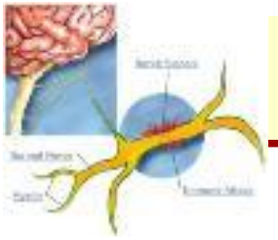
Odesa National Medical University

Department of Pharmacology and Pharmacognosy

PHARMACOLOGY OF DRUGS INFLUENCING ON EFFERENT INNERVATION.

AGENTS INFLUENCING ON CHOLINERGIC RECEPTORS

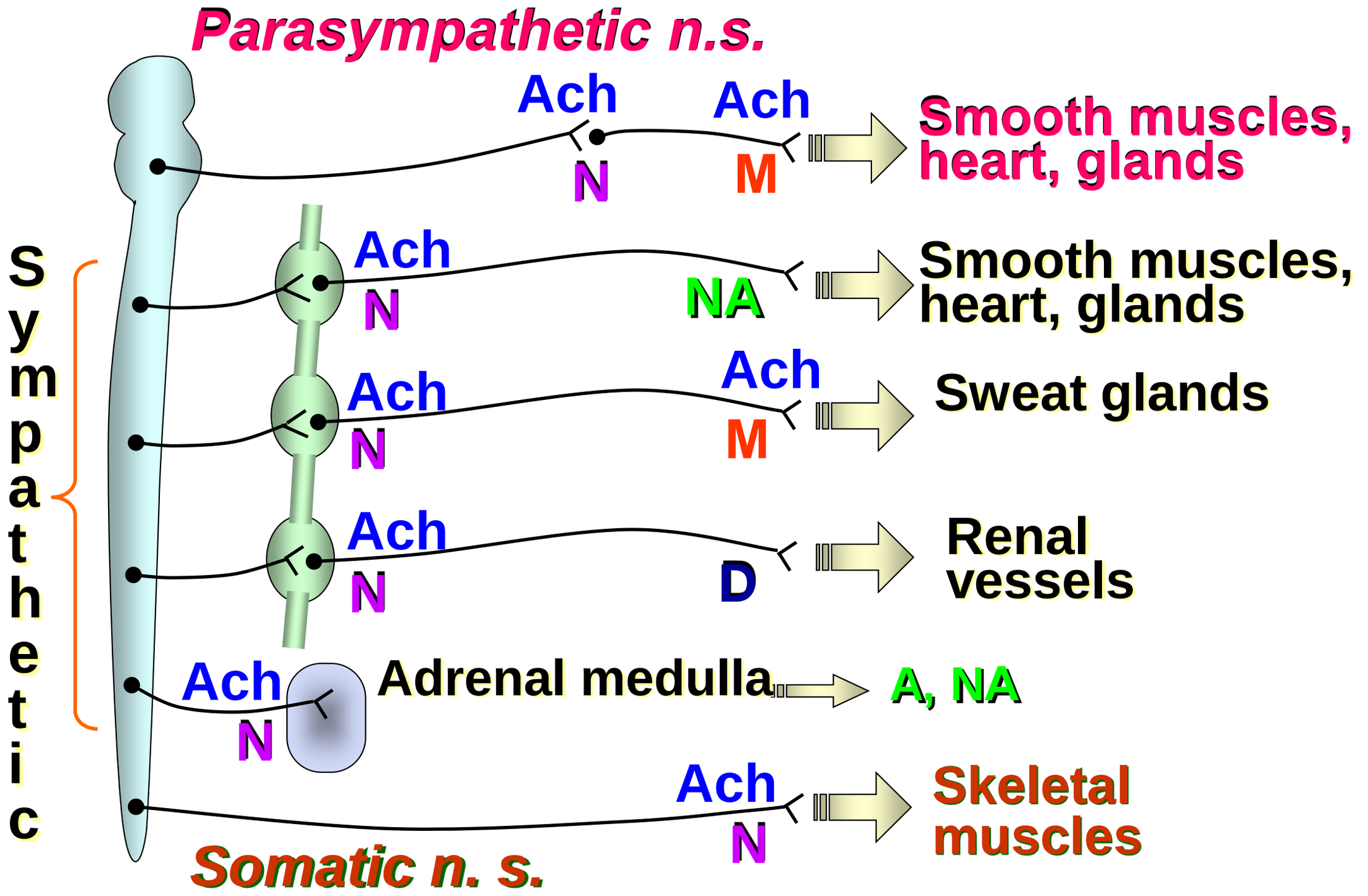
(CHOLINOMIMETICS, CHOLINOBLOCKERS)



