



DIRECT CHOLINERGIC DRUGS

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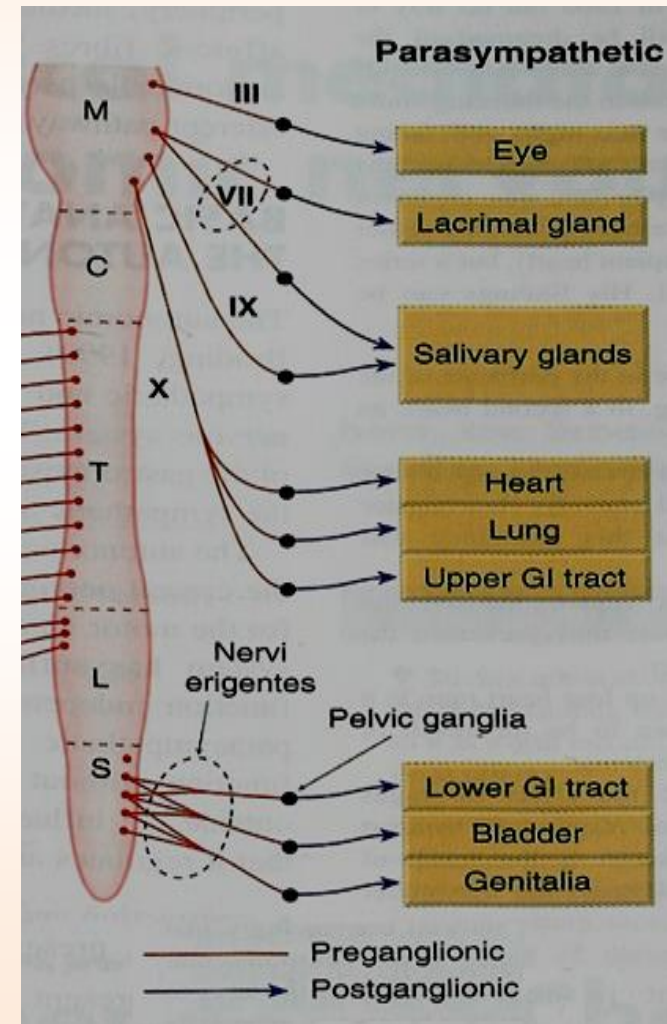
By the end of this lecture the student should know

