DIRECT ACTING CHOLINRTGIC DRUGS

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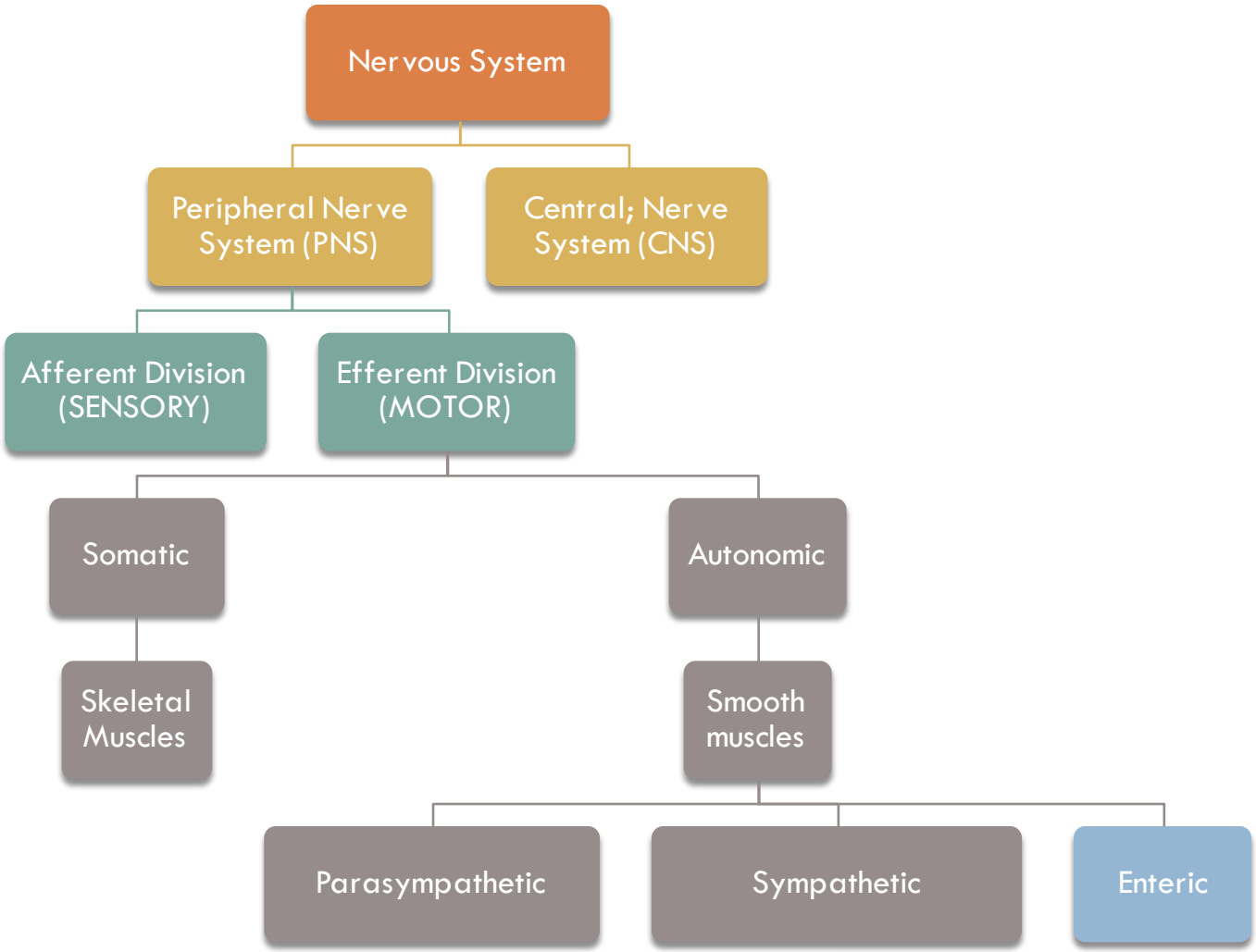
Objectives

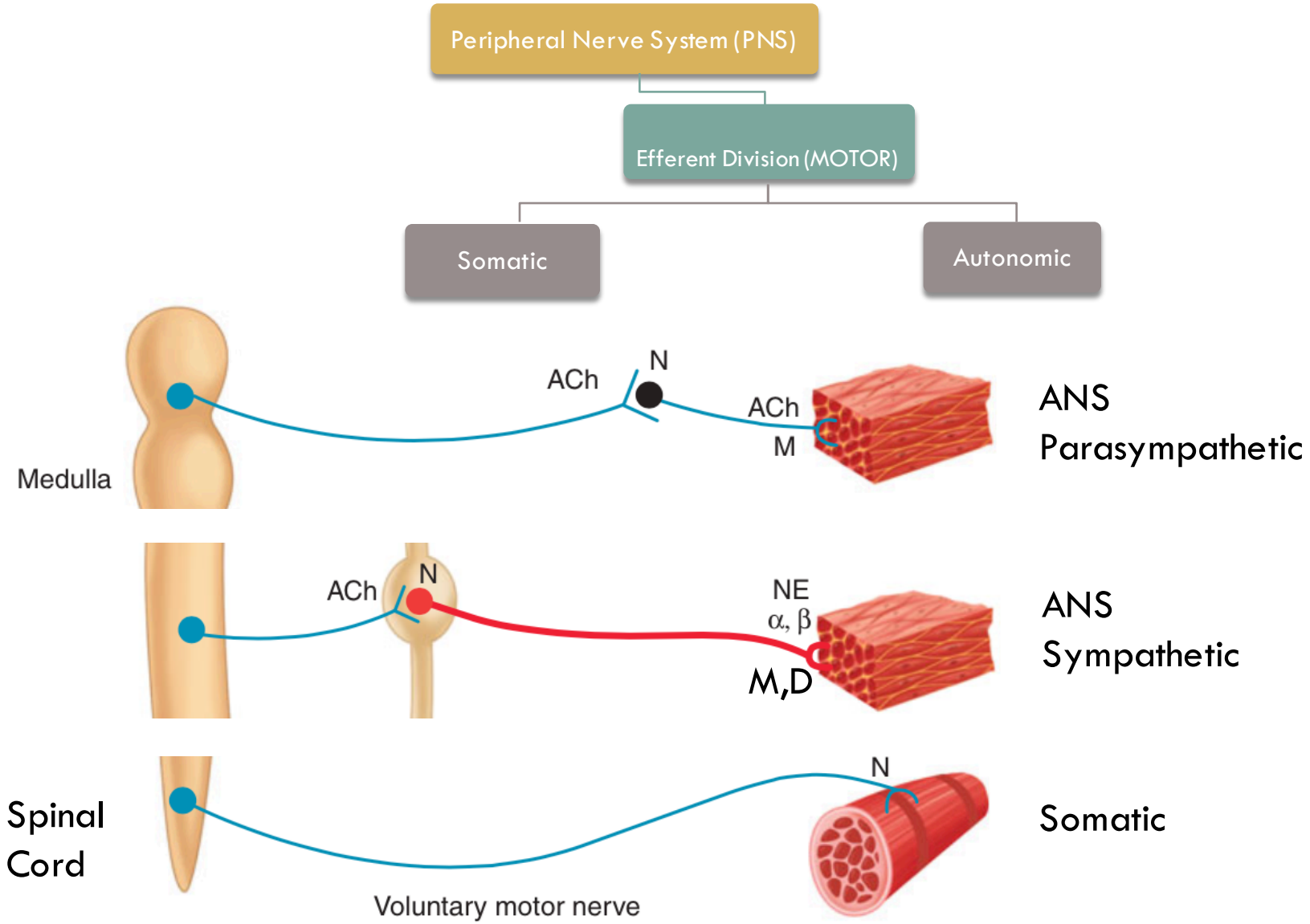
By the end of this lecture the student should able to :

- 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.