NERVOUS SYSTEM

- PERIPHERAL
- CENTRAL
- EFFERENT
- AFFERENT
- VEGETATIVE
- SOMATIC
- SYMPATHETIC
- PARASYMPATHETIC

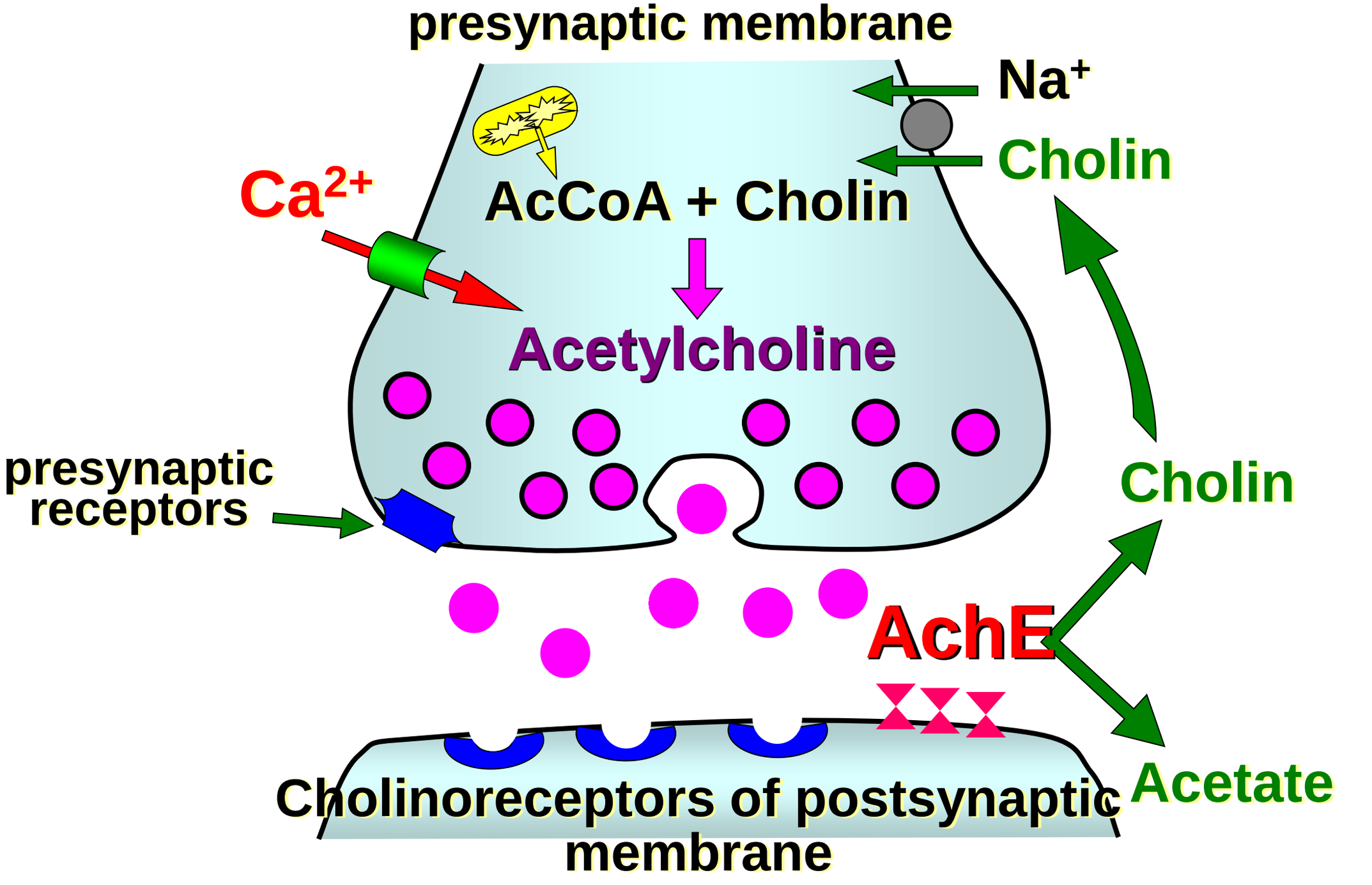
SCHEME ON NEURONAL TRANSMISSION



SITES OF N-CHOLINORECEPTORS

- Central nervous system
- Vegetative ganglia
- Adrenal medulla
- Sinocarotid zone
- Skeletal muscles

