UNIT: CHOLINERGIC DRUGS

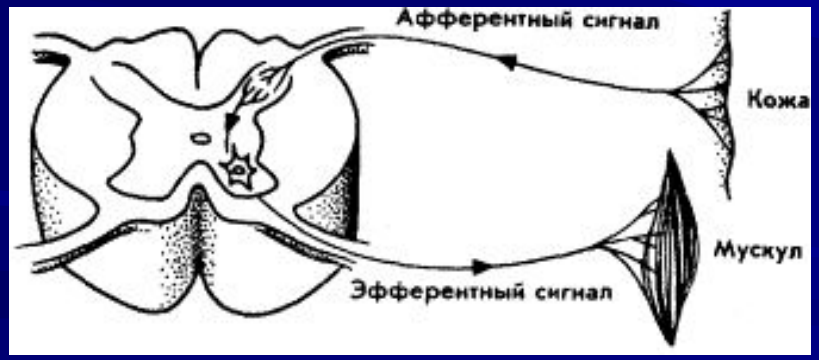
THEME: CHOLINOMIMETIC AND ANTICHOLINESTERASE DRUGS

SMOLENSK STATE MEDICAL ACADEMY

PHARMACOLOGY DEPARTMENT

Peripheral nervous system

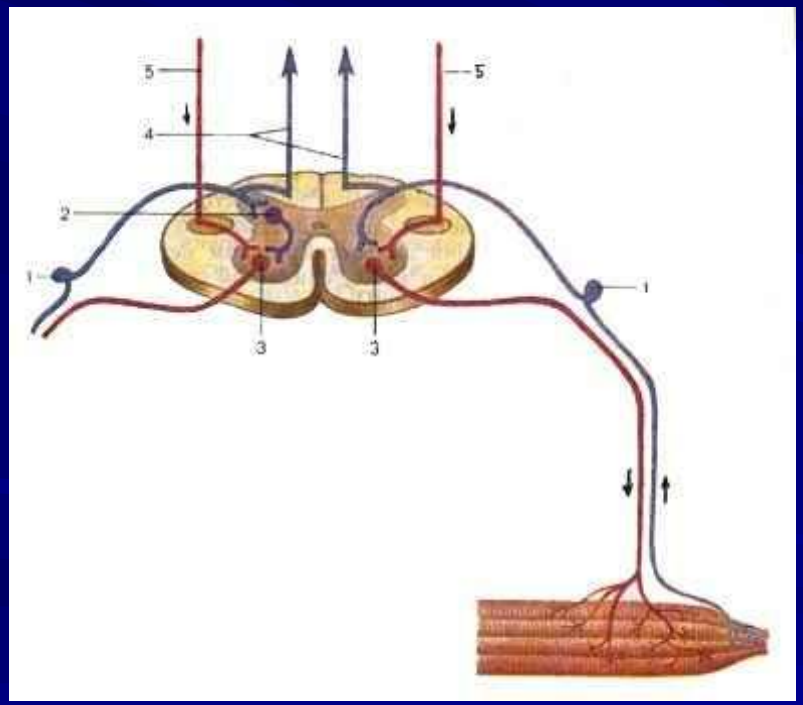
- Peripheral nervous system consists of afferent (sensory) and efferent nerve fibers which participate in regulation of vital activity of an organism



Reflex principle underlies nerve regulation

Peripheral nervous system

- R E F L E X is a response of an organism to irritation of sensory receptors



Each reflex is realized by means of reflex arch

Classification of drugs acing on PNS

- Drugs acting on afferent innervation
- **Drugs inhibiting afferent nerve fibers**
- **Drugs inhibiting afferent nerve fibers**
- Drugs acting on efferent innervation
- Cholinergic agents – acting on cholinergic transmission
- Adrenergic agents – acting on adreneric transmission

Cholinergic synapse

The neurotransmission in a cholinergic synapse is realized by the acetylcholine release from:

Preganglionic nerve fibers	Postganglionic nerve fibers	Efferent nerve fibers
↓	↓	↓
Parasympathetic and sympathetic nerve systems	Parasympathetic nerve system	Somatic nerve system

