorsal division (Coveñas et al. 1986) and glutamatergic and/or aspartatergic cells are abundant in all divisions in the rat (Winer 1991). The chemical heterogeneity of the auditory thalamus does not include glycinergic neurons and axon terminals, which are concentrated in the caudal brain stem. **(E)** Summary of the attributes of MGB divisions. [Adapted and modified from the original source (Calford 1983).]

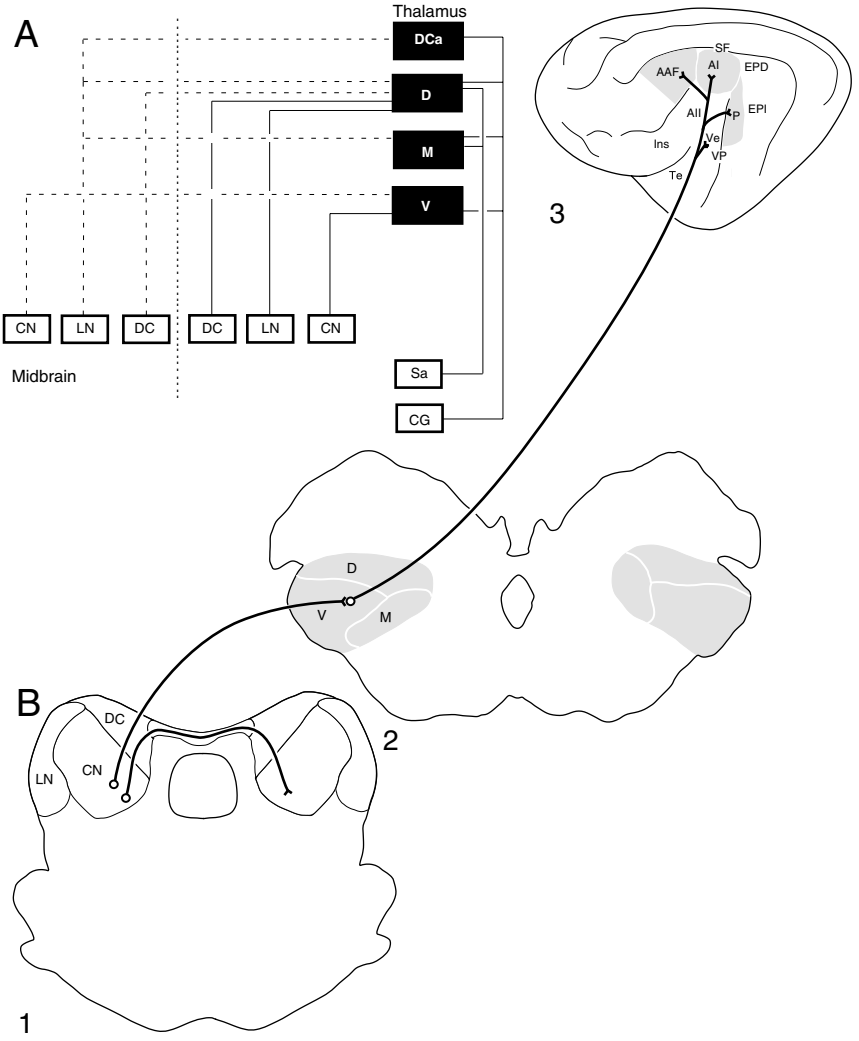

Figure 1.16. Some ascending projections of the auditory midbrain and thalamus. **(A)** A schematic picture of midbrain input to the MGB; the ipsilateral projection is dominant, and there are smaller inputs from the sagulum and central gray whose significance is obscure. Some auditory thalamic subdivisions such as the caudal dorsal nucleus receive little ascending auditory input and receive projections chiefly from the cerebral cortex (not shown) or from midbrain nuclei (such as the sagulum) whose function is uncertain. **(B)** The tectothalamocortical pathway. *1:* Neurons in the central nucleus *(CN)* of the IC project topographically to the ventral division of the MGB (Kudo and Niimi 1980). *2:* Ventral division neurons project ipsilaterally to auditory cortex subdivisions. *3:* All four primary auditory cortical regions (areas AI, AAF, P, and Ve) receive topographic input (Morel and Imig 1987); each area has a unique redistributive pattern of corticocortical connectivity (Fig. 1.17E). [Modified from data in Calford and Aitkin 1983; Parts 2 and 3 from Niimi and Matsuoka 1979.]

and VI, whereas those from the ventral division end largely in layers III and IV (Huang and Winer 2000). Information reaching the cortex from the ventral and medial divisions is segregated and may target different postsynaptic populations, as the neuronal composition and output of the target layers are so varied.

Overall, the MGB is characterized by several parallel projection systems that, at this stage, appear less distinguishable by their auditory task specificity than by nonsensory influences. Strong modulatory influences from cortical feedback and many extracortical sources have been described in all sensory nuclei of the thalamus (Sherman and Guillery 2000). Accordingly, thalamic function may be less related to local receptive field transformation or implementation of feature extraction than to state-dependent modulation and gating of activity forwarded to the cortex (Miller and Schreiner 2000; Winer et al. 2001).

7. The Auditory Cortex

The cerebral cortex (La., *bark*) is a structure whose internal order, stereotyped neuronal organization, and high degree of local microcircuitry are largely conserved from insectivore to primate, despite vast differences in scale (Winer 1992). Its dynamic ability to modify itself through learning and memory suggests that static schemes to subdivide it may be inherently too limited to capture its functional complexity (Weinberg 1997). In the human cortex, for example, from about 50 to several hundred areas have been recognized (von Economo and Koskinas 1925; Brazier 1968). If it were smaller or less critical in behavior, these differences would reflect largely semantic distinctions with little conceptual import. But the human cerebral cortex is the largest organ in the brain: dissected and smoothed, it would be almost 1 m^2 in area and 3600 μm thick with perhaps 10^5 neurons/mm^2. If the human MGB has some 5×10^5 neurons, the auditory cortex has millions more, irrespective of how its boundaries are defined, and the functional attributes of most parts remain unknown because of technical limitations. Moreover, because the cortex is interconnected extensively with itself in recurrent and feedforward networks (White and Keller 1989), the number of prospective neuronal and synaptic interactions assumes impressive proportions relative to the smaller number of permissible connections in the thalamus.

A second feature—laminar organization—distinguishes the cortex from most subcortical centers and adds another dimension to areal classification. Although the types of neuron are presumptively similar from area to area, they are largely segregated on a laminar basis. Horizontal cells, for example, are found only in neocortical layers I and VI and mediate lateral intracortical connectivity, whereas the largest pyramidal cells that may be critical for initiating rapid changes in subcortical targets are exclusively in layer V (Kelly and Wong 1981). This suggests that, within an area, layer-specific processes occur that resemble those in subdivisions of the cochlear nucleus, IC, or MGB. In a sense, the layers then correspond to nuclei in the brain stem, while areas subserve global functions.

The primary auditory cortex (AI) is the best studied of the tonotopic areas

(Brugge and Reale 1985; Aitkin 1990). Like all of the neocortex, it has six layers, with layers III and IV receiving axons arising from cells in the ventral division of the MGB, while layers I and VI are targets of the medial division (Huang and Winer 2000). The layers are linked vertically by interneurons whose axons have intralaminar projections, for example, from layer VI to layer IV (Prieto and Winer 1999) or by specific populations of pyramidal cells with intrinsic connections (Ojima et al. 1992). These pathways are analogous to the layer-specific connections in the DCN between inhibitory interneurons and fusiform cells. Although there are extensive ipsilateral corticocortical connections between areas with similar properties (Imig and Reale 1980) and robust interhemispheric commissural networks (Code and Winer 1985), perhaps >75% of the synapses (LeVay and Gilbert 1976) arise from an immense web of local connections (Matsubara and Phillips 1988; Read et al. 2001). The rules governing these interconnection are known best in the visual cortex, where vertical and horizontal modules are linked in intricate spatiotemporal patterns (Fitzpatrick et al. 1985; Hübener et al. 1997). Thalamic information in AI reaches layer I both directly (via thalamocortical projections) (Mitani et al. 1984) and along short axon polysynaptic intracortical intralaminar connections (Mitani and Shimokouchi 1985). These intrinsic vertical inputs and the monosynaptic thalamocortical projection of ventral division neurons to layer IV (Huang and Winer 2000) contact the long apical dendrites of many cells with perikarya in layers V and VI. Layer V and VI cells give rise to the corticofugal projections to the IC (Kelly and Wong 1981; Winer et al. 1998), thalamus (Winer et al. 2001), olivary complex (Doucet et al. 2002), striatum (Beneyto and Prieto 2001), amygdala (Romanski and LeDoux 1993), and cochlear nucleus (Weedman and Ryugo 1996a), to name just some of their targets (Wong 1991). Thus, thalamic projections to the cortex reach corticofugal neurons with different targets and influence prospectively almost every subcortical auditory nucleus. The complexity of the neural networks involved in this brief summary emphasizes the difficulty of explaining cortical function, as some connections seem to act in a highly redistributive way, whereas others are far more specific. Tracing these patterns of connectivity to the next level is a formidable task (Briggs and Callaway 2001).

A useful way to examine auditory cortex function is to enumerate and assess its physiologic representations. A primary auditory field with a tonotopic representation was found in every species studied (Luethke et al. 1988). In cat primary auditory cortex the gradient of tonotopic organization seen in barbiturate-anesthetized animals is for the most part quite strict (Merzenich et al. 1975) (Fig. 1.17C) but it is perhaps less ordered in awake preparations (Evans and Whitfield 1964; Evans et al. 1965) and at its dorsal and ventral margins (Schreiner and Sutter 1992). Across the tonotopic sequence is arrayed a series of orthogonal bands representing binaural subclasses (Imig and Adrián 1977; Kitzes et al. 1980; Middlebrooks et al. 1980) (Fig. 1.17C: EE, EI). A complete picture of the functional design would include other axes of organization interleaved among or embedded within the tonotopic and binaural axes (Ehret 1997). Evidence for amplitopic organization (Schreiner et al. 1992; Phillips et al. 1995;

Schreiner 1995) as well as representations of sharpness of tuning (Schreiner and Mendelson 1990; Heil et al. 1994; Schreiner 1995) or a systematic distribution of responses to frequency modulated tones (Mendelson et al. 1993; Eggermont 1998) have been seen in primary auditory cortex; these are reminiscent of the multiple, overlapping maps in primary visual cortex (Tusa et al. 1981). Cortical cells generally do not represent amplitude modulation as precisely as thalamic neurons (Creutzfeldt et al. 1980; Miller et al. 2001), and their response areas have a range of sizes and shapes (Phillips et al. 1985). Some subcortical aspects of spectral and temporal processing are further refined in the cortex to extract new information (Miller et al. 2001). The proportion of neurons sensitive to interaural level or phase or with azimuthal sensitivity is equal to or exceeds that in the MGB (Clarey et al. 1992). Many cortical cells respond selectively to the spatial location of tone bursts, with hemifield units among the most numerous (Middlebrooks and Pettigrew 1981). Inhibitory processes profoundly shape their receptive fields (Hendry and Jones 1991; Phillips et al. 1991; Prieto et al. 1994a,b) (Fig. 1.17F). More than 10 auditory cortex subdivisions are known in the cat (Winer, 1992); in primates, whose auditory cortical representation has been explored less fully, almost as many areas have been described (Merzenich and Brugge 1973; Morel and Kaas 1992; Morel et al. 1993; Kaas and Hackett 2000; Cheung et al. 2001). It remains for future work to understand how areas differ. These data will have important consequences for competing paradigms of cortical function. For example, the serial processing model envisages the cortex as a multistage decoding device whereas parallel processing schemes emphasize largely independent processing streams that are conveyed concurrently to different postsynaptic targets (Cowey 1981; Diamond 1983; Rouiller et al. 1991). Although elements of both models are present in auditory cortex (Romanski et al. 1999; Rauschecker and Tian 2000), more explicit tests of the differential predictions of each model will require a more complete picture of cortical operations than is now available.

A central issue is how the cortex affects subcortical centers. Stimulating or inactivating bat auditory cortex strongly affects the delay tuning of IC neurons, reducing the auditory-evoked response to subsequent afferent volleys by 90% (Yan and Suga 1996) and significantly altering the tuning properties of postsynaptic thalamic and collicular neurons (Zhang et al. 1997). Perhaps cortex exerts executive control on subcortical neurons for critical processing in demanding acoustic environments. Such corticofugal control is not limited to primary areas. Indeed, studies of these projections from nonprimary, nontonotopic areas show that they are as strong, focal, and topographic, as that of their primary, tonotopic counterparts (Winer et al. 1998, 1999, 2001). Contemporary models of sensory processing emphasize biological and perceptual roles for the corticofugal systems commensurate with their size (Deschênes et al. 1998; Przybyszewski 1998) (Fig. 1.18).

The notion that topical representations in the cortex are rigid and invariant has recently been challenged in two complementary ways. Exposure to specific sounds in a training paradigm alters the distribution of cortical characteristic

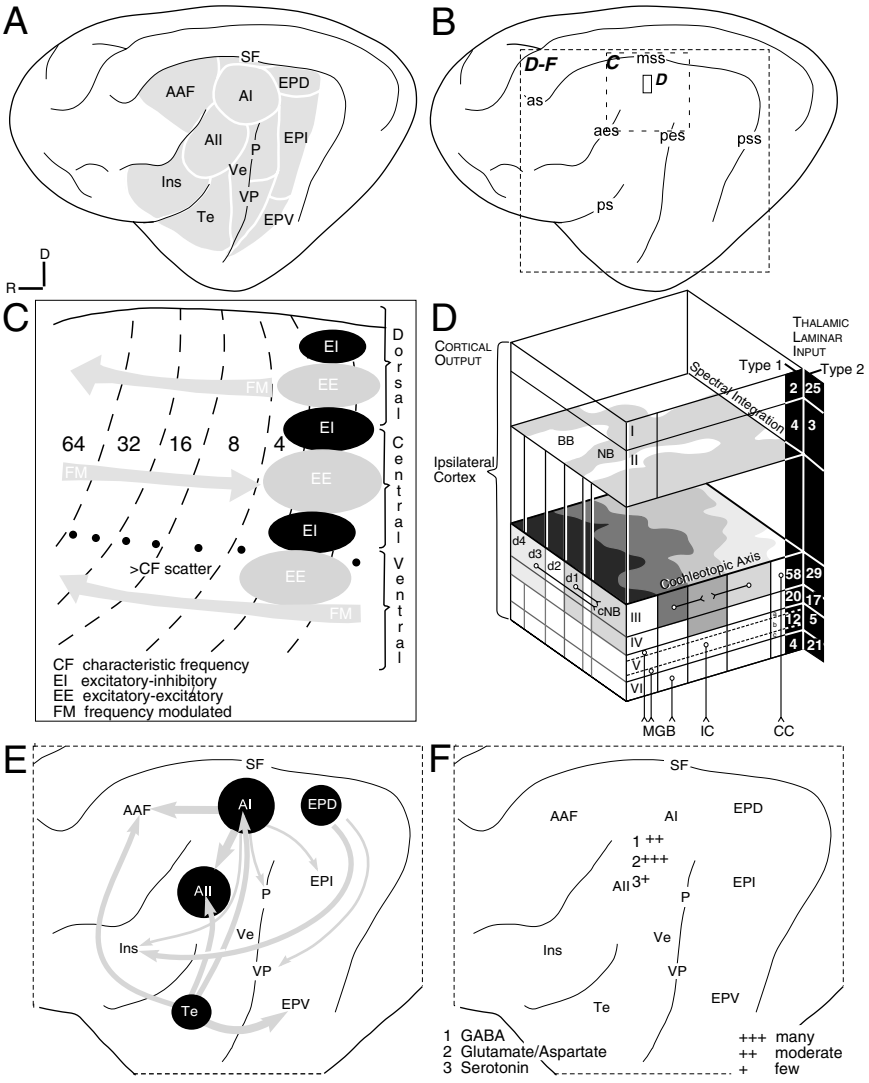

Figure 1.17. Some aspects of auditory cortical organization. **(A)** Areal borders in a lateral view as derived from physiologic (Imig and Reale 1980) and architectonic (Rose 1949; Wallace et al. 1991) investigations. The primary fields are AI, AAF, P, Ve, and VP. Each has a tonotopic organization; the neurons respond mainly to auditory stimuli and they receive topographic projections from the auditory thalamus. Secondary areas are periauditory, include AII (Schreiner and Cynader 1984) and SF (He et al. 1997), and probably are not essential for sound localization (Diamond et al. 1962; Neff et al. 1975). The tertiary areas include limbic-related territories, Ins and Te, near the pseudosylvian sulcus, respond to auditory and nonauditory stimuli (Sindberg and Thompson 1962), and have complex ascending connections with thalamic association nuclei (Niimi and Matsuoka 1979; Winer and Morest 1983). The other fields in the posterior ectosylvian gyrus *(EP)*

frequency (Recanzone et al. 1993), and even relatively brief experience in a ventriloquism task shifts perceptual estimates of sound spatial localization (Recanzone 1998). This implies a rapid retuning of functional domains. A second approach used a stimulation paradigm involving subcortical nonauditory interactions between the cortex and the nucleus basalis, a forebrain limbic center that contains populations of cholinergic and GABAergic neurons; the former project widely to neocortex and elsewhere (Jones et al. 1976). Nucleus basalis stimulation, when paired with appropriate training, has robust and temporally enduring effects on gross tonotopy, single-neuron tuning, receptive field structure, and

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Figure 1.17. *Continued*
have relationships with periauditory-perivisual thalamic nuclei (Bowman and Olson 1988). **(B)** Major sulci in cat auditory cortical areas (Kawamura 1971). **(C)** Selected features of AI functional organization from physiologic studies. Locus of observations is shown in **(B)**. Binaural representation (Middlebrooks et al. 1980) includes alternating bands *(ovals)* superimposed on and crossing the isofrequency contours *(dashed lines)* (Merzenich et al. 1975) throughout AI. Neurons with a preferred direction for frequency-modulated *(FM)* sweeps (Mendelson et al. 1993) also are localized across the isofrequency gradient *(arrows).* The dispersion of characteristic frequency values (CF) is larger in the ventral part of AI *(small black circles)* (Schreiner and Sutter 1992). Other representations are omitted for purposes of clarity. [Redrawn and modified from the original (Ehret 1997).] **(D)** Intrinsic organization of a module in AI (see **B**: *D*). Units with narrowband *(NB)* and broadband *(BB)* frequency selectivities segregate spatially into multiple clusters across the surface of AI. Spatially segregated narrowband clusters are connected via long-range (>1 mm) intrinsic horizontal circuitry as shown with the retrograde labeling pattern (*white circles* denote somata; *lines* denote axons) which aligns with a prominent dorsal cluster of narrowband units (d1–d4). Quality factors *(Q)* at 40 dB above spike threshold were derived from unit responses to pure tone stimuli over a 5-octave range. *Light gray:* low Q_{40}s (wide bandwidth); *white:* high Q_{40}s (narrow bandwidth). The injection and retrograde labeling are largely confined to the white narrowband regions. *a–c:* Sublayers of layer V with differential corticofugal projections. [Adapted and modified from the original source (Read et al. 2002).] The distribution of thalamic laminar projections (right side, white numbers) from type 1 (ventral division) and type 2 (medial division) input is shown numerically as the percentage of boutons/layer after thalamic deposits of tracers. [Adapted and modified from the original source (Huang and Winer 2000).] **(E)** Some ipsilateral corticocortical connections between core, belt, and parabelt auditory areas. Each area receives thalamocortical, ipsilateral corticocortical, and commissural input (Winer 1992). *Arrows* are proportional to the strength of interareal connections. AI acts as a major redistributive hub since it receives projections from a few, mainly lemniscal thalamic nuclei and redistributes their output to other primary fields *(AAF),* to belt areas *(AII),* and to remote parabelt cortex *(EP).* In most instances strong feedback connections are present as well. [Adapted and modified from original sources (Kawamura 1973; Rouiller et al. 1991; Clarke et al. 1993).] **(F)** Concentration of putative neurotransmitters in AI, of which GABAergic neurons comprise about 20% of the population (Prieto et al. 1994a,b), and glutamatergic or aspartatergic cells represent the majority. The serotoninergic innervation consists of axon terminals only (Mulligan and Törk 1988), many of which form perisomatic baskets onto pyramidal cells.

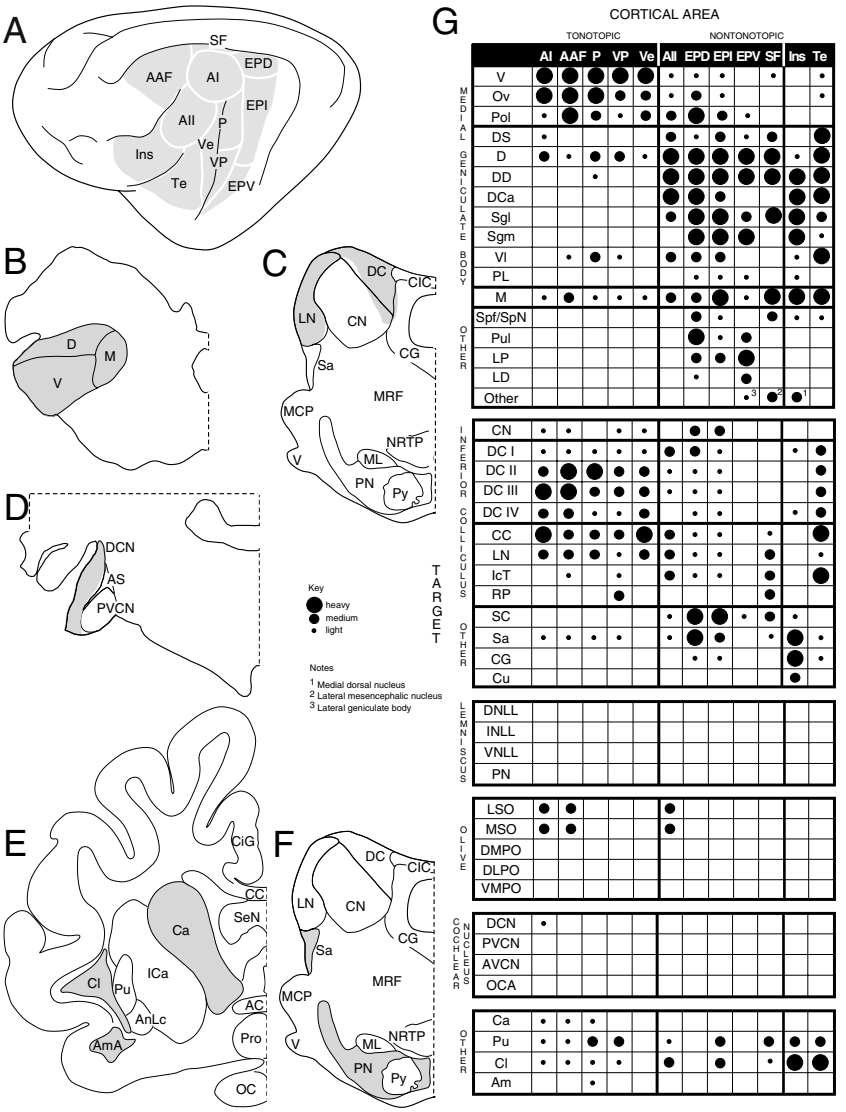

Figure 1.18. Some descending connections of auditory cortex. **(A–E)** Main targets of corticofugal auditory system. **(A)** Cortical auditory areas in the cat (Rose 1949; Imig and Reale 1980, 1981). **(B)** All subdivisions of the MGB receive auditory corticofugal projections (see Fig. 1.18G: MGB); most are topographic, even when they involve thalamic nuclei devoid of fine tonotopic organization (Diamond et al. 1969; Pontes et al. 1975). Few neurons project to both the MGB and the IC (Wong and Kelly 1981); this suggests that the different corticofugal projections have specific laminar origins in rat (Games and Winer 1988) and cat (Prieto and Winer 1999). **(C)** The complementary corticofugal projections to the IC (**G:** inferior colliculus) differ fundamentally from those to the MGB. Thus, input to the lemniscal part (the central nucleus) is sparse, whereas

topical representation in primary auditory cortex (Weinberger 1997; Kilgard and Merzenich 1998b; Kilgard et al. 2001; Kilgard and Merzenich 2002). Thus, even topographically secure areas can show physiologic lability under circumstances that might approximate normal subcortical–cortical interactions (Ohl and Scheich 1997).

In humans several auditory areas have been defined with physiologic (Celesia 1976; Howard et al. 2000), imaging (Belin et al. 2000), neurochemical (Hutsler and Gazzaniga, 1996), connectional (Tardif and Clarke 2001), and histochemical (Hackett et al. 2001) methods. These regions correspond, at least superficially, to their presumed homologues in primates (Brugge 1982). For example, chimpanzees exhibit planum temporale asymmetry (Gannon et al. 1998) much like that in humans (Geschwind and Levitsky 1968), and macaque species-specific vocalizations are impaired by a left, but not a right, hemisphere lesion in a way that recalls expressive aphasia seen after human cortical damage (Heffner and Heffner 1984).

The question of how auditory cortex output influences other parts of the brain can be examined from a neurologic perspective. Cortical disconnection syndromes from infarcts or other trauma leave some functions isolated but otherwise largely intact (Geschwind 1965). In primates the output of the auditory cortex and associated polysensory areas along the superior temporal gyrus reaches wide areas of the parietal lobe and prefrontal cortex (Jones and Powell 1973). Although questions remain about the identity of homologous areas related to language in humans and nonhuman primates (Aboitiz and García 1997), the linguistic deficits in humans consequent to destruction of Wernicke's area—impairments in repetition, comprehension, and naming—are consistent clinical features (Benson 1988) and leave little doubt that auditory cortex functions in-

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Figure 1.18. *Continued*
the ventral division of the medial geniculate body receives a much larger projection (Winer et al. 1998). The other main midbrain targets—the intercollicular tegmentum and lateral nucleus—have roles related to spatial orientation to sound (Oliver and Huerta 1992). A third difference is that giant axon terminals of cortical origin are present in the MGB (Winer et al. 1999) and not in the IC (Diehl and Winer 1996). Cortical influence on nuclei in the ascending auditory system is nucleus–, and perhaps areally, specific. **(D)** The dorsal cochlear nucleus *(DCN)* receives a corticofugal projection. [Adapted and modified from the original sources (Weedman and Ryugo 1996a,b).] **(E)** The corpus striatum and associated nuclei (e.g., claustrum) each receive input from almost all subdivisions of auditory cortex (**G,** *lower part*). [Adapted and modified from the original source (Beneyto and Prieto 2001).] **(F)** Other corticofugal projections reach the sagulum and pontine nuclei. [Adapted and modified from the original source (Brodal 1972).] **(G)** Summary of auditory corticofugal input to the MGB (Winer et al. 2001), IC (Winer et al. 1998), olivary region (Doucet et al. 2002), and cochlear nucleus (Weedman and Ryugo 1996a). The range in the strength, specificity, and origin of the input suggests that the cortex has many roles. *1,* Medial dorsal nucleus; *2,* lateral mesencephalic nucleus; *3,* lateral geniculate body.

clude an essential prelinguistic role analogous to that of the somatic sensory cortex in planning motor behavior. Corticofugal projections thus permit cortical access to some of the earliest parts of the central synaptic sequence in hearing.

By the same token, the auditory cortex has massive feedforward connections that convey its output signals to other cortical and subcortical areas with a role in comprehending and initiating speech. The case can be made for a disjunction between the brain stem auditory system, which encodes the spatial and temporal and spectral qualities of sound, and the thalamus and forebrain, which use this information to derive higher-order representations, namely, biological significance, pattern recognition, and planning for action. The temporal aspects of biological signals contain abundant information that the cortex might extract (Phillips et al. 1991) and that cortical lesions surely impair (Albert and Bear 1974). The primal sketch derived by the brain stem imposes temporal structure on these premotor and cognitive aspects of hearing. The auditory cortex, in conjunction with the frontal lobes and speech sensory-motor cortex, is responsible for the fluidity, precision, and salience of speech in the context of language.

The role of the auditory system up to and including primary cortex can be viewed as to establish a stable representation of a multidimensional feature space that allows extraction of object form, attribute, and location from the sound background for a reconstruction of the environmental scene. Higher sensory cortical areas utilize these representations for the recognition of objects and the formation of reference-independent categories of objects, their relationship to environment and self, multisensory integration, assignment and evaluation of behavioral significance according to context, and the transition to action (Dinse and Schreiner 2002).

8. Themes for Discussion

1. Most auditory centers receive projections from other areas (convergence) and project to many others (divergence). This can entail multiple levels of function within a nucleus so that more than one processing task is superimposed on single neurons, or functions are allocated to ensembles of cells specialized for a specific computational role.
2. The diverse structure of auditory neurons and the rich array of auditory nuclei contrast with the relative homogeneity of peripheral input and the remarkably small number of receptors.
3. Parallel and serial forms of processing emerge as organizing principles at the level of the cochlear nucleus, and they prevail throughout the auditory system. Corticofugal feedback and feedforward connections violate any simple or unidirectional principles of serial organization.
4. Single auditory neurons participate in several representations. Their complete receptive field profile should include, but not be limited to, considerations of aurality, onset/offset behavior, participation in tonotopic or amplitopic representations, and sharpness of tuning. This range is a chal-

lenge to single neuron feature detection models of sensory processing. How many and which of these dimensions are required to classify neurons?

5. The auditory forebrain has two forms of inhibition: intrinsic processes are local to a nucleus, and extrinsic inhibition links remote nuclei/areas. The latter projections are robust in the auditory system, and virtually nonexistent in other modalities. The role that remote inhibition plays in auditory processing is not yet understood.
6. The forebrain auditory system has powerful and direct connections with premotor neurons in the striatum and the pons, each of which is involved in ongoing movement. What is the impact of auditory information on these structures?
7. One role of the auditory system might be as the anticipatory stage for the higher-order communication system, analogous to the function of the premotor cortex in primate movement.
8. It may not be possible or even appropriate to delegate functions to nuclei, as functions are global constructs, while neurons and nuclei and circuits are restricted to local operations.
9. The auditory "system" is composed of several subsystems (for example, olivocochlear, thalamocortical, etc.), each with a distinct connectivity, function, structure, and physiology. The apparent unity of these operations is an inference, not necessarily an implicit or emergent property of these neurons. The presence of so many nuclei is consistent with the view that function is widely dispersed yet highly localized.
10. Some auditory nuclei are strongly conserved in phylogeny, while others are far more variable (Butler and Hodos 1996; Glendenning and Masterton 1998). This principle applies both to size and to internal circuitry. The cochlea is, arguably, the most variable of all the structures. The ancestral forms common to mammals must have diverged rapidly to occupy specific behavioral niches (Baird 1974).
11. The descending auditory connections are among the largest and the most elaborate in any modality. They reach the earliest stage (cochlear nucleus) monosynaptically and increase progressively in size (corticofugal) until they are one of the largest projections in the brain. How do the actions of the several descending systems differ?
12. Much of the central auditory system has no, or only a rudimentary, tonotopic organization. This principle seems to reach its apex in the forebrain, where only a part of the representation for hearing has maps like those so prevalent in the brain stem. This feature appears as early as the PVCN, where broadly tuned cells occur. Are these classes analogous to the two visual systems in mammals (Schneider 1969)?
13. Comparatively few types of neuron are present in the auditory system. These are conserved across nuclei and analogous types are found in different species. Some neurons closely resemble their visual and somatic sensory counterparts, especially in the thalamus and the cortex. Other features of auditory system organization, such as the endbulbs and calyces of Held, are unique

to it and the vestibular system. What is the relationship between these types of neuron and the information they process?

14. The auditory system is the only sensory modality with two chemically distinct central neurotransmitters (GABA and glycine) that may serve an inhibitory/disinhibitory role. Although these transmitters occur in other pathways, they are nowhere as prominent (especially glycine) as they are in the auditory system. Is more than one form of inhibition operating in the auditory system?
15. GABA is present, in varying amounts, through the entire auditory pathway from cochlea to cortex. Glycine as a transmitter is limited to the locus between the cochlear nucleus and the inferior colliculus, and all glycinergic neurons are subcollicular. What is the significance of the nucleus-specific distribution of these and other putative transmitters?
16. The concept of a relay nucleus requires critical scrutiny as all central nuclei transform and modify the information that passes through them (Stanley et al. 1999). It remains to be seen how processing in the IC differs from that in the cerebral cortex (Langner 1992; Eggermont 1998, 2001).
17. The auditory system is the only modality with direct projections from the hippocampus. These could integrate working memory with prior auditory experience. Audition is the only sensory modality with significant direct limbic affiliations.
18. The MGB has monosynaptic projections to the amygdala in the limbic system. This permits polysensory parts of the auditory system to influence smooth muscle as amygdalohypothalamic pathways have significant impact on the autonomic nervous system. It suggests a special saliency for auditory input.
19. There are species differences in the size and internal organization of auditory nuclei, especially in the cochlear nucleus and superior olivary complex. Some of these differences extend to neural circuitry and may entail species-specific patterns of processing. This has implications for the evolution of this circuitry and for understanding species differences.
20. Considerations of tonotopy have dominated thinking about the functional organization of hearing at the expense of considering how other aspects of the stimulus or response patterns such as spontaneous rate, amplitude, latency, and others are organized globally.
21. The auditory system seems to contain three types of neurons as defined on connectional and neurochemical grounds. Two types are common throughout the nervous system: a large projection cell that uses glutamate or aspartate as a transmitter (type I), and a smaller local circuit neuron that uses GABA or glycine as their main transmitter (type II). The third type resembles the projection neuron in size, but uses GABA or glycine as a transmitter, and projects remotely (type III). Neurons with a type III profile are rare or nonexistent in other modalities. What role do they have in audition?
22. Only the auditory system has a robust centrifugal pathway that is conserved phylogenetically. In other modalities it is either nonexistent in all taxa (so-

matic sensory system) or present in a highly selective way in a few species only, such as avian isthmooptic projections to retinal ganglion cells (Cowan et al. 1961). A possible parallel is the projection from spinal γ motoneurons onto intrafusal fibers in the somatic motor system (Matthews 1972). Why are these centrifugal systems so prominent in hearing?

23. Localization theory suggests that functions reside in particular sites that are linked by connections. Computational theory emphasizes interactions between areas. Localization theory depends on maps but the nature of their interactions or the properties that underlie synaptic plasticity are largely unknown. Computation theory depends on operations that cannot readily be related to either neuronal connections or realistic behavior. There is evidence that neural coding properties are labile and experience dependent, but the nature of the code is a matter of debate (Eggermont 2001).
24. Biologically naturalistic stimuli can reveal facets of neural response profiles that more artificial stimuli cannot (Phillips 1989). Studies using pure tone stimuli in anesthetized preparations must be extended to include awake, behaving animals.
25. A general theory of communication should encompass the range of auditory behavior from cricket stridulation (Robert et al. 1992) to song learning in birds (Margoliash 1987) to language acquisition in humans (Nobre and Plunkett 1997). If a grand unified theory is impossible, then the common and unique features of the several communication systems should be identified.

Acknowledgments

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Abbreviations

AAF	anterior auditory field
AC	anterior commissure
aes	anterior ectosylvian sulcus
AI	primary auditory cortex
AII	second auditory cortical area
Am	amygdaloid nuclei
AMa	anterior amygdaloid nucleus
AnLc	ansa lenticularis
AS	dorsal and intermediate subdivisions of the acoustic striae
as	anterior suprasylvian sulcus

AVCN	anteroventral cochlear nucleus
BB	broadband
Ca	caudate nucleus
CC	caudal cortex of the inferior colliculus *or* corpus callosum
CF	characteristic frequency
CG	central gray
ChAt	choline acetyltransferase
CiC	commissure of the inferior colliculus
CiG	cingulate gyrus
Cl	claustrum
CN	central nucleus of the inferior colliculus
cNB	central narrowband region
Cu	cuneiform nucleus
C_Z^+	positive interelectrode difference
C_Z^-	negative interelectrode difference
D	dorsal division of the medial geniculate body *or* dorsal
DC	dorsal cortex of the inferior colliculus
DC I-IV	layers of the dorsal cortex of the inferior colliculus
DCa	caudal pole of the medial geniculate body
DCN	dorsal cochlear nucleus
DD	deep dorsal nucleus of the medial geniculate body
DLPO	dorsolateral periolivary nucleus
DMPO	dorsomedial periolivary nucleus
DNLL	dorsal nucleus of the lateral lemniscus
DS	dorsal superficial nucleus of the medial geniculate body
EE	excitatory/excitatory
EI	excitatory/inhibitory
EO/F	excitatory/occluded/facilitated
EO/mon	excitatory/occluded/monaural
EPD	posterior ectosylvian gyrus, dorsal part
EPI	posterior ectosylvian gyrus, intermediate part
EPV	posterior ectosylvian gyrus, ventral part
FM	frequency modulated
GABA	γ-aminobutyric acid
IC	inferior colliculus
ICa	internal capsule
IcT	intercollicular tegmentum
INLL	intermediate nucleus of the lateral lemniscus
Ins	insular cortex
LD	lateral dorsal thalamic nucleus
LGB	lateral geniculate body
LLN	lateral lemniscal nuclei
LN	lateral nucleus of the inferior colliculus
LNTB	lateral nucleus of the trapezoid body
LP	lateral posterior nucleus

LSO	lateral superior olive
M	medial division of the medial geniculate body *or* medial
MCP	middle cerebellar peduncle
MGB	medial geniculate body
ML	medial lemniscus
MNTB	medial nucleus of the trapezoid body
MRF	mesencephalic reticular formation
MSO	medial superior olive
mss	middle suprasylvian sulcus
NB	narrowband
NRTP	reticular tegmental nucleus of the pons
OC	optic chasm
OCA	octopus cell area
Ov	*pars ovoidea* of the ventral division of the medial geniculate body
P	posterior auditory field
pf	parallel fiber
pes	posterior ectosylvian sulcus
PL	posterior limitans nucleus
PN	pontine nuclei
Pol	lateral part of the posterior group
Pro	preoptic area
ps	pseudosylvian sulcus
pss	posterior suprasylvian sulcus
Pu	putamen
Pul	pulvinar nucleus
Py	pyramidal tract
PVCN	posteroventral cochlear nucleus
RP	rostral pole of the inferior colliculus
Sa	sagulum
SC	superior colliculus
SeN	septal nuclei
SF	suprasylvian fringe
Sgl	suprageniculate nucleus, lateral part
Sgm	suprageniculate nucleus, medial part
Spf	subparafascicular nucleus
SpN	suprapeduncular nucleus
Te	temporal cortex
V	ventral division of the medial geniculate body *or* trigeminal nerve *or* ventral
V_{dc}	ventral division, dorsocaudal part
Ve	ventral auditory field
V_l, Vl	ventral division, lateral part
V_o	ventral division, oral part
VMPO	ventromedial periolivary nucleus

VNLL	ventral nucleus of the lateral lemniscus
VP	ventral posterior auditory field
I–VI	components of auditory brain stem evoked potential *or* layers of auditory cortex

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Chapter 2
Neuronal Organization in the Inferior Colliculus

Douglas L. Oliver

1. Key Issues Regarding Inferior Colliculus Neuronal Organization

An understanding of the neuronal organization of the inferior colliculus (IC) requires an exploration of how the types of neurons, the microcircuitry, and the synaptic organization of the IC interact to define functional zones. The IC was originally divided using anatomical methods to identify the neurons and their inputs with the hope that these subdivisions would correspond to functional zones. The central nucleus, the largest of the subdivisions, has been the focus of most studies of IC neuronal organization and its neuron types and the inputs are best known. Understanding the neuronal organization of the IC in terms of subdivisions has been a problem when it is uncertain how other parts differ from the central nucleus. Because IC subdivisions must be related to the constituent neurons and their inputs, the first part of this chapter discusses how the central nucleus and surrounding structures differ in this regard. One way to address the possible functional differences is through the study of IC microanatomy, our second topic. Within the central nucleus the microanatomical arrangements suggest that the inputs may create modules with specific combinations of inputs. Because a module may contain neurons performing similar types of processing, the types of functional zones present in each subdivision will define the function of that subdivision and clarify the differences between it and others. A third aspect of neuronal organization is the definition of the neuron type. Neurons have a functional as well as a morphological profile. Hence, neurons defined by their axonal targets, neurotransmitter content, and intrinsic membrane properties should reveal fundamental aspects of IC neuronal organization. The final facet of neuronal organization to be discussed is the synaptic organization—the types of synapses and patterns of synaptic input that are manifest on different neuron types or in different functional modules. Synaptic organization leads to the final question regarding neuronal organization. How is auditory processing influenced by the interaction of synaptic inputs with the intrinsic properties of the IC neurons?

2. The Problem of Subdividing the Inferior Colliculus

The IC is one of the largest structures in the mammalian midbrain. It forms the posterior half of the corpora quadrigemina in the midbrain tectum: four bulges on the dorsal surface of the midbrain (Fig. 2.1). Grossly, the IC is readily distinguished from the superior colliculus that constitutes the anterior half of the tectum. Likewise, it is distinguished from the midbrain tegmentum readily in frontal or transverse sections. Tectum and tegmentum develop from different stem cells (Senut and Alvarado-Mallart 1987). The tectum is an alar (sensory) plate derivative whereas the tegmentum is a basal plate derivative, which suggests a motor function.

Despite the ease with which the IC is distinguished from other midbrain structures, understanding the internal or functional organization of the IC has not been so obvious. Like many other brain structures, sharply defined internal boundaries are not always evident.

2.1. The Central Nucleus and a Surrounding Cortex Are the Major Inferior Colliculus Subdivisions

The simplest parcellation recognizes a central nucleus (ICC; Fig. 2.2) that is surrounded by a cortex. Most historical accounts as well as most modern studies follow this basic design. For example, Ramón y Cajal (1995) referred to a nucleus of the IC covered by a dorsal cortex (DC; Fig. 2.2) that includes the commissural connections. He described a lateral cortex (LC; Fig. 2.2) which is a thin layer of gray matter beside ICC that is covered by the brachium of the IC (BI; Fig. 2.2). The brachium contains axons that project to the medial geniculate body in the diencephalon and descending fibers to the IC from the neocortex. Although the name "central nucleus" has been in use for many years, the precise IC region associated with it has depended on the methodological approach and its interpretation.

The anatomical subdivisions of the cat (Oliver and Shneiderman 1991; Oliver and Huerta 1992) and human (Waitzman and Oliver 2002) IC have been reviewed and the references cited include a discussion of adjoining tegmental structures. Here, we address the IC structure from a comparative perspective and evaluate different views on the organization of the subdivisions.

2.2. Midbrain Subdivisions Reflect the Methods Used to Identify Them

Neuroanatomical studies have traditionally relied on Nissl stains or myelin stains to identify subdivisions (Figs. 2.2 to 2.4). These stains are complementary, as Nissl stains show cell bodies while myelin stains reveal axons, and increased

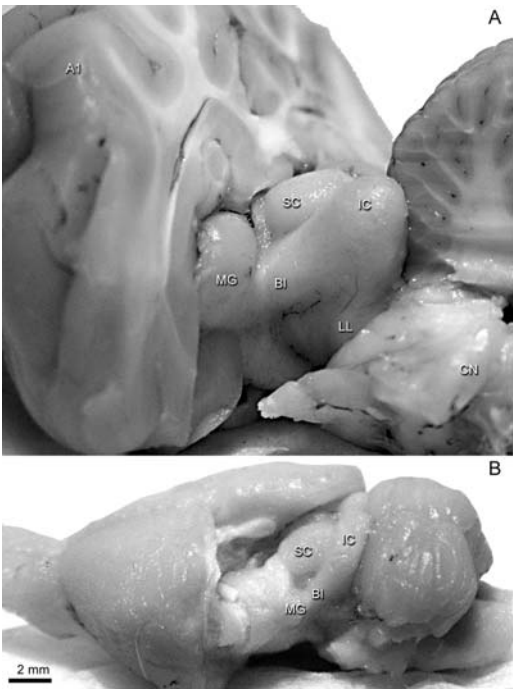

Figure 2.1. Gross anatomy of the cat **(A)** and rat **(B)** midbrain. *A1,* Primary auditory cortex; *BI,* brachium of the inferior colliculus; *CN,* cochlear nucleus; *IC,* inferior colliculus; *LL,* lateral lemniscus; *MG,* medial geniculate body; *SC,* superior colliculus. The scale bar represents 2 mm.

axon density usually reflects lower neuronal cell body density (Berman 1968; Olszewski and Baxter 1982; Paxinos and Watson 1998). Nissl and myelin stains, although widely used, can only hint at the functional subdivisions and internal complexity in the IC.

Golgi impregnations reveal details of IC neurons that are not discernible by other methods. They reveal more distinguishing features of unique neuron types, local differences in the structure of the neuronal distribution, and the differences in local dendritic neuropil organization. Golgi studies have been essential to identifying more specialized regions in the IC (Rockel and Jones 1973a,b; Fitzpatrick 1975; Oliver 1984b; Morest and Oliver 1984; Faye-Lund and Osen 1985; Meininger et al. 1986; Ramón y Cajal 1995). Unfortunately, Golgi stains are incompatible with many histological approaches. Thus, more refined methods that identify morphologically distinct cell types must be used to recognize subdivisions and to confirm their identity independently.

Molecular methods may ultimately identify subdivisions. For example, parvalbumin, a calcium binding protein, has a high concentration in ICC whereas calbindin and calretinin, other calcium binding proteins, concentrate in the dorsal cortex (ICD; see Section 2.6). Cytochrome oxidase, a metabolic marker, concentrates in the ICC (Dezso et al. 1993; González-Lima and Cada 1994; González-Lima et al. 1997; Poremba et al. 1997) rather than in the ICD.

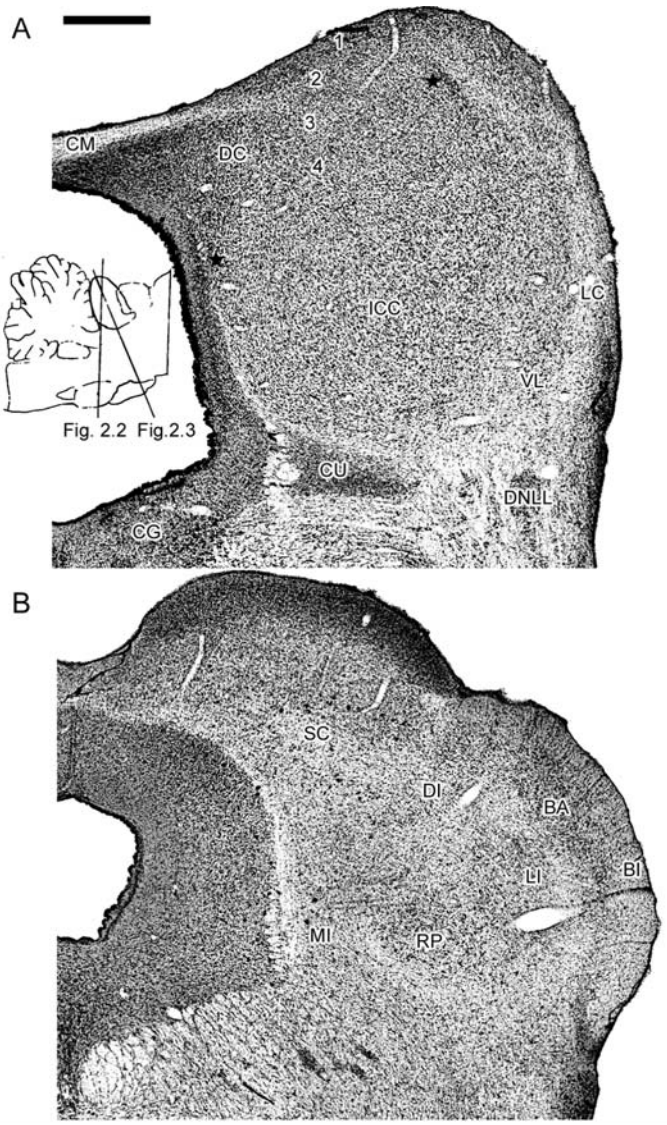

Figure 2.2. Nissl cytoarchitecture of the cat IC in the Horsley–Clarke stereotaxic plane. The *inset* shows the planes of section. **(A)** Mid-IC level through the DNLL. **(B)** A more rostral section at the level of the rostral pole nucleus (RP). *BA,* Nucleus of the brachium; *BI,* brachium of the inferior colliculus; *CG,* central gray; *CM,* commissural, commissure; *CU,* cuneiform nucleus; *DC,* dorsal cortex; *DI,* dorsal intercollicular tegmentum; *DNLL,* dorsal nucleus of the lateral lemniscus; *ICC,* central nucleus; *LC,* lateral cortex; *LI,* lateral intercollicular tegmentum; *MI,* medial intercollicular tegmentum; *SC,* superior colliculus; *1–4,* layers of the dorsal cortex; *VL,* ventral lateral nucleus. The scale bar represents 1 mm.

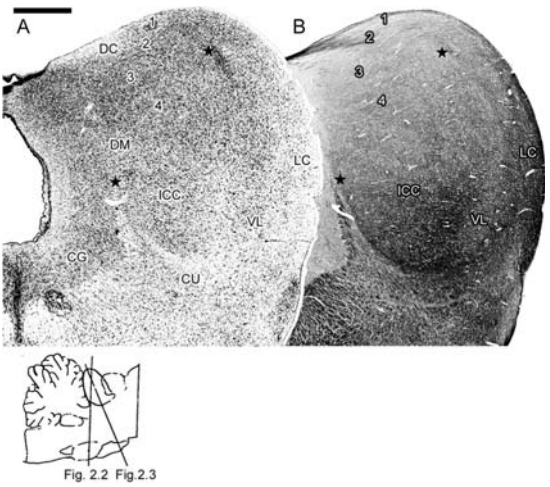

Figure 2.3. Cat IC in the anatomical transverse plane of section. The *inset* shows the plane of #2. **(A)** Nissl stain. **(B)** Heidenhain fiber stain. The scale bar represents 1 mm.

Subdivisions can also be identified electrophysiologically. Microelectrode studies showed that ICC neurons had low thresholds and vigorous responses to simple acoustic stimuli, and their spectral properties and response latencies often distinguished them from ICD (see Chapter 11). ICC neurons have the sharpest tuning and shortest latencies (Aitkin et al. 1975), suggesting its functional primacy.

However, the presence of a tonotopic map does not distinguish the ICC from the surrounding cortex. In other brain regions there is often a reversal in the sequence of frequencies at a subdivision border. Such a reversal is found at the border of the ICC and lateral cortex but *not* at the border of the ICC and ICD or caudal cortex. This has frustrated any sharp distinction between the ICC and dorsal cortex in electrophysiological studies, as the best frequency of a neuron cannot conveniently determine electrode position relative to the ICC border. Electrophysiological methods must often be complemented by other independent methods such as post hoc histology to identify recording sites in smaller subdivisions.

Two methods combine elements of histological approaches and acoustic stimulation and may distinguish subdivisions. The first uses the accumulation of 2-deoxyglucose (2DG) in presynaptic endings during synaptic activity (Nudo and Masterton 1986). A second method is the detection of the Fos protein, a nuclear transcription factor, or its mRNA (Sheng et al. 1993; Fields et al. 1997). Both approaches can reveal activity evoked by acoustic stimuli in presynaptic endings (2DG) or in single neurons (Fos). The challenge in using these methods to identify IC subdivisions is the choice of an appropriate stimulus. One approach uses different spectral, temporal, and binaural features of acoustic stimuli to evoke differential responses in the ICC and surrounding structures.

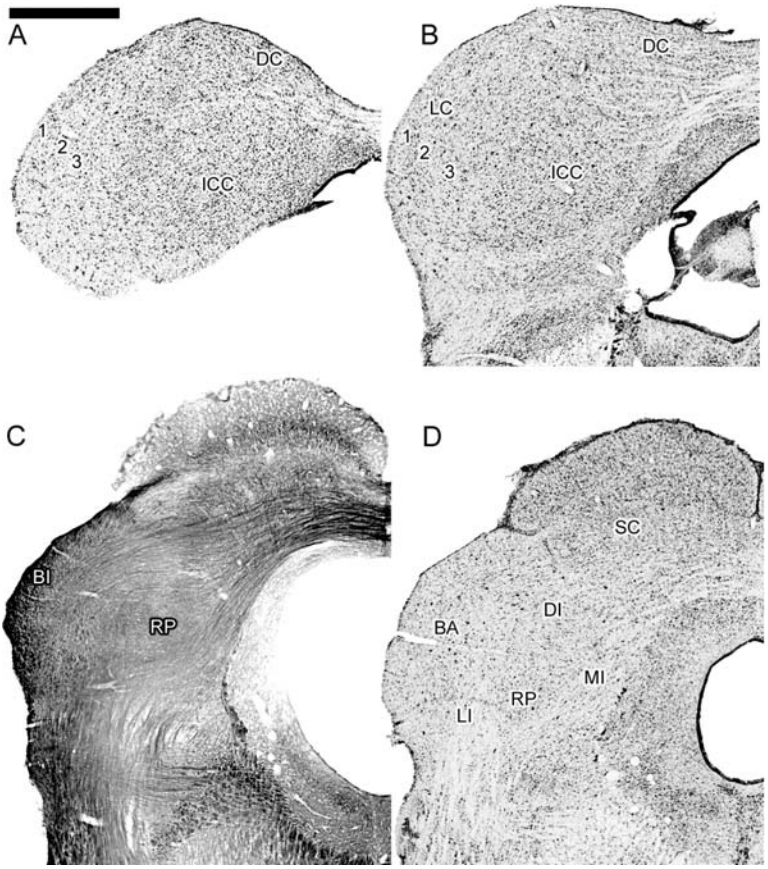

Figure 2.4. Rat IC. **(A)** Caudal central nucleus. *1–3*, layers of the lateral cortex. **(B)** Rostral central nucleus. **(C)** Myelin stain at the level of rostral pole. **(D)** Nissl preparation. The scale bar represents 1 mm.

2.3. How Is the Central Nucleus Defined?

The main subdivision of the mammalian IC is the central nucleus (Figs. 2.2 to 2.4). Its main feature is the fibrodendritic lamina, an entity comprised of disc-shaped neurons and the laminar plexus of afferent axons terminating in it.

2.3.1. Morphology of Central Nucleus Neurons

The main feature of ICC neurons is their highly oriented dendritic field. These disc-shaped neurons are by far the most common cell type and have been observed in almost every species studied. Similar neurons have been described in Golgi preparations of the cat (Oliver 1984b), mouse (Meininger et al. 1986), bat

(Zook et al. 1985), rat (Faye-Lund and Osen 1985; Malmierca et al. 1993. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.), and human (Geniec and Morest 1971) and after intracellular injections of horseradish peroxidase (Kuwada et al. 1997b; Oliver et al. 1991). In the cat most ICC neurons are disc-shaped and have dendritic fields parallel to one another (Figs. 2.5A and 2.6). This arrangement imparts a distinct appearance in Golgi stains that distinguishes the ICC. Disc-shaped neurons have dendritic

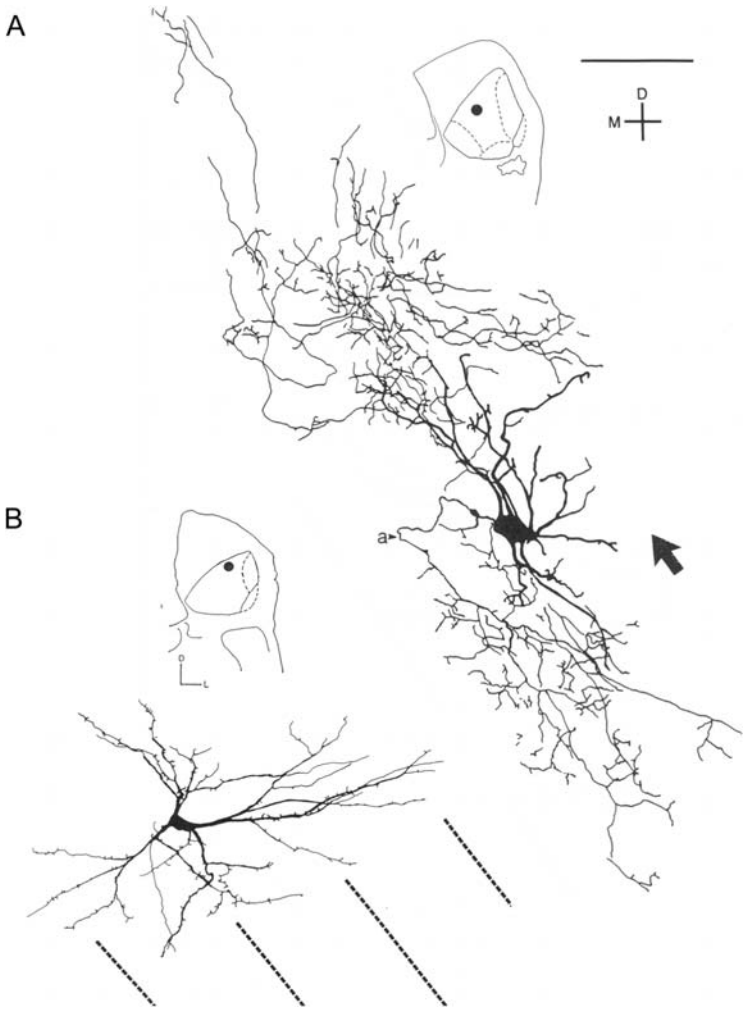

Figure 2.5. Disc-shaped **(A)** and stellate **(B)** cell types in the ICC labeled by intracellular injections of horseradish peroxidase in the adult cat. The approximate position of the cells is shown in the *inset (closed circle).* Laminar orientation is shown by arrow in **(A)** and by lines in **(B)**. *a*, axon. The scale bar represents 100 μm. (From Oliver et al. 1991.)

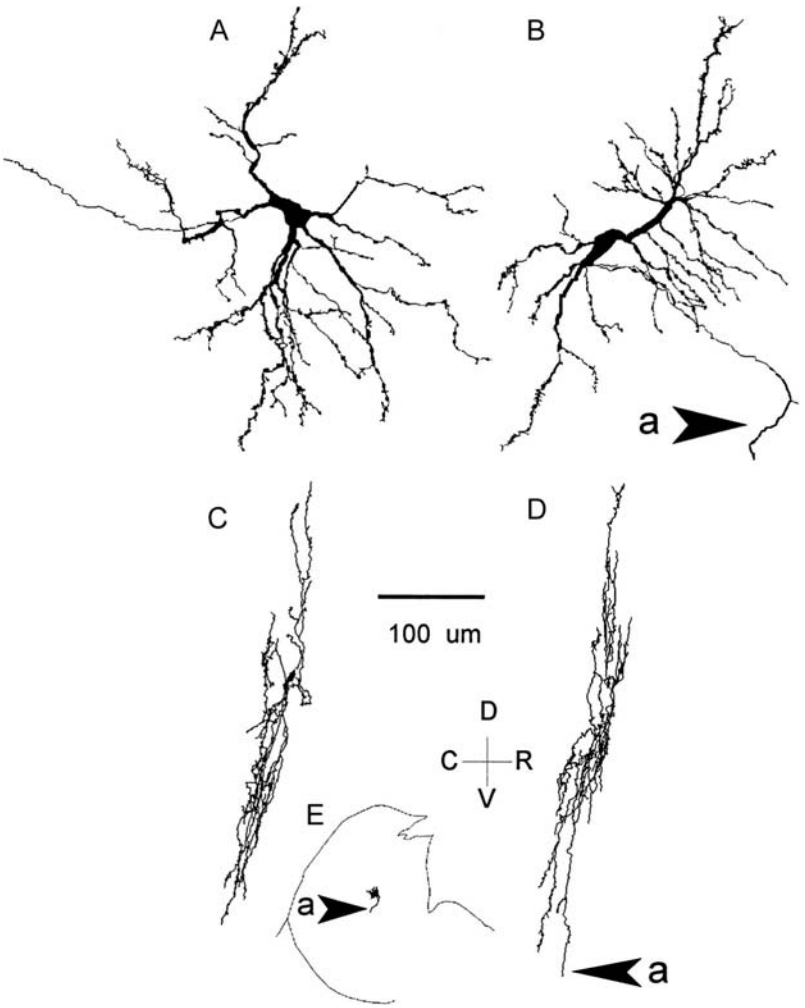

Figure 2.6. Two disc-shaped cells in the ICC of the cat after intracellular injection of horseradish peroxidase. **(A, B)** The cells are shown *en face* in the original parasagittal plane of section. **(C, D)** The same cells after 90° rotation to show the most highly oriented edge-on view of the dendritic field. **(E)** Location of the neuron. (From Kuwada et al. 1997.)

fields about 50 to 70 μm in diameter at the narrowest dimension although the longest axis may be a millimeter (Fig. 2.6). These dimensions may be species-specific. Disc-shaped cells form rows with cells stacked end-to-end or overlapping with long axes of the dendritic fields in parallel. In the rat the high-frequency part of ICC has layers where most disc-shaped neurons, called flat cells in that species, alternate with the less oriented less-flat cells (an oriented

stellate neuron is 100 μm in diameter) (Malmierca et al. 1993). Here, the laminar unit is proposed to be one flat cell and one less-flat neuron, yielding a laminar thickness of about 150 to 170 μm (Fig. 2.7). In the lower-frequency part in the rat and throughout the cat ICC, alternating cell types have not been observed and the laminar unit is likely a multiple of the diameter of the disc-shaped dendritic field. In Nissl stains the disc-shaped morphology is not apparent, as

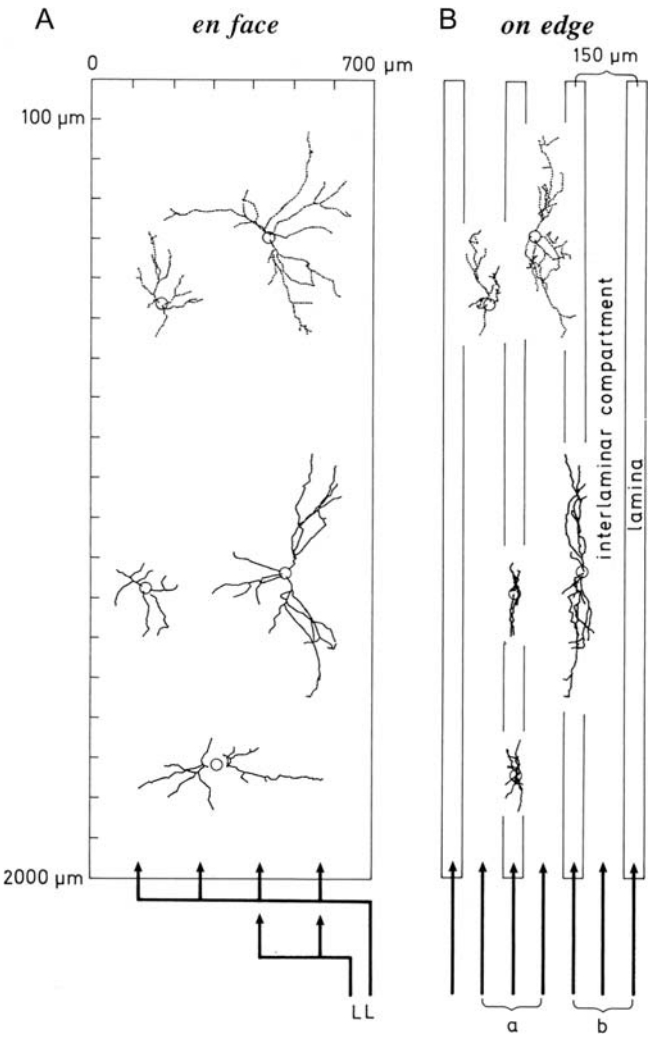

Figure 2.7. Alternating flat and less-flat cells create laminae in the rat central nucleus. **(A)** The *en face* view shows less-flat cells *(top)* and flat cells *(bottom)* with different-sized dendritic fields. **(B)** The on edge view shows the narrowest dimension of the neurons after 90° rotation. (From Malmierca et al. 1993.)

the dendrites are invisible but the somatic orientation is often still evident. Most ICC neurons have dispersed Nissl bodies (granular endoplasmic reticulum) and a smooth nuclear envelope, and presumably correspond to disc-shaped cells (Oliver 1984b; Ribak and Roberts 1986).

A second major cell type defined by morphology in ICC is the stellate (cat; Fig. 2.5B) or less-flat (rat; Fig. 2.7) neurons, which represent <25% of the population and often have radiating dendritic fields that are spherical. Dendrites typically extend beyond the single fibrodendritic lamina into adjacent laminae. Other cell types have ovoid dendritic fields oriented perpendicular to the long axis of the disc-shaped cells (cat) or parallel to the flat cells (the less-flat cells in rat). Nissl stains reveal that presumptive stellate cells have more Nissl bodies (stacks of granular endoplasmic reticulum) and an irregular or infolded nuclear envelope.

The identification of functionally relevant neuron types remains a challenge to research in this field. There are probably more than two types of ICC cells distinguished only on anatomical grounds. They can also be discriminated by size (disc-shaped cells are large to medium or small) and by the complexity of the dendritic branching (stellate cells have simple or complex dendritic branching patterns) (Malmierca et al. 1993). The incidence of dendritic spines (Paloff et al. 1992) and the number and types of axosomatic synaptic input may vary (Oliver 1984b; Ribak and Roberts 1986; Paloff et al. 1989). Observations on the neurotransmitter content, axonal targeting, and intrinsic membrane properties (see Section 4) support the notion that the definition of functional cell types must include data beyond classical morphological models.

2.3.2. Synaptic Inputs to the Central Nucleus

Inputs to the ICC ascend from neurons in the lower auditory brain stem, including the cochlear nuclear complex consisting of the dorsal (DCN; Figs. 2.8 and 2.9) anteroventral (AVCN) and posteroventral (PVCN) cochlear nuclei (see

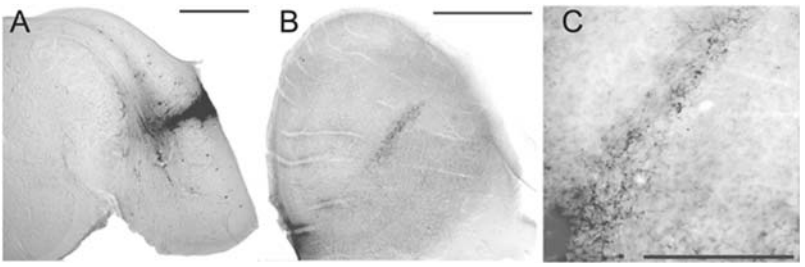

Figure 2.8. Projections from cat dorsal cochlear nucleus to the inferior colliculus. **(A)** Injection of biotinylated dextran amine in dorsal cochlear nucleus. **(B)** A single layer of dextran-labeled axons in the central nucleus of the inferior colliculus. **(C)** Higher magnification view of labeling. The scale represents 1 mm in **(A, B)**; the scale bar represents 0.5 mm in **(C)**. (From Oliver et al. 1997.)

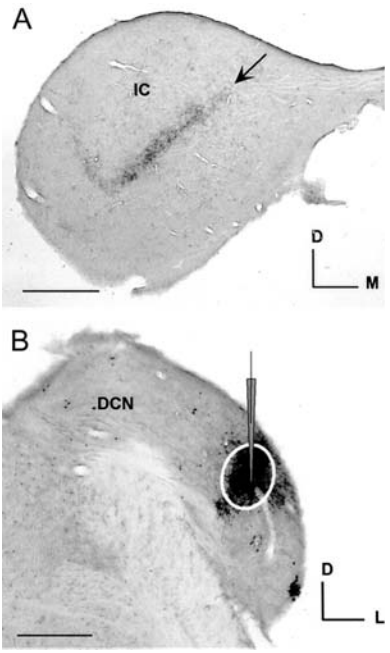

Figure 2.9. Projection from dorsal cochlear nucleus (*DCN*) to the inferior colliculus in the rat. **(A)** Band of labeled axons in the ICC *(arrow).* The lateral band of axons in the external (lateral) cortex is orthogonal to the medial band. **(B)** Injection of dextran in the 4.5 kHz region of dorsal cochlear nucleus. The scale bar represents 0.5 mm. (From Malmierca et al. 2002.)

Chapter 3), and from the superior olivary complex, which includes the medial superior olive (MSO; Fig. 2.10) and the lateral superior olivary nuclei (LSO; Chapter 4). Smaller inputs originate in the medial nucleus of the trapezoid body and from periolivary nuclei, including the superior paraolivary nucleus, and the lateral and ventromedial nuclei of the trapezoid body. The lateral lemniscal nuclei (dorsal and ventral nuclei; DNLL and VNLL, respectively) also provide many afferent axons to ICC (Brunso-Bechtold et al. 1981; Oliver and Shneiderman 1991) and represent the largest single source of input fibers. These projections have been described in small mammals (Merchán et al. 1994; Merchán and Berbel 1996; Malmierca et al. 1998).

Excitatory inputs to the ICC outnumber inhibitory inputs. Electron microscopic autoradiographic studies have identified the synaptic endings from different brain stem sources. These afferent endings are defined as excitatory inputs by the morphology of their synapses—their endings contain clear, round synaptic vesicles (R-type) that make asymmetrical synaptic contacts. It is possible to determine the relative prevalence of different types of axonal boutons from different sources. The MSO provides the largest single source of excitatory synaptic inputs (37%) in the cat followed by the ipsilateral LSO (26%), the contralateral LSO (18%) (Oliver et al. 1995), and the cochlear nucleus (DCN: 11%; AVCN: 13% to 18%) (Oliver 1984a, 1985, 1987). The sum of R-type endings from all sources is about 60% of the ICC axonal endings.

Inhibitory inputs are substantial and are a remarkable feature of ICC neuronal organization. Synaptic terminals that contain γ-aminobutyric acid (GABA) or

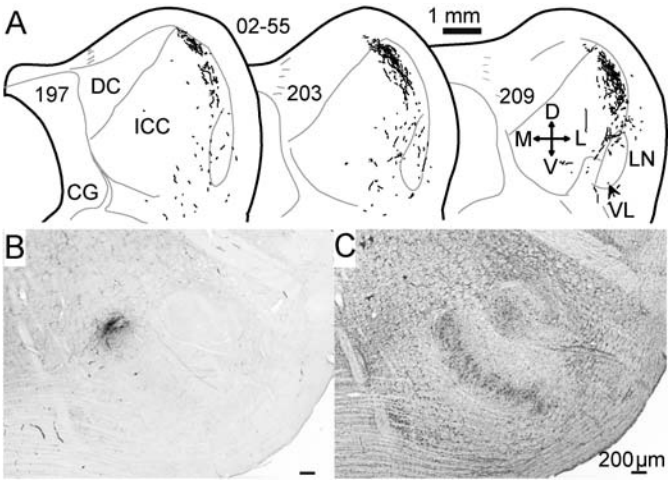

Figure 2.10. Medial superior olivary projections in the cat. **(A)** Plots of dextran-labeled axons terminating in the most dorsolateral ICC laminae corresponding to the lowest frequency representation. A few fibers cross the border into the dorsal cortex. Others may terminate in the most dorsal part of the ventrolateral nucleus. **(B)** Injection of dextran amines in the dorsal 150 Hz region of the medial superior olive. **(C)** Adjacent Nissl-stained section. (From Loftus et al. 2004.)

glycine as a neurotransmitter comprise 40% of the presynaptic endings (Oliver 2000). Electron micrographic studies find many endings with the morphology associated with inhibitory synapses—pleomorphic synaptic vesicles (PL-type) that make symmetrical synaptic contacts (Shneiderman and Oliver 1989). Many of these contain GABA (Shneiderman et al. 1993; Oliver et al. 1994) and originate in the DNLL (Hutson 1988; Shneiderman et al. 1988; Zhang et al. 1998; Chen et al. 1999) and they account for 26% of the PL-type endings (Shneiderman and Oliver 1989). A second source of inhibitory endings is the ipsilateral LSO projection, which contains glycine (Saint Marie et al. 1989; Saint Marie and Baker 1990; Glendenning et al. 1992) and also accounts for 26% of ICC endings (Oliver et al. 1995). A third and probably inhibitory projection is the VNLL, whose neurons contain both glycine and GABA (Saint Marie et al. 1997; Riquelme et al. 2001). These endings have not been identified at the electron microscopic level nor have the local axons from IC GABAergic neurons (see Section 4.2).

Although the inputs to ICC have been identified at the electron microscopic level, their synaptic role in processing auditory information remains an area of intense interest. For example, it is unclear whether these inputs are distributed homogeneously. Further evidence on ICC microanatomy suggests that inputs are segregated and raises the possibility that excitatory and inhibitory inputs have different densities in different functional modules (see Section 3.2.2). Likewise,

as the definitions of cell types expand to include transmitter content and intrinsic properties, it will be important to determine whether different cell types receive the same proportions of excitatory and inhibitory input.

2.3.3. Axonal Components of the Fibrodendritic Laminae

The major axonal components of the fibrodendritic laminae are lemniscal axons. Many axons in Golgi preparations run parallel to the dendrites of the disc-shaped neurons but the identity of these axons cannot be determined. In experimental material the contribution of the ascending fibers to the fibrodendritic laminae can be determined. Axons from lower brain stem sources form ventrolateral-to-dorsomedial oriented rows parallel to the dendritic fields of the disc-shaped neurons. Small injections of clusters of neurons in auditory brain stem structures with anterograde tracers (biotinylated dextran amines, [^{3}H]leucine) reveal axonal bundles that run from the caudal to rostral direction through much of the ICC (Figs. 2.8 to 2.10). In essence a single band of axons represents the narrowest laminar dimension, about 200 μm wide. In the cat the axonal laminae can extend 4 mm rostrocaudally and reach 2 mm in height (Fig. 2.11). These run from caudolateral-to-rostromedial at approximately 45° to the rostrocaudal plane and from ventrolateral to dorsomedial in the dorsoventral plane. The rostrocaudal laminar length may be species-specific. However, the width of single bands of axons from the DCN (compare Figs. 2.8 and 2.9) is similar in cat and rat and resembles that for AVCN and for cat LSO and MSO axons (Fig. 2.10).

A third component of the fibrodendritic laminae are axons from local IC neurons (see Chapter 5). Axons from both disc-shaped and stellate cells form local collaterals before leaving the IC. Disc-shaped cells injected with intracellular deposits of horseradish peroxidase (HRP) have axons that remain in the same lamina as the parent cell and the local axonal plexus is parallel to the dendritic field (Fig. 2.5A) (Oliver et al. 1991). IC neurons may also project to other ipsilateral laminae. Stellate neuron axons in Golgi impregnations in the cat or after intracellular filling in the rat contribute to fibrodendritic laminae other than the one in which the cell body resides (Fig. 2.12A). Thus, ICC neurons of all types have axons that contribute to ICC laminar organization. An important unresolved issue here is whether the ICC contains true interneurons with axons that are confined solely to the ipsilateral IC (see Chapter 22). Although there is evidence for local axonal collaterals, it is more difficult to prove that the axon remains within the ICC. No neuron with a unique morphology has been identified as a true interneuron and the evidence from HRP intracellular filling suggests that all neurons have axons with local collaterals, even those whose targets are outside of the IC or in the contralateral IC (Oliver et al. 1991).

A fourth component of the fibrodendritic lamina is commissural fibers (see Chapter 5). Small injections of *Phaseolus vulgaris* leucoagglutinin (PHA-L) or biotinylated dextran amines (BDA) on one side of the IC can label single contralateral laminae (Saldaña and Merchán 1992; Malmierca et al. 1995). The contralateral laminar labeling is at the same best frequency as the injected lam-

ina. Thus, the homotypical laminae on each side of the central nucleus appear to be interconnected.

2.4. The Lateral Cortex

The lateral cortex is lateral to the central nucleus (LC; Fig. 2.2A) and has also been called the external nucleus (Berman 1968), external cortex (Faye-Lund and Osen 1985), and lateral zone (Geniec and Morest 1971). Part of it may receive input from the lateral lemniscal nuclei, but it lacks disc-shaped cells. In the cat and human the LC includes the lateral nucleus and the ventrolateral nucleus (Geniec and Morest 1971; Morest and Oliver 1984).

The LC has a fibrous outer layer 1 and a small-celled layer 2. In the cat it is easily defined relative to the low-frequency parts of ICC by its lower neuronal density (Fig. 2.2A: LC). The LC is also apparent in myelin stains because the fibers that become the brachium of the IC aggregate and the outer fibrous layer thickens rostrally (Fig. 2.3). Layer 2 of the LC is apparent in many species because of high acetylcholinesterase concentrations (rat: Paxinos and Watson 1998). The main inputs to the lateral nucleus are from the ipsilateral ICC, the auditory cortex, the spinal cord, and dorsal column nuclei of the somatic sensory system (Morest and Oliver 1984; Oliver and Huerta 1992). These terminate primarily in LC layer 2 and lateral lemniscus fibers do not enter layers 1 or 2 (Oliver et al. 1999) (see below).

In the cat and human the lateral cortex includes the ventrolateral nucleus (Figs. 2.2 and 2.3: VL) wedged between the ventral part of the lateral nucleus and the fibers of the lateral lemniscus as they enter the ventral central nucleus (also called the interstitial zone). VL has large and small cells and a cellular density intermediate to that in the central or lateral nuclei. Thus, it can appear as a third layer beneath the small-celled second layer of the lateral nucleus in the ventral IC. Rostrally, VL is usually segregated from ICC by the lateral lemniscal axons. More caudally, however, lemniscal fibers are fewer and the separation is less obvious. The cat VL receives lemniscal inputs from the cochlear nucleus and the MSO and LSO (Shneiderman and Henkel 1987). These are laminar projections. When labeled experimentally they form a "medial band" of axons in ICC parallel to the disc-shaped neurons, and a shorter "lateral band" in VL oriented orthogonal to those in ICC (Shneiderman and Henkel 1987).

In the rat the LC (Fig. 2.4A, B: LC) is called the external cortex (Faye-Lund and Osen 1985; Paxinos and Watson 1998). The many studies of rats make it useful to compare this region to that in the cat. The external cortex is a three-layered structure. Layers 1 and 2 resemble the cat LC, the fibrous layer and the small cellular layer, respectively. Layer 3 of rat LC corresponds to the ventrolateral nucleus. Studies of both the local connections and the lemniscal inputs to the IC in rat show laminated input to both the ICC and to layer 3 of the external cortex (see Chapter 5). As in the cat ICC and VL, the medial band of lemniscal fibers terminates parallel to the ICC laminae and the lateral band of fibers in the external cortex is nearly orthogonal (Fig. 2.9). Single lateral bands

are as wide as the medial bands. The lemniscal inputs to the external cortex are tonotopically organized with lower frequency bands located dorsally (Loftus et al. 2004b).

One explanation for the different appearances of the IC in the rat and cat is the absence of laminae in rat ICC and lateral cortex tuned to frequencies <1 kHz and the attenuation of laminae tuned to 1 to 5 kHz. In the rat, the ICC is separated from the lateral nucleus by the VL (layer 3 of LC). In contrast, in the cat the frequencies <5 kHz and especially <1 kHz occupy much of the dorsolateral ICC. The portions of the IC lateral to this low-frequency ICC region have little or no ventrolateral nucleus intercalated between it and the lateral nucleus, and lateral bands of lemniscal axons tuned to frequencies <2 kHz diminish. Because in the rat few IC responses are <3 kHz (Clopton and Winfield 1973), the comparable low-frequency part of ICC is presumably absent or attenuated, perhaps explaining the species difference. A similar effect may be present in mice, whose low-frequency hearing is likewise minimal.

Questions remain concerning the LC particularly. Not least among these is the persistent use of different names for what may be the same structure. We propose that the term "lateral cortex" be adopted as a substitute for external cortex, as it clearly denotes this lateral portion of the IC, it distinguishes it from other rostral, medial, and dorsal regions, and it identifies its cortical affiliations.

The function of the LC is uncertain. This may be because observations from the deeper portion (VL nucleus, layer 3), which receives lemniscal inputs, are often combined with data from the superficial portion, which receives little ascending input but is a major target of ICC. Electrophysiological studies have not characterized these areas systematically and consequently there is little basis on which to compare their neuronal response properties. One possible function, suggested below, is that the lateral nucleus of the LC extends rostrally as the nucleus of the brachium of the IC and this amalgamated structure has a role in multimodal integration (Malmierca et al. 2002).

2.5. *Structures Rostral to the Central Nucleus*

Rostral to the ICC the laminae disappear and the nucleus of the rostral pole (RP; Figs. 2.2B and 2.4C, D) emerges. In many species the RP receives the most anterior lemniscal fibers and these terminate on stellate neurons. The RP is evidently related to auditory function owing to its lemniscal inputs and it projects to the superior colliculus, providing auditory signals to the visual–motor system (Harting and Van Lieshout 2000). However, few studies have considered the responses of these neurons to sound stimuli.

The intercollicular tegmentum surrounds the RP (Figs. 2.2B and 2.4C, D) and it is named according to its location in the dorsal (DI), medial (MI), or lateral (LI) intercollicular tegmentum (Morest and Oliver 1984). These complex tegmental structures are the part of the mesencephalic reticular formation that separates the IC from the superior colliculus. The borders of ICC, RP and tegmental structures are best seen in sagittal or horizontal planes where the fibrous teg-

mental architecture contrasts with the denser cell packing of the ICC. The functions of the intercollicular tegmentum at the level of the IC remain obscure, but it may be involved with multimodal integration. Like the second layer of LC, the intercollicular tegmentum receives inputs from the somatosensory system (RoBards et al. 1976; RoBards 1979; Wiberg et al. 1987), from the auditory nerve root (Lopez et al. 1999), and more rostral portions of the mesencephalic reticular formation that are involved in visual–motor function (Waitzman and Oliver 2002). The intercollicular tegmentum may therefore be involved with multimodal integration.

The nucleus of the brachium of the IC (BI; Figs. 2.2B and 2.4C, D) may be involved in gaze control. Whereas the brachium of the IC (BI; Figs. 2.2B, 2.4C, D) contains the tectothalamic fibers from the IC and corticotectal fibers from the neocortex (Kudo and Niimi 1980; Winer et al. 1998), the BI is a cellular structure that receives inputs primarily from the IC. It is continuous caudally with the LC. The nucleus of the brachium projects in a reciprocal topographical manner to the superior colliculus (King et al. 1998; Doubell et al. 2000). The BI may also serve as an interface for routing auditory information from the ICC to the superior colliculus. Because of this role and its position in the auditory pathway the nucleus of the brachium (perhaps including the lateral nucleus) may be homologous to the "external cortex" as defined in the barn owl, where convergent inputs from ICC create a spatial map of sound location that is conveyed to the optic tectum (Knudsen 1983a,b). The nature of the auditory signals sent by BI to the superior colliculus in the mammal is unknown.

2.6. Structures Dorsal and Caudal to the Central Nucleus

Dorsal to the ICC is the dorsal cortex (DC; Figs. 2.2A, 2.3, and 2.4B, C). Earlier studies (Berman 1968; Rockel and Jones 1973b) recognized a "pericentral nucleus" that is largely confined to the outer margin of the IC and resembles the LC in that it has a fibrous outer layer and a parvocellular inner layer. These layers correspond to layers 1 and 2 of the cat's DC (Morest and Oliver 1984). The deeper layers of DC (layers 3 and 4; Figs. 2.2A and 2.3) were considered the dorsomedial part of ICC in some prior accounts (Rockel and Jones 1973b). Layer 3 is continuous with the fibers of the commissure of the IC and the deeper layers have successively larger cells. The caudal cortex is limited to the superficial 200 to 300 μm IC caudal to ICC (Morest and Oliver 1984; Oliver and Morest 1984). Much like the pericentral nucleus, it has two outer layers but the most superficial fibrous layer is less prominent. Where it is caudal to the DC in the dorsomedial IC, layer 2 of the caudal cortex borders layer 3 of the DC.

Golgi studies have shown that the deeper layers of DC continue beneath the pericentral region until it meets the ICC. Their border is clear, as the orientation of the dendritic fields shows disc-shaped neurons of the fibrodendritic laminae in the ICC ending at the border of the DC, where nonoriented neurons become prominent (see Fig. 11 in Morest and Oliver 1984). Fiber stains and anterograde

transport studies reveal the transition from the ICC, as the axonal populations change here. For example, DC neurons have unoriented axons while disc-shaped ICC neurons have axons confined to a lamina (Oliver et al. 1991). Inputs to ICC are primarily from the brain stem with minor (or no) inputs from the neocortex and a modest input from the contralateral IC (see earlier). This pattern is reversed in the deepest layer of dorsal cortex (layer 4), where the neocortical and commissural inputs are predominant (Chapters 5 and 8). Only modest inputs from the DCN and the DNLL reach DC layer 4 (Oliver 1984a; Shneiderman et al. 1988). These fibers are often smaller collaterals of the lemniscal axons whose principal terminal fields are in the ICC. Input to the DC from the SOC is absent.

Defining the dorsal border of ICC experimentally remains problematic and there is a question as to whether there is a sharp functional border. As noted earlier, there is no reversal of the tonotopic map at this border. However, changes in the populations of inputs and possibly in the intrinsic properties of the neurons (Smith 1992; Li et al. 1998) suggest that the response properties of neurons in these regions differ. For example, DC neurons have broader tuning than ICC neurons (Aitkin et al. 1975, 1994).

Certain histochemical stains and immunocytochemical probes may be useful to identify this border. In many species a high parvalbumin concentration delineates the ICC from the DC and the latter has high concentrations of calbindin and calretinin. Comparisons are available for human, gerbil, bat, guinea pig, macaque, dolphin, rat, and mouse (Seto-Ohshima et al. 1990; Ohshima et al. 1991; Coleman et al. 1992; Vater and Braun 1994; Yasuhara et al. 1994; Caicedo et al. 1996; Lohmann and Friauf 1996; Glezer et al. 1998; Idrizbegovic et al. 1999; Spencer et al. 2002; Tardif et al. 2003). Molecules such as cytochrome oxidase also have high concentrations in the ICC (Dezso et al. 1993; González-Lima and Cada 1994; González-Lima et al. 1997; Poremba et al. 1997) and NADPH-diaphorase is concentrated in the dorsal and lateral cortex (Paxinos 1999). These latter proteins may be expressed in the presynaptic lemniscal axons in the IC and these axons may not all terminate precisely at the ICC border, suggesting a concentration gradient at the DC border.

2.7. *Future Research on Defining Functional Subdivisions in the Inferior Colliculus*

Other endogenous proteins may better serve as architectonic guides to IC parcellation. The premise that IC subdivisions represent homogeneous functional zones based on either unique neuron types or fixed combinations of inputs suggests that cell-specific molecules or inputs may identify the subdivisions. At this point, however, single IC subdivisions remain to be identified by single molecules. Moreover, the premise that the identity of an IC subdivision is represented as a single functional module is tenuous.

A complementary approach that deserves attention is the molecular specificity of different IC cell types or cells of different lineage. Thus, if DC neurons originate from different stem cells or develop at different times than those in

the ICC it could explain why the dendrites of their neurons differentiate later (Morest 1969). Because ICC and DC neurons often differ in dendritic morphology, perhaps there are molecules related to this phenotype that would demarcate IC subdivisions. Different IC neurons have different patterns of ion channel expression, as suggested by firing patterns related to unique combinations of potassium and calcium currents (Sivaramakrishnan and Oliver 2001). Thus, probes for ion channel subunits or combinations of subunits may specify subdivisions.

3. Microanatomy of the Central Nucleus

There are units of IC neuronal organization finer than the subdivisions described earlier. The microanatomy within each subdivision may define functional modules that control important aspects of information processing. We have proposed that synaptic domains are functional modules formed by the segregation of in-

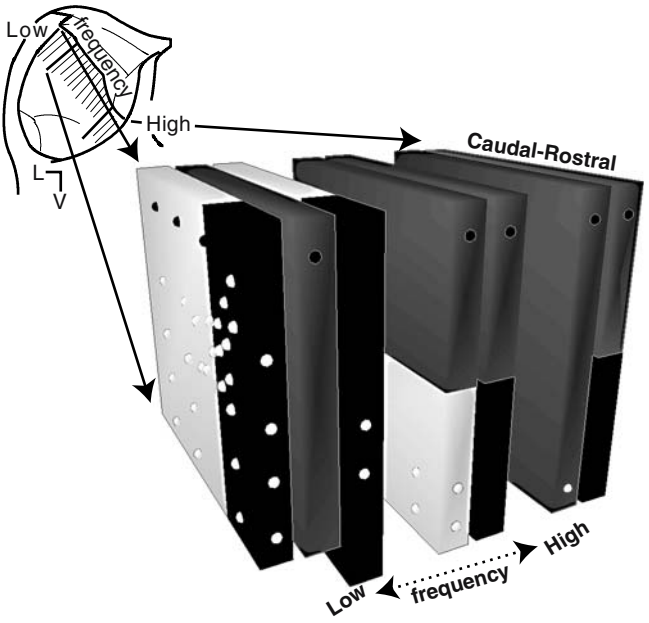

Figure 2.11. A model of ICC synaptic domains in the ICC. Each functional module is denoted by a different shade and represents a different excitatory brain stem input (*light gray,* medial superior olive; *dark gray,* cochlear nucleus; *black,* lateral superior olive). Inhibitory inputs (lateral superior olive, *white spheres;* dorsal nucleus of the lateral lemniscus, *black spheres*) terminate in particular domains and avoid others. The distribution of some modules is highly related to the tonotopic map since some inputs are absent at the ends of the frequency ranges.

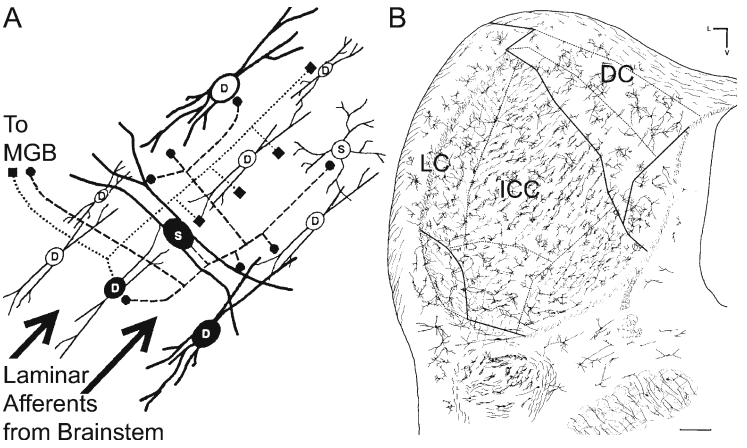

Figure 2.12. Microanatomy of ICC. **(A)** Disc-shaped neurons (D) align to form laminae that are reinforced by the local axons of these cells and parallel to the brain stem laminar afferents. Stellate cells (S) have dendrites and axons that interact with several laminae. Both disc-shaped and stellate cells can synthesize GABA *(black cells)* while others may be glutamatergic. GABAergic neurons can project to the medial geniculate body as do the nonGABAergic cells *(not shown).* **(B)** Golgi-impregnated section of the cat IC shows the subdivisions and ICC laminae at lower magnification. Most laminae run from ventrolateral to dorsomedial. For other abbreviations see Figs. 2.1 and 2.2. (From Oliver 1984. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.; Oliver et al. 1994.)

puts from different sources (Oliver and Huerta 1992; Oliver 2000). Synaptic domains are a basic feature of organization in the inferior and superior colliculus. Thus, small groups of neurons share a common set of synaptic inputs and are likely to share a similar function. In the ICC a single lamina may actually be composed of two or more synaptic domains (Fig. 2.11). Each DC layer may represent a functional module or a layer may contain multiple domains similar to the deep layers of the superior colliculus. Because the LC, VL, and RP nuclei also have unique combinations of inputs, they should be considered functional modules. Future study may show that they contain more than one domain. ICC functional modules have been the most thoroughly studied. Consequently, this section focuses on ICC modules and their role in processing auditory information.

The ICC has a three-dimensional organization defined by its microanatomy. Its laminae consist of arrays of disc-shaped neurons and parallel axons from brain stem and local sources (Fig. 2.12; cf. Section 2.3.2). In the cat the laminae are long sheets running obliquely to the rostrocaudal plane and several millimeters high. The bands of labeled axons seen after small injections in the brain stem or intracellular injections of single IC neurons suggest that single laminae are discrete units approximately 200 μm wide (Figs. 2.8 to 2.11). This unit organization is probably driven by the axonal components, as single dendritic

fields are usually one half to one third the diameter of the axonal bands (Oliver and Morest 1984; Malmierca et al. 1993).

Given this stereotyped ICC microanatomy, the synaptic domains may be related to the dimensions of a single lamina. The most obvious functional parameter related to the laminae is tonotopic organization. This varies in the dimension parallel to the width of the laminae. We first discuss the evidence that the spectral properties of ICC cells are related to the laminar microanatomy. Whether synaptic domains create other functional modules will be the second topic of this section.

3.1. What Is the Structural Basis of Tonotopic Organization?

The elementary organization of the ICC tonotopic map is clear from auditory physiology and experimental neuroanatomical studies. The lowest frequencies are represented dorsolaterally and the highest frequencies are ventromedial (Merzenich and Reid 1974; Schreiner and Langner 1997). Anatomical experiments show that brain stem neurons tuned to different frequencies project to corresponding positions of the ICC tonotopic map and these axonal laminae form discrete units approximately 200 μm wide.

Studies with 2DG show the activation pattern of axons activated by pure tones. Because 2DG is taken up by presynaptic axons during synaptic activity (Nudo and Masterton 1986), this method reveals the three-dimensional organization of the axons when they are activated by sound (Brown et al. 1997b). Their spatial pattern recapitulates the morphology of the axonal laminae. Most sound-activated axons are in the medial band in ICC and the lateral band in the VL is weaker or unlabeled. These studies also show that the width of the axonal band activated by tone increases with stimulus intensity (Brown et al. 1997a). The minimum width of the band activated by near-threshold stimuli should be related to the spatial dimensions of the axons. However, it is difficult to relate the activation pattern to the microanatomy of the laminae because 2DG labeling is usually performed with carbon-14 emission, producing substantial cross-scatter that reduces resolution of the method to a level too coarse to resolve single axons. Because the 2DG accumulates in the presynaptic axons only, the firing of single neurons is not detected.

Microelectrode recordings from single and multiple neurons provide higher resolution and are consistent with a frequency organization based on discrete laminae. The characteristic frequency changes in steps of 175 ± 83 μm in penetrations perpendicular to the tonotopic axis (the dorsolateral to ventromedial direction) and each step is approximately 0.28 octaves (Schreiner and Langner 1997; see Chapter 11). Such frequency steps would constrain the maximum number of laminae available for ICC frequency coding. Thus, 35 to 40 laminae would be required to encode the 9 octaves audible in the cat (Schreiner and Langner 1997). This study suggests that an entire lamina may represent a narrow

range of characteristic frequencies, a "frequency-band lamina" rather than representing a single frequency, the "iso-frequency lamina" concept. However, this method does not address whether the laminar organization is effective in organizing the spectral properties of ICC at sound intensity levels above threshold.

It is now possible to relate the activity of the entire population of the ICC laminae to frequency coding using sound-activated Fos protein. Most neurons produce this nuclear transcription factor when stimuli induce regular bursts of firing for prolonged periods. The production of cFos mRNA and Fos protein is proportional to the amount of firing in the cochlear nucleus and dorsal root ganglion (Sheng et al. 1993; Fields et al. 1997; Saint Marie et al. 1999; Yang et al. 2003b). Consequently, the amount of protein reflects stimulus intensity (Yang et al. 2003b).

The sound activation of Fos protein can address whether the population of neurons activated by single tones is confined to a single lamina, independent of the stimulus intensity (Yang et al. 2003a). Interestingly the maximum band of neurons activated by a single sinusoidally amplitude modulated (SAM) tone (8 or 16 kHz; 14 Hz modulation) is limited to approximately 180 μm wide (Fig. 2.13A). The width of the band is virtually the same for 47- to 80-dB stimuli, although at 27 dB the band narrows (Fig. 2.13B, C). Because the laminar dimension is similar to that suggested by the microelectrode recordings in the cat,

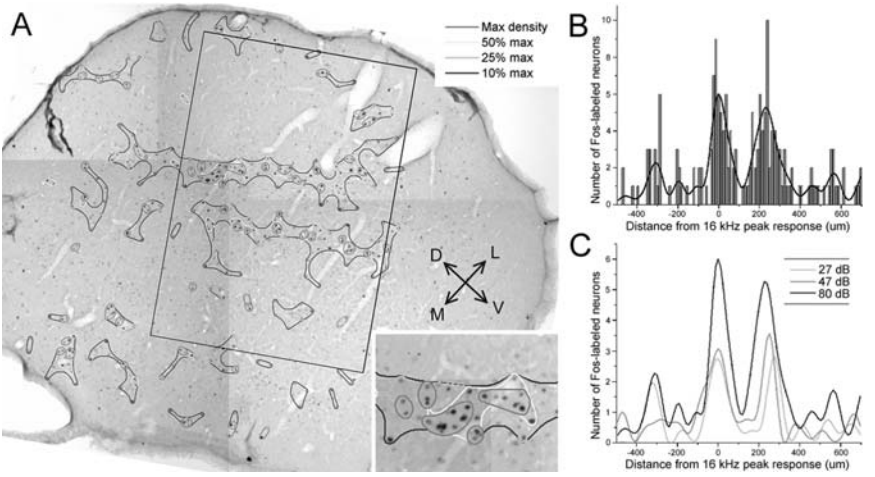

Figure 2.13. Fos protein in the rat IC activated by sounds of two different frequencies. **(A)** Montage showing Fos-immunopositive neural nuclei in the ICC, DC, and LC. The *inset* shows nuclei at higher magnification. Labeled ICC and LC neurons form bands. Isodensity contours show clusters of cells within bands activated by monaural 80-dB amplitude-modulated tones. **(B)** Histogram showing density of labeled cells in the box in **A**. Peaks correspond to the bands of labeled cells. **(C)** Smoothed curves fitted to the histograms generated by stimuli of different intensities. (From Yang et al. 2003a.)

the microanatomy of ICC laminae may constrain the spread of excitation in the frequency domain. Lateral inhibition may limit the number of neurons activated by a tone to those within the same lamina; however, the mechanisms for this inhibition are still unclear.

A second question addressed by sound activation of Fos is the laminar role in processing spectral information. For example, what frequency separation is necessary for two stimuli to activate independent ICC neural populations? Two populations of neurons were activated by two SAM tones (as above) one octave apart (Yang et al. 2003a, 2004). At levels from 27 to 80 dB the centers of the bands of labeled neurons were separated by 240 μm. Similarly two bands of neurons were evident after stimulation with 37 dB tones separated by 0.5 octave and their centers were half the distance of those in the one octave cases. However, when two tones were separated only by 0.25 octave at 27 to 37 dB the sound-activated neurons formed one band approximately 200 μm wide.

These experiments suggest that ICC laminar microanatomy may play an important role in spectral information processing and may be related to critical bands (Ehret and Merzenich 1985; Schreiner and Langner 1997). The laminae could permit independent neural populations to respond to stimuli separated by at least 0.5 octave across a relatively broad range of stimulus intensities. Two stimuli spectrally more separated are less likely to interact, as they activate discrete populations. For stimuli within 0.25 octave the activation is confined to a single population of neurons within a lamina. This population may respond to all stimuli within this range of frequencies while also encoding subtle differences in the activity pattern related to the stimulus spectrum. Stimuli that activate the same population of neurons in a lamina are likely to be identical perceptually because the neurons cannot distinguish them.

3.2. How Does Microanatomy Organize Inferior Colliculus Neurons with Different Binaural Response Properties?

Because there is only one tonotopic map in the ICC, the processing of other types of auditory information faces a severe problem. All neurons with a similar best frequency (within 0.25 octave) may be within the same frequency-band lamina. Thus, all ICC neurons with similar tuning are at the same point on the tonotopic map. If each receives identical inputs from all of the lower auditory brain stem, they might have the same response properties. However, this is clearly not the case (see Chapters 11 to 14).

Functional classes of neurons have been identified using several sets of criteria. Early studies classified IC neurons based on interaural level differences (ILD) (EE: bilateral excitation; EI: ipsilateral suppression; EO: monaural only) (Semple and Aitkin 1979; Irvine 1986, 1992). Further studies have clarified the binaural response properties and enlarged the earlier classifications (Kelly and Sally 1993). Binaural neurons sensitive to interaural time disparity (ITD) com-

prise at least two types, both related to ITD sensitivity in the SOC. For peak-type neurons the ITD functions across frequencies align at or near maximal discharge (Kuwada and Yin 1983; Yin and Kuwada 1983a,b; Kuwada et al. 1984, 1987; Stanford et al. 1992) similar to those in MSO (Yin and Chan 1990; Batra et al. 1997a,b). In contrast, trough-type IC neurons align at or near the minimal discharge (Batra et al. 1993) like those in the LSO (Joris and Yin 1995; Joris 1996). In contrast, monaural neurons (Irvine 1986, 1992) must constitute a separate class, as a monaural response would be impossible with the convergence of monaural and binaural inputs. Spectral response properties have been used to classify these neurons (Ramachandran et al. 1999; Le Beau et al. 2001). The frequency-tuning curve shape (V-, I-, or O-shaped) may be correlated with certain binaural inputs (Ramachandran and May 2002). For example, low-BF neurons with V-shaped tuning curves often show peak-type responses, consistent with an input from MSO. I- and O-shaped response classes may receive their primary excitatory synaptic inputs from LSO and DCN, respectively (Ramachandran et al. 1999; Davis 2002).

A critical unresolved issue is how the combination of brain stem inputs contributes to the response properties of IC neurons. One clue is that the inputs to the IC differ by their frequency ranges. For example, MSO is a low-frequency structure with most of its neurons in the range from 100 Hz to about 5 kHz (Guinan et al. 1972). By comparison, the DCN is a high-frequency structure with little representation <1 kHz (Spirou et al. 1993). A particularly complex pattern is shown by the LSO, as the contralateral projection to the IC is heavier at high frequencies and the ipsilateral projection is stronger for low frequencies (Glendenning and Masterton 1983). Such differences in frequency range suggest one reason why synaptic domains across the IC will likely receive different combinations of inputs.

The synaptic domain hypothesis predicts that neurons with similar response properties will occupy the same functional module and receive similar brain stem inputs. For example, IC neurons aggregate when they have similar properties for coding interaural level differences (Roth et al. 1978; Semple and Aitkin 1979). The following sections consider the evidence for synaptic domains as defined by the major excitatory inputs to the IC from the MSO, LSO, and cochlear nucleus.

3.2.1. The Medial Superior Olivary Domain and the Representation of Azimuth

One type of synaptic domain in the ICC may be dominated by MSO input. MSO neurons compute ITD and their receptive fields indicate the location of azimuthal sound sources (Yin and Chan 1990; Batra et al. 1997a,b). The MSO projections neurons are the major source of ITD information to the midbrain. Despite the importance of this pathway, how ITD information is passed from the MSO to the IC is unclear. For example, if the ITD is mapped in the MSO along the rostrocaudal axis, as is often assumed, is this map transmitted to the

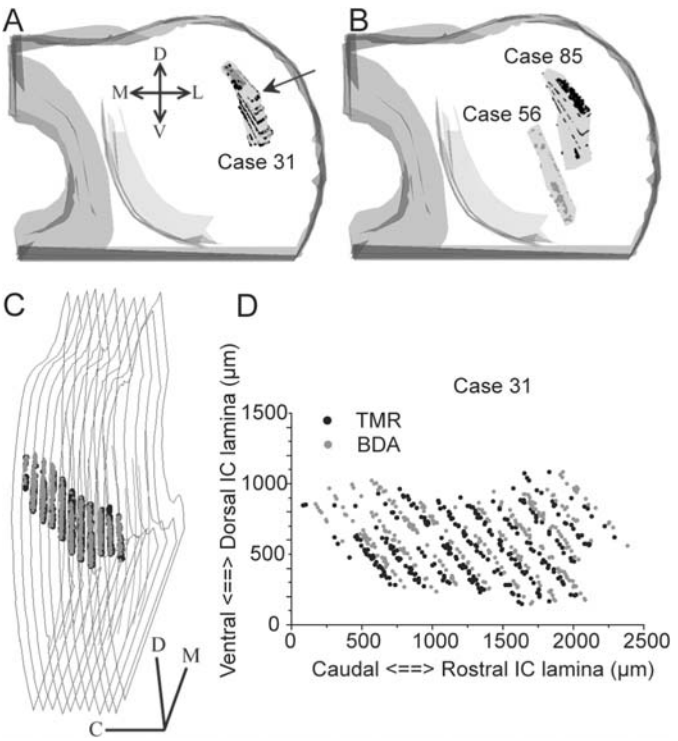

Figure 2.14. Three-dimensional reconstructions of MSO axonal boutons terminating in a lamina in the cat IC. **(A, B)** Single laminae from three animals. **(C)** Lateral view of boutons in a lamina. **(D)** *En face* view of the bouton distribution in **(C)** shows the absence of a simple density gradient related to injection site location. In **(A)**, **(C)**, and **(D)** the boutons are from two injections of different dextran anterograde transport markers in the same MSO at the same best frequency, one rostral and the other caudal. Boutons are labeled with either biotinylated dextran amines (BDA) or dextran labeled with tetramethylrhodamine (TMR). (From Oliver et al. 2003.)

rostrocaudal dimension of the IC laminae? The evidence for spatial topography in the MSO–IC projections was examined in the cat by making recordings of ITD sensitivity and small injections of BDA in different MSO locations and tracing the axons to the IC laminae (Figs. 2.14 and 2.15; Oliver et al. 2003). Two deposits in the same animal allow overlap and segregation of terminal fields to be studied. Different rostrocaudal locations on the same MSO frequency plane do not terminate at restricted points on the IC lamina. Instead, the MSO axons terminate along the length of a lamina (Figs. 2.14A to C, 2.15C). Within the lamina the axonal boutons are not distributed at uniform density or in a linear gradient (Fig. 2.14D). Consequently, there are neither point-to-point connections

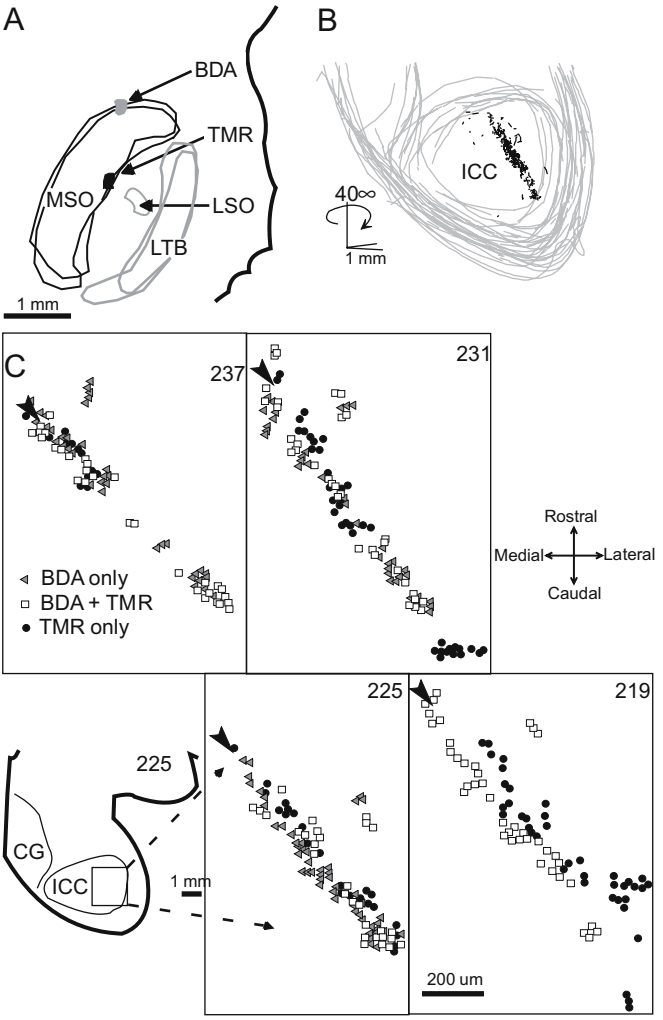

Figure 2.15. Axons from two points in the MSO with the same best frequency converge on the same IC lamina. **(A)** Injections of different dextrans. **(B)** Three-dimensional reconstruction of the colliculus to show the laminar labeling from these injections. **(C)** Axonal labeling in serial sections through the ICC (see *inset*). (From Oliver et al. 2003.)

nor a gradient of connections to convey information from a map of space in the MSO to a comparable map in the IC laminae.

These results suggest that the dimension of the lamina orthogonal to the frequency axis does not necessarily represent a monotonic spatial map of a sensory dimension. For the MSO projections to the IC, the transmission of information about azimuthal sound location does not rely on a rerepresentation of a spatial map of azimuth in the MSO that is conveyed to the IC. Consequently, the azimuthal response of an IC neuron may be unrelated to its laminar position. Instead, the results suggest that a complex nontopographical neural network codes the position of a sound source in the IC. The MSO domain is a key component of this network for the IC, as it identifies a population of neurons on a lamina that receive inputs and participate in the network to code sound location.

3.2.2. Lateral Superior Olivary Domain vs. the Medial Superior Olivary Domain

Do MSO inputs remain segregated from other major excitatory inputs to the ICC laminae? Excitatory LSO inputs have different binaural properties. As mentioned earlier, binaural response properties that mimic these inputs would be difficult to find in IC neurons if excitatory LSO and MSO inputs always converged on the same IC neuron. For example, peak-type ITD responses would be expected in IC neurons that receive excitatory inputs from MSO, but not excitatory trough-type ITD inputs from the LSO. To be consistent with the synaptic domain hypothesis, excitatory inputs from the MSO and the LSO should remain segregated. To test the hypothesis that the inputs from MSO and LSO would not converge in the same IC lamina, ITD-sensitive MSO and LSO cells with a similar characteristic frequency, but different binaural responses, were labeled with different anterograde tracers to trace the axons that project from these sites to the ICC.

The results suggest that the excitatory inputs from MSO and contralateral LSO remain separate (Loftus et al. 2002, 2004a). The MSO projections on one side were compared to the projections of the opposite LSO, as MSO axons project only to the ipsilateral IC, while the LSO excitatory projections are mostly contralateral. The LSO target in IC is more rostral than the MSO target (Fig. 2.11, black; Fig. 2.16A). The MSO termination zone is longer and has more boutons than the rostral LSO target (Fig. 2.11, light gray; Fig. 2.16B, C). This is consistent with injections of retrograde tracers in the caudal, low-frequency ICC, where neurons have peak-type ITD responses. Both the retrograde and anterograde labeling suggests that IC neurons with peak-type responses to ITD are in synaptic domains with excitatory inputs from the MSO whereas neurons with trough-type ITD responses are in another synaptic domain receiving mainly excitatory contralateral LSO input.

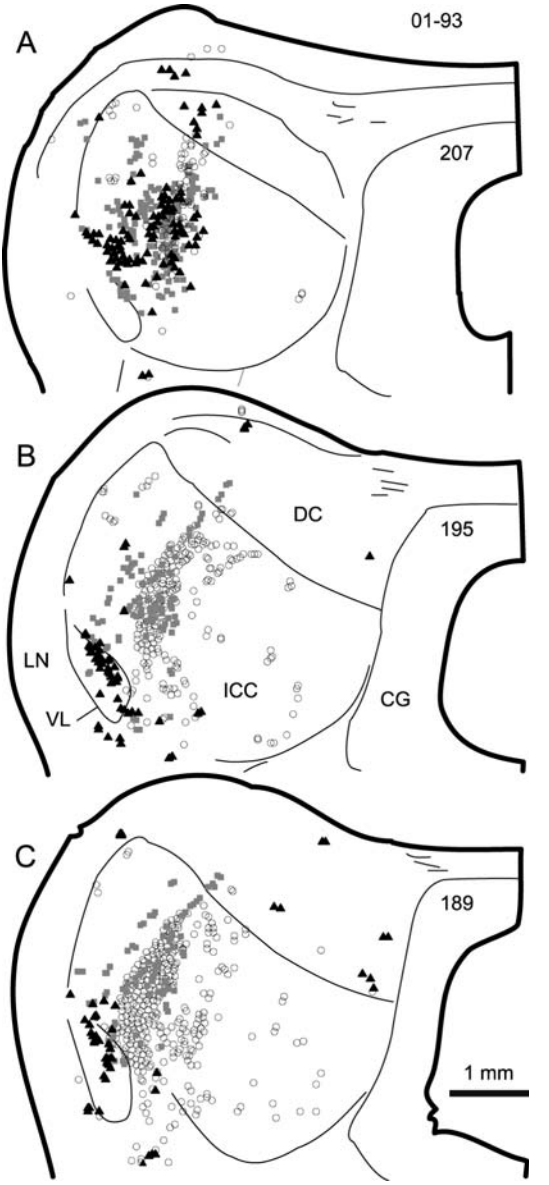

Figure 2.16. Summary of projections from the superior olives to the IC. One injection was made in the left MSO, and the second in the right LSO at an overlapping frequency range. Presumed excitatory ipsilateral MSO inputs *(open circles)* dominate **(B, C)** except in the most rostral levels **(A)** where excitatory inputs from the contralateral LSO dominate *(closed triangles).* Presumed inhibitory inputs from the ipsilateral LSO *(gray filled squares)* are superimposed on those from the medial superior olive. LN, Lateral nucleus; other labels as in Figs. 2.1 and 2.2. (From Loftus et al. 2004.)

These experiments also suggested that the MSO and LSO domains may have other forms of organization as well, including different inhibitory influences. The LSO projects to both the contralateral and ipsilateral IC, but only the contralateral projection is excitatory. The ipsilateral LSO projection is glycinergic. A comparison of both LSO projections was made by superimposing the bouton data from the right IC onto the left IC for each section. In contrast to the excitatory LSO and MSO inputs, which remained separate, the ipsilateral inhibitory LSO projection is denser, terminates in a broader area, and largely overlaps the MSO target zone (Fig. 2.16). Thus, there appears to be one synaptic domain with excitatory inputs from the MSO, and postsynaptic IC neurons also receive inhibitory input from the LSO. There appears to be a second synaptic domain where excitatory LSO inputs are prevalent. These are summarized in the model of the synaptic domains (Fig. 2.11) as the MSO domain (lightly shaded) and LSO domain (black). The inhibitory LSO input is shown as white spheres.

3.2.3. Comparing Central Nucleus Monaural and Binaural Domains

The third major excitatory input to the IC originates in the cochlear nucleus. It arises from multiple cell types in each major division of the cochlear nucleus. Although it is tempting to consider the cochlear nucleus inputs to the IC as a single entity, that would be a gross oversimplification (see Chapters 1 and 3) and DCN, AVCN, and PVCN neurons may not participate in the same synaptic domains. How the inputs from the divisions of the cochlear nucleus complex are related to each other in the IC remains an unresolved issue.

Because a proportion of IC neurons are monaural they likely receive direct input from the cochlear nucleus. They should lack input from binaural lower auditory brain stem neurons. This characteristic is most likely to occur in the high-frequency parts of ICC devoid of MSO afferents. In the rat IC cochlear nucleus axons were labeled with anterograde transport of BDA while tectothalamic IC neurons in the same animals were identified by retrograde transport from the medial geniculate body, and their dendrites were labeled by subsequent intracellular injection of Lucifer Yellow in formaldehyde-fixed brain slices. Cochlear nucleus inputs terminate directly on tectothalamic neurons (Oliver et al. 1999) and this synaptic input fulfills the first requirement for a monaural pathway extending from the cochlear nucleus to the thalamus.

The second requirement for a monaural pathway and for monaural IC neurons is a synaptic domain without binaural input. To address this issue the distribution of afferent axons from the DCN and LSO to the contralateral IC was compared (Oliver et al. 1997). DCN and LSO neurons were characterized by responses to monaural and binaural acoustic stimulation and a deposit was made in each structure with different markers. Both injection sites had cells with overlapping best frequencies. The results showed that DCN and LSO axons are superimposed in part of the contralateral ICC, in laminae in the ventral part of the central nucleus (Fig. 2.11, high frequency, black). However, in the dorsal part of the

same layer LSO axons are absent (Fig. 2.11, dark gray). These data suggest two types of synaptic domains in the high-frequency ICC laminae. One contains binaural neurons that combine the properties of inputs from the contralateral LSO and DCN. A second functional module may contain monaural neurons that have cochlear nucleus inputs and none from binaural structures.

3.3. Unresolved Issues About Microanatomy and Functional Zones in the Central Nucleus

The synaptic domain hypothesis remains a viable explanation for the anatomical organization of the inputs to the ICC. Unresolved issues remain concerning the microanatomy and the organization of the inputs to functionally defined neuron types. Chief among them is the relative contribution of inhibitory inputs to the microanatomy and to each synaptic domain. It is not clear whether modules defined by excitatory inputs receive different combinations of inhibitory input. Inhibitory inputs to the IC are GABAergic axons from the DNLL and glycinergic axons from the ipsilateral LSO. Lemniscal and olivary nuclei influences on ITD sensitivity may differ (Kuwada et al. 1997). Some ITD-sensitive neurons receive predominantly DNLL inputs while others receive mostly ipsilateral LSO inputs. Future experiments will determine if separate groups of IC neurons are postsynaptic to these two inhibitory brain stem inputs.

The contribution of inhibitory inputs to monaural processing also remains unclear. The VNLL is actually a complex of nuclei whose neurons have predominantly monaural responses (Aitkin et al. 1970; Covey 1993; Batra and Fitzpatrick 1999), although one subregion has binaural responses (Batra and Fitzpatrick 2002). Many VNLL neurons contain glycine, GABA, or both and they represent a major input to the ICC that is probably inhibitory (Brunso-Bechtold et al. 1981; Merchán and Berbel 1996; Malmierca et al. 1998). Anatomical studies suggest that the ventral nucleus inputs are laminar rather than diffuse, as suggested earlier (Whitley and Henkel 1984). However, it is unclear to which synaptic domains they contribute.

The local components of the functional modules also remain uncertain. It is unknown how the synaptic domains relate to ICC local axons. Although the existence of Golgi type II interneurons is unresolved (see Section 2.3.2 and Chapter 22) there could be local intra- or intermodular input. It is also unclear how the local environment within a module influences the postsynaptic neurons that reside there. Perhaps the combination of inputs that define a module can also influence number and types of synaptic receptors and ion channels in the postsynaptic neurons (see below).

While synaptic domains are defined largely by the excitatory inputs from binaural or monaural sources, the present relationship of these zones to other facets of auditory processing remains to be clarified. Because inputs from different brain stem sources may differ in their spectral properties, the specific combination of inputs may be related to the spectral properties of single IC neurons. Likewise, the brain stem inputs to IC may differ in their ability to code

complex temporal patterns. Whether functional zones that differ in binaural properties also differ in their spectral and temporal properties remains an open question.

A final question is how ICC synaptic domains relate to functional modules in other subdivisions of IC. Because a frequency reversal does not mark the border between the ICC and the DC, other response properties may distinguish them from the upper tier of ICC synaptic domains. Only the basic inputs of these regions have been determined. The predominant inputs to the upper domains in the ICC are from the cochlear nucleus and nuclei of the lateral lemniscus. In contrast, the predominant input to the adjacent deep dorsal cortex is from the neocortex. Much remains to be learned about the microanatomy of the dorsal cortex and how it differs from that in the ICC.

4. Functional Definitions of Neuron Types in the Central Nucleus

Up to this point the discussion of functional modules has focused almost exclusively on the inputs. However, the postsynaptic neurons in each module will integrate information from each input. Different types of IC neurons may influence how the inputs are integrated. Although IC neurons were originally defined primarily by their dendritic morphology into disc-shaped and stellate categories, this binary classification does not begin to account for all the functional properties observed. IC neurons also differ in their axonal targeting, the types of neurotransmitters produced, and in their electrical properties. These factors must be considered in any definition of IC neuron types to better understand their role in auditory information processing.

4.1. Neuron Classifications Based on Axonal Targeting

One criterion for IC neuron types is a unique axonal target. The main IC target is the ipsilateral medial geniculate body (MGB) (see Chapter 7). ICC axons terminate primarily in the ventral division whereas axons from the dorsal cortex project to the deep part of the dorsal division. Some neurons from all subdivisions have axons that terminate in the medial division of MGB. Other IC targets are the ipsilateral nucleus of the brachium, the contralateral IC (see Chapter 5), and the contralateral MGB. Descending IC projections terminate in the periolivary nuclei of the superior olive and the cochlear nucleus (see Chapter 6).

Despite the fact that the targets of the IC are known, we have only a rudimentary knowledge of the cell types that participate in these connections. For example, both disc-shaped and stellate neurons project to the ipsilateral MGB (Oliver 1984b). It is not clear whether these two cell types carry the same information to the MGB and whether their termination patterns are similar. Even less is known about the cell types that participate in tectal or descending projections. Understanding which cell types participate in each IC projection will

allow us to determine whether the same information is transmitted from the IC to each target.

4.2. GABA Projection Neurons in the Inferior Colliculus

A second functional criterion for defining IC neurons is the neurotransmitter content. Two types of IC neurons project to the MGB. One type is excitatory and probably uses glutamate as the neurotransmitter. The second type is inhibitory and uses GABA as a neurotransmitter. In the cat about 20% of the IC projection neurons to the MGB are GABAergic (Winer et al. 1996). In the rat 40% of the IC neurons projecting to the MGB contain GABA (Peruzzi et al. 1997). GABAergic projection neurons are distributed throughout the IC subdivisions except in the caudal cortex and intercollicular tegmentum (Fig. 2.17). This matches the distribution of GABA immunostaining without reference to axonal target. Some of the IC neurons projecting to the contralateral IC also contain GABA (González-Hernández et al. 1996). However, all of the targets have not been investigated and it is not known whether these two populations of IC neurons project to other targets.

This dual population of GABAergic and presumed glutamatergic projection neurons is a distinctive feature of the IC. GABAergic neurons are often the largest neurons in the IC (Oliver et al. 1994). Most GABA-containing neurons are disc-shaped neurons although some with stellate morphology are also seen.

Figure 2.17. Distribution of GABAergic and nonGABAergic IC neurons projecting to the rat MGB. **(A)** Caudal section showing ICC and caudal cortex. **(B)** Section through middle ICC. Tectothalamic neurons are labeled by retrograde transport and are GABA-positive *(black circles)* or GABA-negative neurons *(open squares)*; there are also GABA-positive neurons *(open triangles)* that are not retrogradely labeled. (From Peruzzi et al. 1997.)

However, the dendritic morphology of GABAergic neurons has not been correlated with projections. It is suspected that disc-shaped and stellate GABAergic neurons project from the IC to the MGB.

GABAergic IC neurons may have a special role in auditory processing at the thalamic level. Monosynaptic inhibitory postsynaptic potentials (IPSPs) from the IC often reach the MGB before the excitatory postsynaptic potentials (EPSP) (Peruzzi et al. 1997; Bartlett and Smith 2002). Additional IPSPs are seen after the EPSP. The fast IC GABAergic input may actively control the timing of the onset of excitation in the MGB and the slow GABAergic input may contribute to the suppression of firing along with other mechanisms such as GABAergic inhibition from the thalamic reticular nucleus. These data suggest that the IC projection to the thalamus is more complex than the thalamic inputs in other sensory systems (Bartlett et al. 2000). Retinal inputs to the lateral geniculate and the spinal cord or dorsal column inputs to the ventrobasal complex are assumed to be purely excitatory. Only in the thalamic motor nuclei is there a mixture of inhibitory and excitatory inputs and an interplay between them that seems to underlie the temporal responses of the thalamic neurons (Peruzzi et al. 1997).

There are several questions regarding GABAergic neurons. As mentioned earlier, there are both disc-shaped and stellate GABA-containing IC neurons. However, it is unknown if both project to the same MGB targets. Further, the GABAergic IC neuron and its role as an inhibitory neuron has not been related to the auditory responses of IC neurons. For example, in the context of binaural response types (see Section 2.3.2), it is unknown whether GABAergic neurons favor MSO domains, LSO domains, or monaural domains.

4.3. Neuron Types Defined by Intrinsic Membrane Properties

A third basis for defining IC neurons is their intrinsic membrane properties. ICC neurons have distinct discharge patterns to intracellular current injection (Peruzzi et al. 2000) and their responses are correlated with distinctive current/voltage relationships (Sivaramakrishnan and Oliver 2001). Six physiological classes of IC cell are revealed by intracellular recording with either sharp electrodes or whole-cell patch-clamp techniques in rat brain slices. Neurons formed two groups based on their responses to the offset of hyperpolarizing currents. One group exhibits a rebound calcium-dependent depolarization in addition to sodium action potentials (Sivaramakrishnan and Oliver 2001), while the other group lacks the rebound response (Fig. 2.18). The rebound neurons form three subtypes based on their responses to depolarizing currents—a transient response (few action potentials, rapidly adapting), a sustained slowly adapting response, and a regular nonadapting response (Fig. 2.18, rebound). Nonrebound neurons also have three subtypes—an onset response with one spike (Fig. 2.18, onset), a sustained-regular response, and a pause-buildup response (Fig. 2.18, pause-buildup). The latter appears only when the depolarization is preceded by a hyperpolarization (see Chapter 10).

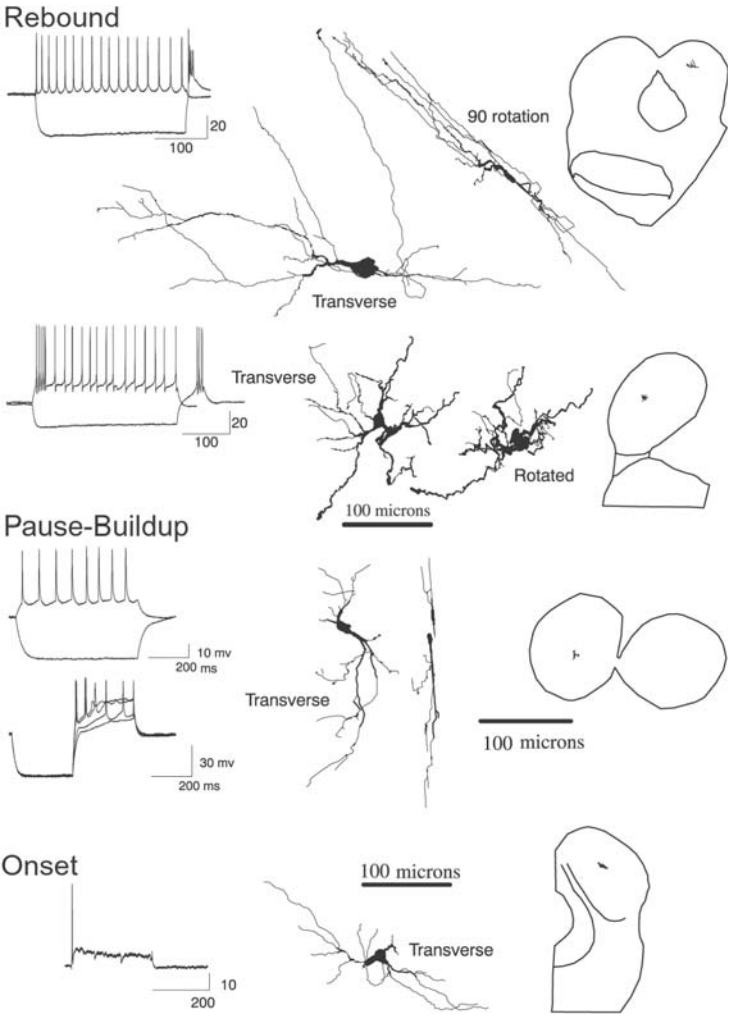

Figure 2.18. Firing patterns of neurons in the IC brain slice preparation. For each type the discharge pattern to depolarizing and hyperpolarizing intracellular current injections are shown **(left)**. Neurons **(middle)** whose responses are shown were filled with neurobiotin (rebound onset) or Lucifer yellow (pause-buildup). IC location of the neuron appears on the inset **(right)**. (From Peruzzi et al. 2000. Reprinted from Neuroscience with permission from Elsevier.)

The six IC firing patterns are generated by a unique K^+ current and set of cellular parameters (Sivaramakrishnan and Oliver 2001; cf. Chapter 10). For example, the IC rebound-adapting cell likely has an SK-type K^+ channel as it has a Ca^{2+}-activated K^+ current that is blocked by apamin. The rebound-transient cell also has a Ca^{2+}-activated K^+ current, but of the BK-type, as it is

blocked by charybdotoxin. Likewise, the pause-buildup cell has a response that can be directly related to an A-current K^+ current, while the onset response requires a high-threshold delayed rectifying K^+ current such as *Kv3.1* (Perney et al. 1992). The rebound-regular and the sustained-regular cells have primarily delayed rectifier currents and show no evidence for the additional currents mentioned earlier. However, the rebound-regular cell has a rebound response that may reflect a high density of a T-type Ca^{2+} channel that produces a Ca^{2+} influx after hyperpolarization offset.

The intrinsic properties of IC neurons entail several questions. There is little understanding of the molecular basis of these membrane properties and the distinct combinations of ionic currents are still poorly understood. Such currents likely depend on the precise subunit combinations that compose the channel and different subunit combinations may produce subtle differences in their current properties. Identification of expression patterns will have an enormous practical impact beyond the immediate issue of membrane properties, as they will identify intrinsic molecular markers for functional IC cell types.

The relationship of morphology to the firing patterns needs to be resolved. The cell types based on intrinsic properties do not correspond to the simple disc-shaped or stellate morphological classifications. Most neurons in the small sample were flat cells (Fig. 2.18) and the data suggests subtypes with different intrinsic properties (Peruzzi et al. 2000; Sivaramakrishnan and Oliver 2001). A small sample of less-flat rat stellate cells does not allow conclusions about the firing patterns. However, some morphological features besides dendritic orientation may be related to discharge pattern. Dendritic branching patterns, size, or the incidence of spines may be correlated with the intrinsic properties and the dendritic electrotonus of different cell types.

It is also not known how the firing patterns relate to the cell's projection. In some brain regions intrinsic properties are associated with cell types with different targets, as in the cochlear nucleus, where the spherical bushy cells project to the MSO while the stellate cells project to the IC, and octopus neurons project to the VNLL but not to the main targets of the other cells. In the midbrain the tectothalamic neurons may have a different firing pattern than cells projecting to the superior olive. One possible purpose of correlated firing properties and targeting is that each neuron type can convey different types of information to its target.

Finally, the relationship of the firing pattern to GABA needs to be clarified. Elsewhere in the nervous system GABAergic and glycinergic neurons often play a special role in the microcircuitry. If GABAergic neurons have firing properties that distinguish them from other cells, the temporal pattern of inhibition may differ from that of excitation. To resolve this issue the organization of the synapses of the types of IC cells must be determined.

5. Synaptic Organization of Central Nucleus Neurons

The previous section suggests that IC neurons are more complex physiologically than their early morphological designations indicated. If different types of neurons also receive different types of synaptic inputs it would further enhance the functional differences between them. Understanding synaptic inputs to the different IC neuron types and how the intrinsic membrane properties of these cells further modify the synaptic input to shape a neural response is vital.

5.1. Do Inferior Colliculus Neuron Types Receive Similar Synaptic Inputs?

Synaptic input is important for IC signal processing but little is known about the synaptic inputs to the different neuron types. Here synaptic input refers specifically to the excitatory or inhibitory postsynaptic current (EPSC or IPSC) elicited in the IC cell by stimulating the presynaptic ending and its interaction with ligand-gated receptors on the postsynaptic cell. IC neurons have various receptors for glutamate, glycine, and GABA (see Chapter 9) and the function of the synapses will depend on their subunit composition and their effect on the postsynaptic IC cell, as it does elsewhere in the brain (Barnes-Davies and Forsythe 1995; Wang et al. 1998; Gardner et al. 2001; Schmid et al. 2001). Thus, the $GABA_A$ receptors are responsible for fast Cl^--mediated IPSCs at GABAergic IC synapses. The patterns of expression for $GABA_A$ subunits provide the best evidence for neurons of different size having different combinations of $GABA_A$ subunits (Shiraishi et al. 2001). Such differences suggest that there may be different types of GABA synapses in the IC just as in the neocortex (Gupta et al. 2000).

A related issue is activity-dependent changes in IC synapses that differ among the different IC cell types. Glutamate inputs to IC neurons can show long-term potentiation (LTP) (Zhang and Wu 2000; Wu et al. 2002) similar to *N*-methyl D-aspartate- (NMDA) dependent LTP elsewhere in the nervous system. It is important to resolve whether such changes are equally common to all cell types.

The important implication for IC neuronal organization is that synaptic properties are vital parameters for the function of neuron types. Each type of neuron must be defined by the interactions of multiple parameters—the location in a particular synaptic domain, the axonal target, the cell's morphology, the intrinsic membrane properties, and the types of synaptic input. Because of unique AMPA, NMDA, or $GABA_A$ subunit compositions, activity could modify synaptic strength or the nature of the synaptic inputs, and consequently output could vary by the cell type. The relative number and location of glutamate, GABA, and glycine synapses also vary according to cell type. Each factor would contribute to the information processing carried out by the different IC neuron types.

5.2. Can Intrinsic and Synaptic Properties Interact to Create the Responses of Inferior Colliculus Neuron Types?

The cellular mechanisms that regulate synaptic integration are essential to understanding IC function in sound processing. Membrane properties can facilitate or degrade the temporal pattern of synaptic inputs evoked by sound and thus shape the synaptic inputs to which the cell ultimately responds. Neurons defined by different intrinsic properties may interact with the synaptic inputs in different ways that may especially influence the timing of responses.

The IC represents a transition stage for temporal coding in the auditory system. Timing here is better suited for coding the envelopes of complex signals (SAM tones; Batra et al. 1989), communication calls (Klug et al. 2002), and duration (Casseday et al. 2000) information than for coincidence detection (Fitzpatrick et al. 1997). Although the sources of input to IC neurons may phase lock and fire at high rates (Batra et al. 1997a,b; Spitzer 1998; Spitzer and Semple 1998), synaptic properties or intrinsic membrane properties of IC neurons could transform this information. Synaptic inputs may alter time codes because facilitation or depression occurs in some cell types, related perhaps to the relative contributions and kinetics of NMDA and AMPA components (see Chapter 10). Membrane properties are also important, as some IC cells follow stimuli at higher rates (Peruzzi et al. 2000).

We do not yet know the relative contributions of synaptic inputs and membrane properties to temporal processing in the different IC cells. Ultimately, the IC cell's response may reflect both the intrinsic membrane properties (voltage-gated and Ca^{2+}-activated ion channels) and synaptic inputs (presynaptic mechanisms and postsynaptic ligand-gated receptors). Ca^{2+}-activated conductances in particular can disrupt the normal cadence of neuronal firing in response to synaptic input, as they often enhance adaptation related to increased Ca^{2+} influx. The presence of Ca^{2+}-activated K^+ currents in some cell types suggests that their membrane properties may alter the response to synaptic input, transforming afferent input and shaping the temporal aspects of the response.

A final question relates to both synaptic inputs and intrinsic membrane properties and it is whether the neural responses to sound in vivo reflect different synaptic inputs or different membrane properties. The link between brain slice data, usually obtained from young animals, and sound processing in the adult is tenuous. Experiments are necessary in which IC cell types are identified in adult animals with the same criteria used in the brain slice experiments. Such an experiment may explain how the IC neuronal response is related to the cell-specific synaptic input and its sources.

6. Summary

How are the types of IC neurons related to the synaptic domains? The synaptic domain hypothesis defines functional IC modules and seeks to establish a relationship between the auditory response properties of a neuron and the sources of its brain stem inputs. Within these domains the cell types are defined by their membrane properties, dendritic morphology, K^+ channel subunits, and transmitter content. Whether particular IC cell types are associated with specific synaptic inputs remains to be resolved in future experiments. If so, it suggests a special relationship between the sources of the brain stem projections, the synaptic inputs, and the postsynaptic IC cells that coexist within a synaptic domain.

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Abbreviations

a	axon
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole propionate
AVCN	anteroventral cochlear nucleus
BI	brachium of the inferior colliculus
CG	central gray
DC	dorsal cortex
DCN	dorsal cochlear nucleus
2DG	2-deoxyglucose
DI	dorsal intercollicular tegmentum
DLL, DNLL	dorsal nucleus of the lateral lemniscus
EPSP	excitatory postsynaptic potential
GABA	γ-aminobutyric acid
IC	inferior colliculus
ICC	central nucleus of the inferior colliculus
ILD	interaural level differences
IPSP	inhibitory postsynaptic potential
LC	lateral cortex
LI	lateral intercollicular tegmentum
LL	lateral lemniscus
LSO	lateral superior olive
LTB	lateral nucleus of the trapezoid body

MGB	medial geniculate body
MI	medial intercollicular tegmentum
MSO	medial superior olive
NMDA	*N*-methyl-D-aspartate
PVCN	posteroventral cochlear nucleus
RP	rostral pole
SAM	sinusoidally amplitude modulated
VL	ventrolateral nucleus
VNLL	ventral nucleus of the lateral lemniscus

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Chapter 3
Projections from the Cochlear Nuclear Complex to the Inferior Colliculus

Nell Beatty Cant

1. Introduction

The substantial projections from the cochlear nuclei to the inferior colliculus (IC) do not seem to have been generally recognized as a common mammalian characteristic until about the late 1960s. Although they were described in some of the earliest experimental studies of the auditory pathways (Woollard and Harpman 1940, q.v., for a discussion of the earlier literature on the subject; Barnes et al. 1943), the prevailing view appeared to be that most of the axons leaving the cochlear nucleus terminated in the superior olivary complex or nuclei of the lateral lemniscus and that the projections to the IC were sparse. Certainly, the matter appeared to be unresolved in 1953, as Stotler stated flatly in his influential article on brain stem auditory pathways in the cat that "all neurons reaching the level of the inferior colliculus are of the third order." It was not until the late 1960s and early 1970s that studies with sensitive degeneration techniques (cf. Nauta 1993) demonstrated conclusively that both the dorsal and ventral cochlear nuclei project directly to the contralateral inferior colliculus (cat: Warr 1966, 1969, 1972; Fernandez and Karapas 1967; van Noort 1969; Osen 1972; Rhesus monkey: Strominger and Strominger 1971; Strominger 1973; chimpanzee: Strominger et al. 1977; kangaroo rat: Browner and Webster 1975). In some cases, sparse ipsilateral projections were also reported.

Degeneration studies established that the main target of both the dorsal and ventral cochlear nuclei in the IC is the central nucleus, that the projections from these two sources overlap, and that they are topographically organized, with the cochlea systematically represented from apex to base. Since the late 1970s, neuroanatomical methods based on retrograde and anterograde axonal transport of various tracers have allowed detailed studies of the projections from the cochlear nuclei to the IC in a wide variety of species (Table 3.1). These tracing studies, supplemented by electron microscopy, have provided descriptions of both the cell types contributing to the projections and also the distribution and arborization patterns of their axons within the IC. An overview of the projections from the cochlear nuclei to the IC is presented in Section 2. The discussion is based mainly on the results of large injections of retrograde or anterograde tracers in

Table 3.1. Neuroanatomical studies of projections from the cochlear nucleus to the inferior colliculus by species, 1978–2003.

Species	Authors and year of study
CAT	Roth, Aitkin, Andersen, and Merzenich 1978 Adams 1979, 1983 Aitkin, Kenyon, and Philpott 1981 Brunso-Bechtold, Thompson, and Masterton 1981 Oliver 1984, 1985, 1987 Aitkin and Schuck 1985 Maffi and Aitkin 1987 Oliver and Beckius 1993 Oliver, Beckius, Bishop, and Kuwada 1997
RAT	Beyerl 1978 Druga and Syka 1984 Tokunaga, Sugita, and Otani 1984 Coleman and Clerici 1987 Alibardi 1998, 1999 Oliver, Ostapoff, and Beckius 1999
MOUSE	Ryugo, Willard, and Fekete 1981 Ryugo and Willard 1985 Frisina, Walton, Lynch-Armour, and Byrd 1998
MARSUPIAL	Aitkin and Kenyon 1981 Willard and Martin 1983 Aitkin, Byers, and Nelson 1986
GERBIL	Nordeen, Killackey, and Kitzes 1983a,b Moore and Kitzes 1985
FERRET	Moore 1988
MOLE	Kudo, Nakamura, Tokuno, and Kitao 1990
GUINEA PIG	Schofield and Cant 1996 Alibardi 2000
CHINCHILLA	Josephson and Morest 1998
BAT: Mustache bat	Zook and Casseday 1982, 1985, 1987 Ross, Pollak, and Zook 1988 Frisina, O'Neill, and Zettel 1989 Ross and Pollak 1989 Wenstrup, Mittmann, and Grose 1999
Horseshoe bat	Schweizer 1981 Vater and Feng 1990

the IC or cochlear nuclei, respectively. In Section 3, the laminar organization of inputs to the IC as revealed by small tracer injections is discussed.

2. Projections from the Cochlear Nucleus to the IC

2.1. Comparison with Other Sources of Ascending Input

The major sources of ascending auditory inputs to the IC are the cochlear nuclei, the nuclei of the superior olivary complex, and the nuclei of the lateral lemniscus (see Chapter 1). Some of the relevant neuroanatomical studies (those that contain information about the projections from the cochlear nuclei) are listed in Table 3.1. In some of these studies, counts were made of the numbers of neurons labeled in brain stem nuclei after large injections in the IC of retrograde tracers (substances that are taken up by axon terminals and transported through the parent axons back to the cell body of origin). Results from these studies have been replotted on common axes in Fig. 3.1 so that they can be compared directly. The figure shows that the pattern of labeling in the brain stem after large tracer injections is quite consistent across studies and species. (The results of small tracer injections are considerably more variable [see Section 3.3]). In terms of the numbers of neurons that are labeled, the projections from the contralateral cochlear nuclei are matched only by the projections from the ipsilateral ventral nucleus of the lateral lemniscus in most species. In the Japanese mole and the mustache bat (Fig. 3.1F, G), the number of labeled cells in the cochlear nuclei and superior olivary complex may be more nearly equal than in the other species, but the apparent differences among species could also be a function of differences in the sizes of the injection sites (see Section 4.3). The number of cells in the contralateral ventral cochlear nucleus that project to the IC is consistently larger than the number in the contralateral dorsal cochlear nucleus.

The contralateral projections are topographically organized. Cells in the ventral (low-frequency) parts of the cochlear nuclei project to the dorsolateral IC, and cells in the more dorsal (high-frequency) parts of the cochlear nuclei project to the ventromedial IC. Osen (1972) noted that the parts of the cochlear nucleus that represent middle frequencies project more caudally in the IC than do the parts with the lowest and highest frequency representations. In most species, a few cells in both the dorsal and ventral cochlear nuclei project to the ipsilateral IC. The ipsilateral projections appear to be mainly to the dorsolateral (or low-frequency) part (Nordeen et al. 1983a; Oliver 1984, 1987). In the chimpanzee, the ipsilateral projections were described as "substantial" (Strominger et al. 1977).

2.2. Cell Types that Project to the Inferior Colliculus

The cochlear nuclear complex contains a number of well-characterized cell types that can be distinguished based on a wide variety of criteria (reviewed by Cant

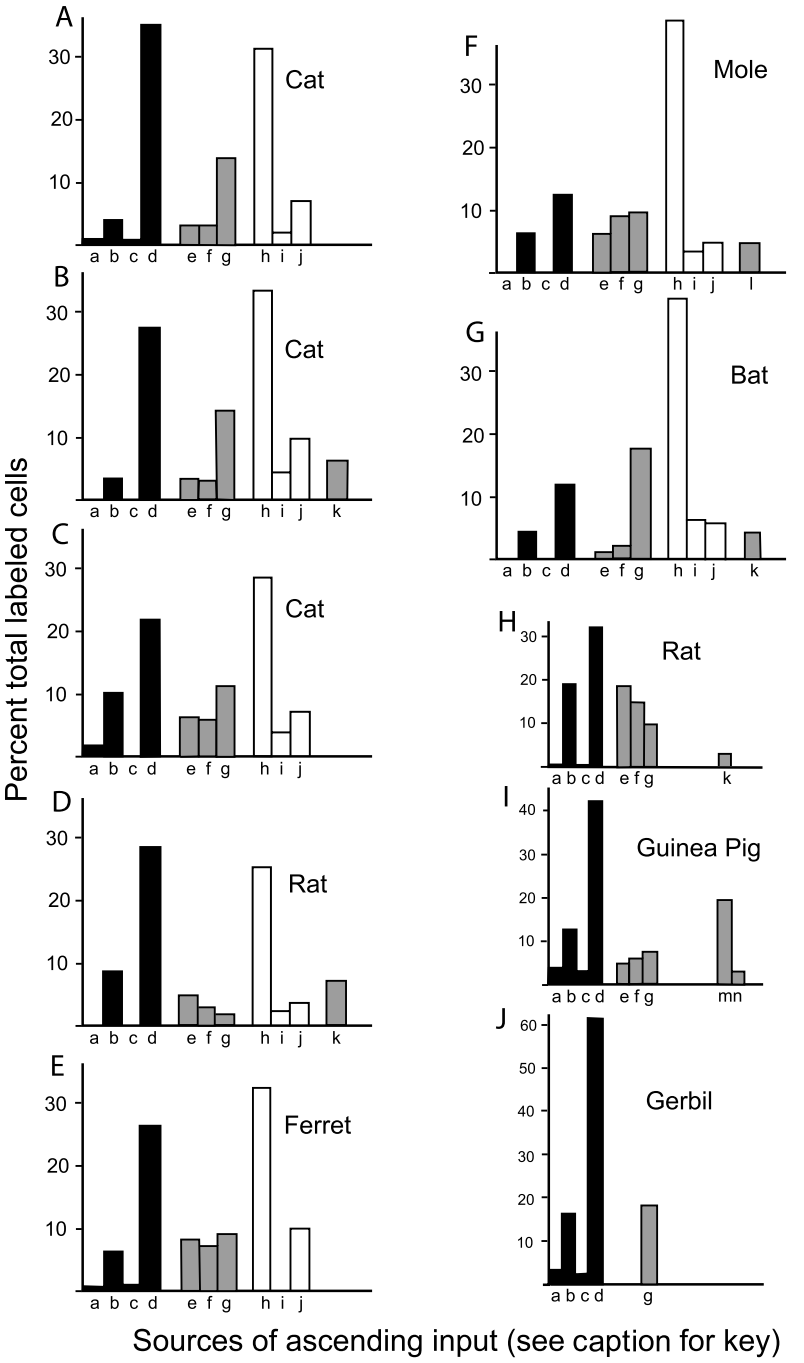
A
Cat
B
Cat
C
Cat
D
Rat
E
Ferret
F
Mole
G
Bat
H
Rat
I
Guinea Pig
J
Gerbil
Percent total labeled cells
Sources of ascending input (see caption for key)

Figure 3.1. Summary of results of 10 studies in seven species in which large injections of retrograde axonal tracers were placed in the IC. In each study, counts were made of the number of labeled cells in some or all of the sources of ascending inputs to the IC. For those studies in which the counts were reported as the numbers of labeled cells in each structure, the data have been converted to percent of total labeled cells counted in the structures shown. In some cases, counts were also made in other sources of input, such as the contralateral IC. If possible, these were not included in the calculation of the percent of labeled cells. **(A)** Cat (Adams 1979). The result from pressure injection of horseradish peroxidase (HRP) in ventral IC. Counts made in a sample of one twelfth of the total tissue; $N = 3799$. **(B)** Cat (Roth et al. 1978). The result from pressure injection of HRP in dorsal IC. The largest injection (in terms of numbers of labeled cells) in a series of six; 2-kHz region; counts made in 60% of the tissue; $N = 6305$. **(C)** Cat (Kudo and Nakamura 1988, quoted in Kudo et al. 1990). The result from a pressure injection of HRP conjugated to wheat germ agglutinin (HRP-WGA). Information about the counts not available. **(D)** Rat (Tokunaga et al. 1984). The result from pressure injection of HRP in the IC. The largest injection (in terms of numbers of labeled cells) in a series of four; counts made in every other section; $N = 4754$. **(E)** Ferret (Moore 1988). The result from multiple pressure injections of HRP-WGA in the IC. Counts made in every other section; numbers corrected for uncounted sections; $N = 41{,}605$. This does not include 15,435 neurons labeled in the contralateral IC; those cells were not included in the calculation of the percent labeled cells shown here. **(F)** Japanese mole (Kudo et al. 1990). The result from a pressure injection of HRP-WGA in IC. Counts made in every other section; average of counts from four different animals; total $N = 12{,}291$. **(G)** Mustache bat (Ross et al. 1988). The result from an iontophoretic injection filling most of the 60-kHz region of the IC. Counts made in every other section; estimated $N = 2000$–2300. A small percentage of the counted labeled cells were in the contralateral IC; data not included here. **(H)** Rat (Druga and Syka 1984). Pressure injection of HRP in the IC. Counts made in three animals and summed; sampling rate not given; total $N = 3608$. **(I)** Guinea pig (Schofield and Cant 1992). The result from a pressure injection of fluorescent tracers. Counts made in every sixth section; $N = 4122$. **(J)** Gerbil (Nordeen et al. 1983a). The result from a pressure injection of HRP in the IC. Counts in every other section; estimated $N = 4300$. For all panels, the *black bars* show the cell counts for the cochlear nucleus: *a,* ipsilateral dorsal cochlear nucleus (DCN); *b,* contralateral DCN; *c,* ipsilateral ventral cochlear nucleus (VCN); *d,* contralateral VCN. Gray bars *(middle)* show the cell counts for nuclei in the superior olivary complex: *e,* ipsilateral lateral superior olivary nucleus (LSO); *f,* contralateral LSO; *g,* ipsilateral medial superior olivary nucleus (MSO). *White bars* show the cell counts for nuclei of the lateral lemniscus: *h,* ipsilateral ventral nucleus of the lateral lemniscus; *i,* ipsilateral dorsal nucleus of the lateral lemniscus (DNLL); *j,* contralateral DNLL. *Gray bars* (end) show cell counts in other nuclei counted in specific studies: *k,* periolivary nuclei (PO); *l,* contralateral MSO (a substantial projection in the mole); *m,* ipsilateral PO; *n,* contralateral PO. Note the change in scale for panels **(H–J)**. Labeled cells in the nuclei of the lateral lemniscus were not counted in these studies, resulting in larger percentages in the other nuclei.

and Benson 2003). Even in studies based on degeneration techniques, it was recognized that only some of these cell types project to the inferior colliculus (Warr 1966, 1969, 1972; van Noort 1969). In all species studied (Table 3.1), it has been demonstrated that both fusiform and giant cells of the dorsal cochlear nucleus send axons to the IC. In fact, it appears that all of the large cells in the dorsal cochlear nucleus participate in the projection (Ryugo et al. 1981; Moore 1988). The projection from the ventral cochlear nucleus arises from neurons throughout its extent, including all but the most anterior part of the anteroventral cochlear nucleus and the octopus cell area in the posteroventral cochlear nucleus. It is generally agreed that multipolar (or stellate) cells are the major source of projections from the ventral cochlear nucleus, that octopus cells do not terminate in the IC, and that few if any globular cells or large spherical cells project that far. The case is less clear for small spherical cells in the anteroventral cochlear nucleus. A number of authors report that small, round cells in this part of the complex project to the IC, and some refer to these as small spherical cells, implying that they have a bushy cell morphology (cf. Cant and Benson 2003). Because the dendrites of the cells usually are not filled with the tracer, it is generally not possible to be sure that these really are spherical bushy cells, although Adams (1979) did illustrate one well-filled spherical bushy cell labeled after a large injection of horseradish peroxidase in the IC of the cat. Electron microscopic studies have provided no evidence for such a projection, however. In three species, all cells labeled retrogradely from the IC were identified in the electron microscope as type I stellate (or multipolar) cells (cat: Cant 1982; chinchilla: Josephson and Morest 1998; rat: Alibardi 1998). The cells that project from the ipsilateral cochlear nucleus have been identified as fusiform, giant, and multipolar cells (Adams 1979; Oliver 1984, 1987).