CHOLINERGIC SYNAPSIS

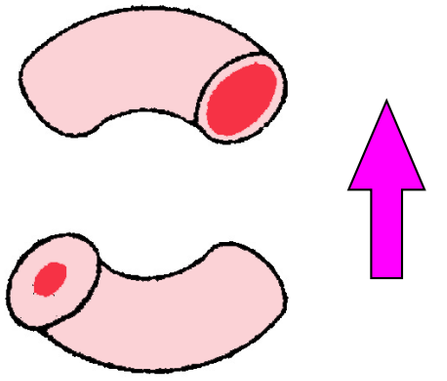


CLASSIFICATION OF CHOLINOMIMETICS

M-	N-	M-, N-	
		direct action	indirect (anticholinesterases)
Pilocarpine Aceclidine	 Nico-rette Cytiton	Acetyl-choline Carbo-choline	*reversible:* Neostigmine Physostigmine Galantamine Pyridostigmine *irreversible:* POC, insecticides

ACTIONS OF M-CHOLINOMIMETICS

heart «–» ino, «–» chrono, «–» dromotropic



blood vessels dilation

bronchi spasm

GIT peristaltics – increasing, sphincters – relaxation, secretion - increasing

urinary bladder detrusor – increasing, sphincters – relaxation

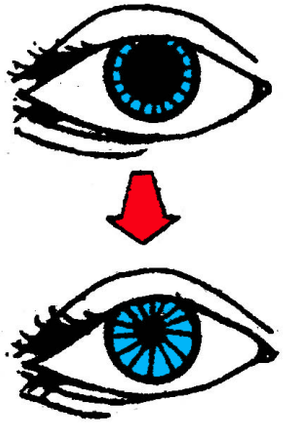
ACTIONS OF M-CHOLINOMIMETICS

glands

(sweat, lachrymal, salivary, bronchial) **increasing secretion;**

eye

miosis,
spasm of accommodation,
increasing of intraoccular pressure



CNS

hyperkinesis

USES OF M-CHOLINOMIMETICS

indications:

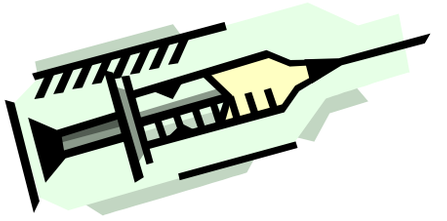
- Glaucoma *(pilocarpine)*
- Atony, paralytic obstruction of intestine *(aceclidine)*
- Atony of urinary bladder *(aceclidine)*

contra-indications:

- Bronchial asthma
- Peptic ulcer of stomach
- Mechanic obstruction of intestine
- Bradyarrhythmia
- Epilepsy

ANTICHOLINESTERASES

Neostigmine, physostigmine, galantamine, pyridostigmine



ACTIONS

- M-cholinomimetic effects
+
- Neuro-muscular transmission – increasing

INDICATIONS

- Glaucoma *(physostigmine)*
- Atony of urinary bladder, atony and paralytic obstruction of intestine *(neostigmine)*
- Myasthenia, paralysis, paresis, polyomyelitis, after-trauma recovery period *(galantamine, neostigmine)*
- Decurarization *(galantamine, neostigmine)*

ACUTE POISONING BY MUSCARINE

Symptoms:

- CNS excitation (hallucination)
- bradycardia, atrio-ventricular blockage
- bronchospasm
- vomiting, diarrhea
- sweating, hypersalivation
- miosis, spasm of accommodation, lacrimation

First aid:

I.V. administration of antidote – ATROPINE (10-15 mg !)

