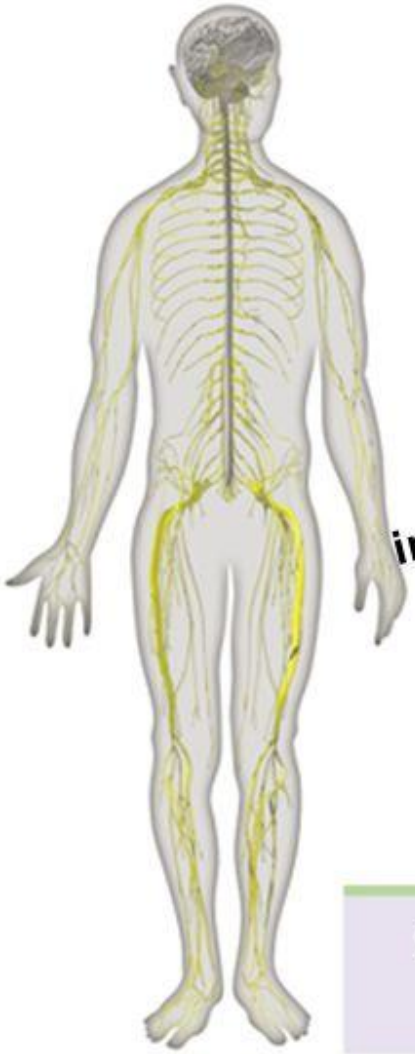
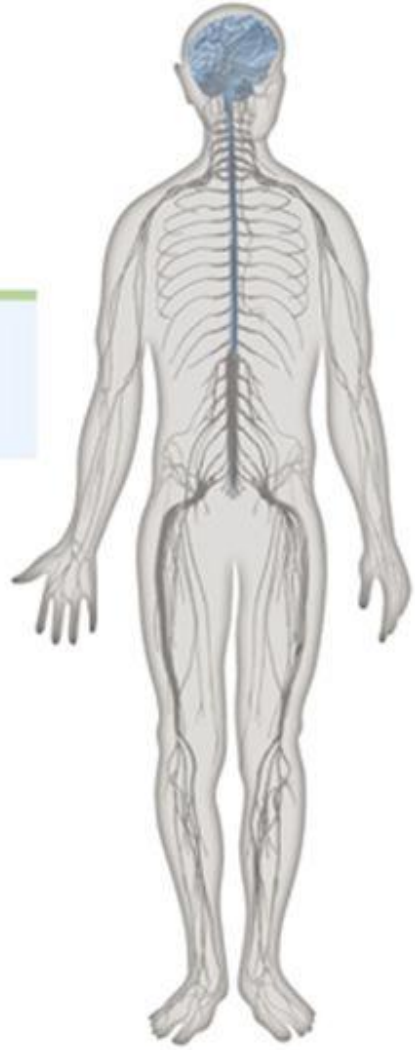
Drugs affecting efferent innervation

Cholinomimetics,

Anticholinesterase drugs

The Nervous System





Nervous system

Peripheral

Central (brain and spinal cord)

involuntary

voluntary

Autonomic (controls self-regulated action of internal organs and glands)

Somatic (controls voluntary movements of skeletal muscles)

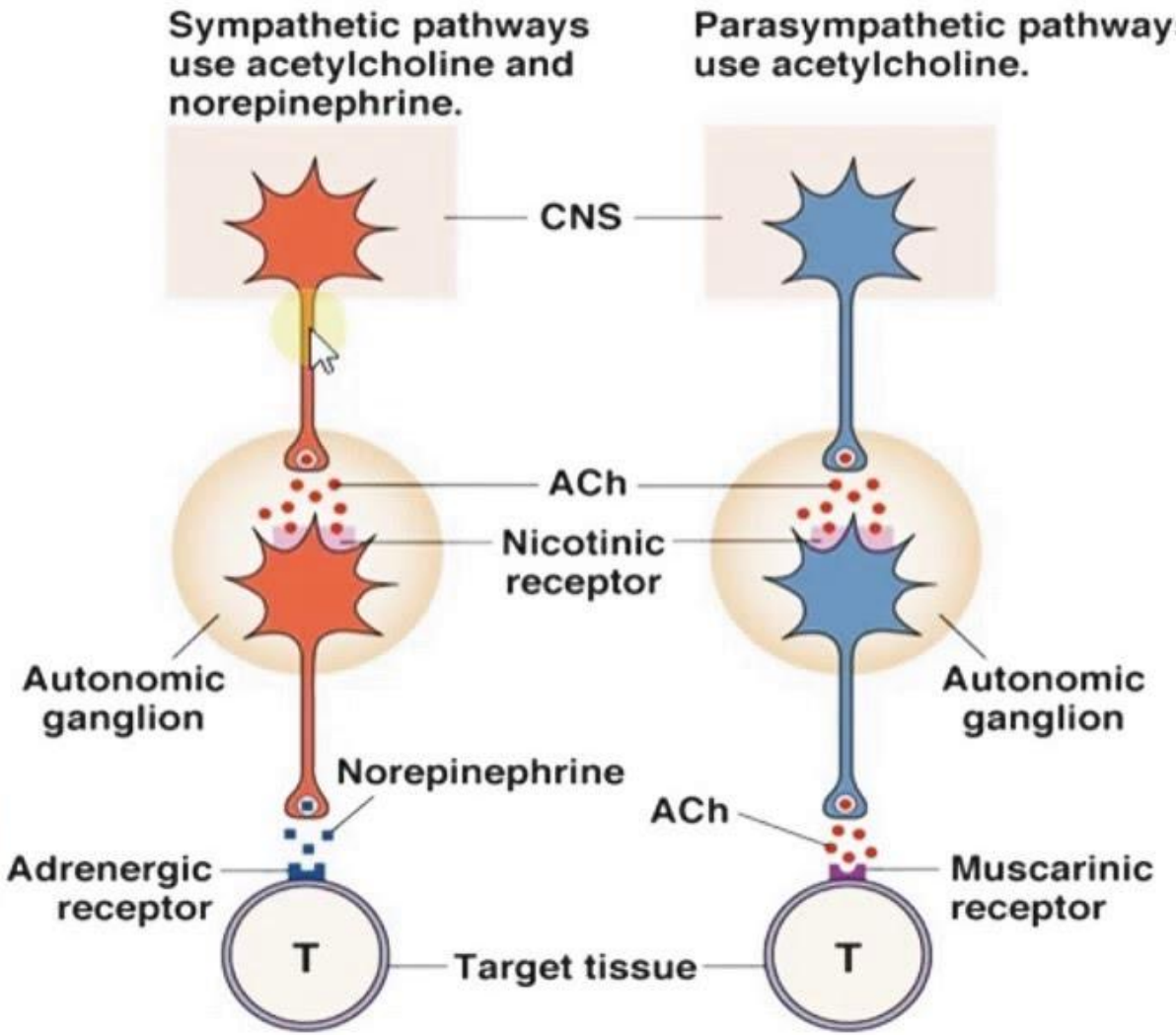
Sympathetic (arousing)

Parasympathetic (calming)

- Efferent innervation of the body occurs via autonomic nerves (innervating visceral organs, blood vessels and glands) and motor nerves of skeletal muscles.
- Autonomic innervation is subdivided into cholinergic (parasympathetic) and adrenergic (sympathetic).
- There are two main mediators: acetylcholine and norepinephrine).

