Poltava State Medical University

Pharmacology of drugs that influence efferent innervation. Cholinergic drugs

CONTENTS

1. Autonomic nervous system, its structure and function
2. Cholinergic agonists. Direct-acting cholinomimetics and anticholinesterases
3. Cholinergic antagonists. M-cholinoblockers. N-cholinoblockers (ganglionic blockers and myorelaxants)
4. Control tasks

AUTONOMIC NERVOUS SYSTEM

Autonomic nervous **system regulates the function of internal organs.**

It is divided into two sections:

- ***sympathetic system***
- ***parasympathetic system***

They exert opposite actions.

SYMPATHETIC SYSTEM (SANS)

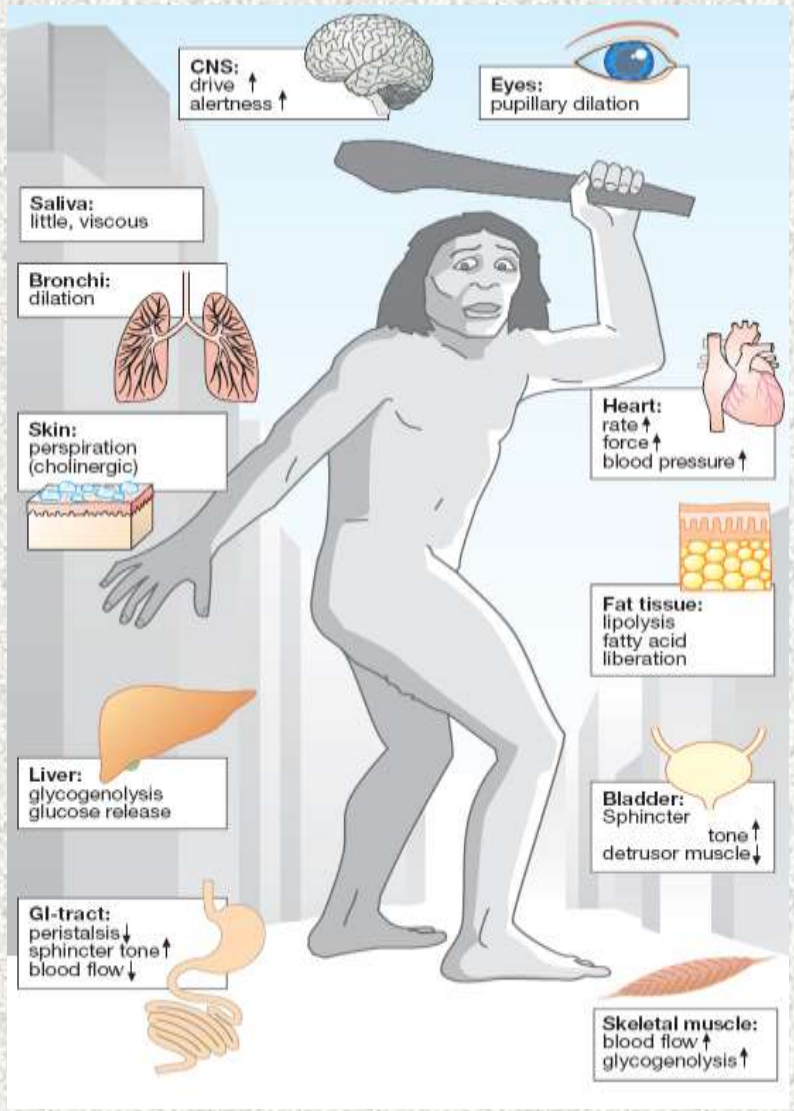
Centers **(the 1st neuron):**

thoraco-lumbal region of the spinal cord.

Ganglia **(the 2nd neuron):**

near the spinal cord (Thruncus sympaticus)

RESPONSES TO SYMPATHETIC ACTIVATION



PARASYMPATHETIC SYSTEM (PANS)

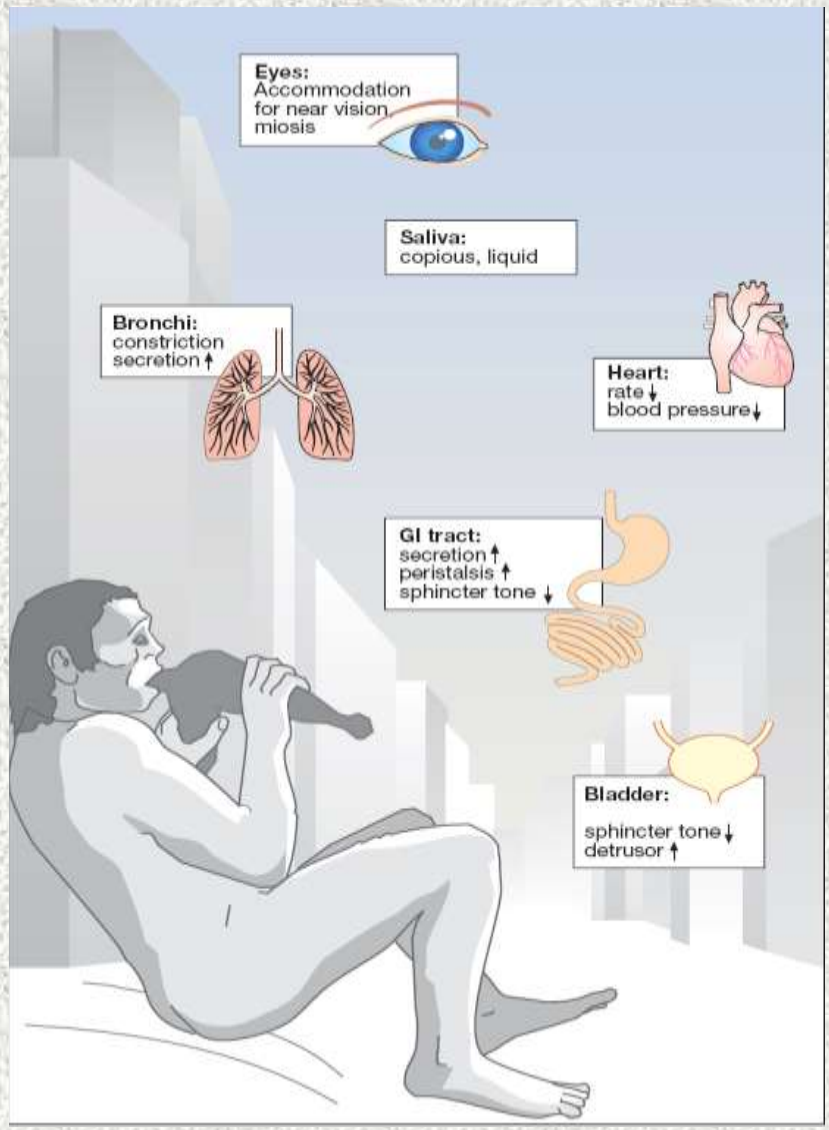
Centers **(the 1st neuron):**

medulla of brain, sacral region of the spinal cord.

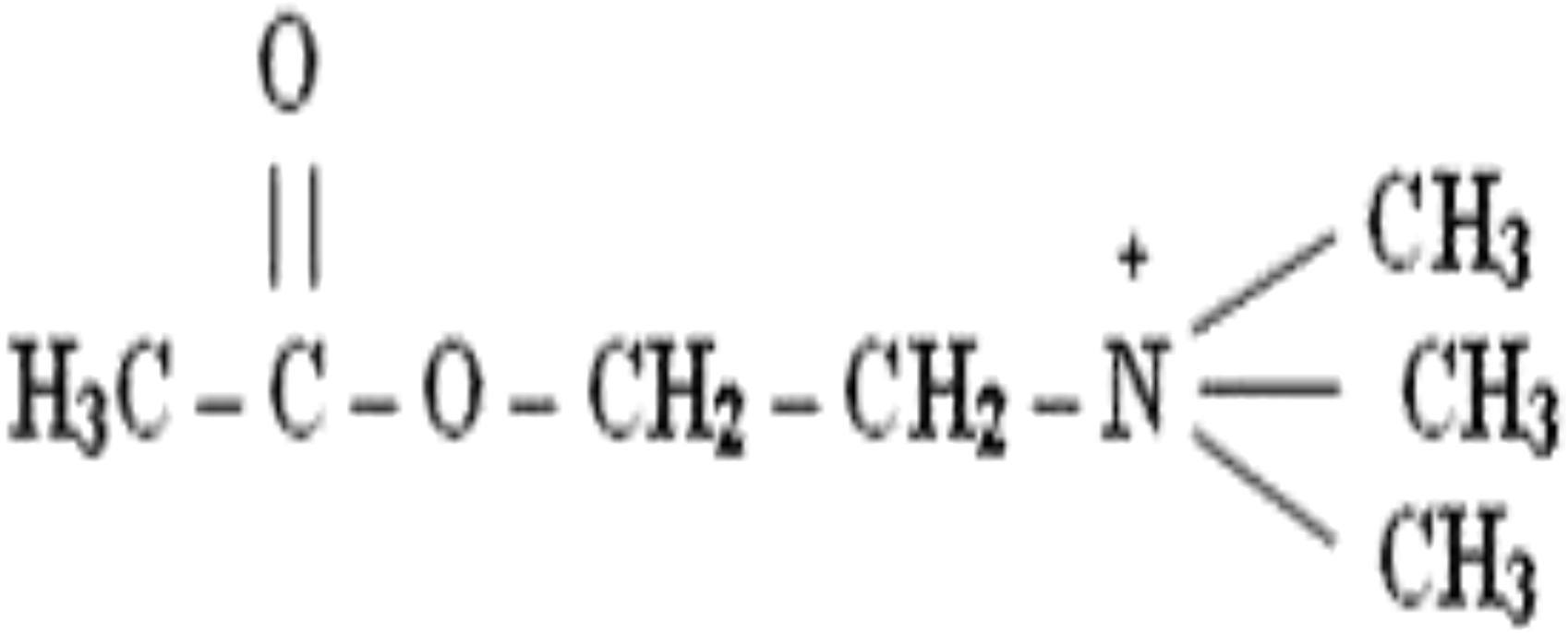
Ganglia **(the 2nd neuron):**

in the tissues of effector organs or near them.