ACUTE POISONIG BY POC

Symptoms:

- See muscarine poisoning +
- Tonic-clonis convulsions

First aid:

- ✓ cholinesterase re-activators – aloxim, dipyroxim, isonitrosin
- ✓ administration of atropine

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CHOLINERGIC ANTAGONISTS

M-CHOLINOBLOCKERS

Classification	Centrally acting agents	Agents of mixed action	Peripherally acting agents
Agents	Amizyle, cyclodole	Atropine, scopolamine, beladonna extract	Methacine, pirenzepine, iptatropium bromide

LOCALIZATION OF CHOLINOBLOCKERS ACTION

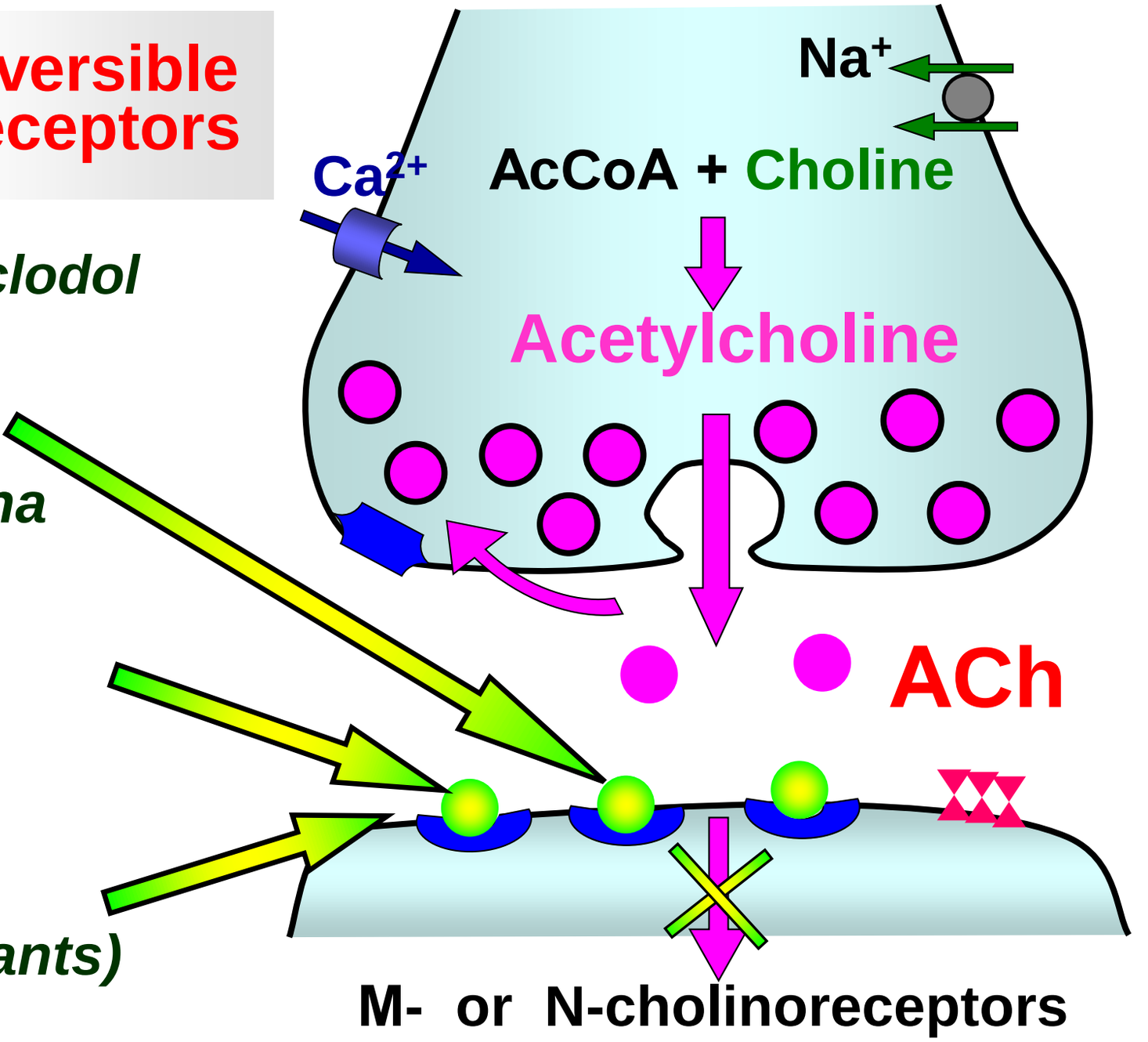
Direct action – reversible blockers of the receptors

