



DIRECT CHOLINERGIC DRUGS

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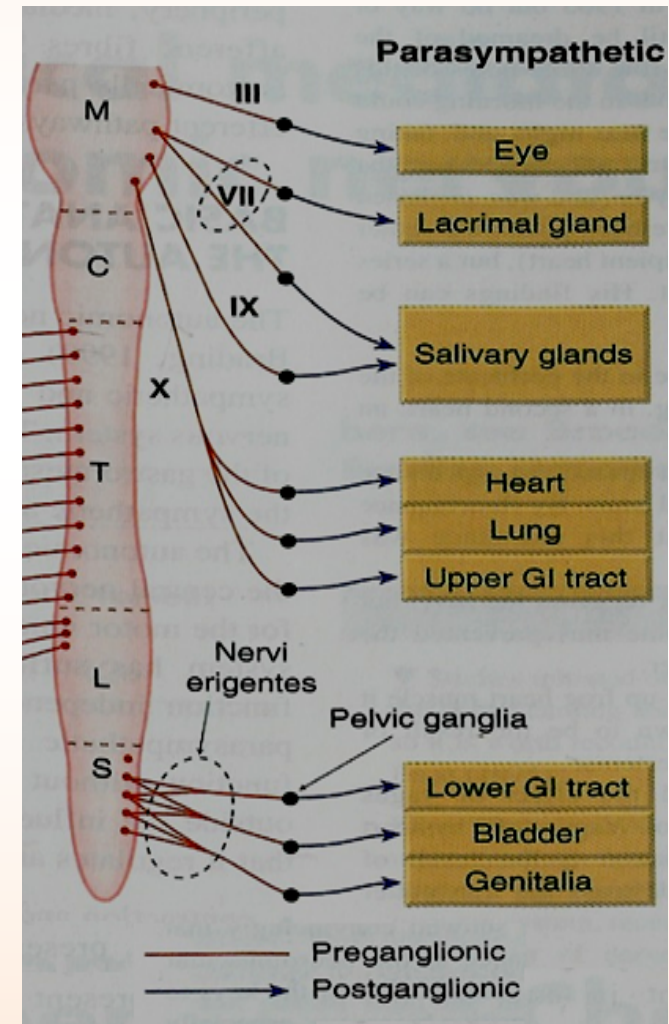
By the end of this lecture the student should know

