Veterinary pharmacology1

Symphatetic Nervous System drugs (Part 1)

Department of Pharmacology, Toxicology and Environmental Protection

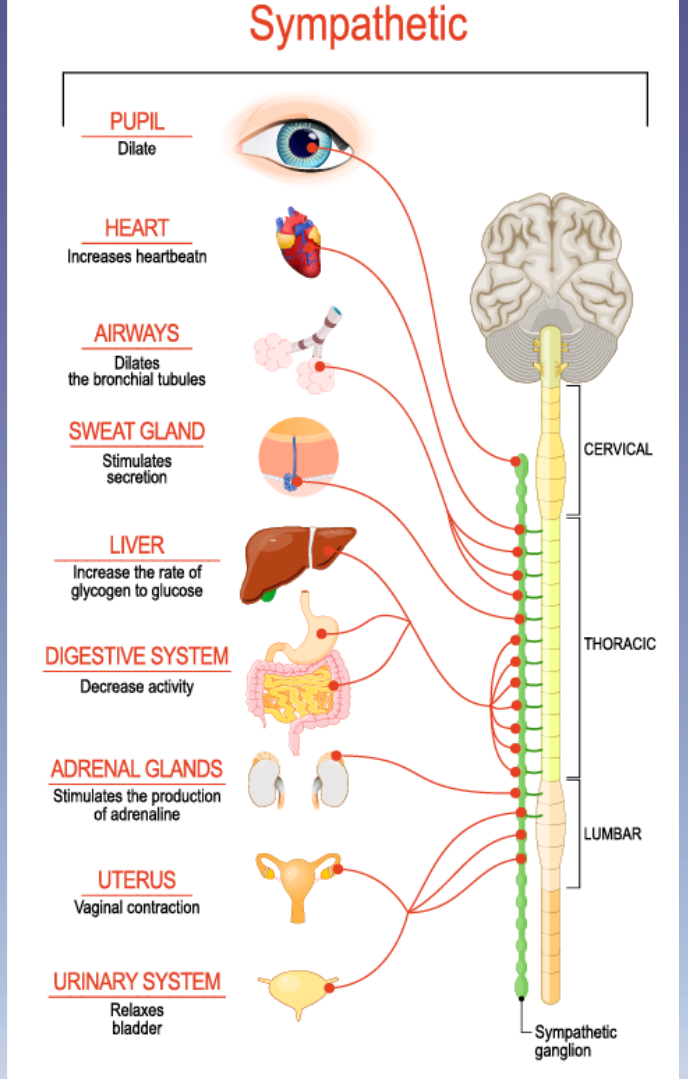
Sympathetic nervous system

(łac. pars sympathica divisionis autonomici systematis nervosi)

participates with the parasympathetic system in the functioning of the autonomic nervous system. Responsible for mobilizing the body and maintaining homeostasis

Functions of the sympathetic nervous system:

- stimulation
- activation
- fight



Adrenergic receptors

α−adrenergic receptors

- α1 receptors
- α2 receptors

β−adrenergic receptors

- β1 receptors
- β2 receptors
- β3 receptors

$\alpha 1$ – adrenergic receptors

Receptors located in smooth muscles, mainly vascular smooth muscles. Stimulation of these receptors causes contraction:
- increase in blood pressure
- spasm of the circular muscles

The most powerful natural agonists are NOREPINEPHRINE AND EPINEPHRINE

Exogenous agonists include: NORPHENEPHRINE, PHENYLERPHINE, AND METOXAMINE

Antagonists of $\alpha 1$ - adrenergic receptors. PRAZOSIN AND TERAZOSIN

α2 – adrenergic receptors

They are located at the adrenergic endings of the sympathetic nervous system and are autoreceptors. Stimulating them inhibits the activity of the sympathetic nervous system.

Stimulation of these receptors results in:

- inhibition of membrane adenylate cyclase activity
- autoreceptors (activated by a neurotransmitter secreted from the neuron on which they are located)
- their activation results in a reduction of norepinephrine release - inhibitory effect

The endogenous agonists are NOREPINEPHRINE AND EPINEPHRINE

Exogenous neurotransmitters are: XYLASE

The antagonist of these receptors is YOHIMBINE

β1 – adrenergic receptors

Receptors located in the heart muscle. They are responsible for:
- stimulation of the strength and frequency of contraction of the heart muscle
- they activate non-cardiac lipoprotein lipases
- they increase the release of renin from the dense macula in the kidneys
- activate the RAA system

Agonists are:

DOBUTAMINE AND ISOPRENALINE

The antagonists are:
METOPROLOL
ATENOLOL

β2 – adrenergic receptors

They are found mainly in smooth muscle.
They are responsible for:

- Relaxation of the smooth muscles of the bronchi, blood vessels, and the gastrointestinal tract

- Activation of glycogen phosphorylase

Agonists:
SALBUTAMOL
PHENOTEROL
ISOPRELIN

Antagonists:
BUTAKSAM BUTOXAMINE

β3 – adrenergic receptors

They are found mainly in adipose tissue cells and are responsible for:

- They intensify lipolysis
- They intensify glycogenolysis
- They increase the secretion of glucagon
- They are responsible for thermogenesis in skeletal muscles

Agonists: ISOPRENALINE

Antagonists: BUPRANOLOL

Drugs that act on adrenergic receptors

SYMPATHOMIMETICS

substances stimulating the sympathetic nervous system by acting on adrenergic receptors. They resemble naturally occurring neurotransmitters in structure and operation, including adrenaline or norepinephrine. They work by increasing the concentration of neurotransmitters at the synapses

SYMPATICOLITICS

substances that indirectly inhibit the sympathetic nervous system by impeding the release of noradrenaline into synaptic gaps or preventing the storage of catecholamines in nerve endings