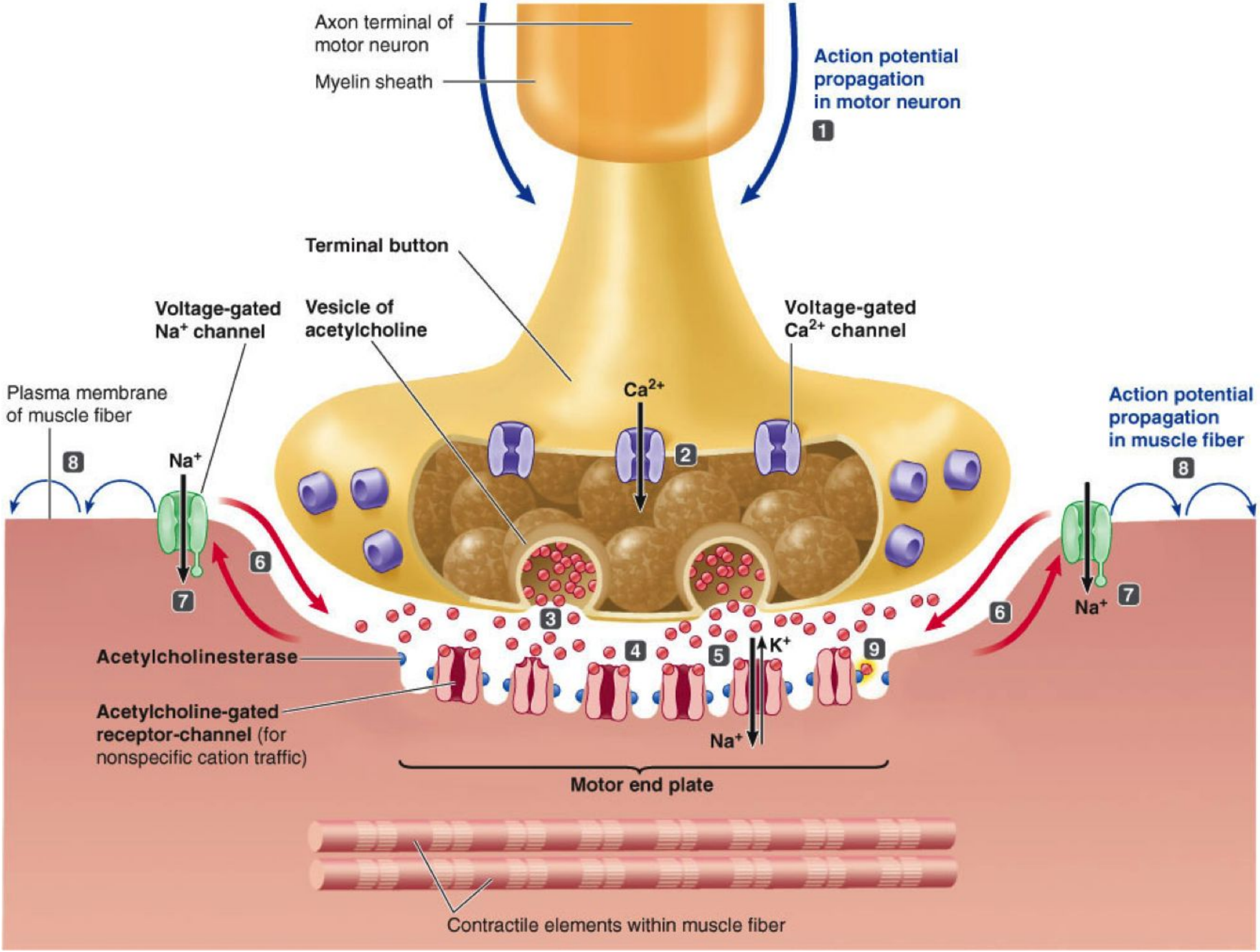
- The efferent pathway of the autonomic nerves consists of two neurons: preganglionic and ganglionic (postganglionic).
- The bodies of preganglionic neurons in the cholinergic system have craniosacral localization. Cranial nuclei are located in the midbrain and medulla oblongata. Cholinergic fibers are inside the pairs of cranial nerves (III, VII, IX, X).
- In the sacral part preganglionic neurons originate from the lateral horns of the spinal cord gray substance.

The Autonomic Nervous System



- In the adrenergic system, the bodies of preganglionic neurons are mainly located in the lateral horns of the thoracolumbar part of the spinal cord.
- Axons of preganglionic neurons terminate at the autonomic ganglia in the synaptic contacts with ganglionic neurons.
- Sympathetic ganglia are located outside the bodies organs, and parasympathetic are mostly located inside the organs.

- Choline is accumulated in cholinergic presynaptic nerve endings via an active transport mechanism linked to a Na+ pump. Acetylcholine is synthesized from choline and acetyl-CoA and accumulated in synaptic vesicles.
- Ach is released from synaptic vesicles.
- Ach interacts with its receptors, but it is inactivated by acetylcholinesterase.


Axon terminal of motor neuron
Myelin sheath
Action potential propagation in motor neuron
1
Terminal button
Voltage-gated Na+ channel
Vesicle of acetylcholine
Voltage-gated Ca2+ channel
Plasma membrane of muscle fiber
Ca2+
Action potential propagation in muscle fiber
8
Na+
2
6
7
3
4
5
K+
9
Acetylcholinesterase
Acetylcholine-gated receptor-channel (for nonspecific cation traffic)
Motor end plate
Contractile elements within muscle fiber