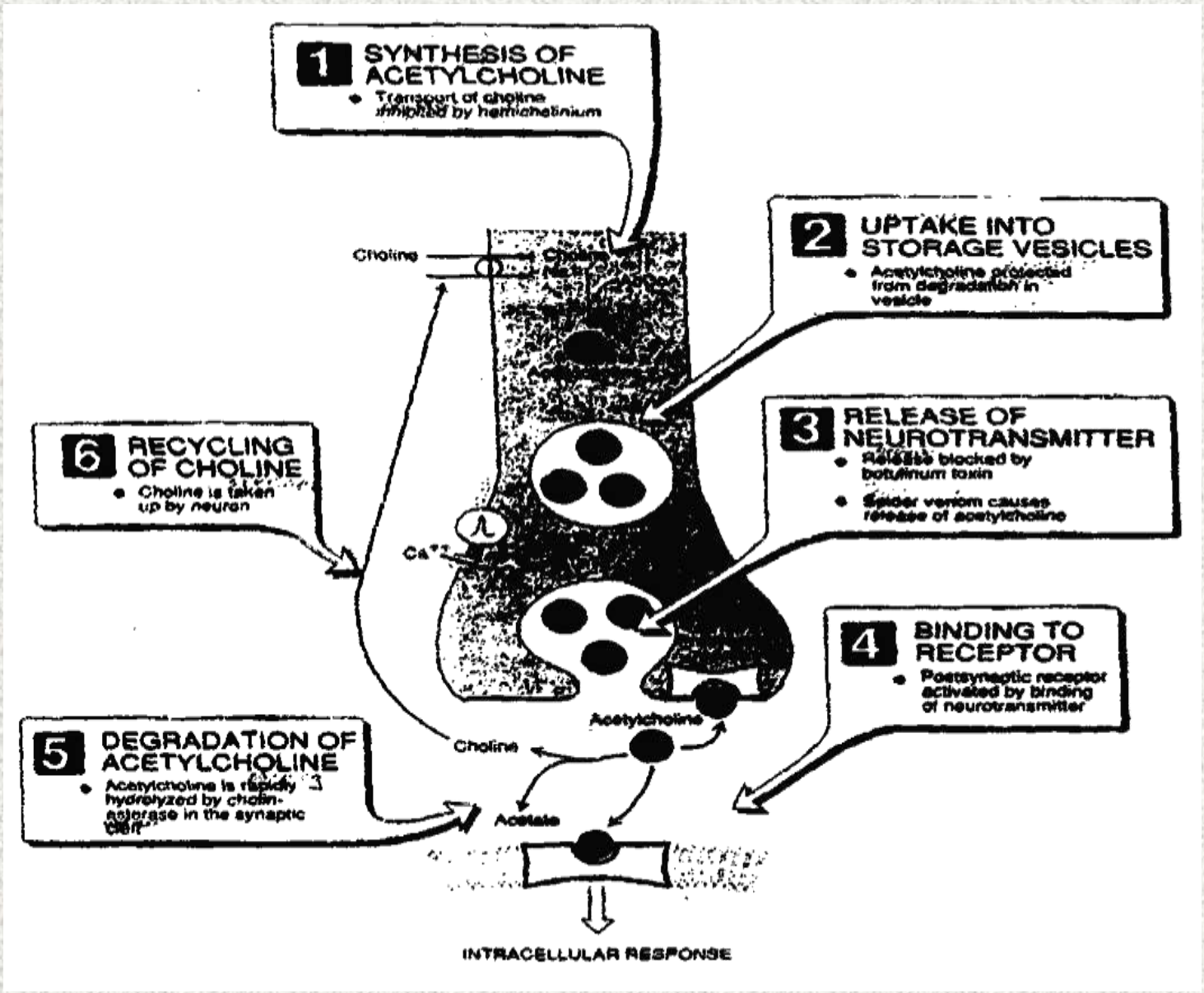
RESPONSES TO PARA-SYMPATHETIC ACTIVATION



ACETYLCHOLINE AS NEUROTRANSMITTER IN PANS



CHOLINERGIC SYNAPSE



CHOLINERGIC RECEPTORS

M-cholinoreceptor:

- **Agonists are acetylcholine and muscarine.**
- **Antagonist is atropine.**

N-cholinoreceptor:

- **Agonists are acetylcholine and nicotine (low dose).**
- **Antagonist is nicotine (bigger dose).**

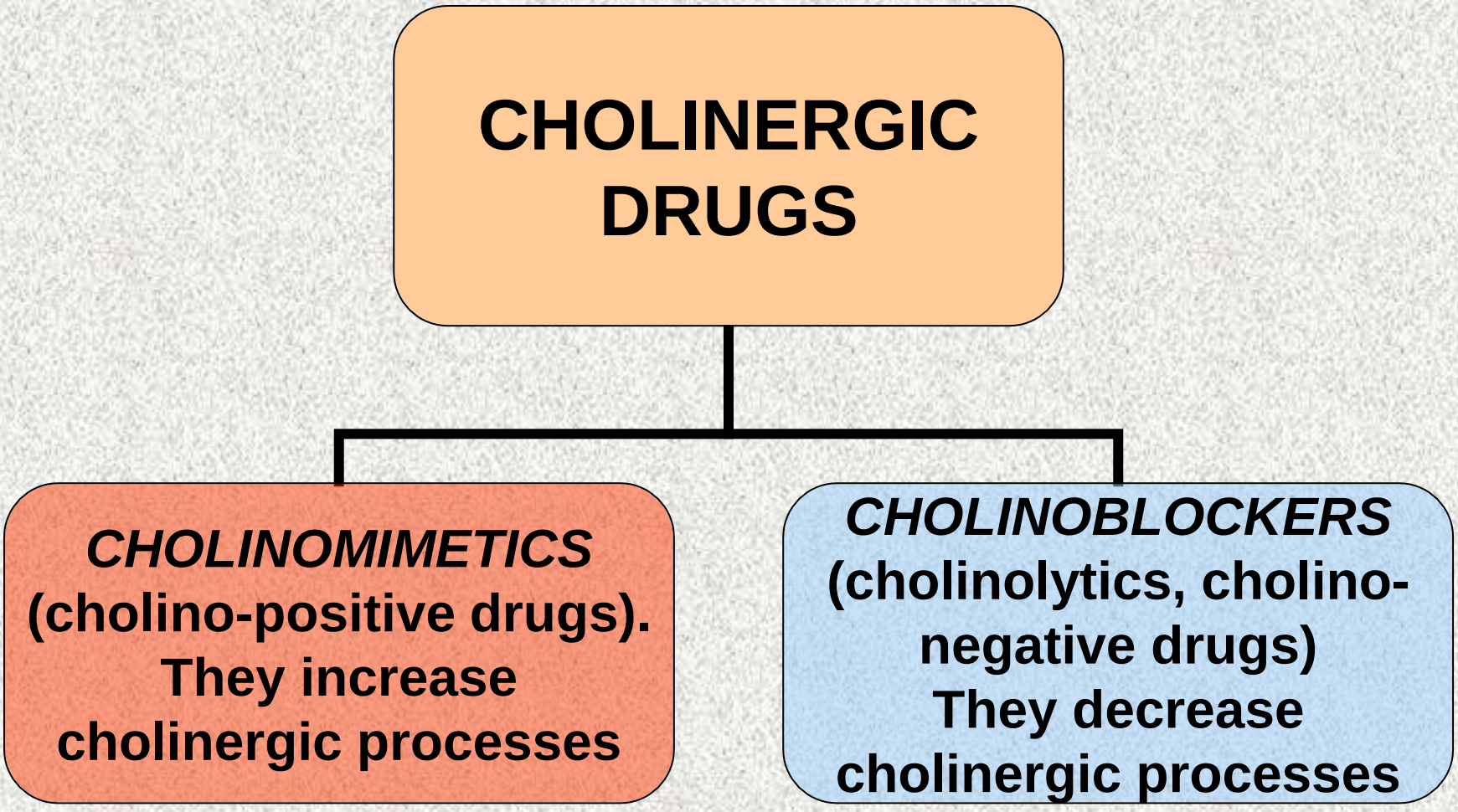
LOCATION OF N-CHOLINORECEPTORS

- CNS
- Adrenal medulla
- Carotid glomerulus
- Sympathetic and parasympathetic ganglia
- Skeletal muscles

LOCATION OF M-CHOLINORECEPTORS

- CNS
- Eye
- Heart
- Blood vessels
- Bronchi (smooth muscles, glands)
- Gut (smooth muscles, glands)
- Urinary bladder
- Uterus
- Sweat glands

CHOLINERGIC DRUGS



CHOLINOMIMETICS: Classification

A. M-,N-cholinomimetics

1. Direct-acting

– Acetylcholine

– Carbachol

2. Indirect-acting (anticholinesterases)

– Neostigmine (Proserine)

– Physostigmine

– Pyridostigmine

– Galanthamine

– Isoflurophate (Phosphacol)

B. M-cholinomimetics

– Pilocarpine

C. N-cholinomimetics

– Cytiton

– Lobeline

DRUGS WITH M-CHOLINOMIMETIC EFFECTS
(DIRECT-ACTING M-,N- AND M-CHOLINOMIMETICS)

M-cholinomimetic effects	Indications
Miosis **(constriction of the eye pupils).** ***Spasm of accomodation*** **(regulation of eye lens on near vision).** ***A decrease in intra-eye pressure*****.**	**Glaucoma**
Stimulation of glands secretion. ***An increase in salivation.***	**Xerostomia**
An increase in smooth muscles tone.	**Atonia of intestine and urinary bladder after surgeries**
Bradycardia. ***Blood vessels dilatation.***	**Some kinds of tachyarrhythmia**

DIRECT-ACTING M-,N- AND M-CHOLINOMIMETICS:

PECULIARITIES OF PREPARATIONS

- ***Carbachol*** (Carbacholine) has a chemical structure similar to acetylcholine, but is non destroyed by cholinesterase; is direct acting M-, N-cholinomimetic with prevalence of M-cholinergic activity; now is applied topically for treatment of glaucoma (eye drops).