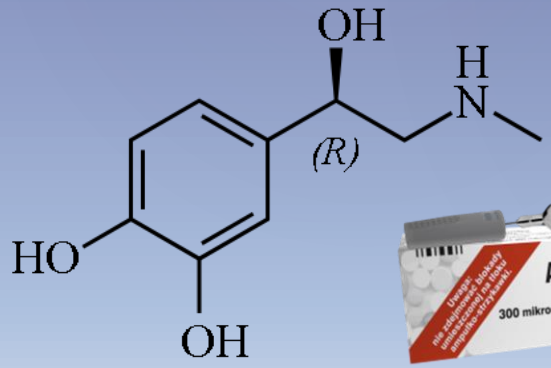
SYMPATHOMIMETICS

SYMPATYKOMIMETICS = ADRENOMIMETICS ACTING ON ALPHA AND BETA RECIPES

EPINEPHRINE

Alpha1 stimulation: narrowing of the blood vessels of the skin, mucous membranes and kidneys.

β1 increase: myocardial contractility and acceleration of its activity, increase in stroke and minute capacity, increase in blood pressure.



It is included in complex and anesthetic preparations. Amine causes the β2-adrenomimetic effect - relaxation of the smooth muscles of the bronchi, intestinal blood vessels and the muscles of the uterus.
It inhibits the release of histamine from mast cells, also the conversion of carbohydrates and lipids - an increase in glucose and free fatty acids in the blood.

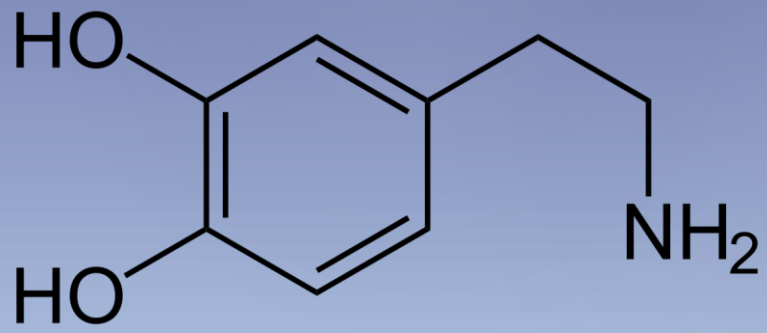
Purpose: anaphylactic shock, decreased circulation in vital organs, e.g. kidneys. Reanimation after anesthesia, local reduction of swelling of the conjunctiva and nasal mucosa, prolongs the effect of local anesthetics

Overdose: Tachycardia and arrhythmia.

SYMPATYKOMIMETICS = ADRENOMIMETICS ACTING ON ALPHA AND BETA RECIPES

DOPAMINE

It has a partially sympathomimetic effect on α-receptors and a weaker effect on β-adrenergic receptors.



A precursor to the synthesis of norepinephrine and epinephrine. A neurotransmitter synthesized at dopaminergic nerve endings in the periphery and the central nervous system. It acts via dopaminergic receptors found in the renal, coronary, splanchnic, and cerebral vessels.

Stimulation of these receptors leads to vasodilation. Increased cardiac contractility and increased heart rate. Transient increase in blood pressure.

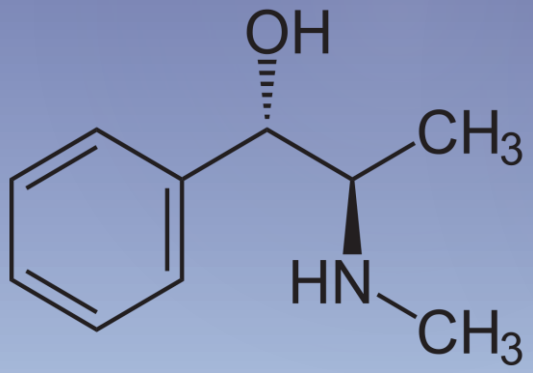
Uses: Anaphylactoid and cardiac shock, after replenishing circulating blood volume. Improves blood flow to internal organs.

Overdose: Tachycardia and arrhythmia.

SYMPATYKOMIMETICS = ADRENOMIMETICS ACTING ON ALPHA AND BETA RECIPES

EFEDRINE

It directly stimulates α- and β-adrenergic receptors



Alkaloid contained in Ephedra vulgaris. It causes the release of norepinephrine in the sympathetic nerve endings and the neurons of the CNS
It works like an epinephrine, but for a longer time, it constricts the blood vessels and increases blood pressure. It widens the bronchi, accelerates the heart rate. It causes motor agitation and anxiety.

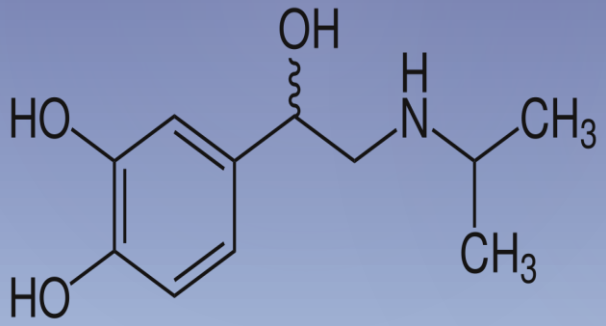
Application: bronchial asthma, circulatory system disorders
- to stimulate breathing and circulation in the case of neonatal asphyxia, as well as depression of the respiratory and circulatory system after the use of surgical drugs and sedative-hypnotic drugs.

Overdose: tachycardia, disturbance of the atrium of the heart rhythm, motor stimulation.