- *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

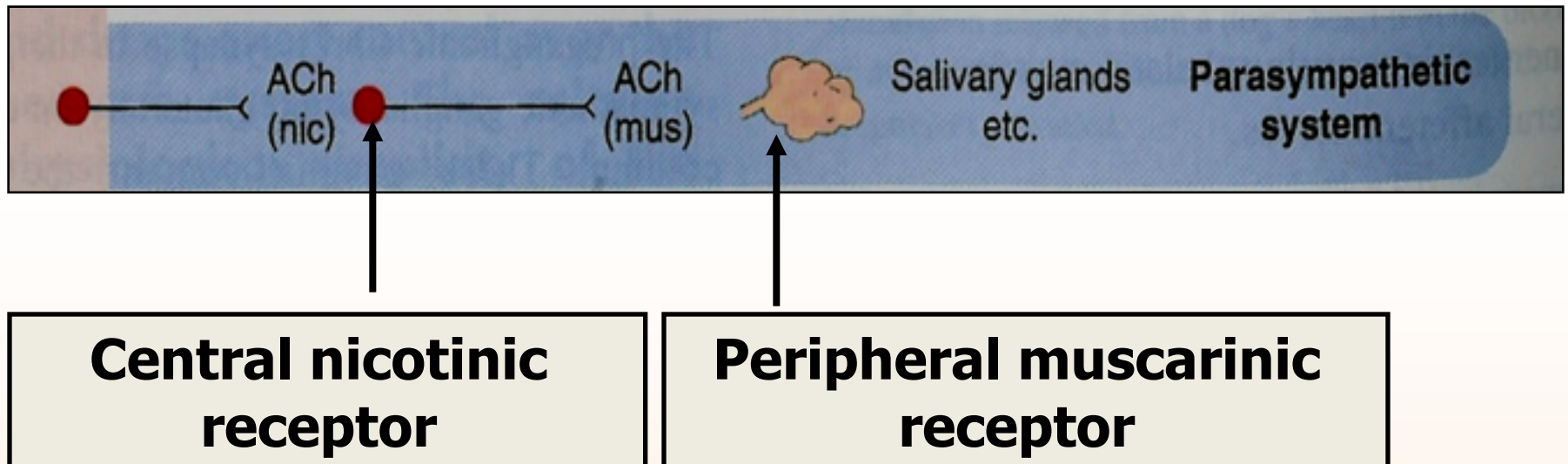
Direct Cholinergic drugs

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



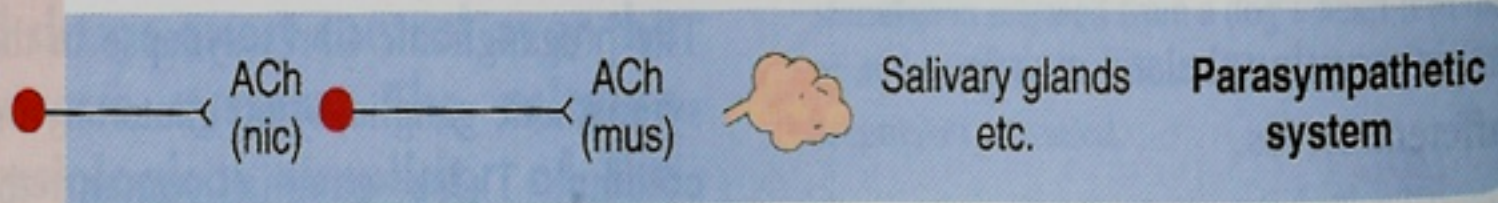
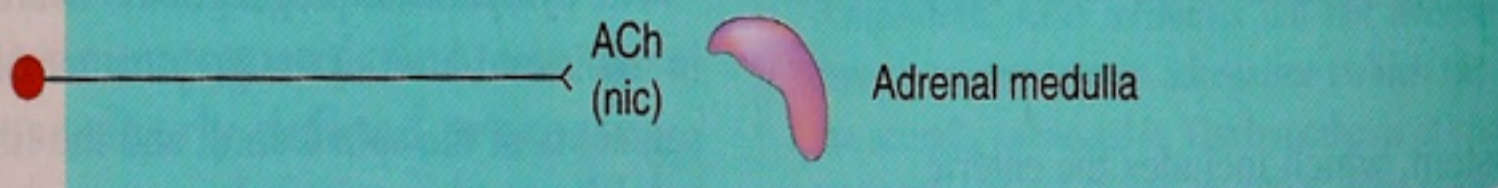
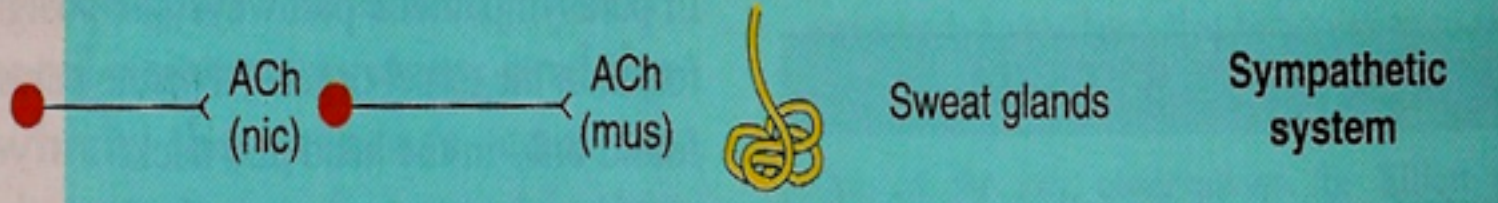
Nicotinic receptors