The ventral cochlear nucleus contains several types of multipolar cells. Those that project to the contralateral IC appear to be the type I multipolar cells (or type I stellate cells; cf. Cant and Benson 2003). It seems likely that most, if not all, of the type I cells participate in this projection (Josephson and Morest 1998). The same neurons in the ventral cochlear nucleus that project to the IC send collateral branches to the dorsal cochlear nucleus (Adams 1983). Multipolar cells in the ventral cochlear nucleus also give rise to projections to the superior olivary complex and the ventral nucleus of the lateral lemniscus (see Chapter 4). Although they have not been identified with certainty, the cells that give rise to these projections are probably also type I multipolar cells (Smith et al. 1993), but it is not known whether individual cells project to all of the targets. Some fusiform or giant cells in the dorsal cochlear nucleus may send axonal branches to both the ipsilateral and contralateral IC, but bilateral projections from cells in the ventral cochlear nucleus have not been described (Schofield and Cant 1996).

Axons arising from the fusiform and giant cells leave the cochlear nucleus in the dorsal acoustic stria. After crossing the midline, they enter the lateral lemniscus and travel in its medial part or in the adjacent tegmentum (Osen 1972; Willard and Martin 1983; Oliver 1984). The projections from the contralateral

ventral cochlear nucleus travel mainly in the trapezoid body, where they make up part of the thin fiber component, cross the midline, and enter the lateral part of the lateral lemniscus (Warr 1966; Osen 1972; Willard and Martin 1983). Ipsilateral projections from the cochlear nucleus travel in a small fiber bundle known as the lateral trapezoid body tract (Warr 1972).

2.3. Synaptic Terminals in the Inferior Colliculus

Electron microscopic studies of the terminals from both the anteroventral and dorsal cochlear nuclei in the IC demonstrate that they contain round synaptic vesicles and make asymmetrical contacts with their targets, the morphology associated with excitatory synapses (Oliver 1984, 1985, 1987). The fine structure of the inputs from the posteroventral cochlear nucleus to the IC has not been reported, but presumably they are also excitatory, as the collaterals of their axons that project into the dorsal cochlear nucleus (Adams 1983) give rise to terminals with round synaptic vesicles (Smith and Rhode 1989). Alibardi (1998) also concluded that the neurons in the posteroventral cochlear nucleus that project to the IC are excitatory, based on the variable presence of immunoreactivity for glutamate and the absence of immunoreactivity for the inhibitory neurotransmitters glycine and γ-aminobutyric acid (GABA). The ventral nucleus of the lateral lemniscus contains almost as many neurons that project to the IC as the cochlear nuclei (Fig. 3.1), but because a large proportion of the cells in the ventral nucleus of the lateral lemniscus are inhibitory (Riquelme et al. 2001), it is apparent that, in terms of numbers of neurons, the contralateral cochlear nucleus represents the major brain stem source of excitatory inputs to the IC.

Although the number of cells projecting to the IC from the cochlear nuclei may be much greater than the number of cells projecting from the main superior olivary nuclei, many of which are also excitatory (e.g., Oliver et al. 1995), the number of terminals that is made by axons from the different sources may be more comparable. For example, in areas where the terminals from the ipsilateral medial superior olivary nucleus terminate most densely, they may account for up to 36% of the terminals with round synaptic vesicles in that area. Terminals with round vesicles from the ipsilateral and contralateral lateral superior olivary nucleus can reach 26% and 18%, respectively. These values can be compared to the maximum density of terminals from the contralateral anteroventral cochlear nucleus (13%) and the contralateral dorsal cochlear nucleus (11%). Interestingly, in the lateral part of the central nucleus, the synapses formed by the ipsilateral anteroventral cochlear nucleus can contribute up to 18% of the terminals with round vesicles, although the number of neurons projecting from the ipsilateral cochlear nucleus is always very small (Fig. 3.1). It is not yet known how the regions with the maximum density of inputs from any one source overlap with those from other sources (see Section 3).

The inputs from the cochlear nuclei form synapses on the dendrites of both disc-shaped cells and stellate cells, the main types in the central nucleus (see Chapter 2). Occasionally, terminals are also found on the cell bodies of the

stellate cells. Little is known about differential innervation of different types of IC neurons (defined in terms of morphology, physiological response properties, neurotransmitter chemistry, connections, other sources of input, or any other criteria). Oliver et al. (1999) showed that at least some of the inputs from the contralateral cochlear nucleus terminate directly on neurons that project to the medial geniculate nucleus.

3. Distribution of Cochlear Nuclear Inputs within the Inferior Colliculus

The topography related to frequency is the most obvious organizational principle in the IC, and most, if not all, inputs to the IC are organized with respect to frequency. The part of each brain stem nucleus that represents the apex of the cochlea (low frequencies) projects to the dorsolateral IC and the part that represents the base of the cochlea (high frequencies) projects to the ventromedial IC, with a systematic progression of the intermediate regions (e.g., Osen 1972; Adams 1979). This topography has given rise to the concept that the IC is organized into a series of laminae, each of which receives inputs from a limited frequency range and is continuous across the major subdivisions of the IC (cf. Oliver and Morest 1984; Saldaña and Merchán 1992; Brown et al. 1997). Within this framework of tonotopic organization, however, there is evidence for other levels of organization. Some studies have focused on differences in the organization of inputs from one subdivision to the next, while others have provided evidence for partial segregation of inputs within the central nucleus of the IC.

3.1. Projections to the Major Subdivisions of the Inferior Colliculus

The main target of both the ventral and dorsal cochlear nuclei in the IC is the central nucleus, where the projections from these two parts of the cochlear nuclear complex appear to overlap almost completely (Osen 1972; Oliver 1984). In addition, both the dorsal and ventral cochlear nuclei send projections into the deep layers of the dorsal cortex, although the terminations appear to be more sparse than those to the central nucleus (Oliver 1984; Coleman and Clerici 1987; Zook and Casseday 1987). In the dorsal cortex, the projections from the ventral cochlear nucleus may arborize more widely than those from the dorsal cochlear nucleus (Oliver 1987). The dorsal cochlear nucleus also projects to the external cortex of the IC in rats (Coleman and Clerici 1987; Oliver et al. 1999), mice (Ryugo et al. 1981), and opossums (Willard and Martin 1983) but not in the cat (Aitkin et al. 1981). Like those to the central nucleus, the projections to both the dorsal and external cortices appear to be topographically organized (Ryugo et al. 1981; Oliver 1984, 1987).

Because the main sources of inputs to each subdivision of the IC are different (cf. Chapter 1), the inputs from the cochlear nuclei must converge with those from different sources in the various parts of the IC. For example, in the central nucleus, the projections from the cochlear nuclei overlap to a large extent with the projections from the superior olivary complex, the other major source of ascending excitatory inputs to the IC (Oliver et al. 1995; Oliver 2000; see Chapter 4). However, the superior olivary complex does not project into the dorsal or external cortices of the IC (Henkel and Spangler 1983; Shneiderman and Henkel 1987; Oliver et al. 1997) so that in some parts of the IC, inputs from the olivary nuclei and the cochlear nuclei may be convergent and in other parts, cells could be influenced by the cochlear nuclei but not by the olivary nuclei. Likewise, the main targets in the IC of the auditory cortex are the dorsal and external cortices (Chapter 8). Here, the neurons that receive inputs from the cochlear nuclei might be more subject to descending control than those in the central nucleus, which receives relatively little cortical input.

3.2. Organization Within the Central Nucleus

The proportion of labeled cells located in each source of ascending input to the IC is quite consistent both across studies and also across species after large injections of tracers (Fig. 3.1). However, when small (usually iontophoretic) injections of retrograde tracers are made into the central nucleus of the IC, the results are considerably more variable in terms of the proportions or even the presence of labeled cells in the different sources (Roth et al. 1978; Brunso-Bechtold et al. 1981; Aitkin and Schuck 1985; Maffi and Aitkin 1987; Ross and Pollak 1989; Wenstrup et al. 1999; cf. Oliver et al. 1995). For example, in some small regions, projections from the superior olivary nuclei may dominate. In the most extreme example reported, after an injection of a tracer in the lateral IC, 98% of the labeled cells were located in the ipsilateral medial superior olivary nucleus (Aitkin and Shuck 1985). In general, however, it is rare that so many labeled cells are located in only one source of input. In other cases, cells in the cochlear nuclei and nuclei of the lateral lemniscus might be labeled with little or no labeling in the superior olive. Across species and studies, almost every possible combination of inputs has been seen, although some are more common than others.

Studies with anterograde tracers also provide evidence for segregation of inputs within the central nucleus. Many inputs to the IC from the cochlear nucleus form bands that are parallel to the isofrequency laminae (Oliver 1984, 1987). In some cases, the bands from two sources overlap, as is the case for inputs from the contralateral dorsal cochlear nucleus and the contralateral lateral superior olivary nucleus (Oliver et al. 1997). Other inputs appear to lie in adjacent and possibly nonoverlapping bands, as is the case for the inputs from the ipsilateral and contralateral lateral superior olivary nuclei (Shneiderman and Henkel 1987). The inputs from the ipsilateral medial superior olivary nucleus and the ipsilateral cochlear nucleus may remain partially separate in the dorsolateral part of the IC

(Oliver and Beckius 1993). In that same part of the IC, some of the inputs from the contralateral and ipsilateral cochlear nuclei also appear to remain separate (C.G. Benson and N.B. Cant, unpublished results in the gerbil).

A dramatic example of segregation of inputs within a frequency lamina is provided by studies of the mustache bat, which exploited the fact that the 60-kHz "layer" is greatly expanded in this species (Wenstrup et al. 1986; Ross et al. 1988; Ross and Pollak 1989). When tracer injections filled most of the 60-kHz region, the pattern of labeling was very similar to that seen in other species (Fig. 3.1G), although more labeled cells were located in the nuclei of the lateral lemniscus than in the cochlear nuclei and the numbers of cells in the cochlear nucleus and the superior olivary complex were approximately equal (Ross et al. 1988). (Whether these differences from the common mammalian pattern are a result of specializations in the bat or occur because the injections are still relatively small is not clear.) However, when small, discrete injections were made systematically throughout the 60-kHz lamina, Ross and Pollak (1989) found different patterns of projections in four different regions that could be related to differences in the physiological response properties of the neurons in each region. Their results show that both connectivity and physiological response properties change systematically across this isofrequency representation.

In one of the first studies of projections to the IC employing tracer injections (and physiological recording), Roth and colleagues (1978) suggested that, "Within the cochleotopic and laminar framework of the central nucleus, it would seem that other rules of order must exist." Other investigators have reached the same conclusion. Maffi and Aitkin (1987) proposed that the central nucleus is made up of "core zones" in which inputs from specific brain stem nuclei are dominant. Based on their demonstration of a systematic difference in the proportions of labeled cells in the cochlear nuclei vs. the superior olivary complex when horseradish peroxidase injections were made in the caudal vs. rostral IC, Brunso-Bechtold and colleagues (1981) concluded that an organization based on "nucleotopy" was superimposed on the cochleotopic organization of the IC. The apparent differential organization of inputs forms the basis for the hypothesis that the central nucleus is organized into "synaptic domains" as put forth by Oliver and Huerta (1992; Oliver 2000). In this conception, the synaptic domains are defined as small groups of neurons that share the same populations of synaptic inputs. A given synaptic domain may lie next to another synaptic domain with the same frequency characteristics but with different sets of inputs and, presumably, different physiological properties (see Chapter 2).

Consistent with the conclusions based on neuroanatomical studies, the physiological response properties of IC neurons have been shown to vary with location, and neurons with similar properties tend to cluster together (Roth et al. 1978; Semple and Aitkin 1979; Wenstrup et al. 1986; Brückner and Rübsamen 1995). As noted earlier for the mustache bat, differences in the sources of inputs covary with differences in the physiological types found in various parts of the central nucleus. A similar progression of response types across isofrequency laminae was demonstrated in the gerbil (Brückner and Rübsamen 1995). The

properties of some unit types in the IC of the cat appear to reflect a dominant input from only one of the many brain stem sources of inputs (Davis et al. 1999; Ramachandran et al. 1999; Davis 2002).

4. Conclusions

Neurons in the IC receive inputs from a wide variety of brain stem, forebrain, commissural, and intrinsic sources. Learning exactly how these inputs are organized at the level of the individual neurons that make up the IC represents a major challenge for future studies. Although at the light microscopic level, many of the inputs overlap to a greater or lesser extent, it is not known whether individual cells receive synapses from all of the axons in their vicinity or only from some of them. Although the potential for convergence of multiple inputs at the level of the IC is generally emphasized, there is ample potential for divergence and segregation of inputs from different sources at the level of the individual cells, especially because the IC may contain over five times as many neurons as the cochlear nuclei, superior olivary complex, and nuclei of the lateral lemniscus combined (Kulesza et al. 2002).

Given the many sources of inputs to the IC, the possibilities for combinations of inputs to any particular neuron are staggering. Even if the inputs from the cochlear nuclei alone are considered, there are a number of possible combinations. The cell types in the cochlear nuclei that project to the IC—the fusiform and giant cells in the dorsal cochlear nucleus and multipolar cells in the ventral cochlear nucleus—each have different physiological response properties and appear to encode different types of information (Rhode and Greenberg 1992). It is curious that no major differences in the organization of the terminal fields of these three cell types have been described, but it is certainly possible that there are important differences at the level of the synaptic organization of the cells in the IC. Potential interactions between ipsilateral and contralateral inputs from the cochlear nuclei add to the number of possibilities, as all three major cell types that project contralaterally also project ipsilaterally. Although the number of cells projecting to the IC from the ipsilateral cochlear nucleus is small, they may provide a substantial proportion of the inputs in the dorsolateral region. The inputs from the cochlear nuclei to the IC could also be combined in many different ways with the ascending inputs from the superior olivary complex and nuclei of the lateral lemniscus (see Chapter 4), commissural connections (see Chapter 5), and descending projections from the forebrain (see Chapter 8).

Adding to the complexity of organization made possible by the multitude of inputs is the intrinsic complexity afforded by the many different cell types that make up the IC. As discussed elsewhere, neurons in the IC may differ in their morphology (see Chapter 2), projection targets (see Chapters 5 and 6), transmitter expression (see Chapter 9), biophysical properties (see Chapter 10), and physiological response properties (see Chapters 11 to 13). It is reasonable to expect that cell types defined based on these differences will also differ in their

sources of input and synaptic organization, but at present very little is known about the synaptic organization of any particular cell class.

Neuroanatomical methods based on axonal transport of tracers have constantly improved since their introduction in the 1970s, and can still be used profitably to address many of the outstanding questions about the auditory pathways. Double and triple labeling experiments, combined with electron microscopy or physiological recording and marking techniques, can answer many important questions about the specific sources of inputs to specific cell types and provide substantive hypotheses for further work. These are tried and true methods, but they are technically difficult and progress is slow. It is exciting, therefore, that in the near future, new methods based on work in genetics and molecular biology can be expected to have a major impact on our ability to examine neural circuitry. For example, transgenic mice have been produced that express axonally transported tracers under the control of cell-type specific promoters (Yoshihara et al. 1999). In these animals, the projections of one specific cell type may be studied in isolation from those of other cell types. Similar methods are already being applied to some sensory systems (Braz et al. 2002; Kinoshita et al. 2002), and there is every reason to expect that such technology will vastly improve our ability to trace specific circuits in the complex pathways of the auditory system.

Knowledge of the connectivity and synaptic organization of specific cell types is essential for advancing our understanding of how physiological response properties emerge and, ultimately, of how each pathway contributes to overall auditory function. Although questions remain that can be addressed with currently available neuroanatomical techniques, we can look forward to an exciting new era of investigations of brain stem auditory circuitry as new techniques of molecular biology are used to address these questions.

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Chapter 4
Superior Olivary Complex and Lateral Lemniscal Connections of the Auditory Midbrain

BRETT R. SCHOFIELD

1. INTRODUCTION

The inferior colliculus (IC) receives the majority of its ascending auditory inputs from the superior olivary complex (SOC) and the nuclei of the lateral lemniscus (NLL). These nuclei receive their inputs from the cochlear nucleus (CN), which also projects directly to the IC (see Chapter 3). Thus, there are parallel ascending pathways from the CN to the IC. These pathways analyze different aspects of acoustic information and send that information to the IC, where it is combined in ways that remain largely mysterious. Indeed, some of the most pressing questions in auditory research concern the functions of these parallel pathways and the nature of their convergence in the IC.

An important tool for understanding the functional organization of the ascending pathways has been conceptualizing them as monaural and binaural systems (Kudo and Nakamura 1987; Pollak and Casseday 1989; Helfert and Aschoff 1997; Casseday et al. 2002). Although this approach has been useful, it has been limited by a paucity of data on many of the relevant nuclei, especially the periolivary nuclei and the ventral and intermediate nuclei of the lateral lemniscus. The purpose of the present chapter is to examine new data on these nuclei and to present a new view of the monaural and binaural pathways. We begin with a brief review of the nuclei of the SOC and NLL and their projections to the IC, with an emphasis on recently acquired data. We then discuss the monaural and binaural systems and consider several aspects of their convergence in the IC. For additional information, and particularly for discussions of the identification of nuclei in different species, several reviews of the SOC and NLL are available (Schwartz 1992; Helfert and Aschoff 1997; Oliver 2000; Thompson and Schofield 2000; Smith and Spirou 2002; Casseday et al. 2002; Oertel and Wickesberg 2002).

2. The Superior Olivary Complex

Figure 4.1A illustrates the SOC nuclei. We consider the medial superior olivary nucleus (MSO) and the lateral superior olivary nucleus (LSO) to be the principal nuclei, and the remainder to constitute the periolivary nuclei (PON). Following a brief description of MSO and LSO circuitry (reviewed by Oliver 2000), we

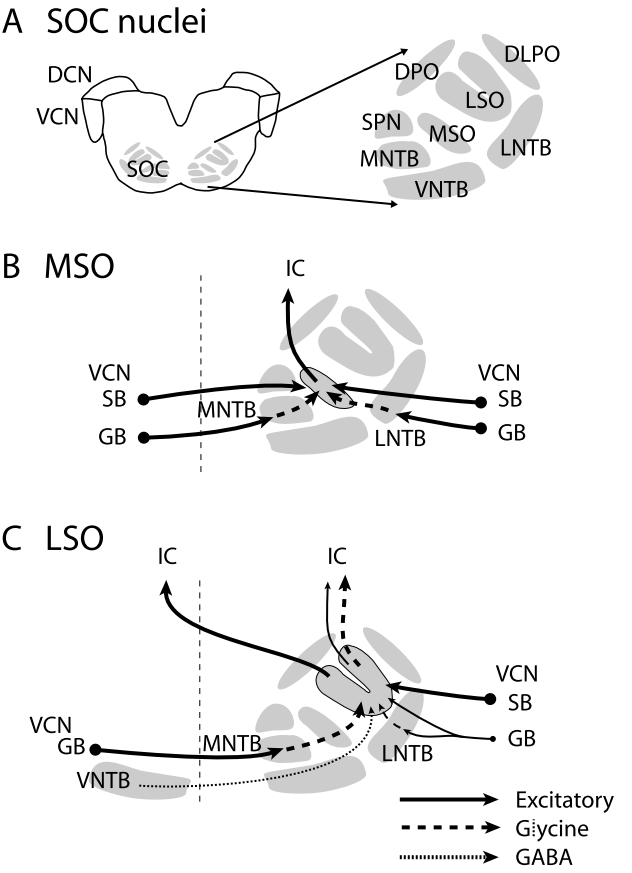

Figure 4.1. The superior olivary complex and the circuits of the principal nuclei. **(A)** Schematic drawing (outlined from a guinea pig brain) showing the location of the major nuclei of the SOC. **(B, C)** Schematic drawings showing the major inputs to the MSO and the LSO. In this and subsequent drawings, *arrows* indicate major projections, with *line thickness* indicating relative size. The major neurotransmitter (or the postsynaptic effect) is indicated by the legend. GABA and glycine are generally inhibitory; the excitatory neurotransmitter(s) are less well known but for many pathways are believed to be glutamate or a related substance. The midline is represented by a *thin, dashed vertical line.*

focus on the PON and especially on the superior paraolivary nucleus (SPN), which is emerging as an important element in this system (Fig. 4.1A).

2.1. The Medial Superior Olive

The MSO receives bilateral excitation and inhibition (Fig. 4.1B). The excitation originates from spherical bushy (SB) cells, while the inhibition arises from globular bushy (GB) cells whose axons activate glycinergic cells in the medial or lateral nuclei of the trapezoid body (MNTB and LNTB, respectively), that project in turn to the MSO. The projections are organized tonotopically, with a relative overrepresentation of low frequencies.

The majority of MSO cells are excited by both ears and are particularly sensitive to interaural time differences. These cells likely play an important role in encoding azimuthal location of a sound.

Most MSO cells project ipsilaterally to the IC, where the axons terminate in bands in the central nucleus (ICc). Although a few MSO cells may use γ-aminobutyric acid (GABA) or glycine (Helfert et al. 1989; Winer et al. 1995), most appear to use an excitatory neurotransmitter (Kumoi et al. 1993; Oliver et al. 1995).

2.2. The Lateral Superior Olive

The major excitatory input to the LSO arises from SB cells in the ipsilateral VCN (Fig. 4.1C). The major inhibitory input arises from the MNTB, which is driven by GB cells in the contralateral VCN. Additional inputs, presumed to be inhibitory, arise from the ipsilateral LNTB and contralateral VNTB. Finally, small inputs arise from GB cells in the ipsilateral VCN and from multipolar cells in the VCN on both sides (not shown; Helfert and Aschoff 1997; Doucet and Ryugo 2003). As for the MSO, the inputs to the LSO are organized tonotopically; however, in the LSO the system is biased toward high frequencies.

Most LSO cells are excited by ipsilateral stimulation and inhibited by contralateral stimulation. These cells are particularly sensitive to interaural level differences (and less so to time differences). This sensitivity and the bias toward high frequencies have led to the idea that the LSO analyzes interaural differences that are critical for azimuthal localization of high-frequency sounds. A few binaurally excited cells are also present.

The projections from the LSO to the IC are bilateral, with ipsilateral and contralateral projections originating from different cells. In cats and several other species, the ipsilateral projection arises preferentially from the lateral limb of the LSO, while the contralateral projection arises more heavily from the medial limb (Helfert and Aschoff 1997). The opposite bias is true in ferrets (Henkel and Brunso-Bechtold 1993); the significance of this species difference remains to be determined. In any case, the crossed and uncrossed projections help to establish what Glendenning and colleagues (1981) called an “acoustic chiasm,”

referring to the fact that most cells in the midbrain and above respond to sounds in the contralateral sound field. The contralateral projection from the LSO is excitatory, whereas the ipsilateral projection contains a large glycinergic component and a smaller, presumably excitatory, component (Saint Marie et al. 1989). A small, bilateral projection may also originate from GABAergic cells (González-Hernández et al. 1996). Both the ipsilateral and contralateral projections terminate in bands in the ICc and in the deeper layers of the dorsal cortex of the IC (reviewed by Oliver 2000).

The LSO and MSO are widely considered as the first site of binaural convergence, even though binaural effects are observable in the CN and the cochlea. However, the LSO and MSO are the "lowest" nuclei to exhibit exquisite sensitivity to interaural disparities. These nuclei, along with their inputs and outputs, form the core of the binaural system and play an essential role in sound localization.

2.3. The Periolivary Nuclei

The periolivary nuclei (PON) are a group of nuclei surrounding the LSO and the MSO. They contain a variety of cell types that vary in morphology, inputs, projections, immunocytochemical properties, and physiologic responses (Schwartz 1992; Helfert and Aschoff 1997). Collectively, the PON are a significant source of projections to the IC (Fig. 4.2A). We first describe projections of the PON in general and then consider the SPN in detail.

Ascending inputs to the PON originate primarily from multipolar, octopus, and globular bushy cells of the VCN (reviewed by Thompson and Schofield 2000). Additional ascending inputs to particular PON can originate from other SOC nuclei.

All the periolivary nuclei project to the ipsilateral IC (Fig. 4.2B) (Adams 1983). Many of the nuclei, particularly the LNTB, send a smaller projection to the contralateral IC as well. Little is known regarding termination patterns in the IC. Ipsilateral projections from all nuclei appear to terminate in the central nucleus, and there is apparently a small projection to the dorsal and external cortices (González-Hernández et al. 1996).

There have been few studies of the responses of periolivary cells to acoustic stimuli (Guinan et al. 1972a,b; Irvine, 1986; Finlayson et al. 1997; Kuwada and Batra 1999). Binaural effects are common, and include various combinations of excitation and inhibition driven from either ear. Guinan et al. (1972a,b) distinguished 10 types of responses; in general, each unit type could be found among multiple nuclei, and each nucleus contained units of different response types. The heterogeneity suggests that the periolivary nuclei send a variety of signals to higher levels.

In few cases are the projections of the recorded PON cells known (Irvine 1986; Helfert and Aschoff 1997). The latter comment applies to principal cells of the MNTB and to medial olivocochlear cells; because neither of these cell types project to the IC, these studies provide no insight into the responses of

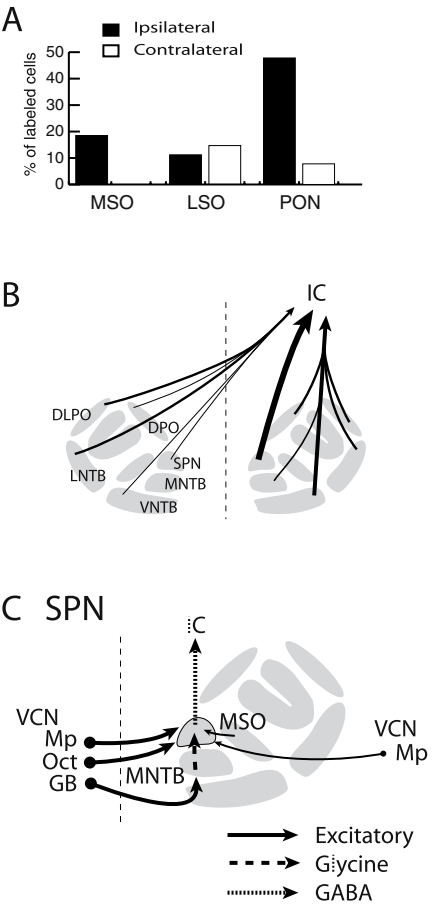

Figure 4.2. Periolivary projections to the inferior colliculus. **(A)** Graph showing the distribution of labeled cells in the SOC after injection of a retrograde tracer into one IC in a guinea pig (Schofield and Cant 1992). Cells in the PON were totaled to illustrate that olivocollicular cells in the PON can outnumber those in the principal nuclei (MSO and LSO). **(B)** Summary diagram showing general pattern of periolivary projections to the IC. *Line thickness* indicates in relative terms the number of cells giving rise to each projection (transmitters are not indicated in this figure). **(C)** Schematic diagram showing the major inputs to the SPN.

olivocollicular cells. One exception to this rule is the SPN, which provides a substantial projection to the IC and is discussed in detail later.

Several neurotransmitters have been implicated in periolivary projections to the IC. GABA is present in ipsilaterally projecting cells in the SPN (Kulesza and Berrebi, 2000) and in "other periolivary nuclei" (apparently including both VNTB and LNTB; González-Hernández et al. 1996) in rats. Presumptive glycinergic cells projecting to the ipsilateral IC have been identified in the SPN (guinea pig and chinchilla; Saint Marie and Baker, 1990) and, in smaller numbers, in the LNTB and MNTB (chinchilla; Saint Marie and Baker 1990). Other prospectively neuroactive substances, such as somatostatin and enkephalin, are associated with PON cells, but it is not known if they are present in olivocollicular cells. These substances are considered neuromodulators and could play an important role in modifying activity in the IC.

2.4. The Superior Paraolivary Nucleus

Inputs to the SPN are distinctly different from those to the MSO and LSO. The largest input arises from multipolar (Mp) and octopus (Oct) cells of the contralateral VCN, with additional inputs from Mp cells in the ipsilateral VCN (Fig. 4.2C; Schofield 1995). Additional inputs arrive from the ipsilateral MNTB and MSO (Kuwabara and Zook 1992; Smith et al. 1998).

Several reports describe response properties of SPN units (rat: Finlayson and Adam, 1997; Kulesza et al. 2003; rabbit: Kuwada and Batra 1999; gerbil: Behrend et al. 2002; Dehmel et al. 2002). Common denominators are a clear best frequency, and that the units appeared to be arranged tonotopically. There are considerable differences in the reported patterns of responses, with offset responses prevailing in some studies and rare in others. In most studies, monaural responses were more common than binaural responses. The binaural responses are of particular interest for the present discussion because they were quite different from those typical of the classic "binaural" nuclei (i.e., MSO and LSO). Few SPN cells are reported as sensitive to interaural differences of time or intensity (a hallmark of MSO and LSO units) (Behrend et al. 2002). Furthermore, many SPN units have transient responses (at onset or offset) and respond well to sinusoidally amplitude-modulated tones. These properties have led to a general conclusion that SPN units are specialized for analysis of temporal features of sound (Behrend et al. 2002; Kulesza et al. 2003).

Most SPN cells appear to be inhibitory. In rats, potentially all SPN cells are GABAergic (Kulesza and Berrebi 2000); in other species, there also appear to be glycinergic cells (Helfert et al. 1989). Both GABAergic and glycinergic cells appear to project to the IC (Saint Marie and Baker 1990; González-Hernández et al. 1996).

The SPN sends a large projection to the ipsilateral IC (rat: Coleman and Clerici 1987; mouse: Ollo and Schwartz 1979; Willard and Ryugo 1983; gerbil: Nordeen et al. 1983); in some species, a small contralateral projection is also present (guinea pig: Schofield 1991; chinchilla: Saint Marie and Baker 1990; North American opossum: Willard and Martin 1983). The projections appear to be organized tonotopically (Kelly et al. 1998; Saldaña and Berrebi 2000). Although there is general agreement that the projections terminate in the central nucleus, there are reports of input to the dorsal cortex and external cortex (rat: González-Hernández et al. 1996; Coleman and Clerici 1987; guinea pig and gerbil: Cant et al. 1999).

Several authors have distinguished the SPN from other PON (González-Hernández et al. 1996; Saldaña and Berrebi 2000) and the latter authors have stressed the similarities of the SPN to other principal nuclei. In rats (the only species for which cell counts are available), the number of SPN neurons supports this argument (Table 4.1). SPN contains about 2400 neurons per side, compared to 2500 neurons in the LSO and 1100 in MSO. Because virtually all SPN neurons project to the IC in rats (Saldaña and Berrebi 2000), the SPN certainly qualifies as a substantial source of projections to the IC.

Table 4.1. Summary of the number of neurons in six nuclei in the SOC of the rat.

Nucleus	Number of neurons[a]	Percentage
MNTB	6000	32.2
MSO	1100	5.9
LSO	2500	13.4
SPN	2400	12.9
VNTB	4500	24.2
LNTB	2100	11.3
Total	18,600	100

[a]Unbiased stereologic estimates of the number of neurons, rounded to nearest hundred, in each nucleus. (From Kulesza et al. 2002.)

Is the SPN equivalent to the dorsomedial periolivary nucleus (DMPO)? A prominent SPN is present in many animals, including rat, guinea pig, gerbil, mouse, mole, North American opossum, and chinchilla (Willard and Martin 1983; Willard and Ryugo 1983; Kudo et al. 1990; Saint Marie and Baker 1990; Schwartz 1992). In other animals, a much less prominent nucleus in the same location has been called the DMPO (e.g., cat, ferret, primate; Moore 1988; Schwartz 1992). Kuwabara et al. (1991) suggest that the SPN and the DMPO are distinct: the DMPO receives input from GB cells of the contralateral CN (cf. Morest, 1968; cat), whereas such inputs are absent in the SPN.

In summary, the SPN, and the PON overall, are a significant source of projections to the IC. Most of these projections terminate ipsilaterally and appear to use inhibitory neurotransmitters. Where do the PON fit into the monaural/binaural scheme? The PON have traditionally been included with the MSO and LSO within the binaural system. Without question, several of the PON play essential roles in the binaural pathways; the best known example is the MNTB and its projections to the MSO and LSO. We believe that the MNTB plays an essential role in the monaural pathways as well, and that some PON should be considered components of both monaural and binaural systems. Other nuclei, such as the SPN, are more appropriately considered part of the monaural system. We return to these issues after reviewing the nuclei of the lateral lemniscus.

3. Nuclei of the Lateral Lemniscus

The lateral lemniscus contains ventral, intermediate, and dorsal nuclei (VNLL, INLL, and DNLL, respectively) that differ in cytoarchitecture, connections, and immunocytochemical properties. DNLL and VNLL are recognized across species. The INLL is sometimes considered a dorsal division of the VNLL (see discussion in Oertel and Wickesberg 2002), but we will treat it as a separate structure. The VNLL is often further divided into two or more parts (Fig 4.3A).

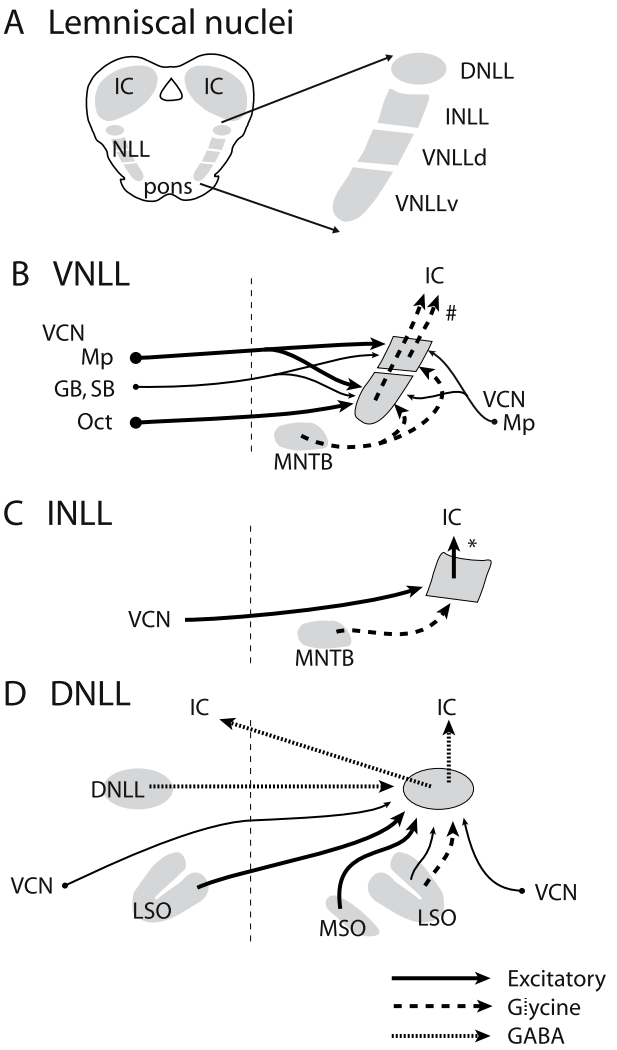

Figure 4.3. Lateral lemniscal nuclei and their connections. **(A)** Schematic diagram of the NLL. **(B–D)** Schematic diagrams showing the inputs and collicular projections of the two major subdivisions of the VNLL **(B)**, the INLL **(C)**, and the DNLL **(D)**. Conventions as in Fig. 4.2. #, includes GABAergic and excitatory projections; *, includes GABAergic and glycinergic projections.

We will discuss two large subdivisions, dorsal (VNLLd) and ventral (VNLLv), as described in guinea pigs (Schofield and Cant, 1997).

3.1. Ventral Nucleus of the Lateral Lemniscus

The VNLL receives bilateral inputs from the VCN and ipsilateral input from the MNTB (Fig. 4.3B; Oertel and Wickesberg 2002). Note that, although most inputs are shared by the two subdivisions of the VNLL, VCN octopus cells project only to the contralateral VNLLv. The octopus cell axons have large endings (Adams 1997; Schofield and Cant 1997) and presumably play an important role in distinguishing the response properties of cells in the two subdivisions. Additional inputs (not shown) arise in several periolivary nuclei (Glendenning et al. 1981).

In contrast to most other brain stem auditory nuclei, there is no clear tonotopic order in the VNLL (Glendenning and Hutson 1998). Most VNLL cells are excited by contralateral stimulation; many are also affected by ipsilateral stimulation, and are thus binaural (Batra and Fitzpatrick 2002). Some binaural cells are sensitive to interaural time disparities, but the transient responses of these cells distinguish them from MSO cells. A variety of response patterns have been described, including onset, offset, and sustained.

The VNLL of some bats is divided into two parts with distinct cell types and response properties (Covey and Casseday 1991). The multipolar subdivision has primarily sustained responses, whereas the columnar division has onset responses. Furthermore, these cells appear to be exclusively monaural. These properties may be particularly important for bat echolocation, and may explain the specialized appearance of the VNLL in bats. However, the basic analyses, focused on temporal processing, are likely to be useful to nonecholocating animals as well. In fact, proposed functions for the VNLL (and INLL) include "timing" (Glendenning and Hutson 1998), pattern recognition (Oertel and Wickesberg 2002), and duration and delay tuning (Casseday et al. 2002). The emphasis on temporal features reflects, in part, the inputs from octopus cells, which are specialized to respond as onset detectors across a wide range of frequencies (Trussell 2002).

A majority of VNLL cells appear to use glycine or GABA as a neurotransmitter, suggesting that the VNLL provides an inhibitory projection to the IC (Thompson et al.1985; Saint Marie and Baker 1990; Winer et al. 1995). In addition, a smaller number of cells may use the excitatory neurotransmitter glutamate (Saint Marie 1996). It is interesting that these presumptive glutamatergic cells are located medially in the VNLL (Fig. 3 of Saint Marie 1996), in a region that Batra and Fitzpatrick (1997) have characterized as containing a large percentage of binaural cells that are sensitive to interaural time disparities.

Numerous studies have identified the VNLL as the brain stem nucleus that contains the greatest number of labeled cells after injection of a retrograde tracer into the IC (e.g., Brunso-Bechtold et al. 1981). The projections from the VNLL are diffuse (as opposed to banded) and are widespread, terminating heavily in

the central nucleus and dorsal cortex and less so in the lateral nucleus (Whitley and Henkel 1984; reviewed by Helfert and Aschoff 1997). These projections are almost exclusively ipsilateral. The many GABAergic and glycinergic cells in this nucleus make the VNLL the largest single source of inhibition to the IC.

3.2. The Intermediate Nucleus of the Lateral Lemniscus

The INLL receives input primarily from the contralateral VCN and the ipsilateral MNTB (Fig. 4.3C) (Oertel and Wickesberg 2002).

The most detailed information on INLL responses comes from studies on bats (Covey and Casseday 1991). INLL units are excited by contralateral stimulation and respond throughout the stimulus duration. These properties resemble those of the multipolar subdivision of the VNLL in the same bats (discussed earlier), leading Covey and Casseday (1999) to conclude that these two nuclei convey to the IC similar information about stimulus duration and intensity.

Immunohistochemical studies suggest that INLL contains some cells that use GABA or glycine, but most probably use an excitatory neurotransmitter.

The projection from the INLL to the IC is largely ipsilateral and terminates diffusely in the central nucleus and dorsal cortex (Whitley and Henkel 1984). The pathway appears to be organized tonotopically (Zook and Casseday 1982).

Both the VNLL and the INLL have been implicated in temporal processing. As discussed later, this broad category of analysis has been applied generally to the monaural system, of which INLL and VNLL are considered major components. In contrast, the DNLL differs in its inputs and its response properties, and is considered part of the binaural system.

3.3. The Dorsal Nucleus of the Lateral Lemniscus

The DNLL receives inputs bilaterally from the VCN and SOC (Fig. 4.3D). The olivary inputs arise from the LSO on both sides and from the MSO on the same side (see Pollak et al. 2003). Additional inputs may arise from the ipsilateral VNLL and INLL (not shown). All ascending axons reach the DNLL via the lateral lemniscus. An additional input arises from the contralateral DNLL, whose axons arrive via the commissure of Probst.

Most DNLL cells are binaural, and excited by the contralateral ear and inhibited by the ipsilateral ear (EI cells). A small number of cells are binaurally excited. DNLL appears to be organized tonotopically, although the precise arrangement may vary between species (Helfert and Aschoff 1997).

The DNLL contains primarily, perhaps exclusively, GABAergic cells (Adams and Mugnaini 1984). These cells comprise separate populations that project to the ipsilateral or contralateral IC and are organized tonotopically. In the contralateral IC, DNLL axons form bands that terminate in the central nucleus and extend into the dorsal cortex. The projection terminates more diffusely ipsilaterally (Shneiderman et al. 1988; reviewed by Helfert and Aschoff 1997). Projections to external cortex (lateral nucleus) may be present.

As mentioned earlier, the DNLL has been associated with binaural processing and sound localization. In the next section, we review the monaural and binaural systems and consider how recent data impact these ideas.

4. Organization of the Ascending Pathways

The ascending pathways to the IC have been conceptualized as monaural and binaural systems (Kudo and Nakamura 1987; Pollak and Casseday 1989; Helfert and Aschoff 1997; Casseday et al. 2002). In most accounts, the monaural system has included the direct projections from the CN as well as indirect projections from multipolar and octopus cells in the VCN through the VNLL and INLL. The binaural system has included spherical bushy and globular bushy cells in the VCN as well as the nuclei of the SOC (particularly the MSO, LSO, and MNTB) and the DNLL. We present here a modified view of these systems, taking into account new data, particularly concerning the SPN and the VNLL. While maintaining the concept of monaural and binaural systems, we propose to dissect the SOC further and to consider its components individually. Some SOC nuclei belong to the monaural system and others to the binaural system. Further, some nuclei, and some CN cell types, should be considered common elements of both systems.

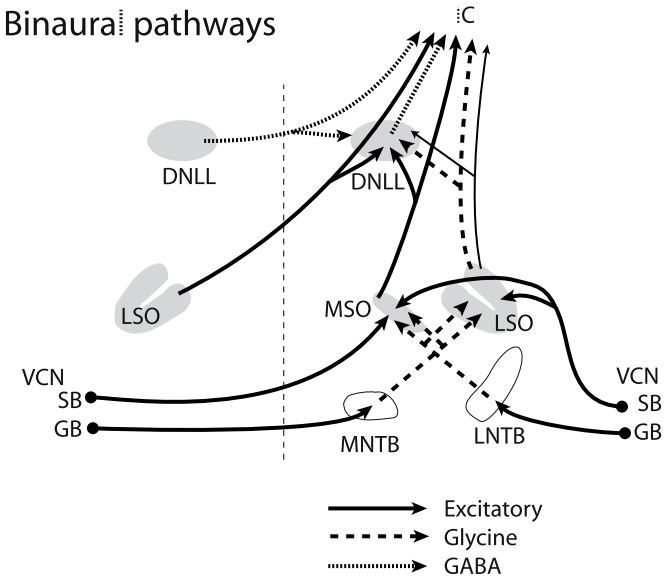

Figure 4.4. Summary of the binaural pathways through the SOC and NLL to the inferior colliculus. Conventions as in Fig. 4.2.

4.1. Nuclei of the Binaural System

Our view of the binaural system is similar to previous proposals except that we do not include the entire SOC (Fig. 4.4). The key nuclei are the MSO, LSO, and DNLL. The inputs originate from spherical bushy and globular bushy cells in the VCN. Cells in both the MNTB and LNTB contribute to binaural as well as monaural pathways. The binaural pathways include crossed and uncrossed projections from the SOC and provide for both excitation and inhibition (the latter including both GABAergic and glycinergic projections) in the IC.

4.2. Nuclei of the Monaural System

The INLL and VNLL are customarily included with direct projections from the CN to the IC as part of the monaural system. In an earlier study, we discussed numerous similarities between the SPN and VNLL (Schofield and Cant 1997), parallels that led Helfert and Aschoff (1997) to include the SPN (which they called the dorsomedial periolivary nucleus) with the monaural system. Subsequent work has expanded the list of similarities between SPN and VNLL. Like the VNLL, the SPN has widespread projections to all IC subdivisions (Cant et al. 1999). Inputs to both nuclei arise largely from the contralateral CN, and less so from the ipsilateral CN and SOC. The CN inputs arise from multipolar cells bilaterally and from octopus cells contralaterally. Both nuclei have a preponderance of cells with monaural responses. Furthermore, the binaural responses in each of these nuclei are different from those in the binaural system (i.e., MSO, LSO, and DNLL). Not surprisingly, the data have led to similar conclusions regarding functions of the SPN and the VNLL.

The monaural pathways include the direct projections from the CN (Fig. 4.5A; see Chapter 3) and consist of SPN, VNLL, and INLL. Note the variety of VCN cell types involved; of these, the multipolar and octopus cells are most prominent in the monaural pathways. Most information arriving at the IC via these pathways originates from the contralateral ear. The monaural pathways, like the binaural ones, provide excitatory as well as inhibitory projections to the IC.

4.3. Nuclei of the Monaural and Binaural Systems

The MNTB has often been considered a principal nucleus of the SOC, and is generally considered part of the binaural system. Unlike the MSO and the LSO, the MNTB is not a major source of projections to the IC. In fact, the small projection it does send to the IC originates from nonprincipal cells (Schofield 1994), about which we know very little. The MNTB principal cells, in contrast, are well known as the targets of globular bushy cell calyces, and as the source of projections to the MSO and LSO. The principal cells also project to each of the nuclei associated with the monaural system as well as to the VCN (Fig. 4.6; Spangler et al. 1985; Kuwabara and Zook 1992; Schofield 1994; Smith et al. 1998). It seems appropriate to consider the MNTB (or at least the majority of

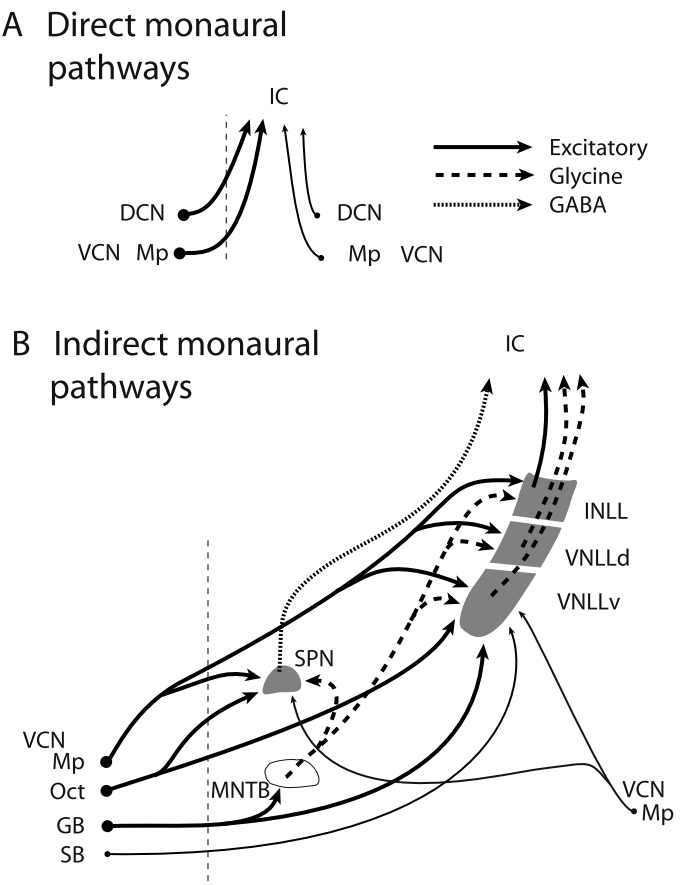

Figure 4.5. Summary of monaural pathways to the IC. **(A)** Direct projections from the cochlear nuclei (see Chapter 3). **(B)** Indirect monaural projections through the SOC and NLL. Conventions as in Fig. 4.2.

its neuronal population, the principal cells) as contributing to both the monaural and binaural systems, and not to assign it exclusively to one or the other.

4.4. Connections Between the Monaural and Binaural Systems

There are multiple points of interaction between the monaural and binaural systems. VCN multipolar cells are probably the most numerous single input to the monaural pathways, but they also project to the LSO (Doucet and Ryugo 2003) and they are probably the source of VCN projections to the DNLL. Both VNLL and INLL project to the DNLL (Glendenning et al. 1981). Thus, there are several

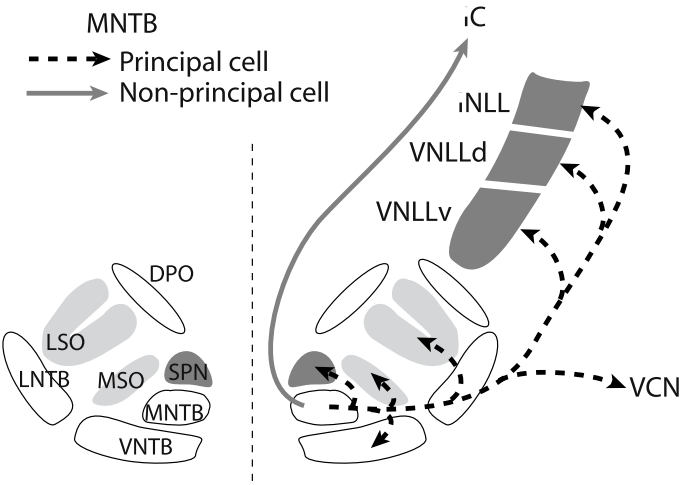

Figure 4.6. Schematic diagram showing projections from MNTB principal cells and non-principal cells. Nuclei associated with the monaural pathways are shown in *dark gray* and binaural pathways in *light gray*.

unexpected instances of "monaural" components projecting to binaural nuclei. There are also examples of the converse arrangement, that is, binaural inputs to monaural nuclei. For example, spherical bushy cells project not only to the MSO and LSO but also to the VNLL. Finally, the MSO projects to the SPN. Identifying the functions of these interactions will be important for understanding the ascending systems and should temper categorical assignments of specific cell types to particular systems with more caution than they ordinarily receive.

4.5. Proposed Functions of Monaural and Binaural Systems

The direct projections from the CN are the largest source of ascending excitatory inputs to the IC. The indirect monaural pathways provide excitatory inputs as well as the largest source of ascending inhibitory inputs to the IC (via the VNLL). The binaural system also gives rise to excitatory and inhibitory projections. Despite their interconnections, the differences in physiologic responses of the monaural vs. the binaural nuclei indicate that the two systems send different information to the IC. For each system, the proposed functions are suggested by the physiologic properties of both the constituent nuclei and those of the CN cells that provide inputs.

The binaural pathways have long been considered integral to analysis of interaural differences that are important for sound localization (particularly with regard to azimuth). A question that arises (for both binaural and monaural systems) is, Why are there so many nuclei and multiple, seemingly redundant,

pathways? In the binaural system, both the LSO and the DNLL contain many EI cells with inhibitory projections to the ipsilateral IC (Fig. 4.4). Pollak et al. (2003) demonstrate that these projections are not redundant. In fact, the DNLL projection confers new binaural properties on the target IC cells, allowing the IC cells to respond to stimuli to which they would not otherwise respond. These new properties could contribute to a variety of functions, such as analysis of stimulus motion.

Functional roles for the monaural pathways have generally received less attention than those of the binaural system. The VNLL and INLL have been implicated in "timing" (Glendenning and Hutson 1998), pattern recognition (Oertel and Wickesberg 2002), and temporal processing and duration and delay tuning (Casseday et al. 2002). The latter authors discuss mechanisms by which the VNLL and INLL could contribute to tuning for sound duration, rate of frequency or amplitude modulation, delay between an echolocation pulse and its echo, and selectivity for upward or downward frequency modulations. The similarities between the SPN and the VNLL lead to the conclusion that the SPN may be involved in some of these same functions. Both the SPN and the VNLL are substantial sources of inhibitory projections to the ipsilateral IC. Are these pathways redundant? We hypothesize that, like the DNLL and LSO projections in the binaural system, the SPN and VNLL projections confer different properties on their targets in the IC. Future experiments will be needed to test this idea.

5. Relationship between afferents and the Inferior Colliculus

5.1. Large-Scale Order: Nucleotopic Organization

The majority of data pertinent to this issue are from the ICc, and the following discussion is focused on that division. Results from both anterograde and retrograde tracing studies indicate that some projections to the ICc terminate more broadly than others. Projections from the VNLL, for example, terminate widely in ICc. MSO and LSO projections are more dense rostrally, whereas those from the CN are more dense caudally. This organization has been called "nucleotopic" (Brunso-Bechtold et al. 1981). In addition, the ICc itself and most of its inputs are organized tonotopically. Thus, projections from the low-frequency-biased MSO target the low-frequency (dorsal) part of ICc, whereas those from the LSO are denser in the high- frequency (ventral) regions. The consequence of nucleotopic and tonotopic organization is that different parts of the ICc receive different combinations of inputs, leading to local order and small regions with distinct circuitry.

5.2. Local Order and Microcircuitry

A frequent finding in physiologic studies is the clustering of units with similar response types (Roth et al. 1978). The scale of this clustering is much smaller

and finer than that of nucleotopic order discussed earlier, and occurs within an isofrequency lamina. Furthermore, the responses of many clusters are similar to those of lower centers, suggesting that IC cells simply "mirror" a dominant input. This applies particularly to temporal response patterns (e.g., onset vs. sustained) and to binaural interactions. Interestingly, some IC cells may, in fact, mirror a single, dominant input. Aitkin and Schuck (1985) recorded from a small low-frequency region of the IC in which the cells had response properties resembling those of the MSO. A small injection of retrograde tracer into this region labeled cells primarily in the MSO, consistent with the idea that the IC cells were mirroring MSO inputs. Using different techniques, Davis (2002) suggested that some IC cells are dominated by input from the contralateral dorsal cochlear nucleus (DCN). These projections are part of the monaural system, and thus there have been suggestions of mirroring in both monaural and binaural systems.

However, "mirroring" cannot explain all instances of similar responses. Kuwada et al. (1997) have shown that the same temporal discharge pattern can be generated by the intrinsic membrane properties of a neuron or by convergent excitatory and inhibitory inputs as well as by mirroring. The significance is that different mechanisms could result in different responses to more complex stimuli; for example, different types of onset units should respond differently in a reverberant environment. A similar situation applies to binaural properties. An EI cell (excited by the contralateral ear and inhibited by the ipsilateral ear) may mirror an EI input or integrate inputs that carry the excitation and inhibition separately (Pollak et al. 2003).

Several patterns of convergence have been suggested by experiments combining physiologic with anatomical and/or pharmacologic methods. IC cells could receive convergent input from the contralateral DCN and the ipsilateral MSO, LSO, or DNLL, or the contralateral DNLL (Semple and Aitkin 1981; Aitkin and Schuck 1985). Inputs from the ipsilateral MSO have been suggested to converge with those from ipsilateral LSO and ipsilateral or contralateral DNLL (Aitkin and Schuck 1985; Vater et al. 1995; Kuwada et al. 1997). Finally, inputs from the contralateral DNLL may converge with a contralateral monaural input (likely arising from DCN or VCN; Pollak et al. 2003). Anatomical tracing after very small injections in the IC suggest additional possibilities (Kudo and Nakamura 1987; Ross and Pollak 1989). Understanding and testing these possibilities, which essentially represent functional subdomains, will require a clear picture of circuitry within a lamina.

An important insight into microcircuitry followed from the discovery that several large projections to the IC terminate in bands. As described earlier, projections from the CN, MSO, LSO, and DNLL are banded whereas those from the VNLL and INLL are not (patterns for the PON are not known). The bands are on the order of a few hundred micrometers wide, providing a small-scale order of segregation (or overlap or periodicity) of specific inputs. Studies employing two different anterograde tracers have shown that the bands from the ipsilateral LSO and the contralateral LSO are interdigitated (Shneiderman and Henkel 1987). A disc-shaped cell situated in the middle of a band may receive just one of the inputs whereas a stellate cell, with dendrites that span

multiple bands, could receive convergent inputs. The detailed arrangement of bands from different sources, and their overlap with nonbanded inputs, gives rise to small regions, "synaptic domains," with unique patterns of microcircuitry (see Chapter 2).

A great deal of work remains to be done to identify the various patterns of convergence, to understand how they give rise to IC response patterns, and to recognize their contributions to auditory function.

6. Future Directions

We have reviewed the olivary and lemniscal inputs to the IC, and have suggested some revisions to the classic dichotomous scheme of monaural and binaural categorical pathways. These pathways ascend in parallel to the direct projections from the CN, which provide the IC with a massive, excitatory drive. The indirect pathways through the SOC and the NLL provide additional excitatory inputs as well as major inhibitory inputs that use both GABA and glycine. We conclude by enumerating a few of the questions that still remain.

1. To what extent, and to what purpose, do the monaural and binaural pathways, and their individual components, converge in the IC?
2. With respect to the principal SOC nuclei, what function is served by contralateral, or bilateral, projections from individual MSO cells? What purpose might be served by excitatory projection from the LSO to the ipsilateral IC: does it exist, and if so, what does it do? What function do binaurally excited LSO cells serve?
3. Does the SPN serve a unique function? What cells serve the same purpose in animals without an SPN? Is the SPN absent in some species? What about projections from other PON?
4. MNTB principal cells are well studied and are the source of the connections reviewed in the preceding (Fig. 4.6). However, it is the nonprincipal cells in the MNTB that project directly to the IC (Schofield 1994). These cells probably receive input from the contralateral VCN and thus form a small, disynaptic pathway from the VCN to the IC. A similar disynaptic pathway appears to traverse other periolivary nuclei, including the dorsal periolivary nucleus, the VNTB, and the LNTB (Thompson and Schofield 2000). Very little is known about the physiologic properties of the "periolivocollicular" cells, so it is premature to assign them to monaural or binaural systems or to reach definitive conclusions as to their role.

   We have focused on the ICc because most of the available data concern that subdivision. Difficulties in establishing criteria for distinguishing the IC subdivisions have complicated efforts to understand it. Such criteria will be essential before we can more fully understand IC function.
5. Can identification of SOC and NLL cell types provide functional insight, as it has for the VCN and for olivocochlear cells?

6. How do the ascending pathways converge, merge, and segregate from intrinsic and commissural projections (see Chapter 5), and how are these many pathways integrated with information from descending projections from the auditory cortex and thalamus (Chapter 8)?
7. How do the various ascending pathways relate to the outputs of the IC? This issue appears to be underappreciated. The ascending IC projections are often viewed from the perspective of transmission of information to the thalamus and thus to cortex. The IC projects to numerous nonthalamic targets, including the SOC and CN, reticular formation, and superior colliculus and pontine nuclei, and has motor as well as sensory functions (see Chapter 6). It seems likely that the diversity of physiologic properties characteristic of IC cells may be a reflection of the different functions served by the IC. One could predict that different pathways comprise units with different response properties (or at least differing proportions of the major response types).

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Abbreviations

CN	cochlear nucleus
DCN	dorsal cochlear nucleus
DLPO	dorsolateral periolivary nucleus
DMPO	dorsomedial periolivary nucleus
DNLL	dorsal nucleus of the lateral lemniscus
DPO	dorsal periolivary nucleus
EE	excited by both ears
EI	excited by contralateral ear, inhibited by ipsilateral ear
GABA	γ-aminobutyric acid
GB	globular bushy cell of the ventral cochlear nucleus
IC	inferior colliculus
ICc	central nucleus of the inferior colliculus
INLL	intermediate nucleus of the lateral lemniscus
LNTB	lateral nucleus of the trapezoid body
LSO	lateral superior olivary nucleus
MNTB	medial nucleus of the trapezoid body
Mp	multipolar cell of the ventral cochlear nucleus
MSO	medial superior olivary nucleus
NLL	nuclei of the lateral lemniscus
Oct	octopus cell of the ventral cochlear nucleus

PON	periolivary nuclei
SB	spherical bushy cell of the ventral cochlear nucleus
SOC	superior olivary complex
SPN	superior paraolivary nucleus
VCN	ventral cochlear nucleus
VNLL	ventral nucleus of the lateral lemniscus
VNLLd	dorsal division of ventral nucleus of the lateral lemniscus
VNLLv	ventral division of ventral nucleus of the lateral lemniscus
VNTB	ventral nucleus of the trapezoid body

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Chapter 5
Intrinsic and Commissural Connections of the Inferior Colliculus

Enrique Saldaña and Miguel A. Merchán

1. Introduction

1.1. Intracollicular Connections

The inferior colliculus (IC) is regarded as a nearly obligatory relay center for the information ascending from subcollicular auditory centers. Few axons bypass the IC en route to the auditory thalamus (Ramón y Cajal 1904; Henkel 1983; Malmierca et al. 2002), and most lateral lemniscal fibers end in the IC. Because of these convergent projections, the complexity of the inputs to the IC (see Chapters 3 and 4) contrasts with the apparent simplicity of midbrain projections to the thalamus (see Chapter 7).

The rat IC contains approximately 350,000 neurons, almost five times that in auditory subcollicular nuclei, and five times the number in the medial geniculate body (MGB) (Kulesza et al. 2002). These numbers suggest that, before arriving at the MGB, auditory information is extensively processed in the IC. Such processing is shaped by interactions between IC neurons, which are mediated by intracollicular connections.

Intracollicular connections, which are the focus of this chapter, are monosynaptic interactions between ipsilateral or contralateral IC neurons. Connections between neurons in the same IC are intrinsic, whereas those between the colliculi are commissural and travel in the commissure of the IC (CoIC). In this account intrinsic and commissural connections are considered together, as most if not all IC neurons with commissural connections also have intrinsic connections. Moreover, intrinsic and commissural connections share similar patterns of distribution. The chapter also contains data about the organization of intracollicular connections of the cortical subdivisions of the rat IC, and the distribution of commissural IC neurons. All references are to the rat unless stated otherwise.

We use the now-classic cytoarchitectural parcellation of the rat IC (Faye-Lund and Osen 1985) with slight modifications (Saldaña and Merchán 1992). The IC contains a central nucleus (CN) surrounded dorsally and dorsocaudally by the dorsal cortex (DC), and rostrolaterally by the external cortex. For clarity, we

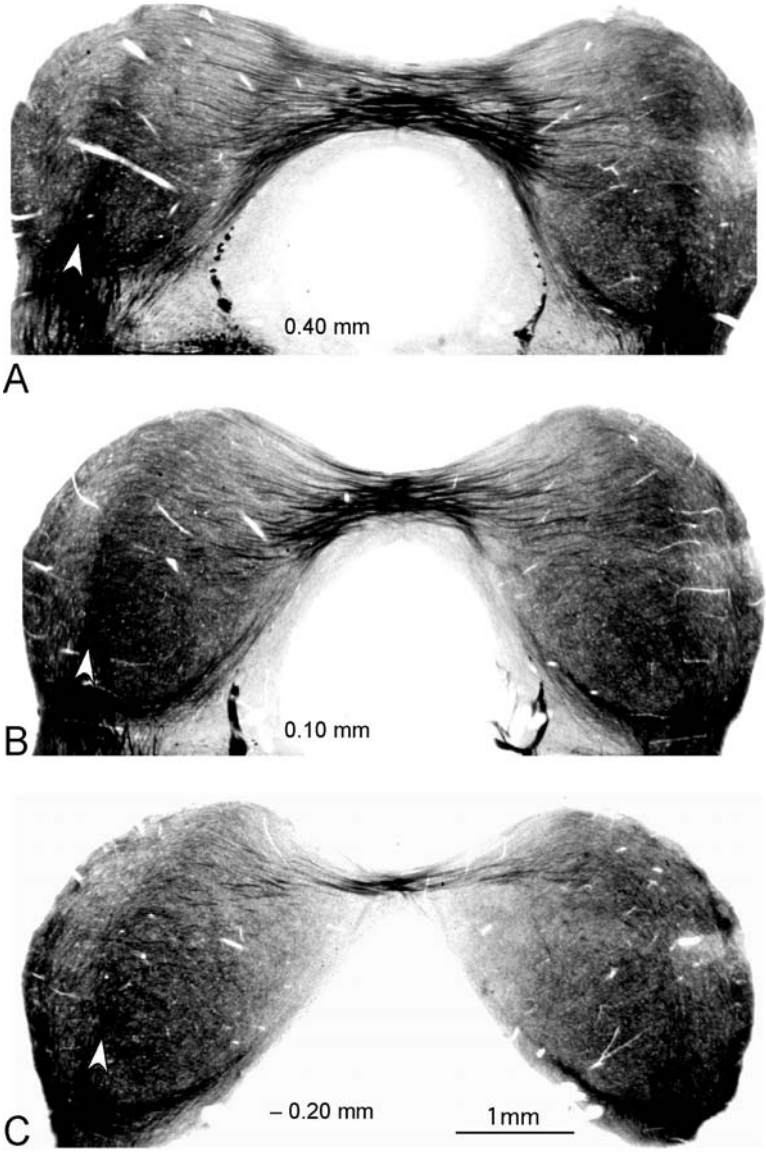

Figure 5.1. Micrographs of glutaraldehyde-fixed, 60-μm-thick coronal sections through the rat midbrain tectum. Sections were postfixed with osmium tetroxide, which stained myelinated fibers black. The numbers at the bottom of the section indicate the approximate rostrocaudal coordinate of the section in the interaural coronal plane. Fiber fascicles of CoIC are well defined and the IC neuropil is fiber rich, in contrast to the lightly stained periaqueductal gray matter. The *white arrowheads (left side)* indicate lateral lemniscal fascicles entering the IC.

refer to external cortex rostral to the CN as the rostral cortex (RC), and to the portion lateral to the CN as the external nucleus (EN).

1.2. The Commissure of the Inferior Colliculus

1.2.1. Anatomy and Topography

Despite subtle interspecies variations in volume and anatomical relationships, the main structural features of the CoIC are shared by most mammals (Figs. 5.1 and 5.2; see Chapter 22). The CoIC is a prominent transverse fiber tract that, at very caudal levels, consists of thin fascicles that constitute the roof of the recess of the fourth ventricle (Fig. 5.1C). Rostrally, it becomes a thick tract corresponding to the enlarged caudal portion of the tectal commissure (Faye-Lund and Osen 1985) and it is separated from the cerebral aqueduct by the thin rim of caudal periaqueductal gray matter (Fig. 5.1A, B). The CoIC is largest in the rostral third of the IC (Fig. 5.1A, B), where most commissural axons decussate. Whereas most CoIC axons project horizontally and in parallel, more caudal fascicles have variable, ascending or descending, oblique trajectories (Fig. 5.1C).

The rostral position of the CoIC is best seen in horizontal sections (Fig. 5.2) which show commissural axons traveling rostrally across the midline and then turning caudally in the contralateral IC. The horizontal plane shows that commissural axons cross in a nearly transverse plane (Fig. 5.2D), and that there is direct continuity between the rostroventral CoIC and the commissure of the superior colliculus (Fig. 5.2C).

1.2.2. Commissural Projections of the Inferior Colliculus

CoIC carries information bidirectionally (Held 1891, 1893; Moore and Goldberg 1966; van Noort 1969) and most CoIC axons belong to IC neurons. However, the CoIC contains some axons from other sources or destined for other targets. Tracer deposits in the MGB or the severed brachium of the IC (BIC) label projections to the contralateral MGB (Kudo and Niimi 1978; Aitkin and Phillips 1984; Oliver 1984; Hutson et al. 1991). Injection of anterograde tracers into the IC confirms crossed tectothalamic projections traveling in CoIC (Kudo and Niimi 1980; Andersen et al. 1980a; Hutson et al. 1991). It is unknown whether such axons also project in the contralateral IC before reaching the brachium.

The CoIC may contain also axons from subcollicular auditory centers (Ramón y Cajal 1904). Tracing studies in mice, rats, and cats suggest that the CoIC contains sagulum and/or lateral lemniscal fibers (González-Hernández et al. 1987; Henkel and Shneiderman 1988; Hutson et al. 1991; Bajo et al. 1993). Rat superior paraolivary nucleus cells project to the ipsilateral IC and proceed dorsomedially over the CoIC before ending in the contralateral DC (Fuentes et al. 1999). We are not aware of reports of axons in the CoIC from neural centers caudal to the superior olivary complex. The CoIC contains also auditory corticocollicular axons (Saldaña et al. 1996).

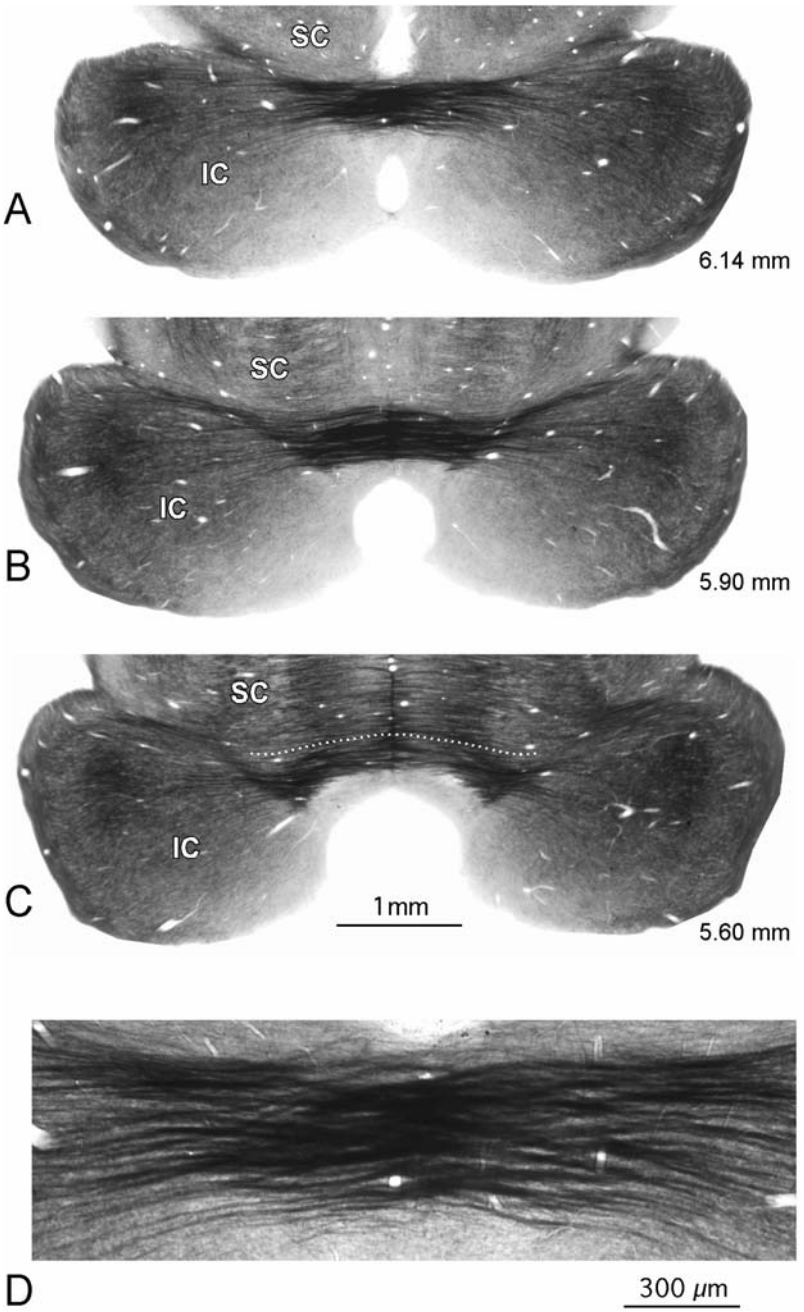

Figure 5.2. **(A, B)** Glutaraldehyde-fixed, 80-μm-thick horizontal sections of the rat midbrain tectum. Sections were postfixed with osmium tetroxide. Rostral is at the *top*. The *dotted white line* **(C)** indicates the border between the CoIC and the commissure of the superior colliculus. **(D)** Detail of the CoIC in the same section shown in **(A)**.

Whether the projections from different sources are segregated within the CoIC is unknown. There is rostrocaudal or dorsoventral topography for commissural IC axons with more rostral IC neurons crossing the CoIC more rostrally (Saldaña and Merchán, unpublished observations). Likewise, CN axons of neurons with low characteristic frequency (dorsolateral neurons) course more dorsally than higher characteristic frequency neurons (Saldaña and Merchán 1992; Figs. 5.5, 5.6).

2. Intracollicular Projections of the Central Nucleus and the Dorsal Cortex

2.1. Central Nucleus Projections

A study of the organization of the intrinsic and commissural connections of the albino rat (Saldaña and Merchán 1992) injected the anterograde tracer *Phaseolus vulgaris*-leucoagglutinin (PHA-L) into the CN. Axons (Fig. 5.3) from a discrete CN deposit formed two ipsilateral, rostrocaudally oriented laminar plexuses of terminal fibers in IC, a main (medial) plexus (iMP), and an external (lateral) plexus (iLP), and two more plexuses in the contralateral IC, a main (medial) plexus (cMP), and an external (lateral) plexus (cLP). Few terminals were outside the plexuses. The iMP extended dorsomedially and ventrolaterally from the injection site, parallel to the CN fibrodendritic laminae of the CN, a well-known cytoarchitectonic arrangement in which flattened terminal fields of incoming fibers intermingle with similarly oriented, flattened dendritic trees of the resident cells (see Chapter 2). This iMP was continuous in CN and DC and extended rostrally into the RC. The iLP was narrower than iMP and in the EN, iLP was nearly parallel to the surface of the nucleus, with its ventral pole deeper than its dorsal end. Each contralateral plexus was symmetrical with the ipsilateral plexus. The main and the external plexuses met caudally at their ventral poles, forming a dorsally open three-dimensional structure. The fiber density was variable in the plexuses: iLPs were most prominent.

These features were common to all experiments (Saldaña and Merchán 1992), irrespective of the CN injection site. Individual differences in plexus thickness, extent, position, and orientation were related to the features of the injection site. First, plexus size and density was a function of injection site size. Second, plexus size and shape depended on the deposit's location in the CN tonotopic axis (Fig. 5.4). Injections in the ventromedial CN, whose neurons have a high characteristic frequency, labeled the iMP ventromedially, near the IC–periaqueductal gray matter border, while the iLP was ventrolateral in EN, near the pial surface. With more dorsolateral injection sites at lower characteristic frequency, the iMP moved dorsolateral, and the iLP was more dorsal and more medial.

Such intracollicular projections are not unique to the rat, and a similar organization is present in the IC of mouse (González-Hernández et al. 1986; Frisina et al. 1997, 1998), gerbil (Doroshenko and Cant 1994), chinchilla (Caspary and

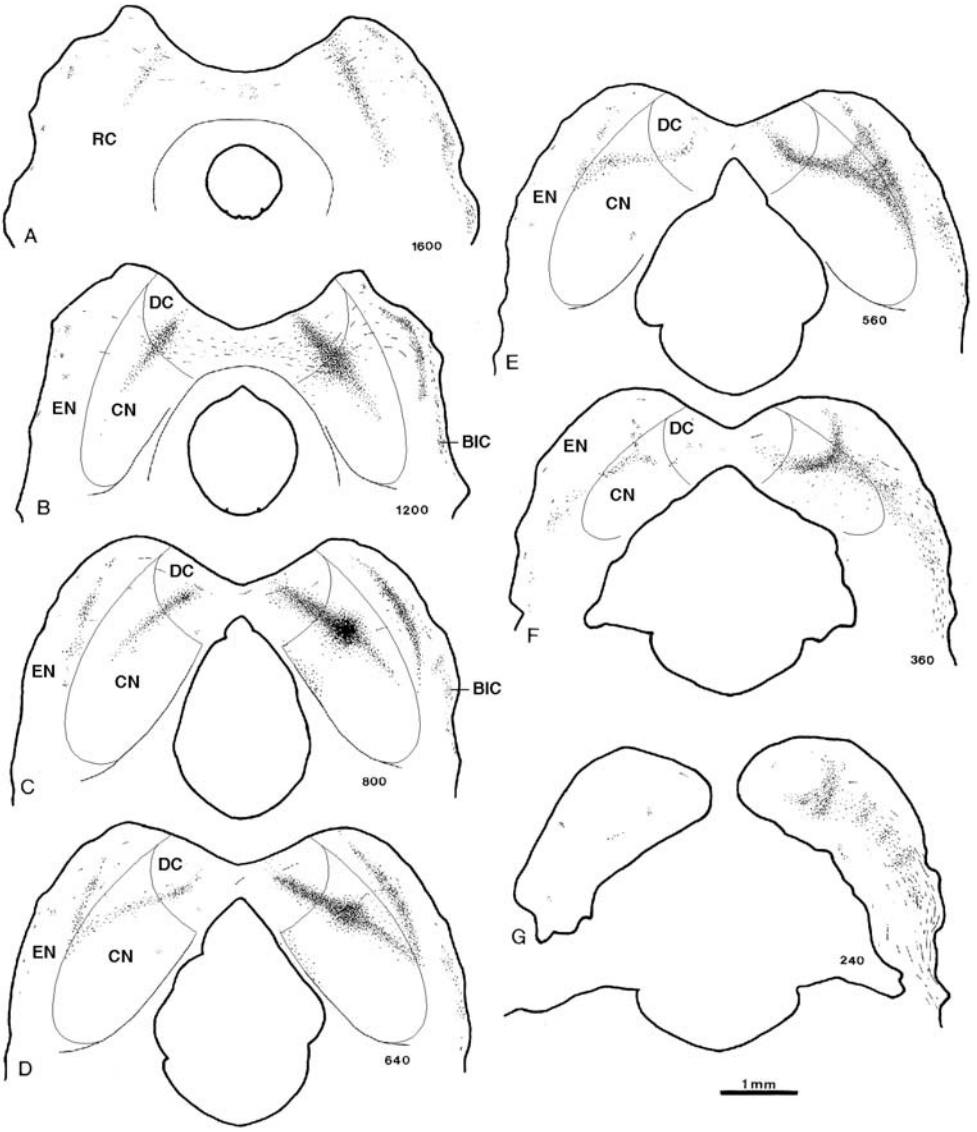

Figure 5.3. Camera lucida drawings of coronal sections showing the terminal intracollicular labeling pattern from a small PHA-L injection in the right CN. The numbers *(right side)* are the distance from the caudal pole of the IC in microns. In the IC, *lines* represent fibers of passage, and *stippling* denotes terminal fields. The injection site is near **C**. Intracollicular terminal fields are symmetrical, and the commissural labeling is weaker. The four axonal plexuses of terminal fibers span most of the IC rostrocaudally, and enter the RC. The iMP and cMP are continuous across the CN and DC. (Adapted from Saldaña and Merchán 1992. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

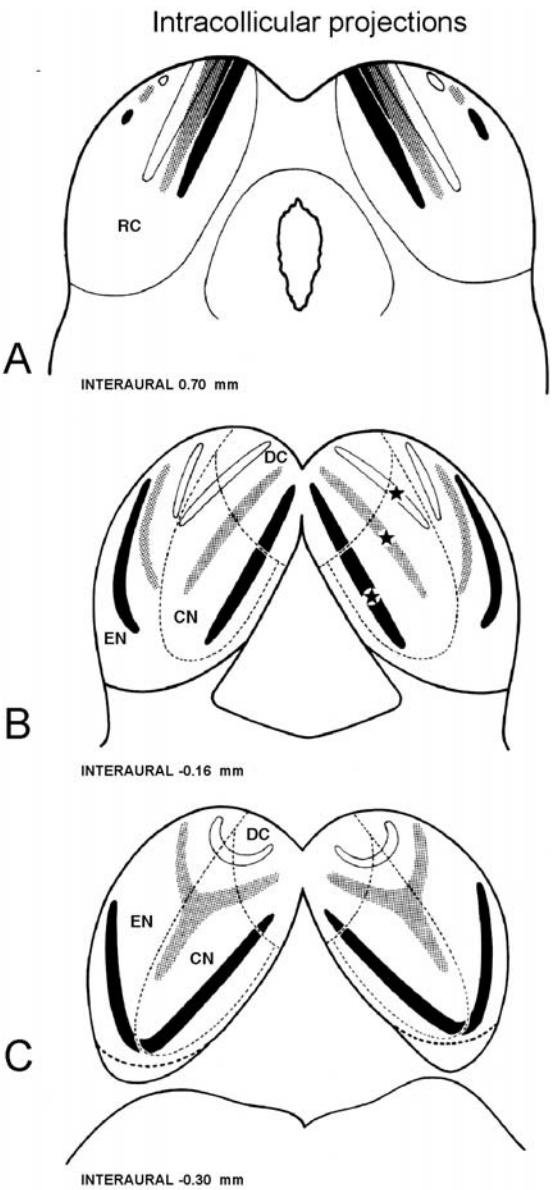

Figure 5.4. Schematic representation of the topographic distribution of intracollicular connections of the CN. The *black, gray,* and *white* areas represent territories targeted by discrete groups of CN neurons (*star* in **B**). *Black areas:* territories with input from ventromedial (high-frequency) CN neurons. *Gray areas:* targets of central (medium-frequency) CN neurons. *White areas:* targets of dorsolateral (low-frequency) CN neurons. The distribution of intracollicular fibers suggest that the laminae cross the divisions and involve most of the IC. These fibrocellular laminae curve around a point located dorsally. (Adapted from Saldaña and Merchán 1992. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

Helfert 1993; Saint Marie 1996), guinea pig (Malmierca et. 1995), cat (Brunso-Bechtold et al. 1981; Malmierca et al. 1998), and bat (Vater and Feng 1990).

Intracollicular connections studied with biocytin deposits into physiologically identified CN loci showed a similar pattern of intracollicular CN projections in the guinea pig and the rat (Malmierca et al. 1995). Three-dimensional reconstructions of the plexuses provided a clearer picture of the near-concentric organization in IC (Fig. 5.5).

Further analysis of earlier results (Saldaña and Merchán 1992) and injections of PHA-L or biotinylated dextran (BDA) in rat CN show that plexuses labeled by injections in rostral isofrequency regions are denser rostrally than caudally, and the converse is true for the caudal deposits (Saldaña and Merchán, unpublished observations). Likewise, plexuses labeled by a ventral injection are denser ventrally. Thus, despite the widely divergent nature of the intracollicular projections of the CN, they involve preferentially neurons at rostrocaudal and dorsoventral levels near those of the parent cell bodies, a topographic arrangement whose functional significance will require further investigation.

2.2. *Dorsal Cortex Projections*

Because the ipsi- and contralateral targets of intracollicular fibers from the CN extend into the DC, it is of interest how DC intracollicular projections relate to those of CN. A PHA-L injection into rat central DC spared both the fiber-rich superficial layer of the DC and the CN (Fig. 5.6). It was centered at medium or medium-to-low characteristic frequency (CF). The labeled fibers created a medial and a lateral laminar plexus in each IC that spanned the IC rostrocaudally and merged caudally at their ventral ends, a pattern like that of the intracollicular CN projections. These plexuses were denser dorsally (compare Figs. 5.3 and 5.6). With more ventromedial (higher CF) or more dorsolateral (lower CF) DC injections, the plexuses resembled those labeled by injections in comparable CN tonotopic regions (Fig. 5.7A).

The organization of the DC intracollicular projections is remarkably similar to that of CN intracollicular projections, which accentuates the connectional parallels between the CN and the DC. Accordingly, the DC sends topographic (tonotopic) projections to all four ipsi- and contralateral IC subdivisions.

2.3. *Implications for Inferior Colliculus Organization*

The pattern of intrinsic and commissural connections described in the preceding for CN and DC leads to several conclusions.

2.3.1. Strength of Intracollicular Inputs

Intracollicular projections are robust and may constitute one of the major inputs to IC neurons. They are an essential component of CN fibrodendritic laminae revealed by studies of the morphology of single intrinsic Golgi impregnated

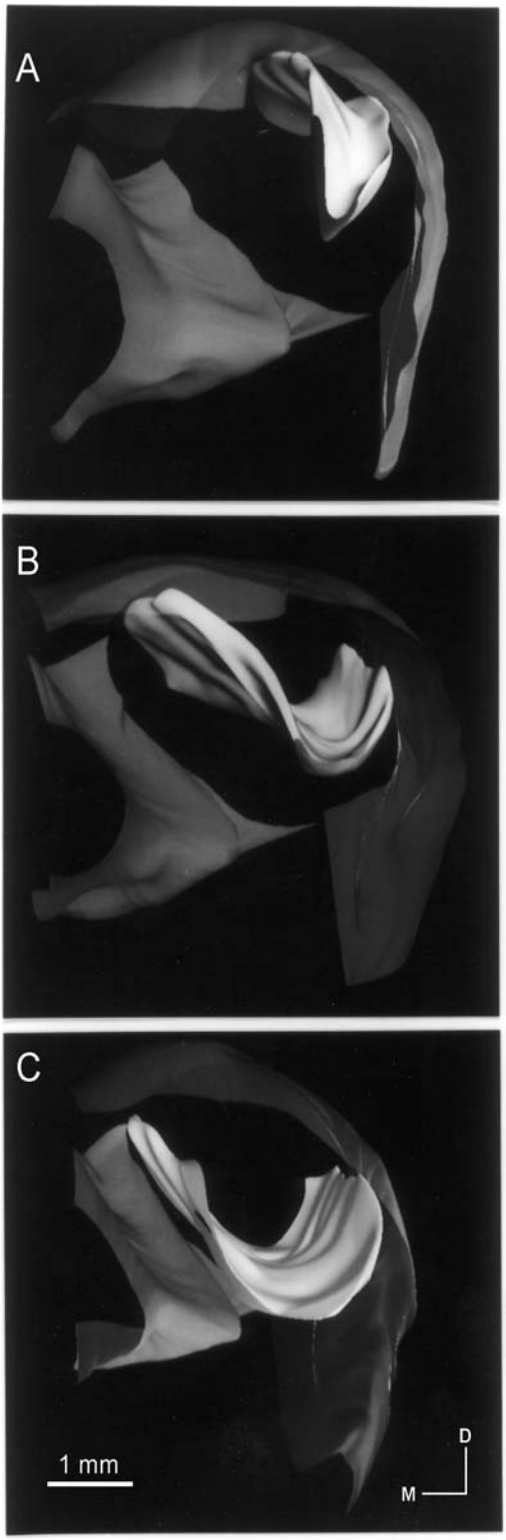

Figure 5.5. Three-dimensional reconstructions of guinea pig fiber plexuses of intrinsic CN axons at CFs of 0.5 kHz **(A)**, 6 kHz **(B)**, and 21 kHz **(C)**, respectively. The medial and lateral plexuses merge and form a complex, dorsally open structure. (Adapted from Malmierca et al. 1995. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

axons (Herrera et al. 1988, 1989) or neurons and axons filled with horseradish peroxidase (HRP) injected intracellularly (Oliver et al. 1991).

2.3.2. Divergence of Intracollicular Inputs

Neurons in specific CN and DC regions project divergently to the four divisions of the ipsi- and contralateral IC (CN, DC, EN, and RC), confirming the idea from retrograde tracing experiments that the commissural projections chiefly connect homotopic IC regions (Adams 1980; Schweizer 1981; Zook and Casseday 1982; Druga and Syka 1984; Tokunaga et al. 1984; Coleman and Clerici 1987; Ross et al. 1988; Ross and Pollak, 1989; Frisina et al. 1989; González-Hernández et al. 1996; Zhang et al. 1998). The commissural projection is more than merely reciprocal or homotopic because the contralateral IC targets includes areas homotopic to the iLPs (González-Hernández et al. 1986; Malmierca et al. 1995; Frisina et al 1998).

2.3.3. Topography of Intracollicular Inputs

The topographic (tonotopic) arrangement of the main plexuses show that CN and DC neurons project to CN and DC bilaterally at similar CF. We thus propose that the intracollicular projections enhance frequency specificity (see later), and that they may have other roles as well.

2.3.4. Possible Internal Topographies in Nuclei

The topography in the CN and DC projections to the EN raises the possibility that the EN possesses an unexpected tonotopic arrangement, whose isofrequency axes would parallel the IC surface, and whose main tonotopic axis is approximately mediolateral.

2.3.5. Contribution to Laminar Organization

The IC contains fibrocellular laminae. Each lamina is defined as the territory receiving input from CN and DC neurons with similar CF. Such laminae resemble the CN and DC plexuses or intracollicular input which curves around a point situated dorsally. Every fibrocellular lamina contains neurons and a precisely ordered axonal plexus. Fibrodendritic CN laminae may represent the central part of the fibrocellular laminae, but the latter are larger and extend into the other IC subdivisions. IC intrinsic and commissural projections are an essential component of the fibrocellular laminae, although other projection systems may also contribute. The distribution of the corticocollicular projections mimics that of the intracollicular connections (Fig. 5.7C), and this may apply to the cat (Andersen et al. 1980b).

Various lemniscal projections may follow a similar pattern, including those from the dorsal cochlear nucleus (Willard and Martin 1983; Malmierca et al. 2002) and the superior paraolivary nucleus (SPN) (Willard and Martin 1983; Fuentes et al. 1999). Input from the SPN forms two laminar plexuses in the

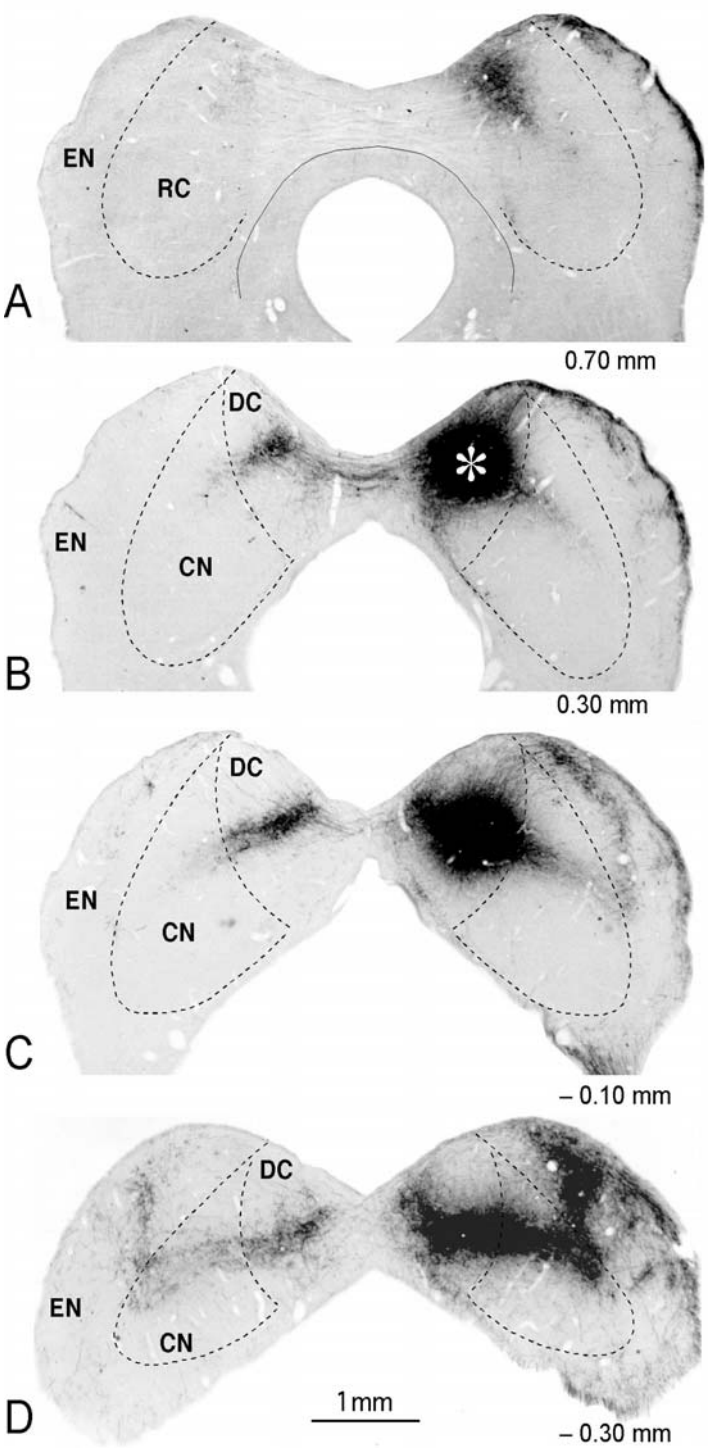

Figure 5.6. DC intracollicular projections after a small injection of PHA-L. **(A–D)** Micrographs of coronal sections. The numbers are the distance from interaural zero. The distribution of the terminal fibers plexus resembles that formed by CN axons (compare with Figs. 5.3 and 5.4).

ipsilateral IC, whose topography matches that of the iMP and iLP (Fig. 5.7B), and a weak CoIC projection. The SPN projection to the IC is topographic, and the size and shape of the terminal plexuses matches that of the intracollicular and corticocollicular projections. Thus, specific SPN cells project divergently to topographically matched neurons in the IC fibrocellular lamina.

3. Intracollicular Projections of the External Nucleus

Do EN neurons contribute to the same fibrocellular laminar distribution of intrinsic, commissural, ascending, and descending projections? The labeling in a representative experiment with a PHA-L deposit in EN (Fig. 5.8) showed terminal ipsilateral IC input to the EN extending rostrocaudally and dorsoventrally; in the DC and the dorsal part of the RC; and along the ventromedial IC border. Commissural terminal fields were sparser, and their distribution mirrored the ipsilateral projection. CN contained few fibers of passage bilaterally, and had few terminals. Thus, the EN projects to EN, DC, and RC bilaterally, and not to the CN. EN intracollicular projections do not contribute to the fibrocellular laminae of the IC, accentuating connectional differences between the medial (CN and DC) and the lateral (EN) IC.

Comparing PHA-L injections of EN with DC or CN deposits suggests that the intracollicular projections of the EN are weaker. That the EN innervates preferentially peripheral regions of the IC is of interest because these regions are the main recipients of the corticocollicular projections (Saldaña et al. 1996) and the EN is an early link in the "belt" auditory pathway.

The absence of significant projections from the EN to the CN is in partial agreement with studies using [^{3}H]leucine in the cat (Kudo and Niimi 1980) and with work in the rat (Chernock and Winer 2003) that show few cells retrogradely labeled in rat EN after CN injections of gold conjugated to cholera toxin β subunit. In contrast, several accounts find abundant retrogradely labeled cell bodies in the ipsi- and/or contralateral EN following HRP injections into the CN (Willard and Martin 1983; Willard and Ryugo 1983; Druga and Syka 1984; Tokunaga et al. 1984; Coleman and Clerici 1987; Frisina et al. 1998). A parsimonious explanation may be methodological: HRP injection sites tend to be large, so the possibility that the tracer spread or was incorporated by fibers of passage cannot be dismissed.

4. Intracollicular Cells of Origin

4.1. Neurons with Intrinsic Connections

Golgi studies of the IC show that most neurons with well-impregnated axons have ipsilateral collaterals (cat: Rockel and Jones 1973a,b; rat: Herrera et al.

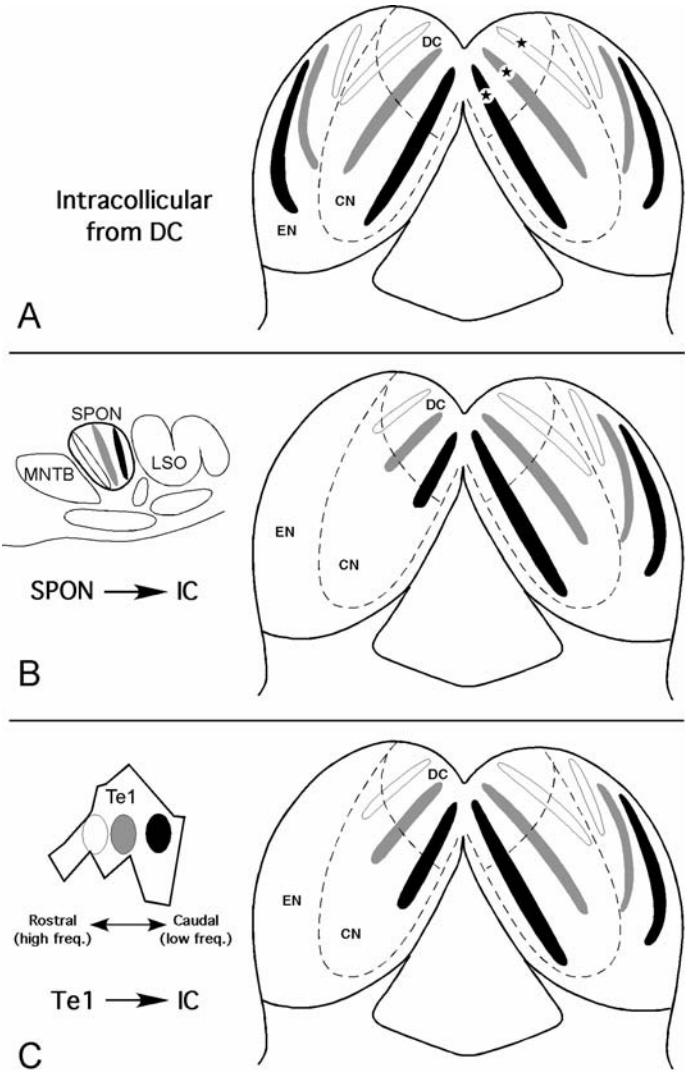

Figure 5.7. Schematic IC representation of the distribution of the terminal plexuses formed by axons from the right DC **(A)**, the right superior paraolivary nucleus **(B)**, and the right primary AC **(C)**. *Black, gray,* and *white areas* represent the IC territories targeted by a discrete group of neurons (*star* in the DC in **A**, *shadowing* in *insets* **B** and **C**). *Black areas:* territories receiving high-frequency projections. *Gray areas:* zones with medium-frequency input. *White areas:* loci targeted by low-frequency neurons. The distribution of IC ascending and descending projections mimics the topography of the CN and DC intracollicular projections except in the contralateral EN, which does not receive cortical or superior paraolivary nucleus input. (Adapted from Saldaña et al. 1996. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

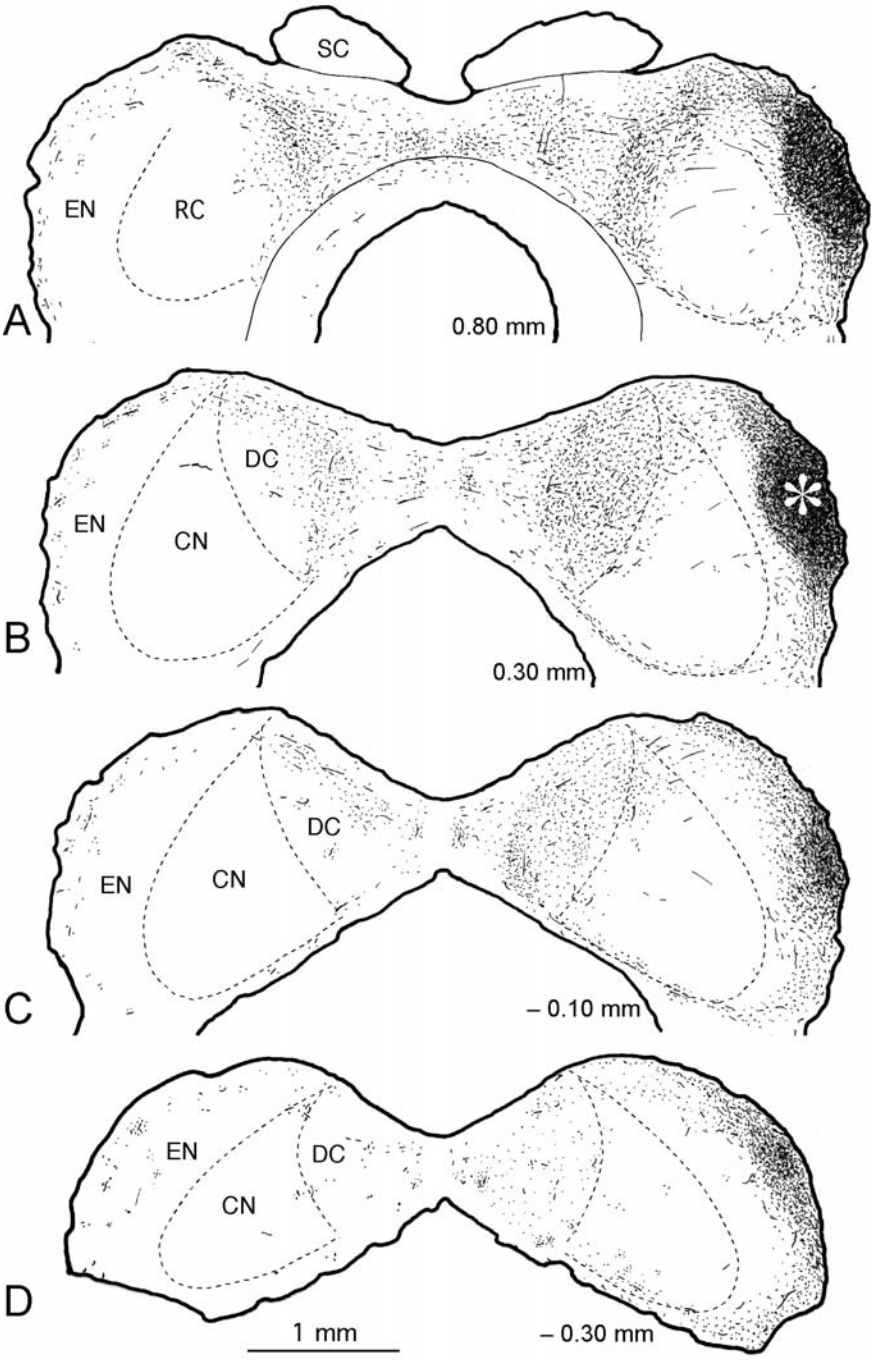

Figure. 5.8. Camera lucida drawings of bilateral coronal sections showing intracollicular terminal labeling from an EN PHA-L injection. *Numbers* are the rostrocaudal locus. *Lines* represent fibers of passage, stippling the terminal fields. The injection site center is marked *(asterisk).* **(B)** The main features are input to the ipsilateral EN, DC, and RC; a weak, symmetrical commissural projection; and no ipsi- or contralateral CN projection.

1988, 1989; González-Hernández et al. 1989). Intracellular injection in cats and rodents demonstrates that most IC neurons with filling of distal axon segments, including those whose axons enter the BIC, the CoIC or the lateral lemniscus, possess intrinsic axonal collaterals (Oliver et al. 1991; Smith 1992; Wagner 1994, 1996; Reetz and Ehret 1999; Peruzzi et al. 2000). Therefore, with the reservations imposed by the limited sample inherent to the Golgi method and to intracellular filling in mind, many if not all IC neurons have intrinsic connections. This is supported by the IC injection of retrogradely transported tracers, which label IC neurons belonging to virtually all morphologic types in rodents, bats, cats, and other small mammals (Tokunaga et al. 1984; Coleman and Clerici 1987; Saint-Marie 1996; Frisina et al. 1998).

Two conclusions can be drawn. Numerically, intrinsic connections may constitute the largest source of input to IC neurons, as the number of IC-projecting neurons in other auditory centers falls short of the number of labeled intrinsic IC neurons; and IC neurons with intrinsic connections are diverse in morphology, connections, neurochemistry, and physiology (see Chapter 2). This diverse morphology is evident in two representative cat IC neurons with very different intrinsic axonal arborization (Figs. 5.9 and 5.10) labeled by intracellular HRP injection (Oliver et al. 1991).

4.2. Neurons with Commissural Connections

Although there are no estimates of the total number of IC commissural neurons, nor has the number of CoIC axons been determined, the contralateral IC is surely among the main IC projection sources. For instance, the number of ferret IC neurons labeled after HRP injections in the contralateral IC was more than twice the number of neurons labeled in any other auditory center (Moore 1988).

Much like neurons with intrinsic connections, IC commissural neurons are heterogeneous in form and distribution. This is apparent in mammals as diverse as opossum (Willard and Martin 1983), mouse (González-Hernández et al. 1986; Frisina et al. 1998), rat (Druga and Syka 1984; Tokunaga et al. 1984; Coleman and Clerici 1987; González-Hernández et al. 1996), chinchilla (Saint Marie 1996), cat (Adams 1980), ferret (Moore 1988), and bat (Schweizer 1981). Although principal (disc-shaped) CN neurons have crossed projections, most commissural neurons are described as multipolar or stellate. While this trend may reflect differences in the relative proportion of different neuron types, multipolar neurons might also possess more extensive contralateral axonal arbors, or take up tracer more efficiently.

Four commissural neuron types were distinguished in the albino mouse on the basis of somatic size and their dendritic pattern: small-to-medium sized spiny cells, small-to-medium sized spineless cells, medium-sized sparsely spinous neurons, and large cells (González-Hernández et al. 1986). The profusion of intrinsic axon collaterals of the commissural neurons was also marked.

Commissural neuron projections may have various target nuclei. Rat IC contains some neurons that project to both the contralateral IC and the ipsilateral

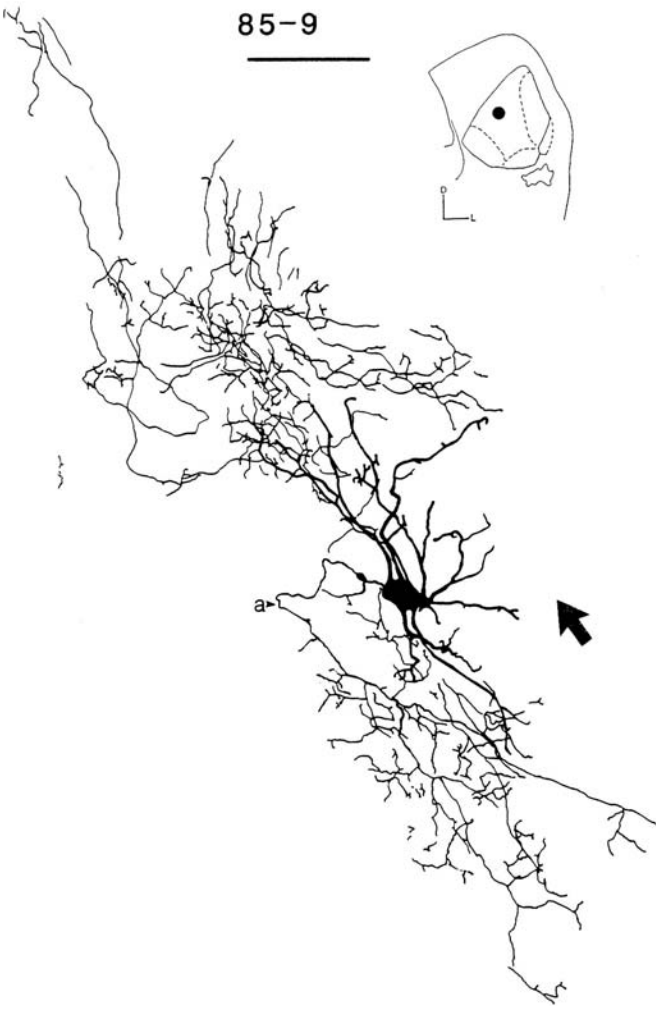

Figure 5.9. A cat CN neuron labeled in vivo by intracellular HRP injection. The neuron is shown in the coronal plane and its IC position is indicated *(inset). Black arrow,* the orientation of CN fibrodendritic laminae. The highly oriented dendritic tree and the profusely ramified axonal arborization *(thinner lines)* both parallel the isofrequency laminae. The calibration bar represents 100 μm. (From Oliver et al. 1991. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

MGB (González-Hernández et al. 1991). The axonal branching of some mouse IC commissural neurons suggests that they project in the ipsilateral brachium and/or lateral lemniscus (Reetz and Ehret 1999). Some commissural axons send collaterals to CoIC to end in the tectal commissural column (Saldaña and Viñuela 2002).

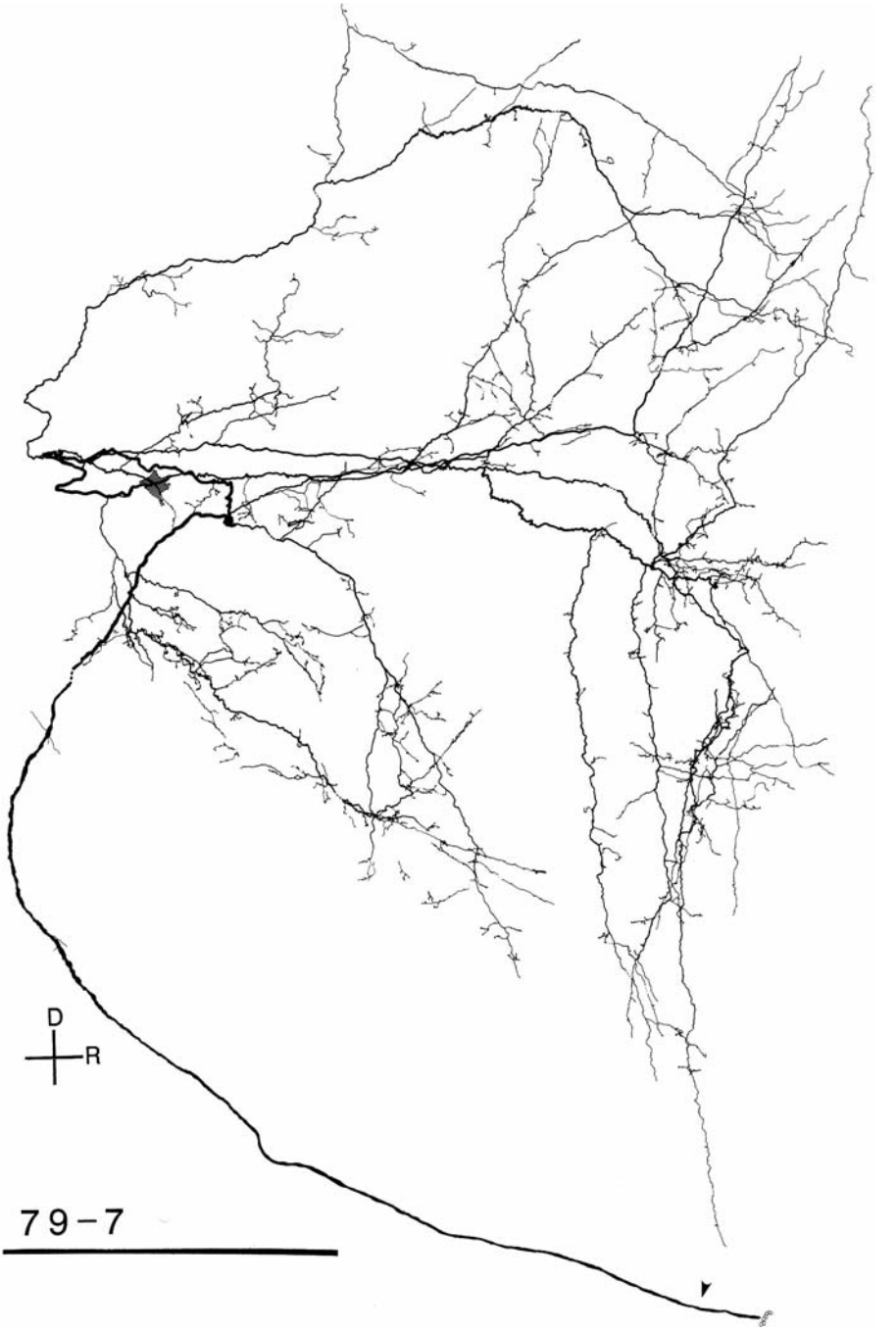

Figure 5.10. The axonal arborization of a cat CN neuron labeled by an intracellular injection of HRP in vivo. The neuron is shown in the sagittal plane, the cell body is *cross-hatched,* and the dendrites are omitted to reveal the axonal arbor. The main axon *(arrowhead)* courses laterally toward the brachium of the IC. This neuron's intrinsic axonal branches bear more than 2000 presumed synaptic boutons. The calibration bar represents 500 μm. (From Oliver et al. 1991. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

4.3. Distribution of Commissural Neurons

Early degeneration studies speculated that the commissural projections might originate throughout the IC (van Noort 1969), a possibility now confirmed. Large HRP injections that fill most of the IC-labeled neurons retrogradely in all contralateral IC subdivisions (Schweizer 1981; Ross et al. 1988; Fig. 5.11). Experiments with discrete injection of retrograde tracers invariably found retrogradely labeled neurons in contralateral IC areas that included, but were not necessarily restricted to, the area homotopic to the deposit. Moreover, all anterograde transport experiments label contralateral IC fibers, irrespective of the location of the ipsilateral IC injection (Kudo and Niimi 1980; Malmierca et al. 1995).

Although all IC regions are a source of commissural projections, commissural neurons are distributed nonuniformly. To label all cat CoIC neurons retrogradely, HRP was deposited into a cut made in the CoIC (Aitkin and Phillips 1984; Hutson et al. 1991) and commissural neurons were concentrated ventrolaterally at posterior levels, and more dorsally at anterior levels. A similar trend is found in the rat (Fig. 5.11).

5. The Function of Intracollicular Connections

The density of intracollicular connections could enable IC neurons to modulate the activity of other collicular neurons. Many IC neurons may receive lateral lemniscal information through local connections rather than through lemniscal synaptic input (Smith 1992; Wagner 1996; Moore et al. 1998; Reetz and Ehret 1999).

It seems unlikely that the CoIC is associated with some aspect of sound localization, as transecting the CoIC and/or the corpus callosum of trained cats had little or no effect on the animal's ability to localize a sound source (Moore et al. 1974). This result is consistent with results in the ferret after unilateral IC ablation (Kelly and Kavanagh 1994).

5.1. The Physiologic Role of Commissural Connections

The morphologic diversity of IC neurons with commissural projections suggests that they might be equally varied neurochemically and electrophysiologically, and the intrinsic and commissural projections of the IC may contain excitatory and inhibitory fibers (Saldaña and Merchán 1992). Preliminary immunoelectron microscopic results in the chinchilla suggested that the commissural axons are immunoreactive for γ-aminobutyric acid (GABA) and glutamate (Caspary and Helfert 1993). Later morphologic data disagree as to the neurochemical status of these projections. A combined tract tracing and the immunocytochemical approach found many double-labeled cells in the contralateral IC (González-Hernández et al. 1996). This is consistent with the presence of fibers immuno-

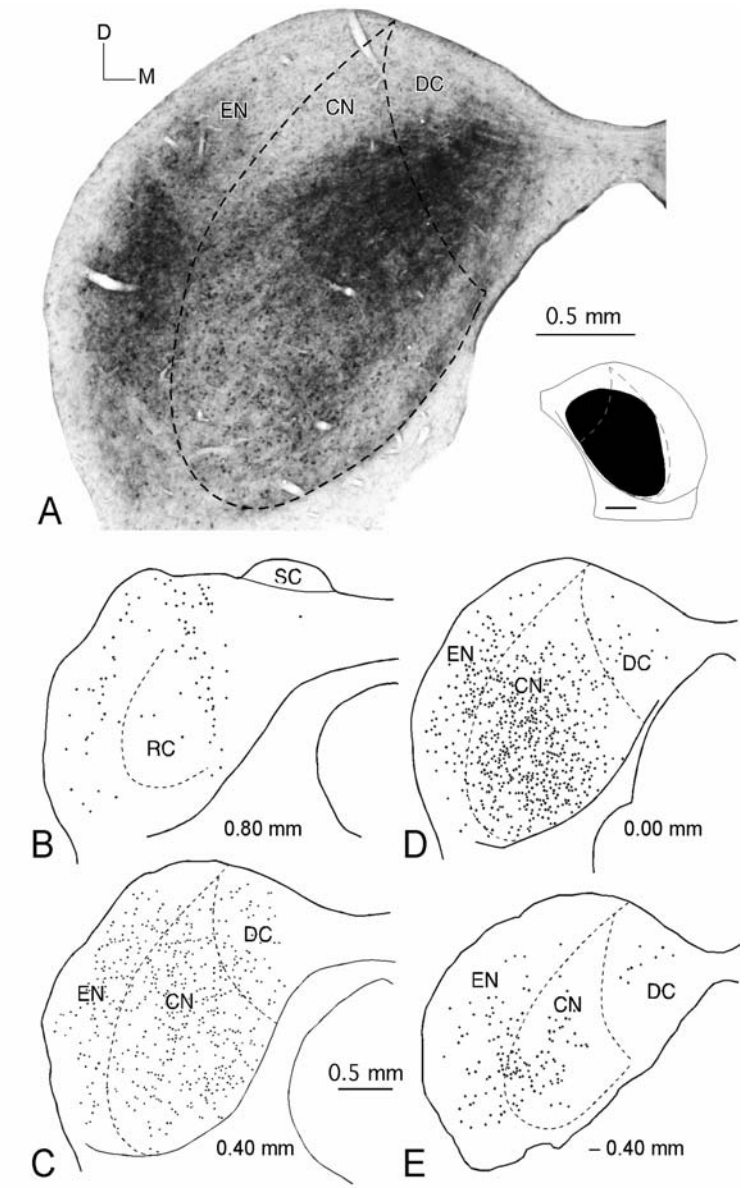

Figure. 5.11. Distribution of commissural neurons. *(Inset)* A BDA deposit *(black area)* spared only the lateral and dorsolateral CN and involved most of the DC. **(A)** A coronal section of the contralateral IC at the level of the injection site. Retrogradely labeled neurons are embedded in anterogradely labeled commissural fibers. **(B–E)** Commissural neurons in sections 400 μm apart. A *dot* represents one neuron; the position of each labeled cell body was noted. Drawing made at ×193 with a plan ×10 objective (numerical aperture 0.30).

reactive for glutamic acid decarboxylase, the synthesizing enzyme for GABA (Vetter and Mugnaini 1985). However, similar experiments combining retrograde transport of a fluorescent tracer and immunocytochemistry for GABA revealed no commissural double-labeled neurons, despite their abundance in the lateral lemniscal nuclei (Zhang et al. 1998).

Using a different approach, many chinchilla neurons are retrogradely labeled following deposits of D-[^{3}H]aspartate in the contralateral IC, which suggests that they are glutamatergic and that (at least some parts of) the commissural projections are excitatory (Saint Marie 1996). Some commissural neurons are immunopositive for enkephalin and neuropeptide Y (Nakagawa et al. 1995).

Support for a mixed excitatory–inhibitory commissural projection comes from electrophysiologic studies of living slices in vitro, which examined the effects on IC cells of electrical stimulation of the CoIC. DC neurons respond with an early inhibitory postsynaptic potential (IPSP) followed by a longer latency excitatory postsynaptic potential (EPSP); the pharmacologic evidence suggests that the IPSP reflects a direct, commissural GABAergic input, while the EPSP arises from direct, crossed input that activates non-*N*-methyl-D-aspartate-type (non-NMDA) glutamate receptors (Smith 1992). Similarly, most gerbil CN neurons receive both excitatory and inhibitory CoIC input, although GABAergic inhibition dominates (Moore et al. 1998). Furthermore, CoIC shock stimulation evokes short-latency PSPs in mouse IC, and these potentials may be excitatory or inhibitory (Reetz and Ehret 1999).

That the CoIC exerts both excitatory and inhibitory effects is corroborated by recent investigations in vivo. CN electrical stimulation and the injection of the glutamate-receptor agonist NMDA into CN both produced excitatory or inhibitory effects on the acoustically evoked activity of contralateral RC neurons, and this effect occurred in both normal and genetically epilepsy-prone rats (Chakravarty and Faingold 1997). These manipulations changed the neural discharge rate but did not affect sustained or onset discharge patterns. By the same token, silencing one IC reversibly by local microinjections of the glutamate receptor blocker kynurenic acid modified the spectral properties of contralateral IC neurons (Malmierca et al. 2003). In most neurons, blocking the contralateral IC increased the frequency response area to monaural (contralateral) or binaural stimulation, although decreased frequency response areas were also recorded (Fig. 5.12). One limitation of these in vivo studies is that they do not reveal if the neurons whose activity is modified by the contralateral IC manipulation receive direct commissural input or if other, interposed neurons are required. Moreover, IC stimulation or blockade alters the stream of information ascending to the cerebral cortex, and so may interfere with descending control of collicular activity.

5.2. Neocortical Control of Intracollicular Circuits

The corticofugal system modulates the sensitivity of IC neurons to sound frequency, amplitude, and duration (Suga and Ma 2003). For frequency selectivity,

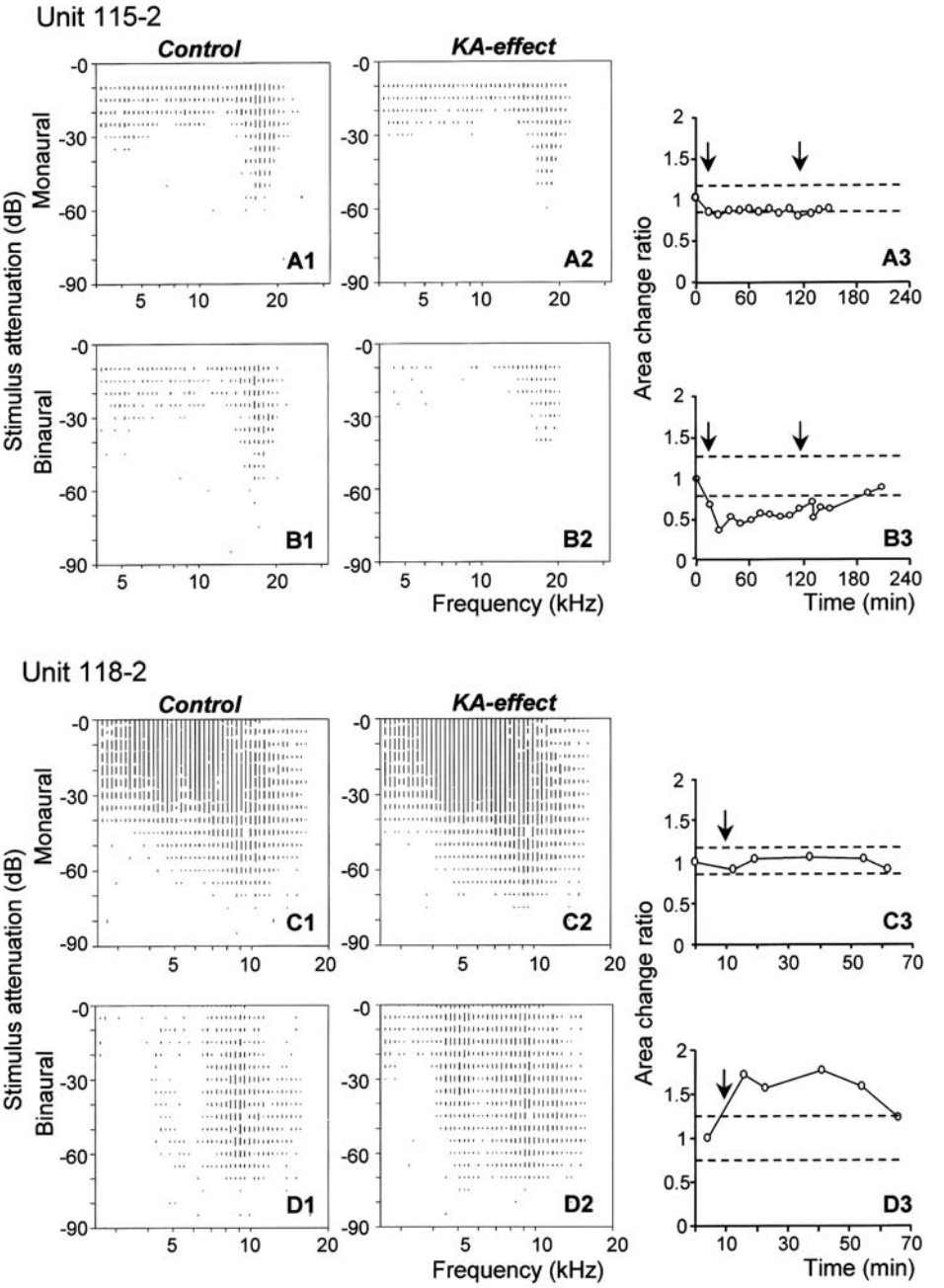

Figure. 5.12. Blocking reversibly the activity of one IC with kynurenic acid changes the frequency response area of commissural neurons. In unit 115-2 *(upper half),* the contralateral blockade reduced the frequency response areas elicited by monaural (A1–A3) and binaural stimulation (B1–B3). In unit 118-2 (lower half), blockade increased the frequency response areas for monaural (C1–C3) and binaural stimulation (D1–D3). (Reproduced from Malmierca et al. 2003.)

the auditory neocortical activity evokes both facilitation and inhibition of auditory responses. The amount of facilitation and inhibition varies as a function of the relationship in frequency tuning between neocortical and IC neurons. A neuron's response is augmented at its CF and inhibited at other frequencies (see Chapter 8). Corticocollicular and intracollicular projections are topographically (tonotopically) matched (Andersen et al. 1980b; Saldaña et al. 1996). Corticocollicular projections are excitatory (Feliciano and Potashner 1995), and intracollicular projections have both excitatory and inhibitory effects (see Section 5.1), so that the facilitation and inhibition of IC neurons produced by auditory cortex activation can be best explained in terms of interactions mediated by intracollicular connections governed by corticocollicular modulation.

6. Themes for Discussion

1. Different IC neurons receive their main inputs from different sources. How do the IC intrinsic and commissural connections relate to the origin of their inputs?
2. Available data on the commissural connections come from bulk transport experiments. What is the morphology and distribution of individual commissural axons?
3. Within the IC, different afferent projections terminate preferentially on different parts of the target neurons (cell body, proximal or distal dendrites). For example, some lateral lemniscal inputs provide a significant input to more proximal portions of IC neurons, including cell bodies, than do corticocollicular fibers. What part(s) of the neuron is/are targeted preferentially by intracollicular connections?
4. The EN receives topographic ascending as well as intracollicular and descending projections. Are the efferent projections of the EN topographically organized?
5. The EN is usually regarded as a center for multisensory integration. How do the nonauditory projections intersperse within the EN with the topographic projection from the CN and the DC?
6. The CN has been implicated in the genesis of audiogenic seizures and the EN/RC in the propagation of the epileptic crises. Does the CN-to-EN projection play a role in the physiopathology of these seizures?
7. Neurons within an IC isofrequency region differ in other physiologic parameters. The distribution of some of these parameters within the IC is orthogonal to the isofrequency planes of the nucleus (Schreiner and Langner 1988). Is there a relationship between the orderly pattern of intracollicular connections and the representation of parameters other than frequency?
8. What information is conveyed by commissural fibers? What is the biologic significance of the CoIC?

9. The results reviewed here suggest that the IC consists of concentric fibrocellular laminae that involve all collicular subdivisions. Principal (disc-shaped) neurons are likely integral elements of these CN laminae. What neurons form the cellular substrate of the fibrocellular laminae in the cortical subdivisions of the IC?
10. Are there comparative variations in the organization of intracollicular projections? Some big brown bat EN neurons are excited by corticocollicular fibers and inhibit CN neurons, which are facilitated by corticofugal input (Jen et al. 1998). However, the morphologic data suggest that, in the rat, the EN does not project significantly to the CN.

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Abbreviations

BDA	biotinylated dextran amine
BIC	brachium of the inferior colliculus
CN	central nucleus of the inferior colliculus
CoIC	commissure of the inferior colliculus
DC	dorsal cortex of the inferior colliculus
EN	external nucleus of the inferior colliculus
EPSP	excitatory postsynaptic potential
GABA	γ-aminobutyric acid
GAD	glutamic acid decarboxylase
HRP	horseradish peroxidase
IC	inferior colliculus
IPSP	inhibitory postsynaptic potential
LSO	lateral superior olive
MNTB	medial nucleus of the trapezoid body
NMDA	*N*-methyl-D-aspartate
PHA-L	*Phaseolus vulgaris*-leucoagglutinin
RC	rostral cortex of the inferior colliculus
SC	superior colliculus
SPON	superior paraolivary nucleus
Te1	primary auditory area of rat cerebral cortex

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Chapter 6
Descending Connections of the Auditory Midbrain

Ann M. Thompson

1. Introduction

The inferior colliculus (IC) integrates acoustic information from many auditory nuclei and relays the processed information to higher centers. In addition, the IC is the source of robust projections to lower auditory nuclei, as well as to a number of nonauditory brain regions. Identification of these subcollicular targets and the behavioral effects of manipulating the IC have implicated the IC in modulating certain ascending and descending auditory pathways as well as premotor centers. However, the functional impact of the descending IC pathways remain poorly understood. The following overview presents some of the descending IC projections within a functional context.

This chapter begins with descriptions of the IC projections to lower auditory nuclei and the functional auditory circuits that are likely recipients of these projections. Then, the nonauditory brain stem centers that receive direct and indirect projections of the IC are described. The potential IC inputs to brain circuits mediating various behaviors are also discussed. It should be noted that the pathways presented have been described mostly in the rat, but also in a few other mammalian species. For clarity, a generalized mammalian scheme is presented but species differences likely exist. Further, some projections have been found only in species with specialized hearing, for example, bats and owls (see Chapter 17), and these potentially unique projections are noted where appropriate.

2. Primary Auditory Targets

2.1. Nuclei of the Lateral Lemniscus

Axons of IC neurons exit the midbrain ventrolaterally and enter the ipsilateral lateral lemniscus (LL). As the fibers descend in the LL, many terminate in the dorsal nucleus (DNLL) (Caicedo and Herbert 1993; Thompson and Thompson 1993; Wenstrup et al. 1994; Malmierca et al. 1996). As the fibers continue to

descend, minor terminations are made in the intermediate (INLL) and then in the ventral nucleus of the lateral lemniscus (VNLL) (Thompson and Thompson 1993; Malmierca et al. 1996). The part of the IC giving rise to the projection to the ipsilateral nuclei of the lateral lemniscus is the central nucleus (ICc; Fig. 6.1B; Caicedo and Herbert 1993; Malmierca et al. 1996). On the contralateral side, the only IC projection is a minor one to the VNLL arising from the ICc or the dorsal cortex (ICd) (Thompson and Thompson 1993).

Among the projections to LL nuclei, those to the DNLL predominate. The DNLL projects to the central nucleus of the IC bilaterally (see Chapter 2); many

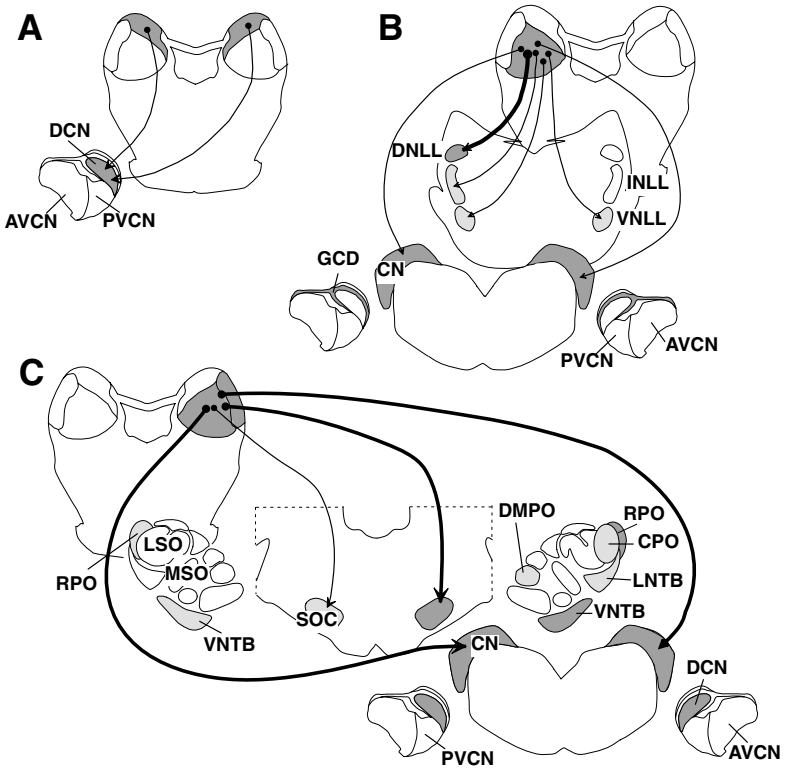

Figure 6.1. Descending IC auditory projections. The predominant targets are indicated by *thicker arrows* and *darker shading;* see the text for details. **(A)** The dorsal cortex of the IC *(gray)* projects to the DCN bilaterally. **(B)** The main target of the central nucleus is the ipsilateral DNLL and secondarily the GCD of the DCN. **(C)** The central and lateral IC nuclei project to the SOC and the CN. The major SOC target is the ipsilateral VNTB and the RPO. Minor periolivary targets are the ipsilateral CPO, the LNTB, the DMPO, and the contralateral rostral periolivary region (RPO) and the ventral nucleus of the trapezoid body (VNTB). Within the CN, the DCN is the main target of the ICc and ICl. The projection is bilateral.

of its cells use γ-aminobutyric acid (GABA) as a transmitter and help to shape the responses of IC neurons (Ehret 1997). It is also notable that the projection to the DNLL is the only projection to LL nuclei that is tonotopic (Caicedo and Herbert 1993; Malmierca et al. 1996).

Descending IC fibers also target neuronal cell groups situated near the LL nuclei. One such cell group, the sagulum, lies lateral to the DNLL. IC axons enter the sagulum near the beginning of their descent in the LL. The IC areas projecting to the sagulum include the lateral nucleus (ICl), ICd, and ICc (Caicedo and Herbert 1993; Malmierca et al. 1996; Beneyto et al. 1998). Although the ipsilateral projection predominates, the ICd and/or the ICc also project to the contralateral sagulum. Descending IC axons also terminate in the horizontal cell group located ventral to the dorsal nucleus of the lateral lemniscus as described in the rat (Caicedo and Herbert 1993). Other IC axon collaterals terminate in ipsilateral perilemniscal regions, for example, within the LL but outside its primary nuclei. The source of the perilemniscal projections is the ICc and/or the ICd (Caicedo and Herbert 1993; Thompson and Thompson 1993).

2.2. *Superior Olivary Complex Inputs and Connections with the Olivocochlear System*

Some IC fibers descending in the LL enter the trapezoid body and terminate in the superior olivary complex (SOC). Not all of the SOC nuclei receive IC input; the IC projects predominantly to the periolivary regions with little or no input to the principal nuclei (Fig. 6.1C). On entering the rostral part of the SOC, IC fibers terminate in the rostral periolivary region (RPO) (Caicedo and Herbert 1993; Thompson and Thompson 1993; Malmierca et al. 1996; Schofield and Cant 1999). Many other fibers travel ventrally to enter and terminate in the ventral nucleus of the trapezoid body (VNTB) (Thompson and Thompson 1993; Vetter et al. 1993; Malmierca et al. 1996; Schofield and Cant 1999). Some fibers end in the lateral nucleus of the trapezoid body and the caudal periolivary region (Caicedo and Herbert 1993; Thompson and Thompson 1993). Other fibers maintain their dorsal position in the trapezoid body and terminate in the dorsomedial periolivary region (superior paraolivary nucleus of rodent; Thompson and Thompson 1993; Schofield and Cant 1999). Although not often observed and comparatively sparse, IC projections to the margins of the lateral superior olive (LSO), the LSO itself (Thompson and Thompson 1993), and the medial nucleus of the trapezoid body (Carey and Webster 1971) have been noted. The several origins of the descending IC pathway to the SOC include the ICl (especially layer 3) and ICc nuclei (Caicedo and Herbert 1993; Malmierca et al. 1996). These descending IC cells are glutamatergic and likely have an excitatory influence on SOC target neurons (Saint Marie 1996).

Two periolivary regions, the VNTB and the RPO, also receive input from the contralateral IC (Malmierca et al. 1996; Schofield and Cant 1999). The axons cross the midline in the ventral part of the trapezoid body. The contralateral projections are sparser than the ipsilateral projections.

The periolivary regions, where most IC axons terminate, contain the efferent (centrifugal) neurons of the medial olivocochlear system (MOC) (Warr 1992). MOC neurons project to the cochlea where they innervate outer hair cells (OHCs). The terminal endings of descending IC neurons make synaptic contacts with MOC neurons (Vetter et al. 1992; Thompson and Thompson 1993). This indicates that, by its descending projections to the SOC, the IC may influence cochlear function mediated by MOC neurons and OHCs. This is further supported by neurophysiologic studies indicating that the IC, by exciting MOC neurons, influences OHC responses (Scates et al. 1999; Braun 2000; Mulders and Robertson 2000, 2002). Because the IC projection to the SOC is mainly ipsilateral, and because most MOC neurons project to the contralateral cochlea, the IC likely influences the cochlea of the opposite ear (Fig. 6.2). The IC receives most of its direct ascending auditory input from the contralateral side and, therefore, this can be considered a feedback pathway. In addition, MOC neurons send collaterals to the cochlear nucleus (CN), allowing for IC modulation of these neurons.

Periolivary regions also contain olivocochlear nucleus neurons (OCNs) that project to the CN complex. Olivocochlear nucleus neurons are a specific target of the descending IC system (Schofield and Cant 1999). Olivocochlear nucleus neurons that receive IC inputs project bilaterally and hence form a route by which the IC may modulate the ascending auditory pathway simultaneously and bilaterally at the level of the cochlear nuclear complex (Fig. 6.2). The effect may be excitatory if glutamate is the neurotransmitter of this pathway and the synaptic targets of these cells are themselves excitatory.

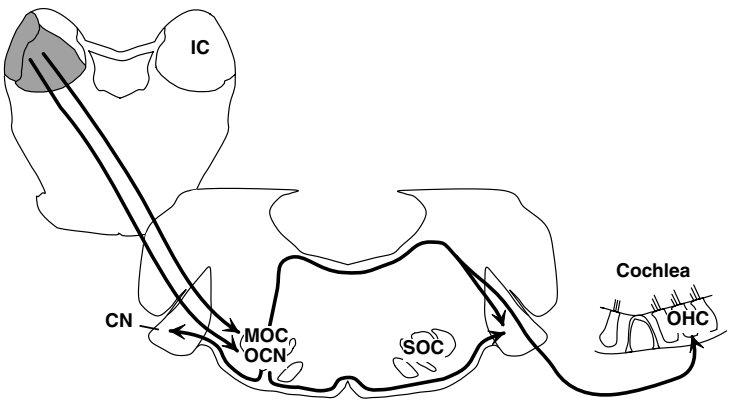

Figure 6.2. Descending IC projections to the centrifugal auditory pathways innervating the CN and cochlea. The MOCs near the SOC are the main target. MOCs project to the cochlea bilaterally, mainly contralaterally, and terminate on outer hair cells (OHCs). Via its projections to MOCs, the IC may modulate cochlear processing. The IC also projects to olivocochlear nucleus (OCN) neurons in the SOC that, in turn, project to the CN. It is unknown whether IC projections to the CN reach cells that themselves project to the IC.

2.3. Inputs to Extrinsic and Intrinsic Circuits of the Cochlear Nucleus Complex

Of the descending IC projections, the one to the CN complex has been the most studied. Descending IC axons enter the CN complex via the LL and then the trapezoid body. As the fibers reach the ventral CN within the trapezoid body, they turn dorsally, between the descending trigeminal nerve root and the anteroventral cochlear nucleus (AVCN), to enter the dorsal cochlear nucleus (DCN). Among the main cochlear nuclear complex subdivisions, the DCN is the major target of descending IC fibers (Fig. 6.1A, C; Vater and Feng 1990; Saint Marie 1996; Schofield 2001). The projection to the DCN is bilateral, with a slight ipsilateral preponderance (Kane and Conlee 1979; Caicedo and Herbert 1993; Schofield 2001). At least one component of the IC pathway to the DCN is GABAergic (Alibardi 2002).

Within the ipsilateral DCN, most IC axons terminate in the fusiform cell layer and deeper layers (Kane and Conlee 1979; Conlee and Kane 1982; Shore et al. 1991; Malmierca et al. 1996). In the ipsilateral fusiform cell layer, IC terminal endings are associated with granule cell dendrites and these terminals have small, round vesicles and short, asymmetric densities (type 1a glomerular endings; Kane 1977). Besides those scattered throughout the DCN, granule cells within the granule cell domain (GCD) may also receive IC input (Malmierca et al. 1996; Shore and Moore 1998). The IC projection to the GCD is bilateral. The small cell cap, adjacent to the GCD, may also receive IC input (Malmierca et al. 1996).

Through its terminations onto the dendrites of granule cells in the fusiform cell layer and input to the granule cell domain, the IC influences the intrinsic circuitry of the CN complex (Fig. 6.3). The cochlear nucleus intrinsic circuits are comprised of a number of cell types, including granule cells (see Chapter 1). Granule cells are remarkable as they receive a wide variety of inputs from within the auditory system (including auditory cortex, type II auditory nerve fibers, medial olivocochlear efferents), and also from the vestibular and somatosensory systems (Wright and Ryugo 1996), the pontine gray (Ohlrogge et al. 2001), and the brain stem serotonergic system (Hurley and Thompson 2001). Therefore, the descending IC pathway to granule cells is but one part of an intricate, multimodal circuit that likely has a role in modulating the responses of CN neurons.

The IC also provides inputs to giant cells and the dendrites of fusiform cells situated in the deeper layers of the DCN (Kane 1977). The ipsilateral IC projects to the innermost part of the molecular layer where the axons terminate onto the fusiform cell apical dendrites (Kane and Conlee 1979; Shore et al. 1991; Malmierca et al. 1996). Both fusiform and giant cells are principal neurons of the DCN and project to the contralateral IC (see Chapter 3). Therefore, by its descending inputs to fusiform and giant cells, the IC can influence the ascending auditory pathway that originates in the DCN. Moreover, because the granule cells project directly and indirectly (via cartwheel cells) to fusiform cells (Young

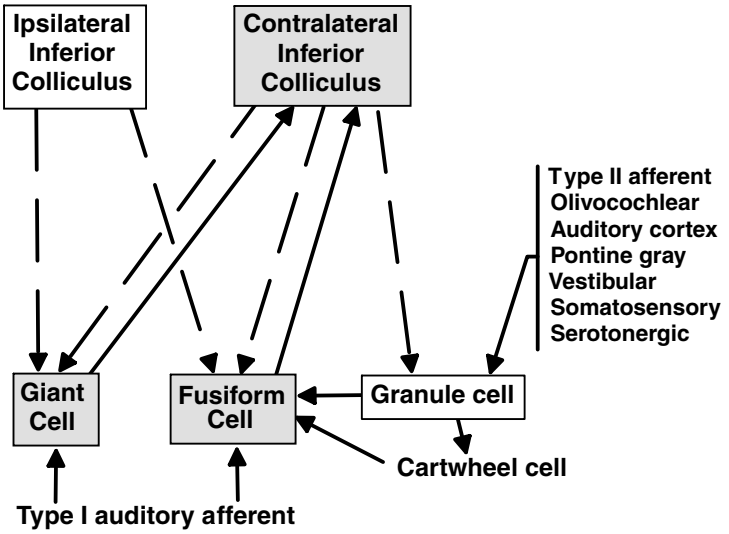

Figure 6.3. Interaction of descending connections with ascending and intrinsic CN circuits. The DCN is a major auditory target of the IC. Both the ipsilateral and contralateral IC provide input to giant and fusiform cells *(dashed arrows),* both of which receive direct input from the cochlear type I auditory afferents and send monosynaptic input to the contralateral IC *(solid arrows).* The IC also projects to an intrinsic cochlear nucleus circuit through the ipsilateral GCD, and to the fusiform cell layer where other granule cells are found. Granule cells receive many acoustic and nonacoustic inputs and project directly and indirectly (via cartwheel cells) to fusiform cells, possibly propagating IC influences to the ascending CN output via the fusiform cell. Although the function of fusiform cells is not fully understood, they may be involved in vertical sound localization.

and Davis 2002), granule cells may be an indirect route for the IC to influence the ascending output of the DCN.

ICc and ICd neurons are the primary source of the descending projections to the CN complex (Caicedo and Herbert 1993; Schofield 2001). Some cell-specific pathways have been identified. Giant neurons in the deep DCN receive input from ipsilateral ICc neurons (Conlee and Kane 1982; Shore et al. 1991). The ICc is also the source of input to the granule cell domain (predominantly ipsilaterally; Shore and Moore 1998). The ICd projects to the CN complex bilaterally (Ostapoff et al. 1990; Schofield 2001). Some of the projections arise solely from the ICd whereas others terminate solely in the DCN (Fig. 6.1A). The CN granule cell domain receives only ICc input (Fig. 6.1B).

The types of IC neurons that are the source of descending projections to the CN complex have also been identified in the guinea pig. The projections originate from multipolar (stellate) cells in the ICc and ICl, from disc-shaped ICc neurons (Schofield 2001), and multipolar neurons residing mostly in ICd layers 2 and 3.

The projections from the ICc to the DCN are topographic and/or tonotopic in rodents and carnivores (Kane and Conlee 1979; Saldaña et al. 1989; Caicedo and Herbert 1993; Malmierca et al. 1996). Unlike those arising from the ICc, the ICl (external cortex) projections terminating in the CN complex are diffuse, and probably not tonotopic (Caicedo and Herbert 1993). These descending inputs to the DCN likely modulate fusiform cells to enhance vertical sound localization (Fujino and Oertel 2003).

The projections to the contralateral DCN are independent of those to the ipsilateral side (Schofield 2001). Electron microscopic evidence supports the independence of the contralateral projection because, unlike those on the ipsilateral side, the majority of IC synapses in the contralateral fusiform cell layer appear to be axodendritic (type 5a) and to terminate on fusiform cells (Kane 1977).

There is little evidence that the IC projects to the ventral cochlear nucleus (VCN). Interpretation of some anatomical findings is problematic because collicular axons traverse the VCN en route to the DCN. The IC has a sparse projection bilaterally to the most anterior part of the octopus cell area in the posteroventral cochlear nucleus (PVCN) (Kane and Conlee 1979). Other results (Caicedo and Herbert 1993; Saint Marie 1996) indicate a sparse projection (at least from the ICc and/or ICl) to the AVCN and PVCN.

3. Projections to Motor Pathways and Structures Involved in Orientation Behaviors

3.1. The Superior Colliculus and Pinna Movements

Various lines of evidence indicate that the IC controls pinna movements. The IC does not project directly to the facial (VII) motor nucleus (FMN), which innervates the pinna muscles, but there are several indirect routes whereby the IC could influence these muscles. The predominant route for such influence is through the ipsilateral deep superior colliculus (SC) (Fig. 6.4).

The deep SC receives convergent visual, auditory, and somatosensory input and it is involved in the control of orienting movements of the head, eyes, and pinnae in response to stimuli from different modalities (Irvine 1992; Oliver and Huerta 1992). IC fibers enter the brachium of the SC and terminate in the deep layers (Frisina et al. 1989; Appell and Behan 1990; Jiang et al. 1997). The IC source of most projections to the deep SC is the ICl (Covey et al. 1987; Thiele et al. 1996; King et al. 1998). The SC also receives sparse inputs from the ICc, in particular the dorsomedial part (Covey et al. 1987; Zhang et al. 1987; Frisina et al. 1997). A major source of input to the deep SC may be the rostral pole (rostral nucleus) of the IC (Harting and Van Lieshout 2000).

The IC also projects to deep layers of the contralateral caudal SC (Appell and Behan 1990). These crossed projections are sparser than the ipsilateral projections. The IC inputs to the contralateral deep SC originate from the ICc

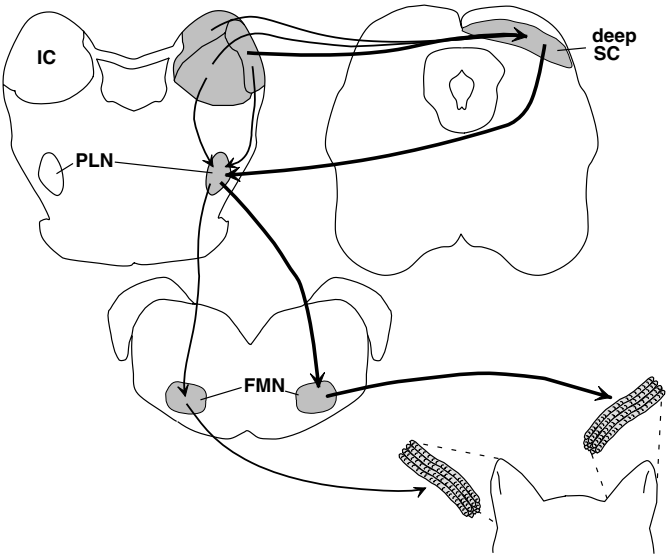

Figure 6.4. IC inputs to premotor centers involved in pinna movements. The paralemniscal zone *(PLN)* is the premotor center for pinna movements and it projects to the facial motor nuclei *(FMN)* to innervate pinna muscles. The IC influence on pinna movements involves the superior colliculus. All three IC regions project to the deep SC with the lateral nucleus projection the heaviest. The deep SC, in turn, projects to the PLN ipsilaterally. The PLN projects predominantly to the ipsilateral FMN. A smaller projection from the central and lateral nuclei of the IC to the ipsilateral PLN may be an alternate route to the FMN.

(ventromedial part) and ICl subdivisions in several species (Covey et al. 1987; Zhang et al. 1987; Jiang et al. 1997; King et al. 1998). The projections from the IC to the deep SC may be glutamatergic and thus excitatory (Saint Marie 1996).

From the deep SC, the indirect IC pathway to FMN continues to the ipsilateral lateral paralemniscal zone (PLN) (Stein et al. 1984; Metzner 1996). The PLN, in turn, projects to the contralateral FMN (Fig. 6.4; Henkel and Edwards 1978; May et al. 1990; Takeuchi et al. 1993; Chen et al. 1995; Schuller et al. 1997).

The IC itself projects to the PLN. As described in cat, the PLN extends from the retrorubral nucleus (associated with the substantia nigra) to the VNLL (Henkel 1981; Herbert et al. 1997). The cat PLN receives input from the ICl ipsilaterally (Henkel 1981). A PLN has been defined in the horseshoe bat that is rostral and medial to the DNLL and INLL and it may receive input from the ipsilateral ICc (Metzner 1993, 1996).

It is also possible that IC inputs are relayed to pinna muscles via descending projections to other targets. Some lower IC targets project to the PLN and/or the FMN directly. For example, both the FMN (Hinrichsen and Watson

1983) and PLN (Takeuchi et al. 1993) receive projections from the periaqueductal gray. Other IC targets that project to the PLN are the sagulum and the dorsomedial periolivary nucleus of the SOC (Henkel 1981). Deep layers of the SC also project to the contralateral FMN (Hattox et al. 2002).