Organization of The Nervous System



ANS , Efferent division of the PNS



ANS , Parasympathetic

ANS
Parasympathetic

- Preganglionic neurons
  - Long
  - Synapses with postganglionic at or near organ
  - ACh is neurotransmitter
  - Nicotinic receptor on postganglionic
- Postganglionic
  - Short
  - Synapses on the organ
  - ACh is neurotransmitter
  - Muscarinic receptor on the organ
- Cholinergic fibers: act by releasing acetylcholine

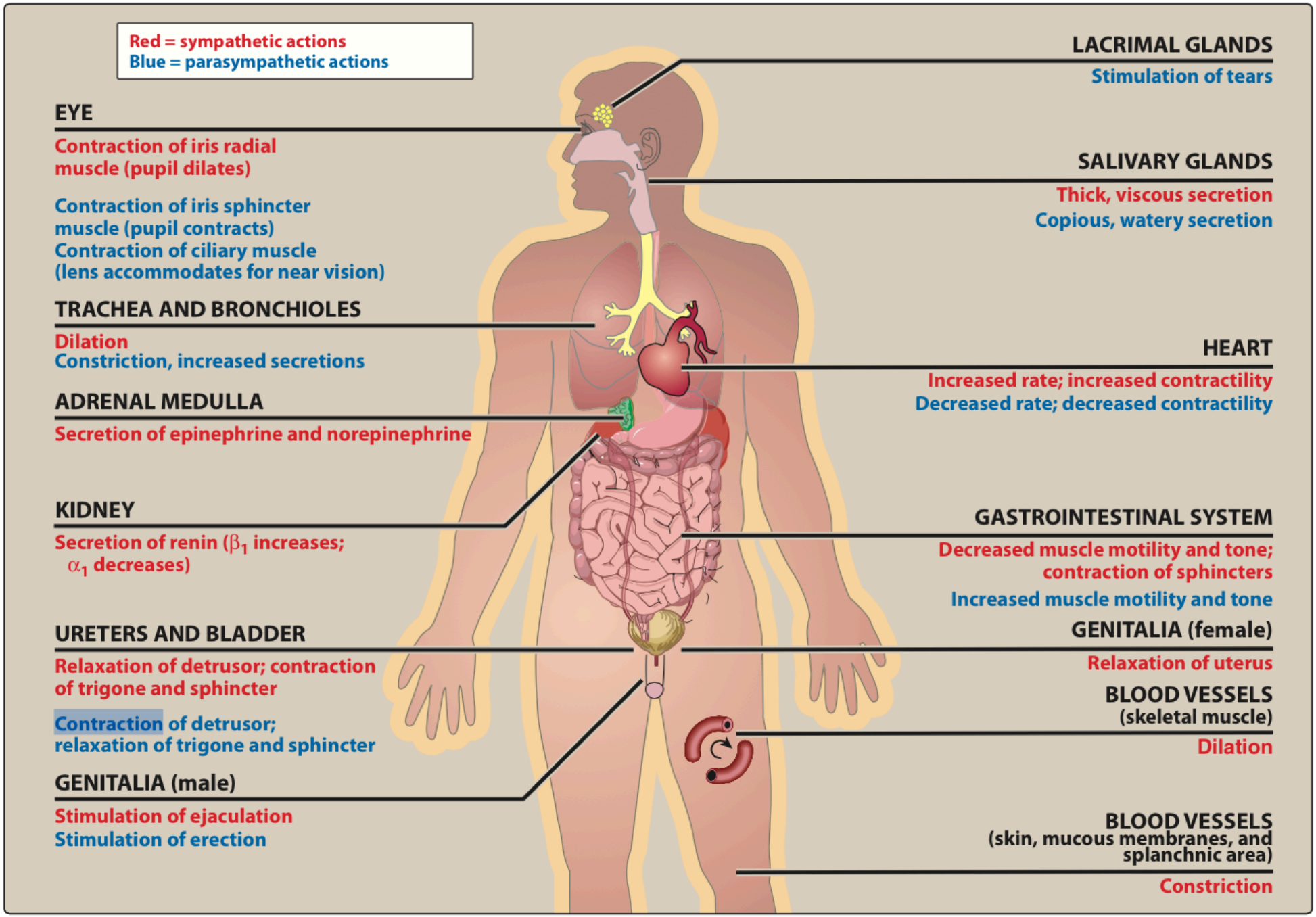
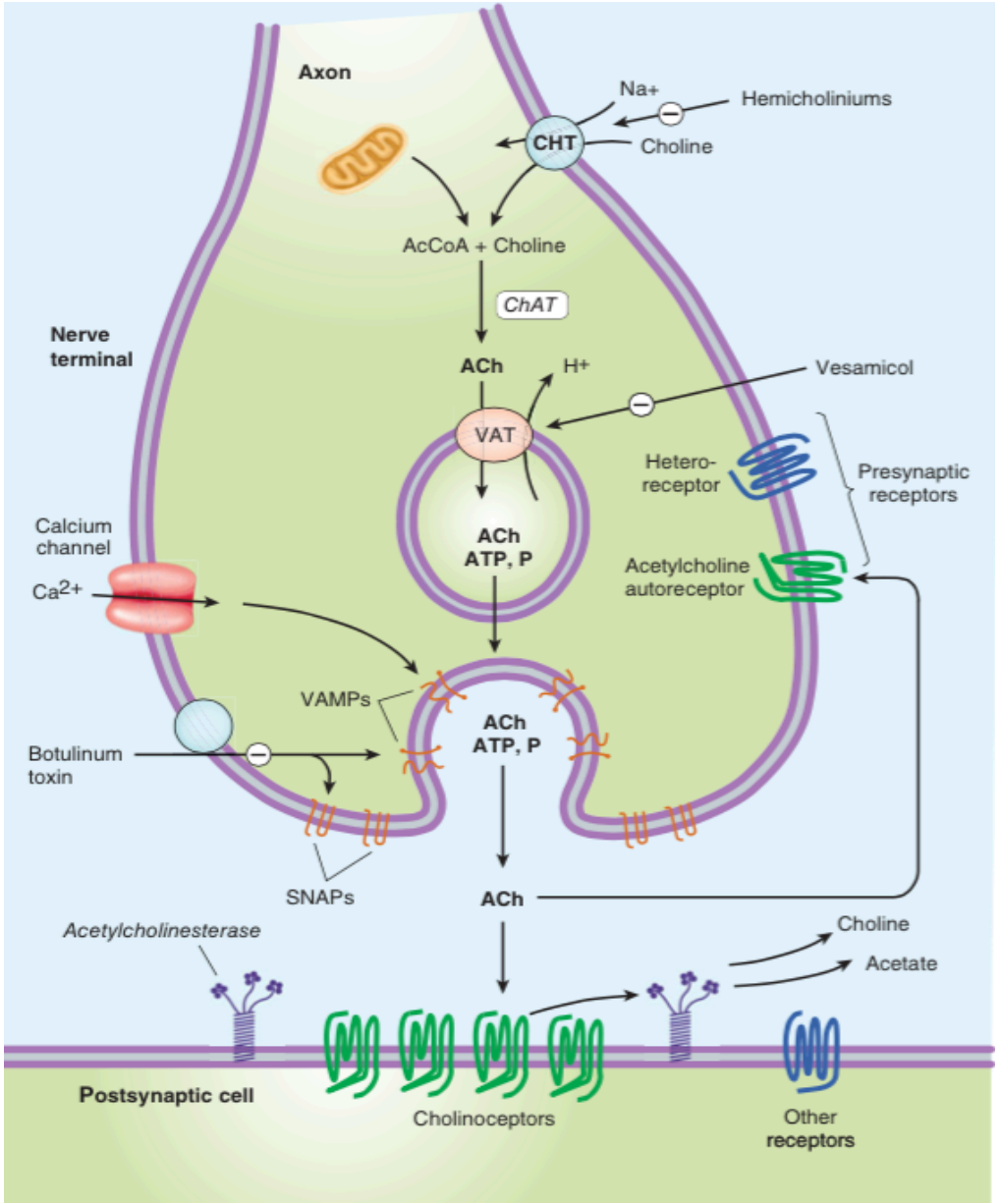
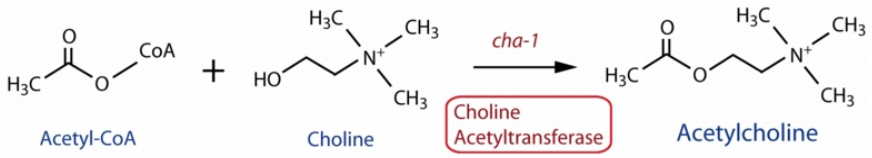


