



DIRECT CHOLINERGIC DRUGS

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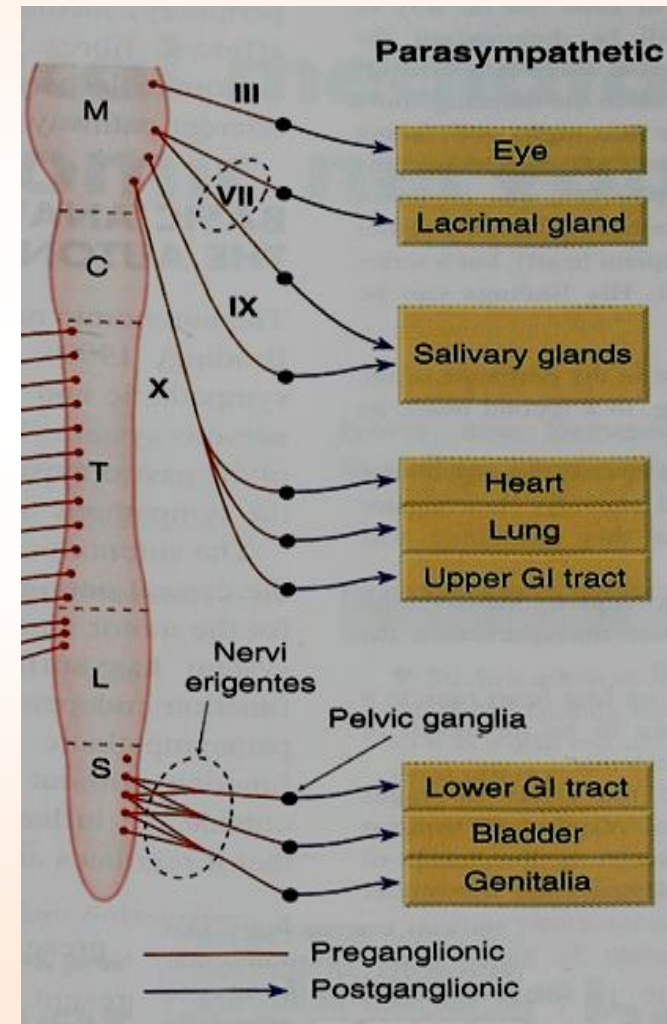
By the end of this lecture the student should know

- *Mention the different types, locations and actions of cholinergic receptors.*
- *Identify the mechanism of action of direct acting cholinomimetics.*
- *Describe the pharmacokinetics of cholinergic drugs.*
- *Identify pharmacological actions and uses of cholinomimetics.*

Cholinomimetics

Parasympathomimetics

Drugs that produce actions similar to stimulation of parasympathetic system or similar to Ach.



Types of cholinomimetics

Direct cholinomimetics

cause direct stimulation of cholinergic receptors.

Indirect cholinomimetics

acts indirectly by inhibiting **acetyl cholinesterase** thus prevent the hydrolysis of Ach. They are called (**cholinesterase inhibitors or anticholinesterases**).

Parasympathomimetics (cholinergic drugs)

Direct

Acetyl-choline
Methacholine
Carbachol
Bethanechol
Pilocarpine

Indirect

Reversible

Physostigmine
Neostigmine
Edrophonium

Irrversible

Organophosphorus
Echothiophate (used in glaucoma)
War gases and Parathion

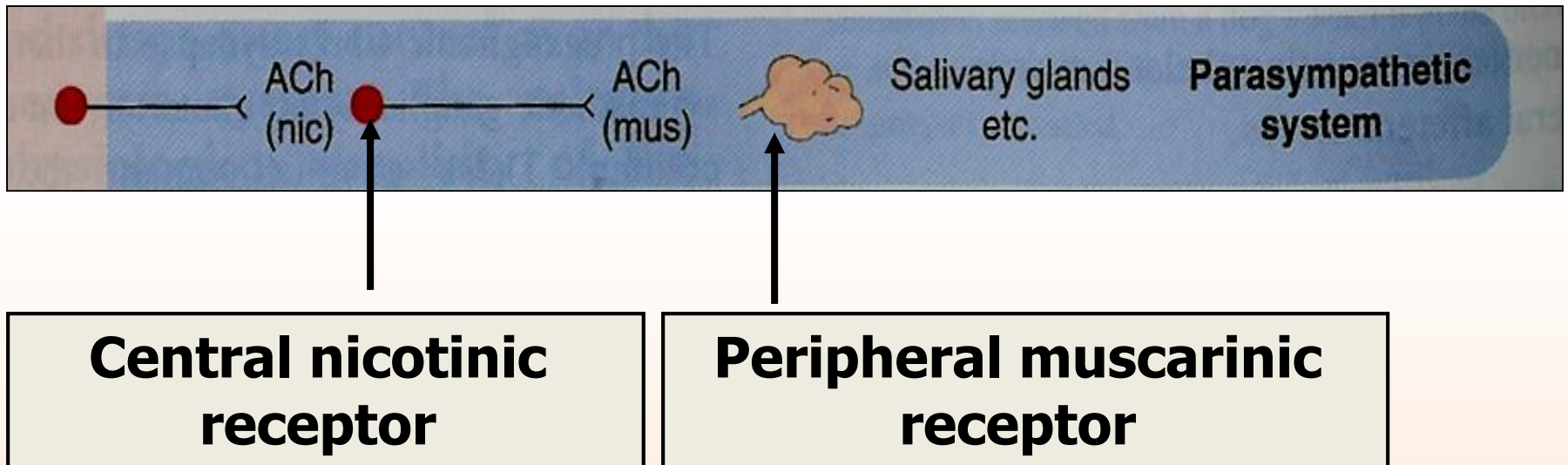
Direct Cholinergic drugs

Cholinergic drugs acts upon two types of receptors

- **Nicotinic receptors**
- **Muscarinic receptors**

Cholinergic or parasympathetic receptors

- Nicotinic receptors (**N**) = central receptors.
- Muscarinic receptors (**M**) = peripheral receptors