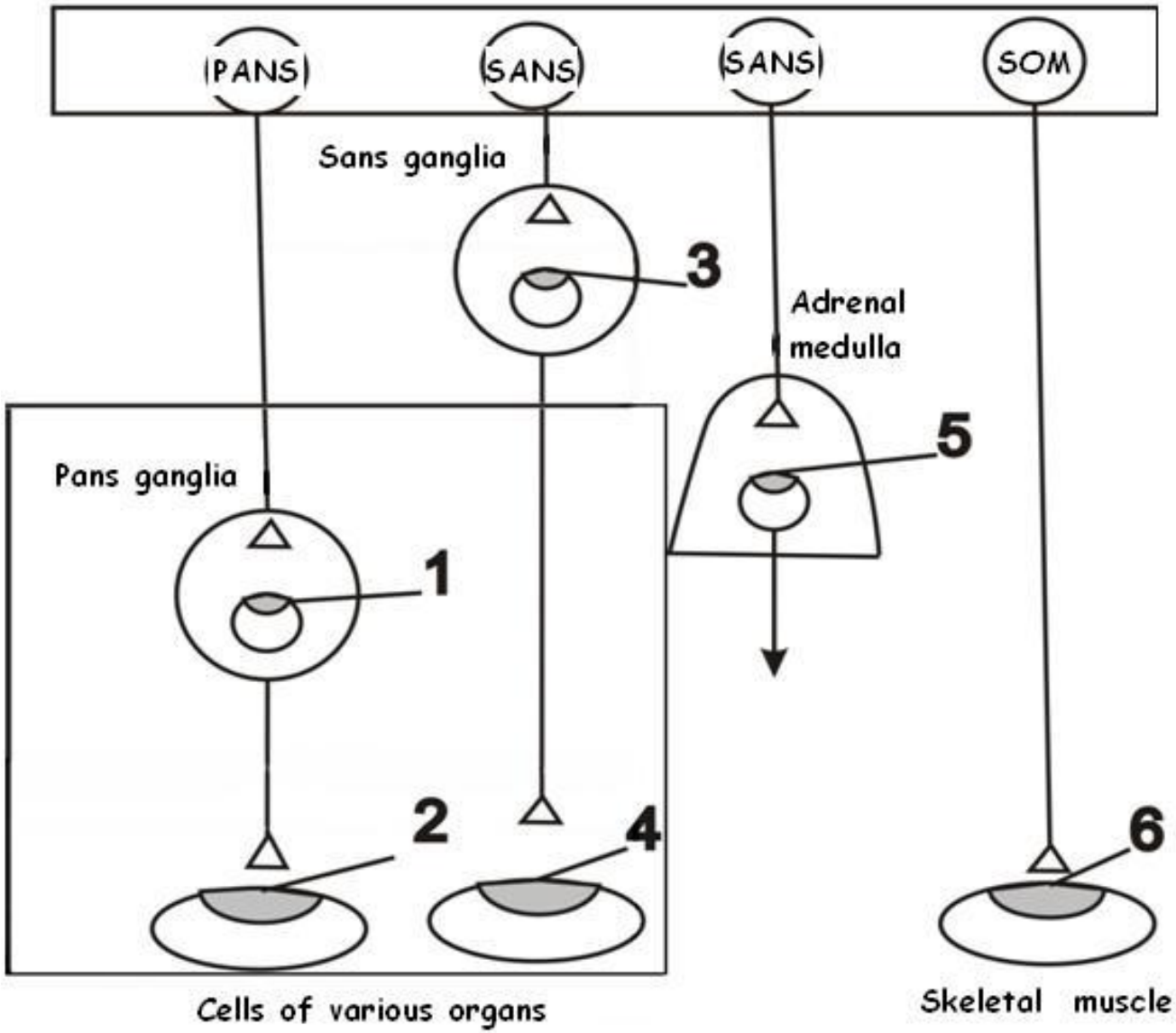
Types of cholinergic receptors: N are nicotine-sensitive M are muscarine-sensitive

Nn (1) are:

- in ganglia,
- in the carotid sinus,
- in the adrenal medulla.

Nm(2) are in skeletal muscles

- M1 are located in the Central nervous system, enterochromaffin cells of the stomach.
- M2 are in the heart.
- M3 are in smooth muscles of organs, glands of external secretion, endothelium of vessels.



N1 – 1,3,5
N2 – 6
M – 2
AR – 4

Mechanism of stimulators of M-cholinoceptors

M1 and M3:

- Activation of Ga proteins
- Activation of phospholipase
- Formation of Inositol-1,4,5 triphosphate
- Increase of Ca content in the cell
- Excitation effects

M2:

- Activation of Gi proteins
- Inhibition of adenylate cyclase
- Reduction of cAMP
- Inhibition of protein kinases
- Reduction of Ca content in the cell
- Oppression of the heart

Classification of ChM:

Direct cholinomimetics:

- **N, M-ChM:** Acetylcholine, Carbacholine
- **M-ChM:** Pilocarpine, Aceclidine
- **N-ChM:** Cytisine (Tabex), Nicotine (Nicorette)

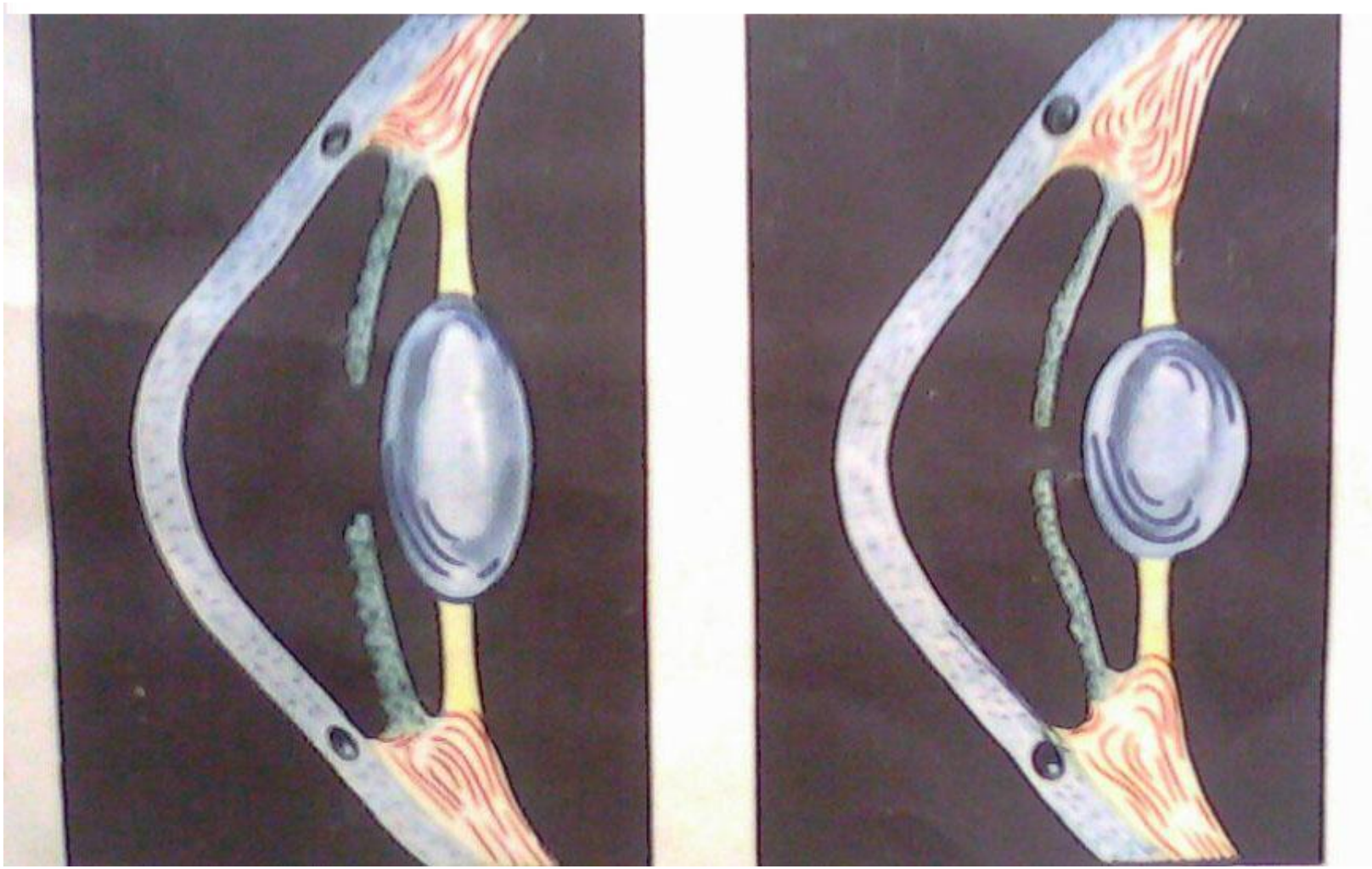
Indirect cholinomimetics (anticholinesterase drugs): Neostigmine, Galantamine, Rivastigmine

- Acetylcholine stimulates his receptors. But it is not used as a drug due to its very short action (several minutes). Acetylcholine is used in experimental pharmacology.
- Carbacholine is analogue of acetylcholine, it is more stable than acetylcholine. It lowers intraocular pressure and is used for the treatment of glaucoma.