M-, H- (central) ***(cyclodol (trihexyphenidyl))***

M-
(atropine, belladonna preparations , scopolamine etc

M_1-
(pirenzepine)

H- ***(ganglionic blockers, myorelaxants)***



PHARMACODYNAMICS OF M-CHOLINOBLOCKERS

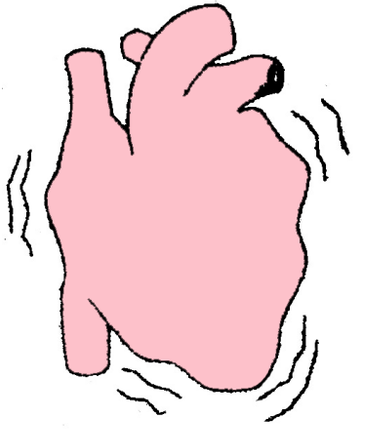
together with depression of parasympathetic tonus, raising of sympathetic tonus

CNS ***(tertiary amines)***

In therapeutic doses – sedative, in toxic – excitation, hallucination, aggitation, convulsions;
↓ tremor, vestibular disturbances

heart **(in moderate doses)**

«+» chronotropic (especially in young people), improvement of AV-conductivity;
↑ oxygen demand of myocardium



blood vessels **in toxic doses– vasodilation**

PHARMACODYNAMICS OF M-CHOLINOBLOCKERS

GIT

peristaltic – decreasing,
sphincters – contraction,
secretion – decreasing

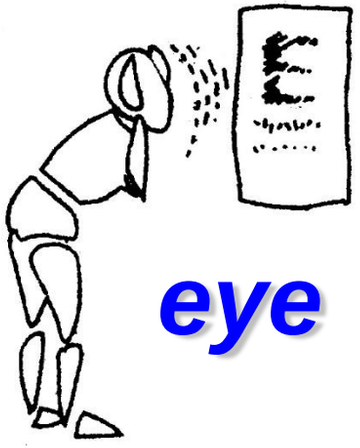
urinary bladder

detrusor – relaxation,
sphincters – contraction

bronchi

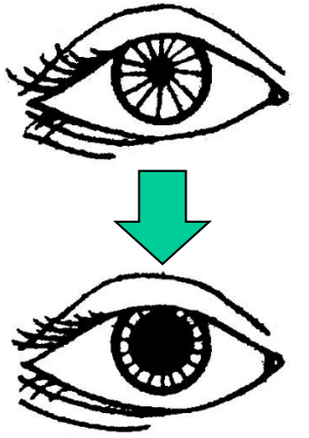
dilation, decreasing of secretion

PHARMACODYNAMICS OF M-CHOLINOBLOCKERS



eye

mydriasis,
paralysis of accommodation *(cycloplegia, far sightness)*, ↑ intraocular pressure, photophobia, ↓ secretion



atropine (upto 12 days) > scopolamine (3-5 days) > homatropine (15-20 hrs) > platyphyllin (5-6 hrs, without cycloplegia) > tropicamid (2-6 hs)

glands

(sweat, lachrymal, salivary, gastrointestinal, bronchial) **↓ secretion, ↑ body temperature (small children !)**

Also possess weak local anesthetic and analgesic actions

USES OF M-CHOLINOBLOCKERS

- **Preanesthetic medication *(atropine)***
- **Vagus hyperactivity at heart**
- **Bronchial asthma, chronic obstructive pulmonary disease *(ipratropium, tioptropim)***
- **In opthalmology with diagnostic *(platyphyllin, homatropine)* and treatment purpose *(atropine)***
- **Peptic ulcer of stomach, hyperacidic gastritis *(pirenzepine*)**
- **Spasm of smooth muscles *(platyphyllin, metacin*)**
- **Diarrhea *(belladonna agents, atropine*)**
- **Motion sickness *(agents, containing scopolamine)***
- **Parkinson disease *(central M-cholinoblockers - cyclodol*)**
- **Poisoning by muscarine, anticholinesterases *(atropine)***

