

Odesa National Medical University
Department of General and Clinical Pharmacology
and Pharmacognosy

PSYCHOTROPIC PREPARATIONS
THAT STIMULATE CNS
(ANTIDEPRESSANTS,
PSYCHOSTIMULATING
PREPARATIONS)



ANTIDEPRESSANTS (thymoleptics, thymoanaleptics)

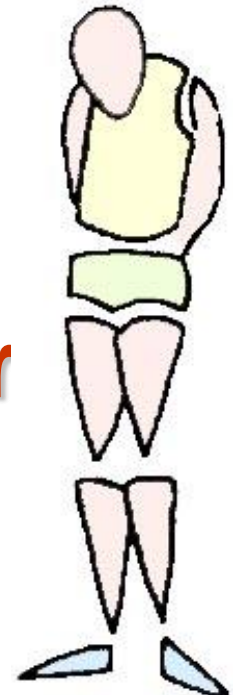
(from Gr. thymos — soul, ana — movement upwards, lepticos — able to apprehend)

- psychotropic drugs which relieve depression, “correct” a pathologically changed mood, return interest to the life, activity and optimism

Types of depressions:

Endogenous – in case of **psychical diseases (psychosis)**

Exogenous (reactive) – in case of **sever psychical trauma, incurable disease, fatigue**



PATHOGENESIS OF DEPRESSIONS

in the centers of the limbic system ↓ content of monoamines — serotonin, norepinephrine and dopamine

Serotonin — neurotransmitter of “well-being”:

- ✚ ↑ mood (**thymoleptic** effect itself)
- ✚ normalize control after the impulsive drive
- ✚ normalize sexual practices
- ✚ ↑ level of aggressiveness
- ✚ facilitation of falling asleep
- ✚ regulation of sleep cycles
- ✚ ↓ appetite
- ✚ ↓ sensitivity to pain



HISTORY OF ANTIDEPRESSANTS

1951 г. The given properties are revealed in hydrazide of isonicotinic acid derivative — iproniazide
N. Kline used this “side” effect for the treatment of depression

1957 г. R. Kuhn studying imipramin – applied a term “thymoanaleptic” action while studying imipramine — a derivative of tricyclic compounds

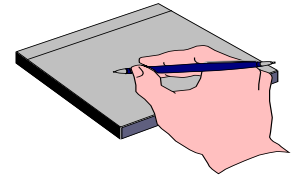
1960 г. J. Axelrod revealed a mechanism of antidepressive action of imipramine (the Nobel Prize)

At the same time the first home-produced antidepressant azafen (laboratory of M. N. Shchukina, Moscow) was obtained, then — pirazidol