- ***Pilocarpine*** is an alkaloid from Pilocarpus pinnatifolius, is M-cholinomimetic; has strong systemic M-cholinomimetic activity, but is toxic; is now used only for the treatment of glaucoma (eye drops, eye ointment, or eye membranes), seldom is used in xerostomia.

PILOCARPUS PINNATIFOLIUS CONTAINING PILOCARPINE

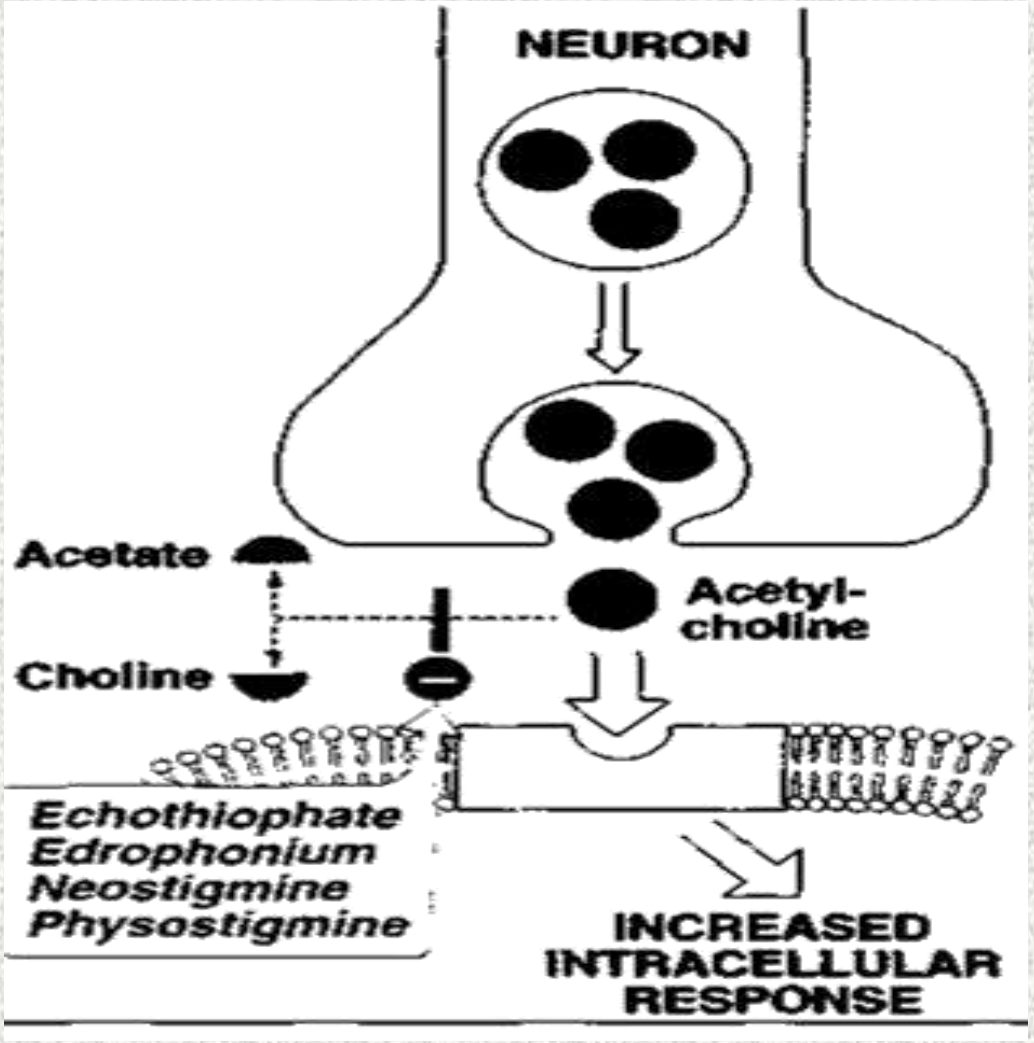
DIRECT-ACTING M-, N- AND M-CHOLINOMIMETICS: SIDE EFFECTS

- Hypersalivation
- Pain in the abdomen
- Diarrhea
- Spasm of bronchi
- Bradycardia
- Frequent urination
- Sweatiness

ANTICHOLINESTERASES

ANTICHOLINESTERASES **are indirect-acting M-,N-cholinomimetics with reversible or irreversible type of action.**

ANTICHOLINESTERASES:
MECHANISM OF ACTION



ANTICHOLINESTERASES:
PHARMACODYNAMICS

- all typical M-cholinomimetic effects in the internal organs
- an increase in neuromuscular transmission resulting from the accumulation of acetylcholine at the neuromuscular junctions

ANTICHOLINESTERASES:
INDICATIONS

- Neurological diseases (paralysis, neuritis)
- Myasthenia gravis
- Atonia of the intestine and urinary bladder after surgeries
- Some kinds of arrhythmia
- Acute poisonings with atropine and anti depolarizing myorelaxants
- Glaucoma
- Xerostomia

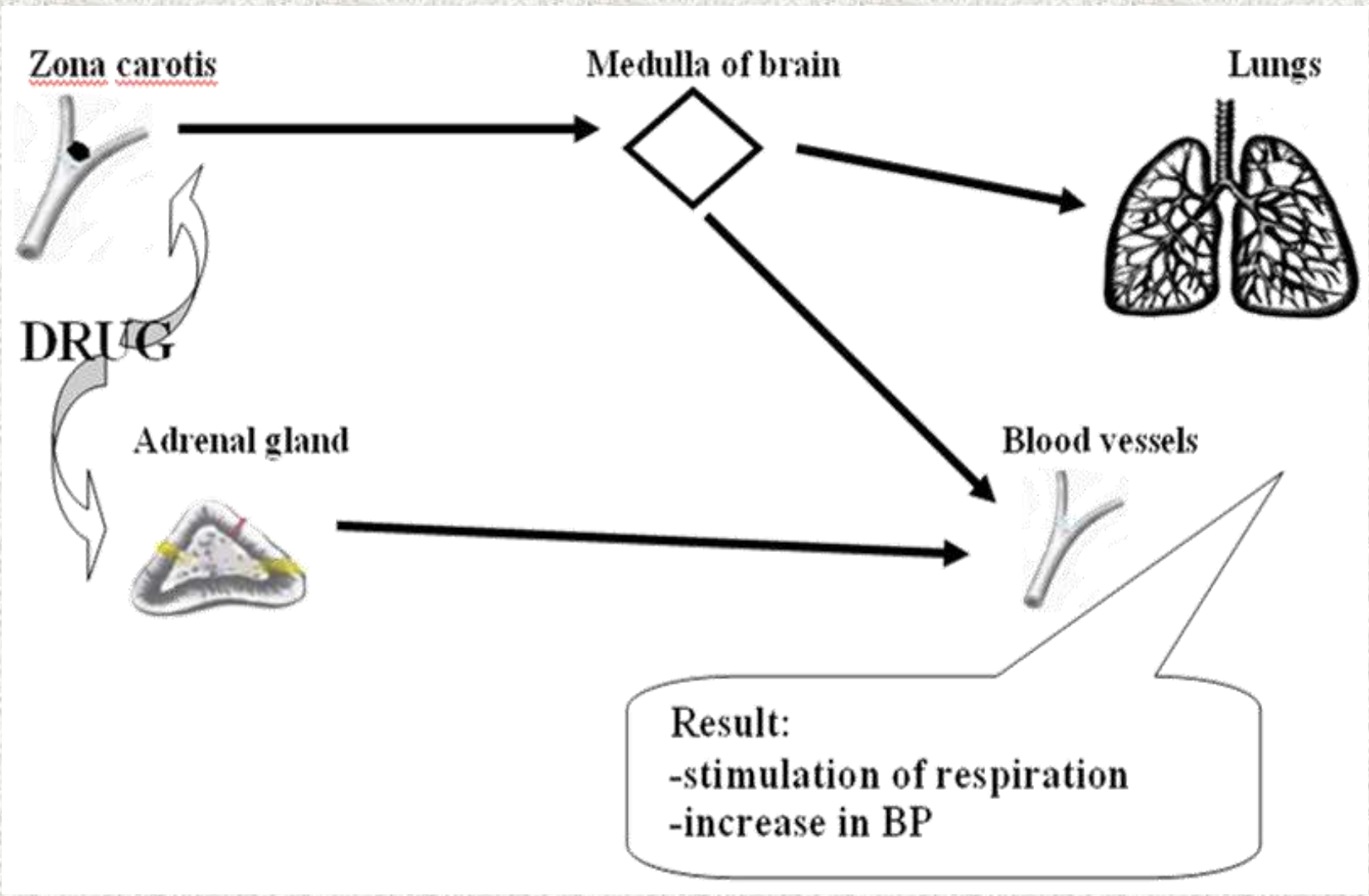
ANTICHOLINESTERASES:
PECULIARITIES OF PREPARATIONS

- ***Physostigmine*** **is an alkaloid from Phyzostigma venenosum; is well absorbed; penetrates CNS; has reversible action; is used for the treatment of glaucoma, intoxication by atropine, cholinoblockers and tricyclic antidepressants, early stages of Alzheimer's disease; is toxic.**
- ***Galantamine*** **is an alkaloid from Galanthus Woronowi; is administered SC, IM; penetrates CNS; has reversible action; is used for the treatment of paralysis, neuritis and other neurological diseases; is not used in glaucoma due to its irritative action.**
- ***Neostigmine*** **is a synthetic preparation; is administered orally, SC, IV, topically (eye drops); does not penetrate CNS; has reversible action (4-6 hrs); is used for paralysis, neuritis, myasthenia gravis, atonia of intestine and urinary bladder, some kinds of arrhythmia, glaucoma, poisoning with atropine, overdose of tubocurarine; may be used for stimulation of labor.**
- ***Pyridostigmine*** **acts longer, but is less active than neostigmine; is used orally for treatment of neurological diseases and myasthenia gravis.**
- ***Phosphacol*** **is irreversibly acting anticholinesterase with long-lasting action; is toxic and use only for glaucoma (eye drops).**