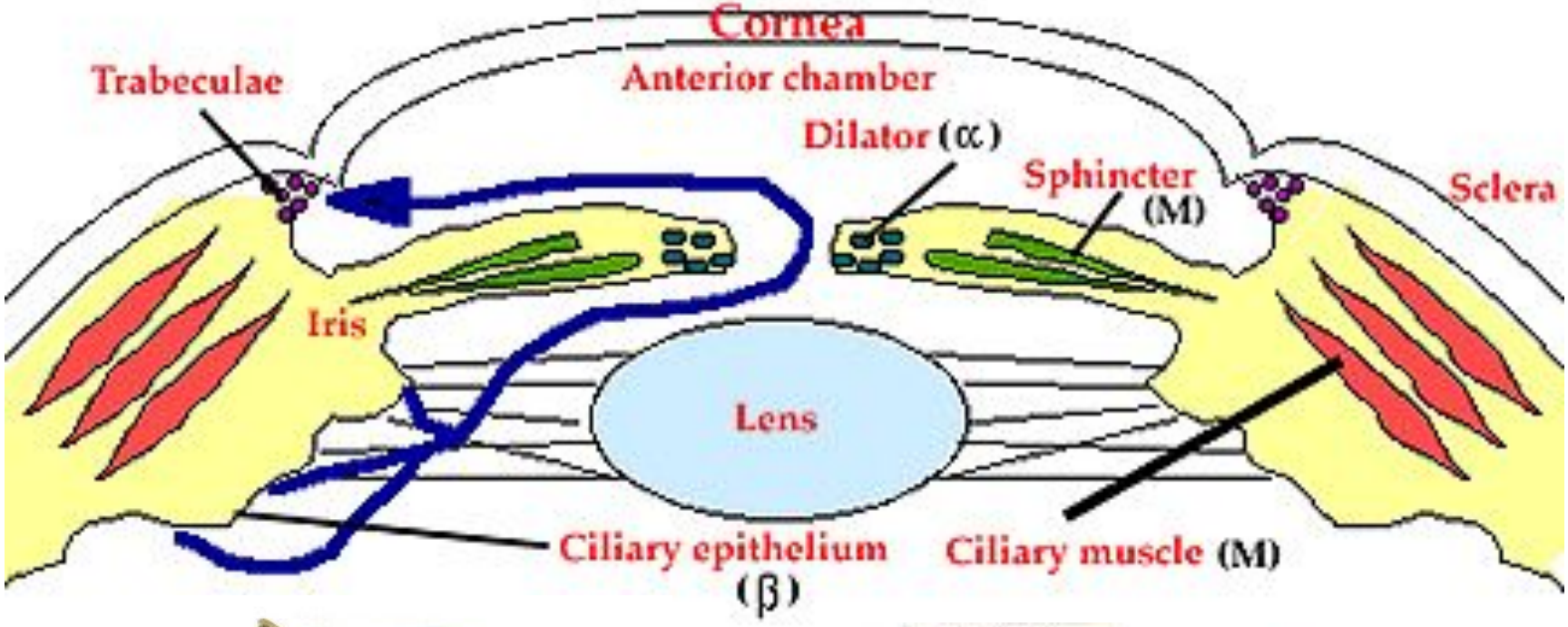
Pilocarpine is an alkaloid, but it is obtained synthetically. It has a direct M-cholinomimetic action. It affects the eye in the following ways:

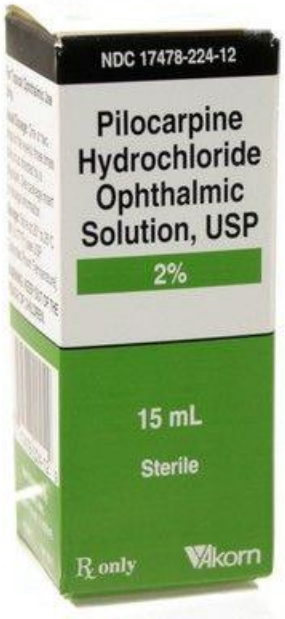
- Causes constriction of the pupils or miosis (contraction of the iris circular muscle – m. cphincter pupillae);
- Causes spasm of accommodation (constriction of the cilliary muscle relaxes the cilliary zonule (ligament of Zinn). Lens curvature increases. The eye is adjusted to the near point of vision.

Pilocarpine



- Decreases intraocular pressure (iris becomes thinner, the angles of the anterior chamber are opened to a greater extent; outflow of the intraocular fluid through the iridocorneal angle space (Fontana's space) to the scleral venous sinus (Schlemm' canal) is improved.
- In clinical practice pilocarpine is administered locally in the form of eye drops to treat glaucoma. It is not used for systemic action.


Cornea
Trabeculae
Anterior chamber
Dilator (α)
Sphincter (M)
Sclera
Iris
Lens
Ciliary epithelium (β)
Ciliary muscle (M)


NDC 17478-224-12
Pilocarpine Hydrochloride Ophthalmic Solution, USP
2%
15 mL
Sterile
℞ only
Akorn


Alcon
Isopto® Carbachol 3%
(carbachol ophthalmic solution)
15 mL Sterile
Alcon
Isopto® Carbachol 3%

Aceclidine is a synthetic drug. It causes:

- bradycardia, inhibition of atrioventricular conduction, ↓of blood pressure;
- ↑smooth muscle tone (bronchi, intestine, gallbladder, bile ducts, bladder, uterus);
- ↑secretion of exocrine glands (bronchi, intestine, salivary, lacrimal, nasopharyngeal glands).

- **Indications f**or use: glaucoma (pilocarpine, aceclidine), xerostomia, atony of the bladder, intestines, weakness of labor (aceclidine).
- **Contraindications:** bronchial asthma, ulcer, AV-blockade.