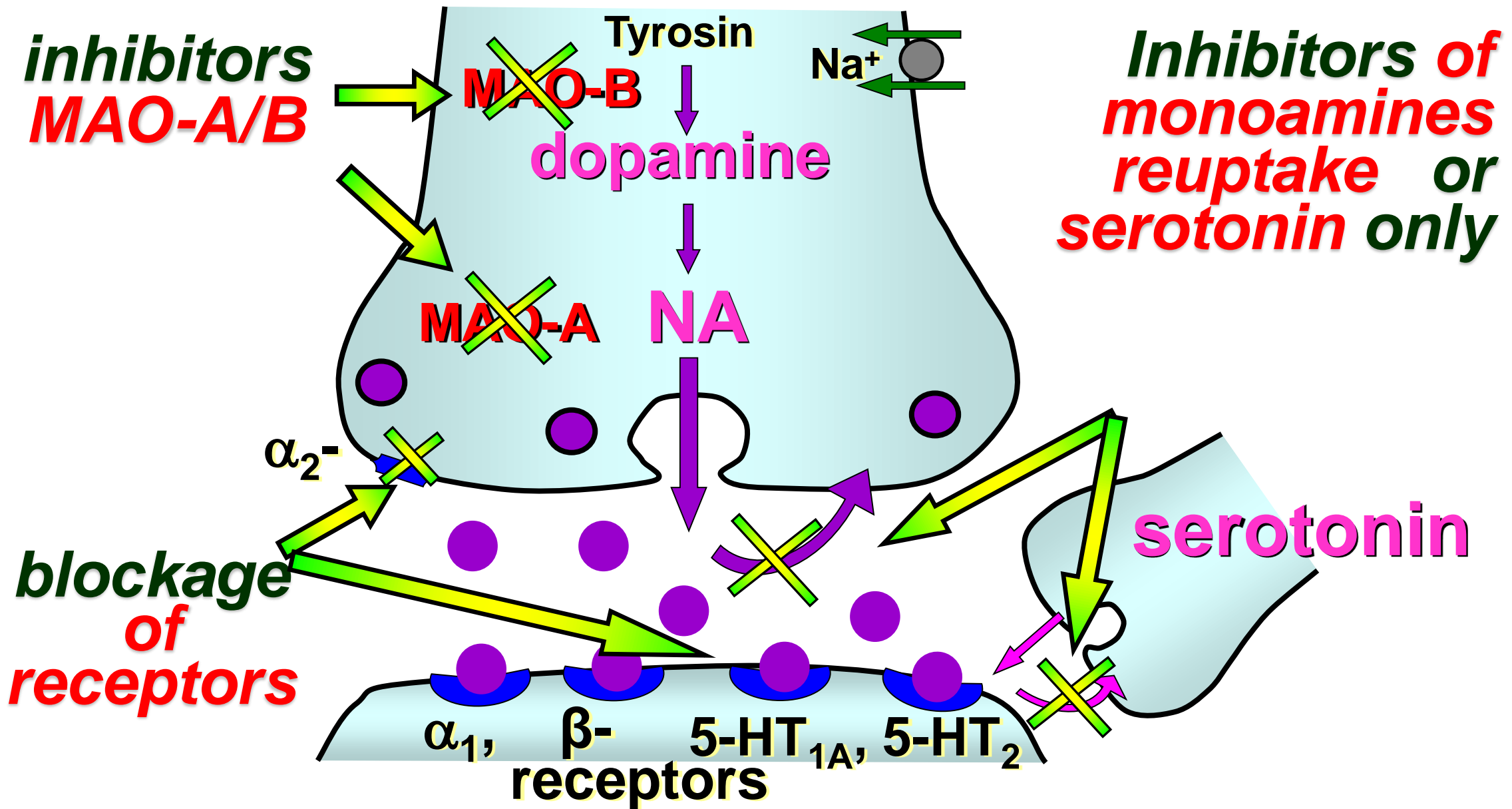
CLASSIFICATION OF ANTIDEPRESSANTS

- **inhibitors of monoaminoxidase (MAO):**
необратимые – ниаламид; обратимые – пиразидол, моклобеמיד и др.
- **inhibitors of neuronal reuptake of monoamines :**
 - *nonselective action: tricyclic (TCA, typical) – imipramine (imizine), amitriptyline, clomipramine; heterocyclic (atypical) – maprotiline*
 - *selective (elective) serotonin reuptake inhibitors (SSRI): fluoxetine (prozac), fluvoxamine, paroxetine, etc.*
- **with the receptor mechanism of action:**
mirtasapine, mianserine (blockers of presynaptic α_2 -, depressing serotonin release, and postsynaptic 5-HT-receptors, modulating a serotonergic transmission) **etc.**
- **reuptake activators(!): thianeptine**



MECHANISM OF ANTIDEPRESSANT ACTION

potentiation and regulation of monoaminergic transmission in the CNS



SELECTIVITY OF ANTIDEPRESSANTS

Along with reuptake inhibition, a series of drugs block central and peripheral M-, α - and H₁-histamine receptors

| <i>groups</i> | reuptake inhibition | | | postsynaptic receptors blockade | | |
|--------------------------------|---------------------|------|----|---------------------------------|------------------|------------|
| | NA | S | DA | M- | H ₁ - | α - |
| typical (TCA): | | | | | | |
| - imipramine | +++ | +++ | + | +++ | ++ | ++ |
| - amitriptyline | +++ | +++ | + | +++ | ++ | +++ |
| atypical (tetracyclic): | | | | | | |
| - maprotyline | ++++ | + | + | + | + | ++ |
| SSRI | - | ++++ | - | - | - | - |

MAO inhibitors do not have cholinolytic activity!



