DIRECT CHOLINERGIC DRUGS

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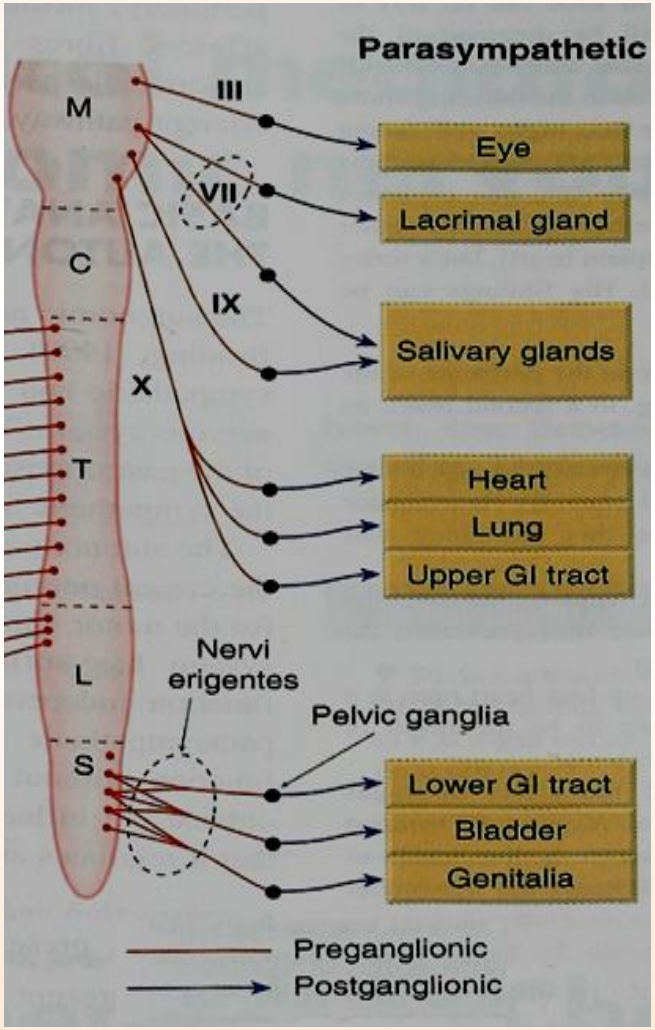
By the end of this lecture the student should know

- ***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.