MEDICINAL PLANTS CONTAINING ANTICHOLINESTERASES:

PHYZOSTIGMA VENENOSUM (left); GALANTHUS WORONOWI (right)

N-CHOLINOMIMETICS:
MECHANISM OF ACTION



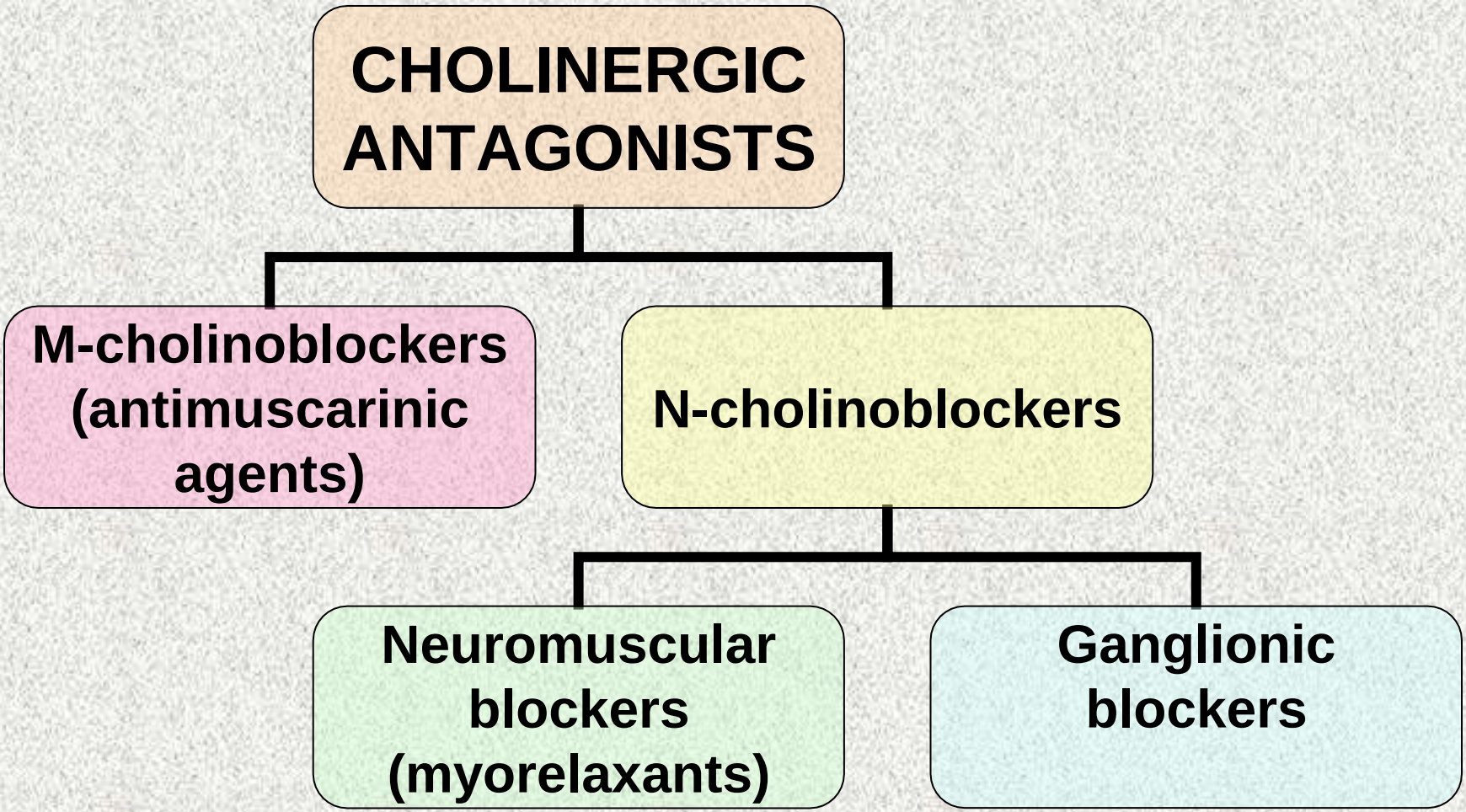
N-CHOLINOMIMETICS:
INDICATIONS

- **Respiratory arrest (IV)**
- **Asphyxia (IV)**
- **Treatment of tobacco abuse (orally, combined tablets)**

N-CHOLINOMIMETICS:
PECULIARITIES OF PREPARATIONS

- ***Cytiton*** **is the name of cytizine solution; is administered IV, acts 3-5 min; stimulates N-cholinoreceptors; reflexly stimulates respiration and increase BP; is used for emergence help in respiratory arrest and collapse.**
- ***Lobeline*** **is an alkaloid; is administered IV and acts during 3-5 min; mechanism of action is similar to Cytiton; is used for emergence help in respiratory arrest, asphyxia, asphyxia of newborns, rarely in pneumonia; is not used for collapse due its ability to cause transitory decrease in BP resulting from stimulation of n. vagus center.**

CHOLINERGIC ANTAGONISTS



M-CHOLINOBLOCKERS:
CLASSIFICATION

A. Non-selective preparations

1. Natural agents

– Atropine

– Hyoscine

– Platyphylline

2. Synthetic and semisynthetic agents

– Hyoscine butylbromide

- Prifinium bromide (Riabal)

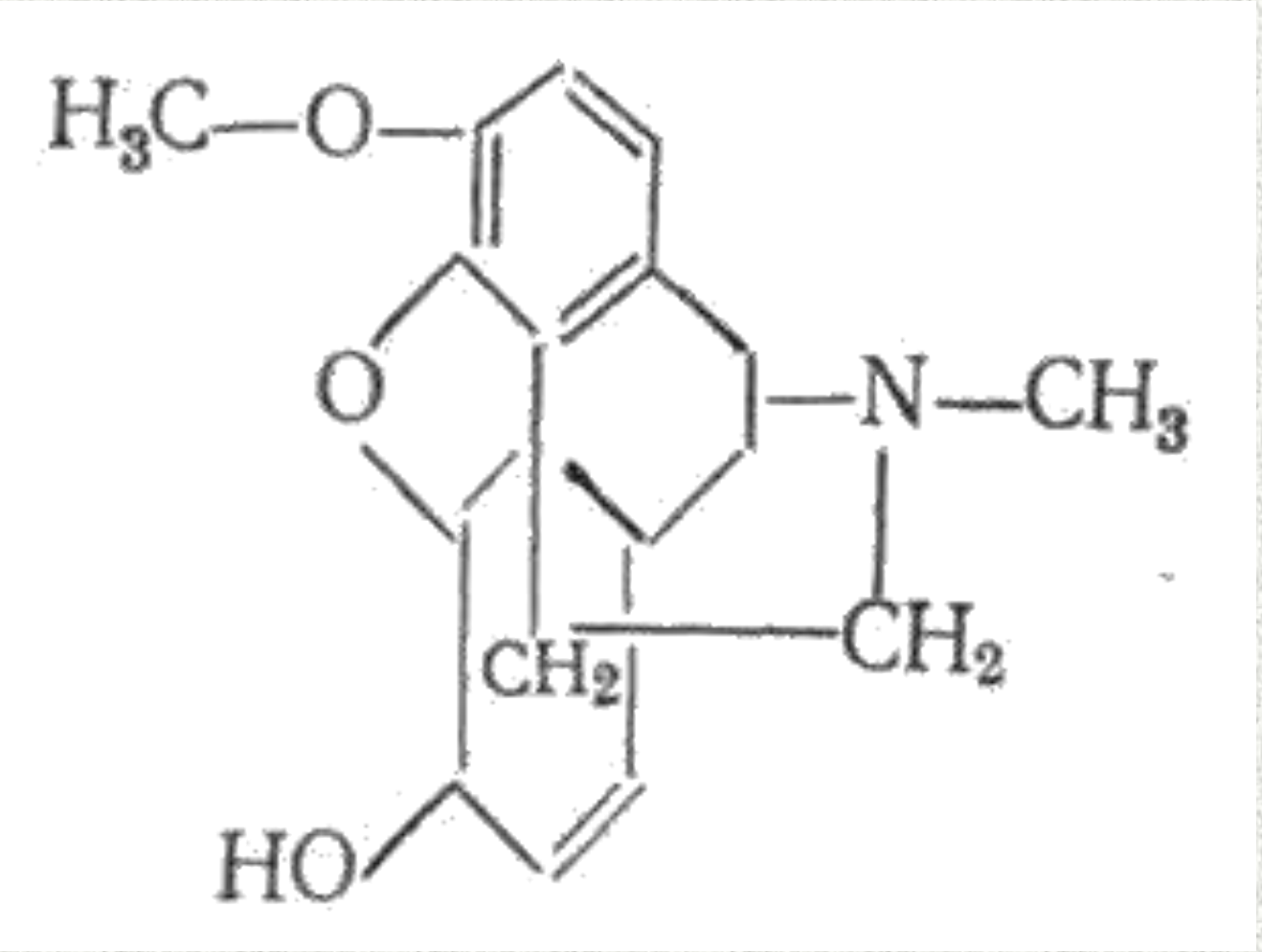
– Ipratropium bromide (Atrovent)

- Tropicamide

B. Selective preparations

– Pirenzepine (Gastrocepin).