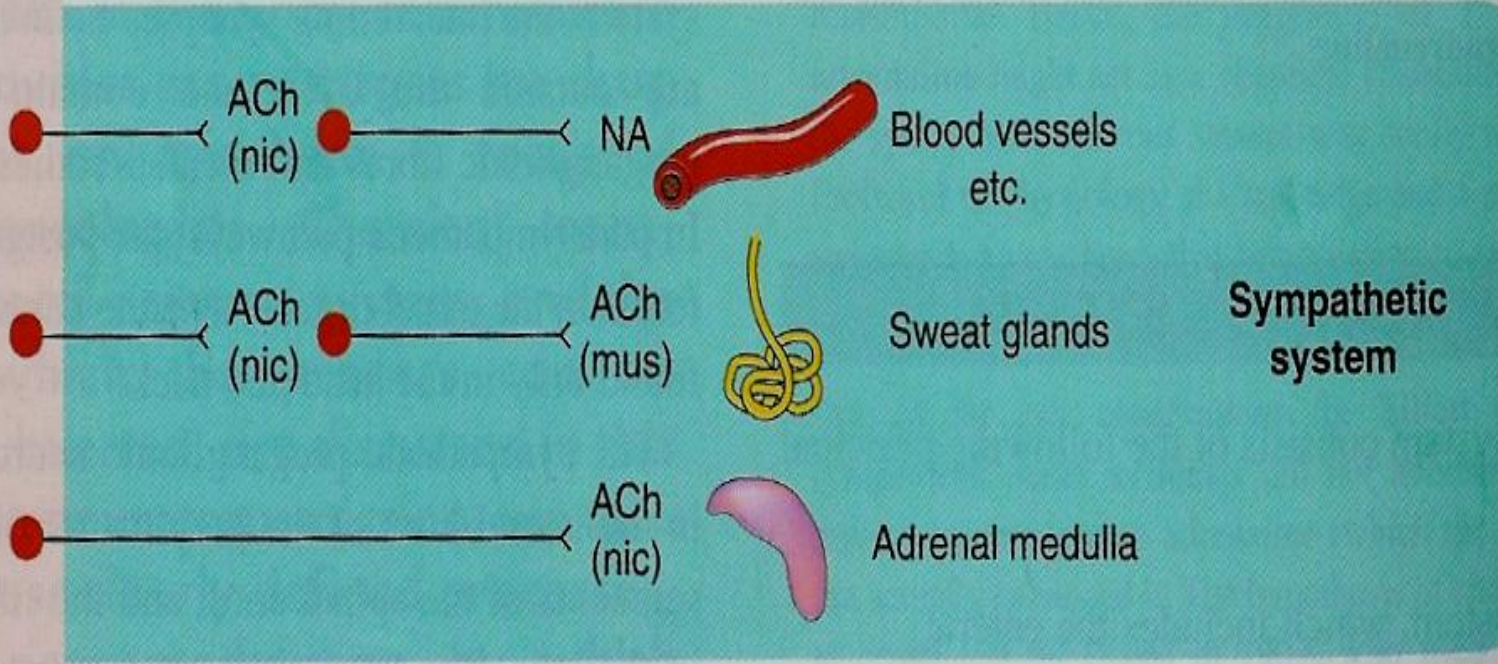
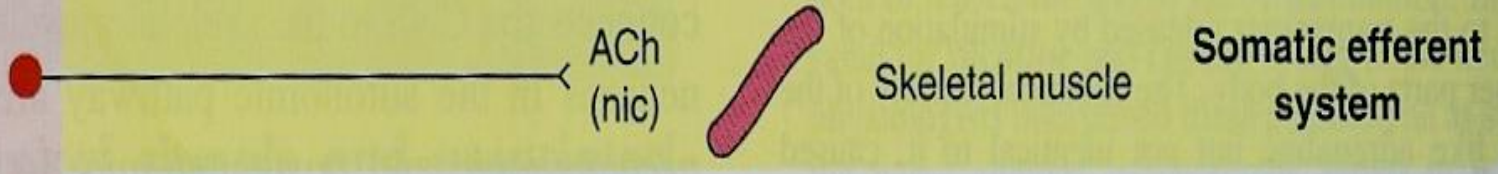
Nicotinic receptors