PHARMACODYNAMICS OF ANTIDEPRESSANTS

**sedative,
antianxious**

thymoleptic

**thymoretic
(stimulant)**

+ ↓ negative
emotions, fears

an ability ↑
mood
(≈ in 10-15
days)

+ ↑ psycho-
motorics
(≈ in 5-7 days)

clomipramine

amitriptyline

fluoxetine

MAO inhibitors

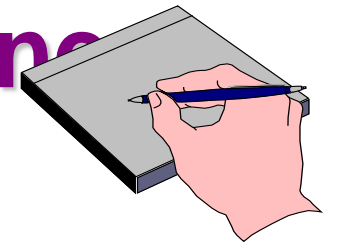
blockade of
M-, H₁-, α-
receptors

↑ serotonin-
ergic
transmission

↑ adrenergic
transmission

CLINICAL CLASSIFICATION OF ANTIDEPRESSANTS

- **thymmeretics (with stimulant action)** – majority of MAO inhibitors (nialamide, moclobemide), imipramine, fluoxetine, sidnofen, etc.
- **sedative (with sedative action)** – amitriptyline, fluoracizine, fluvoxamine, mianserine
- **”balanced” action (bipolar, modulating)** – pyrazidol, clomipramine, majority of SSRI (paroxetine)



PHARMACODYNAMICS OF ANTIDEPRESSANTS

- **own analgesic action and and potentiate analgesic action (mainly TCA)**
- **hypothermia (TCA)**
- **antiemetic (TCA)**
- **nootropic (pyrazidol)**
- **anxiolytic (drugs with the receptor mechanism of action — nafazodone)**
- **hypotensive (TCA, nialamide)**





INDICATIONS TO ANTIDEPRESSANTS

- **depressions in mentally ill patients**
- **reactive and post-traumatic depressions, after neuroinfections, poisonings (lead, etc.)**
- **neurotic reactions with elements of depression, asthenia, nervous anorexia or bulimia, insomnia, narcolepsy, etc.**
- **psychosomatic diseases (irritable colon syndrome, peptic ulcer, etc.)**
- **chronic pain syndromes**
- **vegetodiencephalic crises**
- **syndrome of chronic fatigue, etc.**

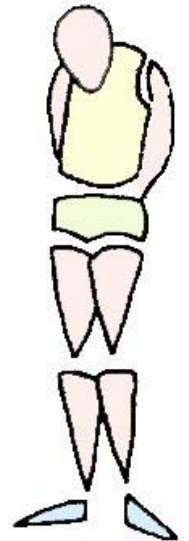
PRINCIPLES OF ANTIDEPRESSANTS RATIONAL ADMINISTRATION

correct choice depending on the form and clinical course of the process

- ✓ at asthenodepressive syndrome – **thymneretics** or balanced action drugs
- ✓ at the anxious-depressive syndrome – **sedatives** from TCA or SSRI CMO3C

correct choice of doses and treatment regimen

- ✓ presence of a «**therapeutic window**» in TCA ⇒ gradual ↑ of dose, starting from c min
- ✓ administration of thymneretics – in the morning, sedatives – in the evening
- ✓ gradual ↑ of the effect (with severe endogenous – after 1,5 months)



2-3 weeks



PRINCIPLES OF ANTIDEPRESSANTS RATIONAL ADMINISTRATION

● combined therapy

- ✓ **TCA + MAO inhibitors or their quick substitution are banned!** (sympathetic crisis, death); turn from TCA to MAO inhibitors — 3–7 days; from MAO inhibitors to TCA — 2–3 weeks
- ✓ **SSRI + MAO inh.** → «serotonin» crisis (hyperthermia, seizures, coma, death)
- ✓ **SSRI, MAO inhibitors** ⇒ slow down biotransformation of other drugs
- ✓ **undesirable simultaneous administration of TCA with beta-blockers, antacids, H₁-blockers, contraceptives, CNS depressants, alcohol, etc.; MAO inhibitors and thymoretics – with adrenomimetics, products containing tyramine (cheese, etc.)**

PHARMACOKINETICS OF ANTIDEPRESSANTS

Administration: TCA are absorbed in GIT incompletely, undergo presystemic elimination, MAO inhibitors and SSRI – well-absorbed

Bioavailability: 30-90 % (depending on group)

Plasma protein binding: 73-98 %

Distribution: well penetrate the tissues

Biotransformation: (generalized for TCA, heterocyclic and SSRI):