SYMPATYKOMIMETICS = ADRENOMIMETICS ACTING ON BETA1 AND BETA2 RECEPTORS

ISOPRENALINE

It stimulates the β 1 and β 2 receptors

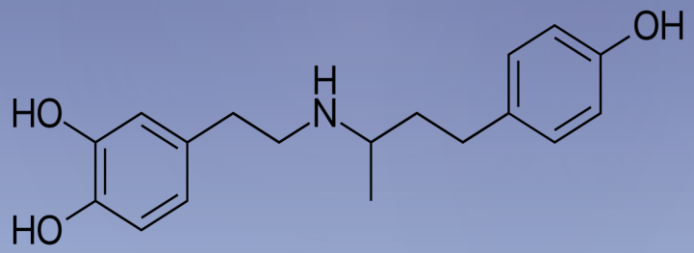


It causes relaxation of smooth muscles, especially the bronchi and blood vessels, lowers blood pressure, narrows venous vessels, causes glycogenolysis and has a lipolytic effect. It is absorbed from the gastrointestinal tract, from the lymphatic alveoli. It is metabolized in the body under the influence of MAO and COMT.

Application: bradycardia, conduction disturbances, atrioventricular block
Overdose: tachycardia with arrhythmia. Interactions: do not administer under halothane anesthesia as it results in atrial fibrillation.

SYMPATYKOMIMETICS = ADRENOMIMETICS ACTING SELECTIVELY ON BETA1 RECEPTORS

DOBUTAMINE



The drug acts selectively, increasing contractility and increasing stroke capacity. It has no effect on blood pressure, does not cause heart rhythm disturbances, and does not increase heart rate.

Administered in acute heart and circulatory failure.
Overdose: tachycardia with arrhythmia and increase in blood pressure

ADRENOMIMETICS ACTING ON BETA2 RECEPTORS

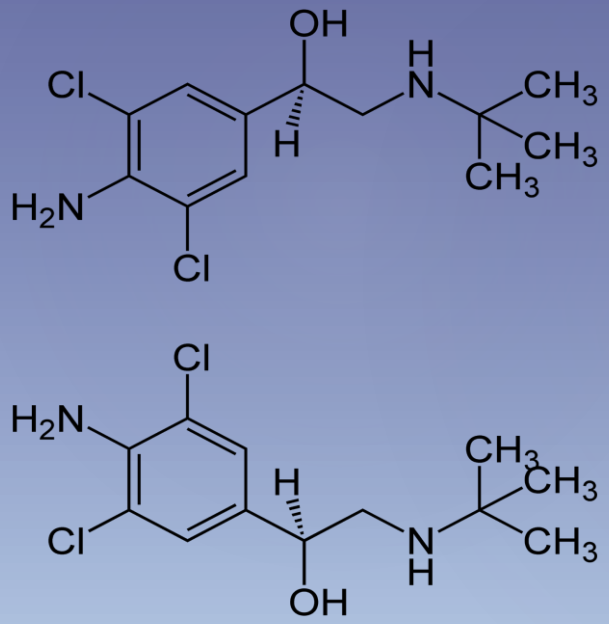
BRONCHLITICS drugs that relax the bronchial muscles.
Used for bronchospastic conditions, they are mainly used in human medicine and in veterinary medicine they are used to treat horses. This group of drugs includes:
-terbutaline
-fenoterol
-salbutamol
-spiropent, known in veterinary medicine as Clenbuterol

TOKOLITICS drugs that inhibit the contractile activity of the uterine muscle.
They are used in gynecology and obstetrics.

Clenbuterol is used in two ways, because it also relaxes the muscles of the uterus (known as Planipart), and also:
-bufenine used in human medicine as a drug that improves organ circulation
-isoxuprine.

BRONCHOLITICS

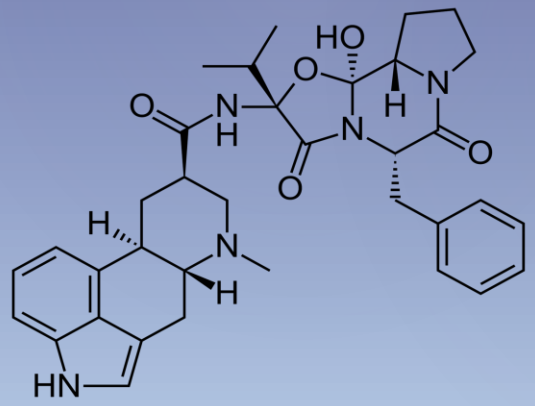
CLENBUTEROL



Mainly used for cattle and horses.
Application: acute and subacute respiratory diseases, with bronchial spasticity.
Side effects: peripheral vasodilation and increased heart rate, muscle tremors, sweating in horses

TOKOLITICS

ISOXUPRINE



Used in all animal species as a medicine that relaxes the uterine muscle.

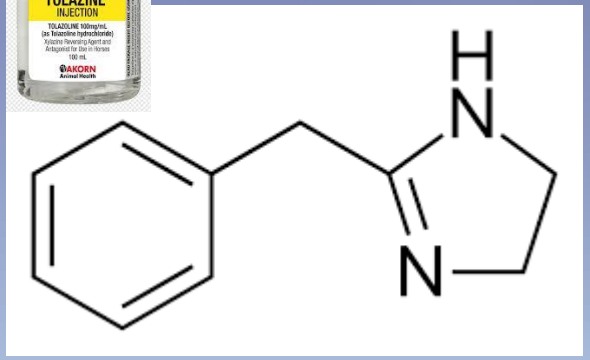
APPLICATION:

- Cervical spasm
- Too much pressure in labor
- Caesarean section to correct the position of the fetus
- With a prolapse of the uterus
- To maintain the threatened pregnancy 3-4 weeks before delivery

Alpha-blockers

- Drugs which suppress the effects of catecholamines and other sympathomimetic drugs on adrenergic receptors
- They block the alpha-adrenergic receptor
- SYNTHETIC: tolazoline, phentolamine (imidazoline derivatives), phenoxybenzamine (haloalicoamine derivative)
- NATURAL: yohimbine, ergot alkaloids