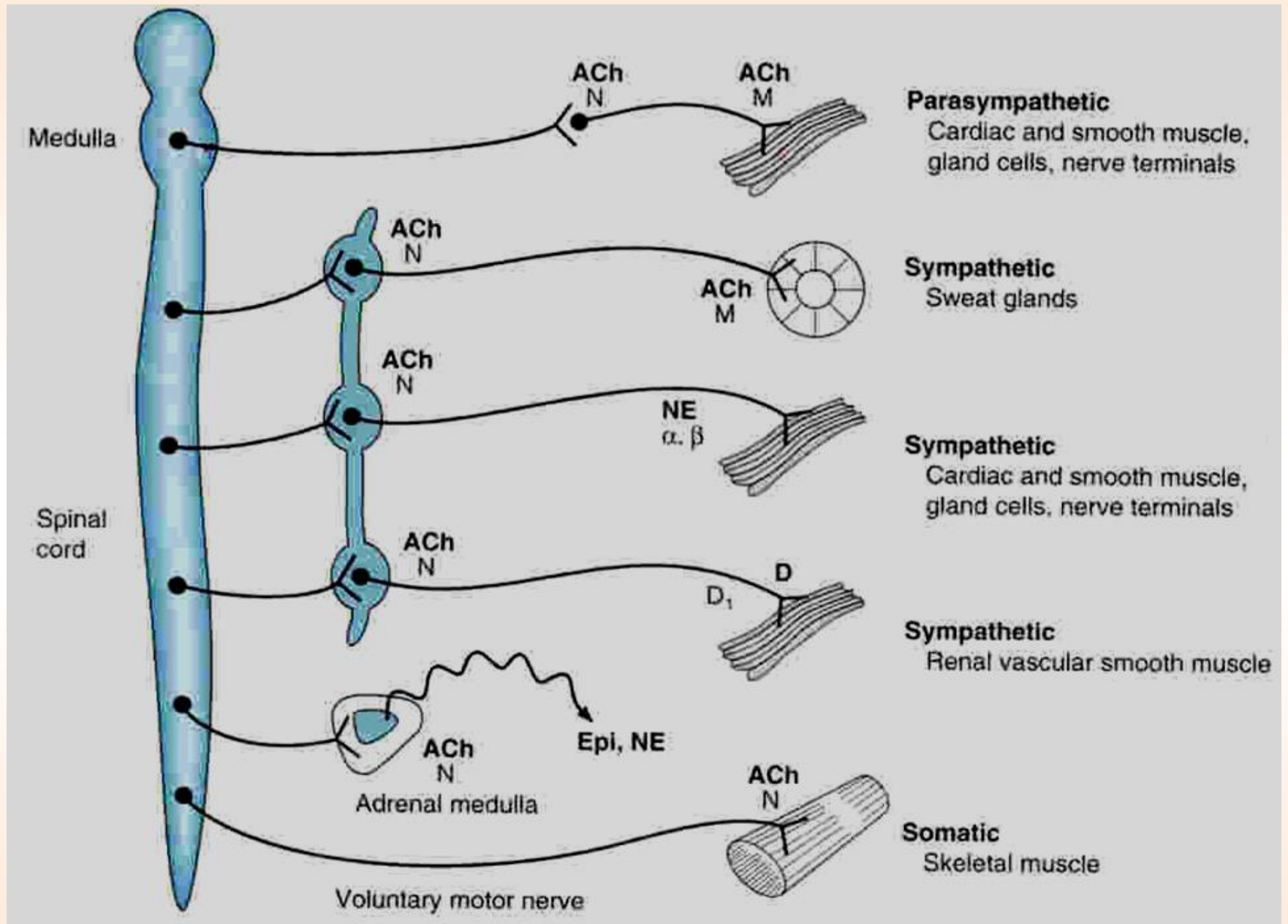
Type I receptors : ion channel linked receptors

Located in:






- **Skeletal muscles (neuromuscular junction, Nm)**
- **Autonomic ganglia (sympathetic and parasympathetic ganglia, Nn).**
- **Adrenal medulla (Nn).**
- **CNS (Nn).**

CENTRAL NERVOUS SYSTEM





Comparison of Autonomic and Somatic Motor Systems

| | Cell bodies in central nervous system | Peripheral nervous system | Neurotransmitter at effector | Effector organs | Effect |
|---------------------------------|---|---|------------------------------|--|---|
| SOMATIC NERVOUS SYSTEM |  | Single neuron from CNS to effector organs Heavily myelinated axon | ACh |  Skeletal muscle | + Stimulatory |
| AUTONOMIC NERVOUS SYSTEM |  | Two-neuron chain from CNS to effector organs Lightly myelinated preganglionic axons | NE |  Smooth muscle (e.g., in gut), glands, cardiac muscle | + - Stimulatory or inhibitory, depending on neurotransmitter and receptors on effector organs |
| | | Ganglion Unmyelinated postganglionic axon Epinephrine and norepinephrine Adrenal medulla Blood vessel | | | |
| PARASYMPATHETIC |  | Lightly myelinated preganglionic axon Ganglion Unmyelinated postganglionic axon | ACh | | |

▲ Acetylcholine (ACh) ● Norepinephrine (NE)

Muscarinic receptors

Type II receptors : G-protein linked receptors

- **Five subclasses ; M_1 , M_2 , M_3 , M_4 and M_5**
- **M_1 , M_3 , M_5 are excitatory or stimulatory in function (stimulation)**
- **M_2 , M_4 are inhibitory in function (inhibition).**
- **Located at all target organs that are innervated by postganglionic parasympathetic fibers (e.g, heart, CVS, eye, bladder, etc).**

Muscarinic receptors

| Receptor | Locations | Pharmacological actions |
|--------------------------------|--|---|
| M1 Excitatory | CNS gastric parietal cells | CNS excitation Gastric acid secretion |
| M2 Inhibitory | Heart | Cardiac inhibition (Bradycardia) |
| M3 Excitatory | Vascular endothelium Exocrine glands Smooth muscles (GIT, urinary tract, bronchial muscles) | <ul style="list-style-type: none">• Release of nitric oxide (NO), vasodilatation• Secretion of glands• Smooth muscle contraction |
| M4 & M5 | CNS | memory, arousal, attention and analgesia |

Cholinergic or parasympathetic receptors

| Nicotinic receptors Central cholinceptors | Muscarinic receptors Peripheral cholinceptors |
|---|---|
| Almost excitatory | Excitatory or inhibitory |
| Autonomic ganglia Nn sympathetic & parasympathetic stimulation | On all peripheral organs innervated by postganglionic parasympathetic fibers |
| Adrenal medulla Nn release of catecholamines (adrenaline & noradrenaline) | <ul style="list-style-type: none"> ▪ Heart (bradycardia, M2) ▪ Exocrine glands (secretion, M3) ▪ Smooth muscles (contraction, M3) (GIT, urinary tract, bronchial muscles, uterus) |
| Skeletal muscles Nm contraction | |

Pharmacological actions of direct cholinergic drugs

Actions that are similar to the effects of parasympathetic system activation.