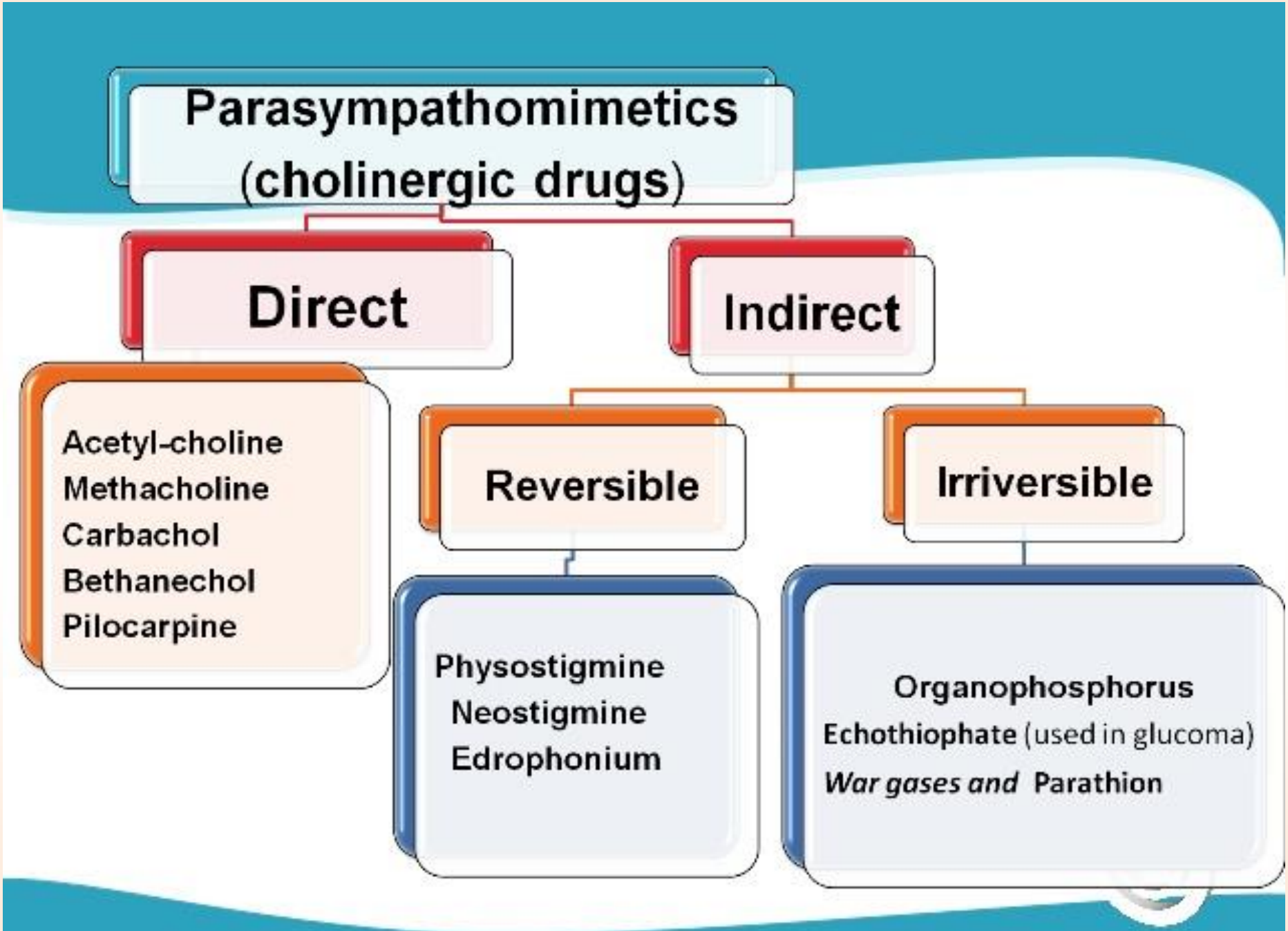
Types of cholinomimetics

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
Indirect
Acetyl-choline
Methacholine
Carbachol
Bethanechol
Pilocarpine
Reversible
Irriversible
Physostigmine
Neostigmine
Edrophonium
Organophosphorus
Echothiophate (used in glucoma)
War gases and Parathion