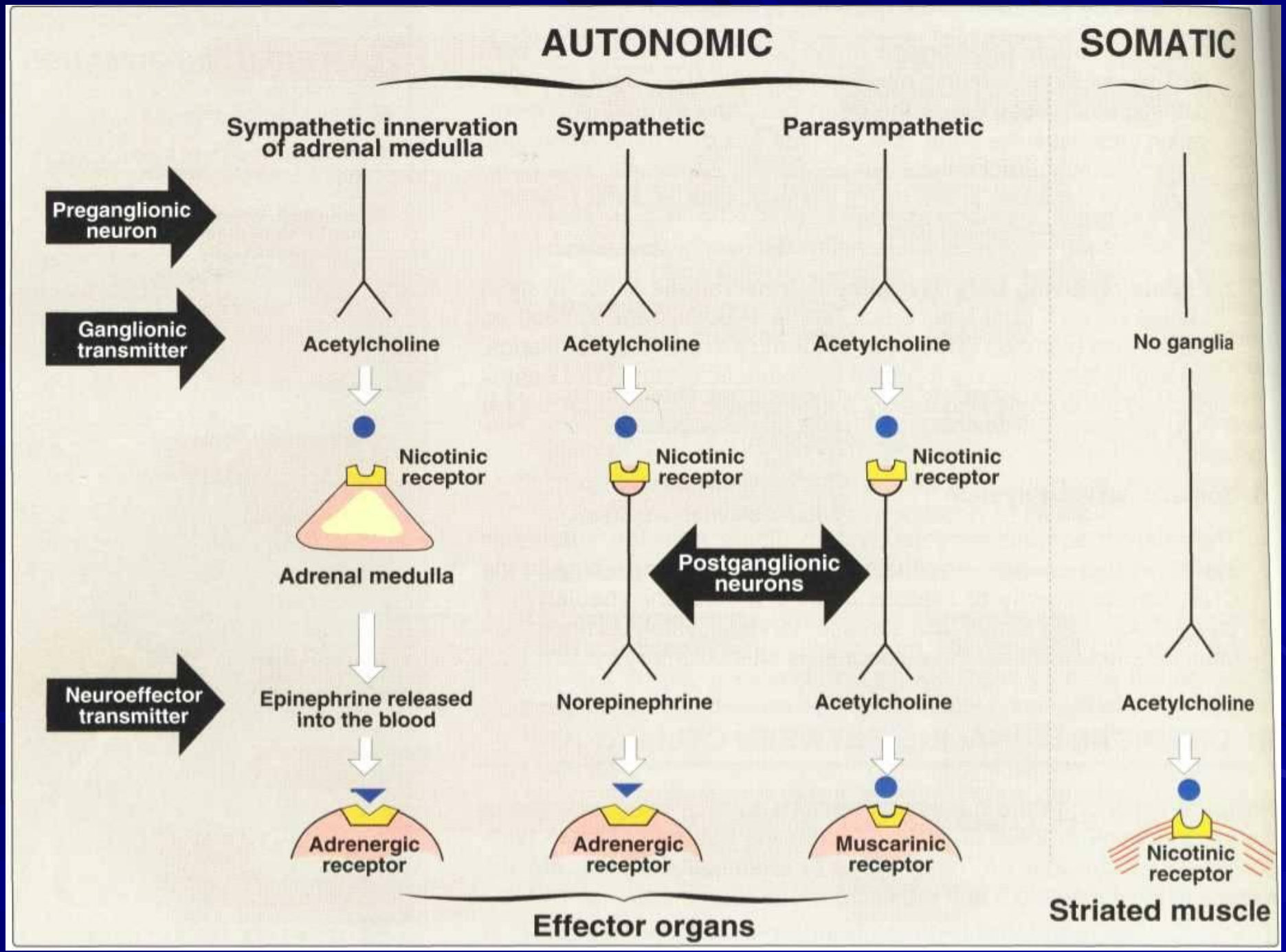
and acetylcholine acts on cholinoceptors located on:

Cells of adrenal medulla

Autonomic ganglia

Cells of internals

Striated muscles


AUTONOMIC
SOMATIC
Sympathetic innervation of adrenal medulla
Sympathetic
Parasympathetic
Preganglionic neuron
Ganglionic transmitter
Neuroeffector transmitter
Acetylcholine
Acetylcholine
Acetylcholine
No ganglia
Nicotinic receptor
Nicotinic receptor
Nicotinic receptor
Adrenal medulla
Postganglionic neurons
Epinephrine released into the blood
Norepinephrine
Acetylcholine
Acetylcholine
Adrenergic receptor
Adrenergic receptor
Muscarinic receptor
Nicotinic receptor
Effector organs
Striated muscle

Neurotransmitter acetylcholine is synthesized in a cholinergic nerve ending from:

acetyl-CoA

choline

choline acetyl transferase catalyzes the reaction

The synthesized neurotransmitter is transported into into vesicles where is packed
(in vesicles acetylcholine is protected from degradation)

The transmitter release occurs, when voltage-sensitive calcium channels
in the presynaptic membrane become opened,
providing influx of calcium ions.

It happens when an action potential arrives
at a nerve ending

Increase in endocellular concentration of calcium occurs and in turn, it causes the fusion of vesicles with membrane surface and release of their content (Ach, co-transmitters- ATP) into the synaptic cleft by exocytosis.