Figure 3.3
Actions of sympathetic and parasympathetic nervous systems on effector organs.

Cholinergic Transmission

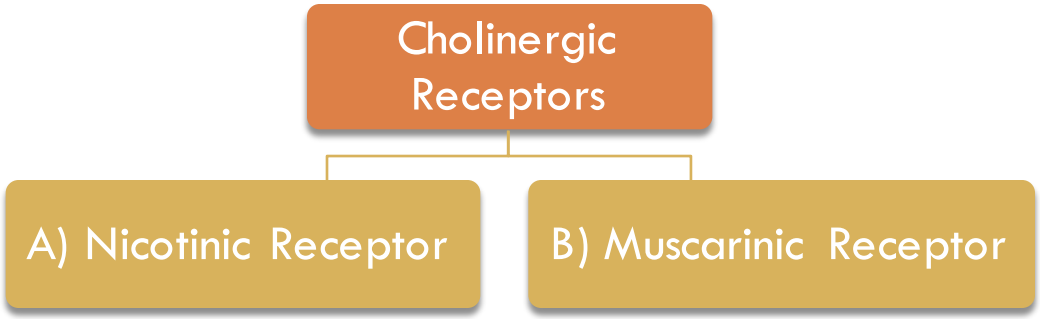


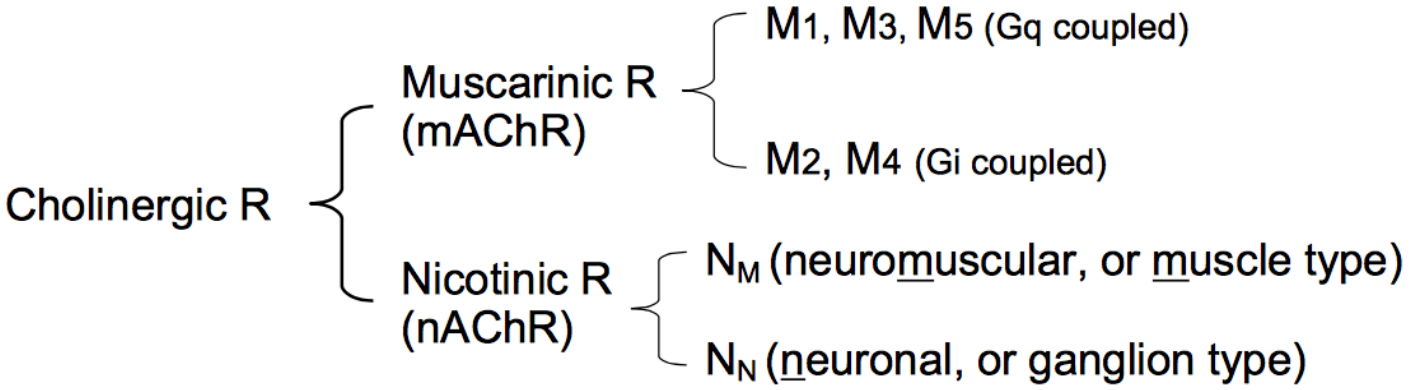
- Choline Transportation
- AcCoA Synthesis



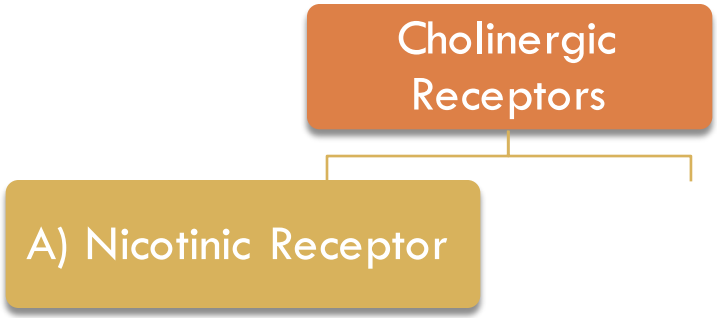
- Acetylcholine Transportation
- Acetylcholine Release
- Acetylcholine metabolism
- Half-life of is very short
- Q? why do we need to know
- Targets for pharmacologic therapy (interventions)
  - Synthesis, storage, release, and termination of action of the transmitter, and receptor effects
- Inhibitors

Autonomic Receptors



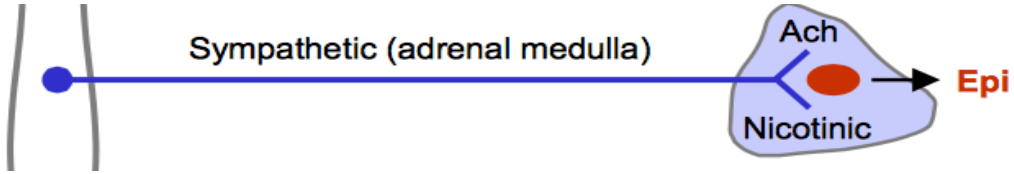


Autonomic Receptors (Cholinergic)