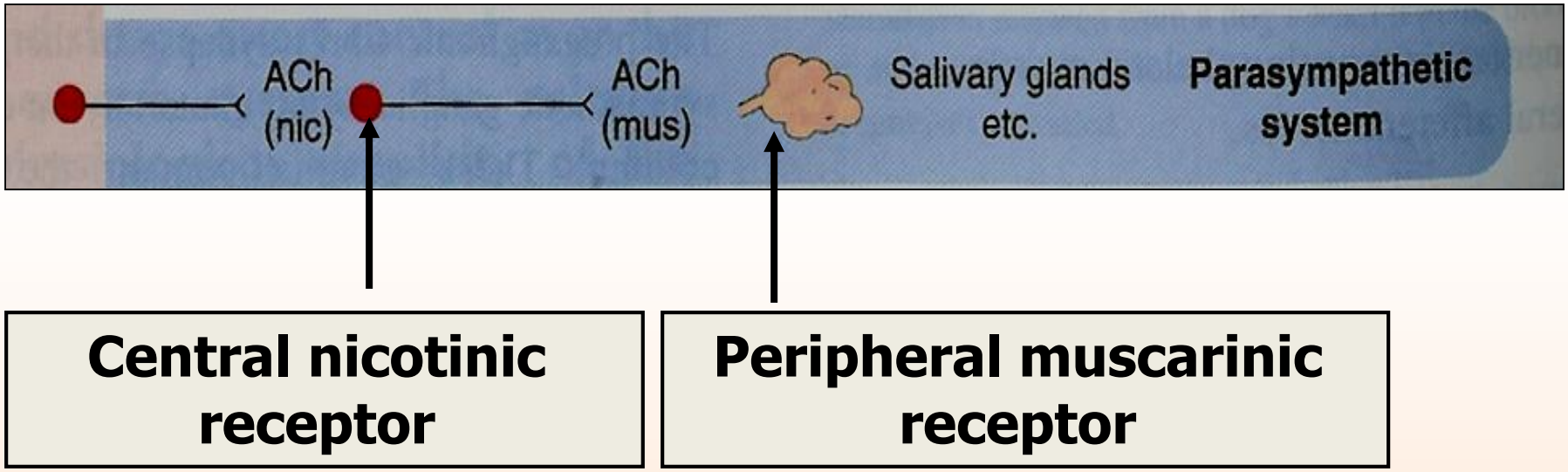
Direct Cholinergic drugs

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

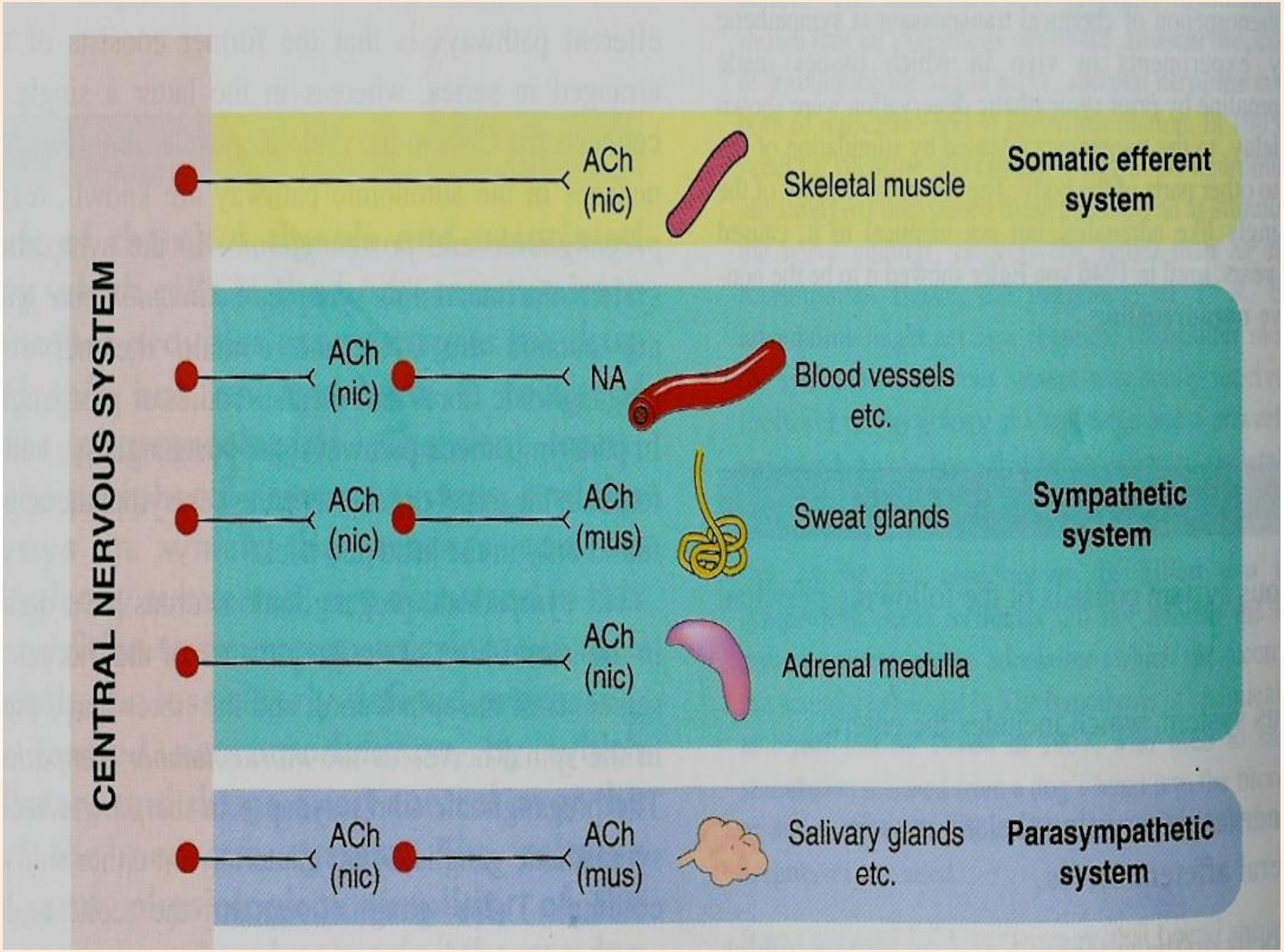


Nicotinic receptors

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
ACh (nic)
Skeletal muscle
Somatic efferent system
ACh (nic)
NA
Blood vessels etc.
ACh (nic)
ACh (mus)
Sweat glands
Sympathetic system
ACh (nic)
Adrenal medulla
ACh (nic)
ACh (mus)
Salivary glands etc.
Parasympathetic system