M-CHOLINOBLOCKERS

Actions

Reduce tonus of smooth muscles of internal organs and inhibit secretion of exocrine glands; cause mydriasis and cycloplegia; increase intraocular pressure, cause tachycardia and central cholinolytic action

Therapeutic uses

Bronchial asthma, spasm of smooth muscles, stomach and duodenum ulcer, premedication, cardiac arrest, diagnostic and treatment of ocular diseases, motion sickness, Parkinson's disease, vomiting, nausea

Adverse effects

Dryness of mouth, tachycardia, constipation, attack of glaucoma

ACUTE POISONING BY ATROPINE

Symptoms:

- adults – 100 mg, children – 10 mg (2-3 belladonna berries)
- CNS excitation (hallucination, delirium, agitation), followed by depression
- tachycardia
- mydriasis
- dry, warm and red skin and mucosa
- hyperthermia (especially children < 2 years). Dose of atropine 2 mg can be lethal !

First aid:

- ✓ symptomatic
- ✓ Intravenous physostigmine (1-4 mg for adults, 0,5-1 mg for children!)

GANGLIONIC BLOCKERS

- ✓ short acting (15-20 min) – hygronium, arphonad
- ✓ intermediate acting (1-6 hrs) – benzohexonium, pentamine, pachycarpin
- ✓ long acting (6-12 hrs) – pirilen

PHARMACOKINETICS

Absorption: quaternary amines (benzohexonium, pentamine, hygronium) badly absorbed in GIT ⇒ I.V., I.M. administration; tertiary amines (pirilen, pachycarpin) well ⇒ + oral way

Distribution: tertiary well cross BBB ⇒ central effects (psychical disturbances, tremor etc); quaternary amines don't cross BBB

Excretion: mainly, through kidneys

GANGLIONIC BLOCKERS

PHARMACODYNAMICS

block of N-cholinoreceptors of vegetative ganglia, so-called "pharmacological denervation"

blood vessels: **sharp hypotension, especially up-right (orthostatic collapse !)** ***because of :***

- **depression of venous tonic innervations ⇒ dilation of veins ⇒** decreasing of cardiac preload
- **depression of arterial innervations ⇒ dilation of arteries ⇒ ↓** BP
- **Depression of central cardiac stimulation ⇒ ↓** cardiac output ⇒ **unloading of left ventriculus**

GANGLIONIC BLOCKERS

PHARMACODYNAMICS

heart: ↓ contractility, moderate tachycardia

GIT: peristaltics – ↓, sphincters – contraction, secretion of gastric and intestinal glands – ↓

urinary and reproductive: urine retention, ↓ erection

uterus: stimulation of contractive activity (pachycarpin)

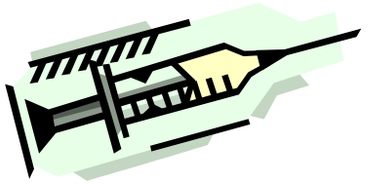
eye: mydriasis, paralysis of accommodation (cycloplegia, far sightness), ↑ intraocular pressure

CNS: tertiary – sedation, tremor, psychical disturbances

Практически все эти эффекты не нашли клинического применения (одновременные неконтролируемые нарушения сердечно-сосудистой функции) и рассматриваются как отрицательные !

GANGLIONIC BLOCKERS

THERAPEUTIC USES



- hypertonic crisis
- pulmonary edema
- moment-to-moment (artificial) hypotension during surgery
- delivery (pachycarpin)

OVERDOSING

- acute hypotension
- tachycardia
- unconsciousness
- dry warm skin

MYORELAXANTS (NEURO-MUSCULAR BLOCKERS

- ***Drugs relaxing the skeletal muscles***
  - **Peripheral** (curare-type)
  - **Central** (for treatment of spasticity): tranquilizers (diazepam), baclofen, etc.