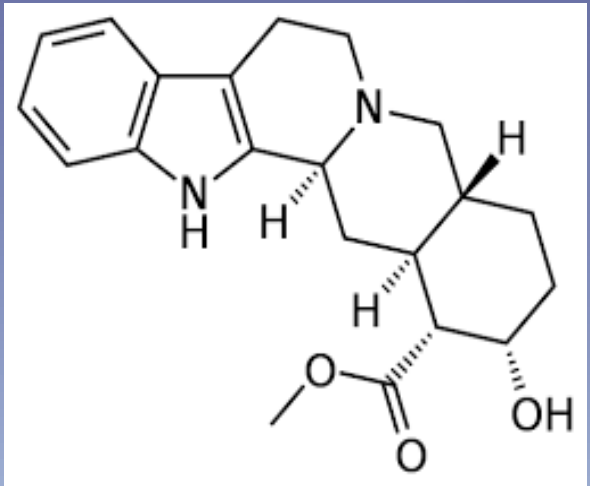
FENTOLAMINE/ TOLAZOLINE



- Strong alpha1 and alpha2-adrenolytic effects
- blocks serotonin receptors and increases the release of histamine
- it acts directly on the smooth muscles of the arteries - it lowers blood pressure
- enhances the release of norepiphedrine by blocking alpha2-adrenergic receptors
- causes contractions of the smooth muscles of the intestines and increases the secretion of gastric acid

APPLICATION:
the later phase of shock - to improve blood perfusion in vital organs (liver, kidneys and visceral circulation)

YOHIMBINE

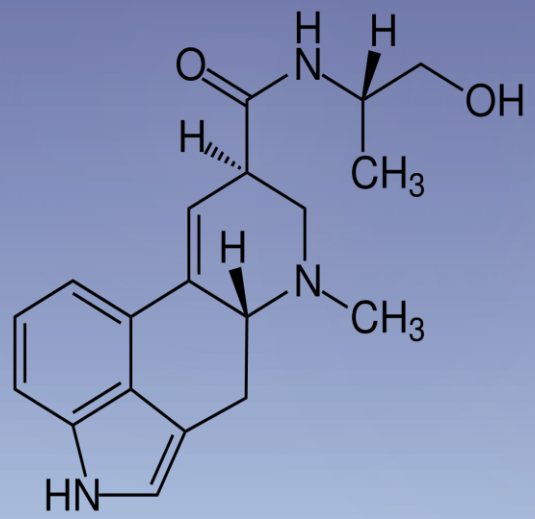


- ALKALOID OBTAINED FROM THE Bark of Corynanthe yohimbe
- Increases male sex drive
- It blocks the action of peripheral and central alpha-adrenergic receptors
- enhances the release of norepinephrine from presynaptic terminals - an antagonist of alpha2-adrenergic receptors
- Increases heart rate increase in arterial blood pressure
- The effects of yohimbine occur as a result of interaction with the alpha2-adrenergic agonists: xylazine, detomidine
- It shortens the sleep time after barbiturate anesthesia, and the sedation time

ERGOT ALKALOIDS - oxytotics

- The spore of the red mace mushroom alkaloids derived from lysergic acid
- Structures similar to: noradrenaline, serotonin, dopamine
- Contractile effect on smooth muscles
- In oxytotic drugs - contracting the uterus
- Eg. **ergometrine, methylergometrine**
- For inhibiting lactation - **bromocriptine**

ERGOMETRIN AND METHYLERGOMETRIN



- The contracting ergot alkaloid has no alpha-blocking effect

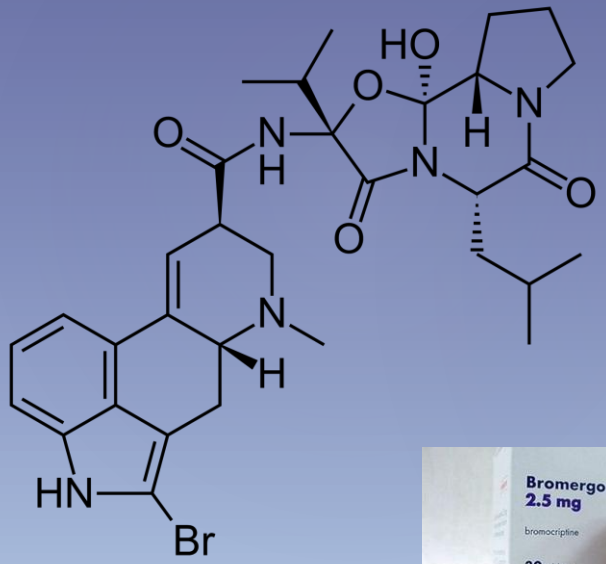
APPLICATION:

- postpartum uterine atony
- bleeding in the postpartum period
- retention of puerperal excrements
- delayed uterine involution

CONTRAINDICATIONS:

- during pregnancy categoty X
- prolonged contraction of the uterus can damage the fetus

BROMOCRYPTIN



- A semi-synthetic derivative of ergot alkaloids
- the nature of the D2 dopaminergic agonist
- inhibits the release of prolactin from the anterior pituitary gland
- only when other methods fail
- common side effects
- reduces the secretion of ACTH (with hyperadrenocorticism)

APPLICATION:

- false pregnancy, Cushing's syndrome

SIDE EFFECTS:

- vomiting, loss of appetite, behavioral changes

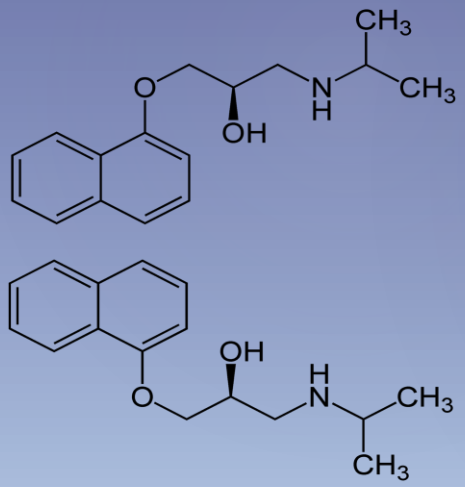
Beta blockers

- They abolish the action of beta-adrenomimetics on beta1 and beta2 receptors and the action of beta2 agonists, i.e. sulbutamol, terbutaline, fenoterol, bamethane, isoxuprine
- In addition to their beta-receptor antagonism, beta-blockers also have a non-specific effect

e.g.