3.2. Premotor/Motor Circuits and the Acoustic Startle Response

The acoustic startle response is characterized by the coordinated contraction of many craniofacial and skeletomotor muscle groups in response to a loud, brief sound. Sounds initiating the response enter the acoustic startle system via cochlear root neurons (CRNs). CRNs are found in the CN complex and they project to the ventrocaudal pontine reticular formation (VPRF) (Fig. 6.5; Lee et al. 1996; Nodal and López 2003). CRNs are not the only input to the VPRF; the latter

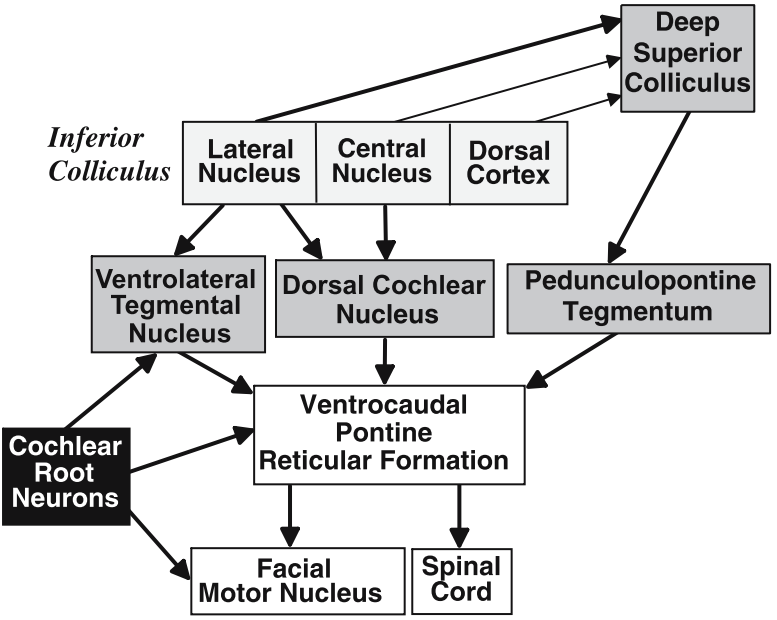

Figure 6.5. Connections within acoustic startle reflex pathways. The IC is one of two auditory centers providing acoustic input to a premotor center, the ventrocaudal pontine reticular formation, involved in the acoustic startle reflex. Cochlear root neurons provide for the rapid reflex component. Unlike the direct input of cochlear root neurons, the path of IC neurons to the ventrocaudal pontine reticular formation is indirect and involves three routes: these are via the ventrolateral tegmental nucleus, the dorsal cochlear nucleus, and the pedunculopontine tegmentum (via the deep superior colliculus). Each receives input primarily from the lateral and central IC nuclei. Each IC target projects to the ventrocaudal pontine reticular formation, the premotor center providing input to the spinal cord and facial motor nucleus, the brain stem hubs for the startle response.

receives many types and sources of input that could modulate this reflex. As an essential premotor center of the startle reflex, the VPRF integrates the information it receives and redistributes it to motoneurons in both the FMN and spinal cord, which control the muscles involved in the reflex.

Several studies have shown that the IC has a role in modulating the startle reflex (Leuman et al. 2001; Swerdlow et al. 2001; Yeomans et al. 2002). Like the FMN, spinal cord motor centers do not receive direct input from the IC. The FMN and the spinal cord probably receive input from the IC indirectly via the VPRF. The IC projections to the VPRF also may be indirect and may be relayed through at least three brain regions, including the ventrolateral tegmental nucleus, the pedunculopontine tegmental nucleus, and the DCN (Fig. 6.5). The ventrolateral tegmental nucleus is medial to the LL at the level of the VNLL and anterior to the rostral periolivary region of the SOC (Kandler and Herbert 1991). Neurons in the ICl project to the ventrolateral tegmental nucleus. The DCN is also a candidate as it receives descending IC input (as described earlier), and it projects to the VPRF. The third potential route is a bit more indirect, traveling through the deep SC and then to the pedunculopontine tegmentum.

Besides the anatomical evidence, behavioral data confirm the role of the IC and these three relay stations in the acoustic startle (Leuman et al. 2001; Swerdlow et al. 2001; Yeomans et al. 2002). Through one or more of these pathways, the IC may be involved in suppressing the acoustic startle response. In addition, the IC may modulate the startle response via its projections to the pontocerebellar pathway (Kandler and Herbert 1991). Finally, the IC may serve as a gating mechanism to coordinate the startle response with descending input from higher brain centers (see Chapter 8).

3.3. Inputs to Pontine Nuclei and the Coordination of Responses to Sound

Some IC axons descend in the ipsilateral LL to enter the pontine gray. These are probably independent of axons that enter the SOC and that target auditory nuclei (Schuller et al. 1991). In the ipsilateral pontine gray, specific IC targets include the lateral, dorsolateral, and ventrolateral nuclei in several species (Mower et al. 1979; Burne et al. 1981; Aas 1989; Frisina et al. 1989; Wenstrup et al. 1994). Although the primary source of the IC projections to the pontine nuclei is the ICc, the ICl and ICd also contribute (Frisina et al. 1989; Schuller et al. 1991; Caicedo and Herbert 1993). The IC projection to the ipsilateral dorsolateral pontine nuclei is glutamatergic (Saint Marie 1996). In the mustached bat, the projections from the ICc to the ipsilateral dorsolateral and lateral pontine nuclei are topographic (Wenstrup et al. 1994).

Through its descending projections to the pontine gray, the IC (principally the ipsilateral central nucleus but also ICl) forms part of the pontocerebellar auditory pathway. Other auditory inputs to the pontine gray originate in belt

areas of the auditory cortex (Schuller et al. 1991) and the AVCN and PVCN (Kandler and Herbert 1991; Thompson 1998). It is thought that, in the cerebellum, sensory information is coordinated with motor feedback from the eyes, head, and body to control their movements (Schuller et al. 1991). Therefore, the pontine nuclei are believed to be the route by which the auditory system projects to the cerebellum to enable coordinated responses to sound.

It has also been hypothesized that, through its projections to the deep SC, the IC plays a role in sound orientation (Olazábal and Moore 1989). Neurons from the anterodorsal IC, in particular, may be involved. Interestingly, both the deep SC and this region of the IC receive input from the substantia nigra, which is presumed to have a modulatory role in orienting movements to visual and auditory stimuli.

4. Projections to the Periaqueductal Gray and Vocalization

There is also evidence that the IC projects to the periaqueductal or central gray (PAG) (Schweizer 1981). The origin of this projection is the ICc bilaterally (Frisina et al. 1989). The dorsomedial ICc is a prominent source of input (Frisina et al. 1997). The ICc projection does not appear to terminate throughout the entire PAG, as the ipsilateral IC projections are restricted to its dorsolateral part. The neurons that project ipsilaterally may also project to the contralateral IC via collaterals that leave the main IC axons before they enter the commissure (Kudo and Niimi 1980).

It has been suggested that the direct IC projections to the PAG have a role in modulating vocalizations (Jürgens 2002). The PAG enables vocalizations through its projections to the nucleus retroambiguus, which projects to abdominal muscle motoneurons that increase abdominal pressure, and to nucleus ambiguus motor neurons that innervate the soft palate, pharynx, and larynx. It is hypothesized that the IC influences vocalizations implicated in communication and echolocation calls in certain bats (Casseday and Covey 1996; Fenzl and Schuller 2002).

There are also indirect routes by which the IC may affect vocalizations. One such potential route is via the deep SC, which projects to the nucleus ambiguus (Metzner 1996). Another indirect route is via the PLN, which also projects to the nucleus ambiguus (Metzner 1996). The reticular formation and the nucleus of the brachium of the IC may also contribute to the vocalization circuits (Pieper and Jürgens 2003).

5. Projections to Structures Involved in Emotive Behaviors

The amygdala processes many types of aversive inputs and has been considered as a critical nexus for decision-making related to aversion (Brandão et al. 2003). The IC may affect input to the amygdala via its connections with the deep SC

and the dorsal PAG (Casseday et al. 2002), although the IC does not project directly to the amygdala. The likely IC source of the polysynaptic projections that ultimately reach the amygdala is the ICc (Pandossio and Brandão 1999). Therefore, the ICc, via its projections to the deep SC and the dorsal PAG, could influence the cascade of responses to aversive stimuli. Another potential route is from IC structures other than the ICc and that terminate in parts of the dorsal and medial divisions of the medial geniculate body (MGB) (Calford and Aitkin 1983; Wenstrup et al. 1994), which project in turn to the amygdala (Shinonaga et al. 1994).

6. Inputs to the Paragigantocellular Nucleus and Arousal

Another set of descending IC projections end in caudal areas of the ipsilateral pontine reticular formation. These target the rostral part of the paragigantocellular nucleus, which is medial to the FMN (juxtafacial), and the gigantocellular reticular nucleus (Andrezik et al. 1981; Van Bockstaele et al. 1989; Caicedo and Herbert 1993). The IC inputs to the paragigantocellular nucleus arise from the ICc, ICd, and ICl (Caicedo and Herbert 1993; Van Bockstaele et al. 1993), whereas the projections to the gigantocellular reticular nucleus are more restricted, originating only from ICl.

The rostral paragigantocellular nucleus itself receives projections from many brain systems including somatic sensory, autonomic, and auditory systems (Van Bockstaele et al. 1993). Auditory input to it may be from the IC directly or from the IC indirectly via the PLN. The IC, perhaps with the PLN, may thus provide auditory input to the rostral paragigantocellular nucleus, where it is integrated with other sensory input. The integrated sensory information is likely then relayed to the locus coeruleus, a critical center for coordinating arousal (Berridge and Waterhouse 2003).

7. Conclusions

This review summarizes several monosynaptic and multisynaptic descending projections of the IC to the brain stem. Within the ascending auditory system, the IC targets the DCN and the DNLL. Most of the projections to these nuclei originate in the ICc, activate inhibitory neurons, and are arranged tonotopically and/or topographically. Both the DNLL and the DCN project to the IC. Therefore, these two descending IC pathways form a reciprocal circuit that could enhance auditory signal processing necessary for sound localization and speech processing. The descending IC pathway to the SOC feeds into the olivocochlear system and thus could modulate cochlear function.

Among other targets of descending IC pathways, the most notable is the deep SC. It is an integral component of the descending IC input to various targets.

This is likely the route by which the IC influences reflexive and other motor behaviors including pinna movements, acoustic startle reflexes, responses to aversive stimuli, and vocalizations.

The IC is also probably involved in modulating proprioceptive adjustments to sound by its descending projections to the cerebellum, via the pontine nuclei. This permits auditory access to many brain stem and spinal pathways that affect muscle tone and the initiation of movement. The IC also likely contributes to global arousal by forwarding acoustic information, albeit indirect, to a major arousal center, the locus coeruleus.

In conclusion, the descending IC connections may serve many roles, including auditory processing. They provide key information to various brain regions necessary for survival. The functions of the descending IC pathways should also be considered in context with the incoming projections from the forebrain (see Chapter 8). This circuitry connects the IC with higher and lower parts of the central nervous system (Huffman and Henson 1990). The IC serves an important role in gating information from higher to lower centers of the brain (Ehret 1997). More studies are necessary to delineate further the function of the descending IC system. In particular, the components and connections of the brain circuits necessary for survival and that rely on the descending IC pathways for acoustic information compel further investigation.

Abbreviations

AVCN	anteroventral cochlear nucleus
CN	cochlear nucleus
CPO	caudal periolivary region
CRN	cochlear root neuron
DCN	dorsal cochlear nucleus
DMPO	dorsomedial periolivary nucleus
DNLL	dorsal nucleus of the lateral lemniscus
FMN	facial motor nucleus
GCD	granule cell domain
INLL	intermediate nucleus of the lateral lemniscus
LNTB	lateral nucleus of the trapezoid body
LSO	lateral superior olive
MGB	medial geniculate body
MOC	medial olivocochlear system
MSO	medial superior olive
OCN	olivocochlear nucleus neuron
OHC	outer hair cells
PAG	periaqueductal gray
PLN	paralemniscal zone
PVCN	posteroventral cochlear nucleus
RPO	rostral periolivary region
SC	superior colliculus

SOC	superior olivary complex
VNLL	ventral nucleus of the lateral lemniscus
VNTB	ventral nucleus of the trapezoid body
VPRF	ventrocaudal pontine reticular formation

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Chapter 7
The Tectothalamic System

JEFFREY J. WENSTRUP

1. INTRODUCTION

As the midbrain auditory center, the inferior colliculus (IC) integrates ascending auditory brain stem projections with descending projections from the auditory cortex, aminergic inputs, and, in some species, limbic projections. Although physiologic properties of IC neurons clearly reflect their inputs, many neurons display novel responses arising by integration of these inputs. The IC then projects to the auditory thalamus, to lower auditory nuclei, and to nuclei at the sensorimotor interface. This chapter focuses on the projection of the IC to the medial geniculate body (MGB), its main target.

Like the IC, the MGB integrates input from multiple ascending and descending sources, but these are more restricted. Its major input is from the IC but it also receives auditory brain stem input and nonauditory input. Its principal output is to auditory cortical areas, while other significant targets include the amygdala and the frontal cortex.

Representations of acoustic signals differ among MGB subdivisions. This chapter considers the IC contribution to subdivisional differences. Are these a function of different ascending inputs, or the different operations each subdivision performs? How does the organization of acoustic responses differ between the IC and the MGB? For information on MGB structure and function, please see reviews (Clarey et al. 1992; Winer 1992; Wenstrup 1995; de Ribaupierre 1997).

2. PROJECTIONS OF THE INFERIOR COLLICULUS TO THE MGB

2.1. ORGANIZATION OF THE TECTOTHALAMIC PROJECTION

The MGB contains dorsal (D), ventral (V), and medial (M) divisions (Fig. 7.1). V is the MGB component of the ascending lemniscal pathway. Its connections relate it to the central nucleus of the IC (CN) and primary auditory cortex (AI).

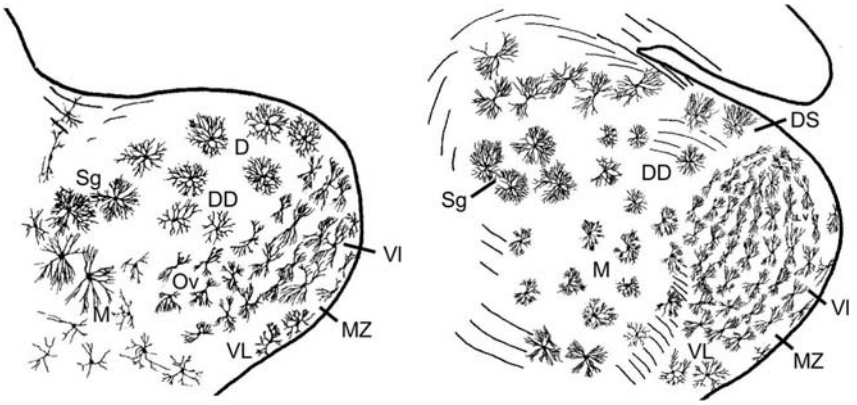

Figure 7.1. Neuronal architecture of MGB in cat, based on Golgi-impregnated neurons. The section at left is more caudal. *D,* Dorsal nucleus; *DD,* deep dorsal nucleus; *DS,* superficial dorsal nucleus; *M,* medial division; *MZ,* marginal zone; *Ov,* ovoid part of the ventral division; *Sg,* suprageniculate nucleus; *VL,* ventrolateral nucleus of the dorsal division; *Vl,* lateral part of the ventral division. (Adapted from Morest 1964.)

Physiologically, its cells have robust, short-latency auditory responses with sharp frequency tuning. The dorsal division contains, at minimum, dorsal (D), deep dorsal (DD), superficial dorsal (DS), ventrolateral (VL), and suprageniculate (Sg) nuclei. D nuclei have diverse inputs, outputs, and functional properties, and show major species variations. They receive most input from regions outside the CN and project to secondary auditory cortical areas. Sg and the rostral dorsal nucleus also project to the amygdala, mediating emotional responses to auditory stimuli. Auditory responses in D are typically weaker, more broadly tuned, and more plastic than in V, but the diversity and species variability also distinguish it. M, rarely subdivided, receives input from the lateral (La) or external nucleus of the IC and brain stem auditory nuclei. It projects widely to the auditory cortex and the amygdala. Auditory responses in M, again relative to V, usually have longer latency and broader frequency tuning.

The IC projection to MGB is complex (Fig. 7.2). Restricted tracer deposits in mustached bat CN show projections to four or more MGB subdivisions, including V, M, and at least two D nuclei (Wenstrup and Grose 1995). Across species, the IC projects to each MGB subdivision, but the projections of IC subdivisions differ. The CN projects most strongly to V, M, and DD. The dorsal cortex (DC) projects to D, including D and VL nuclei. The La projects to D and M. The IC also projects to perigeniculate regions including the cat posterior thalamus (Andersen et al. 1980), rat posterior paralaminar nucleus (LeDoux et al. 1987; Linke 1999), and the cat and bat pretectum (Kudo et al. 1983; Frisina et al. 1989; Wenstrup et al. 1994; Fig. 7.2B). The tectothalamic projection shows considerable species variability (Table 7.1).

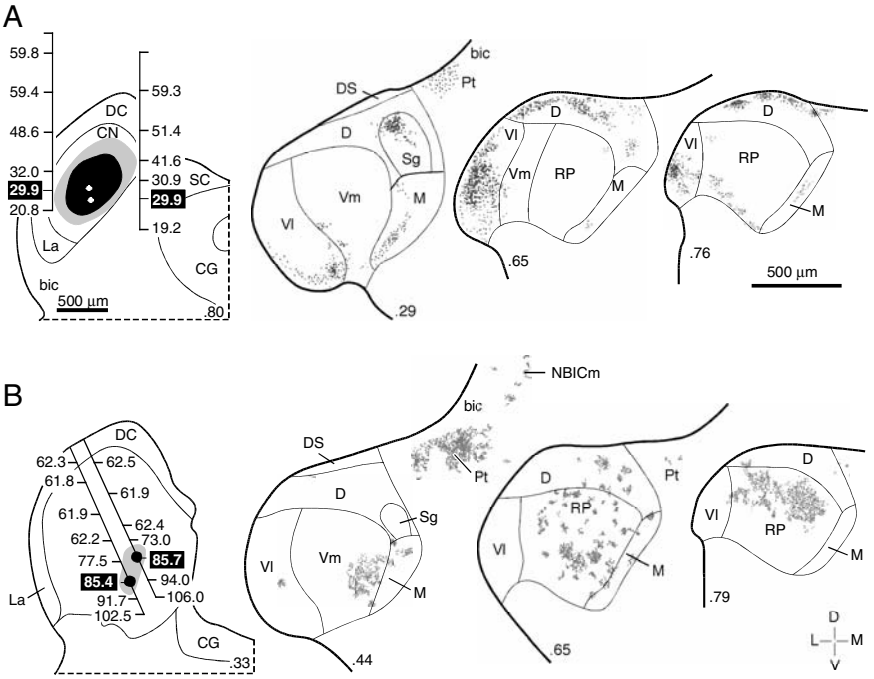

Figure 7.2. Projections to MGB from two frequency-band representations of the central nucleus of IC in the mustached bat. In IC sections *(left)* are electrode penetrations, characteristic frequencies at multiunit recording sites (in kHz), and tracer deposit sites *(black regions).* Anterograde MGB labeling *(dots)* was plotted in a caudal *(left)* to rostral *(right)* series of transverse sections. Numbers *(lower left)* show the IC or MGB section level. **(A)** Widespread projections from the 29- to 30-kHz IC representation terminate in the midbrain and thalamus. Significant MGB labeling occurs in V (lateral part), M, D, Sg, and the rostral pole nucleus (of the dorsal division). **(B)** Different input to MGB and pretectum from the 85- to 86-kHz IC representation. Labeling in MGB includes the medial part of V, M, D, and two zones of RP. *bic,* Brachium of the IC; *Pt,* pretectum; *RP,* rostral pole nucleus of the dorsal division. (Adapted from Wenstrup and Grose 1995.)

The IC–MGB projection is predominantly ipsilateral. In cats and rats, 5% to 10% of tectothalamic cells are contralateral (Aitkin and Phillips 1984; Rouiller and de Ribaupierre 1985; González-Hernández et al. 1991). V receives the strongest contralateral IC input. In mice, guinea pigs, and bats, there is little or no evidence of a contralateral projection (Wenstrup 1995; Frisina et al. 1997; Malmierca et al. 1997).

What sets of IC and other inputs are received by each MGB subdivision? This question is best addressed by retrograde transport studies using restricted tracer deposits, but such studies have been rare. Additional evidence comes from

Table 1: Species Differences in IC Inputs to MGB Subdivisions

MGB Nucleus	Species[1]	CN	DC	La
Ventral	All	●	•	•
Medial Division	C	●	–	●
	MB	●	×	×
	R	•	•	●
	TS	•	•	●
Dorsal	C	•	●	•
	MB	●	–	–
	R	–	•	●
	TS[2]	–	–	–
Deep Dorsal	C	●	•	•
	MB[3]	●	–	–
	R	×	×	×
	TS	–	●	–
Suprageniculate	C	–	–	–
	MB	•	•	
	R	•	•	●
	TS	–	–	–
Ventrolateral	C	–	●	•
	MB	×	×	×
	R	–	●	●
	TS	–	●	–

• ● ● Relative strength of projection

– No projection to MGB subdivision

× Undetermined

[1]*C*, cat; *MB*, mustached bat; *R*, rat; *TS*, tree shrew

[2]DC input is to the anterodorsal nucleus

[3]Correspondence to DD suggested by Olsen and Suga, 1991a and Wenstrup 1999

anterograde transport studies, in which the convergence of input must be assessed across several experiments. Nonetheless, it is clear that MGB subdivisions receive different but overlapping sets of inputs.

Alone among MGB divisions, V receives a nearly unitary ascending projection. Strong input is from the CN, with weak DC and La projections (Calford and Aitkin 1983; LeDoux et al. 1985; Rouiller and de Ribaupierre 1985), a conclusion corroborated by anterograde transport and lesion studies (Oliver and Hall 1978; Andersen et al. 1980; LeDoux et al. 1985). The CN to V projection is topographic/tonotopic, although it has been documented in few species. In cat (Kudo and Niimi 1978; Andersen et al. 1980; Calford and Aitkin 1983) and mustached bat (Wenstrup et al. 1994), low-frequency CN representations end in the lateral part of V, with higher frequency input medially. This differs in the guinea pig: low-frequency dorsal CN regions target dorsal and medial V, while higher frequency, ventral CN regions project to the ventrolateral V (Malmierca et al. 1997). These projection patterns agree with the tonotopy revealed in physiologic studies of V (see Section 5).

While preserving tonotopy, the CN–V projection may alter the representation of bands of different frequencies. In mustached bats, frequency organization is preserved but proportional representation is substantially altered. Thus, CN frequency bands analyzing frequency-modulated components of sonar signals send only a small projection to V; most output terminates in D (Frisina et al. 1989; Wenstrup et al. 1994; Wenstrup 1999). Such an unequal division of CN output to different MGB subdivisions may occur in other species. In cats, for example,

the DD nucleus receives input from high-frequency but not low-frequency CN regions (Andersen et al. 1980; Calford and Aitkin 1983; Rouiller and de Ribaupierre 1985).

The CN projection may contribute to regional differences in responses across V (Rodrigues-Dagaeff et al. 1989; Cetas et al. 2001), but reorganization of CN output is not well documented. In cats, single CN tracer deposits form discontinuous labeling patterns in V (Andersen et al. 1980), suggesting that CN loci project divergently. Such patterns may confer different binaural response regions onto V (Andersen et al. 1980; Middlebrooks and Zook 1983). In the guinea pig discontinuities in the CN–V projection are not apparent (Malmierca et al. 1997).

IC inputs to D are more complex because each subdivision receives distinct sets of auditory midbrain inputs and major species variations occur. In cats and tree shrews, the DC projects to rostral parts of the D nucleus (Oliver and Hall 1978; Andersen et al. 1980; Calford and Aitkin 1983; Rouiller and de Ribaupierre 1985). In rats, the La projects more strongly than the DC to the D nucleus (LeDoux et al. 1985). Mustached bat CN frequency bands corresponding to constant-frequency elements of sonar signals have the strongest input to the D nucleus (Wenstrup et al. 1994; Wenstrup and Grose 1995).

The DD nucleus receives input from the CN, DC, and La, with major species differences. In cats input is from the higher frequency CN, with lesser DC and La input (Andersen et al. 1980; Calford 1983; Rouiller and de Ribaupierre 1985). Similarly, the mustached bat has strong, higher frequency CN input to a region corresponding to the DD (Olsen and Suga 1991a; Wenstrup 1999); these regions receive lesser input from La and the pericollicular tegmentum and none from the DC (Wenstrup et al. 1994; Wenstrup and Grose 1995). In contrast, tree shrews (Oliver and Hall 1978) and rodents (Frisina et al. 1997; Malmierca et al. 1997) send little CN input to DD, with the main input from the DC (Oliver and Hall 1978).

The suprageniculate nucleus (Sg) receives variable input across species. In cats, Sg retrograde tracer deposits labeled only the nucleus of the brachium of IC (nBIC) and the superior colliculus (SC) (Calford and Aitkin 1983), but such limited projections may reflect tracer insensitivity. Degeneration or anterograde transport methods show brain stem inputs traversing the lateral tegmentum (Morest 1965), some from the vicinity of the ventral nucleus of the lateral lemniscus (Henkel 1983). In mustached bats, the Sg receives SC input and significant auditory midbrain and brain stem inputs, including those from the nucleus of the central acoustic tract (NCAT) (Casseday et al. 1989), part of the La or the midbrain tegmentum (Gordon and O'Neill, 2000), and the CN (Frisina et al. 1989; Wenstrup et al. 1994). In rats, the major input is from the SC and specific layers of the La (LeDoux et al. 1987; Linke 1999), with a smaller DC input and little from the CN. Both visual and somatic sensory inputs converge on the Sg (LeDoux et al. 1987).

M integrates a broad range of inputs, with major projections from the La and the CN (Calford 1983) and other auditory projections from the lateral tegmental system (Morest 1965; Oliver and Hall 1978), sagulum (Hutson et al. 1991),

ventral nucleus of the lateral lemniscus (Henkel 1983), and the dorsal cochlear nucleus (Malmierca et al. 2002). There is no evidence for tonotopic projections to M (Wenstrup et al. 1994; Malmierca et al. 2002) but there is a coarse frequency map in the cat (Rouiller et al. 1989). This may arise from the La, which receives topographic CN input (Saldaña and Merchán 1992). Like Sg, M receives multisensory input, including somatic sensory (LeDoux et al. 1987) and vestibular (Blum et al. 1979) projections.

2.2. Cellular Features of the Tectothalamic Projection

Disc-shaped IC neurons form the major tectothalamic cell type. In the cat CN, 80% of projection neurons are varieties of disc-shaped cells; stellate cells are also present (Oliver 1984). In rats, only disc-shaped CN cells project (Oliver et al. 1999), but both stellate and disc-shaped cells project from the La and the DC (Oliver et al. 1999). Sagulum neurons projecting to the MGB include small stellate and larger multipolar neurons (Beneyto et al. 1998).

Although most tectothalamic input is likely glutamatergic, a major finding was the discovery of a γ-aminobutyric acid (GABA)-ergic IC–MGB projection. In cats 20% (CN) to 30% (La) of tectothalamic neurons are GABAergic (Fig. 7.3A) (Winer et al. 1996). In rats about 45% of CN tectothalamic cells are GABAergic (Fig. 7.3A) (Peruzzi et al. 1997). Tectothalamic GABAergic neurons had sizes and morphologies corresponding to those of IC GABAergic cell types (Oliver et al. 1994; Winer et al. 1996). On average, GABAergic BIC axons were larger than nonGABAergic axons (Saint Marie et al. 1997). These results suggest that IC monosynaptic feedforward inhibition to MGB may precede excitatory input. This is a major departure from the patterns of thalamic somatic sensory and visual inputs, where ascending GABAergic inputs are sparse (De Biasi et al. 1990; Pow et al. 1994). The functional properties of this GABAergic input are considered below.

The morphology of tracer-filled tectothalamic axons corroborate earlier Golgi and degeneration findings (Morest 1964; Majorossy and Réthelyi 1968). IC terminals in the MGB are knoblike or en passant endings (Fig. 7.3) with a range of sizes. In V, both types occur, although knoblike clusters dominate (Fig. 7.3B: 1) (Pallas and Sur 1994; Wenstrup et al. 1994; Bartlett et al. 2000). These endings are complex, as observed in ferrets and mustached bats (Fig. 7.3B: 3). As in cats (Morest 1965), preterminal axons in mustached bats are aligned with dendrites of tufted neurons (Fig. 7.3B: 3) (Wenstrup et al. 1994; Winer and Wenstrup 1994a,b). This arrangement is thought to conserve a precise frequency representation in V. In the rabbit MGB, a close relationship between dendritic/cellular laminae and the fine frequency representation of V has been documented (Cetas et al. 2001, 2002).

D neurons receive small, en passant terminals and larger knoblike endings (Fig. 7.3B: 2). These are similar across species, even when the input source differs, with terminals in cats, rats, and bats matching closely, despite the fact that the major input arises in different IC subdivisions (Morest 1964; Wenstrup

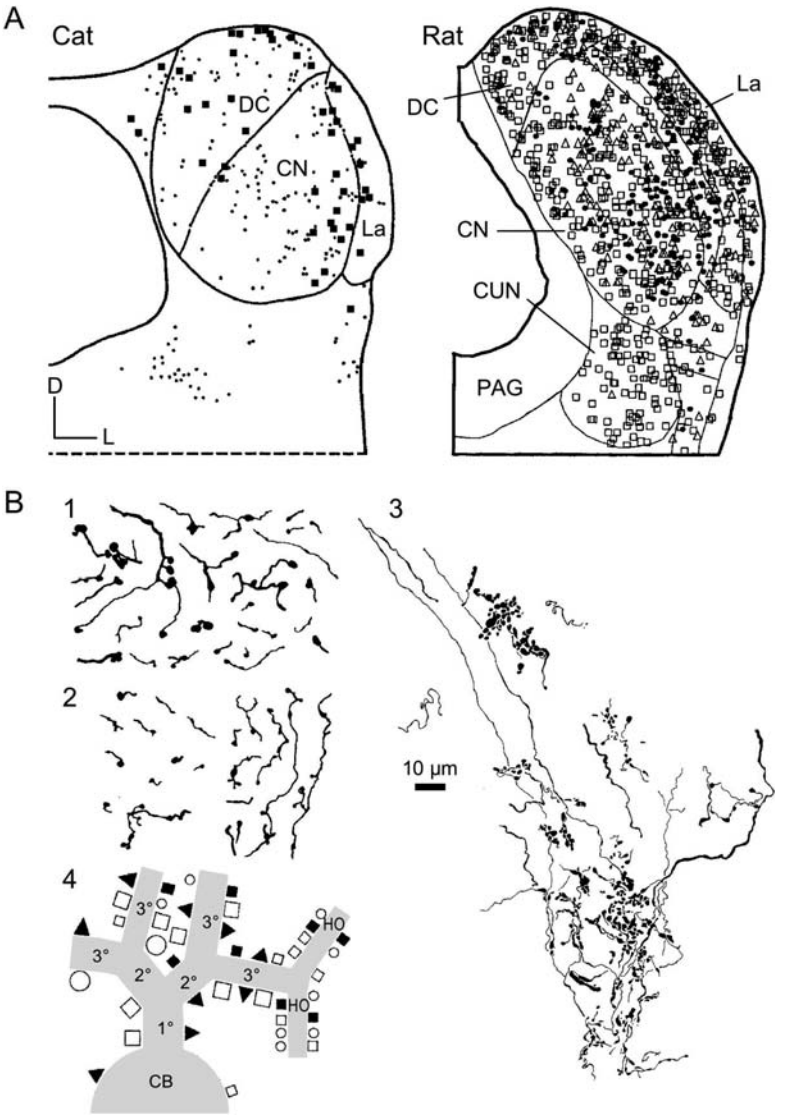

Figure 7.3. Cellular features of the tectothalamic projection. **(A)** GABAergic IC neurons projecting to MGB in cats and rats. *Filled squares (left)* show cells labeled both by MGB injections of a retrograde tracer and by anti-GABA antibody. *Small dots,* cells labeled only by the retrograde tracer. (Adapted from Winer et al. 1996. Copyright 1996 National Academy of Sciences, USA.) *Right, filled circles* show cells labeled both by MGB injections of retrograde tracer and by anti-GABA antibody. *Open squares,* cells labeled only by the retrograde tracer; *open triangles,* GABA-positive cells. (Adapted from Peruzzi et al. 1997.) **(B)** IC inputs to the MGB. Boutons from rat ventral *(1)* and dorsal *(2)* divisions after IC tracer deposits. (Adapted from Bartlett et al. 2000.) *3,* Labeled terminals and preterminal axons after tracer deposits in lower frequency representation of the mus-

et al. 1994; Bartlett et al. 2000). Likewise, the cat Sg is dominated by fine, en passant boutons from the SC and the nBIC (Calford and Aitkin 1983), while CN afferents to Sg in mustached bats are strikingly similar (Wenstrup et al. 1994). The relationship between these morphologic features and response properties remains unclear.

Terminals in the rat MGB were studied with electron microscopy, GABA immunohistochemistry, and tract tracing (Fig. 7.3B: 4) (Bartlett et al. 2000). Tectothalamic axodendritic endings are plentiful, and axosomatic terminals sparse, as in earlier studies (Morest 1964). Their distribution onto MGB neurons depends partly on their size and neurotransmitter. Larger glutamatergic terminals end on primary through tertiary dendrites; a few smaller, presumptive glutamatergic terminals are axosomatic; and most small terminals end on distal dendrites. In D, there are more small, presumptive glutamatergic IC terminals on thinner dendrites. GABAergic terminals are typically smaller and target secondary and higher order dendrites. Thus, some GABAergic IC input may be slow or weak, although GABAergic IC axons are larger than nonGABAergic axons (Saint Marie et al. 1997). Such IC termination patterns may underlie temporal patterns of excitation and inhibition (Bartlett and Smith 1999).

Noncollicular terminals are either large GABAergic terminals, probably from thalamic reticular nucleus cells, or glutamatergic corticothalamic terminals (Winer et al. 1999; Bartlett et al. 2000). Compared to tectothalamic inputs, corticothalamic terminals are smaller and target higher order dendrites. There are species differences in the confluence of collicular, thalamic reticular, and cortical input in MGB. In cats and monkeys, triadic synaptic arrangements involving GABAergic interneurons, collicular afferents, and corticothalamic terminals are common (Jones and Rockel 1971; Morest 1975; Majorossy and Kiss 1976). In contrast, rats and some bats have few intrinsic GABAergic MGB neurons (Winer and Larue 1988, 1996; Vater et al. 1992; Winer et al. 1992) and consequently few triads (Bartlett et al. 2000).

In summary, the tectothalamic projection shows common features across species, but also major differences that challenge understanding of the structure–function relationships of this projection. Most puzzling is the lack of consistent alignments among phylogenetic groups with respect to anatomic features of the projection. For example, considering the projection from CN to D, rodents are at one extreme (no CN input), mustached bats at the other (strong CN input),

Figure 7.3. *Continued*
tached bat's IC follow the laminar arrangement of MGB principal cell dendrites. (Adapted from Wenstrup et al. 1994). The scale bar applies to *1–3. 4,* Schematic distribution of rat IC and other terminals onto MGB neurons show few axosomatic contacts. *Squares,* IC inputs of different sizes; *circles,* auditory cortical terminals of different sizes; *triangles,* large inputs of unknown origin; *filled symbols,* GABAergic terminals; *open symbols,* glutamatergic terminals. Numbers in **(B)**: *4* indicate order of dendrites. *CB,* Cell body; *HO,* higher order dendrites. (Adapted from Bartlett et al. 2000. Copyright 2000 with permission from Elsevier.)

and cats are intermediate. GABAergic MGB neurons are rare in rats and some bats, while cats and monkeys have >20%. The functional implications of these species differences are not understood.

3. Synaptic and Intrinsic Properties of Medial Geniculate Body Neurons

It has long been recognized that auditory input to the MGB triggers interactions between excitation and inhibition (Nelson and Erulkar 1963; Aitkin and Dunlop 1968). Cellular bases for these interactions were investigated using rat MGB explant (Hu et al. 1994; Hu 1995) or slice (Peruzzi et al. 1997; Bartlett and Smith 1999) preparations. When the BIC is shocked, V and D neurons show fast, reliable excitatory postsynaptic potentials (EPSPs) that are insensitive to changes in stimulation rate and have little temporal jitter. In the absence of inhibition, EPSP latencies average <2.5 ms and are completely blocked by simultaneous application of antagonists to *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptors. Such EPSPs reflect monosynaptic glutamatergic IC inputs to V and D, and probably M (Webber et al. 1999).

In V, all IC-evoked EPSP or spike responses were blocked by AMPA receptor antagonists, but few were reduced by NMDA antagonists (Fig. 7.4A) (Hu et al. 1994). In contrast, EPSPs in D were reduced by both NMDA and AMPA receptor antagonists (Fig. 7.4A). The NMDA-mediated responses could sometimes evoke action potentials in D without AMPA receptor–mediated depolarization. In M, AMPA and NMDA receptor antagonists each blocked most action potentials evoked by BIC stimulation (Webber et al. 1999).

Postsynaptic effects of IC GABAergic input to the MGB are varied (Fig. 7.4B) (Peruzzi et al. 1997; Bartlett and Smith 1999). In about one third of V and D cells there was no evidence of $GABA_A$ receptor-mediated IPSPs before or after the EPSP evoked by BIC stimulation (type EX/0). Most such neurons also lacked $GABA_B$ receptor-mediated inhibition activated by the IC afferents. In some 38% of V and D cells, $GABA_A$-mediated IPSPs occurred before the glutamatergic EPSP (type IN/EX), while in 14% the IPSPs followed the EPSP (type EX/IN). In 11%, IPSPs were not accompanied by EPSPs after BIC activation (type 0/IN). Neurons showing $GABA_A$-mediated inhibitory postsynaptic potentials (IPSPs) also had longer latency and longer $GABA_B$-mediated IPSPs.

MGB action potentials elicited by BIC activation result from interaction among excitatory, inhibitory, and intrinsic cellular properties. Like other thalamic neurons (Jahnsen and Llinás 1984; see Sherman 2001), MGB neurons have distinct firing modes associated with levels of alertness (Fig. 7.4C) (Steriade and Llinás 1988; McCormick and Feeser 1990). For MGB in vitro preparations (Hu et al. 1994; Tennigkeit et al. 1996), one mode is tonic discharge to intracellular current pulses, followed by a return to near-resting membrane potentials.

Discharge latency is short (a few milliseconds) following EPSPs or applied current, and the interspike interval is longer. Tonic mode occurs in neurons at slightly depolarized resting membrane potentials. At slightly hyperpolarized potentials, they may still fire tonically but latency increases significantly and spike probability declines. If the membrane potential is further hyperpolarized, cells discharge in burst mode; Na^+/K^+ action potentials at short interspike intervals ride atop a slower depolarization resulting from a low-threshold Ca^{2+}-dependent spike (Steriade et al. 1990; Hu 1995; Tennigkeit et al. 1996). Action potential latency is longer and more variable than in the tonic mode.

In both rat explant (Hu et al. 1994; Hu 1995) and anesthetized guinea pig preparations (He and Hu 2002), lemniscal V neurons fired tonically, whereas nonlemniscal D neurons fired in burst mode. Hu and colleagues related several physiologic characteristics of D neurons to the burst mode firing: longer EPSPs, more NMDA receptor–mediated glutamate excitation, more negative resting membrane potentials, and no depolarizing "sag" mediated by the I_h current. They concluded that such intrinsic and synaptic properties explain major differences between MGB lemniscal and nonlemniscal systems, including firing mode, latency, regularity of firing, and perhaps plasticity.

Other studies have challenged these conclusions. In rat slices, single V neurons show a range of firing modes, latencies, and temporal discharge patterns that are dependent on the cell's membrane potential and the applied current (Fig. 7.4C) (Tennigkeit et al. 1996, 1997). Cells shift from burst to tonic mode with additional stimulation during the burst mode response, and can be influenced by metabotropic receptors to glutamate, GABA, and acetylcholine (Mooney et al. 1995; Tennigkeit et al. 1998, 1999). Few differences in intrinsic membrane properties were seen in V and D neurons, or even between stellate and tufted neurons (Bartlett and Smith 1999). An exception was the concentration in V of the hyperpolarization-activated depolarizing I_h current, which may impede burst mode firing by reducing membrane hyperpolarization. These studies do not support a sharp distinction between D and V neurons with regard to intrinsic properties or firing mode. Perhaps the firing mode is more indicative of alertness levels (Tennigkeit et al. 1996, 1997) as in other thalamic nuclei. Burst mode firing may have an alerting function that provides lower quality information to the cerebral cortex, whereas tonic mode firing may typify high-quality analyses of auditory features in awake animals (Tennigkeit et al. 1997; Sherman 2001). Such a speculation cannot be tested in vitro.

Response properties of guinea pig MGB neurons were tested in awake, sleeping, and anesthetic states with electroencephalograph (EEG) monitoring. Bursts occurred in awake animals, but increased during slow-wave sleep and were most common under barbiturate anesthesia (Massaux and Edeline 2003). In awake animals, there was more V burst firing than in D, M, and the lateral part of the posterior complex (Pol), but no differences during slow-wave sleep. Frequency selectivity during slow-wave or paradoxical sleep was sharper than in awake animals, although sensitivity and spike number declined (Edeline et al. 2000). There was no correlation between burst mode firing and changes in frequency

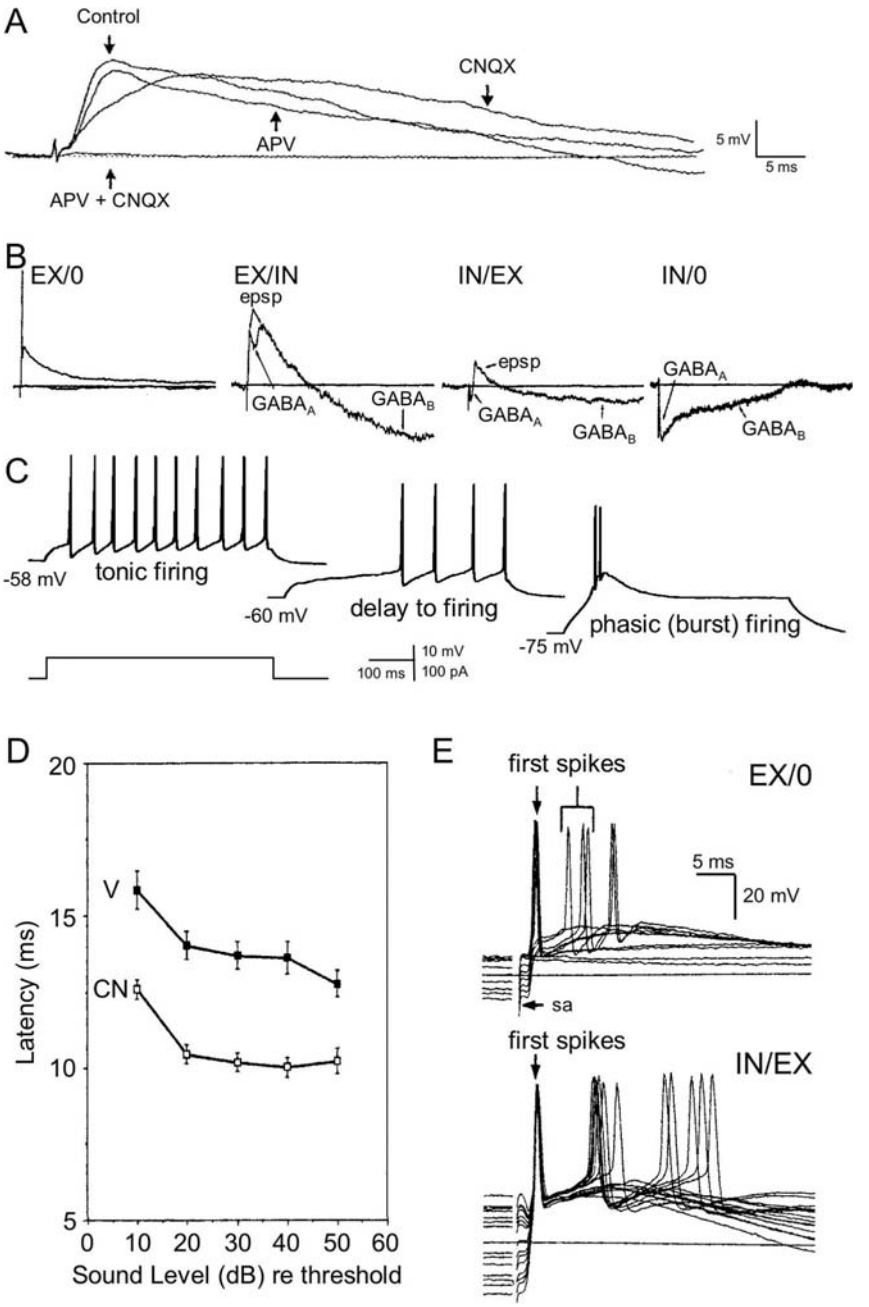

Figure 7.4. Physiologic properties of MGB neurons. **(A–C, E)** Synaptic and intrinsic behavior from in vitro preparations. **(A)** Postsynaptic potentials in D neuron after electrical stimulation of BIC. Bath-application of CNQX and APV separately remove early

receptive fields. These studies strongly suggest that burst firing mode is part of the repertoire of both lemniscal and nonlemniscal MGB neurons, and demonstrate firing mode dependence on levels of alertness. They imply that the information about acoustic stimuli conveyed by burst firing neurons is as precise (for sound frequency) as in neurons firing tonically.

The interplay of synaptic and intrinsic properties in MGB neurons thus transforms their temporal discharge pattern. Such patterns are shaped by a neuron's membrane potential and regulated both by intrinsic properties and short and longer term actions of synaptic inputs. Multiple firing modes occur throughout the MGB and do not distinguish any subdivision, even though neurons in a subdivision may burst more under particular experimental conditions or levels of alertness.

4. Transformations in Functional Properties

MGB auditory responses differ across subdivisions. Typically, V neurons display sharp tuning, short latencies, and reliable responses to sound. D neurons have longer latencies, broader tuning, and less reliable and more labile responses. M neurons vary, with population means often between those of V and D. Some D and M neurons respond to other sensory modalities. These differences hold across species and different levels of anesthesia, although species differences and anesthesia effects can be profound. This contributes to the view that both the tectothalamic projection and MGB functional properties embody parallel (but incompletely segregated) ascending systems whose origin, termination, and functional properties differ. Physiologic support for this hypothesis is plentiful (Calford 1983; Lennartz and Weinberger 1992; Bordi and LeDoux 1994a; Edeline et al. 1999).

This section considers whether MGB neural responses depend on de novo processing within MGB or reflect the IC responses or other inputs. Addressing

Figure 7.4. *Continued*
and late synaptic response components, respectively. Combined, they eliminate the postsynaptic response, showing that glutamate mediates IC excitatory input. (Adapted from Hu et al. 1994.) **(B)** Postsynaptic responses after BIC stimulation show excitatory and inhibitory IC inputs. The vertical scale differs across four neurons. (Adapted from Bartlett and Smith 1999.) **(C)** Firing modes of the V neuron depend on intracellular potential. (Adapted from Tennigkeit et al. 1997.) **(D)** First-spike latency difference in CN and V neurons from in vivo recording of free-tailed bats (Adapted from Klug et al. 2000.) **(E)** IC GABAergic input stabilizes first-spike latency of MGB neurons. EX/0 neuron *(above)* and IN/EX neuron *(below)* spikes elicited by BIC stimulation. Each cell was tested over a range of membrane potentials, which alter neuronal firing mode. The EX/0 neuron displays large changes in first-spike latency over a range of membrane potentials, whereas the IN/EX cell has no change in latency over a range of membrane potentials. *sa*, stimulus artifact. (Adapted from Bartlett and Smith 1999.)

this issue requires two types of experiments, of which few examples exist. The first includes in vivo MGB microiontophoretic studies that test auditory responses before and during application of neurotransmitter antagonists, a method that has identified novel transformations in the IC. The second type of study directly compares IC and MGB recordings in the same species under identical anesthetic and recording conditions. Because both species and experimental variables create significant response disparities, comparisons in which these factors differ are problematic.

4.1. Temporal Properties

4.1.1. Latency and Temporal Response Patterns

MGB neurons differ significantly in response latencies, from $<$10 ms to $>$100 ms. Likewise, there are different temporal response patterns, including onset (ON), sustained, offset (OFF), ON–OFF, and variable patterns (Calford 1983; Rodrigues-Dagaeff et al. 1989; Rouiller et al. 1989; Edeline et al. 1999). For both first spike timing and the temporal spiking pattern, differences exist among subdivisions. Thus, V latencies are shortest and least variable, and temporal response patterns the most homogeneous. D latencies are longest and most variable, while M responses and those in Pol are intermediate. Large differences exist even in V, where latency, temporal response pattern, and other features form caudorostral gradients (Rodrigues-Dagaeff et al. 1989).

Regional differences may be amplified by anesthesia. Large differences in latencies were found in barbiturate-anesthetized cats (Calford 1983). In awake guinea pigs whose level of alertness was monitored with EEG recordings, smaller regional differences persist (Edeline et al. 1999); V, M, and Pol latencies are longer than in the cat while D latencies are substantially shorter. Species differences, and possibly experimental procedures, confound comparisons from awake guinea pigs and little brown bats. In this bat, regional latency differences are small, averaging 8.9 ms in V and 12.8 ms in D and M (Llano and Feng 1999).

In awake free-tailed bats, latencies in V range from 15.9 to 12.8 ms for characteristic frequency (CF) sounds 10 to 50 dB above threshold, respectively, exceeding values in CN by 3 to 4 ms (Fig. 7.4D) (Klug et al. 2000). Axonal and synaptic delays may explain such latency differences, as average EPSP latencies in V after BIC electrical stimulation are 1.1 to 3.8 ms, depending on early GABAergic inhibition (Bartlett and Smith 1999). In awake mustached bats, different types of D neurons (Olsen and Suga 1991b; O'Neill and Brimijoin 2002) reveal strong auditory responses at latencies only a little longer than auditory midbrain or brain stem responses (Portfors and Wenstrup 1999; Gordon and O'Neill 2000). Thus, in awake animals there is little evidence of major response latency transformations except those introduced by axonal and synaptic delays. This is supported by an extensive physiologic survey of IC properties

(Syka et al. 2000) in ketamine/xylazine-anesthetized guinea pigs. Although the use of anesthesia precludes a direct comparison to an MGB study (Edeline et al. 1999), each IC subdivision displays a broad range of latencies. Thus, the IC input latencies, brief synaptic delays, and the effects of GABAergic IC inputs probably account for the range of latencies across MGB subdivisions. In addition, GABAergic input can maintain constant response latencies under different firing modes (Fig. 7.4E; Bartlett and Smith 1999).

In all subdivisions in awake guinea pigs, ON responses form the largest group although these are fewer in D (Edeline et al. 1999). Sustained responders, substantially fewer than ON cells, form the next largest group. OFF, ON-OFF, and other categories are least common. A similar preponderance of ON responses occurs in awake little brown bats (Llano and Feng 1999), barbiturate-anesthetized guinea pigs (He 2001), and cats under barbiturate or light nitrous oxide anesthesia (Calford 1983; Rodrigues-Dagaeff et al. 1989). Although IC discharge patterns vary across species and anesthetic regimens, sustained response patterns seem more common than in MGB (Bock et al. 1972; Ehret and Moffat 1985; Semple and Kitzes 1985; Aitkin et al. 1994). This suggests that one tectothalamic transformation increases responsiveness to dynamic rather than static stimuli.

Such transformations in temporal discharge properties appear unrelated to state-dependent changes in discharge mode caused by neuronal intrinsic and synaptic properties (see Section 3). It has been suggested that ON patterns elicited by auditory stimuli in anesthetized animals indicate burst mode firing (Tennigkeit et al. 1996). This does not appear to be the case, however. Even in EEG-monitored awake guinea pigs, in which most responses are in "tonic" firing mode, ON patterns predominate (Edeline et al. 1999, 2000; Massaux and Edeline 2003). Discharges during tonic mode firing are probably restricted either by inhibitory inputs or by the ON pattern of excitatory inputs, rather than by mode of firing.

4.1.2. Response to Signal Periodicities

Temporal sensitivity to signal periodicities has been studied using periodic amplitude modulations, repetitive click or tone burst trains, or responsiveness to paired click or tonal stimuli. Although many central auditory neurons discharge synchronously to stimulus modulations or repetitive stimuli, this capacity diminishes at successively higher levels (Langner 1992). MGB neurons show modest ability to synchronize to temporal events in sounds (Aitkin and Dunlop 1968; Rodrigues-Dagaeff et al. 1989) and this correlates with sharp frequency tuning (Lennartz and Weinberger 1992). However, there are few direct comparisons between IC and MGB responses in awake animals.

In awake little brown bats, temporal sensitivity to rate variations in tone burst trains was examined in the IC, the MGB, and the auditory cortex. Among MGB cells, modulation rate transfer functions based on response synchrony had a low-

pass cutoff at about 64 pulses/s. V neurons had the highest cutoffs, but these were different only from M neurons (Llano and Feng 1999). Comparable studies of IC and auditory cortex found synchronization cutoffs of 163 and 37 pulses/s, respectively (Condon et al. 1994, 1997), suggesting a progressive reduction in the preservation of fine temporal information in the tectothalamocortical pathway. In a few MGB neurons, the response to a second tone was facilitated but discharge synchrony decreased. Responsiveness to pulse trains improved when a slower amplitude modulation was imposed on the pulse train (Llano and Feng 1999). This response, which was more noticeable in AI, may reflect a change from temporal to rate coding of signal periodicities at higher levels of the auditory system.

MGB neurons recorded in vitro show either response depression or facilitation to the second of two shocks to the BIC (Bartlett and Smith 2002). The effect was related to the presence and timing of IC glutamatergic and $GABA_A$ receptor-mediated events. Type EX/O neurons in MGB, for which a large IC glutamatergic EPSP is unaccompanied by IC $GABA_A$-mediated IPSPs, showed only paired-pulse depression. These are thought to originate from larger glutamatergic IC synaptic inputs. The depression occurred despite chemical blockade of $GABA_A$ and $GABA_B$ receptors and was apparent for either AMPA or NMDA receptor–mediated EPSPs. Paired-pulse MGB depression is likely mediated presynaptically. In other thalamic nuclei with little ascending GABAergic input, paired-pulse depression is the rule (Eysel 1976; Mishima 1992). In MGB, however, V and D neurons could show paired-pulse facilitation, the dominant effect among IN/EX neurons. The facilitation depended on NMDA receptors, but its relation to $GABA_A$-mediated inhibition is unclear. Such neurons had smaller EPSPs and presumably smaller IC glutamatergic synapses on the MGB cell. These results suggest a complex relationship between synaptic ending size, glutamate pharmacology, and the presence and timing of inhibition.

Functional magnetic resonance imaging (fMRI) in awake humans shows decreased responsiveness to higher modulation rates (Giraud et al. 2000; Harms and Melcher 2002), supporting earlier work in various animal models (see Langner 1992). The major change between IC and MGB is that fMRI IC activation is nearly continuous during noise burst trains from 1 to 35 Hz. The MGB response at higher rates is largest at the burst train onset. The change in fMRI activation between IC and MGB is part of a transformation from the IC to the cortex, in which activation at higher repetition rates is phasic.

In summary, compared to IC cells, MGB neurons have longer latencies, greater discharge probability to sound onset, and lower discharge synchrony to repetitive stimuli. There is little experimental evidence that latencies extend beyond predicted axonal and synaptic delays. However, other temporal features such as onset responses and synchronized responses to transients are likely modified by MGB processing and interactions between excitatory and inhibitory IC inputs. Finally, a major transformation in the MGB appears to be the state-dependent modification of discharge mode, which affects latency, temporal discharge pattern, and perhaps other temporal response indices.

4.2. *Spectral Properties*

Cells in V and Pol typically have the sharpest frequency tuning, while in D and M tuning is broader (Calford 1983; Bordi and LeDoux 1994a; Edeline et al. 2000). "Broad" tuning includes multiple forms of spectrally complex responses, such as preferences for broad- vs. narrow-band stimuli, multipeaked tuning curves, inhibitory frequency bands, and combination sensitivity. The anesthetic and the behavioral state affect frequency tuning, such that the complexity of spectral responses, even in V, is often greater in lightly anesthetized or awake animals (Allon et al. 1981; Morel et al. 1987; Edeline et al. 2000). Frequency tuning differences persist across divisions in awake guinea pigs but are weaker (Edeline et al. 1999, 2000). Despite divisional differences in frequency tuning, little evidence exists of transformations in tuning sharpness and spectrally complex responses from the IC to the MGB.

4.2.1. Sharpness of Frequency Tuning

One study has directly addressed how MGB inhibitory interactions contribute to frequency tuning. Blockade of $GABA_A$ receptor–mediated inhibition affects frequency tuning of sharply tuned neurons in the MGB of awake mustached bats (Suga et al. 1997); recording sites were in either V or D, both of which receive their major input from CN (Wenstrup et al. 1994; Wenstrup and Grose 1995). Local bicuculline application broadened frequency tuning in 37% of neurons and often increased dynamic range at CF. The authors concluded that inhibitory interactions sharpened frequency tuning in a minority of cells. The small number of GABAergic MGB cells in this bat (Vater et al. 1992; Winer et al. 1992) suggests that the inhibition is of midbrain origin. Because tuning sharpness in MGB neurons was intermediate between auditory nerve and the AC, Suga and colleagues suggested that frequency tuning is sharpened at several levels of the ascending auditory pathway.

4.2.2. Spectral Integration: Responses to Two-Tone Stimuli

Two-tone stimuli, combining tones of different frequencies, permit an assessment of neural responses to complex sounds. Two-tone responses were studied in the context of monaural sound localization cues in barbiturate-anesthetized cats (Imig et al. 1997). Monaurally directional neurons, using monaural cues to create spatial selectivity, are about 17% of cells in V and Pol. They derive their spatial selectivity from inhibitory spectral interactions; their complex frequency receptive fields have one or more inhibitory bands and some display multipeaked excitatory tuning curves. In comparable IC recordings, slightly more monaural IC directional neurons were found than in MGB, but with somewhat weaker sideband inhibition (Poirier et al. 2003). Thus, the spectral interactions characteristic of monaurally directional MGB and auditory cortex (AC) neurons are present in IC. Although the barbiturate anesthetic used in these studies may

enhance inhibitory response elements, the results support the conclusion (Suga et al. 1997) that some frequency sharpening occurs in the MGB.

4.2.3. Combination Sensitivity

Combination sensitivity refers to neural responses showing preference for particular spectrotemporal combinations of acoustic elements (Suga et al. 1978; Fuzessery and Feng 1983; Margoliash and Fortune 1992; Rauschecker et al. 1995; Ohlemiller et al. 1996). These neurons require distinct frequency-tuned inputs and special temporal properties to achieve their response selectivities. Such integrative features are usually viewed as a forebrain attribute for audition, vision, or somatic sensation. In the mustached bat, however, this integrative feature originates in IC or at subcollicular levels (Mittmann and Wenstrup 1995; Portfors and Wenstrup 1999, 2001b; Wenstrup and Leroy 2001).

A comparison of IC and MGB found sharper temporal sensitivity and stronger facilitation among combination-sensitive MGB neurons (Yan and Suga 1996). In contrast, other studies in the IC (Portfors and Wenstrup 1999) and the MGB (Wenstrup 1999) found no significant differences in facilitatory interactions. They suggested that the earlier IC data reflect multiple-unit responses that, summed across different neurons, failed to show the strength and sharp temporal features of facilitation observed in single-unit recordings. Additional studies (Leroy and Wenstrup 2000) found that other forms of spectrally complex responses observed in MGB (Wenstrup, 1999) are also seen in the IC, including interactions between frequency bands not used in biosonar and noise-selective responses. Thus, most evidence suggests that basic features of combination-sensitive responses in the mustached bat originate in IC or below and undergo little MGB modification.

4.2.4. Frequency Modulation

Responses to temporal modulations of stimulus frequency have rarely been investigated in the MGB, limiting comparison to the more extensive IC literature. Studies of selectivity for direction and rate of frequency sweeps in the nuclei of the lateral lemniscus (NLL), IC, and MGB of awake mustached bats (Gordon and O'Neill 2000; O'Neill and Brimijoin 2002) found that a ventral region of the external nucleus of the IC (ICvx) more strongly prefers upward frequency sweeps than either NLL or CN neurons, although responses to CF tones are generally strong. Directional preferences likely result from a low-threshold inhibitory sideband above the unit's CF. ICvx, with short latency responses in the range of 5 to 8 ms, receives its main input from the nucleus of the central acoustic tract (NCAT) and projects to both the SC and the Sg, which also are NCAT targets. More Sg neurons display preferences for upward than downward frequency sweeps, but respond well to CF tones, like ICvx neurons. Overall, the preference for upward sweeps is less in Sg than in ICvx. Perhaps this reflects the range of inputs to Sg from NCAT (sweep selectivity unknown), ICvx (upward preference), and CN (less directional preference) (O'Neill and Brimijoin

2002). The range of Sg response latencies (5 to 25 ms) is consistent with this range of inputs. Upward sweep selectivity may contribute to the bat's analysis of social vocalizations. These studies suggest that diverse response properties within an MGB subdivision result from diverse auditory inputs, rather than from diverse computations performed on the tectothalamic input.

4.3. Binaural Sensitivity and Spatial Selectivity

MGB binaural and spatial processing has been studied mostly in cats, but these studies are far fewer in number than those in IC and AC. All MGB subdivisions show a range of responses to binaural sounds (Calford 1983). Sensitivity to interaural phase disparities (IPDs) is rare in D, common in V and M, and abundant in Pol (Ivarsson et al. 1988). Because the latter study employed nitrous oxide anesthesia, comparison with IC studies using barbiturate anesthesia is problematic (Kuwada and Yin 1983; Irvine and Gago 1990; Delgutte et al. 1999). However, the MGB may have a more continuous distribution of IPD sensitivity, whereas IPD-sensitive IC neurons favor the contralateral field (Kuwada and Yin 1983). Similarly, more neurons are driven by the ipsilateral ear, although the numbers are small. The increased representation of the ipsilateral sound field may result from contralateral auditory tectothalamic projection in cats (Clarey et al. 1992).

Monaural and binaural mechanisms create spatial selectivity in higher frequency neurons of the cat IC (Poirier et al. 2003), MGB (Imig et al. 1997; Samson et al. 2000), and AC (Samson et al. 1993, 1994). Monaural directional neurons retain azimuthal location selectivity with one ear plugged. Monaural cues from frequency-dependent head-related transfer functions may be encoded by IC, MGB, and AC units with distinct excitatory and inhibitory frequency domains revealed by two-tone stimuli (Imig et al. 1997). Binaural directional neurons lose azimuthal selectivity when an ear is plugged. They use binaural level cues encoded through inhibitory and/or facilitatory mechanisms that compare binaural inputs. The relative proportion of directional neurons based on monaural vs. binaural cues is constant in the IC, MGB (V and Pol), and AC (area AI). Further, there is little change in numbers of inhibitory frequency domains of monaurally directional neurons or in the strength of spectral inhibition. The chief alteration between IC and MGB is an increased proportion of neurons with enhanced responses to ipsilateral sound.

5. Physiologic Organization

Do organizational features change between IC subdivisions and their MGB counterparts? In V, as in CN, the dominant feature is tonotopy. CF increases from lateral to medial and caudal to rostral in V for cats (Aitkin and Webster 1972; Imig and Morel 1985), squirrel monkeys (Gross et al. 1974), and mustached bats (Wenstrup 1999) (Fig. 7.5A). In lagomorphs and rodents, CF

increases from dorsal to ventral, with species variants (Redies and Brandner 1991; Bordi and LeDoux 1994a; Cetas et al. 2001). These patterns agree with each species' organization of CN inputs and with the arrangement of dendrites and tectothalamic terminals, insofar as these are known (see Sections 2.1, 2.2).

In the mustached bat, however, the IC–MGB projection reorganizes frequency. In the CN, the frequency organization is disproportionate but in accord with the cochlear map (Zook et al. 1985; O'Neill et al. 1989). However, anatomic (Frisina et al. 1989; Wenstrup et al. 1994; Wenstrup and Grose 1995) and physiologic (Wenstrup 1999) evidence shows that the tectothalamic projection radically alters this organization. V maintains an ordered CF progression, but certain frequency bands that enjoy large CN representations, those devoted to analyzing frequency-modulated (FM) elements of sonar signals, are diminished in V (Fig. 7.5A) and are, instead, represented in the rostral part of D. Whether such alterations occur in other species is unknown. This seems unlikely in rodents as CN projects mainly to V. In cats, divergent CN projections to V, DD, Pol, and M, and the high-frequency bias in DD neurons, raise this possibility.

Within V, several response gradients or zones of response segregation occur in cats (Calford and Webster 1981; Rodrigues-Dagaeff et al. 1989), guinea pigs (Redies and Brandner 1991), and rabbits (Cetas et al. 2001). In cats, there are related caudorostral gradients of responsiveness to clicks, noise and tone bursts, sharpness of tuning, temporal response pattern, and responsiveness to repetitive stimulation. More rostral cells perform more precise spectral and temporal analyses; they usually are more sharply tuned, respond to a broader range of stimuli, have shorter latencies, display ON responses to noise and tone bursts, and respond better to click trains. These gradients are independent of CF, suggesting that they occur within frequency band representations. Binaural response categories have a patchy distribution. The caudorostral functional gradient was matched by differential connections to AC. Whether these gradients reflect IC arrangements or are imposed by reorganizing the tectothalamic projection is unknown (Rodrigues-Dagaeff et al. 1989).

Few reports of response organization in D are available, although He (2001) described a topographic distribution of OFF and ON–OFF responses in barbiturate-anesthetized guinea pigs. About 18% of D cells had invariant OFF responses to auditory stimuli, whereas 22% showed ON–OFF properties. OFF neurons lay in parts of D, M, and the shell subdivision surrounding V. This may be a novel MGB organization because it is absent in the IC of ketamine-anesthetized guinea pigs (Syka et al. 2000). Interpretation of these results is not straightforward, however, as anesthetic regimens affect temporal response patterns. In the MGB of awake guinea pigs, OFF cells comprise only 3% of the recorded population, with ON–OFF cells forming another 3% (Edeline et al. 1999).

In the mustached bat, D contains an organization of frequency bands representing higher harmonics of the FM component of the sonar call (from 48 to 59 kHz, from 72 to 89 kHz, and from 96 to 119 kHz) (Wenstrup 1999). Two

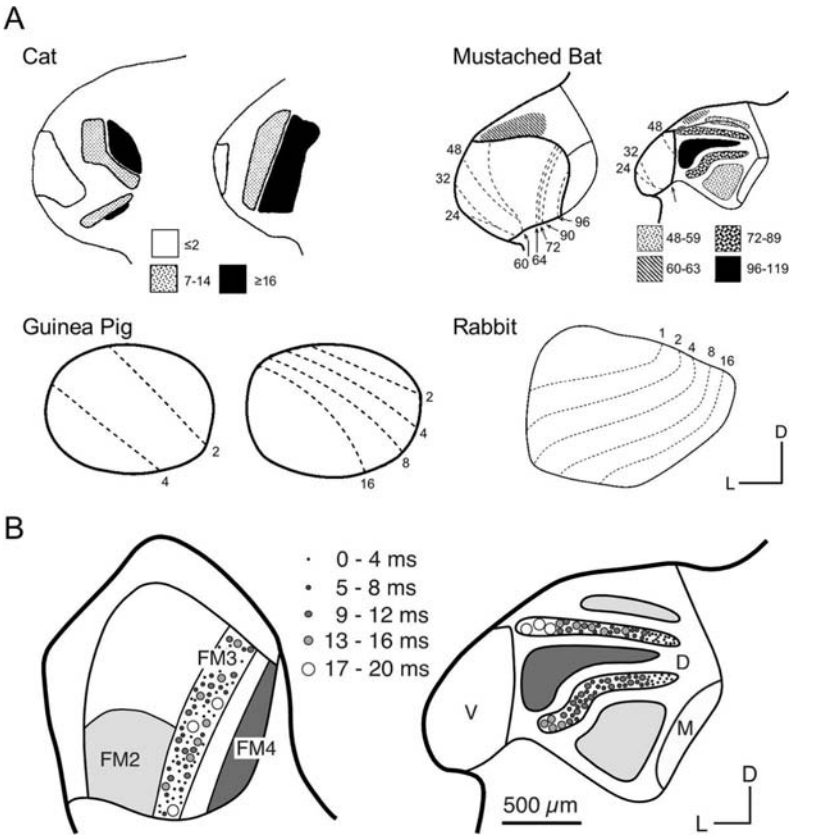

Figure 7.5. MGB functional organization. **(A)** Schematic tonotopy in V of four mammals in transverse sections. Caudal sections are on the *left,* rostral on the *right. Numbers,* characteristic frequency. A tonotopic pattern is present in each species, but the orientation varies. (Cat, adapted from Imig and Morel 1985; mustached bat, adapted from Wenstrup 1999; guinea pig, adapted from Redies and Brandner 1991; rabbit, adapted from Cetas et al. 2001.) **(B)** Transformation of frequency tuning and delay sensitivity from IC *(left)* to MGB *(right)* in the mustached bat. Frequency reorganization shown for three bands corresponding to harmonic components of FM sonar signal (FM2, 48 to 59 kHz; FM3, 72 to 89 kHz; FM4, 96 to 118 kHz). Reorganization of delay tuning is shown only for FM3 representation. *Dots,* best delay of neurons to combinations of the fundamental FM component in the sonar pulse (FM1, 24 to 29 kHz) and the delayed FM3 component of echoes. (Adapted from Portfors and Wenstrup 2001a. Copyright 2001 with permission from Elsevier.)

features are noteworthy (Fig. 7.5B). First, for each of the three frequency bands, there are two segregated maps in the rostral D and they are not arranged in a frequency gradient. Nearly all the neurons are combination-sensitive, tuned to delays between a 24 to 29 kHz signal (the fundamental FM component of sonar signals) and a later higher harmonic FM signal crossing the unit's CF. A second feature concerns delay sensitivity. Neurons within each frequency map display a rough organization of delay sensitivity not seen in CN single-unit studies (Portfors and Wenstrup 2001a). Thus, novel organizations of frequency and delay sensitivity may be created by the tectothalamic projection, setting the stage for thalamocortical projections that result in functionally distinct AC areas. The cortical neurons tuned to both sonar harmonics and delay after a 24 to 29 kHz signal are thought to analyze the sonar echo delays (O'Neill and Suga 1982; Suga et al. 1983; Fitzpatrick et al. 1998).

In M of lightly anesthetized cats, there is a tonotopic gradient, especially rostrally (Rouiller et al. 1989). It is weaker than in V, with no organization of response properties orthogonal to the tonotopic axis. M response properties vary widely but no other systematic representation is reported.

In the rostral and medial MGB, responses to other sensory modalities occur (Wepsic 1966; Phillips and Irvine 1979). Somatic sensory responses occur in rat Sg, M, rostral parts of D, the adjacent posterior intralaminar nuclei, and the posterior complex (Bordi and LeDoux 1994b). These and multimodal (auditory and somatic sensory) responses concentrate in the rostral MGB, in agreement with the distribution of somatic sensory input to the auditory thalamus (LeDoux et al. 1987). Some neurons could be activated antidromically from the lateral amygdala, indicating a role in conditioned emotional responses to sounds (Bordi and LeDoux 1994b).

In summary, anatomic and physiologic studies in several species show that the tonotopic organization present in CN is conferred on V, and it may be substantially altered by the tectothalamic projection. Within V, auditory responses and cortical connections show significant caudorostral variation, suggesting different functional roles. In other MGB divisions, there are few indications that responses are organized or segregated, in part because it has been difficult to identify, especially in D, the stimuli that optimally excite the neuronal population.

6. Synthesis and Perspective

Multiple auditory pathways through the thalamus form multiple streams of auditory information processing that serve many behavioral and perceptual capabilities. Underlying these auditory streams are distinctive anatomic and physiologic features of different MGB subdivisions. The major question is the origin of these streams. Are they created de novo in the MGB or do lower auditory nuclei impose their functional properties and organization onto MGB neurons? There are several conclusions related to this question.

6.1. Transformations in Temporal Processing from Midbrain to Thalamus

The transformations noted earlier are common throughout the ascending auditory pathway and do not distinguish MGB integration. Thus, MGB latencies are longer, the neurons synchronize less well to repetitive acoustic transients, and transient discharge patterns may increase. Feedforward GABAergic inhibition may contribute to these phenomena. Such inhibition characterizes many auditory nuclei, but it is unusual in the thalamus. In contrast, multiple firing modes are a hallmark of thalamic neurons and distinguish them from other auditory nuclei. These state-dependent MGB firing modes alter both latency and discharge pattern.

A mystery related to inhibition and temporal properties among MGB neurons is the role of intrinsic vs. tectothalamic GABAergic inhibition (see Chapters 1, 2, and 22). There are species differences in the source and size of these inputs. How are differences in these forms of GABAergic inhibition manifest in temporal or other encoding features of MGB neurons?

6.2. Serial Transformations in Other Integrative Response Properties

There is no evidence that novel forms of spectrotemporal integration such as multiple excitatory or inhibitory tuning peaks, combination sensitivity, duration tuning, directional selectivity to FM sweeps, or of binaural integration are created in the MGB, and the evidence that response selectivities are substantially sharpened is modest. Creation or extensive modification of response properties are more characteristic of processing in the IC and the AC.

There are several caveats to this conclusion. First, an exception may be the auditory and somatic sensory responses of the rostral and medial parts of the MGB. Because these regions receive both auditory and somatic sensory input, some neurons may integrate inputs to form bimodal responses. However, at least one input, the IC lateral nucleus, is multimodal, making it difficult to discern whether such integration occurs in the MGB. A second caveat is limited understanding of the functional relevance of auditory responses in M and D, regions that have received little attention and require further scrutiny. Identifying their optimal stimuli, delineating the functional properties of their cortical or subcortical targets, and understanding the genesis of their responses as related to their inputs remain as future challenges.

6.3. Emergent Response Properties

The reorganization of IC and other projections in MGB creates pathway-specific assortments of response properties that distinguish projections to auditory cortex and other targets. This reorganization takes several forms. One is the rearrangement of IC outputs to create novel organization in MGB subdivisions and, in

turn, cortical areas. This is evident in the mustached bat, where projections from CN reorganize to create functionally distinct MGB subdivisions that then project to specific cortical regions associated with the analyses of particular information-bearing elements in biosonar signals. Another form is the convergence of input from multiple sources that creates regions with a broad range of response properties, as in the medial and rostral MGB. In this view, the MGB does not create novel response properties, but instead creates novel ensembles of response properties. A major challenge is to understand the functional roles played by these ensembles of neurons.

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Abbreviations

AC	auditory cortex
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BIC, bic	brachium of the inferior colliculus
CF	characteristic frequency
CG	central gray
CN	central nucleus of the inferior colliculus
CUN	cuneiform nucleus
D	dorsal division *or* dorsal nucleus of the medial geniculate body
DC	dorsal cortex of the inferior colliculus
DD	deep dorsal nucleus of the medial geniculate body
DS	superficial dorsal nucleus of the medial geniculate body
EPSP	excitatory postsynaptic potential
FM	frequency-modulated
fMRI	functional magnetic resonance imaging
GABA	γ-aminobutyric acid
IC	inferior colliculus
ICvx	ventral region of the external nucleus of the inferior colliculus
IPD	interaural phase disparity
IPSP	inhibitory postsynaptic potential
La	lateral nucleus of the inferior colliculus
M	medial division of the medial geniculate body
MGB	medial geniculate body
nBIC	nucleus of the brachium of the inferior colliculus
NBICm	nucleus of the brachium of the inferior colliculus, medial part
NCAT	nucleus of the central acoustic tract

NLL	nuclei of the lateral lemniscus
NMDA	*N*-methyl-D-aspartate
PAG	periaqueductal gray
Pol	lateral part of the posterior complex of the thalamus
Pt	pretectum
SC	superior colliculus
Sg	suprageniculate nucleus of the medial geniculate body
V	ventral division *or* ventral nucleus of the medial geniculate body
VL	ventrolateral nucleus of the medial geniculate body
Vl	ventral division, lateral part
Vm	ventral division, medial part

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Chapter 8
Three Systems of Descending Projections to the Inferior Colliculus

JEFFERY A. WINER

1. INTRODUCTION

The inferior colliculus (IC) is the first site in which the several parallel streams established in the cochlear nucleus (Warr 1982) converge (Aitkin and Phillips 1984) before sending this information to the auditory thalamus (see Chapter 7) and cortex (Winer 1992). There is parallel convergence of ascending inputs from γ-aminobutyric acid-positive (GABAergic) and glycinergic subcollicular pathways that reach the IC (Winer et al. 1995) and terminate there (Saint Marie and Baker 1990) or GABAergic inputs that reach the medial geniculate body (MGB) (Winer et al. 1996). The emphasis on the IC as the midbrain hub for ascending input has obscured the fact that it is the target of descending forebrain projections from three systems. The first arises in 11 of the 12 areas that constitute the cat auditory cortex (Winer et al. 1998) and is the corticocollicular system (CC); its physiological role is not well understood despite the fact that the cortex can affect many facets of IC operations. A second, smaller system also has widespread origins but represents far fewer neurons: the thalamotectal system (TT) arises from a widely distributed and diverse set of phylogenetically ancient nuclei in the posterior and intralaminar thalamic regions (Kuwabara and Zook 2000). Nothing is known about the physiological impact of the TT system. A third input arises from the bat lateral amygdaloid nucleus (Marsh et al. 2002), which is a multisensory limbic center and itself the target of auditory and somatic sensory cortical projections in rat (Romanski et al. 1993) and of ascending input from two MGB subdivisions (Shinonaga et al. 1994). No physiologic evidence is available on the role of the amygdalocollicular system (AC). It is not implausible to suggest that the CC, TT, and AC systems collectively represent parallel descending influences that converge on IC subdivisions largely outside the lemniscal pathway represented in the central nucleus. Ultimately, the cortical output targets many of the same subcortical nuclei that provide input to the cortex (Winer et al. 2001), and to other more remote nuclei early in the ascending chain of serial processing in rat (Doucet et al. 2002).

A reconsideration of descending input to the IC is timely, as the CC and TT pathways are rarely compared. The CC input merits attention because it arises

from so many subdivisions of auditory cortex and is thus massive, while the TT system is widespread, diffuse, and far smaller. This CC input to some IC subdivisions is larger than the ascending auditory input, suggesting a role other than modulatory. Physiologic studies find powerful and diverse cortical influences on IC neural responses. Because the posterior thalamus targets many of the same IC subdivisions as does the auditory cortex input, there may be local interactions between corticofugal and thalamofugal systems. The auditory corticofugal projection is comparable in size to the corticospinal pathway; perhaps it has subcortical effects analogous to those in the motor system, except within an auditory frame of reference. The TT pathway remains to be integrated within the family of descending systems. Finally, the AC pathway implies a new kind of functional centrality for the IC as inputs from the cortex, posterior thalamic nuclei, and limbic forebrain, as well as classic ascending projections, all converge in the midbrain subdivisions. Unless noted otherwise, citations refer to the cat.

2. Origins of the Corticocollicular System

At least 11 cortical areas with some auditory affiliation project onto the IC. This input varies on an areal basis (Fig. 8.4A). The strongest CC projection is from the primary (tonotopic) subdivisions of auditory cortex, although nontonotopic regions have more targets in the midbrain and a wider range in projection strength. Limbic-affiliated cortical areas, for example, differ in their CC projections, suggesting that otherwise comparable regions have distinctive corticofugal patterns (Winer et al. 1998).

Layer V is the only laminar source of CC input from the primary auditory cortex (AI). Layer V in AI has three subdivisions, and the CC system arises in sublayers Vb and Vc (Winer and Prieto 2001). The most superficial and the deepest parts of layer V give rise to corticogeniculate axons (Prieto and Winer 1999). Layer V thus projects in the corticocollicular and the corticothalamic systems, besides participating in the commissural (Code and Winer 1985), corticopontine (Brodal 1972), and corticostriatal (Reale and Imig 1983; Beneyto and Prieto 2001) pathways. Thus, despite the laminar specificity of layer V projections, the CC system is only one of its several outputs.

2.1. Types of Neurons

All CC neurons are pyramidal in rat (Games and Winer 1988), cat (Winer and Prieto 2001), and monkey (Winer et al. 2002). CC pyramidal cells range from medium-sized to the largest in AI, and CC axons may have corresponding differences in form, conduction velocity and, perhaps their postsynaptic targets (cf. Section 2.3). These neurons are glutamatergic (Feliciano and Potashner 1995). Many large pyramidal neurons have apical dendrites that extend to layer I to receive both specific (layers III to IV) and nonspecific (layer I) thalamocortical input (White and Hersch 1982; Huang and Winer 2000). Such cells can fire in

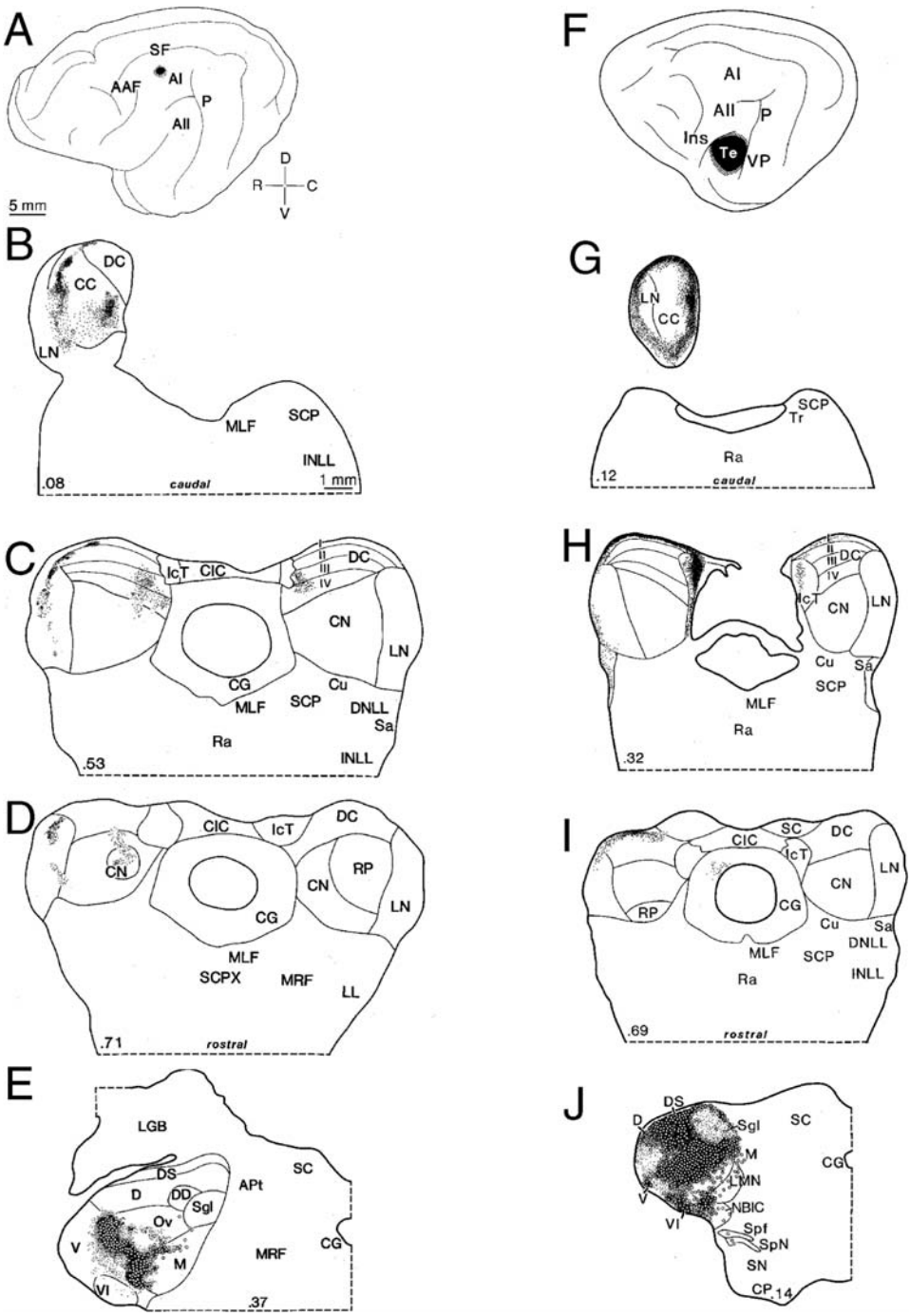

Figure 8.1. Corticofugal projections to the IC **(A–D; F–I)** and MGB **(E, J)** from deposits in AI (*black area* in **A**) and temporal (*black area* in **F**) cortices. Both projections are topographically specific and produce focal terminal labeling in different IC subdivisions. MGB-labeled neurons *(***J**, *open circles)* mingle with anterogradely labeled axon terminals. (Winer et al. 1998, 2001.)

an intrinsic bursting mode and have a sparser local projection in AI, whereas those with shorter apical dendrites have more regular spiking behavior and intricate local projections in rat (Hefti and Smith 2000).

2.2. *Topography*

The distribution of CC axon terminals in the IC is topographic, irrespective of the cortical origin of the projection (Winer et al. 1998). Because most auditory cortical areas have no tonotopic arrangement (Imig and Reale 1980; Schreiner and Cynader 1984), the projections from a limbic-related area (Fig. 8.1F–I) were as orderly and focal as those from tonotopic areas (Fig. 8.1A–D). Perhaps organizing principles other than tonotopy regulate the CC projection topography, and nuclear specificity is a general quality of corticofugal projections.

A second feature is that the CC system targets IC subdivisions that themselves receive modest input from subcollicular auditory structures (Brunso-Bechtold et al. 1981). The wealth of brain stem input to the IC (Warr 1982) is thus partly segregated from cortical projections. This is not the case in the MGB (Calford and Aitkin 1983; Winer et al. 2001).

2.3. *Corticocollicular Axons*

CC axons vary in size and shape and may have a distribution specific to each target. For example, fibers targeting the lateral nucleus are much thicker and may form elaborate terminal nests (Fig. 8.2A: 7). In contrast, the input to the central nucleus is unique because it is conspicuously lighter (Fig. 8.2C: 4), because the axons are so slender (<1 μm in diameter; Fig. 8.2B: 1) and have relatively few boutons, and because many fibers parallel the axis of central nucleus laminae (Fig. 8.2B: 7). The density of input and the distribution of the axons corroborates results found with other tracers (Fig. 8.1A–D, F–I). Perhaps the cortical neurons projecting to separate midbrain subdivisions and their terminal architecture is specific to each nuclear target. Further subtypes of layer V neurons may exist that are analogous to the subclasses of layer VI pyramidal neurons in visual cortex (Briggs and Callaway 2001). Combined, these characteristics support the idea of multiple parallel descending pathways.

3. Cortical Effects on Midbrain Physiology

About one half of a sample of rat IC cells responded to electrical pulses delivered to the cortex; most had brief excitatory responses, and in some this preceded a longer lasting inhibition. Inhibition suppressed spontaneous or sound-evoked discharge (Syka and Popelář 1984). AI stimulation evoked excitatory postsynaptic potentials, inhibitory postsynaptic potentials, or a sequence of both in IC neurons projecting to the MGB; the inhibitory potentials had a longer latency (Mitani et al. 1983). Perhaps colliculogeniculate neurons are un-

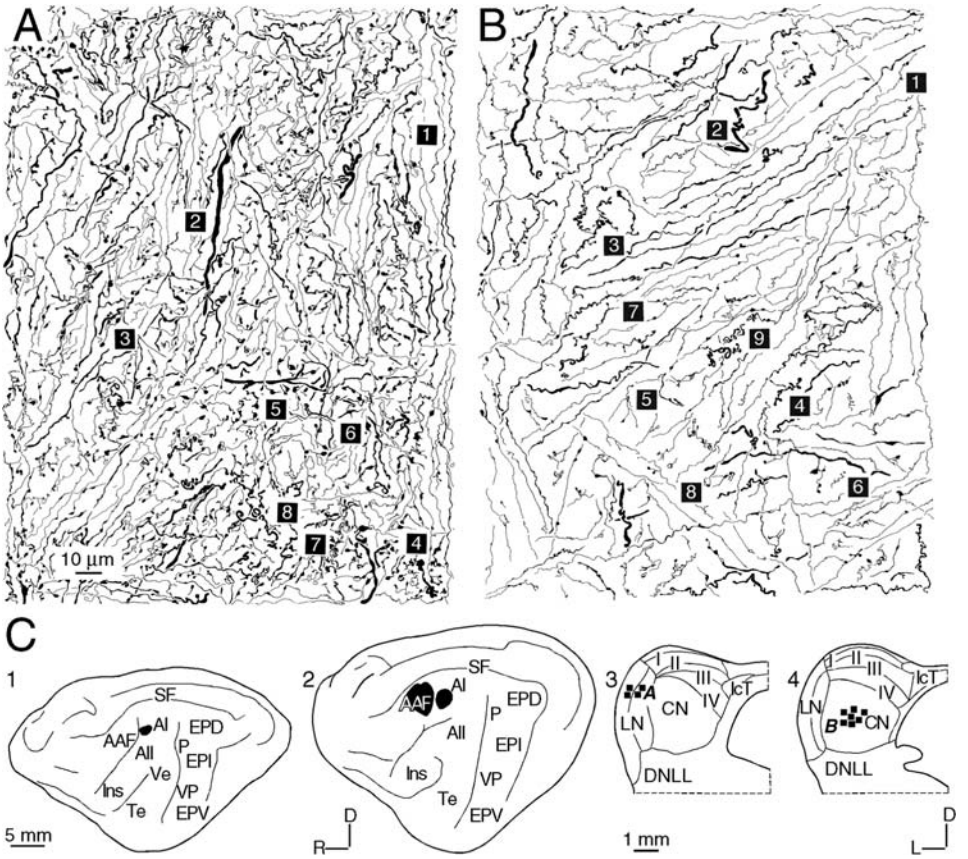

Figure 8.2. Corticofugal axons in IC subdivisions (**C**: 3,4) after deposits of biotinylated dextran amines in AI (**C**: 1) or AI and AAF (**C**: 2). **(A)** Axons in the lateral nucleus. Four sections were required for this panel (**C**: 3, small squares). *1,* Vertically oriented fibers; *2,* thick preterminal axon; *3,* clustered boutons; *4,* a massive terminal; *5,* fibers cross the plexus at right angles; *6,* medium-sized (1–2 µm thick) fibers; *7,* terminals forming complex nests; *8,* fibers with a corkscrew trajectory. **(B)** Central nucleus axons were sparser, thinner, and had fewer boutons than fibers in other subdivisions. Seven sections were required for this panel (**C**: 4, *small squares*). *1,* The main type is a fine fiber (<1 µm thick) with sparse beads, and oriented parallel to the fibrodendritic laminae; *2,* thicker preterminal branch; *3,* elaborate terminal appendages; *4,* grape-like boutons; *5,* the delicate terminal plexus of a thin fiber (cf. *1*); *6,* extremely fine fibers about 0.5 µm thick; *7,* laminar orientation of fibers; *8,* more terminal boutons of fine axons (cf. *5, 6*); *9,* corkscrews in the neuropil. Protocol for **(A, B)**: planapochromat, numerical aperture 1.32, ×2000. **(C)** Deposit sites *(black)* in AI *(1)* and AAF/AI *(2). 3, 4,* Locus of IC axons in the lateral nucleus *(LN)* and central nucleus (*CN*).

der direct cortical control, and the cortex can modulate thalamic neurons through three routes: directly via corticogeniculate projections and indirectly, through the IC and the thalamic reticular nucleus (Crabtree 1998).

Echolocating bats have been the subject of physiologic work on the CC system (Suga et al. 2000). Enhancement of local cortical activity by electrical stimulation in the big brown bat decreased collicular rate-intensity functions and the size of the spatial response area, increased thresholds, and sharpened tuning. Suppression of local cortical activity with lidocaine elevated rate-intensity functions and increased the size of the response area, lowered threshold, and broadened the frequency tuning curve (Sun et al. 1996). Iontophoretic studies using GABA or bicuculline in the IC elicited many of these effects by local pharmacologic administration (Jen et al. 1998). Perhaps cortical axons preferentially target local IC inhibitory circuits responsible for these processes. In the mustached bat, echo-delay processing is enhanced by CC stimulation (Yan and Suga 1996a), while MGB neurons sharpen the delay-tuning curves significantly (Yan and Suga 1996b). Frequency specific shifts in IC frequency reorganization occur in mice after cortical stimulation (Yan and Ehret 2001), and in bats cortically evoked shifts in IC organization emerge before those in auditory cortex (Gao and Suga 2000). Overall, both global and specific changes in receptive field properties and physiologic organization are under CC control.

4. Models of Corticofugal Functional Organization

The corticofugal projections to the auditory midbrain and thalamus might exceed those ascending from the brain stem. This raises two questions: are these descending pathways parallel and as specific functionally as their ascending counterparts, and how do they differ in species in which the corticofugal system is reduced?

4.1. Feedback

The classic view of corticothalamic projections emphasizes their feedback role (Frigyesi et al. 1972). Although this is a reasonable hypothesis it does not explain why these projections are necessary or reciprocal or how they interact (Deschênes et al. 1998), nor can it explain why some axons have larger zones of influence than the topographically matched retinal input (Murphy et al. 1999). With respect to the CC system, the feedback hypothesis is even less compelling because the cortex cannot regulate temporal processes that are briefer than the CC conduction time (cf. Section 4.2), and because many IC neurons that the cortex might be expected to influence, for example, those in the central nucleus, likely receive more extensive intracollicular than cortical input, at least in rodents (Saldaña and Merchán 1992; Malmierca et al. 1995).

4.2. Steps Toward a Theory of Descending Control

There is no global theory of corticofugal operations that places corticothalamic, CC, and other corticofugal projections in a unified context. Such a theory is vital because the targets of this system include the striatum and the pons and other centers that do not have the same functions. Moreover, the corticothalamic and the corticocollicular projections must have different roles because the auditory thalamus and midbrain are connected bidirectionally. A global view should relate corticofugal to corticocortical connections because these systems interact. A model is proposed that postulates a predictive role in which CC input provides instructive commands for processes such as dynamic retuning of receptive fields, postural adjustments, preparations for head and neck reflexes concerned with spatial localization, and the integration of descending auditory and ascending somatic sensory information in the IC. Alternative hypotheses emphasize descending control (Przybyszewski 1998) or signal selection (King 1997). The present account differs in its emphasis on the anticipatory and predictive aspects of corticofugal control, and it is consistent with the notion that feedback responses are temporally rapid in other neural systems and may influence events earlier in the chain of local processing (Hupé et al. 2001).

Several ideas flow from this model. To be predictive, the outflow must be temporally remote from immediate sensory events; this is the case with the time course of evoked potentials. Second, there should be, and there are, significant differences in the corticothalamic and CC projections; each has unique laminar origins and axonal structure, and they differ in their strength of input to the main targets, namely, the ventral division of the MGB (the input to which is massive) and the central nucleus of the IC (whose input is far smaller). Much cortical input to the central nucleus may synapse first in the lateral nucleus (or external cortex), perhaps influencing multisensory operations that are poorly understood. A third requirement is that the cortical areas with descending projections should have extensive feedforward inputs to the higher order areas, which they do. This enables cortex to craft strategic responses long after the initial sensory events, and far in advance of actual movement, much as the premotor cortex enables movement sequence preparation. This theory must account for auditory cortex projections to the basal ganglia, which might coordinate musculoskeletal and audiospinal frames of reference for complex behaviors such as prey acquisition, predator avoidance, mating, freezing, startle, and motor aspects of vocalization dependent on sensory feedback. A fifth prediction is that dynamic midbrain processes such as vigilance or state-dependent changes might require neurons capable of firing in the bursting mode; such neurons are abundant in layer V of AI. These requirements cannot confirm the validity of predictive autonomy as a principle of midbrain function, but they do provide a context for further exploration.

5. The Thalamotectal System

The discovery of the thalamotectal (TT) system was fortuitous and unexpected. It was fortuitous because labeled neurons were found in the auditory thalamus after IC tracer deposits designed to label ascending midbrain axons (Adams 1979) and unexpected because there are no analogous descending projections in other modalities.

Elegant work in a slice preparation first revealed TT organization by filling cells in the medial or dorsal divisions of the gerbil MGB and tracing their axons to the IC (Kuwabara and Zook 2000). Some of the strongest projections were from the medial division to the external nucleus (50% of 14 intracellularly filled neurons), and descending axons were traced to regions near the superior olivary complex.

The TT system arises from the MGB, posterior thalamus, and rostral midbrain, and it targets the central nucleus, dorsal cortex, and lateral nucleus (external cortex) of the IC in rat, cat, and monkey (Winer et al. 2002). Ipsilateral origins are the medial division of the MGB, central gray, and substantia nigra. Bilateral sources include the peripeduncular nuclei, the posterior intralaminar thalamic nuclei, the nucleus of the brachium, the lateral tegmentum, and the deep superior colliculus. TT neurons are diverse in form (Fig. 8.3), often having long, smooth, thin dendrites that branch rarely and resemble thalamic intralaminar cells (Winer et al. 1988). Some TT cells also receive input from the IC, suggesting a reciprocal relationship between ascending and descending systems.

5.1. Speculation on the Thalamotectal System

The role of the TT system is unknown. Thus, functional hypotheses must largely be based on the properties of the projection neurons and their IC targets. A few examples demonstrate the prospective breadth of these relationships (Casseday and Covey 1996).

Neurons in the medial division of the MGB have broad tuning curves, respond both to auditory and nonauditory input (Aitkin 1973), show long-term potentiation (Gerren and Weinberger 1983), project to many layers in all subdivisions of auditory cortex (Huang and Winer 2000), and receive cortical inputs of variable strength from several areas (Winer et al. 2001). In contrast, the deep layers of the superior colliculus integrate multimodal input (Huerta and Harting 1984), its projections reach the nucleus of the brachium of the IC (Doubell et al. 2000) and the intralaminar thalamic nuclei (Krout et al. 2001), and they may enable certain types of seizures via their connections with the IC (Yang et al. 2001). The propensity of posterior thalamic neurons for oscillatory and temporally protracted activity suggests roles in processes ranging from seizure to cognition (Llinás and Paré 1997) to autonomic function (Endepols and Walkowiak 1999).

Figure 8.3. Corticocollicular **(A)** and thalamotectal **(B)** neurons after IC tracer deposits in the rat. **(A)** Corticollicular neurons are exclusively pyramidal *(1–3)* and some have dendrites that reach layer I *(3). Inset*, deposit site (*solid*) and tracer diffusion (*stippled*). Protocol as in Fig. 8.2. **(B)** Neurons projecting to the IC from perithalamic territories include cells in the superior colliculus *(1),* nucleus of the brachium *(2),* and posterior limitans nucleus *(3, 4).* Many *(1–4)* have long, rather smooth dendrites and a simple branching pattern reminiscent of tegmental cells.

5.2. The Amygdalocollicular System

This pathway is documented in two bat species, one of which (*Antrozous pallidus*) is highly visual and uses passive echolocation (Fuzessery et al. 1993) and gleaning (Brown et al. 1978) to acquire prey, while the other (*Pteronotus p. parnellii*) has a remarkable echolocation repertoire (Suga 1964; Fitzpatrick et al. 1998). Neurons in the magnocellular basal amygdaloid nucleus were labeled bilaterally after tracer deposits in IC subdivisions that included the central nucleus (Marsh et al. 2002); the number of labeled cells approximated that in auditory cortex, suggesting a massive, rather than a modulatory, projection.

6. A New Kind of Convergence

The three descending systems considered here terminate preferentially in the external nucleus and dorsal cortex of the IC. This implies that there is convergence of descending influences analogous to that reported for ascending pathways, that the descending pathways act as parallel systems that complement their ascending counterparts, and that there are multiple forebrain systems in hearing without a precise analogue in the visual and somatic sensory systems.

7. Directions for Future Research

Understanding how the CC and TT systems accomplish their functional tasks will require a number of complementary approaches.

7.1. The Corticocollicular System

Direct optical imaging of the neurons during behavioral tasks could provide insight into the sublaminar pattern of activation in the CC system. If there are parallel CC pathways, such an approach might identify them on a temporal basis.

Pharmacologic inactivation of single or small groups of cortical neurons in specific sublayers may have contrasting effects on the midbrain.

Mapping corticocolliculofugal connections with transneuronal tracers could demonstrate the downstream targets of CC neurons. Such experiments address issues of connectional and functional parallelism.

Comparing the synaptic arrangements in different IC subdivisions is an essential step in understanding how midbrain neurons and their associated circuits are under cortical control. For example, cortical influence on the central nucleus of the IC and the ventral division of the MGB may differ. Insights into intrinsic IC circuits could relate them directly to CC input.

The massive CC convergence should be correlated with inactivation studies of single areas, sets of areas, and of hemispheres.

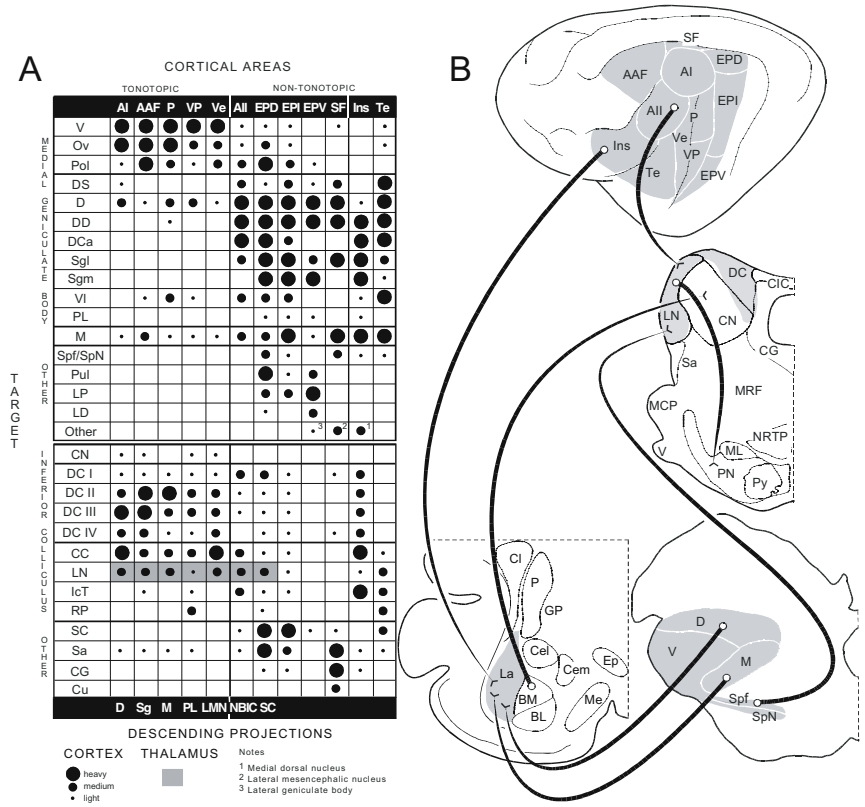

Figure 8.4. **(A)** Summary of auditory corticofugal anterograde projections (origins: *white letters at top;* targets: *left side*) to the MGB *(upper half)* and inferior colliculus *(lower half),* and thalamotectal projections (origins: *white letters at bottom;* terminations: *gray stippling*). In the thalamus, the ventral division receives a heavy input, while the central nucleus *(CN)* of the IC receives less. Likewise, the limbic components *(Ins, Te)* of non-tonotopic auditory cortex have different thalamic and midbrain projection patterns (Winer et al. 1998, 2001). **(B)** Schematic showing possible nuclear convergence of cortical *(upper panel)* and thalamic *(lower panel)* projections to the lateral nucleus of the IC. Such input might reach the CN and affect ultimately pontine neurons, not to mention prospective commissural and tectofugal effects. The links between the amygdala and the inferior colliculus have been demonstrated only in bats (Marsh et al. 2002) and are here projected onto cat amygdaloid subdivisions (Krettek and Price 1978).

7.2. The Thalamotectal System

Selective, reversible inactivation of TT projections could shed light on how thalamic neurons affect IC cells. This should be contrasted with the effects of cortical blockade alone and of simultaneous midbrain and cortical inactivation.

Creating transgenic species devoid of TT projections for physiologic study might reveal the functional contributions of this system and the effects of its genetic deletion.

Exploring the interactions between descending systems and ascending, commissural, and intrinsic pathways could reveal polysynaptic relationships. As the resolution of imaging methods improve, the locus and order of temporal activation patterns should be explored.

7.3. The Amygdalocollicular System

Dual simultaneous recordings in the lateral amygdala and the IC during feeding, procreation, and social behavior including vocalizations should reveal their interactions. Reversible inactivation of the amygdala through cooling or pharmacologic means could elucidate its role in complex social behaviors.

Transneuronal tract tracing with rabies virus should permit visualization of tectofugal projection neurons that themselves are the target of AC input, thus connecting subsequent synaptic chains into a more explicit and extended functional linkage that might include tectopontine or tectocochlear centers.

Abbreviations

AAF	anterior auditory field
AC	amygdalocollicular system
AI	primary auditory cortex
APt	anterior pretectum
AII	second auditory cortex
BL	basolateral amygdaloid nucleus
BM	basomedial amygdaloid nucleus
C	caudal
CC	corticocollicular system *or* caudal cortex of the inferior colliculus
Cel	lateral division of central amygdaloid nucleus
Cem	medial division of central amygdaloid nucleus
CG	central gray
CIC	commissure of the inferior colliculus
Cl	claustrum
CN	central nucleus of the inferior colliculus
CP	cerebral peduncle
Cu	cuneiform nucleus
D	dorsal nucleus of the medial geniculate body *or* dorsal

DCa	caudal dorsal nucleus of the medial geniculate body
DC	dorsal cortex of the inferior colliculus
DCI–IV	dorsal cortex layers I–IV
DD	deep dorsal nucleus of the medial geniculate body
DNLL	dorsal nucleus of the lateral lemniscus
DS	dorsal superficial nucleus of the medial geniculate body
EC	external cortex of the inferior colliculus
EPD	posterior ectosylvian gyrus, dorsal part
EPI	posterior ectosylvian gyrus, intermediate part
EPV	posterior ectosylvian gyrus, ventral part
Ep	entopeduncular nucleus
GABA	γ-aminobutyric acid
GP	globus pallidus
IC	inferior colliculus
IcT	intercollicular tegmentum
INLL	intermediate nucleus of the lateral lemniscus
Ins	insular cortex
La	lateral nucleus of the amygdala
LD	lateral dorsal nucleus
LGB	lateral geniculate body
LL	lateral lemniscus
LMN	lateral mesencephalic nucleus
LN	lateral nucleus of the inferior colliculus
LP	lateral posterior nucleus
M	medial division
MCP	middle cerebellar peduncle
Me	medial amygdaloid nucleus
MGB	medial geniculate body
ML	medial lemniscus
MLF	medial longitudinal fasciculus
MRF	mesencephalic reticular formation
NBIC	nucleus of the brachium of the inferior colliculus
NRTP	reticular tegmental nucleus of the pons
Ov	*pars ovoidea* of the ventral division
P	posterior auditory field *or* putamen
PL	posterior limitans nucleus
PN	pontine nuclei
Pol	rostral pole of the medial geniculate body
Pul	pulvinar nucleus
Pu	putamen
Py	pyramidal tract
R	rostral *or* red nucleus
Ra	raphe
RN	red nucleus
RP	rostral pole nucleus of the inferior colliculus

Sa	nucleus sagulum
SC	superior colliculus
SCP	superior cerebellar peduncle
SCPX	decussation of the superior cerebellar peduncle
SF	suprasylvian fringe area
Sg	suprageniculate nucleus
Sgl	suprageniculate nucleus, lateral part
Sgm	suprageniculate nucleus, medial part
SNL	substantia nigra, *pars lateralis*
SNR	substantia nigra, *pars reticulata*
Spf	subparafascicular nucleus
SpN	suprapeduncular nucleus
Te	temporal cortex
Tr	trochlear nerve
TT	thalamotectal system
V	*pars lateralis* of the ventral division *or* ventral *or* trigeminal nerve
Ve	ventral auditory area
Vl	ventrolateral nucleus of the medial geniculate body
VP	ventral posterior auditory area
I–IV	layers of the dorsal cortex

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Chapter 9
Pharmacology of the Inferior Colliculus

Jack B. Kelly and Donald M. Caspary

1. Introduction

The inferior colliculus (IC) receives convergent projections from a diversity of sources within the auditory pathway and is an important midbrain structure for processing acoustic information. The characteristics of the neurotransmitters and neuromodulators acting at synapses on the somata and dendrites of IC neurons are critically important in shaping responses to both monaural and binaural stimuli. The ways in which IC neurons encode information about complex sounds are determined in large measure by the neurotransmitters and receptors that regulate and control synaptic responses as well as the circuitry and biophysical properties of the neurons and their processes (see Chapter 10). The present chapter examines how the principal amino acid neurotransmitters, acting through ionotropic receptors, influence IC coding. We briefly consider how other identified neurotransmitters and neuromodulators influence the response properties of IC neurons and circuits.

We first provide an overview of the major transmitters released from the principal extrinsic projections and intrinsic pathways and then describe how these neurotransmitters shape the acoustic message as it ascends. The primary excitatory neurotransmitter, released onto IC neurons from ascending, descending, and perhaps intrinsic inputs is the excitatory amino acid, glutamate, acting at both α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) receptors (Adams and Wenthold 1979; Bergman et al. 1989; Faingold et al. 1989a). Many extrinsic and intrinsic IC circuits utilize the amino acid, γ-aminobutyric acid (GABA), as the principal inhibitory neurotransmitter. Also, the inhibitory amino acid glycine is released from several ascending IC inputs (Faingold et al. 1991a; Winer et al. 1995). Other neuroactive substances released onto IC neurons and their dendrites include the catecholamines, serotonin and norepinephrine, as well as acetylcholine, and many peptides. Our emphasis, however, is on the pharmacology of the amino acid neurotransmitters: glutamate, GABA, and glycine.

2. Glutamatergic Inputs into the Inferior Colliculus

There remains little doubt that glutamate is the primary excitatory transmitter throughout the IC (Adams and Wenthold 1979; Faingold et al. 1989b; Bergman et al. 1989; Saint Marie 1996). Neurochemical and functional studies document its release, uptake, and action on both AMPA and NMDA receptors (Feldman and Knudsen 1994; Suneja et al. 2000; Kelly and Zhang 2002; Ma et al. 2002a; Wu et al. 2002). Other studies have specified the subunit makeup of the AMPA receptor and the NMDA receptor in the different IC subdivisions (Marianowski et al. 2000; Parks 2000) and have suggested that the NMDA receptor plays a role in regulating response plasticity (Feldman et al. 1996; Kelly and Zhang 2002; Wu et al. 2002). Physiologic studies have begun to assess the relative impact of parallel ascending excitatory inputs onto neurons in the central nucleus of the inferior colliculus (ICC) (Davis 2002; Davis et al. 2003).

2.1. Ascending Excitatory Inputs

The ventral cochlear nucleus (VCN) is generally considered the main excitatory projection to the IC (Helfert et al. 1991; see Chapter 3). Multipolar/stellate cells in both anterior and posterior VCN project directly to the contralateral IC with collateral projections to other auditory nuclei en route. Most of these neurons are likely excitatory and glutamatergic (Wenthold 1991; Wenthold et al. 1993; Romand and Avan 1997).

Fusiform cells of the dorsal cochlear nucleus (DCN) project to the IC directly and contribute specific excitatory response properties to subpopulations of IC neurons (Davis 2002). Fusiform cells display strongly nonmonotonic rate-intensity functions around their characteristic frequency (CF) and have stereotyped temporal response properties that include buildup or pauser-buildup response patterns observed in their post-stimulus time histograms (PSTHs), that is, the temporal distribution of their action potentials over the time course of stimulus presentation. Fusiform cells show temporal locking to the envelope of sinusoidally amplitude modulated sounds with a greater discharge synchrony than expected from the modulation waveform, that is, they have modulation transfer function gains >1. This temporal locking is not altered by $GABA_A$ receptor blockade in ICC, suggesting that the high level of response synchrony is established in DCN. Some, but not all, of these temporal properties are reflected in the responses of a subpopulation of contralateral IC neurons, which provides functional evidence for a direct input from DCN fusiform cells (Caspary et al. 2002; Davis 2002). Ascending excitatory inputs from the contralateral lateral superior olive (LSO) and the ipsilateral medial superior olive (MSO) are generally considered to be sources of glutamatergic activation of IC neurons

(Casseday et al. 1988; Glendenning et al. 1992; Feldman and Knudsen 1994; Suneja et al. 2000; Kelly and Zhang 2002; Wu et al. 2002). LSO projections convey binaural information to recipient IC neurons, shaping, at least in part, their responses to interaural intensity differences, especially for high-frequency sounds (Li and Kelly 1992; Sally and Kelly 1992; Park and Pollak 1994). MSO projections impart information about interaural timing differences/interaural phase differences especially pertaining to low-frequency binaural coding. It is important to note that additional shaping of binaural responses occurs in the IC and thus the coding is not complete at the superior olive (Faingold et al. 1989a, 1993; Li and Kelly 1992; Sally and Kelly 1992; Kelly and Li 1997).

2.2. Descending Excitatory Inputs

The corticocollicular inputs and, to a lesser extent, geniculocollicular inputs likely are glutamatergic. However, the functional nature of this excitation, especially in the ICC, is not well understood. Layer V pyramidal neurons in auditory cortex, which project to the IC dorsal cortex (ICD), external nucleus (ICX), and central nucleus (ICC), likely possess fairly robust excitatory responses within a conventional V-shaped frequency tuning curve (Turner et al. 2003). Whether these descending inputs are in alignment/register with the frequency tuning of their midbrain targets is unknown. Whether inhibitory neurons in the ICD and the ICX convert these descending excitatory inputs into inhibition in the ipsilateral and contralateral ICC also remains an open question (Jen et al. 2001).

2.3. Extrinsic Inhibitory Inputs to the Inferior Colliculus

In cats and mustache bats about 20% of the IC neurons are GABAergic (Oliver et al. 1994; Winer et al. 1995). In rats 20% to 40% of the neurons in the three major subdivisions of the IC are GABA- or glutamic acid decarboxylase (GAD)-positive (Mugnaini and Oertel 1985; Caspary et al. 1990) and approximately 44% of the synapses are GABAergic (Helfert et al. 1999). GABAergic extrinsic, intrinsic, and commissural projections terminate as either focused or diffuse inhibitory inputs on IC neurons (Adams and Mugnaini 1984; Shneiderman et al. 1988, 1993; Helfert et al. 1989; Saint Marie et al. 1989; Shneiderman and Oliver 1989; Huffman and Henson 1990). Particularly high levels of GABA exist in the IC (Tachibana and Kuriyama 1974; Banay-Schwartz et al. 1989b) and many neurons that label for GABA/GAD likely affect neuronal responses through intrinsic or commissural projections (Fisher and Davies 1976; Adams 1979; Contreras and Bachelard 1979; Mugnaini and Oertel 1985; Nagai et al. 1985; Thompson et al. 1985; Moore and Moore 1987; Roberts and Ribak 1987a,b; Carr et al. 1989; Wenthold 1991; Smith 1992; Vater et al. 1992; Oliver et al. 1994; González-Hernández et al. 1996; Zhang et al. 1998; Jen et al. 2001; see Chapter 10).

GABAergic inputs arise from several extrinsic sources, including a projection from the contralateral dorsal nucleus of the lateral lemniscus (DNLL) and a smaller ipsilateral DNLL projection (Adams and Mugnaini 1984; Li and Kelly 1992; Vater et al. 1992b; Faingold et al. 1993; Shneiderman et al. 1993). In the rat, the superior paraolivary nucleus of the superior olivary complex sends direct GABAergic input to the ipsilateral ICC (Kulesza et al. 2003). Nearly half of the neurons in LSO are glycinergic and send direct input to the ipsilateral IC (Helfert et al. 1989; Saint Marie et al. 1989; Glendenning et al. 1992; Vater et al. 1992b; Vater 1995; Ostapoff et al. 1997). Inhibitory input also arises from the medial geniculate body (Vater et al. 1992b) and perhaps the auditory cortex (Adams and Wenthold 1979; Jen et al. 2001). Connectional studies using small injections of tracers into tonotopically identified target areas suggest that GABAergic projections from the DNLL and the collicular commissure may be tonotopically aligned with their ICC targets (Saldaña and Merchán 1992; Merchán et al. 1994; Malmierca et al. 1996; Bajo et al. 1999). These observations have important implications for the shaping of frequency-response tuning curves and the coding of modulated stimuli.

2.4. *Role of* γ-Aminobutyric Acid in the Central Nucleus

All criteria needed to establish GABA as an IC neurotransmitter have been satisfied. High levels of the synthetic enzyme GAD and the degradative enzyme GABA transaminase are found in the ICC (Fisher and Davies 1976; Adams and Wenthold 1979; Contreras and Bachelard 1979; Nagai et al. 1985; Vater et al. 1992b; Raza et al. 1994). GABA is released from ICC slices/punches in a Ca^{2+}-dependent manner (López–Colomé et al. 1978; Banay-Schwartz et al. 1989b; Caspary et al. 1990; Shneiderman et al. 1993) and a high-affinity GABA uptake system exists in the ICC (Shneiderman et al. 1993; Raza et al. 1994; Suneja et al. 1998). Immunocytochemical probes for conjugated GABA and GAD show dense labeling in somata, fibers, and axon terminal puncta within the ICC, which has among the highest GAD labeling in the auditory brain stem (Tachibana and Kuriyama 1974; Mugnaini and Oertel 1985; Thompson et al. 1985; Moore and Moore 1987; Carr et al. 1989; Caspary et al. 1990).

The $GABA_A$ receptor was initially demonstrated in binding studies (Glendenning and Baker 1988), and high $GABA_A$ receptor binding levels are seen in the rat brain, especially for the benzodiazepine, flunitrazepam (Fig. 9.1A), and the $GABA_A$ receptor channel marker at the picrotoxin site, *t*-butylbicycloorthobenzoate (TBOB) (Fig. 9.1C). Muscimol binding in the IC (Fig. 9.1B) is less dramatic than in the cerebellum, where it may selectively bind different $GABA_A$ subunit constructs.

The $GABA_A$ receptor is a heteromeric pentamer with >20 subunits. The adult wild-type $GABA_A$ receptor likely consists of $2\alpha_1 2\beta_2\gamma_2$ (Chebib and Johnston 1999) and the $GABA_A$ receptor subunit construct will partly determine the response to presynaptically released GABA at IC neuronal synapses. The subunit makeup of the $GABA_A$ receptor in IC subregions is known (Milbrandt et al.

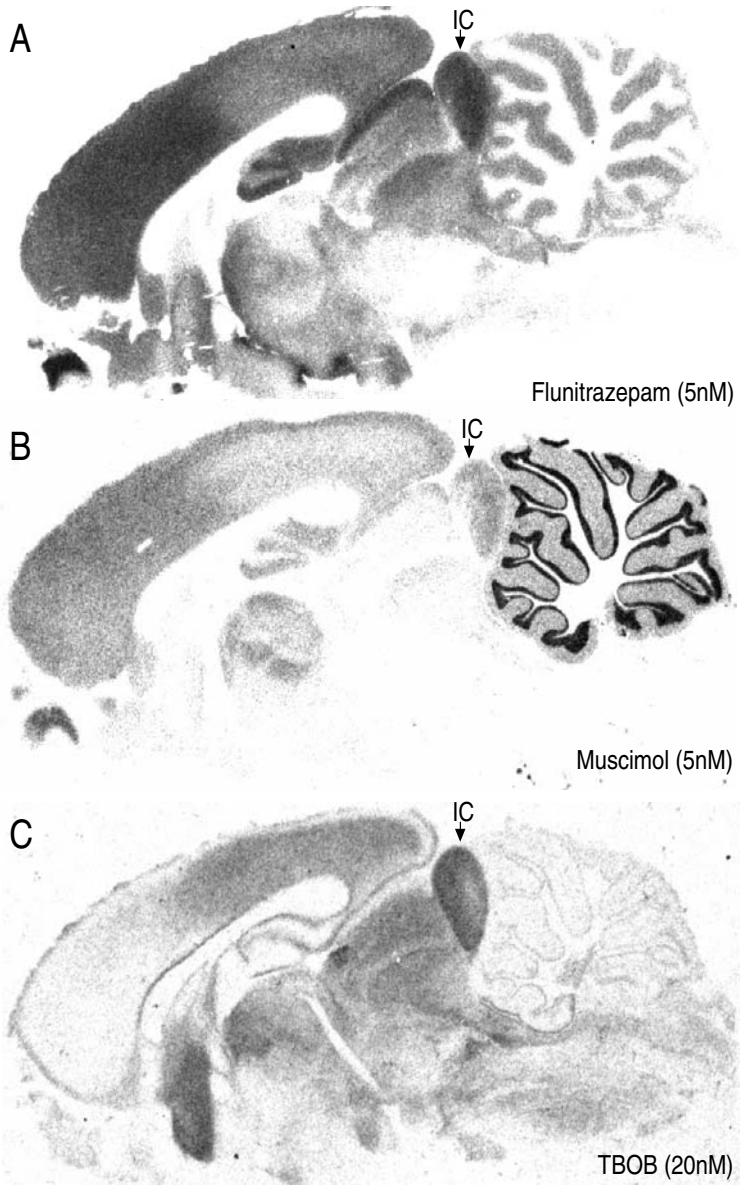

Figure 9.1. Receptor binding of three $GABA_A$ receptor ligands to sites in rat IC (for abbreviations, see the list). Flunitrazepam binds benzodiazepine sites located between the α and γ $GABA_A$ subunits. TBOB (*t*-[^{3}H]butylbicycloorthobenzoate) is thought to bind in the $GABA_A$ receptor channel at the picrotoxin or cage convulsant site, and muscimol is thought to bind at the GABA binding loci on the α subunit. The distribution of these three ligands in a sagittal view of the rat brain is very different. Both TBOB and flunitrazepam show very high levels of binding in IC relative to other brain structures and their distributions within the IC are different.

1997), as is the distribution of $GABA_A$ receptor subunits, for different ICC cell types (Shiraishi et al. 2001). $GABA_B$ receptor binding occurs throughout the rat's IC (Milbrandt et al. 1994) and is prominent in the dorsomedial IC of the bat (Fubara et al. 1996). Whether these receptors are presynaptic sites capable of modulating excitatory or inhibitory inputs or postsynaptic sites opposite GABA terminals is unknown (Bormann 2000). Physiologic studies provide functional and pharmacologic support for the importance of $GABA_A$ and $GABA_B$ receptors in ICC.

3. Brain Slice Studies of Synaptic Pharmacology

In vitro brain slice methods are a powerful tool for investigating synaptic pharmacology. Stable intracellular recordings from one cell over an extended period allow the effects of drugs, for example, selective receptor agonists and/or antagonists, to be evaluated by adding them to the solution bathing the tissue slice. Drug concentration can be precisely controlled and the drug effects can usually be reversed by washing the slice in normal saline. Furthermore, the neurons that provide physiologic data can be filled intracellularly with biocytin, neurobiotin, or Lucifer yellow. Recordings made in either current-clamp or voltage-clamp modes using either sharp electrodes or whole-cell patch-clamp electrodes allow manipulation of the intracellular environment by modifying the solution in the recording pipette to assess membrane properties in detail.

In brain slice studies, synaptic responses are usually evoked by current-pulse stimulation of the tracts that terminate on the neurons from which recordings are made. Such stimulation usually elicits complex synaptic effects involving multiple inputs from potentially diverse sources. Moreover, each current pulse activates synaptic inputs synchronously and may not resemble the timing or input combinations associated with natural acoustic stimulation. Nevertheless, the brain slice procedure provides important insight into the pharmacology of neural circuits that contribute to hearing.

Electrical stimulation of the lateral lemniscal pathways projecting to the ICC evokes excitatory and inhibitory postsynaptic responses converging on a common neural population (Wagner 1996; Moore et al. 1998; Reetz and Ehret 1999; Ma et al. 2002a). Most ICC neurons receive both excitatory and inhibitory input from ascending fibers.

Excitatory responses are mediated by AMPA and NMDA receptors, which are usually present on the same postsynaptic neuron, possibly at the same terminals, and can be activated by the same current pulse stimulus (Ma et al. 2002a). With the brain slice in normal saline, two postsynaptic excitatory response components can be distinguished based on their time of occurrence following current-pulse stimulation. An initial early response with short latency is followed by a more slowly developing late response that produces a second peak in the excitatory postsynaptic potential (EPSP) or postsynaptic current (EPSC). Application of AMPA receptor antagonists, for example, 6-cyano-7-

nitroquinoxaline-2,3-dione (CNQX) or 1,2,3,4-tetrahydro-6-nitro-2,3-dioxo-benzo[*f*]quinoxaline-7-sulfonamide (NBQX) causes a decrease in the amplitude of the early synaptic response. The early response can be blocked by these AMPA antagonists without eliminating the later response.

The later postsynaptic response can be selectively blocked by the NMDA receptor antagonists, (±)-2-amino-5-phosphonovaleric acid (APV) or (±)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP). These drugs can eliminate the late response while leaving the early response intact. Thus, the early and late excitatory synaptic currents in the ICC can be separated pharmacologically. A more accurate assessment of the timing of these excitatory currents comes from recordings in which inhibitory responses are blocked by receptor antagonists. AMPA receptor-mediated EPSPs have shorter rise times than NMDA receptor-mediated EPSPs (means: 5.4 and 22.8 ms, respectively) and shorter decay times (35.6 and 92.1 ms), shorter times to peak response (19.5 ms and 62.9 ms), and smaller half-widths (42.6 and 120.8 ms) (Ma et al. 2002a). The NMDA receptor-mediated response is greatly enhanced in a Mg-free saline solution and, with Mg, the response size is dependent on the cell's membrane voltage. In contrast, the AMPA receptor-mediated response is unaffected by Mg concentration and is not voltage dependent. The size of the late NMDA receptor-mediated response is increased by depolarization and decreased by hyperpolarization of the cell membrane relative to the resting potential. The sensitivity of ICC neurons to membrane voltage manipulation varies considerably from cell to cell, suggesting cell populations with different input–output characteristics (physiologic gain) (Ma et al. 2002b).

For most ICC neurons, both AMPA and NMDA receptor-mediated responses can be elicited at the cell's resting potential and it is unnecessary to activate AMPA receptors or depolarize the cell membrane to demonstrate a long-lasting NMDA receptor-mediated response. An NMDA receptor-mediated current can often be found even when the AMPA receptor-mediated response is blocked by AMPA receptor antagonists, suggesting that both AMPA and NMDA receptor-mediated excitatory responses are available at or near the threshold for hearing and play important roles in processing sensory information even at low stimulus intensity. This expectation has been confirmed by in vivo recordings from ICC neurons in response to acoustic stimulation (Zhang and Kelly 2001, 2003).

Inhibitory responses in the ICC elicited by lemniscal stimulation are mediated by $GABA_A$ or glycine receptors (Moore et al. 1998; Reetz and Ehret 1999; Ma et al. 2002a). Bath application of the selective $GABA_A$ receptor antagonists, bicuculline or picrotoxin, reduces or eliminates inhibitory postsynaptic potentials (IPSPs) in most ICC neurons. However, the glycine receptor antagonist, strychnine, also reduces postsynaptic inhibition in many cases. Probable sources of glycinergic inhibition are the ipsilateral LSO and the ventral nucleus of the lateral lemniscus (VNLL) (Vater et al. 1997; Riquelme et al. 2001). Probable sources of GABAergic input are the lateral lemniscal nuclei, VNLL and DNLL (Adams and Mugnaini 1984; Li and Kelly 1992; Vater et al. 1992b; Faingold et al. 1993; Shneiderman et al. 1988, 1993), the superior paraolivary nucleus (Ku-

lesza et al. 2003), or intrinsic connections within the ICC. Any of these could contribute to postsynaptic responses depending on the placement of the stimulating electrode.

The glycinergic projection from the ipsilateral LSO and the GABAergic projection from the contralateral DNLL play functionally parallel roles in inhibiting ICC neurons. Because of their unique binaural innervation pattern, LSO neurons are strongly excited by ipsilateral acoustic stimulation and inhibited by contralateral stimulation. ICC target neurons are excited by crossed (glutamatergic) efferent projections and inhibited by uncrossed (glycinergic) LSO projections. Thus a sound source on the left would thus excite neurons in the right ICC and inhibit those in the left ICC. In contrast, DNLL neurons are typically excited by contralateral and inhibited by ipsilateral stimulation. The crossed GABAergic projection from the DNLL inhibits responses in the opposite ICC. Thus, a sound on the left would excite the right DNLL, which would in turn inhibit the left ICC. Both the ipsilateral (glycinergic) LSO projection and the contralateral (GABAergic) DNLL projection serve to enhance the contrast in neural activity between left and right ICC through a lateral inhibitory process and amplify (or at least maintain) differences in the response strength on each side of the brain. Both inhibitory projections would reinforce the functional contralaterality of auditory processing in the midbrain and above.

Many ICC neurons receive convergent input from the lateral lemniscus and the opposite IC via commissural projections (Moore et al. 1998). In the gerbil, current-pulse stimulation of either the lateral lemniscus or the commissure of the IC can evoke postsynaptic responses in the same ICC neuron. Commissural evoked responses can be either excitatory or inhibitory; the former are exclusively GABAergic and can be blocked by bicuculline. Thus, the IC commissure might also contribute to the functional laterality of responses.

$GABA_B$ receptors also contribute to synaptic responses in ICC. In brain slice studies, when AMPA and NMDA receptor-mediated excitatory responses and glycinergic inhibitory responses are eliminated pharmacologically, the remaining inhibitory responses can be completely blocked by bicuculline and are not affected by the $GABA_B$ antagonist, phaclofen (Ma et al. 2002c). On the other hand, the $GABA_B$ receptor agonist, baclofen, decreases IPSP amplitude and this effect can be blocked by phaclofen. Baclofen did not affect the membrane conductance of ICC neurons whereas the $GABA_A$ receptor agonist, muscimol, greatly increased conductance. This result suggests that $GABA_B$ receptors in the ICC influence synaptic transmission primarily by presynaptic modulation of transmitter release. Presynaptic $GABA_B$ receptors can affect synaptic inhibition by controlling the amount of transmitter acting at postsynaptic $GABA_A$ receptor sites.

Also, presynaptic $GABA_B$ receptors can regulate excitatory neurotransmitter release in the ICC (Wu et al. 2004) as well as in other structures in the brain (Potashner 1979; Misgeld et al. 1995; Brenowitz et al. 1998; Lim et al. 2000).

Results from brain slice recordings show that ICC PSPs can be potentiated by strong repetitive (tetanic) stimulation of the lateral lemniscus (Zhang and Wu 2000). These effects persist over several hours of recording and resemble, in

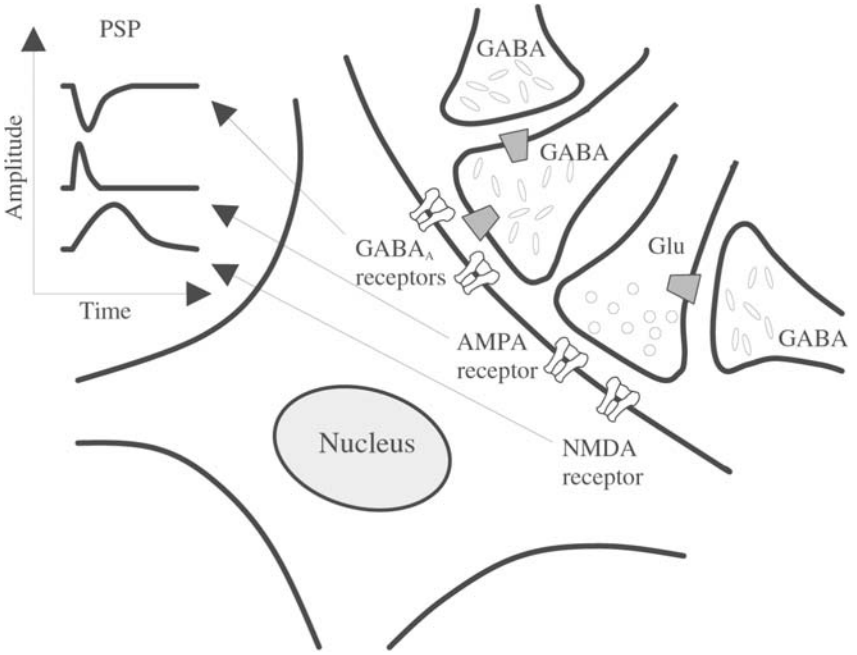

Figure 9.2. Schematic view of GABA and glutamate receptor sites in the ICC based on physiologic recordings and pharmacologic manipulations in brain slice studies of auditory midbrain neurons. The magnitude and sign of postsynaptic potentials *(PSP)* are determined by the balance and timing of excitatory and inhibitory inputs from glutamatergic *(Glu)* and GABAergic terminals. Excitation is mediated by both AMPA and NMDA receptors eliciting relatively early and late excitatory postsynaptic potentials, respectively (upward deflections in the schematic representation of typical responses to current-pulse stimulation). Inhibition is mediated by GABA acting on $GABA_A$ receptors, resulting in an inhibitory postsynaptic potential (a downward deflection in the representative traces). The presynaptic release of both GABA and glutamate is regulated by the activation of $GABA_B$ receptors located on the axon terminals. The normal mechanism for activation of the $GABA_B$ receptors is known. GABA release is likely regulated by $GABA_B$ receptors at the synaptic cleft (autoreceptors), but regulation by presynaptic inhibitory terminals cannot be excluded. Glutamate release might be regulated by presynaptic GABAergic terminals (as indicated), but receptor sites without corresponding axon terminals cannot be excluded. Ionotropic (AMPA, NMDA, and $GABA_A$) receptors are shown as *nonshaded transmembrane pores*. Metabotropic ($GABA_B$) receptors appear as *solid trapezoidal symbols*. Not shown are the receptors for glycine and other neurotransmitters/modulators that affect auditory midbrain physiologic responses.

most respects, the long-term potentiation (LTP) reported elsewhere in the brain (Bliss and Collingridge 1993; Bear and Malenka 1994). The NMDA receptor antagonist, APV, blocks LTP induction in this preparation, indicating that the NMDA receptor plays a key role in ICC synaptic plasticity as it does in other brain centers. $GABA_B$ receptor antagonists block LTP induction, whereas the $GABA_B$ receptor agonist, baclofen, facilitates it, probably by a downward regulation of presynaptic GABA release (Zhang and Wu 2000).

Figure 9.2 shows the probable convergence of synaptic input onto ICC neurons and the potential roles of various receptor types in regulating excitation and inhibition as determined from brain slice studies.

Recordings from brain slice preparations of the IC have examined the dorsal cortex (ICD) and external nucleus (ICX) as well as the ICC (Pierson et al. 1989; Smith 1992; Li et al. 1998, 1999), but reveal little evidence of pharmacologic differences at the synaptic level. In the ICX, ICD, and ICC, excitatory convergence is mediated by glutamate and inhibition largely by GABA. Whether these synapses exhibit unique characteristics that reflect each subdivision's functional specialization will require further study.

4. In Vivo Studies of the Inferior Colliculus

The pharmacology of ICC neurons has been studied in vivo by recording sound-evoked responses before, during, and after drug release at the recording site, usually by iontophoresis. These studies have the advantage of showing the contribution of specific receptors to activity elicited by natural acoustic rather than direct electrical stimulation. Moreover, adult, peripherally altered, and aged animals can be used. The chief disadvantage is the difficulty of controlling drug concentration at the recording site. Although application of the agent is proportional to the current or pressure magnitude over a range of values, an accurate assessment of drug concentration at its site of action is problematic. Concentration decreases as a cubic function of distance, causing a diminishing concentration gradient as the drug spreads from the pipette tip (Foeller et al. 2001). The site of action of a drug on a given neuron is dependent on the size of the molecule, on whether the ligand is actively incorporated by neurons or glia, and on the location of the pipette relative to receptors being studied. Because many IC neurons have substantial dendritic arbors that extend far from the recording site, distal receptors are likely less affected than more proximal dendritic and somatic receptors. Morphologic knowledge of the receptor location is important for interpreting iontophoretic results.

Early studies of in vivo pharmacology show the significant contribution of glutamate and GABA in determining neural acoustic response properties in the IC (see Faingold et al. 1991b). Glutamate plays a major role in evoking excitatory responses to tones or other acoustic stimuli and GABA mediates most inhibitory responses. Application of the $GABA_A$ antagonist, bicuculline, increases sound-evoked firing rate in most neurons, as does glutamate, whereas

glutamate antagonists (e.g., APV) reduce it. Other transmitters, however, affect the level of neural activity, with glycine contributing to the inhibition of responses and acetylcholine, serotonin (5-hydroxytryptamine), and norepinephrine modifying the responses in the IC.

4.1. AMPA and NMDA Receptors and Their Antagonists

Contralateral acoustic stimulation of neurons in the rat ICC involves both AMPA and NMDA glutamate receptor subtypes (Zhang and Kelly 2001, 2003). Iontophoretic release of the selective AMPA receptor antagonist, NBQX, decreased excitatory responses to contralaterally presented 100-ms tone bursts in most IC neurons and blocked responses entirely in some. The blocking effect was present during both early (20-ms) and late (20- to 120-ms) periods of a sustained response to the tone bursts. The selective NMDA receptor antagonist, CPP, also had a blocking effect on most ICC neurons and this effect was strongest during the late part of the response. Thus, the AMPA and NMDA receptor antagonists had distinct and selective effects on specific components of a sustained spike discharge to a contralateral tone, as expected from the different time constants of these receptor types noted in brain slice preparations. The NMDA receptor contribution to auditory responses in rat ICC has been described previously (Faingold et al. 1989b, 1991b), and the differential effect of NMDA and non-NMDA glutamate receptor types has been reported for the barn owl's auditory midbrain homologue of the mammalian IC (Feldman and Knudsen 1994).

Both AMPA and NMDA receptors contribute to responses evoked by acoustic stimulation at all sound pressure levels above threshold, as indicated by rate-intensity curves derived from responses to contralateral tone bursts (Zhang and Kelly 2001; Kelly and Zhang 2002). AMPA and NMDA receptor antagonists reduced the firing rate of most ICC neurons throughout their dynamic ranges. These data show that NMDA receptors can mediate responses at low to moderate levels of acoustic stimulation, and therefore probably play an important role in processing sensory information.

AMPA and NMDA receptors also contribute to the responses of ICC neurons to sinusoidal amplitude-modulated (AM) tones (Zhang and Kelly 2003). The selective antagonists (NBQX for AMPA, CPP for NMDA receptors) reduced the firing rate of most ICC neurons to AM stimuli across a wide range of modulation frequencies, but did not have selective effects at different modulation frequencies. The shape of the modulation transfer functions for firing rate (MTF_{FR}) was unchanged during drug application although overall firing rate was greatly reduced. Furthermore, the synchrony of spike discharges to the modulation cycle was largely unaffected by either receptor antagonist. Thus, the modulation transfer functions for vector strength (a measure of response synchrony, MTF_{VS}) were usually not changed. This suggests that temporal locking to the envelope of AM signals is coded below the level of the IC (Fig. 9.3).

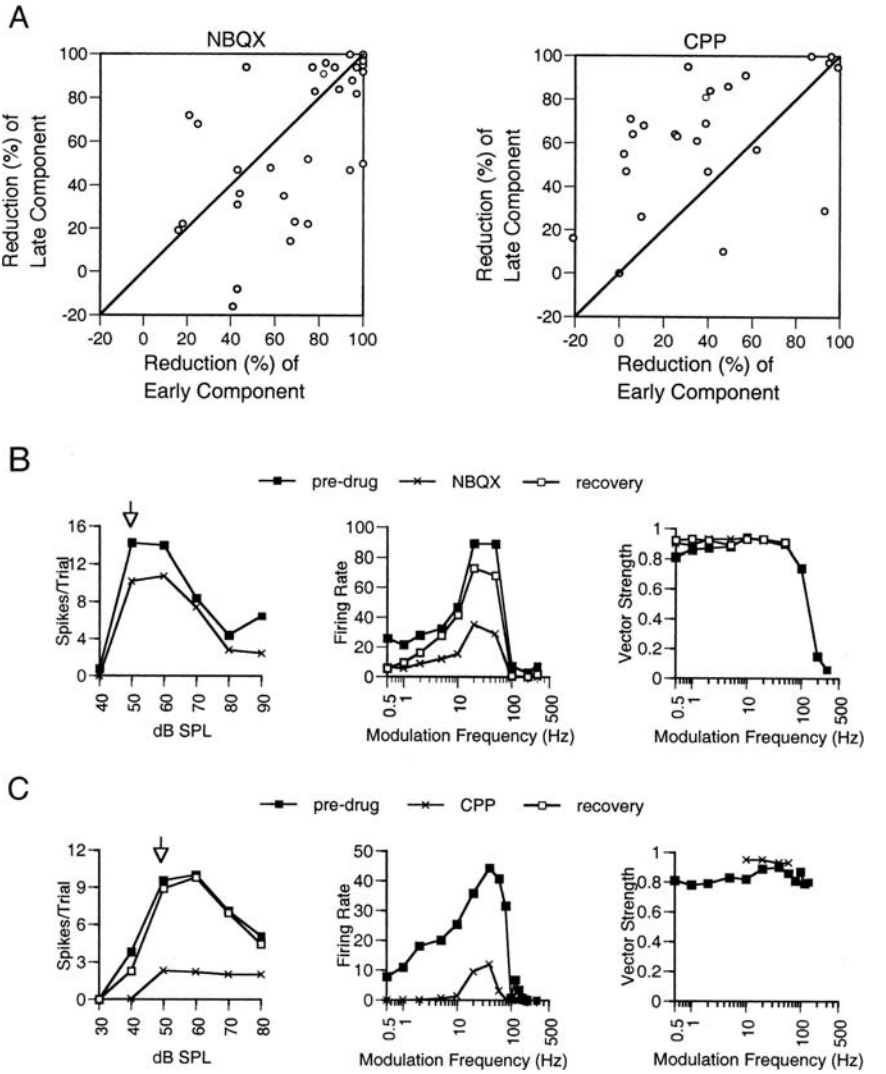

Figure 9.3. The contribution of AMPA and NMDA receptors to excitatory responses recorded from the ICC. **(A)** Both the AMPA receptor antagonist, NBQX, and the NMDA receptor antagonist, CPP, reduced the number of spikes in response to a 120-ms tone burst presented to the contralateral ear. The AMPA receptor antagonist reduced the response during both early (first 20 ms) and late (subsequent 100 ms) parts of the response with a slightly greater early effect, whereas the NMDA receptor antagonist had a greater effect on the late response. **(B, C)** Both NBQX and CPP reduced firing across a wide range of tone burst intensities as indicated by the rate-level curves *(panels on the left side).* Responses to sinusoidal AM tones were also reduced by both AMPA and NMDA antagonists as shown by the modulation transfer functions for firing rate (MTF_{FR}) *(middle panels)* for NBQX and CPP. Neither drug substantially reduced the synchrony of firing to the period of the modulation envelope, as indicated by the modulation transfer functions for vector strength (MTF_{VS}) *(panels on the right side).* The *arrows (left panels)* (rate level curves) indicate the level at which modulated sounds were presented. (Adapted from Zhang and Kelly 2001, 2003.)

4.2. GABA Shapes Receptive Fields and Frequency-Response Tuning Curves

The importance of GABA in regulating IC physiologic responses is well established. GABA application onto cat or rat IC neurons reduces the tone-evoked firing rate for almost all cells that respond to acoustic stimulation (Watanabe and Simada 1973; Faingold et al. 1989a, 1991a,b). Similar results are found with application of the GABA uptake inhibitor, nipecotic acid. The shapes of the rate-intensity functions for CF tones were altered from nonmonotonic to more monotonic during application of $GABA_A$ receptor blockers (Faingold et al. 1991a). Near-threshold responses were less affected by $GABA_A$ receptor blockade than above-threshold responses (Faingold et al. 1991a; Yang et al. 1992; Le Beau et al. 1996, 2001; Palombi and Caspary 1996a,b).

Similar studies in bat, guinea pig, and chinchilla describe receptive field (frequency tuning curve) changes after blockade of $GABA_A$ receptors in the IC (Vater et al. 1992a; Yang et al. 1992; Palombi and Caspary 1996a; Le Beau et al. 2001). There are two populations of ICC neurons, in roughly equal numbers, that respond differently to $GABA_A$ antagonists. One response type displays significant firing rate changes only in the excitatory response area of the monaural (contralateral) receptive field. These changes resemble the nonmonotonic CF rate-intensity curves that become more monotonic on $GABA_A$ receptor blockade (Faingold et al. 1991a). Such neurons had large increases in near-CF discharge rates as stimulus intensity within their receptive fields was increased, with little or no change in firing rate outside or lateral to the boundaries of the predrug receptive field (Vater et al. 1992a; Yang et al. 1992; Palombi and Caspary 1996a; Le Beau et al. 2001). Thus, one large population of IC neurons did not display GABA-mediated lateral inhibition (Palombi and Caspary 1996a). $GABA_A$ receptor blockade in the second group resulted in similarly large near-CF changes in firing rate at higher intensities within the receptive field, but with a broadening of the frequency range represented in the excitatory tuning curve. Some neurons had significant low-side expansion of their frequency tuning curves (Yang et al. 1992; Le Beau et al. 2001).

Two response types occur in guinea pig IC, one with V-shaped tuning curves and the other with more complex frequency tuning properties (Le Beau et al. 2001). $GABA_A$ receptor blockade did not alter frequency tuning of cells with V-shaped frequency-response curves, although it did increase firing rate within the excitatory response area. The frequency-response properties of the complex IC neurons were altered by $GABA_A$ receptor blockade, becoming more V-like and showing increased discharge rate within the excitatory response area.

There is no compelling evidence from these studies for the presence of neurons in IC with "pure" lateral inhibition, that is, cells with a change in firing confined to frequencies above or below the excitatory response area with no change inside this area (Fig. 9.4). There are no neurons for which GABA antagonists increase firing outside the boundaries of the predrug excitatory tuning

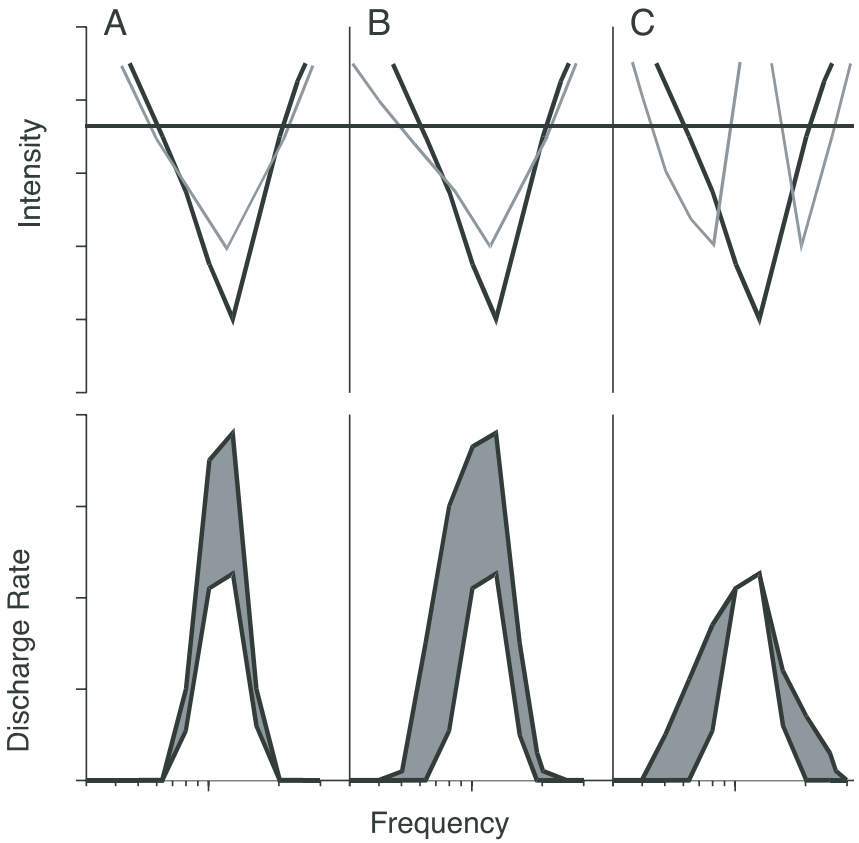

Figure 9.4. Three possible models of the relationship in the frequency domain between excitatory and inhibitory inputs converging onto an ICC neuron. Theoretical frequency tuning curves *(top)* are shown for the excitatory *(black)* and inhibitory *(gray)* input neurons. The *horizontal line* indicates a mid-level intensity. Theoretical isointensity contours *(bottom)* are shown before and during bicuculline methiodide application at this intensity. In **(A)**, the putative inhibitory inputs are aligned tonotopically with the excitatory inputs; blockade of $GABA_A$ receptors by bicuculline would increase the rate of firing within the excitatory response area, with the greatest effect near CF, but without increasing the range of effective frequencies. This first response type was observed in 30% to 50% of ICC neurons in the studies reviewed in the text. **(B)** The inhibitory inputs are aligned with, but extend lateral to, the excitatory inputs; blockade by bicuculline would increase both the firing rate within the excitatory response area and the range of effective frequencies, especially on the low-frequency side. This second response type was observed for 30% to 50% of the neurons tested in the reviewed studies. **(C)** Inhibitory inputs flank excitatory inputs; bicuculline blockade increases the response area width with no discharge rate increase near CF. No iontophoretic studies of ICC neurons showed this response pattern following $GABA_A$ receptor blockade.

curve without also increasing the firing to frequencies within the tuning curve, particularly near the cell's characteristic frequency.

The absence of neurons with "pure" lateral inhibition suggests that inhibitory inputs arising from neurons with CFs exclusively above or below (i.e., tonotopically misaligned with) the excitatory response areas of their IC target neurons do not exist (Palombi and Caspary 1996a). Collectively, these contralateral monaural findings suggest at least two populations of IC neurons classified by response type (Fig. 9.4). Both frequency-response curve types show powerful $GABA_A$ receptor-mediated inhibition within the excitatory receptive field, near-CF, suggesting that extrinsic and intrinsic inhibitory inputs onto ICC neurons are in tonotopic alignment with excitatory target cells and have tuning curves with similar breadth (i.e., similar Q values) (Fig. 9.4A). The second response curve type reveals some "lateral inhibition" likely due to inhibitory inputs arising from projection neurons with broader tuning (lower Q values) than their excitatory IC target neurons (Fig. 9.4B). In some cases high Q-value inhibitory neurons with slightly offset CFs could increase the complexity of ICC frequency-response maps (Le Beau et al. 2001).

4.3. GABA Shapes Binaural Responses

In vivo and in vitro studies indicate that some binaural coding can occur within the IC itself. Binaural responses shaped by excitatory–inhibitory interactions (usually elicited by stimulation of the contra- and ipsilateral ear, respectively) are altered by local IC $GABA_A$ receptor blockade (Vater et al. 1992a; Park and Pollak 1993; Klug et al. 1995; Zhang et al. 1999). One probable origin of the inhibitory binaural influence on these cells is through the crossed GABAergic DNLL projection (Adams and Mugnaini 1984; Chen et al. 1999). Cutting the crossed DNLL projection, that is, severing the commissure of Probst, or pharmacologic block of excitation of DNLL cells that give rise to this projection, results in a release from binaural inhibition in the rat IC (Li and Kelly 1992; Faingold et al. 1993; Kidd and Kelly 1996; van Adel et al. 1999; Kelly and Kidd 2000). This projection could supplement or sharpen binaural responses originating in subcollicular nuclei or create *de novo* binaural interactions within the IC (Park and Pollak 1993; Kelly and Li 1997). Local GABAergic circuits could also contribute to binaural processing in the IC.