They produce:

- 1. Nicotinic actions**
- 2. Muscarinic actions**

Nicotinic actions

➤ **Skeletal muscles:**

➤ **Low concentration → muscle contraction**

➤ **High concentration → persistent depolarization & relaxation (depolarization block).**

➤ **Stimulation of Autonomic ganglia (sympathetic & parasympathetic).**

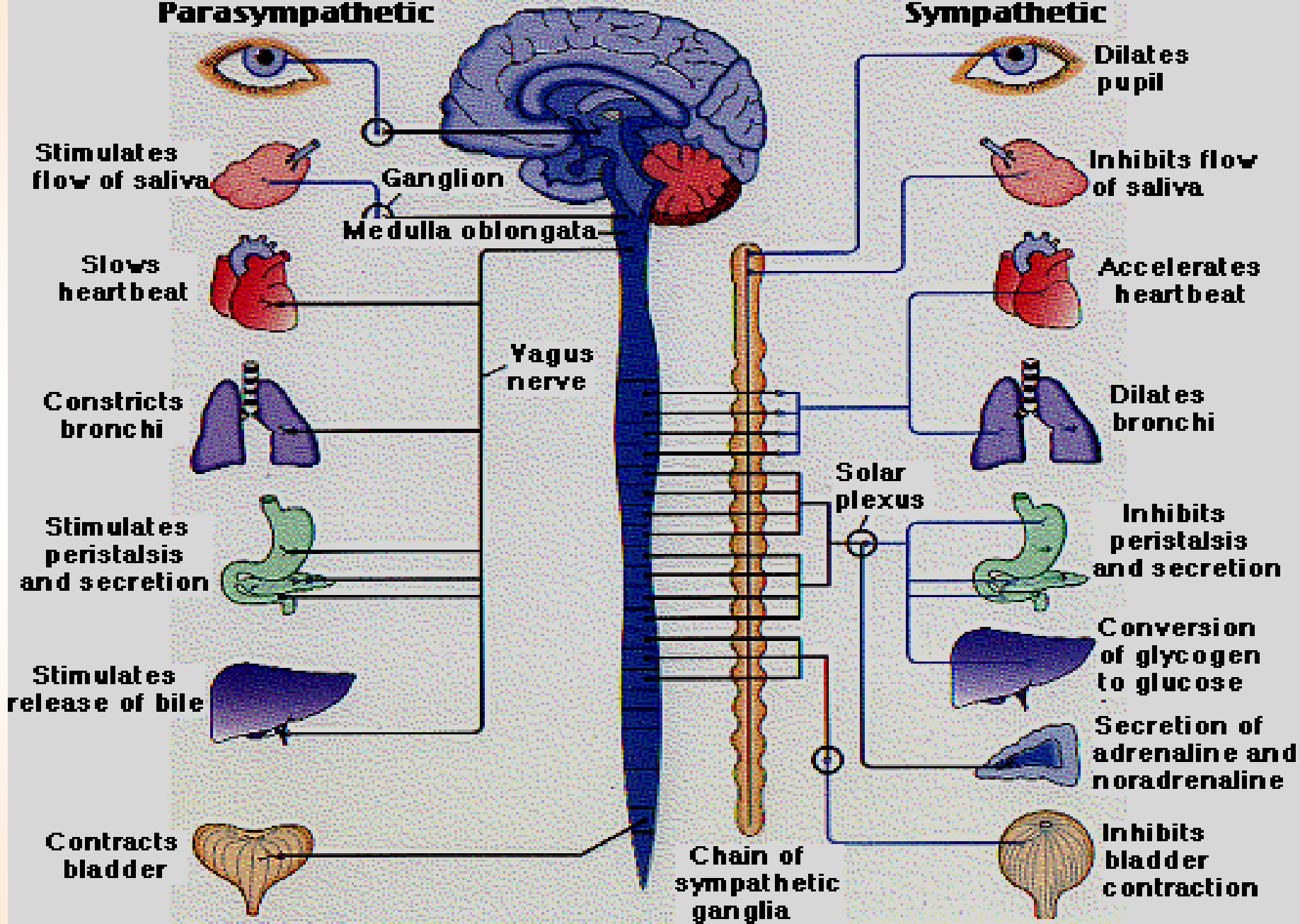
➤ **Stimulation of adrenal medulla: release of catecholamines (Adrenaline & Noradrenaline).**

Muscarinic actions

| Organs | Cholinergic actions |
|------------------------------|--|
| Eye | Contraction of circular muscle of iris (miosis)(M3) Contraction of ciliary muscles for near vision (M3) Decrease in intraocular pressure (IOP) |
| Heart Endothelium | bradycardia (decrease in heart rate) (M2) Release of NO (EDRF) |
| Lung | Constriction of bronchial smooth muscles Increase in bronchial secretion M3 |
| GIT | Increase in motility (peristalsis) Increase in secretion Relaxation of sphincter – defecation M3 |
| Urinary bladder | Contraction of muscles Relaxation of sphincter M3 Urination |
| Exocrine glands | Increase of secretions of exocrine glands sweat, saliva, lacrimal, bronchial, intestinal secretions M3 |