- residual beta-adrenoceptor agonist activity - intrinsic sympathomimetic activity, e.g. weak cardiostimulant activity of pracolol or oxsprenolol
- Non-receptor effect - they stabilize the cell membrane, which is similar to the effect of local anesthetics

Propranolol



- It has an affinity for both beat 1 and beta2 adrenergic receptors
- Easily penetrates the blood-brain barrier
- It depresses the CNS by blocking the above-mentioned receptors
- It has an anxiolytic effect
- In the respiratory system, it leads to bronchospasm - the predominance of the parasympathetic system
- Glaucoma treatment - lowers intraocular pressure
- It inhibits the processes of glycogenolysis and lipolysis
- Can trigger the birthing action
- Speeds up peristalsis and can cause diarrhea

Propranolol

Application

- Prevention of heart disorders with tachycardia with arrhythmia
- In healthy animals, prophylactically before the expected load: loading, transport, mating, childbirth
- Tachycardia with supraventricular arrhythmia in dogs and horses
- With overdose of beta-adrenergic drugs
- Increases the tone and contractile activity of the uterine muscle

DERIVATIVES OF PROPANOLOL

They block the β1 and β2 receptors used in the treatment of high blood pressure, ischemic heart disease and arrhythmias (wide use in cardiology):

Oxsprenolol

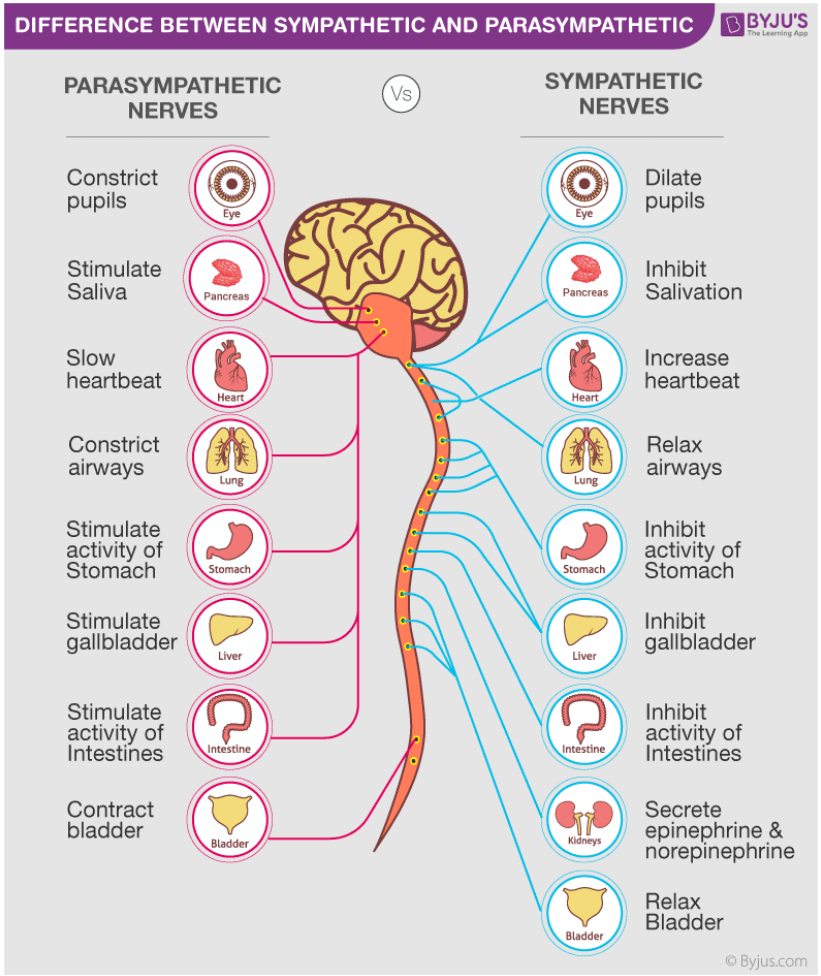
Pindolol

Sotalol

Practolol

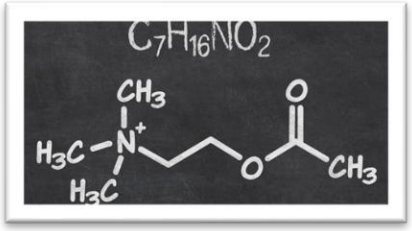
Atenolol

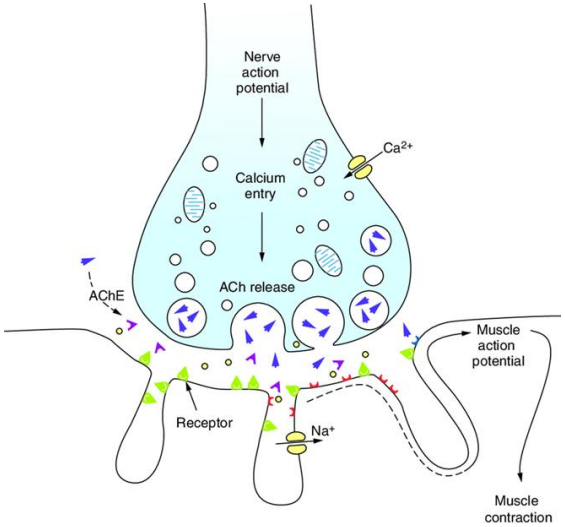
Parasympathetic Nervous system drugs (Part 2)



- acts antagonistically towards the sympathetic nervous system
- it predominates in states of rest, enabling regeneration and energy storage
- Acetylcholine (Ach) is a neurotransmitter that is released at the ends of pre-ganglionic parasympathetic fibers and at the ends of post-ganglionic fibers.