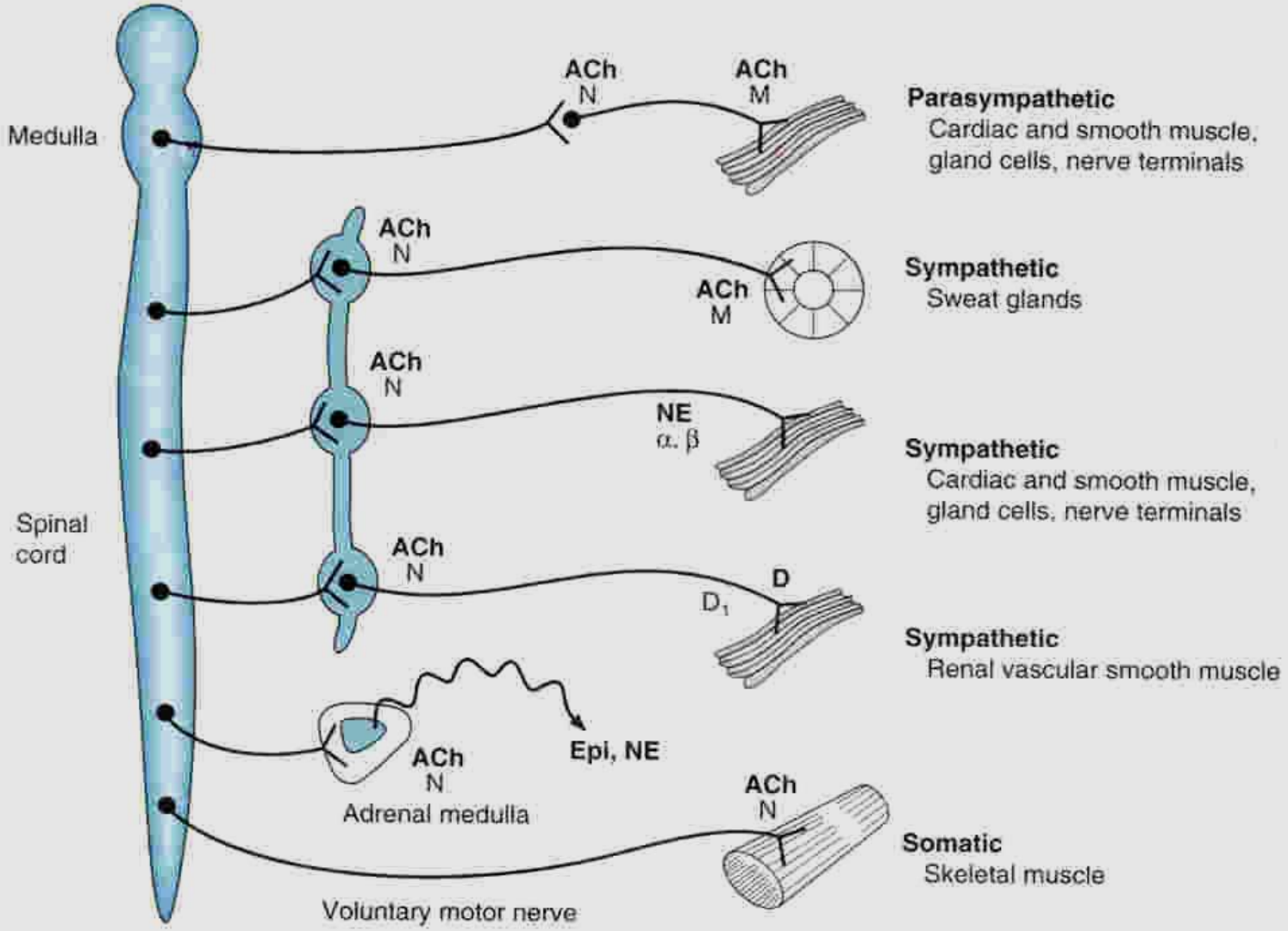


Figure 6–1. Schematic diagram comparing some anatomic and neurotransmitter features of autonomic and somatic motor nerves. Only the primary transmitter substances are shown. Parasympathetic ganglia are not shown because most are in or near the wall of the organ innervated. Note that some sympathetic 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	• Secretion of glands • Smooth muscle contraction • Vasodilatation (via nitric oxide)
M4 & M5	CNS	memory, arousal, attention and analgesia

Cholinergic or parasympathetic receptors

Nicotinic receptors Central cholinoceptors	Muscarinic receptors Peripheral cholinoceptors
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.