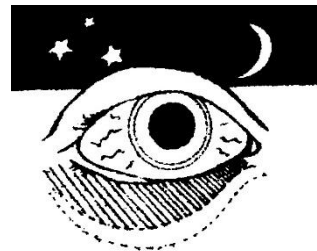
- 1) **hydroxylation and conjugation** to glucuronoids; 2) **dimethylation up to active metabolites formation.** MAO inhibitors: **acetylation, distinction by genotype !**

Excretion: by kidneys, partly with bile

ADVERSE EFFECTS OF ANTIDEPRESSANTS

● CVS:

- **TCA** – orthostatic hypotension (blockade of α -adrenoreceptors), arrhythmias, \downarrow conductivity, sudden death
- **thymoretics-TCA** and especially **MAO inh.** – adrenomimetic reactions, «cheese» syndrome (\uparrow heart rate, BP, arrhythmias)



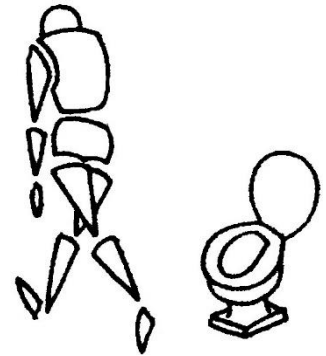
● CNS: psychic excitation (insomnia, delirium, hallucinations, etc.) – more frequently **thymoretics**; **depression** with alcohol, sedatives)

● **rebound syndrome** – suicides, especially in teenagers



ADVERSE EFFECTS OF ANTIDEPRESSANTS

- **toxico-allergic** (гепатиты, нарушение кроветворения, аллергия и пр.)
- **cholinolytic** (dry mouth, mydriasis, sedation, constipation, difficulty of urination, etc.) - **TCA**
- **antihistaminic** (sedation, ↑ weight) – **TCA**
- **others** (sexual dysfunction, ↓ appetite, weight, tremor, etc.) – **SSRI**



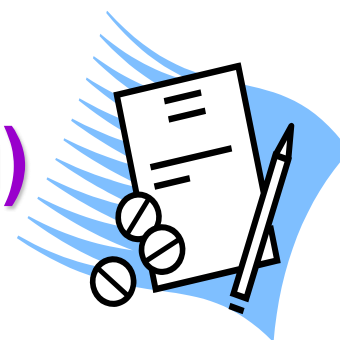
НОРМОТИМИКИ

препараты лития – лития оксибутират, лития карбонат (лителионит-дюорель, микалит)

- предупреждают возникновение как маний, так и депрессий при маниакально-депрессивных и шизофренических психозах, оказывают лечебное действие при маниах
- ионы Li частично замещают Na^+ и K^+ в клетках; как антагонисты Ca^{2+} и Mg^{2+} ↓ активность зависимых от них ферментов, ↓ гиперфункции моноаминергических систем и возбудимости нейронов

нежелательные эффекты:

- ✚ тремор конечностей, сонливость, головные боли
- ✚ диарея (может быть очень тяжелой)
- ✚ полиурия, жажда, нарушение баланса электролитов (потеря Na^+ , K^+ , Mg^{2+} и воды) и функции почек
- ✚ дисфункция щитовидной железы



PSYCHOSTIMULATORS

or psychomotor stimulators –

psychotropic drugs which have agitation effect, quickly mobilize functional and energy reserves of an organism, at first CNS, stimulating mental and physical working-ability of ill and healthy people (with fatigue)



classification

- ▶ phenylalkylamines – amphetamines (phenamine)
- ▶ sidnonimins – sydnocarb
- ▶ Derivatives of purinea (xanthins) – caffeine, caffeine-benzoates sodium

HISTORY OF PSYCHOSTIMULATORS



Caffeine

(tea, coffee, cacao, cola, etc..)

Cocaine

(coca leaves)