ACETYLCHOLINE

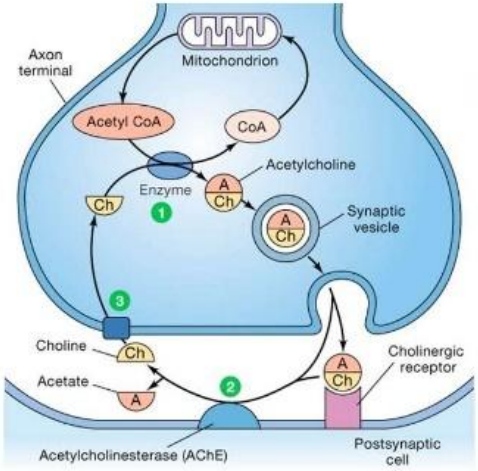




- is a neurotransmitter for cholinergic receptors
- it is formed from choline and coenzyme A under the influence of acetylcholine transferase
- for the release of which the presence of calcium ions is necessary
- small amounts of acetylcholine are continuously released into the synapse, which gives rise to subliminal potentials.
- when nerve impulses are conducted, acetylcholine is released in greater amounts and acts on receptors

The action of acetylcholine at the synapse is interrupted by enzymatic degradation. A specific acetylcholinesterase is responsible for this.

Acetylcholine is broken down into choline and acetic acid.



Choline is reabsorbed into the presynaptic part and is used for the re-synthesis of acetylcholine.

Cholinergic receptors

Cholinergic receptors are found in ganglion synapses of the autonomic system, cells of the executive organs and CNS synapses.

There are nicotinic (N) and muscarinic (M) cholinergic receptors

Cholinergic N receptors are variously arranged:

- at the synapses of the ganglia in the sympathetic and parasympathetic parts of the autonomic system; are called N-ganglion cholinergic receptors

These receptors are also found in the medulla of the adrenal glands; their stimulation leads to the release of epinephrine and norepinephrine in the blood.

- in the neuromuscular endings of skeletal muscles; are called N-muscle cholinergic receptors

Stimulation of these receptors by acetylcholine or other agonists leads to an increase in cation flux and to membrane depolarization, resulting in skeletal muscle contraction.

An agonist of N cholinergic receptors is nicotine, which stimulates N receptors in low doses.

Large doses permanently bind to the receptor and the so-called depolarization block.

Drugs that have agonist effect:

- nicotine
- acetylcholine
- tetramethylammonium

Drugs that inhibit acetylcholinesterase activity, e.g. neostigmine

Antagonistic effects on these receptors have:

- hexamethonium
- tubocurarine
- galamine
- pancuronium

CHOLINERGIC MUSCARINIC RECEPTORS

Depending on their location, M receptors are divided into at least 5 subtypes.

The location of the various M receptor subtypes varies:

M1 receptors are present in the CNS, the ganglia of the autonomic system and in the secretory cells of the gastrointestinal glands, mainly the stomach.

M2 receptors are located in the CNS, the heart's conductive system, in the heart muscle and on smooth muscle cells.

M3 receptors - found on the cells of the secretory glands and smooth muscle cells.

Presynaptically located M receptors are also distinguished, known as autoreceptors. Stimulating them reduces the release of acetylcholine into the synapse.

These receptors have an **agonist effect**:

- acetylcholine
- muscarine
- bethanechol
- carbachol
- pilocarpine

They show an **antagonistic effect** on these receptors

- atropine
- scopolamine

Parasympathetic drugs

These are all drugs that affect cholinergic receptors:

- direct and indirect drugs (agonists) = parasympathomimetics
- cholinergic antagonists = parasympatholytics

Due to the way they act on receptors, we divide them into:

DIRECTLY ACTING	INDIRECTLY ACTING
they directly stimulate cholinergic receptors; the most common muscarinics	inhibit the decomposition of acetylcholine, increase the concentration of the neurotransmitter in the synaptic cleft and thus have an effect on effector cells
acetylcholine, carbachol, muscarine, arecoline	physostigmine, neostigmine

Parasympathomimetics directly acting

Due to the predominance of the muscarinic effect, representatives of this group of drugs are primarily used in intestinal and bladder atony, and locally in glaucoma.

Muscarine itself is not used as a drug due to its severe toxicity.

Drugs of this group have a chemical structure similar to acetylcholine and therefore they can bind directly to receptors and trigger a programmed effect.

They have many side effects.

Acetylcholine (Ah)

is a physiological neurotransmitter.

It has a stimulating effect on nicotinic and muscarinic cholinergic receptors.

It is broken down very quickly by acetylcholinesterase,

and after parenteral administration it has a strong depressant effect on the circulatory system.

Therefore, it is not used in animal medicine.

KARBACHOL (BIOLENT)

It is a choline ester with carbamate acid that works stronger and longer than acetylcholine.

It stimulates nicotinic and muscarinic receptors. It comes in the form of injection solutions, it is administered subcutaneously, it works for about 1 hour. It has a small spread between therapeutic and toxic doses.

It is used in the atony of the stomach, intestines and bladder.

The symptoms of side effects are mainly due to the muscarinic effects: vomiting, diarrhea, polyuria, bradycardia. Central nicotine symptoms are absent as carbachol does not cross the blood-brain barrier.

The antidote for side effects is atropine.