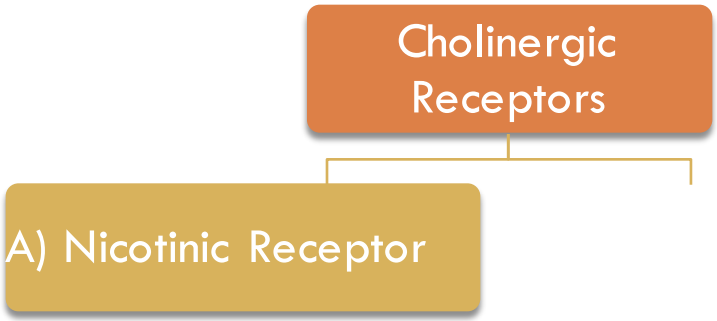
- Nicotinic Receptor (nAChRs)
  - Similar to those induce by nicotine
- Locations:
  - At neuromuscular junctions of skeletal muscle (N_M)

  - On Adrenal medulla (N_N)

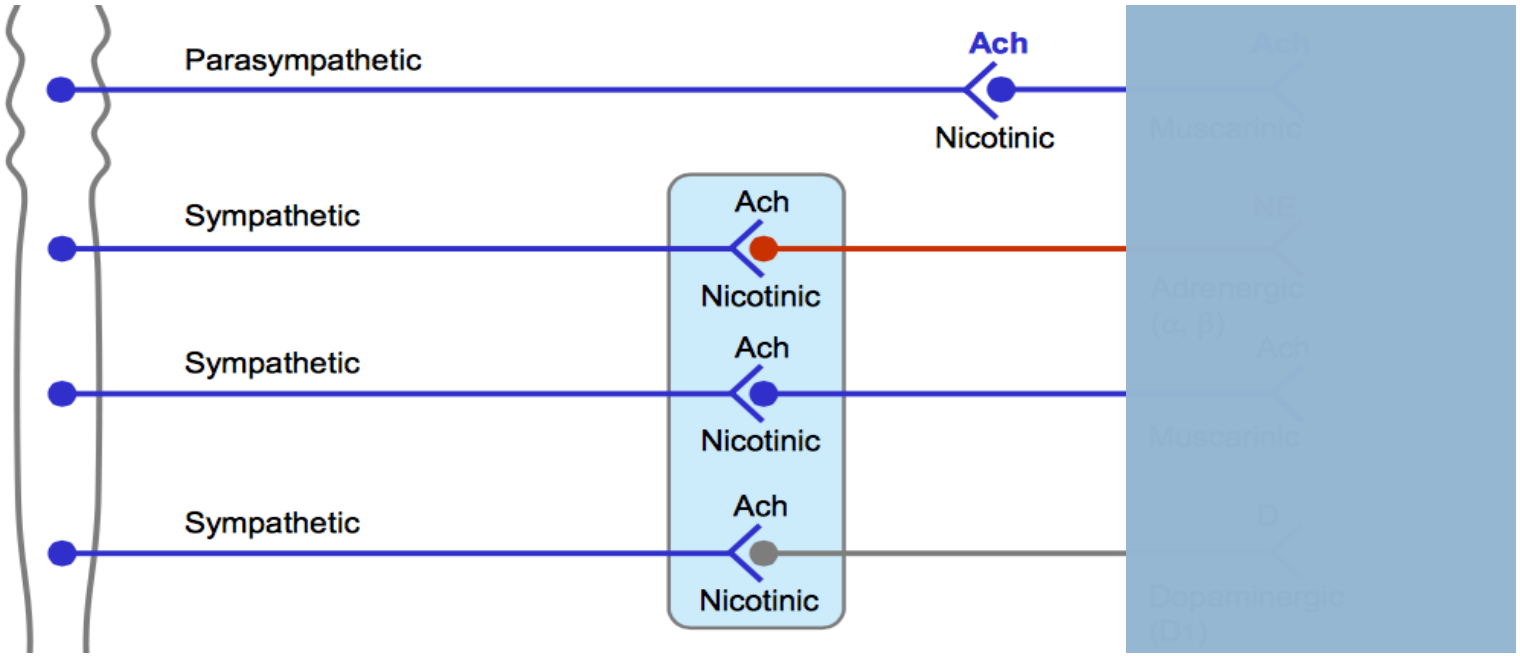


  - In CNS (N_N)

Autonomic Receptors (Cholinergic)



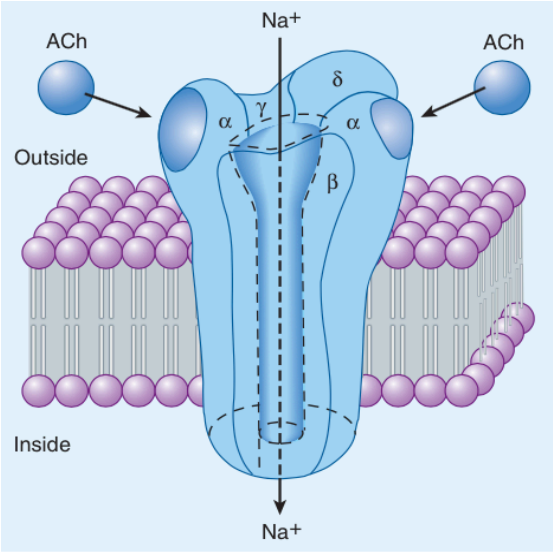
- Locations:
  - Ganglionic neurons in the autonomic ganglia (N_N)



Autonomic Receptors (Cholinergic)

A) Nicotinic Receptor

- Type:
  - Ligand-gated ion (Na+) channel
  - ACh binds to the α subunits
  - 2 acetylcholine molecules
  - Structurally and functionally similar to the Na^+ Channel

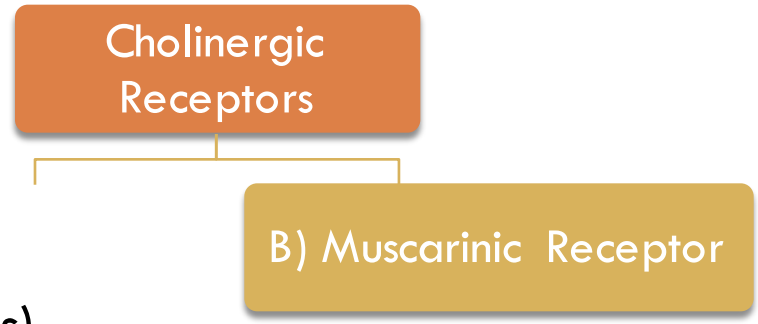


Autonomic Receptors (Cholinergic)

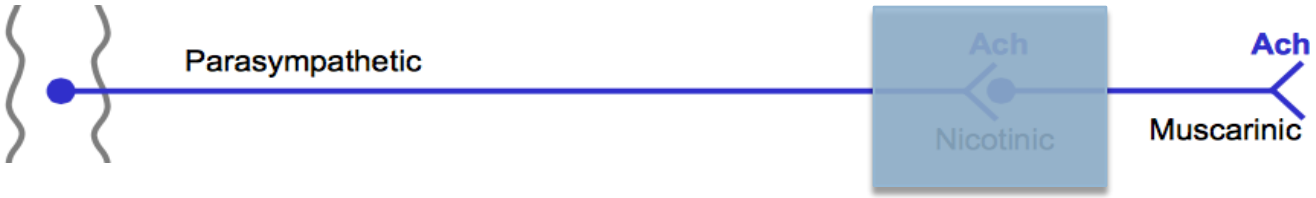
- Primary location of nicotinic receptors and their actions

Receptor	Locations	Pharmacological actions
N_N	Autonomic ganglia	sympathetic & parasympathetic stimulation
N_N	Adrenal medulla	release of catecholamines (adrenaline & noradrenaline)
N_M	Skeletal muscles	Low concentration → muscle contraction High concentration → persistent depolarization & relaxation (depolarization block).