Myorelaxants of peripheral action — the drugs relaxing the skeletal muscles due to depression of neuromuscular transmission at the level of postsynaptic membrane of the end plate

Classification

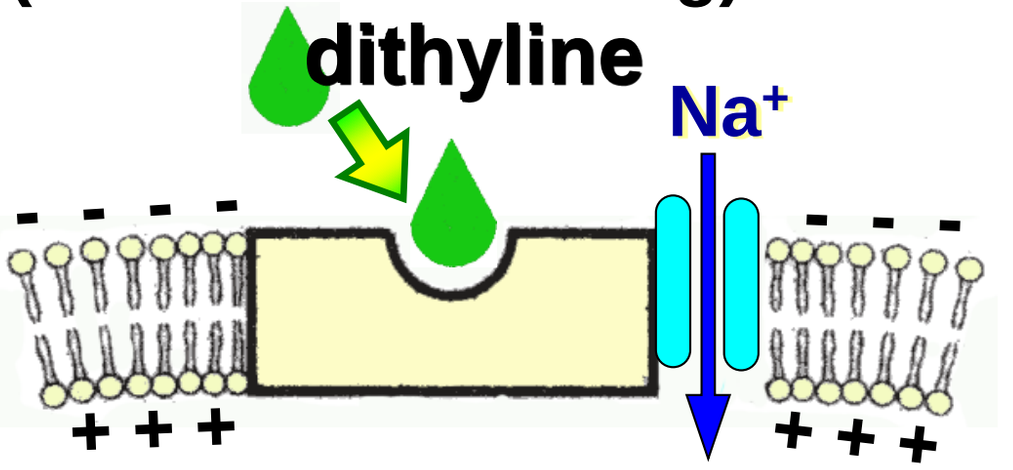
- **Nondepolarizing (competitive) action** — tubocurarine, pipecuronium bromide (arduan), pancuronium bromide, vecuronium bromide, etc.
- **Depolarizing action** — dithyline (succinylcholine, succametonium chloride, listenone)
- **Mixed action** — dioxonium

PHARMACODYNAMICS OF MYORELAXANTS

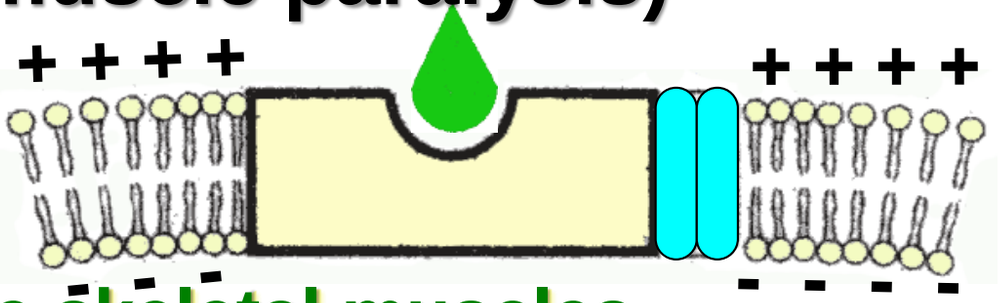
Nondepolarizing:
compitetive blockade
of N-cholinoceptors
on postsynaptic membrane
of the skeletal muscles ⇒ removal
of block by the anticholinesterase
drugs (↑ Ach content)