ATROPINE:
CHEMICAL STRUCTURE



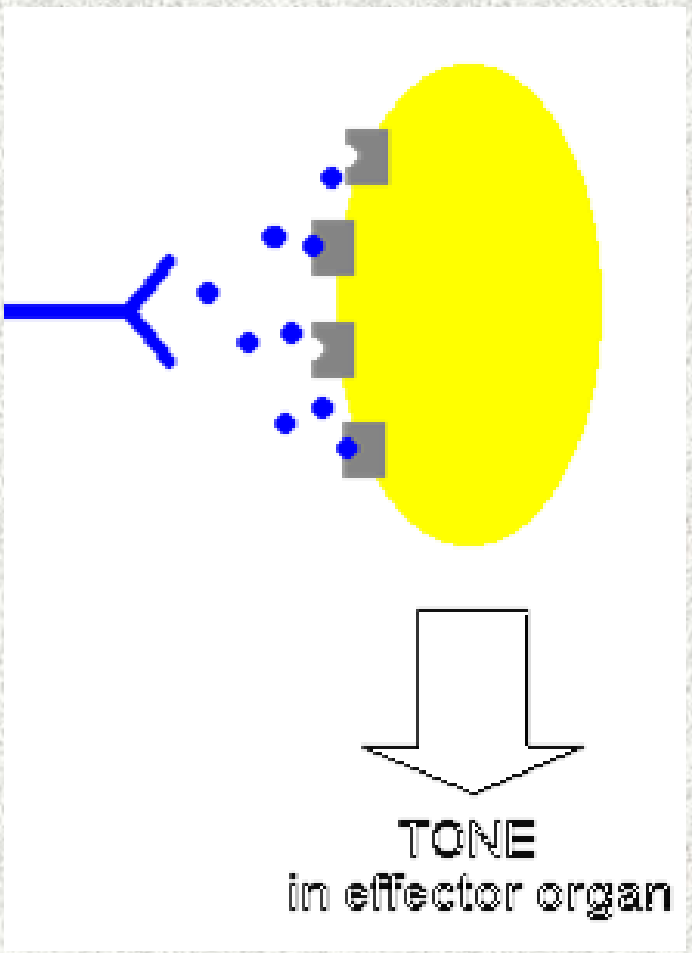
ATROPINE:
ATROPA BELLADONNA CONTAINING ATROPINE

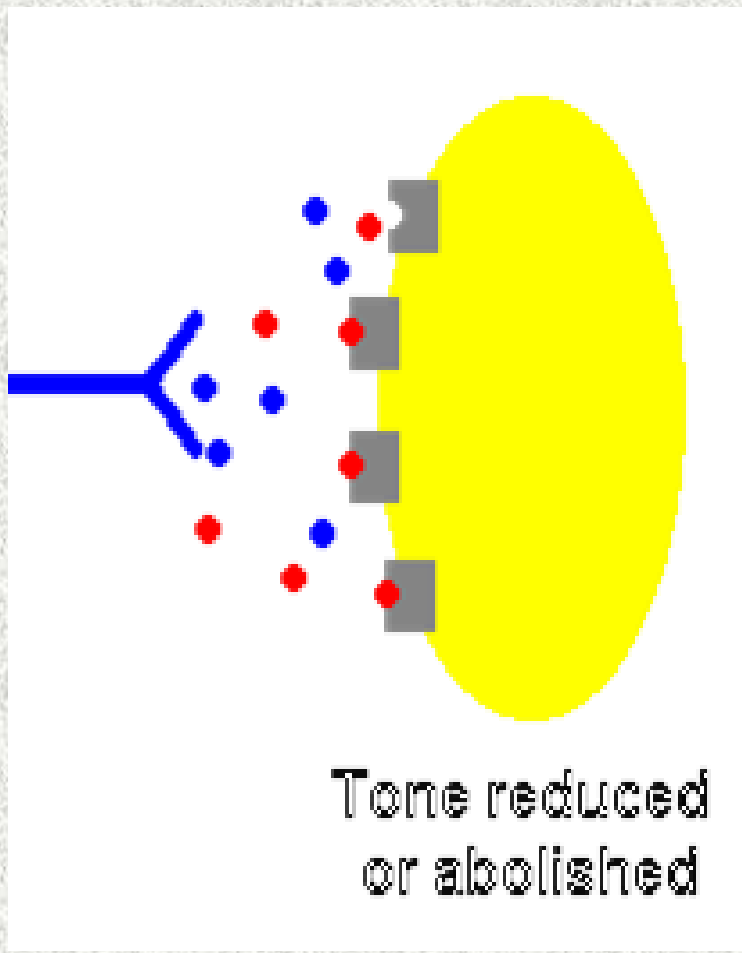
ATROPINE:
PHARMACOKINETICS

- is administered orally, IM, SC; is applied topically (eye drops)
- is absorbed in the gut
- is bound with plasma proteins (18%)
- penetrates CNS and placenta
- is metabolized in the liver by atropinase
- is excreted with urine
- has T ½ = 2 hrs; acts on internal organs during 4 hrs; influences the eye during 7-10 days.

ATROPINE :

MECHANISM OF ACTION (SYNAPSE WITHOUT (LEFT) AND WITH ATROPINE (RIGHT)





ATROPINE:
PHARMACODYNAMICS

- *in the site of application:* **weak local anesthesia**
- *in the CNS:* **therapeutic doses - sedation and antiparkinsonian effect, big doses - excitation, hallucinations, coma**
- **in the eye: mydriasis, cycloplegia (paralysis of accomodation), increase in intraocular pressure**
- *in the cardiovascular system:* **therapeutic doses – tachycardia**
- *in the respiratory system:* **dilation of bronchi, a decrease in secretion of bronchial glands**
- *in the gut:* **reduce of secretion of saliva and gastric juice, a decrease in the tone and motility; antispasmotic activity**
- *in the urinary system:* **relaxation of smooth muscles of the urinary bladder and urinary pathways**
- **inhibition in secretion of sweat**
- *antidote properties* **in acute poisonings with M-cholinomimetics, anticholinesterases and toxic mushrooms containing muscarine**
- **reduce in vagal action of morphine and general anesthetics.**

ATROPINE:
ACTION ON THE EYE

NORMAL CONDITION

INSTILLATION OF ATROPINE

ATROPINE:
INDICATIONS

- Trauma of the eye, inflammation in the eye
- Diagnostic of eye diseases, measurement of refraction for selection of eye glasses
- Bradycardia, A-V block
- Hypersalivation
- Gastric ulcer, gastritis with acid hypersecretion
- Acute pancreatitis
- Cholecystitis
- Colic
- Enuresis
- Premedication
- Acute poisonings with muscarine-containing mushrooms, M-cholinomimetics, anticholinesterases, and morphine.

ATROPINE:

SIDE EFFECTS AND CONTRAINDICATIONS

SIDE EFFECTS

1. Photophobia
2. Blurred vision
3. An increase in intraocular pressure
4. Tachycardia
5. Dry mouse
6. Constipation
7. Retention of urine
8. Flushed skin
9. Rise in body t^{o}

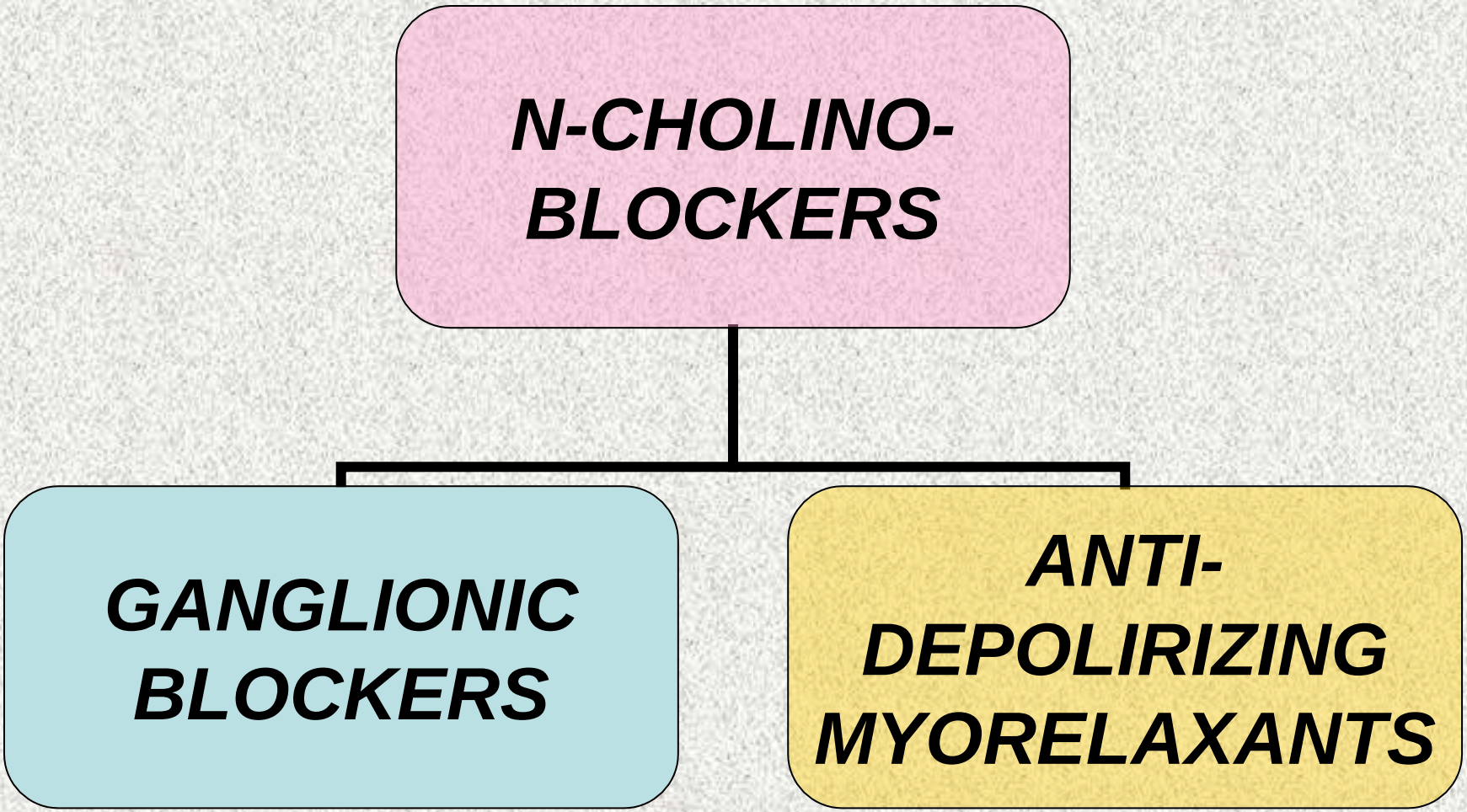
CONTRAINDICATIONS

1. Glaucoma
2. Tachycardia, tachy-arrhythmia
3. Atonia of the GI tract
4. Prostate hyperplasia
5. Hepatic insufficiency
6. Hyperthyroidism
7. High body temperature
8. Toxicosis of pregnancy
9. Cerebral pathology in children
10. Childhood or old age