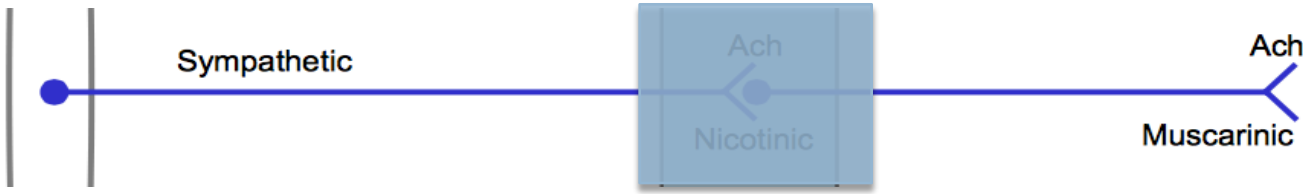
Autonomic Receptors (Cholinergic)



- Muscarinic Reciptors (mAChRs)
  - Similar to those induce by muscarine
- Locations:



all target organs e.g, heart, CVS, eye, bladder, GIT

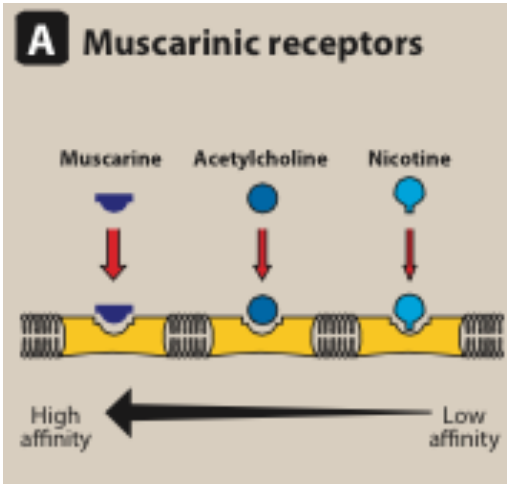


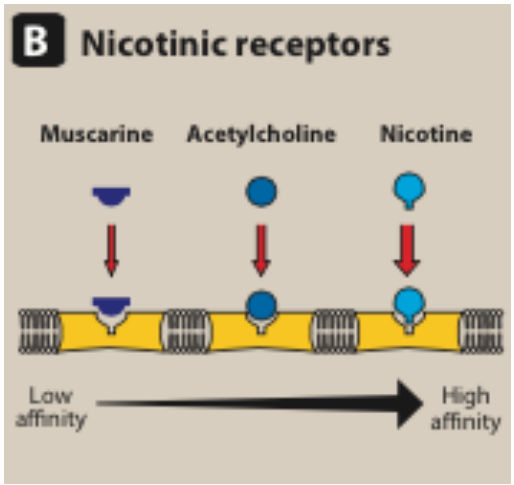
Sweat glands

Autonomic Receptors (Cholinergic)

B) Muscarinic Receptor

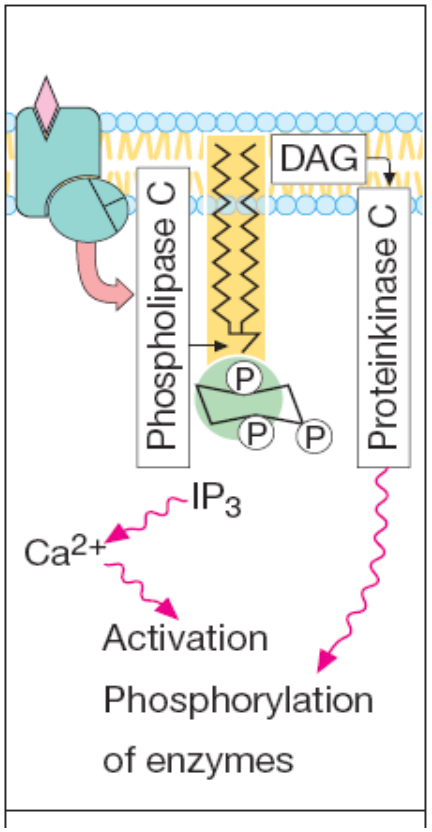
- Type
  - Muscarinic receptors are GPCRs
  - Five Subtypes: M_1, M_2, M_3, M_4, M_5
  - Odd-numbered members M_1, M_3 : Excitatory
  - Even-number M_2, M_4 : Inhibitory
  - Affinity to ACh



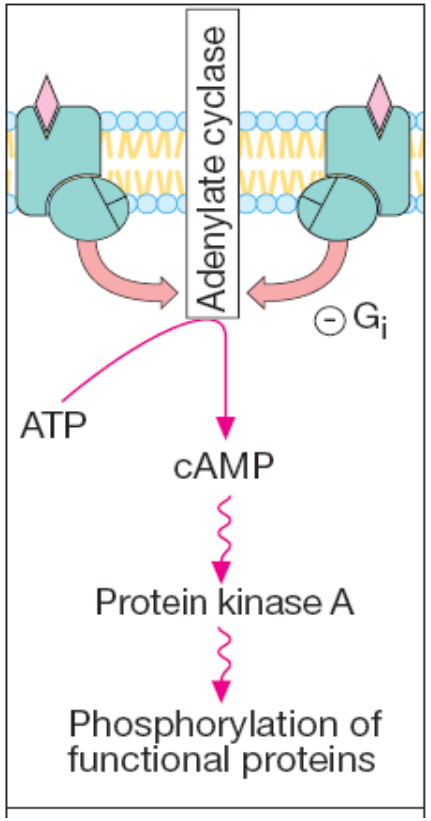


Autonomic Receptors (Cholinergic)