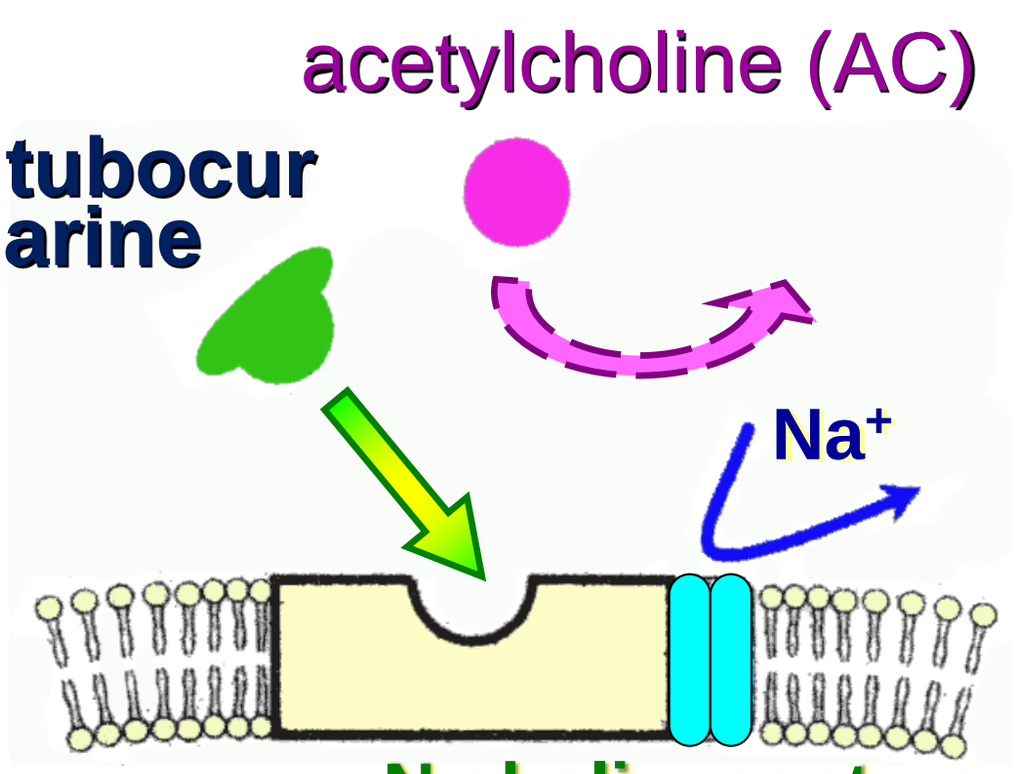
Depolarizing: activate N-cholinoreceptors (like Ach), causing prolong depolarization of postsynaptic membrane ⇒ ↓ block of pseudocholinesterase

Phase I — depolarization
(muscular twitching)



Phase II — desensitization
(muscle paralysis)





N-cholinoceptors of the skeletal muscles

PHARMACODYNAMICS OF MYORELAXANTS

Skeletal muscles:

nondepolarising: **during first 1–5 min there is muscle weakness, followed by muscles paralysis in the following order: first - muscles of the eyes, jaws, then extremities, trunk, diaphragm (breathing arrest); recovery appear in the reverse order**

♦ ***depolarizing:***

phase I (within 1 min) — temporary fasciculation (muscular twitching), especially of the chest, stomach, following by

phase II — relaxation of muscles of the neck, extremities, face, throat, diaphragm

MYORELAXANTS APPLICATION

- Relaxation of the muscles of larynx and throat during intubation for the inhalation anaesthesia and artificial lung ventilation
- Relocation and reposition of bone fragments in case of fractures
- Surgical operations on the abdominal and chest organs under anaesthesia with artificial ventilation of lungs
- Convulsions in case of poisoning by substances which depress the respiratory center, in case of meningitis, cerebral and cranial traumas for transition to AVL
- Spasticity with Parkinson disease, encephalitis and other dysfunctions of the pyramidal and extrapyramidal system

MYORELAXANTS

Adverse effects

- **Bronchi**: *tubocurarine* — bronchial spasm
- **Electrolyte balance:** *dithyline* — hyperkaliemia
- **Eyes:** *dithyline* — ↑ intraocular pressure
- **GIT:** *dithyline* — ↑ intragastric pressure ⇒ vomiting
- **Muscular pains in the postoperative period:** *dithyline* (in 20% of people)
- **Long-term block (> 2 hrs instead of 2–10 min) and apnoea:** *dithyline* in people with genetic insufficiency of cholinesterase
- **Interactions:** potentiation of action — by inhaled general anesthetics, antibiotics-aminoglycosides, by the low doses of locally anesthetics (high doses weaken block)

MYORELAXANTS DISTINCTIONS

Action	Compitetive	Depolarizing
Mechanism of action	Competition with Ach	Steady membrane depolarization
Interaction with Ach	↓ Block	↑ Block
Removal of block (decurarization)	Anticholinesterase drugs (proserin)	Blood transfusion (pseudocholinesterase)
Loss of K+ by the muscle	No	Present
Fibrillations	No	Marked (phase I)
Penetration to the muscular tissue	Does not penetrate	Penetrates deeply
Anaesthesia influence	Strengthens	Does not influence