Aceclidine Atropine

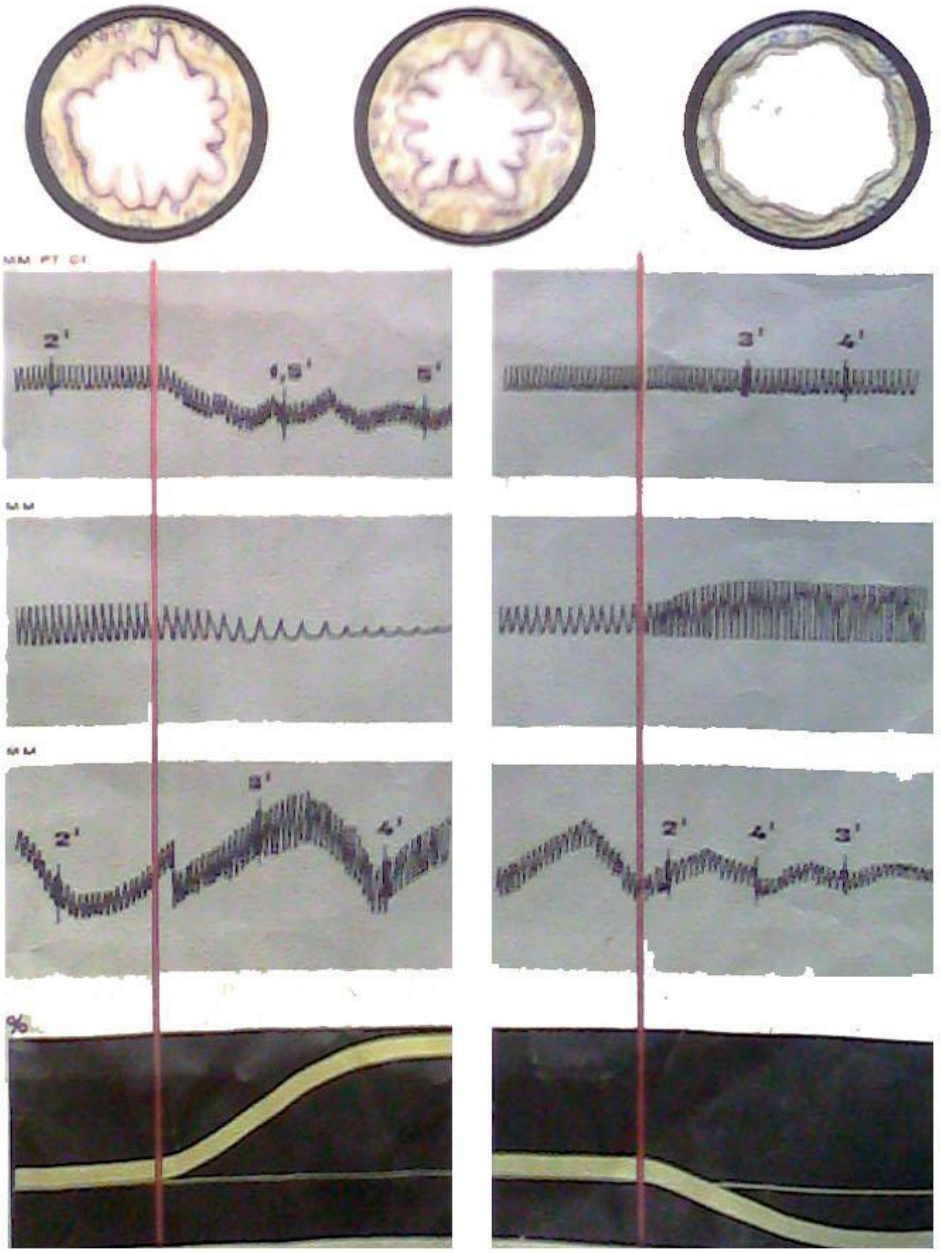
the tone of
the bronchi

blood pressure

heart rate

the tone
of the intestine

the secretion of
the salivary glands



Clinic of a poisoning with Amanita :

- Dyspeptic disorders (abdominal pain, diarrhea, vomiting),
- Difficulty breathing (bronchospasm, wheezing, increased secretion of the bronchial glands),
- Profuse sweating, moist, cool skin,
- Bradycardia, miosis, myopia, pain in superciliary arcs,
- Central nervous system - excitation, disorientation.

Help: Atropine

Anticholinesterase drugs

Drugs of revesible action bind with anionic and esteratic sites of the enzyme. They inhibit it for several hours. They prevent the hydrolysis of acetylcholine and increase its level. Acetylcholine stimulates its receptors. Among this drugs there are alkaloids or tertiary amines (galantamine) and

quaternary amines (neostigmine). Alkaloids go through the BBB, neostigmine doesn't.

- Drugs of irreversible actions connect with esteratic site of enzyme by covalent bond. Cholinesterase activity is restored after synthesis of its new molecules. These substances are released from the bond very slowly.
- There are insecticides, herbicides, fungicides, combat toxic substances-sarin, Zaman, Vi-gases among these substances.

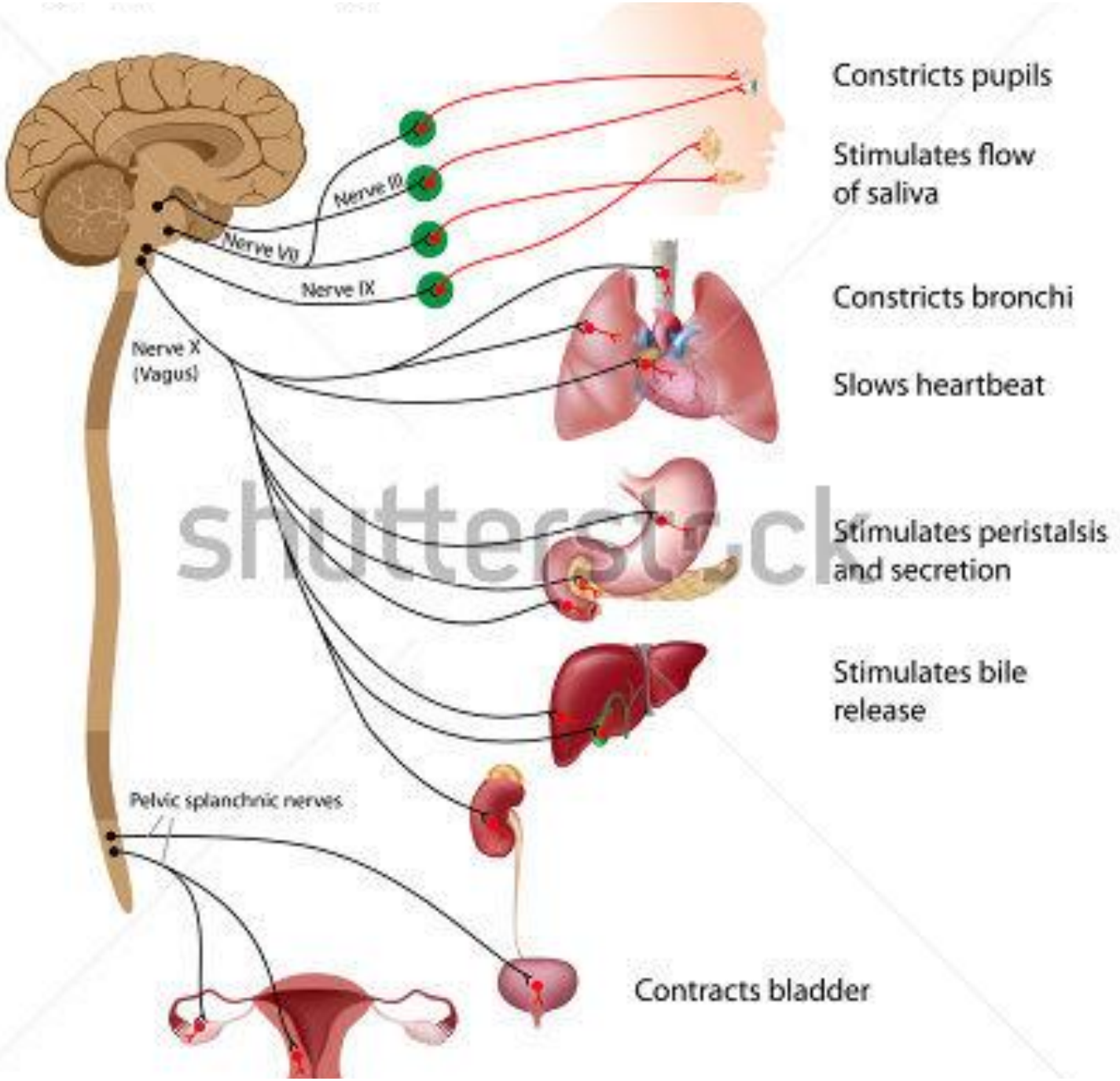
Main effects

Ocular effects: miosis, ↓intraocular pressure, spasm of accommodation.