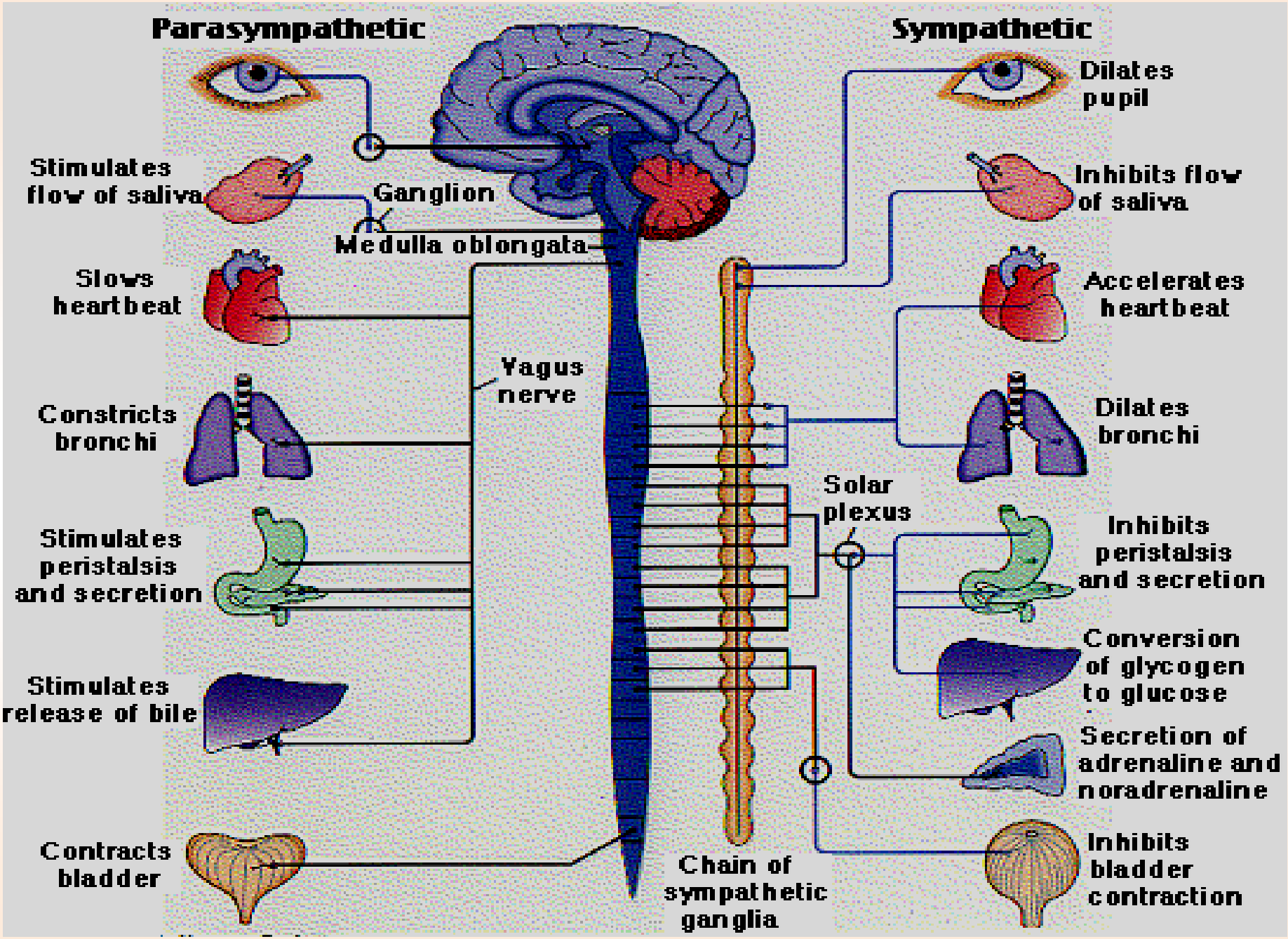
nicotinic actions and muscarinic actions