Nicotine

(tobacco)

in 1819 year **Runge** selected caffeine

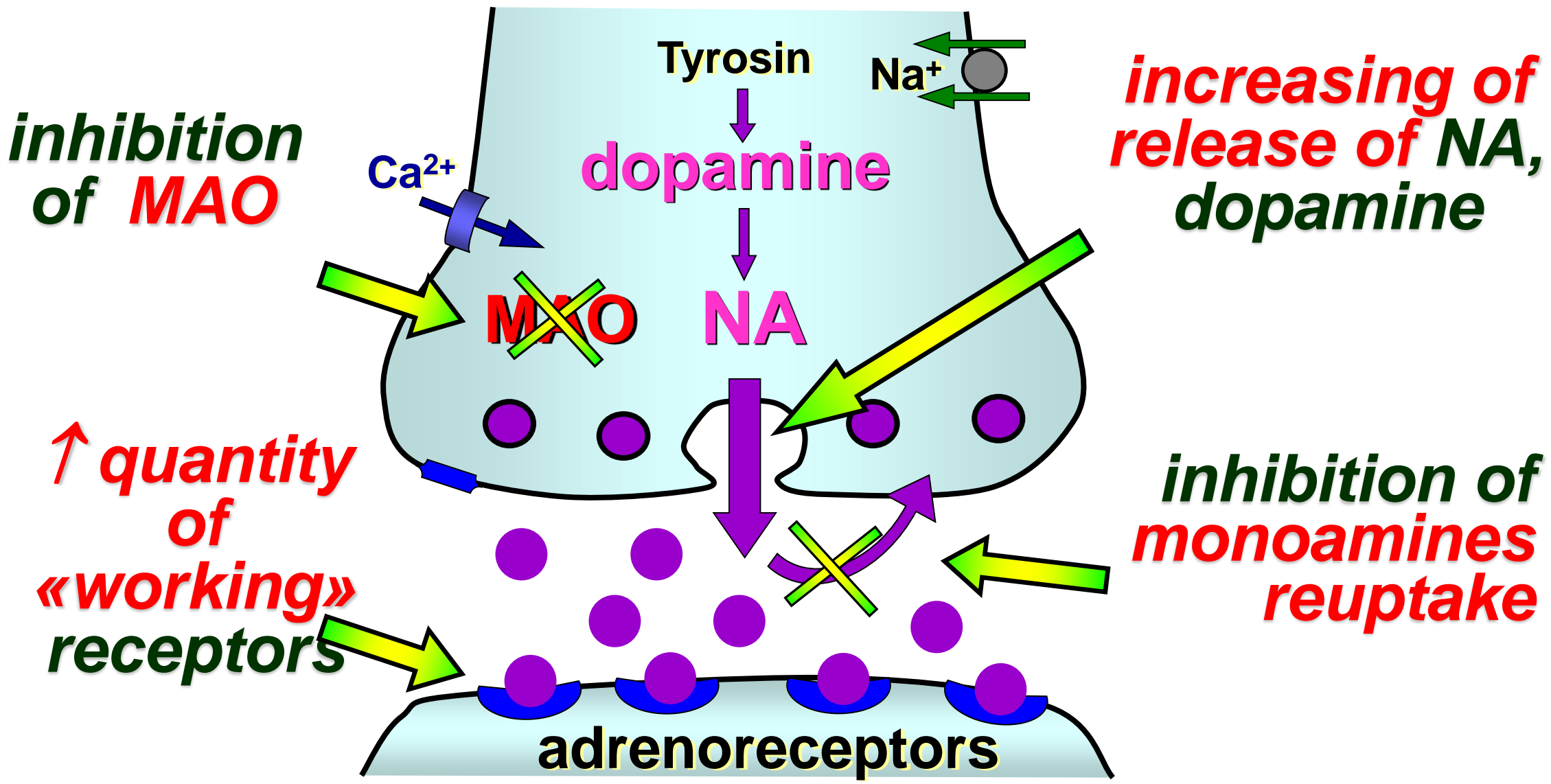
in 1887 year **Edeleano** synthesized

an analogue of alkaloid catinone of coca leaves (*Catha edulis*) – amphetamine



MECHANISM OF PHENYLALKYLAMINES ACTION

Significant activation of adrenergic transmission at all the levels: from CNS to the cellular metabolism





PHARMACODYNAMICS OF PHENYLALKYLAMINES

● **CNS:**

➤ **neurophysiologic processes:**

- ✓ ↑ wakefulness of the brain – ↓ fatigue, put off a necessity in sleep for 10–12 hrs, ↑ perception (activation of reticular formation (RF), thalamus)
- ✓ ↑ emotional-motivation reaction – burst of energy, initiative, ↑ mood (↑ limbic system, hypothalamus)
- ✓ revival of motions – ↑ motive activity, lack of loading control (↑ RF)