PILOCARPINE

- It is an alkaloid obtained from the leaves of the Pilocarpus jaborandi plant.
- It stimulates the M and N receptors.
- It penetrates the blood-brain barrier.
- This drug strongly stimulates the parasympathetic system, increasing the secretion of the glands.
- In addition, it accelerates intestinal peristalsis and exerts a strong muscarinic effect on the circulatory system.
- This drug should not be used systemically.

- It is used in glaucoma.
- Polycarpine applied topically to the conjunctival sac, narrows the pupil and increases the outflow of aqueous humor to the eyeball.

PARASYMPATHOMIMETICS WITH INDIRECT ACTION

They work by inhibiting the activity of acetylcholinesterase, causing an increase in acetylcholine concentration in the synaptic cleft, which leads to the intensification and prolongation of the cholinergic effects.

We divide them into two groups:

- drugs that inhibit the reversible activity of acetylcholinesterase,

e.g. physostigmine, neostigmine

- drugs that inhibit "irreversibly" acetylcholinesterase activity,

e.g. fluostigmine, ecothiopathy

PHYSOSTIGMINE

It is a natural alkaloid found in Calabrian broad beans (Physostigma venenosum). The drug is absorbed from the gastrointestinal tract and crosses the blood-brain barrier.

It is applied topically to the conjunctival sac in glaucoma. It is also used as an antidote in poisoning with parasympatholytics, e.g. atropine; sometimes also in overdosing on antihistamines and neuroleptics.

When applied systemically, the cholinergic receptors are stimulated and there are strong muscarinic symptoms.

The antidote is atropine.

NEOSTIGMINE

It is a synthetic compound that does not cross the blood-brain barrier. It must be used parenterally to obtain effective concentrations.

It has a strong effect on the smooth muscle of the intestines and bladder. It directly stimulates N-cholinergic receptors in the neuromuscular junction.

Used topically in the treatment of glaucoma; systemically in the atony of the intestines and bladder. In dogs, it is used for myasthenia gravis together with immunosuppressants. In combination with atropine, it is used as an antidote in myorelaxantia poisoning.

The antidote is atropine.

Indication for systemic use - obstruction of the gastrointestinal tract, urinary tract, bronchial asthma.

DRUGS THAT INHIBIT "IRREVERSIBLY" ACETYLCHOLINESTERASE ACTIVITY

This group of compounds includes organic esters of orthophosphoric acid, which as a result of phosphorylation bind permanently to the ester part of acetylcholinesterase.

Due to their high toxicity, these compounds can be used mainly as insecticides.

Due to the second action of organophosphorus compounds, some of them have found application in the treatment of glaucoma: fluostigmine and ecothiopathic disease.

Fluostigmine (Diflupyl) in the form of drops has properties similar to neostigmine.

Ecothiopathy (Phospholine) is characterized by prolonged action (1-4 weeks).

Quick and easy absorption, crossing the blood-brain barrier and practically "irreversible" action of these compounds favor the occurrence of poisoning.

Symptoms of intoxication as a result of agitation:

M-cholinergic receptors: miosis, drooling, vomiting, diarrhea, intestinal colic, involuntary urination, bradycardia, low blood pressure and life-threatening bronchospasm

N-muscle receptors: muscle tremors, muscle stiffness, paralysis

central cholinergic receptors: ataxia, convulsions, coma with respiratory disorders.

In the first 24 hours after intoxication, attempts may be made to use acetylcholinesterase reactivators, i.e. obidoxime or pralidoxime. Since the reactivators do not cross the blood-brain barrier, diazepam (Relanium) is used to relieve central symptoms.

Acetylcholine antagonists

Due to the different target points of acetylcholine's action, this neurotransmitter is characterized by several specific antagonists. These include compounds that block the appropriate cholinergic receptors.

1. Compounds that block M-cholinergic receptors = parasympatholytics
2. Compounds that block cholinergic N -receptors = ganglioplegics
3. N-muscle receptor blocking compounds = myorelaxantia

1. Parasympatholytic drugs

Parasympatholytics are compounds which block postsynaptic M cholinergic receptors and thus inhibit the muscarinic symptoms of acetylcholine and other agonists of this receptor.

So far, there are no drugs with a parasympatholytic effect by inhibition of synthesis, storage disorders or acetylcholine release.

The prototype drug for this group is atropine.

Atropine (Atropinum sulfuricum)

It is an alkaloid found in plants of the Solanaceae family, such as:

Atropa belladonna

Hyoscyamus niger

Datura stramonium

- This drug is an antagonist of the cholinergic muscarinic receptors: M1, M2, M3.
- Atropine is well absorbed from the gastrointestinal tract and, at higher doses, easily crosses the blood-brain barrier.
- In addition to abolishing the peripheral effects of acetylcholine, atropine in higher doses causes a strong stimulation of the CNS.

<u>The sensitivity of individual effector organs varies</u>

- the sweat and salivary glands are the most sensitive; very small doses are sufficient to limit their activities
- at higher doses, the following are observed: pupil dilation, tachycardia, accommodation disorders, difficulty swallowing, weakened gastrointestinal peristalsis and urine output

- It is used topically in ophthalmic diagnostics to dilate the pupil.
- There are indications for general use, including spastic inflammation of the stomach and intestines, hyperacidity, as a premedication against surgical anesthesia (protection against vagotonic circulatory disorders), bradycardia with arrhythmia.
- Moreover, atropine is an antidote to parasympathomimetic poisoning.

- With the general use of atropine, there may be, inter alia, tachycardia, inhibition of salivation, gastric acid and bronchial mucus, bronchodilation, mydriasis.

- In case of poisoning, loss of consciousness, coma and respiratory paralysis may occur.

Scopolamine (Hyoscine)

- It is an alkaloid found in black hen (Hyoscyamus niger).
- It has a similar structure and properties to atropine. It causes psychodepressive states in humans.
- Scopolamine may be depressant in dogs and cats, while in large animals it causes arousal states.
- In medicine, mainly its derivatives are used, e.g. scopolamine bromide.