- Muscarinic receptors are GPCRs
  - M_1, M_3, and M_5



  - M_2 and M_4



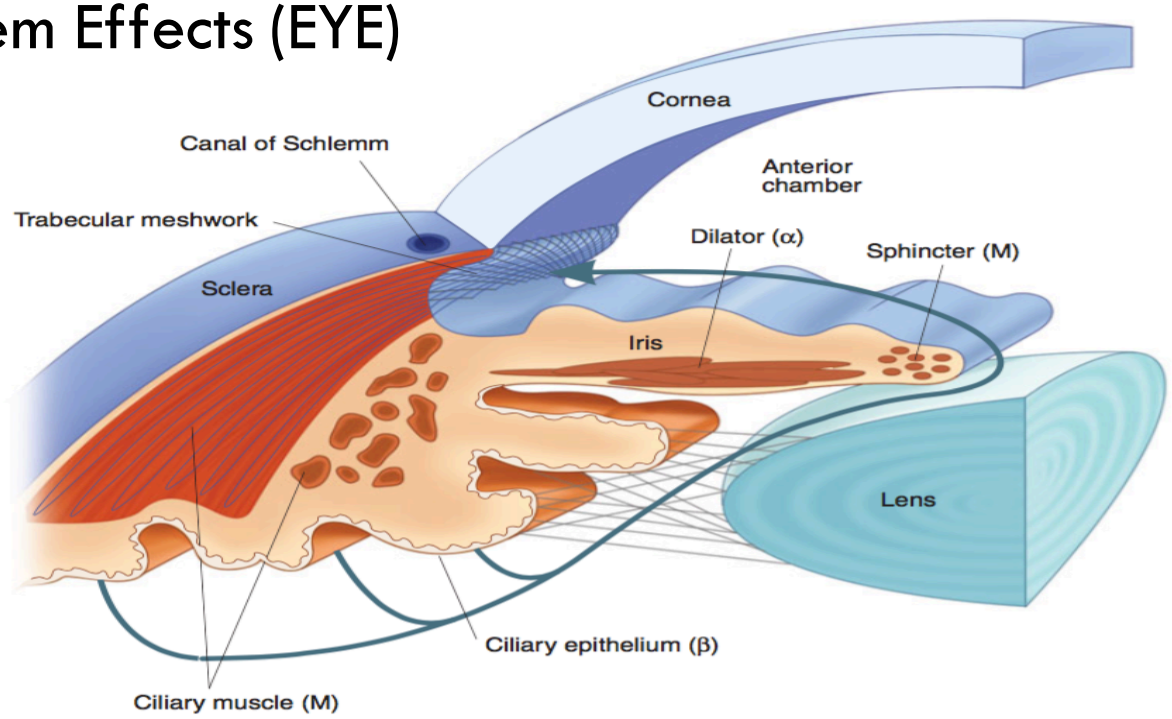
Autonomic Receptors (Cholinergic)

- Primary location of muscarinic receptors and their actions

Receptor	Locations	Pharmacological actions
M_1 Excitatory	**CNS** gastric parietal cells	CNS excitation Gastric acid secretion
M_2 Inhibitory	**Heart**	Cardiac inhibition (Bradycardia)
M_3 Excitatory	Exocrine **glands** **Smooth muscles** (GIT, urinary tract, bronchial muscles) **Eye** Vascular endothelium	• Secretion of glands •Relaxation of sphincter ?? • Smooth muscle contraction •Circular& ciliary muscle Contraction • Vasodilatation (via nitric oxide)
M_4 & M_5	CNS	memory, arousal, attention and analgesia

Drugs In/direct-acting on Ach receptors

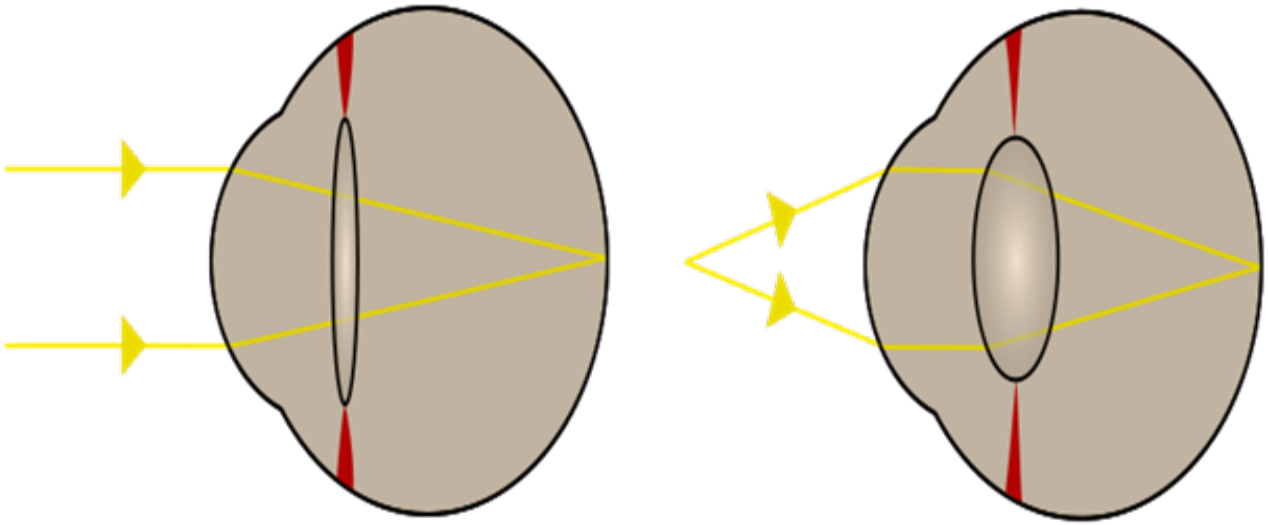
- Organ System Effects (EYE)



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.

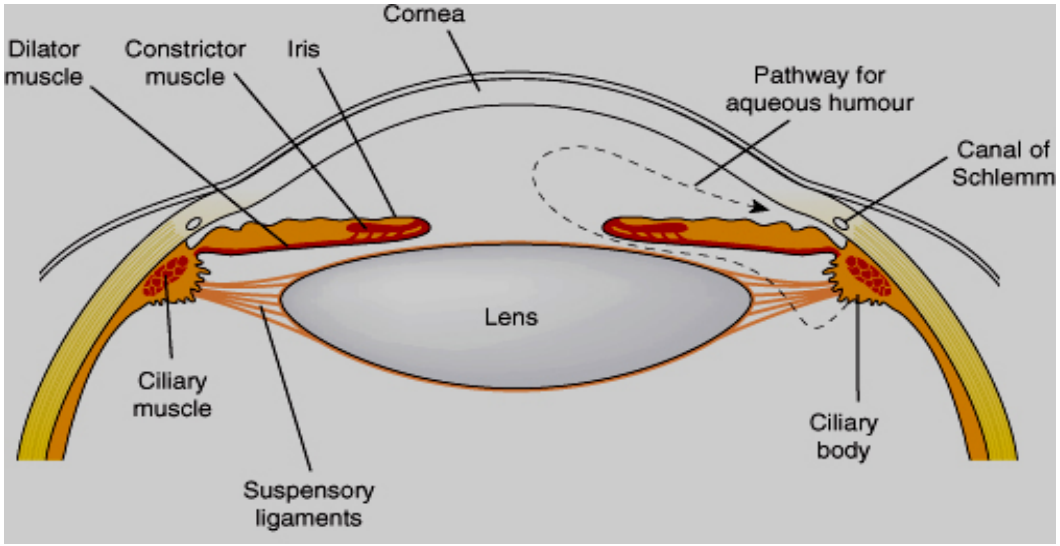
Ach receptors

- Organ System Effects (EYE)
  - When the ciliary muscle contracts, the lens **bulge** more → this parasympathetic reflex is essential to **accommodate for near vision**