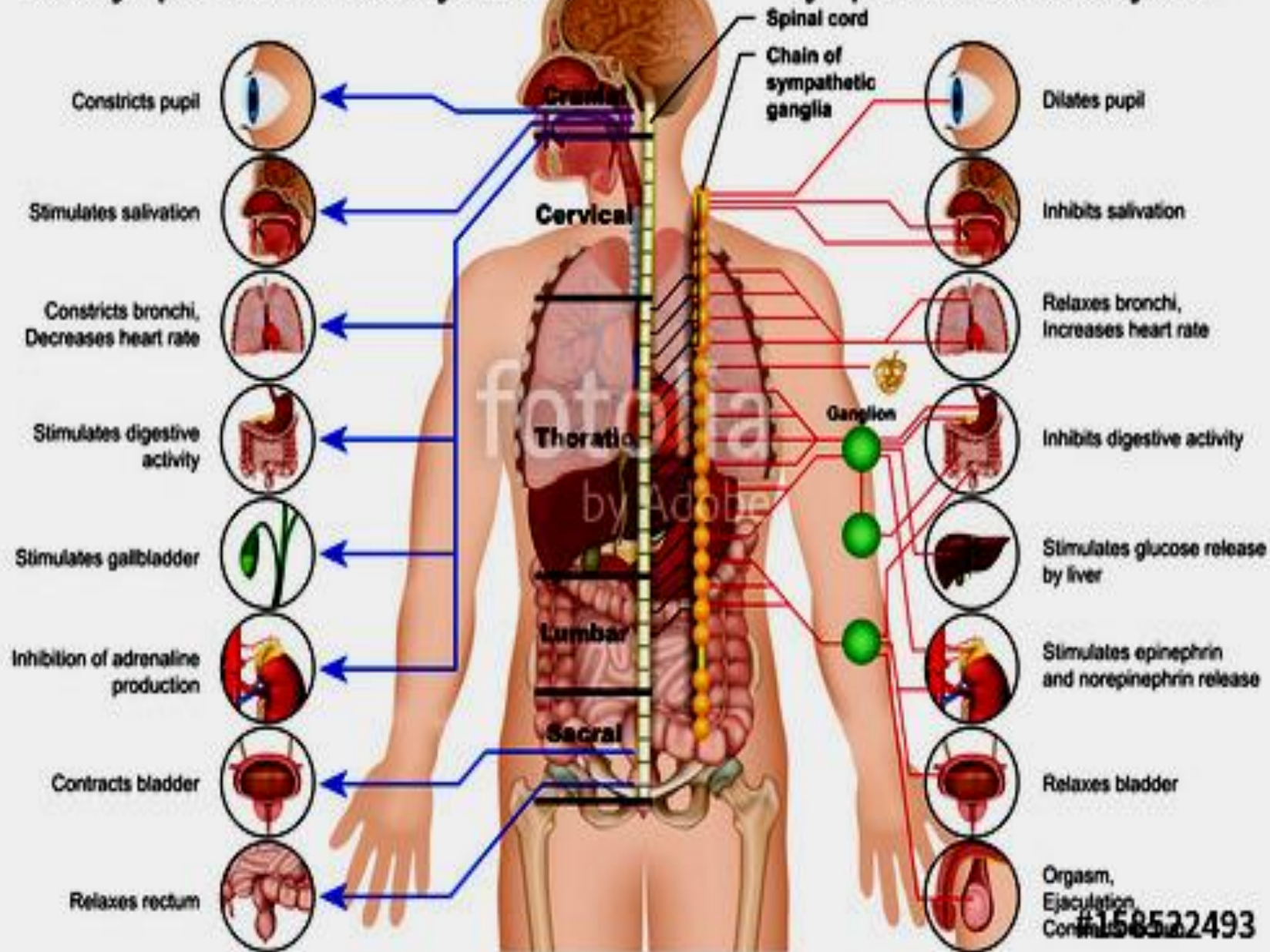
Parasympathetic

Sympathetic



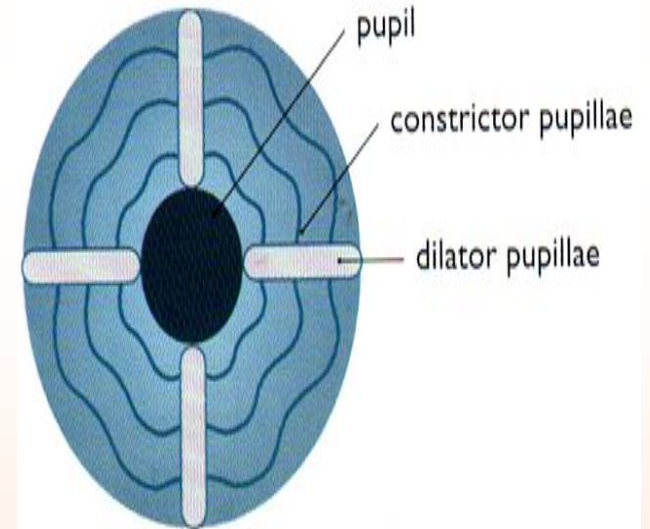
Parasympathetic nervous system

Sympathetic nervous system

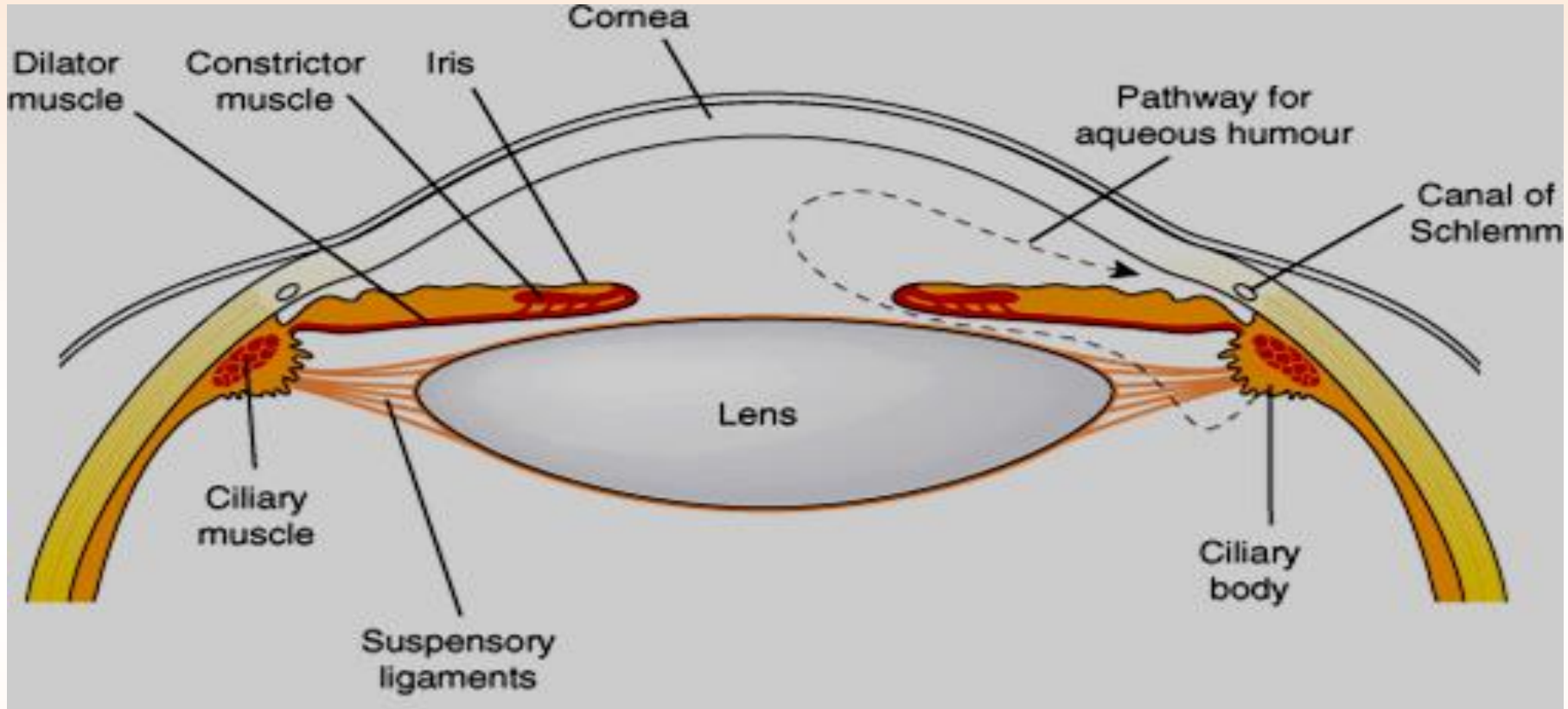


EYE

The parasympathetic innervates the **constrictor pupillae** (**circular muscles of iris**) which is important for adjusting the pupil in response to change in light intensity & regulating the intraocular pressure.



Decrease in IOP by parasympathetic drugs



The aqueous humor is secreted by the epithelium of ciliary body. It is produced by a combination of active transport of ions