➤ **psychophysiologic processes:**

↑ attention, short-term (!) memory, ↑ stereotype work, but a creative one suffers (“leap of ideas”, errors)



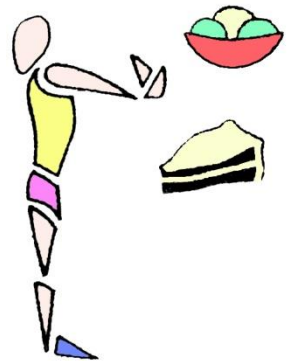
PHARMACODYNAMICS OF PHENYLALKYLAMINES

● CNS:

- ➡ ↓ the hunger center ⇒ anorexigenic effect
- ➡ ↑ the respiratory center

● Metabolism:

- ➡ mobilization of ATP resources and creatine phosphate in the CNS, the heart, the liver, the skeletal muscles
- ➡ ↑ glycogenolysis and lipolysis, delivery utilization of glucose and fatty acids ⇒
- ➡ in the blood ↑ glucose, piruvate, lactate, metabolic acidosis
- ➡ disjoining of phosphorylation and oxidization, ↑ necessity of organs in O₂, macroergs synthesis inhibition
- ➡ uneconomical energy expenditure, ↑ the body temperature, rapid exhaustion





PHARMACODYNAMICS OF PHENYLALKYLAMINES

CVS:

- ▶ «+» ino-, chrono-, batmo-, dromotropic effects
⇒ tachyarrhythmia
- ▶ ↑ ABP, stroke and minute volume

Features:

- ▶ the degree of activating is proportional to the dose
- ▶ under complicated conditions (high temperature of environment), with deep fatigue, prolonged stress **the application is dangerous** (rapid exhaustion of monoamine depot, heart failure)
- ▶ rebound syndrome, dependence
- ▶ in 10–15% of people there is paradoxical reaction (alarm, malice, depression, drowsiness, etc.)

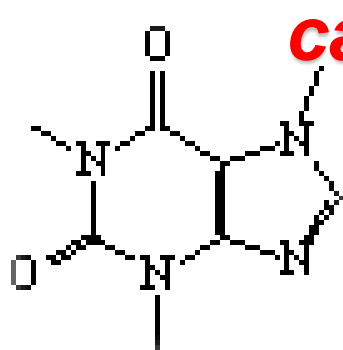




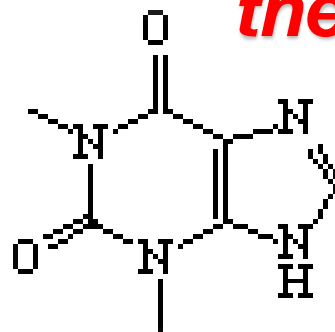
XANTHINE DERIVATIVES

(oxidized purines, analogues of uric acid)

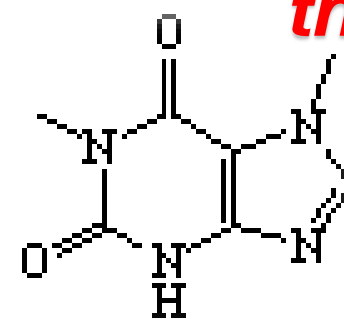
- ✓ **alkaloids: caffeine** (1,3,7-trimethylxanthine), **theobromine** (3,7-dimethylxanthine), **theophylline** (1,3-dimethylxanthine),
- ✓ **hemisynthetic: aminophylline** (euphylline) (theophylline + ethylenediamine!), **diprophylline**, **pentoxiphylline** (trental, agapurine) etc.



caffeine



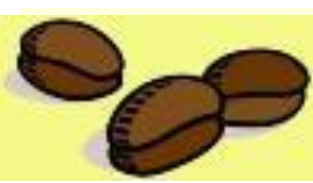
theophylline



theobromine

Sources of obtaining

- ➡ **caffeine:** tea (about 5%), coffee (2–2.5%), cola nut (2%), etc., and by the synthetic way from the uric acid
- ➡ **theobromine:** seeds of a chocolate tree (2 %)
- ➡ **theophylline:** tea