Selective responses to the direction of virtual motion generated by binaural phase cues can be recorded from IC neurons (Spitzer and Semple 1998). Similar results are found with dynamic binaural level cues (Sanes et al. 1998). Blocking GABAergic inhibition by local application of bicuculline increases the IC neurons' sensitivity to dynamic binaural motion cues (McAlpine and Palmer 2002). This effect is attributed to adaptation-of-excitation, a process by which the initial level of excitation influences the magnitude of subsequent binaural responses (McAlpine et al. 2000). The release from inhibition by bicuculline enhances the level of excitation and creates an exaggerated response to dynamically changing binaural phase cues.

The role of GABA in shaping responses to binaural time differences was examined in the barn owl's IC (Fujita and Konishi 1991). Bicuculline increased firing rate and decreased the selectivity of responses to binaural input and GABA had the opposite effect. These results suggest that GABAergic inhibition in IC sharpens neural responses to interaural time differences. The underlying mechanism for such sharpening is probably similar to that proposed for mammalian IC neurons. GABAergic inhibition in the barn owl's auditory midbrain also plays a role in adjusting responses to the spatial location of a sound source through sensory experience (Zheng and Knudsen 1999). Furthermore, in the frog's auditory tectum (IC) bicuculline altered the direction-dependent tuning of neurons to sound frequency (Zhang et al. 1999).

4.4. GABAergic Effects on Responses to Modulated Sounds

Neurons in the IC are responsive to both sinusoidal AM and frequency-modulated (FM) stimuli (Rees and Møller 1983). Bicuculline substantially increased discharge rates to modulated sounds, as expected from studies with unmodulated tone bursts. Some neurons increased their firing equally across all modulation frequencies with no change in the selectivity for particular rates of modulation. For other cells the increase in firing rate was proportional to the excitatory response produced prior to drug release (Le Beau et al. 1996; Burger and Pollak 1998; Koch and Grothe 1998; Caspary et al. 2002; Zhang and Kelly 2003). In these cells, the effect of bicuculline at specific modulation rates was greatest at modulation frequencies that produced the strongest excitation before bicuculline. Still other neurons increased their activity preferentially at low modulation frequencies (Caspary et al. 2002; Zhang and Kelly 2003; Fig. 9.5).

The pattern of increased firing produced by bicuculline at different modulation rates might be determined in part by the receptor mechanism underlying the excitatory response. Excitation based on AMPA receptor activation would likely be level independent so that the release from GABAergic inhibition would cause a constant increase in firing rate. On the other hand, excitation based on NMDA receptors would depend on the background level of activity and the extent of membrane depolarization. Thus, the release from inhibition produced by bicuculline would likely result in a larger increase in firing at modulation frequencies that produced more excitation before drug release. The finding that most neurons in rat IC are driven by both AMPA and NMDA receptors lends some support to this idea (Zhang and Kelly 2003). The proportion of AMPA to NMDA receptor-mediated excitation for an ICC cell might determine its response gain to increasing levels of activity due to acoustic stimulation or GABAergic release from inhibition. The response to modulated or unmodulated sounds would depend on the combined influence of AMPA, NMDA, and $GABA_A$ receptor-mediated interactions.

Some neurons in ICC have band-reject MTF_{FR} profiles, that is, they respond well to high- and low-modulation frequencies but have low response rates to

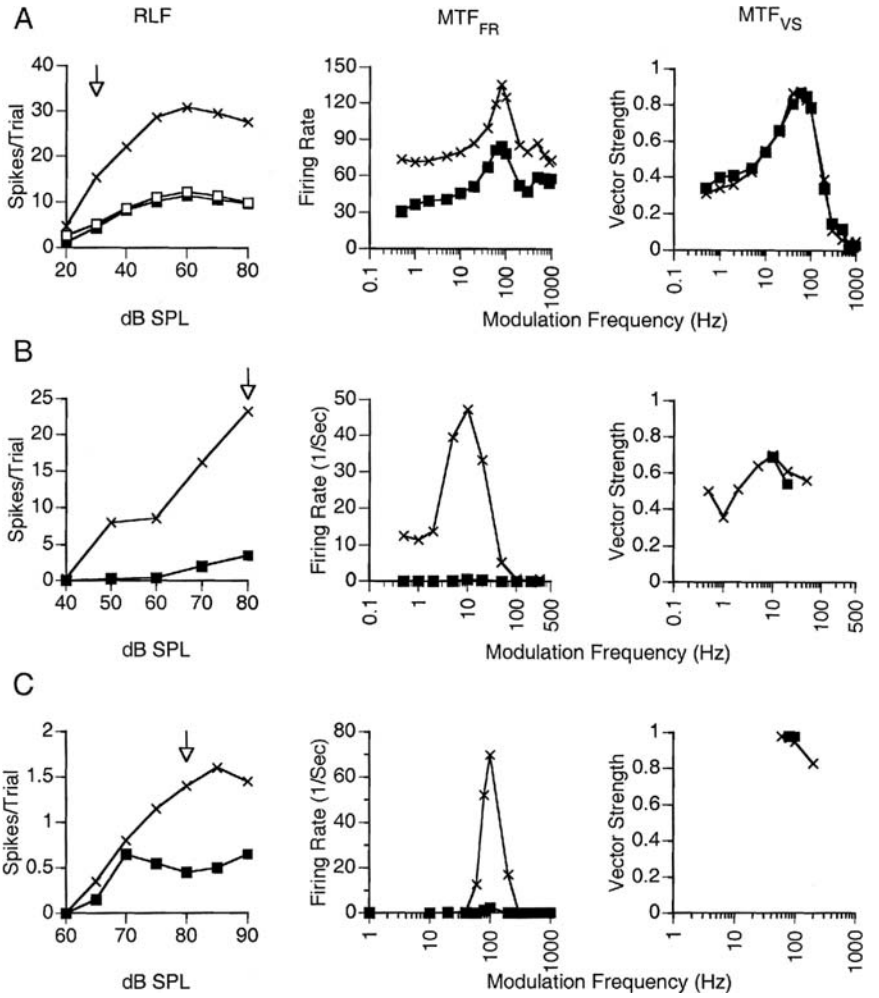

Figure 9.5. The effects of bicuculline on responses to CF tone bursts and sinusoidal AM tones. Iontophoretic application of bicuculline methiodide increased firing rates to both tones and modulated sounds, but had little effect on the synchrony of discharges to the envelope of the AM tone as indicated in the rate level functions *(RLF)* and modulation transfer functions for firing rate *(MTF_{FR})* and vector strength *(MTF_{VS}) (panels from left to right)* for three ICC neurons **(A–C)**. For the neuron in **(A)**, bicuculline increased firing by about the same amount for all modulation frequencies. For the two neurons in **(B)** and **(C)**, the increase in firing was more nearly proportional to the firing level before drug application. For the neuron in **(B)** the increase was more pronounced for modulation rates below than above best-modulation frequency. For all panels the predrug level is indicated by filled squares (■), the drug condition by crosses (X) and the postdrug recovery by open squares (□). (Adapted from Zhang and Kelly 2003.)

middle frequencies (Krishna and Semple 2000; Zhang and Kelly 2003). For these neurons, bicuculline increased the overall firing rate, but did not eliminate the band-reject feature of the MTF_{FR}. In some cases, the increase in activity was constant across a wide range of modulation frequencies, but in others it was greater at modulation rates that produced high firing levels before drug application (Fig. 9.6). These results suggest that the consequences of release from inhibition might be related to the type of underlying excitation, that is, whether the excitatory input is based on AMPA or NMDA receptors and in what pro-

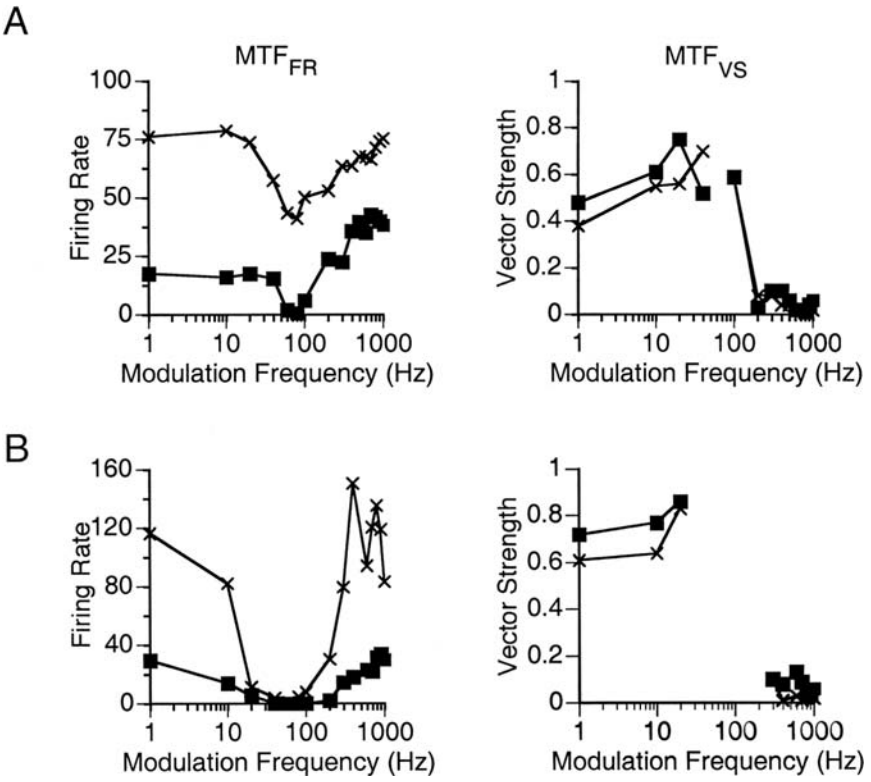

Figure 9.6. The effect of bicuculline on two neurons **(A, B)** with band-reject modulation transfer functions *(MTF_{FR})* in response to a sinusoidal AM tone presented to the contralateral ear. Both neurons responded well to high and low modulation frequencies before drug application, but had much weaker responses to intermediate modulation frequencies. For the neuron shown in **(A)**, bicuculline methiodide increased firing by nearly equal amounts at all AM frequencies. In contrast, for the neuron shown in **(B)**, the increase in firing was nearly proportional to the level of activity prior to drug application. The band-reject profile of the *MTF_{FR}* was preserved in both cases. In neither case was the discharge synchrony to the modulation envelope greatly affected by the drug. For other conventions, see Fig. 9.5. (Adapted from Zhang and Kelly 2003.)

portion. The band-reject feature of the MTF_{FR} for many ICC neurons appears to be shaped primarily by neural circuits at lower levels of the auditory system rather than local GABAergic synapses.

Bicuculline blockade of $GABA_A$ receptors did not strongly affect the synchrony of discharges locked to the modulation envelope of AM tones, even when firing rate was strongly affected (Zhang and Kelly 2003). Vector strength remained high at most modulation frequencies and the temporal pattern of synchronous discharge was similar before and during bicuculline release; similar results were seen in the mustached bat (Burger and Pollak 1998) and chinchilla (Caspary et al. 2002). Thus, response synchrony is not disrupted by local imbalances in excitation and $GABA_A$ receptor-mediated inhibition in IC created by receptor antagonists. Response synchrony is likely governed by the synchronized discharge of inputs from extrinsic sources (likely the DCN), local circuits in the ICC, and/or the intrinsic membrane properties of the neurons from which recordings are made.

$GABA_A$ receptors help shape ICC responses to sinusoidal FM tones in the big brown bat (Koch and Grothe 1998, 2000). $GABA_A$ receptor blockade reduced the sharpness of tuning to the rate of FM in 60% of the cells, affecting the upper and lower cutoff frequencies of the MTF. The sharpness of tuning was increased in 30% of the cells. Bicuculline also reduced response synchrony to the modulation envelope in many cells owing primarily to a prolonged discharge during the modulation cycle. Temporal selectivity to modulation rate was affected by the strength of binaural inhibition in about half the neurons in the ICC, and local $GABA_A$ receptor blockade altered this binaural dependency in some cells (Koch and Grothe 2000).

Many pallid bat ICC cells have directional FM sensitivity dependent on local $GABA_A$ receptors, and this can be abolished or reduced with bicuculline application (Fuzessery and Hall 1996). Koch and Grothe (1998) also reported that bicuculline abolished the FM directional sensitivity of some neurons in the big brown bat ICC.

4.5. GABAergic Effects on Responses to Sound Duration

Many IC neurons in bats (Fuzessery and Hall 1999; Casseday et al. 2002) and other mammalian species (chinchilla: Chen 1998; mouse: Brand et al. 2000) are selectively tuned to sounds of a specific duration. Some cells respond maximally to short-duration sounds (short-pass tuning) and others prefer a specific duration rather than longer or shorter durations (band-pass tuning). A "coincidence model" has been proposed for ICC neural duration tuning in the big brown bat based on the convergence of delayed ascending excitatory and inhibitory inputs. Bicuculline application locally in ICC greatly reduces or eliminates the response selectivity of duration-tuned neurons (Casseday et al. 1994, 2000).

Likewise, many cells in the pallid bat IC are duration tuned. Bicuculline often abolishes duration selectivity, emphasizing the importance of local GABA receptors. However, in some cells duration selectivity is not abolished by bicu-

culline. A revised coincidence model was proposed to explain the response properties of these duration-tuned cells (Fuzessery and Hall 1999).

4.6. Glycinergic Inhibition

Although both anatomical and brain slice studies show that there are glycinergic inputs to the ICC, only a few studies have examined in detail how glycine receptors shape responses to acoustic stimulation. Both GABA and glycine contributed to binaural responses in the mustached bat's ICC (Klug et al. 1995) and their respective antagonists, bicuculline and strychnine, were each effective in partially blocking binaural inhibition (see also Vater et al. 1992a). Furthermore, glycinergic inhibition influenced responses to FM stimuli much like GABA, but less strongly (Koch and Grothe 1998, 2000). Strychnine altered frequency tuning curves in guinea pig IC (Le Beau et al. 2001; see Section 4.2) and affected duration tuning of IC neurons in the big brown bat much like bicuculline, but more weakly (Casseday et al. 1994, 2000). The greater efficacy of the $GABA_A$ receptor blockade when compared with glycine receptor blockade is consistent with brain slice and binding studies of the afferent projections to ICC, which show a $GABA_A$ receptor dominance (Zarbin et al. 1981; Milbrandt et al. 1996; Moore et al. 1998; Ma et al. 2002c). However, the relative expression of GABAergic and glycinergic inhibition might be related to the recording site location within the IC (see Chapters 2 and 5).

4.7. Role of the $GABA_B$ Receptor

The presence of $GABA_B$ receptors in the IC is supported by the actions of the $GABA_B$ receptor agonist, baclofen, and the receptor antagonist, phaclofen (Faingold et al. 1989a, 1991a), as well as receptor binding (Milbrandt et al. 1994, 1996) and brain slice (Zhang and Wu 2000; Ma et al. 2002c) studies. Baclofen reduced firing moderately and phaclofen slightly increased responses to acoustic stimulation (Faingold et al. 1989a, 1991a; see also Burger and Pollak 1998). The reduced firing produced by baclofen, however, cannot be attributed with certainty to a postsynaptic inhibitory action. Indeed, there is no indication of a postsynaptic effect of the $GABA_B$ agonist baclofen in a brain slice preparation of the rat's IC. Rather, baclofen had an effect on GABAergic inhibition through presynaptic modulation of inhibitory transmitter release (Ma et al. 2002c; see Fig. 9.2).

Activation of $GABA_B$ receptors can also reduce the strength of synaptic excitation in the rat's IC as shown by dose-dependent suppressive effects of baclofen on excitatory postsynaptic currents recorded in brain slices with whole-cell patch clamp techniques (Wu et al. 2004). Thus, the decreased response to acoustic stimulation produced by baclofen in vivo might be due to a presynaptic $GABA_B$ receptor-mediated reduction in excitatory transmitter release rather than postsynaptic inhibition.

4.8. Serotonin

Serotonin [5-hydroxytryptamine (5-HT)] has a modulatory effect on the responses of many neurons in the ICC (see Hurley et al. 2002). Simple and complex response properties were altered by serotonin application (Hurley and Pollak 1999, 2001), which reduced tone-evoked responses in 60% of the IC neurons in the Mexican free-tailed bat. The firing decrease was often uniform across frequency, although some frequency-specific effects did occur. The role of serotonin in arousal and attention to particular sounds remains to be examined. Further studies with specific serotonin receptor antagonists are needed to determine the receptor specificity of the effects, and behavioral studies are called for to assess the extent to which the action of serotonin in IC depends on the animal's central state.

5. Modification of Synaptic Function

5.1. Effects of Decreased Peripheral Acoustic Input on Normal Inhibitory Function

Studies of animals exposed to extremely high levels of noise show increased IC evoked potential amplitude and increased single-unit activity to suprathreshold acoustic stimuli following exposure (Willott and Lu 1982; Salvi et al. 1990; Gerken et al. 1991; Szczepaniak and Møller 1995; Wang et al. 1996; Syka and Rybalko 2000; see Chapters 19 and 20). These findings suggest a global loss of synaptic inhibition, as acoustic nerve and VCN show reduced responses to suprathreshold stimuli after noise exposure (Gerken et al. 1991). Damage to the auditory periphery evokes a selective down-regulation of normal inhibitory GABAergic IC function. A loss of bicuculline sensitivity is seen in IC surface-recorded evoked potentials from noise-exposed animals (Szczepaniak and Møller 1995). Bilateral deafness decreases in vivo GABA release and fewer neurons show electrically evoked suppression of activity (Bledsoe et al. 1995). GAD levels were reduced 2 to 30 days following noise exposure (Abbott et al. 1999; Milbrandt et al. 2000) and at 24 hours and 7 days after cochleotomy (Mossop et al. 2000). Studies of GABA uptake and release following ossicle removal or cochlear ablation reveal complex changes in GABA and glycine neurochemistry (Suneja et al. 1998). Collectively, these studies show significant changes in normal GABA function after peripheral manipulations that decrease acoustic input.

5.2. Age-Related Changes in the Inferior Colliculus

It is unknown whether age-related changes in GABA neurotransmission reflect *de novo* adjustment in the central auditory system or embody a gradual loss of peripheral input, or both. A full discussion is beyond the scope of this review (see Chapter 19). However, the significant decreases in endogenous IC GABA

and GABA release are not evident in CN (Banay-Schwartz et al. 1989a,b; Caspary et al. 1990; Raza et al. 1994). GABA levels, GAD levels, and $GABA_B$ receptor binding each decrease with age, and there is neuropil rearrangement in aging Fischer 344 (F344) rats (Banay-Schwartz et al. 1989a,b; Caspary et al. 1990; Gutiérrez et al. 1994; Milbrandt et al. 1994, 1996; Raza et al. 1994; Helfert et al. 1999). Comparison of single-unit recordings from ICC in anesthetized young (3 to 4 months) and aged (24 months) F344 rats shows significantly more monotonic ICC rate-intensity responses in the aged animals, and an 18% increase in the breadth of isointensity functions at 30 dB above threshold (Palombi and Caspary 1996a–c). Analogous physiologic changes occur in C57 and CBA mice (Willott 1986; Willott et al. 1988a,b, 1991; McFadden and Willott 1994; Walton et al. 1998).

5.3. Age-Related $GABA_A$ Receptor Subunit Changes

The $GABA_A$ receptor is a heterogeneous family of ligand-gated Cl^- ion channel receptors that generally mediate inhibition in the adult brain. $GABA_A$ receptors likely exist as pentameric subunit complexes that can be allosterically modulated by numerous pharmacologic agents (Sieghart 1992a,b, 1995; Wafford et al. 1993; Rabow et al. 1995; Mohler et al. 2002). Molecular cloning reveals the presence of 6-α, 4-β, 3-γ, 1-δ, and 2-ε $GABA_A$ receptor subunits (Macdonald and Olsen 1994; Rabow et al. 1995; Sieghart 1995). Specific subunits have regionally selective distributions in several species (Burt and Kamatchi 1991; Luddens and Wisden 1991; Doble and Martin 1992; Persohn et al. 1992; Poulter et al. 1992; Wisden et al. 1992; Wynne et al. 1995; McKernan and Whiting 1996). It is thought that as few as 10 combinations exist in significant numbers in the CNS (McKernan and Whiting 1996). In situ hybridization studies describe age-related changes in $GABA_A$ receptor subunit composition in rat IC (Milbrandt et al. 1997), with significant age-related increases in α_2 and γ_1 subunit mRNA along with small declines in α_1, β_2, and γ_2 subunit mRNA in two strains (Caspary et al. 1999). Coexpression of the γ_1 subunit with α_1 and β_2 subunits in oocytes produces a $GABA_A$ receptor complex with more sensitivity to GABA than receptors with the γ_2 subunit (Ducic et al. 1995), and binding studies find significant age-related enhancement of GABA modulation of binding at the picrotoxin $GABA_A$ receptor site (Milbrandt et al. 1996). These findings suggest altered $GABA_A$ receptor pharmacology in aged animals. Such changes seem to differ in the three main IC subregions (Milbrandt et al. 1997). Altered $GABA_A$ receptor expression levels are supported by immunocytochemical measures of protein levels for selected $GABA_A$ receptor subunits, with significant increases in γ_1 subunit protein and a decrease in α_1 subunit protein with age (Caspary et al. 1999).

A direct functional measure of this subunit change was made by examining the ability of GABA to flux Cl^- ions in microsac/synaptosome preparations from rat IC. The GABA-mediated influx was significantly increased in samples from

aged animals (Caspary et al. 1999). These findings contrast with previous whole-brain synaptosome chloride uptake studies, which found reduced Cl^- uptake with aging (Concas et al. 1988). The Cl^- flux findings strongly support an age-related change in $GABA_A$ receptor subunit composition likely resulting in altered coding in the IC of aged animals. $GABA_A$ receptor changes may reflect a compensatory up-regulation of postsynaptic inhibitory function after significant loss of presynaptic GABA release.

5.4. *Quantitative Receptor Autoradiography*

There is significant muscimol binding in the IC (Glendenning and Baker 1988), and several ligands related to normal $GABA_{A\ and\ B}$ receptor pharmacology bind with high affinity in the IC of young and aged animals (Milbrandt et al. 1994, 1996). No significant age-related changes in IC $GABA_A$ receptor binding are found with single concentrations of tritiated $GABA_A$ receptor ligands (muscimol, TBOB, and flunitrazepam) (Milbrandt et al. 1996). However, as noted earlier, modulation of binding at the picrotoxin site with different concentrations of bath-applied GABA caused a dose-dependent shift to the left in the GABA modulation curve, indicating an age-related increase in the potency of GABA inhibition at this site. In contrast to the complex changes at the $GABA_A$ receptor, $GABA_B$ binding was significantly reduced in the ICs of aged rats, likely indicative of the loss of normal presynaptic GABA function (Milbrandt et al. 1994).

6. Conclusions and Directions for Future Research

It is evident that the excitatory and inhibitory amino acids and their respective receptors are critically involved in shaping the response properties of neurons in the three subdivisions of the IC. Extrinsic projections and intrinsic circuits releasing glutamate and GABA are decisive in determining the activity of neurons projecting from the IC to the medial geniculate body and auditory forebrain. Glycine also plays a role in shaping responses to acoustic stimulation, and other neurotransmitters or neuromodulators, such as serotonin, can influence the responses of IC neurons. The coding properties of IC cells are determined by the relative balance and timing of their excitatory and inhibitory inputs as well as their inherent characteristics, for example, membrane properties and biophysics. The amino acid neurotransmitter systems and the other modulators show plastic changes as the acoustic input changes over time with age or with selective peripheral damage. Such changes appear to be a compensatory increase in gain, ensuing from a loss of excitatory input, that remodels the relative balance of excitation and inhibition centrally. It remains to be determined whether these plastic changes are reversible or amenable to further adjustment using pharmacologic probes.

An important goal for future research is the identification of specific cell types within the IC that receive projections from various sources and the further characterization of their receptor pharmacology and circuitry. For example, do different cell types in IC show variations in the proportion of AMPA and NMDA receptors that might determine the gain of excitatory responses? Do the GABAergic and glycinergic projections from subcollicular auditory nuclei target different IC cell types, and do these transmitters serve the same physiologic functions? Do the ipsilateral and contralateral DNLL projections make synaptic contact with the same or different ICC neuronal populations? How do the ascending projections from cochlear nucleus, superior olive, and lateral lemniscal neurons interact with commissural projections or descending projections from the medial geniculate or cortex? A major challenge for future research will be to provide definitive answers to these intriguing questions.

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Abbreviations

AM	amplitude-modulated
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
APV	(±)-2-amino-5-phosponovaleric acid
CF	characteristic frequency
CN	cochlear nucleus
CNQX	6-cyano-7-nitroquinoxaline-2,3-dione
CPP	(±)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid
DCN	dorsal cochlear nucleus
EPSC	excitatory postsynaptic current
EPSP	excitatory postsynaptic potential
FM	frequency-modulated
GABA	γ-aminobutyric acid
GAD	glutamic acid decarboxylase
IC	inferior colliculus
ICC	central nucleus of the inferior colliculus
ICD	dorsal cortex *or* dorsal nucleus of the inferior colliculus
ICX	external nucleus of the inferior colliculus
IPSP	inhibitory postsynaptic potential

LSO	lateral superior olive
MSO	medial superior olive
MTF_{FR}	modulation transfer function for firing rate
MTF_{VS}	modulation transfer function for vector strength
NBQX	1,2,3,4-tetrahydro-6-nitro-2,3-dioxo-benzo[*f*]quinoxaline-7-sulfonamide disodium
NMDA	*N*-methyl-D-aspartate
PSTH	post-stimulus time histogram
RLF	rate level function
TBOB	*t*-[^{3}H]butylbicycloorthobenzoate
VCN	ventral cochlear nucleus

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Chapter 10
Biophysical Properties of Inferior Colliculus Neurons

Shu Hui Wu

1. Introduction

The inferior colliculus (IC) is a pivotal nucleus in the central auditory pathway. It receives and integrates ascending afferent projections from almost all of the major auditory nuclei in the lower brain stem (see Chapters 3 and 4). Auditory information that has been encoded in specific temporal or spatial configurations in the lower brain stem nuclei is further analyzed, relayed, or transformed in the IC. The wealth of afferent inputs includes excitatory and inhibitory projections. The cochlear nucleus (CN), medial superior olive (MSO), and contralateral lateral superior olive (LSO) are sources for major excitatory inputs. The dorsal nucleus of the lateral lemniscus (DNLL), ipsilateral LSO, and ventral nucleus of the lateral lemniscus (VNLL) are sources for major inhibitory inputs. The IC also receives descending projections from the auditory cortex (AC) and medial geniculate body (MGB) (see Chapters 7 and 8), and local inputs from neurons within the IC (see Chapter 5). In addition, the IC receives converging auditory, somatosensory, visual, and motor information. Thus, IC neurons are influenced by ascending, descending, and internal excitatory and inhibitory synaptic inputs while processing auditory and other signals.

Information processed by IC neurons is sent to the MGB and the AC. The synaptic potentials of IC neurons are therefore transformed into action potentials that will further excite or inhibit their target neurons. The input–output transformation in a neuron is a result of interaction between biophysical properties of the neuron and synaptic inputs to it. The biophysical properties, that is, properties of intrinsic electrical membrane and synaptic receptors, shape the output signals from the IC neurons.

Electrical membrane properties of the neuron have passive and active components. The passive electrical properties, such as the resting potential, membrane input resistance and time constant, are relatively invariant, but crucial for electrical signaling. They determine whether a synaptic potential will elicit a suprathreshold depolarization at the spike-generating zone at the axon hillock. Passive properties also influence the conduction speed of an action potential. The voltage-gated ion channels and synaptic receptors on the cell membrane are

active components that allow rapid changes in membrane potential caused by ionic currents flowing across the cell membrane. The input signals activate ion channels and synaptic membrane receptors, which in turn produce excitatory or inhibitory synaptic potentials. This is a dynamic process in which cellular intrinsic properties interact with neural connections to produce a complex response profile that is arguably unique to each class of neuron.

In this chapter the passive and active membrane properties of IC neurons are summarized, and the question of how IC neurons integrate and process incoming signals based on their biophysical properties is considered. Suggested directions for future research in the cellular biophysics of IC neurons will provide a guide for better understanding neuronal mechanisms of auditory processing.

2. Electrical Membrane Properties

Electrical membrane properties are usually studied by using intracellular recordings from neurons in rodent IC brain slices. Firing patterns and voltage changes across the cell membrane are examined with current-clamp recordings by injection of depolarizing and hyperpolarizing current. Ionic currents underlying the firing pattern are investigated with voltage-clamp recording.

2.1. Firing Patterns and Potassium Currents

Different IC neurons respond selectively and specifically to intracellular injection of depolarizing and hyperpolarizing current (Wagner 1994; Li et al. 1998; Reetz and Ehret 1999; Peruzzi et al. 2000; Wu et al. 2002). Depolarizing current injection activates voltage-sensitive ion channels and generates action potentials, eliciting either onset, sustained-regular, or adapting firing patterns (Wagner 1994; Peruzzi et al. 2000). Some cells show a depolarizing rebound after injection of hyperpolarizing current and others show a pause in response to injection of depolarizing current following hyperpolarizing current. Different firing patterns are correlated with different combinations of specific K^+ channels. Many of the details of the firing patterns discussed in Sections 2.1.1 to 2.1.4 are based on a study by Sivaramakrishnan and Oliver (2001) in which the firing pattern and associated K^+ currents were examined in single neurons of the central nucleus of the IC (ICC) with both current- and voltage-clamp recordings.

2.1.1. Sustained-Regular Pattern

In the study by Sivaramakrishnan and Oliver (2001) neurons with a regular discharge pattern showed sustained firing with constant interspike intervals throughout the period of depolarizing current injection (Fig. 10.1A). Membrane depolarization caused a similar increase in both firing frequency and the magnitude of the 4-aminopyridine (4-AP)- and tetraethylammonium (TEA)-sensitive K^+ currents, suggesting that the sustained-regular firing pattern results from

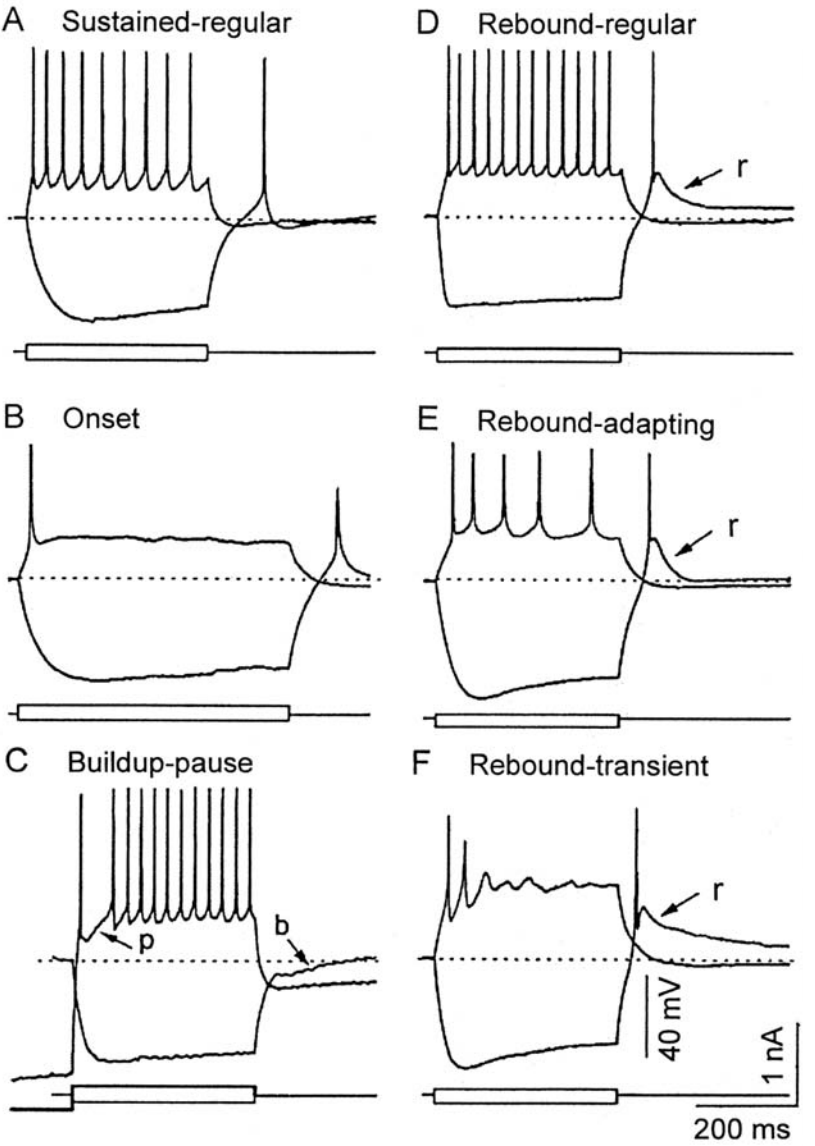

Figure 10.1. The six firing patterns of ICC neurons (for abbreviations, please see the list). In each panel, the *bottom two traces* are the injected depolarizing and hyperpolarizing current pulses, respectively, and the *top two traces* are the voltage responses to each current pulse, respectively. In **(C)**, the thick and thin current traces represent the current that elicited the top and bottom voltage traces, respectively. *Dotted lines* indicate resting membrane potentials. *b*, buildup response; *p*, pause in firing; *r,* Ca^{2+}-dependent rebound. (Adapted from Sivaramakrishnan and Oliver 2001. Copyright 2001 by the Society for Neuroscience.)

4-AP- and TEA-sensitive delayed rectifying K^+ currents (Rudy et al. 1999). In vivo these neurons can readily encode information about sound duration and intensity by a linear increase in firing rate because of their intrinsic linear rate-current function.

2.1.2. Rebound Pattern

Rebound neurons had a period of depolarization after cell membrane hyperpolarization. This rebound was eliminated by reducing extracellular Ca^{2+} concentration. With Na^+ and K^+ channel blockers, depolarizing current injection into the rebound cell produced regenerative Ca^{2+} spikes far longer (around 100 ms) than typical Na^+ action potentials.

Rebound cells responded to depolarizing stimulation with regular, adapting, or transient firing (Fig. 10.1D–F). Like the sustained-regular cells, rebound-regular cells had a delayed rectifying K^+ current, which helps to repolarize the cell during an action potential and to maintain regular firing during depolarizing stimulation. These cells may encode sound intensity because their linear rate-current function resembles that of the sustained-regular cells.

Rebound-adapting neurons fired action potentials with nonuniform interspike intervals to depolarizing current injection. Spikes were initially close together, but became more separate during the injection period. The outward K^+ currents in these neurons were partially blocked by apamin, a blocker for small-conductance, voltage-independent Ca^{2+}-activated K^+ current (Hugues et al. 1982), and reduced by low extracellular Ca^{2+} concentration. The smallest apamin-sensitive currents were evoked at the membrane potential for which the greatest adaptation occurred, suggesting that apamin-sensitive Ca^{2+}-activated K^+ currents contribute to sustained firing during membrane depolarization.

Rebound-transient cells fired transiently during depolarizing current injection. Transient firing was converted to sustained firing by carybdotoxin (CTX), a blocker of the voltage-dependent BK channel. This type of K^+ channel has a large single-channel conductance and is activated by increase in intracellular Ca^{2+} (Vergara et al. 1998). In rebound-transient ICC neurons the outward K^+ currents had a Ca^{2+}-dependent component that was rapidly inactivated after activation and was blocked by CTX. Thus, CTX-sensitive Ca^{2+}-activated K^+ currents are likely responsible for transient firing in rebound-transient neurons.

The depolarizing rebound increases the probability of a Na^+-dependent anode-break spike following membrane hyperpolarization, which may underlie the OFF response to acoustic stimulation noted in IC neurons in vivo (Covey et al. 1996; Kuwada et al. 1997). The rebound mechanism may permit precise temporal coding of ongoing complex sounds such as an amplitude-modulated tone (Kuwada and Batra 1999).

The inhibition-induced rebound mechanism may also underlie sound duration tuning (Casseday et al. 1994, 2000; Covey et al. 1996; Ehrlich et al. 1997). Some IC neurons in bat, rat, and mouse respond preferentially to a specific range of sound durations (Chen 1998; Brand et al. 2000). These neurons may have

excitatory and inhibitory input components that occur in a certain temporal sequence (see Chapter 17). For a preferred sound duration, the OFF excitation that follows the onset inhibition coincides and summates with the delayed excitation, generating a suprathreshold response (Casseday et al. 1994). The OFF excitation is likely the depolarizing rebound observed in rebound neurons in vitro.

2.1.3. Buildup-Pause Pattern

When depolarizing current injection was preceded by a hyperpolarizing current step, buildup-pause neurons delayed the onset of sustained firing or developed a pause between first spike and subsequent firing (Fig. 10.1C). As the prehyperpolarization increased, the pause and magnitude of the A-type K^+ current (I_A), which is characterized as a fast transient and rapidly inactivating K^+ current (Connor and Stevens 1971), increased in parallel. Perhaps the delay or pause at the beginning of sustained firing follows activation of I_A after removal of its inactivation by prehyperpolarization.

As the I_A in the buildup-pause neurons decayed to zero about 80 to 100 ms after activation, the pause would be elicited only if the interval between inhibitory and excitatory stimuli were $<$100 ms. Like sustained-regular and rebound regular cells, the buildup-pause neuron can encode sound intensity because of its linear rate-current function. The buildup-pause neurons are suited to register successive excitatory stimuli or pairs of inhibitory and excitatory stimuli (Sivaramakrishnan and Oliver 2001).

2.1.4. Onset Pattern

Onset cells fire only once at the onset of a depolarizing current injection. The K^+ current activated at –50 to –40 mV, known as low-threshold K^+ current, probably underlies the onset firing pattern. The high-threshold (–10 to +10 mV) K^+ current also exists in the onset neurons. It may help them to repolarize rapidly even if the cell responds to synaptic inputs with a large excitatory potential. Basta and Vater's (2003) study shows that some onset neurons in the mouse's ICC had onset firing to depolarizing current injection only when the neuron was at a hyperpolarizing membrane potential (near –80 mV). In these neurons the inward current that was sensitive to tetrodotoxin, a specific blocker of voltage-gated Na^+ channels, appeared only at –80 mV. The results suggest that the onset firing in these neurons could be attributed to the prehyperpolarization-activated Na^+ current. Only 14% of IC neurons in their study showed a prehyperpolarization-evoked onset pattern. Nevertheless, this Na^+ conductance may enable gating of excitatory synaptic inputs in a narrow time window after inhibitory inputs (Basta and Vater 2003).

In summary, IC neurons represent at least six physiological types based on firing patterns to combinations of depolarizing and hyperpolarizing current injections. Sustained-regular and rebound-regular neurons have only the delayed rectifier K^+ current, and other neurons have more specific K^+ currents besides

the delayed rectifier K^+ current (Table 10.1). In Sivaramakrishnan and Oliver's study (2001) the Ca^{2+} rebound was seen in 57% of cells after hyperpolarizing current injection. Nearly half of these showed a rebound-adapting firing pattern. The regular and transient patterns in the rebound cells were 11% and 21%, respectively. Sustained-regular and buildup-pause patterns comprised 19% and 15% of the population, respectively, while onset cells were 9%. Other studies find that the sustained discharge pattern is prevalent in IC neurons (Table 10.2) (Li et al. 1998; Reetz and Ehret 1999; Bal et al. 2002).

Synaptic inputs may be processed differently by each physiological neuron type (Sivaramakrishnan and Oliver 2001). Input signals can be modified substantially in rebound-adapting, rebound-transient, buildup-pause, and onset neurons, and less so in rebound-regular and sustained-regular neurons. The firing pattern can be changed when inhibition precedes excitation in rebound and buildup-pause neurons, but not in onset and sustained-regular cells. Sustained-regular cells can relay information about sound intensity and duration, and onset cells likely encode the precise onset of sound signals.

Onset, sustained-regular, and rebound-adapting neurons are all found in the IC cortex (Li et al. 1998; Peruzzi et al. 2000). The active membrane properties of IC cortex neurons resemble those of ICC neurons (Smith 1992). Most IC cortex neurons generate Na^+ overshooting action potentials followed by a biphasic afterhypolarization (AHP) with a fast and a slow component (Li et al. 1998). The AHP is attributed to Ca^{2+}-activated K^+ currents because it is abolished by CTX and its shape is altered by extracellular Ca^{2+} removal (Smith 1992; Sivaramakrishnan and Oliver 2001). An obvious feature of intrinsic membrane properties of IC cortex neurons is a slow depolarizing Ca^{2+}-

Table 10.1. Specific K^+ current present in IC neurons with different firing patterns.[a]

Firing pattern	Apamin-sensitive I_k(Ca)	CTX-sensitive I_k	High-threshold I_k (0.2 m*M* TEA-sensitive)	A-type of I_k
Sustained-regular	Not present	Not present	Not present	Not present
Rebound-regular	Not present	Not present	Not present	Not present
Rebound-adapting	30% of total K^+ current	Not present	Not present	Not present
Rebound-transient	Not present	55% of total K^+ current	Not present	Not present
Buildup-pause	9% of total K^+ current	Not present	Not present	56.5% of total K^+ current
Onset	No Ca^{2+}-dependent K^+ current	No Ca^{2+}-dependent K^+ current	45% of total K^+ current	Not present

[a]From Sivaramakrishnan and Oliver (2001). Neurons with any of these six firing patterns all have delayed rectifier K^+ current which can be blocked by 2 m*M* 4-AP or TEA.

Table 10.2. Proportion of sustained and onset IC neurons.

Study	Type of recording	Sustained[a,b]	Onset
Wagner (1994)	Intracellular	62	38
Li et al. (1998)	Intracellular	77	23
Reetz and Ehret (1999)	Intracellular	55	45
Peruzzi et al. (2000)	Intracellular	71	29
	Whole-cell patch clamp	66	34
Sivaramakrishnan and Oliver (2001)	Whole-cell patch clamp	91	9
Bal et al. (2002)	Intracellular	84	16

[a]Sustained neurons include regular, adapting, and transient types.
[b]Values are percentages.

dependent hump in response to depolarizing current injection. This hump is often observed in IC dorsal cortex (ICD) neurons, less so in IC external cortex (ICX) cells, and never in ICC neurons. The hump reflects Ca^{2+} current flowing through Ca^{2+} channels (Smith 1992). The absence of the hump in ICC cells may be caused by a strong Na^{+} current that masks a weak Ca^{2+} current (Li et al. 1998), as ICC neurons do exhibit Ca^{2+} spikes after Na^{+} and K^{+} channels are blocked (Sivaramakrishnan and Oliver 2001). In any event, the voltage-dependent Ca^{2+} current and Ca^{2+}-activated K^{+} current contribute to action potential shape and firing behavior in a similar way for ICC and ICX cells. The apparent calcium hump in ICD neurons indicates more Ca^{2+} channel activity, which may partly explain their lower firing rate.

2.2. *Passive Membrane Properties*

The average range of input resistance of IC neurons is 44 to 116 MΩ in intracellular recordings (Wagner 1994; Reetz and Ehret 1999; Bal et al. 2002) and 240 to 644 MΩ in whole-cell patch clamp recordings (Sivaramakrishnan and Oliver 2001). The higher input resistance with the latter is consistent with the smaller leak current in the whole-cell patch configuration. In whole-cell patch clamp recordings by Sivaramakrishnan and Oliver (2001) the onset neurons had the highest input resistance. The sustained-regular, buildup-pause, and rebound-regular cells had similar input resistances, which were intermediate to onset and rebound-adapting–transient groups. The rebound-adapting and rebound-transient cells had similar input resistances, which were the lowest among IC cell types. The membrane time constant of many IC neurons is 2 to 8 ms in intracellular recordings (Wagner 1994; Reetz and Ehret 1999), resembling that of many auditory brain stem neurons (Hirsch and Oertel 1988; Wu and Kelly 1991, 1995). However, onset neurons have a far shorter time constant than the sustained cells (Wagner 1994), and a shorter time constant for depolarizing than to hyperpolarizing current injection. These membrane properties allow onset cells to respond to input signals faster than the other cell types. Onset neurons can follow

a short train of current pulses at approximately 200 Hz, whereas rebound cells saturate at 50 Hz (Peruzzi et al. 2000).

Differences in passive membrane properties and firing characteristics among ICC, ICX, and ICD neurons have been noted (Li et al. 1998). The input resistance of sustained-firing type of neurons in ICX and ICD is higher than that of ICC neurons. The time constant of sustained type of ICD neurons is longer than that of ICX and ICC neurons. Among the three subdivisions, ICX neurons have the highest spontaneous activity and firing rate in response to depolarizing current injection. The threshold for sustained firing is closer (10 to 20 mV) to the resting potential in ICX and ICC than in ICD neurons. These differences suggest that ICX neurons are more excitable than ICC and ICD neurons, which is consistent with their higher audiogenic seizure susceptibility (Li et al. 1998).

3. The Relationship Between Cell Physiology and Morphology

3.1. The Central Nucleus

ICC neurons have been classified morphologically as disc-shaped (or flat cells) and stellate cells (or less-flat cells) on the basis of their dendritic shape and branching (Peruzzi et al. 2000; see Chapter 2). Electrophysiologically identified categories, that is, rebound, buildup-pause, and so forth do not correlate with the morphologic classification of cells (Peruzzi et al. 2000; Bal et al. 2002). The passive membrane properties of flat and less-flat cells show no significant differences for input resistance, time constant, membrane capacitance, or resting potential (Reetz and Ehret 1999; Bal et al. 2002). However, other morphologic features correlate with electrophysiological profiles (Peruzzi et al. 2000). For example, rebound cells have larger somatic areas and diameters than buildup-pause neurons, which may explain their lower input resistance. Buildup-pause neurons have fewer and simpler dendritic branches than onset and rebound neurons. Axons of some biocytin-labeled IC neurons in mouse brain slices in Reetz and Ehret's study (1999) showed branches, which were parallel to ICC isofrequency laminae and could be traced into the IC brachium, commissure of Probst, ICX, ICD, lateral lemniscus, and IC commissure. But a correlation between the intrinsic electrophysiology and axon arborization has not been found.

3.2. The Inferior Colliculus Cortex

The relationship between the membrane properties and morphology of IC cortex neurons in rat has been examined only in multipolar cells (Smith 1992). The labeled neurons show similar electrical membrane characteristics, responding to depolarizing current injection with a sustained, adapting firing pattern and depolarizing rebound following hyperpolarizing current injection. The results indicate the presence of voltage-dependent Na^+, Ca^{2+} and Ca^{2+}-activated K^+

channels in these neurons (Smith 1992). Future study of physiological properties in different morphologic types of cells is essential for understanding how IC cortical neurons process ascending and descending inputs and influence intra- and intercollicular targets.

4. Ion Channel Characteristics

The intrinsic membrane conductance of an IC neuron, which is attributed to the type, number, and kinetic properties of ion channels, plays a key role in preserving and modulating auditory signals. Electrophysiological, pharmacological, and molecular–biological studies have revealed the features of a wealth of ion channels in IC neurons.

4.1. Potassium Channels

Traditionally, K^+ channels have been classified on the basis of their electrophysiological characteristics. However, molecular–biologic advances have allowed the cloning of the α subunit genes of the rapidly activating, delayed-rectifier (i.e., the Kv channel), which has four subfamilies: *Kv1* to *Kv4* (Coetzee et al. 1999). Each subfamily has different genetic isotypes, for example, *Kv1.1* to *1.7*, *Kv2.1* to *2.2*, *Kv3.1* to *3.4,* and *Kv4.1* to *4.4* subunits, that may encode distinct K^+ channels (Blaine and Ribera 1998; Song 2002).

An in situ hybridization study showed expression of both *Kv1.1* and *1.2* in mouse IC (Grigg et al. 2000). An immunocytochemical study in big brown bat found a gradient of *Kv1.1* labeling from ventrolateral to dorsomedial IC (Rosenberger et al. 2003). The labeled cells were multipolar and confined to the ventral IC. The low-threshold K^+ current in rat IC onset neurons resembles the current through *Kv1.1* channels, which are expressed strongly in CN bushy cells and octopus cells, and in principal cells of the medial nucleus of the trapezoid body (MNTB) (Grigg et al. 2000). This K^+ channel activates rapidly at membrane potentials of –50 to –30 mV, and then slowly inactivates (Brew and Forsythe 1995; Dodson et al. 2002). The low-threshold K^+ current in these auditory neurons accounts for the steep decrease in membrane input resistance near the resting potential and the brevity of synaptic potentials, both specializations for conveying precise timing information (Wu and Oertel 1984; Manis and Marx 1991; Wu and Kelly 1991; Golding et al. 1999; Svirskis et al. 2002). Whether IC neurons with *Kv1.1* also process precise temporal information should be examined in future studies.

IC neurons have weaker *Kv1.1* and *Kv1.2* expression than MNTB neurons, but stronger *Kv1.2* expression than CN bushy and octopus cells (Grigg et al. 2000). The physiological observation that a small number of IC neurons (onset type) have a low-threshold K^+ current probably flowing through the *Kv1.1* channels (Sivaramakrishnan and Oliver 2001) seems consistent with the finding of weak *Kv1.1* expression in the IC. Most IC neurons have a sustained firing pattern

and may express the *Kv1.2* channel. As these channels activate more slowly and at a more positive voltage than *Kv1.1* channels, the *Kv1.2* channel in the sustained firing neurons would allow temporal summation of multiple synaptic inputs, but not precise synaptic transmission of phase-locked information (Grigg et al. 2000).

A high level of *Kv3.1* mRNA expression has been observed in rat IC neurons (Perney et al. 1992; Weiser et al. 1994; Li et al. 2001). Liu and Kaczmarek's study (1998) shows that depolarization caused parallel increases in *Kv3.1* mRNA level and in the amplitude of a voltage-dependent high-threshold, noninactivating K^+ current, strongly suggesting the presence of functional *Kv3.1* channels in IC neurons. *Kv3.1* currents have a high threshold (–10 to –20 mV) for activation, and fast kinetics for both activation and deactivation. These currents are very sensitive to external TEA and 4-AP (Luneau et al. 1991; Critz et al. 1993; Perney and Kaczmarek 1997; Wang et al. 1998). In IC onset neurons the outward K^+ current has a high-threshold component whose activation kinetics and pharmacologic properties resemble those of the *Kv3.1* channel. This current likely flows through *Kv3.1* channels (Sivaramakrishnan and Oliver 2001).

The physiological profile of *Kv3.1* current is ideal to allow neurons to fire action potentials at high frequencies, as these channels open quickly once their threshold is reached, often near the peak of an action potential. The K^+ current influx then rapidly repolarizes the cell membrane and truncates action potential duration. On repolarization, *Kv3.1* channels close rapidly because of deactivation, thus minimizing the action potential refractory period and enabling the generation of subsequent action potentials (Li et al. 2001). Some auditory neurons that fire at high rates express *Kv3.1* channels strongly (Perney and Kaczmarek 1997; Wang et al. 1998). For example, CN bushy cells and MNTB principal cells can fire action potentials in response to electrical stimulation of their synaptic inputs up to about 500 Hz (Wu and Kelly 1993; Oertel 1997), and both express a high level of *Kv3.1* mRNA (Li et al. 2001). Similarly, IC onset neurons, which probably have *Kv3.1* channels, can also follow a train of short depolarizing current pulses at frequencies up to 200 Hz (Peruzzi et al. 2000).

Kv3.3 mRNA is also strongly expressed in the rat IC (Weiser et al. 1994; Li et al. 2001). The *Kv3.3* channel has activation kinetics, voltage sensitivity, and pharmacology similar to those of the *Kv3.1* channel, but differs in inactivation rate (Rudy et al. 1999). *Kv3.1* transcripts express a delayed-rectifier type current with very little inactivation, while *Kv3.3* transcripts express transient currents with moderate inactivation (Weiser et al. 1994). Although *Kv3.3* mRNA is expressed in IC neurons, the inactivating high-threshold K^+ current flowing through *Kv3.3* channels has not been detected (Liu and Kaczmarek 1998).

Kv9.1, one of the genes that encode the α subunit of the voltage-dependent K^+ channel, is co-expressed in IC but cannot form functional potassium channels alone. However, if *Kv9.1* is coexpressed with the *Kv2.1* channel that generates slowly inactivating delayed rectifier K^+ currents, the *Kv2.1* channel activation rate decreases, and the voltage dependence of inactivation and activation shifts

toward more negative membrane potentials (Richardson and Kaczmarek 2000). Because *Kv2.1* is expressed in IC (Hwang et al. 1993), the *Kv2.1* channel may be modulated by *Kv9.1,* which might affect firing patterns significantly (Richardson and Kaczmarek 2000).

The *Kv4* gene subfamily has been proposed as the key component of the classic A-type K^+ channel for A-current (I_A). *Kv4* channels activate and inactivate at subthreshold potentials, and recover from inactivation more quickly than other inactivating *Kv* channels. An in situ hybridization study (Serôdio and Rudy 1998) found high *Kv4* expression in the dorsal cochlear nucleus (DCN) and a low level in the IC. The DCN pyramidal cells express the fast A-type current with kinetic properties appropriate to support their pause-buildup firing pattern (Kanold and Manis 1999). Only about 15% of IC neurons have buildup-pause firing pattern (Sivaramakrishnan and Oliver 2001), which may explain the weak expression of mRNA of the *Kv4* gene.

4.2. Calcium-Activated Potassium Channel

IC neurons express two types of Ca^{2+}-activated K^+ channel, a large conductance, BK-type (or Maxi-type) and a small conductance, SK-type. The characteristics of BK- and SK-type currents were investigated in adapting- and transient-rebound neurons (Sivaramakrishnan and Oliver 2001). Neurons with a transient firing pattern had a voltage-dependent BK current that was rapidly inactivated after activation and blocked by CTX. Elimination of the BK current abolished AHP and altered the transient discharge to more sustained firing. Thus, the transient firing behavior and the AHP are attributed to the BK current. Neurons with an adapting firing pattern possessed an SK current, which showed little voltage dependence, had a threshold comparable to that of the total K^+ current, and was blocked by apamin. The SK current determined the degree of firing adaptation and maintained sustained firing to a depolarizing current injection.

How BK and SK currents contribute to the spike AHP of IC neurons has not been systematically investigated. IC neurons have two types of spike AHP with different time courses. The fast AHP (l to 10 ms) was common, whereas the slower AHP (10 to 100 ms) was found in only 20% of IC neurons (Li et al. 1998). The duration of spike AHP is one of the determinants for the maximal neural firing frequency. The AHP time course in different IC neurons and identification of the responsible Ca^{2+}-activated K^+ currents require further study.

4.3. Other Potassium Channels

Immunocytochemical and cloning studies have revealed other K^+ channels besides the *Kv* channels in IC neurons. For example, mRNA for rat *eag2,* a member of the *ether-à-go-go* family of K^+ channel genes, is expressed abundantly in the rat IC and midbrain (Ludwig et al. 2000). This gene encodes the prototype of a family of voltage-gated K^+ channels distinct from those of the *Kv* channel group. These channels have a strong voltage-dependence of activation, which is

sensitive to extracellular Mg^{2+} concentration (Terlau et al. 1996), and can be blocked by low cytosolic Ca^{2+} (Meyer and Heinemann 1998). The significance of plentiful IC rat *eag2* gene expression is not clear.

The ATP-sensitive K^+ channel (K_{ATP}) and inward rectifier (K_{IR}) belong to another superfamily of K^+ channels. Outward K^+ currents activated by the purinoceptor agonists are seen in cultured rat IC neurons (Ikeuchi and Nishizaki 1995b). The purine receptors in IC have been identified as the P_{2Y} subtype. Unlike K_{ATP} channels in other neurons, in which the K_{ATP} channel is activated by a G-protein–coupled second messenger system (Barnard et al. 1994; Ikeuchi and Nishizaki 1995a), the P_{2Y} purinoceptor gated K^+ channels in IC neurons are activated by direct coupling to the βγ subunits of G-protein (Ikeuchi and Nishizaki 1995b). The physiological significance of the K_{ATP} channel in IC neurons is unknown.

The IC also expresses an inward rectifier K^+ channel (K_{IR}). Immunocytochemical and in situ hybridization studies show staining of G-protein gated inward rectifier K^+ channel protein, the GIRK1 protein (Bausch et al. 1995), and its mRNA (Karschin et al. 1994) in IC neuron somata and dendrites. K_{IR} channels conduct very little current at physiological potentials but pass far more current when the cell is at a membrane potential negative to the K^+ equilibrium potential. Opening these channels also depends on extracellular K^+ concentration. GIRK1 and μ opioid receptors are colocalized over the same neurons in many brain regions, including the IC. These results suggest that μ opioid receptors may regulate K^+ conductance by activation of GIRK1 (Bausch et al. 1995). The significance of K_{IR} channels in IC neurons remains to be determined.

4.4. Calcium Channels

Ca^{2+} currents are implicated in the generation of rebound after hyperpolarization and in the depolarizing hump elicited by subthreshold positive current injection in IC neurons (Smith 1992; Sivaramakrishnan and Oliver 2001). A biophysical and pharmacologic study of Ca^{2+} currents found several types of voltage-sensitive Ca^{2+} channels in the 2- to 8-day-old rat IC (N'Gouemo and Rittenhouse 2000). All neurons expressed a high-threshold voltage-activated Ca^{2+} current that activated around –40 mV. Low- (activated at –70 mV) and mid-threshold (activated at –50 mV) voltage-activated Ca^{2+} currents were present in 33% and 40% of the recorded neurons, respectively. In IC there are four types of high threshold Ca^{2+} channels: L-type, N-type, P/Q-type, and a type that is resistant to a combination of the antagonists for all three types of high-threshold Ca^{2+} channels. How the various Ca^{2+} channels contribute to membrane excitability, action potential genesis, discharge pattern, firing threshold, and neurotransmitter release in the IC is not clear. Nevertheless, intracellular Ca^{2+} can influence many neural processes by regulating membrane and cytosolic proteins, such as ion channels, exchangers, pumps, and enzymes. Therefore, the significance of Ca^{2+} current in electrical activity, biochemical processes, and plasticity in IC should be investigated further.

5. Synaptic Receptors

This section focuses on the physiological properties of synaptic receptors in IC neurons activated by excitatory and inhibitory amino acids, including glutamate, γ-aminobutyric acid (GABA) and glycine; biogenic amines, such as serotonin (5-hydroxytryptamine, 5-HT); and acetylcholine (Ach).

5.1. Ionotropic Glutamate Receptors

Excitatory synaptic transmission in the IC is probably mediated by glutamate through ionotropic glutamate receptors. Intracellular and patch clamp recordings from ICC neurons in rat, mouse, and gerbil brain slices have found that both α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) receptors, the two main ionotropic glutamate receptors, mediate excitatory synaptic responses evoked by electrical stimulation of the lateral lemniscus or the IC commissure (Wagner 1996; Moore et al. 1998; Ma et al. 2002a). Excitatory commissural transmission to the ICD is also mediated by AMPA and NMDA receptors (Li et al. 1999).

Excitatory postsynaptic potentials (EPSPs) examined by Ma et al. (2002a) had two components—the early and the late. They were blocked by the AMPA antagonists, for example, 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) or 6,7-dinitroquinoxaline-2,3-dione (DNQX), and the NMDA receptor antagonist, D, L-2-amino-5-phosphonovaleric acid (APV), respectively (Fig. 10.2). These results suggest that the early part of the EPSP is mediated by AMPA receptors, and the later part by NMDA receptors. The temporal properties of these two types of glutamate receptors in ICC neurons are distinct (Ma et al. 2002a). Rise time, decay time, and half-width of AMPA component were 20% to 30% of the values for the NMDA component. Removing extracellular Mg^{2+} greatly enhanced only the NMDA component in the EPSP, suggesting that the NMDA receptors are suppressed by extracellular Mg^{2+}. AMPA and NMDA receptors in ICC neurons also differ in voltage dependence. The NMDA receptor-mediated response was voltage dependent and it was smaller when the membrane was hyperpolarized. The current-voltage *(I/V)* relationship for AMPA receptor-mediated EPSPs was linear, whereas that for the NMDA receptor-mediated EPSPs was nonlinear (Fig. 10.3) (Ma et al. 2002a). The rectification of the *I/V* curve for NMDA responses is attributable to a voltage-dependent block of the NMDA receptors by extracellular Mg^{2+}. These features of AMPA and NMDA receptors in ICC neurons resemble those of ionotropic glutamate receptors in other neurons, for example, hippocampal pyramidal cells (Mayer et al. 1984; Hestrin et al. 1990). However, unlike the glutamate receptors in hippocampal pyramidal neurons, in which NMDA receptors usually do not activate at the cell's resting potential (Hestrin et al. 1990), NMDA receptor-mediated responses in ICC are elicited at the cell's resting membrane potential and are not eliminated by blocking AMPA receptor-mediated responses (Ma et al. 2002a). NMDA re-

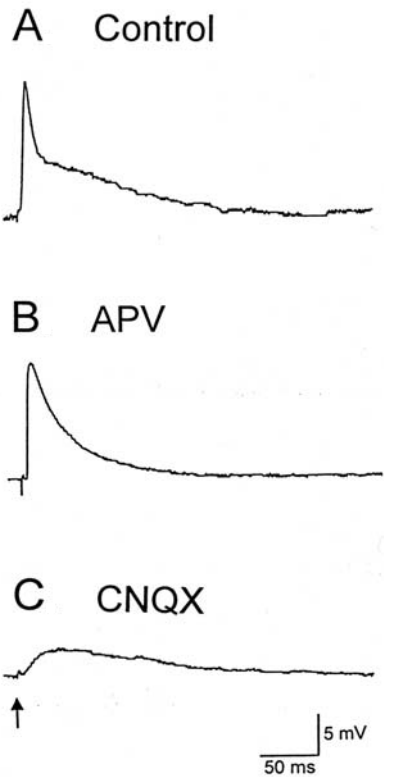

Figure 10.2. Excitatory synaptic response of ICC neurons is mediated by both AMPA and NMDA receptors. **(A)** In a brain slice perfused with normal saline an EPSP was elicited by electrical stimulation of the lateral lemniscus with an early and fast, and a later and slower, component from an ICC neuron. **(B)** APV application (100 μ*M*) suppressed the later part of the EPSP. **(C)** The early part of the EPSP was blocked by CNQX (10 μ*M*). The brain slice was perfused with strychnine (0.5 μ*M*) and bicuculline (10 μ*M*) while APV and CNQX were applied. Arrow, stimulus artifact.

ceptors in the IC may have lower sensitivity to Mg^{2+} blockade, therefore requiring less membrane depolarization for activation, as demonstrated in hippocampal stratum radiatum giant neurons (Kirson and Yaari 2000).

The recombinant heterodimeric NMDA receptors that contain NR2A or NR2B subunits are more strongly blocked by Mg^{2+} than those with NR2C or NR2D subunits (Kuner and Schoepfer 1996). Thus, the lower Mg^{2+} sensitivity of IC NMDA receptors may be attributable to expression of more NR2C and NR2D subunits than NR2A and NR2B subunits. How subunit composition affects Mg^{2+} sensitivity and voltage dependence of NMDA receptors in IC neurons requires further investigation. NMDA receptor subunits also undergo maturational changes, that is, down-regulation of NR2B and NR2D subunits, and up-regulation of NR2A (Kirson et al. 1999). In rat ICC neurons, the NMDA components decline relative to AMPA components during 1 to 2 weeks postnatal and then stabilize at 13 to 16 days (Ma et al. 2002a) and probably throughout adulthood. The ontogeny of the subunit composition of NMDA receptors in IC neurons is unknown.

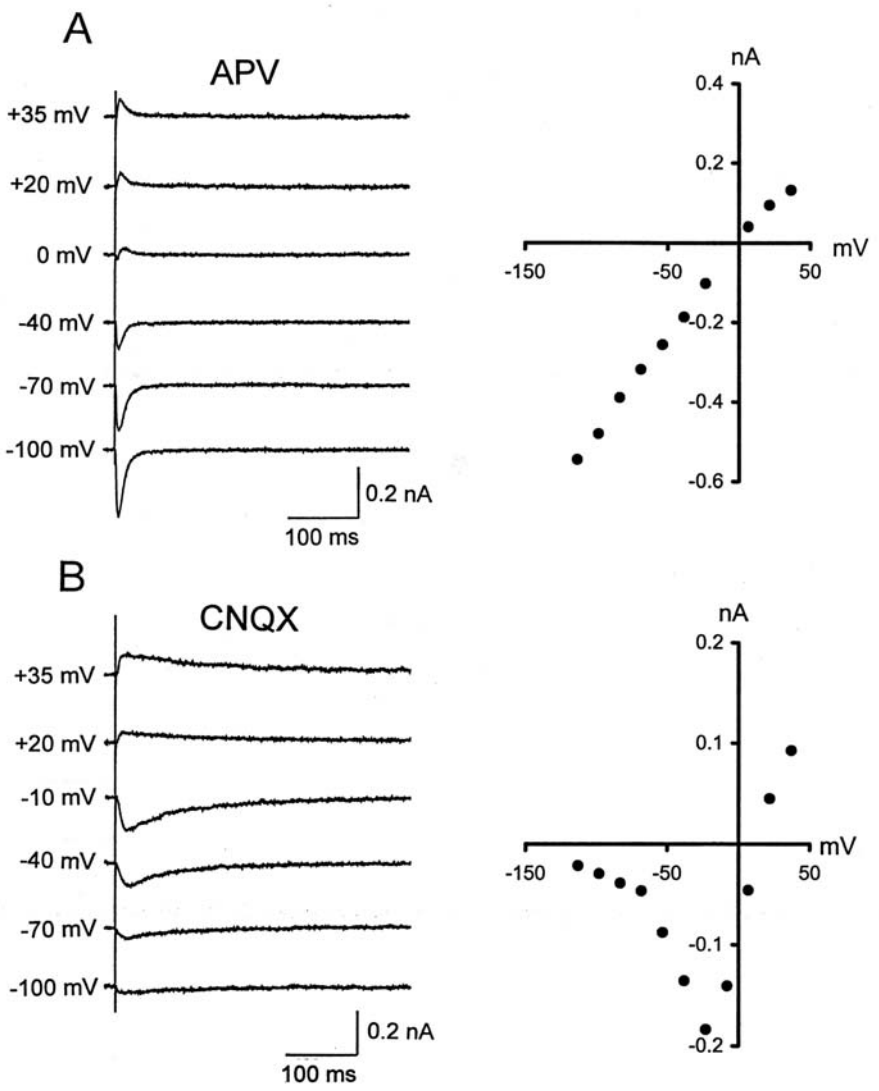

Figure 10.3. Current-voltage relationship of AMPA and NMDA receptor–mediated EPSCs in an ICC neuron. **(A)** *Left panel:* AMPA receptor–mediated EPSCs at various membrane potentials after blocking the NMDA receptor–mediated EPSCs with APV (100 μ*M*). *Right panel:* The *I/V* curve obtained from the peak amplitude of the isolated AMPA EPSCs was linear. **(B)** The NMDA receptor–mediated EPSCs from the same neuron at various membrane potentials after blocking the AMPA receptor–mediated EPSCs with CNQX (15 μ*M*). The ensuing current-voltage curve was highly nonlinear at negative voltages. In both conditions the slice was perfused with strychnine (0.5 μ*M*) and bicuculline (10 μ*M*). (Adapted from Ma et al. 2002a. Reprinted from Hearing Research with permission from Elsevier.)

The function of NMDA receptors in the IC is not fully understood. NMDA receptors are required for induction of long-term potentiation (LTP), a long-lasting increase in synaptic strength evoked by tetanic stimulation, in rat IC brain slices (Zhang and Wu 2000; Wu et al. 2002). Activation of NMDA receptors influences expression of newly learned auditory responses in the barn owl IC homologue (Feldman and Knudsen, 1998) and is involved in auditory responses in rat (Zhang and Kelly 2001; Kelly and Zhang 2002; see Chapter 9). In Zhang and Kelly's study (2001) iontophoretic application of AMPA or NMDA antagonists onto ICC cells of adult rats reduced responses to tone bursts and amplitude-modulated sounds. AMPA receptor antagonists selectively reduced the number of spikes evoked during the early response whereas the NMDA receptor antagonists reduced spikes evoked later. The NMDA receptor may amplify stimulus-evoked responses when the cell is depolarized by AMPA receptors and set the gain of neuronal responses to increasing stimulus intensity. The slow kinetics of NMDA receptors may provide a wide window for processing the inputs converging onto IC neurons at variable delays and with different time courses (Kelly and Zhang 2002). These hypotheses can be examined in vivo with direct application of NMDA.

NMDA receptors are implicated in audiogenic seizures (see Chapter 21). ICC and ICD neurons generate sustained or paroxysmal depolarization and epileptiform activity (burst discharges) after reduction of extracellular Mg^{2+} or application of NMDA (Pierson et al. 1989; Smith 1992; Wagner 1996; Li et al. 1998; Ma et al. 2002a). NMDA receptors in the IC may also be involved in the propagation of generalized tonic–clonic seizures (Yasuda et al. 2000). The increased audiogenic seizure susceptibility in some mice correlates with the overexpression of NR2C subunits (Marianowski et al. 1995) that reduce Mg^{2+} block of the NMDA receptor, thus promoting epileptic events.

5.2. γ-Aminobutyric Acid Receptors

GABAergic inhibition plays a vital role in normal IC auditory processing as well as in audiogenic seizure genesis. It affects firing rate, tuning curves, rate-level functions, duration tuning, and binaural responses (Faingold et al. 1989; Vater et al. 1992; Yang et al. 1992; Park and Pollak 1993, 1994; Pollak and Park 1993; Casseday et al. 1994; Klug et al. 1995; Fuzessery and Hall 1996; Le Beau et al. 1996; Palombi and Caspary 1996; Burger and Pollak 1998; Koch and Grothe 1998; Zhang et al. 1999). Blocking GABA uptake in the ICC or applying $GABA_A$ or $GABA_B$ receptor agonists significantly reduces audiogenic seizure severity in genetically epilepsy-prone rats (Faingold et al. 1994a,b). Conversely, bicuculline application to the ICC of normal rats can produce a short-term susceptibility to audiogenic seizures (Millan et al. 1986). GABA-mediated inhibition is thus a critical mechanism in genetic and induced forms of audiogenic seizures (Faingold 2002).

Intracellular studies in rat and gerbil brain slices have found that IPSPs of ICC neurons evoked by lateral lemniscal or commissural stimulation are medi-

ated predominantly by $GABA_A$ receptors (Smith 1992; Moore et al. 1998; Ma et al. 2002a). The reversal potential of synaptically evoked GABAergic inhibitory postsynaptic currents (IPSCs) and GABA-activated currents corresponds to the equilibrium potential of Cl^- ions, indicating that ICC GABAergic inhibition is mediated by Cl^- ions (Hosomi et al. 1997). The kinetics of $GABA_A$ receptors resemble those of AMPA receptors (Wu et al. 2004a). GABAergic IPSCs rise rapidly and peak within 10 ms, and have a half-width of only 20 to 30 ms. The fast decay time constant (about 30 ms) of GABAergic spontaneous IPSCs in juvenile IC cells (Kraushaar and Backus 2002) may reflect a high level of expression of the α_1 subunit of $GABA_A$ receptors (Sato et al. 2000; Kraushaar and Backus 2002).

The time course of the GABAergic response resembles that of the AMPA receptor–mediated excitatory response, allowing IC neurons to integrate excitatory and inhibitory synaptic inputs arriving simultaneously. When GABAergic inputs arrive earlier than excitatory inputs, activation of $GABA_A$ receptors can drive the cell's membrane potential toward the GABA reversal potential by preopening Cl^- channels (Wagner 1996). Therefore, the GABAergic response not only counteracts the AMPA component, but also suppresses the late and slow activation of the NMDA receptors. As shown in whole-cell patch clamp recordings (Ma et al. 2002a; Wu et al. 2004a), eliminating GABAergic inhibition enhanced the AMPA receptor mediated response and prolonged the NMDA receptor–mediated response, resulting in epileptic-like discharges (Fig. 10.4). Similar results have been found in ICX and ICD neurons (Smith 1992; Li et al. 1998). Thus, GABAergic inhibition normally suppresses NMDA receptor–mediated depolarization. Reducing this inhibition depolarizes the neuron over a longer time course and leads to epileptic-like discharges.

Iontophoresis of GABA or the $GABA_A$ agonist, muscimol, to IC neurons in brain slices of rat and gerbil pups ($<$14 days old) can elicit biphasic responses, that is, membrane de- and hyperpolarization. This is interesting because GABA usually acts on the $GABA_A$ receptor, hyperpolarizing the membrane potential. The membrane depolarization by GABA or muscimol in young IC neurons was accompanied by an increase in intracellular Cl^- and Ca^{2+} (Lo et al. 1998; Frech et al. 1999). The Ca^{2+} influx activated by GABA was dependent on extracellular HCO_3^- (Frech et al. 1999), which implies an HCO_3^- efflux during GABA activation. Active Cl^- uptake and HCO_3^- efflux could shift the GABA reversal potential to a more positive level, which may account for the depolarizing effect of GABA during development. Increased intracellular Ca^{2+} by GABA may be secondary to activation of voltage-dependent Ca^{2+} channels, which can influence the growth and refinement of prospective inhibitory synaptic connections (Segal 1993).

The possibility that $GABA_B$ receptors are involved in synaptic transmission in the IC has been studied in in vivo and in vitro experiments. The $GABA_B$ receptor agonist, baclofen, did not affect membrane input resistance (Ma et al. 2002b), resting potential, or K^+ membrane conductance (Hosomi et al. 1997). These negative effects along with the short time course of the GABAergic IPSPs

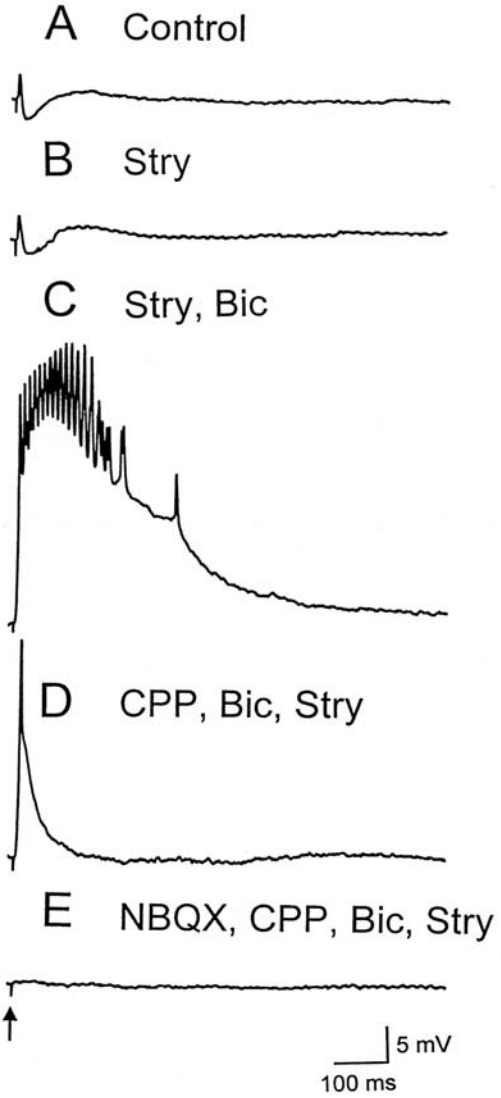

Figure 10.4. Strong suppression of synaptic excitation by GABAergic inhibition in an ICC neuron. **(A)** In a brain slice perfused with normal saline, lateral lemniscal stimulation elicited a small early EPSP, an IPSP, and a late EPSP. **(B)** After strychnine (0.5 μ*M*; Stry) application there was little change in the synaptic response. **(C)** With bicuculline (10 μ*M*; Bic) the EPSP grew larger and longer, and multiple spikes appeared. **(D)** The late EPSP and associated action potentials were eliminated by CPP (20 μ*M*), the NMDA receptor antagonist, but an early EPSP and a short latency action potential were still present. **(E)** The early EPSP and its related spike were completely blocked by the AMPA receptor antagonist, NBQX (2 μ*M*). (Adapted from Ma et al. 2002a.)

and the IPSP reversal potential, which is close to the cell's resting potential, suggest that GABAergic synaptic transmission in the ICC is not mediated by metabotropic $GABA_B$ receptors. However, baclofen reduced the GABAergic IPSP amplitudes of ICC neurons in brain slices and phaclofen reversed this effect (Ma et al. 2002b). These results suggest that GABAergic inhibition is modulated by presynaptic $GABA_B$ receptors via regulation of GABA release (Ma et al. 2002b). $GABA_B$ receptors also affect synaptic plasticity. LTP induction in IC brain slices requires $GABA_B$ receptor activation (Zhang and Wu 2000). Electrophysiological studies in vivo show that $GABA_B$ receptors influence excitatory transmission in the IC (Faingold et al. 1991; Vaughn et al. 1996). Baclofen reduced sound-evoked responses, while $GABA_B$ receptor antagonists increased them. Systemic baclofen application reversed potentiation of click-evoked responses to intense sound (Szczepaniak and Møller 1996). A regulatory effect of $GABA_B$ receptors on glutamate release was proposed (Kelly and Zhang 2002) and tested in in vitro brain slices. EPSCs of IC neurons were reduced by baclofen, and this effect was reversed by the $GABA_B$ receptor antagonist, CGP 35348 (Wu et al. 2004b). Thus, $GABA_B$ receptors can modulate $GABA_A$ receptor–mediated inhibition as well as glutamatergic excitation in the IC.

5.3. Other Synaptic Receptors

5.3.1. Glycine Receptors

Electrophysiological studies suggest that glycinergic inhibition plays a role analogous to GABAergic inhibition in shaping frequency-response areas, sharpening tuning for frequency modulation, sound duration coding, and binaural processing (Klug et al. 1995; Koch and Grothe 1998; Casseday et al. 2000; Le Beau et al. 2001; Lu and Jen 2001). However, differential effects for the $GABA_A$ and glycine receptor antagonists, bicuculline and strychnine, were reported. Excitatory tuning curves in some IC neurons in the horseshoe bat were changed by bicuculline, but not by strychnine (Vater et al. 1992). Bicuculline was more effective in abolishing the inhibitory frequency tuning curves and influencing the excitatory frequency tuning curves than strychnine (Lu and Jen 2001). Most of the bicuculline-sensitive cells were located more dorsally than those influenced by strychnine (Lu and Jen 2001), consistent with regional differences in $GABA_A$ and glycine receptor density (Sanes et al. 1987; Fubara et al. 1996). Physiological properties of glycine receptors resemble those of $GABA_A$ receptors in juvenile and mature IC neurons: activation of both $GABA_A$ and glycine receptors inhibits mature neurons by triggering Cl^- influx and hyperpolarizing the cell's membrane. During embryonic and neonatal development, glycine and GABA depolarize IC neurons and increase intracellular Ca^{2+} concentration (Ehrlich et al. 1999; Kotak and Sanes 2000).

However, IC glycine receptors develop more slowly than $GABA_A$ receptors. In immature rats (3 to 8 days postnatal) glycine receptors activate and deactivate significantly more slowly (Kraushaar and Backus 2002) than those in ventral

CN and spinal motor neurons (Jonas et al. 1998; Harty and Manis 1998). Slow kinetics may reflect immature glycine receptors with $\alpha 2$ subunits (Takahashi et al. 1992; Singer et al. 1998). Slowly deactivating glycine receptors may prolong depolarization and enhance intracellular Ca^{2+} stores, perhaps affecting inhibitory synaptic ontogeny (Kraushaar and Backus 2002). Slowly developed glycine receptors may retard glycinergic relative to GABAergic neurotransmission, which matches the later arrival of glycinergic afferents from the lower auditory brain stem.

5.3.2. Serotonin Receptors

Serotonin (5-HT) modulates neural responses in bat to tone bursts and complex, behaviorally relevant sounds such as FM sweeps and species-specific vocalizations (Hurley et al. 2002). Iontophoretic application of serotonin onto IC neurons in vivo often depressed tone-evoked responses (Faingold et al. 1991; Hurley and Pollak 1999), facilitated or suppressed FM sweep responses, and had frequency-specific effects on response areas (Hurley and Pollak 2001). These effects are thought to be more complex than gain control because serotonin can change frequency tuning (Hurley et al. 2002). Autoradiographic labeling of the 5-HT_{1A} receptor agonist shows the highest level of binding in the IC compared to other auditory brain stem nuclei (Thompson et al. 1994). The 5-HT_{1A} and 5-HT_2 receptors are implicated in defensive behavioral responses after direct agonist injection in the auditory midbrain (Melo and Brandão 1995).

Serotonin acts on 5-HT receptor subtypes through various ionic mechanisms (Peroutka 1988; Bobker and Williams 1990), for example, activation of the 5-HT_{1A} receptor hyperpolarizes the cell's membrane potential, which is mediated by increased conductance to K^+ ions. The 5-HT_{1B} and 5-HT_{1D} receptors may have presynaptic inhibitory effects on glutamate, GABA, and serotonin release. Activation of the 5-HT_2 receptor has a depolarizing excitatory effect owing to decreased K^+ conductance. Activating ionotropic 5-HT_3 receptors causes depolarization by directly opening the receptor for cations. Serotonin enhances the cationic current, I_h (which activates over hundreds of milliseconds on hyperpolarization), via undefined 5-HT receptor subtypes. Whether the complex effects of exogenous 5-HT on IC neurons reflect activation of different 5-HT receptor subtypes is not clear. Future studies should characterize the physiological properties of 5-HT receptor subtypes and determine regional differences in receptor physiology because 5-HT input and receptors are concentrated in the peripheral IC (Thompson et al. 1994; Hurley and Thompson 2001).

5.3.3. Acetylcholine Receptors

Nicotinic and muscarinic Ach receptors in IC are revealed by labeling receptors and mRNA of receptor subunits (Schwartz et al. 1982; Cortés and Palacios 1986; Regenold et al. 1989; Morley and Happe 2000). The role of Ach in IC physiology has been studied by iontophoretic application of Ach receptor agonists and antagonists in in vivo electrophysiological studies (Farley et al. 1983; Fain-

gold et al. 1991). Discharges elicited by the nonspecific agonists, Ach and carbachol, were enhanced in some neurons and decreased in others; temporal patterns, tuning curves, and rate-level functions were unaffected. Application of the nicotinic receptor antagonist, hexamethonium, enhanced activity in most cells and decreased tone-evoked activity in others. The nonspecific muscarinic antagonist atropine and the specific M1 receptor antagonist, pirenzepine, decreased responses in most neurons whereas the M2 receptor antagonist, gallamine, often increased activity. These results suggest that cholinergic inputs constitute a dynamic regulatory system, which controls the overall firing rate and modulates more specific excitatory and inhibitory circuits (Habbicht and Vater 1996). Perhaps Ach modulates acoustic responses via subtypes of Ach receptors that are differentially expressed pre- or postsynaptically. Further investigation should characterize physiological properties of Ach receptor subtypes in the IC.

In summary, excitatory synaptic transmission in the IC is glutamatergic via AMPA and NMDA receptors. The AMPA receptors subserve the early and fast part of the synaptic response, whereas NMDA receptors control the later and slower component. Fast inhibitory transmission is mediated by GABA and glycine via $GABA_A$ and glycine receptors. Glutamatergic excitation and GABAergic inhibition can be modulated by presynaptic $GABA_B$ receptors. Serotonin and Ach receptors have a regional modulatory role in synaptic transmission, perhaps through various receptor subtypes.

6. Future Directions

Understanding the biophysical profile of IC neurons has just begun. Only basic information about intrinsic electrical membrane properties and synaptic receptor characteristics is available. Much more work is needed in order to understand how the biophysical features of IC neurons contribute to auditory processing.

Ion channels that underlie the intrinsic membrane properties play a key role in shaping neural input–output functions. However, the output signal from a neuron embodies the cell's intrinsic electrical membrane properties and the activation of specific synaptic receptors. Therefore, synaptic inputs and synaptic receptors (or subtypes) in IC neurons with specific intrinsic membrane properties should be defined. Molecular–biologic study combined with physiological analysis of ion channels and synaptic receptors in IC neurons will drive such work. As a profile of subtypes and subunits of ion channels and synaptic receptors emerges, biophysical study of the channels and receptors will clarify the molecular mechanisms of auditory signal processing. Systematic studies of membrane and synaptic properties, combined with the anatomy of IC neurons in the three major subdivisions, are essential to understand how cell structure, physiological characteristics, and synaptic connections interact and are integrated.

Abbreviations

Ach	acetylcholine
AHP	afterhyperpolarization
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
4-AP	4-aminopyridine
Bic	bicuculline
CN	cochlear nucleus
CNQX	6-cyano-7-nitroquinoxaline-2,3-dione
CPP	(±)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid
CTX	charybdotoxin
DNLL	dorsal nucleus of the lateral lemniscus
DNQX	6,7-dinitroquinoxaline-2,3-dione
EPSC	excitatory postsynaptic current
EPSP	excitatory postsynaptic potential
FM	frequency-modulated
GABA	γ-aminobutyric acid
GIRK1	G-protein gated inward rectifier K^+ channel
5-HT	5-hydroxytryptamine (serotonin)
IC	inferior colliculus
ICC	central nucleus of the inferior colliculus
ICD	dorsal cortex of the inferior colliculus
ICX	external nucleus of the inferior colliculus
IPSC	inhibitory postsynaptic current
IPSP	inhibitory postsynaptic potential
K_{IR}	inward rectifier K^+ channel
LSO	lateral superior olive
LTP	long-term potentiation
MNTB	medial nucleus of the trapezoid body
MSO	medial superior olive
NBQX	1,2,3,4-tetrahydro-6-nitro-2,3-dioxo-benzo[*f*]quinoxaline-7-sulfonamide
NMDA	*N*-methyl-D-aspartate
SAM	sinusoidal amplitude modulation
Stry	strychnine
TEA	tetraethylammonium
VNLL	ventral nucleus of the lateral lemniscus

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Chapter 11
Spectral and Intensity Coding in the Auditory Midbrain

Günter Ehret and Christoph E. Schreiner

1. Introduction

This overview emphasizes general properties of spectral and intensity processing in the inferior colliculus (IC) common to mammals such as the cat, mouse, rat, guinea pig, Mongolian gerbil, chinchilla, rhesus monkey, and various species of bats. Considerable data are available for the domestic cat (*Felis catus*) and mice (*Mus musculus*, laboratory strains) so that these species can serve as representative unless specified otherwise (for special spectral processing regimens in bats see Chapters 14 and 17). Functional distinctions exist among IC subdivisions (Aitkin 1986). Accordingly, we employ a basic anatomical framework of three major divisions: the central nucleus (ICC), the external nucleus (EN), and the dorsal cortex (DC). In this framework, the ICC contains layer IV of the DC as defined in Golgi studies of the cat (Morest and Oliver 1984) and mouse (Meininger et al. 1986).

1.1. Principles of Spectral Analysis and Coding

A defining step for the organization of the entire auditory system is the spectral decomposition of the acoustic waveform in the cochlea (Patuzzi 1996). All subsequent operations directly reflect this peripheral process or are a consequence of specific central auditory filtering and transformations acting on the residue of this initial process. The orderly frequency representation along the basilar membrane, the tonotopy, is the basis of the concomitant order for characteristic frequency (CF) found in many nuclei and centers of the auditory pathways, including the ICC and extending to the primary auditory cortex. Thus, the cochlear tonotopy is the first and most general principle of spectral analysis and coding. Although the cochlear transformation of the signal is not identical to a Fourier analysis, the parallels between them are sufficiently compelling to warrant analysis of the resulting transmission channels as a bank of parallel spectral filters. Therefore, many characterizations of auditory neuronal elements are cast in the language of frequency filtering, using metrics such as center frequency,

frequency selectivity or filter bandwidth, and response magnitude. The response timing of the individual frequency channels—reflected in phase-locking of action potentials to individual cycles of a frequency—also affects auditory processing, but is confined to relatively low frequencies, and is not considered further. Here, we deal with properties of frequency filtering of IC neurons. A profile of the spectral receptive field (SRF) is a first analytic step in characterizing a neuron type or a nucleus.

1.2. Principles of Intensity Analysis and Coding

Relative and absolute stimulus magnitudes are two parameters in the spectral analysis of sounds with profound influence on auditory processing and perception. Mean sound pressure level (SPL) may influence neural responses in three ways: it can change spectral filter width, alter neural response strength in terms of firing rate, and modify temporal response parameters such as latency and precision of action potential timing relative to the stimulus waveform. Intensity effects on filter bandwidth are closely related to spectral receptive-field shape. Response magnitude effects are commonly discussed in terms of rate-level functions (RLs), that is, the total number of spikes/stimulus plotted against mean stimulus level. From RLs, measures of response threshold, intensity selectivity, and dynamic range can be derived.

Another aspect of stimulus magnitude is the amplitude distribution across the sound spectrum. The relative intensity of spectral minima and maxima, or the "contrast" with regard to their mean amplitudes, and the time course of these amplitude changes across the spectrum, must be encoded and represented. It is evident that amplitude coding in a complex spectral environment, the most natural listening condition, is inseparable from coding in the spectral domain.

2. Spectral Receptive-Field Properties

2.1. Excitatory/Inhibitory/Facilitatory Areas

Traditionally, spectrally simple sounds that are readily parameterized and manipulated are used for the exploration of receptive-field (RF) characteristics. Pure tones of various frequency and intensity combinations can demonstrate the excitatory SRF (eSRF) by identifying the parameter combinations that elevate firing rate above the spontaneous activity. The border of the eSRF represents the excitatory frequency tuning curve (eFTC) (Fig. 11.1A) and its shape is assessed by several measures:

- Characteristic frequency (CF): frequency producing a response at the lowest sound pressure levels (SPL)
- Best frequency (BF): frequency evoking the most spikes at a given SPL (CF and BF are not always identical)
- Minimum threshold (MT): SPL at CF

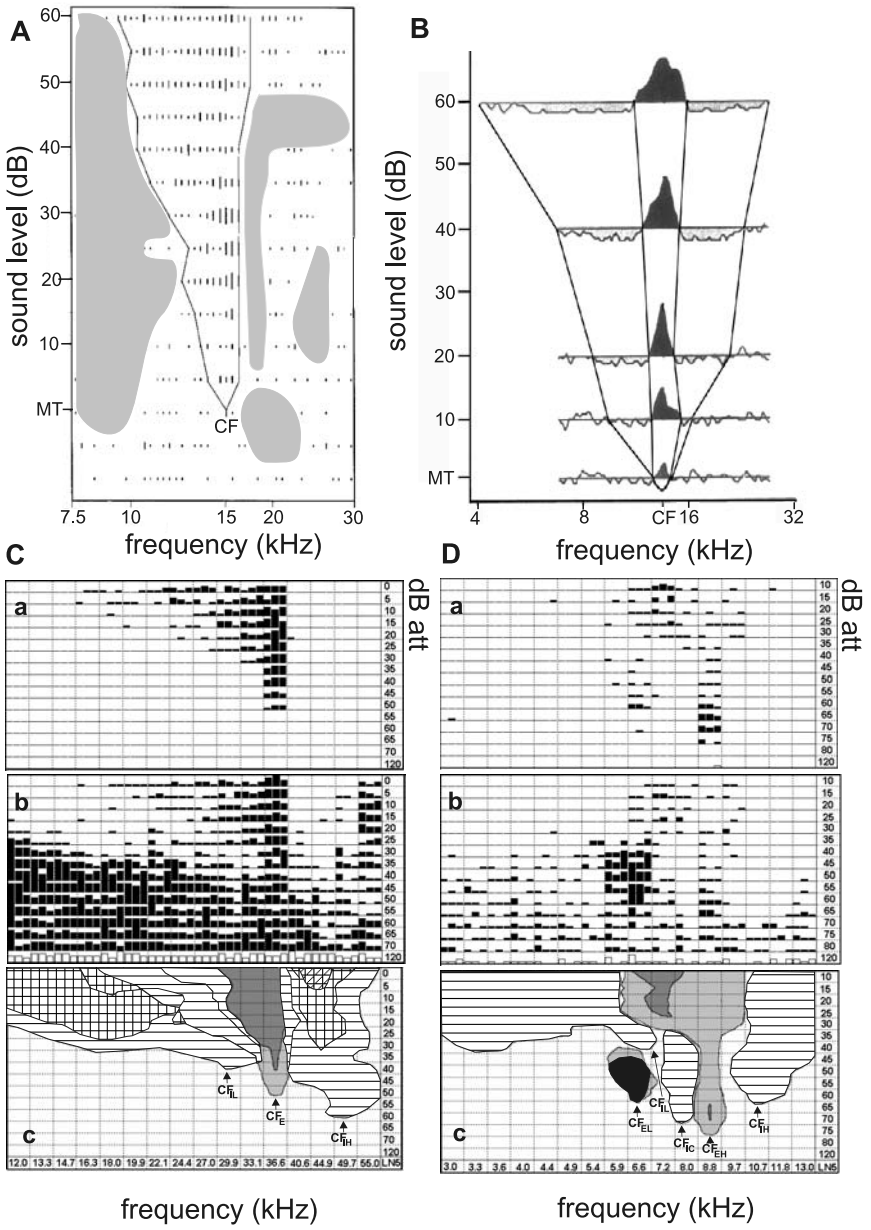


Figure 11.1. Spectral receptive fields *(SRFs)* of neurons in the central nucleus of the inferior colliculus (ICC). **(A)** Map of the SRF of a mouse neuron. Spike rates are shown as short vertical bars. The excitatory frequency tuning curve *(eFTC)* borders an area of increased responsiveness (above the spontaneous activity), the excitatory SRF *(eSRF). Shaded gray areas*: inhibitory SRFs (*iSRF*; suppressed spontaneous activity). (M.A. Ego-

- Bandwidth (BW): frequency width of FTC at various levels above MT
- Quality factor *(Q)*: the relative sharpness of tuning CF/BW at a fixed stimulus level (e.g., *Q10*dB is based on BW 10 dB above MT)
- The slopes of the low- and the high-frequency sides of the eFTC (expressed in dB/octave); also related to sharpness of tuning

A tone at a frequency and/or level outside the eSRF may have no effect on response rate or decrease it below spontaneous activity. The latter effect is called "one-tone inhibition" and reveals inhibitory areas surrounding the eSRF (Fig. 11.1A, B) if the spontaneous activity is sufficient to reliably detect an activity decrease (Suga 1964; Willott and Urban 1978; Wang et al. 1996; Ramachandran et al. 1999).

A more comprehensive approach uses a "two-tone paradigm" (e.g., Egorova et al. 2001): one tone excites the neuron at its CF (10 to 20 dB above threshold) while a second tone of variable frequency and level is presented simultaneously, with or shortly before the CF tone. This second tone can increase excitation to the constant CF tone (summation or facilitation of excitation; Fig. 11.1D), decrease or suppress the response to the CF tone (inhibition; Fig. 11.1C, D), or it can have no visible effect. Thus, the two-tone paradigm can identify the superposition of inhibitory and facilitatory receptive fields (iSRFs, fSRFs, respectively) with the eSRF. Inhibitory areas outside the eFTC are called "inhibitory side bands." The shapes of iSRFs and fSRFs are quantified by similar measures as eSRFs and eFTCs.

Facilitatory SRFs have rarely been studied (Fuzessery and Feng 1983; Ehret and Merzenich 1988a; Egorova et al. 2001; Jen et al. 2002) except in the highly specialized mustached bat IC (Mittman and Wenstrup 1995; Wenstrup et al. 1999; Portfors and Wenstrup 2002) (see Chapter 17). Few cells show spectral facilitation (about 11% in the mouse, 18% in the big brown bat). In the mouse, facilitation is often found within about 1 octave of CF (Egorova et al. 2001).

Figure 11.1. *Continued*
rova and G. Ehret, unpublished observations). **(B)** Response rates to tone bursts relative to spontaneous activity (horizontal lines at five sound levels) at various frequency-level combinations indicate a narrow excitatory area *(black)* around the characteristic frequency *(CF)* bordered by inhibitory areas *(gray)* of a cat type I neuron. Lines demarcate the borders of the eSRF and the two iSRFs. (Modified from Ramachandran et al. 1999.) **(C, D)** Spike rates *(black bars)* of two mouse neurons in response to *(a)* tone bursts of various frequency-level combinations, *(b)* combinations of two tones, one at the CF and 10 dB above minimum threshold, the other at various frequency-level combinations. (Modified from Egorova et al. 2001.) *(c)* eSRFs are marked in various gray levels (proportional to response rate); iSRFs are marked with different hatching reflecting grades of inhibitory strength. The *black area* in **(C)** indicates a facilitatory SRF (fSRF). CF_E, Excitatory CF; CF_{IL}, CF_{IH}, inhibitory CFs below and above the CF_E, respectively. The neuron in **(D)** has two excitatory CFs, CF_{EH} and CF_{EL}, both separated by a central inhibitory area with a CF_{IC}. *dB att,* Attenuation steps in dB; *MT,* minimum threshold.

Facilitation in the IC indicates that spectrally related tones can enhance responses.

2.2. Shapes of Excitatory and Inhibitory Receptive Fields

Basic differences have been found between IC subdivisions with regard to SRF and FTC shapes. In the DC and especially the EN, the frequency selectivity is low, with broad eFTCs, low Q-values, and irregularly shaped eFTCs (Fig. 11.2) (Aitkin et al. 1975, 1978; Willott and Urban 1978; Binns et al. 1992; Syka et al. 2000). Studies specifying iSRFs and iFTCs for DC and EN neurons remain to be done.

In the ICC, eSRFs have been studied extensively (Rose et al. 1963; Suga 1969; Gersuni et al. 1971; Ehret and Moffat 1985a; Casseday and Covey 1992; Wang et al. 1996; Ramachandran et al. 1999; Egorova et al. 2001; Le Beau et al. 2001). iSRFs measured in a two-tone paradigm have been investigated in comparatively few studies (Suga 1969; Ehret and Merzenich 1988a; Vater et al. 1992; Fuzessery 1994; Egorova et al. 2001; Lu and Jen 2001). eSRFs and iSRFs have varied shapes (Figs. 11.1, 11.3, and 11.6A) that sometimes reflect differences in stimulus presentation (monaural vs. binaural, short vs. long durations or rise times, simultaneous vs. asynchronous two-tone presentation) and data evaluation (different criteria for thresholds of excitatory and inhibitory thresholds). However, the rather uniform eFTC shapes of auditory nerve fibers (Kiang et al. 1965; Liberman 1978; Fig. 11.3A) are transformed into ICC FTCs that deviate substantially from the peripheral frequency filtering (Figs. 11.3 and

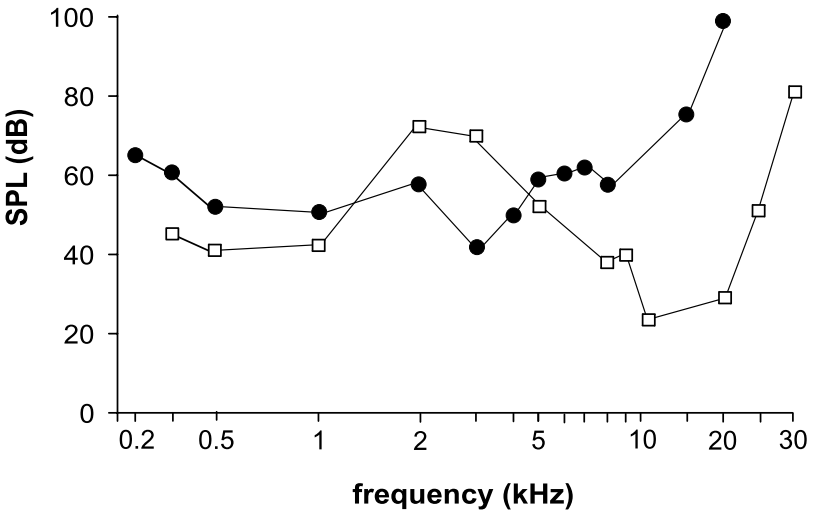


Figure 11.2. Excitatory frequency tuning curves from the external nucleus of the cat inferior colliculus. (Modified from Aitkin et al. 1975.)

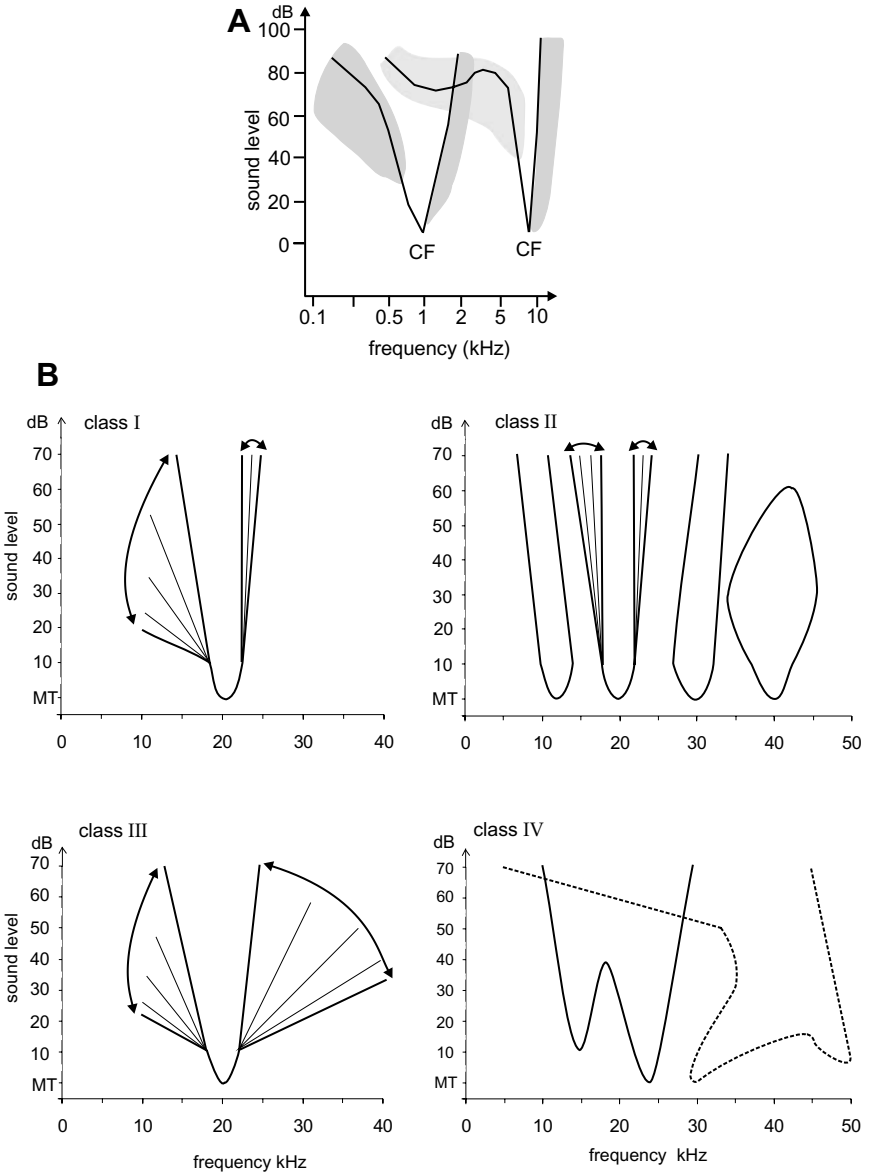


Figure 11.3. **(A)** Examples of excitatory tuning curves of auditory nerve fibers with a low and a high characteristic frequency *(CF)*. Areas of lateral suppression are shaded. (Modified from Ehret 1996.) **(B)** Classification (classes I to IV) of ICC neurons according to the shapes of their excitatory frequency tuning curves *(eFTCs)*. Some variability of the tuning-curve slopes and shapes within each class is indicated. (Modified from Egorova et al. 2001.)

11.6A). With the simultaneous two-tone paradigm, grades of inhibition and heterogeneous iSRF shapes are seen in almost all ICC neurons. Owing to the glycinergic and γ-aminobutyric acid-positive (GABAergic) projections to the ICC (see Chapters 2, 4, and 9) and the intrinsic network with many GABAergic neurons (see Chapters 2, 5, and 9), inhibition is a prominent feature (Oliver et al. 1994; Winer et al. 1995; Le Beau et al. 1996, 2001).

The eSRFs and iSRFs of mouse ICC neurons have properties that define four classes of cells (Egorova et al. 2001) (Figs. 11.3B and 11.6A). All may have fSRFs.

Class I neurons closely resemble the excitatory and lateral suppression areas of auditory nerve fibers (Sachs and Kiang 1968). Their essential properties are: (1) strongly asymmetric eFTCs with steep high-frequency slopes and shallow low-frequency slopes; (2) inhibitory areas below and above CF that are asymmetric with higher inhibitory thresholds below the CF; (3) inhibitory areas that can overlap eSRFs only partially.

Class II neurons are dominated by inhibition. Their main features are: (1) inhibitory areas that are nearly symmetrical, with similar inhibitory thresholds below and above CF and that always invade eSRFs, often completely overlapping them; (2) the eFTCs have either steep slopes on both sides, are skewed toward the low- or high-frequency side at high levels, or are closed (with an upper response threshold); (3) inhibitory and excitatory thresholds and CFs are in close register.

Class III neurons have weak inhibition. Their other attributes are: (1) symmetric and shallow eFTC slopes; (2) inhibitory areas are small, inhibition is weak, and inhibitory areas are often only on one side of the eSRF; (3) excitatory and inhibitory thresholds are unrelated.

Class IV neurons have complex eSRFs and iSRFs, always with several eSRFs or multiple CFs.

iSRFs have not been determined in most ICC studies. Profiles of sound processing in the spectral domain are, however, incomplete without such measures and considerations of the graded influence of inhibition implicit in any RF classification. The gradient of eFTC slopes is an estimate of the extent and strength of inhibition, without direct measurement of iSRFs (Egorova et al. 2001). Most (93%) class I to III neurons can be classified by the slope criterion alone. Class I cells have low-frequency slopes $<$150 dB/octave and high-frequency slopes $>$250 dB/octave. Class II neuron low-frequency slopes are $>$150 dB/octave and high-frequency slopes $>$250 dB/octave. Class III neurons have low-frequency slopes $<$150 dB/octave and high-frequency slopes of $<$250 dB/octave. The critical slope values for classifying neurons may be species-specific. It is encouraging that the assignment of ICC neurons into four classes extends to other ICC studies for comparative purposes, and for functional considerations such as amount and extent of inhibition. Inhibition-dominated class II neurons have similar proportions in mice (27% to 28%; Egorova et al. 2001; Ehret et al. 2003), cats (27%; Ehret and Merzenich 1988a), and guinea pigs (26%; Le Beau et al. 2001). This suggests comparable inhibitory innervation patterns and functions. Class IV neurons are sparse in mice (6% to 10%; Egorova et al. 2001;

Ehret et al. 2003), guinea pigs (2%; Le Beau et al. 2001), and big brown bats (3%; Lu and Jen 2001), and high (40%) in the mustached bat (Portfors and Wenstrup 2002). Combinations of the harmonics of biosonar calls play a decisive role in echolocation, and selective adaptations may create combination-sensitive neurons and irregular FTCs (Mittmann and Wenstrup 1995; Leroy and Wenstrup 2000).

In the decerebrate cat, a related tuning curve classification (Ramachandran et al. 1999) is based on excitatory FTCs and inhibition of spontaneous activity (one-tone inhibition). Type "I" neurons combine a narrowly tuned I-shaped excitatory SRF with flanking inhibitory regions (Fig. 11.1B), like some class II neurons defined previously. Type "V" neurons show more broadly tuned, V-shaped excitatory areas with no inhibition of spontaneous activity (much like some class I/III neurons). Type "O" units have frequency response maps dominated by inhibition except for a circumscribed (O-shaped) island of excitation near CF and MT, also resembling some class II cells. The distribution of these classes seems to be method-specific: type O neurons comprise some 70% of ICC neurons in decerebrate cats (Ramachandran et al. 1999) but only 5% in nondecerebrated and anesthetized cats (Ehret and Merzenich 1988a) and 8% in nondecerebrated and anesthetized mice (Egorova et al. 2001). Differences between the two classification schemes will likely resolve when similar methodologies are applied across species.

Detailed descriptions of RFs in DC and EN are sparse, especially for inhibitory properties. Excitatory SRFs are broadly V-shaped or irregular (cat: Aitkin et al. 1975; guinea pig: Syka et al. 2000), suggesting many class III and IV neurons. Because class IV receptive fields are rare in the dorsal cochlear nucleus (Rhode and Smith 1986; Spirou and Young 1991) and superior olivary complex (Guinan et al. 1972) and ICC, they are likely the result of interactions between ascending (and descending) inputs.

3. Frequency Organization

3.1. The Central Nucleus

Virtually all ICC neurons are frequency tuned, although tuning sharpness differs from auditory nerve fibers. The one-dimensional cochlear frequency map is transformed into a three-dimensional map in the ICC (Fig. 11.4A). ICC tonotopy consists of two frequency gradients. The first is steep with stepwise changes from low frequencies (dorsal and dorsolateral ICC) to high frequencies (ventromedial ICC; Fig. 11.4B). This gradient, typical for most mammals, is orthogonal to the cellular laminae (see Chapter 2) and their input projections (see Chapters 3 to 5) and has been demonstrated with electrophysiologic measurements of single- or multiunit CFs (Merzenich and Reid 1974; Fitzpatrick 1975; Roth et al. 1978; Semple and Aitkin 1979; Stiebler and Ehret 1985; Poon et al. 1990; Romand and Ehret 1990; Casseday and Covey 1992; Brückner and Rübsamen 1995; Schreiner and Langner 1997), with activity-dependent glucose labeling

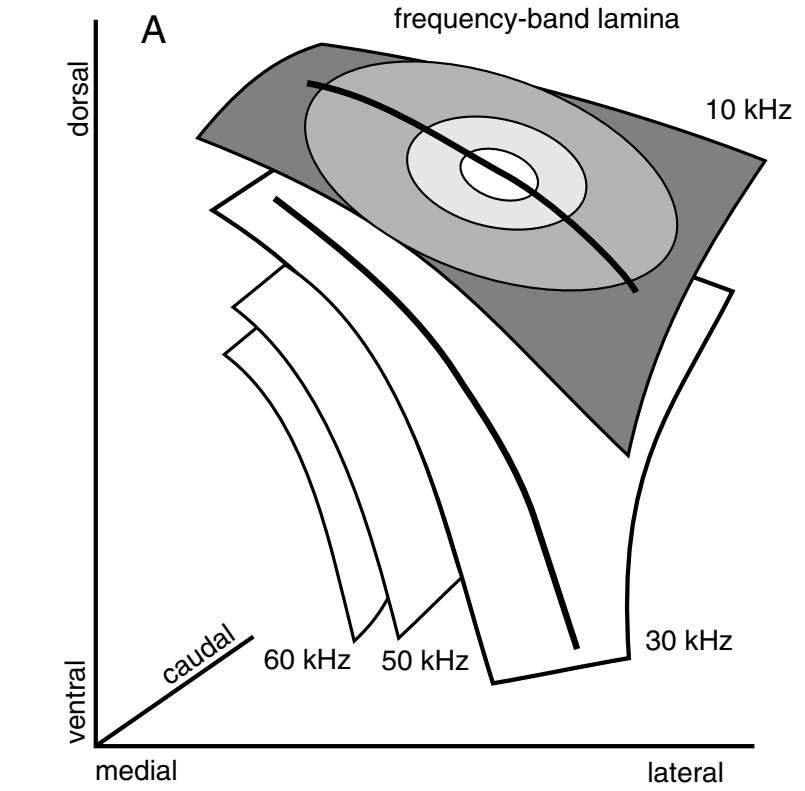
by [^{14}C]2-deoxyglucose autoradiography (Servière et al. 1984; Webster et al. 1984; Huang and Fex 1986; Martin et al. 1988; Ehret and Romand 1994; Brown et al. 1997), and with immediate–early gene activation using c-Fos immunocytochemistry (Ehret and Fischer 1991; Friauf 1992; Reimer 1993). This tonotopic organization forms a stack of "isofrequency sheets" of variable sizes and shapes covering the frequency spectrum of hearing (Fig. 11.4A). Isofrequency sheets parallel the ascending projections to the ICC (see Chapter 2). Cochlear CF space is often distorted in the ICC with frequency ranges important in communication or echolocation overrepresented (bat: Casseday and Covey 1992; mouse: Stiebler and Ehret 1985).

The second frequency gradient, described in cat ICC, is a shallow continuum within the isofrequency sheets (Schreiner and Langner 1997). Low CFs are dorsomedial and higher CFs lateral and ventrolateral (Fig. 11.4A: arrows). The frequency range covered within an isofrequency sheet is about one critical band (Schreiner and Langner 1997; see below). Thus, the sheets of the classic dorsoventral tonotopic gradient constitute "frequency-band laminae" (Merzenich and Reid 1974; Schreiner and Langner 1997). They are larger than synaptic domains, the microarchitectonic compartments of ICC laminae (see Chapter 2).

3.2. The Dorsal Cortex and External Nucleus

The frequency representations in DC and EN have not been studied in the same detail as in the ICC. Historical differences in the definition of the DC have confounded a clear picture of its CF organization. Some studies show a frequency gradient from high (dorsal) to low (ventral at the border to the ICC) (Merzenich and Reid 1974; Servière et al. 1984), whereas others indicate that the ICC frequency-band laminae encroach dorsomedially into the DC, thus creating a continuous tonotopic organization for both subnuclei, at least in DC layers III and IV (Stiebler and Ehret 1985; Schreiner and Langner 1988; Romand and Ehret 1990). This physiologic ambiguity has a parallel anatomical component, with inputs from the lateral superior olive and other medullary structures (Oliver 1987) encroaching far beyond the architectonically recognized border of ICC (Morest and Oliver 1984; Oliver and Morest 1984) into layer IV of

Figure 11.4. **(A)** Three-dimensional plot of frequency-band laminae (10, 30, 50, 60 kHz) of the left-side ICC of the mouse. (Modified from Stiebler and Ehret 1985.) The *long thick lines* on the 10- and 30-kHz lamina indicate the direction of the shallow gradient of frequency increase (mainly from medial to lateral) within a lamina, as found in the cat (Schreiner and Langner 1997.) The concentric increase in the darkness of shading (10-kHz lamina) relates to the increase of the minimum threshold *(MT)* of neurons on a lamina (Stiebler 1986). **(B)** Electrode penetration from dorsal to ventral through the ICC of the cat showing a stepwise increase of the neuronal characteristic frequency *(CF)*. The CF plateaus comprise frequency-band laminae. (Modified from Schreiner and Langner 1997 and unpublished data.)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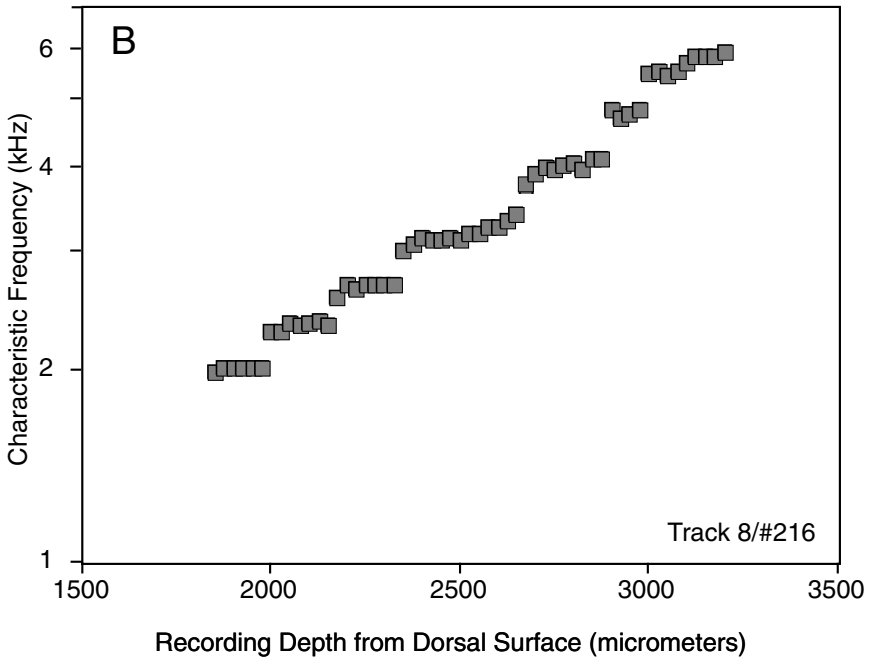
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the DC and perhaps beyond. In small mammals such as the mouse, a clear CF-based distinction between the DC and the ICC may not have been seen because of the thin DC (only layers I to III) (Meininger et al. 1986). Consequently, the ICC itself may not contain a representation of the lowest CF range because this area may be regarded as DC on the basis of anatomical criteria. Further study is necessary.

In the EN, a frequency gradient runs from high (lateral) to low (medial) in the cat (Rose et al. 1963; Roth et al. 1978) and in the mouse from low (lateral and dorsal) to high (medial and ventral) (Stiebler and Ehret 1985). Despite species differences there is agreement from studies in the possum (Aitkin et al. 1978), rat (Clopton and Winfield 1973), and gerbil (Kitzes 1984) that EN tonotopy is separate from that of ICC. Moreover, the CF ranges of DC and EN neurons are incomplete, with the high-frequency part absent or underrepresented. In the mouse EN, for example, CFs >35 kHz have not been found while in the ICC CFs extend to >60 kHz (Stiebler and Ehret 1985; Romand and Ehret 1990).

4. Spectral Resolution and Integration

A basic principle of auditory processing is the decomposition of complex sounds into perceptually distinct frequency components or narrow frequency bands such as formants (Fletcher 1940; Scharf 1970; Patterson 1974). Each cochlear hair cell and most central auditory neurons respond only to a limited part of the spectrum, the RF bandwidth, and can distinguish or "resolve" these frequencies from those outside its range. Frequency components within an RF cannot be distinguished, and their acoustic energy is summed for further processing, a process defined as spectral integration. Much of the ascending auditory pathway can thus be interpreted as a bank of band-pass filters. At any given CF, the bandwidths of auditory nerve fibers are uniform, although intensity dependent (Rhode and Smith 1985). In view of the various excitatory, facilitatory, and inhibitory shapes of IC receptive fields, the uniformity of the peripheral band-pass filters and thus a common mechanism of spectral resolution, is either lost in the IC or transformed. The choice of experimental stimuli and of analytic methods influences the picture of spectral integration. We discuss three approaches: responses to pure tones, to tones in noise, and to various spectral envelopes of broadband signals.

4.1. Sharpness of Pure-Tone Tuning Curves

A common metric of the neuronal frequency resolution is the quality factor Q. Small Q-values reflect broad tuning or low frequency resolution, and large values narrow tuning and high resolution. The range of Q_{10dB}-values in IC neurons is enormous, from <0.05 to >43 (cat: Aitkin et al. 1994; rat: Kelly et al. 1991; guinea pig: Syka et al. 2000; mouse: Egorova et al. 2001). A portion of the

large variability (Fig. 11.5A) stems from the frequency dependence of Q-values established in the cochlear filtering.

Frequency resolution differs between subdivisions. The median Q_{10dB} in the ICC for cat is 4 (Aitkin et al. 1994), for guinea pig 2.5 (Syka et al. 2000) and for the big brown bat 4.4 (Jen et al. 2002), which is higher than in the EN of these species (cat: 2; guinea pig: 1.1; big brown bat: 2.2).

The categories of ICC tuning curve shapes (see Section 2) also reflect differences in frequency resolution (Egorova et al. 2001). Class II neurons have high (5 to 10) Q-values that are largely intensity independent (Fig. 11.5A). Q-values of class I neurons resemble those of class II neurons at 10 dB above threshold, but decrease at 80 dB. Class III Q-values decrease from about 6.5 to 0.5 (Fig. 11.5A) with increasing sound intensity. Similarly, sharply tuned cat ICC type I neurons have Q_{10dB}-values from 2 to 8 and Q_{40dB}-values from 1 to 7 with little

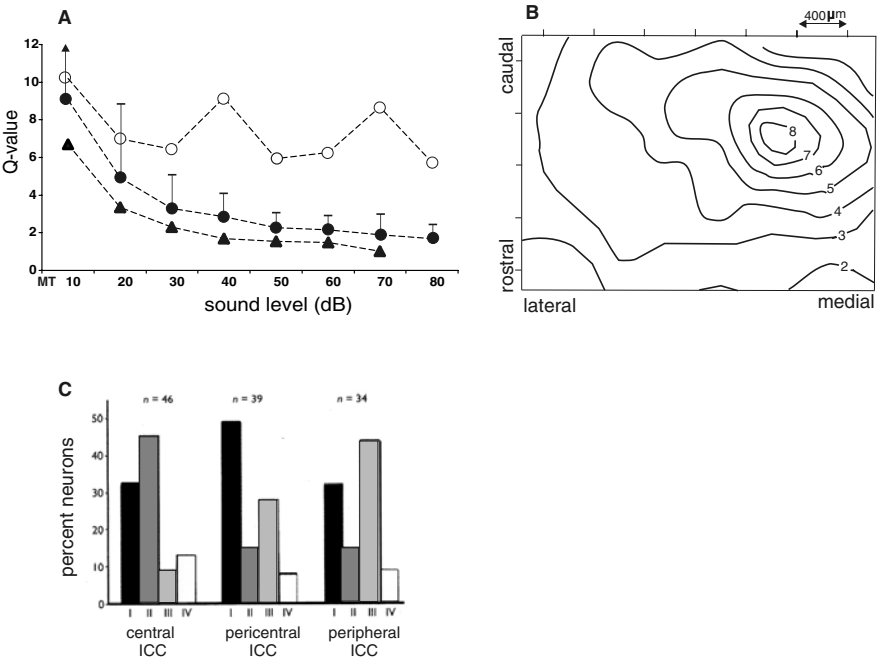


Figure 11.5. Sharpness of frequency tuning. **(A)** Average Q-values (see Section 2.1) as a function of the sound level for class I *(filled circles),* class II *(open circles),* and class III neurons *(triangles)* in the mouse ICC. (Modified from Egorova et al. 2001.) **(B)** View on the horizontal projection of a frequency-band lamina of the cat ICC. The lines are iso-Q_{10dB} contours. The average Q_{10dB} decreases from about 8 near the center to around 2 near the peripheral margin of the lamina. (Modified from Schreiner and Langner 1988.) **(C)** Distribution of neurons of the tuning-curve classes I to IV as a function of their location in the central, pericentral, or peripheral area of frequency-band laminae of the mouse ICC. (Modified from Ehret et al. 2003.)

intensity dependence, whereas type V neurons show much broader and intensity-dependent tuning ($Q_{10dB} < 3$; $Q_{40dB} < 1.5$; Ramachandran et al. 1999). This range in Q behavior suggests that frequency resolution may serve different roles in different functional tasks.

The processing of sensory information through filters of different widths, a multiresolution analysis, is a general concept in sensory processing (Graham 1989). Such a multitask filtering operation may be expressed in the spatial organization of tuning sharpness and eFTC shape in the ICC. Multiunit recordings show a continuous spatial eFTC bandwidth gradient across frequency-band laminae (Stiebler 1987; Schreiner and Langner 1988; Fig. 11.5B), with higher frequency resolution in the center and declining resolution toward the laminar periphery, suggesting processing subdomains within laminae. This bandwidth gradient likely embodies the distribution of the different eFTC classes (Ehret et al. 2003; Hage and Ehret 2003). An abundance of sharply tuned class II neurons in the laminar center decreases toward the laminar periphery, while the number of broadly tuned class III neurons increases from center to periphery (Fig. 11.5C). Frequency resolution gradients are also present in the thalamocortical system (Read et al. 2001), suggesting that they are a general feature in central auditory organization.

4.2. Critical Bands: Spectral Resolution

Psychophysical considerations have led to the concept of a bank of auditory filters or "critical bands" that subserve many perceptual aspects such as tone discrimination in noisy environments and the summation of loudness (Fletcher 1940; Zwicker et al. 1957; Scharf 1970; Moore 1997). Critical bands determined from narrow-band masking experiments cover equal distances of about 0.7 to 1 mm of the basilar membrane (BM) (Greenwood 1961, 1990; Ehret 1983, 1988). Thus, mice whose BM is short (about 7 mm; Ehret and Frankenreiter 1977) have fewer critical bands (<10; Ehret 1976) and poorer spectral resolution than cats (some 22 mm BM; Schuknecht 1960; some 24 critical bands; Pickles 1975, 1979; Nienhuys and Clark 1979), and humans (around 32 mm BM; von Békésy 1960; approximately 41 critical bands; Schafer et al. 1950; Margolis and Small 1975).

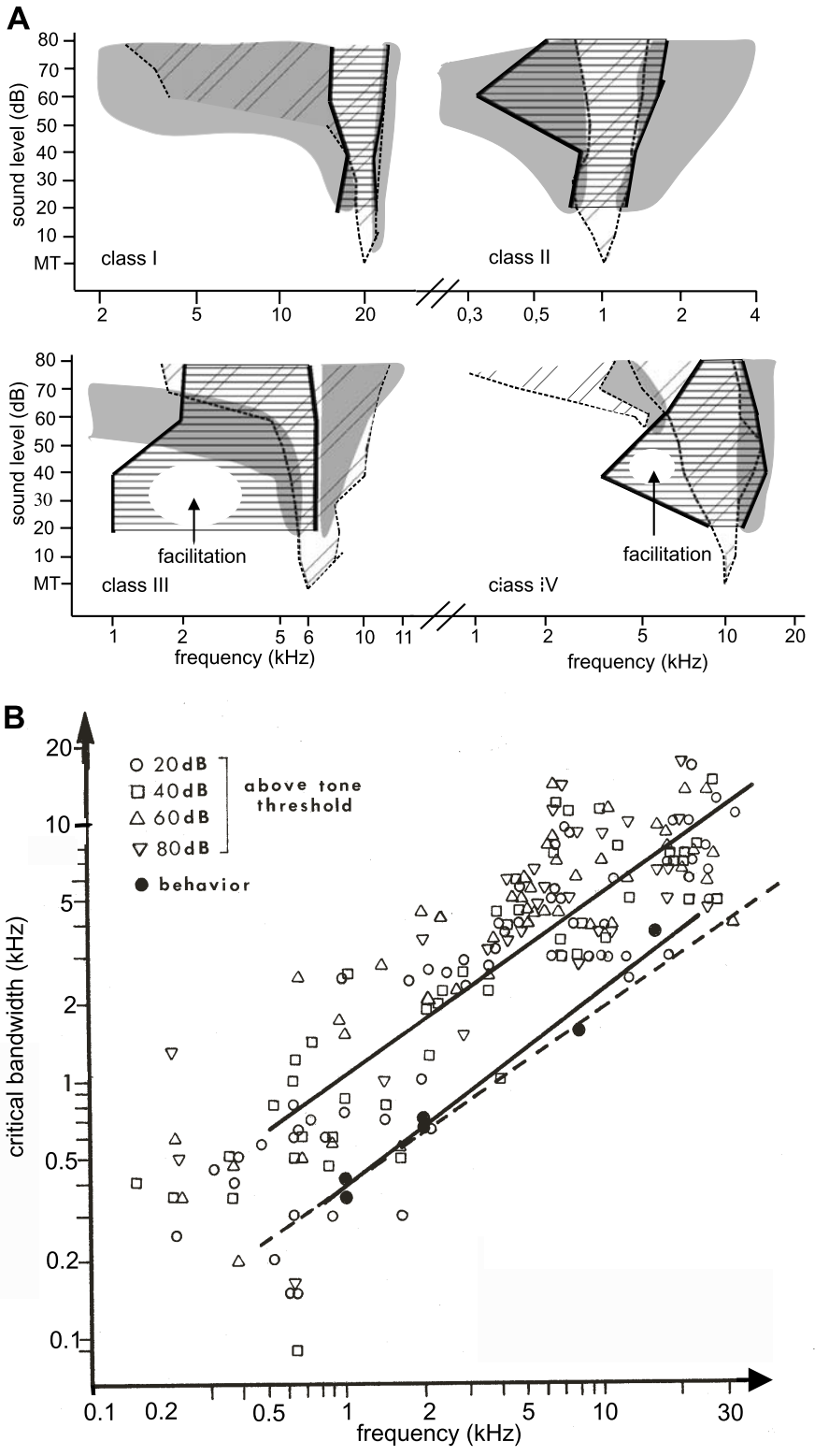
Auditory filter shape, bandwidth, and level dependence rests on the choice of test stimuli and psychophysical method. Accordingly, filter estimates in neurons must faithfully emulate psychophysical test conditions to be useful. For the ICC, two sets of data fulfill this condition (cats: Ehret and Merzenich 1985, 1988a; mice: Vartanian et al. 1999; Egorova et al. 2002). They show that ICC neural critical bandwidths follow the same rules as psychophysical critical bands (i.e., frequency dependence and level tolerance) when determined with a CF-centered tone and narrowband noise masker (Fig. 11.6A, B). Thus, critical-band related perceptual phenomena such as masking of tonal signals by noise (Fletcher 1940; Scharf 1970), the transition from consonance to dissonance evoked by shifting frequency components in a tone complex (Plomp and Levelt 1965), and changes

in the identification of vowels and animal vocalizations by shifts of frequency components (Flanagan 1972; Ehret and Haack 1982) are embedded in the spectral filter properties of ICC neurons. Perceptual critical-band properties are absent in auditory nerve fibers (Ehret 1995), and human auditory brain stem and middle-latency responses suggest that they first emerge in the IC (Zerlin 1986; Burrows and Barry 1990).

Several anatomical properties of the ICC are congruent with spectral integration within the frequency range of critical bands. For example, ICC frequency-band laminae cover a CF range similar to one critical bandwidth. Also, for any point within a frequency-band lamina, the CF distance to the neighboring laminae is about one critical bandwidth (Schreiner and Langner 1997; Fig. 11.4B). ICC neurons with disc-shaped or flat dendritic configurations constrain their integration to a limited part of the isofrequency domain (cf. Chapter 2) (Oliver and Morest 1984; Malmierca et al. 1993) and may process spectral components within a critical band. By contrast, multipolar or stellate cells with dendritic trees orthogonal to frequency-band laminae (Oliver and Morest 1984; Meininger et al. 1986; Wagner 1994; Reetz and Ehret 1999) may process information across frequency-band laminae (Oliver et al. 1991; Reetz and Ehret 1999), a feature perhaps essential for the analysis of spectral shape and other perceptual phenomena (Hall et al. 1984; Moore 1997; O'Connor et al. 1999). Critical band analyses of neurons in the DC and EN are not yet available.

4.3. Spectral Envelope Coding: Spectral Integration

The structural complexity of natural sounds and nonlinear mechanisms in auditory processing disbar simple stimuli alone, such as pure tones, from providing a complete characterization of spectral integration (Smolders et al. 1979; Nelken et al. 1999; Theunissen et al. 2000; Escabí and Schreiner 2002). Broadband stimuli derived from a few essential components in natural sounds can be effective for a more comprehensive characterization of spectral RF properties. Broadband sounds with sinusoidal spectral envelopes ("ripple spectra") represent a class of complex stimuli intermediate between narrow-band artificial sounds and broadband natural vocalizations (Schreiner and Calhoun 1994; Shamma et al. 1995; Kowalski et al. 1996; Escabí and Schreiner 2002). They retain white noise criteria necessary for measuring reverse correlations (Eggermont et al. 1983): these include a flat power spectrum and an impulsive autocorrelation function and can probe the responsiveness of neurons in an unbiased manner. The resulting spectrotemporal receptive field (STRF) is a profile of the spectral and temporal envelope features to which a neuron responds. The SRF or spectral component of the STRF profile can quantify neuronal responses to complex spectra (e.g., formants speech) and can reveal the RF arrangement of excitation and inhibition (Kowalski et al. 1996; Calhoun and Schreiner 1998; Versnel and Shamma 1998; Miller et al. 2002; Qiu et al. 2003). This approach allows the study of spectral integration properties to dynamic broadband sounds with a rich spectral structure and thus under more natural conditions. The ability of IC


A
sound level (dB)
80
70
60
50
40
30
20
10
MT
class I
class II
2
5
10
20
0,3
0,5
1
2
4
sound level (dB)
facilitation
class III
facilitation
class IV
1
2
5
6
10
11
frequency (kHz)
1
2
5
10
20
frequency (kHz)
B
critical bandwidth (kHz)
20
10
5
2
1
0.5
0.2
0.1
20 dB
40 dB
60 dB
80 dB
above tone threshold
behavior
0.1
0.2
0.5
1
2
5
10
30
frequency (kHz)

neurons to represent specific spectrotemporal feature combinations is a relatively common property in central auditory stations in species with specialized acoustic behavior (see Chapters 14, 16, and 17). With the STRF approach, stimulus feature selectivity can be generalized and applied to acoustically less specialized species.

The spectral integration properties found with ripple spectra parallel and expand those seen with tones. In cat ICC neurons tuned to 8 to 16 kHz, SRF bandwidths varied from 0.14 to 4.8 octaves with most (93%) bandwidths below about 2.0 octaves (Qui et al. 2003). Unlike pure-tone estimates, these bandwidth estimates were not strongly level dependent (Escabí et al. 2003), recalling critical-band measurements demonstrating spectral integration to be level independent (Ehret and Merzenich 1985, 1988a). SRF bandwidth distribution was unimodal (mean 1 octave). The best ripple density, the number of spectral envelope peaks/octave that produces a maximal neural response (Schreiner and Calhoun 1994; Klein et al. 2000; Escabí and Schreiner 2002) was low (mean = 0.61 cycles/octave) for most ICC neurons, indicating a preference for broadly spaced spectral features. The wide range of best ripple-density (0.02 to 2.11 cycles/octave), also reflects a wide range of spectral integration/selectivity. It is unclear how these measures relate to psychophysical or physiologic estimates of critical bands. Comparison of spectral envelope preferences in the ICC, the ventral division of the medial geniculate body, and primary auditory cortex reveals that general spectral integration properties seem well conserved in the lemniscal pathway between the IC and the auditory cortex (Miller et al. 2001, 2002; Qiu et al. 2003).

4.4. Origins of Spectral Tuning and Resolution

Cochlear filtering represented in the RFs of auditory nerve fibers is the basis for spectral tuning in higher centers of the auditory pathways. Careful removal of a narrow frequency channel at the level of the spiral ganglion can result in a narrow gap at corresponding frequencies in the eFTCs of ICC neurons (Snyder et al. 2000; Snyder and Sinex 2002). Auditory nerve fibers have relatively uniform eSRFs with areas of lateral suppression (Sachs and Kiang 1968; Schmiedt

Figure 11.6. **(A)** Excitatory spectral receptive fields *(eSRFs, cross-hatched areas)* bordered by the eFTC *(thin lines),* inhibitory SRFs *(iSRFs, shaded areas),* critical bandwidths (horizontal hatching bordered by thick lines), and facilitation areas *(arrows)* of class I to IV neurons of the cat ICC. The critical bandwidths are nearly independent of the FTC shapes. (Modified from Ehret and Merzenich 1988a and unpublished observations.) **(B)** Frequency dependence of critical bandwidth from cat ICC neurons (*open symbols,* measurements at various tone levels) and from behavioral measurements (*closed symbols;* Pickles 1975, 1979). Average behavioral and neural regression lines *(thick lines)* follow virtually the same functions if the neural data are adjusted to compensate for overmasking *(dashed line).* (Modified from Ehret and Merzenich 1985.)

1982; Delgutte 1990) but no facilitation areas (Fig. 11.3A). Brain stem neurons have far more diverse eSRF (eFTC) shapes, and reflect the presence of inhibition (Guinan et al. 1972; Young et al. 1988; Rhode 1991) and facilitation (Palmer et al. 1995; Winter and Palmer 1995). These diverse eSRF, iSRF, and fSRF shapes converge onto the IC and, in some cases, may be directly inherited by IC neurons (Ramachandran et al. 1999; Egorova et al. 2001).

The SRF of a given ICC neuron may be dominated by brain stem input as well as intrinsic biophysical properties (see Chapter 10). For example, many class I (I-type) ICC neurons (Ramachandran et al. 1999; Egorova et al. 2001) may inherit eSRF properties of type I cells in the ventral cochlear nucleus (Young et al. 1988) projecting to the ICC (Romand and Avan 1997). Similarly, many closed eSRFs of ICC neurons (type O; Ramachandran et al. 1999) are derived from O-shaped eSRFs of dorsal cochlear nucleus neurons, as blocking this projection reduces the incidence of O-neurons in the ICC by nearly 80% (Davis 2002). Further, medial superior olive neurons with broader tuning (Goldberg and Brown 1969; Guinan et al. 1972) project to the lateral ICC (Aitkin and Schuck 1985; Kudo and Nakamura 1988) and may engender the many broadly tuned class III neurons there. Pharmacologic blockade of GABAergic input to ICC neurons showed that inhibitory interactions can arise from subcollicular cells projecting to the ICC and from intrinsic ICC neurons. These inputs may affect SRFs in class I and II neurons (Yang et al. 1992; Pollak and Park 1993; Fuzessery and Hall 1996; Palombi and Caspary 1996; Lu and Jen 2001). Further, neurons with complex FTCs (class IV) likely arise from the convergence of neurons with class I and/or class II properties and somewhat different CFs (Egorova et al. 2001). Thus, SRFs of ICC neurons can be inherited from ascending projections and generated locally by excitatory–inhibitory interactions. The weight of both factors on a given neuron may depend on the location of the neuron in the three-dimensional fibrodendritic (see Chapter 2) and critical band (Schreiner and Langner 1997) space in the ICC. The origin of neural critical bandwidths with properties of psychophysical critical bands is associated with ICC neural filtering properties. Perhaps the genesis of critical-band properties reflects the shape of converging neuronal SRFs. This seems at first to be the case only for neurons with level-tolerant, sharp tuning (some class II or I-type neurons) because of the differences in shapes of FTCs and critical-band filters in class I, III, IV (and some class II) neurons (Fig. 11.6A). The steep slopes of the critical-band borders may derive from class I and class III eSRFs; however, they are shaped by inhibitory and facilitatory iSRF and fSRF influences (Ehret 1995). The suggestion that neural critical bands are sculpted from eSRFs mainly by inhibition (Ehret and Merzenich 1988a) has been supported in the mouse ICC (Egorova et al. 2002, 2003), where a strong correlation between critical-band cutoff frequencies and the CFs of inhibition (Figs. 11.1C and 11.6A, class I and II) occurs. In class II neurons, the border frequencies of the critical bands align almost perfectly with the peak frequencies of the iFTCs below and above the CF.

In summary, both spectral filtering (FTCs) and spectral resolution/integration are based on the same kind of processing in the ICC. The shapes of eFTCs can be considered a special case of "critical–band" filters for a one-tone stimulus. Whenever a multitone or complex spectrum is processed, inhibitory and facilitatory influences are activated from off-CF components that refine the neural response into a critical band. Accordingly, the properties of the composite SRF of a neuron (eSRF + iSRF + fSRF) determine its functional capabilities as spectral integrator.

5. Intensity Coding

The total dynamic range of the human ear comprises about 130 dB SPL in the frequency range of best hearing. Within this range, loudness can be matched across frequencies, and small intensity steps can be discriminated. Because loudness estimates are rather independent of the sound's spectral composition (Zwicker and Feldtkeller 1967; Scharf 1978; Moore 1997), the neural coding of sound level and level differences seems to be largely independent of the type of sound.

The coding of sound level in the auditory nerve rests on three mechanisms: (1) there is an approximately 60-dB range of response threshold across AN fibers with similar CFs (Liberman 1978); increasing sound level recruits more auditory nerve fibers with similar CFs. (2) AN fiber RLs vary in shape and dynamic range between 20 and 70 dB for CF tones (Sachs and Abbas 1974; Jackson and Relkin 1998). Dynamic ranges for tones above CF can exceed 70 dB. Thus, some AN fibers vary their response rate to tones over many levels. (3) With increasing amplitude, excitation spreads along the basilar membrane, especially toward the high-frequency end so that louder sounds recruit more AN fibers of increasing CFs (Zwicker and Feldtkeller 1967).

For the first two mechanisms, sound level at a given cochlear position (or CF) is coded over the 130-dB dynamic range by jointly considering the number of activated fibers and their activity levels. The code for AN sound intensity could equal the integrated activity of a small neural ensemble of similar CF. The third mechanism may enhance this population code at higher levels (Chatterjee and Zwislocki 1998) and may underlie the just-noticeable-intensity differences in psychoacoustical tests, which decrease with growing sound level (Maiwald 1967; Ehret 1989). Can the distribution of response thresholds and shapes of RLs illuminate how sound intensity is coded in the IC?

5.1. *Response Sensitivity (Thresholds)*

The stimulus with the lowest SPL to evoke a neural response characterizes neural sensitivity (minimum threshold, MT) to sound pressure level. The behavior of response thresholds in psychophysics and for onset-responses, from auditory

nerve fibers to cortical neurons, is well described by the temporally integrated pressure envelope of a stimulus, in particular its onset envelope (Heil and Neubauer 2001, 2003). The site of this integration process is postulated to be at the inner hair cells and auditory nerve fiber's synapse (Heil and Neubauer 2003). Usually, neuronal responses are expressed as a function of the steady-state SPL although a metric that emphasizes dynamic stimulus aspects may be more appropriate (Heil 1997).

IC minimum thresholds for CF tones range over 60 to 80 dB in the cat (Aitkin 1991) and 35 to 45 dB in mice (Ehret and Moffat 1985a; Stiebler 1986). Because MTs may vary with the physiological state and anesthesia (Ehret and Moffat 1985b; Zurita et al. 1994), a large threshold range at a given CF may embody the animal's status rather than the actual MT range in a behaving animal. MTs are frequency dependent and typically follow the behavioral detection thresholds (Ehret and Moffat 1985a; Kelly et al. 1991; Egorova et al. 2001). The lowest contralateral values are –10 and +10 dB SPL for most species, and ipsilateral thresholds are about 10 to 20 dB higher (Aitkin 1991). Neurons of different spectral response types can also be characterized by MT differences: cat type V neurons have MTs 8 to 10 dB above that of type I and type O cells (Ramachandran et al. 1999). Mouse class III neurons have MTs 10 to 15 dB higher than cells of other classes (Egorova et al. 2001). The median MTs in the DC and the EN are 4 to 7 dB above ICC values (Palombi and Caspary 1996; Syka et al. 2000). Considering the spectral integration within critical bands, MTs for complex sounds such as noises are much lower than pure-tone MTs, if expressed as spectrum level (level/Hz) (Ehret and Moffat 1985a).

Tone MTs of cells in a frequency-band lamina vary systematically in mouse ICC, with lowest MTs in the center and progressively higher values peripherally (Stiebler and Ehret 1985; Stiebler 1986; Fig. 11.4A). Analogous topographic variations occur in the auditory cortex (Sutter and Schreiner 1995). Systematic spatial variations of intensity parameters may contribute a central (cortical) place-code component for loudness representation (Heil et al. 1994).

5.2. *Intensity Selectivity*

The shape of RLs for superthreshold tones reveals several characteristics to increasing stimulus amplitude (Fig. 11.7). A segment of monotonic increase of firing rate with intensity shows a near-linear relationship between rate and SPL in all ICC neurons. However, few neurons maintain such growth at higher stimulus levels (Fig. 11.7A; Table 11.1). Most saturate at a certain intensity (plateau RLs, Fig. 11.7B), decline in rate (nonmonotonic RLs, Fig. 11.7C), or show variable behavior (complex RLs, Fig. 11.7D). Nonmonotonic RLs are intensity tuned, as the maximum rates are limited to a narrow range of stimulus levels. In most studies, these represent the preponderant tonal RL type in ICC (Table 11.1). Each type of RL to tones (Fig. 11.7) is found in varying proportions in the DC and EN (Table 11.1).

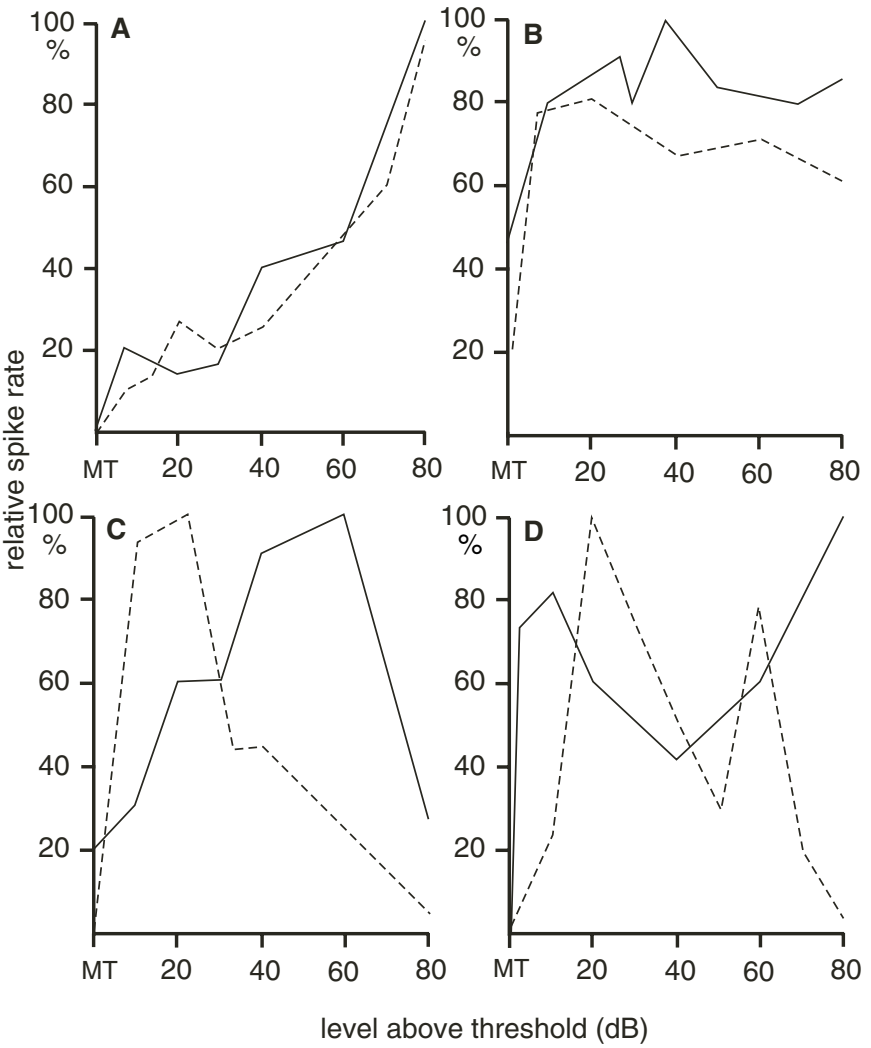


Figure 11.7. Examples of rate-level functions (RLs) in response to tone bursts from the cat ICC showing monotonic **(A)**, plateau **(B)**, nonmonotonic **(C)**, and complex **(D)** shapes. *MT,* Minimum threshold. (Modified from Ehret and Merzenich 1988b and unpublished data.)

Table 11.1. Ranges of percentages for pure-tone rate-level functions of four basic types in IC subdivisions in cats (Ehret and Merzenich 1988b; Aitkin 1991; Aitkin et al. 1994), mice (Ehret and Moffat 1985a), rats (Palombi and Caspary 1996), and guinea pigs (Rees and Palmer 1988; Syka et al. 2000).

	Monotonic	Nonmonotonic	Plateau	Complex
ICC	6–28	15–66	5–35	7–26
EN	32–43	24–32	24–30	11–16
DC	6–39	21–59	4–58	0–31

The level eliciting maximal discharge is the "best" level. Best levels of nonmonotonic neurons occur at any superthreshold level in the cat (Ehret and Merzenich 1988b; Irvine and Gago 1990; Aitkin 1991) and have a range 10 to 40 dB above MT in rat and guinea pig (Rees and Palmer 1988; Palombi and Caspary 1996). Dynamic range is the extent of superthreshold sound levels over which an increased response rate occurs (Fig. 11.7). Dynamic ranges of monotonic neurons can exceed 80 dB (Ehret and Merzenich 1988b; Irvine and Gago 1990), while those of other RL types fall within about 50 dB (Aitkin 1991).

The large variability of the RL type percentages (Table 11.1) has several causes, including methodologic differences between studies and possible species differences. Studies available are constrained by a limited range of sound levels ($<$85 dB) tested; failure to consider the tone burst repetition rate (Galazyuk et al. 2000); or the fact that RLs were not calculated separately from the onset and the sustained response of neurons, which results in different RL shapes (Rees 1992). Moreover, differential criteria for assigning neurons to different RL types have been used. RL shapes often depend on stimulus type (Ehret and Merzenich 1988b; Aitkin 1991; Syka et al. 2000; Palombi and Caspary 1996), on the sound angle incidence (Semple and Kitzes 1985; Irvine and Gago 1990), on behavioral state (Ryan and Miller 1977), and on corticofugal influences (Syka et al. 1988; Zhang and Suga 1997; Jen et al. 1998; Suga et al. 2000; Zhou and Jen 2000; Yan and Ehret 2001, 2002; see Chapter 8). Hence, the shapes of RLs in response to tones and other stimuli are diverse and reflect many variables.

RL shape may be predicted in part from the SRF shape. Class II or type O neurons with a closed eSRF or class II neurons with an eSRF skewed toward higher or lower frequencies at high sound levels (Fig. 11.3) must have nonmonotonic (or complex) RLs to CF-tone bursts because, at higher SPLs, the CF may be outside the eSRF border. Thus, the RL shape embodies the same factors molding RFs (convergence of excitatory, inhibitory, and facilitatory input). Intracellular recordings and current injection of IC cells showed that monotonic, nonmonotonic, and plateau RLs may be locally produced by different ionic regimens interacting with membrane properties (Smith 1992; Wagner 1994; Reetz and Ehret 1999; Peruzzi et al. 2000; Sivaramakrishnan and Oliver 2001; Bal et al. 2002).