and ultrafiltration of interstitial fluid. The fluid flows over the surface of the lens, out through the pupil into the anterior chamber. Flows through the trabecular meshwork into Schlemm's canal and is collected in the scleral veins. **Parasympathomimetics produce contractions of circular muscles of iris thus pulling ciliary muscles away from the trabecular meshwork and Schlemm's canal thus facilitating drainage and reducing intraocular pressure.**

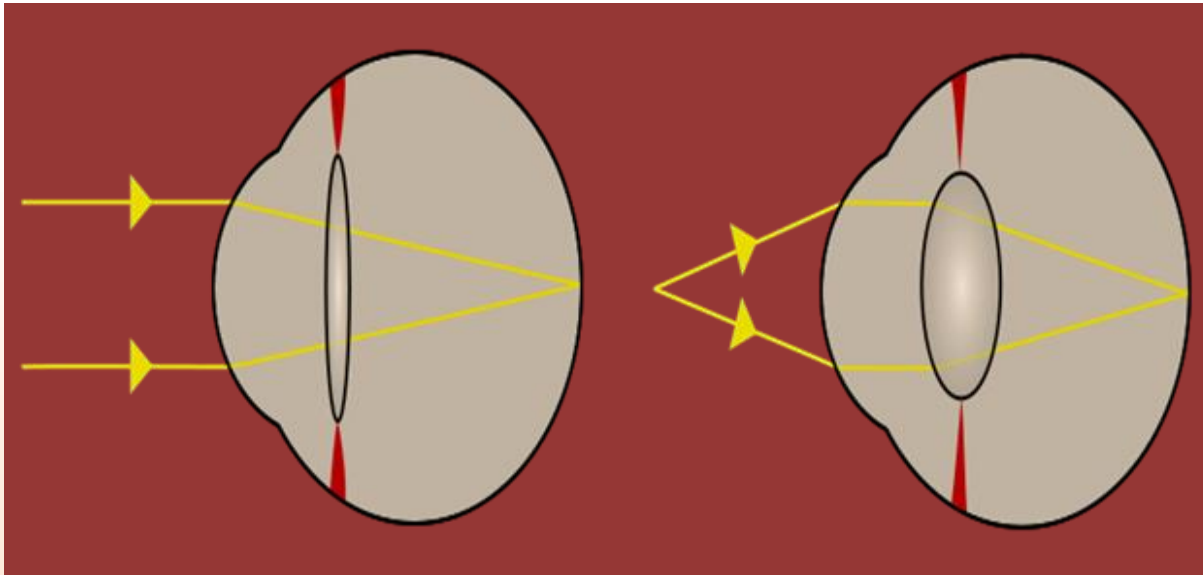
Aqueous humor secreted by **ciliary body**, is removed continuously by drainage into the **canal of Schlemm**.