Resorptive:

- ↑ smooth muscle tone (bronchi, intestine, gallbladder, bile ducts, bladder, uterus);
- ↑secretion of exocrine glands (bronchi, intestine, salivary, lacrimal, nasopharyngeal glands).

- Bradycardia, ↓ AV conduction, ↓ of blood pressure in therapeutic doses, but tachycardia, ↑ blood pressure (in large doses). Effect on the heart contraction rate is not only associated with excitation of its M-cholinoceptors, but also with the stimulation of cholinoceptors in the sympathetic ganglia, adrenal medulla and centers of the medulla oblongata).
- Improvement of neuromuscular transmission (nicotinic effect also).


Nerve III
Nerve VII
Nerve IX
Nerve X
(Vagus)
Pelvic splanchnic nerves
Constricts pupils
Stimulates flow of saliva
Constricts bronchi
Slows heartbeat
Stimulates peristalsis and secretion
Stimulates bile release
Contracts bladder

Central effects

- They increase the content of ACH in neocortex and hippocampus, increase motor and mental activity, normalize impaired mental activity.
- Indications for use: Alzheimer's disease, in post-stroke conditions, accompanied by a decrease in intelligence (rivastigmine, donepezil, galanthamine).

Indications for use

- Glaucoma,
- Atony of the intestine, bladder,
- Weakness of labor,
- Myasthenia gravis, paresis, paralysis, Alzheimer's disease,
- Overdose of anticholinergics (atropine and muscle relaxants, poisoning by alkaloids of Belladonna, Datura, Henbane).

Poisoning with anticholinesterase drugs of irreversible actions. Clinic. Treatment

- Myosis, myopia;
- Increased sweating, wet cold skin;
- Salivation, vomiting, diarrhea, abdominal pain;
- Suffocation (bronchospasm, hypersecretion of the bronchial glands);
- Bradycardia, tachycardia; increase / decrease in blood pressure;

- Muscle twitches, tremors, cramps;
- Excitation of the CNS.
- In severe cases: Central nervous system inhibition, ↓ BP.
- Death from paralysis of the respiratory center.

Treatment

1. Organophosphates must be removed from the sites of introductions. The skin and mucous membranes should be washed with 3-5% solution of sodium bicarbonate. The stomach is lavaged, adsorbing and laxative drugs are given, high siphon enemas are administered.
2. Elimination with urine should be accelerated by means of the forced diuresis.
3. Hemosorption, hemodialysis, peritoneal dialysis.

Antidotes:

- Atropine in high doses blocks M-cholinoceptors.
- Cholinesterase reactivator: Trimedoxime and isonitrosinum. They interact with organophosphates residuals that are bound with acetylcholinesterase, releasing the enzyme and restoring its physiological activity. They are effective during the first few hours after poisoning

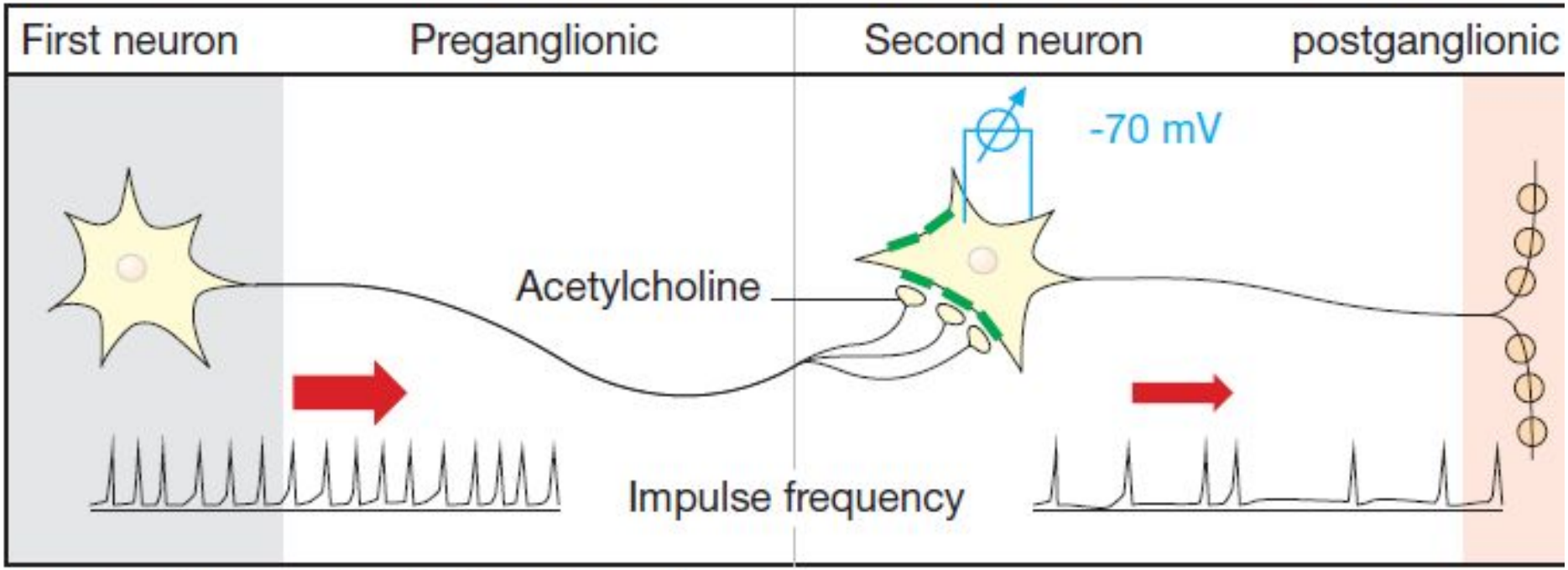
Nicotine is an alkaloid of tobacco leaves. It is used in experimental pharmacology to analyze the mechanism of drugs action.

Nicotine affects both central and peripheral N-cholinoceptors. It has a two-phase effect because it stimulates N-CR in low doses but it blocks them when it is used in high doses.