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).**

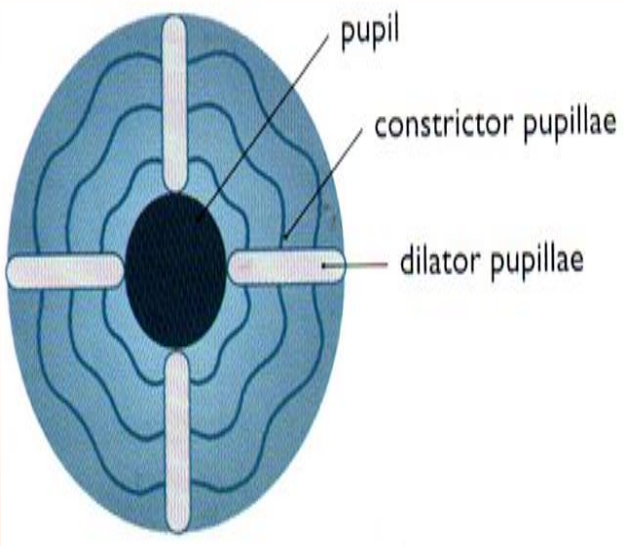
Muscarinic actions

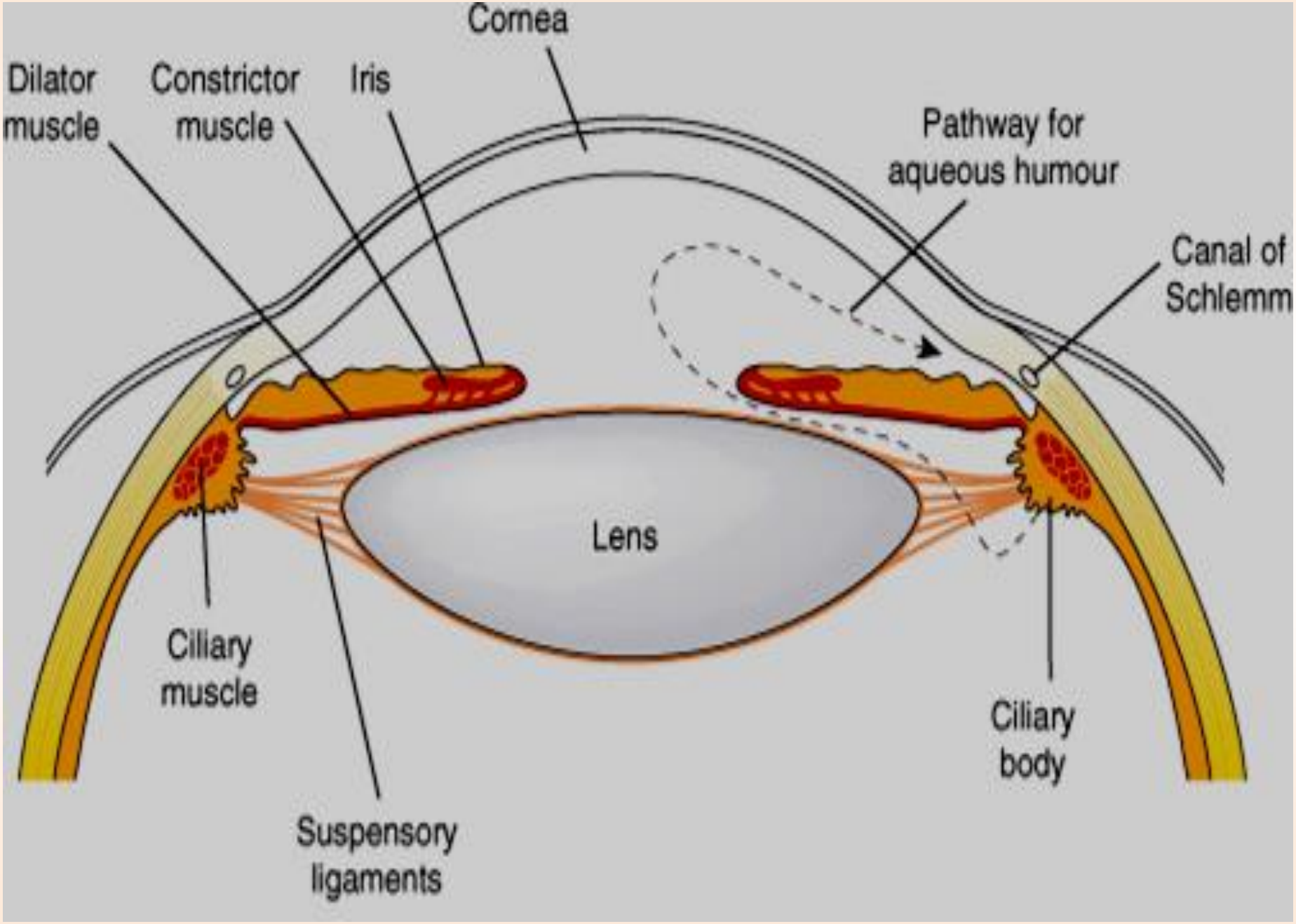
Organs	Cholinergic actions
Eye	Contraction of circular muscle of iris (miosis)(M3) Contraction of ciliary muscles for near vision (M3) Decrease in intraocular pressure (IOP)
Heart endothelium	bradycardia (decrease in heart rate) (M2) Release of NO (EDRF)
Lung	Constriction of bronchial smooth muscles 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
Dilates pupil
Stimulates flow of saliva
Ganglion
Medulla oblongata
Inhibits flow of saliva
Slows heartbeat
Accelerates heartbeat
Vagus nerve
Constricts bronchi
Dilates bronchi
Solar plexus
Stimulates peristalsis and secretion
Inhibits peristalsis and secretion
Conversion of glycogen to glucose
Stimulates release of bile
Secretion of adrenaline and noradrenaline
Contracts bladder
Chain of sympathetic ganglia
Inhibits bladder contraction

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.