- *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

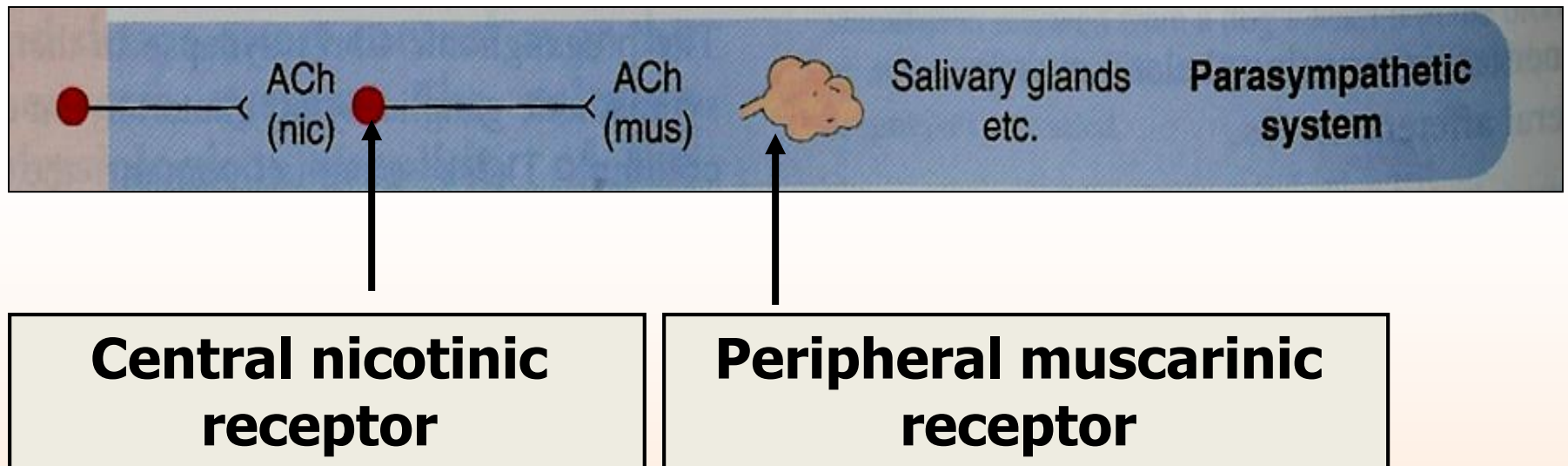
Cholinergic drugs

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



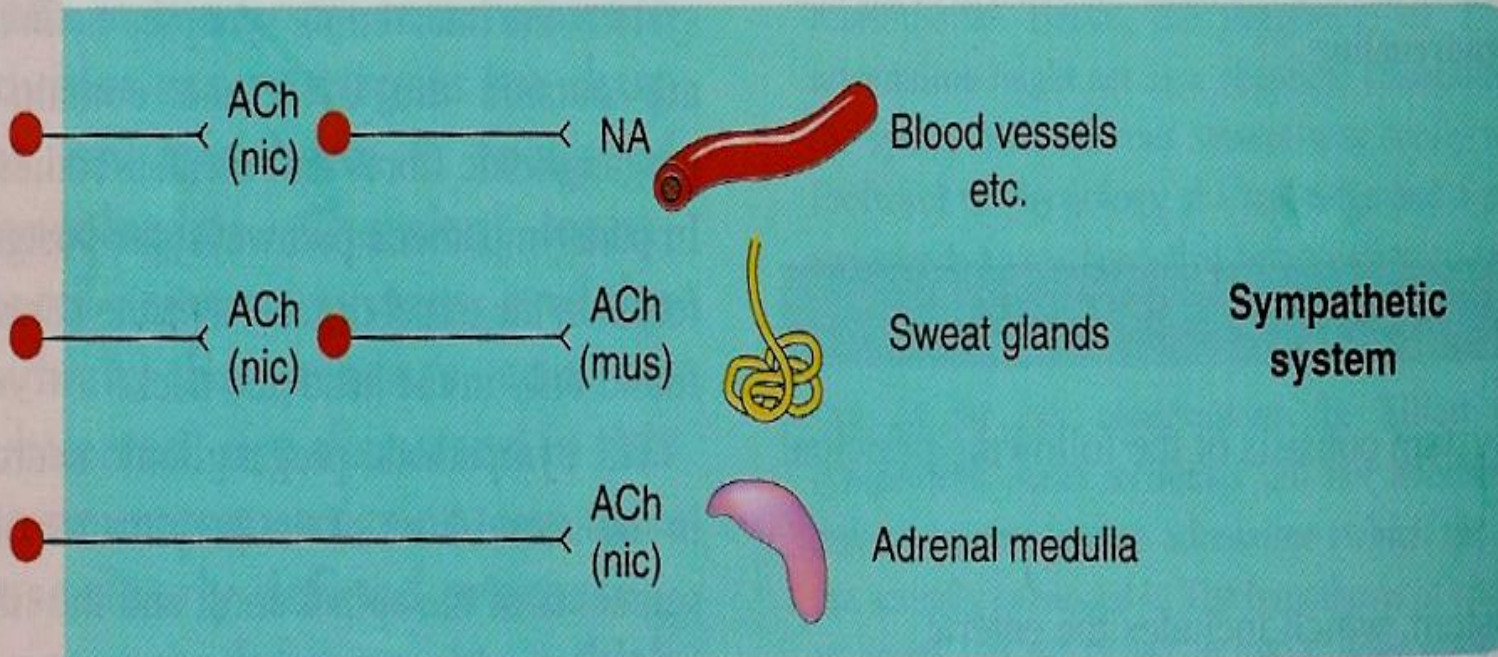
Nicotinic receptors

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



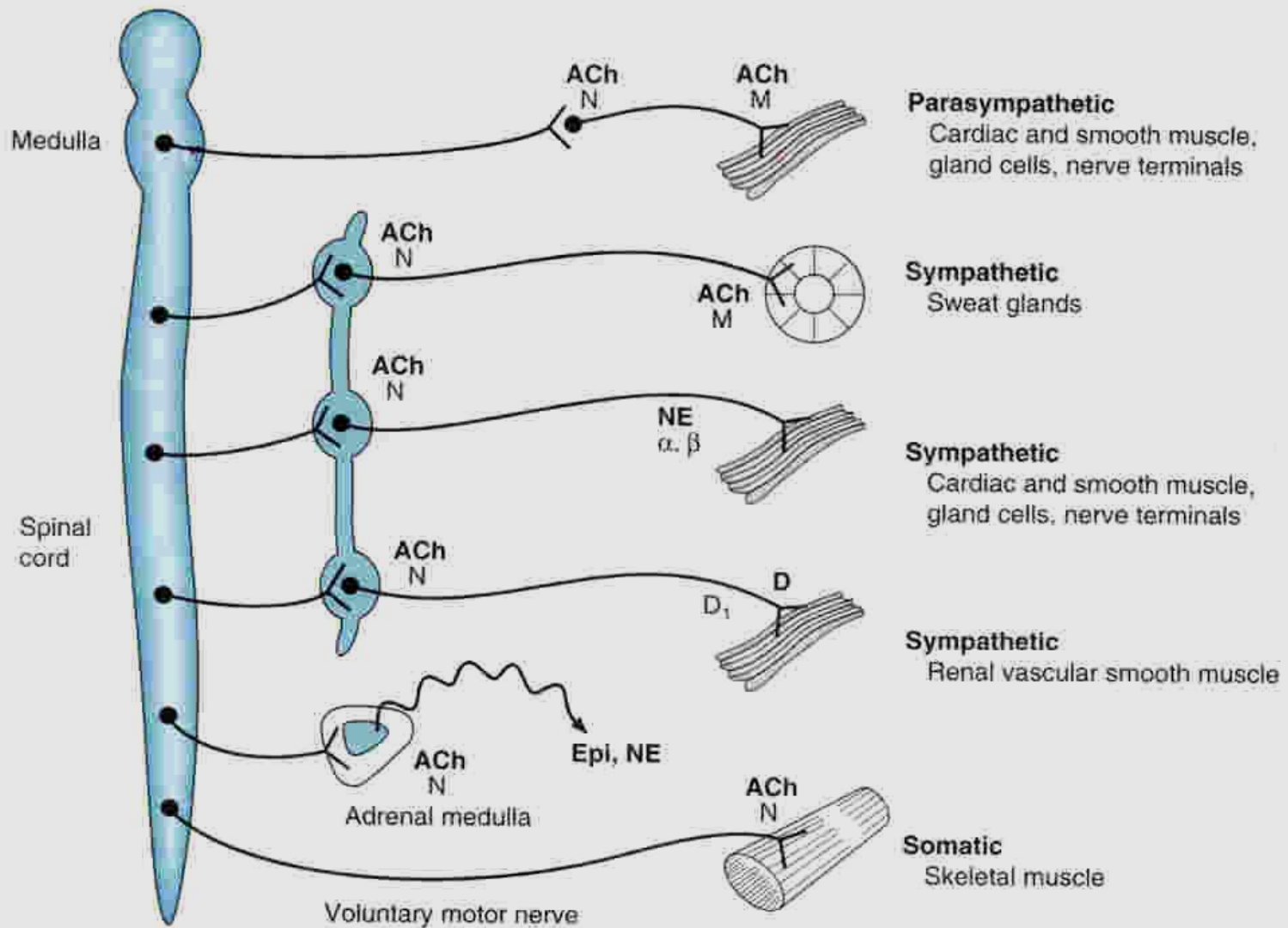


Figure 6–1. Schematic diagram comparing some anatomic and neurotransmitter features of autonomic and somatic motor nerves. Only the primary transmitter substances are shown. Parasympathetic ganglia are not shown because most are in or near the wall of the organ innervated. Note that some sympathetic postganglionic fibers release acetylcholine or dopamine rather than norepinephrine. The adrenal medulla, a modified sympathetic ganglion, receives sympathetic preganglionic fibers and releases epinephrine and norepinephrine into the blood. (ACh, acetylcholine; D, dopamine; Epi, epinephrine; NE, norepinephrine; N, nicotinic receptors; M, muscarinic receptors.)