M-CHOLINOBLOCKERS:
PECULIARITIES OF OTHER PREPARATIONS

- Scopolamine is an alkaloid containing in Scopolia. central action is greater and longer than the same of atropine; it inhibits VIII pair of cranial nerves, produces sedation and short-memory blocking, has antiparkinsonian effect; is used for prevention and treatment of motion sickness, Parkinson's disease, and for premedication.
- Platyphylline is an alkaloid from Senecio platyphylus; central action is less than the same of atropine; dilates blood vessels and lowers BP; may be used to treat spasms of blood vessels and hypertension.
- Pirenzepine is a selective M1-cholinoblocker inhibiting gastric secretion; does not penetrate CNS and placenta; is used for the treatment of ulcer of stomach and duodenum, prevention of peptic ulcers caused by stress; side-effects are minimal in comparison with atropine.
- Ipratropium bromide is a non-selective M-cholinoblocker in the form of aerosol; is not absorbed in lungs and acts on M-cholinoreceptors only in bronchi; dilates bronchi; is used for prevention of bronchial asthma attack; may cause unpleasant taste.

N-CHOLINOBLOCKERS



GANGLIONIC BLOCKERS

GANGLIONIC BLOCKERS **are preparations which block N-cholino-recepors in symphathetic and parasympathetic ganglia.**

GANGLIONIC BLOCKERS:
CLASSIFICATION

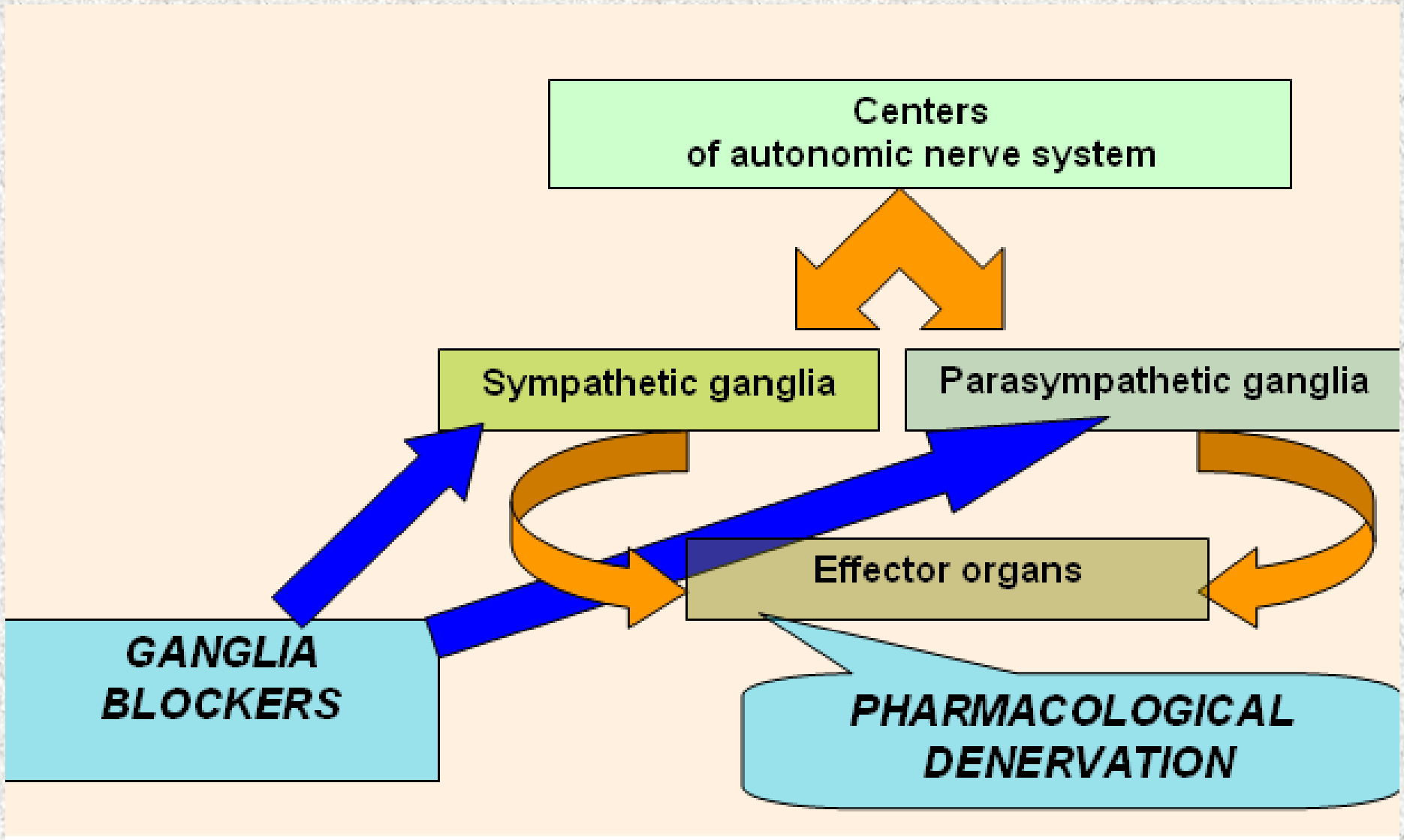
1. Quaternary amines

- Hexamethonium (Benzohexonium)
- Hygronium
- Pentamine

2. Tertiary amines

- Pachycarpine
- Pirilene

GANGLIONIC BLOCKERS:
MECHANISM OF ACTION



GANGLIONIC BLOCKERS:
PHARMACODYNAMICS

- dilation of blood vessels, redistribution of blood in the body, lowering of BP
- dilation of bronchi
- decrease in secretion and motility of the gut, reduce in spasm of smooth muscles
- decrease in tone of urinary bladder and urinary pathways
- increase in sensitivity of myometrium to oxytocin and stimulation of uterus contractions in the labor
- decrease in sweat secretion
- changes in intraocular pressure.

GANGLIONIC BLOCKERS:
INDICATIONS

- Hypertensive emergence
- Hypertension (rarely)
- Controlled hypotension in surgeries
- Edema of lungs
- Edema of brain
- Bronchial asthma attack
- Colic
- Ulcer of the stomach (rarely).

GANGLIONIC BLOCKERS:
SIDE EFFECTS AND CONTRAINDICATIONS

SIDE-EFFECTS

1. ***Hypotension***
2. ***Orthostatic collapse (postural hypotension)***
3. ***Dry mouth***
4. ***Constipation***
5. ***Retention of urination***
6. ***An increase of intraocular pressure in patients with closed-angle glaucoma.***

CONTRAINDICATIONS

1. ***Hypotension, collapse***
2. ***Severe atherosclerosis***
3. ***Closed-angle glaucoma***
4. ***Atony of the gut***
5. ***Adenoma of prostate***
6. ***Severe diseases of heart, liver, and kidney.***

GANGLIONIC BLOCKERS:
PECULIARITIES OF PREPARATIONS

- ***Hexamethonium (Benzohexonium)*** **is administered orally, IM, IV; does not penetrates CNS; acts during 3-4 hrs; has all typical properties.**
- ***Hygronium*** **is a short-acting potent ganglia blocker; is administered by IV infusion; is used for controlled hypotension in surgeries, edema of lungs, edema of the brain, severe hypertensive crisis.**
- ***Pentamine*** **is less potent than hexamethonium, acts during 1,5 hrs, is administered IV, IM for emergence help in acute hypertension, bronchial asthma attack, colic, for controlled hypotension in surgeries.**

MYORELAXANTS

Myorelaxants (neuromuscular blockers) **are cholinergic drugs that interfere with transmission of nervous impulses in the synapses of skeletal muscles causing their relaxation.**