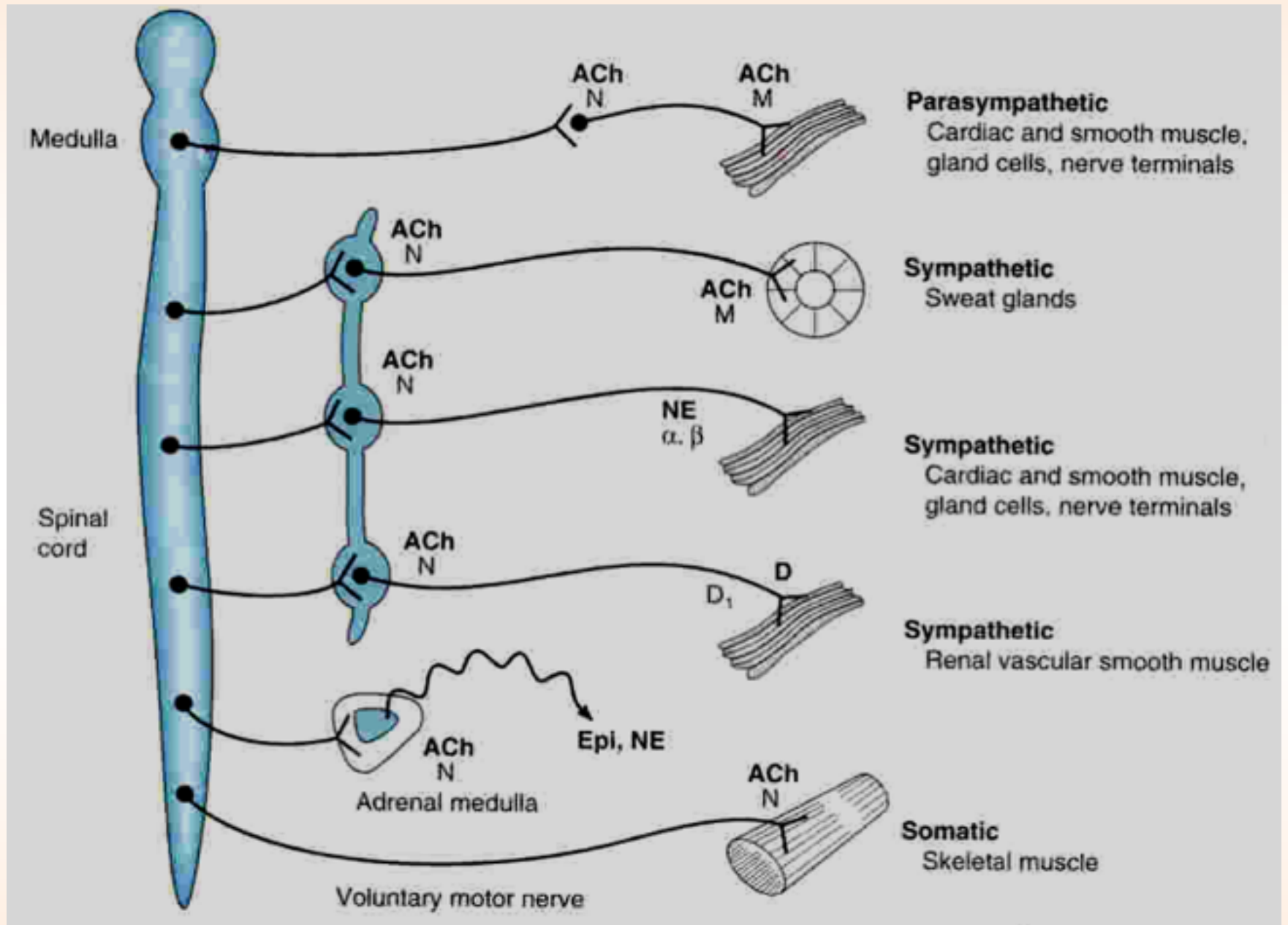
Type I receptors : ion channel linked receptors

Located in:

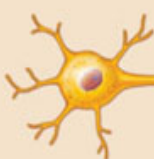

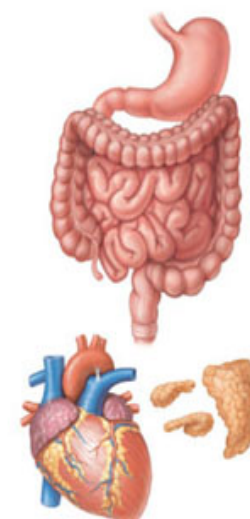
- **Skeletal muscles (neuromuscular junction, Nm)**
- **Autonomic ganglia (sympathetic and parasympathetic ganglia, Nn).**
- **Adrenal medulla (Nn).**
- **CNS (Nn).**

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	SYMPATHETIC	Two-neuron chain from CNS to effector organs Lightly myelinated preganglionic axons	Ganglion ACh	Unmyelinated postganglionic axon NE	 Stimulatory or inhibitory, depending on neurotransmitter and receptors on effector organs
		Adrenal medulla ACh			
PARASYMPATHETIC		Lightly myelinated preganglionic axon	Ganglion ACh	Unmyelinated postganglionic axon ACh	

▲ Acetylcholine (ACh) ● Norepinephrine (NE)

Muscarinic receptors

Type II receptors : G-protein linked receptors

- **Five subclasses ; M₁, M₂, M₃, M₄ and M₅**
- **M₁, M₃, M₅ are excitatory or stimulatory in function (stimulation)**
- **M₂, M₄ are inhibitory in function (inhibition).**
- **Located at all target organs that are innervated by 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">• Vasodilatation (via nitric oxide)• 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)

Heart (bradycardia, M2)
 exocrine glands (secretion, M3)

Skeletal muscles Nm
 contraction

Smooth muscles (contraction, M3)
 (GIT, urinary tract, bronchial
 muscles, uterus)