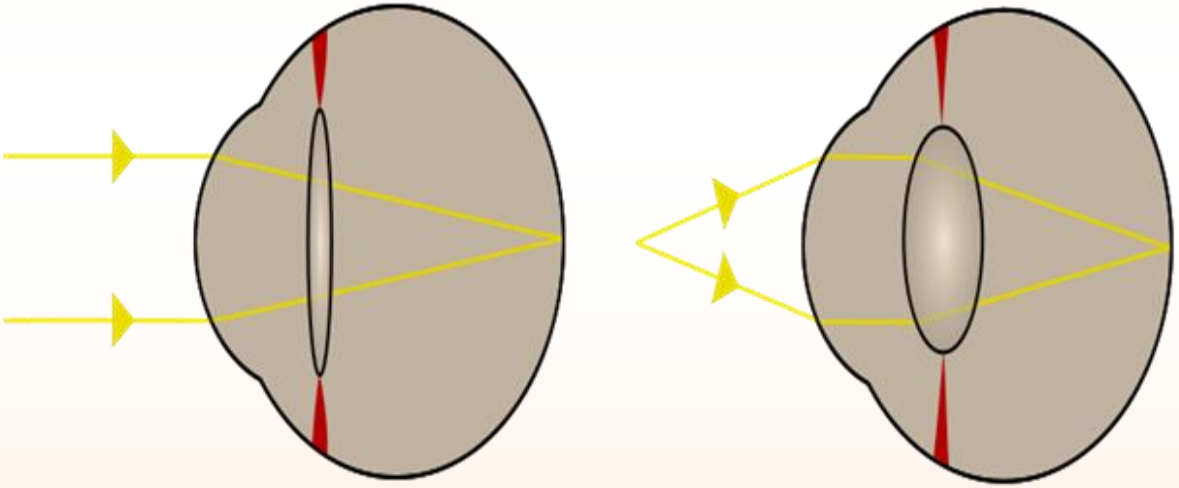

Cornea
Dilator muscle
Constrictor muscle
Iris
Pathway for aqueous humour
Canal of Schlemm
Lens
Ciliary muscle
Ciliary body
Suspensory ligaments

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

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

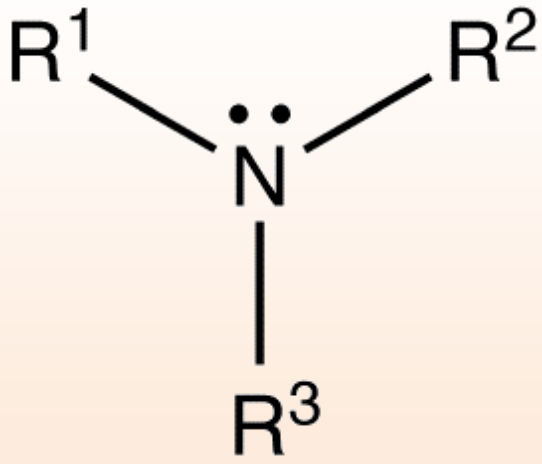


Eye	Parasympathetic Nervous System
Iris **radial muscle** **circular muscle**	No effect Contraction (miosis) M3
Ciliary muscle	Contraction M3
Accommodation	for near vision
Intraocular pressure(IOP)	Decrease

Direct Cholinomimetics

– **Naturally occurring alkaloids e.g.**

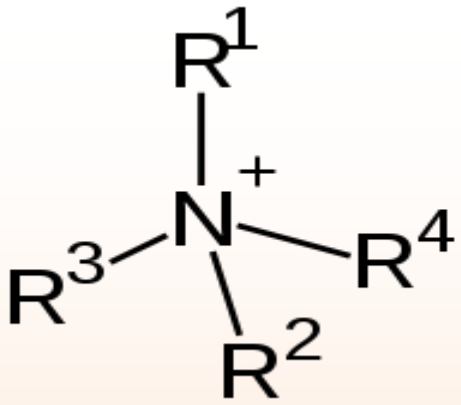
e.g. pilocarpine, nicotine (tertiary amines).



Direct Cholinomimetics

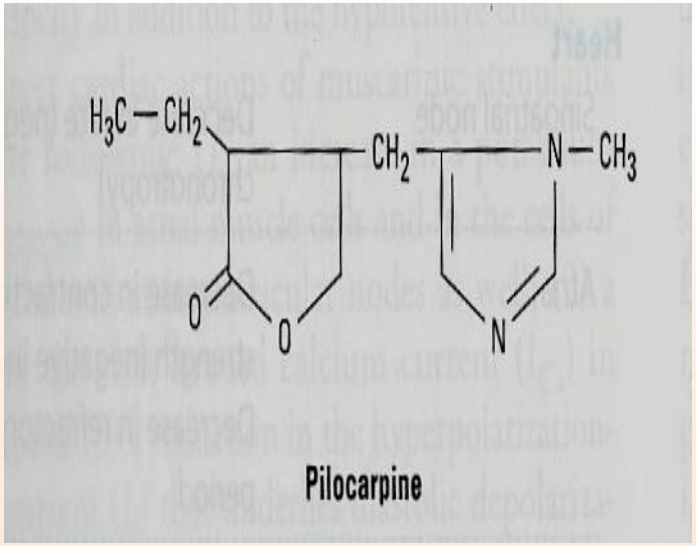
- **Natural alkaloids**

- **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

Pilocarpine (continue…)