MYORELAXANTS:
CLASSIFICATION

1. Non-depolarizing agents

– d-Tubocurarine chloride

- Pipecuronium bromide

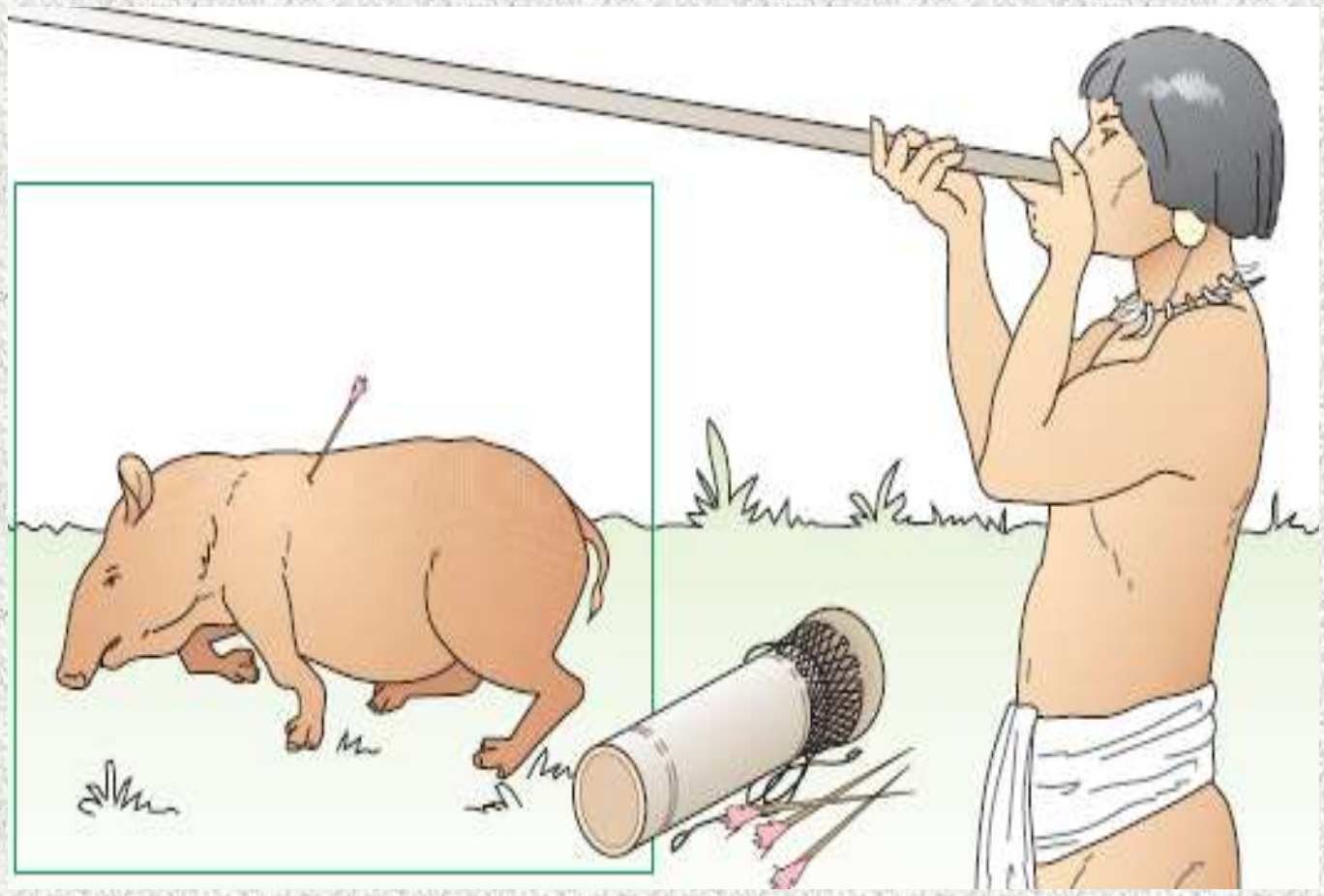
– Rocuronium bromide

2. Depolarizing agents

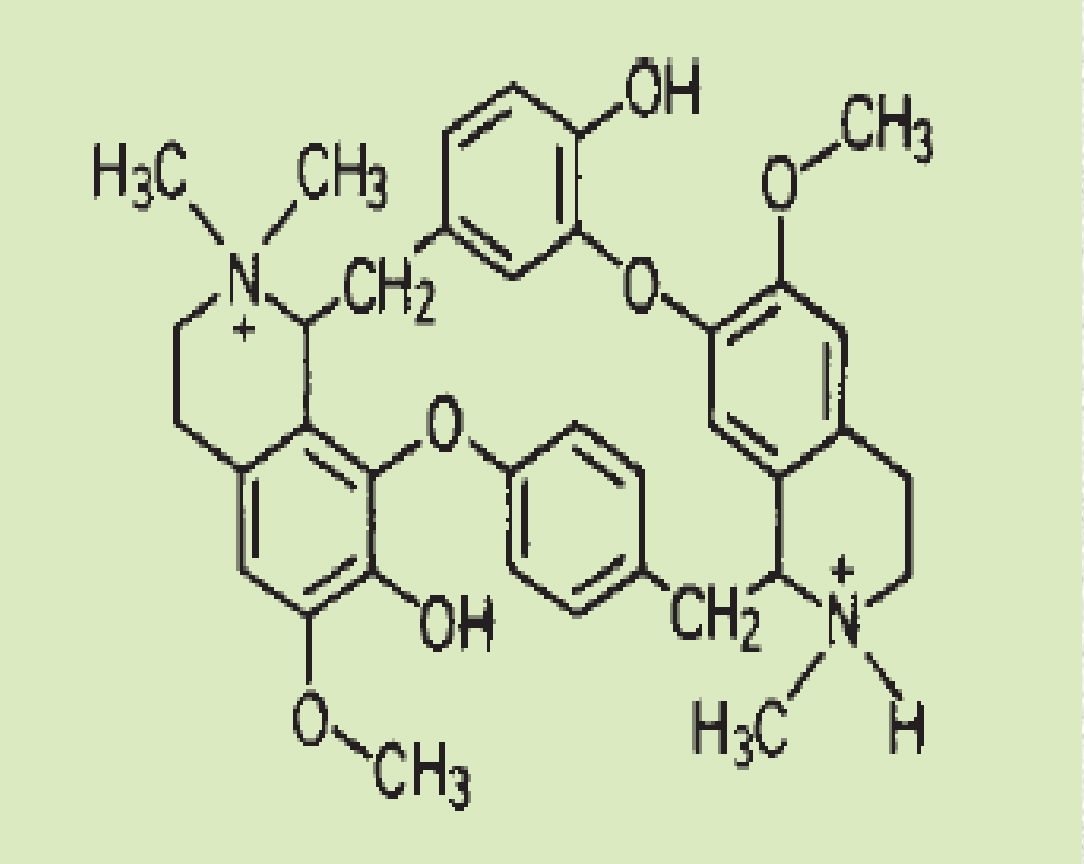
Succinylcholine (Dithyline)

TUBOCURARINE:

AN ALKALOID FROM PLANT-DERIVED ARROW POISON OF SOUTH AMERICAN NATIVES



TUBOCURARINE:
CHEMICAL STRUCTURE

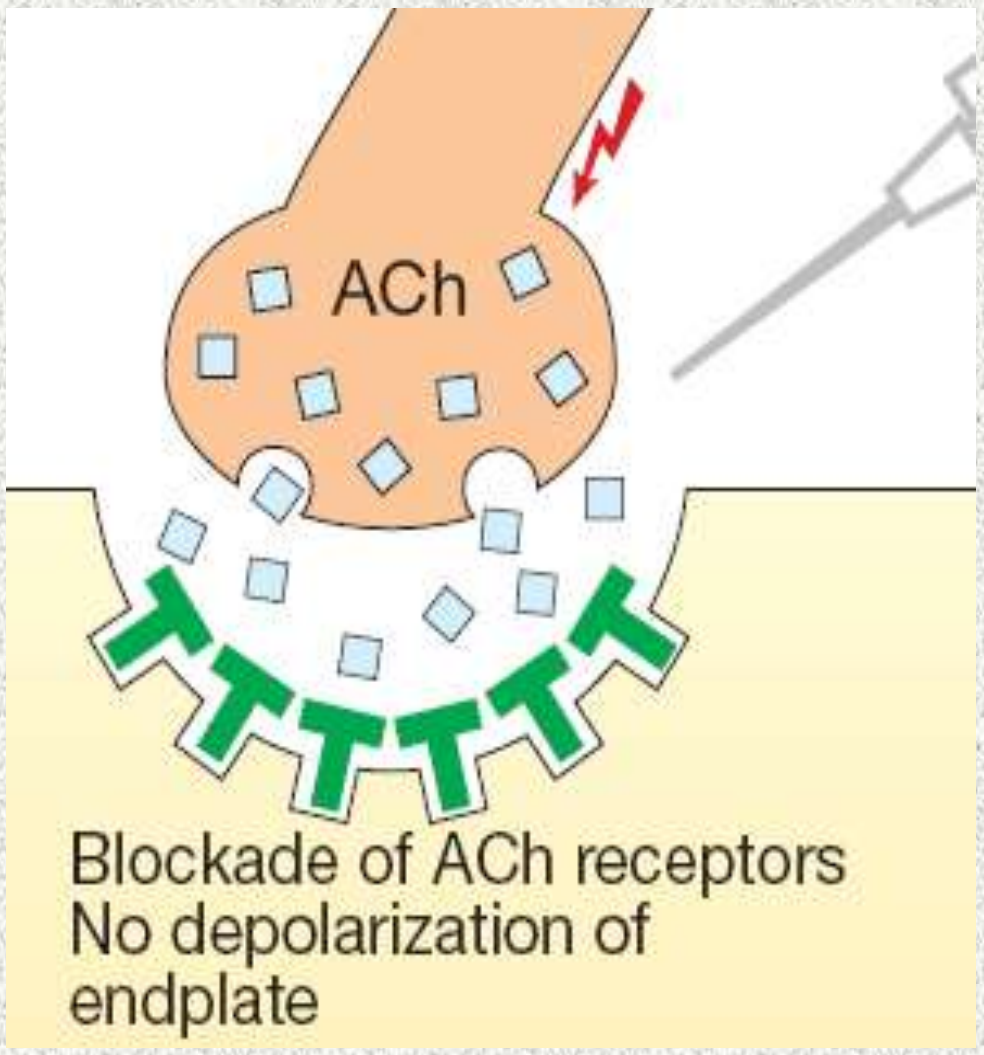


TUBOCURARINE:
PHARMACOKINETICS

- is administered IV
- is not absorbed in the gut due to presence of quaternary nitrogen atoms
- does not penetrate CNS
- total myorelaxation is developed in 20-30 min and lasts about 20-40 min, restoration of muscle tone lasts

  20-30 min

TUBOCURARINE:
MECHANISM OF ACTION



TUBOCURARINE:
PHARMACODYNAMICS AND INDICATIONS

PHARMACODYNICS

muscular paralysis in the muscles of fingers, neck, face, extremities, trunk, then in the intracostal muscles, and diaphragm (with inability to breath).