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).**

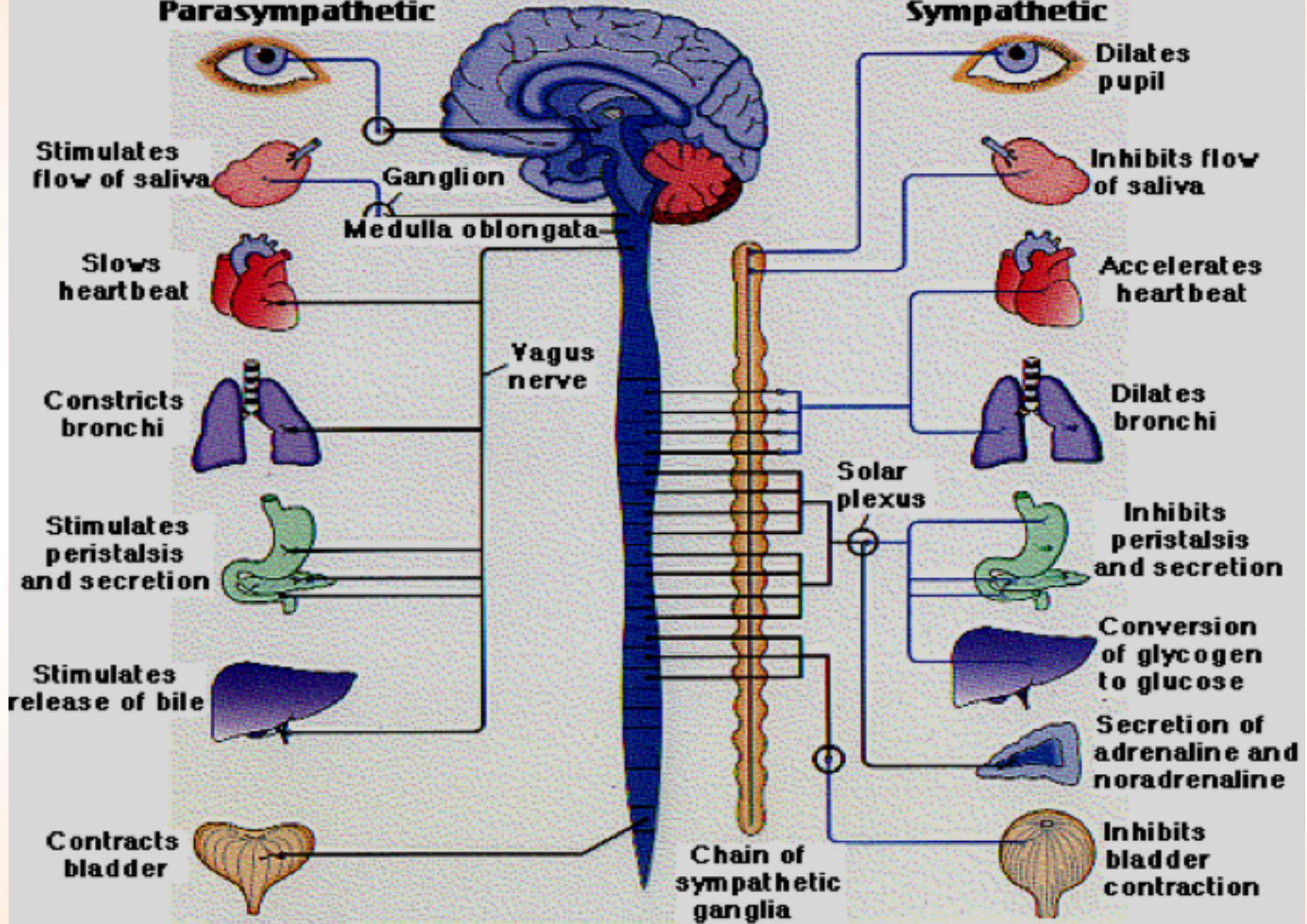
➤ **Stimulation of adrenal medulla: release of catecholamines (Adrenaline & Noradrenaline).**

