Odesa National Medical University
Department of 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

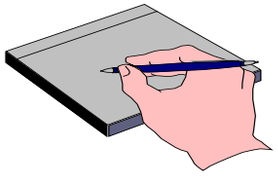
1957 г. R. Kuhn studying imipramin – applied a term “thymoanaleptic” action while studing imipramine — a derivative of trycyclic compounds

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

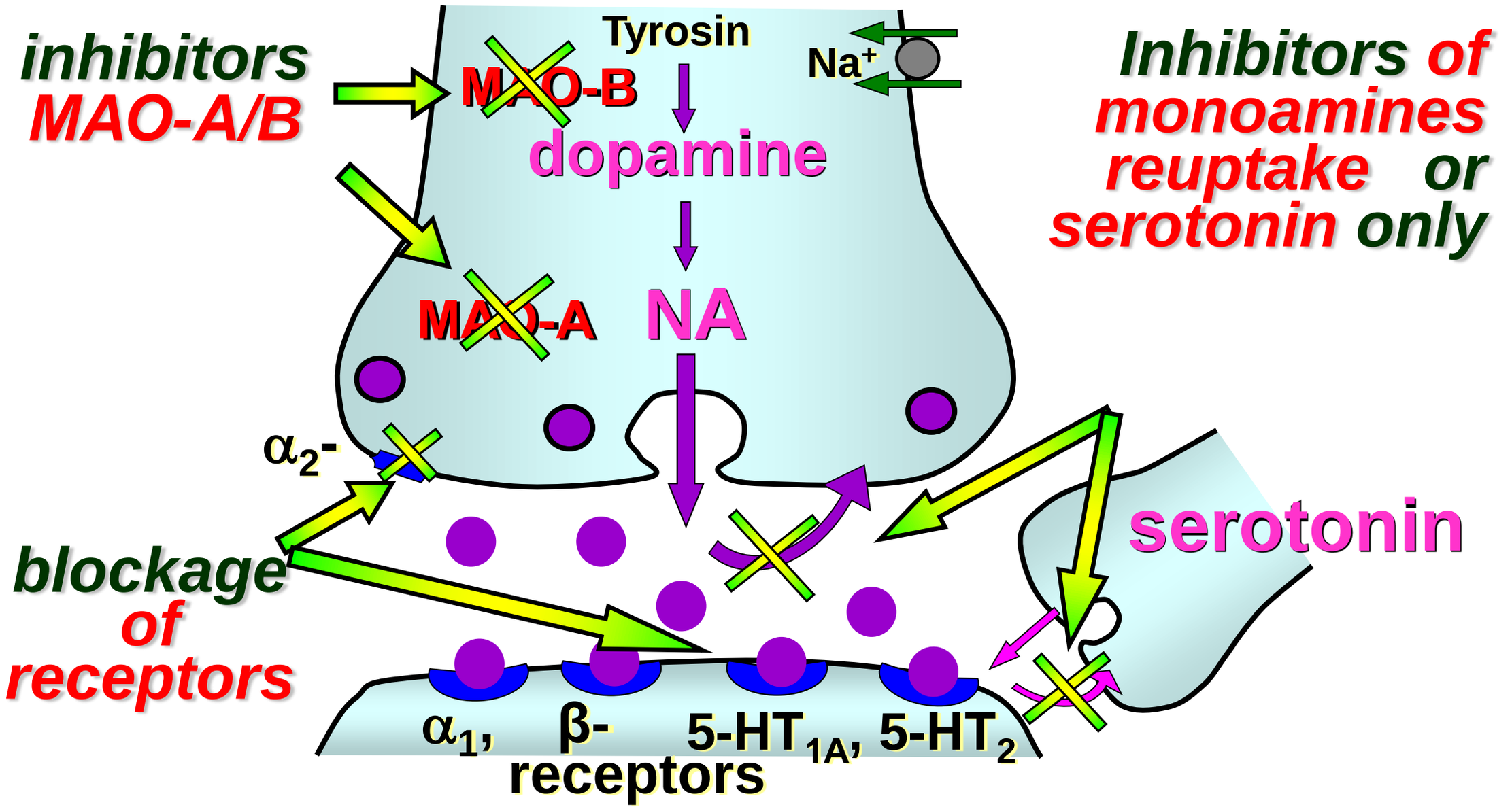
CLASSIFICATION OF ANTIDEPRESSANTS

- **inhibitors of monoaminooxidase (MAO):** ***необратимые*** **– ниаламид;** ***обратимые*** **– пиразидол, моклобемид 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 serotoninergic 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 H_1-histamine receptors

groups	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** — **thymeretic (stimulant)**

+ ↓ negative emotions, fears

an ability ↑ mood (≈ in 10-15 days)