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 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	Exocrine glands Smooth muscles (GIT, urinary tract, bronchial muscles) Vascular endothelium	<ul style="list-style-type: none">• Secretion of glands• Smooth muscle contraction• Vasodilatation (via nitric oxide)
M4 & M5	CNS	memory, arousal, attention and analgesia

Cholinergic or parasympathetic receptors

<p>Nicotinic receptors Central cholinceptors</p>	<p>Muscarinic receptors Peripheral cholinceptors</p>
<p>Almost excitatory</p>	<p>Excitatory or inhibitory</p>
<p>Autonomic ganglia Nn sympathetic & parasympathetic stimulation</p>	<p>On all peripheral organs innervated by postganglionic parasympathetic fibers</p>
<p>Adrenal medulla Nn release of catecholamines (adrenaline & noradrenaline)</p>	<p>Heart (bradycardia, M2) exocrine glands (secretion, M3)</p>
<p>Skeletal muscles Nm contraction</p>	<p>Smooth muscles (contraction, M3) (GIT, urinary tract, bronchial muscles, uterus)</p>

Pharmacological actions of cholinergic drugs

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

nicotinic actions and muscarinic actions

Nicotinic actions

➤ Skeletal muscles:

➤ **Low concentration → muscle contraction**

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

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

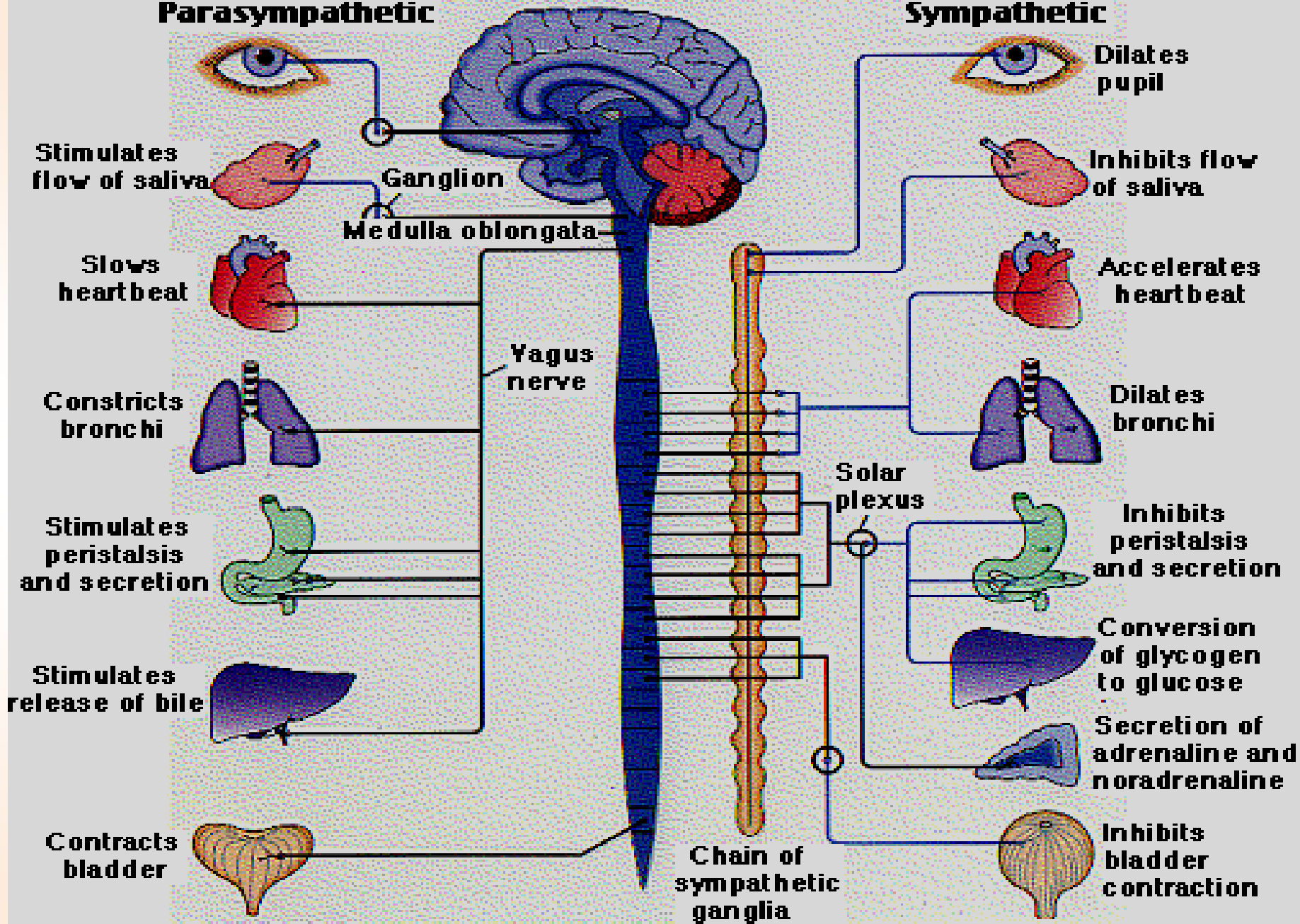
➤ **Stimulation of adrenal medulla: release of catecholamines (Adrenaline & Noradrenaline).**