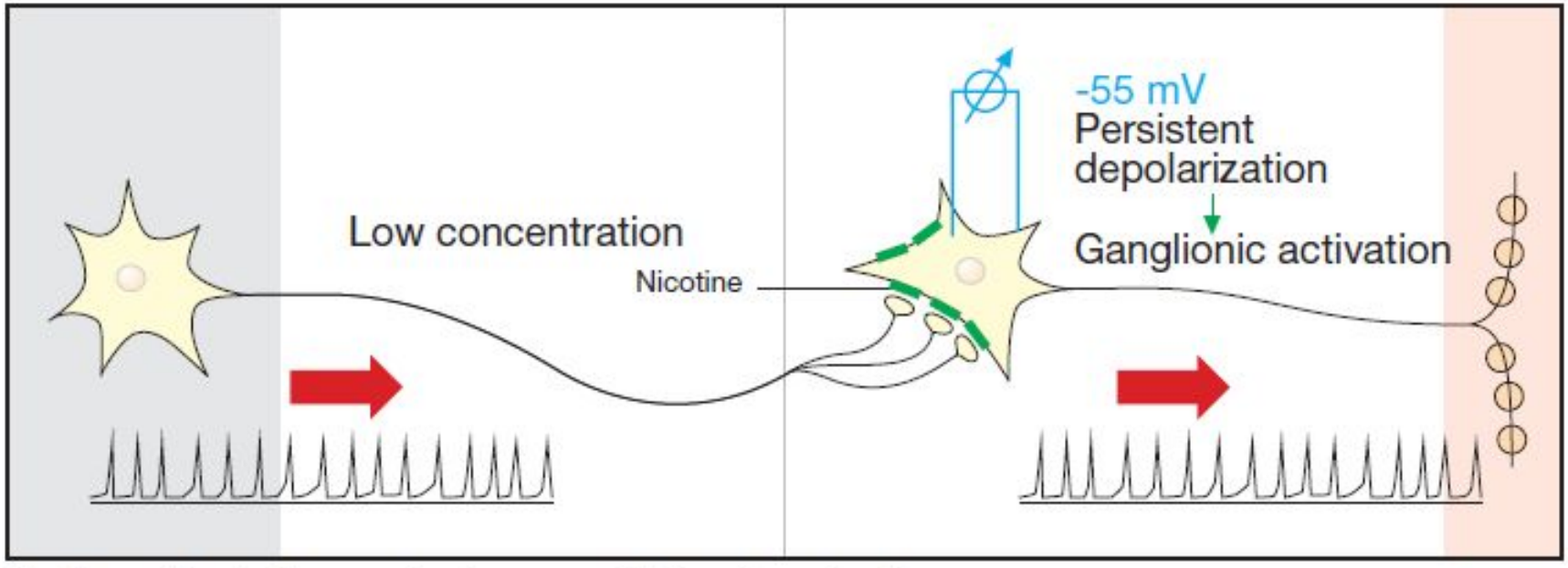
Tolerance and dependence develop to nicotine.

- Nicotine interacts with N-CR of the autonomic ganglia and changes the functions of organs.
- N. stimulates the chemoreceptors of the sinocarotid zone and reflexively activates respiratory and vasomotor centers. In high doses N. causes the inhibition of these centers.
- In low doses N. stimulates N-cholinoceptors of the chromaffin cells of the adrenal glands and increases the release of epinephrine. In high doses it causes the opposite effect.

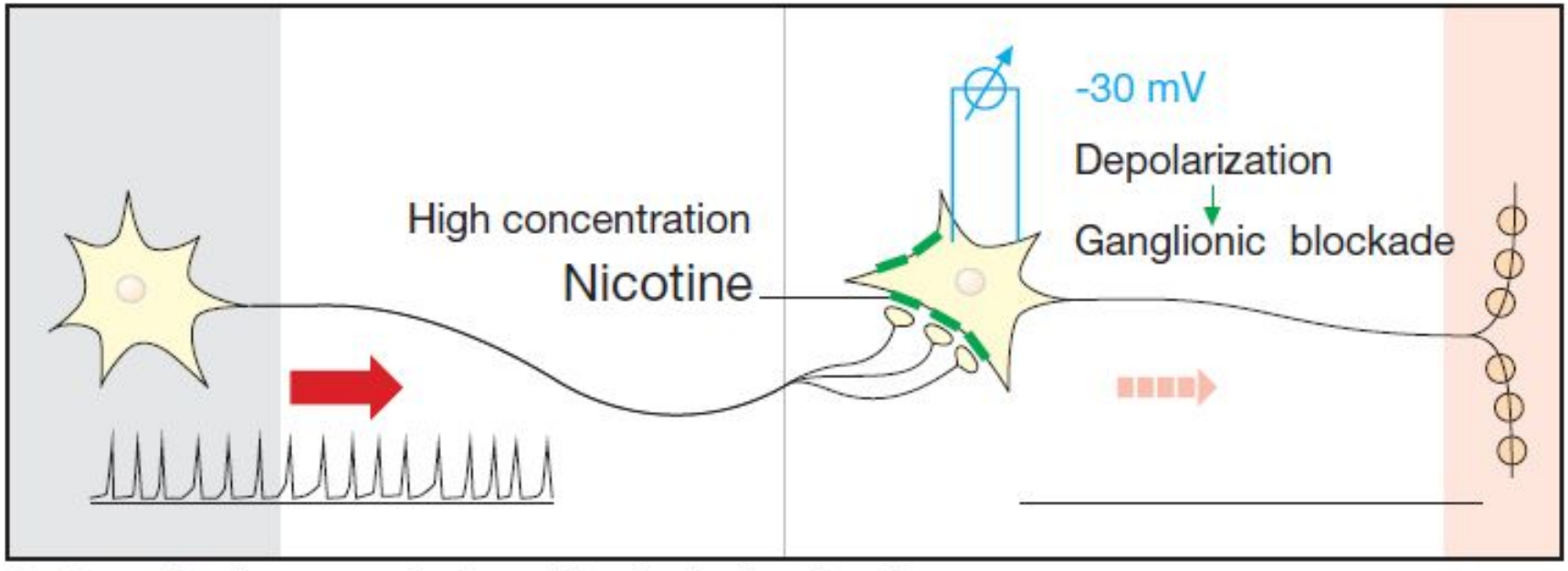
- Nicotine has a marked effect on the CNS. It increases the release of dopamine into the Central nervous system, a person experiences the pleasure of smoking. If a person does not smoke, dopamine levels drop and the person feels unwell. Dependence to nicotine develops.