INDICATIONS

1. **Myorelaxation under the conditions of general anesthesia**
2. **Seizures caused by seizure poisons and some infections.**

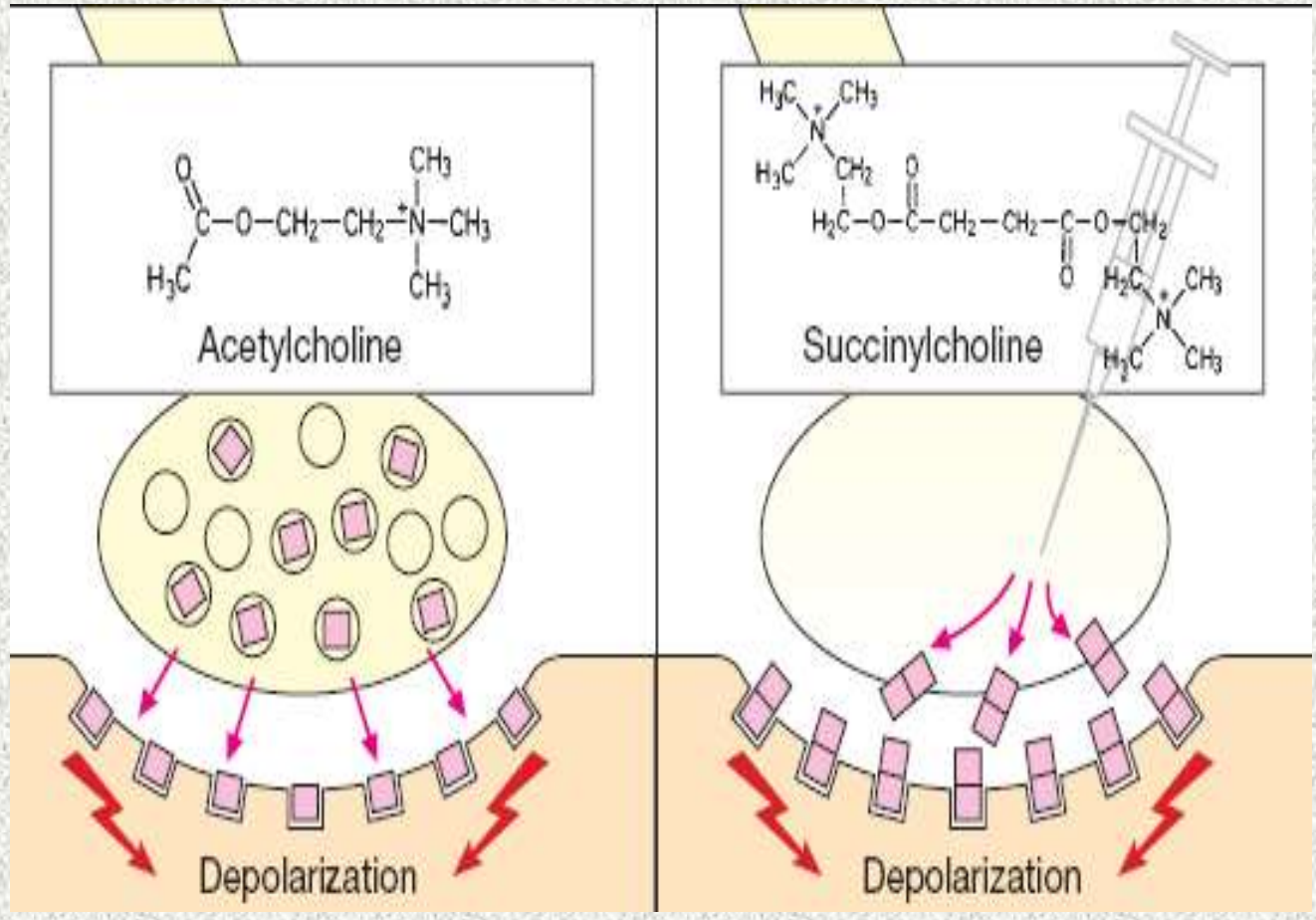
TUBOCURARINE:
SIDE EFFECTS

- ✓ Spasm of bronchi and urticaria (due to histamine release from mast cells)
- ✓ Lowering of BP (due to weak ganglia blocking activity).

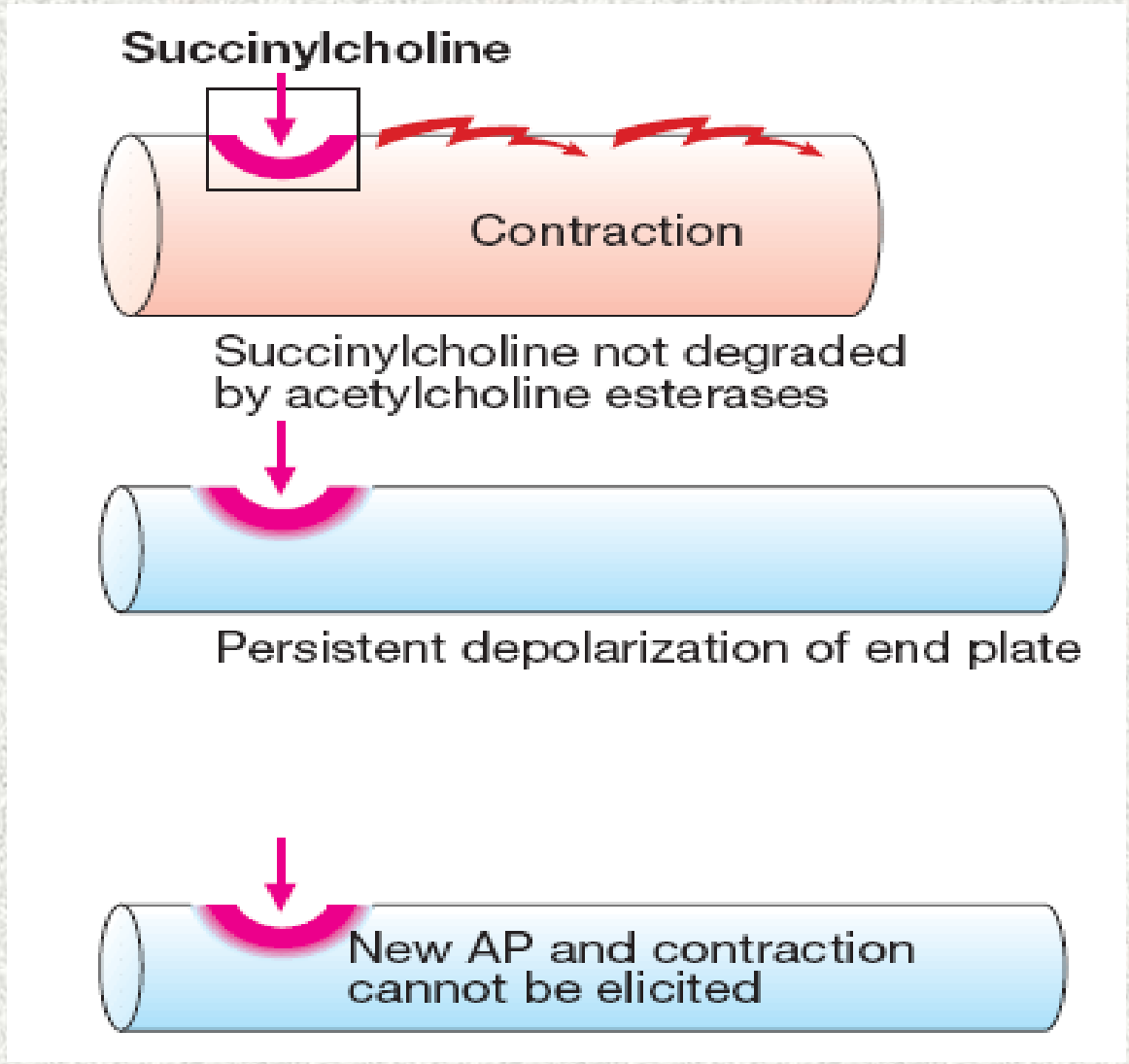
✱The duration of action of d-tubocurarine can be shortened by administration of neostigmine or other anticholinesterase.

SUCCINYLCHOLINE

It is a double acetylcholine molecule, agonist of N-cholinoreceptors, *depolirizing agent*.



SUCCINYLCHOLINE:
MECHANISM OF ACTION



SUCCINYLCHOLINE

- ***PHARMACODYNAMICS*: is administered IV; has short duration of action; total myorelaxation and stop of breathing lasts 3-5 min; is destroyed by butiryl cholinesterase in blood**
- ***PHARMACODINAMICS*: myorelaxation**
- ***INDICATIONS*: short surgeries, intubation of thrachea, endoscopy, reposition of bone fractures**
- ***SIDE EFFECTS*: fibrillation of skeletal muscles at the start of action, hyperkalemia, cardiac arrhythmia, increase of intraocular pressure, pain in skeletal muscles after the surgery**
- ***IDIOSYNCRASY*: long-lasting apnea in patients deficient on butiryl cholinesterase.**

  ✱**Emergence help is hemotransfusion and artificial lungs ventilation.**

CHOLINERGIC DRUGS IN DENTISTRY

- Pilocarpine, neostigmine are used for xerostomia
- Neostigmine and other anticholinesterases are used for paresis and paralysis of the tongue and facial muscles
- Atropine is used for a decrease of hypoersalivation
- Myorelaxants may be used for trismus (a painful condition in which the chewing muscles of the jaw become contracted and sometimes inflamed, preventing the mouth from fully opening)

CONTROL TASKS

- A patient after the stroke has paralysis of the hand and leg. To restore the movements the patient was treated with cholinomimetic. Which of the listed drugs was used for this purpose?

A. Neostigmine

B. Pilocarpine

C. Lobeline

D. Muscarine

E. Nicotine. (A)

- A patient with glaucoma is prescribed with M-cholinomimetic as eye membranes. Its usage in clinic is limited by strong systemic activity and toxicity. Which drug is prescribed?

A. Neostigmine

B. Pilocarpine

C. Lobeline

D. Platyphylline

E. Galanthamine. (B)

CONTROL TASKS

- Use of eye drops in a patient with trauma of the eye results in mydriasis, regulation of the eye for far vision for 10 days. What group of drugs causes such effect?

A. M-cholinergic agonists

B. M-cholinergic antagonists

C. N-cholinergic agonists

D. Reactivators of cholinesterase

E. None of the listed groups (B).

- Succinylcholine has caused long-lasting apnoea in a patient with deficit of pseudocholinesterase. Emergence help in this case is:

A. Neostigmine

B. Reactivators of cholinesterase

C. Forced diuresis

D. Blood transfusion and apparatus lungs ventilation

E. Adrenalin (intracardialy) (D)

THE END

Thank you

for attention!