Muscarinic actions

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

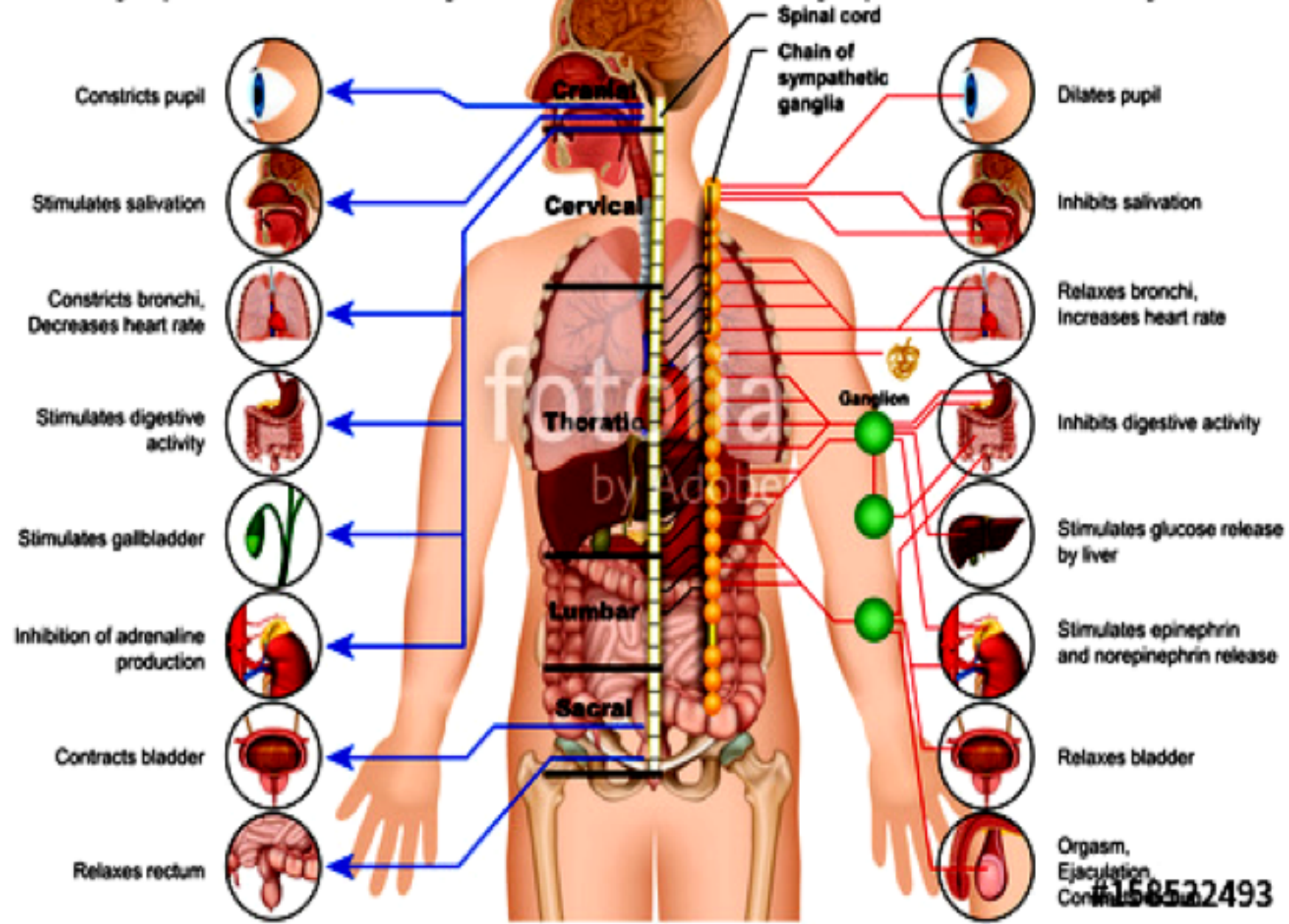
Parasympathetic

Sympathetic



Parasympathetic nervous system

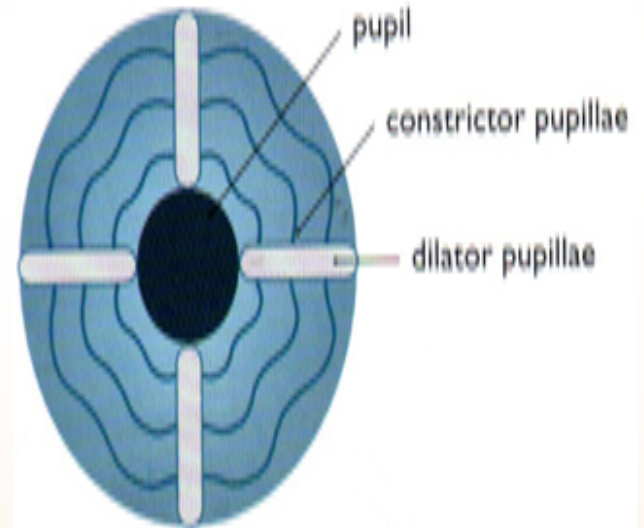