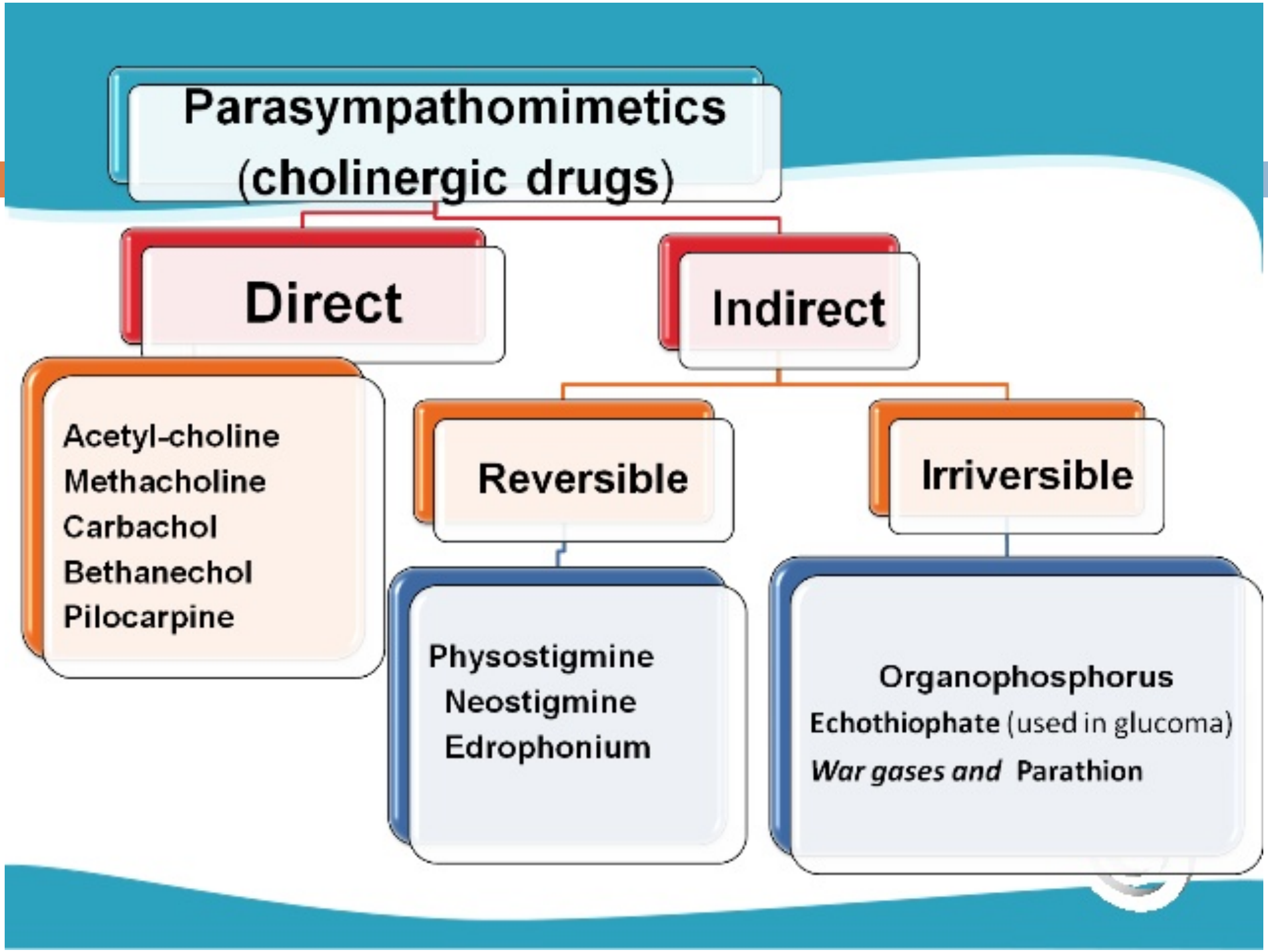
Ach receptors

- Organ System Effects (EYE)
- **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

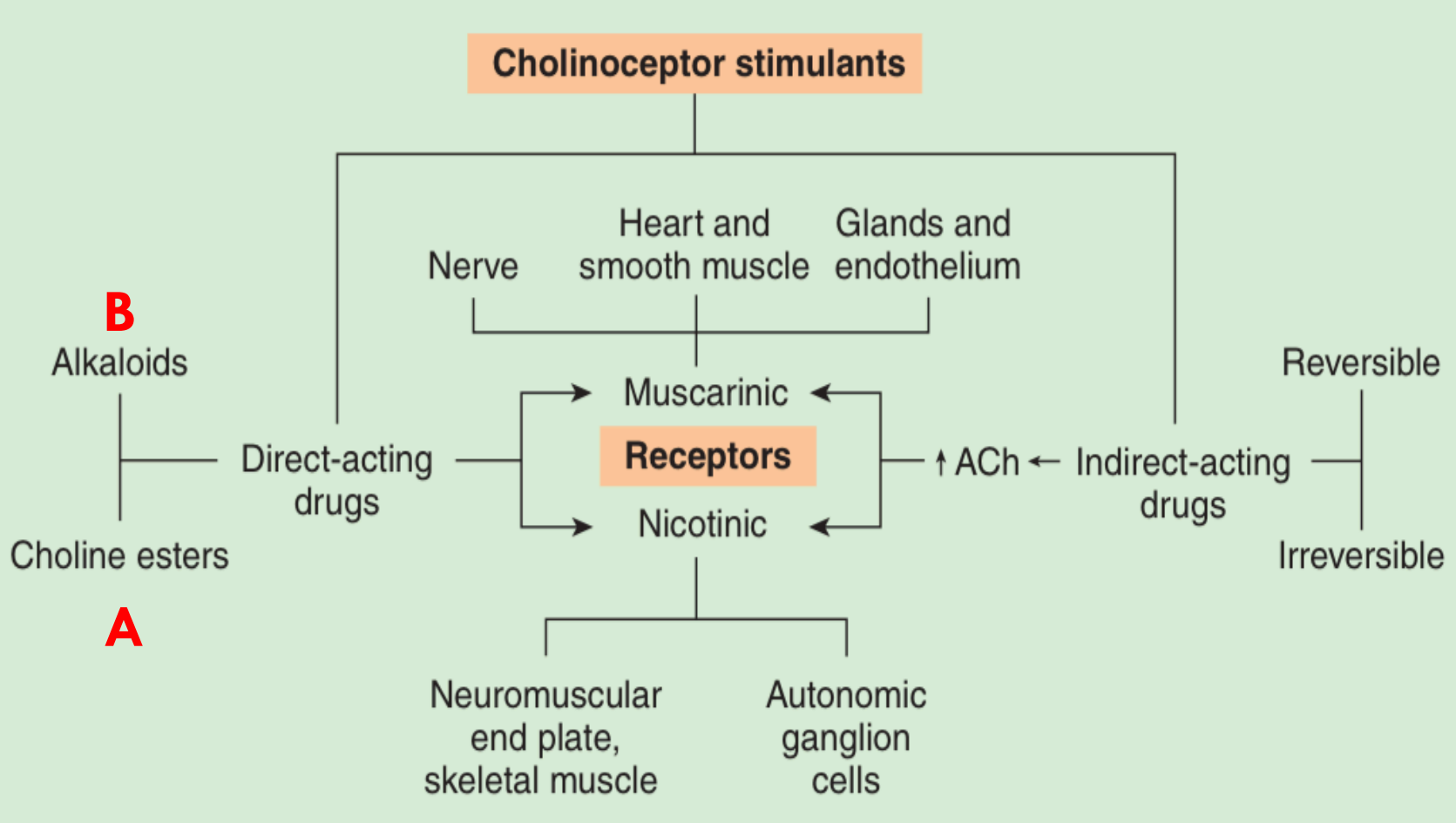


Pharmacological actions of cholinergic drugs

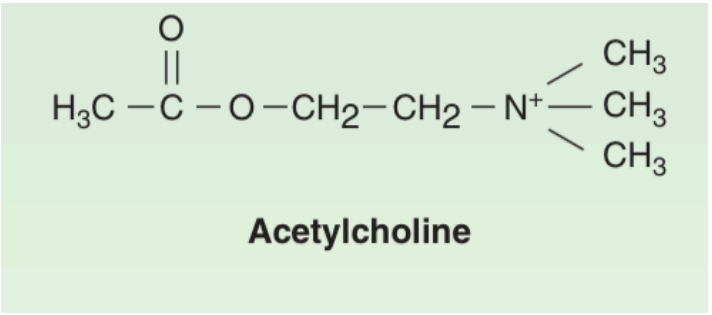
- Actions that are similar to the effects of parasympathetic system activation.
  - nicotinic actions
  - muscarinic actions
- Cholinergic drugs acts upon two types of receptors
  - nicotinic receptors
  - muscarinic receptors