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

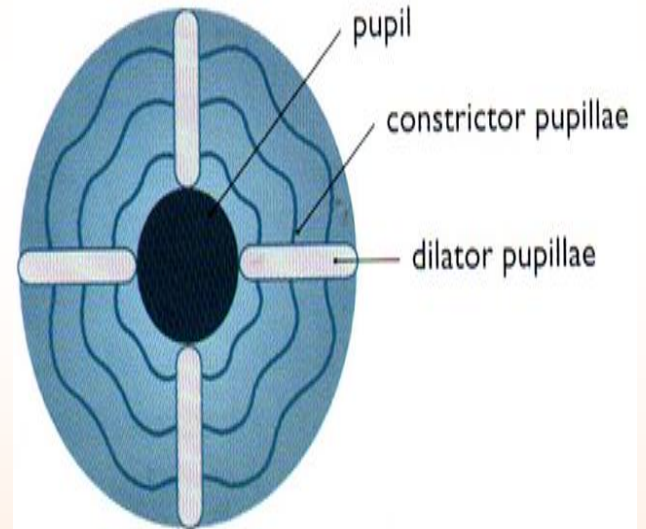
Parasympathetic

Sympathetic

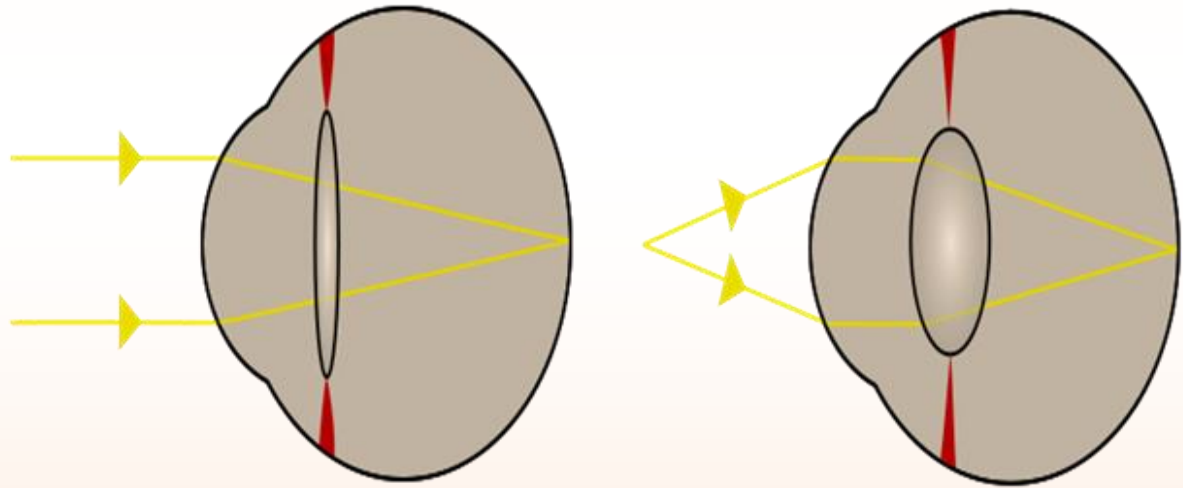


EYE

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.