5.3. *Contrast Sensitivity*

The ability of the auditory system to encode amplitude differences has been studied almost exclusively in the context of intensity discrimination and loudness coding (Evans and Palmer 1980; Ehret and Merzenich 1988b; Viemeister 1988). The range of amplitude values present during a short segment of natural sounds, its contrast, can be substantial (Attias and Schreiner 1998), and varies considerably over time (e.g., during speech) and between sound environments (Escabí et al. 2003). The decibel amplitude distribution of spectrotemporal contrast in natural sounds is approximately normal (Fig. 11.8A). Perhaps the operating range of IC neurons, reflected in the RLs, is matched to the natural amplitude statistics, and thus can efficiently process sounds and thereby detect and segregate signals. ICC neurons are tuned to naturally occurring contrast distributions (Escabí et al. 2003). Moreover, mean intensity and contrast coding appear to be independent. Like RLs for stimulus level, rate-contrast functions are monotonic or nonmonotonic but are independent of the type of RL function in the cell (Fig. 11.8B). This independent response behavior for two stimulus amplitude measures (mean and variance) suggests that both are relevant features of the acoustic landscape and its neural representation. Understanding the role of contrast in

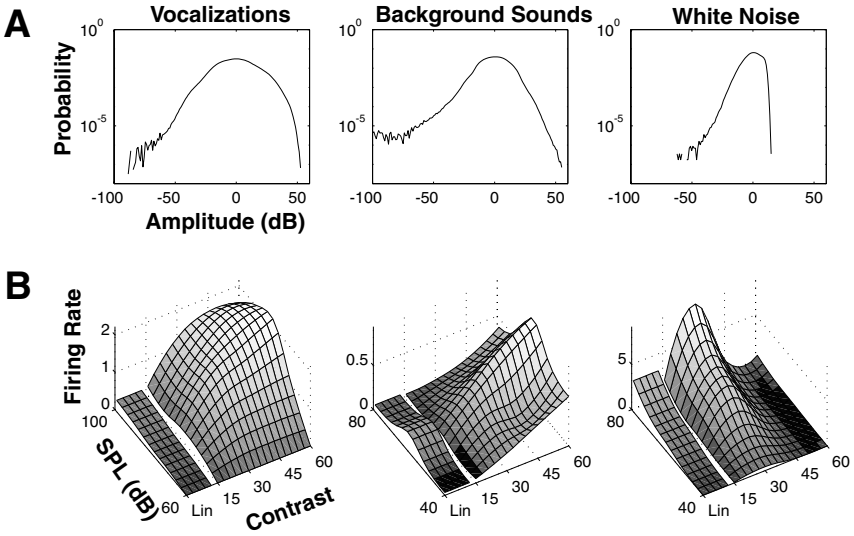


Figure 11.8. **(A)** Probability distributions of amplitude values in three different sound classes. The width of the distributions corresponds to the contrast of the sounds. Note the differences in width between white noise and natural signals. **(B)** Firing rate profiles for three different neurons in the ICC for "ripple-spectra" (broadband stimuli with noise-like spectral envelopes) that were systematically and independently varied in mean intensity and contrast. (Adapted from Escabí et al. 2003.)

auditory processing from the perspective of natural contrast distributions must receive further attention.

5.4. Models of Sound Intensity Coding

The available evidence for sound intensity coding at the IC does not allow conclusive statements about how sound intensity, level or loudness, and intensity differences or contrasts are coded. At present, three fundamental ideas about intensity coding are plausible (Irvine 1992; Ehret 1997): (1) Small groups of neurons with monotonic, sound-type independent RLs over 80 dB or more code sound intensity and level variation by their integrated spike response. (2) Neurons with nonmonotonic RLs aggregate by their best levels at ICC loci in frequency-band laminae and map sound intensity by their location. A similar spatial code for sound level occurs in a specialized field of the mustached bat's auditory cortex (Suga 1977; Suga and Manabe 1982). (3) From maps of absolute response thresholds in frequency-band laminae (Stiebler 1986), a model of the transfer of cochlear sound parameters to the three-dimensional ICC space predicts a spatial code for sound intensity, that is, a shift of the maximum of the neural response from the center of a frequency-band lamina to its periphery with increasing amplitude (Herrnberger et al. 2002). Implications of this model include systematic neural arrangements with monotonic and nonmonotonic RLs in frequency-band laminae. These three propositions about midbrain intensity coding incorporate RL variability and predict that an average-rate code for sound intensity derived from a large proportion of ICC neurons is unlikely (Ehret and Merzenich 1988b). Onset and sustained responses could have unique contributions to intensity and contrast coding. The biological significance or semantic content of environmental and communication sound is often coded independently of intensity. This suggests as yet unidentified mechanisms in the auditory pathways that separate the influence of the total sound level from that of biologically significant level differences or contrasts. However, as total level can mediate arousal, emotions, and motivations, information about it must be coded, and may be transmitted, independently of semantic information, to higher brain centers.

6. Conclusions and Questions for Future Research

The coding of sound frequency and intensity are fundamental tasks of auditory processing and have been extensively studied in the IC. Despite the impressive body of studies available for RF properties, many aspects of the midbrain contribution to various sound processing tasks are unknown. The convergence of input from many sources and the several types of spectral/intensity RFs creates an interpretational dilemma. The segregation of subcollicular pathways in the

cochlear nucleus complex, superior olivary complex, and nuclei of the lateral lemniscus can be construed in terms of specialized tasks that require certain dedicated structural and functional substrates of neural organization. After the massive convergence at the midbrain level, this paradigm is simply no longer appropriate without a deeper grasp of the nature, purpose, or task-specificity of the convergence. Parallel output from an abundance of subcollicular nuclei appears compressed in the ICC onto a single tonotopic substrate, giving a new meaning to the term convergence, with no counterpart in either the visual or somatosensory systems (Ehret 1997). The challenge still is to decipher how the neurons of this substrate are specialized in their structure, physiology, and network properties to serve the many functional demands of sound processing.

We note here just a few immediate tasks directly related to matters of spectral and intensity processing:

1. What are the relationships between the morphologic and physiologic types of neurons and functional maps within ICC frequency-band laminae and those in the DC and the EN?
2. How are the composition and pattern of input projections from lower auditory centers related to the type of IC neuron (morphologic, physiologic, biophysical, functional)? Are there unique circuitries between neighboring neurons and potential laminar and subnuclear synaptic domains?
3. IC neurons are modulated by neurotransmitter-specific inputs such as the cholinergic and noradrenergic systems (Faingold et al. 1991; see Chapter 9) and by descending projections from the auditory cortex and thalamus (see Chapter 8). How do these influence sound processing under natural conditions in awake and behaving animals, and what role do they play in auditory scene analysis, hearing impairment, and neural plasticity?

Abbreviations

BF	best frequency
CF	characteristic frequency
DC	dorsal cortex of the inferior colliculus
eFTC	excitatory frequency tuning curve
EN	external nucleus of the inferior colliculus
eSRF	excitatory spectral receptive field
fSRF	facilitatory spectral receptive field
FTC	frequency tuning curve
GABA	γ-aminobutyric acid
IC	inferior colliculus
ICC	central nucleus of the inferior colliculus
iFTC	inhibitory frequency tuning curve
iSRF	inhibitory spectral receptive field
MT	minimum threshold
RF	receptive field

RL	rate-level function
SPL	sound pressure level
SRF	spectral receptive field
STRF	spectrotemporal receptive field

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Chapter 12
Temporal Coding in the Auditory Midbrain

Adrian Rees and Gerald Langner

1. Introduction

1.1. The Biological Significance of Temporal Coding

The cochlear frequency analyzer is a remarkable biological machine, and within the approximately 30,000 parallel spectral channels of its output in the cochlear nerve temporal stimulus components are highly conserved. In many communication sounds such as speech, it is often the changes in amplitude and frequency that carry information rather than their absolute values (Fig. 12.1; Rosen 1992; Shannon et al. 1995; Smith et al. 2002). Here, we consider the temporal modulations essential for auditory perception and show that the inferior colliculus (IC) is critical in the representation and transformation of temporal information from peripheral levels.

1.2. Temporal Information Content of Natural Sounds

Temporal information in sound stimuli occurs over a wide time scale from a few Hertz up to about 1000 Hz (Joris et al. 2004). Temporal information is important in auditory perception in two ways. Dynamic changes bear information and denote differences between sounds, as in speech consonants in which the direction of a frequency change distinguishes consonants while changes in voice fundamental frequency, or prosody, denote interrogatives or indicate mood. Temporal information may also help to separate sound sources by stream segregation.

1.3. Temporal Coding for Stimulus Segregation and Grouping

The auditory system can separate and identify concurrent sound sources that contain many, overlapping frequency components. Frequency decomposition in the auditory periphery operates on the sum of all the sound waves reaching the ear. The recovery of a sound source requires a grouping or streaming of its frequency components, allowing them to be perceived as a whole (Bregman

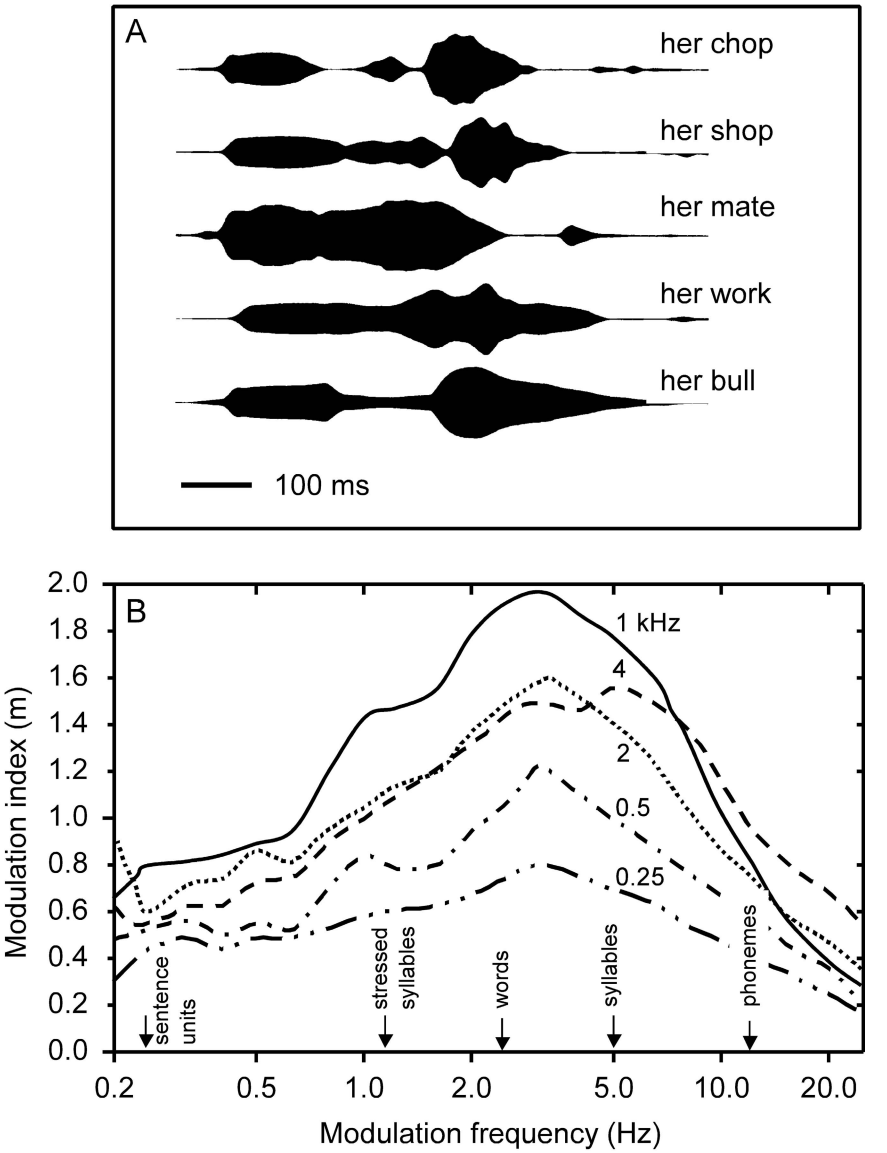


Figure 12.1. Amplitude modulation in human speech. **(A)** Waveforms of utterances from adult male speaker low-pass filtered to show their amplitude envelopes. (Adapted from Rosen 1992.) **(B)** Average modulation envelope spectra extracted from 1 minute of connected speech from 10 male speakers. Modulation index for one-third octave bands centered on the carrier frequency shown adjacent to each curve. *Arrows* indicate the dominant modulation frequency associated with different speech components. (Replotted from Plomp 1983.)

1990). Cues contributing to this identification process include onset and offset times and ongoing temporal envelopes (Darwin and Carlyon 1995). Frequency glides may fuse components into a stream, and tracking the fundamental frequencies of harmonic complexes is important in stream segregation (Moore 2003).

Other psychophysical phenomena suggest interactions between the envelopes of components widely separated in carrier frequency, including comodulation masking release (Hall et al. 1984) and modulation detection interference (Yost and Sheft 1989, 1993). Both phenomena imply that interactions must occur between different frequency channels to extract common envelope patterns. The IC may play a crucial role in this process.

1.4. Temporal Coding of Pitch

When the frequency range of harmonic sounds is sufficiently broad to activate different frequency channels, the neural responses in many channels will be elicited by a waveform that is a superposition of the several frequency components within the channel. Because all harmonic sound components are integer multiples of its fundamental frequency, their superposition periodicity on the basilar membrane will correspond to that of the fundamental frequency or a multiple of it. Analyzing this periodicity and comparing temporal information over different frequency channels enhances the auditory system's capacity to detect communication signals in a noisy environment (Cherry and Sayers 1956).

A by-product of this temporal analysis is periodicity pitch. The timbre of a periodically modulated sound depends on its spectral envelope while the sound's perceived pitch may be identical to a pure tone whose frequency equals that of the sound's temporal envelope. Pitch depends also on the periodic sound's spectral content, as in the first and second effect of pitch shift with inharmonic amplitude modulation (AM) signals (Schouten 1940, 1970; Schouten et al. 1962). Periodicity pitch may be perceived similarly by humans and animals (cats: Chung and Colavita 1976; Heffner and Whitfield 1976; birds: Cynx and Shapiro 1986; monkeys: Tomlinson and Schwarz 1988; Wright et al. 2000; chinchilla: Shofner and Yost 1997; Shofner 2000). Neuronal mechanisms for periodicity pitch likely rely on the temporal encoding up to 5 kHz in the auditory nerve (Greenberg 1988), which is the upper limit of musical pitch (Semal and Demany 1990).

2. Aspects of Temporal Information Coding

2.1. Temporal Responses of Inferior Colliculus Neurons to Tones and Noise

Before considering IC neural responses to temporally varying stimuli, we note their temporal firing patterns to constant pure tones or noise bursts, which have

been studied in many species (Rose et al. 1963; Ryan and Miller 1978; Syka et al. 2000).

The most obvious distinction is between cells that fire only to the stimulus onset and those with sustained firing patterns. The proportions of units in these classes vary between studies, perhaps because of species variations, anesthesia, stimulus duration, repetition rate, or the cell's locus in the IC. Onset units comprise about 50% of the cells in anesthetized cats (Rose et al. 1963) and tranquillized mice (Walton et al. 1998) and 27% in the guinea pig central nucleus of the IC (CNIC) (Syka et al. 2000).

Pauser, on-sustained, chopper, and sustained/buildup response subgroups exist within the broader classes (Willott and Urban 1978; Ehret and Moffat 1985; Le Beau et al. 1996; Rees et al. 1997; Syka et al. 2000). However, response patterns are not fixed for a neuron under all stimulus conditions and response patterns may differ for frequencies remote from the characteristic frequency (CF) or for other stimulus levels (Ehret and Moffat 1985).

IC response patterns are strongly influenced by both γ-aminobutyric acid (GABA) and glycinergic inhibition (Faingold et al. 1989; Vater et al. 1992; Le Beau et al. 1996). Blockade of inhibition by bicuculline or strychnine elevates firing rate and may change its response pattern. Half of the cells changed their firing pattern with bicuculline, of which 70% of these became choppers (Le Beau et al. 1996). Intracellular recordings in vitro (see Chapters 2, 9, and 10) or in vivo (Nelson and Erulkar 1963; Covey et al. 1996; Kuwada et al. 1997) are revealing the underlying mechanisms for these changes. The inhibitory currents driving the response patterns frequently precede the excitatory input to the cell (Nelson and Erulkar 1963; Covey et al. 1996; Pedemonte et al. 1997) and specific ion channels influence the intrinsic neural membrane properties and their response patterns.

2.2. *Synchronization Code*

Temporal stimulus waveform information can be represented by the temporal synchronization of neuronal responses to the stimulus envelope. Period histograms reveal the spike-timing relative to the stimulus modulation period. A quantitative measure derived by circular statistics represents the period of a signal as a circle, a spike by a vector $\vec{a}_i$ with unit length, and the phase angle by vector orientation (Goldberg and Brown 1969). The sum $\vec{R} = \sum_{i=1}^{N} \vec{a}_i$ over all N spike vectors of a response to a periodic signal is the mean synchronization, and the mean phase angle. Normalization gives the so-called vector strength $r = \left| \sum_{i=1}^{N} \vec{a}_i \right| / N$, a measure of average synchronization, which equals 1 for maximal and 0 for no synchronization.

If the IC participates in temporal processing, its input should be synchronized to stimulus envelope fluctuations. Synchronized responses are not "reproductions

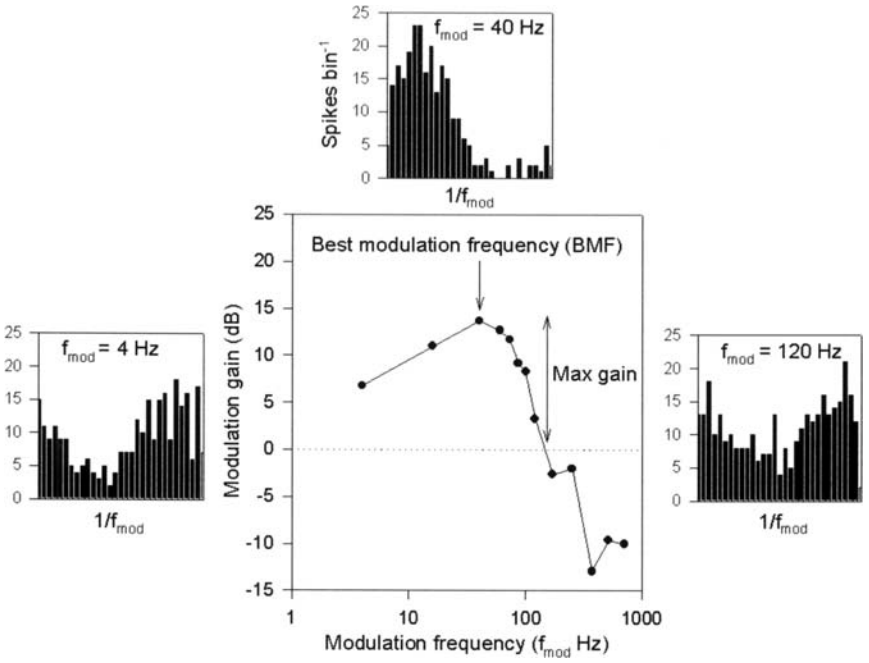


Figure 12.2. Synchronized response to amplitude modulation for a single neuron in IC of guinea pig. Period histograms show distribution of spike firing over one cycle of modulation for three modulation frequencies (f_{mod}). *Center:* Modulation transfer function for synchronized response. (Adapted from Rees and Sarbaz 1997.)

of the waveform" (Møller 1974), because they are restricted to a small portion of the modulation cycle. Envelope fluctuations of acoustic signals are amplified in neuronal response fluctuations in the rat IC, with a gain up to 20 dB (Rees and Møller 1983; Rees and Palmer 1989; Fig. 12.2). Similarly, potentials evoked by modulation frequencies <100 Hz in the frog midbrain show enhanced AM coding relative to auditory nerve evoked potentials (Hillery 1984). Synchronization deteriorates at higher levels in the auditory system, significantly reducing temporal resolution. However, some midbrain neurons can synchronize to modulation frequencies up to 800 or 1000 Hz (Schuller 1979, 1984; Rose and Capranica 1985; Epping and Eggermont 1986; Lesser et al. 1986, 1990; Langner and Schreiner 1988) or even up to 1200 Hz (Langner 1983).

2.3. *Rate Code*

A second feature for neuronal periodicity coding is average response rate. Many IC neurons fire maximally for a particular modulation frequency (Langner 1983; Müller-Preuss et al. 1994). In cat most IC units were rate-tuned, some up to 1000 Hz, while tuning in synchronization above 300 Hz was rare (Langner and Schreiner 1988; Fig. 12.3), suggesting a midbrain synchronization-to-rate trans-

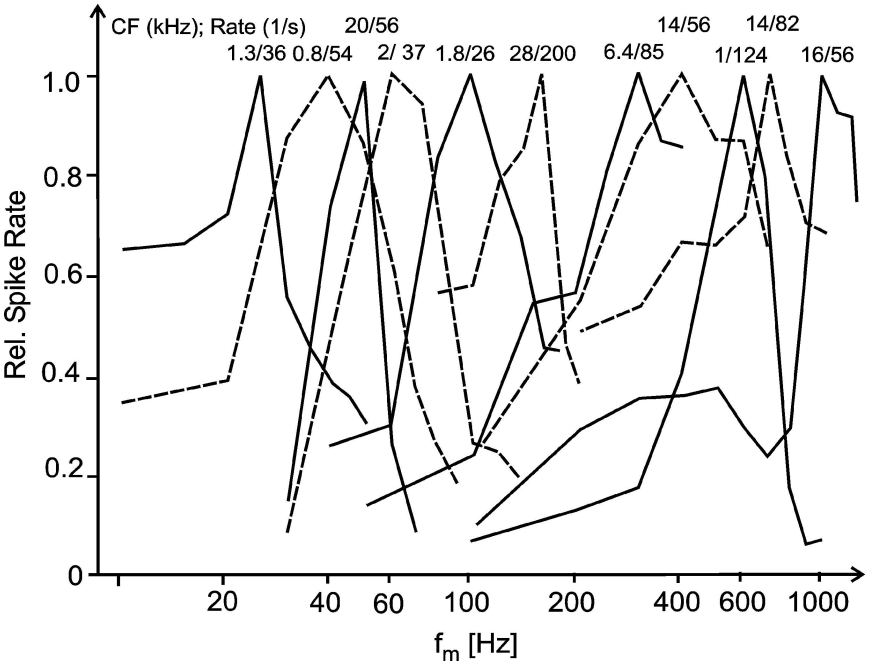


Figure 12.3. Normalized band-pass modulation transfer functions of neurons in cat CNIC. In contrast to more peripheral auditory nuclei, many units in the CNIC are tuned in terms of average firing rate. Numbers above the curves indicate the CF of the unit that also served as carrier frequency of the AM stimuli and the maximal firing rate corresponding to the tip of the MTF. (Adapted from Langner and Schreiner 1988.)

formation for higher modulation frequencies. In guinea pig and gerbil, fewer units show rate tuning and modulation cutoff frequencies match those for synchronization measures (Rees and Palmer 1989; Krishna and Semple 2000).

Neurons in the dorsal and posteroventral cochlear nucleus show near-constant average rates across modulation frequency (Kim et al. 1990). The auditory midbrain might transform synchronized envelope information into a rate/space representation (Langner 1981; Epping and Eggermont 1986; Pinheiro et al. 1991; Langner 1992) as seen when guinea pig IC mean rates were largest at modulation frequencies that elicited maximal synchronization (Rees and Palmer 1989). Additional representation of temporal information in the timing of neural activity or the transmission of low (< 200 Hz) modulation frequencies to higher centers may also be present.

2.4. *Across-Frequency Analysis*

Psychoacoustic experiments show that across-frequency-channel processes occur (see Section 1.3) with a particular role for harmonicity (Treurniet and Boucher 2001). Bat IC (and higher level) neurons may respond to frequencies outside

their pure tone response area when presented in conjunction with other components of their sonar or social calls (Wenstrup and Grose 1995; Mittmann and Wenstrup 1995; Misawa and Suga 2001). This combination sensitivity can be generated within the IC (Wenstrup and Leroy 2001). Guinea pig IC neurons receive input from a wide frequency range that may sum nonlinearly for two-tone stimuli (Thornton and Rees 2001). In chinchilla IC, integration related to harmonically structured social calls is common (Biebel and Langner 2002).

3. Amplitude Modulation Coding

Sinusoidal amplitude modulations (SAMs) are useful test stimuli for investigating periodicity coding. A signal's AM spectrum contains the carrier frequency (f_c) and two side-bands, $f_c + f_m$ and $f_c - f_m$ which cochlear frequency analysis cannot resolve at low modulation frequencies (f_m). The SAM envelope frequency corresponds naturally to f_m and, when the carrier is an integer multiple of the modulation frequency, it may be "harmonic." Therefore, SAM stimuli contain critical features of temporally varying sounds.

3.1. Modulation Transfer Functions

For linear systems the average response to an AM is independent of the modulation frequency as seen in the auditory nerve (Rose and Capranica 1985) and for many dorsal cochlear nucleus (DCN) neurons and posteroventral cochlear nucleus (PVCN) neurons (Schreiner and Snyder 1987; Kim et al. 1990), but not for IC neurons (Langner 1983; Langner and Schreiner 1988; Krishna and Semple 2000).

For nonlinear systems such as the auditory system, the best way to measure the modulation transfer function (MTF) is with AM, presenting one modulation frequency at a time (Schroeder 1981). Synchronization MTFs are derived by calculating vector strength, whereas rate MTFs are measured from the average discharge rate. Responses to AM show changes in synchronization and average discharge rate as a function of modulation frequency described as band-pass or low-pass MTFs (Rees and Møller 1983; Reimer 1987; Langner and Schreiner 1988; Rees and Palmer 1989). The maximum of a band-pass MTF or the cutoff frequency of a low-pass MTF is the "best modulation frequency" (BMF). In cat IC, 33% of the cells had band-pass synchronization MTFs and 48% had low-pass characteristics (Langner and Schreiner 1988). Seventy percent of cat IC single units had rate MTFs with a band-pass characteristics, 7% low-pass characteristics (Langner and Schreiner 1988). Other MTF-types distinguished are high-pass, band-reject, or nonselective/complex (Bibikov and Gorodetskaya 1980; Walkowiak 1984; Rose and Capranica 1985; Langner and Schreiner 1988).

If the temporal code representation of periodicity is partly transformed into a rate code in the midbrain, then activation strength signals stimulus periodicity, just as pure tone frequency is signalled by the response at a particular place in the tonotopic map (Langner et al. 2002). Because the CNIC is tonotopically and

periodotopically organized, neural activation signals simultaneously a certain carrier frequency and a certain envelope periodicity.

3.2. Factors Affecting Amplitude Modulation Coding

Many aspects of midbrain AM responses are insensitive to signal intensity variations and modulation depth. Kitten CNIC cells synchronize to AM waveforms across stimulus levels and modulation depths, and mean firing phase during the modulation cycle is nearly independent of level and modulation depth (Brugge et al. 1993). Other cells show changes in MTF shape and BMF with mean intensity as MTFs shift from band-pass to low-pass at low sound intensities (Rees and Møller 1987; Krishna and Semple 2000). Modulation depth changes do not affect MTF shape and peak value although IC cells in many species are sensitive to AM and may synchronize to modulation depths of only 2% (Schuller 1979; Bibikov and Nizamov 1996; Biebel et al. 1998).

To encode AM information temporally, a frequency filter needs a bandwidth exceeding twice the modulation frequency to avoid sideband attenuation. Because peripheral tuning curve width increases with CF, an increased upper frequency limit of encoded modulations is expected and has been found (Langner and Schreiner 1988). At CFs$<$4 kHz, virtually all units have BMF values below CF/4, which corresponds to the upper boundary of the psychophysical existence region of periodicity pitch (Terhardt 1970). In conclusion, spectral tuning width of auditory nerve fibers may restrict the upper frequency limit of modulation and periodicity pitch coding. It is difficult to see the relationship between CF and BMF in a sample of neurons with only few BMFs $>$100 Hz (Rees and Møller 1987; Krishna and Semple 2000).

AM signal carrier frequency may also influence MTFs. Small changes of the carrier frequency around a neuron's BF not only affect slopes of MTF shapes but also may alter BMFs systematically (Langner 1983; Langner and Schreiner 1988).

3.3. Influence of Background Noise on Amplitude Modulation Coding

At stimulus levels that generate a band-pass MTF, broadband noise reduces the modulation gain at low modulation frequencies, changing the MTF from band-pass to low-pass. It is as if adding noise reduces the effective level of the modulated stimulus.

Noise shifts IC pure-tone rate-level functions toward higher stimulus levels (Rees and Palmer 1988). For a modulated stimulus at an average level that gives a band-pass MTF in quiet, broadband noise shifts the rate-level function and moves the stimulus lower on the cell's input–output function. This change yields a low-pass transfer function, like that for a low-level stimulus in quiet (Fig. 12.4). A concomitant change in modulation gain at low modulation frequency with the shift in the rate-level function supports this idea (Rees and Palmer 1989).

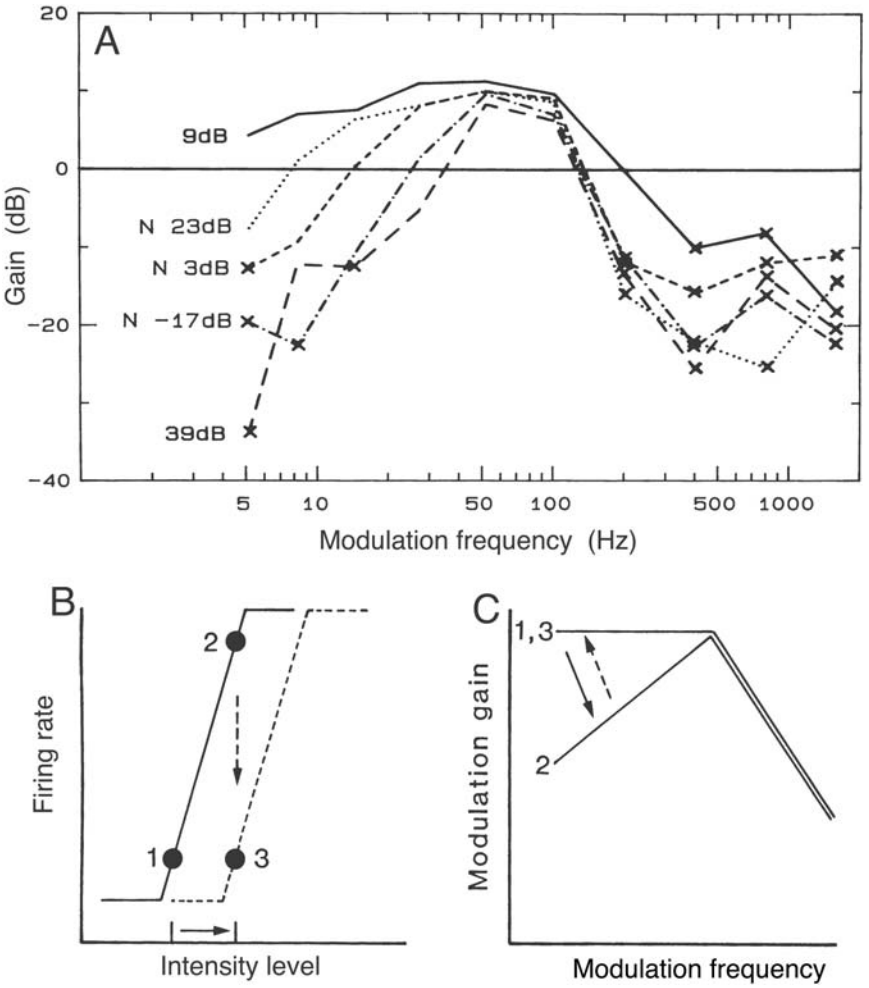


Figure 12.4. Influence of broadband noise on the synchronized responses to sinusoidal amplitude modulation in guinea pig IC. **(A)** Synchronization modulation transfer functions at two different carrier levels (9 dB, *solid line*, and 39 dB re threshold, *long dash*) and for the 39 dB carrier level presented in different levels of broadband noise (*N* parameter, noise spectrum level). Carrier frequency and unit best frequency = 4.25 kHz, modulation depth = 50%. **(B, C)** Schematic representations of the rate-level functions **(B)** and MTFs **(C)** to explain the shift from band-pass to low-pass MTF in **(A)**. Point *1* on the rate-level function shows the position of the carrier giving a low-pass MTF. An increase in the level of the carrier *(solid arrow)* shifts the modulated stimulus to a higher level on the rate-level function (**B**:*2*), and gives rise to a band-pass MTF (**C**:*2*). Addition of broadband noise causes the rate-level function to shift to the right *(dashed function)* and the modulated stimulus now falls on a lower position on the rate-level function (**B**:*3* and *dashed arrow*) resulting in the MTF changing from band-pass to low-pass MTF (**C**:*3* and *dashed arrow*). (Adapted from Rees and Palmer 1989.)

3.4. Responses to Nonsinusoidal Modulations

Most studies of AM encoding use sinusoidal modulation waveforms, but advantages accrue in dissociating stimulus periodicity from envelope parameters such as waveform rise-time and asymmetry. That such properties are important can be seen in response histograms to SAM that often have a more peaked than sinusoidal appearance (Nelson et al. 1966; Rees and Møller 1983; Krishna and Semple 2000). At maximal modulation depths, peak position may change relative to the stimulus waveform and even become bimodal, consistent with the neurons tracking the amplitude envelope at low depths and other parameters, such as the amplitude change rate, at high depths. Sensitivity to rate of amplitude change is evident for exponential and triangular modulation envelopes (Poon and Chiu 1997; Fig. 12.5). Some responses to exponential envelopes showed two histogram peaks compared to one peak for triangular modulation. In most cells spikes occurred during the rising and falling phase, suggesting that these effects embody nonmonotonic or skewed frequency response areas. Four AM unit types were identified: type I units followed the modulation envelope; type II units followed only to the rising phase and were dependent on AM intensity, velocity, and range; type III combined features of types I and II while type IV responded to rising and falling intensity (Chiu and Poon 2000). Asymmetries in the rate and temporal responses of IC neurons are also seen for ramped and damped sinusoids (Neuert et al. 2001). Units with onset firing patterns showed high asymmetry to these stimuli, with most unresponsive to damped stimuli except at the shortest half-life. Sustained units showed little response asymmetry. More cells had asymmetrical rate responses to such stimuli than in the ventral cochlear nucleus (Pressnitzer et al. 2000), demonstrating enhanced IC response asymmetry.

The sensitivity of rat IC neurons to AM periodicity is similar for sinusoidal and for nonsinusoidal modulations studied with tones amplitude modulated with pseudorandom noise (Møller and Rees 1986; Rees and Møller 1987). MTFs obtained by cross correlating neural discharge with the noise modulator estimate the linear response component and closely resemble the SAM transfer function (Møller and Rees 1986). Responses to pseudorandom AM reveal that the linear component explains less of the total response than it does for cochlear nucleus cells (Møller and Rees 1986). Most nonlinear IC responses were even-order and might therefore represent asymmetries to rising and falling amplitude. Comparison of responses to a speech utterance in cat auditory nerve, cochlear nucleus, and IC with responses predicted by the linear component of the site's modulation response found that only IC responses departed significantly from the linear prediction (Delgutte et al. 1998).

3.5. Relationship of Amplitude Modulation Coding to Other Neuronal Properties

IC neurons show several temporal firing patterns when stimulated with pure tones (see Section 2.1). Onset and sustained neurons respond to continuous AM

tones under anesthesia (Rees and Palmer 1989) even at modulation depths well below 100%. In awake chinchilla, a phasic response often predicts narrowly tuned MTFs, whereas an additional tonic component indicates broader MTFs (Langner et al. 2002). However, in bats and rats onset units are the least likely to respond to AM and onset units were least responsive to AM (Condon et al. 1996; Palombi et al. 2001). These differences may represent species differences or anesthesia effects.

IC neurons also differ in the firing regularity of their responses to pure tones (Rees et al. 1997). Some fire regularly with preferred interspike intervals and their interval period is highly correlated with temporal best modulation frequency (Rees and Sarbaz 1997). In contrast, cells with band-pass modulation rate tuning usually fired irregularly to tones.

3.6. Spatial Representation of Envelope Periodicity

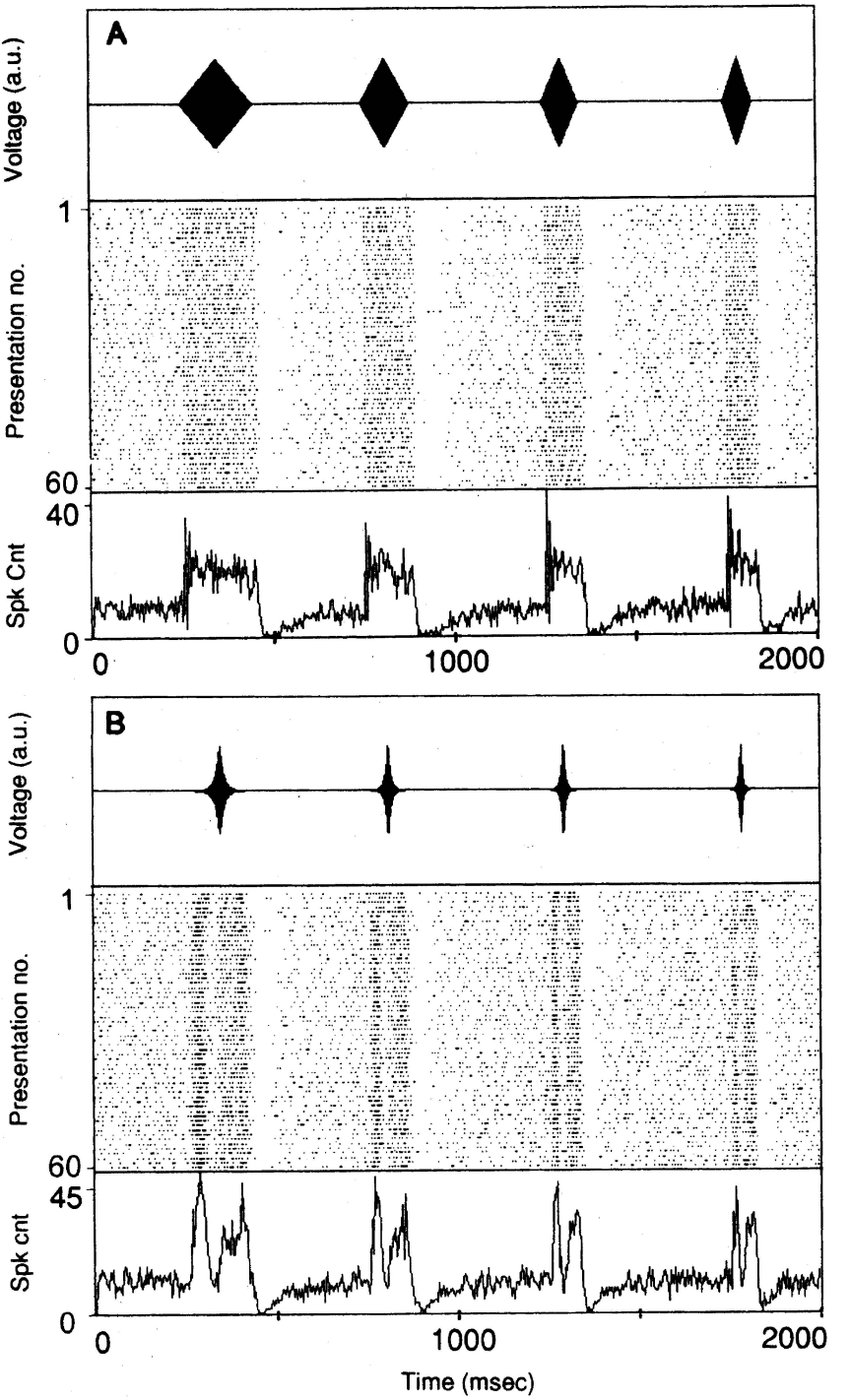
3.6.1. Periodotopy

By providing a substrate for relative position and spatial shifts of excitation, neuronal maps optimize information processing in the corresponding signal space (Suga and O'Neill 1979). The periodotopic map based on the temporal analysis of periodicity information in the CNIC is such a map (Fig. 12.6).

Systematic distributions of responses to AM rate are found in several species (Langner and Schreiner 1988; Langner et al. 1992, 2002; Heil et al. 1995). Periodotopy occurs in CNIC frequency-band laminae. In cat, low BMFs are represented medially and high BMFs laterally; even more lateral subareas with low BMFs, probably in the external nucleus of the IC (ENIC), resulted in the interpretation of concentric periodicity representation (Schreiner and Langner 1988). However, it turned out that recordings in CNIC alone show a simple mediolateral gradient orthogonal to the main dorsoventral tonotopic gradient (Langner et al. 2002; Fig. 12.6). The local BMF increased from about 20 Hz medially to CF/4 (for CF $<$4 kHz) laterally. Moreover, within the frequency-band laminae, the periodicity map is organized orthogonal to the intralaminar tonotopic fine structure (Langner 1992; Fig. 12.7).

Single-unit findings are supported by c-fos mapping (Büttner et al. 1997) and metabolic labeling with [^{14}C]2-deoxyglucose (Langner 2004). Spatial representation of periodicity information is also transferred to higher centers of the avian forebrain (Hose et al. 1987), cat cortex (Langner 1997), and human auditory cortex (Langner et al. 1997).

Figure 12.5. Responses of IC neuron to triangular and exponential amplitude modulation envelopes. **(A)** Triangular modulation waveforms (arbitrary units, a.u.) of a pure tone at 4.8 kHz and 30 dB above threshold *(upper)* and neuronal responses to this stimulus shown as a dot raster plot *(middle)* and a histogram of spike counts *(spk cnt, lower)*. The response is single-peaked for the triangular, and double-peaked for the exponential, envelope indicative of a response to the rate of change of amplitude. (Adapted from Poon and Chiu 1997.)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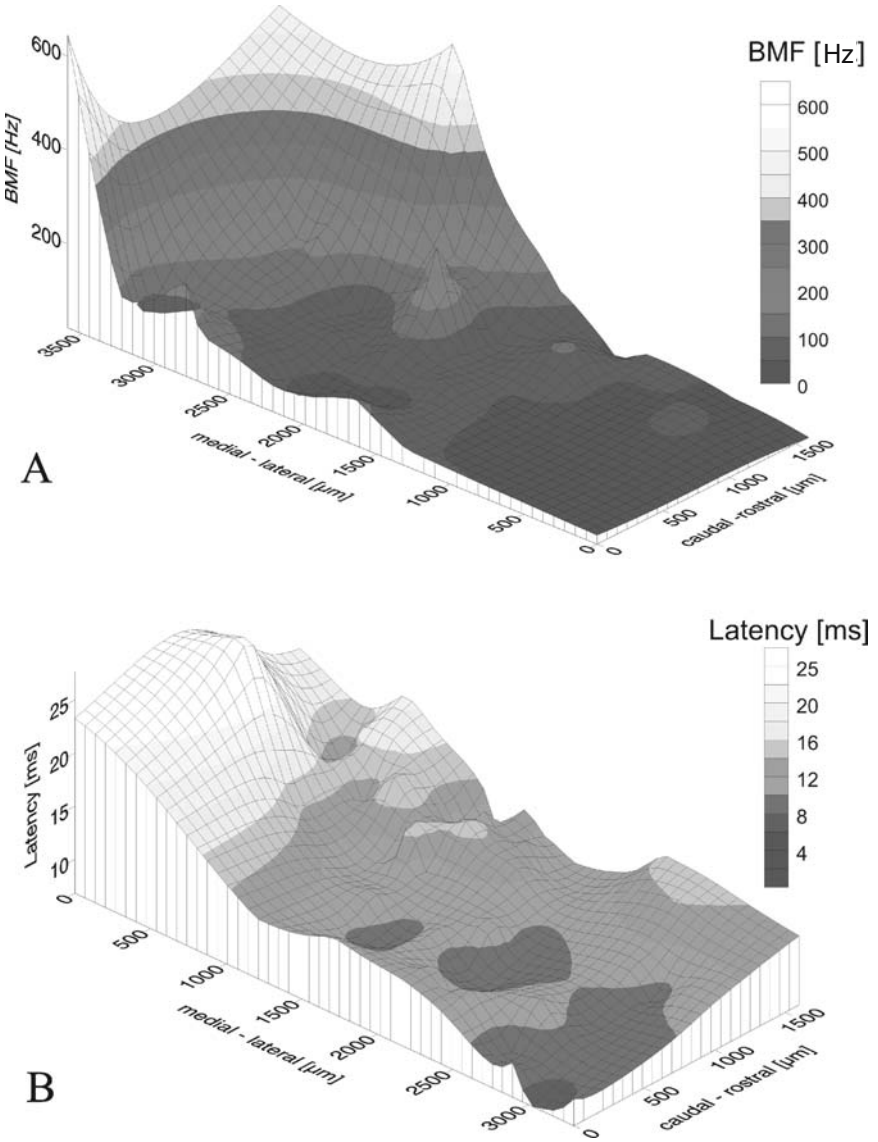

Figure 12.6. Mapping of periodicity and latency in the CNIC. **(A)** Distribution of 52 BMFs in a frequency-band of the chinchilla CNIC. The plane corresponds to the frequency-band lamina of 6 kHz, while the vertical axis represents approximately 5 octaves of BMFs. Low-BMF neurons are located medially and high-BMF neurons laterally. **(B)** Latency map for the same 52 neurons plus latencies from an additional 31 units. Neurons with long latencies are located medially and neurons with short latencies laterally. Note the different viewing orientations in **(A)** and **(B)**.

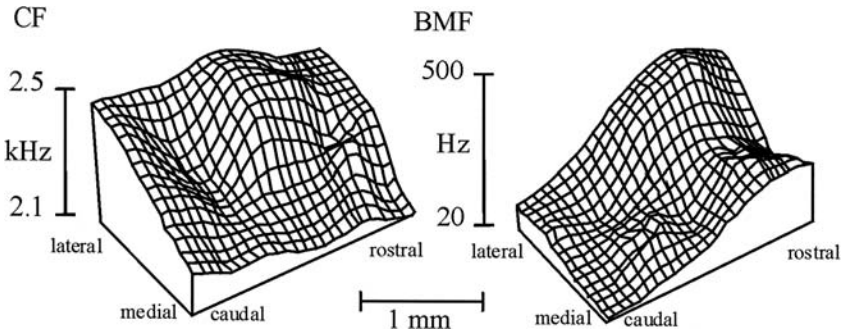

Figure 12.7. Orthogonality of tonotopy and periodotopy in a frequency-band lamina of cat CNIC. In this particular lamina, CFs increased from approximately 2.1 kHz rostromedially to CFs approximately 2.5 kHz located laterally; lowest BMFs were observed in a caudomedial corner and highest BMFs in the rostrolateral corner.

Periodicity, like frequency, seems to be mapped logarithmically in the CNIC, providing scaling invariance in mapping and integration of information from broad band harmonic sounds (Fig. 12.8). Together with the orthogonality of tonotopic and periodotopic gradients, this suggests the periodotopic axis as a second functional axis of the auditory system (Langner 2004).

3.6.2. Relationship of Periodotopy to Other Neuronal Maps

CNIC maps for other auditory parameters, such as onset latency for pure tone responses, also exist. The spatial gradient for onset latency closely resembles that of periodicity maps and, accordingly, is orthogonal to the tonotopic map in many species (Schreiner and Langner 1988; Hattori and Suga 1997; Walton et al. 1998; Biebel and Langner 2002). On average, neurons with low BMFs have long onset latencies and neurons with high BMFs have short onset latencies (Langner et al. 1987, 2002; Condon et al. 1996). Because of the linear relation between latency and 1/BMF (Langner et al. 1987) it would, therefore, suffice to measure latency and calculate a periodicity map by latency information. In bats the latencies within the CNIC could correspond to the echo delays (Yan and Suga 1996). However, no map of IC best echo delays was found, although latency was organized topographically (Portfors and Wenstrup 2001).

Other parameters mapped in the CNIC include threshold (Stiebler and Ehret 1985), tuning curve bandwidth, and binaural input characteristics (Schreiner and Langner 1988; see Chapter 11). However, none of these parameters is represented in a monotonic map with a single gradient as are periodicity and latency.

3.7. Putative Mechanisms for Amplitude Modulation Coding

Models using a combination of short-term adaptation, refractory properties, intrinsic oscillations, coincidence detection, or temporal integration can explain

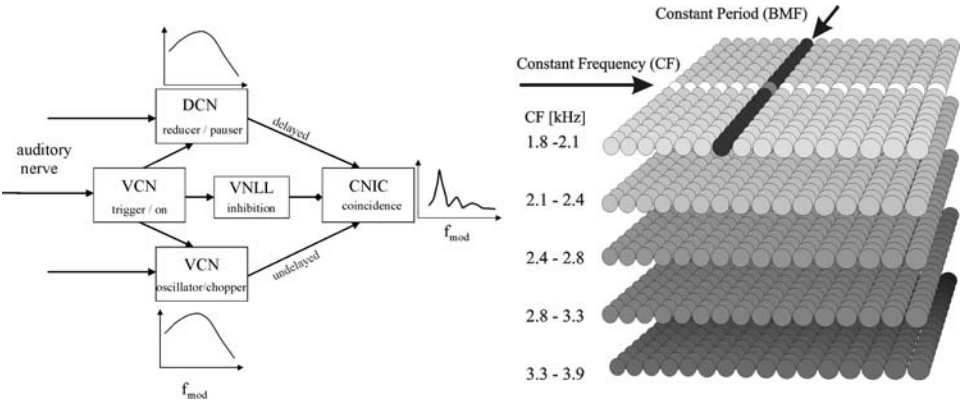

Figure 12.8. A functional and topographic model of periodicity processing. **(Left)** A black-box version of a correlation model. After the frequency analysis of the cochlea and further processing in DCN and VCN periodicity information converges with different delays on coincidence neurons in the CNIC. Oscillator (chopper) in the VCN and reducer (pauser) responses in the DCN are extremely broadly tuned, but precisely synchronized to the signal envelopes by means of a trigger (onset-) neuron. The relatively long delay—resulting from the integration time of the reducer circuit—has to be compensated by the period of the signal and the period of the oscillation for the coincidence unit to be activated and is crucial to its BMF. Although the coincidence of inputs from DCN and VCN provides a correlation between the fine-structure (or carrier) of the signal and its envelope modulation an additional synchronized inhibition provided by neurons in the VNLL shapes the resulting comb-filter into a band-pass MTF. To cover the relevant spectral and temporal ranges many such circuits are necessary in parallel for the periodicity analysis. **(Right)** A topographic model of the CNIC. In accordance with anatomical findings the model suggests that coincidence units (disc-cells) are arranged in neuronal laminae, oriented approximately orthogonal to the main frequency gradient. In each of about 30 to 40 frequency-band laminae, CF increases over a small range of frequencies orthogonal to the main frequency gradient of the CNIC, while BMF increases along an isofrequency-line from about 10Hz to CF/4 (<1000 Hz) with the highest BMFs located at the lateral border of the CNIC. The CF-ranges given for each of the five selected laminae result from a mapping study of the CNIC of cat (Schreiner and Langner 1997).

many aspects of modulation coding (Langner 1983, 1992; van Stokkum 1987, 1989).

A "cancellation model" for a hypothetical "neural comb filter" employs neural delay lines, as already suggested by Licklider (1951), and inhibitory synapses (de Cheveigné 1993). A similar model network that matches the periodicity of tuned neurons in the fish auditory midbrain (*Pollimyrus*) uses coincidence of excitatory and inhibitory input and post-inhibitory rebound, enhanced by neural oscillations (Large and Crawford 2002).

To explain why the periodicity pitch of AM signals (Schouten 1970) and the BMFs of midbrain neurons depend on the carrier and the modulation frequency (Langner 1983; Langner and Schreiner 1988), a model was proposed which

performs a correlation between signal fine-structure and envelope (Langner 1981, 1983, 1988, 1992; Borst et al. 2004). Neuronal elements include a trigger, an oscillator, a reducer unit (reducing high-frequency information), and a coincidence detector. These elements may correspond to ventral cochlear nucleus (VCN) on-type chopper neurons, DCN pauser neurons, and disc-shaped CNIC neurons (Langner and Schreiner 1996). The trigger unit is activated by each modulation cycle and synchronizes the oscillator and the reducer. The oscillator responds with regular interspike intervals for each modulation cycle. The reducer makes use of synchronized activity of many nerve fibers in accordance with the volley principle (Wever 1949) and provides regular intervals calibrated to signal fine structure with phase delays equal to an integer multiple of the carrier period. The output is from coincidence units that receive input from the oscillator and the reducer circuit. Therefore, the coincidence unit responds when carrier and envelope frequency are correlated and the envelope period matches the reducer delay. Finally, to avoid responses to periods corresponding to integer fractions of the preferred period resulting in comb-filter type MTFs (Langner 2004), the coincidence unit requires additional inhibitory input synchronized to the envelope period. An appropriate inhibitory input to the IC may arise from neurons in the ventral nucleus of the lateral lemniscus (VNLL) (Vater et al. 1997; Covey and Casseday 1999; Riquelme et al. 2001). In support of this idea, VNLL cells receive giant synapses mainly from on-type neurons in cat, human (Adams 1997), and bat (Vater et al. 1997) CN.

In an alternative model, BMF preferences of CNIC neurons reflect convergence of inputs from VCN choppers with the same chopping frequency and, therefore, sensitivity to the same modulation frequency (Hewitt and Meddis 1994). Indeed, in many CNIC neurons a chopper-like intrinsic oscillation occurs after signal onset and often to each modulation cycle (Langner 1983; Langner and Schreiner 1988; Condon et al. 1996). However, the intervals of these onset oscillations are usually only a fraction (about 1/6) of the BMF periods of the neurons and their oscillation alone cannot explain unit BMF preference (Langner et al. 2002). However, after a certain latency in the onset response additional spike clusters occur at regular intervals in ongoing responses (Langner 1983). In contrast to onset oscillations, these intervals correlate with the neuron's BMF (Rees and Sarbaz 1997).

4. Frequency Modulation Coding

Frequency modulations (FMs) are important elements of many natural sounds including vocalizations and speech and of bat sonar signals. The earliest reports of IC function described FM-selective IC neurons, including some that respond to dynamic frequency changes but not to pure tones.

4.1. Responses to Sinusoidal Frequency Modulations

Many units responding to sinusoidal FM (SFM) do so with an approximately sinusoidal modulation of their neural discharge (Nelson et al. 1966; Casseday

et al. 1997). Such neurons show great sensitivity to FM with a substantial modulation of the response at depths of <10% of the carrier. As with AM sounds, rat IC neurons have lower best modulation frequencies (<100 Hz) for SFM than cochlear nucleus cells, and similar BMF ranges for the two types of modulation (Rees and Møller 1983). Indeed, as an FM sweeps through the neuron's tuning curve it effectively generates an AM.

Some bat neurons are SFM-selective and responded best or only to SFM (as opposed to frequency sweeps); the larger group of nonselective units had best-SFM frequencies <180 Hz (Casseday et al. 1997). Some units were also modulation-depth selective. As for many IC responses, it is difficult to establish whether such specializations arise within the IC or below it. However, similar stimuli analyzed in the lateral lemniscal nuclei show significantly higher BMFs (Huffman et al. 1998), suggesting that further processing occurs in the IC. Similar findings are reported for SAM (Yang and Pollak 1997).

IC inhibition helps to limit neural responses to low SFM rates. $GABA_A$ or glycine receptor antagonists increased the upper, and/or decreased the lower, cutoff values of the SFM rate response, but in only one-third of the units was the change >50% (Koch and Grothe 1998). Whether these mechanisms alone can account for SFM selectivity differences between the IC neurons and those in more peripheral structures is unknown.

4.2. *Responses to Frequency Modulation Sweeps*

Frequency sweeps are powerful tools for studying FM responses in the IC (Suga 1965; Clopton and Winfield 1974; Fuzessery 1994; Gordon and O'Neill 1998; Hage and Ehret 2003). These stimuli, unlike SFM, enable rate of frequency change to be dissociated from stimulus periodicity and permit identification of directional preference for frequency glides. They are important for studying responses in echolocating bats whose calls contain frequency sweeps. Evidence for directional selectivity as well as specificity to FM was first reported by Suga (1965, 1969). Specific IC regions contain higher percentages of FM-sensitive neurons. In the pallid bat (*Antrozous p. pallidus*), which combines echolocation and passive listening, about 50% of the ventral (high frequency) IC neurons prefer the descending frequency sweeps in its echolocation call and about a third responded only to them and not to pure tones or noise bursts. In contrast, in the dorsal, low-frequency IC, few such neurons were found (Fuzessery 1994). In the mustached bat (*Pteronotus p. parnellii*) many units responding to upward frequency glides were found in a specific part of the external nucleus (Gordon and O'Neill 2000).

Two studies have addressed the relationship between the response to sweeps and IC frequency band laminae. In rat, 34% of units responded to FM sweeps but not to *continuous* pure tones and 43% responded to both (Poon et al. 1992). Cells responding only to FM preferred higher rates and wider ranges of frequency change than other neurons. Most FM-specialized cells also had a strong preference for the FM sweep direction. Anatomically, FM-specialized cells were

multipolar with larger, more extensively branched dendritic fields and more dendritic spines. FM cells were found in all three IC subdivisions, with a higher proportion in EN and fewest in DC. FM response differences may thus depend on cellular morphology and IC location. The best FM ranges were highly correlated with the degree of dendritic extension along the tonotopic IC axis (Poon et al. 1992). However, other rat data found little evidence for FM selective cells and only small changes in response strength for different directions of sweep (Felsheim and Ostwald 1996) and selectivity for sweep speed showed band-pass tuning in many neurons. The use of exponential rather than linear sweeps in the latter study might account for discrepancies between them.

Selectivity for frequency sweep speed is represented topographically in mouse IC (Hage and Ehret 2003). The proportion of cells responding to high sweep speeds increased with distance from the laminar center, as did the firing rate to high, and to a lesser extent, medium sweep speeds. These distributions correlated with those for the units' frequency response area type, sharpness of tuning, and temporal response pattern (see Chapter 11). The authors propose that a common feature underlying all these distributions is a gradient of increasing inhibition from the lamina edge to its center. Some spatial segregation of directional selectivity is seen, although its precise form and correspondence with sweep speed representation is less clear (Hage and Ehret 2003).

4.3. Putative Mechanisms for Frequency Modulation Coding

Asymmetric side band inhibition has long been hypothesized to be involved in determining FM directional specificity (Suga 1965; Gordon and O'Neill 1998). The principle is that an FM-selective cell fails to respond when the frequency trajectory of a stimulus crosses an inhibitory region of its frequency receptive field before entering the excitatory region. Variants on this theme have been proposed to explain complexities such as the unresponsiveness of such FM-specialized neurons to pure tones (Fuzessery and Hall 1996). These accounts either postulate two subthreshold excitatory inputs with different latencies that sum only when a frequency sweep travels in one direction, or combinations of excitatory and inhibitory inputs. The appropriate time delays may be created by inputs with different latencies (Fuzessery 1994; Casseday et al. 1997) or by differences in spatial distributions of frequency specific inputs along the cell's dendrites (Rall 1962; Erulkar et al. 1968). A frequency sweep in one direction results in greater spatiotemporal integration of the postsynaptic potential than an opposite sweep.

The postulated role of inhibition opens the model to testing with transmitter antagonists. Blockade of GABAergic inhibition in the pallid bat reduced directional selectivity for FM sweeps in some cells without changing selectivity for FM over tones or noise (Fuzessery and Hall 1996). However, in another bat (*Eptesicus fuscus*), few cells changed their directional selectivity to SFM with

GABA or glycinergic antagonists (Koch and Grothe 1998). These results suggest differences in FM processing between species, or stimulus differences (SFM vs. linear sweeps) but limitations of iontophoresis may also be significant.

Serotonin also modulates responses to FM stimuli in free-tailed bats (*Tadarida brasiliensis*) (Hurley and Pollak 1999). Both depression and facilitatory effects were observed, depending on the stimulus parameters. Thus, IC responses may be influenced by neuromodulatory systems.

5. Other Aspects of Temporal Coding

5.1. Responses Influenced by Temporal Gaps

The ability to detect a gap in an otherwise continuous signal is a useful psychophysical measure of temporal resolution (Viemeister and Plack 1993; Moore 2003). The advantage of such measures of temporal resolution is that, for a broadband noise, the magnitude spectrum is unaffected by the introduction of a brief gap allowing temporal acuity to be assessed without spectral changes.

The effect of temporal gaps on IC responses has been studied in mouse (Barsz et al. 1998; Wilson and Walton 2002). Mouse behavioral gap detection thresholds resembled thresholds derived from CNIC responses (Fig. 12.9). Onset units responded to each noise burst in the stimulus, while tonic units showed a reduced discharge during the gap and increased firing at the second noise burst onset (Walton et al. 1997). Phasic off-units and inhibitory units responded during the gap. Onset and primary-like tonic units showed the shortest detection thresholds of 1 to 2 ms. Neural gap thresholds for phasic-off and tonic inhibitory units were 3 to 6 times higher than for other unit types (Wilson and Walton 2002).

Gap thresholds for most units increase as the fall- and rise-times of the noise on either side of the gap are increased and the gap blurs (Barsz et al. 1998). Neural gap thresholds are higher in aged mice (Walton et al. 1998) which may provide a model for investigating the mechanisms underlying similar age-related changes in human temporal acuity (Viemeister and Plack 1993). A loss of inhibition may contribute to these changes, as behaviorally measured gap detection thresholds in aged gerbils improved after systemic drug application that enhanced the GABAergic system (Gleich et al. 2003).

5.2. Responses Affected by Tone Duration and Echo Delays

In echolocating bat, neurons sensitive to sound duration intervals (Pinheiro 1991; Fuzessery and Hall 1999) and echo delay (Feng et al. 1978; Yan and Suga 1996) exist in the IC. Bats vary the duration of their biosonar calls during different stages of hunting with the sounds usually becoming shorter and more frequent as they acquire their prey. The echo delay-time allows the bat to compute target distance.

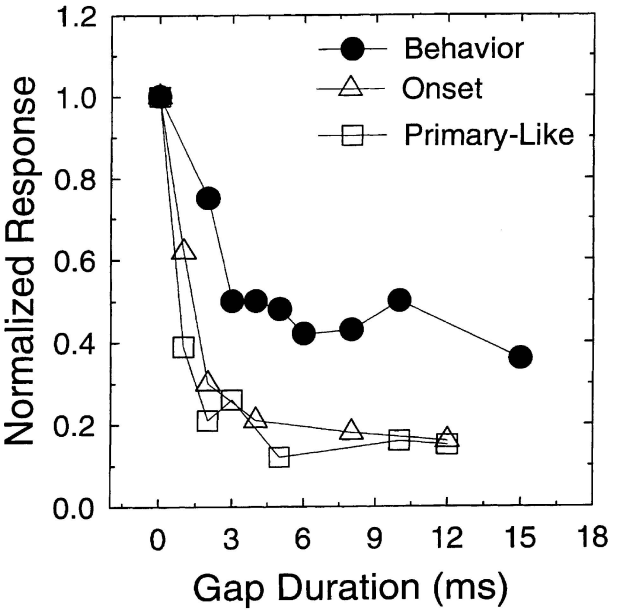

Figure 12.9. Similarity of behavioral *(closed symbol)* and neurophysiological *(open symbols)* measurements of responses to gaps in broadband noise. Behavioral data obtained from five mice using inhibition of the acoustic startle reflex as the paradigm. Neurophysiological data taken from two neuronal types (onset $n = 13$, primary-like $n = 3$) in CNIC in unanesthetized mouse. For onset units, the response is the reciprocal of the increase in firing immediately following the gap. The response for the primary-like units is the decrease in firing during the gap. In both cases the data are normalized to the equivalent time window in the response to noise with no gap present. (Adapted from Walton et al. 1997.)

Approximately 30% of big brown bat neurons increase firing rate significantly with sound duration. Some duration sensitive neurons responded to pure tones, others only to frequency sweeps. The tuning functions were band-pass and the duration selectivity matched the durations of the sounds emitted with most cells preferring durations $<$10 ms (Casseday et al. 1994; Ehrlich et al. 1997). Similar results were seen in pallid bats (Fuzessery and Hall 1999).

Inhibition is essential for duration tuning (Casseday et al. 1994). $GABA_A$ or glycine antagonists reduce or eliminate duration tuning, but in cells tested with both GABA predominated (Casseday et al. 2000). Intracellular measurement of synaptic currents in vivo, using whole-cell patch clamp, shows an excitatory–inhibitory interplay consistent with duration tuning (Covey et al. 1996). Sound onset evokes a short latency sustained inhibition and long latency excitation. The end of the inhibition is followed by an intrinsic rebound excitation or other source of excitation associated with offset. However, the cell fires only when this rebound coincides with the long-latency excitation evoked by stimulus onset.

At other latencies the excitation is either suppressed by inhibition or occurs after the rebound excitation. The cell's preferred duration is thus determined by the sound latency evoked by the long latency excitation (Ehrlich et al. 1997; see Chapter 17).

Evidence for duration tuned neurons also comes from studies of chinchilla and mouse (Chen 1998; Brand et al. 2000). About half the mouse neurons showed long, short or band-pass functions for duration, but most varied with other stimulus properties. It is unknown whether the underlying mechanisms resemble those in bat, but intracellular current measurements in cat IC neurons found one essential component of the model, namely that some cells receive inhibition before excitation (Nelson and Erulkar 1963). It has been suggested that the mechanism for sensitivity to duration might underlie psychophysical masking. In the big brown bat the unit response to the best duration tone was suppressed when it preceded or followed a tone that evoked only inhibition. Thus, inhibition with a shorter latency than excitation may contribute to backward masking (Faure et al. 2003).

Bat IC neurons may be sensitive to the delay between the emission of a biosonar signal and the echo return (Feng et al. 1978; Mittmann and Wenstrup 1995). Their preferred delays ($<$10 ms) are within the range a bat would experience while echolocating. Mechanisms, like those proposed for periodicity analysis (see Section 3.7), involving time-dependent excitation and inhibition (Saitoh and Suga 1995), that elicit firing when coincidences occur between the emitted sound and an echo component, could explain how these detectors operate.

6. Conclusions and Directions for Future Research

Hearing depends on the accurate perception of temporal information. From pitch perception to sound localization and speech discrimination, time and timing are critical in auditory perception. We have focussed on how temporal *changes* in amplitude, frequency and duration of sounds are encoded in the responses of IC neurons.

Several themes are noteworthy. First is the emergence of response properties that are not apparent below the IC. For AM coding, one theme is the appearance of modulation frequency selectivity signalled by average firing rate, besides synchronized firing to the modulation envelope at lower auditory stations. Although this implies that temporal information is recoded as a rate-based stream at the IC, we emphasize that many IC neurons have strongly synchronized responses to AM envelopes, sometimes well above 100 Hz, and many neurons do not show tuned responses to modulation frequency when transfer functions are derived from average rate measures. Indeed, for processing sounds with temporal information (as in source streaming and grouping) it might be important to retain

a temporal component in the response to identify different frequency components that share common temporal features.

Coding information by average rate may compensate for the reduction in frequency limit for synchronized firing to modulation envelopes for IC neurons compared to auditory nerve fibers and CN neurons. This trend, apparent in the periodic responses to both AM and FM, continues in the thalamus and the cortex. A likely extension of coding information by rate is that the coded parameter is represented topographically across the IC laminae. Evidence has been presented for such representations of AM rate and frequency sweep speed, and these may underlie the generation of specific auditory percepts. A particular pitch may originate when the appropriate frequency channels are stimulated with the appropriate envelope periodicity. Periodicity pitch and frequency information—defining sound timbre—are orthogonal percepts, a relationship in accord with the finding that periodotopy and tonotopy have complementary IC representations.

For both FM and AM there is evidence that the IC is the first site in the auditory pathway for neural selectivity to the direction of frequency or amplitude change, and some units may respond exclusively to frequency dynamics rather than to static frequencies. Similarly, duration tuning appears to first emerge at the IC. An extensive inhibitory component present in both the synaptic input to IC and in a significant proportion of its neurons plays an important role in the genesis, and perhaps the spatial representation, of these selectivities. Concomitant with the specialization and refinement in the temporal response properties of IC neurons, is the robust representation of nonlinear components in their responses. These have to date been described in general terms, such as the nonsinusoidal responses of many cells to sinusoidal modulations. A key aspect of future studies will be a more rigorous and quantitative analyses of these nonlinearities.

With respect to stimuli, most studies have used relatively simple sounds such as sinusoidal or linear modulations of pure tones often centered on the BF of the unit under study. Given the significant nonlinearities in IC responses, some features of temporal processing in the IC will likely become apparent only with the use of more complex sounds that contain multiple frequency components and combine more than one temporal property. This approach will be vital for addressing hypotheses about across-frequency interactions within the IC and the creation of auditory streams. A fundamental requirement for addressing many of the questions about temporal information processing in the IC is an understanding of how its circuits are organized, and how the membrane properties of neurons shape their responses. Auditory information coded in many nuclei and by numerous brain stem neuronal types converges in the IC. For some models, like the periodicity model of Langner, one constraint is that different inputs to the IC contact the same neurons and that their spatial and temporal coincidence is essential for auditory processing. On the other hand, other inputs may target specific domains within the IC to create local networks representing specific stimulus parameters. For example, neurons preferentially coding localization and

others coding periodicity may participate in such local networks and may be important for auditory streaming.

To resolve these conundrums, we need a clearer and more complete description of IC microcircuitry to specify the functional and structural relationships between its neurons, the different subdivisions in which they reside, and the synaptic inputs they receive. Some of this information is emerging from in vitro studies; complementary intracellular in vivo analyses, that enable the temporal characteristics of both excitatory and inhibitory postsynaptic currents to be measured in response to physiological stimuli, will be vital to this agenda.

Abbreviations

AM	amplitude modulation
BMF	best modulation frequency
CF	characteristic frequency
CN	cochlear nucleus
CNIC	central nucleus of the inferior colliculus
DCN	dorsal cochlear nucleus
ENIC	external nucleus of the inferior colliculus
FM	frequency modulation
GABA	γ-aminobutyric acid
IC	inferior colliculus
MTF	modulation transfer function
PVCN	posteroventral cochlear nucleus
SAM	sinusoidal amplitude modulation
SFM	sinusoidal frequency modulation
VCN	ventral cochlear nucleus

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Chapter 13
Binaural and Spatial Coding in the Inferior Colliculus

Alan R. Palmer and Shigeyuki Kuwada

1. Introduction

1.1. The Importance of the Inferior Colliculus in Binaural Processing

The inferior colliculus (IC) is a critical center for binaural processing because the outputs of the primary binaural processors, the medial and lateral superior olives (MSO and LSO), terminate in the IC. The MSO and LSO also project to the nuclei of the lateral lemniscus, which in turn project to the IC. Direct monaural inputs from both cochlear nuclei, as well as second-order monaural inputs from the ventral nucleus of the lateral lemniscus, can also converge with the binaural inputs in the IC. Thus, there is considerable opportunity for binaural as well as monaural convergence. Because of this potential for multiple-source interaction, the responses of IC neurons cannot be a simple reflection of a single source (see Chapter 2).

1.2. Binaural Cues and Functions of Binaural Hearing

There are generally considered to be three major cues for the localization of sound: interaural time (ITDs) and level differences (ILDs) and spectral cues. Although often treated as independent, because in some circumstances only one cue is available, for any spectrally rich sound all of these cues are simultaneously present and consistent. Interaural time differences are created by the differences in arrival time of the sound at the two ears. The largest ITD depends on head size and in humans it is approximately 700 μs (Nordlund 1962; Shaw 1974; Blauert 1983). The upper frequency limit for ITD cues is limited by head size, that is, when the wavelength of the sound is shorter than the head width. In humans, this limit is about 1300 Hz. Above this frequency the effect of the head in "shadowing" the sound reaching the ear further from the sound source creates ILDs as well as multiple peaks (ambiguity) in the ITD function. In low-frequency sounds ILDs are small because their wavelengths are much larger than the head width. However, even at low frequencies sound sources very near

the ear (in the near field) can generate considerable ILDs. In humans, the ILDs at high frequencies can exceed 20 dB (Shaw 1974; Blauert 1983). The utility of this cue is maximized in animals with small head widths by extending their high-frequency hearing (Masterton et al. 1969). Spatially dependent spectral cues are generated by interference at the eardrum between sound waves traveling directly from the source with those reflected from the torso and pinna. The effect of the interfering waves is to produce peaks and notches in the spectra of wide-band sounds, the frequency position of which depends on the spatial position (Blauert 1983). The filtering effect of the head and body in the sound field can be measured in the ear canal as the head-related transfer function (HRTF). For any sound source, the sound reaching the two ears will be filtered by the HRTF, appropriate for that position in space at that ear, to produce interaural spectra that contain ITDs, ILDs, and spectral information specific to the sound position.

Many advantages accrue from listening with both ears rather than only one ear, for example, improved detection and increased loudness of sounds. Other advantages stem directly from the ability to localize the sound source, such as the detection of moving sound sources. Whether this is a simple process of sequentially evaluating spatial position or involves specialized motion detectors is still in debate (Grantham 1997). Finally, there are benefits in source isolation and segregation. In our everyday environment we experience not only direct sound, but also many echoes that usually do not interfere with our listening to the primary source. This reduced perceptual salience of echoes depends on processing the differences at the two ears and identifying sources that arrive earliest (the precedence effect; Wallach et al. 1949). Binaural hearing also helps in segregating target sounds from interfering backgrounds that derive from spatially separated sources. A well investigated surrogate for this ability is the binaural masking level difference in which spatially separating masker sounds from target sounds improves target detection (Hirsh 1948a,b; Licklider 1948).

2. Processing of Interaural Time Differences for Low-Frequency Sounds

2.1. Types of Interaural Time Difference Sensitivity and Their Possible Origin

It is important to distinguish between two types of ITD, onset and ongoing. The onset ITD is the initial difference produced by the sound reaching the ears at different times, while the ongoing ITD is produced by ongoing differences in the pattern of pressure variations at the two ears. In humans, the ongoing ITDs are much more potent than onset ITDs in determining the position of a lateralized image (Tobias and Schubert 1959; Buell et al. 1991). Consistent with this observation, neurons sensitive to ongoing ITD (those showing a cyclic ITD function with a period equal to that of the stimulating tone; Fig. 13.1) generally display no sensitivity to onset ITDs (Kuwada and Yin 1983). Although the ev-

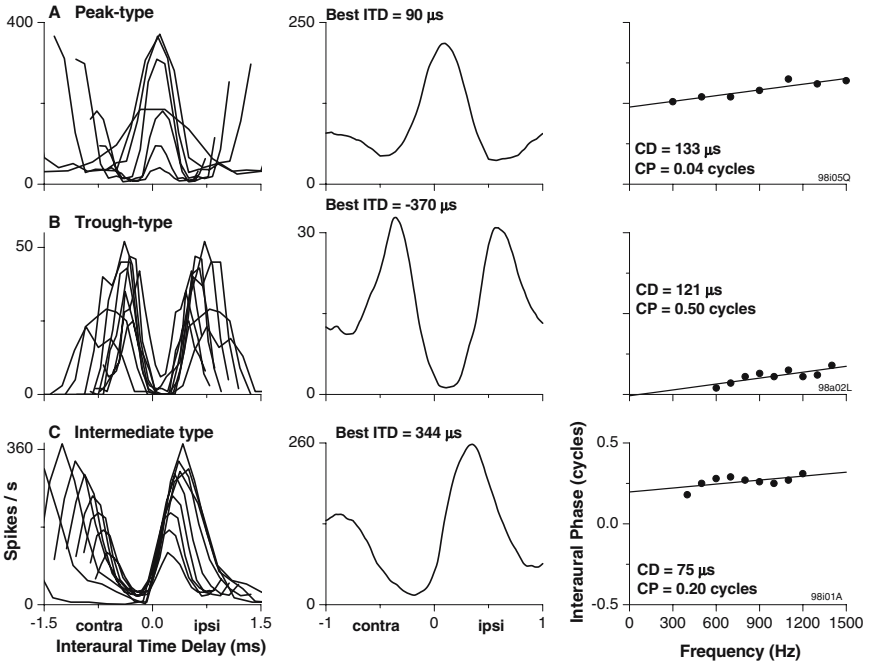

Figure 13.1. Types of ITD functions. Examples of types of response to changes in ITD across frequency in IC neurons sensitive to low-frequency sounds. *Left column:* each ITD function is the response to a particular stimulus frequency. *Middle column*: "composite curves" obtained by averaging the ITD functions *(left column).* The peak of the composite curve is fit by a parabola and the center of the parabola is an estimate of the neuron's best ITD (BD). *Right column*: plots of the mean phase of the response vs. the stimulating frequency. The slope of the best fit line represents the characteristic delay (CD), and the intercept is the characteristic phase (CP). **(A)** Peak-type response: the CP is near 0, the CD occurs near the peak of each ITD function, and the BD of the composite curve resembles the CD. **(B)** Trough-type response: CP is near ± 0.5, the CD occurs near the trough of each ITD function, and the BD differs substantially from the CD. **(C)** Intermediate-type response: the CP is near ± 0.25, the CD occurs between the peaks and troughs of the ITD function, and the BD differs from the CD, but not as much as for the trough-type neuron. (From Kuwada et al. 1987.) *Contra,* Contralateral; *Ipsi,* ipsilateral.

idence for neural sensitivity to ongoing ITDs is abundant and has been observed at all levels of the auditory pathway (Kuwada et al. 1997), sensitivity to onset ITDs has been studied by few investigators (e.g., Harnischfeger 1980; Caird and Klinke 1983, 1987; Kelly and Phillips 1991). Such investigations are complicated by the fact that even transient stimuli can give rise to cyclic ITD functions (Carney and Yin 1989). This occurs because brief sounds can "ring" the basilar membrane and evoke a spike discharge that is synchronized to the fiber's best frequency (Kiang et al. 1965; Carney and Yin 1989).

Rose and colleagues (1966) described three types of ongoing ITD-sensitive neurons in the IC that are currently referred to as peak-, trough-, and intermediate-type. Quantitative criteria were established for these three types (Yin and Kuwada 1983; Fig. 13.1) that require the neuron's sensitivity to ITDs be measured at several frequencies. For peak-type neurons, the peaks (maxima) of the ITD functions for different stimulus frequencies align at or near a particular ITD (Fig. 13.1, top row), for trough-type neurons the alignment is at or near the trough (minima; Fig. 13.1, middle row), and for intermediate-type neurons the alignment is intermediate (Fig. 13.1, bottom row). The alignment of ITD functions is determined by a linear fit to the plot of the mean interaural phase vs. stimulating frequency (Fig. 13.1, right column). The slope of the fit is the characteristic delay (CD) and the phase intercept at 0 Hz is the characteristic phase (CP). In the Jeffress scheme (see Section 2.2), the CD would correspond to the difference in conduction times of the neural path lengths from each ear to the binaural coincidence detector, that is, the ITD required for coincident arrival of the inputs. The CP is a measure of whether the alignment occurred at the peak (CPs near 0 or 1 cycle), trough (CPs near 0.5 cycles), or at an intermediate position (CP near 0.25 or 0.75 cycles). The most common ITD functions display a peak with flanking slopes (Figs. 13.1A and 13.2D), and can be evoked by tones or more complex stimuli such as amplitude-modulated tones, noise, clicks, and vowels (Kuwada and Yin 1983; Yin et al. 1986a; Carney and Yin 1989; Palmer et al. 1990; D'Angelo et al. 2003; Sterbing et al. 2003a).

Averaging the ITD functions (Fig. 13.1, left column) for all the stimulating frequencies to which the neuron was ITD sensitive generates the composite curve, which is representative of the neuron's ITD sensitivity to a broad-band sound (Yin et al. 1986a). The neuron's best ITD (BD) is estimated by fitting a parabola to the peak of the composite curve (Fig. 13.1, middle column). A neuron's BD can be predicted by the equation: best ITD = CD + CP/best frequency of ITD sensitivity (Fitzpatrick et al. 2000, 2002).

In a Jeffress type scheme, peak-type ITD sensitivity arises from excitatory inputs from each side, whereas trough-type sensitivity is created by excitatory inputs from one side and inhibitory inputs from the other (Fig. 13.2). Thus, it is tempting to assume that peak-type neurons in the IC reflect inputs from the MSO, because MSO neurons receive excitatory input from the cochlear nucleus neurons of each side. Similarly, trough-type IC neurons could reflect LSO inputs because LSO neurons receive excitatory inputs from the ipsilateral cochlear nucleus, and inhibitory inputs from the contralateral cochlear nucleus via the medial nucleus of the trapezoid body. Intermediate-type neurons are not compatible with a Jeffress type scheme and yet constitute a sizeable portion of ITD-sensitive IC neurons. Their phase-vs.-frequency plots are often complex and often of the intermediate type. There is compelling empirical and modeling evidence (McAlpine et al. 1998; Shackleton et al. 2000) that intermediate-type IC neurons are created by the convergence of inputs from different coincidence detectors from the same nucleus (e.g., MSO) or different nuclei (MSO and LSO). Because of the high likelihood that IC neurons receive ITD-sensitive inputs from many

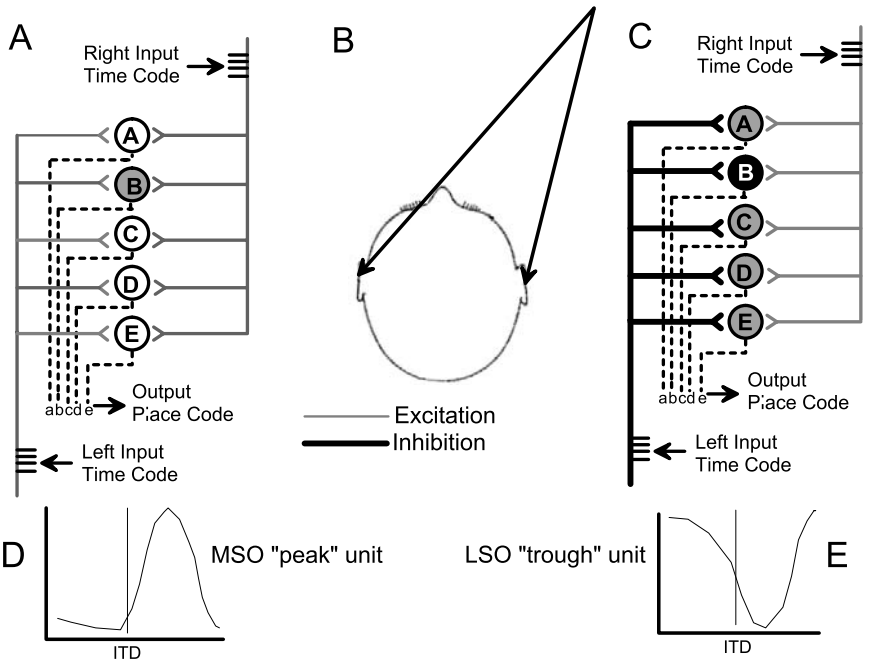

Figure 13.2. Jeffress model for peak ITD sensitivity and its variant for trough units. **(A)** The classic Jeffress network has excitatory inputs arranged in a delay line and that feed coincidence detectors (circles labeled A–E) to convert interaural time differences to a place code for position (output axons labeled a–e). Activation is shown for a spatial position on the right as in **(B)**. **(C)** A putative Jeffress network with inhibition from one side giving rise to suppression when the inputs are coincident (labels as in **A**). **(D)** A typical "peak" unit response from the Jeffress network. **(E)** A typical "trough" response from the variant of the Jeffress network.

different nuclei, the type of ITD sensitivity observed is not easily attributable to a single input, even for peak- and trough-type neurons.

It has been suggested on the basis of frequency tuning and ITD and ILD sensitivity that IC neuronal responses are dominated by parallel inputs from different lower level brain stem nuclei (Davis et al. 1999, 2003; Ramachandran et al. 1999; Ramachandran and May 2002). Thus, cells with V-shaped responses areas ("type V") tend to be found at low frequencies, have excitatory input from both ears, and have "peak" type ITD functions. The dominant input to these cells is hypothesized to be the MSO. Cells with level tolerant narrow tuning ("type I") tend to have trough- or intermediate-type carrier and envelope ITD functions, receive excitatory input from the contralateral ear and inhibitory input from the ipsilateral ear, and are sensitive to ILDs. These are hypothesized to be dominated by inputs from the LSO. Finally, units with an island of low-level excitation caused by strong best frequency inhibition at higher levels ("type O")

are a more diverse group that often show very weak binaural sensitivities, but could show ITD or ILD sensitivity and were hypothesized to be dominated by input from the dorsal cochlear nucleus.

2.2. The Jeffress Model for Interaural Time Delay Sensitivity

The human ear is exquisitely sensitive to ITDs. For noise and clicks the just noticeable difference in ITD is 5 to 12 μs and for tones it is 20 to 30 μs, dependent on frequency and duration (Tobias and Zerlin 1959; Durlach 1972). An obvious question is, What aspects of the neural ITD function carry the salient information to code the ITD in an external sound source? The dominant model for the way in which ITDs are processed in the brain was proposed by Jeffress (1948) (Fig. 13.2A), who postulated a network of neurons that acted as coincidence detectors, receiving excitatory input from the two ears. Originally he suggested the medial geniculate body (Jeffress 1948), but later correctly suggested that it likely took place in the MSO (Jeffress 1958). Input to the coincidence detector from both sides occurring within a short time window leads to summation of the excitatory postsynaptic potentials and generation of an action potential. A variant of this scheme (Fig. 13.2C) has inhibitory input from one ear. When excitation and inhibition are coincident the cell firing is prevented. With this variant (Fig. 13.2C), responses of ITD-sensitive neurons are consistent with Jeffress's notion of coincidence detectors. To enable such cells to respond maximally (or minimally, Fig. 13.2C) to specific spatial locations, Jeffress proposed that the cells were connected to each ear by axons of differing length to provide a delay line. Only when the internal delay compensated exactly for the later arrival of the sound at one ear would a specific coincidence detector fire. Thus, the specific coincidence detector activated provides a code for a specific spatial position and the array of coincidence detectors converts ITDs into a place code representing all azimuthal sound locations.

A sound source would optimally activate neurons with ITD functions whose peaks correspond to the ITD created by the sound source, as well as other neurons whose ITD functions overlapped with the optimally activated functions, all contributing to increasing the activity at a locus in the neural ITD array. This viewpoint is supported in a study in the unanesthetized rabbit showing that such arrays in the SOC, IC, and auditory thalamus could achieve high acuity in ITD discriminability (Fitzpatrick et al. 1997).

2.3. Distribution of Best Interaural Time Delay Sensitivities

Subsequent work focussed on the value of the ITD evoking the maximum output of the coincidence detectors. Whether in response to best frequency tones or to broadband noise, the numbers of IC neurons with the various best delays (BD) tended to peak at relatively long ITDs, representing sensitivity preferentially to

sounds in the contralateral hemifield, and this applies when different animals were examined (Fig. 13.3A, B; Palmer et al. 1990; McAlpine et al. 1996b). Later studies suggested that within such plots, at least for the gerbil and guinea pig, there was a frequency dependence: BDs near 0 ITD were found in neurons with high best frequencies, while longer BDs were found in neurons with lower best frequencies (Fig. 13.3C). This was confirmed when CD to tones (Fig. 13.3C; McAlpine et al. 1996b) or BD in response to noise (McAlpine et al. 2001) was measured as a function of best frequency.

Despite large differences in head width and therefore the physiological ITDs available to the animal, the shapes of the ITD functions and the distribution of their BDs are similar across many mammals. Furthermore, even the sharpest ITD function can span several hundred microseconds and the bulk of their BDs are off the midline. So, for animals with small head widths, an external sound source would not activate the peak of the ITD functions, and even if the peak was located near 0 ITD, the modulation of the response would be negligible across the physiological ITDs available to such animals.

In guinea pigs, even at high best frequencies, BDs were on the edge of the estimated physiological range, whereas the medial slopes of the ITD functions were well within. Their physiological range was estimated to be ± 150 μs, al-

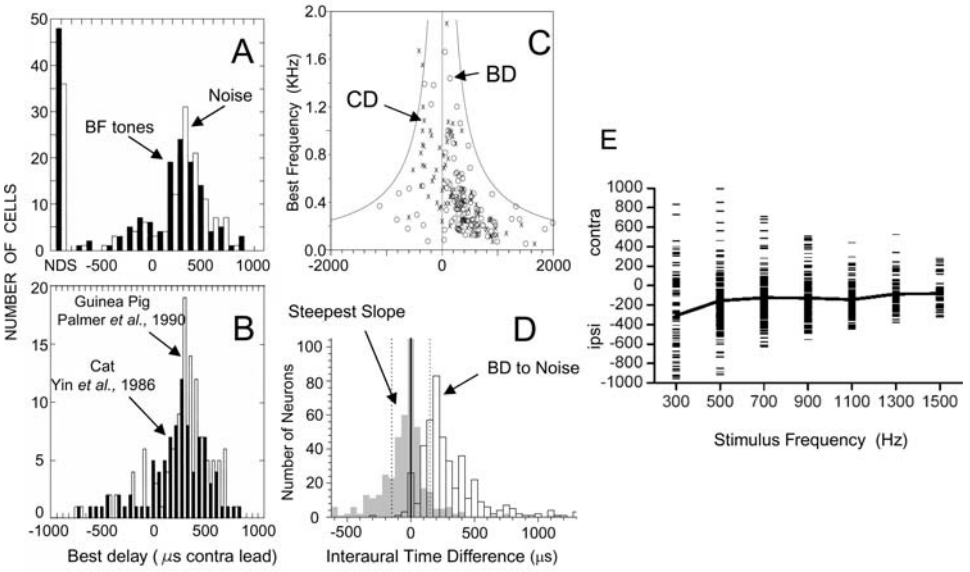

Figure 13.3. Distributions of best delays from different animals and the frequency dependence of BD. **(A)** The distribution of BD to BF tone and noise stimulation. (From Palmer et al. 1990.) **(B)** The distribution of noise BDs in the cat and guinea pig. (From Yin et al. 1986a; Palmer et al. 1990.) **(C)** The variation of BD and CD for BF tones with BF. *Open circles* show BD, *crosses* show CD. (From McAlpine et al. 1996b.) **(D)** The distribution of BDs and steepest slopes of noise ITD functions. (From McAlpine et al. 2001.) **(E)** The distribution of BDs as a function of stimulus frequency in rabbit.

though another report measured it to be about ±330 μs at frequencies <1600 Hz (Sterbing et al. 2003b). Taking this larger range, guinea pig neurons with best frequencies >400 Hz have their BDs within the physiological range (McAlpine et al. 2001), albeit near its extreme end.

A consequence of the frequency dependence of ITD sensitivity is that the steepest slopes of the delay functions at any frequency pass through the physiological range of the animal (Fig. 13.3D). Several other reports, however, show BD distributions (from composite curves) that, although still displaced toward the contralateral hemifield, have modes between 90 and 200 μs (cat: Yin and Kuwada 1983, 1984; rabbit: Kuwada et al. 1987; Stanford et al. 1992) and that contain many neurons with BDs at and near 0 ITD. A sampling bias or perhaps even species difference may contribute to the differences between the cat/rabbit BDs and those of the guinea pig. The best frequency dependence of the BD is marked when frequencies <300 Hz are plotted, which are more prevalent in the guinea pig than in the cat and rabbit. Above 300 Hz, the data sets are much more similar with BDs closer to 0 ITD. For example, a plot of BD vs. dominant frequency (highly correlated to best frequency) (Joris et al. 2005) resembles Fig. 13.3C but extends only down to about ±300 Hz and has a greater representation of neurons with BDs near 0 ITD. Furthermore, when BDs distributions are viewed at individual stimulus frequencies many neurons have BDs near 0 delay at all frequencies (Fig. 13.3E). Differences between studies may be methodological, and, if so, may shed light on ITD processing under normal listening conditions. The data in Fig. 13.3E are plotted as a function of stimulus frequency, which usually was not the best frequency of the neuron. In Jeffress' original network formulation this would make no difference (i.e., all BDs are available at all best frequencies). However, if the BD dependence on best frequency is general, the distribution of best frequencies will be germane, as a preponderance of high best frequencies will lead to BD distributions closer to 0 ITD. Certainly, some rabbit near-0 BDs could be from the low-frequency tails of high best-frequency neurons. Thus, the plot of BD at each stimulating frequency would encompass the distribution across best frequency for all neurons sampled that responded to that frequency. The importance of this (developed later) is that, under normal sound stimulation levels, the population of neurons will be activated at their tail region or at their best frequency. Under these conditions, depending on the best frequency distribution, the population response may indeed be dominated by neurons with BDs near 0 ITD.

From a Jeffress perspective, the full range of ITD tuning should be present in every frequency channel, but this was not the case in the guinea pig. However, McAlpine et al. (2001) used a low stimulus level (10 to 20 dB above the neurons' threshold) to reveal the shifts in BD with frequency. Even at moderate levels (60 to 70 dB), low-frequency ITD functions can be generated in high-frequency neurons, presumably by stimulating their low-frequency tails. In the rabbit, ITD functions evoked at 70 dB SPL show tuning to a range of BDs within this animal's physiological range at all frequencies (Fig. 13.3E). So, using near-threshold levels may not capture the population of ITD-sensitive neurons evoked at higher stimulus levels. However, the high-frequency neurons recruited at su-

prathreshold levels likely have short BDs (near 0), but their ITD tuning width will largely be determined by the stimulus period (Fitzpatrick and Kuwada 2001). Thus, although the population at high levels will contain many neurons responding maximally near 0 to low-frequency stimuli, many of these will not provide much variation in discharge as ITDs change within the physiological range. However, even under these circumstances neurons with BDs remote from 0 ITD and, hence, with steep slopes through 0 ITD, should still provide good resolution.

A distribution of BDs that is densest off the midline becomes a problem for the Jeffress model if its centroid is far from 0 ITD and/or the ITD functions are extremely sharp. In mammals, neither is the case as shown by averaging the delay functions from many neurons and plotting them as well as their mirror images (Fig. 13.4A). Averaging the two population ITD functions reveals a central peak at 0 ITD and is a simple consequence of the medial tails of each side overlapping. If the peaks were widely separated and the ITD functions were extremely sharp, then this overlap would be minimal and no activity could be evoked at 0 ITD.

2.4. Alternatives to the Jeffress Model

Stillman (1971) first proposed that the steeply sloping part of the ITD functions in the kangaroo rat might be an important feature because the peaks of the ITD functions occurred outside the natural range of ITDs in this species. Consistent with this suggestion, Skottun (1998) and Shackleton et al. (2003) showed empirically that the slope of the ITD function has sufficient information to discriminate changes in ITD with high acuity. The steepest part of the slopes, independent of best frequency, fell near 0 ITD (McAlpine et al. 2001) because of the best-frequency dependent shift in BD (see Section 3.2.5). This finding, the paucity of BDs near 0 in the guinea pig, and the finding that inhibition can systematically shift the peaks of ITD functions, questions the validity of the Jeffress delay line model and has led to reconsiderations of alternative coding schemes that compare activity in two neural populations (possibly on either side of the brain) evoked by a sound with a particular ITD (McAlpine et al. 2001). Such a view is like the count-comparison models (von Békésy 1960) and refined within an anatomical and physiological context (van Bergeijk 1962).

McAlpine et al. (2001) recognized that their count-comparison scheme, in its simplest form, is incompatible with lesion/localization studies. Unilateral lesions of the IC, brachium of the IC, and auditory cortex have shown that the deficits in localizing sounds are confined to the contralateral sound field and localization appears normal in the ipsilateral sound field (Jenkins and Masterton 1982). Certainly, hemisphere comparisons remove the inherent ambiguities generated by other factors, such as sound level, that change the neural activity. However, direct access in one hemisphere to a monaural level dependent signal could achieve the same disambiguation.

A further caveat in making use of changes on the slopes occurs when the peak of the ITD function lies within the physiological range. In the cat and

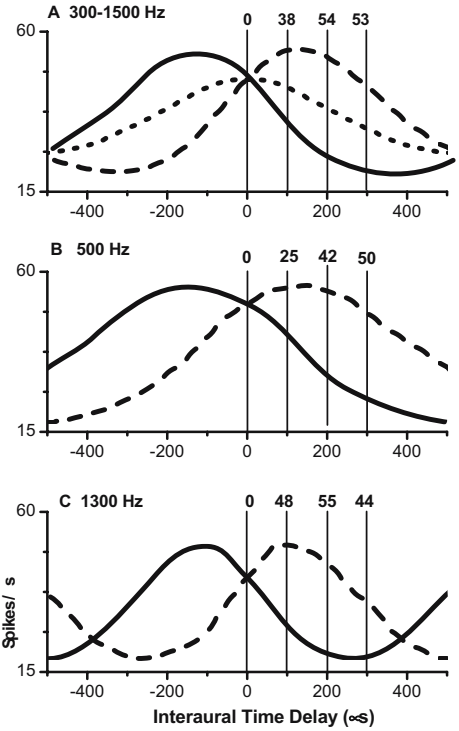

Figure 13.4. A count comparison scheme applied to ITD-sensitive IC neurons in the unanesthetized rabbit. **(A)** The ITD functions from 300 to 1500 Hz were averaged to depict the activity to a sound containing all these frequencies (i.e., noise). This averaged function *(black line)* was also flipped to depict the activity in the contralateral IC *(coarse dashed line)*. The difference (count comparison) between the activity of the two sides at ipsilateral delays of 100, 200, and 300 μs is expressed as a percentage. The two ITD functions were averaged to show that the resultant function *(fine dashed line)* had maximal activity near 0 ITD. If these peaks were further displaced from 0 ITD, such averaging would lead to a function with minimal activity at 0 ITD. **(B, C)** The ITD functions only at 500 Hz or 1300 Hz were averaged. In all cases, the peak of the ITD function is within the rabbits' physiological range. In such cases, a count comparison scheme provides an ambiguous code for ITD that degrades as frequency increases.

rabbit and likely in human, most IC neurons display BDs within their physiological ranges. As the ITD increases, activity along the upslope and the downslope of the ITD function can produce the same count comparison difference, at very different ITDs. This is a situation (Fig. 13.4) in which the ITD functions from the IC of the unanesthetized rabbit for all frequencies between 300 and 1500 Hz are averaged (Fig. 13.4A), or only those at 500 Hz (Fig. 13.4B) or 1300 Hz (Fig. 13.4C). The averaged ITD functions in one IC are flipped to display also the averaged ITD function in the opposite IC. The activity evoked

at 0-, 100-, 200-, and 300-μs delays appears as a percentage difference between the activities in the two. An ITD of 100 and 200 μs (Fig. 13.4A) increases neural activity by 16%, whereas the increase between ITDs at 200 and 300 μs is only 1%. At 1300 Hz, the count-comparison scheme becomes more ambiguous, that is, activity increases by 7% between a 100- and 200-μs ITD, but decreases by 11% between a 200- and 300-μs ITD. For these animals, under such stimulation conditions, a slope/count comparison scheme leads to an ambiguous code.

Although the measured ITD functions can produce ITD discriminability (Fitzpatrick et al. 1997; Skottun 1998; Shackleton et al. 2003) that matches or approaches that seen in humans, under similar behavioral testing conditions rabbits, gerbils, kangaroo rats, and guinea pigs show poorer localization ability than humans and the cat (Heffner and Heffner 1985, 1987, 1988a,b; Heffner 1997). This brings into question the processing capabilities of different animals, our inability to assess properly their ITD acuity, or our focus on neural codes that do not correlate with their behavioral acuity.

The controversy over whether the system uses the slopes or peaks of the ITD function centers around peak-type responses, as these features are within or close to the physiological delays an animal would experience. In contrast, the peaks of trough-type neurons almost invariably occur outside the animal's physiological range and their troughs show little, if any, modulation over this range. These features suggest that troughs are unlikely to play a role in sound localization. A proposed role for trough-type neurons rests on the idea that the maxima of peak-type and peaks of trough-type neurons formed a continuous ITD axis (Fig. 13.3) (Fitzpatrick et al. 2000, 2002). The ITDs of peak-type neurons fell within the physiological range and therefore may participate in sound localization, whereas the peaks of trough-type neurons occurred outside and could be used for analysis of features such as the spaciousness of the acoustic environment (Batra et al. 1997b).

2.5. *Mechanisms to Generate Interaural Delays*

The Jeffress circuit model for ITD sensitivity accounts for many aspects of the psychophysics, and several of its tenets such as coincidence detection and characteristic delay are well supported by the physiological data. In the owl and chick, there is excellent evidence that the anatomical substrate for a delay line exists and, although apparently different in these two birds, that it operates much as Jeffress envisaged (Konishi et al. 1988; Rubel and Parks 1988; Carr and Konishi 1990; Carr 1993). However, the evidence for a delay-line system in mammals is more equivocal. This issue has been addressed by reconstructing the paths of axons to the MSO; however, the difficulty of these confirmatory experiments means that even those few reports (Smith et al. 1993; Beckius et al. 1999) are neither comprehensive nor, unfortunately, entirely convincing. There are several ways in which the necessary delays could arise such as graded length collaterals on both sides, graded axon lengths on both sides, or graded

collaterals or axons on only one side (Beckius et al. 1999). Both studies show evidence that axons that could provide the necessary graded delays and both conclude that the anatomical substrate for a delay line system is present in the cat.

Another method of generating interaural delays that does not involve axonal length variation was proposed by Schroeder (1977), expanded and formally modeled by Shamma et al. (1989), then by Bonham and Lewis (1999) and Shackleton et al. (2000), and investigated physiologically (Joris et al. 2005). Phase changes created by the conduction time of the activity along the basilar membrane to different frequencies are used directly by mismatching the best frequencies of the inputs to the coincidence detectors from each ear. Cross-correlation functions between auditory nerve fibers with different best frequencies have delays that vary in appropriate ways and over suitable ranges to account for ITD sensitivity measured in the IC (Joris et al. 2005).

Another way of generating interaural delay exists (Brand et al. 2002). Blocking inhibitory inputs to MSO neurons shifted the BD toward 0 ITD. They proposed that inhibition rather than axonal delay accounts for the empirically observed CD. The phase-locked, but ITD-insensitive inhibition shifts the peak of the ITD curve from 0 to about 1/8 of the period of the best frequency tone, thus providing the dependence of BD on best frequency. In support of this role for inhibition, in neonatal animals all BDs are near 0 ITD and they move away from 0 with development, unless deprived of spatial information (Seidl and Grothe 2003). Together, these studies suggest that in some species ITDs at low frequency may not be processed by a delay-line system, but rather an inhibitory input to MSO tunes the BD away from 0 ITD and optimally positions the slope in the physiological range.

2.6. *Tuning to Interaural Time Delay*

The ITD tuning widths systematically narrow at progressively higher stations along the auditory pathway. This frequency-by-frequency narrowing (Fig. 13.5A) appears in the composite curves (Fig. 13.5B) for the SOC, IC, and auditory thalamic neurons in the unanesthetized rabbit, all at 70 dB SPL. Equating for frequency range across structures (300 to 1000 Hz), the mean widths decreased 25% between the SOC and IC, and the total sharpening between the SOC and auditory thalamus was 50%.

For peak-type neurons, the widths of the peak of their composite curves decreases between the SOC and auditory thalamus, but for trough-type neurons, their widths remain relatively constant above the SOC (Fig. 13.5B). The widths in the SOC are probably overestimated because ITD sensitivity in this sample was not seen $>$1000 Hz, whereas in the samples at higher structures, many neurons had ITD sensitivity to 1500 Hz and more (Fig. 13.5A). With this caveat the decrease in peak width was 35% between the SOC and IC and, like the peak-widths by frequency (Fig. 13.5A), the total extent of sharpening in peak width from SOC to thalamus was 50%.

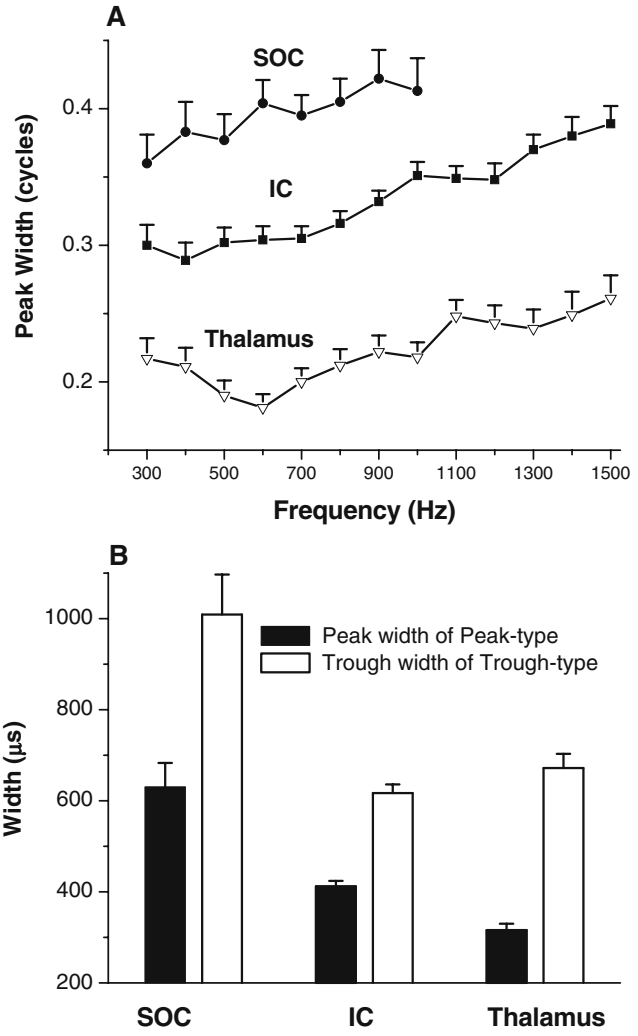

Figure 13.5. Peak width of ITD functions for neurons in the SOC, IC, and auditory thalamus as measured 50% from maximal discharge. **(A)** Peak width in cycles of interaural phase as a function of stimulus frequency. **(B)** Peak width (μs) of composite curves of peak- and trough-type neurons.

Such sharpening of ITD functions could be due to many mechanisms (Kuwada et al. 1997). For example, inhibitory, peak-type inputs from the ipsilateral dorsal nucleus of the lateral lemniscus (DNLL) could interact with excitatory peak-type MSO inputs to create sharper peak-type IC responses, or inhibitory, peak-type contralateral DNLL inputs interacting with excitatory peak-type inputs from the opposite MSO could create an asymmetrical, sharper ITD function

(Fig. 13.1C). Similar sharpening could be created by peak-type inputs from the contralateral IC. Although this projection appears to be excitatory, it could sharpen if it acted through inhibitory interneurons. Other candidates are inhibitory, trough-type LSO or DNLL inputs interacting with excitatory, peak-type MSO inputs. IC sharpening may also be due to projections within the IC. Most, if not all, IC neurons display axon collaterals (Oliver et al. 1991) and 19% use γ-aminobutyric acid (GABA) (Oliver et al. 1994). Finally, sharpening may involve coincidence between similarly tuned ITD inputs converging onto an IC neuron.

Even in the auditory thalamus ITD functions are still broad and encompass about half of the physiological range of the rabbit (Fitzpatrick et al. 1997; Skottun 1998; Shackleton et al. 2003). Perhaps the auditory system uses neural ensembles, that is, a population code, to localize sound in space. A position-variable type model used to test the efficacy of the population code found that fewer neurons are required to detect ITD changes. The auditory thalamic sharpening appears optimal as further artificial sharpening degraded acuity (Fitzpatrick et al. 1997).

2.7. Dynamic vs. Static Interaural Time Delay

Many studies varied ITD in discrete steps (i.e., statically) to measure neural ITD sensitivity and early comparisons of cat static and dynamic ITD sensitivity (generated by binaural beat stimuli) revealed only small differences (Yin and Kuwada 1983). However, in gerbil, when dynamic ITD stimuli were presented that corresponded to azimuthal movement of low-frequency sound sources through restricted arcs (e.g., 90° centered at various azimuthal positions), sensitivities different from those with static ITDs emerged (Spitzer and Semple 1991, 1993). Such responses (Fig. 13.6A) show histograms locked to the cycle of repeating interaural phase modulations with the responses to the two directions shaded differently. The responses from such histograms as a function of the interaural phase difference (IPD: the ITD transformed into the phase difference for the frequency presented; Fig. 13.6B, dashed line) show the static IPD sensitivity. Some IPD values give static responses that are quite different from the same IPD presented dynamically. Furthermore, the same IPD in two different dynamic stimuli can vary from near minimum to near maximum discharge. In the extreme, IPD sensitivity curves could peak at very different IPD values when the IPD was static or part of a dynamic stimulus (Fig. 13.6C). A component of the sensitivity to the direction of dynamic IPD stimuli was consistent with adaptation (McAlpine et al. 2000). However, the static/dynamic differences (Spitzer and Semple 1991, 1993) greatly exceed those found by other authors, even using similar paradigms and this may reflect species and/or anesthesia differences manifest as different strengths of GABAergic inhibition. Larger effects were seen when tonic GABAergic inhibition to ITD-sensitive cells in the guinea pig was blocked, consistent with the adaptation of excitation hypothesis (McAlpine and Palmer 2002). Thus, adapting inhibitory inputs seem to be also required.

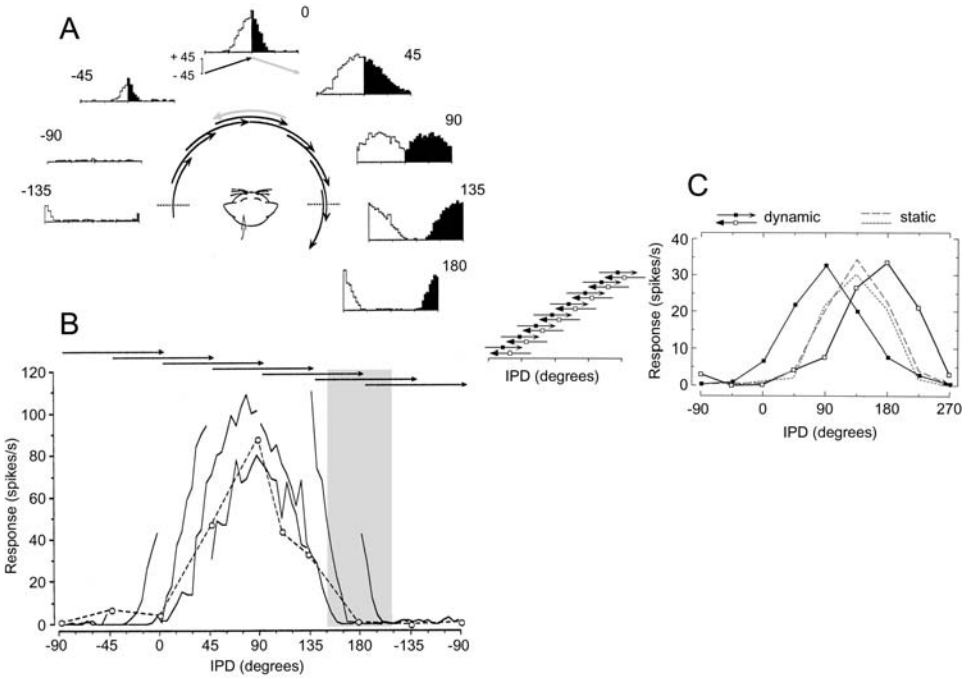

Figure 13.6. Dynamic and static ITD sensitivity compared. IC neural responses to static and dynamic variation in interaural phase difference (IPD). **(A)** The *curved arrow* shows the simulated movements generated by the phase modulations. The *unfilled bins* in the histograms show the response during clockwise motion and the *filled bins* the response during the motion in the opposite direction (center IPD values shown). **(B)** Response as a function of IPDs computed from the histograms in **(A)**. *Dashed lines* show responses to static presentation and the *solid lines* that from the different presentations of dynamic IPD stimuli. (From Spitzer and Semple 1993). **(C)** Complete separation of the sensitivity curves to IPD when the response to specific IPDs are computed from dynamic stimuli or from static stimuli. (From M. Semple, personal communication.)

3. Processing Interaural Time Delays in Envelopes of High-Frequency Sounds

Humans can resolve small differences in ITDs conveyed by the fine structure of sinusoids for frequencies to about 1200 Hz. Beyond this, ITD sensitivity decreases rapidly and disappears >1400 Hz (Zwislocki and Feldman 1956). However, if the sound is amplitude modulated, ITDs are detected at much higher frequencies by using the ITDs in the envelopes of complex, high-frequency sounds (Leakey et al. 1958; David et al. 1959; McFadden and Pasanen 1976; Nuetzel and Hafter 1976; Bernstein and Trahiotis 1985a,b, 1994). Neurons sen-

sitive to ITDs in envelopes exist at many auditory stations (SOC: Yin et al. 1984; Yin and Chan 1990; Joris and Yin 1995; Joris 1996; Batra et al. 1997a,b; IC: Crow et al. 1980; Batra et al. 1989, 1993; auditory cortex: Fitzpatrick et al. 2000). The mechanism underlying envelope ITD sensitivity is similar in principle to that for low-frequency tones, beginning with envelope coding (discharges phase- or temporally locked to the envelope frequency) in the auditory nerve (Joris and Yin 1992) that is transmitted to cochlear nucleus bushy cells. These inputs converge onto the binaural SOC neurons that use a coincidence mechanism to become optimally tuned to a particular ITD.

3.1. Types of Envelope Interaural Time Delay Sensitivity and Their Frequency Distribution

The types of ITD sensitivity for low-frequency tones (peak-, trough-, and intermediate-type; Figs. 13.1 and 13.2) are also seen in the envelopes of amplitude-modulated, high-frequency tones (Batra et al. 1997a,b; Fitzpatrick et al. 2000, 2002), although ITD sensitivity in envelopes differs from that to tones: its lower and upper frequency limits are much lower (Fig. 13.7). In the rabbit, ITD envelope sensitivity begins at around 25 Hz (the lowest frequency tested) and the optimal frequency is approximately 150 Hz. In contrast, tone sensitivity begins at about 200 Hz (in the guinea pig <100 Hz) and the optimal frequency is nearly 900 Hz (Fig. 13.3). The frequency region where this encoding declines corresponds to the point where most neurons respond to envelopes. Combining tones and envelopes, ITD sensitivity extends from 25 to 2000 Hz.

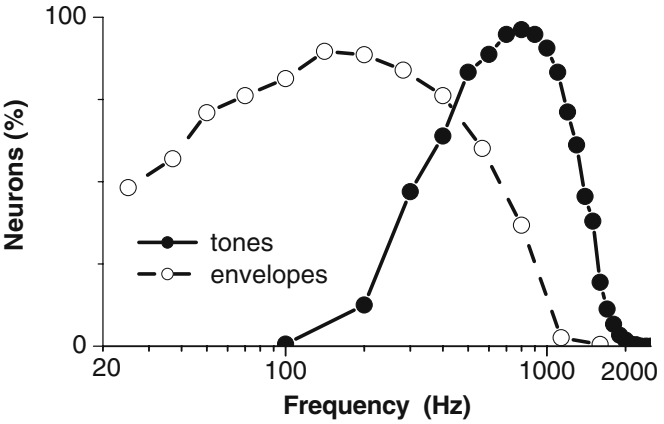

Figure 13.7. The ranges of carrier and modulation frequencies over which rabbit IC neurons were sensitive to ITDs. Each point is the percentage of cells that showed ITD sensitivity at a tonal or modulation frequency. By using both tones and envelopes the frequency range is continuous from 25 Hz (the lowest modulation frequency tested) to about 2000 Hz.

Most neural and psychophysical studies used higher carrier frequencies in ITD envelope studies than those used to study ITD sensitivity to sound fine structure. Neurons with ITD sensitivity to fine structure and those preferring envelopes overlapped over a common range of best frequencies (Joris 2003). These findings are in accord with a model using normalized interaural correlation and with human data showing that envelope sensitivity occurs at a far lower carrier frequency than the best tonal ITD sensitivity (around 1300 Hz). The transition of ITD sensitivity in the fine structure to that of envelopes approximates a low-pass filter with an approximately 425 Hz cutoff (Bernstein and Trahiotis 1996a,b).

3.2. Coding of Envelope Interaural Time Delays

This broad ITD tuning suggests that at low envelope frequencies response modulation is nearly negligible over the physiological ITD range, leading to the speculation that envelope ITD sensitivity is a manifestation of dynamic interaural level sensitivity (Joris and Yin 1998). Envelope sensitive neurons, especially those that are trough-type, can have BDs far beyond the animal's physiological range. Such BDs could be activated by low interaural correlations from sound reflections in a reverberant environment. These neurons may not be involved in sound location per se, but in analyzing the properties of the auditory space. Based on the broadness of ITD functions evoked by envelopes, behavioral ITD sensitivity is predicted to be poor. Surprisingly, human listeners detect changes in the ITDs in envelopes <200 μs for a sinusoidal envelope of 64 Hz and even less for a 64-Hz "transposed" envelope that provides the high-frequency channels with information similar to that available in low-frequency channels (Bernstein and Trahiotis 2002, 2003). Models using normalized interaural correlations are in accord with such behavioral acuity as are neural studies showing high sensitivity to changes in interaural correlation (Yin et al. 1986b).

4. Processing of Interaural Level Differences

4.1. Types of Interaural Level Difference Sensitivity

The first major site of binaural interaction takes place in the superior olive in the brain stem. LSO neurons receiving excitatory input from one ear and inhibitory input from the other are sensitive to ILDs (Goldberg and Brown 1969). As the inhibition (I) is from the contralateral ear and the excitation (E) is ipsilateral, such cells are IE. Owing to the crossed projection to the IC from the high-frequency part of the LSO, at higher levels of the auditory pathway the cells responsive to ILDs are designated as EI (excited contralaterally and inhibited ipsilaterally). Two different and largely complementary stimulus paradigms are used to investigate ILD sensitivity. In one, the contralateral stimulus is held at a constant level while the ipsilateral stimulus level is varied (excitatory mon-

aural intensity constant: EMI). For EI cells this method reveals the inhibitory effects of ipsilateral stimulation. A second paradigm varies the levels at the two ears symmetrically in opposite directions to provide ILD variations about an average binaural intensity level (ABI–constant). This better mimics ILD variation as a sound source traverses azimuthal positions, increasing level at one ear as it decreases at the other (Irvine 1986, 1991).

Most EI cells in the IC with monotonic rate-level functions to monaural, contralateral sounds have a stereotypical sigmoid-shaped sensitivity to ILDs with EMI or ABI (Fig. 13.8A). The response is maximal over an ILD range at which

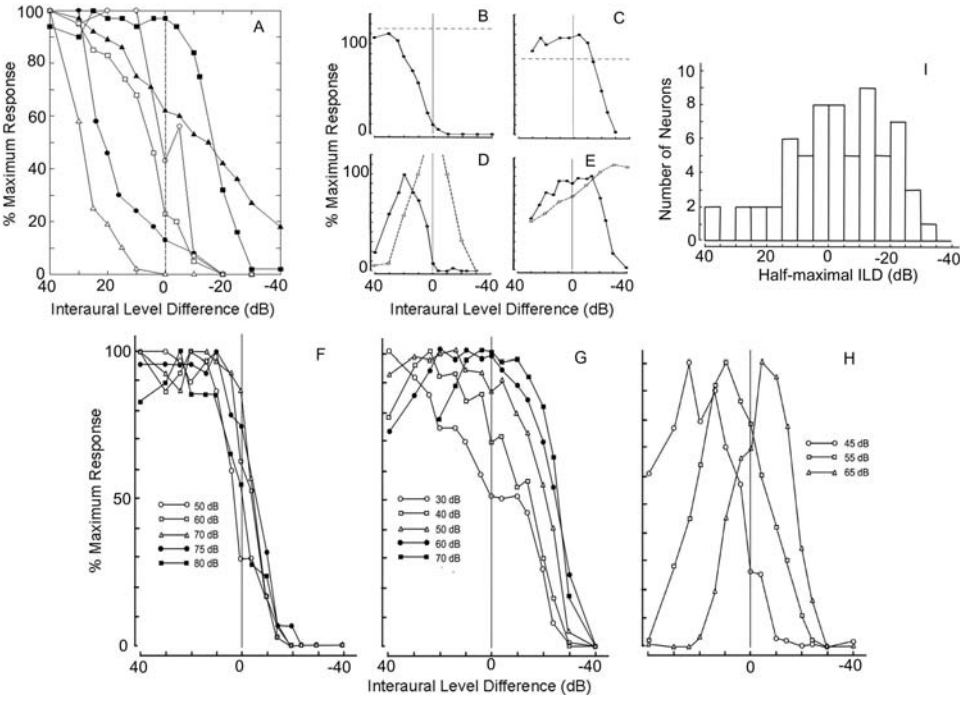

Figure 13.8. Types of ILD curves and their distribution. **(A)** Normalized spike rate as a function of ILD for 6 IC neurons for BF tones showing the variation in the position of the half-maximum ILD value. (Modified from Irvine 1986.) **(B, C)** Normalized spike rate as a function of ILD for two cells measured using a constant BF tone at the contralateral ear (response shown as *dashed line*). **(D, E)** As for **(B, C)** for the same two neurons but measured with the average binaural intensity constant. (**B, E** modified from Irvine 1991.) **(F, G)** Normalized spike rate as a function of ITD for three cells. **(F)** A monotonic neuron whose ILD sensitivity is invariant with ABI. **(G)** A monotonic cell with a shift to the right as the ABI is increased. **(H)** A nonmonotonic unit shifts to the left with increased ABI. (**F–H** modified from Irvine and Gago 1990.) (**I**) Distribution of the half-maximal ILD values. (From Irvine and Gago 1990.)

the contralateral excitatory sound level is greatest, and it is partially or totally suppressed over ILDs at which the ipsilateral inhibitory ear is loudest. Between these extremes neural output varies directly with the ILD.

For neurons with nonmonotonic rate-level functions to monaural contralateral stimuli the ILD functions using EMI and ABI methods are usually different. The ILD function with the fixed contralateral tone may be sigmoid (Fig. 13.8B, C) whereas the ABI-derived ILD function for the same neurons is highly nonmonotonic (Fig. 13.8D, E) (Irvine and Gago 1990). Because the ABI paradigm moves from left to right in the plot (+40 to –40 dB ILD) the contralateral stimulus is declining while the ipsilateral stimulus grows, so that the ILD function is the net result of level dependent ipsilateral and contralateral influences. The responses to the contralateral stimulus (Fig. 13.8, dashed lines) show that ILD functions reflect facilitatory action of the ipsilateral input at positive ILDs, and the converse at negative ILDs, when the ipsilateral tone was louder (Irvine 1987). Mixed responses to stimulation of both ears are also reported (Irvine 1991).

Analyses of sound level variations on ILD sensitivity are available in gerbil, mustached bat, cat, and other species (Semple and Kitzes 1987; Wenstrup et al. 1988; Irvine and Gago 1990) and show that level affects all but a few neurons (Fig. 13.8F). The commonest variation as ABI increased was for the sigmoid-shaped ILD function to shift to the right, that is, for activity to encroach on the region where ipsilateral inhibition dominated the ILD function at lower ABIs (or into the ipsilateral spatial hemifield: Fig. 13.8G). More dramatic changes occur in neurons with nonmonotonic ILD functions (Fig. 13.8H) and a few cells have nonmonotonicity in their responses to ILD and to ABI (Semple and Kitzes 1987; Irvine and Gago 1990). For such neurons the maximal discharge rate is often evoked only by a limited ILD and ABI range.

4.2. Distribution of Interaural Level Differences

We do not know what aspect of ILD sensitive neural activity is important for ILD and spatial position discrimination. Perhaps ILD is encoded by a population response. As the azimuthal position of a sound source moves from the ipsilateral to the contralateral hemifield, IC neurons will first be strongly inhibited by the ipsilateral ear input, then progressively activated, and eventually saturate. A growing population of cells is activated by the variation in the position of the ILD range over which the neuron is sensitive (Fig. 13.8A). The transition region ranges between domination by the different ear inputs and is quantified as the ILD value at half-maximum output. Its distribution for cat central nucleus cells (Fig. 13.8I) spans the range of ILDs that this animal naturally experiences (Irvine and Gago 1990). Such a population code might depend only on those cells whose medial ILD borders are invariant with ABI or on a more complex representation using all information, including that on changes with ABI.

An alternative to population coding suggests that neurons have both a preferred ILD and ABI (Semple and Kitzes 1987). The position at which a cell is

maximally activated might provide an ILD place code. Although the data are limited there is evidence for a systematic variation in the position of the half-maximum ILD, moving from rostral to caudal along a single IC frequency lamina (Irvine and Gago 1990), and the ILD functions more rostrally show sharper transitions and stronger inhibition.

4.3. Mechanisms of Interaural Level Difference Sensitivity

Undoubtedly much of the initial ILD information processing takes place in the LSO, and the excitation from the ipsilateral ear and contralateral ears endows many high-frequency LSO cells with their ILD sensitivity (Goldberg and Brown 1969; Boudreau and Tsuchitani 1970; Tollin and Yin 2002a,b). However, other mechanisms clearly give rise to, or modify, the ILD sensitivity in the IC. Evidence includes deactivation of the superior olivary complex (even bilaterally) or DNLL, which does not abolish ILD sensitivity (Li and Kelly 1992a,b; Sally and Kelly 1992), and deactivation within the IC of local inhibition or of inhibitory inputs to the IC leaves some ILD sensitivity intact but can modify or abolish the ILD of many cells (Pollak et al. 2002). It is suggested that, owing to the level dependency of first spike latency, that ILD sensitivity ensues from brain stem coincidence detectors operating like the ITD-sensitive MSO cells (Jeffress 1948). Testing this model by counteracting the level dependent latency shift abolished the ILD sensitivity only in some IC and LSO cells (Irvine et al. 1995, 2001). Using virtual space stimuli, the spatial receptive fields of LSO cells are generated by their sensitivity to the ILDs in a band of frequencies around the cells' characteristic frequency; however, LSO spatial tuning accounts for only 75% of that in IC (Tollin and Yin 2002a,b). These data and the mixed facilitation and inhibition in ILD functions at the IC suggest that diverse supraolivary mechanisms shape midbrain ILD sensitivity.

5. Role of the Inferior Colliculus in Perceptual Phenomena

5.1. Binaural Masking Level Differences

The ability to detect a signal masked by a noise is strongly influenced by the relative interaural similarity between signal and masker. When a signal, identical at the two ears, is masked by a noise identical at the two ears, inverting either can achieve a 12- to 15-dB improvement in signal detection (Hirsh 1948a,b; Licklider 1948). For unmodulated tonal signals the mechanism for this binaural masking level difference (BMLD) might reside in low-level ITD-sensitive cells, because large BMLDs occur only at low frequency and BMLDs depend on the relative phase at the ears. Large BMLDs occur at higher frequencies when the signal envelope fluctuates from mechanisms analogous to those at low frequency,

but involves cells sensitive to envelope ITDs (Bernstein and Trahiotis 1992; van de Par and Kohlrausch 1997).

Early attempts to find a neural mechanism for this unmasking by comparing activity to identical noise (N0) and tone (S0) at the two ears with that to identical noise (N0) but inverted signal (Sπ) were not successful, although reduced MSO discharge to N0Sπ stimuli was consistent with coincidence detection models (Langford 1984). Subsequent studies tracking masked thresholds while varying masker or signal ITD showed greatest ITD masking for the masking noise evoking most activity (Caird et al. 1991; McAlpine et al. 1996a). Tracking methods were, however, limited to discharge rate increases, and only when full rate-level functions to the signals and fixed levels of masker noise were employed with signal detection methods did a more consistent picture emerge. IC responses to BMLD signals are entirely consistent with their ITD sensitivity to noise and tones (Jiang et al. 1997a,b; Palmer et al. 2000). In most neurons with peak or intermediate ITD functions and near-0 BD, S0 tones can be detected by increased discharge and Sπ tones by a decrease (Fig. 13.9A). These BMLDs are consistent with the psychophysics. Trough units show the inverse. Identical noises (N0) and noise inverted at one ear (Nπ) drive neurons according to their respective ITD functions and S0 tones are again detected by an increased discharge above this rate (Fig. 13.9B). Masked thresholds are obtained from rate-level functions using signal detection standard separation methods (Sakitt 1973) (Fig. 13.9A, B: arrows). Such masked thresholds for populations of neurons responding to N0S0, N0Sπ, and NπS0 signals at 500 Hz show the lowest thresholds near the signal frequency and N0S0 masked thresholds tend to be >N0Sπ (Fig. 14.9C) or the NπS0 (Fig. 14.9D). This is further emphasized by taking the average masked thresholds for different BMLD stimuli (Fig. 13.9E, F), which is smaller than that in human psychophysics. However, that N0S0 vs. N0Sπ BMLD is larger than N0S0 vs. NπS0 BMLD is consistent with the hierarchy in humans (Hirsh 1948a,b). Different neural populations contribute to detection of the tonal signal in different binaural configurations (Jiang et al. 1997a,b). The empirical neural responses to BMLD stimuli are consistent with both the type of ITD sensitivities and with the predictions from interaural cross-correlation models.

5.2. *The Precedence Effect*

This term signifies that the auditory system can discern the actual location of sound sources despite the mass of reflections and echoes that arrive soon after the direct waves strike the ears (Wallach et al. 1949). The precedence effect has been studied by presenting two brief, successive sounds through two spatially separated speakers or through headphones. The leading sound, the "conditioner," simulates the direct wavefront whereas the second, or delayed sound, the "probe," simulates a reflection or an echo. Speakers are usually placed in front of the listener and on either side of the midline, and the sound from the probe speaker is systematically delayed. Under headphones, ITDs commonly provide

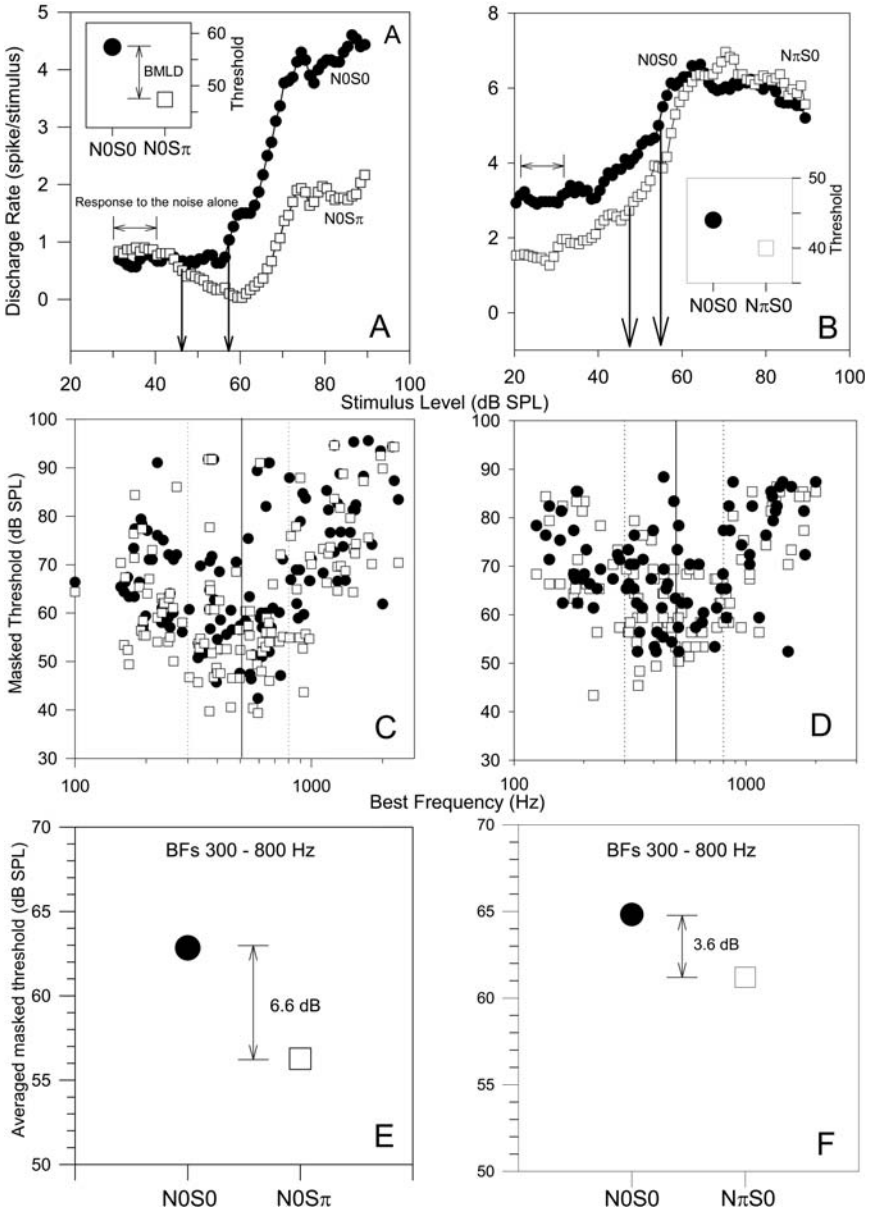

Figure 13.9. Responses of IC units to BMLD stimuli. **(A)** Rate level functions to S0 and Sπ tones at 500 Hz in the presence of N0 noise masker. The arrows show the masked thresholds determined by signal detection methods. The inset shows the value of the MLD. **(B)** As for **(A)**: rate-level functions to S0 tones at 500 Hz in the presence of N0 and Nπ noise masker. **(C)** Masked threshold for N0S0 *(filled circles)* and N0Sπ *(open squares)* for IC neurons responding to a 500-Hz tone. *Vertical line,* 500 Hz; *dashed lines,* 300 and 800 Hz. **(D)** As for **(C)** for N0S0 *(filled circles)* and NπS0 *(open squares).* **(E)** Average masked thresholds across the 300–800-Hz neurons from **(C)**. **(F)** Average masked thresholds across 300- to 800-Hz neurons from **(D)**. (Modified from Jiang et al. 1997a; Palmer et al. 2000.)

different lateralities of the conditioner and probe. Behaviorally, a sequence of perceptual events occurs as the interval between two identical sounds from different locations increases (Zurek 1987; Blauert 1983; Litovsky et al. 1999). When the "conditioner-probe interval" (CPI) is approximately 1 ms, the listener hears a single, fused auditory event and judges its location to be between the conditioner and probe. This is the window of "summing localization" and the perception follows the physical cues present from the combination of the sources (Blauert 1983). When the CPI exceeds 1 ms, the listener still hears a fused auditory perception but the location is assigned to the conditioner. This is the start of the precedence (or localization dominance) window. The end of the precedence window occurs at "echo threshold," or the CPI at which the probe is heard as a separate sound in its own location. For clicks, echo threshold occurs at CPIs ranging from 2 to 10 ms, and headphone studies have shorter values (from 2 to 4 ms) than free-field studies. Far beyond echo threshold, the probe is heard more faintly than the conditioner (Blauert 1983). Although many data have been obtained from humans, experiments in rats (Kelly 1974) and cats (Cranford and Oberholzer 1976; Populin and Yin 1998; Tollin 2003) indicate similar phenomena.

The neural basis for the precedence effect has been studied in several species and structures (Yin 1994; Fitzpatrick et al. 1995, 1999; Keller and Takahashi 1996; Parham et al. 1996, 1998; Wickesberg 1996; Litovsky and Yin 1998a,b; Wickesberg and Stevens 1998). The CPI at which the neural response to the probe is 50% of that to the conditioner (the half-maximal delay) has been used as a measure of the neuron's recovery time. Within the summing localization window (CPI $<$1 ms), IC neurons sensitive to sound-source location in cats and owls respond to "phantom images" in accord with the physical cues present during this window (Yin 1994; Keller and Takahashi 1996).

The recovery functions for neurons in the auditory nerve, cochlear nucleus, superior olivary complex, IC, and auditory cortex in unanesthetized animals show median recovery times in the first three stations that are within the precedence window ($<$3 ms). In contrast, in the IC and auditory cortex they increase to 6 and 20 ms, respectively (Fig. 13.10). Anesthesia increases the recovery times of IC and auditory cortex neurons. In the unanesthetized rabbit and behaving cat IC (Fitzpatrick et al. 1995; Tollin 2003) the median 50% recovery was near or within the precedence window ($<$10 ms) while in anesthetized cats median recovery times extend beyond (17 to 28 ms; Yin 1994; Litovsky and Yin 1998a,b). In the unanesthetized rabbit auditory cortex median recovery times are about 20 ms (Fitzpatrick et al. 1999) and those in the anesthetized cat are approximately 100 ms (Reale et al. 1995).

While the precedence effect was long thought to involve inhibitory mechanisms (Lindemann 1986) modeling studies (Hartung and Trahiotis 2001; Trahiotis and Hartung 2002) indicate that cochlear filter interactions and hair cell–based compression and adaptation account for the results of many precedence experiments, including behavioral data (Wallach et al. 1949) and neural responses (Fitzpatrick et al. 1999).

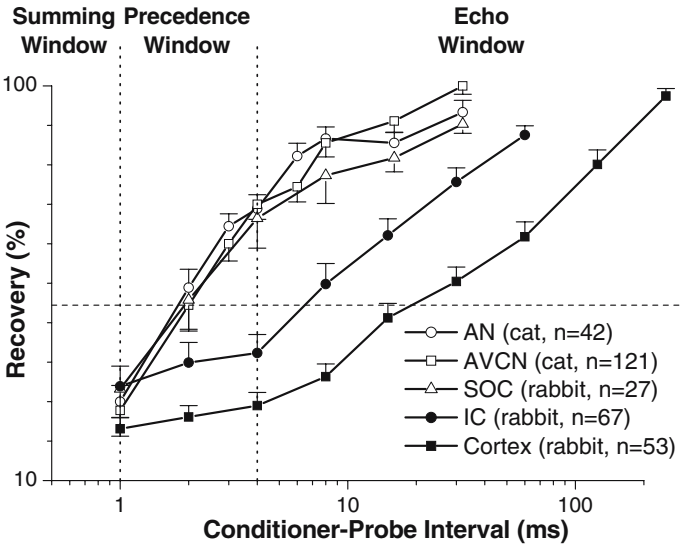

Figure 13.10. Population recovery functions to click pairs at different levels along the auditory pathway. n=Number of cells. Those from the auditory nerve (AN), AVCN, and SOC were all similar and short, with 50% recovery times of about 2 ms. By echo threshold (4 ms CPI) the recovery was near 70%. For the IC, recovery was much slower, with 50% at approximately 7 ms and nearly 40% recovery at echo threshold. In the auditory cortex the recovery was slower yet, with 50% recovery at 20 ms and 25% recovery at echo threshold. Neurons in the AN and AVCN were from an unanesthetized, decerebrate cat, and the others from an unanesthetized rabbit.

The IC and cortical neurons with long recovery times have behavioral correlates, including a reduction in the discriminability of the ITD in the probe (Shinn-Cunningham et al. 1993; Tollin and Henning 1998), and reduced perceived loudness of the probe compared to the conditioner (Blauert 1983) for a period well beyond echo threshold. Such neurons may participate in coding features unrelated to the precedence effect, for example, spaciousness or timbre. Inhibition may modulate such neurons since inactivating glycinergic (M. Paterson, personal communication) or GABAergic inhibition (Zhou and Jen 2003) can reduce IC recovery time in guinea pig and big brown bat neurons, respectively.

5.3. Binaural Pitch

Pitch not only is important for musical perception, but also is probably the strongest cue for segregation of sounds (Darwin 1997). Some pitches are created solely from the binaural cues that result when narrow frequency bands within binaurally identical noise (correlated), have a reduced correlation (i.e., decorrelation, Culling et al. 1998). Huggins pitch is a binaural pitch associated with the frequency at which decorrelation is caused by a rapid phase difference between two dichotic noise sources (Cramer and Huggins 1958). This pitch resem-

bles a binaural unmasking effect resulting from the decorrelation of activity within the frequency channels at which the phase difference occurs (Culling et al. 1998). Physiological and modeling experiments show that IC neural responses are consistent with this interpretation, showing firing rate changes and decorrelation effects consistent with the cross correlation model of binaural hearing (Hancock and Delgutte 2002). The neural responses to stimuli generating binaural pitches are entirely consistent with models of binaural cross correlation.

6. Future Directions

Detailed descriptions are now available that account for many elements of the auditory signal that are used in specific binaural contexts represented in the auditory midbrain. However, there has been much emphasis on abstracted binaural cues presented via earphones as a tool for understanding underlying mechanisms. This would seem to be a propitious point to advocate the inclusion of more ecological and realistic listening situations. The effort to link perception to the responses recorded in anesthetized animals can be taken only so far and recordings in the unanesthetized animal engaged in behaviors such as localizing may provide new and more relevant information on the brain processes underlying these behaviors. Remarkable abilities such as sound source segregation and the binding of their components into a single auditory object ultimately depend on auditory midbrain processing and require consideration of the animal's reactions to the sounds. Virtual auditory environments may represent an enabling technology to allow new stimulus paradigms and for the study of IC spatial receptive fields (Sterbing et al. 2003b). The use of individualized HRTFs is critical for accurate assessment of spatial receptive fields, which are smaller than those reported when using nonindividualized HRTFs.

Some binaural abilities will no doubt be reflected only in population measures of activation or even synchronized or correlated population activity. If so, such representations will require simultaneous monitoring of many neurons, approaches that are becoming routinely available. Finally, we encourage the use of naturally occurring and meaningful sounds and analysis of the necessarily complicated responses that are evoked. This approach will probably entail study of the auditory ecology of animal models that have proved so successful in the case of the bat and barn owl.

Abbreviations

ABI	average binaural intensity
AN	auditory nerve
AVCN	anteroventral cochlear nucleus
BD	best delay
BMLD	binaural masking level difference
CD	characteristic delay

CP	characteristic phase
CPI	conditioner-probe interval
DNLL	dorsal nucleus of lateral lemniscus
E	excitation
EMI	excitatory monaural intensity constant
GABA	γ-aminobutyric acid
HRTF	head-related transfer function
I	inhibition
IC	inferior colliculus
ILD	interaural level difference
IPD	interaural phase difference
ITD	interaural time difference
LSO	lateral superior olive
MSO	medial superior olive
Nπ	inverted noise
N0	noise
S0	signal
SOC	superior olivary complex
Sπ	inverted signal

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Chapter 14
Coding of Communication Sounds in the Inferior Colliculus

Christine V. Portfors and Donal G. Sinex

1. Introduction

Many animals, including humans, use species-specific vocalizations to convey biologically relevant information to members of the same species. These communication sounds (referred to as speech sounds in humans and vocalizations in nonhuman animals) are often complex in frequency and time. A fundamental function of the auditory system is to process these complex sounds and impart specific meanings to each sound that are important for communication behaviors. It is unclear how communication sounds are processed and represented in the auditory system, and in particular, it is unclear how these sounds are differentiated from other types of complex sounds. The majority of previous studies have examined processing of communication sounds in the auditory forebrain (Margoliash and Fortune 1992; Ohlemiller et al. 1996; Wang 2000), but the inferior colliculus (IC) likely plays an important role in the neural analysis of communication sounds. We consider the representation of communication sounds in the IC and discuss current evidence for neural specializations in the IC for encoding communication sounds.

The degree to which auditory neurons are specialized in encoding vocalizations has been debated since about 1980 (Symmes 1981). In the auditory cortex, some neurons exhibit specializations that affect the representation of vocalizations so that they are encoded differently than other types of complex sounds. These neural specializations include selectivity for the species' own vocalizations (Wang and Kadia 2001), selectivity for particular types of vocalizations (Wang 2000), reduced responsiveness to spectrally or temporally modified vocalizations (Wang et al. 1995) and experience-dependent plasticity (Wang et al. 1995). Although some specializations are apparent, it is still uncertain whether the information in vocalizations is represented in the auditory cortex by the pattern of spatially distributed activity, by subsets of highly selective, highly specialized neurons ("call detectors"), or by a combination of these mechanisms (Wang 2000; Rauschecker and Tian 2000).

In contrast, peripheral neurons do not exhibit specializations that lead to different representations of speech or vocalizations compared to other types of

complex sounds. Instead, their responses to communication sounds are largely a function of their frequency selectivity, as determined by cochlear mechanics (Robles and Ruggero 2001). For example, auditory nerve fibers respond to complex sounds with an overall temporal pattern that resembles a band-pass–filtered version of the stimulus (Sinex and McDonald 1988).

Consequently, the question arises as to where in the ascending auditory system specializations for encoding communication sounds emerge. Most studies have focused on the representation of communication sounds in the auditory cortex because the forebrain is thought to be inherently more complex than brain stem auditory nuclei (Schreiner 1998; Rauschecker and Tian 2000) and therefore a likely site for the emergence of specializations for encoding complex sounds (Rauschecker et al. 1997).

Few studies have examined responses of IC neurons in mammals to species-specific communication sounds (Aitkin et al. 1994; Klug et al. 2002; Portfors et al. 2002; Šuta et al. 2003). However, the IC, with its ascending inputs from nearly every nucleus in the caudal brain stem (see Chapters 3 to 5), and its descending (see Chapter 8) and intrinsic (see Chapters 2 and 6) connections, is a rich substrate for the integration of spectral information. This convergence of information makes the IC a plausible candidate in the representation and transformation of communication sounds. Understanding the midbrain's role will provide useful information about hierarchical processing of communication sounds in the auditory system, and clarify the species-specific neural mechanisms involved in processing of vocalizations. Moreover, studies of IC neural responses to speech sounds in nonhuman animals will increase understanding of how speech sounds are processed in the absence of linguistic experience.

A brief summary of the production and acoustic characteristics of communication sounds is followed by a review of studies of the representation of communication sounds in the IC. Contemporary studies in mammals are emphasized and the representation of human speech is considered. Finally, the prospects for future studies are discussed.

2. Acoustic Properties of Speech and Vocalizations

For simplicity, the term *vocalizations* is used to refer to the communication sounds produced by nonhuman animals, and *speech* is reserved for human sounds. The distinction is made on acoustic grounds alone. Questions about how animals use vocalizations, and the extent to which the use of vocalizations resembles humans' use of speech, are beyond the scope of this chapter and are treated elsewhere (Hauser et al. 2002).

The "source-filter theory" (Fant 1960) provides a useful framework for understanding the production and acoustic characteristics of speech and vocaliza-

tions. When these sounds are produced, air from the lungs is forced through the larynx, providing a source of energy, and resonances of the supraglottal vocal tract filter the source spectrum and shape the sound spectrum. Vocal tract resonant frequencies are determined by its physical characteristics, and by the locations and elasticity of constrictions produced primarily by the tongue, teeth, and lips.

Forcing air through vocal folds that are held close together causes them to open and close repetitively, with each opening producing a "glottal pulse." A sequence of glottal pulses produces a quasi-periodic waveform, and the rate at which glottal pulses occur determines the fundamental frequency (F0) of the sound. In speech, F0 varies between 100 and 250 Hz (Peterson and Barney 1952) whereas F0 varies much more in vocalizations, within and across species. Values range from several hundred Hertz (guinea pig: Šuta et al. 2003; macaque: Rendall et al. 1998) to several kHz (marmoset: Wang et al. 1995) to several tens of kiloHertz (mustached bat: Kanwal et al. 1994; mouse: Portfors 2003). Varying subglottal air pressure and the position and tension of the vocal folds causes changes in F0 (Borden et al. 2003). Modulations of F0 can be minimal (Fig. 14.1A) or extensive (Fig. 14.1B). The line spectrum of the glottal waveform is shaped by the transfer function of the upper vocal tract, so that the sound that is radiated from the lips may have a distinctive pattern of spectral peaks and valleys. The peaks are produced by resonances of the vocal tract, called "formants." In speech, the locations of formants vary (Fig. 14.1A) and provide powerful cues that contribute to phonetic judgments.

Nonhuman animals have much less control over the configuration of the vocal tract (Schön Ybarra 1996), so formants in their vocalizations are relatively static. However, nonhuman animals may still use the information in formants to identify individuals and body size of conspecifics (Fitch 1997).

If the vocal folds are held partially open and air is forced through a constricted vocal tract, the resulting sound will be aperiodic and may be perceived as noisy. Aperiodic segments occur in speech (Fig. 14.1A) and also in vocalizations (Kanwal et al. 1994). As with voiced sounds, the shape of the emitted spectrum reflects the spectrum of the aperiodic source and the transfer function of the vocal tract.

Speech and vocalizations also vary over time. In speech, temporal information arises because the configuration of the vocal tract rarely reaches a steady state, and one consequence is that the amplitude envelope fluctuates at a rate typically between 5 and 50 Hz (Rosen 1992). During vocalizations, vocal tract configuration is more stable, but F0 may change dramatically. In some vocalizations, short spectrally similar segments are repeated in bursts (Kanwal et al. 1994) so the temporal envelope may fluctuate at a rate similar to that of speech. Spectral and temporal changes are linked because both are natural consequences of the same movements of the articulators and changes in voicing.

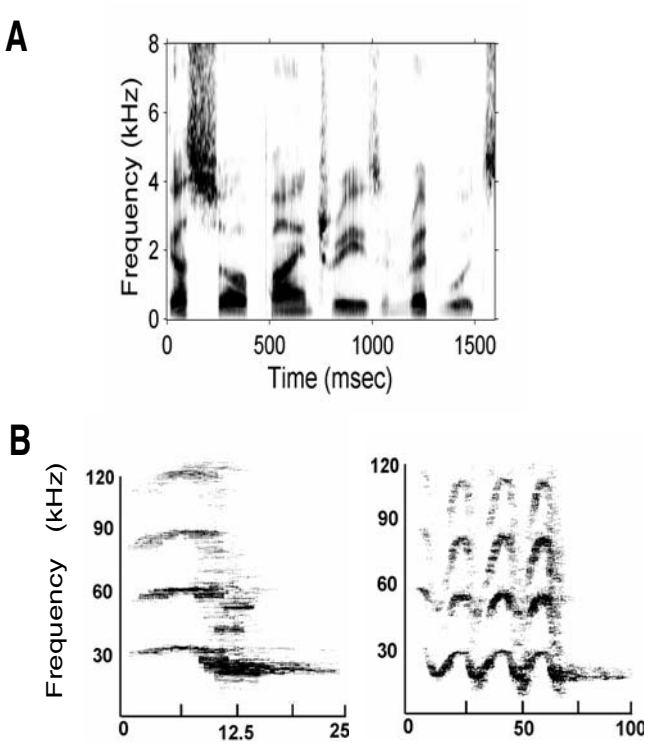

Figure 14.1. Spectrograms of speech and of nonhuman vocalizations. **(A)** Spectrogram of the sentence "Gus saw pine trees and redwoods." Acoustic properties of representative consonants and vowels can be seen. For example, the fricative consonant, /s/, produced with aperiodic excitation of the vocal tract, is characterized by a broad peak at about 5 kHz (150 to 250 ms). During vowels, formant frequencies occur at lower frequencies, and formant transitions are usually visible between segments (for example, F2, F3, and F4 rise between 800 and 900 ms, preceding the vowel /i/ in "tree"). During voiced segments, individual glottal pulses appear as vertical striations. In speech, formant frequencies vary but F0 is relatively stable, as indicated by the approximately equal spacing between glottal pulses. In vocalizations, the opposite is usually true. The sentence material is from the DARPA TIMIT Acoustic-Phonetic Continuous Speech Corpus. **(B)** Two mustached bat communication calls. The frequencies in the calls are much higher than human speech, but the calls are complex in frequency and time.

3. Representation of Vocalizations in the Inferior Colliculus

3.1. Responses to Complex Stimuli that May Underlie Processing of Vocalizations

Very few studies have explicitly examined neural responses to communication sounds in the IC of mammals, but there are many examples of responses to

complex acoustic stimuli in the IC that may underlie processing of vocalizations. Single neurons demonstrate complex response properties to spectrally and temporally complex acoustic stimuli that involve amplitude modulation (Rees and Møller 1987; Sinex et al. 2002), frequency modulation (Schuller 1979), duration (Casseday et al. 1994), and the temporal interval between stimuli (Walton et al. 1998). More than half of the IC neurons of the mustached bat (*Pteronotus p. parnellii*) show nonlinear facilitation or inhibition to the combination of two sounds in different frequency bands (Portfors and Wenstrup 1999). These combination-sensitive neurons are a distinct class (Portfors and Wenstrup 1999) and were initially described as specialized for echolocation behaviors. However, they are now thought to play a more general role in processing of spectrally and temporally complex sounds (Leroy and Wenstrup 2000).