Normal intraocular pressure is 10-15 mmHg above atmospheric pressure . Abnormally raised pressure (**glaucoma**)→**retinal detachment**.

Cholinergic drugs →**Miosis** →↓ intraocular pressure in patient with glaucoma

Cholinergic drugs & accommodate for near vision

When the ciliary muscle contracts, the lens **bulge** more → this parasympathetic reflex is essential to **accommodate for near vision**

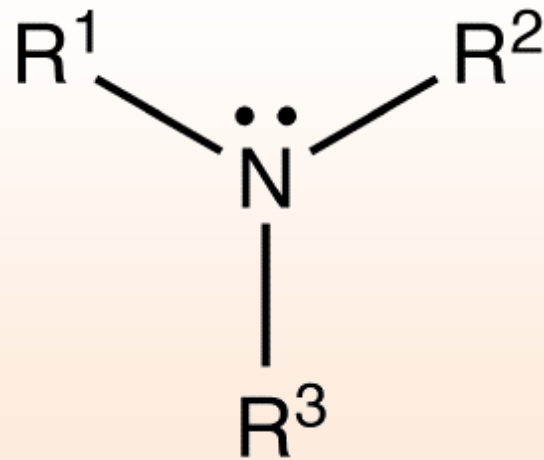


| Eye | Parasympathetic Nervous System |
|---|---------------------------------------|
| Iris radial muscle circular muscle | No effect Contraction (miosis) M3 |
| Ciliary muscle | Contraction M3 |
| Accommodation | for near vision |
| Intraocular pressure(IOP) | Decrease |

Direct Cholinomimetics

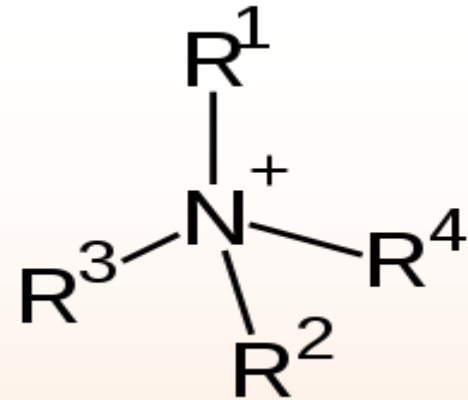
– Naturally occurring alkaloids e.g.

e.g. pilocarpine, nicotine (tertiary amines).



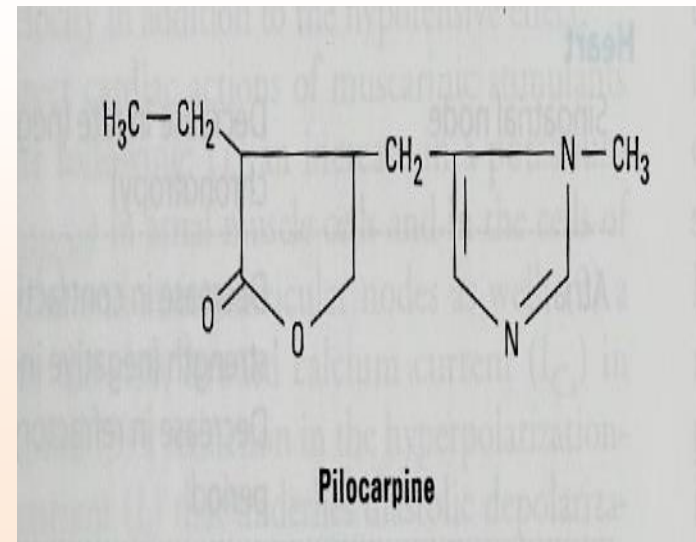
Direct Cholinomimetics

- Natural alkaloids
- Synthetic choline esters (**Quaternary ammonium compounds**)
 - Acetylcholine
 - Carbachol
 - Bethanechol
 - Cevimeline



Pilocarpine (natural alkaloids)

- Tertiary amine **non polar = lipophilic**
- well absorbed, good distribution
- **Cross BBB (has central effects).**
- Not metabolized by cholinesterase
- Long duration of action
- Excretion is enhanced by acidification of urine
- Direct muscarinic agonist
(mainly on eye & secretion).



Pilocarpine (continue...)

Uses:

- **Xerostomia (*dry mouth*).**
- **Drug of choice in emergency glaucoma **applied as eye drops.****

Adverse effects:

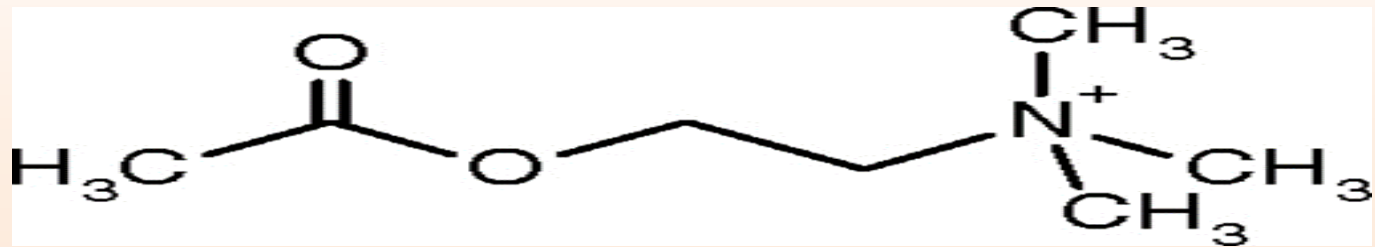
- **Profuse sweating**
- **Salivation**
- **Bronchoconstriction**
- **Diarrhea (increase GIT motility)**
- **CNS effects**