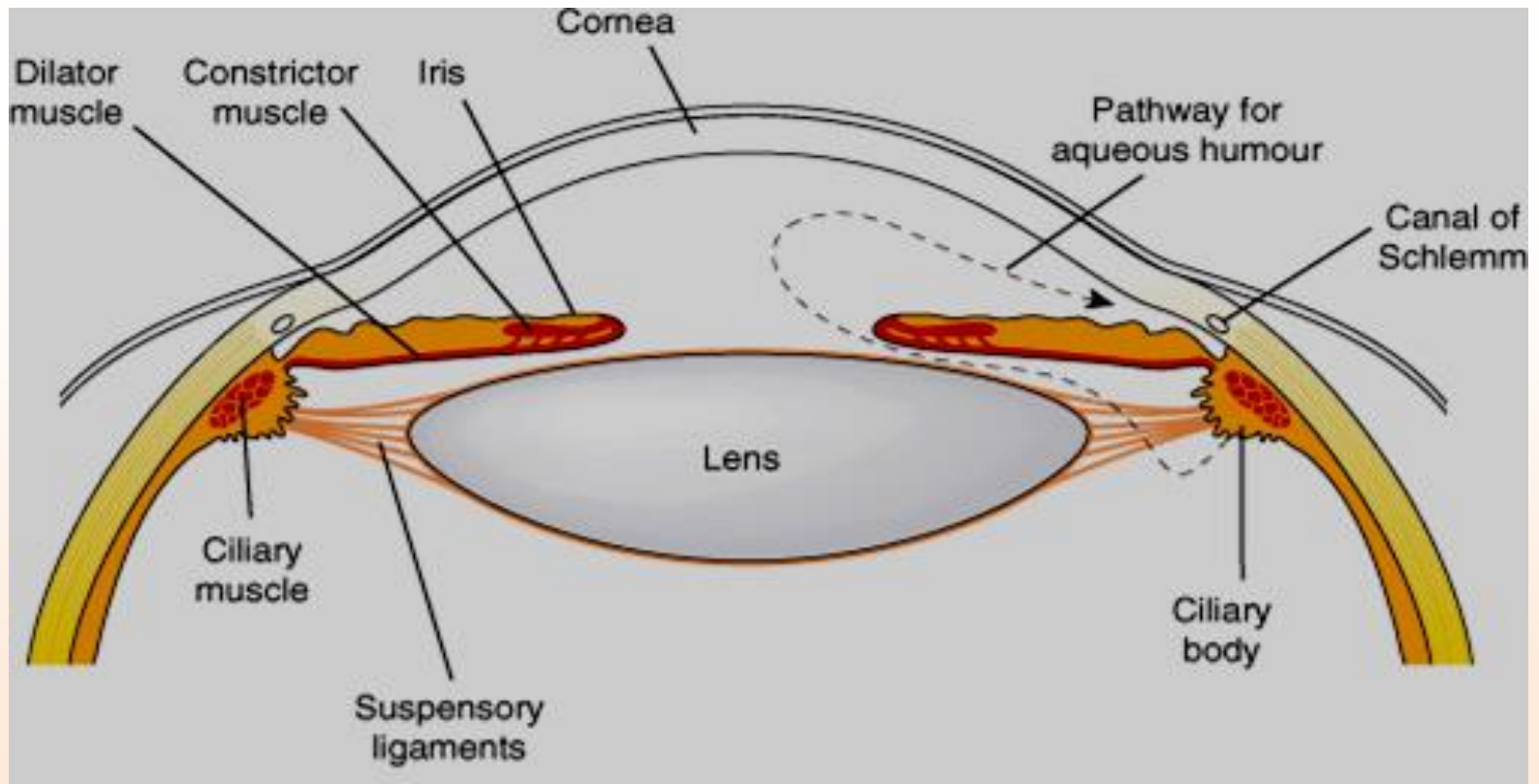
When the ciliary muscle contracts, the lens **bulge** more → this parasympathetic reflex is essential to **accommodate for near vision**