3.2. Responses to Vocalizations in the Central Nucleus of the Inferior Colliculus

Two studies have suggested that some IC neurons in bats respond selectively to species-specific vocalizations. It is useful to distinguish between "selectivity" and "specialization" when discussing neural responses to communication sounds. Selectivity implies that the neuronal response can be reasonably well predicted based on the same cell's response to simpler sounds, whether presented alone or in combination with other sounds. Specialized responses, in contrast, are not well predicted. In the IC, neural responses to vocalizations can be fairly well predicted based on excitatory and inhibitory frequency response areas.

Excitatory frequency tuning curves of neurons in the IC of the Mexican free-tailed bat (*Tadarida brasiliensis mexicana*) were measured and their responses to 10 different vocalizations assessed (Klug et al. 2002). These responses were not well predicted by the excitatory tuning curves because most neurons responded to a subset of the vocalizations even though most of those to which the neurons were unresponsive had energy in the neuron's excitatory frequency response area. However, responses to vocalizations were much better predicted when inhibition was blocked by iontophoretic application of bicuculline or bicuculline and strychnine, which caused the neurons to respond to many vocalizations and eliminated their selectivity. These data suggest that IC neurons show selectivity to vocalizations, and that one mechanism underlying this selectivity is inhibition.

Selective responses in the IC of the mustached bat IC were also found with a two-tone paradigm to assess excitatory and inhibitory frequency response areas of single neurons, and then predict their responses to fourteen different mustached bat communication calls (Portfors et al. 2002). The benefit of a two-tone paradigm is that the sound frequencies that elicit inhibition are determined, and the neural response to a communication call can be predicted, based on whether the call has energy in the frequency range that elicits an inhibitory response. To test the frequencies of inhibition, one sound is presented at the frequency that elicits the best response from the neuron while a second sound that varies in frequency is presented (Portfors and Wenstrup 2002). Neurons with inhibitory

frequency response areas were selective to certain communication calls whereas those without inhibitory frequency response areas responded to many of the communication calls.

Neurons with inhibitory response areas too remote from the excitatory frequency area to be considered as side-band inhibition present an interesting mechanism for suppressing responses to certain vocalizations. For example, consider a neuron with a narrow excitatory frequency-tuning curve centered at 50 kHz, and with two inhibitory frequency regions that flank the excitatory response area, and a third inhibitory region centered at 19 kHz (Portfors et al. 2002). Without knowing the areas of inhibition, we would predict that this neuron would respond to all calls that had energy in the 50-kHz regions. However, this neuron actually responded to only 1 of 14 vocalizations even though other calls had energy in the cell's excitatory tuning curve. The vocalization to which the neuron responded was a three harmonic, frequency-modulated call with the second harmonic passing through the 50-kHz range. The fundamental frequency of the call never entered the low-frequency inhibitory region of the neuron. The other vocalizations either did not have energy in the excitatory region of the neuron or had energy in the low-frequency inhibitory region (18- to 23-kHz range) that suppressed the excitatory response. Therefore, inhibitory frequency response areas are effective in providing for selectivity to vocalizations in the mustached bat IC. To understand the mechanisms underlying neural selectivity to communication calls, then, it is necessary to understand how both the excitatory and inhibitory frequency response areas of neurons are organized and interact.

However, excitatory and inhibitory frequency tuning cannot explain selectivity in all neurons. Another mechanism that may provide for selectivity to vocalizations is combination-sensitive facilitation (Portfors et al. 2002) in which a neuron responded only to one call (a multiharmonic, upward frequency modulated sweep) regardless of intensity (Fig. 14.2A, B). The high selectivity could be explained by the neuron's combination-sensitive facilitatory response to pairs of tones. The neuron responded weakly to tones near 57 kHz, was unresponsive to any low-frequency tones, and responded well to the combination of a 57-kHz and a 29-kHz tone presented simultaneously (Fig. 14.2B). The vocalization to which this neuron selectively responded contained energy in both the 57-kHz and 29-kHz bandwidths and these frequency components overlapped in time. The cardinal features of this response were the weak or nonexistent response to the individual components (tones or call elements) and the robust facilitatory response to the combination of the frequency components. These features caused the neuron to respond poorly or not at all to vocalizations that had energy in only one of the frequency bands and to respond well to the vocalizations with energy in at least two of the frequency bands, as long as the spectral components of the vocalization were in the proper temporal relationship. Thus, the combination-sensitive properties of some mustached bat IC neurons provided for selectivity to particular vocalizations.

Interestingly, mouse IC neurons also show inhibitory and facilitatory combination sensitivity (Portfors 2003) suggesting that neural selectivity to species-specific vocalizations may occur in species other than bats. In contrast, however,

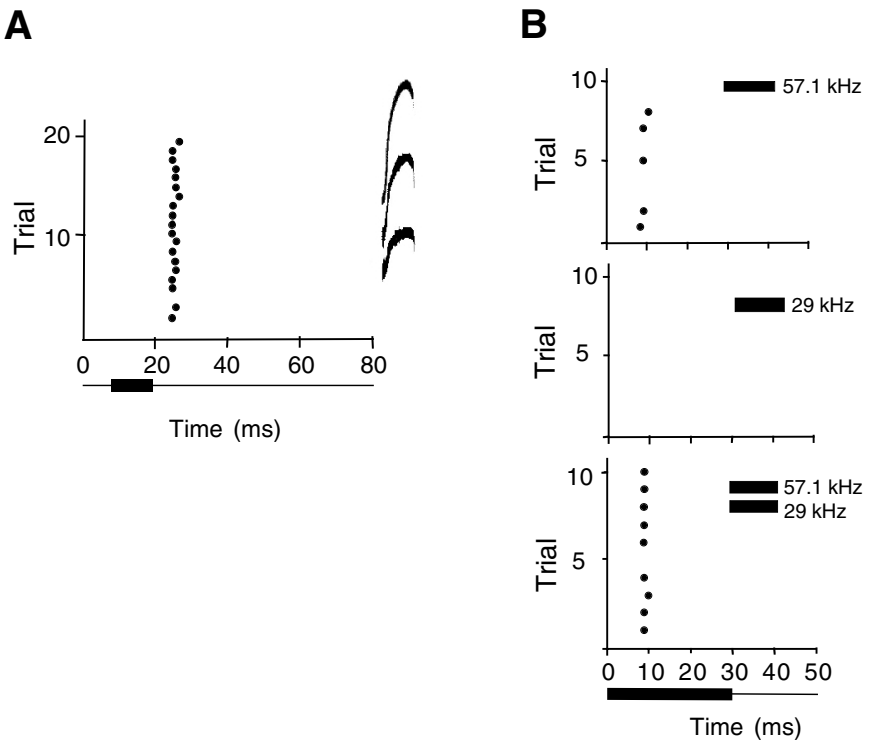

Figure 14.2. Responses of an IC neuron illustrating that combination sensitivity can explain some neuronal selectivity to social vocalizations. **(A)** Raster plot of the neuron's response to its preferred vocalization (a three-harmonic, upward frequency modulated sweep as shown in the figure). **(B)** Raster plots show that such response selectivity may be explained by the neuron's response to single tones and combinations of tones. The cell responded weakly to a 57.1-kHz tone alone, did not respond to a 29 kHz tone, and was strongly facilitated by the combination of the tones. The facilitatory frequency tuning explains the neuron's selectivity to vocalizations because only one vocalization had sufficient energy in both of the facilitatory frequency bands in the appropriate temporal relationship to elicit a strong response. *Black bars* under raster plots indicate onset time and duration of stimulus.

are other findings that guinea pig IC neurons showed little selectivity to four vocalizations (Šuta et al. 2003). Most neurons responded to all the vocalizations, but they did show some selectivity in that they preferred vocalizations to pure tones or noise bursts. The temporal firing patterns matched the sound envelope of the vocalization, suggesting that the neurons encoded the spectrotemporal aspects of the vocalizations. The reasons for different findings between species are unknown.

An important aspect of encoding of vocalizations in the IC is that individual neurons showed different selectivity to vocalizations both in terms of how many

vocalizations elicited a response from each neuron and the particular vocalizations eliciting a response. It has been suggested that because neurons show different types of selectivity, each vocalization should evoke a unique pattern of activity across the population of IC neurons, and this activation should be greater than if the individual IC neurons showed no selectivity (Klug et al. 2002).

3.3. Responses to Vocalizations in Other Inferior Colliculus Subdivisions

When the responses of neurons in all IC subdivisions of the cat IC to four different vocalizations were recorded, many cells responded more vigorously to vocalizations than to tones, in particular neurons in the external nucleus (EN), but they were not selective for individual vocalizations. Instead, the increased response to vocalizations appeared to reflect a general preference for broadband sounds (Aitkin et al. 1994). The authors proposed that the EN neurons strongly preferring vocalizations might be part of a premotor pathway involved in the initiation of vocalization. Further studies will be required to substantiate this idea.

4. Representation of Speech in the Inferior Colliculus

Few reports of the representation of selected speech sounds by IC neurons in the anesthetized cat are available (Watanabe and Sakai 1978; Delgutte et al. 1998). In both studies, envelope information was prominently represented by IC neurons. In one study the discharge rate of auditory nerve fibers and cochlear nucleus neurons generally followed the envelope of the speech in the frequency band near the neurons' characteristic frequencies (CFs). In contrast, IC neurons responded phasically to the same stimulus, with activity restricted to the onsets of syllables and the release bursts of stop consonants. Quantitative comparisons of spectral properties of the speech to discharge patterns were not reported, but the findings suggest that IC neurons provide a good representation of temporal cues (Delgutte et al. 1998).

A series of studies of the representation of consonant–vowel syllables differing in voice-onset time (VOT) has been carried out in the chinchilla IC (Chen et al. 1996; Chen and Sinex 1999; Sinex and Chen 2000). VOT is the delay between the release of a stop consonant and the onset of voicing, and it determines the identity of stop consonants such as /d/ and /t/ that are produced at the same place of articulation (Lisker and Abramson 1964). Small changes in VOT near the /d/-/t/ perceptual boundary are highly audible, but larger changes away from the boundary are not (Abramson and Lisker 1970). This finding, coupled with the observation that chinchillas exhibit psychophysical acuity for VOT that is quantitatively similar to that of humans (Kuhl 1981), led to the hypothesis that certain sounds are advantageous for vocal communication be-

cause they naturally elicit distinctive responses in the mammalian auditory system (Kuhl 1986). Studies of the neural representation of VOT continua were undertaken in the chinchilla to determine how these sounds are processed in the absence of confounding linguistic experience. That is, the goal was explicitly to examine nonspecialized processing of acoustic cues for consonant voicing.

Examples of the representation of syllables differing in VOT are shown in Fig. 14.3. The top row shows waveforms of syllables with VOTs of 30 and 70 ms, heard by humans as /da/ and /ta/, respectively. The responses of an IC neuron to two syllables (Fig. 14.3, bottom row) can be compared to those of an auditory nerve fiber with the same CF, 0.8 kHz, to the same syllables (Fig. 14.3, middle row). The IC neuron responded phasically at the onset of voicing in each syllable and also exhibited a less obvious response to the steady-state vowel. In contrast,

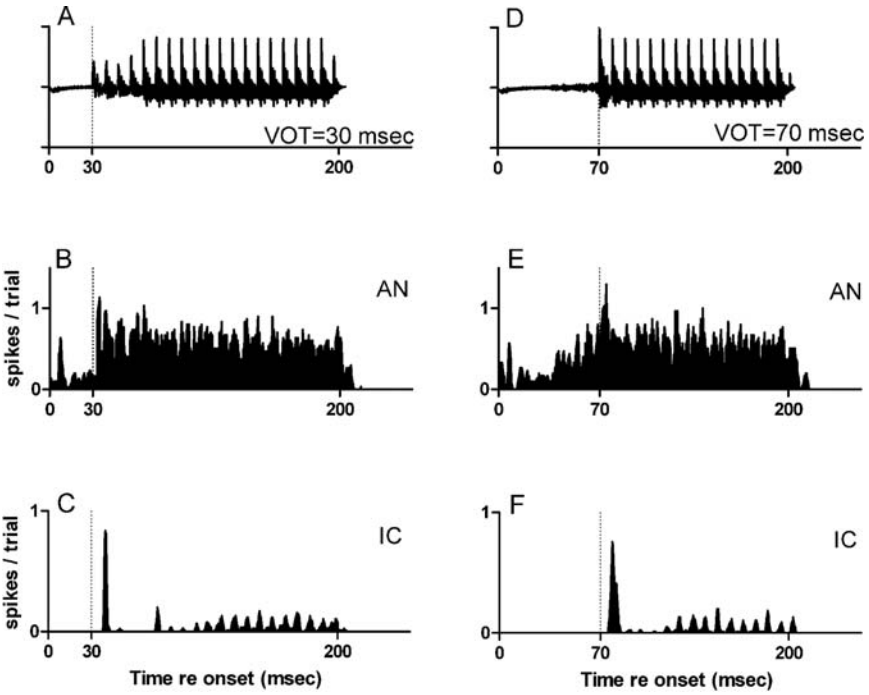

Figure 14.3. Responses to syllables differing in VOT. VOT is indicated in each panel by a vertical dashed line. **(A)** Waveform of a synthesized syllable with VOT of 30 ms. The syllable is heard as /da/. **(B)** Discharge pattern of a chinchilla auditory nerve fiber to the syllable shown in **A**. Fiber 8713-66; CF: 0.8 kHz; threshold: 11 dB SPL. **(C)** Discharge pattern of a chinchilla IC neuron to the syllable shown in **A**. Neuron 9311-78; CF: 0.8 kHz; threshold: 25 dB SPL. **(D)** Waveform of a synthesized syllable with VOT = 70 ms. The syllable is heard as /ta/. **(E)** Discharge pattern of the same auditory nerve fiber shown in **(B)**, for the syllable shown in **(D)**. **(F)** Discharge pattern of the same IC neuron shown in **(C)**, for the syllable shown in **(D)**.

the auditory nerve fiber discharged additional spikes at the release of the syllable, and higher sustained discharge rates throughout the vowel. Clearly, the representation of the onset of voicing was less precisely marked by the peripheral neuron.

The characteristic discharge patterns of individual IC neurons to VOT syllables reflect the acoustic properties of the syllable but are strongly affected by characteristics of individual neurons such as frequency selectivity, threshold, the temporal pattern of responses to steady-state tones, and binaural sensitivity (Chen et al. 1996; Chen and Sinex 1999). Because neurons with similar CFs differ in these other characteristics, the same syllable may elicit a range of discharge patterns, and IC neurons do respond in complex ways to changes in VOT. For example, some low-CF neurons represent VOT nonmonotonically, showing higher discharge rates for the syllables with intermediate VOT for which psychophysical acuity would be highest (Chen and Sinex 1999). Discharge rates of individual auditory nerve fibers do not vary as strongly with VOT (Sinex and McDonald 1988), suggesting that this difference is a consequence of more complex spectral integration at the level of the IC.

5. Conclusions

The studies reviewed here are consistent with the view that the processing of communication sounds is organized in a hierarchical fashion (Rauschecker et al. 1997). Responses observed in the IC are generally more complex than those in the peripheral auditory system (Sinex and McDonald 1988; Chen et al. 1996; Delgutte et al. 1998) but appear less complex than the cortical representation (Ohlemiller et al. 1996; Esser et al. 1997). There is also a suggestion that, in the bat and perhaps in other species with stereotypical vocalizations, some IC neurons have intricate patterns of spectral and temporal integration that are especially well matched to the acoustic properties of the species-specific vocalizations (Portfors et al. 2002; Portfors 2003). The generality and significance of combination sensitivity for the processing of vocalizations in other species should be evaluated in future studies to elucidate the extent of common neural mechanisms across nonhuman species.

In nonhuman vocalizations, the range of sounds that may occur is far more restricted than is the case with speech. When individual vocalizations are somewhat stereotyped, and there are limits to the number of different sounds that must be processed, strategies such as combination sensitivity may be very efficient. Although there have been suggestions that combination sensitivity may contribute to the processing of speech sounds (Suga 1996; Sussman et al. 1998), it is not clear that the same strategy would be as effective for representing the phonetic elements of speech in a sound-selective way. This is because the range of sounds that occur in speech is enormous. There are only modest constraints on the possible relationships between elements such as formant frequencies for

an individual talker, and even greater variation exists across talkers and languages. Thus, it seems unlikely that combination-sensitive neurons that can encode each potential variation exist, at least at the level of the IC. If some form of combination sensitivity does exist in higher structures, at or beyond the primary auditory cortex, it seems likely that the properties of those neurons might be language dependent. That is, experience with one's native language may alter the selectivity of neurons (cf. Wang et al. 1995), such that some sounds are encoded more effectively and some less effectively. Previously we noted that studies of the representation of speech in nonhuman animals are most useful for addressing the role of mechanisms that are not species-specific and not language dependent. Thus, if combination-sensitive processing does occur in the human, imaging studies of extraordinary resolution will likely be required to reveal them.

6. General Issues and Future Considerations

6.1. Species-Specific Differences and Similarities

Selectivity to species-specific vocalizations in the mammalian IC has been found only in bats. Responses in the cat IC to vocalizations are more complex than responses to tones, but there is little evidence of specific neuronal selectivity to particular vocalizations (Aitkin et al. 1994). Similarly, responses in the guinea pig IC show little selectivity to vocalizations (Šuta et al. 2003). This may be a valid species-specific difference or may reflect the choice of vocalizations presented or the experimental paradigm. Only further experiments in other species will resolve these questions. An important consideration, however, is the choice of vocalizations used as stimuli. To dissect critically how the IC encodes species-specific vocalizations and determine the extent of neural selectivity and/or specializations, a full array of vocalizations should be explored as stimuli. This includes all the different categories of calls in a species' repertoire and also sufficient calls per category to counterbalance the variability seen in the repertoire of calls emitted, both within and between individual animals. Presenting only a few "exemplar" calls as representative stimuli may provide a misleading impression of both neural selectivity and specializations in the IC.

As shown in both species of bats, excitatory and inhibitory frequency response areas are important in providing for selectivity to vocalizations, and it is expected that these features of frequency tuning will also be important in other species (Portfors 2003). The importance of combination sensitivity as a mechanism for selectivity in species other than the mustached bat is unclear. Although there is evidence of nonlinear interactions in the response properties of cat (Escabí and Schreiner 2002) and Mexican free-tailed bat (Klug et al. 2002) IC neurons, the appropriate tests to investigate combination sensitivity have not been done. In the mouse IC some neurons are combination sensitive (Egorova et al. 2001;

Portfors 2003), but their role in selectivity for vocalizations is unclear. Certainly assessing the excitatory, inhibitory, and facilitatory frequency response areas of IC neurons on a more secure comparative basis will increase our understanding of the mechanisms underlying midbrain selectivity to species-specific vocalizations.

6.2. *Selectivity for Vocalizations vs. Specialization for* Vocalizations

The evidence supporting the idea of neural selectivity to communication calls in the IC suggests that the neural responses to communication calls could be predicted reasonably well from their discharges to simpler stimuli. This implies that the responses are selective, but not specialized, for encoding species-specific vocalizations.

There is little consensus about the degree to which central auditory neurons are specialized for vocalizations, and this is partly a reflection of the difficulty in determining what a nonspecialized response should look like. Neurons in the IC certainly exhibit selectivity for vocalizations, but to claim that the neuron is specialized, it is first necessary to establish which response patterns could have been predicted given adequate information about the same neuron's responses to simpler sounds. Thus, "adequate" information should be obtained when assessing responses to complex sounds. This could include measures of (at least) the form of the temporal discharge pattern elicited by a pure tone, the distribution of responses to tone pairs, and temporal interactions such as the spectrotemporal receptive field (STRF, Escabí and Schreiner 2002). For example, some IC neurons show excitatory or inhibitory combination sensitivity that affects their responses to vocalizations. If combination sensitivity had not been documented, the response of such neurons might mistakenly have appeared to express specialization for vocalizations rather than selectivity. Similar misinterpretations could potentially be made for neurons with excitatory–inhibitory temporal interactions of the type revealed by the STRF. The current perspective suggests that IC neurons are selective for vocalizations, but not specialized. If stronger claims for specialization are to be made in the future, they should be supported with correspondingly extensive and rigorous measurements with simpler sounds.

Abbreviations

CF	characteristic frequency
F0	fundamental frequency
IC	inferior colliculus
STRF	spectrotemporal receptive field
VOT	voice-onset time

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Chapter 15
Acoustic Behavior and Midbrain Function

Tom C.T. Yin and Bradford J. May

1. Introduction

This chapter provides an overview of the role of the central nucleus of the inferior colliculus (ICC) in auditory behavioral tasks. This question must be addressed to understand the function of this large structure. The substantial literature on the anatomy, physiology, and pharmacology reflect its importance as a nexus for ascending and descending auditory information processing.

A primary goal is to relate these anatomical and physiological properties of the ICC to acoustically dependent animal behavior. For this, studies of the ICC that incorporate behavior are critical and must address the relationship between neuronal activity and behavior. Given the difficulty in quantifying behavior in animals and recording neural activity in humans, many early studies related human psychophysics to recordings from anesthetized animals (Siebert 1970). This is not an ideal combination, as the behavioral "function" of a neuron in the awake brain and anesthetized brain is different. These ambiguities are compounded when the animal's auditory behavioral ability is unknown.

Traditionally, the behavioral function of neural tissue has been inferred from the effects of activation (electrical stimulation in intact animals) or inactivation (lesions or cooling) on neurons. Such manipulations, although useful, are constrained by the virtual impossibility of electrically stimulating neurons with naturalistic stimuli and because lesions cause loss of neurons but also elicit compensatory responses in the brain.

The development of techniques to record from neurons in awake, behaving animals, particularly in the visual system, has enabled striking advances in relating neural activity with behavior. Major advances in understanding include the neural basis for saccadic eye movements (Wurtz 1996; Sparks 2002), the linkage between single-cell responses and visual motion perception (Parker and Newsome 1998), the neuronal substrate for directed visual attention (Maunsell and Cook 2002), and neuronal processing of intended movements (Andersen and Buneo 2002). Studies in the somatosensory system have related single-neuron discharges to the perception of vibration (LaMotte and Mountcastle 1975; Vallbo and Johansson 1984). Deciphering the relationship

between perceptual state and neural activity is a central goal of modern neurobiology.

Unfortunately, the auditory community has lagged behind the visual and the somatosensory communities in relating neural activity and behavior in animals. It was noted that "Remarkably, we have been unable to identify studies of the auditory pathways in which neural signals have been measured at the same time as the subject is performing at near-threshold levels in a detection or discrimination task" (Parker and Newsome 1998, p. 260). The few behavioral studies of the ICC and its input systems from a functional point of view limit our understanding of its function.

This chapter summarizes experiments that have been directed toward the functional organization and processing in the ICC with respect to behavior, sound localization, and on the coding of localization cues. Classically, the duplex theory posits that the important cues for sound localization are interaural time and level disparities (Rayleigh 1907). Since about 1980 it has become clear that additional cues are necessary for localization in elevation, as can be readily appreciated by considering localization of sources that vary in elevation along the midsagittal plane, where interaural cues are minimal. The spectral filtering by the head, shoulders, and external ears is now considered important for localization in elevation (May 2000) while the interaural cues are critical for azimuthal localization (Yin 2002).

2. Sound Localization and the Inferior Colliculus

2.1. Contralateral Encoding of Space

Most mammalian sensory and motor systems are organized in a contralateral fashion: the left brain receives input from the right side of the body and extrapersonal space, and controls the muscles on the right side of the body. This contralateral representation is documented in the visual, somatosensory and skeletal motor systems, for example, the precise partial decussation of fibers at the optic chiasm, such that the right side of visual space is projected to the left lateral geniculate body and visual cortex, is well known. That the auditory system follows a similar contralateral representation is less obvious but not unexpected.

However, the auditory system differs markedly from the visual and somatosensory systems in the manner in which space is encoded. In vision and touch the spatial location of the stimulus is naturally encoded by receptor location: the retinal map of the visual field and the somatosensory receptors in the skin are naturally topographically arranged. Retinotopic and somatotopic organization is preserved in both systems by the anatomical projections at successive nuclei to the sensory cortices, and in both systems there is a precise projection of the appropriate fibers across the midline such that the cortex has a topographical representation of the contralateral visual field and body.

On the other hand the auditory system initially encodes frequency, not spatial location. The auditory system must compute the location of the stimulus based on the interaural cues of time, intensity, as well as spectral cues. The result of this neuronal computation also provides for a contralateral representation of auditory space.

2.2. *Coding of Interaural Localization Cues*

2.2.1. Interaural Time Disparities

It has been known since about 1900 that the interaural time (ITD) and interaural level differences (ILD) of sounds in free field provide the critical cues for localization of sound sources along the horizontal dimension (Rayleigh 1907). Numerous studies have shown that ITDs are first encoded by cells in the medial superior olive (MSO; Goldberg and Brown 1969; Yin and Chan 1990), which receives bilateral input from the spherical bushy cells of the anteroventral cochlear nucleus (AVCN; Fig. 15.1A; Warr 1966; Tolbert et al. 1982; Cant and Casseday 1986; Smith et al. 1993). Cells in the MSO project to the ICC so that ITD sensitivity is also a common feature of low-frequency ICC cells (Rose et al. 1966; Kuwada and Yin 1983). The physiological properties of these cells are described in more detail elsewhere (see Chapter 13) (Yin 2002).

For pure tone stimuli, which were used by most of the early studies, auditory nerve fibers preserve timing information in the stimulus by discharging over a limited range of phase angles of the input sinusoid, a feature usually called phase locking. Phase locking in mammals is limited to low frequencies <3 to 4 kHz (Johnson 1980) and it is preserved, indeed, enhanced, by AVCN spherical bushy cells (Joris et al. 1994) so that the bilateral inputs arriving at the MSO are highly phase-locked. A fundamental feature of binaural ITD-sensitive MSO cells is that they behave like coincidence detectors in accord with the original model (Jeffress 1948): they respond maximally when the inputs from the left and right sides coincide in time (Goldberg and Brown 1969; Yin and Chan 1990; Batra et al. 1997). Thus, when both ears are stimulated at the same frequency and the delay between the onset of the tones is varied, an MSO cell will respond maximally at a particular interaural phase angle, which corresponds to the condition when the arrival of the left and right inputs is in coincidence. For each ear a time delay results from the angular position of the stimulus with respect to the midsagittal plane, cochlear delays, and the path length between the AVCN on that side to the MSO cell. When the time delays on the two sides are equal, then the inputs arrive in phase and the MSO cell will discharge maximally.

A fundamental concept, first proposed on the basis of observations in only four cells, was characteristic delay (CD) (Rose et al. 1966). CD refers to what happens in a cell as the frequency of the tone is varied since changes in frequency also result in changes in phase. Thus, the interaural phase difference of the stimulus at which the maximal response is obtained may vary with the stimulus frequency for any given MSO cell. A cell that shows CD is one in

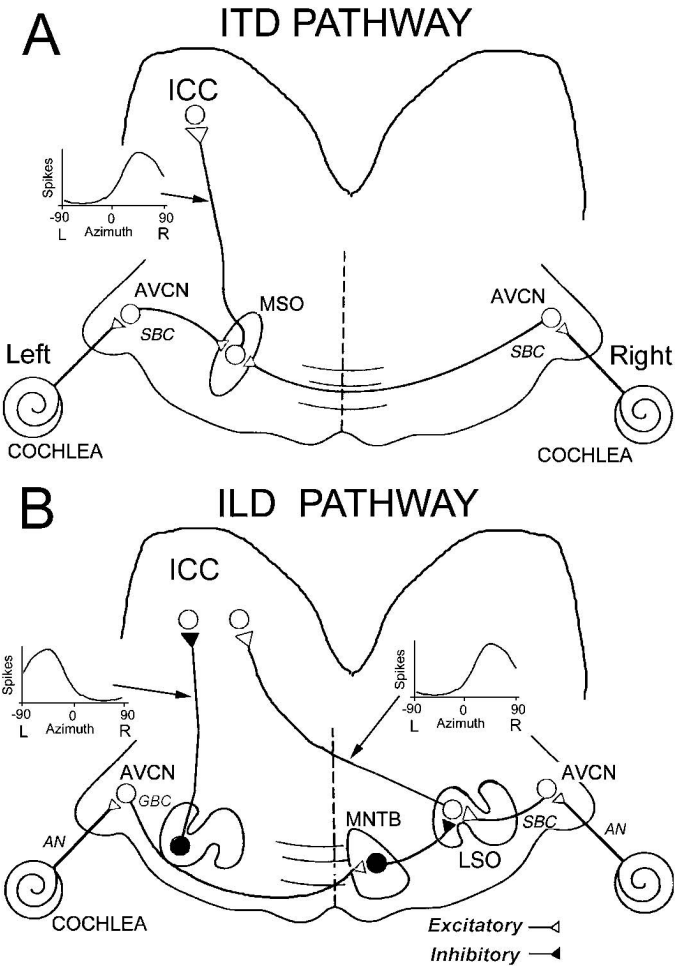

Figure 15.1. Parallel circuits in the superior olive for encoding interaural time **(A)** and interaural level **(B)** disparities in the medial and lateral superior olive, respectively. *AN,* Auditory nerve; *AVCN,* anteroventral cochlear nucleus; *GBC,* globular bushy cell; *ICC,* central nucleus of the inferior colliculus; *LSO,* lateral superior olive; *MNTB,* medial nucleus of the trapezoid body; *MSO,* medial superior olive; *SBC,* spherical bushy cell. Inset diagrams indicate how the neuron would be expected to respond to sound sources delivered in free field.

which the same relative discharge rate (e.g., maximum) is reached at the same ITD at all stimulus frequencies (Rose et al. 1966). This concept was quantified by showing that cells with CD had a linear relationship between interaural phase and stimulus frequency (Yin and Kuwada 1983). The slope of the phase-frequency plot corresponds to the CD while the phase intercept is the characteristic phase (CP) and specifies whether the point of common relative discharge is at the peak (CP = 0.0 or 1.0), trough (CP = 0.5), or in-between. Cells sensitive to ITD and exhibiting CD have been described in the MSO, ICC, dorsal nucleus of the lateral lemniscus (DNLL), medial geniculate body, and primary auditory cortex (Kuwada et al. 1987; Reale and Brugge 1990; Yin and Chan 1990; Stanford et al. 1992).

For stimuli with multiple spectral components, such as noise, a composite curve can be calculated by averaging all the ITD curves at the different frequencies. This composite curve resembles the ITD obtained using the broadband stimulus (Yin et al. 1986; Palmer et al. 1990). This relationship suggests that the individual frequency components of the stimulus are summed in near-linear fashion. An important feature of these responses to broadband stimuli is that the maxima of the composite curves of MSO cells tend to fall in the contralateral sound field, that is, with the ipsilateral ear delayed. This is expected, as the bushy cell axons from the contralateral AVCN must travel further to reach the ipsilateral MSO and hence coincidence would be expected if the contralateral stimulus is given a lead in time. Because the MSO projects to the ipsilateral ICC, we predict that ICC cells would also respond best to sound stimuli in the contralateral sound field, which is indeed the case. Thus, in ICC there is a representation of the contralateral sound field in terms of ITD (Fig. 15.1A).

2.2.2. Interaural Level Disparities

The other important cue for localization in the horizontal plane is created by the reflection and diffraction of sound by the head, shoulders, and external ears. Because the degree of reflection depends on sound wavelength, and hence on its frequency, the ILD cue is highly frequency dependent, with significant ILDs only at high frequencies where the wavelength is short (Blauert 1997). The neural circuit thought to be important for encoding ILDs involves lateral superior olive cells (LSO) which receive excitatory input from the ipsilateral spherical bushy cells and inhibitory input from the medial nucleus of the trapezoid body (MNTB), which is in turn driven by globular bushy cells of the contralateral AVCN with a large calyx of Held synapse on the MNTB cells (Fig. 15.1B; Warr 1966, 1972; Cant and Casseday 1986; Guinan and Li 1990; Smith et al. 1991, 1993). Thus, LSO cells are excited by a sound source in the ipsilateral sound field, where the excitation exceeds the inhibition, and inhibited when the source is in the contralateral sound field (Fig. 15.1B; Tsuchitani and Boudreau 1966; Tollin and Yin 2002a,b; Tollin 2003).

The projection of the LSO to the ICC is unusual and complex. LSO axons project bilaterally to the ICC, but some axons are glutamatergic and excitatory

while others are glycinergic and inhibitory (Glendenning and Masterton 1983; Saint Marie et al. 1989). In the cat the crossed projection originates primarily from the medial, high-frequency limb and is excitatory while the uncrossed projection from the lateral, low-frequency limb is both excitatory and inhibitory. Because LSO cells are excited by sound sources in the ipsilateral sound field, an excitatory crossed projection or an inhibitory uncrossed projection will result in ICC neurons that are excited by sound sources in the contralateral sound field (Fig. 15.1B; Glendenning et al. 1992). Note two caveats to this scheme. First, the inhibitory uncrossed projection will not result in an ICC cell that responds to sounds in the contralateral field alone: it needs to act on spontaneous activity or other driven excitation. Second, the excitatory uncrossed projection (not shown in Fig. 15.1B) provides inputs to the ICC that are excited by sounds in the ipsilateral sound field. Thus, most, but not all, ICC cells receive inputs that are responsive to stimuli in the contralateral, but not the ipsilateral, sound field.

Most binaural ICC cells respond to ITDs and ILDs that represent the contralateral sound field, like their visual and somatosensory counterparts. To ensure a unified perception of space, it is not surprising that all modalities follow the contralateral representation of space. What is remarkable is that the auditory system achieves this representation using a computational scheme that involves a massive, but precisely ordered, array of bilateral cochlear nucleus projections to the LSO, and in turn from the LSO to the ICC. This representation is important behaviorally because it predicts that a lesion above the level of the superior olive should affect localization in the contralateral sound field with little ipsilateral effect.

2.3. Perception and Processing of Spectral Cues for Sound Localization

Anatomical projections for the binaural processing of ITD and ILD cues converge on the superior olive from the two cochlear nuclei (Ramón y Cajal 1909; Cant and Gaston 1982; Glendenning et al. 1985; Cant and Casseday 1986). By contrast, sound localization pathways with a selectivity for spectral information do not have overt anatomical features and have been inferred from the unusual spectral integration properties of populations in dorsal cochlear nucleus neurons (Nelken and Young 1997; Spirou et al. 1999; Imig et al. 2000) and ICC (Ehret and Merzenich 1988; Leroy and Wenstrup 2000; Davis et al. 2003). The anatomical specializations that subserve spectral processing may appear less differentiated than those for the binaural brain stem, but the functional enhancements are equally important in natural behavioral contexts where survival mandates the accurate localization of complex sounds.

2.3.1 The Head-Related Transfer Function of the Cat

Our description of spectral cues for sound localization emphasizes the large body of behavioral and physiological evidence from domestic cats. These directional

cues are described by the head-related transfer function (HRTF), which is the filter function characterizing relative spectral changes in complex sound propagating from the free field to the ear drum (Wightman and Kistler 1989a,b; Musicant et al. 1990). With ITD and ILD cues that are inherent in binaural comparisons of the HRTF, directionally dependent spectral features encode sound source location (Kulkarni and Colburn 1998). These spectral cues are critical for monaural sound localization, but binaural comparisons of HRTF spectral shapes also provides spatial information (Rice et al. 1992).

The HRTFs of a representative adult cat (Rice et al. 1992) were measured by recording sound energy near the ear drum with a miniature implanted microphone (Fig. 15.2). Rather than focusing on the specific directional properties of individual functions, several functions from the horizontal and median planes are juxtaposed to show generalized localization cues. One transfer function (Fig. 15.2, bold line) in both data sets indicates the ear's filtering effects for a broadband sound directly in front of the head (0° AZ, 0° EL). By convention, a 0-dB gain indicates the HRTF has neither amplified nor attenuated the sound relative to its free-field sound pressure level.

The HRTFs suggest three domains of spectral information. Frequencies <5 kHz are amplified, rising to an energy peak at about 4 kHz. Middle frequencies (5 to 20 kHz) usually have one deep and narrow energy trough, or spectral notch. Frequencies >20 kHz manifest a complex spectral shape with multiple peaks and notches. HRTF gain falls with increasing frequency, implying a reduced salience for the high-frequency spectral cues of broadband sounds.

Directional features of the HRTF are revealed by comparing transfer functions across sound locations. The functions represent different azimuthal locations in the horizontal plane ($\pm 75°$ in 15° increments) (Fig. 15.2A) as well as different elevations in the median plane (–30° to 90° in 7.5° increments) (Fig. 15.2B).

The HRTFs (Fig. 15.2) suggest that its low-frequency components are either amplified by the pinna when the sound source azimuth is in the near field, or attenuated by the head's "sound shadow" when it is in the far field. The difference in gain between the ears is equivalent to the ILD cue. This frequency region is virtually unaffected by elevation changes in the median plane.

The mid-frequency HRTF spectrum provides rich directional information for both azimuth and elevation. As a sound source moves in the horizontal or median plane, changes in location are reflected in notch frequency. This feature is critical for encoding sound source elevation, but it also may contribute to the identification of azimuth because horizontal plane spatial acuity improves with increasing stimulus bandwidth (Heffner and Heffner 1988).

The high-frequency HRTF displays complex and less systematic filtering properties. Consequently, directionally dependent relationships between energy peaks and notches have not been established. Nevertheless, high-frequency sounds tend to impart the perception of high elevation (Pratt 1930; Butler and Belendiuk 1977; Blauert 1997), presumably because they are less attenuated by the HRTF at such elevations (Wightman and Kistler 1989a; Rice et al. 1992).

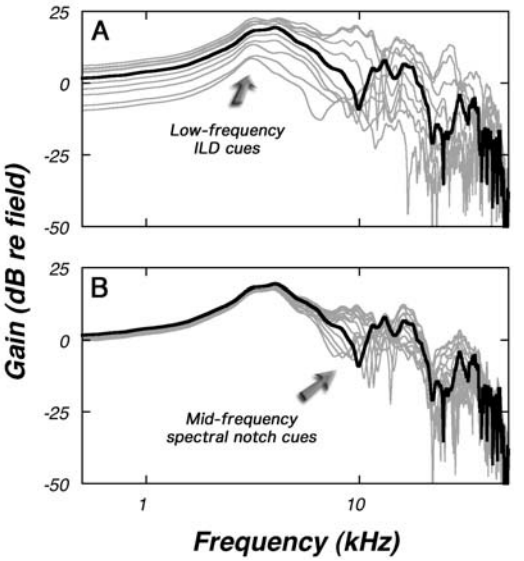

Figure 15.2. Head-related transfer functions (HRTFs) of an adult cat for sound locations in the interaural horizontal plane **(A)** and median vertical plane **(B)**. The transfer function for a sound source directly in front of the subject is repeated in both panels *(bold line).* Filtering effects fall into three frequency domains. At low frequencies, the HRTF gain increases as the sound source moves from contralateral to ipsilateral locations in the horizontal plane. These gain changes create interaural level differences (ILDs). At mid-frequencies, the frequency of a prominent spectral notch increases as the sound rises from low to high elevations in the median plane. At high frequencies, spectral peaks and notches display a less orderly relationship to the direction of the sound source. (Adapted from Rice et al. 1992.)

2.3.2. Role of High-Frequency Spectral Information in Spatial Discrimination

The spectral notches of the HRTF are conveyed to the brain by the discharge rates of auditory-nerve fibers (Poon and Brugge 1993). Computational models suggest a dichotomous role for spectral information in the high- vs. mid-frequency HRTF domains (Nandy and Ben-Arie 1996; May and Huang 1997). Although the high-frequency HRTF components are robust, individual spectral features are not unambiguously associated with discrete sound locations and thus are most effective for the simple detection of a change from one location to another. Mid-frequency spectral notches, in contrast, influence fewer auditory neurons but create more spatially localized response patterns, dictating performance in behavioral tasks that demand the absolute identification of sound source location.

The most common metric for evaluating the perceptual significance of HRTF-borne directional information is the minimum audible angle (MAA; Mills 1958), the threshold for detecting directional changes between paired sound sources. Relative localization tasks are often used in animal behavioral studies because they require less training and are easily related to psychophysical thresholds.

MAA tasks have been used extensively in cats (Martin and Webster 1987; Heffner and Heffner 1988; May et al. 1995). Behavioral results using noise bursts with different frequency domains were used to isolate the frequency dependence of HRTF filtering effects (Fig. 15.3) (Huang and May 1996a). Broadband noise contained spectral cues >5 kHz. Mid-frequency noise was limited to the spectral notch region from 5 to 20 kHz. High-frequency noise conveyed only complex spectral cues >20 kHz. For each stimulus, the MAA was defined as the smallest elevation change that elicited correct responses with a probability corresponding to the signal detection criterion $d' = 1$.

Correlations between directional acuity and the spectral domain of complex sounds have been demonstrated in cats (Martin and Webster 1987; Populin and Yin 1998a) and humans (Musicant and Butler 1984; Carlile et al. 1999; van

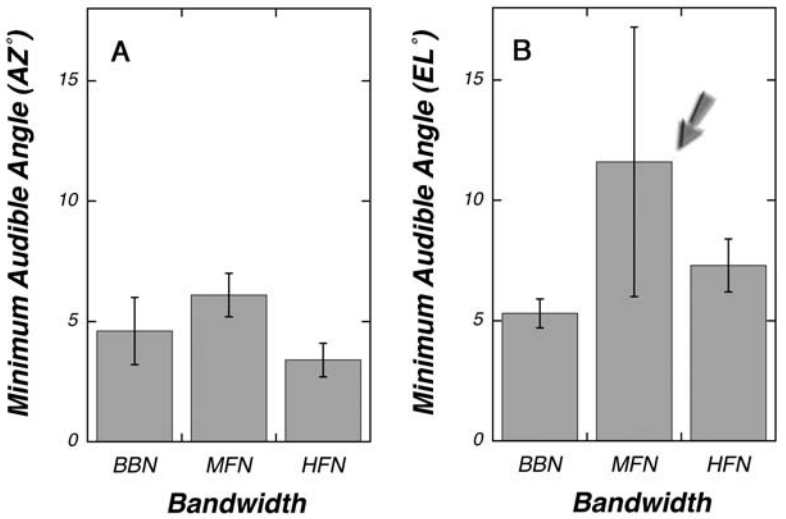

Figure 15.3. Effects of spectral frequency on minimum audible angles (MAAs) in the horizontal **(A)** and median planes **(B)**. MAA is the smallest change in location relative to a reference speaker at 0° AZ, 0° EL that elicited threshold performance ($d' = 1$). Histograms indicate the average thresholds (±SD) of three cats. Largest performance deficits were noted for tests in the median plane with mid-frequency noise (*arrow*). *BBN*, Broadband noise (>5 kHz); *HFN,* High-frequency noise (>20 kHz); *MFN,* mid-frequency noise (5 to 20 kHz). (Adapted from Huang and May 1996a.)

Schaik et al. 1999) and are replicated by responses to mid- and high-frequency noise bursts (Fig. 15.3). As predicted by the quality of directional information inherent in the HRTF (May and Huang 1997), high-frequency noise bursts contain many spectral cues for directional change. Their thresholds were similar to broadband performance. Cats showed deficits when tested with noise that conveyed the more singular mid-frequency notch cue. The relationship between behavioral performance and sound spectra was clearer for sound sources varying in elevation in the median plane than those varying in horizontal plane azimuth.

2.3.3. Role of Mid-Frequency Spectral Cues in Sound Orientation

Natural sound localization behaviors are concerned with the determination of actual locations, not the detection of spectral differences between paired sound sources. The unnatural aspects of the MAA task are circumvented in behavioral paradigms that require the subject to indicate the apparent location of an auditory stimulus by indicating or approaching the sound source. Such procedures are especially useful when directional percepts are predicted to change with modifications of acoustic parameters or lesions. Thus, limiting spectral content to high frequencies provides enough information to convey relative positional changes in the MAA task (Fig. 15.3), but does this manipulation preserve the absolute directionality of an auditory stimulus?

Early studies of cat directional hearing combined an array of sound sources with food or water reward. Sound presentations signaled the active goal box and the subject obtained the reward by approaching the proper speaker (Casseday and Neff 1973). When combined with surgical lesions, this procedure revealed valuable insight into the information processing roles of major auditory centers (Moore et al. 1974; Casseday and Neff 1975; Neff and Casseday 1977).

Unilateral ICC lesions induce only contralateral sound localization deficits in the goal-box task (Strominger and Oesterreich 1970; Goreva and Shcherbakov 1978; Jenkins and Masterton 1982). Robust perceptual deficits are only observed if the subject is forced to make an absolute localization among multiple sound sources (Jenkins and Masterton 1982; Jenkins and Merzenich 1984). Normal performance is achieved if the localization task is a simple spatial discrimination between paired sound sources (Butler and Musicant 1993; Kelly and Kavanagh 1994) and in nonspatial tasks such as the pure-tone discrimination (Neff et al. 1975). In these behavioral contexts, only the multiple speaker goal-box procedure specifically addresses the effects of the lesion on absolute directional hearing.

The dominant role of spectral information in directional hearing exists beyond the horizontal plane. Since flightless animals cannot approach an elevated stimulus, behavioral studies rely on a response in which the subject points to the perceived location of the sound source. In animals, the response is usually based on changes in position of the head (Thompson and Masterton 1978) or eyes

(Populin and Yin 1998a). This reflexive behavior may be used briefly in naive subjects (Sutherland et al. 1998a) or shaped into a food-reinforced operant paradigm for more detailed psychophysical analyses (May and Huang 1996; Populin and Yin 1998a,b; Tollin and Yin 2003a,b).

The effects of spectral content on the accuracy of sound orientation behavior was assessed in cats trained to orient to broadband noise (Fig. 15.4A) (Huang and May 1996b), then probing behavioral performance with occasional bursts of mid-frequency (Fig. 15.4B) or high-frequency noise (Fig. 15.4C). Band-limited stimuli elicited less accurate orientation than broadband noise, but spatially organized responses were maintained when the mid-frequency notches were available. High-frequency probes evoked inconsistent and inaccurate head movements. These deficits confirm that the high-frequency filtering effects of the cat's HRTF fail to impart an absolute directional identity, even though this domain is an excellent source of information for relative directional changes (Fig. 15.3).

The directionally dependent HRTF spectral shapes explain illusory elevation effects seen when paired sounds are presented from two locations in close temporal proximity (Tollin and Yin 2003a). Under summing localization conditions (see Section 3.1.1.), cats unexpectedly localize sounds at higher elevations than predicted by actual locations, a striking effect when both sound sources are located in the horizontal plane. These response errors are correlated with mid-frequency spectral notch alterations arising from the time-delayed summation of energy from the two locations.

Illusions of spatial azimuth and elevation also can be created by synthesizing HRTF-based spectral and binaural cues over headphones (Wightman and Kistler 1989b; Pralong 1996; Langendijk and Bronkhorst 2000). The perceptual realism of the resulting virtual space stimuli implies that the auditory system cannot isolate HRTF directional properties from acoustic source spectrum features. Nevertheless, to function effectively in the biological world, the auditory system must be able to derive the HRTF shape without prior knowledge of the stimulus. This processing dilemma is simplified under normal listening conditions because the amplitude spectra of most natural sounds lack sharp spectral features that may be confused with HRTF-filtering effects (Zakarauskas and Cynader 1993). The source spectrum can be disambiguated further by comparing the multiple directional perspectives provided by the two ears (Rice et al. 1992), head movement (Goossens and van Opstal 1999; Wightman and Kistler 1999), and mobile pinna (Young et al. 1996; Populin and Yin 1998b). Despite these heuristics, optimal localization is achieved when the auditory stimulus is a familiar sound (McGregor et al. 1985; Blauert 1997) and it is filtered by one's own ears (Wenzel et al. 1993; Hofman et al. 1998; Middlebrooks 1999).

2.3.4. Coding of Spectral Cues

Electrophysiological studies of the ICC suggest specializations for processing spectral cues for sound localization. The existence of this discrete information

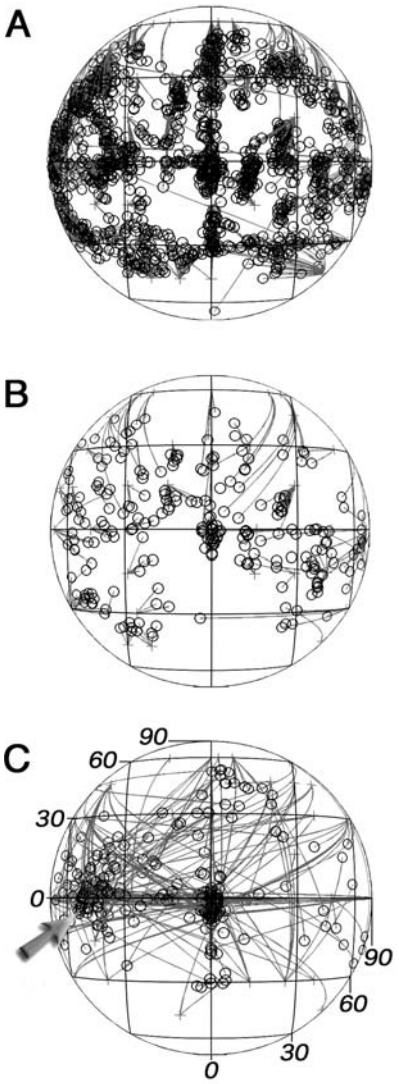

Figure 15.4. Effects of frequency domain on sound orientation behavior. Results from one cat summarized across orientation sessions in which discrete noise bursts were presented from randomly selected speaker locations. *Lines* connect individual responses *(circles)* to stimulus locations *(plus symbols).* Presentations of broadband noise comprised 85% of the trials **(A)**. Noisebands with mid-frequency spectral notches **(B)** or high-frequency complex cues **(C)** were presented during the remaining probe trials. In this behavioral context, large performance deficits were observed for high-frequency stimuli (*arrow*). *Numerical labels* indicate stimulus azimuth and elevation in double-pole coordinates. (Adapted from Huang and May 1996b.)

processing pathway is based on the physiological classification of inhibitory patterns in the ICC of decerebrate cats (Ramachandran et al. 1999). Type V units have a V-shaped receptive field without strong inhibition. Type I units show a narrow I-shaped excitatory field bounded by lateral inhibitory areas. Type O units may be inhibited by any combination of frequency and level except for an O-shaped excitatory area near threshold.

Similarities in the inhibitory features of frequency response maps have linked type O responses to ascending projections from the dorsal cochlear nucleus (DCN; Davis et al. 1999, 2003; Ramachandran et al. 1999; Ramachandran and May 2002). The response map of a representative type O unit is compared with that of its hypothesized input, a type IV DCN neuron (Fig. 15.5A, B) (Young et al. 1992). The conservation of pure-tone responses between the putative target and source neurons suggests that the DCN spectral processing pathways remain functionally segregated in the ICC (Davis 2002).

The largely inhibitory pure-tone type O responses give way to excitation when the neurons are tested with more natural stimuli (Davis et al. 2003). The response class is particularly sensitive to broadband sounds containing HRTF-filtering effects. The spectral cues influencing these responses have been characterized with parametric stimuli that reduce the complex HRTF to a rectangular notch in broadband noise. A tuned excitatory response is elicited when the notch is swept in frequency across the receptive field of the type O unit (Fig. 15.5C). Because notch frequency is a directionally dependent feature of the cat's HRTF, notch-selective neurons can encode sound location (Young et al. 1992; Imig et al. 2000).

The directional sensitivity of type O responses has been demonstrated under closed-field conditions with noise bursts that provide more realistic simulations of binaural and spectral properties of the HRTF (Fig. 15.5E) (Delgutte et al. 1999; Davis et al. 2003). As predicted by the notch frequency sweep (Fig. 15.5C), maximum discharge rates align with a spatial contour that is defined by near-BF spectral notches. Interestingly, the unit exhibits a preferred location along the iso-notch contour that cannot be explained purely by notch directional selectivity. This enhanced spatial tuning may derive from wideband spectral integration properties allowing type O units to analyze the broader spectral context of mid-frequency notches, or a sensitivity to covarying binaural cues in some type O units (Ramachandran and May 2002).

Most type O units are silenced by surgical or pharmacological manipulations that disrupt neural transmission in the dorsal acoustic stria (DAS; Davis 2002), the principal DCN output pathway to the ICC. Although type IV units are distinguished by nonlinear spectral integration properties that endow sensitivity to HRTF-based spectral notches, type O units do not simply recapitulate their DCN inputs. Type IV units (Fig. 15.5D) display a frequency tuned inhibitory response to spectral notches (Young et al. 1992; Imig et al. 2000). Additional excitatory, inhibitory, and binaural inputs are required to transform this DCN pattern into the directionally selective type O unit (Davis et al. 2003).

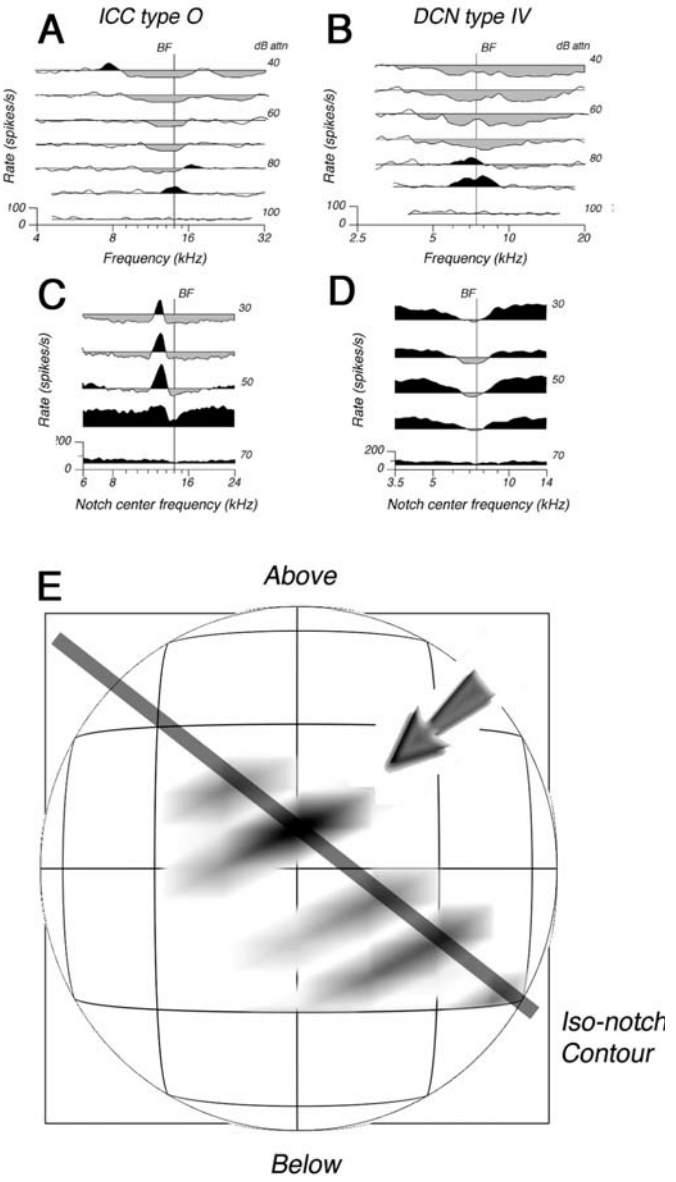

Figure 15.5. Physiological properties of type O units in the ICC and type IV units in the DCN. Each row of the response maps shows driven discharge rates at a different level of attenuation. Inhibitory responses of the two unit types are similar for pure-tone frequency sweeps **(A, B)**, but the type O unit shows a tuned excitatory response for notch frequency that is absent in the type IV unit **(C, D)**. This notch selectivity creates a spatial receptive field when type O units are tested with virtual-space stimuli **(E)**. Responses along the preferred iso-notch contour exhibit a "best location" that implies directional processing beyond notch frequency *(arrow)*. (Adapted from Davis et al. 2003.)

2.3.5. Effects of Dorsal Cochlear Nucleus and Central Nucleus Lesions on Localization Behavior

The functions of DCN projections to the ICC have been investigated by measuring the effects of DAS lesions on localization behavior (Sutherland et al. 1998a,b; May 2000). Unlike trapezoid body lesions that induce deafness, this surgical procedure has little effect on hearing sensitivity in quiet and in background noise (Masterton and Granger 1988; Masterton et al. 1994). Consequently, it is possible to explore the nature of auditory deficits in subjects with bilateral DAS lesions.

A cat with DAS lesions was tested with bandpass noise to restrict spectral cues to HRTF-based notches between 5 and 20 kHz (Fig. 15.6). The subject oriented correctly to random source locations throughout the frontal sound field prior to the lesions (Fig. 15.6A), but had large errors after transecting DCN pathways (Fig. 15.6B) (May 2000). These deficits confirm that DCN/ICC pathways fulfill a critical spectral processing role in feline sound localization (Davis et al. 2003).

Elevation errors are pervasive (Fig. 15.6B). Regardless of the actual elevation of randomly selected sound sources, most responses fell within $\pm 30°$ of the horizontal plane. The under-estimation of sound source elevations exceeded 60° for extreme locations. These results reproduce the elevation-dependent errors induced when spectral cues are constrained in narrowband stimuli (Middlebrooks 1992). In both situations, the perceptual consequences of impaired spectral information are minimized for testing in the horizontal plane by the normal function of the binaural pathways. The remaining deficits suggest that monaural spectral representations within the DCN/ICC pathway also contribute to the perception of azimuth. This dual role is supported by the observation that most monaural ICC units are sensitive to both azimuth and elevation of virtual-space stimuli (Delgutte et al. 1999).

The functional specificity of DAS sound localization deficits has been evaluated by testing cats with MAA procedures (Sutherland et al. 1998a; May 2000) (Fig. 15.6C). Although these three cats had orientation deficits after the DAS lesion, none showed impaired spatial acuity when tested with mid-frequency noise bursts in the MAA procedure, confirming that DAS lesions do not produce general hearing deficits (Masterton and Granger 1988). These results further substantiate the view that relative spatial acuity and absolute directional hearing utilize different cues and processing pathways (Jenkins and Masterton 1982; May and Huang 1997).

2.3.6. The Neurobiology of Spectral Processing

Behavioral and electrophysiological studies suggest that type O units represent a specialized pathway for processing of spectral cues for sound localization. Although type O response patterns are common in decerebrate cats, they are rare in the ICC of some other laboratory species. For example, V-shaped fre-

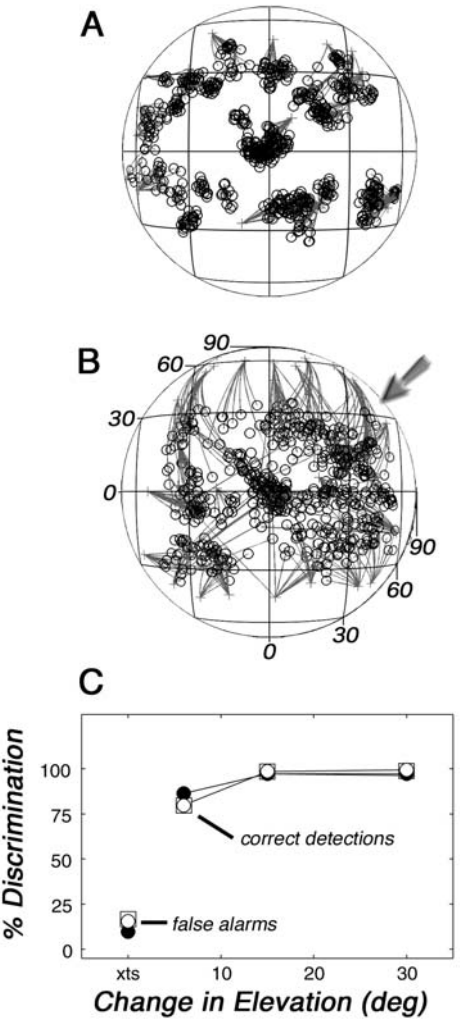

Figure 15.6. Effects of dorsal acoustic stria (DAS) lesions on directional hearing. Orientation responses of a representative cat before **(A)** and after **(B)** bilateral DAS lesions. Elimination of DCN inputs to the ICC disrupted absolute orientation behavior, especially sound source elevation *(arrow)*. Three cats with bilateral DAS lesions had excellent post-lesion performance in MAA procedures **(C)**. Psychometric functions plot the percentage of correct responses relative to changes of elevation in the median plane. False alarms to catch trials without directional changes *(xts)* confirm the low probability of false positive responses in well-trained subjects. (Adapted from May 2000.)

quency response areas comprise most ICC units in anesthetized guinea pigs (Syka et al. 2000; Le Beau et al. 2001). (See Fig. 15.7A.) The remaining non–V-shaped units tend to have narrow tuning like the type I units in decerebrate cats.

Species differences in the prevalence of type O units cannot be explained by the use of anesthesia in guinea pigs, or the surgical elimination of descending projections to the ICC in decerebrate cats. After decerebration, guinea pigs show the same inhibitory patterns described in anesthetized preparations, including a conspicuous absence of type O units in frequency response maps (Fig. 15.7B).

An alternative explanation is that type O units reflect an auditory specialization that is restricted to species that require accurate sound localization, a biological need often associated with predatory lifestyles. The sound localization abilities of laboratory mice support this neuroethological premise. Besides poor directional acuity (Ehret and Dreyer 1984), single-unit recordings suggest an under-representation of type O responses in anesthetized mice (Egorova et al. 2001; Ehret et al. 2003). These species differences do not simply reflect the confounding influences of anesthesia and decerebration on the inhibitory prop-

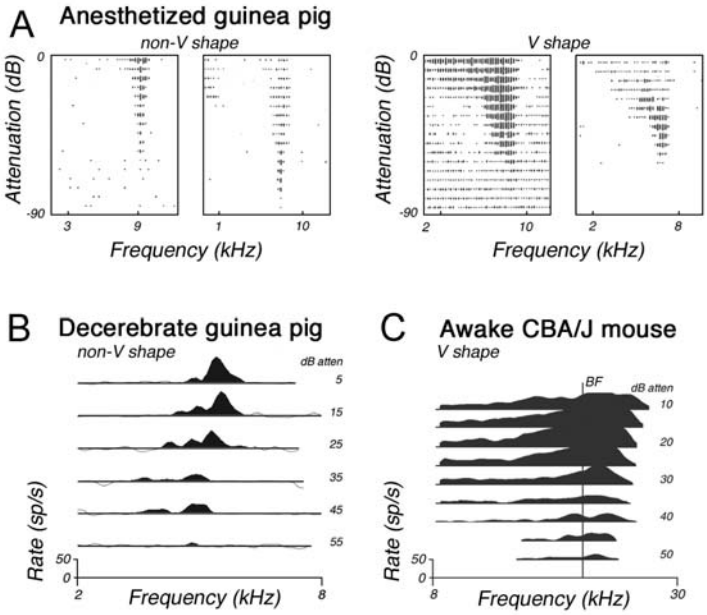

Figure 15.7. Frequency response maps in nonpredatory species. Non–V-shape and V-shape responses are common in anesthetized guinea pigs **(A)**, decerebrate guinea pigs **(B)**, and awake mice **(C)**. Type O units are rare in these species. (**A**: Adapted from Le Beau et al. 2001.) (**B, C**: Unpublished data from BJ May.)

erties of ICC neurons. V-shaped units also represent the most common response type in the ICC of awake, intact mice (Fig. 15.7C; May 2003).

This review relies heavily on research in domestic cats to describe the perception and processing of spectral cues for sound localization. Though regarded as a general model of mammalian hearing, the cat auditory system has evolved to meet the demands of nocturnal predation. These adaptations for prey localization may be species-specific.

Natural behavior provides insights into the functional significance of the common neural pathways and species specializations that remain to be addressed by laboratory studies. An emphasis on comparative behavior, particularly in terms of predator and prey relationships, has contributed greatly to investigations of the brain stem binaural sound localization system (Neff et al. 1975; Heffner and Heffner 1986, 1987, 1989; Moore 1987). A neurobiological perspective ought to prove equally important for understanding the spectral processing pathways of the ICC.

2.4. Effects of Lesions of the Central Nucleus of the Inferior Colliculus on Localization

Physiological studies of the encoding of interaural localization cues suggest that the contralateral sound field is represented in the ICC even though the superior olive has both ipsilaterally and contralaterally driven cells. This dominant innervation has been confirmed by ICC lesions. A contralateral localization deficit followed a unilateral lesion of its output pathway, the brachium of the ICC (Strominger and Oesterreich 1970), and a unilateral lesion that affected LSO output in the lateral lemniscus or ICC caused a deficit in localizing sounds in the field contralateral to the lesion (Jenkins and Masterton 1982) and after large unilateral ICC lesions in the ferret (Kelly and Kavanagh 1994).

Since the ascending projections from the ICC to the medial geniculate body and then to the primary auditory cortex are predominantly uncrossed (see Chapter 7), we predict the same functional contralateral representation in the physiology of thalamic and cortical cells as well as a contralateral deficit in localization following a unilateral lesion of these higher centers. Indeed, most medial geniculate and primary auditory cortex cells have receptive fields in the contralateral sound field (Imig et al. 1990; Brugge et al. 1996; Irvine et al. 1996; Samson et al. 2000) and unilateral auditory cortex lesions create a contralateral localization deficit (Jenkins and Merzenich 1984).

2.5 Effects of Electrical Stimulation of the Inferior Colliculus

There are few studies of behavioral results of electrical stimulation of the ICC. By 1970 (Syka and Straschill 1970; Syka and Radil-Weiss 1971) it was known

that head and eye movements could be evoked by stimulation of the ICC and that these effects used connections to the deep layers of the superior colliculus, a well-known sensorimotor integration site (Wurtz 1996; Sparks 2002).

In rodents the ICC has been implicated as one of the sites for abnormal brain activity in the form of seizures. Stimulation of the ICC by acoustic, electrical, or pharmacological means can evoke seizure activity in particular seizure-prone strains of rodents, the genetically epilepsy prone rat (GEPR; Ribak and Morin 1995; Ross and Coleman 2000). This system has been used as a model for studying the interaction between excitatory and inhibitory neurotransmitters in inducing epileptic activity (see Chapter 21).

3. Physiology in Awake and Behaving Animals

In all of the experiments reviewed in the preceding, the physiological responses to localization cues were recorded in anesthetized or decerebrated animals. How anesthesia affects the responses is not understood and undoubtedly depends on the dosage, type, and the site of recording as well as the species. A major advance since 1960 is the development of techniques to record from awake, behaving animals, which avoids the contaminating effects of anesthesia and allows one to study the neural bases of higher-order cognitive effects.

There are few studies since 1980 in awake behaving preparations, even though several earlier studies used this technique. Responses of monkey ICC cells in an auditory reaction time task were compared to responses to the same stimuli when the monkey was quiescent. Discharge patterns resembled those in acute experiments and rates significantly increased during task performance (Ryan and Miller 1977, 1978). Similar comparisons were also made from the cochlear nucleus to auditory cortex (Ryan et al. 1984). Moreover, in behaving animals there are multisensory interactions as eye position affects some ICC neuron responses as much as sound source location in monkeys (Groh et al. 2001).

3.1. The Precedence Effect

3.1.1. Psychophysics

There has been considerable interest in an auditory illusion known as the precedence effect (PE), or law of the first wavefront (Wallach et al. 1949), shown by placing a subject between two speakers (Fig. 15.8A) and delivering the same transient sound to both speakers with a variable interstimulus delay (ISD) between the sounds. An idealized plot (Blauert 1997) of the perceived location of the sound as a function of ISD (Fig. 15.8B) shows that, if both speakers are activated simultaneously, the observer will localize the sound to a single phantom source midway between them. As ISD gradually lengthens the perceived source moves towards the leading speaker until, at approximately 1 ms ISD the sound is perceived near the leading source. The interval between about ± 1 ms

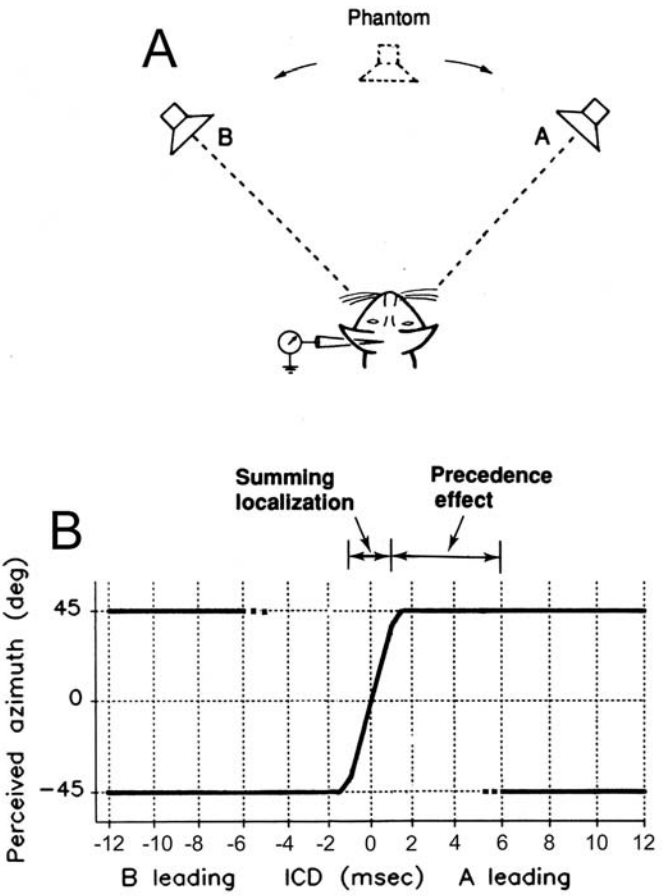

Figure 15.8. The precedence effect. **(A)** Diagram of the stimulus configuration in free field with the subject midway between two speakers (A, B) *(top)* and **(B)** the perceived azimuthal location of the sound as a function of the interclick delay. By convention negative delays correspond to speaker B leading. (Adapted from Blauert 1997 and Yin 1994.)

has been termed summing localization. ISDs between 1 and 5 to 10 ms represent the period of the precedence effect, or localization dominance: the sound is localized to the position of the leading source even though the lagging source is readily localized when presented alone. At longer ISDs the subject hears both sounds at their respective positions, and the shortest ISD at which this occurs is the echo threshold. In practice the echo threshold value is variable and depends on the instructions given to the subject and on the duration and type of acoustic stimulus. Sustained and complex sounds (music, speech) usually have longer echo thresholds.

The term, precedence effect, refers to the way in which the leading sound appears to take precedence over the lagging one in judgments of sound location, as if the lagging sound's location were suppressed by the auditory system. However, the lagging source still plays a role in perception other than localization: for delays in the range of localization dominance, the fused sound can be readily discriminated from the leading sound by a change in timbre, although it is localized to the position of the leading sound. It is thought that the precedence effect is critical for accurately localizing sound in a reverberant environment, such as a room, where any sound will produce time-delayed echoes from many different spatial locations.

An important question regarding the neural bases of PE is how it is experienced by animals. PE has been demonstrated in cats (Populin and Yin 1998a; Tollin and Yin 2003b), birds (Keller and Takahashi 1996; Dent and Dooling 2003), dogs (Ashmead et al. 1986), rats (Kelly 1974), and crickets (Wyttenbach and Hoy 1993). Mean horizontal eye position as a function of ISD of a cat trained to fixate sound sources when presented with pairs of short noise bursts to simulate the PE (Tollin and Yin 2003b) demonstrates this effect (Fig. 15.9). With the head held, all cats consistently undershoot the target (Fig. 15.9A, B: leftward arrows).

The cat (Fig. 15.9) and human (Fig. 15.8B) responses are similar during the localization summing period except that the period is only ± 400 μs in the cat because of its smaller head width. For delays between 1 and 10 ms, the cat showed localization dominance to the position of the leading speaker and at delays >10 ms it often made saccades to the location of the lagging sound or double saccades to both the leading and lagging sounds, resulting in mean responses near 0 and large variability. We infer from this behavior, never seen for

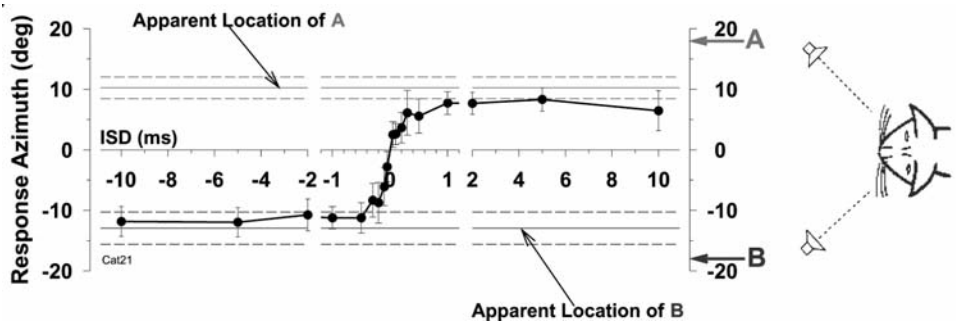

Figure 15.9. Responses of a cat to the PE stimuli. Azimuthal final eye position as a function of interstimulus delay (ISD). The locations of the speakers A and B are indicated by the arrows on the right and the horizontal lines ($\pm$ standard deviation) show the mean eye position for the two speakers when delivered in isolation. (Adapted from Tollin and Yin 2003b, used with permission.)

shorter delays, that the cat was perceiving both sounds and was unsure which to look at. Thus, the cat echo threshold is between 10 and 15 ms.

3.1.2. Physiology

The first studies of the physiological responses to PE stimuli were in anesthetized animals (Yin 1994). ICC cells respond to click pairs delivered dichotically (Fig. 15.10). A +400 μs ITD, an effective stimulus for this cell, was imposed on both pairs of clicks while the interclick delay (ICD) varied from 1 to 101 ms. At long ICDs the response to both pairs of clicks is clear, but as the ICD decreases gradually the response to the lagging click declines until it disappears at ICDs <7 ms, while there is little change in the response to the leading one. A recovery curve plot shows the response to the lagging click normalized by the response to the same click when delivered in isolation (Fig. 15.9B). The delay at 50% recovery is often used as a metric for half-maximal suppression, and in this cell is 11 ms.

Suppression of the response to the lagging click was common in the ICC and has been studied in other species (rabbit: Fitzpatrick et al. 1995; barn owl: Keller and Takahashi 1996) and extends from the auditory nerve to the cortex (Parham et al. 1996, 1998; Fitzpatrick et al. 1999). Spatial location, ITD, level, duration, and binaurality of the leading sound can each affect suppression (Litovsky and Yin 1998a,b; Litovsky and Delgutte 2002). The half-maximal delay values in different cells were variable, with significant differences in the degree of suppression in the anesthetized cat and unanesthetized rabbit (Yin 1994; Fitzpatrick et al. 1995, 1999; Litovsky and Yin 1998a,b).

To investigate whether the differences between the cat and rabbit results were due to the species difference or to the anesthesia, recordings were also made in the ICC while the cat was awake and performing a sound localization paradigm. The distribution of half-maximal delays for cells in the anesthetized cat (Litovsky and Yin 1998b; Fig 15.11, gray bars), for unanesthetized, quiescent rabbit (Fitzpatrick et al. 1995; Fig. 15.11, white bars) and in awake, behaving cats (Fig. 15.11, black bars) are available. The half-maximal delays in the behaving cat (circles representing mean and s.d.) were significantly different than in the anesthetized cat but similar in the awake rabbit and suggest that the differences reflect anesthesia. Mean recovery curves for the population of ICC cells in the awake animal were computed separately for either ipsilateral side or contralateral side-leading speaker and show significantly stronger contralateral leading suppression (Fig. 15.10B). The PE period (Fig. 15.10, shaded region) shows considerable suppression in the response of the population of ICC cells when PE is behaviorally effective.

4. Future Directions

We have focused on the relationship between sound localization behavior and neural response patterns in the ascending pathways of the auditory midbrain.

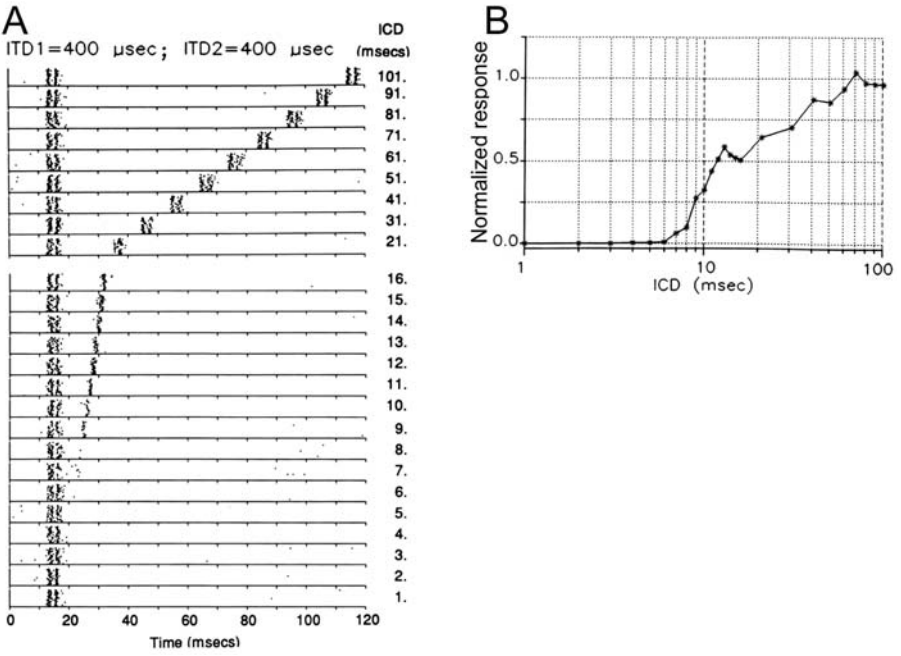

Figure 15.10. Echo suppression in the ICC under dichotic stimulation. **(A)** Dot rasters show the responses to 40 repetitions of ICDs ranging from 1 to 101 ms. Each dichotic click had an ITD of +400 µs. **(B)** Recovery curve of the data in **(A)**. The response to the lagging click was normalized by the response to the same click without the leading click. Half-maximal delay was 12 ms. (Adapted from Yin 1994.)

This emphasis reflects the prominent role the ICC has played in current behavioral and physiological assessments of the inferior colliculus. It is almost certain that the midbrain is involved in other auditory behaviors and that these processes reflect descending influences from higher auditory centers.

Physiological studies find that the auditory processing of a meaningful sound is enhanced by corticofugal pathways that terminate in the dorsal cortex of the inferior colliculus (Zhang et al. 1997; Jen et al. 1998; Yan and Ehret 2001, 2002). When repeating tones are paired with noxious shocks, neurons encoding the fear-conditioned stimulus show an expanded reorganization in the inferior colliculus of big brown bats (Gao and Suga 1998). Analogous changes in frequency tuning are evoked by electrical stimulation of auditory cortex (Chowdhury and Suga 2000), or abolished by pharmacological inactivation of the same locations (Gao and Suga 2000). By contrast, specialized echolocation areas in the inferior colliculus of mustached bats show increased activity and sharper frequency tuning when matching cortical frequency regions are stimulated (Zhang and Suga

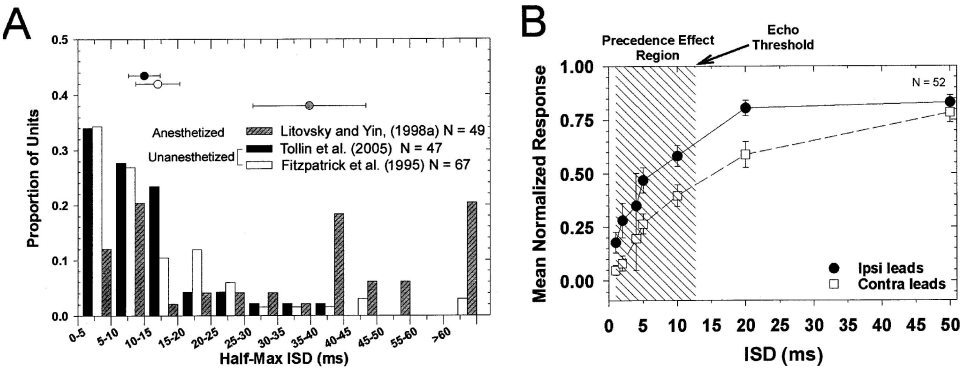

Figure 15.11. **(A)** Histogram of the half-maximal delays in anesthetized cats (Litovsky and Yin 1998b; *gray bars*), awake rabbits (Fitzpatrick et al. 1995; *white bars*), and awake, behaving cats (black bars). The means and standard error of the mean of the distributions are shown by the *circles above*. **(B)** Mean normalized recovery curves of all cells as a function of ISD with the ipsilateral *(filled circles)* or contralateral *(open squares)* speaker leading. (Adapted from Tollin et al. 2005.)

2000), and those of unmatched neurons are suppressed. This compressive reorganization creates a more selective representation of biosonar signals (Suga et al. 2002).

The physiological correlates of attentional filtering were predicted by the classic behavioral paradigms (Jane et al. 1965), in which reciprocal functional roles for the central nucleus and dorsal cortex were proposed. Unlike the deafening effects of ICC lesions, surgical manipulations of the dorsal cortex do not impair sound localization but diminish auditory attention. When redundant auditory and visual cues signal an impending electrical shock, intact cats tend to base their avoidance behaviors on auditory information. This natural "prepotency" of the auditory stimulus is supplanted by visual information in cats with lesions of the dorsal cortex.

Cognitive influences such as learning, attention, and compensation represent exciting new directions for future studies of the physiological underpinnings of acoustic behavior. Within the auditory midbrain, it is becoming increasingly clear that while these complex processes are driven by ascending sensory representations, a set of descending perceptual filters that are suppressed by anesthesia, silenced by decerebration, and altered by experience operate in parallel. From this perspective, acoustic behavior provides an essential context for understanding midbrain function.

Abbreviations

AN	auditory nerve
AVCN	anteroventral cochlear nucleus
CD	characteristic delay
CP	characteristic phase
DAS	dorsal acoustic stria
DCN	dorsal cochlear nucleus
DNLL	dorsal nucleus of lateral lemniscus
GBC	globular bushy cell
HRTF	head-related transfer function
IC	inferior colliculus
ICC	central nucleus of inferior colliculus
ILD	interaural level difference
ISD	interstimulus delay
ITD	interaural time difference
LSO	lateral superior olive
MAA	minimum audible angle
MSO	medial superior olive
PE	precedence effect
SBC	spherical bushy cell

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Chapter 16
Auditory Midbrain of Fish, Amphibians, and Reptiles: Model Systems for Understanding Auditory Function

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1. Introduction

We review studies that identify midbrain mechanisms in fish, amphibians, and reptiles that solve acoustic problems common to all vertebrates, including humans. The homologue of the inferior colliculus (IC) in fish, amphibians, and reptiles is the torus semicircularis (TS) (Nieuwenhuys et al. 1998). The TS, like the IC, "is a nexus of the auditory system because it processes and integrates almost all ascending acoustic information from lower centers, and it determines the form in which information is conveyed to higher regions in the forebrain" (Pollak et al. 2003). To remind the readers of this homology, we will use the term TS/IC.

Limited space precludes full review of the studies available on fish and amphibian auditory midbrain (Fay and Popper 1999). We therefore concentrate on neurophysiological studies of the encoding of vocalizations. Studies of nonmammalian audition have long focused on anuran amphibians (frogs and toads), showing how their auditory system is exquisitely adapted to detecting acoustic signals that diverge in spectral and temporal properties both within and between species. Studies of fish have concentrated on sound producing teleosts, whose detection and interpretation of vocal signals is essential for survival and reproduction.

We consider midbrain auditory circuitry devoted to encoding the temporal structure of vocalizations. "Temporal structure" refers to the modulations of the envelope of the acoustic waveform, either its amplitude (AM) and/or frequency (FM) over time. Temporal "fine structure" is the time course of the waveform beneath the envelope, and is most important when substantial energy is concentrated $<$500 Hz. We emphasize temporal codes because "the production and physical reality of animal signals lie in the time domain . . . the time varying acoustic waveform is the physical signal that is actually produced by the temporally patterned action of the motor system under ongoing control of the central

nervous system. . . . The two systems [vocal and auditory] co-evolved and we should expect them to share the same underlying code for signal generation and recognition" (Capranica 1992). Temporal processing has received increased attention in studies of humans (van Tasell et al. 1987; Shannon et al. 1995) and other mammals (Wang 2000; Klug et al. 2002; Nagarajan et al. 2002). We propose that studies of fish and anurans can reveal the most fundamental mechanisms underlying temporal coding in the more complex vocal communication systems of mammals as well as birds.

We also integrate a review of the reptilian auditory system, which is challenging because of the few sonic reptiles and the paucity of central neurophysiological studies for sonic or nonsonic species. The cardinal features of nonmammalian organization are conserved in mammals.

2. Vocalizing Fish

Sound production is widespread among teleost fishes (Fine et al. 1977), the largest group of living fishes and of vertebrates (Pough et al. 2002). Among sonic/vocal fish, we concentrate on two distantly related teleosts, the marine batrachoidids and freshwater mormyrids, species whose midbrain TS/IC has received the most attention among teleosts (Bass and McKibben 2003). Batrachoidids are a single order and family of teleosts of 19 genera that include midshipman fish and toadfish (Nelson 1984). Mormyrids are a single family of 16 genera (Nelson 1984) known for their electrosensory and electrogenic abilities (Bullock and Heiligenberg 1986).

2.1. Vocal Communication Signals of Teleost Fish

The acoustic communication signals of fish, like those of anurans (see Section 3.1), are diverse in their spectral (broadband or tonal harmonic series) and temporal (amplitude or frequency modulations) properties. Signals of fish are perhaps the simplest because the potential for diversity is constrained by the contraction rates of sonic muscles that vibrate or move one body part against another and the absence of a vocal tract and other resonators, although a resonant, gas-filled swimbladder may be involved in some species (Bradbury and Vehrencamp 1998). The simplicity of fish vocalizations can be mimicked with computer-synthesized signals to identify auditory sensitivities with either behavioral or neurophysiological methods. The acoustic signals of midshipman fish (*Porichthys notatus*) exemplify this simplicity. Males court females with long duration (seconds to >1 hour) advertisement calls, "hums," whose fundamental frequency (F0) is 90 to 100 Hz and which have prominent harmonics and essentially a flat envelope shape (Bass et al. 1999; Fig. 16.1). The temporal structure of hums differs from that of "grunts" which are brief (50 to 100 ms), broadband signals that midshipman males produce during agonistic encounters at rates of only 1 to 2 Hz (grunt "trains," Fig. 16.1). The pulse repetition rate

(PRR) in a grunt is similar to the F0 of hums. The temporal attributes of concurrent hums (acoustic beats) and AM-like grunt trains have shaped the design of behavioral and neurophysiological studies of auditory processing (Bass and McKibben 2003).

The temporal structure of mormyrid sounds has strongly influenced psychophysical and neurophysiological studies, where PRR is the vocal parameter of interest (Fig. 16.1). Mormyrids generate species-specific "moans," "grunts," and "growls" (Crawford et al. 1997). Moans are multiharmonic signals with differences in F0 of 200 to 400 Hz and 100- to 200-ms durations. Grunts are broadband, pulsatile signals with durations of 100 to 400 ms and PRRs of 30 to 60 Hz. Growls extend for seconds with PRRs of about 25 Hz.

2.2. *Torus Semicircularis and Inferior Colliculus Circuitry of Teleost Fish*

Like all terrestrial vertebrates, the teleost inner ear has three semicircular canals and two otolithic end organs, a sacculus and a utriculus (Popper and Fay 1999). Teleosts also have an otolithic lagena, a trait shared with anuran and urodele amphibians, reptiles, and birds. One or more of the otolithic organs may detect acoustic (and/or vestibular) stimuli (Popper and Fay 1999). The sacculus is the main auditory end organ in most teleosts (Popper and Fay 1999) and it encodes acoustic stimuli in amphibians (Lewis et al. 1982) and mammals (McCue and Guinan 1994). The macula neglecta is a nonotolithic end organ of unknown function in teleosts. As it serves an auditory function in cartilaginous fishes (Corwin 1981), it may also in teleosts. Some groups, including mormyrids, are categorized as "hearing specialists" because of accessory structures that enhance the detection of a propagating pressure wave. Although "hearing nonspecialists" or "generalists" such as batrachoidids lack these adaptations, their hearing sensitivity is comparable to that of specialists in the relevant frequency range (McKibben and Bass 1999).

While comparisons of hindbrain and forebrain auditory nuclei in teleost fish to those in tetrapods are not entirely resolved, the homology of TS to the IC is widely accepted (McCormick 1999). Studies of both toadfish and midshipman identify corresponding auditory centers at hindbrain, midbrain, and forebrain levels (Highstein et al. 1992; Bass et al. 1994, 2000, 2001; Edds-Walton et al. 1999; Goodson and Bass 2002). Comparable circuitry is found in vocal mormyrids (Kozloski and Crawford 1998; Prechtl et al. 1998; von der Emde and Prechtl 1999) and nonvocal teleosts in general (McCormick 1999) (Fig. 16.2).

The midbrain's TS/IC has separate auditory and lateral line divisions. Although these divisions are often not obvious in Nissl- and Bodian-stained material, they are apparent using neurophysiological and tract-tracing methods. Medullary auditory and lateral line afferents enter the TS/IC via medial and lateral components, respectively, of the lateral lemniscus. The auditory region, nucleus centralis (TSnc, Fig. 16.2A; Knudsen 1977) occupies medial and dorsal TS/IC regions and caps the lateral line-recipient nucleus ventrolateralis (TSvl,

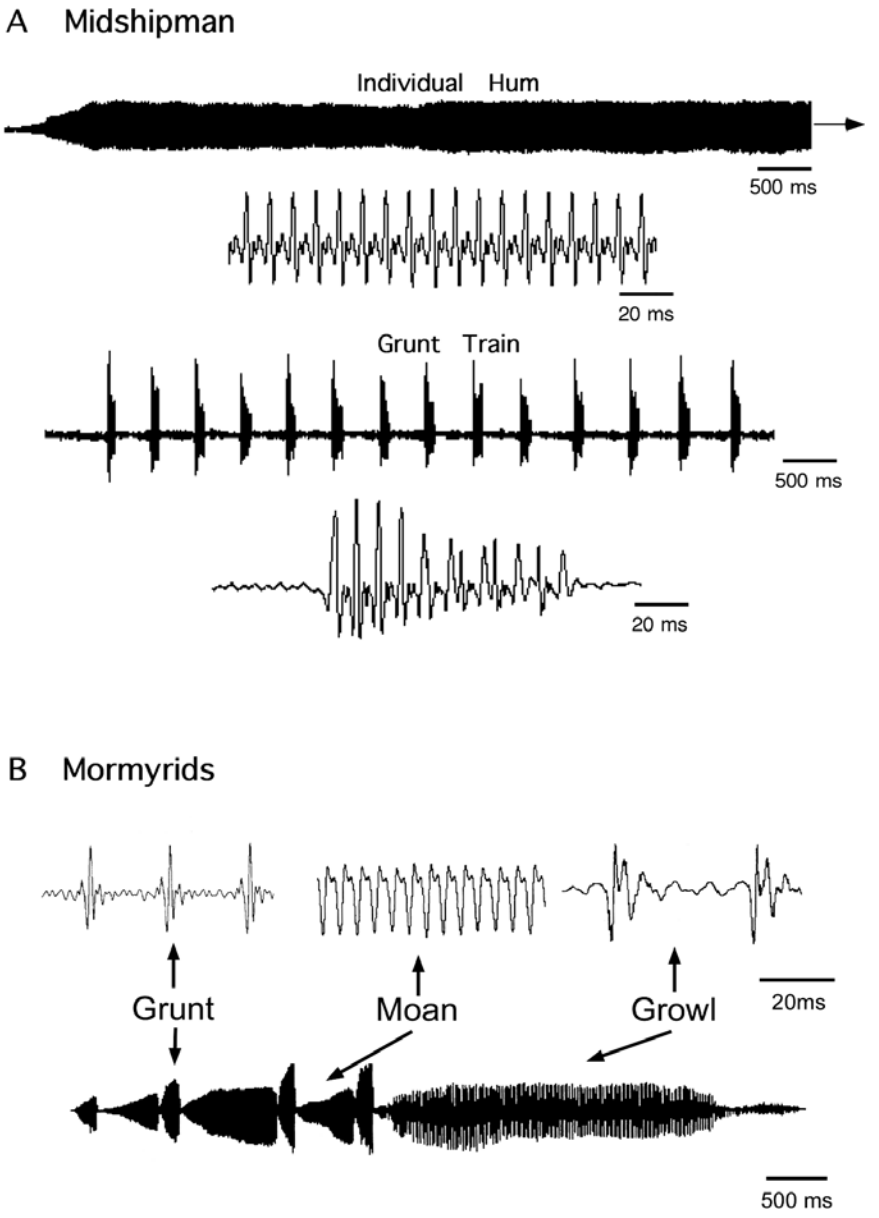

Figure 16.1. Communication signals of vocal fish. **(A)** Oscillograms of a midshipman hum and grunt train on two time scales. (From Bass et al. 1999.) **(B)** Oscillograms of mormyrid grunts, moans and growls on two time scales. (From Crawford 1997.)

Fig. 16.2A). As in anurans and reptiles (see later), TSnc receives input from two medullary auditory nuclei (Fig. 16.2B), one an eighth nerve recipient nucleus, the descending octaval nucleus (DO), and a nearby nucleus, the secondary octaval nucleus (SO) that is DO's main target (Highstein et al. 1992; Bass et al. 1994; Mensinger et al. 1997; Edds-Walton et al. 1999). TSnc is reciprocally connected with multiple hindbrain and midbrain sites including DO, SO, the contralateral TSnc, and several sites involved in vocal production (see Section 2.3). Other brain stem targets of TSnc include a nucleus of the lateral lemniscus, while forebrain targets are the hypothalamus, the posterior tuberculum, and a dorsal thalamic nucleus projecting to the telencephalon (Fig. 16.2B). The precise role of these sites in auditory processing is unknown.

2.3. *Auditory–Vocal Integration*

The pattern of auditory circuitry is similar in nonvocal and vocal teleosts with one important exception: auditory–vocal integration sites have been identified in batrachoidids. Midshipman and toadfish have an expansive vocal pacemaker–motoneuron circuit near the spinal–hindbrain junction that generates rhythmic, oscillatory-like activity similar in frequency and duration to that of natural vocalizations (Bass and Baker 1990, 1991). Each of a pair of midline sonic motor nuclei innervates the ipsilateral sonic muscle attached to the swimbladder walls, a gas-filled chamber involved in buoyancy control (Pough et al. 2002). Vocal pacemaker neurons cluster ventrolateral to the motoneurons and innervate both motor nuclei; their synchronous activation leads to the simultaneous contraction of both sonic muscles (Bass and Baker 1990).

Tracing studies coupled with electrical brain stimulation identify auditory–vocal integration sites at forebrain, midbrain and hindbrain levels (Bass et al. 1994; Goodson and Bass 2000, 2002). The TS/IC projects to low threshold midbrain tegmental activation sites where electrical stimuli evoke fictive vocalizations as monitored by intracranial recordings from the sonic nerve roots (Bass and Baker 1990; Goodson and Bass 2000). These sites include the periaqueductal gray (PAG) and the paralemniscal tegmentum (PL), both of which receive TS/IC input (Fig. 16.2B). As in mammals, the PAG and PL receive auditory input from the IC and are sites of electrically evoked vocalizations (Suga et al. 1973; Metzner 1996; Jürgens 2002). While neurophysiological studies have identified audio–vocal mechanisms in bats (Smotherman et al. 2003), such studies are just beginning in midshipman (Weeg and Bass 2003).

2.4. *Neural Coding of Temporal Parameters*

Like those in other teleosts (Feng and Schellart 1999; Popper and Fay 1999), eighth nerve afferents in batrachoidids and mormyrids provide a periodicity code of frequency by phase locking to temporal modulations of the acoustic waveform's fine structure. As with anuran amphibians (see Section 3.4), the range of

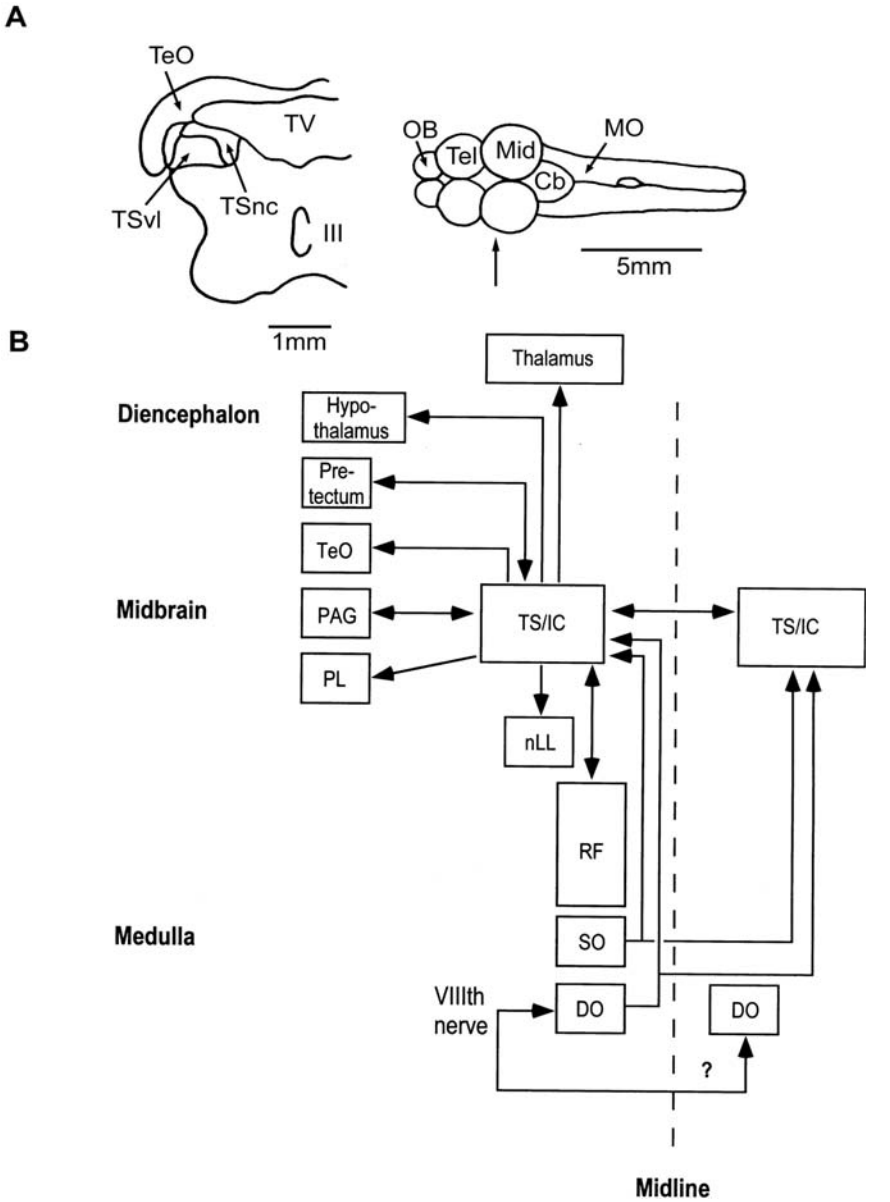

Figure 16.2. TS/IC auditory circuitry in teleost fish. **(A)** A line drawing *(left side)* of a transverse section through the midbrain of midshipman fish (*Porichthys notatus*) showing the position of the auditory division, nucleus centralis (TSnc). Also shown is the lateral line division, nucleus ventrolateralis (TSvl). To the right is a line drawing of a dorsal view of the brain; the *vertical arrow* indicates the approximate midbrain level of the transverse section. **(B)** Schematic diagram of the major components of TS/IC circuitry. Following labeling of one eighth nerve with neurobiotin or biocytin, there is robust filling

frequency sensitivity is consistent with the energy spectrum of each species' calls (Fay and Edds-Walton 1997; McKibben and Bass 1999; Suzuki et al. 2002; Weeg et al. 2002; Sisneros and Bass 2003). Species differences in frequency sensitivity, like the F0s of vocalizations, often reflect differences in recording temperature (Bass et al. 2001). However, other studies of midshipman fish show seasonal changes in frequency sensitivity that are not temperature dependent (Sisneros and Bass 2003). Thus, the onset of male advertisement calling during the breeding season shows upward shifts among females in the frequency sensitivity of their saccular afferents such that it overlaps both the F0 and the most prominent harmonics of the male's hum; afferent sensitivity mainly overlaps only the F0 at other times. Midbrain neurons are more often sharply tuned than primary afferents in both nonvocal and vocal species (Crawford 1993; Lu and Fay 1996; Bodnar and Bass 1997). Seasonal shifts in midbrain frequency sensitivity among vocal species may yet be found.

Studies of midbrain auditory neurons in midshipman have focused on the encoding of acoustic beats because of their prominence in this species' acoustic environment (Bodnar and Bass 1997; Bass et al. 1999). Neighboring males that concurrently hum, generate acoustic beats with a modulation rate determined by the difference frequency (dF) between their F0s (Fig. 16.3). Beats are imitated by two concurrent tones with dFs like the natural range ($<$10 Hz). Playback studies show that beat dF and modulation depth are important parameters for discriminating hums from beats and other vocalizations with low modulation rates (grunt trains, Fig. 16.1) (McKibben and Bass 1998, 2001a).

There is a peripheral-to-midbrain transformation in the temporal coding of a beat's dF and modulation depth. Saccular afferents exhibit robust phase locking to a beat's component tones, and code its modulation rate dF in their temporal modulations of spike rate and synchronization (McKibben and Bass 2001b). By contrast, TS/IC neurons show poor phase locking to tones, but robust phase locking to dFs over their natural range, which is $\pm$10 Hz (Bodnar and Bass 1997, 1999, 2001a). About 35% of midbrain units are broadly tuned across the behaviorally relevant range of $\pm$10 Hz (broad dF-selective, Fig. 16.3B). The remaining units show symmetrical peaks in dF selectivity (narrow dF-selective, Fig. 16.3C); 25% of these units exhibit asymmetrical tuning (narrow dF sign-selective, Fig. 16.3D). This synchronization code cannot be explained by either spike rate profiles (Fig. 16.3E–G) or frequency tuning. Spike synchronization increases with increasing modulation depth; primary afferents increase in both spike rate and spike synchronization (McKibben and Bass 2001b).

Figure 16.2. *Continued*
of medullary (descending octaval; DO) neurons bilaterally, likely due to transneuronal transport (Bass et al. 1994, 2000). Bilateral projections are reported in several teleost taxa (McCormick 1997; Kozloski and Crawford 1998; H. Straka and R. Baker, unpublished observations). ?, evidence for a projection that has not been demonstrated conclusively. For abbreviations please see the list.

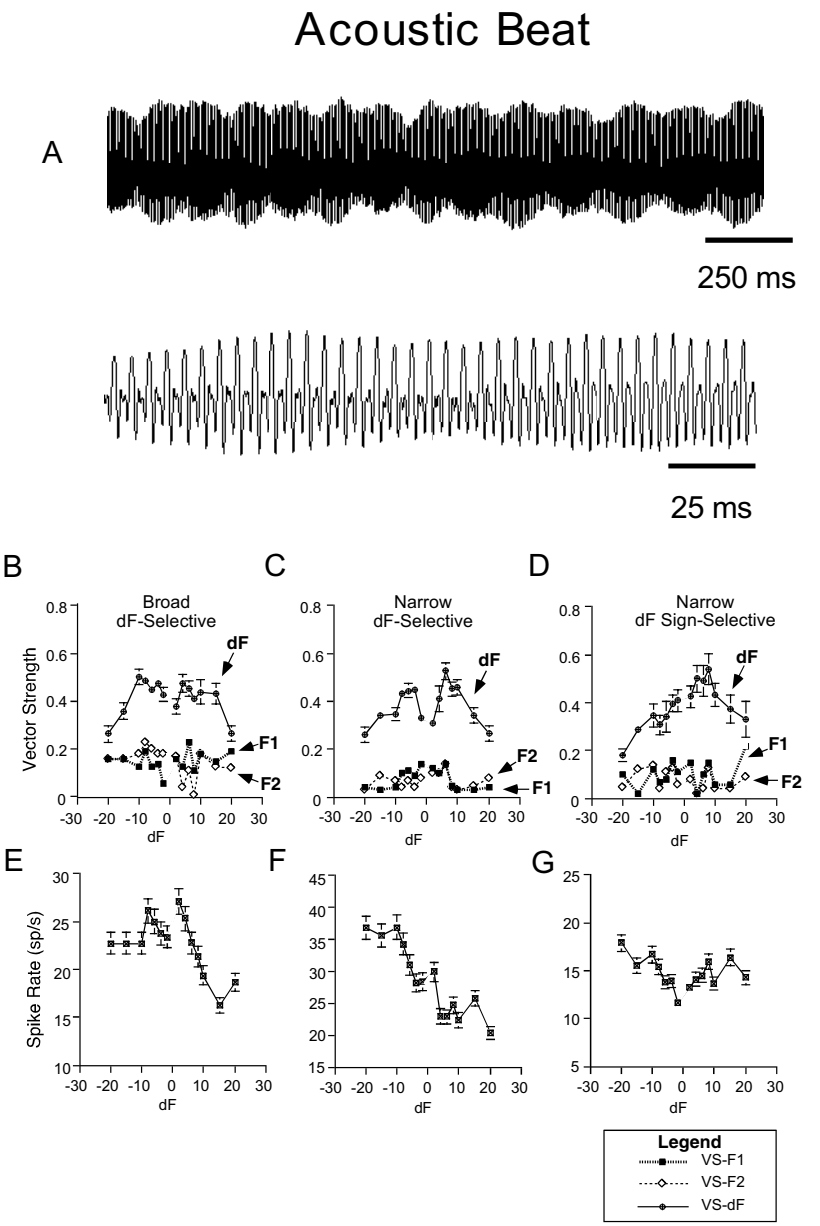

Figure 16.3. Encoding of acoustic beats. **(A)** The temporal waveform of two concurrent hums on two time scales. **(B–G)** Single-unit responses in the auditory midbrain (TSnc) of midshipman fish to beat stimuli. Each stimulus was formed by an F1 of 90 Hz and an F2 of 90 ± 2 to 20 Hz (see legend in lower right). **(B–D)** Plots of vector strength of synchronization (vs. ± SE) over dF stimulus range. Units show a range of dF selectivities, but exhibit low synchronization to the individual components (F1, F2) of a beat. **(E–G)** Corresponding average spike rate (± SE) curves for the same units shown in **(B–D)**. (**B–G** from Bodnar and Bass 1997.)

Other experiments show two midbrain populations of AM-encoding neurons. About 65% of TS/IC neurons have a similar tuning profile for the modulation rate of either beats or AM signals produced by the modulation of a single acoustic waveform's amplitude over time (Bodnar and Bass 1997). Thus, despite differences in fine structure between these signals (beats are formed by the interaction of two waveforms), their envelope shape is often encoded in a similar way. Importantly, 35% of TS/IC neurons distinguish AM-like signals from beats that could contribute to a behavioral distinction between beats and grunts (Fig. 16.1).

In contrast to eighth nerve afferents that show little if any adaptation with increasing sound duration (McKibben and Bass 1999), midbrain neurons show a range of adaptation rates (Bodnar and Bass 2001b). While the lack of evidence for duration selective units is consistent with the behavioral evidence showing that a wide range of tone durations are recognized as hums (McKibben and Bass 1998, 2001a), spike rate variability across midbrain units may contribute to a population code (Bodnar and Bass 2001b).

Mormyrid psychophysical experiments show interclick interval discrimination consistent with the natural variation of PRRs (Marvit and Crawford 2000; Fletcher and Crawford 2001; Fig. 16.1). The click interval sensitivities of midbrain neurons overlap the PRRs of mormyrid moans (5-ms intervals/200 Hz), grunts (20-ms intervals/50 Hz), and growls (40-ms intervals/25 Hz) (Crawford 1997). This temporal code is apparently formed in the midbrain, since medullary neurons have a broad range of interclick interval sensitivities (Kozloski and Crawford 2000). Thus, like midshipman, mormyrid studies provide evidence for midbrain temporal coding.

3. Auditory Midbrain of Anurans

Acoustic communication is vital in the reproductive biology of most anurans. Hence, several robust behaviors can be used to address questions of auditory processing. Phonotaxis and evoked calling paradigms have been particularly important for investigating the auditory system's analytic ability to code the spectral and temporal structure of anuran calls. We emphasize behavioral work that relates to our understanding of the function of the anuran TS/IC (Fay and Popper 1999).

3.1. Vocal Communication Signals of Anurans

Spectrally, most anuran communication signals are narrowband "tonal," broadband, dual-peaked, a harmonic series, or some combination of these. Dual-peaked signals resemble the formant structure of human speech sounds, particularly vowels, which can generally be identified based on their first two formants. In such anuran vocalizations, each spectral peak is within the frequency sensitivity range of one of the two peripheral auditory organs that function primarily for detecting communication signals, the amphibian and basilar

papillae; typically, the higher frequency peak is close to the tuning of the basilar papilla. The bullfrog (*Rana catesbeiana*), for example, produces calls with broad spectral "formants" centered at about 200 Hz and 1400 Hz (Capranica 1965, 1966). The precise positions of these spectral maxima differ among the calls of the various species within this genus. Whereas most interspecific calls differ in spectral and temporal structure, intraspecific call types often are spectrally highly similar and differ chiefly in temporal structure; calls of closely related cryptic species may differ exclusively in their temporal structure.

The basic temporal features of a vocalization are its duration and rise/fall characteristics; the temporal structure of a tonal call can be described by these parameters. Many communication signals of anurans, however, show distinctive, more complex, AM patterns. Sometimes AM reflects the interactions of harmonically related spectral components of the vocalization. In most cases, however, AM results from passive and/or active mechanical processes such as the contractions of thoracic musculature and muscle-related vibrations of the cartilaginous laryngeal elements (Martin 1971; Schneider 1988). The diverse AM patterns probably result from complex active control and passive properties of laryngeal structures. Further involvement of skeletal and respiratory-related musculature in vocalization is absent in teleosts, but enhances potential anuran call diversity and complexity (and in reptiles, birds, and mammals; Bradbury and Vehrencamp 1998). Amplitude modulation ranges from a nearly sinusoidal periodic pattern to discrete sound pulses. The rise and fall characteristics of individual pulses can vary even between the calls of closely related species, and, with PRR, constitute the primary temporal cues that enable discrimination between conspecific and heterospecific calls (Gerhardt 1982, 1988). As discussed later, many intraspecific call types differ virtually exclusively in PRR; individual pulses have similar shapes and spectral composition. Where pulse number is similar between call types, call duration is inversely related to PRR. Anuran PRR is physiologically equivalent to PRR in sonic fish, the number of sound pulses per second. The latter is also the case for F0 in teleosts, but F0 among anurans is determined by vocal cord vibratory properties (Martin 1971). PRR and F0 in teleosts, like PRR in anurans, are established by a central pattern generator (anurans: Schmidt 1976; teleosts: Bass and Baker 1990).

3.2. Behavioral Studies

Evoked calling experiments on bullfrogs demonstrate that energy must be present in the low- and high-, but not in the middle-, frequency regions for stimuli to maximally elicit responses from males (Capranica 1965, 1966). These experiments and others support the concept of a neural AND gate that detects simultaneous low- and high-frequency energy peaks.

Many anuran communication sounds have nearly identical spectral composition but differ in temporal structure. This disjunction occurs in the calls of some closely related species, but is found more commonly in the intraspecific call repertoire of particular species. The intraspecific call types of the Pacific treefrog (*Hyla regilla*) are differentiated virtually completely by temporal structure. Pa-

cific treefrogs produce an "encounter" (aggressive) call and two types of advertisement calls (Allen 1973). These calls consist of pulses, each 10 to 12 ms in duration, repeated at about 25 pulses/s (pps) and 100 pps, respectively (Fig. 16.4A); the exact value depends on temperature. To alter PRR, they change the pulse duty cycle (ratio of pulse duration to interpulse interval). Because the advertisement and encounter pulses are nearly identical in spectral composition, shape, and duration, the calls differ primarily in PRR; calls also differ in duration but this is quite variable (Rose and Brenowitz 2002). Behavioral studies define two discrete sensory "channels" for processing the two call types (Brenowitz and Rose 1994; Rose and Brenowitz 1997). These findings suggest neural filters that are highly selective for PRR. Other behavioral studies (Rose and Brenowitz 2002) indicate that temporal filters tuned to the fast PRRs, as found in the advertisement calls of *H. regilla*, respond only after several consecutive pulses, delivered with 10-ms interpulse intervals (time between onsets of adjacent pulses), have occurred.

An excellent example of temporal differentiation in the calls of closely related anurans is the advertisement calls of two species of gray treefrogs, *H. versicolor* and *H. chrysoscelis*, which differ only by chromosome number and call structure (Gerhardt 1982). Their advertisement calls are spectrally essentially identical, but differ in temporal structure (Fig. 16.4B). The *versicolor* advertisement pulses have slower rise time, longer duration and slower PRR. Female gray treefrogs use both pulse shape and PRR to select a conspecific's advertisement call over that of the other species (Gerhardt 1988; Diekamp and Gerhardt 1995).

Frequency modulation (FM) is especially common among certain anuran genera (e.g., *Leptodactylus* and *Physalaemus*). The call direction and rate of frequency change is species-specific, with some using upsweeps and others downsweeps. The FM frequency range in these calls corresponds to that represented by the sensitivity range of the amphibian papilla. Interestingly, species such as *L. labialis* have calls with concurrent AM and FM (Straughan and Heyer 1976). In the advertisement calls of the Tungara frog, *P. pustulosis*, frequency sweeps downward exponentially from 900 Hz to 300 Hz (Fig. 16.4C) as signal amplitude decreases smoothly. In phonotaxis studies with *P. pustulosis*, females chose the forward call over a time-reversed version (Ryan 1983). Behavioral (evoked calling) studies of males showed that they can discriminate, in an intensity-independent fashion, between synthetic signals that differ only in FM direction (Rose et al. 1988).

3.3. Anuran Torus Semicircularis/Inferior Colliculus Circuitry

Anurans possess amphibian and basilar papillae and there is evidence for an acoustic function for the sacculus. The amphibian papilla is unique to amphibians, while the basilar papilla may be homologous to that of reptiles, birds, and mammals (Lewis and Narins 1999; McCormick 1999). Anuran brain stem auditory regions are homologous to the major auditory areas in the mammalian brain stem (Wilczynski 1988; Feng and Lin 1991; ten Donkelaar 1998a; Mc-

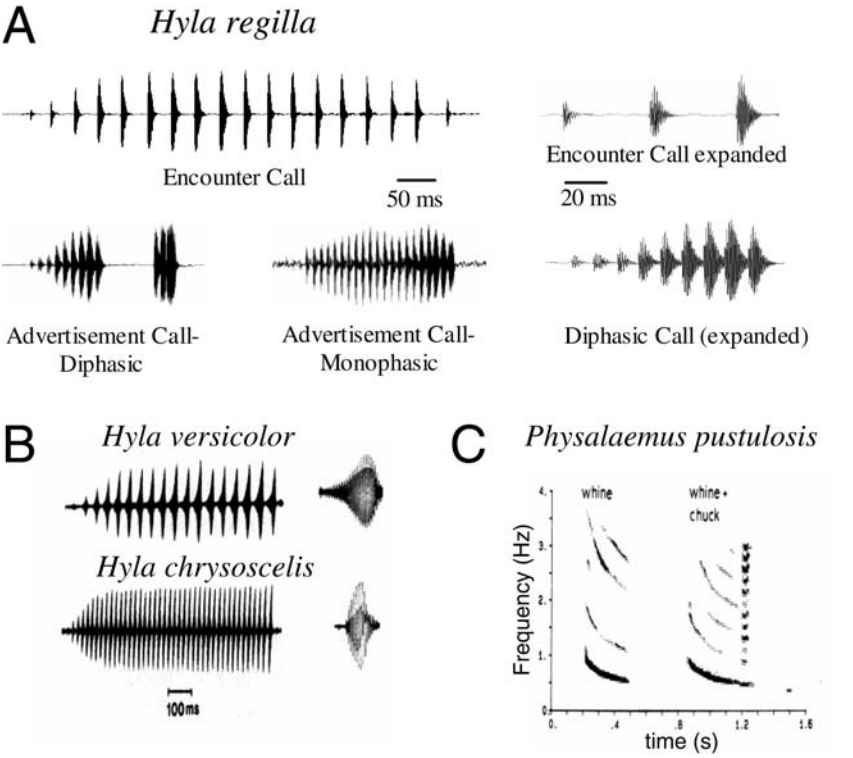

Figure 16.4. Anuran communication signals. **(A)** Oscillograms of encounter and advertisement calls of *Hyla regilla*; advertisement calls consist of diphasic and monophasic types. **(B)** Oscillograms of advertisement calls of *H. versicolor* and *H. chrysoscelis*. **(C)** Spectrograms of advertisement calls of *Physalaemus pustulosis*; the frequency-modulated (whine) portion can be followed by one or more harmonically rich "chucks."

Cormick 1999). The TS/IC has laminar, principal, and magnocellular subdivisions (Fig. 16.5A). Afferents include the dorsal lateral nucleus (DLN, first-order auditory region), the superior olivary nucleus (SO, second-order target of auditory input from the DLN), and the lateral lemniscal nucleus (nLL, also termed the superficial reticular nucleus) near the reticular formation. Portions of the TS/IC also receive afferents from the pretectum, preoptic area and hypothalamus. The TS/IC has reciprocal connections with SO, the nLL and the contralateral TS/IC. The TS/IC projects to three thalamic nuclei (anterior, central, and posterior), some of which also receive SO input (Fig. 16.5B).

3.4. Spectral Processing in Anuran Torus Semicircularis/Inferior Colliculus

The range of spectral sensitivity of units in the anuran TS/IC parallels that seen in the auditory nerve. This range is represented by the frequency sensitivities of

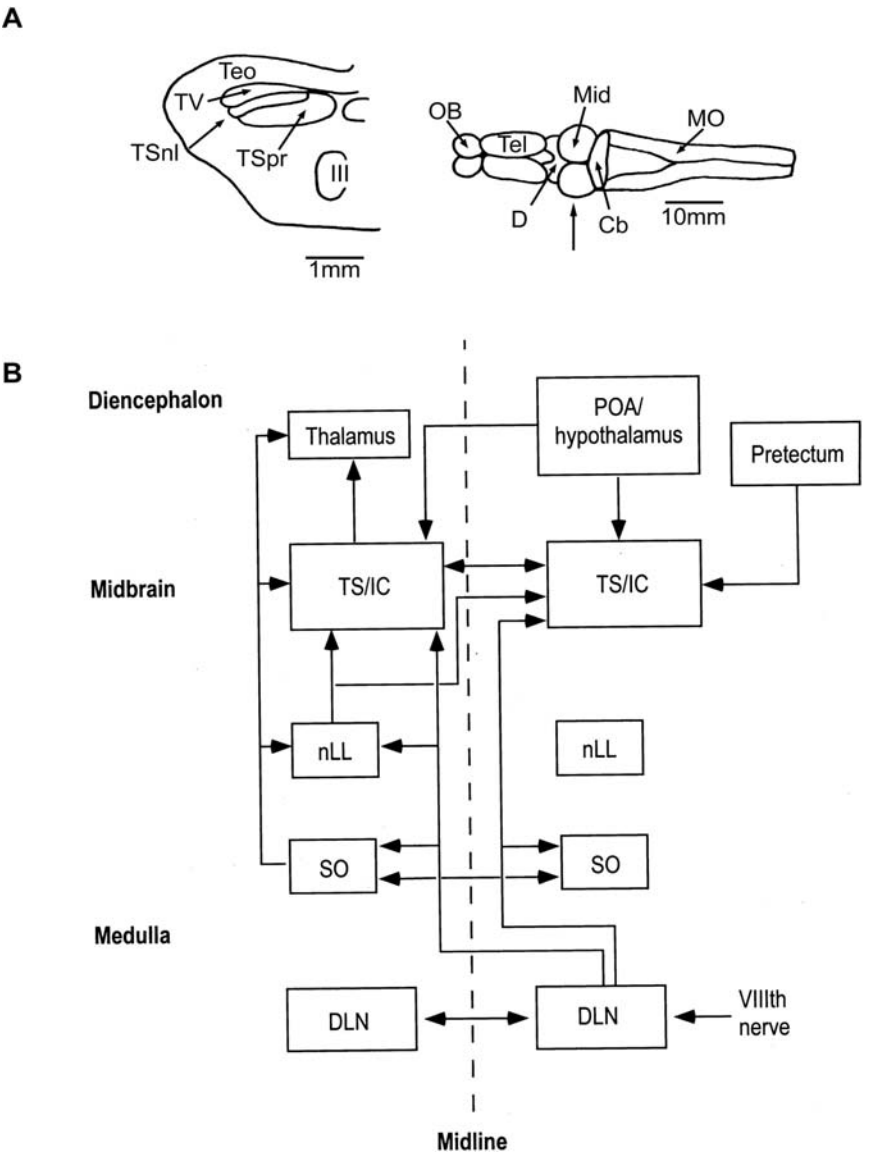

Figure 16.5. TS/IC auditory circuitry in anurans. **(A)** A line drawing *(to the left)* of a transverse section through the midbrain of the bullfrog, *Rana catesbeiana*, showing the position of the laminar (TSnl) and principal (TSpr) nuclei. A magnocellular division has no clearly defined boundaries but includes large cells that lie ventral and lateral to TSnl and TSpr. To the right is a line drawing of a dorsal view of the brain; the *vertical arrow* indicates the approximate midbrain level of the transverse section. **(B)** Schematic diagram of the major components of TS/IC circuitry as described in the text. The TS/IC also receives contralateral SO and nLL input and has bilateral outputs to SO and nLL (not shown for simplicity, but see Feng and Lin 1991). [Line drawings in **A** and **B** based, respectively, on Northcutt (1974) and Wilczynski and Northcutt (1983).]

the amphibian and basilar papillae (Lewis and Lombard 1988). Basilar papilla units are tuned to higher frequencies and excitatory responses cannot be suppressed by higher frequency tones. The tonotopically organized amphibian papilla represents the low- and mid-frequency range, with only the low-frequency sensitive fibers, those innervating rostral segments, showing two-tone suppression. Like auditory-nerve fibers, many TS/IC units have a single region of frequency sensitivity; some cells even show V-shaped excitatory frequency tuning curves. Unlike eighth-nerve fibers, however, many TS/IC neurons have well developed inhibitory receptive fields that are not attributable to peripheral two-tone suppression (Walkowiak 1980; Fuzessery 1988; Hall 1994). Thus, units most sensitive to middle frequencies can be inhibited by frequencies below and/or above their excitatory regions. As a result, a major transformation in coding is that many individual TS/IC neurons in anurans show "level-tolerant" frequency sensitivity in which the excitatory frequency band is a narrow region independent of stimulus intensity; in the most extreme cases, excitatory receptive fields consist of a discrete region in frequency-amplitude "space." Blocking γ-aminobutyric acid-A ($GABA_A$) receptors with bicuculline showed that neural inhibition underlies these complex receptive fields (Hall 1994).

Approximately 3% of TS/IC neurons have two regions of frequency sensitivity (W-shaped tuning curves); in some cases this W function is shallow, indicating that the neuron simply shows very broad frequency tuning (Walkowiak 1980). Although most neurons with W-shaped tuning curves respond when energy is present in either of their excitatory receptive field regions, a few show properties characteristic of an "AND" logical operation, responding only, or in a facilitated manner, when energy is in both frequency bands. Units that require energy in both low- and high-frequency bands represent the neural correlate of the AND gate proposed as the filter matched to the spectral structure of the advertisement call (bullfrogs and leopard frogs). This spectral selectivity can be more generally classified as "formant selectivity." Such selectivity is rare in the anuran TS/IC, but robust in the posterior thalamic nucleus (Fuzessery and Feng 1983).

3.5. Temporal Processing in Anuran Torus Semicircularis/Inferior Colliculus

As discussed previously, the temporal structure of anuran communication signals is important in their reproductive biology. What neural mechanisms underlie the abilities of anurans to discriminate between calls that differ in temporal structure? We next consider how patterns of AM are represented and processed in the auditory system.

Constituting early evidence suggesting midbrain specializations for processing AM signals, some neurons in *R. ridibunda* preferred amplitude-modulated tones to pure tones, and maximally synchronized their spikes to a particular phase of the modulation cycle at rates of 10 to 20 Hz AM (Bibikov and Gorodetskaya 1980). Also, TS/IC units were recorded that responded to a sequence of sound pulses, but not to pure tones (Walkowiak 1980). Sinusoidally amplitude-

modulated (SAM) white noise stimuli were used to further investigate how AM is represented in anurans. With white noise as the carrier, long-term spectral properties of the stimulus do not change with AM rate; selective neural responses, therefore, reflect temporal, not spectral, stimulus features. While auditory-nerve fibers coded AM rate in their discharge periodicities, their mean spike rate was independent of the AM rate; this result is perhaps not surprising because stimulus energy and spectral properties were constant across AM rate. In the anuran TS/IC, however, the firing rate of most neurons depended strongly on the AM rate (Rose and Capranica 1983, 1985). This conclusion is supported by many studies in which AM rate or sound pulse repetition rate was varied (Walkowiak 1988; Diekamp and Gerhardt 1995). For sinusoidal AM, the temporal selectivity of cells is level-tolerant and is classed as low-pass, high-pass, band-suppression, or band-pass. About one third of the cells are band-pass types, responding best over a narrow range of modulation rates ("AM-tuned"). Using tonal carriers as stimuli, almost 70% of TS/IC cells are band-pass to the AM rate (Alder and Rose 2000). Similarly, band-pass selectivity for the AM rate is seen in avian (Albert et al. 1989) and mammalian midbrain cells (Langner 1992; Krishna and Semple 2000; Langner et al. 2002).

Remarkably, anuran TS/IC neurons most sharply tuned to AM poorly encode the modulation rate in their discharge periodicity (quantified by calculating a synchronization coefficient) (Rose and Capranica 1984; Rose 1995). Similarly, in mammals, there is a significant reduction in spike synchronization to the AM stimulus at the midbrain (Langner 1992; Eggermont 2001; Frisina 2001). The transformation from a peripheral periodicity code of AM rate to a temporal filter representation in the midbrain has been observed for fish (see Section 2.4), frogs (Rose and Capranica 1983, 1985), birds (Langner 1981), and mammals (Langner and Schreiner 1988; Pinheiro et al. 1991; Condon et al. 1996). The distribution of AM tuning values for anuran TS/IC neurons is species-specific and nicely related to the range of PRRs in their calls (Rose and Capranica 1984; Rose et al. 1985).

The mechanisms that underlie AM selectivity are only beginning to be understood. Theoretically, band-pass selectivity for SAM waveforms might arise from sensitivity to stimulus rise time and duration. Although some anuran TS/IC neurons are sensitive to stimulus rise time and/or duration, these properties contribute little to their AM selectivity (Gooler and Feng 1992; Alder and Rose 2000). For example, band-pass selectivity exists for square-wave AM, where pulse rise time is constant across AM rates.

Rise-time sensitivity accounts only for the slight differences in the shapes of band-pass functions for square-wave AM vs. sinusoidal AM; at slow AM rates, responses are weaker for sinusoidal AM because cells prefer fast rise times. This preference appears to originate in auditory regions caudal to the anuran TS/IC. Neurons in DLN and SO that respond phasically to tone bursts prefer rise times $<$25 ms (Hall and Feng 1988, 1991; Condon et al. 1991). Their phasic response properties may account for their diminished responses to slow SAM rates (Hall 1994). Bicuculline injections, presumably reversing their phasic properties, can

transform neurons from band-pass to low-pass, and from high-pass to all-pass (Hall 1994).

Processes other than just rise time and duration sensitivity must therefore underlie the band-pass selectivity of TS/IC neurons. This conclusion is perhaps not surprising considering that the intraspecific calls of many anurans differ primarily in PRR, not pulse shape or duration, for example, *H. regilla* (see Section 3.2). As predicted from the behavioral studies described previously, extracellular single-unit recordings confirm that one class of TS/IC neurons responds highly selectively to fast PRRs, as in the advertisement calls, but not to PRRs seen in the encounter call (25 pps) (Alder and Rose 1998, 2000). These neurons respond only after a threshold number of pulses, each separated by a cell-specific interpulse interval (time between the onsets of consecutive pulses) (Fig. 16.6A). The salient temporal feature for eliciting responses is the number of consecutive "correct" intervals rather than mean pulse rate, suggesting an interval-counting process (Edwards et al. 2002). This integration process may account for the impressive selectivity of these units for AM or PRR. Remarkably, a single interval that falls outside a particular range can reset the integration process (Fig. 16.6B–D). This integration process bears some similarity to "sequence sensitivity" in cat auditory cortex (Brosch and Schreiner 2000) and to combination sensitivity in bat auditory cortex (O'Neill and Suga 1979) and in songbird forebrain (Margoliash 1983; Margoliash and Fortune 1992). An integration process of this nature may contribute to AM rate discrimination in humans (Lee 1994).

Surprisingly, the enigmatic "band-suppression" neurons, so called because they respond to slow and fast, but not intermediate, AM rates, are also interval-integrating types (Edwards et al. 2002). Relative to band-pass neurons, these cells require few (median: 2) intervals and have broad interval tolerance. Thus, mechanistically, and perhaps functionally, band-suppression neurons and band-pass interval-integrating neurons may be one physiological class.

Another class, the "recovery neurons," respond well to slow PRRs, but only weakly at the onset of faster PRR stimuli (Alder and Rose 2000). At slow PRRs and AM rates, they respond phasically to each pulse and, therefore, are low-pass when pulse shape, duration and number are held constant, and band-pass to SAM (Fig. 16.7). These findings suggest that recovery processes contribute to their PRR selectivity; after the excitation from a stimulus pulse, a recovery period is required before the next pulse can excite the cell. The phasic nature of these responses may reflect inhibition, as bicuculline can transform neurons from band-pass to low-pass (Hall 1994).

Most TS/IC neurons selective for AM rate are either recovery- or interval-integrating types. Thus, we suggest there are primarily two physiologically distinct classes of AM selective neurons. The mechanisms that underlie the integration process in the "interval-counting" neurons and the recovery process of the "recovery-type" cells are unknown. Temporally selective TS/IC neurons are hypothesized to project to the central thalamic nucleus (Hall and Feng 1987). Thus, parallel spectral and temporal processing continues at the posterior and

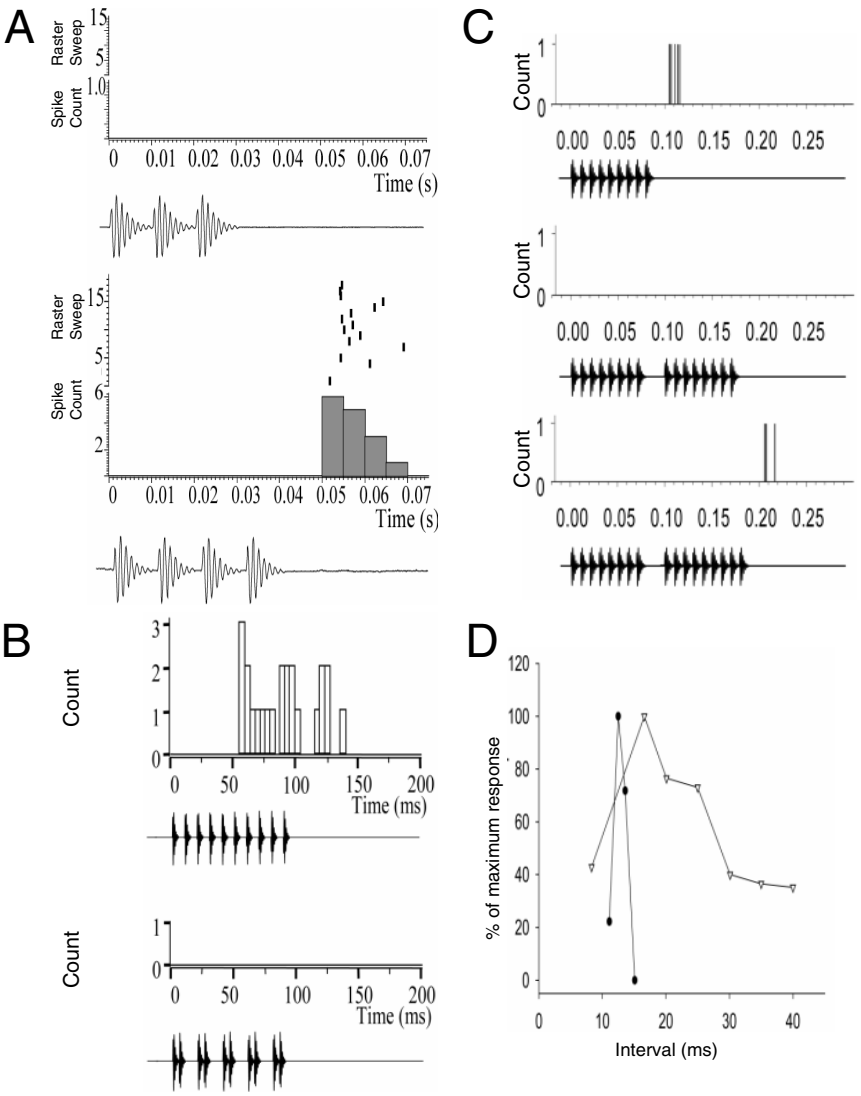

Figure 16.6. Properties of integration-type midbrain neurons that respond selectively to fast PRRs. **(A)** Raster plots and histograms of responses of a unit to multiple repetitions of stimuli having three *(top)* or four *(bottom)* pulses. **(B)** Histograms of responses to stimuli consisting of nine consecutive intervals of 10 ms each *(top),* or alternating 5-ms or 15-ms intervals *(bottom).* **(C)** Effects of a single long (30-ms) interval in resetting the interval-integrating process; this unit had an interval number threshold of 8. **(D)** Normalized response levels of two units as a function of the duration of a single interpulse interval embedded in a series of optimal intervals. (Adapted from Edwards et al. 2002.)

central thalamic nuclei, respectively (Hall and Feng 1987). Further spectral processing involves generating "AND-type" selectivity, where neurons respond only if energy in two spectral bands occurs simultaneously. Central nucleus neurons show temporal selectivity; however, further work is needed to delineate how it differs from temporally selective TS/IC neurons.

4. Reptilian Auditory Midbrain

Residing in the reptilian tectal plate are the modalities of vision, somatic sensation, and audition. Although each modality is represented in an individual target area, sensory channels are not entirely separate and multimodal neurons exist (Kachunts 1982; Belekhova et al. 1985). Vision is represented in the optic tectum (Ulinski et al. 1992) and somatic sensation is located in the caudolateral midbrain roof (Ebbesson 1967; Pritz and Stritzel 1989). As with fish and amphibians, the TS is the midbrain auditory area and the reptilian homologue of the mammalian IC (ten Donkelaar 1998b).

4.1. Morphology and Subdivisions of Reptilian Torus Semicircularis/Inferior Colliculus

The morphology and complexity of the TS/IC varies among species, reflecting the role audition plays in their behavior. The optic tectum rings the TS/IC on all but its ventral surface where it is bounded by the midbrain tegmentum (Díaz et al. 2000). The tectal ventricle separates the optic tectum from the TS/IC. Internal subdivisions exist in the TS/IC. The main auditory portion is the central nucleus (TSnc, Fig. 16.8A). The deep layers of the optic tectum are continuous with TSnc. This feature has been used to distinguish an external or lateral nucleus (also known as nucleus laminaris), continuous with the deep tectal layers, from TSnc (Pritz 1974; Browner and Rubinson 1977; Browner and Baruch 1984) (Fig. 16.8A). In other reptiles an additional subdivision termed cortical (Browner and Rubinson 1977) or superficial (Browner and Baruch 1984) has been described, and in some reptiles (Tegu lizards) the central nucleus is subdivided into two regions (Browner et al. 1981). The topographic relations and individual cellular morphology of each of these subdivisions have been detailed in several species. Selected features of neuronal morphology (Table 16.1) and immunocytochemical/histochemical properties (Table 16.2) are summarized.

4.2. Reptilian Torus Semicircularis/Inferior Colliculus Circuitry

The basilar papilla is the main auditory organ in reptiles; its morphology varies widely especially among lizards (Manley 2000). Many brain stem subdivisions project to the central nucleus of the torus, which is part of a larger scheme (Fig.

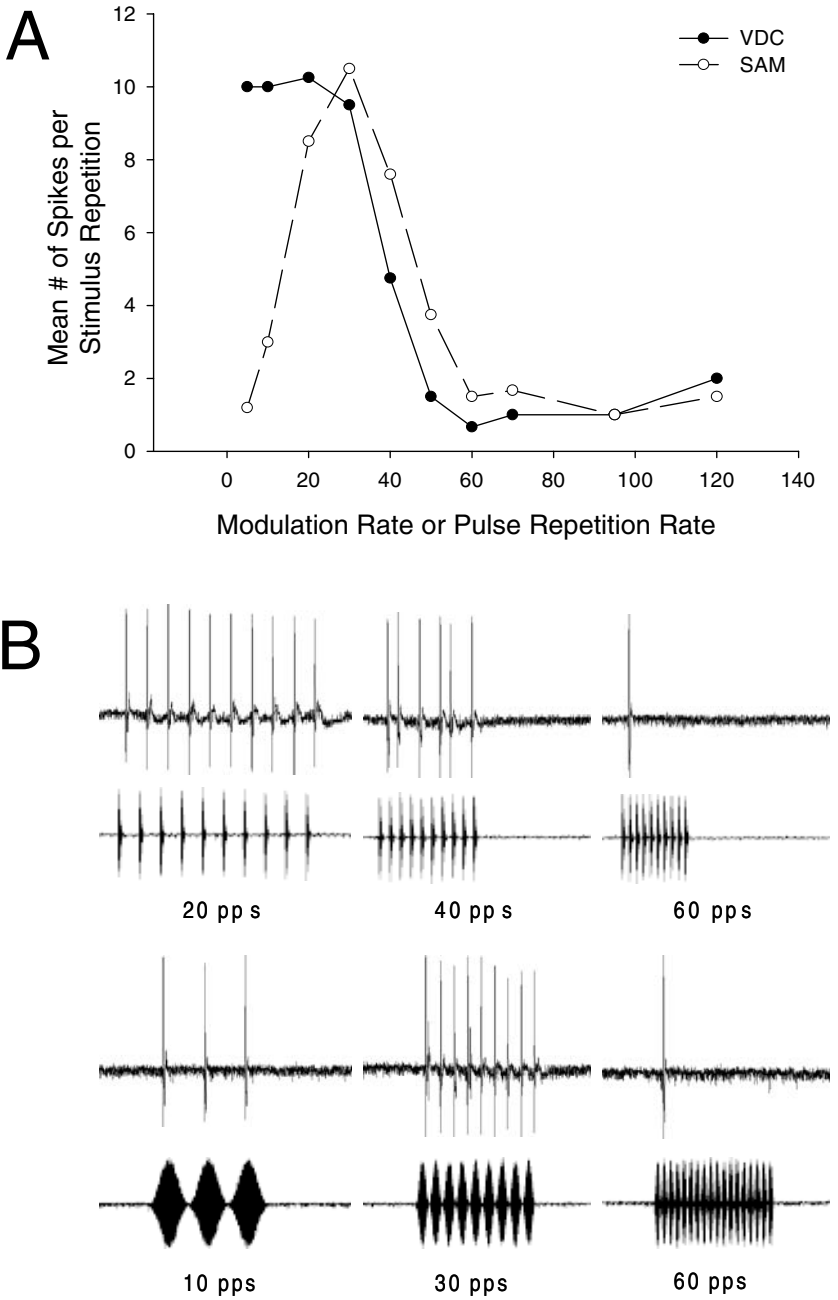

Figure 16.7. "Recovery-type" neuron. **(A)** This unit showed band-pass properties to sinusoidal AM (SAM) rate, but was low-pass for stimuli when only pulse repetition rate was varied (variable duty cycle [VDC], pulse number, shape, and duration were constant). **(B)** Phasic responses of this unit to stimuli of these two types. (From Alder and Rose 2000.)

Table 16.1. Cell types within the TS/IC in several reptiles.

Subdivision	Somatic shape	Somatic diameter (μm)	Spines	Species[a]
Central nucleus	Round	6–25	Few	Turtle
		6–12	Many	Skink
		13–21	Some	Lizard
	Triangular	15–27	Rare	Turtle
		14–28	Few	Skink
		21–27	Moderate	Lizard
	Fusiform	10–26	None	Turtle
		20–30	Few	Skink
		19–21	—	Lizard
Laminar nucleus	Ovoid	9–15	Few	Turtle
		8–12	Many	Skink
		14–20	Few	Lizard
	Triangular	20–40	None	Turtle
		18–28	Few	Skink
		19–36	None	Lizard
	Fusiform	20–40	None	Turtle
		20–40	None	Skink
		18–33	Few	Lizard

[a]Based on data on turtles (Browner et al. 1981), skinks (Browner and Baruch 1984), and lizards (Browner and Rubinson 1977).

16.8B). Brain stem projections to the central nucleus arise bilaterally from the cochlear nuclei, with a contralateral predominance (Foster and Hall 1978; Belekhova et al. 1985; Künzle 1986), bilaterally from the superior olive (Foster and Hall 1978; Belekhova et al. 1985) and from the nucleus of the lateral lemniscus (ipsilateral in iguana, Foster and Hall 1978 and bilaterally in turtles, Belekhova et al. 1985). Ascending connections of TS terminate bilaterally, with an ipsilateral dominance in a caudomedial thalamic nucleus, nucleus reuniens (Pritz 1974; Browner 1983; Belekhova et al. 1985) or medialis (Foster and Hall 1978). Additional ascending terminations target a nucleus embedded in this tectoreuniens fiber tract (Pritz 1974) and a separate, lateral portion of nucleus reuniens, the pars diffusa, as opposed to the heavier terminations in the pars centralis (Pritz 1974).

Descending connections of the TS/IC have not received much attention experimentally. Limited data describe descending efferents as terminating primarily in the ipsilateral midbrain and medullary reticular formation and nucleus of the lateral lemniscus (Foster and Hall 1978). In addition to commissural projections to the opposite central nucleus, axons terminate in the ipsilateral deep layers of the optic tectum (Foster and Hall 1978; Belekhova et al. 1985) (see Chapter 6).

Experimental analyses of nucleus laminaris neural circuitry are likewise limited. Efferents have been traced to the spinal cord (ten Donkelaar and de Boer-van Huizen 1978; Butler and Bruce 1981; Follett 1989), the inferior raphe (ten

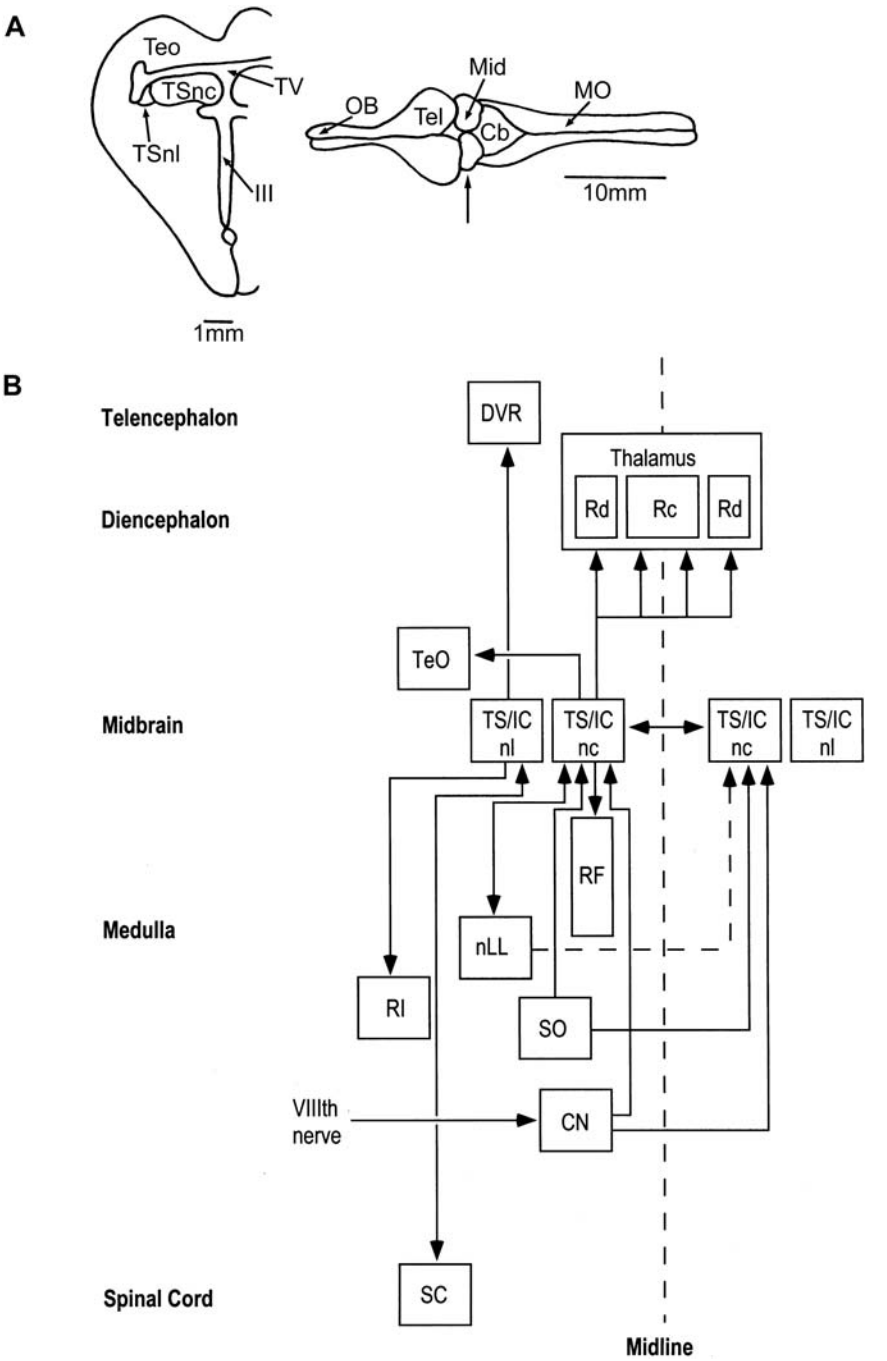

Figure 16.8. TS/IC auditory centers in reptiles. **(A)** A line drawing *(to the left)* of a transverse section through midbrain of the crocodile, *Caiman crocodilus*, showing the position of the central (TSnc) and laminar (TSnl) nuclei. To the right is a line drawing of a dorsal view of the brain; the *vertical arrow* indicates the approximate midbrain level of the transverse section. **(B)** Schematic diagram of the main components of TS/IC circuitry as described in the text. [Line drawings based on Pritz (1974).]

Table 16.2. Immunocytochemical properties of the torus semicircularis of turtles[a]

	Subdivision			
	Central Nucleus		Laminar Nucleus	
Marker	Fibers/Boutons	Cells	Fibers/Boutons	Cells
5-HT	+	−	+++	−
TH	+	−	+++	−
SP	+	−	+++	+
*m*ENK	+	−	+++	+
NPY	+++	+	+++	+
NADPH-d	++	++	+++	+++

Density: +, Light; ++, moderate; +++, heavy; −, not described.

*m*ENK, met enkephalin; 5-HT, serotonin (5-hydroxytryptamine); NADPH-d, nicotinamide adenine dinucleotide-diaphorase; NPY, neuropeptide Y; SP, substance P; TH, tyrosine hydroxylase.

[a]Based on data of Belekhova et al. (2002).

Donkelaar and de Boer-van Huizen 1987), and the anterior dorsal ventricular ridge (ten Donkelaar and de Boer-van Huizen 1988), while afferents come from the spinal cord (Künzle and Woodson 1982).

4.3. Neurophysiological Studies of Auditory Torus Semicircularis/Inferior Colliculus

Electrophysiological studies have investigated response to sound in several reptilian groups. Auditory units have been recorded in lizard central nucleus (Kennedy 1974; Foster and Hall 1978) and in *Caiman crocodilus*, where the most detailed information is available (Manley 1971). In *Caiman*, TS/IC is organized tonotopically. Most units have phasic responses with the characteristic frequency of individual units varying from 70 to 1850 Hz. Tuning curves often were V-shaped. Although unimodal auditory units were identified in the torus of turtles, some cells were bimodal, responding to both audition as well as somatic sensation (Kachunts 1982). Characteristic frequencies ranged from 40 to 6000 Hz with optimal frequencies between 100 and 400 Hz. Three types of discharge patterns were observed: phasic, burst, and sustained (Kachunts 1982).

4.4. Brain Stimulation and Behavior Studies

Regardless of whether some central nucleus units are bimodally responsive to both auditory and somatic sensory stimuli, audition is the dominant modality. However, vocalization, as elicited by electrical stimulation, is localized to the lateral nucleus (Kennedy 1975). Not surprisingly, the lateral nucleus rather than the central nucleus contains androgen receptors (Tang et al. 2001). This is potentially significant because geckos are the only lizards capable of producing

complex sounds involved in social behavior (Carr 1992). Although not yet examined in geckos or other lizards, ultrastructural analyses in turtles, which do vocalize (Carr 1992), revealed lipid-like droplets and agranular endoplasmic reticulum in certain nucleus laminaris neurons. These are features of steroid secreting cells (Drakontides and Browner 1986).

4.5. Common Features of Torus Semicircularis/Inferior Colliculus Organization in Reptiles

This brief review of relevant anatomical, physiological, and behavioral features of the TS/IC notes significant areas where data are either limited or lacking for both the central nucleus as well as the external or laminar nucleus. Nevertheless, certain key features are salient. First, much of the midbrain neural circuitry for audition among reptiles is similar although not identical. Second, nucleus laminaris is probably involved in vocalization and this behavioral feature is likely to be influenced by steroid hormones. Third, unlike in mammals (see Chapter 8), no long efferent tracts of telencephalic origin (either cortex, dorsal ventricular ridge, or striatum) to the torus have yet been described in any reptilian group, or in fish and amphibians.

5. Concluding Comments and Directions of Future Work

Fish model systems present the simplest and perhaps most ancient extant example of how a vertebrate auditory system encodes context-dependent vocal signals. In some teleosts, like the species discussed here, the physical attributes of the acoustic waveform are essentially a direct translation of the temporal attributes of a central pattern generator (CPG). This work has demonstrated a vocal–acoustic network that closely resembles the organizational pattern in mammals, while showing how that circuitry can modulate the output of the vocal CPG. Behavioral studies demonstrate that the recognition of temporal structure is an essential acoustic task: studies of midshipman fish emphasize the importance of recognizing perturbations of the acoustic waveform's envelope shape for distinguishing advertisement calls (hums) that essentially lack any envelope modulation from AM-like signals (beats and grunt trains), while studies of mormyrids provide evidence for the recognition of interclick intervals that compare closely to the PRRs of their calls. As in other sonic vertebrates, the range of frequency sensitivity of both eighth nerve afferents and midbrain neurons is consistent with the energy spectrum of each species' calls. Midbrain auditory neurons in midshipman and mormyrids are well adapted to encode the temporal structure of acoustic waveforms: the midshipman's acute behavioral sensitivity to dF, the modulation rate of acoustic beats, is matched by dF-selective neurons; the mormyrid's sensitivity to PRR is paralleled by interval-selective neurons.