CAFFEINE

mechanism of action

- ➔ Concurrent antagonist of adenosine receptors A₁ (purine P₁) ⇒ ↑ cAMP synthesis
- ➔ Inhibits phosphodiesterase (in large doses), that ↓ cAMP inactivation
- ➔ in the end ↑ intracellular level of cAMP in the CNS, the heart, the smooth and skeletal muscles, fatty tissue

pharmacodynamics

- ✚ C₁H₇N₃O₂ – ↑ release of neuromediators in synapses:
 - dopaminergic – psychostimulation
 - cholinergic of the cortex and medulla oblongata - ↑ intellect and respiratory center
 - adrenergic of the hypothalamus and medulla oblongata - ↑ vasomotor center



CAFFEINE

pharmacodynamics

+ Heart:

- direct cardiostimulating effect – «+» inotropic effect, ↑ organ need in O₂, in the large doses arrhythmia
- tachy- (↑ automatism of s.-a. node) or bradycardia (↑ n. vagus center)

+ Blood vessels:

- constriction of cutaneous, mucous membranes, abdominal organs vessel (influence of the vasomotor center)
- dilation of coronary, pulmonary, skeletal muscles (managed with cAMP participation)
- ↑ ABP with mild hypotension (in the norm changes a little)
- cerebral blood flow in healthy people caffeine can worsen with spasms, migraine — normalizes (spasmolytic action)



CAFFEINE

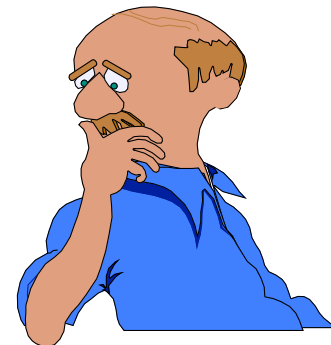
pharmacodynamics

- + **GIT** – gastric secretion stimulation
- + **kidneys** – ↑ diuresis (modestly)
- + **smooth muscles** – relaxation of bronchial muscles and bile-excreting ways
- + **metabolism** – ↑ lipolysis, glycogenolysis, basic metabolism by 10–25%
- + **with drug abuse** – worsening of blood circulation in the extremities, deterioration of IHD clinical course, insomnia, tremor, psychical dependence (caffeinism)



INDICATIONS TO PSYCHOSTIMULATORS

- **temporal ↑ mental work– sydnocarb (2-3 days), caffeine**
- **single ↑ of exercise tolerance under extraordinary conditions – sydnocarb (2-3 days) + rest**
- **neuroses with asthenia – sydnocarb (2-3 weeks)**
- **narcolepsy – sydnocarb, caffeine**
- **for weakening of the action of substances which depress the CNS - sydnocarb, caffeine**
- **hypotesion – caffeine**
- **migraine – caffeine**
- **as analeptic – caffeine**



АКТОПРОТЕКТОРЫ (бемитил)

(лат. actus - движение) – стимулирующие работоспособность и повышающие резистентность организма в осложненных условиях (острое кислородное голодание, охлаждение, гипертермия и пр.) за счет повышения сопряжения окисления и фосфорилирования, снижения потребности в кислороде, ослабления истощения катехоламинов при физической нагрузке

показания:

- +** астения, неврозы,
- +** травмы, инфекции, интоксикации
- +** гипоксия, стресс и др.
- +** экстремальные условия труда
- +** спортивная медицина

NOOTROPICS

(psychometabolic stimulators) – render a selective mnemotropic action (from Gr. mneme - memory, tropos - direction), improving higher integrative functions of the brain — an ability to study, memory, operator activity

classification:

- **pyrrolidone derivatives – piracetam (nootropil) and its analogues (aniracetam, etc.)**
- **GABA-ergic – aminalone, picamilone, fenibut, sodium oxybutyrate**
- **derivatives of different groups – membranoprotectors (piriditol); glutamatergic (glycine)**

MECHANISM OF NOOTROPICS ACTION

- **↑ bioenergetics of the brain :**
 - **↑ ATP and cAMP synthesis, glucose utilization, glycolysis, aerobic breathing**
 - **antihypoxic action (GABA-ergic nootropics)**
- **↑ synthesis and secretion of mediators: dopamine, noradrenaline, acetylcholine**
- **↑ synthesis of protein and membrane phospholipids due to ↑ regeneration of neurons, synthesis of informative neuropeptides, metabolism of phospholipid membranes**

MECHANISM OF NOOTROPICS ACTION

- **↑ cerebral blood flow and hemorrheology:**
 - **dilation of cerebral vessels**
 - **improvement of bloodflow (zone of ischemia)**
 - **↓ aggregation of thrombocytes, thrombi formation, ↑ microcirculation**
- **antioxidant action:** ↓ lipid peroxidation, protection from phospholipids cellular membranes destruction ⇒ facilitation of memory traits fixation
- **↑ mnemotropic effects of memory neuropeptides due to agonism with receptors for memory neuropeptides**

PHARMACODYNAMICS OF NOOTROPICS

only with long administration!