+ ↑ psycho-motorics (≈ in 5-7 days)

clomipramine

amitriptyline

fluoxetine

MAO inhibitors

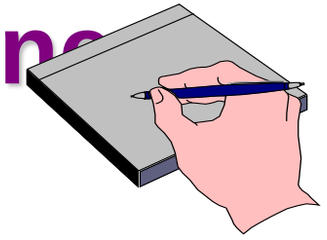
blockade of M-, H_1-, α-receptors

↑ serotonin-ergic transmission

↑ adrenergic transmission

CLINICAL CLASSIFICATION OF ANTIDEPRESSANTS

- **thymeretics (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 – thymeretics or balanced action drugs**
  - ✓ **at the anxious-depressive syndrome – sedatives from TCA or SSRI СИОЗС**

- **correct choice of doses and treatment regimen**
  - ✓ **presence of a «therapeutic window» in TCA ⇒ gradual ↑ of dose, starting from c min**
  - ✓ **administration of thymeretics – 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, H_1-blockers, contraceptives, CNS depressants, alcohol, etc.; MAO inhibitors and thymeretics – with adrenomimetics, products containing thyramine (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, hetero-cyclic and SSRI):**

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

Excretion: **by kidneys, partly with bile**

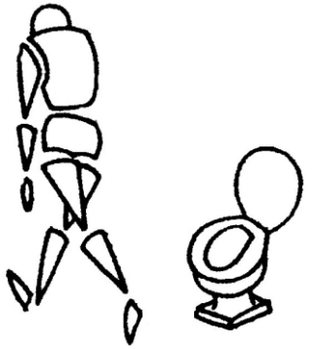
ADVERSE EFFECTS OF ANTIDEPRESSANTS

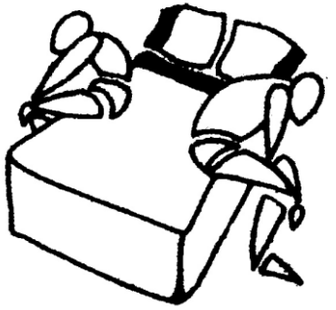
- **CVS:**
  - **TCA – orthostatic hypotension (blockade of α-adrenoreceptors), arrhythmias, ↓ conductivity, sudden death**
  - **thymeretics-TCA and especially MAO inh. – adrenomimetic reactions, «cheese» syndrome (↑ heart rate, BP, arrhythmias)**

- **CNS: psychic excitation (insomnia, delirium, hallucinations, etc.) – more frequently thymeretics; depression with alcohol, sedatics)**
- **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 (литионит-дюрель, микалит)

- предупреждают возникновение как маний, так и депрессий при маниакально-депрессивных и шизофренических психозах, оказывают лечебное действие при маниях
- 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)