The biophysical mechanisms underlying midbrain temporal sensitivity are unknown but studies of the electrosensory system of other teleosts (Fortune and Rose 2001) suggest that fish model systems hold great promise in this regard. Given the evolutionary emergence of the most fundamental mechanisms of vertebrate audition in fishes, such studies will influence both our basic understanding of the evolution and development of auditory and audio–vocal mechanisms and the functional organization of genetic model systems (zebrafish).

The temporal structure of anuran vocalizations are more complex than those of fish, in part because of the specialized coupling between vocal organs, respiratory-related musculature and resonant chambers that enhance the coupling of the vibrations of their vocal organs to terrestrial habitats (Bradbury and Vehrencamp 1998). Intraspecific call types often are spectrally similar and differ only in temporal structure; moreover, the calls of closely related species may only differ in their temporal structure. Studies in anurans first showed that a peripheral periodicity code of AM is transformed in the midbrain into a temporal filter representation. The distribution of AM tuning values for anuran TS/IC neurons are species-specific and match the range of call PRRs. This resembles the peripheral-to-midbrain transformations for the encoding of dF and PRR in fish. Further studies in anurans have revealed two populations of AM neurons encoding interpulse intervals. Theoretical studies suggest that the interplay between excitation and inhibition might underlie temporal selectivity, particularly interval analysis, in hearing (Buonomano 2000; Large and Crawford 2002). In these models, interval analysis stems from differences in the timing, time course and plasticity (Buonomano 2000) of excitatory and inhibitory inputs. GABAergic inhibition is present in the anuran TS/IC (Hall 1994, 1999), but its role in temporal processing is incompletely understood. Intracellular studies should be pivotal in testing these models and revealing the mechanisms that underlie temporal selectivity.

As noted earlier, the temporal structure of acoustic signals is characterized primarily by the changes in amplitude and frequency over time. Anurans offer the opportunity to study the neural representations and processing of these two forms of temporal information in isolation because particular species specialize in the use of AM or FM. Although there have not yet been any neurophysiological investigations of FM processing in anurans, they provide tractable systems in which to study how FM information is represented and the mechanisms that underlie FM selective behavioral responses.

Studies of reptiles remain essential to a more complete understanding of the auditory system of birds and mammals because of their pivotal position in the phylogeny of amniotic vertebrates. The general organization of the central auditory system of reptiles resembles that of birds and, to a lesser extent, that of mammals (Manley 2000). Besides those differences mentioned earlier (such as a lack of direct telencephalic input to the midbrain), multiple forebrain representations and their associated neural circuitry seem to be the rule rather than the exception in birds and mammals (Nieuwenhuys et al. 1998). Similar features have not yet been documented in reptiles with the exception of a second tel-

encephalic auditory area in crocodilians (Pritz and Stritzel 1992). Such anatomical data have prompted the view that the central nervous system of reptiles is dominated by the midbrain (Kappers et al. 1967) but such generalizations for these and other nonmammalian groups must be tempered by the sparse behavioral and physiological evidence available. In keeping with the themes described for fish and amphibians, important questions to be answered in the future include the following. If neural circuitry is similar among lizards, then how does the auditory circuitry of sonic geckos interface with central vocal circuitry? Furthermore, why are so few reptiles, with the exception of geckos, some turtles and crocodilians (Carr 1992), capable of vocalization? For reptiles that do vocalize, what is the role of steroid hormones and how do these relate to behavior? Lastly, what are the auditory specializations for animals that are aquatic and terrestrial as compared with those species that are solely terrestrial?

The nonmammalian auditory systems discussed here and elsewhere (Fay and Popper 1999; Simmons et al. 2003) have just begun to articulate the experiments among fish, amphibians, and reptiles that will reveal neural mechanisms for hearing that are common to all vertebrates. Such model systems will provide clues in infrahuman species about how the human auditory system has evolved to meet environmental challenges common to all vertebrates.

Abbreviations

AM	amplitude modulated
Cb	cerebellum
CN	cochlear nuclei
D	diencephalon
dF	difference frequency
DLN	dorsolateral medullary nucleus
DO	descending octaval nucleus
DVR	dorsal ventricular ridge
F_0	fundamental frequency
FM	frequency modulated
IC	inferior colliculus
Mid	midbrain
MO	medulla oblongata
ms	milliseconds
nLL	nucleus of the lateral lemniscus
OB	olfactory bulb
PAG	periaqueductal gray
PL	paralemniscal tegmentum
POA	preoptic area
pps	pulses per second
PRR	pulse repetition rate
Rc	nucleus reuniens pars centralis

Rd	nucleus reuniens pars diffusa
RF	reticular formation
RI	inferior raphe
SAM	sinusoidal amplitude modulation
SC	spinal cord
SO	secondary octaval nucleus of teleost fish *or* superior olive of anurans and reptiles
Tel	telencephalon
TeO	optic tectum
TS	torus semicircularis
TSnc	central nucleus of the torus semicircularis
TSnl	laminar nucleus of the torus semicircularis
TSpr	principal nucleus of the torus semicircularis
TSvl	ventrolateral nucleus of the torus semicircularis
TV	tectal ventricle
VS	vector strength of synchronization
III	third ventricle

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Chapter 17
The Auditory Midbrain in Bats and Birds

Ellen Covey and Catherine E. Carr

1. Introduction

1.1. Evolution and Phylogeny

Both bats and birds are flying vertebrates that diverged early in evolution. Their flight mechanisms are different, and so are their auditory systems. They share a common ancestor in the Carboniferous era, but their auditory systems evolved in parallel and are not homologous (Clack 1997). However, other ancestral mammalian traits, such as moveable ears, multiple ossicles, and echolocation have modified the ear and the auditory system of bats. We discuss both species because they reveal neuroethological principles that relate neural activity to behavior.

1.2. Behavioral Context

Bats and birds use hearing to localize and analyze sound sources passively, and to communicate with conspecifics (Kanwal et al. 1993; Konishi 2000). Some birds learn song and have forebrain areas to control vocal pathways. Others, like the barn owl, are nocturnal predators with superb sound localization skills. Bats use their extraordinary hearing in concert with stereotyped vocalizations and listen to the echoes from objects. By analyzing how echoes have been modified from the original sound by reflective objects, bats perceive obstacles and capture flying insects in darkness.

1.2.1. Bat Hearing and Echolocation

Bats are Chiroptera, an order closely related to insectivores. Because bats use their sense of hearing to perform tasks that in other mammals are guided by vision, their auditory system has undergone a corresponding species-specific hypertrophy and specialization (Neuweiler 1990). The inferior colliculus (IC) is a structure critical for hearing that has evolved to fulfill unique functional needs for different species of bats.

There are approximately 1000 bat species and each uses a different pattern of vocalization for echolocation (Neuweiler 2000). Bats that hunt for insects in open spaces (e.g., the Mexican free-tailed bat, *Tadarida brasiliensis*) use short-duration frequency-modulated (FM) calls. Bats that hunt in foliage use calls with a long constant-frequency (CF) component and a short FM component (CF-FM calls). The best studied CF-FM species are the mustached bat, *Pteronotus parnellii,* and the horseshoe bats, *Rhinolophus rouxi* and *R. ferrumequinum*. Other species, like the big brown bat, *Eptesicus fuscus*, use either CF- or FM-type calls (Fig. 17.1) depending on circumstances (Simmons 1989; Grinnell 1995).

Bat echolocation calls are modified in predictable ways by objects. The interval between call and echo is proportional to the distance of the reflective object. The attenuation of the echo depends on the object's size and distance. Three-dimensional structures create characteristic interference patterns in the echoes (Simmons 1989). The IC contains neurons sensitive to all these features of echolocation signals.

All bat species listen to sounds passively and most echolocate. Species that glean from surfaces such as the pallid bat, *Antrozous pallidus*, listen to sounds made by prey (Fuzessery et al. 1993). Many bat species have a rich repertoire of communication sounds that differ from echolocation calls in temporal structure (Kanwal et al. 1993).

Because there is so much information on the patterns of sound that are behaviorally relevant, bats have become an important model system in which to study temporal aspects of sound processing. Although bats are specialized mammals, much of what has been learned about their auditory systems can be generalized to other mammals (Covey 2003).

1.2.2. Avian Hearing

Psychophysical tests have measured auditory sensitivity, loudness, and temporal resolving power in several species of birds. These data resemble those for other vertebrates, including humans (Dooling et al. 2000). Birdsong has become a model for complex sound processing, especially in the auditory midbrain (Theunissen et al. 2000). Studies of the owl, a sound-localization specialist, have implications for spatial hearing, while the development of the map of auditory space has become a paradigm for studies of experience-dependent plasticity (Knudsen 2002).

1.2.3. The Auditory Midbrain: A Hub of the Central Auditory System

In birds and mammals, the midbrain occupies a central position in the auditory system, receiving input from many ascending and descending sensory pathways as well as motor and modulatory projections. The IC projects to the thalamus and has abundant motor and premotor targets (Covey and Casseday 1995; Carr and Code 2000). Besides developing selectivity for biologically relevant sounds, the IC likely transforms the high rate of auditory input into a slower rate of

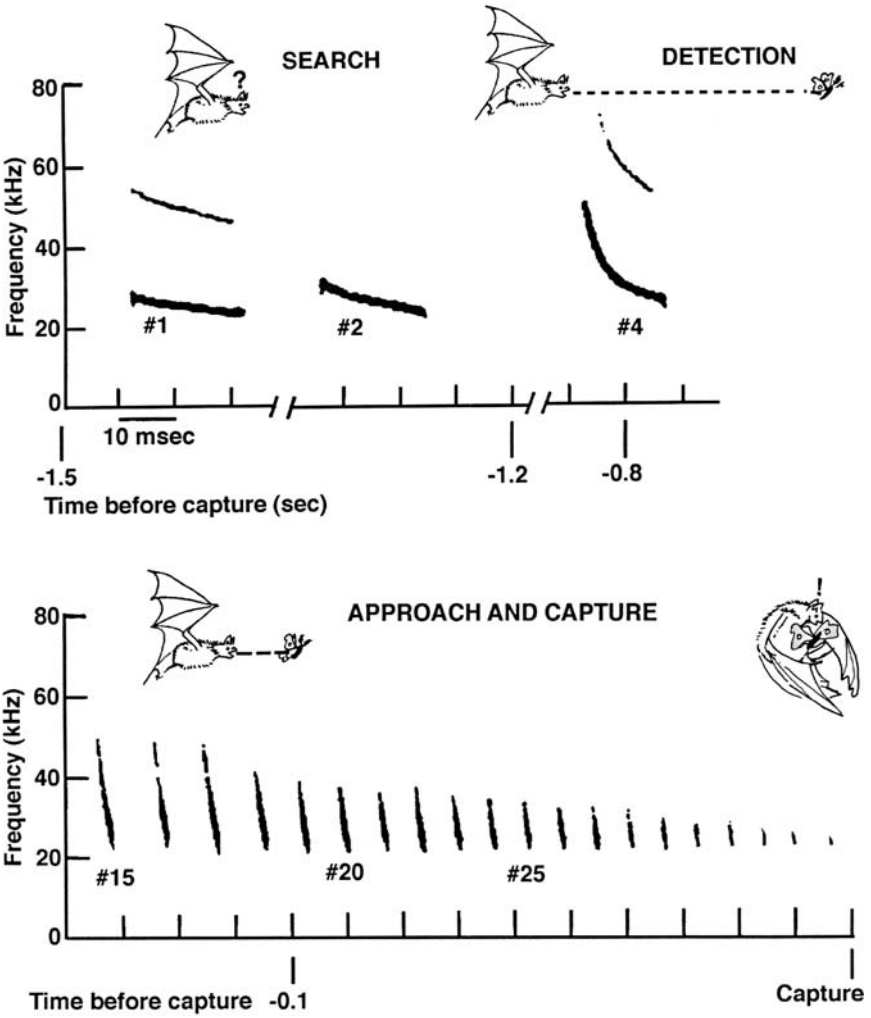


Figure 17.1. Echolocation calls of *Eptesicus* during foraging, pursuit, and insect capture. Calls are 100 dB SPL or more. While hunting the bat emits narrowband quasi-constant frequency calls *(#1, #2)* between 23 and 29 kHz and up to 20 ms or longer. After finding an insect, it emits broadband FM calls *(#4 to #25)* that decrease in duration and increase in rate until the terminal buzz *(#25 to end)* when durations are <1 ms and the repetition rate is up to 150/s. (From Simmons 1989; redrawn from Casseday and Covey 1995.)

output that matches the speed of motor performance (Casseday and Covey 1996).

2. Inferior Colliculus Structure

2.1. Structure and Chemoarchitecture of the Bat Inferior Colliculus

The bat IC is enormous and protrudes between the cerebellum and the cortex. In Nissl-stained material it does not have obvious subdivisions (Fig. 17.2), although most species have a "pericentral" area that contains large neurons and

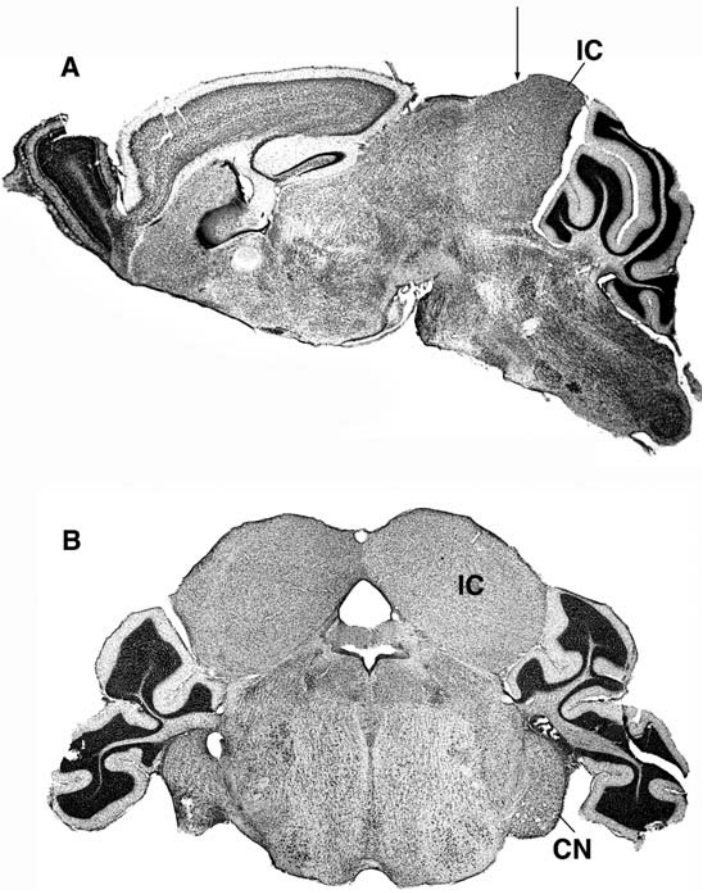


Figure 17.2. Nissl preparations showing the relative size and location of the IC in an echolocating bat, *Eptesicus fuscus*. **(A)** Parasagittal section. **(B)** Frontal section through the caudal one-third of the IC; the caudorostral level is indicated by the *arrow* **(A)**.

probably corresponds to the external nucleus in other mammals (see Chapter 22).

2.1.1. Organization of the Bat Inferior Colliculus

Like that of other mammals, the bat IC contains various cell types, including small disc-shaped cells and large multipolar neurons (Zook et al. 1985; see Chapter 22). *Eptesicus* and other bats with a flexible repertoire of echolocation calls and behavior have a homogeneous IC. *Pteronotus*, a CF-FM bat, has an expanded region of the basilar membrane, the "auditory fovea" (Pollak et al. 1972; Bruns and Schmieszek 1980). There is a corresponding IC "foveal" frequency presentation that is distinguished cytoarchitecturally, the dorsomedial (or dorsoposterior) division (Zook and Casseday 1982; Zook et al. 1985).

2.1.2. Biochemical Gradients in the Bat Midbrain

Chemoarchitectural markers reveal regional differences or gradients within the IC. Immunoreactive synaptic endings (puncta) stained for the inhibitory neurotransmitter γ-aminobutyric acid (GABA) are virtually absent in a crescent-shaped area in the ventrolateral IC, but this same area is immunostained for glycine (Vater et al. 1992b; Winer et al. 1995). Local gradients in GABA and glycine immunoreactivity are organized so that each area is devoted to a single frequency range. This specific isofrequency lamina contains subregions in which neuroactive compounds are abundant or sparse. The distribution of $GABA_A$ and glycine receptors follows the distribution of GABA and glycine puncta; however, $GABA_B$ receptors are concentrated in the dorsomedial IC (Fubara et al. 1996). Because $GABA_A$ receptors provide rapid inhibition and $GABA_B$ receptors subserve longer inhibition, the same neurotransmitter could have different effects in different IC subregions.

The IC receives glutamatergic excitatory input from many sources in the cochlear nucleus (CN) and superior olivary complex (SOC) and modulatory input from neurons containing acetylcholine (Habbicht and Vater 1996) or serotonin (Kaiser and Covey 1997; Hurley and Thompson 2001). Serotonin concentrates in the dorsomedial half of the IC and at the lateral edge.

Other biochemical markers include the Ca^{2+} binding proteins, parvalbumin, calbindin-D28 and calretinin (Zettel et al. 1991; Vater and Braun 1994), and the voltage-gated potassium channel subunit, *Kv1.1* (Rosenberger et al. 2003). Parvalbumin is present in many neurons of all types throughout the IC. Calbindin- and calretinin-positive neurons are concentrated in the dorsomedial IC and external nucleus. Calretinin-positive fibers are densest in an arc above the glycine-rich area, probably from heavy input from calretinin-positive cells in the ventral nucleus of the lateral lemniscus (VLL), which are also glycinergic (Vater et al. 1997).

The *Kv1.1* potassium channel subunit is related to ion channel kinetics implicated in precise temporal processing (Brew and Forsythe 1995). Neurons immunoreactive for *Kv1.1* in *Eptesicus* are mostly in the ventral two thirds of the

IC, decreasing from ventrolateral to dorsomedial (Rosenberger et al. 2003). Many immunolabeled cells are multipolar, indicating that disc-shaped cells have few or no *Kv1.1* ion channels. This regional concentration suggests that multipolar neurons in the ventrolateral IC are distinct and concerned with preserving precise timing.

2.2. Structure of the Auditory Midbrain in Birds

The avian auditory midbrain forms when a caudodorsal portion of the mesencephalic vesicle buckles and thickens to encroach upon the tectal ventricle (Puelles et al. 1994). This massive invagination protrudes beneath the tectal ventricle as the torus semicircularis in nonmammalian species. The torus contains three main parts: the intercollicular area, the toral nucleus, and the preisthmic superficial area (Puelles et al. 1994; Fig. 17.3). The toral nucleus includes the auditory region. It is surrounded rostrally and laterally by the intercollicular area (Wild et al. 1993) and caudally by the caudal preisthmic superficial area (Puelles et al. 1994).

Auditory midbrain nomenclature varies by author and custom. The main recipient of ascending auditory information, Puelles' toral nucleus, has been referred to as the mesencephalic lateral nucleus, pars dorsalis (MLd) (Karten 1967) and as the inferior colliculus (Knudsen 1983). We use the term inferior colliculus, as a major premise of this account is that the functional organization of the avian auditory midbrain parallels that of the mammalian IC.

IC borders and connections have been reevaluated and an intercollicular area between the IC and the tectum identified (Puelles et al. 1994; Fig. 17.3). The intercollicular core, also called DM in songbirds, mediates avian call production and has robust cholinergic immunoreactivity and steroid binding sites (Balthazart 1992; Gahr et al. 1993). Consistent with its function in call production, the intercollicular core receives descending input from the lateral hypothalamus and forebrain archistriatum, specifically the robust archistriatal nucleus, which provides descending motor control of the songbird vocal organ (Wild et al. 1993).

2.2.1. Organization of the Avian Inferior Colliculus

The avian IC contains a large tonotopically organized central nucleus (ICC) and two surrounding nuclei. The central nucleus contains a central core (ICCc) surrounded by lateral (ICCls) and medial (ICCms) shells. Lateral to the central nucleus is the external nucleus (ICX). Surrounding ICC and ICX dorsally is a periventricular lamina, the superficial nucleus (ICS; Wagner et al. 2003). Medial to the ICC is the caudomedial shell and paracentral nucleus, both intercollicular structures (Fig. 17.3B; Puelles et al. 1994).

2.2.2. Neurons and Internal Organization

The bird IC, like that of the bat, contains many large, loosely packed cells with fusiform, stellate, or round somata (Knudsen 1983). In Golgi preparations many

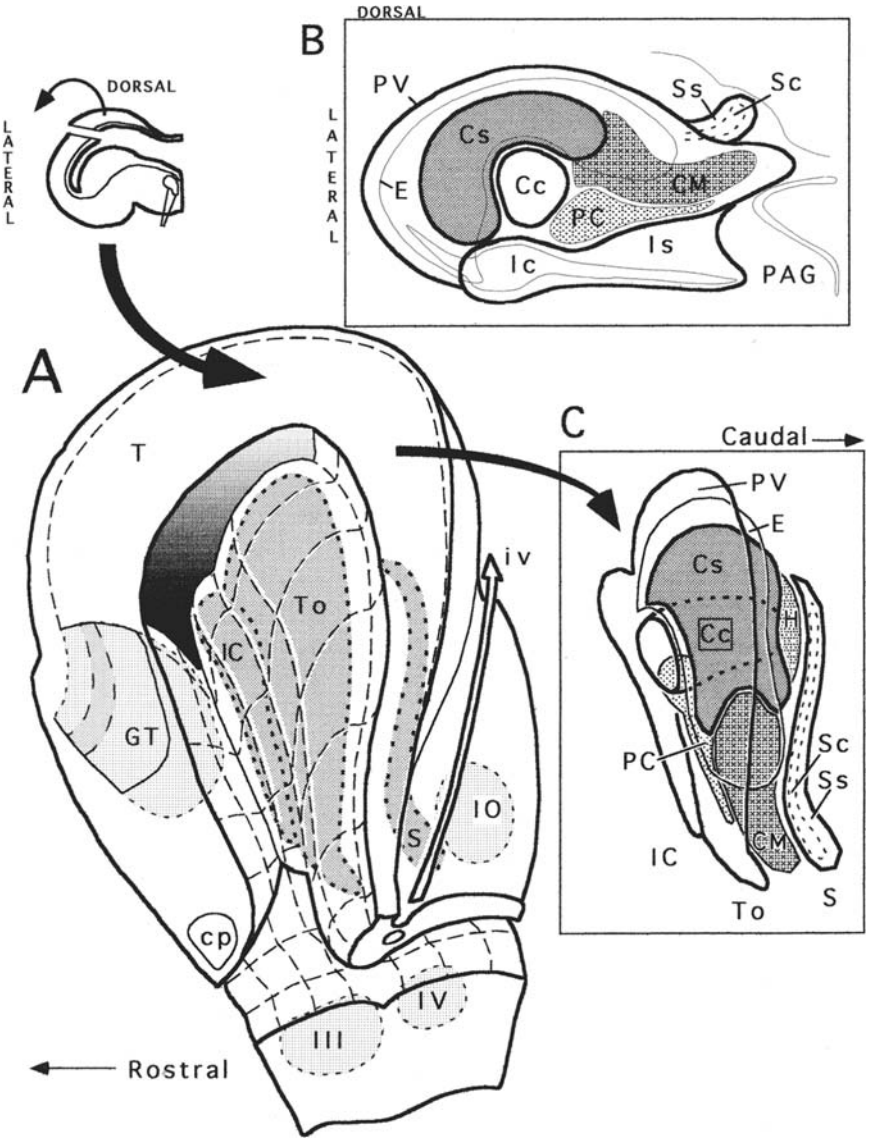


Figure 17.3. Avian auditory midbrain organization. The *inset (upper left)* partially removes the mesencephalic roof. **(A)** Schema of the right torus protruding into the optic lobe ventricle, showing its topographic relationships with tectum *(T),* tectal gray *(GT),* and isthmic structures: isthmo-optic nucleus *(IO)* and trochlear nerve *(iv).* The three toral subdivisions (*IC, To, S*) are *shaded dotted contours*; *black arrow* denotes subdivisions (cf. **C**). **(B)** Subdivisions of the right torus from a rostral perspective as projected in a transverse plane (*directional arrows*: dorsal and medial) and related to the paracentral toral nucleus (*PC*), external toral nucleus (*E*), toral periventricular lamina (*PV*), intercollicular area core (*Ic*) and shell (*Is*), periaqueductal gray *(PAG)*, preisthmic superficial area shell and core (*Ss, Sc*), and preisthmic dorsal brain surface *(right).* **(C)** Toral nucleus subdivisions (as in **A**) showing the posterior location of the hilar nucleus *(H)* and the orientation of the central core *(Cc).* (Modified from Puelles et al. 1994.)

cells are multipolar with stellate or elongate somata (Fig. 17.4). Bipolar and unipolar cells are rare and lie near the margins of the nucleus. Unlike most mammals (see Chapter 2), there is neither fibrodendritic alignment nor preferred orientation. Dendritic fields may be polarized in any dimension and the lemniscal input does not enter or ramify in a laminar fashion (Knudsen 1983). External nucleus cells are smaller than those in the central nucleus, but the same cell types occur.

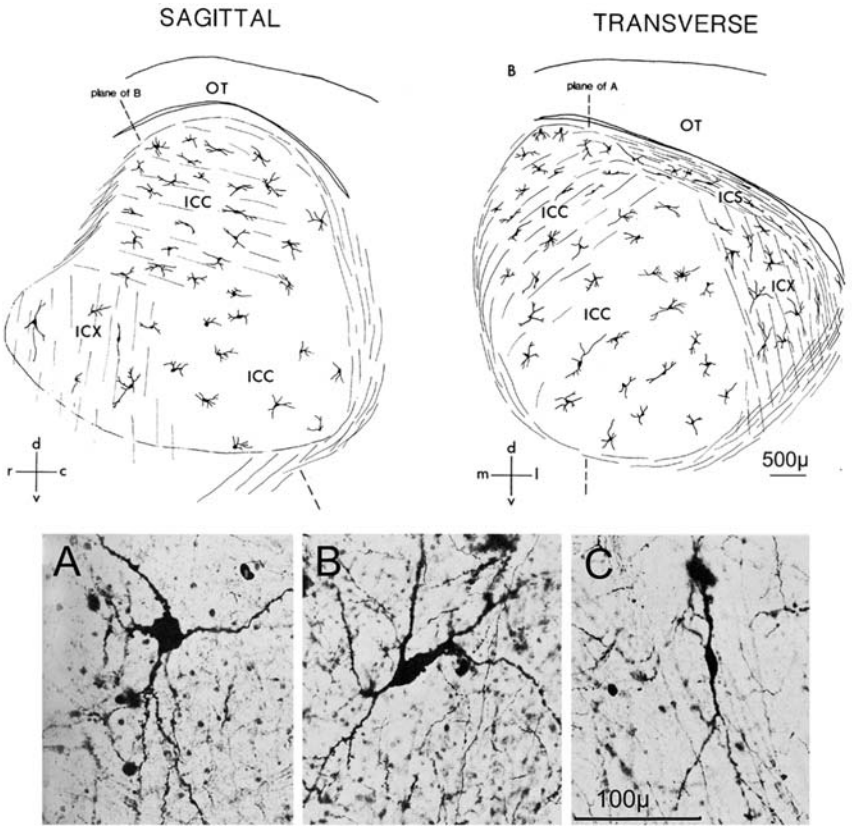


Figure 17.4. IC cell types and subdivisions in Golgi preparations. *Fine lines,* fibers; *ICC,* IC central core, dorsal and ventral; *ICS,* IC superficial nucleus; *ICX,* IC external nucleus; *OT,* optic tectum. **(A)** ICX stellate cell. **(B)** ICX elongate cell. **(C)** ICS bipolar cell. (Modified from Knudsen 1983.)

2.2.3. Biochemical Gradients in the Bird Inferior Colliculus

Biochemical features delineate and support the scheme of architectonic divisions (Fig. 17.5). The differential distributions of these markers identify nuclear subdivisions, which are more apparent than in bats.

In the barn owl and chicken, calretinin immunoreactive fibers from the nucleus laminaris demarcate the laminaris terminal field in the ICCc and thus the pathway used for interaural time difference (ITD) computations (Puelles et al. 1994; Takahashi et al. 1987; Kubke et al. 1999). Acetylcholinesterase defines the medial and lateral shell, and the interaural level difference (ILD) pathway (Adolphs 1993; Puelles et al. 1994). Other markers label other IC subdivisions, including the ICX and ICS (Puelles et al. 1994; Wagner et al. 2003).

GABAergic inhibition is a hallmark of the IC in all vertebrates, including birds (Carr et al. 1989; Fujita and Konishi 1991; Müller 1988; Zheng and Knudsen 1999). ICC contains both the largest number and the largest GABAergic neurons. Cytochrome oxidase distinguishes chicken ICCc from a moderately active ICX (Dezso et al. 1993) and the lateral shell had stronger neuropil reactivity than the central core.

3. Connections of the Inferior Colliculus

3.1. Connections of the Inferior Colliculus in Bats

3.1.1. Afferent Inputs

An enormous variety of projections converge in the IC (Fig. 17.6) (Covey and Casseday 1995; Casseday et al. 2002) and brain stem input extends nearly to the IC surface laterally and dorsally. This section focuses on characteristic features in the context of the physiology of the inputs (see Chapters 2 to 5).

Monaural projections (Fig. 17.6A) arise in the contralateral cochlear nucleus (CN), and indirectly from the ventral (VLL) and intermediate (ILL) nuclei of the lateral lemniscus. Binaural projections come from the medial superior olive (MSO), lateral superior olive (LSO), and dorsal nucleus of the lateral lemniscus (DLL). These projections converge throughout the IC with varying degrees of overlap. Dorsal cochlear nucleus (DCN) input extends through almost all of the IC, and is densest in the dorsomedial one third. Posteroventral cochlear nucleus (PVCN) projections are more prominent than in other mammals, and are uniformly distributed. Input from the anteroventral cochlear nucleus (AVCN) is dense ventrolaterally, declining dorsomedially (Zook and Casseday 1985, 1987).

ILL and VLL are hypertrophied and highly specialized in all species of bats (Covey 1993). The VLL of echolocating bats contains a segregated, functionally specialized population of small neurons, the columnar nucleus (VLLc) (Covey and Casseday 1986, 1991), whose neurons are segregated, permitting their inputs to be readily examined. Each sheet receives convergent input from many CN

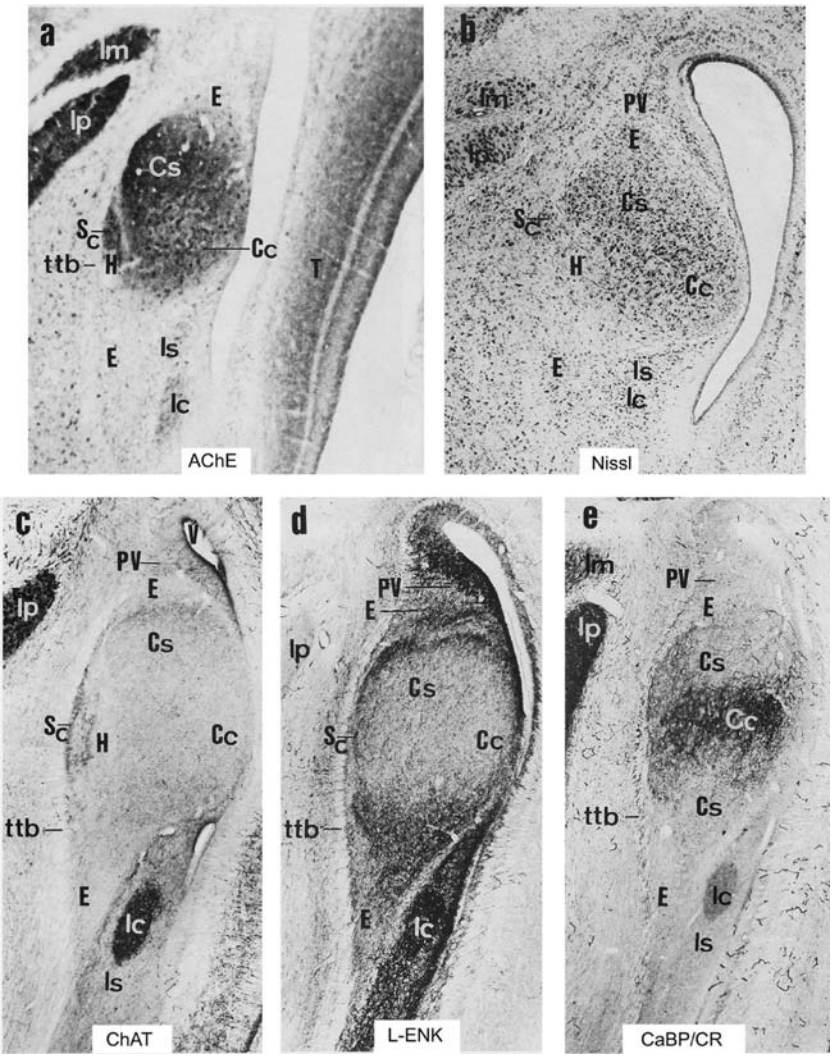


Figure 17.5. Chick IC chemoarchitecture in sagittal sections through the central nucleus core *(Cc).* Dorsal is up, rostral to the right. **(A)** Acetylcholinesterase *(AchE).* **(B)** Nissl stained section. **(C)** Choline acetyltransferase *(ChAT).* **(D)** L-Enkephalin *(L-Enk).* **(E)** Calcium binding protein and/or calretinin. *Cc,* IC central core; *Cs,* IC shell; *E,* external nucleus; *H,* hilar toral nucleus; *Ic,* intercollicular area core; *Im,* nucleus isthmi, pars magnocellularis; *Ip,* nucleus isthmi, pars parvicellularis; *Is,* intercollicular area shell; *PV,* toral periventricular lamina; *Sc,* preisthmic superficial area core; *T,* optic tectum; *ttb,* tectobulbar tract. (Modified from Puelles et al. 1994.)

cells, which represent a broad range of frequencies and project to an equally broad IC territory (Covey and Casseday 1986). The VLLc projection is the most dense and widespread of IC inputs. VLLc neurons are glycinergic, so presumably provide widespread inhibition (Vater et al. 1997). The projections of ILL and the remainder of VLL extend throughout the IC and overlap those of VLLc (Covey and Casseday 1986).

Binaural projections originate from LSO and DLL bilaterally, and MSO ipsilaterally (Fig. 17.6B) (Casseday et al. 1988; Vater et al. 1995) except in *Tadarida*, whose MSO input is bilateral (Grothe et al. 1994). The MSO in most bats probably serves a different function than MSO in species with prominent low frequency hearing (Casseday et al. 1988; Covey et al. 1991; Grothe et al. 1992). Instead of processing interaural time differences, which in bats are probably too small to be a useful cue for sound location, the MSO may represent the amplitude envelope of a high frequency carrier (Grothe et al. 1992). The MSO, LSO, and DLL projections extend throughout IC and overlap with each other and with monaural input (Zook and Casseday 1987; Covey et al. 1991; Vater et al. 1995). Although inputs converge, those from each source form gradients: DCN predominates in the dorsomedial part of each isofrequency lamina, while AVCN, LSO, and NLL predominate ventrolaterally.

3.1.2. Other Afferents

Mammalian IC receives projections arising from auditory cortex (Herbert et al. 1991; Winer et al. 1998), parts of the medial geniculate body (MGB) and posterior thalamus (Senatorov and Hu 2002), and the substantia nigra pars reticulata, globus pallidus, and central gray (Winer et al. 2002). Most of these pathways have not been studied in bats. In *Pteronotus*, layer V cells in auditory cortex project to the dorsomedial IC but not to the ventrolateral part. Input from the basal amygdaloid nucleus in *Pteronotus* and *Antrozous* (Marsh et al. 2002) is distributed throughout most of the IC.

3.1.3. Projections of the Inferior Colliculus

The IC projects to the MGB (Wenstrup et al. 1994; see Chapter 7) and to the superior colliculus (Covey et al. 1987) and pontine gray (Frisina et al. 1989; Schuller et al. 1991; Wenstrup et al. 1994). Input to the pontine gray is comparable in size to the tectothalamic path, suggesting that auditory input to the cerebellum is crucial for aerial species that echolocate.

3.2. Connections of the Avian Inferior Colliculus

Avian IC projections follow the same pattern as other vertebrates, with brain stem input terminating topographically in the contralateral IC (Fig. 17.7; Carr and Code 2000). The surrounding intercollicular area receives descending input from the forebrain archistriatum (Puelles et al. 1994; Wild 1995).

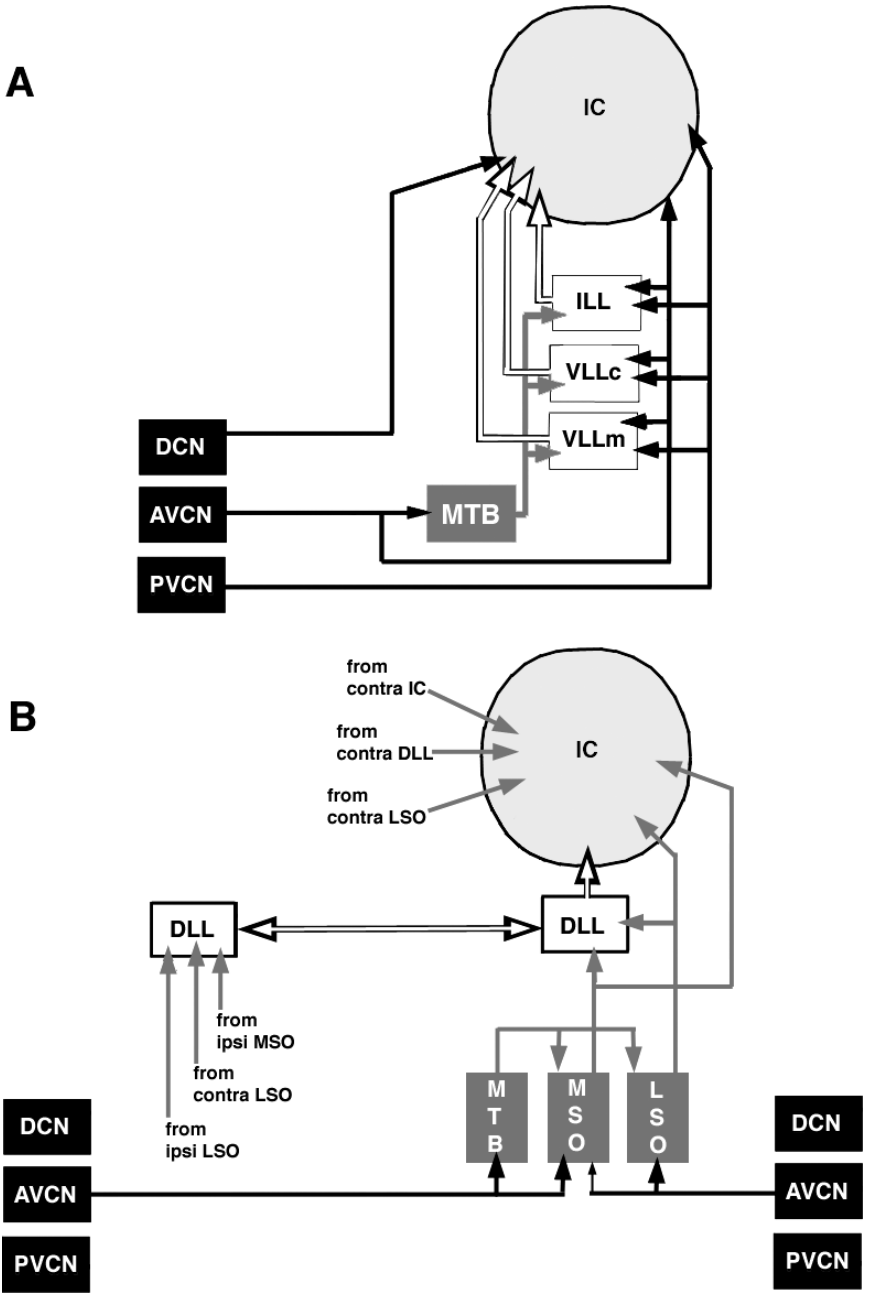


Figure 17.6. Ascending projections to the bat IC. **(A)** Monaural direct and indirect CN pathways to contralateral IC. **(B)** Binaural input from both CN via the superior olivary complex and DLL. *AVCN,* Anteroventral cochlear nucleus; *DCN,* dorsal cochlear nucleus; *DLL,* dorsal nucleus of the lateral lemniscus; *IC,* inferior colliculus; *ILL,* intermediate nucleus of the lateral lemniscus; *LSO,* lateral superior olive; *MSO,* medial superior olive; *MTB,* medial nucleus of the trapezoid body; *PVCN,* posteroventral cochlear nucleus; *VLLc,* ventral nucleus of the lateral lemniscus, columnar division; *VLLm,* ventral nucleus of the lateral lemniscus, multipolar cell division (modified from Woolley and Casseday 2004; see also Karten 1968; Schwartz et al. 1995).

3.2.1. Afferent Inputs

There are two lemniscal projections to the ICC, one from the cochlear nucleus angularis (NA) and another from the cochlear nucleus magnocellularis (NM). The NA projection is direct. The NM projects solely and bilaterally to the brain stem nucleus laminaris (NL) where ITD sensitivity first arises, and the NL projects to the IC. Thus, the NL input is analogous to the mammalian MSO projection. Selective, reversible ablation of each cochlear nucleus shows that the two ascending streams form separate neural channels to encode time and intensity cues for sound localization. Injection of local anesthetic in NM alters the space-specific cells' selectivity for ITD, leaving their ILD selectivity intact. Anesthetizing NA has the opposite effect (Takahashi et al. 1984).

Indirect pathways from the avian SO and lateral lemniscal (LL) nuclei also project to the ICC (Fig. 17.7; Leibler 1975; Conlee and Parks 1986; Takahashi and Konishi 1988a,b; Takahashi et al. 1989; Adolphs 1993). The NL and NA projections are segregated within the ICC, perhaps more so in the barn owl than in the chicken or pigeon (Conlee and Parks 1986; Wild 1995). In the barn owl, the ICC core receives ITD input from the contralateral NL and anterior DLL (Takahashi et al. 1987; Takahashi and Konishi 1988a; Adolphs 1993; Carr and Code 2000). Contralateral NA projects to the lateral and medial shell, conveying both ILD and other information. The lateral shell also receives ITD input from the contralateral core (Takahashi et al. 1989). These ITD and ILD signals converge in the lateral shell, which in turn projects to the ICX (see Section 5). Most of the avian auditory system to the level of the midbrain is binaural and without the specialized monaural pathways found in mammals.

3.2.2. Projections of the Avian Inferior Colliculus

The ICC projects to both the ICX and the thalamic nucleus ovoidalis (Fig. 17.7; Proctor and Konishi 1997; Carr and Code 2000). The ICX projects to the optic tectum where the auditory and visual maps are in register (Knudsen 1983). In the barn owl, the ICX also receives a topographic, visually based instructive signal from the tectum which calibrates the auditory space map (Luksch et al. 2000; Hyde and Knudsen 2002; see Section 6).

Auditory–motor connections are essential for bird vocalizations. The intercollicular area receives auditory input from the IC in the dove (Akesson et al. 1987) and is part of the descending telencephalic archistriatal pathway for vocal control (Wild 1993; see also Jarvis et al. 2000). The ICX projects to the deep layers of the tectum, which projects to the pontine tegmentum, enabling orientation to sound in space (Knudsen and Knudsen 1983; Knudsen et al. 1993). In birds, the connections of the IC to the tectum are probably concerned with sound localization, and in generating the nontonotopic space map in the ICX. The tonotopically organized representation that is transferred to the thalamic pathway in both birds and bats may be concerned with other aspects of sound processing (Bonke et al. 1979; Durand et al. 1992).

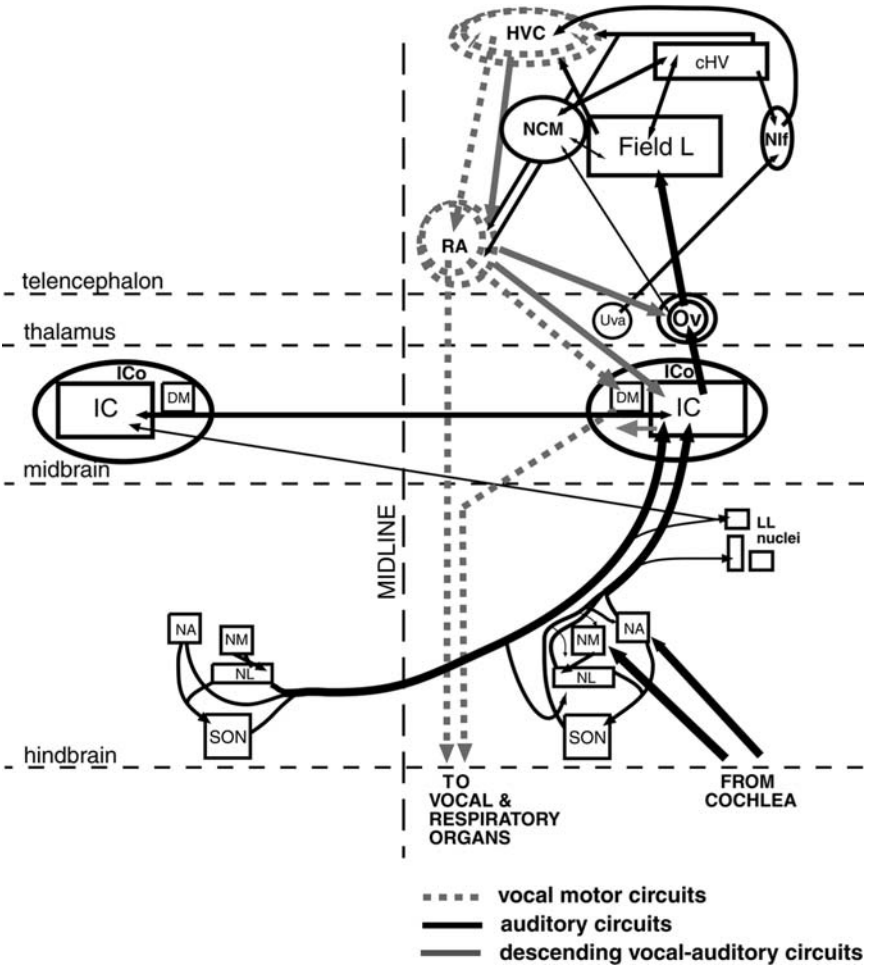


Figure 17.7. Connections of the avian IC. Typical avian auditory system and the passerine song control nuclei. Ascending auditory circuits, *black*; *dashed gray lines,* main descending song control circuit; *solid gray lines,* descending input from the song nuclei (HVC shelf and RA cup) to MLd and Ov. *cHV,* Caudal hyperstriatum ventrale; *DM,* dorsal mesencephalic nucleus and part of ICo; *HVC,* hyperstriatum ventrocaudal (used as a proper name); *IC,* inferior colliculus; *ICo,* nucleus intercollicularis; field L, forebrain auditory area; *LL nuclei,* lateral lemniscal nuclei; *NA,* nucleus angularis; *NCM,* caudomedial neostriatum; *NIf,* nucleus interfacialis; *NL,* nucleus laminaris; *NM,* nucleus magnocellularis; *Ov,* nucleus ovoidalis; *RA,* robust nucleus of the archistriatum; *SON,* superior olivary nucleus; *Uva,* nucleus uvaeformis of the thalamus. IC receives parallel inputs from lower brain stem and projects to the auditory thalamus *(Ov),* as does the ventral nucleus of the lateral lemniscus. (Modified from Woolley and Casseday 2004; see also Karten 1968; Wild 1987; Schwarz et al. 1995; Wild et al. 1997, 2001.)

4. Tonotopic Organization of the Inferior Colliculus

4.1. Tonotopic Organization in Bats

The bat IC, like that of other mammals, is tonotopically organized with low-frequency afferents terminating dorsolaterally and high-frequency input ventromedially. Many bat species have expanded representations of specific frequency ranges that are critical in echolocation (Fig. 17.8).

4.1.1. Tonotopy in Frequency Modulating Bats

Eptesicus is a species without cochlear specializations. The largest area in the ICC is the 20- to 40-kHz representation, with a continuous low-to-high sequence from dorsolateral to ventromedial (Casseday and Covey 1992). *Antrozous* uses echolocation and passive listening to detect and locate prey. IC tonotopy resembles that in *Eptesicus* except that there is a larger representation below 20 kHz and no expanded isofrequency contour. IC regions devoted to echolocation (30 to 60 kHz) and passive listening (<30 kHz) are segregated, with the dorsal and lateral regions serving passive listening and the ventral region serving echolocation (Fuzessery and Hall 1999).

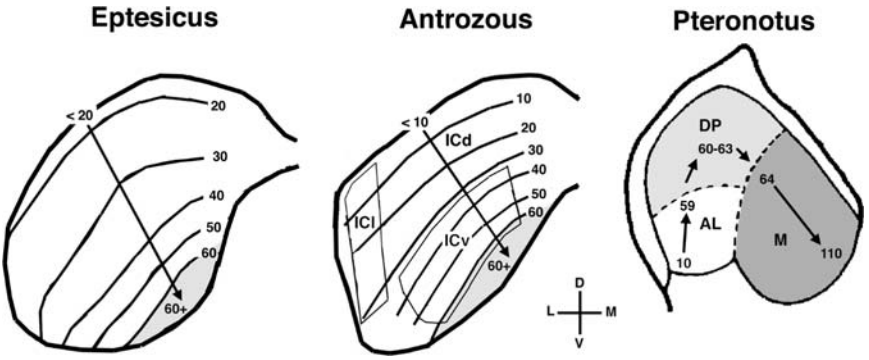


Figure 17.8. Tonotopic organization in the left IC of three species of bats. *White areas,* frequencies <60 kHz; *gray areas,* >60 kHz. In *Pteronotus*, the light gray area is the expanded 60-63 kHz region and the *dark gray area* is 64 kHz and higher. *Arrows,* tonotopic axis from low-to-high frequency. In *Antrozous*: *ICd,* dorsal IC region; *ICl,* lateral IC region; *ICv,* ventral IC region. In *Pteronotus*: *AL,* Anterolateral region IC; *DP,* dorsal posterior IC region; *M,* medial IC region. Orientation: *d,* dorsal; *l,* lateral; *m,* medial; *v,* ventral.

4.1.2. Specialized Tonotopy

The cochlear specializations in *Pteronotus* bias the auditory system at every level toward the second harmonic of the CF echolocation signal, at about 61 kHz (Kössl and Vater 1985; Henson and Henson 1991; Kössl et al. 1999). Thus, 61 kHz occupies its expected place in subcollicular tonotopic sites (Vater et al. 1985; Zook and Leake 1989). However, in the IC, this region is displaced to form the dorsoposterior region (DP), and frequencies >63 kHz are expanded concomitantly, forming a large medial division (M) while those <60 kHz are greatly reduced (Pollak and Casseday 1989). To accommodate this expansion, the sequence is convoluted and semicircular. However, in *Rhinolophus*, another CF-FM bat with an "acoustic fovea" created by cochlear specializations, ICC frequency organization resembles that in FM bats and other mammals (Rübsamen and Schäfer 1990).

4.2. Tonotopy in the Avian Inferior Colliculus

Birds have an IC tonotopic orientation like that in mammals (Carr and Code 2000) with low best frequencies dorsally and higher frequencies ventrally (chicken: Coles and Aitkin 1979; guinea fowl: Heil and Scheich 1986; owl: Wagner et al. 1987, 2002; zebra finch: Woolley and Casseday 2004). There is a monotonic relationship between best frequency and recording depth, although best frequency changes more slowly in the low-frequency region (Wagner et al. 2002).

Owl ICCc frequency tuning curves are typically single peaked and symmetrical, with steep slopes on both flanks (Fig. 17.9A–C). Tuning curve widths are related to best frequency (BF), such that the ratio of tuning width to BF decreases as BF increases (Wagner et al. 2002). They are also related to IC subdivisions: lateral shell neurons have broader tuning curves and ICX cells prefer noise (Knudsen and Konishi 1978; Wagner et al. 1987; Mazer 1997). In the chicken and zebra finch, BFs range from 1 to 6 kHz and tuning curve widths are variable (Coles and Aitkin 1979; Woolley and Casseday 2004; Fig 17.9D–F). Most zebra finch IC neurons have V-shaped tuning curves, with a quarter having multiple peaks, noncontiguous excitatory regions, or narrow tilted or columnar shapes. Double peaked tuning curves occur in about 12% of chicken neurons (Coles and Aitkin 1979), and single- and multipeaked tuning curves are found in awake guinea fowl (Scheich et al. 1977). Temporal response patterns in the chicken and zebra finch revealed several categories (Coles and Aitkin 1979; Woolley and Casseday 2004). In anesthetized finches, 49% of IC neurons had onset responses, 20% primary-like, 19% sustained, and 12% primary-like with notch (Woolley and Casseday 2004).

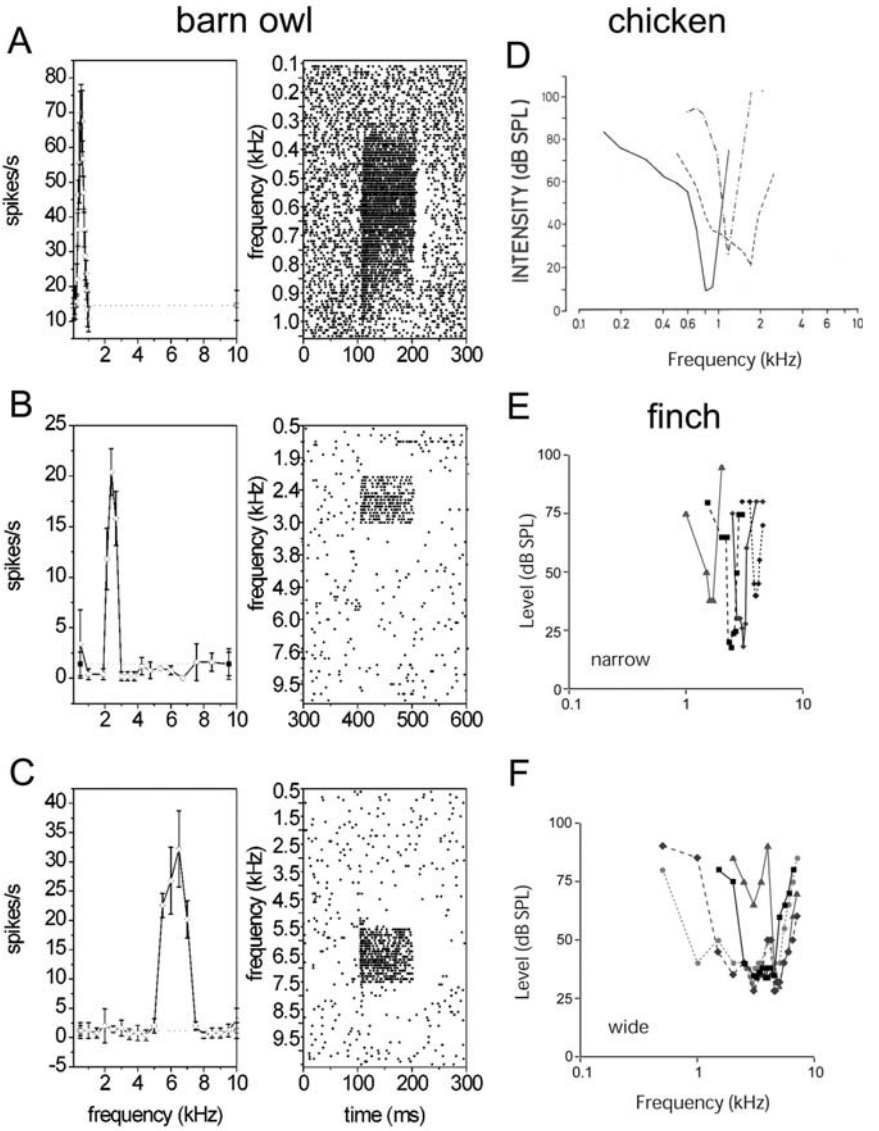


Figure 17.9. Avian IC tuning curves. **(A–C)** The barn owl ICC is tonotopic with best frequency increasing from dorsal **(A)** to ventral **(C)**. *Left column,* isointensity frequency response functions with pure tone stimuli. *Right column,* dot raster plots for the same response functions. **(D–F)** Excitatory tuning curves for chicken and zebra finch. **(D)** Mid-frequency tuning curves in chicken. Narrow **(E)** and broad **(F)** tuning curves in zebra finch. (From Coles and Aiken 1979; Wagner et al. 2002; and Woolley and Casseday 2004.)

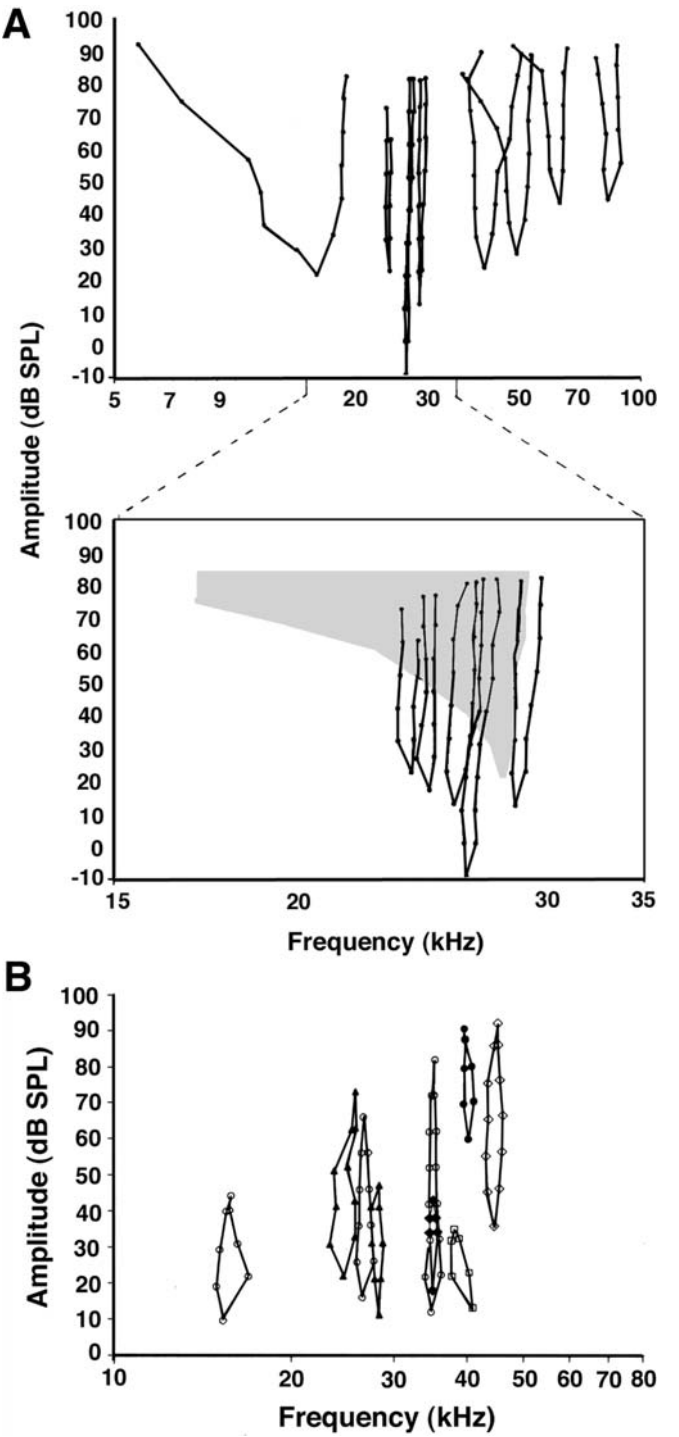


Figure 17.10. **(A)** Response areas in *Eptesicus* IC. The range between 15 and 35 kHz (*lower panel*) is expanded to better illustrate narrow, level-tolerant frequency response areas. *Gray shading,* a V-shaped frequency response area for comparison. **(B)** Neurons with upper thresholds and closed frequency response areas. (From Casseday and Covey 1992.)

5. Response Properties of Inferior Colliculus Neurons

In all vertebrates the auditory midbrain receives excitatory, inhibitory, and modulatory input from many sources, arranged as overlapping and intersecting gradients. The inputs terminate in various ways on different neuronal types, each with specific membrane properties, creating heterogeneous response properties (see Chapters 2, 10, and 11). It is often possible to relate neuronal responses to sound attributes such as frequency, amplitude, duration, the rate and/or depth of modulation in both amplitude and frequency, and the interval separating sounds. It has been possible to localize specialized response properties to particular IC regions in both bats and birds.

5.1. Functional Characteristics of Bat Inferior Colliculus Cells

5.1.1. Frequency and Amplitude Tuning

Single neurons have many types of frequency response areas, including simple V-shaped tuning curves, multipeaked areas, closed response areas with lower and upper thresholds, and narrow, level-tolerant "filter" types (Casseday and Covey 1992). (See Fig. 17.10.)

In CF-FM bats with cochlear specializations, frequency response areas of "foveal" neurons are largely determined by cochlear mechanical properties (Suga et al. 1975). These neurons typically respond to a 1- to 2-kHz frequency band, with their tuning breadth constant across amplitude. This "filter-type" response area (Fig. 17.10A) contrasts with the V-shaped frequency response areas of neurons tuned to other frequencies.

Although *Eptesicus* has no cochlear specializations, it too has neurons with filter-type frequency response areas, tuned to a 1- to 2-kHz band near the bat's quasi-CF calls. Filter-type response areas have not been found below the level of the IC in *Eptesicus* (Haplea et al. 1994). Frequency tuning can be narrowed considerably by synaptic inhibition (Yang et al. 1992; Pollak and Park 1993; Fuzessery and Hall 1996). In FM bats without cochlear specializations, inhibition produces the same filter property that is mechanically derived in other species, an example of convergent evolution. Perhaps narrow, level-tolerant frequency response areas are essential for processing CF or quasi-CF calls and echoes.

Many IC neurons have nonmonotonic rate-level functions: as amplitude grows their activity increases up to a point and declines or saturates (Suga 1968; Casseday and Covey 1992). Because neurons with nonmonotonic rate-level functions have a variety of "best amplitudes" (Fig. 17.10B), some respond only to the loud echolocation call, others only to the faint echoes. Amplitude tuning

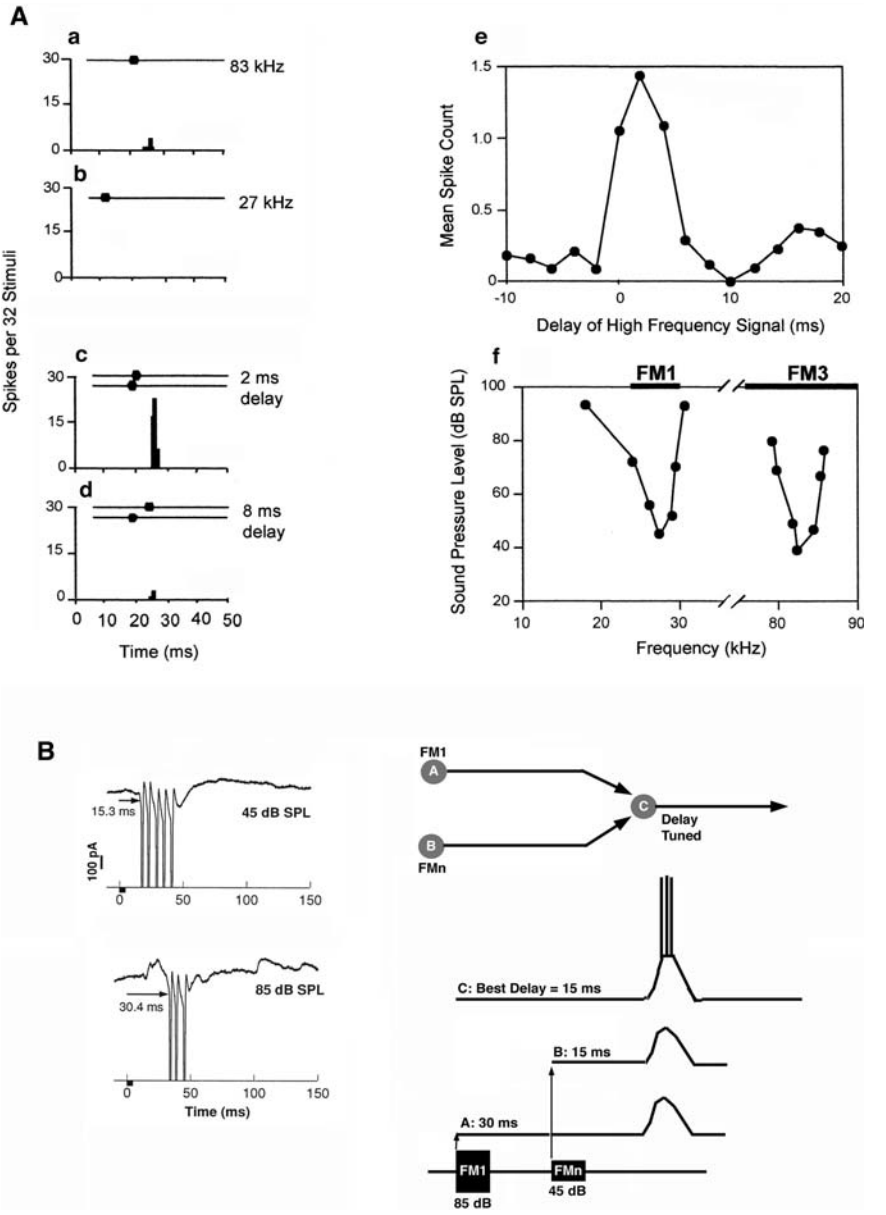


Figure 17.11. **(A)** A combination-sensitive delay tuned neuron in *Pteronotus* IC. *a, b*: Responses to 83-kHz and 27-kHz tones alone. *c, d*: Responses when the 27-kHz tone was followed by the 83-kHz tone at two different interstimulus intervals (ISI). *e*: Mean spikes/tone pair as a function of ISI. *f*: The neuron had one excitatory response area near the fundamental (first) harmonic of the echolocation call and another near the third harmonic. (From Portfors and Wenstrup 1999.) **(B)** Paradoxical latency shift (PLS; left) in *Eptesicus* IC. Latency to an 85-dB tone was almost 15 ms longer than to a 45-dB tone. Diagram *(top right)* of a circuit that could produce delay-tuning if neurons A and B have a similar PLS. Because FM1 is loud in the emitted call, neuron A's latency would be 30 ms, while B's response to the attenuated nth echo harmonic would be 15 ms. The combined EPSP evoked by A in response to the call and in B in response to the echo would be maximal at neuron C when there is a 15-msec echo delay.

might provide a mechanism for segregating responses to calls and echoes for parallel processing (Rübsamen et al. 1988).

5.1.2. Combination Sensitivity and Delay-Tuning

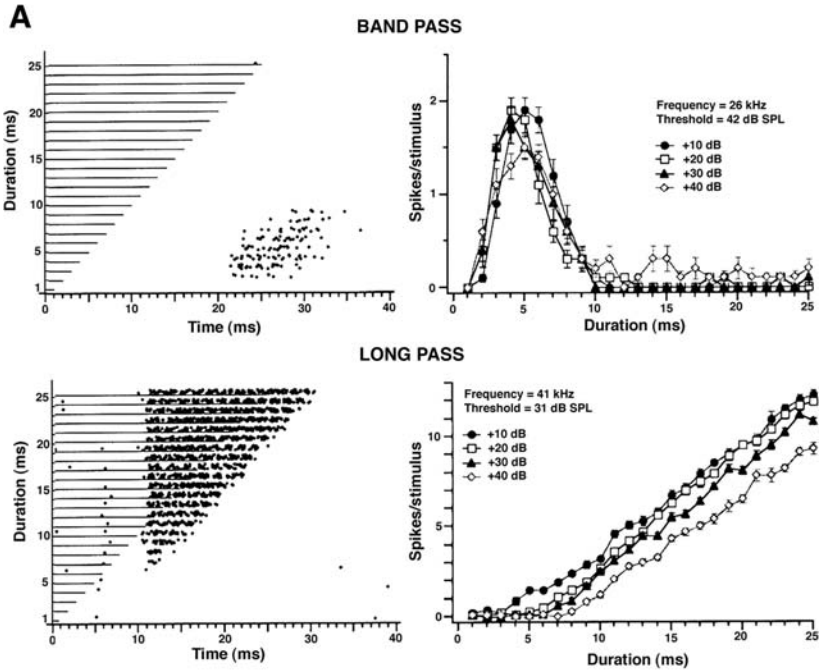
All bat species have IC neurons with multipeaked frequency response areas (Portfors and Wenstrup 2002). Many neurons are facilitated by combinations of sounds at specific frequencies, with the response to both tones significantly larger than the sum of either alone (Fig. 17.11A). Such facilitation is combination sensitivity and was first described in the intercollicular area of *Eptesicus* (Feng et al. 1978) but is common in the auditory cortex (AC) (Suga et al. 1979; O'Neill and Suga 1979), thalamus (Olsen and Suga 1991), and IC (Mittmann and Wenstrup 1995; Dear and Suga 1995; Portfors and Wenstrup 2001). In one form of combination sensitivity, two frequencies facilitate each other only when presented sequentially in a specific temporal relationship (Fig. 17.11A). Because facilitation depends on the interstimulus interval, such neurons are "delay tuned."

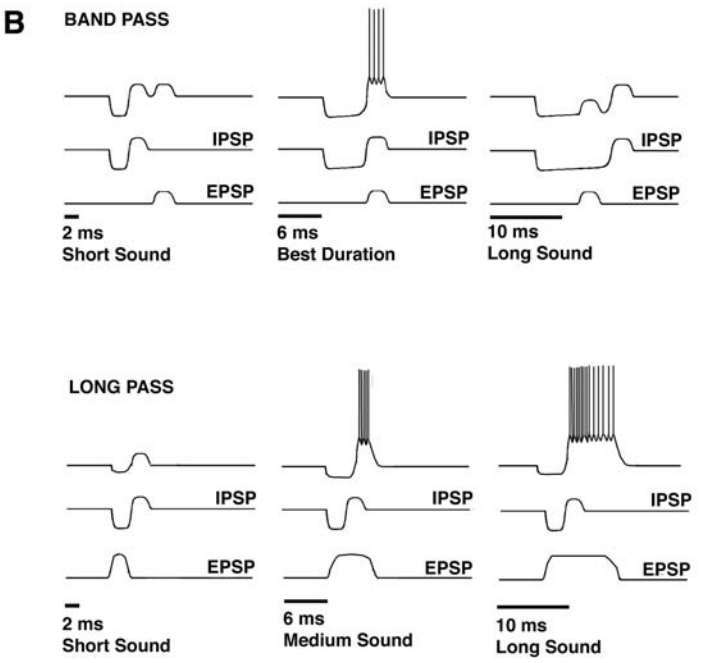
In *Pteronotus*, delay-tuned neurons require tones of different frequencies to produce facilitation. The initial stimulus must often be within the frequency range of the first (fundamental) harmonic of the FM portion of the echolocation call (FM1). Because the FM1 amplitude is weak relative to that of the other harmonics, it likely will be below threshold in the echoes. The second stimulus must be within the frequency range of the second, third, or fourth FM harmonic (FM2, FM3, or FM4, collectively designated FMn). In *Pteronotus* AC, neurons tuned to different delays between FM1 and FMn are organized systematically (O'Neill and Suga 1982). However, there is no topographic organization of best delays in the IC, nor any systematic relation between response latency and best delay (Portfors and Wenstrup 2001), suggesting that "mapping" of best delay occurs at the AC.

The delay between the emitted call and its echo is proportional to the distance of the reflective object; the best delays in IC, MGB, and AC neurons correspond to the range of values for realistic object distances. Therefore, combination-sensitive delay-tuned neurons may be a specialization for echolocation. Other combination-sensitive delay-tuned neurons are facilitated by sounds in frequency combinations that are harmonically unrelated and/or that are outside the frequency range of echolocation calls (Leroy and Wenstrup 2000), and may be involved in processing communication sounds.

5.2. Mechanism for Delay-Tuning

Most work on delay-tuning mechanisms has used *Pteronotus*. One hypothesis that flowed from Jeffress's work (1948) was that delay-tuned neurons act as coincidence detectors, although on a much longer time scale than for sound localization. In this model, the delay-tuned neuron receives delayed excitatory input from FM1 neurons and rapid excitatory input from FMn-tuned neurons, firing only when the FM1-FMn delay compensates for the delay in the FM1


A
BAND PASS
Duration (ms)
Time (ms)
Spikes/stimulus
Duration (ms)
Frequency = 26 kHz
Threshold = 42 dB SPL
+10 dB
+20 dB
+30 dB
+40 dB
LONG PASS
Duration (ms)
Time (ms)
Spikes/stimulus
Duration (ms)
Frequency = 41 kHz
Threshold = 31 dB SPL
+10 dB
+20 dB
+30 dB
+40 dB


B
BAND PASS
IPSP
EPSP
2 ms
Short Sound
6 ms
Best Duration
10 ms
Long Sound
LONG PASS
IPSP
EPSP
2 ms
Short Sound
6 ms
Medium Sound
10 ms
Long Sound

pathway, making the inputs coincident. Delay-tuned neurons respond to certain interpulse intervals with a peak "best delay" (O'Neill and Suga 1982), consistent with partial coincidence of excitatory postsynaptic potentials (EPSPs) at some delays and complete coincidence at the peak of the delay-tuning function. However, glycine antagonists abolish delay-tuning in IC neurons that show facilitation (Wenstrup and Leroy 2001), suggesting that inhibition is involved.

One mechanism might be paradoxical latency shift (PLS) (Sullivan 1982), presumably using neural inhibition. For most cells, latency decreases with increasing sound level, but paradoxical latency neurons respond with longer latencies as sound level grows (Fig. 17.11B). Some *Eptesicus* IC neurons show PLS due to increasing strength and duration of inhibition at higher sound levels (Covey et al. 1996). PLS cells would respond to the loud echolocation call with a longer latency than to the faint echo. The amount of latency shift would determine best delay (Fig. 17.11B). Since the latency shift varies according to sound level, this may be a mechanism for PLS neurons that changes best delay as a function of amplitude, and it might explain why blocking glycinergic inhibition abolishes delay-tuning.

5.3. Duration Tuning

Duration sensitive neurons (Fig. 17.12A) are common in the bat IC. Duration tuned neurons typically have a peak response at some best duration (Pinheiro et al. 1991; Casseday et al. 1994; Ehrlich et al. 1997; Fuzessery and Hall 1999) with best durations near the range of call durations used by bats while echolocating. In *Eptesicus* one third of IC cells are duration tuned. They are mainly in the caudal half of the IC, and have not been found below the IC. The underlying mechanisms involve convergence of excitatory and inhibitory inputs with different latencies and discharge patterns (Casseday et al. 1994, 2000). Blocking inhibition abolishes duration tuning in nearly all such neurons (Casseday et al. 2000) and in a subset of these cells in *Antrozous* (Fuzessery and Hall 1999).

Figure 17.12. **(A)** Duration sensitive *Eptesicus* IC cells. Composite dot rasters *(left)* from band-pass *(top)* and long-pass *(bottom)* cells with 10 presentations/duration *(horizontal bars).* Spike count vs. duration *(right)* at several sound levels. Duration sensitivity is level tolerant. (From Faure et al. 2003.) **(B)** Model for duration sensitivity created by the interaction of excitatory and inhibitory inputs with different time courses and latencies. The band-pass neuron *(top traces)* receives a transient subthreshold EPSP with a 10-ms onset latency and a sustained 4-ms latency IPSP, followed by an excitatory rebound. The neuron does not reach threshold unless sound duration is such that the EPSP coincides with the rebound from inhibition. Best duration reflects latency differences between the EPSP and IPSP. A short-pass neuron would result when the difference is very small. The long-pass neuron *(bottom traces)* receives a sustained EPSP with a 5-ms latency which, alone, is suprathreshold. The neuron also receives a transient IPSP with similar latency. At short durations, the EPSP is cancelled by the IPSP, but at longer durations the later part of the EPSP is unaffected and elicits a response.

All *Eptesicus* duration tuned neurons receive inhibition for the stimulus duration and have a shorter latency than for excitation. At the end of the inhibitory period, corresponding to stimulus offset, an excitatory rebound occurs that, alone, is subthreshold (Covey et al. 1996). If the sound duration allows the rebound to coincide with the transient excitation evoked by sound onset, facilitation occurs and the neuron responds (Fig. 17.12B). Thus, the cell's best duration reflects the difference between the latencies of inhibition and excitation. Consistent with this model, duration tuned neurons respond at the stimulus offset.

Long-pass neurons' duration sensitivity results when a neuron receives sustained excitation and transient inhibition at about the same latency (Faure et al. 2003). At short durations the excitation is sufficiently brief to be nullified by inhibition, and at longer durations it outlasts the inhibition and drives the neuron (Fig. 17.12B).

5.4. Tuning to Frequency and Amplitude Modulations

All bats use FM sweeps in their echolocation call repertoire. Some IC neurons respond only to frequency sweeps and many of these are selective for the direction of frequency change (Suga 1969; Fuzessery 1994). IC neurons preferring either downward or upward FM (Fuzessery 1994) may process communication calls and echolocation signals.

For bats that use CF or quasi-CF calls, insect wing beats can produce periodic amplitude modulations and Doppler shifts in the echo frequency. Echoes of FM calls may contain significant amplitude modulations from interference patterns of reflections from multiple surfaces. Sinusoidal amplitude modulations (SAM) and sinusoidal frequency modulations (SFM) are artificial stimuli that mimic these patterns of amplitude and frequency change. Half of IC neurons respond to sinusoidally modulated stimuli with periodic, phase-locked discharges (Schuller 1979; Casseday et al. 1997). Some *Rhinolophus* foveal cells respond to SAM of as little as 3% depth and to SFMs with modulation depths as small as 0.025%.

IC neurons' discharge patterns in response to pure tones are related to their responses to modulated stimuli. *Pteronotus* ON–OFF neurons are unresponsive to SAM (Lesser et al. 1990) and receive an initial inhibitory input with a shorter latency than that of excitation. When presented with pairs of tones separated by a short interval, both populations experience a phenomenon similar to backward masking. These cells do not code periodic amplitude modulations because the response to the earlier stimulus is suppressed by the short-latency inhibition evoked by the second stimulus. Because many IC neurons receive inhibition before excitation (Covey et al. 1996), backward masking may set the upper limit for modulation rate. IC neurons respond to SAM only up to 100 to 200 Hz (Reimer 1987) even though the presynaptic cells respond to higher modulation rates. Because blocking GABAergic and glycinergic inhibition (Burger and Pollak 1998) has little effect on SAM tuning, intrinsic properties may be more important than inhibition for tuning to AM rate.

Some *Eptesicus* IC neurons respond only to SFM (Casseday et al. 1997), requiring several cycles to become primed. Perhaps each cycle of frequency modulation elicits an inhibitory event followed by a subthreshold excitatory event. If the modulation rate for the excitatory rebound that follows the inhibition from one half-cycle coincides with the excitation evoked by the next half-cycle, the neuron reaches threshold and fires. Blocking inhibition broadens SFM tuning (Koch and Grothe 1998), suggesting that neural inhibition may contribute to tuning to SFM rate.

5.5. Role of the Bat Inferior Colliculus in Binaural Hearing and Sound Localization

Bat IC neurons, like those of other mammals, have many binaural interaction patterns, but there is no evidence of a space map like that in the barn owl. Because most mammals move their eyes, the relationship between the visual and auditory fields is variable. Many mammals also have mobile pinnae, complicating the relation between the head and the auditory field.

Many bats have large, complex, and mobile pinnae that are highly directional and accentuate ILDs. They also produce characteristic spectral patterns that could aid in localization in both azimuth and elevation (Fuzessery and Pollak 1984; Wotton et al. 1995). The response patterns of all IC neurons likely reflect the pinna's characteristics, imparting some spatial tuning, especially at sound levels just above threshold (Grothe et al. 1996).

IC binaural properties are not simply inherited from LSO or MSO, but instead reflect integration of excitatory and inhibitory synaptic input. Both GABAergic and glycinergic inhibition actively shapes binaural response properties (Vater et al. 1992a; Park and Pollak 1993, 1994; Klug et al. 1995; Pollak 1997). Some cells experience inhibition when sound is presented at one ear and excitation when it is presented at the other, and the latency and time course of each is different (Covey et al. 1996). Because binaural processing does not construct a fixed auditory space representation, it may have other roles such as enhancing the detection of signals in noise, reducing echo clutter, or coding sound source motion.

Specific binaural subclasses are excited by inputs from the contralateral ear and inhibited by the ipsilateral ear (EI) or excited by inputs from the contralateral and ipsilateral ear (EE). Cells representing these classes are segregated spatially and there are progressive shifts in the excitatory–inhibitory balance of inputs from the ears that form gradients across the IC. When ILD function 50% points (or cutoffs) are measured across an isofrequency contour, the points create a gradient in which ILD functions extend into ipsilateral space (Wenstrup et al. 1986). However, spatial receptive field (RF) properties interact with sound amplitude, frequency spectrum, modulation pattern, sound source movement, and other stimulus aspects (Grothe et al. 1996), so individual neurons, or even populations, are unlikely sources for unambiguous spatial information.

5.6. Interactive Processing

Convergent inputs differentially tuned to many sound parameters suggest that neural responses are interactive. Stimulus amplitude or spectrotemporal changes affect spatial RF size and shape (Grothe et al. 1996; Wu and Jen 1996) and stimulus repetition rate can influence latency, rate-level functions, thresholds, frequency tuning, and duration tuning (Jen and Chen 1998; Jen et al. 2001; Zhou and Jen 2001). Some interactions depend on GABAergic inhibition (Jen et al. 2002). The sound-evoked sequence of synaptic currents can exceed the sound's duration, imposing context-dependent alterations of the subsequent responses (Covey et al. 1996).

5.7. Plasticity of Responses

IC neural response properties show long-term plastic changes caused by corticocollicular input (Suga et al. 2002; Suga and Ma 2003). Tuning changes can reflect behavioral conditioning (Gao and Suga 1998) or experimental manipulations of AC, including electrical stimulation (Yan and Suga 1996) or inactivation (Yan and Suga 1999). Effects on frequency tuning (Zhang et al. 1997), interstimulus interval (Yan and Suga 1996), and sound duration (Ma and Suga 2001) are seen. Conditioned changes in responses require 15 to 30 minutes of stimulation under constant conditions and last for hours (Ji et al. 2001). Cortical manipulations have similar effects on all parameters tested. In *Pteronotus*, AC electrical stimulation in an area where neurons are tuned to a particular parameter value augments IC responses of cells tuned to that parameter value and decreases that of neurons tuned to different values of the same parameter, perhaps enhancing the representation of a common sound.

6. Functional Characteristics of Avian Midbrain Neurons

Save for barn owls and songbirds, we do not know what acoustic properties are behaviorally salient to birds (Konishi 1985). Nevertheless, IC responses in barn owl, chicken, and zebra finch IC are similar, and principles learned from studies of the barn owl IC may apply to other birds (Knudsen et al. 1979).

Barn owls can localize sound precisely, and their midbrain responses are dominated by binaural computations subserving localization (Keller and Takahashi 1996; Konishi 2000). Their IC neurons are EE or EI (Moiseff and Konishi 1981) and sensitive to changes in ILD and ITD. Similarly, most chicken neurons are binaural, 46% being EI, 21% EE, 8% II (inhibited by either ear), and only 17% are monaural (Coles and Aitkin 1979).

Physiological properties are subdivision specific. The ICCc contains ITD-sensitive neurons and projects to the contralateral lateral shell, where ITD in-

formation is combined with ILD information (Fig. 17.13; Coles and Aitkin 1979; Takahashi et al. 1987a; Wagner et al. 1987; Volman and Konishi 1989; Spezio and Takahashi 2003). Thus, the progression from ICC to ICX is associated with the abstraction of stimulus features required to construct the ICX auditory space map (Mazer 1997).

6.1. Interaural Time Difference Tuning

ITD is the principal cue for auditory azimuth (Moiseff and Konishi 1981) and is computed in two stages: first, brain stem NL neurons act as coincidence detectors to encode interaural phase difference, firing maximally when simultaneously receiving inputs from both ears (Carr and Konishi 1990; Peña and Konishi 2001). At this stage, ambiguities exist about the correspondence between the NL response and the actual ITD in auditory space. The second stage of ITD computation occurs in the IC, where across-frequency integration filters phase-ambiguous side peaks, creating neurons coding the true ITD (Takahashi and Konishi 1986; Peña and Konishi, 2000).

The ICCc receives NL input and contains sharply frequency-tuned ITD sensitive neurons with primary-like responses (Fig. 17.13; Coles and Aitkin 1979; Wagner et al. 1987). In the ICCc one ITD activates a neural array tuned to many different frequencies (Fig. 17.13F; Wagner et al. 1987). This array code is transformed into unambiguous space-specific neuron responses as follows. Each array projects to ITD- and ILD-sensitive neurons in the contralateral lateral shell (ICCls), which project to space-specific neurons in the contralateral ICX, endowing them with ITD selectivity and therefore azimuth coding (Takahashi and Konishi 1986; Mazer 1997; Peña and Konishi 2000).

6.2. Tuning to Level and Interaural Level Difference Processing

Less is known about ILD processing. In the barn owl, the vertical asymmetry in ear directionality makes ILD a cue for the vertical target axis at high frequencies. Level is encoded by CN neurons, most having monotonic rate level functions (Köppl and Carr 2003). ILD sensitivity first emerges in the dorsal nucleus of the lateral lemniscus, posterior part (LLDp) whose neurons are excited by contralateral stimulation and inhibited by ipsilateral stimulation (Takahashi and Keller 1992; Takahashi et al. 1995) and are EI cells coding ILD (Manley et al. 1988; Mogdans and Knudsen 1994). LLDp therefore is analogous to LSO (Tsuchitani 1977; Takahashi et al. 1995). LLDp projects bilaterally to the ICCls, endowing these cells with ILD sensitivity (Adolphs 1993).

LLDp neurons do not unambiguously encode ILD. Although they prefer sound at the contralateral ear, they are also sensitive to changes in average binaural level. ILD tuning gradually emerges in the ICCls (Mazer 1998). Response latencies are about 5 ms near the central core, and $>$10 ms at the ICX

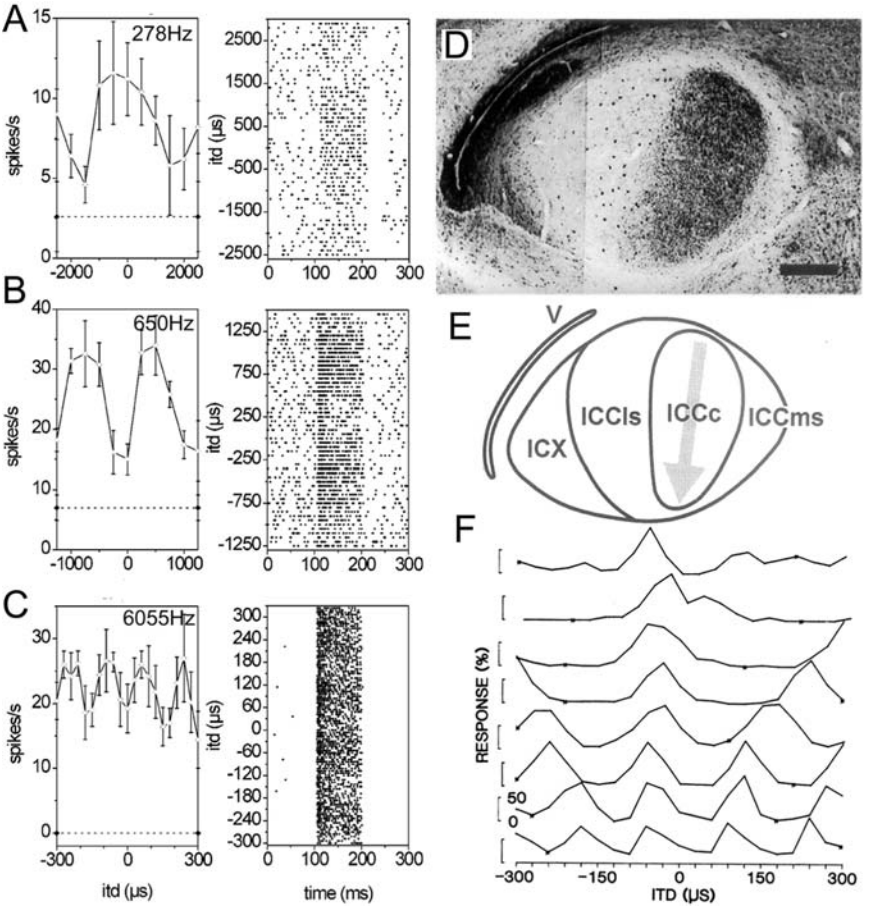


Figure 17.13. **(A)** ITD tuning curves in the barn owl ICCc. *Left,* ITD tuning curves; *right,* raster plots. Positive ITDs are right-ear leading. Tuning curves *(a, b, d)* from low- and high-frequency neurons. **(B)** The stimulus is an 800-Hz tone; all others are broadband noise. Note the cyclical tuning, even in response to noise stimuli, and the inhibition of spontaneous activity at stimulus termination. **(D, E)** Calretinin immunohistochemistry labels the ICCc; *arrow,* best frequency axis. **(F)** The ensemble code for ITD in the ICC. The array is sensitive to interaural phase differences, but each response shows phase ambiguity. (Modified from Wagner et al. 1987, 2002; Kubke et al. 1999.)

border. Frequency tuning widths broaden with increasing lateral position, while ITD and ILD tuning widths sharpen. Almost all ICCls neurons are sensitive to both time and intensity cues (Mazer 1997).

Unlike the ITD coding array in the ICCc, a topographical representation of ILD is never observed in the ICCls (Mazer 1998). Recordings from the space specific neurons show instead that ILD varies as a function of frequency in a

complex manner for any given location (Fig. 17.14A). In ICX, ILD-alone RFs are generally horizontal swaths of activity at the elevation of the cell's normal spatial RF (Fig. 17.14A). An ITD-alone RF forms a vertical swath at the azimuth of the cell's normal RF, which thus lies at the intersection of the ITD- and ILD-alone RFs (Euston and Takahashi 2002). ILD sensitive neurons in the chicken are EI and encode a 10- to 15-dB range (Coles and Aitkin 1979), with responses like those in the barn owl.

6.3. The Map of Auditory Space in the External Nucleus

The ICX space-specific neurons respond to sound only from a particular spatial locus and, when spontaneously active, are inhibited by stimulation of either ear (II) (Fig. 17.15; Knudsen and Konishi 1978; Knudsen and Knudsen 1983; Takahashi and Konishi 1986) and they are selective for combinations of ITD and ILD. Driven by noise, they do not show phase ambiguity, and thus differ from the ICCc ITD sensitive cells that provide their input (Peña and Konishi 2000). The phase-unambiguous response of space-specific neurons has been explained as follows. They receive inputs via the ICCls from many ICCc isofrequency laminae (Knudsen 1983), presumably from the ITD-specific arrays (Wagner et al. 1987). These inputs interact at the postsynaptic cell: peaks signaling the correct ITD superimpose and add, while secondary, ambiguous peaks cancel by interacting with inhibitory sidebands from other or ambiguous frequencies (Takahashi and Konishi 1986; Keller and Takahashi 1996, 2000). The inhibitory interactions between different frequency channels may originate from GABAergic ICX neurons (Fujita and Konishi 1991).

ICX neurons act like analog AND gates for ITD and ILD, such that the two inputs are multiplied (Fig. 17.14B–E). Multiplication of separate postsynaptic potentials (PSPs) tuned to ITD and ILD, rather than an additive process, explains their subthreshold responses to ITD-ILD pairs. Comparing subthreshold PSPs and spike output for the same ICX neurons show that RFs measured in PSPs exceed those measured in spikes in both ITD and ILD dimensions. Thus, a spike threshold mechanism mediates formation of the restricted space specific RF, the stimulus-induced first spike having a lower threshold than subsequent or spontaneous spikes (Peña and Konishi 2001).

The spatially restricted ICX RFs are still much larger than the minimum detectable change in sound source location, which can be 3°. However, changes in neuronal activity across the space map show that most neurons can reliably signal source location changes smaller than the behavioral threshold. Each source is represented in the space map by a focus of activity in a neural population, and source displacement changes their activity pattern (Takahashi et al. 2003). This map of contralateral auditory space projects topographically to the optic tectum (OT), whose visual and auditory space maps are in register (Knudsen and Knudsen 1983). OT activity directs the owl's rapid head movements to auditory and visual stimuli (du Lac and Knudsen 1990).

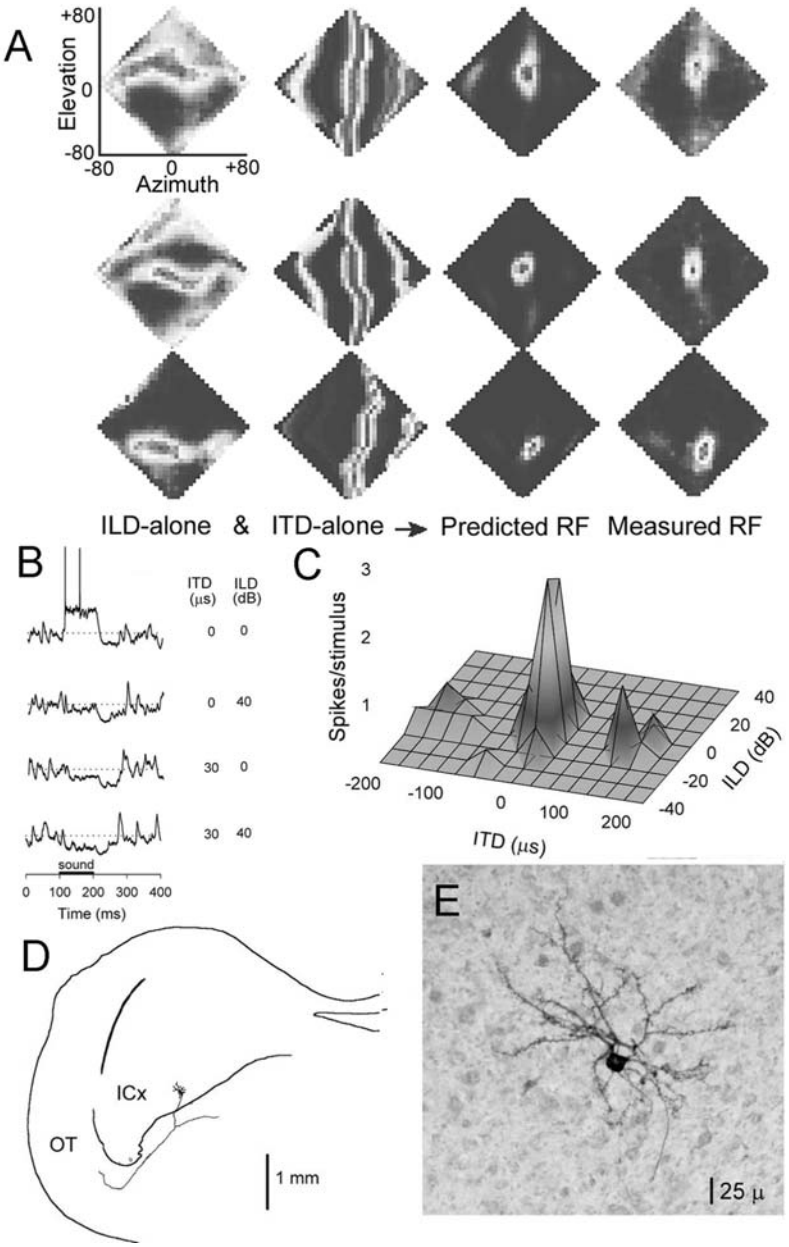


Figure 17.14. Formation of space-specific responses in the barn owl ICX. **(A)** ITD and ILD contributions to the spatial RF of an ICX cell. Diamond, spikes *(gray)* evoked by a source at frontal hemisphere loci. *First column*: ILD-alone RFs for three cells obtained by filtering broadband noise with HRTFs altered to present the ILD spectra for each spatial location while holding the ITD constant at a cell's preferred value. *Second column*:

6.4. The Role of Experience in Formation of the Space Map

The auditory space map has become a paradigm for studies of experience-dependent plasticity (Knudsen 2002). Manipulating sensory experience reorganizes ICX in a manner congruent with behavioral learning, as accurate auditory orienting behavior is a measure for adaptive adjustment in sound localization after peripheral changes in sensory experience such as disrupting auditory cue values for spatial loci by ear plugging (Knudsen et al. 1984; Brainard and Knudsen 1995; Knudsen 1999). Owls with an earplug first err toward the open ear, then recover. On earplug removal, their orienting errors are in the opposite direction, and these resolve with experience. A second manipulation alters visual and auditory correspondence with prismatic spectacles that displace the visual field (Brainard and Knudsen 1998). Such owls learn new associations between auditory and visual cues to recalibrate both worlds.

Learning changes forebrain and midbrain neuron tuning to sound localization cues. In the midbrain space map, the assay for plasticity is precise and can be quantified for each neuron (Fig. 17.15; Knudsen 1982). Adaptive changes are centered in the ICX and depend on changes in axonal projections and adjustments in synaptic strength (Knudsen 2002; Nieder et al. 2003). In young owls with either earplugs or prismatic displacement, ICX tuning to sound localization cues alters adaptively to coordinate the auditory and the visual RFs (Fig. 17.15; Mogdans and Knudsen 1994). Gradually, these new responses strengthen, while those to the prior ITD range disappear. These changes are correlated with axonal remodeling of the topographic projection from the ICC to the ICX. Prism experience appears to induce the formation of modified circuitry in the ICX at least in part through axonal sprouting and synaptogenesis. Normal circuitry also persists, showing that alternative plastic and normal circuits coexist in this network.

Both *N*-methyl-D-aspartate (NMDA) and $GABA_A$ receptor changes are implicated in plasticity. NMDA receptors regulate expression of newly learned responses (Feldman and Knudsen 1998). In an ICX expressing a maximally shifted

Figure 17.14. *Continued*
the ITD-alone RFs. *Third column*: combining the plots in these columns yields the predicted spatial RFs. *Fourth column*: spatial RFs measured directly from the cell. Negative azimuths and elevations denote loci on the left of the midline and below eye level, respectively. (Modified from Takahashi et al. 2003.) **(B)** Space specific neuron showing PSPs to different ITD–ILD pairs. *Dotted lines,* mean resting potential. **(C)** Spiking responses of the same neuron to different ITD–ILD pairs. The large peak is the excitatory center and the flat area around it is the inhibitory surround (compare **B, C**). Negative (–) ITD and negative (–) ILD mean, respectively, sound in ipsilateral ear leading and louder. **(D)** An ICX neuron and its axon projecting to the OT. **(E)** The same neuron labeled with neurobiotin. (From Peña and Konishi 2001.)

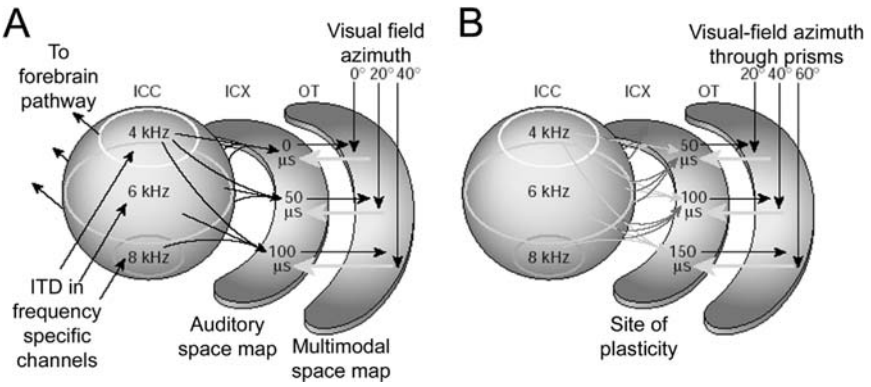


Figure 17.15. The auditory space map in the ICX before **(A)** and after **(B)** shifts produced by early prism experience. **(A)** The ICC-ICX *(black arrows)* projection conveys ITD and other information and converges across frequency channels, creating spatially restricted auditory RFs and a space map. The auditory and visual maps of space merge in OT and receives a reciprocal instructive signal from it. **(B)** The schematic representation of the anatomical change *(dark arrows)* in the ICC–ICX projection resulting from early prism experience. For each axis of prismatic displacement, an abnormal rostralward projection of ICC axons *(dark gray arrows)* appears on one side of the brain and a caudalward projection appears contralaterally (data not shown), although the normal projection persists *(light gray arrows).* (Modified from Knudsen 2002.)

ITD map, focal blockade of GABA elicited the immediate appearance of normal responses. Thus, in a shifted-ITD map, synapses that support normal responses remain patent and coexist with synapses that support learned responses, but responses to the normal synapses are selectively nullified by GABAergic inhibition (Zheng and Knudsen 1999).

Changes in the ICX auditory space map are directed by a topographic map of visual space whose dominance is plausible since the pathway's primary function is to trigger gaze towards auditory targets (Knudsen et al. 1993; Wagner 1993). The power and precision of the visual instructive signal is shown when a small lesion in the tectum eliminates adaptive adjustments (Hyde and Knudsen 2002).

7. Comparing Birds and Bats

The auditory midbrain structures of birds and bats are probably homologous, and serve many similar purposes. The IC integrates information converging on it from many parallel pathways that will ultimately contribute to sound source localization and decoding of the auditory signals. The IC is an important source of output to motor pathways for orientation, vocalization, and other behaviors. It is part of a massive system that extends to the forebrain, and it may participate

in adaptive changes from learning and peripheral modifications. However, the evolutionary paths of birds and bats diverged so long ago that many of the substrates through which these tasks are accomplished are very different. The avian cochlea, central auditory system, and forebrain are organized differently from those of mammals so that the patterns of connections differ considerably between the two groups.

Midbrain organization is more hierarchical in owls, especially with regard to the emergence of an invariant map of auditory space in the different IC subdivisions. The barn owl midbrain is dominated by binaural processing and may have more in common with mammals that do not echolocate. Finally, the streams of processing for sound location and temporal patterns are more sharply segregated in owls. Future work should reveal whether birds and bats share some of the same neural circuits and cellular mechanisms for information processing despite the fact that many structures and pathways are different.

Abbreviations

AVCN	anteroventral cochlear nucleus
CF	constant-frequency
CN	cochlear nucleus
DCN	dorsal cochlear nucleus
DLL	dorsal nucleus of the lateral lemniscus
EE	neuron excited by contralateral and ipsilateral sound
EI	neuron excited by contralateral sound and inhibited by ipsilateral sound
EPSP	excitatory postsynaptic potential
FM	frequency-modulated
GABA	γ-aminobutyric acid
GC	tectal gray
IC	inferior colliculus
ICC	central nucleus of the inferior colliculus
ICCc	central core of the central nucleus of the inferior colliculus
ICCls	lateral shell of the central core of the inferior colliculus
ICCms	medial shell of the central core of the inferior colliculus
ICX	external nucleus of the central core of the inferior colliculus
III	oculomotor nucleus
ILD	interaural level difference
ILL	intermediate nucleus of lateral lemniscus
IO	isthmo-optic nucleus
IPSP	inhibitory postsynaptic potential
ITD	interaural time difference
IV	trochlear nucleus
iv	trochlear nerve
LL	lateral lemniscus

LLDp	dorsal nucleus of lateral lemniscus, posterior part
LSO	lateral superior olive
MGB	medial geniculate body
MLd	mesencephalic nucleus, pars dorsalis
MSO	medial superior olive
NA	nucleus angularis
NL	nucleus laminaris
NM	nucleus magnocellularis
NMDA	*N*-methyl-D-aspartate
PLS	paradoxical latency shift
PVCN	posteroventral cochlear nucleus
RF	receptive field
SAM	sinusoidal amplitude modulation
SFM	sinusoidal frequency modulation
SOC	superior olivary complex
VLL	ventral nucleus of lateral lemniscus
VLLc	columnar nucleus of VLL

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Chapter 18
Development of Auditory Afferents to the Central Nucleus of the Inferior Colliculus

Judy K. Brunso-Bechtold and Craig K. Henkel

1. Introduction

The inferior colliculus (IC) is a requisite site of convergent input for much of the ascending auditory system (Fig. 18.1). Although some ascending fibers bypass this structure, the IC is certainly a synaptic target for the vast majority of parallel auditory pathways ascending from the brain stem (see Chapters 2 and 4). In addition, the IC receives a heavy descending projection from cerebral cortex (see Chapter 8). Consequently, during development an immense population of actively growing axons converges on the IC. Of necessity, this heterogeneous and dynamic input must rapidly and efficiently develop local intrinsic networks to integrate and preserve ascending monaural and binaural frequency and timing cues extracted during neural processing in brain stem nuclei.

The IC is composed of a large central nucleus (CNIC) surrounded by dorsal (DCIC) and external (ECIC) cortical nuclei. The CNIC receives crossed and uncrossed ascending pathways (Fig. 18.1A), each converging in cochleotopic order within a series of fibrodendritic layers. A hallmark of the structural organization of the CNIC is the mosaic of bands and patches of afferent input from different sources projecting to somata and dendrites oriented parallel to the layers (Fig. 18.1B, C) (Geniec and Morest 1971; Rockel and Jones 1973; Fitzpatrick 1975; Morest and Oliver 1984; Oliver and Morest 1984; Faye-Lund and Osen 1985; Zook et al. 1985; Shneiderman and Henkel 1987; Oliver and Shneiderman 1989; Malmierca et al. 1993; Oliver 2000). How this elaborate and precise organization is created from a dynamic population of rapidly growing neurites is unknown but it must be governed by some of the classic ontogenetic principles prevailing elsewhere in the neuraxis (Fig. 18.2). This population of neurites includes axons arriving from a wide range of cell types in various nuclei on both sides of the brain, as well as intrinsic axons and developing dendrites. Once the basic axonal organization is established within the CNIC, their local distribution is refined and they begin to express mature features such as neurotransmitters and their receptors and transporters as well as calcium binding proteins. The development of these features appears to be influenced significantly by neural activity, often demonstrated by the effects of hearing loss.

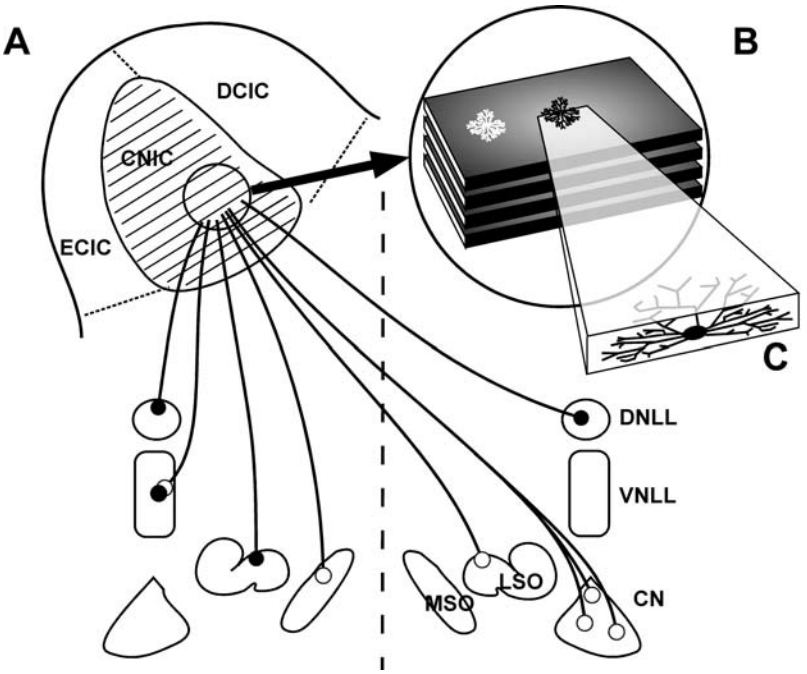

Figure 18.1. Schematic overview of the architecture and afferent projections to the CNIC (simplified to include only ascending projections from principal nuclei). **(A)** Locations of the CNIC, DCIC and ECIC are shown at the *upper left* in an outline of a frontal section. *Diagonal lines* depict the orientation of fibrodendritic layers characteristic of the CNIC. The major excitatory *(open circles)* and inhibitory *(closed circles)* inputs to the layers are shown. **(B)** A portion of CNIC is enlarged to show four layers. Afferents from multiple sources converge in cochleotopic order in layers, forming distinct synaptic compartments among functional sets of inputs. **(C)** A single disc-shaped cell is illustrated in the expanded view of a layer. Cells with flattened dendritic fields are aligned with layered afferent inputs to form input–output circuits that preserve frequency processing. *CN,* cochlear nuclei; *CNIC,* central nucleus of inferior colliculus; *DCIC,* dorsal cortex of inferior colliculus; *DNLL,* dorsal nucleus of the lateral lemniscus; *ECIC,* external cortex of the inferior colliculus; *LSO,* lateral superior olivary nucleus; *MSO,* medial superior olivary nucleus; *VNLL,* ventral nucleus of the lateral lemniscus.

Although the precise mechanisms by which ear removal or hearing loss influence afferent organization and axonal identity remain to be determined, there is an increased awareness of the trophic impact of activity-driven neural events.

2. Development of the Central Nucleus

2.1. Axons and Synapses

Cells within the CNIC are born very early in development (Fig. 18.2), beginning at embryonic day 14 (E14) in rat, 3 weeks before hearing begins (Altman and

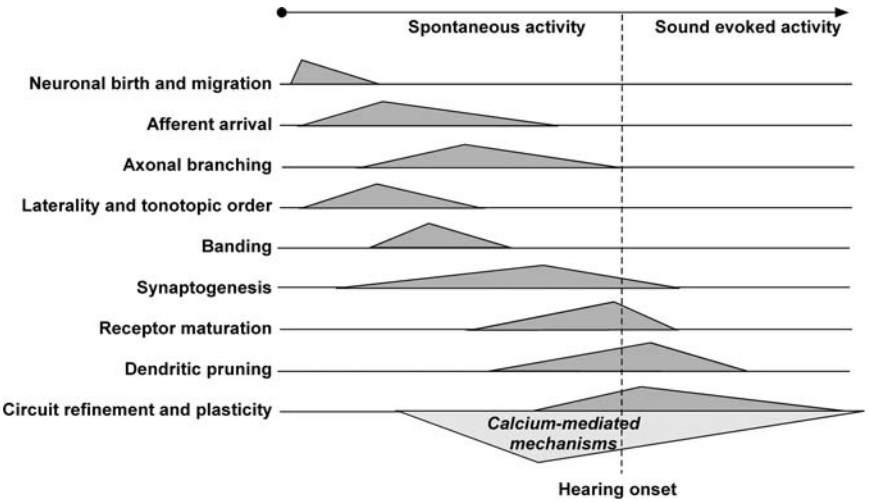

Figure 18.2. Summary of the time course of the developmental events in the IC relative to each other and in relation to onset of hearing.

Bayer 1981). By E13 some cochlear nucleus pioneer axons have extended along the perimeter of the hindbrain (Niblock et al. 1995), reaching the IC by E17 or E18 in rat (Kandler and Friauf 1993). Axons from the dorsal nucleus of the lateral lemniscus (DNLL) extend to the contralateral IC by E19 in ferret (Gabriele et al. 2000a). The medial superior olive (MSO) projection to the IC is present at birth in rat and gradually increases until adulthood (Okoyama et al. 1995). In carnivores as well as in the rat, there is a rich distribution of axons within the IC well before auditory experience (González-Hernández et al. 1989; Kandler and Friauf 1993; Gabriele et al. 2000a; Keiger et al 2003). Initially, projections from DNLL distribute diffusely in the CNIC as linear axons with few side branches or protrusions but oriented parallel to the frequency layers (Fig. 18.3A). Second, still before the onset of hearing, axons from DNLL as well those from lateral superior olive (LSO) begin to form a periodic distribution of fiber-rich bands or layers with intervening axon-sparse interband spaces or sublayers (Fig. 18.3B) (Gabriele et al. 2000a). Similarly the LSO projection in ferret distributes diffusely in the IC in the first postnatal week (Fig. 18.4A, B). One week later, and two weeks before hearing begins, a banded segregation of this projection is apparent (Fig. 18.4C, D) (Keiger et al. 2003).

In the only two afferent systems in which band formation has been studied, the DNLL and the LSO projections to IC, the projections are bilateral. Both the DNLL and LSO projections are banded within the adult IC (Kudo 1981; Shneiderman and Henkel 1987; Shneiderman et al. 1988; Oliver 2000). This pattern is in contrast to that of other projections such as those from the MSO and the ventral nucleus of the lateral lemniscus, which are almost exclusively ipsilateral and have little banding within the CNIC (Henkel and Spangler 1983; Whitley

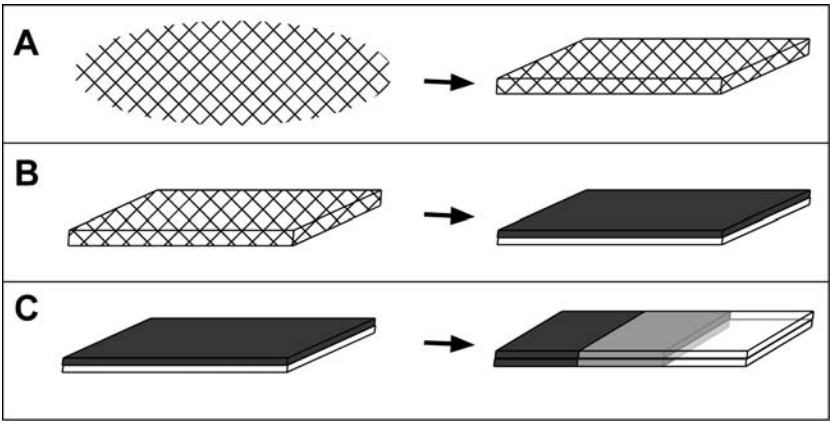

Figure 18.3. A working model of steps in the developmental refinement of layered fibrodendritic circuits in the CNIC. **(A)** Afferent and dendritic elements of IC circuits initially establish their approximate distribution *(hatched area)* and then subsequently are pruned *(arrow)* to match cochleotopic position within fibrodendritic layers. **(B)** Afferent inputs from different ascending channels initially converge on the same layer and then segregate *(arrow)* in the vertical dimension to form sublayers *(black vs. white)*. **(C)** Functional sets of inputs segregate *(arrow)* to form multiple synaptic domains *(black, overlapping, and white zones)* within fibrodendritic layers or sublayers.

and Henkel 1984; Oliver 2000). These observations are consistent with the possibility that competition between converging ipsilateral and contralateral input drives the development of banded projection patterns from the DNLL and the LSO. Although there is a banded pattern of input to CNIC from the dorsal cochlear nucleus (DCN) (Oliver 1984; Oliver et al. 1997), which also projects bilaterally, the contralateral component is significantly larger. This asymmetry of projection raises the issue of whether a projection from another source might overlap with that from ipsilateral cochlear nucleus (CN), presumably firing coincidentally with it and thus participating in a competition for synaptic space potentially occupied by fibers from the contralateral CN.

Rearrangement in the laterality of IC afferents prior to hearing onset is evident in the gradual decrease in the proportion of LSO cells projecting to the contralateral IC in ferret during the first postnatal month (Henkel and Brunso-Bechtold 1993). Initially the DNLL and LSO projections distribute diffusely across the width of the frequency layers and extend broadly along the length of the frequency layers (Fig. 18.3C: left). However, once the segregation of axons into bands and interband spaces has begun, these projections are confined to the length of the frequency layers (Fig. 18.3C: right). In the adult, projections from different sources such as DCN and LSO occupy distinct domains within the layers, consistent with a role for competition among afferent sources in the refinement of intralaminar synaptic domains. Although refinement of the banded

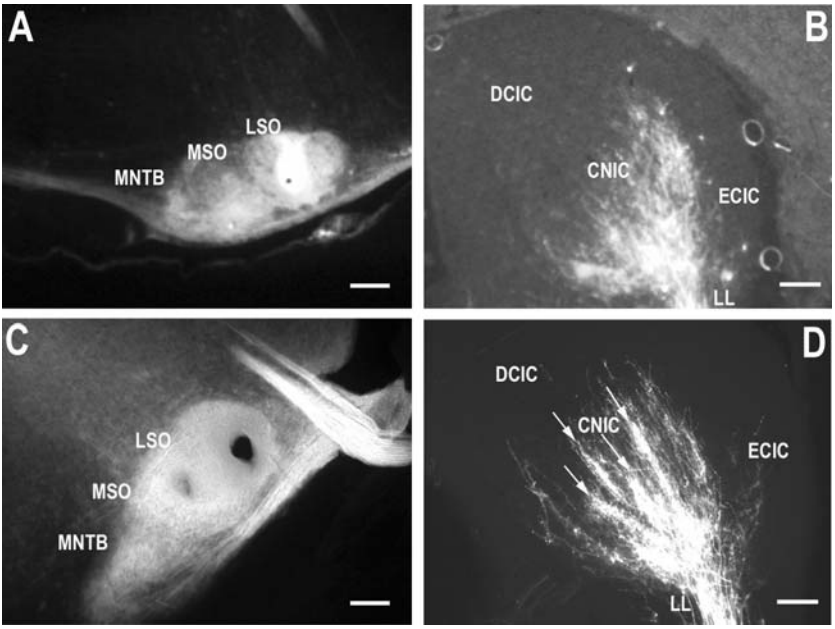

Figure 18.4. DiI labeling of projections from the LSO to the IC in ferret prior to hearing onset at the end of the first postnatal month. DiI-coated cactus needles that were placed in the LSO in lightly fixed ferret brains at P7 **(A)** and P14 **(C)** labeled axons that enter the CNIC from the lateral lemniscus and extend parallel to the isofrequency planes. Axons at P7 **(B)** distribute throughout the ventrolateral portion of the CNIC with early periodicity emerging. By P14 **(D)**, LSO axons within the CNIC form bands *(arrows).* Dorsal is toward the *top* and medial is to the *right*. *CNIC,* Central nucleus of the inferior colliculus; *DCIC,* dorsal cortex of the inferior colliculus; *ECIC,* external cortex of the inferior colliculus; *LL,* lateral lemniscus; *LSO,* lateral superior olive; *MNTB,* medial nucleus of the trapezoid body; *MSO,* medial superior olive. The scale bars represent 150 μm.

distribution of ascending auditory projections undoubtedly continues after ear opening, the basic banded pattern of DNLL and LSO input to the CNIC is evident several days before hearing onset in the rat (Gabriele et al. 2000a) and several weeks before hearing onset in the ferret (Keiger et al. 2003).

As input segregation along afferent bands is taking place, numerous varicosities and side branches emerge along the preterminal axons (Gabriele et al. 2000a). Whether these axonal events are accompanied by a synchronous formation of synaptic connections is currently unclear as little information is available on synaptogenesis within the IC. In fact, the only quantitative studies of synapse development pertain to marsupials for which data are not available about the development or absence of a banded distribution pattern (see Chapter 22, Fig. 22.2B). In the Northern quoll, a marsupial cat, synapses first can be detected

in the IC nearly 2 months prior to the onset of hearing. The ratio of synapses to neurons gradually increases until several days before hearing onset, and then rapidly accelerates to adult levels about 10 days later (Aitkin et al. 1996). Similarly, in the short-tail Brazilian opossum, synapses are apparent at the first age studied, about 1 week before hearing begins, and do not quantitatively change until hearing onset, after which synaptogenesis rapidly accelerates (Aitkin et al. 1997). In the rat, the available information suggests some synapses are present before hearing onset (Pysh 1969).

In the ferret, evidence from our laboratory indicates that synapses in the IC neuropil are present during the first postnatal week and increase steadily in number throughout the month before hearing begins. At postnatal day 4 (P4) IC synapses are distributed sparsely through the neuropil, but are small and immature, without glial encapsulation, and myelin is not present (Fig. 18.5A). In comparison, P28 synapses (Fig. 18.5B) are larger and more likely to be perforated, and have multiple targets. Moreover, myelin is now apparent and glial encapsulation of dendrites and synapses is in progress. Quantitative studies will be required to relate synaptogenesis to the beginning of afferent band formation within the ferret CNIC (Keiger et al. 2003). However, ferret MSO synapses are apparent in the neuropil during the first 2 weeks after birth with rapid somatic synaptogenesis beginning during the third postnatal week and a relatively mature synaptic organization present by ear opening (Brunso-Bechtold et al. 1992). Although quantitative data on synaptogenesis within the CNIC are not

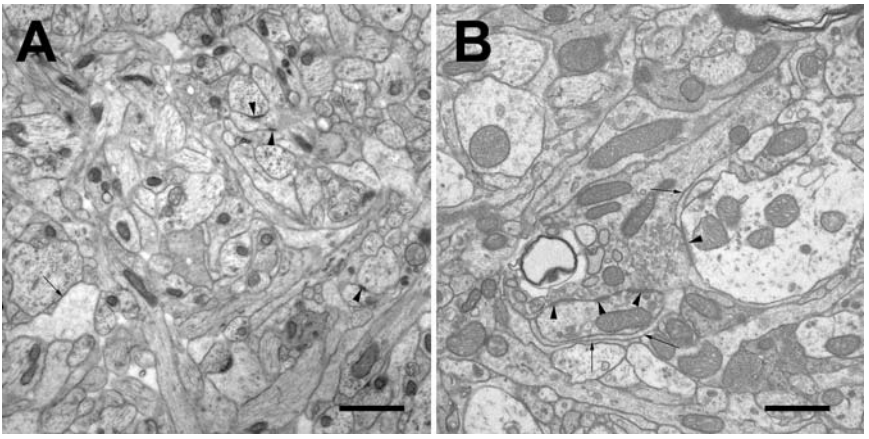

Figure 18.5. Ultrastructure of ferret IC prior to hearing onset. At P4 **(A)**, simple synapses *(arrowheads)* are sparsely distributed throughout the CNIC neuropil. Growth cones *(arrow)* are present, myelin has not yet begun to form, and glial processes only rarely extend along the surfaces of somata and dendrites. At P28 **(B)**, just before hearing begins, synapses *(arrowheads)* are more complex and glial encapsulation *(arrows)* of synapses and dendrites is evident. Myelin formation also is underway. The scale bars represent 5 μm **(A)** and 1 μm **(B)**.

currently available for any mammal, it is reasonable to extrapolate that a basal level of synapses is present during the segregation of afferent input and that increased synaptogenesis coincides with the refinement of afferent projections.

2.2. *Dendrites*

Lamination of dendritic arbors as well as lemniscal axons is a characteristic feature of the CNIC (Fig. 18.1). This arrangement of afferent inputs and postsynaptic cells underlies the orderly coding of frequency in IC layers, with low frequencies represented dorsolaterally and higher frequencies more ventromedially. In rat Golgi material, dendritic features distinguishing disc-shaped and multipolar (stellate) cells in the CNIC and multipolar and giant cells in the ECIC and DCIC are present at birth (González-Hernández et al. 1989). Quantitative analysis of CNIC cells reveals a pronounced flattening of dendritic trees in the plane of these layers after the onset of hearing in kittens and rats (Meininger and Baudrimont 1981; Dardennes et al. 1984). Dendritic trunks parallel to the layers elongate by adding secondary processes while those extending beyond the layer are pruned. Dendritic spines, present on various CNIC cell types, gradually increase in density until one month of age then decline to adult values (Dardennes et al. 1984). Dense layers of lemniscal axons are present at birth in kittens (González-Hernández et al. 1989) and banding of afferent projections in rat (Gabriele et al. 2000a) and ferret (Keiger et al. 2003) emerges well before hearing begins. Thus, the final dendritic maturation in the CNIC, including growth, branching, and spine elimination that occurs after hearing onset, may depend on functional maturation of afferent input (Fig. 18.2).

2.3. *Functional Correlates*

Almost as soon as responses to sound can be recorded in the IC, response properties such as frequency tuning, binaural response patterns, and response types emerge and resemble those in adult animals (Aitkin and Moore 1975; Aitkin and Reynolds 1975; Moore and Irvine 1980, 1981a,b; Blatchley and Brugge 1990; Romand and Ehret 1990). These reflect the early establishment and postnatal maturation described for the presynaptic and postsynaptic structural organization in the IC. Although higher thresholds, lower discharge rates, and broader tuning are evident initially, and in part are secondary to protracted development of the ear, further maturation of threshold and discharge rates undoubtedly depends on subsequent postnatal events that affect the balance of excitatory and inhibitory synaptic circuits and their respective receptor composition. Moreover, refinement of frequency tuning may involve interaction and matching of dendritic compartments with afferent input.

In contrast to the morphological sequence of cochlear maturation in which development of the high-frequency, basal cochlea precedes that of the low-frequency, apical portion, functional studies suggest that low-frequency hearing develops first. It has been proposed that this apparent paradox reflects a devel-

opmental shift in cochlear best frequency, and such shifts in sensitivity of hair cells from low- to high-frequency sounds are reported in many species (Lippe and Rubel 1983; Harris and Dallos 1984; Rubel et al. 1984; Echteler et al. 1989; Sanes et al. 1989; Friauf 1992; Schweitzer et al. 1996; Romand 1997; Mills and Rubel 1998). Evidence in the gerbil supports a developmental shift in the tonotopic map within the LSO and IC in a manner consistent with such frequency shifts in the developing cochlea (Ryan and Woolf 1988; Sanes et al. 1989). However, at a comparable time point in the rat, high- and low-frequency neural activity demonstrated by c-*fos* immunoreactivity is present in the IC as well as in brain stem auditory nuclei (Friauf 1992). No subsequent shift in the position of frequency responsiveness was observed, suggesting that any such frequency shift takes place before ear opening. Reconciling this observation with reports of frequency shifts in the rat cochlea taking place near hearing onset (Hyson and Rudy 1987) or even later (Müller 1991) remains an open issue.

2.3.1. Calcium-Binding Proteins

Calcium-binding proteins in neurons have multiple roles and their presence has been correlated with different functional properties. In immature neurons, calcium-binding proteins may identify the site of important calcium-dependent mechanisms and serve as simple markers of various components of developing auditory circuits (Baimbridge et al. 1992; Andressen et al. 1993). In adult rat, various calcium-binding proteins are distributed differentially in the IC and have unique developmental patterns (Friauf 1994; Lohmann and Friauf 1996). For instance, parvalbumin-immunoreactive neurons are distributed throughout the IC subnuclei in adult rat, but are not present until P8. Parvalbumin-immunopositive cells increase from P8 until P28 when adult levels are reached (Lohman and Friauf 1996). In contrast, calretinin- and calbindin-immunoreactive neurons are present in the IC around birth. Immunostaining for these calcium-binding proteins, as opposed to parvalbumin, declines thereafter and is absent shortly after hearing onset in the CNIC, but persists in other subnuclei (Friauf 1994; Lohman and Friauf 1996).

In addition to the distribution of calcium-binding proteins in neuronal somata within the IC, calretinin and calbindin concentrate selectively in axons afferent to the CNIC (McHaffie et al. 2000; Fuentes-Santamaria et al. 2003). The early distribution pattern of calbindin-immunoreactive endings in kitten (McHaffie et al. 2000) resembles the alternating bands described for lemniscal inputs to the CNIC (Fig. 18.6A). This pattern gradually becomes fainter but more sharply defined during the 2 postnatal months as calbindin-immunoreactive endings are restricted to the central region of the IC layers (Fig. 18.6B), suggesting that the segregation of those projections involves calcium-mediated mechanisms (Fig. 18.2).

2.3.2. Neurotransmitters

Glutamate, glycine, and γ-aminobutyric acid (GABA) are the dominant neurotransmitter systems in the brain stem auditory nuclei afferent to the IC. Iono-

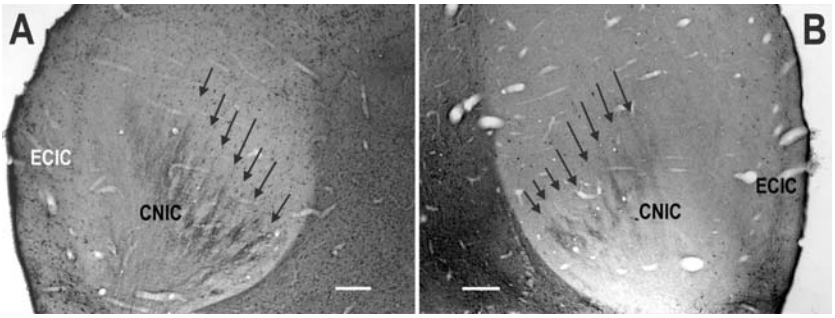

Figure 18.6. Distribution of calbindin immunoreactivity in cat IC during postnatal development. Calbindin immunoreactivity in the CNIC at P1 **(A)** is localized densely in axons forming bands *(arrows)* oriented parallel to the isofrequency planes. By P42 **(B)**, the bands of calbindin immunoreactive axons are sharper but less intense. Dorsal is toward the *top* and medial is to the *right* in **(A)** and to the left in **(B)**. *CNIC,* Central nucleus of the inferior colliculus; *ECIC,* external cortex of the inferior colliculus. The scale bars represent 100 μm.

tropic receptors for these amino acid neurotransmitters have in common that they are heteromeric complexes comprised of different subunits surrounding an ion channel. The specific receptor subunit composition modulates channel kinetics. Receptors for these neurotransmitters have complex individual subunit profiles and distributions in the IC (Sato et al. 2000). These receptor complexes undergo postnatal modification with slight variations in peak expression times of the various components (Fig. 18.2).

The major class of excitatory receptors in the mature IC is the ionotropic glutamate receptors. Both α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) glutamate receptors are present. The functional complements of AMPA receptor subunits (GluR1-4 or A-D) and two of their splice variants (flip or "a" and flop or "b") as well as the NMDA receptor subunits (NR1 and NR2) in the CNIC are developmentally regulated. There is a decrease in the immature, flip isoforms of the AMPA subunits in the IC by hearing onset while the mature, flop isoforms are expressed more highly at or after hearing onset. In contrast, NMDA subunit expression in the CNIC is moderate and relatively constant in postnatal and young adult rats (Caicedo and Eybalin 1999). For the AMPA receptors, there are significantly higher mRNA levels for the immature flip isoform of the GluR2 subunit in the IC compared to LSO and CN (Schmid et al. 2001). Higher GluR2 subunit levels in mature receptors may be related to slower kinetics and lower permeability to calcium ions of these neurons (Hollman et al. 1991; Hume et al. 1991). This calcium permeability of IC glutamate receptors appears to be developmentally regulated and is highest in postnatal rat around hearing onset (Caicedo et al. 1998).

Both GABA and glycine are prominent IC inhibitory neurotransmitters. The composition of $GABA_A$ and glycine receptor subunits changes postnatally, with the expression of mRNA for immature forms of both receptor complexes de-

clining by hearing onset (Laurie et al 1992; Kraushaar and Backus 2002). Although it is often the case that the glycine α-2 receptor subunit is the neonatal form and α-1 the adult form, the α-2 message is weakly expressed at birth in the rat IC and remains low until P21. In contrast, the α-1 subunits of the glycine receptor are absent at birth, expressed weakly at about P8, increase from P12-P20, and reach adult distribution by P28 (Friauf et al. 1997; Piechotta et al. 2001). As the glycine transporter protein GLYT2 is highly expressed in the CNIC at birth, before the mature α-1 subunit appears, and declines to lower levels by P22, this transporter may participate in synapse maturation (Friauf et al. 1999).

Although its function has not been fully explored, a substantial cholinergic input to the CNIC appears postnatally and may be of basal forebrain origin (Gao and Suga 2000; Ma and Suga 2003). This input is mediated primarily by a subclass of nicotinic cholinergic receptors (nAchR) (Morley and Happe 2000). nAchRs in the IC are concentrated on presynaptic endings and may have modulatory affects on neurotransmitter release. In development, nAchRs have important roles in activity-dependent plasticity of synaptic connections (Radcliffe and Dani 1998; Dani 2001; McGehee 2002). Perhaps the developmental regulation of nAchRs in IC is similar to that in auditory cortex where they peak late in postnatal development (Aramakis et al. 2000) during the plastic period when auditory experience shapes functional and structural refinement of synaptic circuits.

Maturation of the neurotransmitter receptor subunit profiles, regardless of type, is a dynamic process and may reflect the organization of heterogeneous inputs to the CNIC. Moreover, cotransmitters such as somatostatin and leu-enkephalin, which modulate activity, are expressed transiently in the IC (Sekitani et al. 1990; Kungel and Friauf 1995; Thoss et al. 1996). The maturation of these profiles occurs well after initial circuits are formed and even after banded patterns in IC emerge (Fig. 18.2). Thus, the early functional role of receptor subunits may be to participate in the formation of afferent bands and early emergence of synaptic domains (see Chapter 2).

3. Role of Activity in Inferior Colliculus Development

Activity-mediated mechanisms that shape IC circuits may depend on either spontaneous activity in the ascending auditory pathways before hearing onset or patterned sound-evoked activity during early hearing (Fig. 18.2). Ascending projections reach the auditory midbrain and elaborate diffuse axonal arbors near their ultimate targets well before hearing onset and undergo subsequent adjustment. The electrophysiological and biochemical environment plays an essential role in influencing the formation of a mature afferent projection pattern in the CNIC. The principal manipulations used to assay activity-specific effects include

cochlear removal and antibiotic infusion, which physically interrupt the link from sensory receptor to auditory targets and cause a sensorineural hearing loss. In contrast, ossicle removal and ear plugging leave the auditory pathway intact, but reduce the afferent signal, causing a conductive hearing loss. Here, we consider only studies that affect the formation of afferent bands within the developing IC.

3.1. Effect of Ear Removal on Inferior Colliculus Afferents

Considerable information is available on the effects of ear removal on projections to, and morphometry of, mammalian CN, LSO, and MSO neurons (Webster and Webster 1977; Trune 1982a,b; Moore and Kowalchuk 1988; Moore 1990; Kitzes et al. 1995; Russell and Moore 1995; Tierney et al. 1997; Hardie and Shepherd 1999). The impact of sensorineural hearing loss on these structures is most dramatic when it occurs prior to hearing onset. This suggests that the effect of early ear removal on the input to the IC extends beyond a change in levels or patterns of activity to physically affect the neuronal populations contributing the axonal input. Thus, unilateral cochlear ablations made before ear opening in ferret significantly decrease cochlear nucleus volume ipsilateral to the lesion in adults and increase the projection from the contralateral CN to the IC on the same side (Moore and Kowalchuk 1988). However, conductive hearing loss does not change CN volume, yet still increases the number of CN neurons contralateral to the lesion that projected to the IC on the same side (Moore et al. 1989). This demonstrates forcefully that early changes in auditory activity can affect the projection pattern to the IC independent of cell loss.

In the gerbil, as in the ferret, early cochlear ablation increases the projection originating in the CN contralateral to the lesion and terminating in the IC on the same side (Nordeen et al. 1981). Moreover, the distribution of the ipsilateral CN projection within the IC is expanded (Moore and Kitzes 1985). In contrast, bilateral cochlear ablations at ear opening cause no significant differences in the projection from the CN to the IC (Moore 1990). Taken together, the effects of unilateral vs. bilateral cochlear ablation suggest the importance of competition between event-driven auditory activity from both ears in establishing the projection of ascending auditory afferents to the IC.

3.2. Effect of Ear Removal on Structural Features of the Inferior Colliculus

Few studies have evaluated structural changes within the IC ensuing from cochlear ablation. In the cat unilateral cochlear ablation near hearing onset did not affect the size of neurons within the IC, while bilateral ablation produced a small but significant decrease (Nishiyama et al. 2000). These authors suggest that the profound changes in subcollicular auditory nuclei are not evident in the

IC following unilateral ear removal because the massive afferent convergence insures sufficient levels of afferent activity to maintain somatic size. Similarly, synaptic density in mature cats and ferrets is unchanged by unilateral cochlear removal at the time of ear opening (Hardie at al. 1998; Fuentes-Santamaria et al. 2003). Interestingly, synapse density was significantly lower in the mature cat IC after bilateral neonatal cochlear ablation, which was interpreted as a global decrease of auditory activity and a consequent effect on trophic support (Hardie et al. 1998).

3.3. Effect of Ear Removal on Afferent Band Formation in the Inferior Colliculus

Even less is known about the impact of cochlear ablation on the development of IC bands and patches of afferents. Changes in the banded projection pattern of DNLL fibers, however, have been studied following unilateral neonatal cochlear removal on P2 in rats, before afferent bands develop (Gabriele et al. 2000b). The rats survived until P12, around onset of hearing, when DNLL input to the CNIC is banded (Fig. 18.7A, B) (Gabriele et al. 2000a). The projection pattern of crossed DNLL axons was visualized with a fluorescent carbocyanine dye tracer, diI (1,1'-dioctadecyl-3,3,3',3'- tetramethylindocarbocyanine perchlorate), which showed a sparse, but banded, distribution of crossed DNLL input in the contralateral IC (Fig. 18.7C). Ipsilateral to the ablation, the crossed DNLL input is considerably heavier; however, no banding pattern is evident (Fig. 18.7D). Thus, before ear opening, cochlear ablation profoundly affects the refinement of afferent projection patterns within the IC. Precisely how cochlear ablation leads to the changes in the banded DNLL input to the IC is unknown. Because cochlear ablation reduces spontaneous activity, it is tempting to ascribe the effect to activity per se or to a difference in the activity-regulated release of neurotrophic factors that regulate the symmetry of afferent patterns.

3.4. Effect of Ear Removal on Inferior Colliculus Function

Functional changes in the IC after early postnatal deafening demonstrate the considerable plasticity latent in the central auditory pathways in young animals and that can persist to a degree even in adults. Thus, frequency-specific IC circuits are altered by partial hearing loss after focal damage to the spiral ganglion (Snyder and Sinex 2002). The several prospective contributions to this process may remain plastic even in adults (Harrison et al. 1998; Snyder et al. 2000) and include plasticity from structural rearrangement, sprouting of afferents in adjacent layers, unmasking of silent synapses, or alterations in synaptic efficacy. These various consequences have just begun to be elucidated. Neonatal lesions restricted to a portion of the gerbil cochlea reorganize the IC tonotopic map (Harrison et al. 1998) and there is evidence that experience dependent changes may be adaptive or restorative (Silverman and Clopton 1977; Knudsen

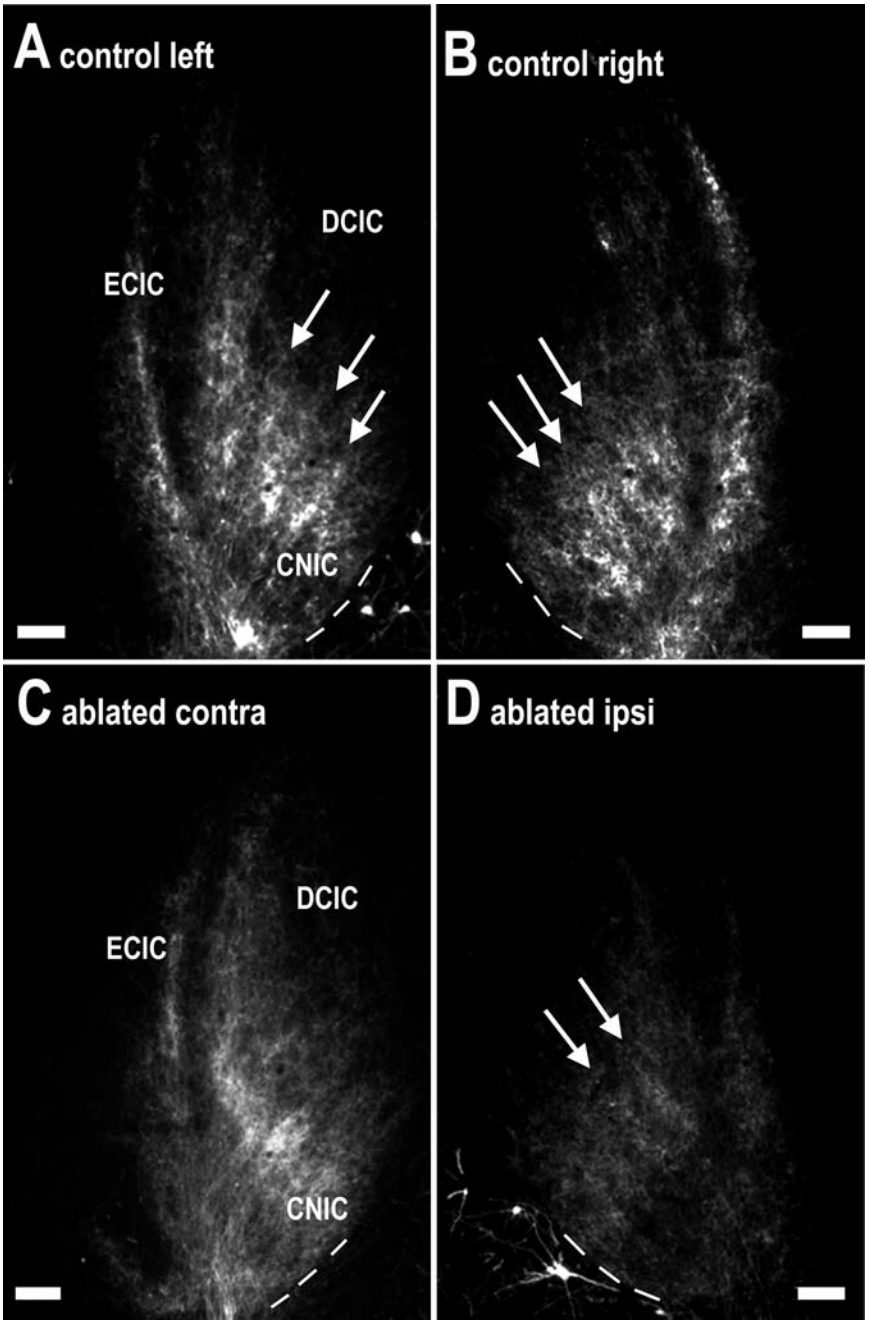

Figure 18.7. DiI-labeled axons in IC of P12 rats following a midline diI pin placement in the decussation of DNLL fibers. Axons from the contralateral DNLL in unoperated, control animals are banded (*arrows,* **A** and **B**). Following cochlear ablation at P2, DNLL axons projecting to the IC contralateral to the ablation distribute densely in an unbanded pattern **(C)**. In contrast, labeled axons projecting to the IC ipsilateral to the ablation are sparser, but a banded distribution *(arrows)* is still evident **(D)**. Dorsal is toward the *top* and medial is to the *right* in **(A)** and **(C)** and to the *left* in **(B)** and **(D)**. The scale bars represent 100 μm.

1999). The mechanisms underlying these changes may include synaptic reorganization as well as adjustments in the efficacy of synaptic function.

Changes in the composition and distribution of IC neurotransmitter receptors that may mediate plasticity of functional properties after either monaural or binaural hearing loss are variable. For instance, whereas GABA or glutamic acid decarboxylase levels in IC decrease following bilateral hearing loss in rats, $GABA_A$ receptor expression (Marianowski et al. 2000) and receptor binding (Milbrandt et al. 2000) are up-regulated. Moreover, in bilaterally deafened rat pups, decreased expression of mature, and increased expression of immature, forms of AMPA subunit mRNA occur, as well as decreased NMDA receptor subunit mRNA (Marianowski et al. 2000). Furthermore, unilateral deafening in adult guinea pig results in modest but transient elevation in the number and activity of AMPA receptors (Suneja et al. 2000).

Unilateral deafening results in a paradoxical increase in excitability of the IC ipsilateral to stimulation of the intact ear (McAlpine 1997). This excitability likely reflects plasticity of lower auditory connections as well as expanded ipsilateral excitatory CN inputs to the IC (Moore and Kitzes 1985; Moore et al. 1989). Moreover, the unmasking of responses in deafened animals, whether immature or adult, may be attributable to down-regulation of inhibitory circuits, particularly intrinsic GABAergic mechanisms (Mossop et al. 2000).

Such activity-dependent changes in receptor distribution and composition affect the dynamics of neurotransmission and could serve to maintain a balance of excitation and inhibition in IC circuits, compensating for peripheral changes in hearing sensitivity. Similarly, prior to hearing onset and during assembly and refinement of IC circuitry, bilateral cochlear ablation increases excitatory postsynaptic currents and decreases inhibitory postsynaptic currents in neonatal gerbil IC (Vale and Sanes 2002). These changes may contribute to altered levels and localization patterns of intracellular calcium that mediate functional and structural adjustments. How such changes in activity or calcium levels contribute to alteration of afferent patterns (Gabriele et al. 2000b) or levels of calcium-binding proteins (Fuentes-Santamaria et al. 2003) in the IC is unknown.

4. Conclusion and Synthesis

We have reviewed several events in the development of pre- and postsynaptic elements of banded circuits in the IC that may contribute ultimately to their formation, refinement, and plasticity (Fig. 18.2). The development of the presynaptic component of these circuits begins with the growth of axons from multiple brain stem auditory sources into the IC. En route to the IC, these growing neurites must make important decisions at decussation points to establish the appropriate laterality and binaural interactions. These decisions may be self-regulated, programmed or the result of either permissive or inhibitory cues in the local microenvironment through which they grow. Once neurites invade the IC, intrinsic cues likely guide the initial establishment of a coarse cochleo-

topic order (Figs. 18.2 and 18.3A). The ascending projections are simple in morphology and distribution, only minimal synaptogenesis has taken place, and the constellation of neurotransmitter receptors is immature. Thus, even before hearing begins, ascending projections segregate into discrete bands of aural dominance (Figs. 18.2 and 18.3B) in an activity-dependent manner, perhaps driven by competition between spontaneously active pathways from each ear. These projections then proliferate within IC in a manner consistent with trophic support mediated by activation of the target neurons. These afferents also must compete within the fibrodendritic framework with similar inputs to establish precise synaptic domains and dendritic alignment (Figs. 18.2 and 18.3C). Thus, local circuits are established by activity-dependent, calcium-mediated mechanisms. Once the basic pattern of afferent bands is established, the many neurotransmitter receptor systems begin their elaboration and auditory-driven activity begins to sculpt individual projection pathways and their synaptic domains via gene expression and cell–cell interactions. Finally, as the head grows or the sensitivity of the two ears changes over time, adaptive changes in circuits and efficacy of synapses maintain or restore relative synaptic throughput within IC synaptic domains.

5. Future Studies

This chapter has emphasized development of ascending afferent projections to the CNIC. However, many basic issues of the development of projections to the other subdivisions of the IC are less well understood. Tracing studies should document the development of descending cortical and intrinsic commissural projections in relation to inputs ascending to the IC. In addition, the question whether the projections to different IC subdivisions develop independently should be investigated.

Further experimental studies are required to understand the role of competition in the development of layered inputs and the segregation of synaptic domains. Moreover, the role of spontaneous and patterned activity in the development of the complex circuitry of afferent projections remains to be explored more fully. Similarly, no information is currently available on the role of growth factors in the early development of IC circuits. Future studies of this issue are critical because activity-based regulation of growth factor expression may be the mechanism through which layered inputs and synaptic domains are established.

Future studies also should address the development and plasticity of synaptic domains within different functional inputs to the IC. Histochemical or immunohistochemical identification of discrete synaptic domains of related input–output elements should aid these studies. Once identified, multiple anatomical methods could assay the spatial relationships of discrete sets of functional inputs. For instance, the banded profiles of calbindin immunostained plexuses that are pronounced in kitten IC provide borders for some type of functional domain

within IC layers. Their boundaries might constitute a template that defines the distribution of receptor expression and maturation, dendritic rearrangement, or spine modification. Such features could be assayed in conditions of altered overall activity, afferent competition, or growth factor expression in order to study their effect on circuit refinement.

Abbreviations

AMPA	α-amino-3-hydroxy-5-methyl-isoxazole-4-propionate
CN	cochlear nuclei
CNIC	central nucleus of the inferior colliculus
DCIC	dorsal cortex of the inferior colliculus
DiI	1-1'-dioctadecyl-3,3,3',3'-tetramethylindocarbocyanine dye
DNLL	dorsal nucleus of the lateral lemniscus
E	embryonic day
ECIC	external cortex of the inferior colliculus
GABA	γ-aminobutyric acid
GluR	glutamate receptor
GLYT	glycine transporter
HRP	horseradish peroxidase
IC	inferior colliculus
LL	lateral lemniscus
LSO	lateral superior olivary nucleus
MNTB	medial nucleus of the trapezoid body
MSO	medial superior olivary nucleus
NMDA	*N*-methyl-D-aspartate
nAchR	nicotinic cholinergic receptors
P	postnatal day
VNLL	ventral nucleus of the lateral lemniscus

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Chapter 19
Inferior Colliculus: Aging and Plasticity

Robert D. Frisina and Ramesh Rajan

1. Introduction

Classic views and theories of the central nervous system (CNS) emphasized that mammalian neural circuitry formed during development remained essentially invariant in adulthood. No new neurons are added, and CNS damage entails neuron loss, resulting in permanent anatomical damage and enduring functional impairments. However, advances in the study of plasticity and aging in the CNS, including the central auditory system, reveal that neural systems can reconfigure themselves with age and in response to the loss of peripheral inputs from sensory end-organs. For instance, peripheral abnormalities induce unmasking, rewiring, or changes in functional responses in the central auditory system, sometimes termed "peripherally induced central changes" (Frisina et al. 2001). Alternatively, in the case of age-related changes in the central auditory system, deficits can occur independently of age-dependent alterations of the inner ear. Instances of these plastic and aging phenomena are presented in this chapter, focusing on those manifested in the inferior colliculus (IC).

2. Age-Related Functional Changes

2.1. Tonotopic Organization

Neuroanatomical and neurophysiological investigations revealed age-related tonotopic plasticity in the auditory midbrain in response to the loss of high-frequency input of cochlear origin (Willott 1984, 1986). The C57Bl/6 mouse strain suffers from accelerated peripheral age-related hearing loss, starting in the base of the cochlea. Like human age-related hearing loss (presbycusis), the C57 syndrome begins with an impairment of the high frequencies, which then spreads to the lower frequencies with age. The C57 high-frequency hearing loss is much more rapid than that of human presbycusis, even when correcting for the different absolute lifespans of mice and men. Specifically, young adult C57s about 6 months old have severe-to-profound high-frequency hearing losses and de-

velop profound deficits at all frequencies in their second year. Because a 6-month-old C57 mouse has an "old" ear but a young brain, it permits the dissection of aspects of presbycusis inherent in the inner ear and largely independent of the aging brain.