The released acetylcholine binds to:

postsynaptic receptors

presynaptic receptors

muscarinic

nicotinic

Binding of acetylcholine to postsynaptic receptors results in a biological response within cells of target organs (the myocardium, g.i.t., excretory glands, eyes, etc)

Binding of acetylcholine to presynaptic receptors results in discontinuation of its release (negative feedback mechanism)

(by acetylcholine action), the **acetylcholinesterase** terminates the Ach action by its hydrolysis with formation of:

choline

acetate

Choline formed is actively uptaken by the axonal membrane (by a Na+:choline cotransporter) and is used for acetylcholine resynthesis again.

Is removed

Flash movie describing nerve impulse conduction in a synapse

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gettyimages
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Cholinergic receptors:

Cholinergic receptors are protein macromolecules having specific sensitivity to acetylcholine.

They are not homogeneous.

Two basic groups of cholinoceptors such as **M-cholinoceptors and N- cholinoceptors** have been identified with the help of natural alkaloids.

Receptors which have high sensitivity to muscarine (alkaloid of the mushroom *fly-agaric*) are called **M - cholinoceptors** (muscarinic receptors).

fly agaric

There are 5 subtypes of muscarinic receptors:

M1, M3 and M5 subtypes lead to cellular excitation (stimulant receptors)

M2, M4 subtypes inhibit cellular excitation (inhibitory receptors)

Localization of muscarinic receptors:

M_1

On ganglion cells and central neurones, escpecially in cortex, hyppocampus and corpus striatum. It plays a major role in mediating gastric secretion, relaxation of LES, in learning, memo- ry, motor functions

M_2

on effector cells of myocardium and presynaptic membrane (cholinergic nerve ending)

M_3

on smooth muscles of g.i.t., bronchi, urogenital system, on eye muscles, on excretory glands

In blood vessels non-innervated muscarinic receptors (off- synaptic M - cholinoceptors) have been found.

Nicotinic (N) – cholinoceptors:

N - cholinoceptors have high sensitivity to nicotine like to acetylcholine.

Nicotine is known as alkaloid of tobacco leaves nicotine.

Localization of nicotinic receptors:

in the CNS,
adrenal medulla,
autonomic ganglia
neuromuscular junctions,
sinocarotid zones

N_N receptors – are located on ganglionic cells

N_M receptors – at skeletal muscle endplate

Tabacco leaves

Classification of cholinomimetics:

Cholinomimetics with direct action:

M, N – cholinomimetics

Acetylcholine
Carbachol
Metacholine

M – cholinomimetics

Pilocarpine
Aceclidine

N – cholinomimetics

Lobeline &Cytitone
"Lobesil &Tabex
Nicotine (TTS, Chewing gum)
Varenicline
Bupropion

Cholinomimetics with indirect action:

Stimulators of acetylcholine presynaptic release

Cisapride
Ceruletide
Pymadine

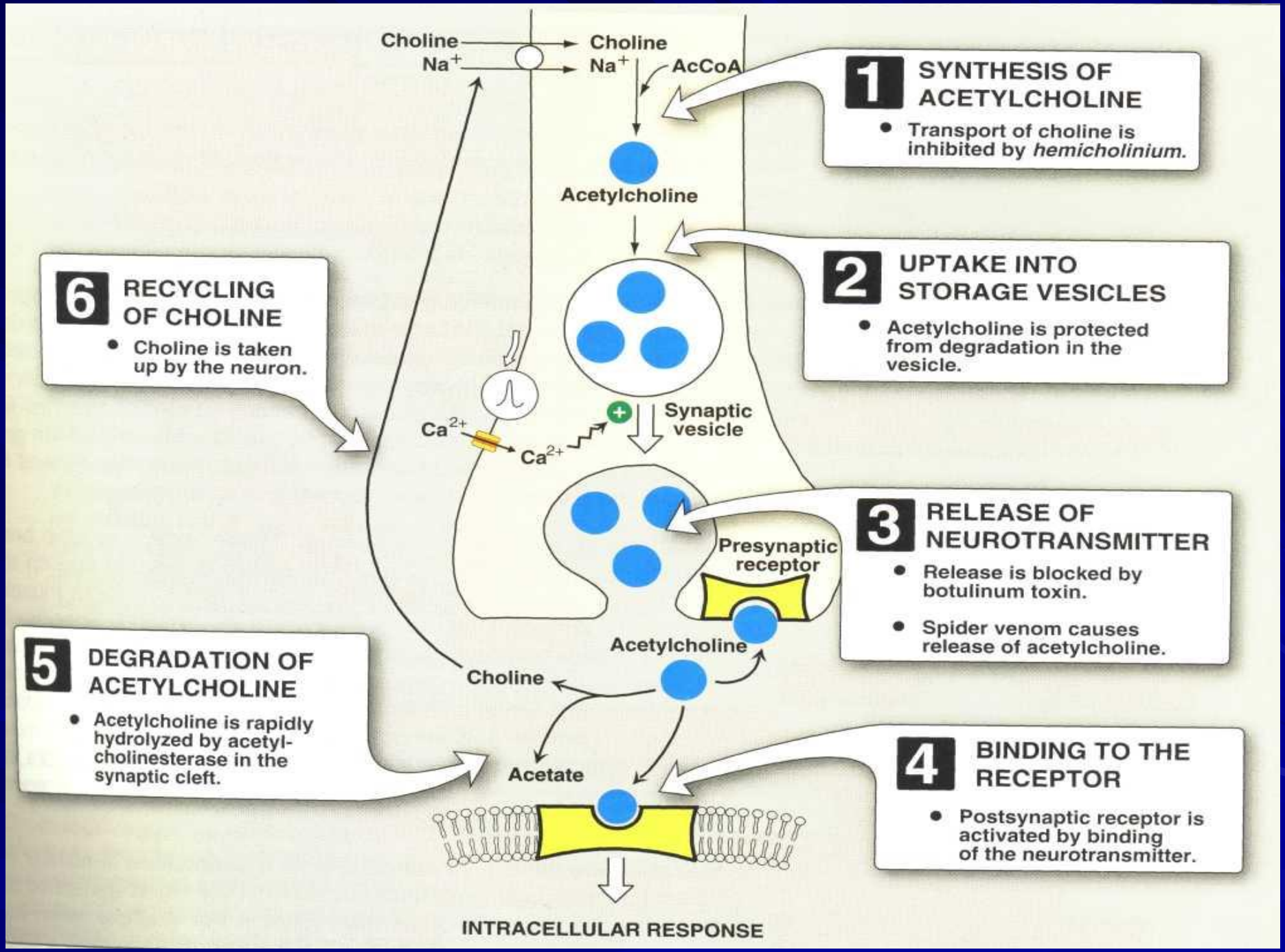
Anticholinesterases

reversible

Neostigmine
Physostigmine
Galantamine
Pyridostigmine
Rivastigmine
Tacrine
Donepezil
Edrophonium

irreversible

Armine
Ecothiophate
Dyplos
Malathion
Diazinon
Tabun, Sarin, Soman


Choline
Na+
Choline
Na+
AcCoA
1 SYNTHESIS OF ACETYLCHOLINE
• Transport of choline is inhibited by hemicholinium.
Acetylcholine
2 UPTAKE INTO STORAGE VESICLES
• Acetylcholine is protected from degradation in the vesicle.
6 RECYCLING OF CHOLINE
• Choline is taken up by the neuron.
Ca2+
Ca2+
Synaptic vesicle
3 RELEASE OF NEUROTRANSMITTER
• Release is blocked by botulinum toxin.
• Spider venom causes release of acetylcholine.
Presynaptic receptor
Acetylcholine
Choline
5 DEGRADATION OF ACETYLCHOLINE
• Acetylcholine is rapidly hydrolyzed by acetyl-cholinesterase in the synaptic cleft.
Acetate
4 BINDING TO THE RECEPTOR
• Postsynaptic receptor is activated by binding of the neurotransmitter.
INTRACELLULAR RESPONSE

Molecular mechanism of cholinomimetic action:

Stimulatory action

M1, M3 -receptors (activating)