Sympathetic nervous system

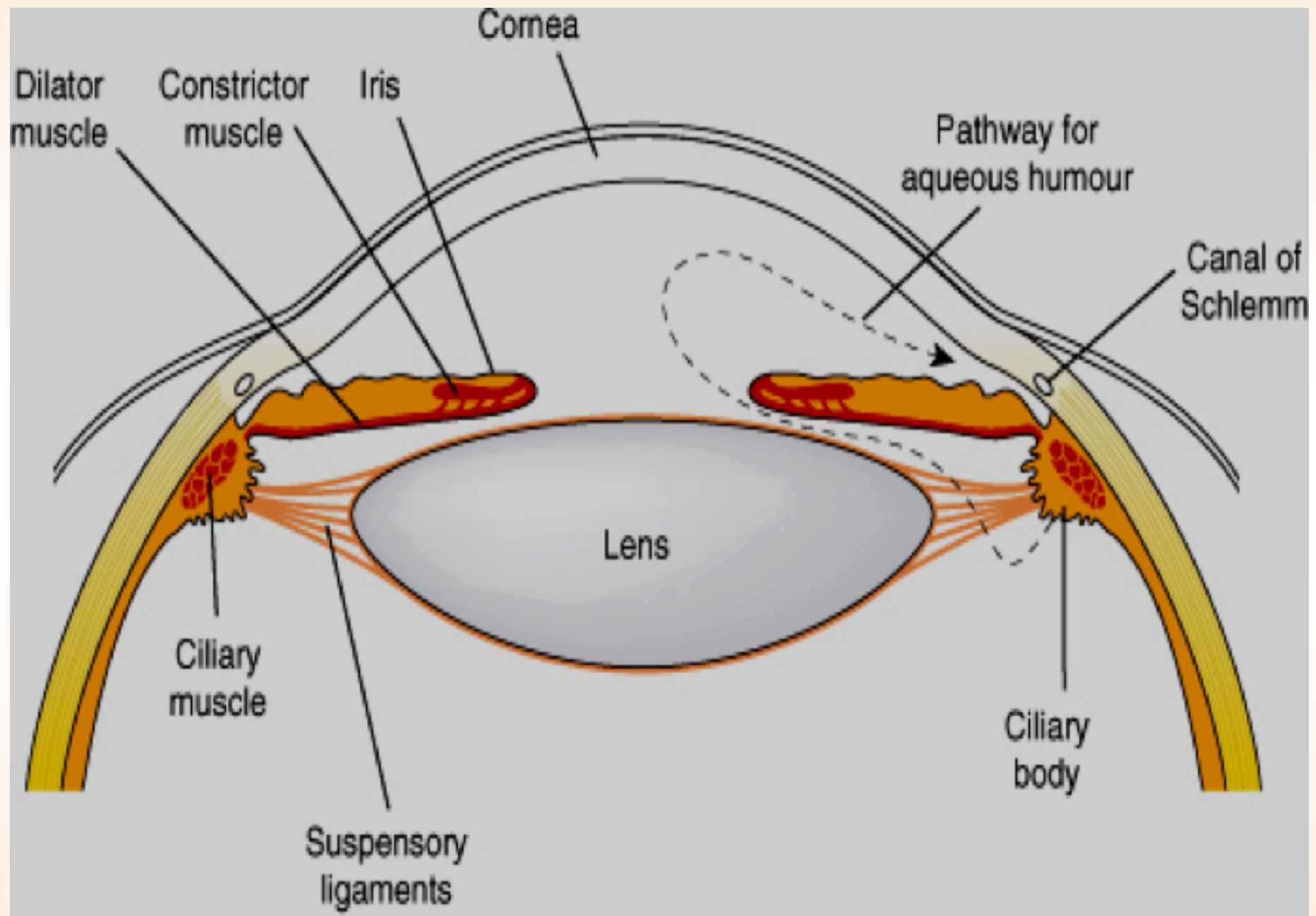


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EYE

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.