The IC tonotopic reorganization was documented by neurophysiological mapping in the central nucleus (ICC) across time in C57 mice (Willott 1984, 1986). In young adults, as in most mammals, there is a dorsoventral gradient of single-unit characteristic frequencies (CFs) orthogonal to the well defined neuroanatomical ICC laminae, with lower CFs dorsally and higher CFs ventrally. With age, high-CF units shift to lower frequencies, although the tuning curve tip sensitivity remains surprisingly good, indicative of a true CF shift and not merely a loss of the sensitive tips of high CF units (Fig. 19.1). Apparently, a development, strengthening, or enhancement process involving new synaptic connections occurs in the formerly high-frequency IC regions and/or its brain stem input nuclei, such that the low CFs become overrepresented in the tonotopic map.

In contrast to the C57, the CBA mouse strain has a slow, progressive age-related hearing loss that is similar (flat) across the auditory frequency range. This strain has been useful for studying age-related changes in the central auditory system when only moderate changes take place in the auditory periphery. Not surprisingly, in contrast to the C57 ICC reorganization, a tonotopic reorganization of the IC in aged CBA mice does not occur (Willott 1991a; Walton et al. 1998).

2.2. *Temporal Processing*

Sound temporal features are essential for effective processing and perception of biologically relevant acoustic stimuli such as speech, animal vocalizations, and music (see Chapters 12 and 14). In presbycusis, aged listeners often have auditory temporal processing deficits that contribute to their impairment in speech comprehension in the presence of background noise (Snell and Frisina 2000; Frisina et al. 2001). Temporal processing deficits may be due to a sloping hearing loss of peripheral origin. When aged persons have good peripheral sensitivity, speech perception problems may involve temporal processing deficits caused by brain stem auditory pathology, including the IC (Frisina and Frisina 1997; Frisina et al. 2001).

Gap stimuli and amplitude-modulated stimuli are two of the most commonly utilized sounds for investigating auditory temporal processing deficits in cases of hearing loss, including presbycusis (Frisina 2001a). Gap detection paradigms involve measuring the minimum detectable silent interval between two sounds. These sounds are sometimes referred to as "markers," or the "masker" and the "target," and may be pure tones or wideband noise bursts. Gap detection experiments assess the smallest gap that a human listener, behaving animal, or single neuron can perceive, encode, or process. Temporal envelope features are represented by amplitude-modulated (AM) sounds. The most common AM stimulus

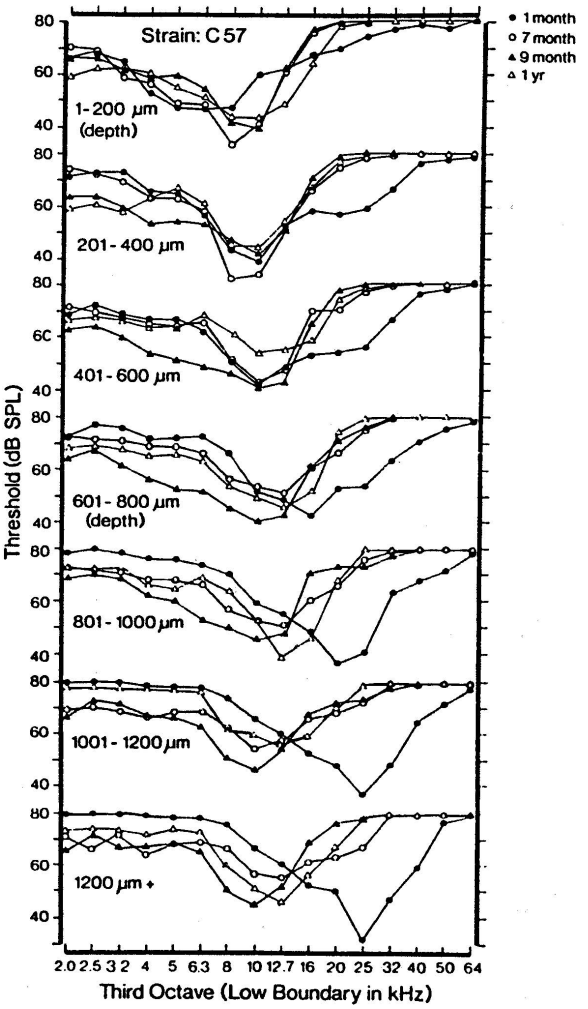


Figure 19.1. The tonotopic (cochleotopic) map of CFs in the C57 mouse IC reorganizes after an age-related decline in inputs from the high-frequency region (basal turn) of the cochlea. Group average frequency-threshold tuning curves (MTCs) for units, as a function of age and dorsoventral ICC depth, show a statistically significant CF shift from high (25 kHz) to middle (10 to 12 kHz) frequencies at the three lowest depths for the 7- to 12-month old subjects relative to the young adults. The number of single-unit tuning curves comprising each of the group average MTCs is: 1 month, $n = 90$; 7 months, $n = 74$; 9 months, $n = 50$; 12 months, $n = 56$. (From Willott 1986.)

envokes a periodic, usually sinusoidal, fluctuation in a tone's or wideband noise's envelope. Here, the threshold for the minimal depth of modulation can be measured or, more commonly in physiological experiments, the strength of the response of a single-unit or multiunit cluster is determined, either in terms of number of action potentials (rate) or timing of the action potentials (synchrony) in response to the AM (see Chapter 12). Both gap and AM coding can change with age in the IC.

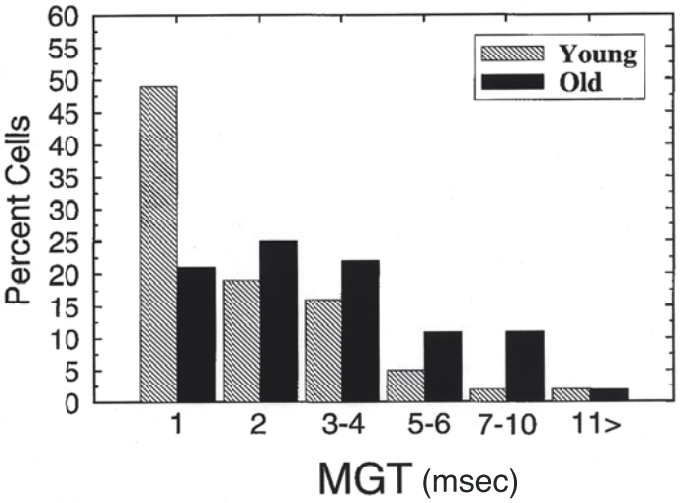
2.2.1. Sound Gaps

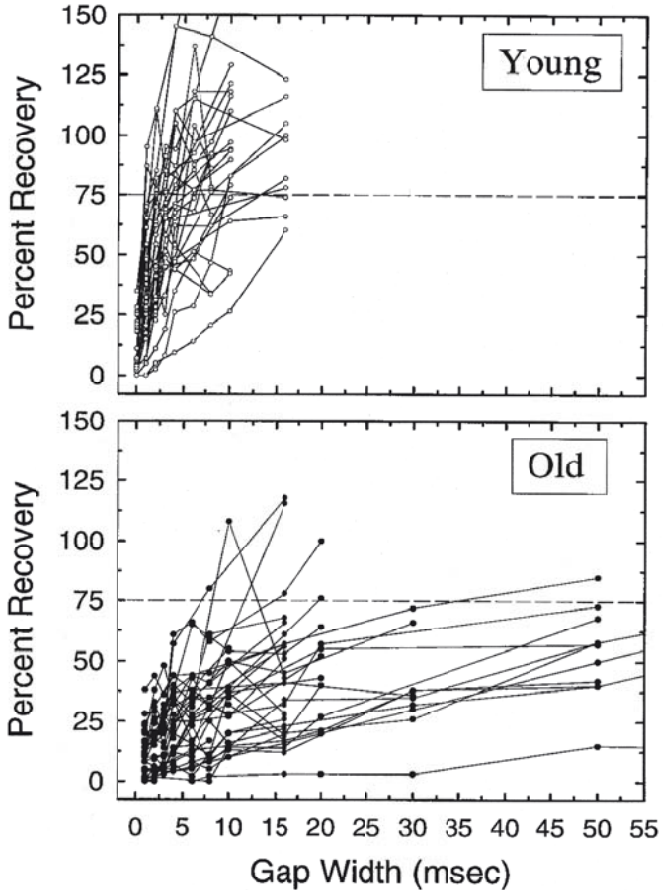
Single-unit gap encoding in the ICC of unanesthetized CBA mice is consistent with behavioral gap detection, both of which degrade with age, starting in middle age (Walton et al. 1997, 1998). Specifically, units with short gap detection thresholds decline, and the strength of their gap responses decreases in the ICC of aged CBA mice (Fig. 19.2). It is unknown what portion of this age effect occurs within the ICC and in brain stem nuclei that project to the ICC. It is likely that much of this age-related temporal processing decline occurs at ICC, as the coding of gaps there is of a different nature than that at subcollicular sites. For instance, at the auditory nerve and cochlear nucleus, gaps are encoded by a decrease in single-unit firing rate during the gap. In contrast, ICC neurons respond to gaps with an increase in neural firing at the end of the gap, and it is this response that declines with age in CBA mice with relatively good peripheral hearing sensitivity.

2.2.2. Amplitude Modulation

The neural encoding of ongoing auditory temporal features is investigated in AM experiments. Using monaural stimuli in anesthetized rats, there were no dramatic changes in ICC sinusoidal AM coding with age, no significant declines in the upper cutoff frequencies of the modulation transfer functions, or any marked changes in other temporal and rate measures of AM coding. However,

Figure 19.2. The proportion of single units in the unanesthetized CBA mouse IC with short gap thresholds decreases in old animals. The percentage of units in young adult and old CBA mice with minimum gap thresholds (MGTs) from 1 to >11 ms for young adult (*hatched, n* = 78) and aged mice (*solid, n* = 108). The distribution shows longer gap thresholds for aged animals. IC cells in young adult units encode gaps with higher firing rates. Neural recovery functions for 30 phasic units in young adult *(top)* and aged *(bottom)* animals. Recovery *(vertical axis)* was measured by computing the number of spikes elicited by the noise burst following the gap, divided by those to the noise burst preceding it, ×100. This calculation included all gap durations for each unit. A 100% recovery *(horizontal dashed line)* designates equal discharges to both bursts. Gap response recovery to the post-gap noise burst is 75% by <10 to 15 ms for almost all young adult units, whereas most aged units do not reach this criterion at even the longest gaps. (From Walton et al. 1998.)


Young
Old
Percent Cells
60
55
50
45
40
35
30
25
20
15
10
5
0
1
2
3-4
5-6
7-10
11>
MGT (msec)


Young
Old
Percent Recovery
150
125
100
75
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0
0
5
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15
20
25
30
35
40
45
50
55
Gap Width (msec)

there was a significant shift in the shape distribution of modulation transfer functions, with a decline in band-pass, and an increase in the low-pass shape, with age, in both the ICC and the external nucleus of the IC. This was interpreted as consistent with the hypothesis that IC inhibition contributes to the formation of band-pass AM transfer functions in young adult animals, and if this inhibition declines with age (see later), then band-pass specificity of AM coding will also degrade (Shaddock-Palombi et al. 2001).

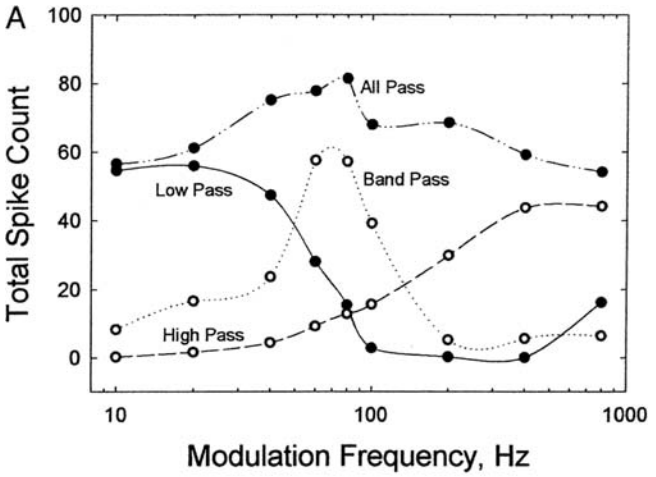
Subsequent sinusoidal AM studies in the unanesthetized mouse ICC used free-field stimuli and also demonstrated the age-related shift from band-pass to low-pass modulation transfer function shapes, originally found in the aged rat (Walton et al. 2002). The various shapes of modulation transfer functions characteristic of the mammalian IC (Fig. 19.3A) shift from a preponderance of band-pass transfer functions in young CBA mice to more low-pass in old mice (Fig. 19.3B). Other aspects of AM processing change with age, such as declining upper cutoff and best modulation frequencies (Fig. 19.3C) of rate modulation transfer functions, and the increased spike rate for pure tone stimulation was amplified in old animals in response to AM stimuli, further supporting a loss of IC inhibition with age.

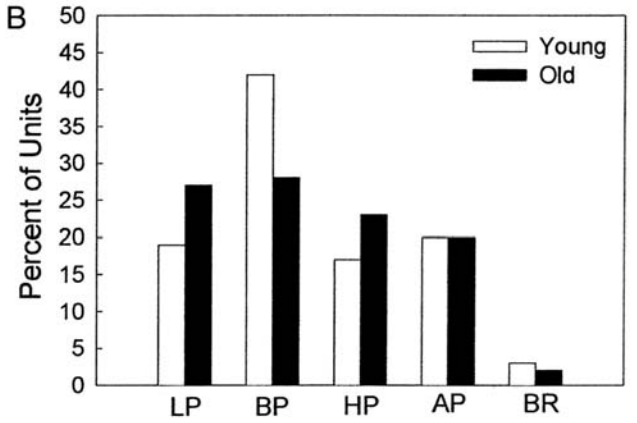
2.3. *Spatial Processing*

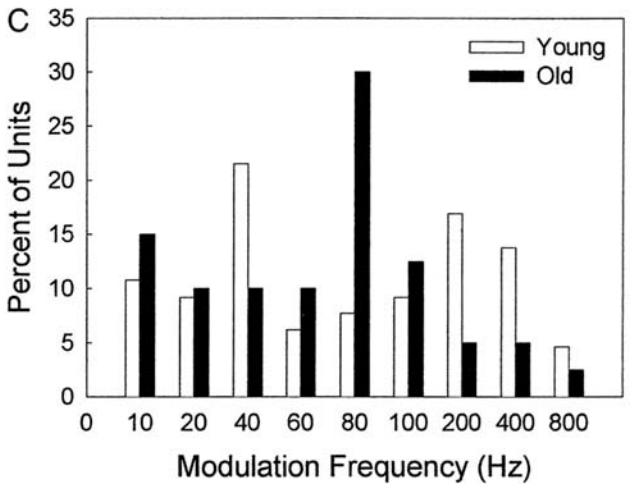
The auditory system uses different neural mechanisms for separating signals of interest, such as speech, from interfering acoustic clutter, such as ambient noise. Spatial localization of a speaker of interest in the context of noise from other speakers is a critical auditory adaptation for enhancing the signal-to-noise ratio in complex acoustic environments. It has been postulated, from clinical research, that this ability degrades with age (Willott 1991b). Consistent with the initial behavioral experiments with human subjects and patients, animal experiments found that sound localization abilities decline with age in C57 mice, and in a manner independent of their high-frequency hearing loss that occurs between young adulthood and middle age (Heffner et al. 2001).

What is the neural basis for age-related declines in the ability of the brain stem auditory system to separate signals from noise spatially? Single IC units in middle-aged C57 mice did not benefit from moving background noise sources away from signal locations, as do cells in young adult C57 mice. At a given

Figure 19.3. Age-related effects on rate encoding of envelope periodicities for IC single units. **(A)** Four different single-unit amplitude modulation transfer functions (MTF) types showing the scheme for MTF filter shape classification. Five categories occur: low-pass with a maximum synchronization index (SIm) of 0.889; band-pass, SIm 0.939; high-pass, SIm 0.946; all-pass, SIm 0.703; band-reject, example not shown. **(B)** Young adult *(open bars)* and aged *(filled bars)* units with each rate MTF filter shape. **(C)** Young adult *(open bars)* and old *(closed bars)* mice units with rate BMFs at each of the nine AM frequencies tested. (From Walton et al. 2002 with permission.)


A
Total Spike Count
All Pass
Band Pass
Low Pass
High Pass
Modulation Frequency, Hz


B
Percent of Units
Young
Old
LP
BP
HP
AP
BR


C
Percent of Units
Young
Old
Modulation Frequency (Hz)

azimuthal location, the amount of masking from the background noise was greater in the older mice, a change that peripherally induced threshold shifts with age could not account for and that implicates age-related declines in the mammalian brain stem auditory spatial localization analysis system (McFadden and Willott 1994a,b).

3. Neuroanatomical and Chemical Changes with Age

3.1. Changes in Input Pathways

Do IC brain stem connections also change in aged mice and, if so, is altered connectivity implicated in this syndrome? A neuroanatomical retrograde tracer, horseradish peroxidase, was injected into the centers of the IC regions from which recordings were obtained in temporal processing experiments (Frisina et al. 1998; Frisina and Walton 2001a,b). Inputs from all three divisions of the contralateral cochlear nucleus, the ipsilateral anterolateral periolivary nucleus, and portions of the ventral nucleus of the lateral lemniscus, each decline with age. These inputs likely contribute to the normal IC temporal processing abilities in young adult animals. As inputs age and decline, the balance of excitatory and inhibitory inputs to IC principal cells may become disrupted and precise temporal processing is diminished, leading to degradations in gap coding. These declines in brain stem inputs to the IC begin in middle-aged mice who have relatively normal auditory sensitivity as measured with auditory brain stem responses (ABRs), a finding consistent with the human mid-life psychophysical declines in temporal processing, even in subjects with otherwise normal audiograms (Snell and Frisina 2000).

3.2. Changes in Inhibitory System

GABA (γ-aminobutyric acid) is one of the main auditory brain stem neurotransmitters, and it is prominent in ICC neurons and synaptic endings where it has been implicated in many aspects of sound processing, including temporal and spatial coding. A study of IC GABAergic systems found that many aspects decline with age (Caspary et al. 1995). Quantitative analyses of GABA immunolabeling in IC perikarya in young and aged Fischer 344 rats found a 36% reduction with age (Caspary et al. 1990) and a reduced basal and K^+-evoked GABA release, in contrast to the normal values in control excitatory neurotransmitter levels and in acetylcholine release. Using quantitative receptor autoradiography, it was shown that declining $GABA_B$ receptor binding occurs in all three divisions of the aged rat IC (Milbrandt et al. 1994) while cerebellar tissue was unchanged. In contrast, $GABA_A$ receptors increased with age, perhaps in compensation for the $GABA_B$ decline (Milbrandt et al. 1996). Immunogold electron microscopy demonstrates that rat IC excitatory and inhibitory synapses

decrease in density with age (Helfert et al. 1999), just as does synaptic density in the IC of C57 mice (Kazee et al. 1995), although not in aged CBA mice (Kazee and West 1999). In conclusion, in rats, most aspects of GABA neurotransmitter biochemistry degrade with age, perhaps causing an imbalance of excitation and inhibition in the IC and concomitant functional impairments such as deficits in auditory signal extraction in background noise.

3.3. Activity-Dependent Changes in Calcium-Binding Proteins

Several competing theories and models address age-related neural degeneration and cell death in the mammalian CNS. These include processes such as calcium excitotoxicity; apoptosis; and damage caused by the harmful by-products of oxidative phosphorylation such as free radicals, stress/inflammatory responses in the brain, and others. Calcium excitotoxicity can result from concentration imbalances in intracellular calcium-binding proteins such as calbindin, calretinin, or parvalbumin. Age-related changes in calcium-binding proteins have been found in the IC (Zettel et al. 1997; Frisina 2001b,c). Antibodies for calbindin and calretinin reveal an age-related decline in IC calbindin immunostaining of CBA and C57 strains. For calretinin, up regulation occurs in the aged CBA IC, but not in aged C57 mice. Perhaps the age-related up regulation of calretinin in CBA mice reflects sound-evoked IC activity, as this up regulation was absent in aged, deaf C57s. This hypothesis was confirmed in CBA mice deafened as young adults and compared to the aged controls (Zettel et al. 2001). Calretinin up regulation in aged, hearing CBAs was absent in the mice deafened as juveniles (Fig. 19.4).

4. Plasticity in the Adult Mammalian Inferior Colliculus Caused by Altered Cochlear Outputs

Plasticity in the IC has been studied at many time points in the lives of experimental animals. This section examines studies in the adult, but not aged, mammalian IC.

The mature IC possesses the neural machinery that, at other brain sites, plays important roles in neural plasticity, including the *N*-methyl-D-aspartate (NMDA) glutamate receptors, the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) glutamate receptor, and $GABA_A$ receptors (Caspary et al. 2002; Kelly and Zhang 2002; Ma et al. 2002; Pollak et al. 2002). Many neuromodulators such as acetylcholine, serotonin, and noradrenaline (Habbicht and Vater 1996; Hurley et al. 2002) are present and can influence neuronal response plasticity in specific brain areas. IC cells express long-term potentiation (LTP), a synaptic phenomenon that is an important form of neural plasticity (Buonomano and Merzenich 1998). Various chemical levels in IC show immediate

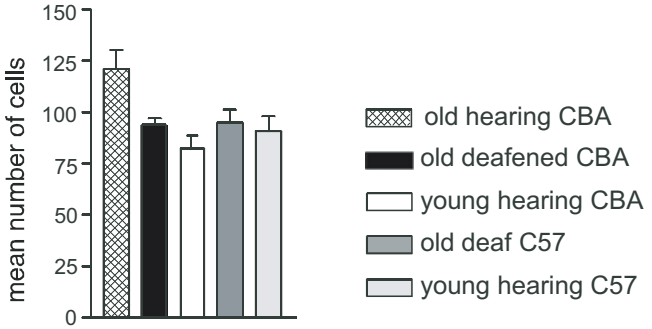


Figure 19.4. Mean cell density of calretinin-stained (CR+) cells per 100 μm² in the dorsomedial IC of aged, deafened CBA mice, aged hearing CBA, young adult hearing CBA, and young adult hearing C57 mice. Aged deafened CBA mice do not show the statistically significant increase in CR+ cells discovered in the aged hearing CBA mice. There was no significant difference between the cross-sectional areas of the dorsomedial IC in any of the ages or strains tested (not shown). Error bars denote standard errors of the mean. (From Zettel et al. 2001.)

changes as well as long-term changes after major alterations in afferent input. It is therefore surprising that, except in aging, there are very few demonstrations of physiological response plasticity in the adult mammalian IC.

An important distinction is made between plasticity and "unmasking" of latent inputs. As noted in the somatosensory CNS after damage or other manipulations to the receptor surface, CNS plasticity cannot simply mean the expression of latent, functionally dormant inputs once these have been released from inhibition (i.e., "unmasked") after removal of a dominant input (Calford and Tweedale 1988, 1991). Instead, plasticity must involve the conversion of implicit but unexpressed inputs into explicit responses expressed as part of the cell's normal suprathreshold repertoire, whereas unmasking entails the expression of explicit inputs that are otherwise blocked by other dominant (often inhibitory) inputs. Plasticity must involve changes in synaptic weights (Calford and Tweedale 1988, 1991; Buonomano and Merzenich 1998) that would not occur in unmasking. This distinction between plasticity and unmasking has been made in auditory cortex (Rajan 2001) and in the IC (Snyder et al. 2000) and will guide this exposition. It does not mean that the IC only has a stereotyped repertoire of hard-wired responses unaltered by major alterations of afferent or efferent input, or that unmasking does not produce functionally important response changes. However, it does provide a conceptual context for thinking about these changes and their causes. Finally, studies of IC plasticity in adults are confined to ICC unless otherwise stated.

4.1. Inhibitory Neurochemistry in the Inferior Colliculus after Cochlear Damage

IC neurochemistry has been examined often after cochlear ablation or total inactivation, and for focal cochlear damage with acoustic trauma. Although the former type of manipulation is not representative of most clinical conditions, it allows assessment of IC neurochemical reorganization after large changes in afferent input.

Many studies examined the effects on $GABA_A$ receptors, as hyperactivity or increased spread of activity often follows cochlear damage (Ryan et al. 1992; Bledsoe et al. 1995; Nagase et al. 2000; Salvi et al. 2000). IC cells express LTP only after blocking of some, if not most, inhibitory inputs such as $GABA_A$ receptors (Hosomi et al. 1995). LTP required NMDA and $GABA_B$ receptor activation—the latter likely acting presynaptically on GABAergic neurons to reduce postsynaptic inhibitory potentials mediated through $GABA_A$ receptors—and blocking of glycinergic receptors (Zhang and Wu 2002). LTP also occurs in brain slices in which GABAergic and glycinergic inhibition was routinely suppressed pharmacologically (Wu et al. 2002). These studies provide the rationale for examining changes in inhibition-related parameters in IC after cochlear damage.

There are considerable changes in GABAergic indices in IC after alterations of cochlear outflow. An immediate (Milbrandt et al. 2000; immediately after, and 42 hours after focal acoustic trauma) or rapid (Mossop et al. 2000; 24 hours and 7 days post-cochleotomy, but not 4 hours post) decrease in levels of glutamic acid decarboxylase (GAD), the rate-limiting enzyme in GABA synthesis, occurs in both membrane and cytosolic fractions (Milbrandt et al. 2000). Return to normal GAD levels follows 30-day (Milbrandt et al. 2000) or 1-year survivals (Mossop et al. 2000). However, GAD levels (primarily GAD67, the GAD isoform of molecular mass 67,000 kDa) in the entire IC increased immediately after focal acoustic trauma (Abbott et al. 1999), returned to near normal levels 2 days post-trauma, then dropped significantly below control levels at 30 days with a permanent hearing loss of 20 to 25 dB in auditory brain stem response thresholds. A similar trend occurs for GAD-immunoreactive cells in all IC divisions, although these changes were rarely significant and 30 days post-trauma the number was similar to that of normal animals. When salicylate was chronically administered in drinking water for 4 weeks or 4 months to produce a very small elevation in rat auditory brain stem evoked response (ABR) thresholds (Bauer et al. 2000), there was a marginal increase in GAD65 levels at 4 weeks treatment and a significant increase at 4 months.

Variability occurs in other indices of GABAergic function. A significant decrease in evoked GABA release occurs 21 days after ototoxic drug-induced bilateral deafness (Bledsoe et al. 1995). Evoked GABA release exceeded control levels in the contralateral IC 2 to 5 days after unilateral cochleotomy or ossicular removal, fell to normal at 59 days, and increased again at 145 days, with no

changes ipsilaterally. There were small decreases in GABA uptake in both ICs after cochleotomy only after the 145-day survival, in contrast with an immediate increase followed by a return to normal (ipsilateral) or subnormal (contralateral) levels after ossicle removal (Suneja et al. 1998). $GABA_A$ receptor function shows similar variability: increased binding when tested with muscimol (Milbrandt et al. 2000) and a small decrease in binding sites but increased receptor affinity to muscimol and not other $GABA_A$ ligands (Bauer et al. 2000). Thus, these studies do not show that a decrease in cochlear outflow consistently reduces IC GABAergic levels or expression.

Glycine is present in low amounts in the IC compared to GABA and has received correspondingly less attention. Little change in glycine release was seen 21 days after ototoxic drug-induced bilateral deafness in rats (Bledsoe et al. 1995). In guinea pigs a small and transient increase in glycine receptor binding occurred only in dorsal cortex (ICD) and the lateral nucleus (LIC) 2 days after unilateral cochleotomy and became normal 31 days later, decreased slightly in all three IC divisions at 60 days, and returned to normal at 147 days. The pattern was similar bilaterally (Suneja et al. 2000a).

4.2. Excitatory Transmitters and Calcium-Related Inferior Colliculus Proteins After Cochlear Damage

Changes in glutamate after unilateral cochleotomy in adult guinea pigs were assessed by measuring the number and/or activity of intracellular AMPA-type glutamate receptors. There was a small, significant decrease in AMPA receptor binding in contralateral IC 2 days post-lesion, a gradual increase to above average 60 days later, and a return to normal at 147 days. The ipsilateral pattern showed a significant decrease starting at 31 days, then followed the contralateral pattern. These changes were predominantly in the ICC and the ICD but not in LIC (Suneja et al. 2000b).

Given the established role of high calcium levels in excitotoxic neuronal cell death, a few studies have examined changes in calcium-related proteins; different effects have been reported for different proteins. Parvalbumin was unchanged from immediately after focal acoustic trauma to 30 days later (Abbott et al. 1999). After unilateral cochleotomy in adult rats, increased immunostaining was found for calbindin, which regulates intracellular calcium and may act as a cytoplasmic calcium buffer and thereby exert a neuroprotective effect. Changes were found only in the IC contralateral to the ablated cochlea, with immunoreactivity increasing from about 23 days post-lesion to a plateau only by 18 weeks (Förster and Illing 2000). Both cochleotomy and focal acoustic trauma also upregulate GAP 43, a growth and plasticity-associated phosphoprotein that binds to calmodulin and acts a substrate of protein kinase C, in IC neurons (Illing et al. 1997; Michler and Illing 2002). GAP 43 influences early synaptogenetic processes and decreases to near-zero levels with maturation; thus, GAP 43 expression after cochlear damage represents its trauma-induced reemergence

and occurs only from day 10 post-lesion and increases to day 30; the ipsilateral increase is greatest until day 30 when contralateral expression predominates. Immediately after acoustic trauma there is a reactive transient decrease in the phosphorylated form of the cyclic adenosine monophosphate (cAMP) response element binding protein (phospho-CREB) in ipsilateral IC and a contralateral increase that persists for up to 239 days and exceeded any subsequent ipsilateral changes. These changes in calcium-related proteins and in CREB are indicative of reactive changes but not plasticity, unless the latter is loosely defined as any change in the parameter under measurement (Michler and Illing 2003).

4.3. Changes in Inferior Colliculus Physiology After Cochlear Damage

Focal cochlear damage, quantified by changes in the compound action potential (CAP) audiogram, was created with acoustic trauma (Popelář and Syka 1982; Syka and Popelář 1982) or by spiral ganglion cell lesions (Snyder et al. 2000; Snyder and Sinex 2002), or lesions to the base of the cochlear partition (Irvine et al. 2003). Several indices, from potentials evoked at the IC surface to the responses of single neurons, before and after lesions, were assessed (Salvi et al. 1992; Wang et al. 1996). Responses were recorded from multineuron clusters across the dorsolateral-to-ventromedial tonotopic IC axis before and after cochlear lesions at similar depths (Snyder et al. 2000). Chronic implanted IC electrodes were used to assess neural responses from multineuron clusters pre- and post-lesion (Snyder and Sinex 2002). Multineuron responses several moths after cochlear lesions were compared to normal animals (Irvine et al. 2003). The results from these studies are presented below according to the type of IC response measured.

4.4. Changes in Evoked Potentials

In the IC contralateral to a damaged cochlea, changes in evoked potential (EP) amplitudes and thresholds to stimulation of the undamaged ipsilateral cochlea and to stimulation of undamaged parts of the contralateral test cochlea were obtained, although not in the same study. After unilateral cochlear deactivation with an ototoxic drug, the IC ipsilateral to the intact ear was now as sensitive and responsive to stimulation as the contralateral IC, whereas normally the contralateral IC is more sensitive. The decreased laterality differences were specifically due to changes in the IC responsiveness ipsilateral to the intact cochlea and occurred with a lag: the difference persisted at 1 to 2 days post-lesion and decreased at 7 days (Popelář et al. 1994).

A second effect was elicited by acoustic trauma (Salvi et al. 1992). Thirty days post-trauma a focal permanent hearing loss was seen with a peak of a 20- to 30-dB loss in CAP thresholds, and EP amplitude enhancement to frequencies below the peak of the cochlear hearing loss occurred, even at nearby frequen-

cies with deficits resembling the peak loss. Enhanced EP amplitude occurred at threshold and at mid-to-high stimulation intensities (>50 dB SPL). At frequencies above and below that of peak cochlear hearing loss, there was a decrease in EP amplitude in the IC at 8 hours post-lesion but not after 1 hour. Deficits could occur at frequencies at which CAP amplitudes (and EP amplitudes from cochlear nucleus) were below normal, or when CAP amplitudes had recovered but the amplitude of the cochlear nucleus EP was still depressed. These results were interpreted as due to relatively rapid, but not instantaneous, changes local to the IC or at least proximal to the cochlear nucleus (Salvi et al. 1992).

In contrast to these EP enhancement effects, other studies (Popelář et al. 1987) found none in awake guinea pigs after white noise trauma, even when the trauma caused a permanent hearing loss. Instead, EP amplitude was depressed and gradually recovered. That study (Popelář et al. 1987) also found EP enhancements in the auditory cortex, but not in the IC, when acoustic trauma was administered when the animals were awake but not when anesthetized. The absence of EP enhancement in the IC cannot simply reflect the use of a click stimulus, as the enhancement was found in the auditory cortex in the same animals. No EP enhancement occurred in the IC after acute noise trauma although the decrease of EP amplitude with increasing tone burst duration was slower in the lesioned animals, an effect mimicked by application of a $GABA_A$ blocker in controls (Szczepaniak and Møller 1995).

4.5. Changes in the Response Properties of Single Neurons

The reduced ipsilateral–contralateral differences after deactivation of one cochlea (Popelář et al., 1994) indicate recruitment of more IC neurons ipsilateral to the intact ear to the ipsilateral stimulus, possibly through a decreased inhibition on binaural input. In keeping with this hypothesis, increased IC neurons responsive to ipsilateral stimulation occur in adult cats with partial high-frequency contralateral cochlear damage (Snyder and Sinex 2002; Irvine et al. 2003) and in adult ferrets after unilateral cochleotomy (Moore et al. 1993). The change was larger after cochlear lesions causing broad high-frequency losses extending over the entire frequency range with 26% to 100% increase in ipsilateral responsive sites in IC (Irvine et al. 2003) than the changes ensuing after more focal damage and <50% increase (Snyder and Sinex 2002).

Any increase in EP amplitudes at frequencies below the peak of cochlear damage in a focally damaged cochlea (Salvi et al. 1992) could indicate a recruitment of more neurons, and a plausible mechanism for such recruitment is decreased monaurally acting inhibition evoked by stimulating a partially damaged cochlea. Discounting for the moment the varied effects of cochlear damage on GABA function in the IC noted earlier, a decrease in such function should affect the frequency-bandwidth of the response areas (tuning curves) because inhibition can shape this property of central auditory neurons (Vater et al. 1992;

Yang et al. 1992; Suga 1995; Palombi and Caspary 1996; Rajan 1998). Consistent with the idea that cochlear damage reduced inhibition in IC cells and could thereby unmask responses in them, 21 days after ototoxicity-induced cochlear deafness, there was decreased IC GABA release and fewer IC cells were inhibited by electrical stimulation of the contralateral cochlea (Bledsoe et al. 1995). Another study, using the same technique and duration of cochlear deafening (Nagase et al. 2000), found more Fos-immunoreactive cells activated by an intense electrical stimulus to the basal cochlea (and fewer activated by a near-threshold stimulus). These results predict that, after cochlear damage, there should be changes in the profile of the response area and/or other response properties of IC neurons that do not simply mimic the peripheral desensitization changes seen in auditory nerve responses. Analyses of response properties (Wang et al. 1996; Snyder et al. 2000; Snyder and Sinex 2002) found changes in response area profiles consistent with a decrease in inhibition after cochlear damage. Acoustic trauma at frequencies above the characteristic frequency (CF) of individual neurons created cochlear hearing losses above the high-frequency edge of the IC neuron's response area (Wang et al. 1996). In essence, rapidly after acoustic trauma there was addition of excitation to the low-frequency side of the response area in about 40% of cells, and this was more likely to occur in mustached bat IC cells whose response areas are shaped by GABAergic inhibition than in neurons whose response areas were less influenced or uninfluenced by GABA. Most often the change was manifest as decreased thresholds in the low-frequency tails of the neuron's response area and occasionally as a broadening of bandwidth along the low-frequency slope between the CF tip and the low-frequency tail of the response area, with no change in the neuron's CF (Yang et al. 1992; Fig. 19.5).

The posttrauma effects (Wang et al. 1996) resemble those seen on tuning curves after applying $GABA_A$ blockers to mustached bat IC neurons (Yang et al. 1992). Following the earlier model (Yang et al. 1992), tuning curve changes were interpreted as an unmasking of low-frequency excitatory inputs normally suppressed by inhibitory inputs tuned to a higher CF than that of the IC neuron under study (Wang et al. 1996). They postulated that the cochlear hearing loss at frequencies higher than the response area of an IC neuron under study, desensitized inhibitory neurons with CFs above that of the IC neuron, thereby unmasking lower threshold responses on the low-frequency side (mainly in the tail) of the IC cell's response area (Fig. 19.5).

Unmasking responses and changes in the response area profile also occurred after focal cochlear damage in IC neurons that previously had (Snyder and Sinex 2002), or would have had (Snyder et al. 2000), a CF at or near frequencies sustaining cochlear hearing losses. A withdrawal of lesion-induced afferent drive at the appropriate frequencies in the response area and addition of excitation at other frequencies, could shift the tuning curve CF. The rapidity of unmasking shows that the IC physiology can change soon after alteration in afferent outflow and argues that the effect cannot be a form of adaptive plasticity (Snyder et al. 2000).

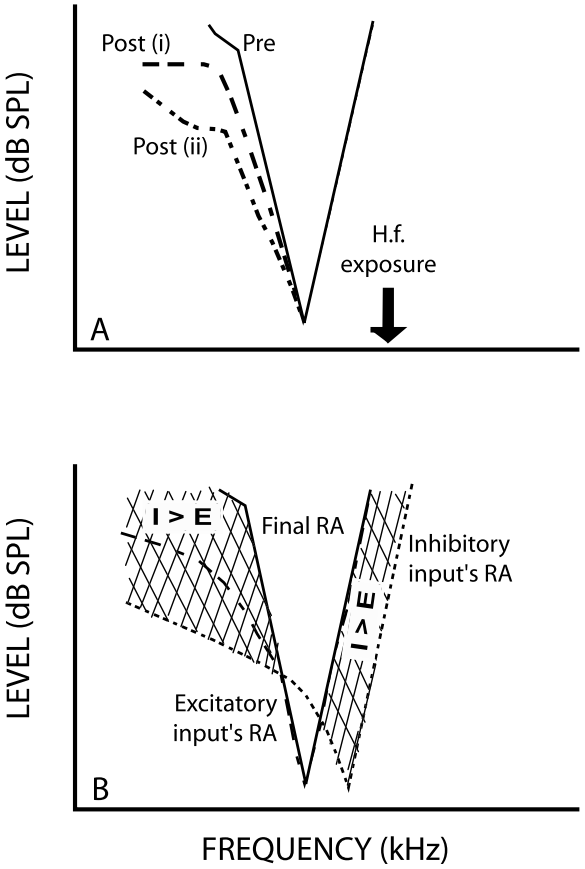


Figure 19.5. Rapid unmasking in the CNIC. **(A)** Prototypical changes in the tuning curves of level-tolerant CNIC neurons after a brief high-frequency loud tone (H.f. exposure) at a frequency above the high-frequency boundary of the IC neuron's tuning curve. (From Wang et al. 1996.) *Pre* is the response area boundary before the loud sound. The two *Post* curves show schematically two common changes seen immediately after the loud tone. In *Post (i)* the major change was the "addition" of a low-frequency "tail" at high intensities, whereas in *Post (ii)* the low-frequency "tail" occurred at lower intensities. *Post (ii)* shows another feature sometimes seen: a broadened response area width toward low frequencies at intensities nearer threshold. There is no change at the characteristic frequency (CF). **(B)** Schematic representation of the model (Wang et al. 1996). The final response area (*Final RA*) of the level-tolerant IC neuron is modeled as consisting of excitatory and inhibitory inputs; for clarity, only one of each input is shown. Both inputs have the same general profile but the inhibitory input is tuned to a higher frequency. In the hatched regions, the inhibitory input has a lower threshold than the excitatory input, and is therefore modeled to be a stronger input ($I>E$) at suprathreshold levels, thus suppressing excitatory input at these frequencies. In the area *Final RA,* excitation is stronger than excitation as is observed with extracellular recording. If a high-frequency loud tone exposure elevated the inhibitory input thresholds, and if this effect was greater on the low-frequency side, low-frequency excitation would be unmasked to produce the *Post* curves in **(A)**.

The physiological unmasking is consistent with a reduction in inhibition; however, studies of IC neurochemistry demonstrate that cochlear damage can decrease or increase indices of GABAergic inhibition (see Section 4.1). The difference does not appear to be methodological: focal acoustic trauma in a single neuron study (Wang et al. 1996) caused immediate physiological unmasking, probably from reduced inhibition, while similar trauma increased GAD levels across the entire IC (Abbott et al. 1999). Perhaps small decreases in inhibitory gain suffice to unmask physiological responses, but these may not be detectable neurochemically, and certainly physiological unmasking was not seen in all cases (Wang et al. 1996; Snyder and Sinex 2002), nor was the pattern of unmasking related to the locus of cochlear damage (Snyder and Sinex 2002).

Other studies (Popelář et al. 1978; Popelář and Syka 1982) found no unmasking of new components in IC neural tuning curves after acoustic trauma, but only threshold elevation which, like the data in studies of unmasking, were obtained in the same neurons before and after acoustic trauma.

Changes in the maximum firing rate of single IC neurons have also been reported after cochlear damage. Acoustic trauma, targeted to produce hearing losses at frequencies in the response area of IC neurons, found a few neurons with an increased maximum firing rate at the CF (Lonsbury-Martin and Martin 1981). Even with acoustic trauma targeted at frequencies above the tuning curve of IC neurons, 70% increased their maximum response rate at CF, possibly through decreased suprathreshold inhibition. Because the same study reported response area changes in about 40% of neurons after acoustic trauma, in at least 30% of neurons, GABA-mediated IC inhibition does not play a significant role in shaping the threshold response area (Wang et al. 1996), although it may have effects at high intensities (Yang et al. 1992; Rajan 2001).

4.6. Relationship of Single-Unit Changes to Evoked Potential Shifts

Does the unmasking of new components in single neuron response areas account for the EP amplitude enhancement after cochlear trauma? Prior work did not provide a definitive answer because the principal unmasking took place at tail frequencies in neurons with CF below the frequency range with hearing loss (Wang et al. 1996). Because EP enhancement occurs (Wang et al. 1996) even for frequencies with significant hearing loss (frequencies near, but below, the peak hearing loss), the unmasking effects (Wang et al. 1996) are at frequencies too far from the damaged frequencies in the EP studies to provide the single-neuron basis for EP enhancement. Unmasking provides a more likely candidate, as it was found in neurons with CF at a frequency with hearing loss. Further, unmasking could often be at low frequencies very near to the pre-lesion CF of the IC neuron (Snyder and Sinex 2002).

Despite this, unmasking of new parts of the response area is unlikely to account for the EP amplitude enhancement because it does not occur as reliably or predictably as does the EP amplitude enhancement (Salvi et al. 1992). The

other factor likely to play a role—and probably a more important role since it appears to be a more common effect than unmasking in the response area profile—is the increase in IC neural maximum firing rates after cochlear damage (Salvi et al. 1992; Snyder and Sinex 2002).

4.7. Cochleotopic Map Changes After Cochlear Damage

This issue has been examined using paradigms described earlier to create focal cochlear hearing losses, assessed subsequently by changes in the CF progression across the dorsolateral-to-ventromedial tonotopic IC axis, examined by multineuron mapping before, and within hours after, a small focal lesion in the basal cochlea. Post-lesion there was a normal CF progression in dorsal IC regions receiving CF input from cochlear frequency regions below the lesion-affected region. Further ventrally there were discontinuities in the CF progression within and adjacent to the region receiving CF input from cochlear frequencies with hearing losses (Snyder et al. 2000). The term *lesion projection zone* (LPZ) denominates the region of a CNS structure that once received input from a receptor region that is now lesioned (Schmid et al. 1996). Despite the awkwardness of the term, because a lesion cannot project anywhere, it suffices as a short and easily remembered descriptor of such a region.

Two types of discontinuities were observed (Fig. 19.6). In one type, starting near the ventral edge of the LPZ, successive points had CFs at the low-frequency edge of the cochlear lesion, indicating an expanded CF map from the low-frequency margin of the cochlear lesion. Next, a succession of points occurred with CF at a frequency at the high-frequency edge of the cochlear lesion, representing an expanded CF map at the high-frequency margin of the cochlear lesion. Further ventrally in IC, there was a normal CF progression. The second type of discontinuity had an LPZ with an expanded CF frequency map at the low-frequency edge of the cochlear lesion and this enlarged map persisted throughout the depth of the IC even when exiting the LPZ and entering regions that, pre-lesion, had CF at frequencies without hearing losses. Thresholds at the new CFs in the expanded CF representations (in the map discontinuities) resembled, and were even more sensitive than, thresholds at the same CF(s) in neurons in the normal parts of the map.

Others have concluded (Snyder et al. 2000) that the rapid changes embody unmasking of suppressed inputs (see Section 4.5) and cannot represent adaptive use-dependent plasticity consequent on sensory deprivation. In the mapping study unmasking resulted in more homogeneous CF representation in the LPZ than would be predicted (see Section 4.4) from the wide scattering of CF with unmasking (Snyder and Sinex 2002). This may relate to the fact that the latter study produced much larger CAP losses (up to 60 dB); it would be interesting to determine whether rapid map changes of the sort seen in the first study, with small CAP losses, would have occurred in the second study.

This issue is particularly germane because further study found that only rarely could an expanded CF map of a lesion-edge frequency be interpreted as not

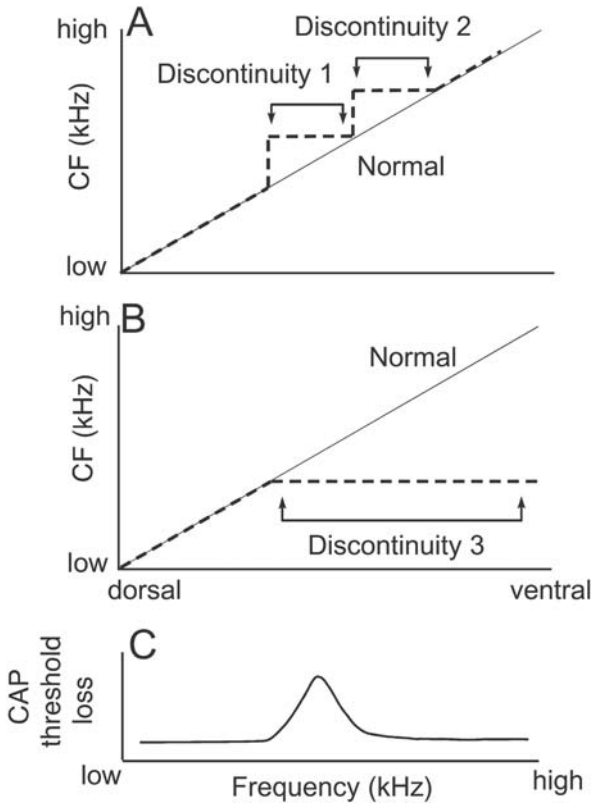


Figure 19.6. Changes in the frequency gradient curves (Snyder et al. 2000) in the CNIC after cochlear lesions. **(A, B)** Schematics of the frequency progression in CNIC when an electrode passes from dorsolateral to ventromedial and characteristic frequencies (CFs) are recorded at regular intervals. The *light line* (*Normal* in **B**) is the normal CF progression across the CNIC frequency axis. The *dashed line* shows the CF progression seen after a cochlear lesion produced a focal hearing loss (shown in **C** as elevations in cochlear compound action potential thresholds). In **(A)**, two discontinuities in CF progression are observed, and in both CFs remain about the same for some distance. Discontinuities include an expanded CF at the low-frequency edge of the cochlear lesioned range, and a CF over-representation at the high-frequency edge. **(B)** A single CF discontinuity at the low-frequency edge of the cochlear lesioned range extended across the remainder of the IC depth.

simply the residue of pre-lesion inputs to the LPZ (Irvine et al. 2003). In this residue argument (Rajan et al. 1993; Rajan and Irvine 1998) thresholds should increase across the expanded CF map in the LPZ (Fig. 19.6). Twenty sequences of recordings in the IC of 8 chronically lesioned animals found that the residue argument accounted for effects in almost every case when CFs were defined from the late component of multineuron responses to tones (time window from 35 ms after tone onset to the end of the 150-ms tone) (Irvine et al. 2003). CFs defined from the onset component (time window 5 to 35 ms after tone onset) were comparable to the 50-ms time window in other studies (Snyder and Sinex 2002; Snyder et al. 2000) for 50-ms duration tones. For two thirds of the sequences the effects were consistent with responses in the LPZ being simply the residue of pre-lesion responses at those sites. Reservations as to why even the remaining one third may not represent plasticity of the type seen in studies in auditory cortex in the same experimental paradigm led to the conclusion that, if IC tonotopic map plasticity occurs, it is rare, unrelated to intersubject variability, and limited to the early responses to tonal stimuli (Irvine et al. 2003).

5. Summary and Conclusions

Despite differences in techniques used to alter cochlear outflow and to record from the IC, and in physiological responses measured in the IC, similar conclusions follow from most such studies: the changes in IC physiology after altering cochlear outflow are best explained as a post-lesion expression of preexisting inputs, either through unmasking of previously suppressed inputs or as the residue of pre-lesion inputs. These studies suggest that there is little native capacity for plasticity in IC physiology in the adult mammal in response to large changes in cochlear outflow, at least in the limited context of the few experimental paradigms available. This conclusion is at odds with the effects seen in IC physiology with presbycusis, and with the dramatic changes in IC physiology seen after neonatal cochleotomy (Moore et al. 1993), or following large and extensive perinatal cochlear lesions with ototoxic drugs (Harrison et al. 1998). The plasticity in the latter two instances may reflect developmental phenomena, as massive cochlear lesions made with ototoxic drugs in adult life do not produce the IC plasticity seen after similar neonatal lesions (Harrison 2001).

Abbreviations

AI	primary auditory cortex
AM	amplitude modulation of sound envelopes
AP	all pass
BF	best frequency
BP	band-pass
C57	C57Bl/6 mouse strain

cAMP	cyclic adenosine monophosphate
CAP	compound action potential
CBA	CBA mouse strain
CF	characteristic frequency
CNS	central nervous system
CR+	calretinin-stained cells
CREB	(phospho-CREB) cyclic adenosine monophosphate response element binding protein
EP	evoked potential
GABA	γ-aminobutyric acid
GAD	glutamic acid decarboxylase
GAP 43	growth associated protein 43
HP	high pass
IC	inferior colliculus
ICC	central nucleus of inferior colliculus
LIC	lateral nucleus of the inferior colliculus
LPZ	lesion projection zone
LTP	long-term potentiation
LP	low-pass
MGT	minimum gap threshold
MTC	frequency-threshold tuning curve
MTF	modulation transfer function
NMDA	*N*-methyl-D-aspartate
SIm	synchronization index maximum

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Chapter 20
Hearing Loss and the Inferior Colliculus

JAMES F. WILLOTT

1. HEARING LOSS AND THE INFERIOR COLLICULUS

It is a given that peripheral hearing loss will dictate which sounds inferior colliculus (IC) neurons can respond to; if the ear does not respond to a sound, neither will the IC. Of interest, then, is how the loss of peripheral sensitivity affects responses to still-audible sounds, and the physiological, histological, metabolic, and neurochemical effects this has upon IC neurons. This chapter addresses these topics with regard to the types of hearing loss occurring in adolescents and adults. Related issues are the effects of cochlear damage on the IC during development (see Chapter 18) and in aging or after peripheral trauma (see Chapter 19), which complement this exposition and explore themes in which peripheral challenge elicits reorganization.

Because the IC does not receive direct input from the auditory nerve, effects of hearing loss on IC physiology and anatomy must be centrally mediated, a function of altered properties of lower-order auditory pathways afferent to the IC. Spatiotemporal patterns of auditory-evoked activity in these pathways, altered by hearing loss, likely affect IC neuron responses and perhaps trigger neural plasticity. Denervation and transneuronal changes resulting from cochlear pathology and hearing loss in adults can also have lasting effects on the cochlear nucleus (CN) and other subcollicular auditory nuclei, including shrinkage of neurons, neuropil reduction, changes in neurotransmitter activity, and other sequelae. These effects depend in turn on whether the hearing loss is sensorineural (and which tonotopic regions of the cochlea are damaged), acute noise-induced, unilateral, conductive, or bilaterally profound. From the perspective of the central auditory system, each type of hearing loss has different consequences. Sensorineural cochlear trauma eliminates and/or diminishes evoked activity in damaged auditory nerve fibers, whereas other "channels" may remain intact. Moreover, a population of deafferented CN neurons is deprived of synaptic input and trophic support, possibly causing degenerative or compensatory changes. Acute noise-induced hearing loss results in a sudden attenuation of auditory input from some or most of the cochlea; however, the transsynaptic effects on the CN are presumably minimal in the short term. Unilateral damage dramati-

cally alters the pattern of neural activity received by binaural neurons of the IC and elsewhere, while depriving one CN of nearly all ascending input. Conductive hearing loss is typically "flat" across frequencies and results in no direct denervation of CN neurons. Severe bilateral sensorineural damage eliminates auditory input to the CN and causes massive denervation without the relative sparing of certain channels seen in less severe sensorineural or unilateral loss. Effects on the IC of each of these types of hearing loss are now addressed.

2. Sensorineural Hearing Loss

Sensorineural cochlear damage causes most hearing disorders, including those associated with some diseases, genetic conditions, aging (presbycusis), ototoxicity, and noise trauma (Schuknecht 1974; Willott 1991). The basal cochlea is often vulnerable and compromised, resulting in high-frequency hearing loss, and this has been the focus of most of the work reviewed here. Of course, this means that high-frequency tonotopic components of auditory pathways afferent to the IC are essentially inactivated, whereas those supporting lower frequencies are not. This imbalance of afferent input has a number of important consequences falling under the rubric hearing-loss–induced (HLI) plasticity—a variety of changes in neural response properties and frequency organization. Several processes may be involved in HLI plasticity including "unmasking" of responses supported by the still-intact circuit components by the removal of inhibitory or occlusive inputs from the now-defunct components, or synaptogenesis whereby the functional axons sprout branches or up-regulate synaptic events at sites "vacated" by the quieted inputs (see Chapter 19).

Two basic types of animal models have been used to study the effects of sensorineural cochlear damage on the IC and other central auditory nuclei: animals in which circumscribed cochlear lesions have been induced by frequency-specific noise trauma or surgery and inbred strains of mice that exhibit specific genetic cochlear pathology. We focus on murine models because the forms and consequences of pathology are considered elsewhere in this volume (see Chapters 19 and 21).

2.1. *Mouse Models*

Inbred mice of the strains C57BL/6J (B6) and DBA/2J (D2), in particular, have provided much information on the effects of hearing loss on the IC and other central auditory nuclei. Both strains undergo genetically determined, progressive sensorineural hearing loss (Ralls 1967; Mikaelian 1979; Henry and Chole 1980; Willott 1981, 1986; Hunter and Willott 1987; Li and Borg 1991; Erway et al. 1993; Parham et al. 1997; Willott et al. 1995, 1997). B6 mice have hearing equal to that of young adults at 2 months of age and show a gradual change in IC properties as high-frequency hearing loss slowly ensues over the next few months. D2 mice, however, have poor sensitivity to high frequencies ($>$16 kHz)

even at 3 weeks, when abnormal IC properties are already observed (Willott 1981). At 2 months of age, auditory brain stem response (ABR) tone thresholds of D2 mice are roughly equivalent to those of 12- to 16-month-old B6 mice. Tones >20 kHz are virtually inaudible and thresholds of lower frequencies are elevated as well. Thus, D2 mice provide an animal model for adolescent-onset, rapid hearing loss, whereas B6 mice have adult-onset, gradual hearing loss.

2.2. *Frequency Maps*

Tonotopic organization of the IC is greatly altered in both B6 and D2 strains (Willott 1981, 1984, 1986, 1996). In normal-hearing mice (as in other mammals), neurons in the dorsolateral IC have sensitive thresholds and vigorous suprathreshold responses to low-frequency sounds. At increasingly ventromedial locations the best frequencies increase. After basal cochlear degeneration has occurred in B6 mice, this is no longer possible because severe high-frequency hearing loss removes the normal input to ventrally located neurons. However, the ventral neurons are not silent; rather, their thresholds for low- and middle-frequency sounds become similar to those in more dorsal IC regions (Fig. 20.1). Thus, neurons throughout the IC tend to respond best to low–middle frequencies.

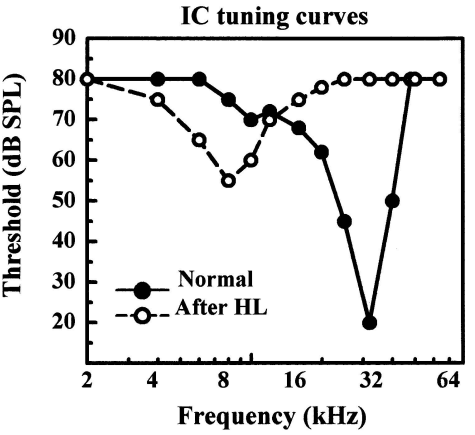

Figure 20.1. Prototypical tuning curves of B6 mouse IC neurons (Willott 1986). The tuning curve *(filled circles)* is typical of that seen in the ventral IC of a young, normal-hearing B6 mouse. The neuron's best frequency (BF) is about 32 kHz and its low-frequency "tail" has high thresholds for frequencies <10 kHz. The same tuning curve would look very different *(unfilled circles)* after high-frequency hearing loss has occurred due to expression of the *Ahl* gene. This neuron no longer responds to its normal BF because of sensorineural damage to the basal cochlea; however, thresholds for lower frequencies are now lower, and the experimentally altered BF is near 8 kHz. The 50-dB BF threshold is comparable to 8-kHz thresholds observed in lower-frequency (more dorsal) tonotopic regions of the IC.

Indeed, more neurons now respond to the lower frequencies than is the case in normal-hearing mice. In D2 mice, tonotopic organization is also absent at a young age in both the ventral cochlear nucleus (Willott et al. 1982) and IC (Willott and Turner 2000). Tuning curves are similar throughout the IC, responding best to middle frequencies, between 12 and 15 kHz. As in hearing impaired B6 mice, ventral IC neurons have lower thresholds for low frequencies than would normally be the case. The tonotopic alteration of frequency threshold maps is one aspect of HLI plasticity, and occurs in the IC of several species when cochlear lesions have been experimentally induced during adulthood (see Chapter 19).

2.3. *Suprathreshold Responses*

Suprathreshold responses of IC neurons were evaluated in normal-hearing young adult B6 mice and middle-aged B6 mice with high-frequency hearing loss (Willott et al. 1988b). Single units were given tones (2 to 64 kHz) and noise stimuli at intensity levels from 80 dB SPL, decreasing by 10-dB steps to threshold. A small age-related increase (2% to 11%) in "sluggish" neurons (driven poorly by sound) occurred, but most neurons were well driven by suprathreshold stimuli in middle-aged mice. Indeed, in the ventral IC of middle-aged B6 mice, robust suprathreshold discharges were evoked by lower frequencies than normal. Similar changes were not observed in normal-hearing, middle-aged CBA mice.

Rate-level (intensity) functions have various shapes including "flat" (minimally affected by increased intensity), "monotonic" (increasing discharge rate as intensity increases), and "nonmonotonic" (decreased discharge rate at some suprathreshold intensities) (Willott et al. 1977). Nonmonotonicity presumably results when inhibition is evoked by stimuli at higher SPLs. IC neurons of both B6 and D2 mice with hearing loss exhibit fewer nonmonotonic intensity functions (Willott 1981; Willott et al. 1988b).

A significant proportion of IC neurons in adolescent D2 mice exhibit hyperactivity in the form of after-discharges (ADs) seen in a post-stimulus time histogram (PSTH) that is representative of those for IC neurons of a normal (Fig. 20.2, left) and a 21-day-old D2 mouse (Fig. 20.2, right). Normally, neurons responding to tones in a sustained fashion cease firing when the tone ends (Fig. 20.2, left). ADs occur when the discharges continue beyond tone termination, sometimes with a brief offset pause (Fig. 20.2, right). Interestingly, D2 mice exhibit violent, often lethal, audiogenic seizures (AGS) at the age when ADs occur (21 to 23 days); by 28 days both ADs and AGS subside. AGS susceptibility is likely to result from hearing loss; moreover, the IC plays a key role in AGS (Fig. 20.2; see Chapter 21).

2.4. *Directional Hearing*

Free-field (binaural) stimuli have been used to evaluate the effects of sensorineural hearing loss on azimuth functions (discharge rates evoked by tone bursts

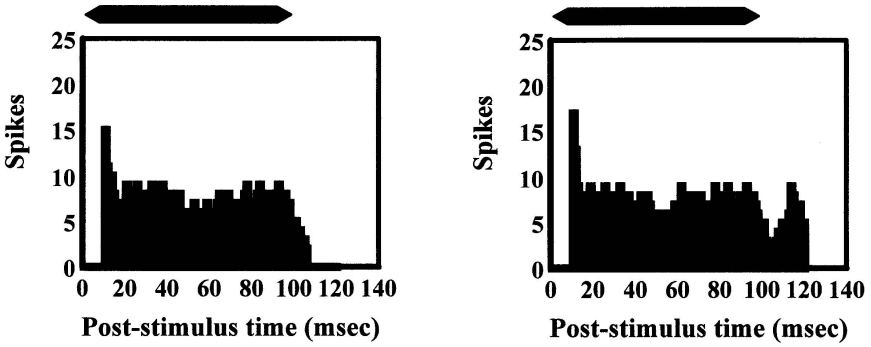

Figure 20.2. Characteristic post-stimulus time histograms (PSTHs) of mouse IC neurons (Willott 1981). The PSTHs depict the number and temporal pattern of action potentials evoked by a 100-ms tone burst *(silhouette above box)* summed for 15 trials. The PSTH *(left side)* is a typical sustained response in a normal-hearing mouse: the neuron fires and continues to do so for the duration of the tone, with little adaptation after onset. When the tone ceases, so does the neuron's responding. The PSTH *(right side)* resembles that of many IC cells in adolescent D2 mice with high-frequency hearing loss: the sustained firing does not stop immediately when the stimulus ceases, but continues as after-discharges. These hyperexcitable IC responses are most prevalent when D2 mice are susceptible to AGS and disappear as hearing loss progresses in severity.

as a function of stimulus azimuth) of IC neurons of B6 mice aged 2, 7, and 12 months (McFadden and Willott 1994a). Irrespective of age, nearly all neurons in the central area of the IC were sensitive to the azimuth of a best frequency (BF) stimulus, as revealed by azimuth functions in which firing rates varied by more than 50% from maximum to minimum at one or more intensities (the criterion used to designate directional sensitivity of an azimuth function). Much like IC neurons in other species, stimuli at azimuths contralateral to the IC recording site evoked excitatory responses, whereas ipsilateral stimuli evoked few discharges or inhibited the neuron. However, in hearing-impaired 7- and 12-month-old mice, more IC neurons had their strongest excitatory response evoked by ipsilateral stimulation, azimuth function "borders" (separating angles evoking high vs. low discharge rates) were more likely to have the high rates being evoked by the more ipsilateral angle, and azimuth functions often met the criterion for direction sensitivity only minimally.

2.5. *Masking*

A single-unit study evaluated the effects of hearing loss on IC responses to a signal (BF tone) in a fixed position, when a continuous broadband masker was presented from different azimuth angles (McFadden and Willott 1994b). For both young and middle-aged B6 mice, BF tone thresholds were significantly elevated in the presence of noise at the three locations employed (–90°, 0°, and +90°).

Separating the signal (fixed at –90°) and masker sources improved masked tone thresholds of young, but not middle-aged, mice with hearing loss. Whereas the differences between normal-hearing and hearing-impaired B6 mice might have been influenced by peripheral or central monaural effects, the data indicated that improvement in thresholds as signal and masker are separated depends on binaural interactions. This implies that altered binaural excitatory–inhibitory interactions (within the IC and/or elsewhere) could contribute to the changes in binaural masking changes described here.

2.6. Comparison of Inferior Colliculus, Auditory Cortex, and Lower Brain Stem

The representation of frequency in the primary auditory cortex (AI) of B6 mice was mapped (Willott et al. 1993) and compared with that obtained from single- and multiple-unit tuning curves from the ventral cochlear nucleus (VCN) and dorsal cochlear nucleus (DCN) (Willott et al. 1991). Reorganization of frequency maps was rapid and striking in cortex, but did not occur in VCN. The sensitization of tuning curve tails, seen in high-frequency IC neurons (Fig. 20.1), was not observed in VCN neurons. Indeed, as thresholds in the tuning curve tails of ventral IC neurons decreased with age, thresholds of VCN tuning curve tails in comparable tonotopic regions became elevated. Although the loss of high-frequency portions of VCN tuning curves inevitably results in lowering the BFs of some high-frequency neurons, that is, a portion of tuning curve tail became the "new" BF, the new BF thresholds of VCN neurons were elevated. In other words, the shift in the high-frequency IC to lower BFs, while maintaining low thresholds, did not occur in the VCN. Thus, VCN neurons appear to exhibit "pseudoplasticity" (Kaltenbach et al. 1996). These studies suggest that HLI plasticity in the IC is intermediate between that of VCN and auditory cortex. Moreover, sensitization of tuning curve tails of IC neurons is not accounted for by similar changes occurring in auditory nerve fibers or VCN neurons that are being conveyed to the IC. Rather, central neural processes appear to be responsible for the changes in the IC.

2.7. Interpretation

Sensorineural hearing loss can have significant effects on the IC of adult mice. The imbalance of neural traffic in high- vs. low-frequency pathways probably contributes to altered tonotopic organization. For example, pathways served by healthy cochlear regions may "out-compete" pathways served by impaired regions for synaptic expression or synaptogenesis on IC neurons. Alternatively, impaired pathways may not engage inhibitory circuits that normally "mask" excitatory responses evoked by lower frequencies. Degenerative, compensatory, or complex transsynaptic changes in the cochlear nucleus, secondary to denervation, may also come into play. For example, (inhibitory) glycinergic neurons in the CN are degraded in older, hearing-impaired B6 mice (Willott et al. 1997),

and this could alter the activity in neural circuits projecting to the IC. Indeed, observations outlined here suggest that inhibition may be diminished in the IC. These changes include fewer nonmonotonic rate-intensity functions, weaker ipsilaterally evoked free field inhibition, and ADs and AGS in D2 mice. In addition, IC neurons of older B6 mice exhibit increased spontaneous activity, which might be expected if tonic inhibition of neurons were reduced (Willott et al. 1988b).

3. Acute Noise-Induced Hearing Loss

Acute exposure to sufficiently intense noise causes immediate elevation of thresholds, and these typically recover partially or completely. Acute effects on the IC are likely to be secondary to impaired cochlear function and resulting changes in input via the auditory nerve. Two topics not addressed here are chronic exposure to intense noise in workplace or military occupations which cause permanent sensorineural hearing loss akin to that discussed in Section 2.7, and exposures to tones or narrow-band noises to demonstrate plasticity (see Chapter 19). The effects on IC responses can be evaluated using a within-subjects design by recording auditory activity before and after noise exposure, or using a between-groups design comparing exposed and control groups.

3.1. Within-Subject, Before-and-After Design

Several studies have obtained responses of IC neurons before and after threshold elevations were induced acutely with noise exposure (Willott and Lu 1982). They recorded PSTHs and tuning curves in normal-hearing mice, exposed them to a threshold-elevating noise, and recorded again from the same neuron (only one neuron per mouse was studied). The neuron responded to tones with a transient onset response: one or two discharges at the beginning of the tone (left) as shown in typical PSTHs (Fig. 20.3). After noise exposure, about one third of the neurons showed evoked discharges after the initial onset response (Fig. 20.3, right side). It was hypothesized that the inhibition which normally suppresses the sustained discharges was diminished by the hearing loss, resulting in the increased discharges. Subsequent studies of this kind have supported the notion that inhibition is reduced (Salvi et al. 2000; Wang et al. 2002). This is confirmed by experiments in which IC responses of chinchillas were studied before and after intense tone exposure designed to attenuate inputs to the neural circuits responsible for activating the inhibitory sidebands above BF. The noise exposure caused a widening of some tuning curves at high sound intensities but had little or no effect on the low-threshold tip of the tuning curves. Among the neurons with strongly nonmonotonic discharge rate level functions, 93% showed a significant increase in discharge rate. Pauser PSTHs often significantly decreased in the inhibitory pause duration and increased in the sustained discharge rate after exposure (Wang et al. 1996).

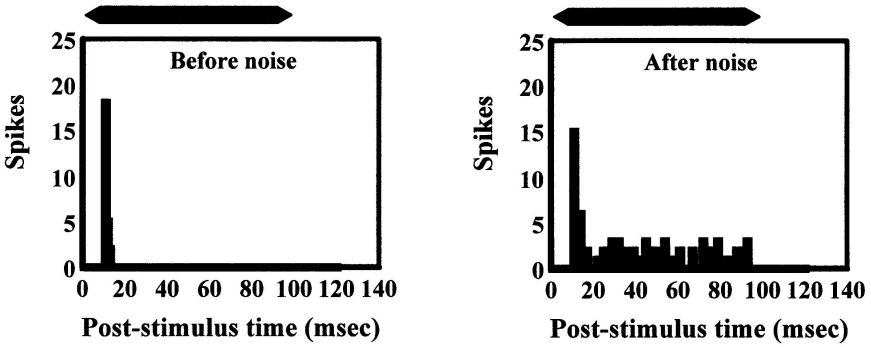

Figure 20.3. A typical acute effect of noise-induced hearing loss on the auditory response of a mouse IC neuron. (From Willott and Lu 1982.) The PSTH *(left side)* depicts a typical onset response in a normal-hearing mouse. Unlike the sustained response (Fig. 20.2, left side), the neuron fires once or twice at the 100-ms tone onset, then ceases firing for the duration of the tone. A likely mechanism for producing an onset response is inhibition of sustained discharges. Immediately after the mouse was exposed to a threshold-elevating noise, the same neuron now responds with a more sustained pattern *(right side)* when noise-induced hearing loss resulted in stronger excitation/weaker inhibition.

3.2. Between-Groups Design

Studies comparing noise-exposed and control groups also provide evidence of diminished inhibition in association with noise-induced hearing loss. This was demonstrated by a significant decrease in glutamic acid decarboxylase immunoreactivity in the IC after exposure of adult rats to high-intensity sound for 10 hours. Complete recovery occurred by 30 days post-exposure. These data suggest that transient changes in γ-aminobutyric acid (GABA) neurotransmission occur in the IC of animals exposed to intense sound (Milbrandt et al. 2000).

Several studies produced noise-induced hearing loss in adolescent mice and monitored the IC responses over several days. This procedure is particularly interesting because such mice become susceptible to AGS within 3 to 5 days, a propensity dubbed as "acoustic priming" for AGS (Henry 1967; Chen and Willott 1983). Thus, the changes in IC responses have a behavioral correlate, as is the case for D2 mice mentioned earlier. Measures of auditory evoked potentials from the IC of adolescent mice, made one day after noise exposure, show thresholds were elevated and suprathreshold amplitudes were reduced (Fig. 20.4). By 4 days, however, evoked potential amplitudes were enhanced compared to controls (Willott and Henry 1974). Extracellular single-unit IC responses in D2 mice revealed abnormal ADs such as those seen in adolescents (Fig. 20.3), and prolonged bursts of action potentials to click stimuli. These studies suggest that, after a period of partial threshold recovery from noise exposure, some IC neu-

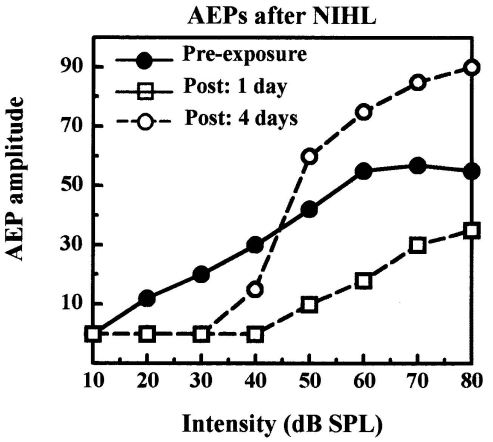

Figure 20.4. Auditory evoked potentials from the IC in three groups of adolescent mice. (From Willott and Henry 1974.) A large electrode recorded evoked potentials in response to noise pips of various SPLs. Three groups were used: nonexposed control *(filled circles);* mice exposed to an intense, threshold-elevating noise and tested 1 day later *(unfilled squares)* or 4 days later *(open circles)*. In mice tested 1 day after noise exposure, thresholds were greatly elevated and evoked potential amplitudes were reduced from control values. Mice tested 4 days after noise exposure had less severe threshold elevations (now responding to 40-dB stimuli). Interestingly, evoked potential amplitudes were larger than in controls at higher SPLs.

rons become hyperexcitable (perhaps because of diminished inhibition), and this results in susceptibility to AGS (Urban and Willott 1979).

3.3. *Interpretation*

Acute noise-exposed hearing loss appears to have some effects on responses of IC neurons resembling those of sensorineural cochlear damage. Correlates of threshold elevations such as the emergence of ADs, increased excitatory driving, and altered tuning curves suggest diminution of inhibitory influences on the IC, similar to sensorineural damage. Because acute noise-induced hearing loss presumably causes little or no central trauma, the response changes probably result from weaker auditory activation of inhibitory pathways by affected regions of the cochlea.

4. Unilateral Deafness

Unilateral deafness can result from trauma or disease in the ear or auditory nerve. Given the importance of binaural input to the IC, this is likely to have significant effects. For example, an imbalance between left and right ear input

might trigger competition for the "functionally vacated" synapses, whereby input supported by the intact ear would prevail. Such effects are especially dramatic when the unilateral deafferentation occurs during early development (see Chapter 19). Neonatal unilateral hearing loss in various species leads to substantial changes in organization of bilateral projections to the IC and bilateral neural responses (Trune 1983; Kitzes and Semple 1985; Moore 1985; Moore et al. 1989).

Unilateral deafening during adulthood has consequences as well. For example, unilateral cochlear removals in adult ferrets led to a rapid increase in the proportion of neurons in the IC ipsilateral to the intact ear that were excited by acoustic stimulation of that ear. Responses in the IC contralateral to the intact ear were largely unchanged (McAlpine et al. 1997). In an activity-sensitive measure, c-*fos* mRNA expression using in situ hybridization was assessed in the adult rat brain following cochlear ablations. After unilateral ablation, acoustically driven c-*fos* expression was eliminated or decreased in the contralateral IC and elsewhere. Recovery was not evident even after 6-month survivals (Luo et al. 1999). A physiological study concluded that unilateral deafening reduced inhibition in the adult gerbil IC as shown by multiple-unit recordings made from electrode penetrations before and after contralateral cochlear ablation. Up to 60% increases in the proportion of recording sites at which neural activity was elicited by ipsilateral stimulation were observed after the ablation. Novel excitatory responses were evident within minutes of ablation. Western blotting for glutamic acid decarboxylase, the precursor to GABA, showed significant decreases in the IC contralateral to cochlear ablation, relative to those in the ipsilateral IC. Their results suggested decreased inhibitory influence of two types: a rapid, stimulus-related, functional unmasking and a delayed reduction in the capacity of GABA synthesis in the IC (Mossop et al. 2000).

5. Conductive Hearing Loss

Occlusion of the outer or middle ears causes threshold elevations across all frequencies, so the most obvious effect would be reduced auditory evoked activity in the IC (assuming there is not amplification of stimuli). Thus, in adults, one might not expect strong effects on IC neurons, such as those brought about by sensorineural or unilateral deafness. Indeed, no effect of conductive hearing loss initiated during young adulthood was found on IC neural somatic size neurons or in other auditory brain stem structures (Webster 1983). Conductive hearing loss decreased 2-deoxy-D-glucose (2-DG) uptake, an activity sensitive metabolic marker studied in the IC of adult gerbils (Tucci et al. 1999, 2001), whereas others found minimal effects (Woolf et al. 1983). No effect of unilateral conductive hearing loss on cytochrome oxidase staining was observed in the adult gerbil IC (Tucci et al. 2002). Even when a conduction deficit was caused by neonatal ossicle removal, there was no detectable difference in relative IC cytochrome oxidase activity (Paterson and Hosea 1993).

Might more interesting, subtle changes occur following conductive hearing loss? Perhaps the elevation of thresholds is not completely linear or differential attenuation of low and high frequencies or changes in resonant frequencies from reduced volume of the ear canal cause small changes in the relative activity related to tonopicity, albeit much less than those occurring with sensorineural damage to cochlear regions. Moreover, complex excitatory–inhibitory responses of IC neurons might be affected, as in this hypothetical example. Sound levels in the ambient acoustic environment range from 0 to 80 dB. An IC neuron with a "nonmonotonic" intensity function responds with excitation to sounds in the 0- to 40-dB SPL range and is inhibited from 40 to 80 dB. After a 40-dB conductive loss, 0- to 40-dB sounds are eliminated and the 40- to 80-dB sounds are effectively attenuated to 0 to 40 dB. This manipulation creates an IC neuron that can respond only with excitation.

6. Complete Bilateral Hearing Loss

The effects of bilateral cochlea ablation or auditory nerve section obviously result in a loss of auditory function in the IC and throughout the central auditory system. Because responses to all frequencies in all monaural and binaural circuits are equally affected, bilateral deafening does not cause the imbalance and synaptic competition in different neural circuit components that follow sensorineural and unilateral hearing loss. Thus, it is not surprising that effects on the IC can be minimal. Ferrets reared with bilateral cochlear removals from before the normal hearing onset were injected with wheat germ agglutinin conjugated to horseradish peroxidase in one IC. Neither the absolute number nor the bilateral symmetry of the labeled neurons differed significantly from normal adult ferrets (Moore 1990). Severe bilateral hearing loss also occurs in B6 mice older than 18 months of age (see section 2). In aged B6 mice, IC labeling with either 2-DG (Willott et al. 1988a) or cytochrome oxidase (Willott 2001) showed little, if any, change. Retrograde transport of wheat germ agglutinin–horseradish peroxidase from IC to CN of B6 mice revealed no evidence of altered projections or change in the number of labeled neurons (Willott et al. 1985). Little effect was observed on the size or the packing density of IC neurons, and there was no age-related neuron loss (Willott et al. 1994a). Another study observed a small but significant decrease in the size of principal neurons in the central nucleus of older B6 mice (Kazee et al. 1995).

This is not to say that bilateral deafness has no effect on the IC, as a study on aged B6 mice found fewer synapses of all morphologic types on principal neuronal somas, and the percentage of somatic membrane covered by synapses decreased by 67% (Kazee et al. 1995). After bilateral deafness of 21 days in guinea pigs there was an increase in evoked *fos*-immunoreactive neurons in IC to contralateral cochlear electrical stimulation, a reduction in IC neurons responding with suppression of activity to electrical stimulation, and decreased GABA release assayed by in vivo microdialysis (Bledsoe et al. 1995). Taken

together, these studies suggest that severe hearing loss may affect synaptic density or organization and inhibition, but does not have dramatic effects on morphology or metabolism. This implies that a uniform reduction in activity is less injurious to IC cells than unilateral contralateral deafferentation; perhaps this reflects upper and lower limits on IC capacity for reorganization after partial and complete reductions in activity.

7. Behavioral Correlates of Inferior Colliculus Changes: Prepulse Inhibition

An issue often overlooked is whether neural plasticity in the IC and elsewhere has significant effects on auditory perception. What, if any, are the effects of altered tonotopicity or suprathreshold excitability? The correlation between IC neural properties and AGS, mentioned earlier, strongly suggest a behavioral outcome of altered IC physiology. Another auditory behavior that is localized to the IC is prepulse inhibition (PPI), a normal behavior exhibited by humans and other species.

In PPI, an audible "prepulse" stimulus (S1) is presented approximately 100 ms before an intense, startle-eliciting stimulus (S2). Whether the S1 is a tone burst, a gap in background noise, or some other acoustic change, it ultimately activates other components of the PPI neural circuitry, including pathways that descend to the reticular formation and inhibit neurons that trigger the startle reflex (Davis 1984; Willott et al. 1994b; Carlson and Willott 1998; Koch 1999; Ison 2001). Activation of the PPI circuit inhibits the startle pathway for several hundred milliseconds, producing an "inhibited" startle reflex with a reduced amplitude. Studies on humans find that PPI magnitude reflects the behavioral salience of the prepulse tones (Hoffman and Ison 1980; Ison 2001).

The IC plays a crucial role in the processing of prepulses and their ability to inhibit the startle response circuit. For example, IC lesions reduce or abolish PPI, whereas electrical stimulation of the IC produces PPI (Leitner and Cohen 1985; Li et al. 1998a,b). It follows, therefore, that changes in the responses of IC neurons to tones have the potential to modulate PPI, when those tones are used as prepulses.

PPI can be expressed by the simple ratio of startle reflex amplitude when a prepulse has been presented (S1 to S2) to startle reflex amplitude without the prepulse (S2-only). A stronger PPI is indicated by a smaller ratio in this computation. Studies of B6 mice have shown that the PPI magnitude changes are correlated with hearing loss and HLI plasticity (Willott et al. 1994b; Willott and Carlson 1995; Carlson and Willott 1996). As high-frequency sensitivity declines in aging B6 mice, the salience of a 24-kHz S1 in PPI also wanes (Fig. 20.5). However, at 5 months of age enhanced PPI is produced by a 12-kHz S1, which has become over-represented in the IC because of HLI plasticity. As B6 mice age from 5 to 12 months and hearing loss extends to 12 kHz and above, the

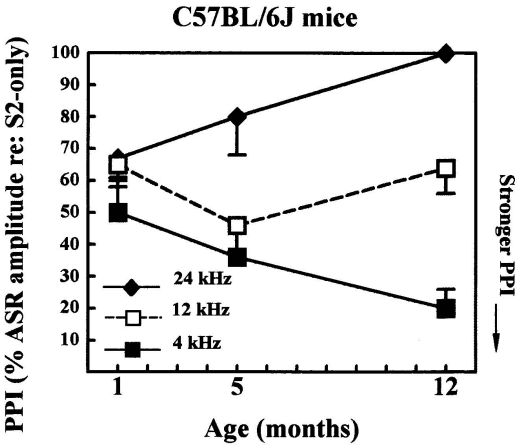

Figure 20.5. Prepulse inhibition in B6 mice (Willott et al. 1994b) aged 1, 5, or 12 months. In normal-hearing 1-month-olds, PPI ranged between 50% and 67% for 70-dB SPL with S1 stimuli of 4, 12, and 24 kHz. At 5 months (when thresholds >20 kHz have become elevated), the 24 kHz S1 is less effective, whereas the 12- and 4-kHz S1s produce stronger PPI. At 12 months, after high-frequency hearing loss has progressed, the 24-kHz S1 is ineffective, the 12-kHz S1 is less effective than it was a 5 months, but the 4 kHz S1 is more effective. The salience of S1 tones parallels changes in IC neuron frequency responses associated with HLI plasticity. At 5 months, more IC neurons respond to 70-dB SPL 12-kHz tones then at 1 month (Fig. 20.1), and 12-kHz tones elicit stronger PPI. At 12 months of age, even more IC neurons respond to 70-dB 4-kHz tones because the changes in frequency representation continue to favor even lower frequencies and 4-kHz tones elicit stronger PPI. (From Willott 1984, 1986.)

improvement in lower-frequency PPI continues to develop (Fig. 20.5). With a 4-kHz S1, PPI is even better in 12- month-olds than in 1- or 5-month-olds. Age-related changes in PPI do not occur in CBA mice, which have minimal hearing loss. Because the IC "drives" the inhibiting modulation of the startle reflex, improved PPI parallels HLI plasticity for the middle and low frequencies.

8. Diminished Inhibition

Much of the evidence presented here suggests that hearing loss results in diminished inhibition in the IC. This may be especially marked when the balance between excitatory and inhibitory processes becomes biased against inhibition: inhibitory processes become impaired and/or excitatory processes become augmented as a function of cochlear damage/hearing loss. Such events may be involved in HLI plasticity, development of susceptibility to AGS, and strengthening of PPI.

Several hypotheses have been offered to explain diminished inhibition (Willott 1996). One possibility is that diminished inhibition occurs in the CN or other structures projecting to the IC. Another hypothesis is that inhibitory portions of neuronal response areas are selectively impaired because of the topographic pattern of cochlear damage (Willott 1981). For example, the response areas of many IC neurons have inhibitory subregions activated by high frequencies. A high-frequency deficit (with relatively intact middle-to-low-frequency hearing) from noise or genetic manipulation would have an especially deleterious effect on activation of these inhibitory regions. When intense or broad band stimuli are presented to normal-hearing animals, both excitatory and inhibitory regions would be engaged simultaneously, affecting discharge rates; however, the same stimuli would activate only the excitatory region in hearing-impaired mice because the inhibitory region would be "lost," and discharge rates would increase. A variant of this hypothesis is that the neurons would be inhibited less than normally by high frequencies in the ambient acoustic environment, which could have long-term effects on the neurons' inhibitory response properties (a use- or activity-dependent phenomenon). It is also feasible that altered auditory activity affects inhibitory circuits directly.

9. Implications

Whatever the mechanisms of diminished inhibition and/or HLI plasticity prove to be, it is clear that the organization and response properties of IC neurons and circuits are altered with hearing loss in adults. We have seen the likely consequences in the form of AGS and altered PPI in mice, and there is no reason to believe that effects of hearing loss on the IC in human adults would not affect auditory perception. The general effect of HLI plasticity/diminished inhibition is to enhance the strength of still-audible sounds. Whether this is advantageous for a person with hearing loss is not yet clear. If the enhanced response is to a signal, this could be positive; if, on the other hand, the response to background noise is enhanced, it may be deleterious. Thus, it seems vital to better understand the processes involved in hearing-loss–induced changes in IC responses as a prelude to developing interventions to modulate or manage them clinically.

Abbreviations

ABR	auditory brain stem response
AD	after-discharge
AGS	audiogenic seizures
AI	primary auditory cortex
BF	best frequency
CN	cochlear nucleus

DCN	dorsal cochlear nucleus
2-DG	2-deoxyglucose
GABA	γ-aminobutyric acid
HLI	hearing-loss–induced
IC	inferior colliculus
PPI	prepulse inhibition
PSTH	post-stimulus–time histogram
VCN	ventral cochlear nucleus

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Chapter 21
The Midbrain and Audiogenic Seizures

Carl L. Faingold

1. Seizures and the Inferior Colliculus

High-intensity acoustic stimuli can elicit motor convulsions (audiogenic seizures, AGS) in several animal species and are common in rodents (Hohenboken and Nellhaus 1970; Jobe et al. 1973; Beck et al. 1987; Gil Verona et al. 1990). Extensive experimentation has established that the inferior colliculus (IC) plays the key role in AGS initiation (Millan et al. 1986; Browning 1994; Nehlig et al. 1995; Faingold et al. 1998; Faingold 1999, 2002, 2004; Garcia-Cairasco 2002). Many techniques demonstrate the primacy of IC in AGS, including c-*fos* expression (McCown et al. 1991; Snyder-Keller and Pierson 1992; Clough et al. 1997; Kwon and Pierson 1997), lesion (Browning 1994; Ribak et al. 1994), focal microinjection (Frye et al. 1983, 1986; Millan et al. 1986; Faingold et al. 1989b,c, 1998; Riaz and Faingold 1994), 2-deoxyglucose (Eckardt et al. 1986), electrical stimulation (Frye et al. 1986; McCown et al. 1995), and neurophysiological studies (Li 1997). High-intensity acoustic stimuli evoke abnormal neuronal firing increases in the IC central nucleus (ICc) of rats with genetic or induced AGS susceptibility (Faingold et al. 1986b; Faingold and Boersma Anderson 1991; Faingold and Riaz 1995). This enhanced output from the IC initiates AGS. Most of the evidence indicates the ICc is the most critical site within the IC, but the other IC subnuclei are also important network components (McCown et al. 1984; Chakravarty and Faingold 1996, 1997; Faingold 2002).

AGS studies in rats began in 1924 (Jobe 1981). Several rodent strains inherit AGS susceptibility, and susceptibility is inducible in rodents by several experimental treatments (Tecott et al. 1995; Ross et al. 2001; Faingold 2002). Seizure mechanisms in rats were extensively studied in inherited forms of AGS (Jobe et al. 1973, 1992; Faingold and Naritoku 1992; Nehlig et al. 1995; Faingold 1999; Garcia-Cairasco 2002). Sustained AGS susceptibility is also produced in young rodents by inducing a hearing deficit during the critical period for hearing development (Ross et al. 2001), through thyroid deficiency, intense acoustic stimulation (priming), and ototoxic drugs (Faingold 2002). Normal adult rodents can be rendered susceptible to AGS by chemical stimulation in the IC (Millan et al. 1986; Faingold 1999) or after sustained focal perfusion of agents that inhibit

neuronal firing (Yang et al. 2001). AGS-like seizures can be evoked by IC electrical stimulation (McCown et al. 1984, 1991, 1995; McCown and Breese 1993), and acoustic priming lowers the threshold for evoking electrically induced seizures (Sakamoto and Niki 2001).

2. Hearing Loss and Audiogenic Seizure Susceptibility

Hearing loss is associated with susceptibility to AGS in many rodents, such as DBA/2 mice (Willott and Turner 2000). Two strains of genetically epilepsy-prone rats (GEPR-3s, GEPR-9s) exhibit elevated hearing thresholds (Faingold et al. 1986a,b, 1990; Penny et al. 1986). Not all genetic forms of AGS involve a hearing deficit. Black Swiss mice exhibit AGS susceptibility without hearing deficits (Misawa et al. 2002). Treatments producing significant hearing loss during the critical period for hearing development render rodents susceptible to AGS (Van Middlesworth and Norris 1980; Chen and Aberdeen 1981; Henry 1984; Pierson and Swann 1988; Kwon and Pierson 1997; Iida et al. 1998; Ross and Coleman 1999; Willott and Turner 2000; Sakamoto and Niki 2001; Kai and Niki 2002). The degree of hearing loss does not correlate well with the intensity of AGS in thyroid-deficient rats and GEPRs (Patrick and Faingold 1989; Faingold et al. 1990). When hearing deficits rise above a certain level, AGS severity declines (Faingold et al. 1990). Acute AGS forms, such as ethanol withdrawal, do not involve hearing deficits (Wecker and Ison 1984). In AGS forms with early-onset hearing loss, the neurotransmitter changes in IC may occur as compensatory mechanisms for decreased acoustic input during the critical period (Faingold 2002). IC neurotransmitter changes brought about by several different mechanisms play critical roles in drug-induced and withdrawal-induced AGS.

3. Genetically Based Audiogenic Seizures

Genetically epilepsy-prone rats (GEPRs) were derived by selective breeding from the Sprague–Dawley strain (Reigel et al. 1986). The two substrains, GEPR-9 and GEPR-3, exhibit consistently different severities of convulsive behavior during AGS (Jobe et al. 1973, 1992; Faingold and Naritoku 1992; Faingold 1999; Raisinghani et al. 2003). AGS mechanisms in GEPRs and other AGS-susceptible rats have been investigated worldwide (Garcia-Cairasco et al. 1998; Simler et al. 1999; Yechikhov et al. 2001). Many mouse strains also exhibit AGS (Faingold 2002). Thus far, genetic abnormalities have been identified only in DBA/2 and Frings mice (Neumann and Collins 1991; Skradski et al. 2001). Several "gene-knockout" mouse strains also exhibit AGS susceptibility (Faingold 2002; Upton and Stratton 2003), but how these abnormalities produce AGS susceptibility is unknown.

Some forms of AGS consistently exhibit generalized clonic seizures (such as GEPR-3s), while others consistently exhibit tonic seizures (such as GEPR-9s) (Reigel et al. 1986; Marescaux et al. 1987). Many similarities in the AGS networks of these closely related seizure forms exist, particularly the critical role of the IC in seizure initiation. However, there are also surprising differences with regard to the involvement of the amygdala (Browning et al. 1985; Garcia-Cairasco et al. 1996; Hirsch et al. 1997; Faingold 1999; Feng and Faingold 2002; Yang and Faingold 2002; Raisinghani and Faingold 2003).

4. Induced Audiogenic Seizures

Long-lasting AGS susceptibility can be induced in normal rodents, commonly in young rodents during the critical period. However, AGS susceptibility induced in mature rodents is typically short lived.

4.1. Developmentally Related Audiogenic Seizures

In young rodents, AGS susceptibility can result from a hearing deficit during the critical period within the first 3 weeks of life (Ross et al. 2001). Approaches that induce AGS during development include thyroid deficiency, intense acoustic stimulation (priming), and ototoxic drugs (Reid and Collins 1986; Ross et al. 2001; Sakamoto and Niki 2001).

4.2. Audiogenic Seizures Induced in Mature Animals

Transient AGS susceptibility can be induced in adult rodents without detectable hearing deficit, including a post-ischemic syndrome (Kawai et al. 1995) and by drug administration (Wada 1970; Chung and Johnson 1983; Bac et al. 1998). AGS also occurs during withdrawal after continued administration of depressant drugs (Faingold 2002). AGS that occur during ethanol withdrawal (ETX) is well studied (Faingold et al. 1998; Atkins et al. 2000). If ethanol intake is prolonged or intense, most species, including humans, will develop convulsive seizures. In rodents such seizures are triggered by acoustic stimuli (Majchrowicz 1975; Faingold and Riaz 1994; Faingold et al. 1998; Koob 2000; Veatch and Gonzalez 2000; Devaud and Chadda 2001; Yang et al. 2003).

In normal rats AGS susceptibility is induced by focal microinjection of agents that enhance excitation or reduce inhibition in IC. The same agents injected into other brain sites do not induce AGS susceptibility (Millan et al. 1986; Bagri et al. 1989, 1999; Faingold et al. 1992). AGS are a major manifestation of withdrawal after chronic administration of alcohol, barbiturates, or benzodiazepines in rodents (Faingold et al. 1998; Oh and Ho 1999). These agents enhance the inhibitory action of γ-aminobutyric acid (GABA), and withdrawal results in AGS susceptibility involving $GABA_A$ receptor ($GABA_AR$) down-regulation and/or de-

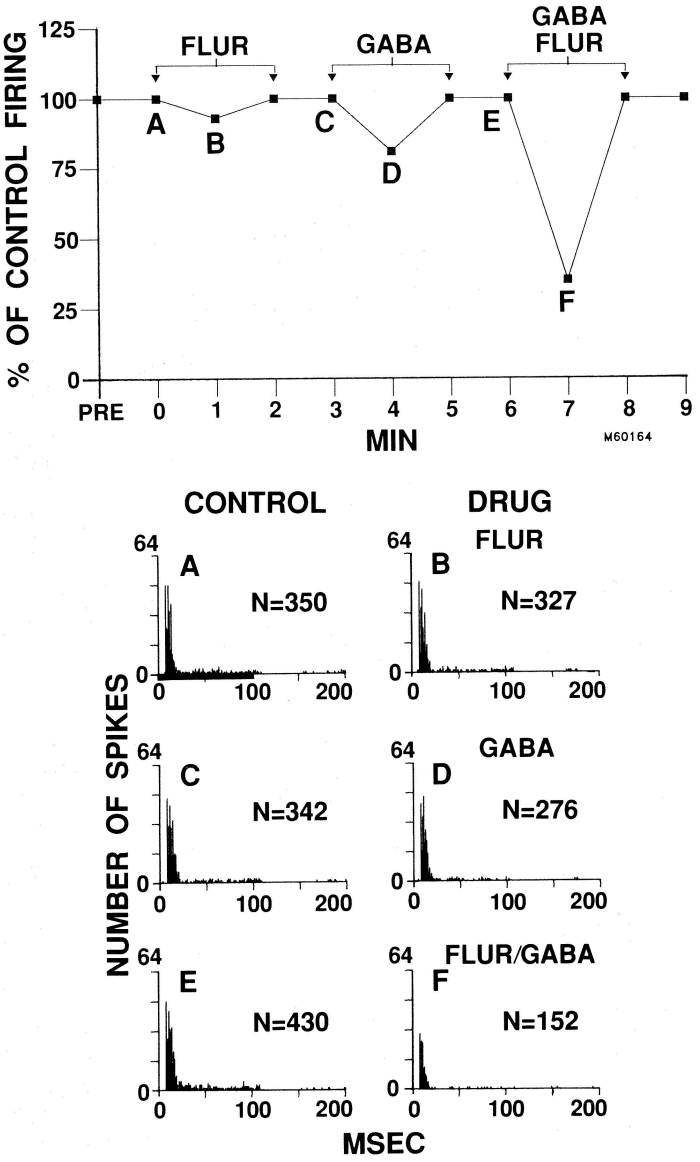

Figure 21.1. Inhibitory effects of iontophoretic application of GABA and a benzodiazepine, flurazepam (FLUR) on the responses of an ICc neuron to acoustic stimuli and the interaction of the agents applied simultaneously. The drug time course appears in the upper panel. The PSTHs are shown below. **(A, C, E)** The control response before drug application. **(B)** FLUR (200 nA, 2 min) alone is relatively ineffective. **(D)** The effect of GABA (40 nA, 1 min). **(F)** Combined application of GABA and FLUR is superadditive. The line below **(A)** is the stimulus duration. *N* is the total number of action potentials in the post-stimulus time histogram (PSTH). Stimulus: 100-ms tone bursts, 60 dB contralateral, 10 kHz. CF threshold: 40 dB SPL. (From Faingold et al. 1991a,b, Lippincott Williams & Wilkins.)

sensitization, which diminishes the effectiveness of GABA-mediated inhibition (Bianchi and Macdonald 2002; Chang et al. 2002; Mozrzymas et al. 2003).

5. Neurotransmitter Mechanisms of Audiogenic Seizures

Several forms of AGS are associated with neurotransmitter abnormalities, most prominently in IC. GABA- and glutamate (GLU)-mediated neurotransmission are implicated in AGS. Monoaminergic abnormalities (norepinephrine, 5-hydroxytryptamine, histamine) are also implicated in AGS (Onodera et al. 1992; Jobe et al. 1994; Yan et al. 1998; Feng and Faingold 2000; Feng et al. 2001), but the IC may not be the most critical site of involvement of these transmitters.

5.1. Role of γ-Aminobutyric Acid

Reduced GABA effectiveness is a critical AGS mechanism (Roberts et al. 1985; Faingold et al. 1986b, 1994a,b; Frye et al. 1986; Ribak et al. 1993). The $GABA_AR$ hyperpolarizes most neurons by fluxing chloride (Sieghart 2000; Kittler et al. 2002). GABA plays a key role in acoustic processing in IC neurons (Faingold et al. 1989b) based on anatomical, neurochemical, neurophysiological, and pharmacological studies (Faingold 2002; see Chapter 9). Direct application of GABA and agents that alter the GABA receptor activation modify IC inhibition (Faingold et al. 1989a, 1991a,b, 2000; Wagner 1996; Hosomoi et al. 1997) (Fig. 21.1).

GABA mediates several forms of inhibition in ICc. Exogenous GABA-mediated inhibition and endogenous acoustically evoked inhibition are increased by agents that enhance the action of GABA. These include a GABA uptake inhibitor and a benzodiazepine (Fig. 21.1). Acoustically evoked GABA-mediated neural inhibition is blocked by a $GABA_AR$ antagonist in vivo (Faingold et al. 1989a, 1991a,b; Casseday et al. 2000; Jen and Zhang 2000). The acoustically evoked inhibitory responses of ICc neurons include binaural inhibition (Fig. 21.2), nonmonotonic rate intensity response, offset-inhibition (Fig. 21.3), and pauser responses (Caird 1991; Covey and Casseday 1999). These inhibitory response patterns are subserved, in part, by local GABAergic inhibitory circuits within the IC and exogenous GABAergic inhibitory projections to IC (Faingold et al. 1989a, 1991a,b, 1993a; Li and Kelly 1992; González-Hernández et al. 1996; Burger and Pollak 2001). Agents that enhance or block the action of GABA will increase or reduce, respectively, inhibition in ICc neurons (Faingold et al. 1989a, 1991a,b; Fuzessery and Hall 1996; Le Beau et al. 1996; Palombi and Caspary 1996; Jen et al. 2001).

An inherent or induced deficiency of GABA-mediated ICc inhibition is a key mechanism subserving AGS susceptibility (Faingold et al. 1986a; N'Gouemo et al. 1996; Faingold 1999; Ishida et al. 2002). GABA transport mechanisms are also abnormal in genetic forms of AGS (Faingold et al. 1994b; Akbar et al.

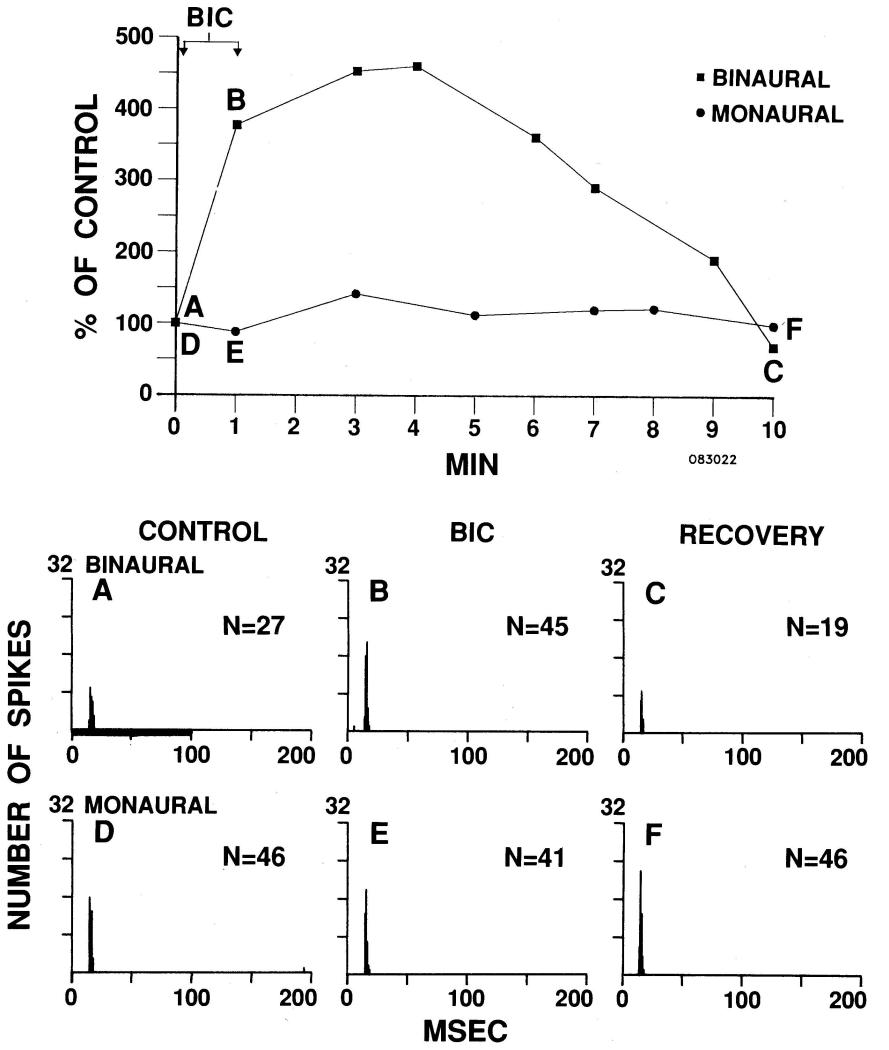

Figure 21.2. The effects of the $GABA_A$ antagonist bicuculline *(BIC)* on the responses of an ICc neuron to monaural and binaural acoustic stimuli at CF. For drug time course and PSTHs see Fig. 21.1. **(A, D)** The control response. Binaural inhibition reduced firing >40% (**A** vs. **D**). The darkened line at the bottom of histogram **(A)** shows stimulus duration. After *BIC* application (100 nA) the inhibitory effect of binaural stimulation is almost completely blocked (**B** vs. **D**), but the monaural response at the same time point is nearly normal **(E)**. **(C)** Recovery of the binaural inhibition after ending *BIC* application. *N* is the total number of action potentials in the PSTH. Stimulus: 100-ms tone bursts, 50 dB contralateral or bilateral, 19.9 kHz. CF threshold: 30 dB SPL. (From Faingold et al. 1991a,b, Lippincott Williams & Wilkins.)

1998). The effectiveness of both acoustically evoked GABA-mediated inhibition and exogenously applied GABA is significantly decreased in both induced and genetically based AGS (Faingold et al. 1986a; Faingold and Boersma Anderson 1991; Li et al. 1994; N'Gouemo et al. 1996). Reduced GABA effectiveness also occurs in other brain sites of GEPRs (Gould et al. 1991, 1995; Evans et al. 1994; Molnar et al. 2000). Application of GABA onto ICc neurons induces dose-related inhibition (Fig. 21.1) that is enhanced by agents that increase $GABA_AR$ activation and diminished by agents that block $GABA_AR$. The effectiveness of iontophoretically applied GABA is reduced in GEPRs and ETX (Faingold et al. 1986a; N'Gouemo et al. 1996). The nonmonotonic rate-intensity function is mediated, in part, by GABA (Faingold et al. 1989a, 1991a,b), and this form of inhibition is diminished in GEPR-9s (Faingold and Boersma Anderson 1991). The failure of the nonmonotonic rate-intensity function commonly seen in GEPR IC neurons mimics the effect of iontophoretic application of bicuculline in normal IC neurons (Faingold 2002).

Binaural inhibition is mediated partly by the action of GABA, and its effectiveness is also diminished in GEPRs (Faingold et al. 1986a; Faingold 2002). When a tone burst is presented a few normal ICc neurons exhibit a response peak at the offset of the stimulus, but an elevated incidence of offset responses occurs in GEPR-9s (Faingold et al. 1986b). The offset response is also induced by iontophoretic application of a $GABA_AR$ antagonist in normal rats (Faingold et al. 1986a) (Fig. 21.3). The offset response also involves diminished GABA-mediated offset inhibition (Faingold et al. 1986a). The source of the offset inhibition is an ipsilateral GABAergic projection to ICc from the superior paraolivary nucleus (SPON) (Kulezsa and Berrebi 2000; Berrebi and Saldaña 2001). SPON neurons respond to acoustic stimuli with excitation at stimulus offset (Kulesza et al. 2002). The GABA projection from SPON appears to mediate offset inhibition. Diminished GABA effectiveness, genetically or pharmacologically induced, contributes to the emergence of the offset peak. A defect in GABA-mediated tonic inhibition, arising in the dorsal nucleus of the lateral lemniscus, which normally suppresses the offset response in ICc neurons, could contribute to the altered response pattern (Faingold et al. 1993a; Burger and Pollak 2001). A form of GABA-mediated inhibition evoked by paired electrical pulses in vitro is also diminished in IC and several other brain sites in AGS-susceptible rats (Dalkara 1986; Li 1997; Evans et al. 2000).

Agents focally microinjected into ICc that increase $GABA_AR$ activation will block AGS in GEPR-9s or during ETX. Microinjection of $GABA_AR$ or $GABA_BR$ agonists blocks AGS. Blocking GABA uptake or breakdown, or enhancing GABA synthesis focally within ICc, also blocks AGS susceptibility (Frye et al. 1983, 1986; Faingold et al. 1994a,b; Riaz and Faingold 1994). GABA uptake is increased in GEPR-9s as compared to controls (Faingold et al. 1994b). These data support the critical importance of a defect in GABA-mediated inhibition in the IC for susceptibility to AGS in GEPR-9s and ETX. A transient susceptibility to AGS is induced in normal rats after focal microinjection of bicuculline (Millan et al. 1986). AGS susceptibility was induced in normal rats on withdrawal after

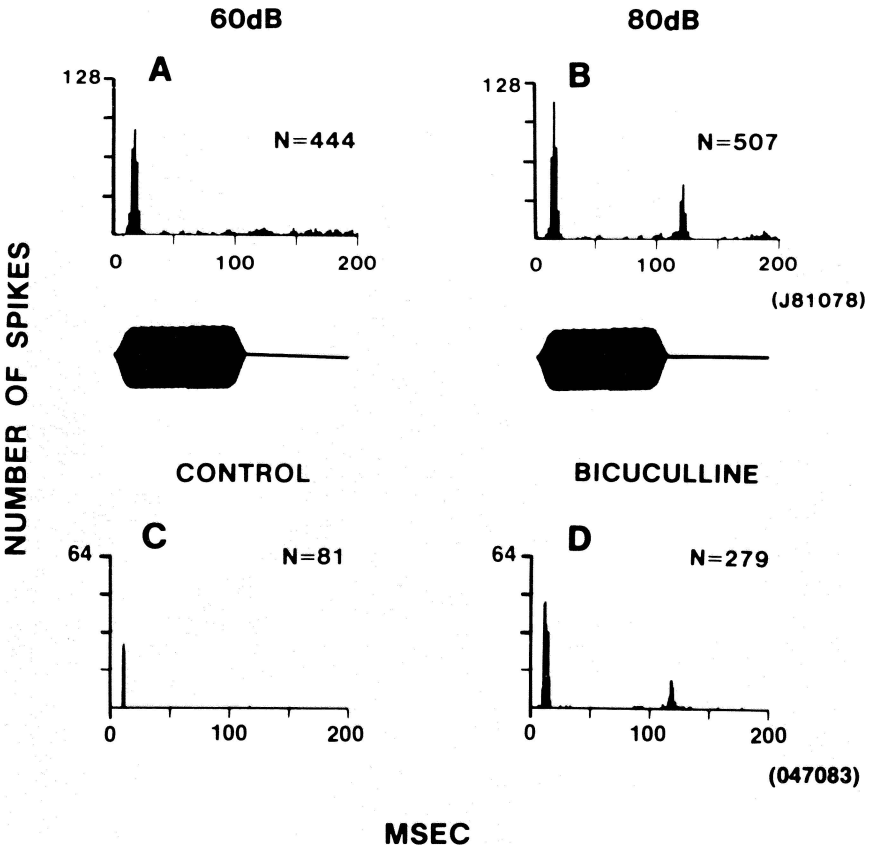

Figure 21.3. PSTHs showing the induction of the onset–offset response in ICc neurons. The responses to increasing sound intensity in the GEPR are shown in the top row. **(A)** At 60 dB an onset response pattern was observed. **(B)** At 80 dB the pattern becomes an onset–offset response, a result that occurred significantly more often in GEPR IC neurons. The bottom row shows the induction of an onset–offset response by *BIC* in a control IC neuron. **(C)** Before *BIC* only an onset response was seen. **(D)** After *BIC* (100 nA for 2 min) the response is onset–offset as above. Typical acoustic stimulus appears in the middle row. *N* is the number of action potentials/histogram. PSTH parameters: 50 stimulus presentations, 1-ms bin width. Stimulus parameters: 63 dB binaural, 6.4 kHz; threshold: 33 dB SPL *(top row),* 7.2 kHz; threshold: 30 dB SPL *(bottom row).* (From Yang et al. 2001, with permission from Elsevier.)

continuous activation of GABA receptors by GABA infusion in ICc for 7 days (Yang et al. 2001). GABA receptor desensitization and down-regulation occur after prolonged exposure to GABA, which reduces GABA-mediated inhibition (Russek et al. 2000). These findings further support diminished GABAergic function in the IC as a critical mechanism for AGS initiation.

Withdrawal after continued systemic treatment with agents that enhance the action of GABA induces seizures in normal rats. Systemic administration of ethanol, barbiturates, or benzodiazepines for sufficient periods results in AGS susceptibility on withdrawal due partly to GABA-related mechanisms (Faingold et al. 1998; Harris 1999; Grobin et al. 2000; Loh and Ball 2000; Davis and Wu 2001; Ueno et al. 2001). $GABA_AR$ activation is strongly implicated in the depressive effects of ethanol (Loh and Ball 2000; Davis and Wu 2001; Criswell et al. 2003; Roberto et al. 2003). The regionally selective effects of ethanol on $GABA_ARs$ may be lost when the neurons are isolated from their normal in vivo neuronal network (Criswell et al. 2003). The inhibitory effect of GABA directly applied onto IC neurons in vivo is enhanced by systemically administered ethanol (Simson et al. 1991). $GABA_AR$ subunit alterations are associated with altered responses to GABA (Buck et al. 1991; Mhatre and Ticku 1992; Devaud et al. 1997; Mihic et al. 1997; Faingold et al. 1998; Loh and Ball 2000).

The importance of GABA in the IC in AGS mechanisms is confirmed further by the ability to block GABA-mediated inhibition with significantly lower doses of bicuculline in genetic and induced AGS-susceptible rats than in normal rats (Faingold et al. 1986a, 2000).

5.2. *The Role of Glutamate*

Glutamate (GLU) is the major excitatory brain neurotransmitter (Hardingham and Bading 2003), and GLU receptors (GLURs) play a critical role in modulating AGS. GLUR antagonists block AGS (Croucher et al. 1984; Faingold et al. 1992; Chapman et al. 2001; De Sarro et al. 2003).

Excitatory neurotransmission is critical in the responses of IC neurons to sound, and considerable data support GLU as a candidate (Feliciano and Potashner 1995; Goldsmith et al. 1995; Suneja et al. 1995, 2000; Saint Marie 1996; Gaza and Ribak 1997; Caicedo and Eybalin 1999). Application of GLUR agonists excite, and antagonists suppress, respectively, IC neuronal firing (Faingold et al. 1989b, 1991a,b, 2000; Smith 1992; Wagner 1996; Li et al. 1999; Jen et al. 2001; Zhang and Kelly 2001, 2003; Goldstein-Daruech et al. 2002) (Fig. 21.4).

GLU and aspartate levels in IC and certain other sites of AGS-susceptible rodents are abnormal (Chapman et al. 1986; Ribak et al. 1988; Lasley 1991; Marianowski et al. 1995). AGS susceptibility results from microinjection of agents that enhance GLUR activation in the IC (Millan et al. 1986; Faingold et al. 1989c; Browning et al. 1991). AGS susceptibility is also induced on withdrawal after continued systemic treatment or focal infusion of GLUR antagonists (Faingold and Riaz 1995; Tsai and Coyle 1998; Dahchour and De Witte 1999; Yang et al. 2001). Significantly greater than normal doses of GLUR antagonists

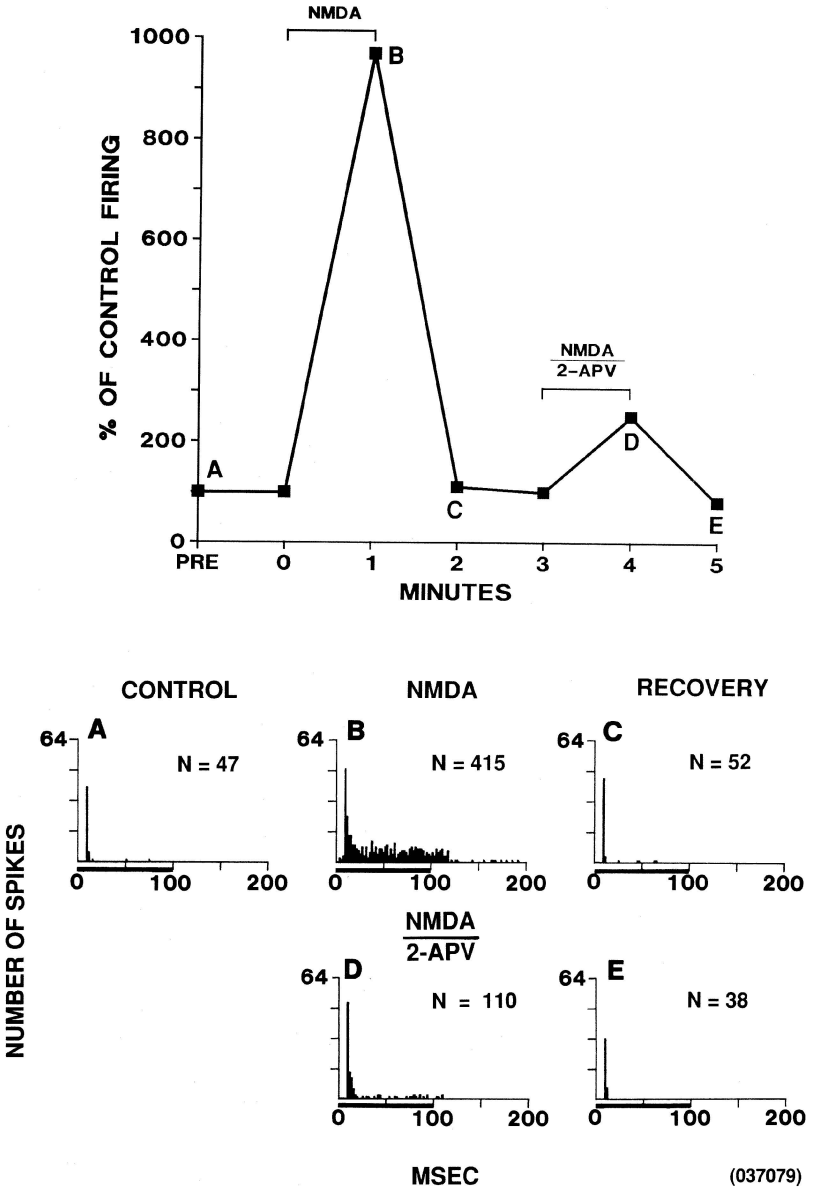

Figure 21.4. The effects of NMDA and the NMDA receptor antagonist, 2-APV, and their interactive effects on the responses of an IC neuron to acoustic stimuli at CF. The *top graph* is the time course, and the bottom PSTHs show the effects on the cell's response pattern. **(A)** The control response. The line below **(A–E)** is stimulus duration. **(B)** The excitatory effect of NMDA (30 nA). **(C)** Recovery from drug effects. **(D)** The same dose of NMDA was repeated with simultaneous application of APV (80 nA), reducing the NMDA effect. *N* is the total number of action potentials in the PSTH. Stimulus parameters: 100-ms tone burst; 30 dB SPL contralateral; 36.0 kHz; 0 dB SPL threshold. (From Faingold et al. 1989, with permission from Elsevier.)

are needed to block GLU-mediated excitation in IC dorsal cortex (ICd) neuron (in vitro) from AGS-susceptible animals (Faingold et al. 2000). (See Fig. 21.5.)

Systemic or focal microinjection into IC of agents that reduce GLUR activation will block AGS in several types of AGS-susceptible rats (Faingold et al. 1988, 1991a,b, 1992, 1993b; Patrick and Faingold 1989; Riaz and Faingold 1994; Higashiyama et al. 1998; Raisinghani and Faingold 2003). Focal microinjection of agents acting on metabotropic GLURs also blocks AGS (Chapman et al. 2001; Yip et al. 2001).

Focal IC microinjection of *N*-methyl-D-aspartate (NMDA) induces temporary susceptibility to AGS in normal rats (Millan et al. 1986; Faingold et al. 1989c; Browning et al. 1991). AGS susceptibility in normal rats is induced on termination of continuous focal perfusion into IC for 1 week with a NMDA receptor antagonist, presumably due to upregulation of NMDA receptors (Yang et al. 2001).

6. Conclusions

IC neurons and the ICc play a critical role in AGS initiation. Chronic susceptibility to AGS is a common rodent neurological disorder that can be genetically mediated (GEPRs) or induced by a hearing deficit produced during the critical period. Transient AGS susceptibility is readily induced by withdrawal from ethanol and other depressant drugs. Most forms of chronic AGS susceptibility are associated with early-onset hearing deficits. Several neurotransmitter abnormalities that occur in the IC involve GABA and GLU. GABA, acting largely at $GABA_A$Rs, plays a major role in various types of normal acoustically evoked inhibition in IC. The effectiveness of these forms of $GABA_A$R-mediated inhibition is reduced in AGS, which can be blocked by enhancing the action of GABA. AGS susceptibility in normal rodents is also induced by decreases in GABA receptor function in IC, and AGS susceptibility in normal rats can be induced by reducing the action of GABA. GLU likely mediates normal IC excitatory neurotransmission, and evidence for increased GLU availability is seen in AGS. AGS susceptibility can be temporarily blocked by GLUR antagonists, while it can be induced in normal animals by enhancing GLUR activation in IC. AGS susceptibility also follows GLUR antagonist withdrawal after continuous IC perfusion. These changes in amino acid neurotransmitters in the IC are proposed to occur either as compensatory mechanisms for hearing loss in many AGS forms, or are induced transiently in adulthood, by treatments such as withdrawal after prolonged treatment with agents such as ethanol.

7. Future Directions

Many questions about the role of the IC in AGS remain unanswered. The genetic defect responsible for AGS susceptibility in GEPRs is unknown. In the two forms of mouse AGS in which the abnormal gene has been identified, the mo-

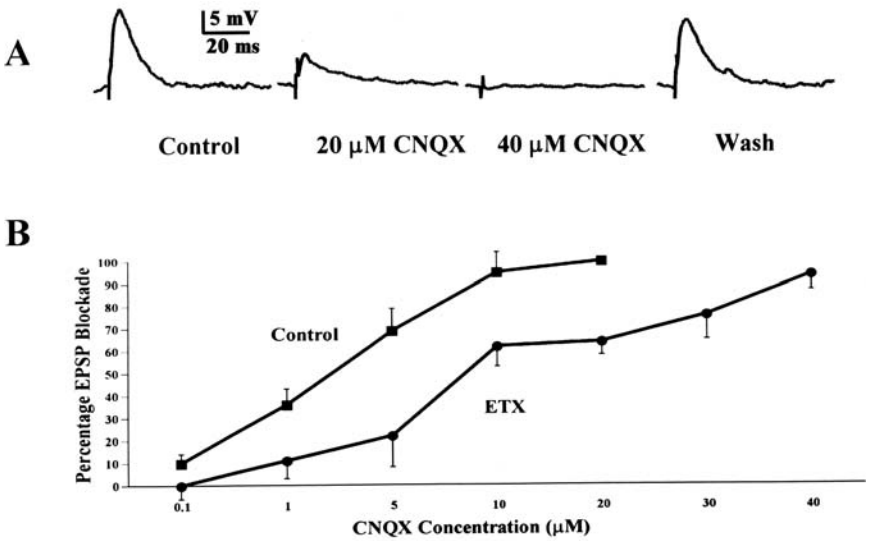

Figure 21.5. **(A)** Inhibition in vitro of ICd neurons' excitatory postsynaptic potentials (EPSPs) by bath application of the non-NMDA excitatory amino acid receptor antagonist, CNQX. CNQX blocks the EPSP during ethanol withdrawal (ETX) in the presence of a competitive NMDA receptor antagonist, AP5 (10 to 70 μ*M*), and bicuculline (0.1 to 30 μ*M*). Membrane potential was held at –90 mV. **(B)** Concentration-response (area, mV × ms) curves for CNQX. The curves for ETX vs. control were significantly different. All data are means ± SEM. (From Faingold et al. 2000, with permission from Elsevier.)

lecular cascade by which the gene abnormality leads to AGS susceptibility is unknown. Understanding how the genetic defects lead to the abnormalities in neurotransmission seen in AGS remains a challenge. Finally, development of experimental approaches to reverse the genetic deficit or prevent its development in AGS-susceptible animals is a major future research goal. Results of these investigations may have important therapeutic implications for genetic diseases of the human nervous system.

Abbreviations

AGS	audiogenic seizures
AMPA	α-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AP7	DL-2-amino-7-phosphonoheptanoic acid
2-APV(AP5)	2-amino-5-phosphonovalerate
BIC	bicuculline
CF	characteristic frequency

CNQX	6-cyano-7-nitroquinoxaline-2,3-dione
CONT	microinjection control
EPSPs	excitatory postsynaptic potentials
ETX	ethanol withdrawal
FLUR	flurazepam
GABA	γ-aminobutyric acid
$GABA_AR$	$GABA_A$ receptor subtype
GEPRs	genetically epilepsy-prone rats
GEPR-3s	moderate seizure strain of genetically epilepsy-prone rats
GEPR-9s	severe seizure strain of genetically epilepsy-prone rats
GLU	glutamate
GLUR	glutamate receptors
IC	inferior colliculus
ICc	inferior colliculus, central nucleus
ICd	inferior colliculus, dorsal cortex
nA	nanoamperes
NMDA	*N*-methyl-D-aspartate
PSTH	post-stimulus time histogram
SPON	superior paraolivary nucleus

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Chapter 22
The Inferior Colliculus: Past, Present, and Future

John H. Casseday, Christoph E. Schreiner, and Jeffery A. Winer

1. Rationale

From an historical perspective, the last few decades have seen a spectacular increase in our knowledge of the inferior colliculus (IC). The topics of the previous chapters cover the range of neurobiology, thus reflecting the complexity of the issues concerning the IC. However, the wide range makes it virtually impossible to provide a synthesis that does justice to all the chapters. Therefore, we address a few salient themes that, through our view, seem to merit analysis or that are otherwise underrepresented in the text. We hope this idiosyncratic view will be a polemic to encourage new ways of thinking about the auditory midbrain.

2. Historical Overview

Much of the early thought on function of the auditory midbrain (Whitfield 1967; Aitkin 1986) was influenced by Ramón y Cajal's concepts of the mammalian auditory midbrain. He described the principal component of lateral lemniscal ascending fibers as a "reflex bundle terminating in the IC" (Ramón y Cajal 1911). The second and large component consisted of fibers that bifurcated, sending a branch to the IC and another to the thalamus. Fibers continuing to the medial geniculate nucleus, the so-called "central acoustic tract," were considered a major constituent (one third or more) of the entire ascending body (Papez 1929). In short, the ascending auditory pathway to the telencephalon bypassed the IC, and the ascending auditory pathways to the IC served as the auditory input necessary for midbrain reflex functions. Thus, the IC was seen as serving hearing in much the same way as the superior colliculus served vision.

However, by the 1960s a different view began to emerge, one that is relatively close to the current view that the IC is an auditory center that is an obligatory synapse for nearly all ascending input to the medial geniculate nucleus (Whitfield 1967). The evidence came from several early tract tracing studies showing

that nearly all fibers in the lateral lemniscus terminated in the IC (Woollard and Harpman 1940; Barnes et al. 1943; Rasmussen 1946). The "central acoustic tract," as first defined, is a quite minor component of the ascending auditory pathway (Casseday et al. 1989).

A critical step came as retrograde transport methods became available in the 1970s and 1980s (Adams 1979). From these studies an appreciation grew for the extent of convergence at the IC, from both ascending and descending auditory pathways (Aitkin 1986; Irvine 1986; Pollak and Casseday 1989; Casseday et al. 2002). Thus, the IC was construed as the "nexus" (Aitkin 1986) or "shunting-yard" (Ehret 1997) of the auditory pathway.

The same neuronal tracing methods called attention to the nonauditory inputs to the IC, some of which had been known from older degeneration techniques, such as the somatosensory inputs to the IC (RoBards et al. 1976), and some of which were newly identified such as projections from the substantia nigra (Olazábal and Moore 1989) and projections from the amygdala (Marsh et al. 2002).

Physiological techniques to block inhibitory transmitters revealed a crucial functional aspect of the convergence, namely, that most, if not all, IC neurons receive auditory evoked inhibition as well as excitation (see Chapters 9 to 13). Further, the timing of the excitatory and inhibitory inputs can be offset from one another, providing a possible mechanism for processing complex temporal information.

Thus, the IC truly merits a descriptive term such as Aitkin's (1986) "nexus" or "hub" for its broad patterns of afferent convergence and for the active reshaping of sound encoding (Casseday et al. 2002). Although the IC is clearly the main route to auditory thalamus and cortex, it also serves motor functions that have to be taken into account when considering its manifold roles (Casseday et al. 1976). Ramón y Cajal's idea of the IC as an auditory reflex pathway was simply incomplete in the important sense that the IC both transmits information to and receives information from "higher" auditory centers. Furthermore, the IC has functions that cannot be viewed as "reflex" in the classic sense, yet must certainly be construed as motor, in that it serves as a route to enable motor action via telencephalic auditory centers or via deep superior colliculus or pontine gray/cerebellar circuits. Naturally, the widespread intrinsic operations of the IC both at a cellular and a local circuit level make their own contributions in sculpting the many functions of this critical hub. These operations are just beginning to be understood (see Chapters 2 to 5).

Pioneering physiological studies (Thurlow et al. 1951) were followed by experiments revealing narrow-band, level-tolerant frequency tuning and inhibitory sidebands in IC cells (Katsuki et al. 1958; Erulkar 1959). Studies by Rose and Hind and colleagues were crucial in establishing tonotopy, binaural response types, and temporal response patterns (Rose et al. 1963). The first intracellular IC recordings provided direct evidence of long-lasting temporal sequences of excitation and inhibition in response to sound (Nelson and Erulkar 1963) showing that ". . . changes in membrane potential are specific to particular tonal frequencies and may outlast the duration of the tone. They serve to set the levels

of excitability of the neurons and to regulate the patterns of firing in response to long-lasting tonal stimuli" (Nelson and Erulkar 1963, p. 921). These observations led to interest in how IC neurons process time varying sounds (Nelson et al. 1966). Likewise, the IC became an early focus of neurophysiological studies of the mechanisms for processing temporal signals by echolocating bats (Grinnell 1963; Suga 1964).

Behavioral-ablation studies drew attention to subcortical mediation of auditory discrimination abilities. Cats with bilateral ablation of the entire auditory cortex had surprisingly little or no difficulty relearning frequency discrimination (Neff et al. 1975). For example, even after bilateral transection of the brachium of the inferior colliculus (BIC) cats could still relearn a frequency discrimination. These early anatomical, physiological, and behavioral studies already revealed the essence of the major themes that define our current understanding of IC structure and function as summarized in this volume.

3. Comparative Neurobiology of the Auditory Midbrain

Most studies of the auditory midbrain are concentrated in a few mammals, the rat, cat, bat, and on one bird, the barn owl. There are many investigations on the amphibian auditory midbrain, virtually all on anuran amphibians (Wilczynski 1988). There is a small but growing literature on fish, but the reptilian auditory midbrain has received far less attention (see Chapter 16). Moreover, the species examined are often chosen for their specializations, for example, the barn owl for sound localization and the bat for temporal processing (see Chapter 17). How can we make meaningful comparisons based on so limited a sample? If the auditory midbrain were a stereotyped structure with a common architectonic, neuroanatomical, neurochemical, neuroethological, neurophysiological, and ontogenetic arrangement, insularity with respect to a few aquatic, terrestrial, and aerial species would be a defensible position.

Nevertheless, the preceding chapters have revealed some features that appear to be common among vertebrates so far examined and might embody general principles of organization that appeared early in evolution (Grothe et al. 2004). One is the organization into a core that is the primary target of ascending auditory pathways and surrounding areas that receive other inputs, some of which may be descending and not all of which are auditory. Another is the presence of multiple ascending auditory pathways, some limbs of which ascend directly while others ascend via a synapse, providing different synaptic delays at their target in the IC (Casseday and Covey 1996). In fish, the pathways are few; in birds and mammals they are many; however, all vertebrates so far examined seem to have direct and indirect pathways. In this context, it is a important to note the recent discovery that in the auditory midbrain of fish, specializations emerge for processing complex temporal features of sound, as is the case in

amphibians and mammals (see Chapter 16) and probably also in songbirds (Woolley and Casseday 2004). A third common feature is the close connection of the auditory midbrain with motor systems, especially those concerned with vocalization. Many of these points have been noted in prior work (Wilczynski 1988), and supporting evidence has grown considerably since then. The issue of how the auditory midbrain participates in processing and influencing species-specific vocalizations is an important venue for further comparative studies in all vertebrates (see Chapter 14).

4. The Mammalian Auditory Midbrain

Even considering only the mammalian IC in more detail, there are many unanswered questions. One might expect to see gross structural differences in the IC of different mammals in view of the enormous comparative differences in the cochlear nucleus (Moore 1980), trapezoid body (Richter et al. 1983), lateral lemniscal nuclei (Covey and Casseday 1995; Merchán et al. 1997), medial geniculate body (MGB) (Morest and Winer 1986), and auditory cortex (Winer 1992). However, at a macroscopic level, the IC in different species looks remarkably similar (Fig. 22.1): each species has a substantial central nucleus in which disc-shaped neurons form conspicuous fibrodendritic laminae (Fig. 22.2) much like those in the cat (Oliver and Morest 1984) and human (Geniec and Morest 1971). In addition, in each species the IC has an external cortex (Fig. 22.1A: bat; 22.1B: owl; 22.1C: rat; 22.1E: macaque), lateral nucleus (Fig. 22.1D: cat), or lateral zone (Fig. 22.1F: human).

Are these subdivisions homologous? With respect to architectonic, neuroanatomical, neurochemical, neuroethological, neurophysiological, and ontogenetic frames of reference—all pertinent to establishing such correspondences (Butler and Hodos 1996)—the evidence is too fragmentary to permit a conclusion. The cytoarchitecture of the lateral rind of the inferior colliculus region—denominated variously as external cortex/lateral nucleus/lateral zone/pericentral nucleus—has been described in the rat (Faye-Lund and Osen 1985). Its neurons have been classified to some extent (Malmierca 1991); certain neurochemical aspects have received attention (Chernock et al. 2004); and a limited amount of physiology (Syka and Popelář 1984; Smith 1992) and a developmental profile have been described (Altman and Bayer 1981). Many of the features in these studies suggest that it differs from the central nucleus, although we do not yet have a sufficiently large or secure database to propose that any given structure is homologous across species.

Three conclusions follow from this analysis: (1) It might be possible to assemble the elements for such a list of definitive criteria for the rat, but the task of looking at many species including bats, owls, cats, primates, and human would be daunting, and inspection of the contemporary literature shows few signs of providing the essential data. (2) Even if such a survey were available, there is little evidence to establish functional correspondences between species,

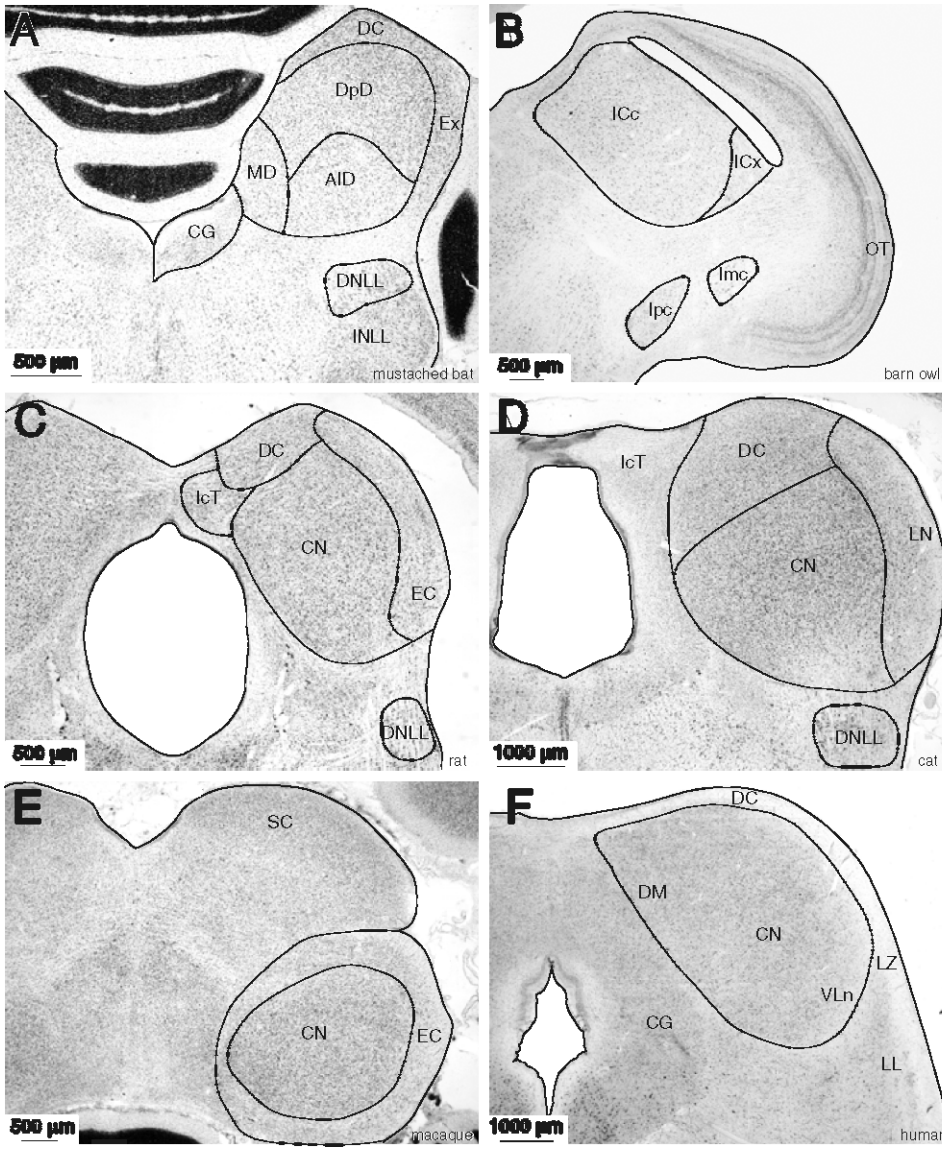

Figure 22.1. Cytoarchitectonic views of inferior colliculus organization in six common experimental species in Nissl preparations. Protocol: 30 µm thick celloidin-embedded or frozen sections counterstained with cresyl violet acetate. **(A)** In the mustached bat, *Pteronotus p. parnellii*, the dorsoposterior division (DpD) is devoted to the approximately 61-kHz second harmonic, and the external cortex (Ex) is a slender rind (Zook et al. 1985). **(B)** The barn owl (*Tyto alba*) central nucleus (ICc) is massive, but has no apparent laminar organization (Knudsen 1983; Takahashi and Konishi 1988). **(C)** Rat external cortex *(EC)* and central nucleus both expand as a consequence of reduction of the dorsal cortex *(DC)* (Faye-Lund and Osen 1985). **(D)** The cat central nucleus *(CN)* shows regional architectonic variation and the dorsal cortex *(DC)* is massive (Oliver 1984; Winer et al. 1998). **(E)** The rhesus monkey (*Macaca mulatta*) has a large central nucleus *(CN)*. (J.A. Winer and D.T. Larue, unpublished observations). **(F)** The human inferior colliculus has a fiber rich lateral zone *(LZ)* and a reduced dorsal cortex *(DC)* relative to the cat *(D)*.

for example, whether the same types of neurons subserve central nucleus binaural processing. (3) No synoptic picture exists for serial, parallel, hierarchical, and multimodal (Aitkin et al. 1994) processing for external cortex/lateral nucleus/lateral zone/pericentral nucleus, and that would distinguish these structures from the central nucleus. The rigorous statement of the comparative position is that all possible comparisons would be required to establish homologies; a more liberal interpretation is that a subset of criteria would suffice (Morest and Winer 1986), much as cladistic studies rest on critical evidence (Eisenberg 1981). Resolution of these questions will require more knowledge about the canonical IC circuits as a prelude to specifying the nature of species differences.

5. The Central Nucleus: *Primus Inter Pares*

Much of the text in this volume is devoted to the central nucleus, which is a defensible emphasis in view of its primacy in hearing and its apparent homology among vertebrates (Grothe et al. 2004). Ultimately, however, the dorsal cortex, lateral nucleus, caudal cortex, rostral pole, and intercollicular tegmentum must each receive attention commensurate with their importance, as an example will show.

Physiological experiments suggest that the auditory cortex can modulate frequency-specific plasticity in the central nucleus of the inferior colliculus in bats (Jen et al. 1998; Suga et al. 2000) and mice (Yan and Ehret 2001). However, the present route for this effect in the central nucleus is unknown, and it may be indirect, requiring the participation of the external cortex/lateral nucleus (but see Chapter 5). The reason is that the most sensitive anterograde tract tracing techniques show only sparse input to the central nucleus in the cat after large cortical tracer deposits, although there are massive projections to the external cortex from many fields in the cat (Winer et al. 1998). In rats there is a difference of opinion in regard to the density of auditory cortex input to the central nucleus, with either a substantial (Saldaña et al. 1996) or a far smaller input (Herbert et al. 1991) comparable to that reported in the cat. A related issue is how the central nucleus is defined. In any case, the circuitry for expressing central feedback either depends on the external cortex/lateral nucleus because abundant intrinsic connections link it to the central nucleus (Saldaña and Merchán 1992), or there may be species differences in cortical input. In principle, the other inferior colliculus subdivisions are no less important with regard to their functional affiliations: for example, the dorsal cortex is implicated in attention (Jane et al. 1965), the intercollicular tegmentum in commissural and multimodal roles (RoBards et al. 1976), the lateral nucleus in the processing of complex sounds (Aitkin et al. 1994), and the rostral pole has significant projections to the superior colliculus (Harting and Van Lieshout 2000), presumably for spatial orientation.

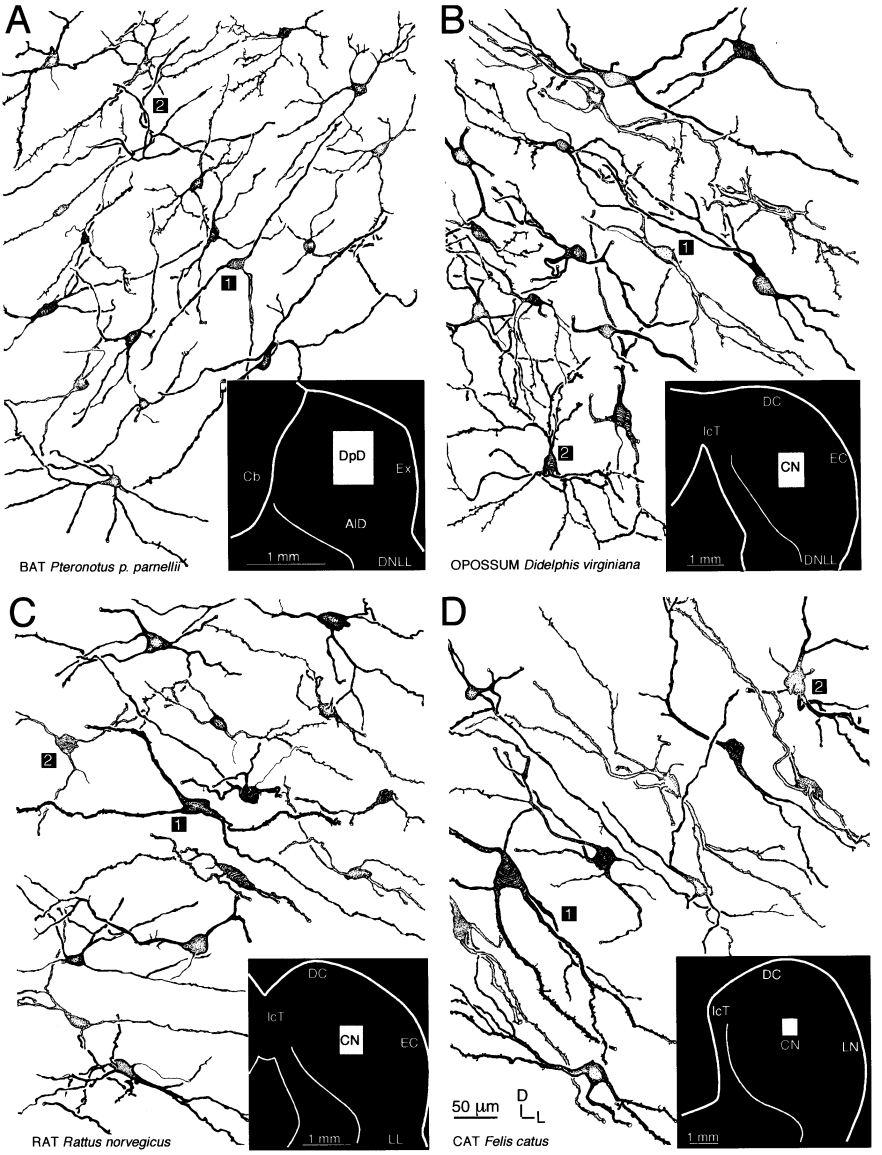

Figure 22.2. The constraints inherent in the Nissl method as an architectonic tool (cf. Fig. 22.1) are readily apparent in Golgi preparations from the central nucleus in four species. Protocol: Golgi-Cox preparations, 140 µm thick celloidin-embedded sections. Planapochromat, numerical aperture 0.65, ×500. **(A)** In the mustached bat (see Fig. 22.1A) a laminar organization is readily apparent in DpD (cf. *black inset*) that is masked in Nissl preparations, including disc-shaped cells *(1)* as well as neurons with dendrites orthogonal to the laminar axis *(2)*. Such neurons are common in the opossum **(B)**, rat **(C)**, and cat **(D)** inferior colliculus. **(B)** In the opossum, many disc-shaped cells have dendritic fields more constrained and flattened than those in *Pteronotus*. **(C)** In the rat there is an especially wide range of sizes and shapes in central nucleus cells that is matched by the cat **(D)**. **(D)** Some cat disc-shaped cells have spiny dendrites *(1)*.

6. The Question of Inhibitory Interneurons in the Inferior Colliculus

This question requires first a definition of interneurons. The classic view assigns neurons to either type I (long axon) or type II (short axon) categories (Golgi 1873), a scheme that applies to all but a few cells, for example, axonless amacrine cells (Masland 2001). Classic type II cells (Ramón y Cajal 1911) have these features: a short, often unmyelinated, axon (Winer and Morest 1983) whose plexus and main sphere of influence is limited to perhaps 1 or 2 mm (Kisvárday et al. 1993); smooth dendrites with a few long, slender, and pedunculated appendages (Winer and Larue 1988); a soma about 10 μm in diameter (Winer 1986); and a primary transmitter of γ-aminobutyric acid (GABA) or glycine (Todd 1996).

With regard to the IC, this dichotomous arrangement encounters several difficulties. Thus, some 20% of central nucleus neurons are GABAergic, and these have subtypes that include both the smallest and the largest neurons (Oliver et al. 1994). Moreover, about the same proportion of cells that are GABAergic also project to the MGB (Winer et al. 1996), and intracellular labeling demonstrates that most neurons injected have a local axonal plexus, reminiscent of type II cells, as well as presumptive tectofugal long axonal projections, which is not characteristic of interneurons (Oliver et al. 1991). Thus, the central nucleus either has no classic type II cells, unlike the cochlear nucleus (Adams and Mugnaini 1987), MGB (Huang et al. 1999), and auditory cortex (Prieto et al. 1994), or it more closely resembles the superior olivary complex and lateral lemniscal nuclei in having GABAergic neurons with long projections (Saint Marie et al. 1989). An IC with no classic interneurons necessarily has a different functional organization than one with GABAergic neurons that have both local and remote projections. For example, the synaptic glomeruli that are a cardinal feature of MGB intrinsic organization and in which Golgi type II cells have an important role (Morest 1975) do not seem to occur in the IC (Rockel and Jones 1973).

7. Context Dependency of Inferior Colliculus Processing

Audition must capture events in time, auditory objects that are fleeting disturbances in air pressure, and reconstruct the nature of the sound source and the information it contains. This task is complicated by the fact that a given auditory object, such as a phoneme, may be embedded in different acoustical and informational conditions, or context, that must be considered when performing the analysis.

The context of an acoustic signal activating neurons in the IC is determined by the intensity distribution across the spectral profile of the signal at every

instant in time, by the time course of intensity changes across the spectrum, including dynamic changes in spectral components, and by the phase relationships and their changes among the spectral components, all of which are influenced by the location of the sound source in the auditory space. That is, under natural hearing conditions, sounds have a dynamic stimulation effect on the IC. Because of intrinsic mechanisms of adaptation and synaptic mechanisms of habituation, the instantaneous response of an IC neuron reflects not only the sound composition at the related instant in time but also the sound history, that is, the recent state of its own activity and that of neurons that provide input to it. For example, IC neurons may respond to bursts of a tone differently depending on whether the amplitude is variable or constant (Neuert et al. 2001), or whether a certain tone is reached by a frequency sweep or a frequency step (Malone and Semple 2001). Further, direction and speed of a frequency sweep may affect the response to a following tone (Suga 1969; Fuzessery 1994; Hage and Ehret 2003). Finally, transitions between sounds with different amplitude histograms (or contrasts) can elicit release from adaptation, thus substantially increasing the salience in the representation of a newly introduced amplitude statistics (Kvale and Schreiner 2004).

Accordingly, time-critical statistical properties of the acoustic environment can have a marked influence on the stimulus/object properties and the dynamics of neural responses. Consequences of these influences emerge when characterizing receptive fields with different stimulus statistics (Escabí and Schreiner 2002) and following a context change (Kvale and Schreiner 2004).

The ability of IC neurons to adapt their performance to the local statistics of the acoustic environment provides several advantages for information processing, including gain control, and enhanced detection, discrimination, and classification abilities. This context sensitivity may hold the key for understanding the transition from a peripheral analysis based on sound properties to a central one oriented to auditory objects.

8. Streams of Function and Functions of Streams

The inferior colliculus is located at a crucial transition in the flow of auditory information processing. Peripheral to the IC, incoming information can be viewed as being segregated into several processing streams that either emphasize specific stimulus aspects, including frequency composition, phase-locking, onsets and other amplitude variations, or compute specific stimulus aspects such as those related to the comparison of inputs to the two ears or the frequency filtering at the pinnae. Thus, the auditory stimulus is decomposed and undergoes parallel analysis. These multiple processing streams can be considered stimulus-based, and the description of the neuronal function is well served by reference to elemental sound attributes.

Rostral to the IC, the main principle of processing appears to be increasingly object-, task-, and perhaps action-related. Examples of identifiable task-specific central processing streams are reflected in the Doppler-shift and echo-delay maps in bats (O'Neill 1995), and the proposed "what" and "where" pathways in primates (Romanski et al. 1999). Other necessary central processing tasks include representational robustness in background noise, object equivalencies across sound source (speaker) variability, and enabling categorical signal classification. Even at the midbrain level, specific stimulus evaluations regarding urgent action-related tasks must be established or at least prepared (Casseday and Covey 1996). Examples include reflexive and other motor behaviors such as pinna movements, acoustic startle reflexes, responses to aversive stimuli, and vocalization (see Chapter 7). Each of these ascending (see Chapters 3 and 4) and descending (see Chapters 6 and 8) functional streams likely relies on specific superpositions of convergent feedforward and feedback information that shape and refine the task-specific processing. Potential segregations of different functional streams may be expressed in the many subdivisions in the midbrain and other nuclei (see Chapter 1), or in the different synaptic domains in the central nucleus of the inferior colliculus (see Chapter 2). It remains for future work to identify the origin, termination, and function of different streams, to establish whether incoming and outgoing projections are sufficiently compartmentalized that they can be unequivocally related to a specific functional stream, and, finally, whether is it even useful to refer to specific functional streams if the task-oriented refinement requires cooperation of several convergent projections at each node of the auditory pathway.

Abbreviations

AlD	anterolateral division of the inferior colliculus
Cb	cerebellum
CG	central gray
DC	dorsal cortex of the inferior colliculus
DM	dorsomedial part of central nucleus
DNLL	dorsal nucleus of lateral lemniscus
DpD	dorsoposterior division of the inferior colliculus
Ex	external nucleus of the inferior colliculus
GABA	γ-aminobutyric acid
ICc	central nucleus of the inferior colliculus
IcT	intercollicular tegmentum
ICx	external nucleus of the inferior colliculus
Imc	nucleus isthmi, *pars magnocellularis*
Ipc	nucleus isthmi, *pars parvicellularis*
LL	lateral lemniscus
LN	lateral nucleus
LZ	lateral zone

MD	medial dorsal division of the inferior colliculus
MGB	medial geniculate body
SC	superior colliculus
Vln	ventrolateral nucleus

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