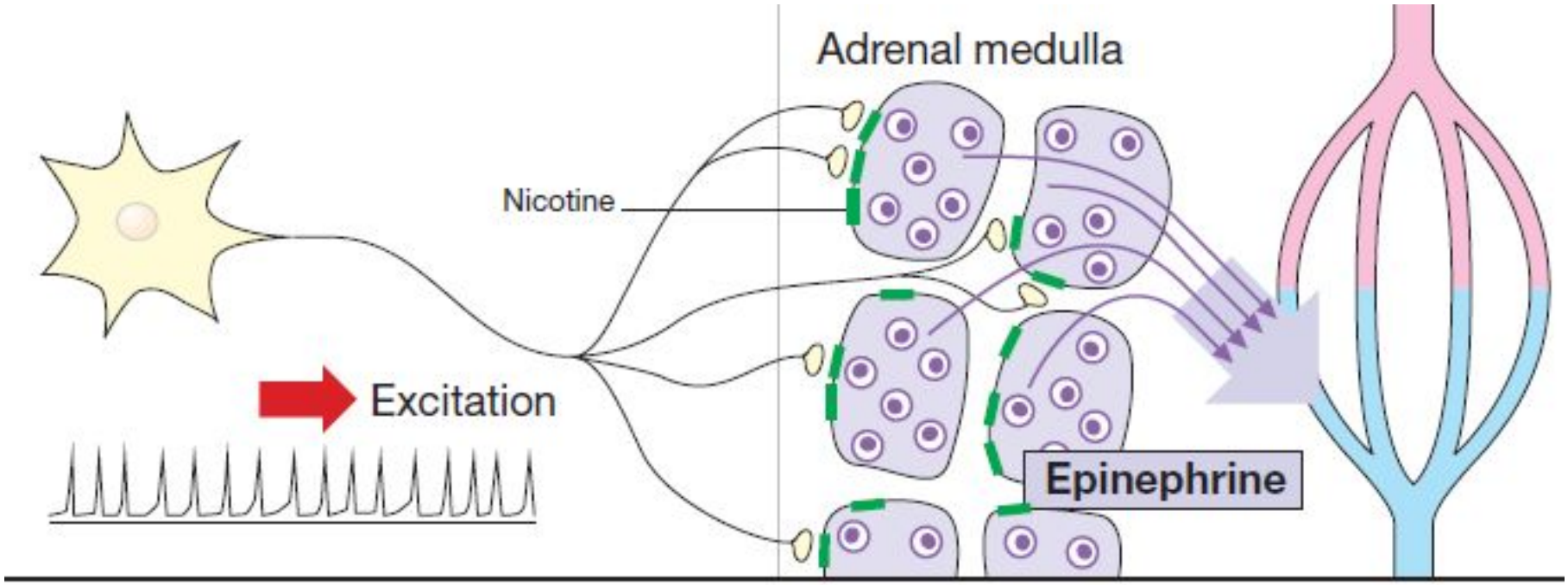
A. Ganglionic transmission: normal state



B. Ganglionic transmission: excitation by nicotine



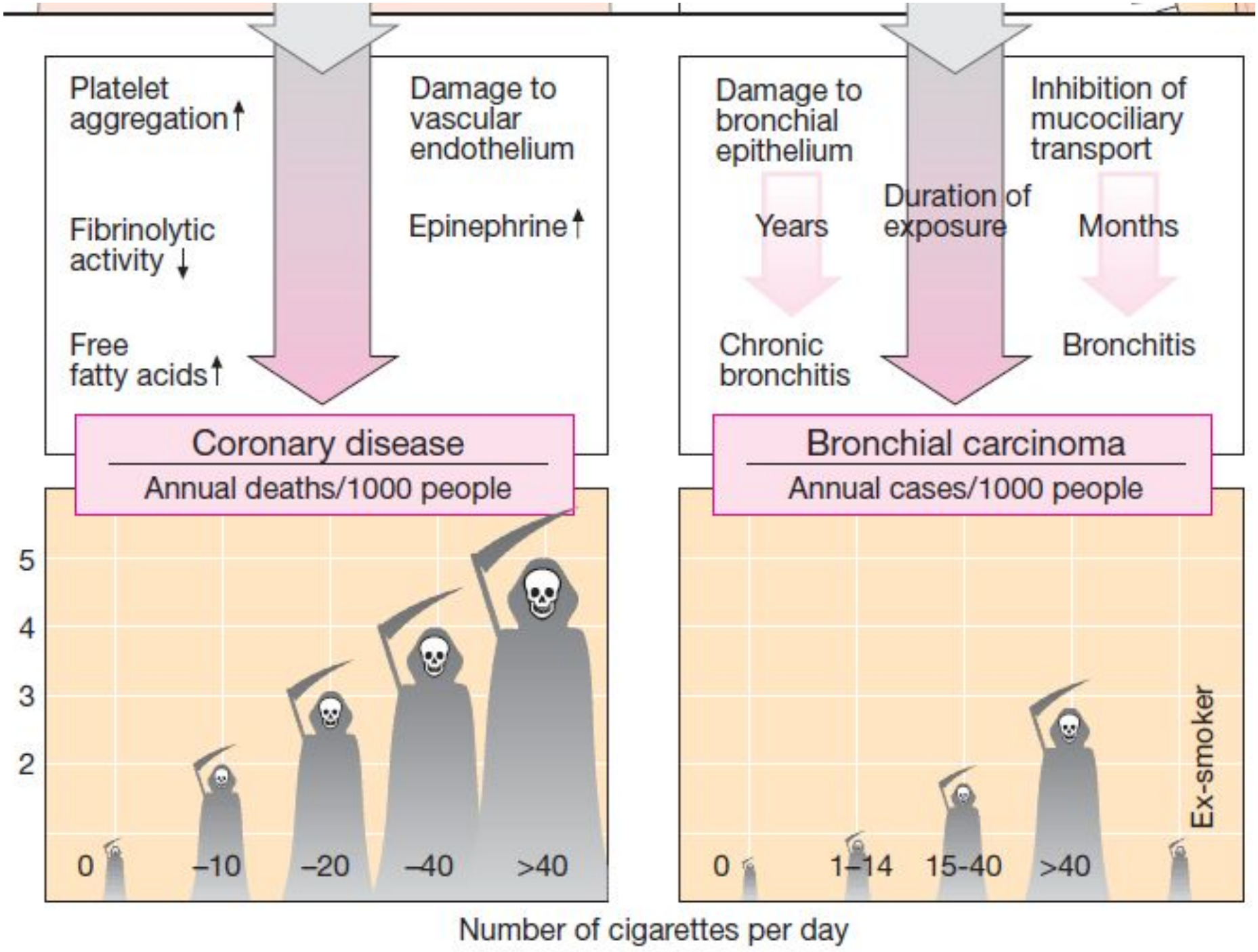
C. Ganglionic transmission: blockade by nicotine



Adrenal medulla: epinephrine release by nicotine

Effects of nicotine

Effects	Low doses	High doses
The heart rate	↓	↑
Blood pressure	↑	↓
Intestinal motility	↑	↓
The secretion of exocrine glands	↑	↓


Platelet aggregation ↑
Fibrinolytic activity ↓
Free fatty acids ↑
Damage to vascular endothelium
Epinephrine ↑
Coronary disease
Annual deaths/1000 people
5
4
3
2
0
–10
–20
–40
>40
Damage to bronchial epithelium
Inhibition of mucociliary transport
Years
Duration of exposure
Months
Chronic bronchitis
Bronchitis
Bronchial carcinoma
Annual cases/1000 people
0
1–14
15-40
>40
Ex-smoker
Number of cigarettes per day

Acute poisoning

- Abdominal pain, vomiting, nausea, diarrhea,
- Raised sweating,
- Headache, dizziness, visual impairment, hearing disorders, disorientation.

In severe cases: lowering of blood pressure, oppression of the heart, oppression of the respiratory center.

Help: Adsorbents, gastric lavage; Anticholinergics; artificial ventilation, symptomatic therapy

- N. in low doses can be used for the treatment of tobacco dependence. It stimulates receptors and helps stop Smoking. We can used for example:

- Cytisine is sometimes used in clinical practice as respiratory stimulant of reflex action. It stimulates receptors of carotid sinus. It stimulates receptors of adrenal medulla, increases the release of epinephrine and increases arterial pressure.
- Indications: depression of breathing (morphine poisoning, carbon monoxide, drowning, injury), to aid “quitting” smoking.

- Cytisine is an analeptic because it restores depressed breathing and reduced pressure. It is effective only after intravenous administration.