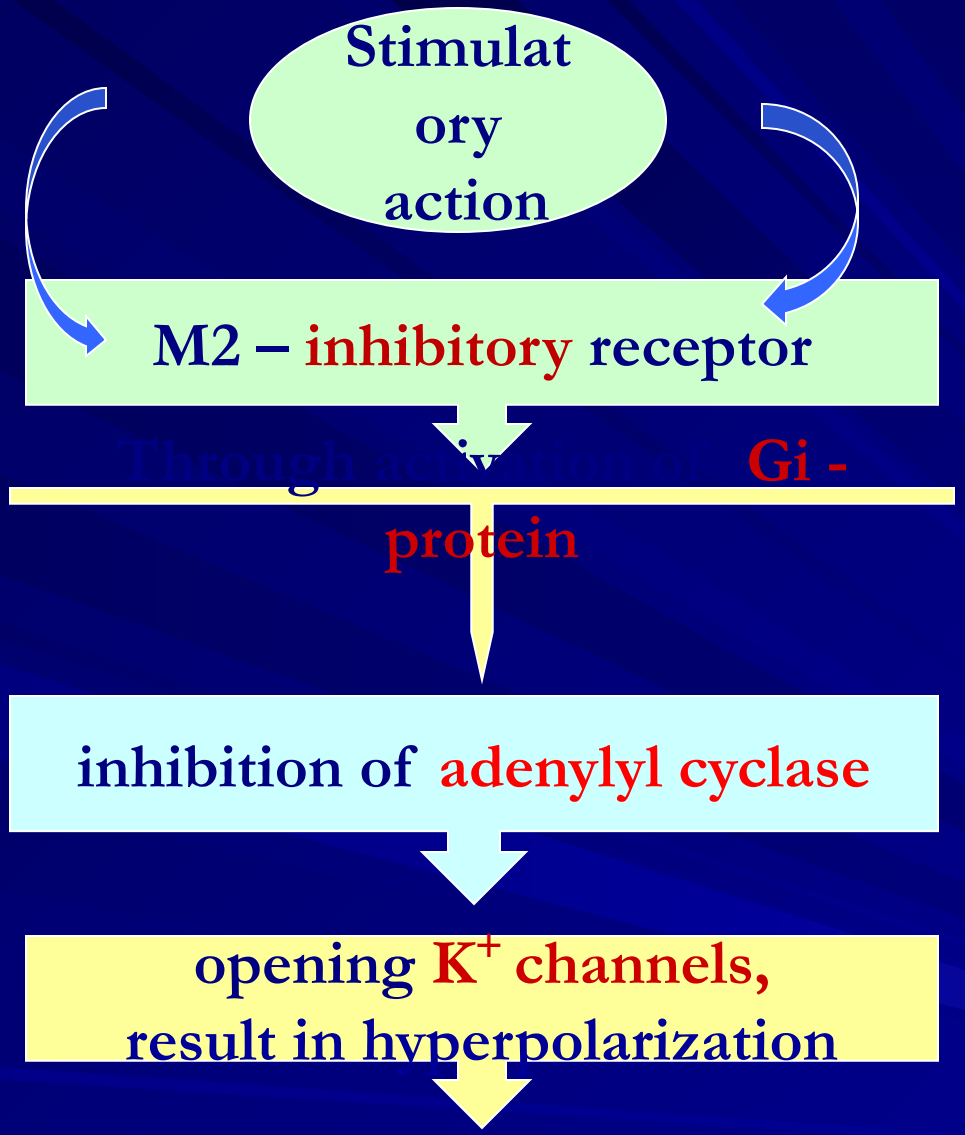
Through Gq protein activate phospholipase "C"

hydrolyses phosphatidylinositol -4,5-bisphosphate (PIP_2)

formation of Diacylglycerol (DAG) Inositol (1,4,5)-triphosphate (IP_3)

influx of Ca^{2+} ions, production of protein kinase C

- depolarization
- Secretion
- Contraction
- Stimulation or inhibition of enzymes



Decrease in heart rate (due to reduction in pacemaker activity and slowing of conduction) & force of contractions

Pharmacological effects of M- cholinomimetics:

M- cholinomimetics take direct selective stimulatory effect on M - cholinoceptors.

Drugs of this group have broad spectrum of action. They cause the following effects:

Ophthalmic effects:

- narrowing of pupils,
- decrease in intraocular pressure,
- spasm of accommodation.

Action on smooth muscles:

Stimulating M3-cholinoceptors of myocytes the drugs cause contraction of smooth muscle organs such as:

- bronchi
- stomach
- intestines
- biliary tract
- urinary bladder (stimulate detrusor and relax the trigon)
- uterus

Effects on cardiac functions:
Stimulating inhibitory M2 – cholinoceptors of the myocardium the drugs produce:

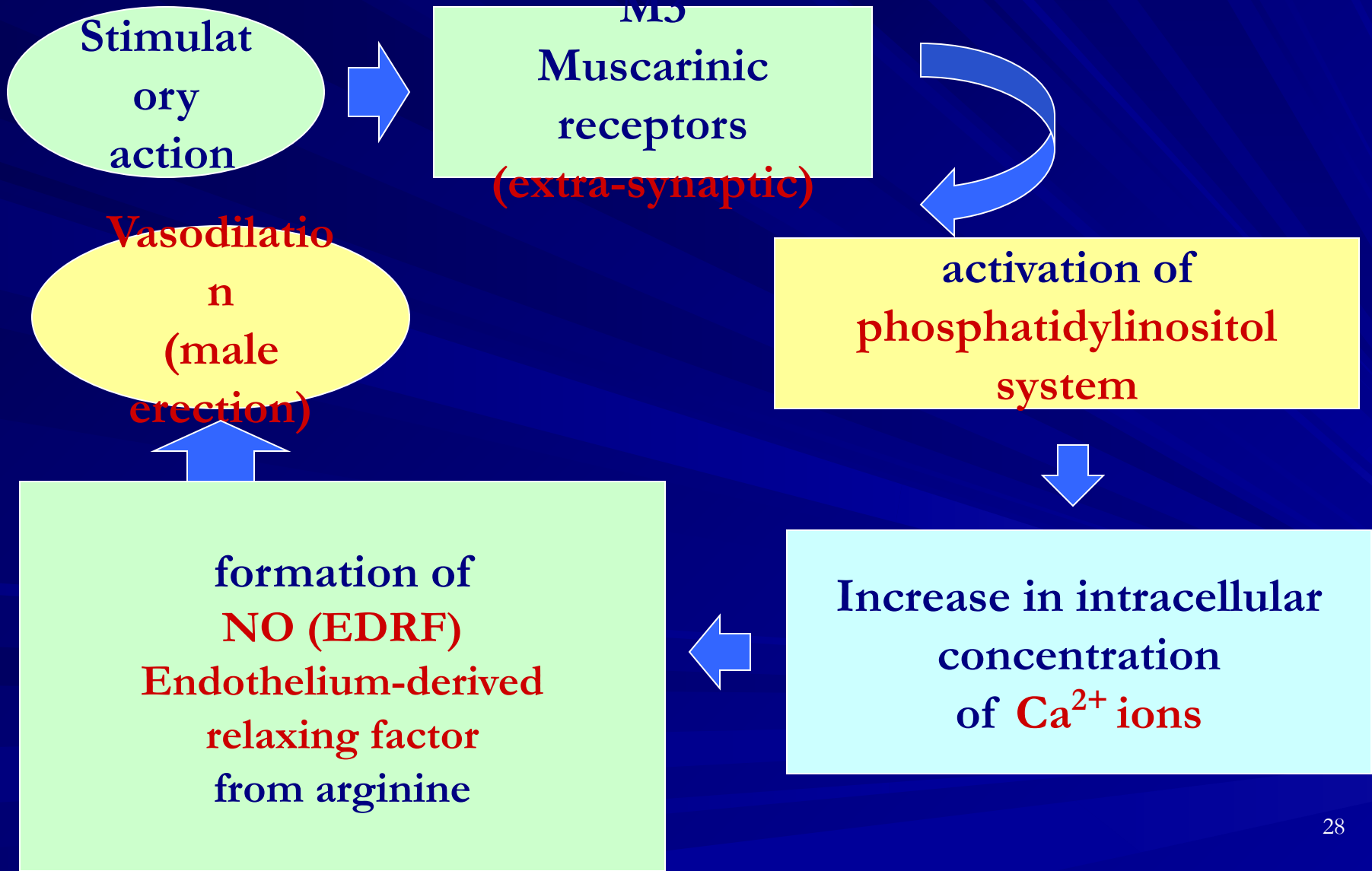
Slowing down of conduction in the atrioventricular node

decrease in excitability of heart cells

decrease in automatism of heart cells

Finally these effects result in bradycardia

Decrease in blood pressure: if the drugs injected i.v



Effects on excretory glands :

Stimulating M3-cholinoceptors of glandular cell membranes, drugs increase secretion of :

- Bronchial glands
- Salivary glands
- Gastric glands
- Sweat glands
- Lacrimal glands

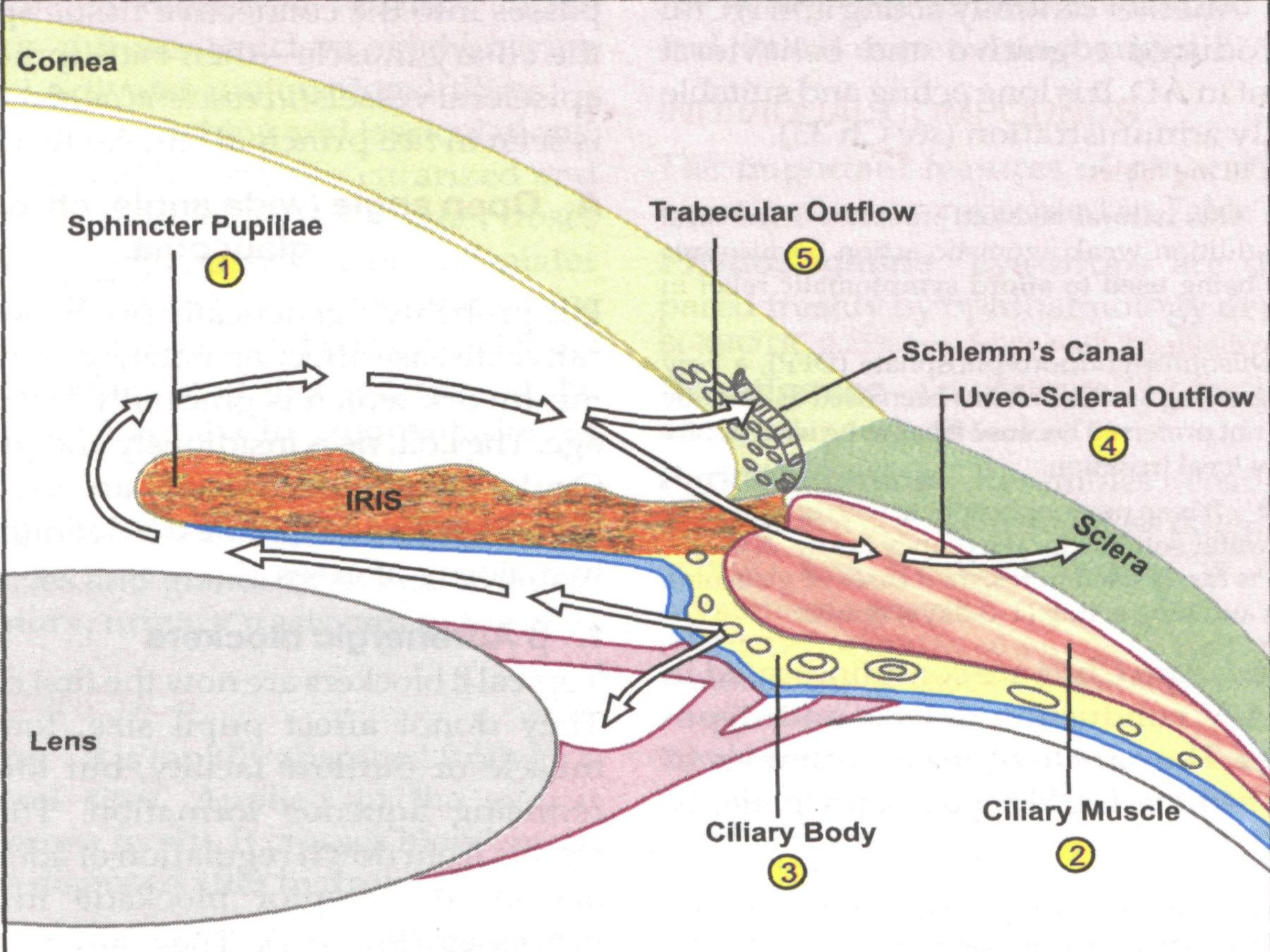
Ophthalmic effects of M- cholinomimetics:

Narrowing of pupils (miosis)

caused by stimulation of M3 – cholinoceptors of the sphincter pupillae and its contraction.

Decrease in intraocular tension

caused by the sphincter pupillae contraction, increase in iridocorneal angle, dilatation of Schlemm's canal and increase in intraocular fluid outflow from anterior chamber of the eye


Cornea
Sphincter Pupillae
1
Trabecular Outflow
5
Schlemm's Canal
Uveo-Scleral Outflow
4
IRIS
Sclera
Lens
Ciliary Body
3
Ciliary Muscle
2

Spasm of accommodation

due to activation of M3 – cholinoceptors of the ciliary muscle.

- Contraction of the eyeball muscle decreases the diameter
- of the muscle.
- Ligament of Zinn between the muscle and the lens relaxes.
- The lens becomes more convex,
- An eye becomes focused on the nearest point of vision.
- At the same time ciliary muscle contraction increases further
- opening of Schlemm's canal
- that improves fluid outflow into venous network
- and helps to decrease in intraocular pressure

Main effects of N- cholinomimetics:

N- cholinomimetics are the drugs which directly stimulate N – cholinoceptors.

The main effects of these drugs are caused by the stimulation of N - cholinoceptors of:

- Sinocarotid zones
- Autonomic ganglia
- CNS
- Chromaffin cells of adrenal glands

Effect of N- cholinomimetics is characterized by the action consisting of two phases. After the stimulation phase, phase of inhibition follows.

Stimulation of N – cholinoceptors of carotid bodies results in reflex stimulation of neurons of the medulla oblongata, first of all, neurons of the respiratory center.

However, after the stimulation N- cholinomimetics can cause inhibition of these neurons and even apnoea (respiratory standstill).

Stimulation of N – cholinoceptors of autonomic ganglia results in:

increase in the sympathetic activity in peripheral bood vessels

increase in the parasympathetic activity in smooth muscles and excretory glands

Stimulation of N – cholinoceptors of the medullary substance of adrenal glands causes increase in adrenaline secretion that results in:

vasoconstriction

increase in arterial and venous pressure

increase in total peripheral resistance

increase in afterload and myocardial oxygen demand

Therapeutic use of N- cholinomimetics:

Therapeutic use of N- cholinomimetics has been limited.

In the past, they were used as reflex stimulators of respiration (respiratory analeptics).

Currently, N- cholinomimetics are used as agents smoking cessation (in case of nicotinic dependence) as they act similarly to alkaloid of tobacco on nicotinic receptors.

Cholinomimetic drugs with indirect action: pharmacodynamics.

Stimulators of acetylcholine presynaptic release:

Their mechanism of action is based on "modulation" of acetylcholine release from nerve endings and an increase in Ach concentration in a synapse.