Uses:

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

Adverse effects:

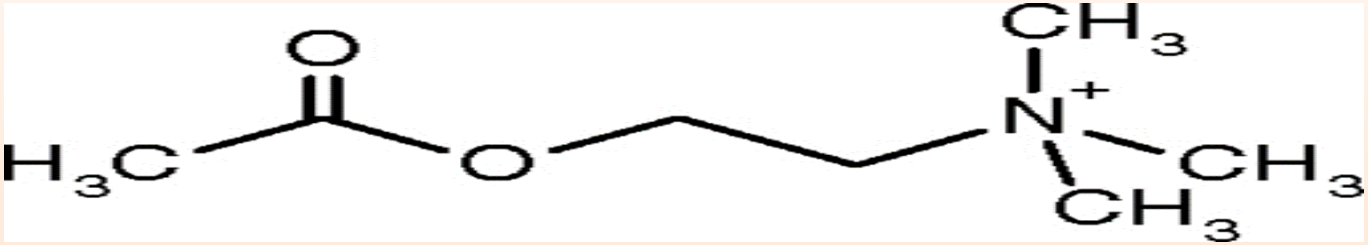
- **Profuse sweating**
- **Salivation**
- **Bronchoconstriction**
- **Diarrhea**
- **CNS effects**

Acetylcholine (Ach)

Muscarinic and nicotinic agonist

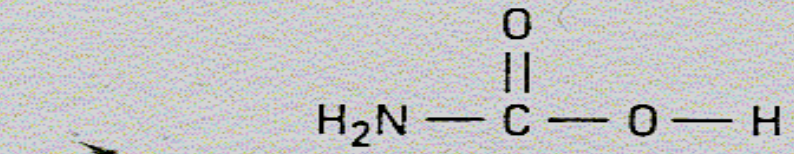
Not used clinically because Ach

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

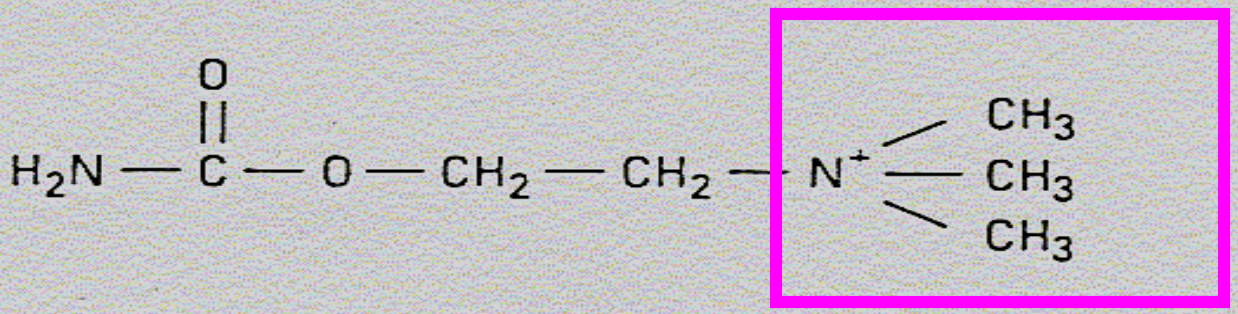


Synthetic choline esters

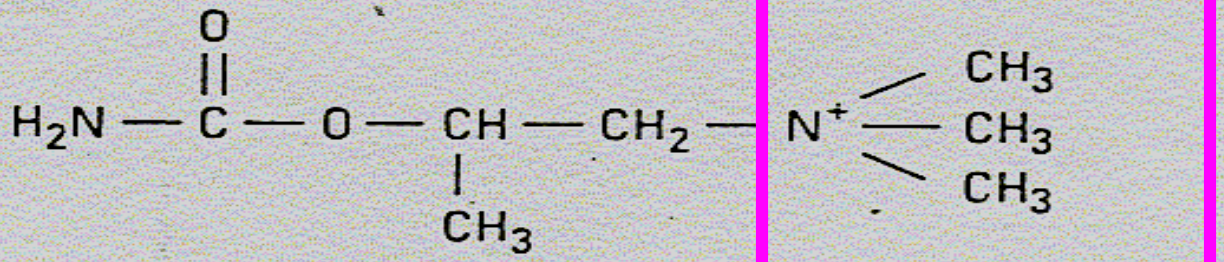
- include drugs as **bethanechol, carbachol**
- Quaternary ammonium compounds contain N^+ **(polar)**
- Poor distribution
- can not cross BBB **(No CNS effects)**
- Not metabolized by cholinesterase.
- Have longer duration of action than Ach.
- Never given I.V. or I.M **BUT** S.C.



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 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