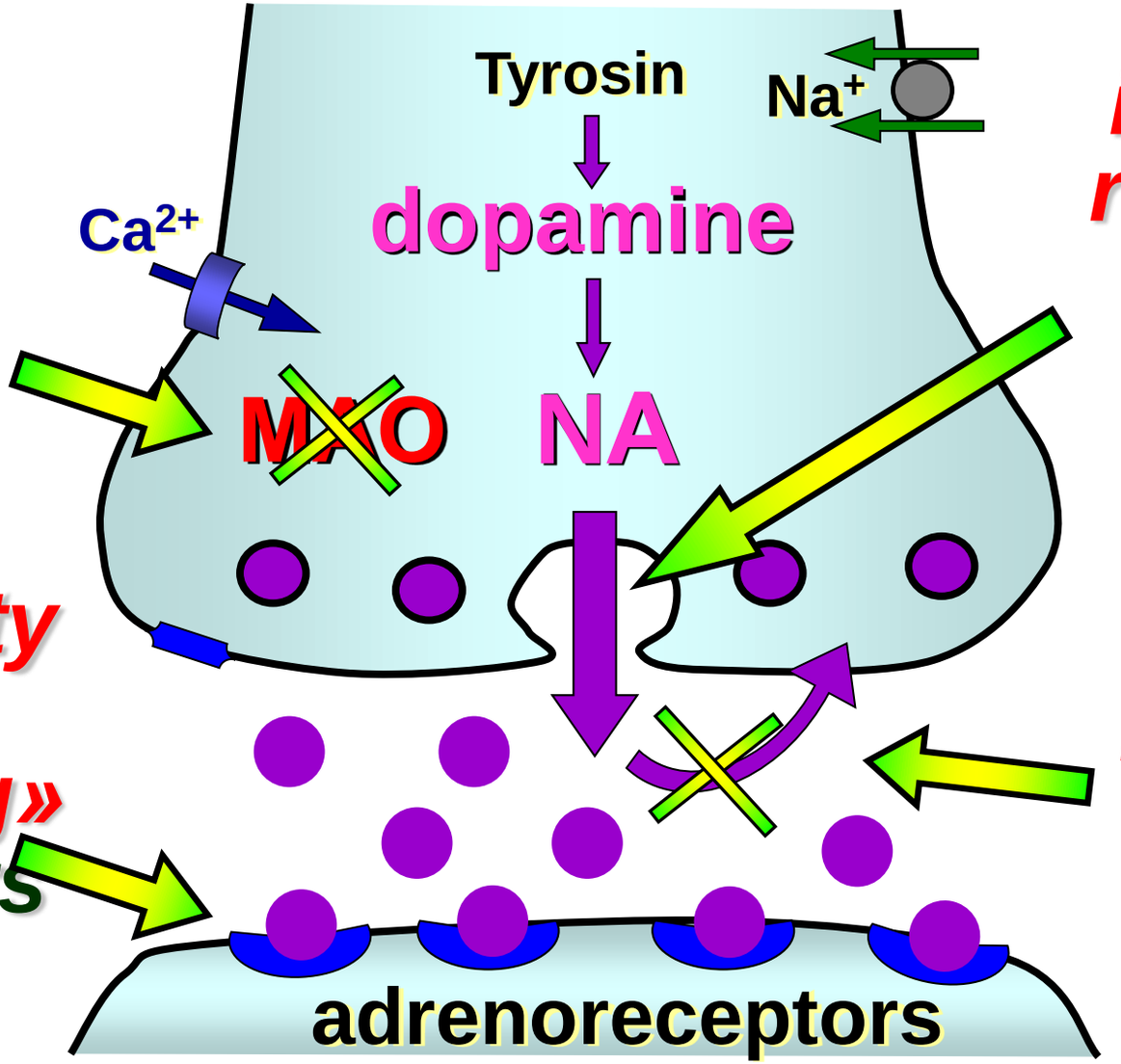
in 1819 year Runge selected caffeine

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



inhibition of MAO

increasing of release of NA, dopamine

↑quantity of «working» receptors

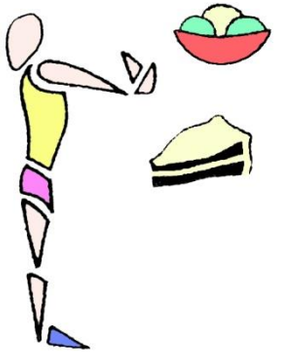
inhibition of monoamines reuptake

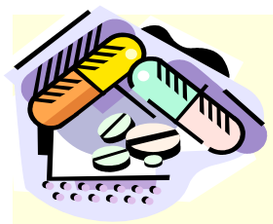
PHARMACODYNAMICS OF PHENYLALKYLAMINES

- **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 ⇒ anorexinogenic 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 O_2, macroergs synthesis inhibition
  - uneconomical energy expenditure, ↑ the body temperature, rapid exhaustion





PHARMACODYNAMICS OF PHENYLALKYLAMINES

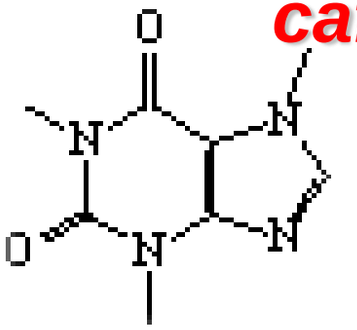
- **CVS:**
  - «+» ino-, chrono-, batmo-, dromotropic effects ⇒ tachyarrhythmia
  - ↑ ABP, stroke and minute volume
- **Features:**
  - the degree of activating is proportional to the dose
  - under complicated conditions (high temperature of environment), with deep fatigue, prolonged stress the application 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

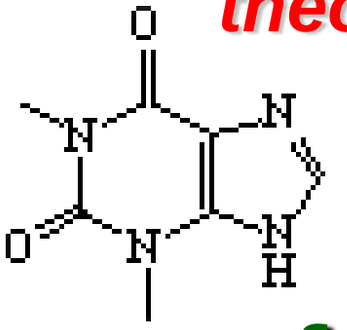
(oxidized purines, analogues of uric acid)

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

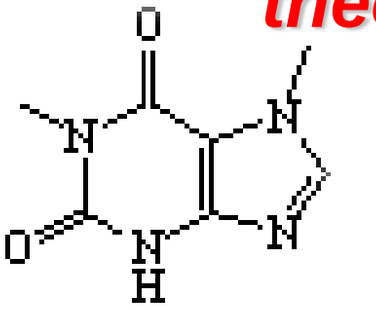
caffeine



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 P_1) ⇒ ↑ 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

- ЦНС – ↑ 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 O_2, 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)

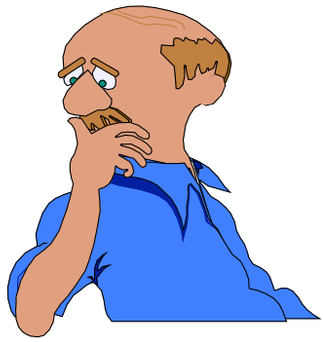
CAFFEINE

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, bemegride, ethimizole***
- **with the mixed mechanism of action – *camphor, sulfocamphocain, cordiamine***

PHARMACODYNAMICS OF ANALEPTICS

- ↑ depolarization of neurons at the expause of ↑ permeability of the Na+ and Ca2+-channels
- ↓ latent period of reflexes
- ↑ expense of macroergs, O_2consumption
- antagonism with inhibiting mediators of the CNS *(bemegride — 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 – bemegride
- poisoning of moderate severity with hypnotics, barbiturates and other depressants of the CNS – bemegride, camphor, cordiamine