Their main pharmacological effects are:

- Considerable increase in tone and motility of the g.i.t. smooth muscle cells that can result in hyperperistalsis of the small and large intestines
- Acceleration of gastric and duodenal emptying and bowel mass movement
- Prevention of duodenogastric and gastroesophageal refluxes, increase in tone of the cardiac sphincter
- Acceleration of contractions of the gallbladder and bile duct smooth muscles
- Relaxation of the Oddi's sphincter and stimulation of excretory function of the pancreas

Therapeutic use of stimulators of acetylcholine presynaptic release

These drugs are used for treatment of:

- postoperative atony of the intestines
- paralytic intestinal obstruction
- gastroesophageal reflux
- dyspepsia
- chronic constipations
- X-ray examination of the g.i.t.

Adverse effects of acetylcholine presynaptic release stimulators:

- Nausea
- Epigastric pains
- Giddiness
- Blood pressure decrease

The main contraindications are:

- intestinal obstruction of an unknown reason
- stomach ulcers
- pregnancy
- obstructive jaundice
- severe cardiovascular diseases

Anticholinesterases

The action of these drugs is directed to acetylcholinesterase in a cholinergic synapse.

Anticholinesterase drugs bind to active centers of acetylcholinesterase and impair hydrolysis of acetylcholine. The mediator is accumulated in synapses and stimulates M and N – cholinoceptors.

The mechanism of acetylcholinesterase inhibition is reversible. After inhibition, enzymatic activity of the enzyme is restored and it continues to control acetylcholine level in synapses.

Irreversible anticholinesterases (Armine, Ecothiophate, Organophosphate and carbamate insecticids, nerve gases for chemical war Tabun, Sarin, Soman inhibit activity of the enzyme without its restoration.

Pharmacological effects of Anticholinesterase drugs:

These drugs produce:

M- cholinomimetic effects

N- cholinomimetic effects

They act on eyes, smooth muscles, secretion of excretory glands and heart work like M-cholinomimetics.

(these effects were described above)

Influence on skeletal muscles:

Anticholinesterase drugs facilitate neuromuscular transmission due to indirect stimulation of postjunctional N– cholinoceptors and increase tone of striated muscles.

Influence on the CNS:

At small doses, anticholinesterase drugs take stimulatory effect, whereas at high doses they produce inhibitory effect on the CNS.

However, only tertiary structure compounds pass cross the blood-brain barrier well.

Physostigmine Galantamine
Aminostigmine Tacrine
Donepezil

Quaternary compounds badly pass cross the blood-brain barrier and practically don't cause effects in the CNS.

Neostigmine Pyridostigmine bromide
Distigmine bromide Ambenonium chloride

Therapeutic use of Anticholinesterase drugs

Anticholinesterase drugs are used for:

1. Treatment of glaucoma: Physostigmine, Armine, Echothiophate
2. Stimulation of peristalsis in postoperative atony of the intestines, paralytic obstruction, atony of the urinary bladder and uterine inertia (powerless labor):
Neostigmine, Distigmine, Physostigmine

3. Treatment and diagnostics of myasthenia gravis:
(chronic autoimmune disease causing muscle weakness:
autoantibodies reduce number of free Nn receptors)
Neostigmine, Pyridostigmine, Ambenonium, Edrophonium

4. As pharmacological antagonists in overdoses of nondepolarizing muscle relaxants: Neostigmine

5. Treatment of overdoses of drugs with anticholinergic action (atropine, phenothiazines, tricyclic antidepressants): Physostigmine, Galantamine

6. Treatment of Alzheimer's disease: Tacrine, Donepezil, Rivastigmine

Adverse effects of anticholinesterase drugs:

- Hypersalivation
- Nausea, spastic stricture of muscles of the intestine and urinary bladder, diarrhea
- Bronchospasm and apnoe
- Bradycardia, arrhythmia
- Frequency of urination
- Miosis
- Twitchings of tongue and skeletal muscles

Cholinesterase reactivators

Drugs of this group restore acetylcholinesterase inhibited by anticholinesterases with irreversible action (organophosphates & carbamates).

The main acetylcholinesterase reactivators are:

- Isonitrozine
- Trimedoxime bromide
- Alloxime
- Pralidoxime
- Obidoxime

Mechanism of acetylcholinesterase reactivator action:

Reactivators contain oxime group (=N-OH). They attach to the anionic site of acetylcholinesterase which remains unoccupied in the presence of organophosphate inhibitor.

Its oxime end reacts with the phosphorous atom attached to the esteratic site: the oxime:phosphonate diffuses away leaving the reactivated ChE.

Acetylcholinesterase reactivators are used as specific antagonists of organophosphorous compounds.

They are ineffective as an antidotes to carbamate antiChEs (Physostigmine, Neostigmine, Carbaryl, Propoxur) in which case the anionic site of the enzyme is not free to provide attachment to it.

Atropine as well as reactivators is the basic pharmacological antidote in anticholinesterase poisoning.

Atropine inhibits bronchospasm, bronchorrhea, bradycardia and blockade of heart conductive system.