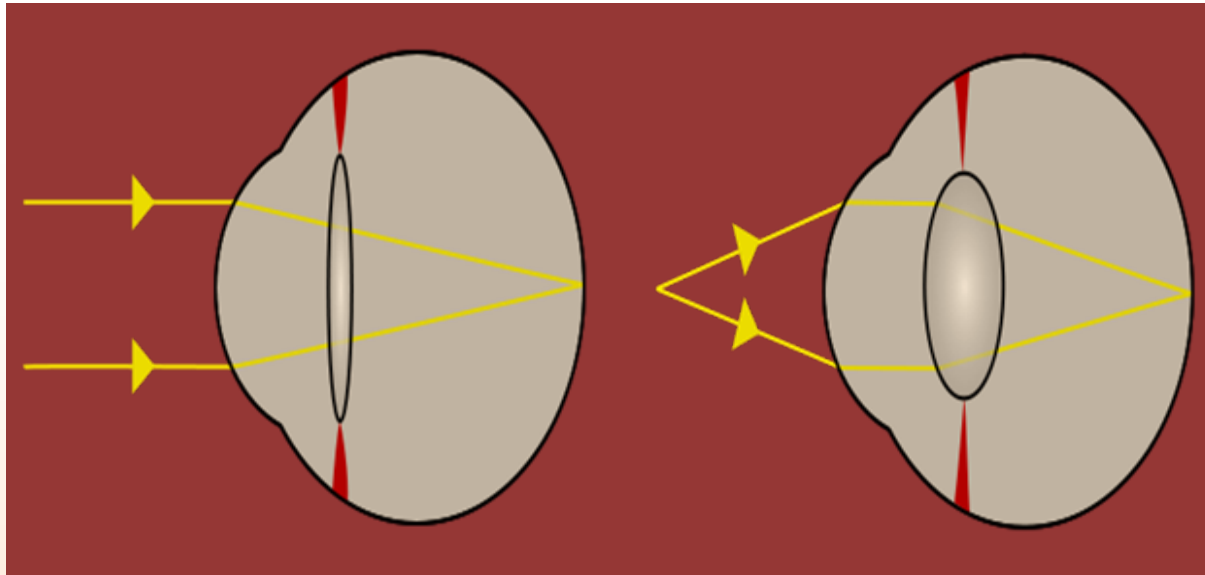
Aqueous humor secreted by **ciliary body**, is removed continuously by drainage into the **canal of Schlemm**.

Normal intraocular pressure is 10-15mmHg 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**

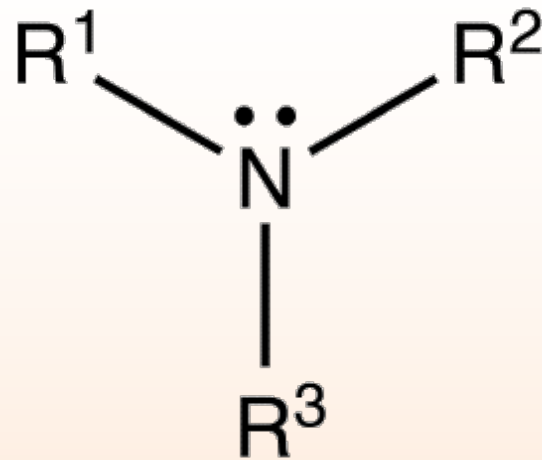


Eye	Parasympathetic Nervous System
Iris radial muscle circular muscle	No effect Contraction (miosis) M3
Ciliary muscle	Contraction M3
Accommodation	for near vision
Intraocular pressure(IOP)	Decrease

Direct Cholinomimetics

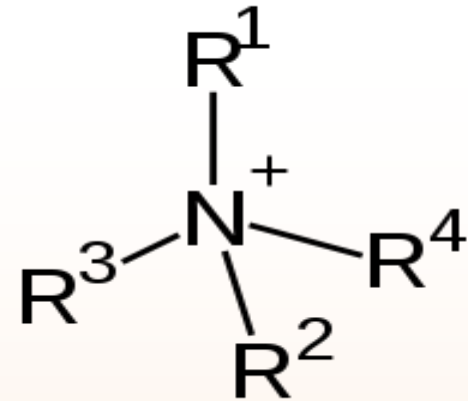
– Naturally occurring alkaloids e.g.

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



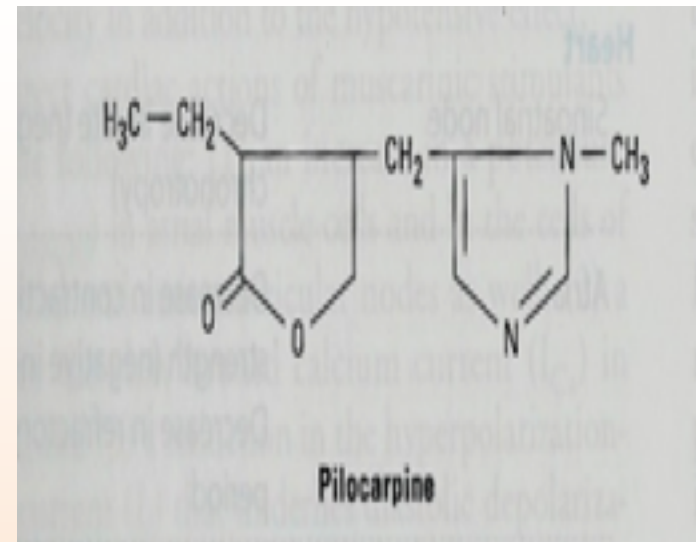
Direct Cholinomimetics

- 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:

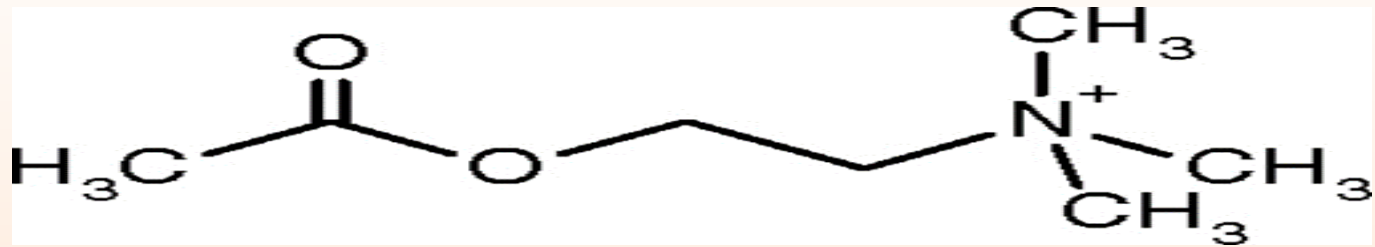
- Profuse sweating
- Salivation
- Bronchoconstriction
- Diarrhea
- CNS effects

Acetylcholine (Ach)

Muscarinic and nicotinic agonist

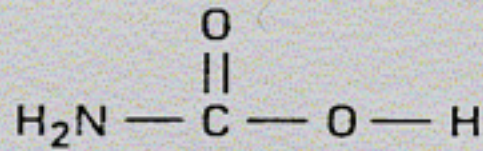
Not used clinically because Ach

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

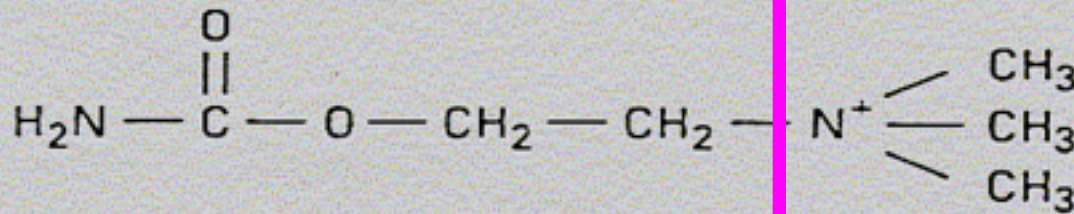


Synthetic choline esters

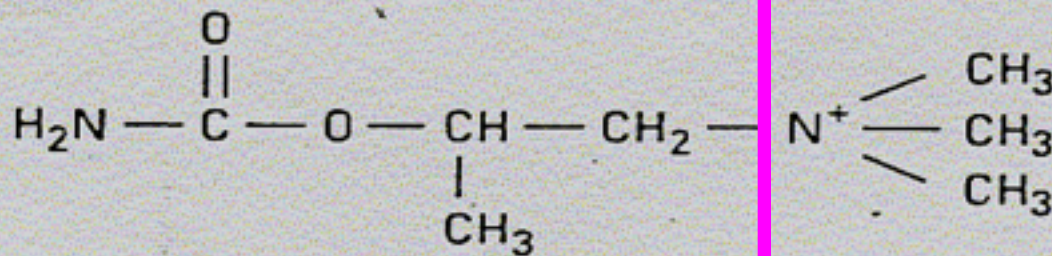
- ❑ include drugs as **bethanechol, carbachol**
- ❑ Quaternary ammonium compounds
contain N^+ (**polar**)
- ❑ Poor distribution
- ❑ can not cross BBB (**No CNS effects**)
- ❑ Not metabolized by cholinesterase.
- ❑ Have longer duration of action than Ach.
- ❑ Never given I.V. or I.M **BUT** S.C.



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 (autoimmune disease characterized by Formation of antibodies 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 Xerostomi a	Sjogren's syndrome

Contraindications of direct cholinomimetics

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

Thank you

A large yellow oval is centered in the image. Three black silhouettes of birds in flight are positioned around the oval: one at the top right, one on the left side, and one at the bottom right. The text "Thank you" is written in a pink, serif font across the middle of the oval.