- ↑ concentration of attention, ability of studying, long-term memory (with asthenias, chronic fatigue, in children with the defects of development, but not in healthy people!)
- ↓ perception of stress in people with neurotic states (stress-protective – piracetam, picamilon + anticonvulsant – phenibut, + moderate psychostimulating – acefen etc.)
- Cerebroprotective, ↑ restorative processes in the damaged brain (rehabilitation after the cranial-cerebral traumas, strokes etc)
- ↑ general tonus and functional activity in elder age groups

ADAPTOGENS

– *Natural drugs rendering unspecific general restorative action on the CNS function, endocrine regulation, metabolic processes and promoting adaptation of an organism to unfavorable conditions*

Schizandra
(*Schizandra*)



Eleuterococcus
(*Eleutherococcum*)



Ginseng
(*radix Ginseng*)



Rose-root
(*Rhodiola r.*)



Leuzea
(*Leuzea*)

ADAPTOGENS

prolong administration!

- ↑ volume and limit of physical work, ↓ fatigue, ↑ tolerance
- ↑ memory, attention, an ability to study (especially in fatigue)
- activate the cerebral cortex, RF
- Psychostimulating effect (↑ glycolysis, oxidization of lipids, etc.)
- ↑ synthesis of glycogen in the liver and skeletal muscles
- ↑ synthesis of DNA, RNA, protein, membrane phospholipids
- ↑ secretory function of adrenal cortex, thyroid gland

INDICATIONS FOR ADAPTOGENS

- ✓ **asthenia** – schizandra, leuzea, eleuterococcus, ginseng
- ✓ **moderate hypotension** - mountain angelica, devil's club, eleuterococcus, ginseng
- ✓ **for elderly people to rise the vital tone and a working ability** - schizandra, leuzea, eleuterococcus, ginseng
- ✓ **For the rise of immunological reactivity of an organism at the period of epidemics**– ginseng, eleuterococcus, rose-root
- ✓ **for healthy people to rise a working ability and accelerate adaptation to mental and physical loading**– ginseng, eleuterococcus, rose-root

ANALEPTICS (reviving)

(from Gr. ana — movement upwards, lepticos — capable to perceive) – tone up respiratory and vasomotor centers of medulla oblongata



classification:

- with the prior influence on the vital centers (respiratory and vasomotor centers) – *caffeine, bemegrade, ethimizole*
- with the mixed mechanism of action – *camphor, sulfocamphocain, cordiamine*

PHARMACODYNAMICS OF ANALEPTICS

- ✱ ↑ depolarization of neurons at the expense of ↑ permeability of the Na⁺ and Ca²⁺-channels
- ✱ ↓ latent period of reflexes
- ✱ ↑ expense of macroergs, O₂ consumption
- ✱ antagonism with inhibiting mediators of the CNS (*bemegrade* — GABA, *caffeine* — adenosine)

- ⇒ ↑ activate depressed respiratory center (for a short term, repetition — seizures !):
- ↑ sensitivity to CO₂, H⁺, reflexes from the carotid sinus, chemoreceptors of the vessels, lungs
 - accelerate and deepen breathing, ↑ minute volume of breathing
- ⇒ ↑ vasomotor center: ↑ tone of arterioles and venules, venous return to the heart, secondary ↑ cardiac output (except for caffeine and camphor)

INDICATIONS TO ANALEPTICS

- ✦ asphyxia of new-borns – ethimizole
- ✦ collaptoid states of central genesis – caffeine, cordiamine
- ✦ transient disorders of cerebral circulation (faints) – sulfocamphocaine, caffeine
- ✦ chronic hypoventilation with CO₂ retention at respiratory diseases – sulfocamphocaine, camphor
- ✦ “convulsive” therapy – bemegrade
- ✦ poisoning of moderate severity with hypnotics, barbiturates and other depressants of the CNS – bemegrade, camphor, cordiamine