Scopolamine butylbromide (Scopolan, Buscopan)

- It is a quaternary derivative of scopolamine and does not cross the blood-brain barrier.
- It has a parasympatholytic effect mainly on the digestive system and the biliary and urinary tract.
- It is used in spastic conditions of the gastrointestinal tract, biliary and urinary tract, diarrhea, and inflammation of the stomach and intestines.
- Parasympatholytic symptoms are less severe than with atropine.

2. Drugs that act on the autonomic ganglia - ganglioplegics

NICOTINE (*NICOTINE SULFATE*)

It is an alkaloid found in tobacco leaves.

It works in two phases on the turns of the autonomous system:

- stimulates N-ganglion receptors
- in high doses it blocks the conduction of impulses in the ganglia as a result of the persistent depolarization of the postsynaptic membrane of the ganglion cells.

It is not broken down by acetylcholinesterase, which prolongs the depolarization state

Nicotine is highly toxic to the CNS. First, it strongly stimulates, then causes a strong depression of the CNS.

As a result of depolarization block, the muscles of the diaphragm and chest are paralyzed, resulting in respiratory depression and death.

Nicotine		
	In small doses	In high doses
the circulatory system	stimulates the autonomic ganglia, reduces the heart rate	paralyzes the autonomic ganglia, the heart rate initially returns to normal, followed by tachycardia
smooth muscles and gastrointestinal glands	vomiting, acceleration of peristalsis, increase in secretory activity of the glands	slowing down of peristalsis, weakening of the secretory functions of the glands
N-muscle receptors	stimulation of receptors in the neuromuscular junction	long-term depolarization of muscles

Synthetic ganglioplegics

- There are many compounds that compete with acetylcholine at the ganglion synapses.
- These include tertiary ammonium compounds, e.g. hexamethonium, pentamethonium, chlorinonsamine; They react with N-ganglion receptors in the ganglion cells, blocking the conduction of impulses in the synapses.
- Unlike nicotine, synthetic ganglioplegics they do not cause initial depolarization.

3. MYORELAXANTIA-MIORELAXANTS

They are skeletal muscle relaxants with peripheral action, inhibiting neuromuscular conduction.

The myorelaxants used disrupt the ability of acetylcholine to stimulate N-muscle cholinergic receptors, resulting in relaxation of skeletal muscles.

One of the drugs that attack the skeletal muscles is curare. Kurara is an extract from various plants of the genus Strychnos. The most important ingredient isolated from curare is d-tubocurarine.

Depending on the mechanism of action, these drugs are divided into two groups:

- compounds that competitively block cholinergic NM receptors, preventing the action of acetylcholine = non-depolarizing miorelaxants
- compounds causing prolonged depolarization of the cholinergic NM receptors = depolarizing myorelaxants

D-TUBOCURARINE - A NON-DEPOLARIZING COMPOUND

- It is practically not absorbed from the gastrointestinal tract.
- When administered intravenously, it works for 30-40 minutes.
- Muscle weakness may last longer due to the slow release of d-tubocurarine from its connections with blood proteins.
- It is used to induce skeletal muscle relaxation during surgical anesthesia.
- Possible occurrence of paralysis of the respiratory muscles, therefore it is recommended to have equipment for artificial respiration when administering them.
- Side effects caused by it are: release of histamine, lower blood pressure and increase in heart rate.
- An overdose is associated with an exacerbation of the symptoms mentioned above. The antidote is neostigmine and pyridostigmine in combination with atropine.

Galamine

It is about 5 times less active than d-tubocurarine, but does not release histamine.

It has a weak parasympatholytic effect, which is manifested by an increase in arterial blood pressure and tachycarida. This relationship is distinguished by the lack of strong side effects.

Pancuronium

it is a drug in the form of bromide, with a 5-fold greater effect than d-tubocurarine.

Does not release histamine. The drug has a weak parasympatholytic effect and has little effect on the ganglia.

Alkuronium

it is a synthetic derivative of the curare alkaloid toxoferrin.

It is slightly more active than d-tubocurarine;

releases little histamine.

It has a weaker antihypertensive effect compared to d-tubocurarine.

Overdose symptoms, contraindications and interactions are the same as for d-tubocurarine.

Muscle relaxants - depolarizing

This group includes suxamethonium and decamethonium, which have a paralytic effect on skeletal muscles.

These compounds, like acetylcholine, depolarize the postsynaptic membrane. However, acetylcholine is immediately hydrolyzed by acetylcholinesterase, whereupon the membrane repolarizes. Suxamethonium depolarizes the motor plate, preventing complete repolarization of the postsynaptic membrane.

These drugs cause filamentous muscle tremors followed by full relaxation of the muscles.

Suxamethonium

- It is broken down very quickly in the blood of humans.
- In animals, enzymatic degradation of the drug over an extended period of time.
- Dogs have an atypical type of pseudocholinesterase, and therefore breakdown of the drug is slowest.
- In cats, the degradation is similar to that in humans (1-2 min).
- Ruminants are sensitive to the drug due to the low levels of pseudocholinesterase in the blood. The undesirable effect depends on the animal species and the organism's baseline condition. Most often it is an adverse effect on the heart, bradycardia, tachycardia, arrhythmia. Administration of hexamethonium or propranolol may reduce the harmful effects on the heart. Drooling sometimes occurs. Pigs may develop hyperthermia.

ACETYLCHOLINE ANTAGONISTS
OF NATURAL AND SYNTHETIC ORIGIN

Group of drugs	Drug	Influence on the receptor
parasymphaticolitics	atropine, scopolamine	M
	homatropine, glycopyrolate	M
ganglioplegics	nicotin (high doses)	Nz
	hexametonium, panametonium	Nz
myorelaxants	D-tubocurarine	Nm
	galamine, pancuronium, alcuronium	Nm
	suxamethonium, decamethonium	Nm