Aqueous humour 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**.

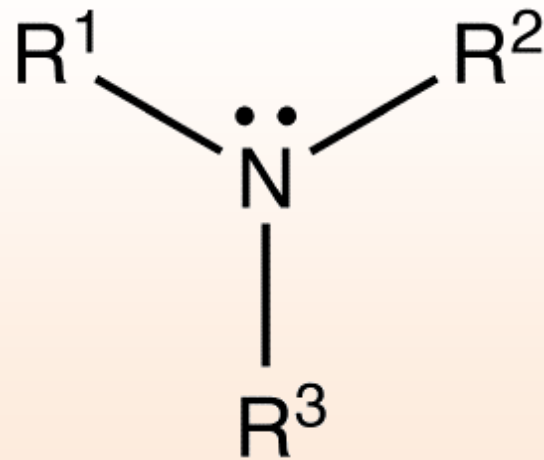
Miosis → ↓ intraocular pressure in patient with glaucoma



Direct Cholinomimetics

– Naturally occurring alkaloids e.g.

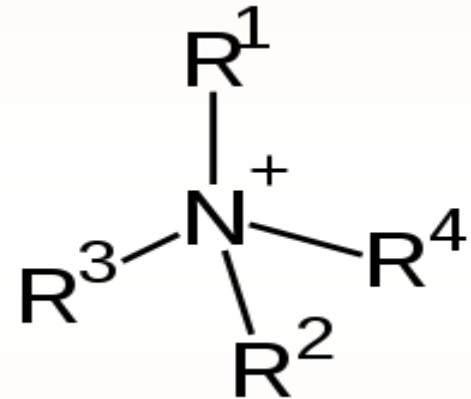
e.g. pilocarpine, nicotine (tertiary amines).



Direct Cholinomimetics

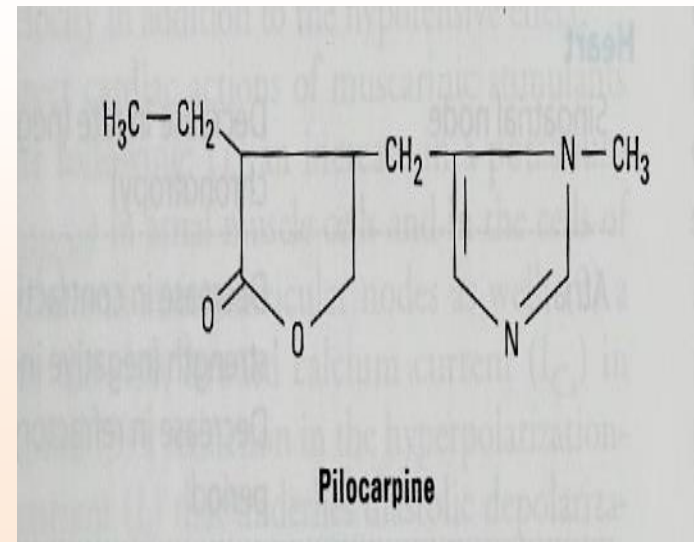
– Synthetic choline esters (**Quaternary ammonium compounds**)

- 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:

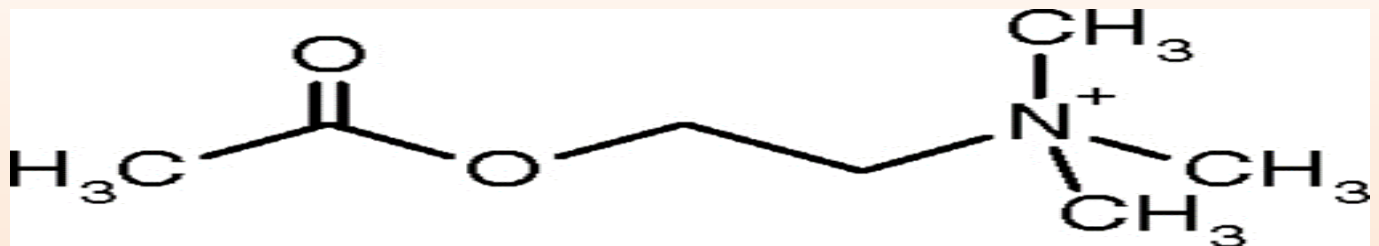
- **Profuse sweating**
- **Salivation**
- **Bronchoconstriction**
- **Diarrhea**
- **CNS effects**

Acetylcholine (Ach)

Muscarinic and nicotinic agonist

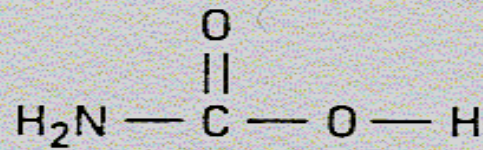
Not used clinically because Ach

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

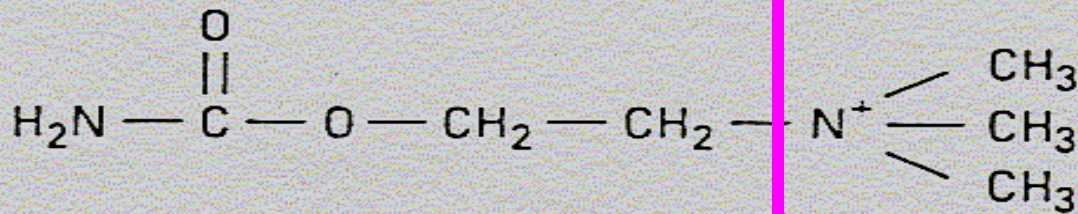


Synthetic choline esters

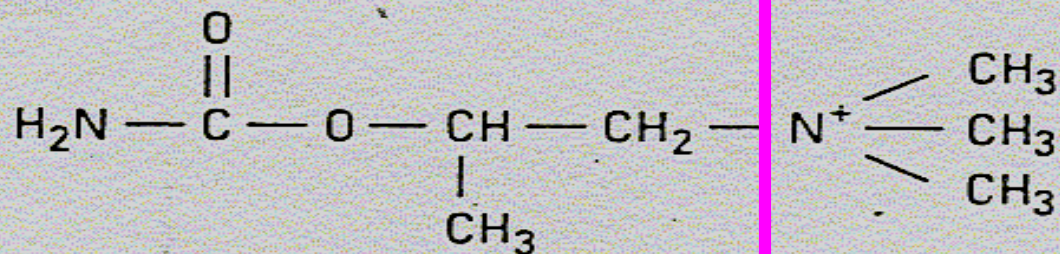
- ❑ include drugs as **bethanechol, carbachol**
- ❑ Quaternary ammonium compounds
contain N^+ (**polar**)
- ❑ Poor distribution
- ❑ can not cross BBB (**No CNS effects**)
- ❑ Not metabolized by cholinesterase.
- ❑ Have longer duration of action than Ach.
- ❑ Never given I.V. or I.M **BUT** S.C.



Carbamic acid



**Carbachol
(carbamoylcholine)**



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

Carbachol

- **Has muscarinic actions similar to ACh**
- **Has nicotinic actions similar to ACh (side effects)**
- **Longer duration of action**
- **Used for treatment of glaucoma**

Bethanechol

- **Has muscarinic actions similar to ACh**
- **Has no nicotinic actions**
- **Longer duration of action**
- **Used for treatment of paralytic ileus & urinary retention.**

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