Acetylcholine (Ach)

Muscarinic and nicotinic agonist

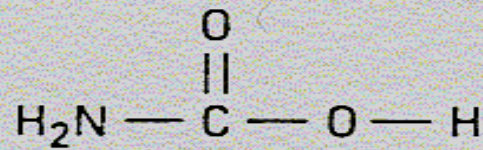
Not used clinically because Ach

- Is not selective as it acts on both **nicotinic and muscarinic receptors**
- Has short duration of action. Why?
- Due to rapid metabolism by **acetylcholinesterase**

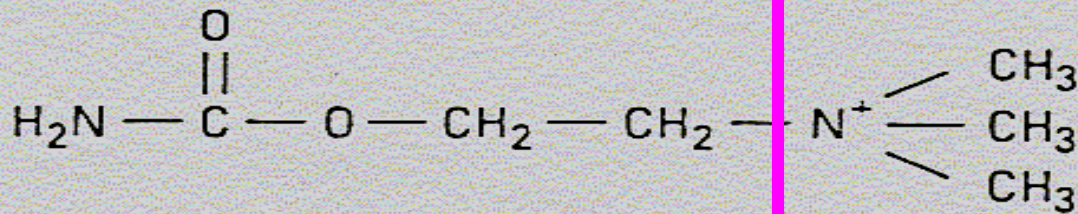


Synthetic choline esters

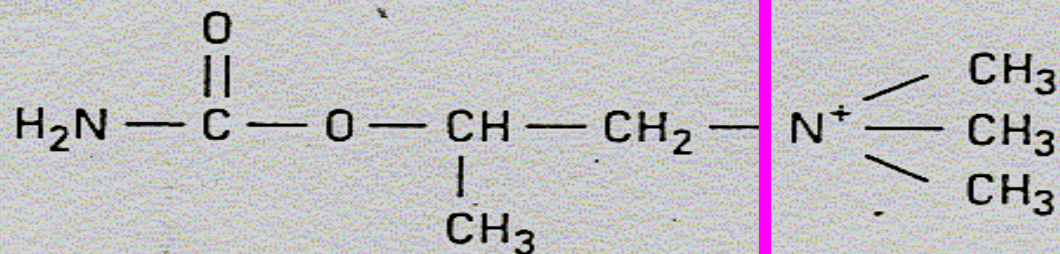
- ❑ include drugs as **bethanechol, carbachol**
- ❑ Quaternary ammonium compounds
contain N^+ (**polar**)
- ❑ Poor distribution
- ❑ can not cross BBB (**No CNS effects**)
- ❑ Not metabolized by cholinesterase.
- ❑ Have longer duration of action than Ach.
- ❑ Never given I.V. or I.M **BUT** S.C.



Carbamic acid



**Carbachol
(carbamoylcholine)**



**Bethanechol
(carbamoyl- β -methylcholine)**

Carbachol

1. Muscarinic actions on Eye, GIT, UT. (see the previous table).
2. Has nicotinic actions (side effects).
3. Resistant to hydrolysis by acetyl cholinesterase
4. Longer duration than Ach.
5. Used for treatment of glaucoma

Bethanechol

- **Prominent muscarinic actions on GIT, UT.**
- **No nicotinic action**
- **Resistant to hydrolysis by acetyl cholinesterase**
- **Longer duration than Ach**
- **Used for**
 - **Paralytic ileus**
 - **Urinary retention in cases of post-operative atony & neurogenic bladder**

Cevimeline

- Direct acting muscarinic agonist (M3)**
- Used for treatment of dry mouth symptom associated with Sjogren's syndrome or radiation therapy**

(autoimmune disease characterized by formation of antibodies that attacks the glands that make tears and saliva leading to dryness Of mouth and eye).

| | ACh | Carbachol | Bethanechol | Pilocarpine |
|---|--|--|---|-------------------------------|
| Chemistry | Quaternary Polar | Quaternary Polar | Quaternary Polar | Tertiary non polar |
| Absorption | NOT | better absorbed than Ach | better absorbed than Ach | Complete |
| Metabolism by cholinesterase | metabolized by cholinesterase | NOT metabolized by cholinesterase | | |
| Duration | Very short | Longer (++) | Longer (++) | Longer (++) |
| administration | I.V. eye drops | Oral, eye drops S.C. | Oral S.C. | oral, eye drops |

direct Cholinomimetic

| | ACh M, N | Carbachol M,N | Bethanechol M | Pilocarpine M | Cevimeline M |
|--------------------|---------------------------------------|---|--|---|-------------------------------------|
| Receptors | Muscarinic Nicotinic | Muscarinic Nicotinic | Muscarinic | Muscarinic | Muscarinic |
| Muscarinic | +++ | +++ | +++ | +++ | +++ |
| Selectivity | NOT | Eye, GIT Urinary bladder | GIT, Urinary bladder | More on eye, exocrine glands | Exocrine glands |
| Nicotinic | +++ | +++ | NO | NO | NO |
| Uses | NO | Glaucoma | Paralytic ileus Urinary retention | Glaucoma Xerostomia | Sjogren's syndrome |

Contraindications of direct cholinomimetics

- 1. Bronchial asthma.**
- 2. Peptic ulcer.**
- 3. Angina pectoris**
- 4. Urinary incontinence**
- 5. Intestinal obstruction**



Thank you