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

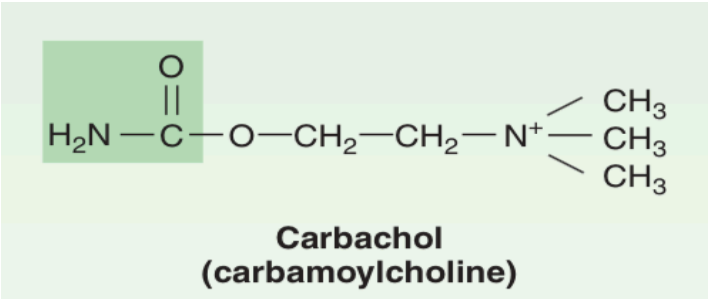
Parasympathomimetic (Cholinergic Drugs)



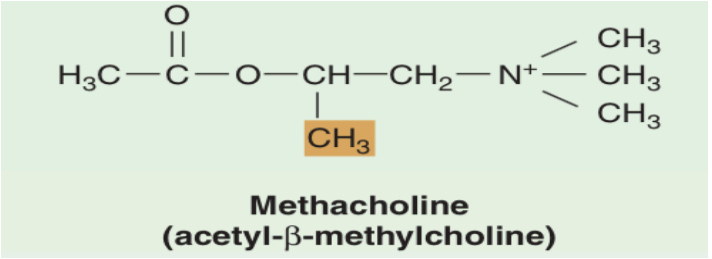
Drugs direct-acting on Ach receptors (CHOLINOCEPTORS)



Acetylcholine

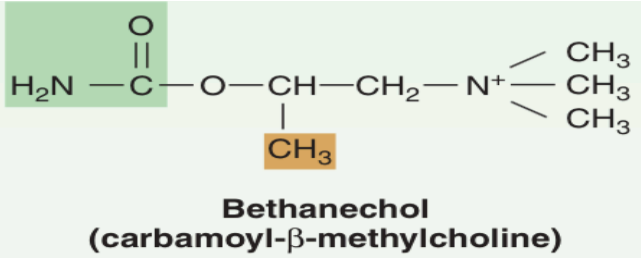


Carbachol
(carbamoylcholine)

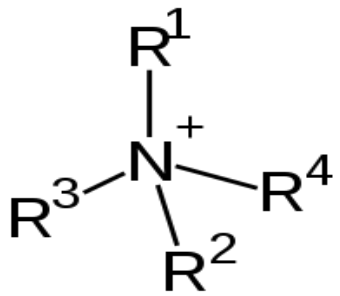


Methacholine
(acetyl-β-methylcholine)

- **A** Choline esters
  - Charged quaternary ammonium group- Activity **(polar)**
  - Poor distribution
  - can not cross BBB (No CNS effects)
  - Not metabolized by cholinesterase.(except Ach)
  - Have longer duration of action than Ach.
  - β-methyl group : Selectivity to M receptor
  - Never given I.V. or I.M But S.C Why??
  - Cevimeline

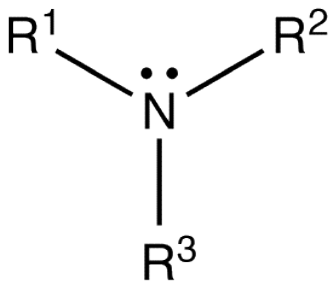


Bethanechol
(carbamoyl-β-methylcholine)

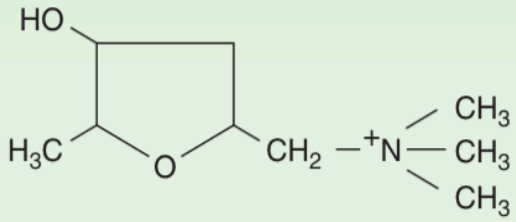


Drugs direct-acting on Ach receptors (CHOLINOCEPTORS)

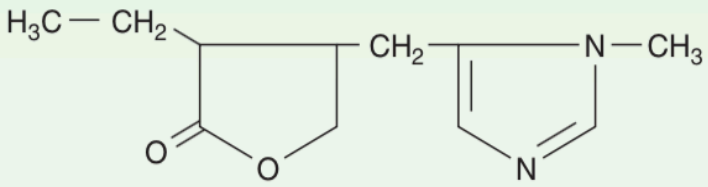
- **B** Tertiary natural alkaloids – Muscarine quaternary
  - Well absorbed except Muscarine , Excreted by the kidneys



Action chiefly muscarinic

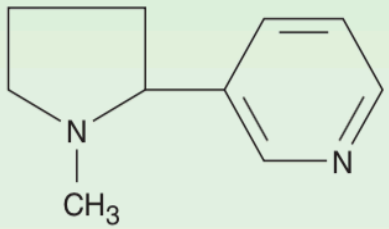


Muscarine

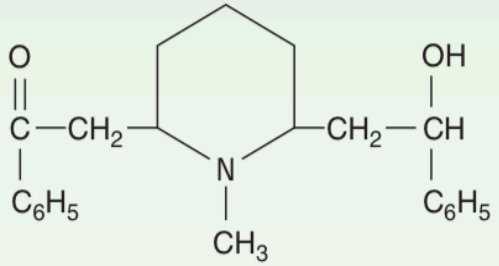


Pilocarpine

Action chiefly nicotinic



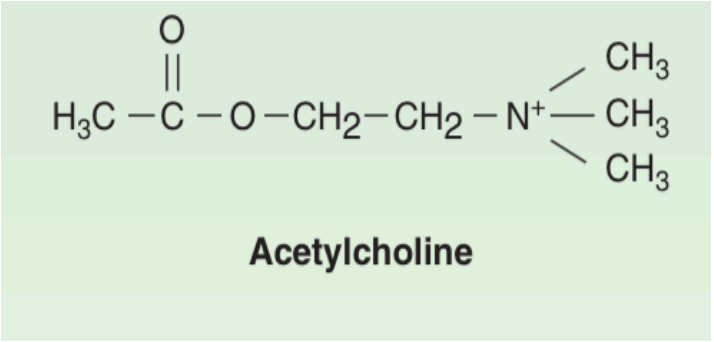
Nicotine



Lobeline

Drugs direct-acting on Ach receptors (CHOLINOCEPTORS)

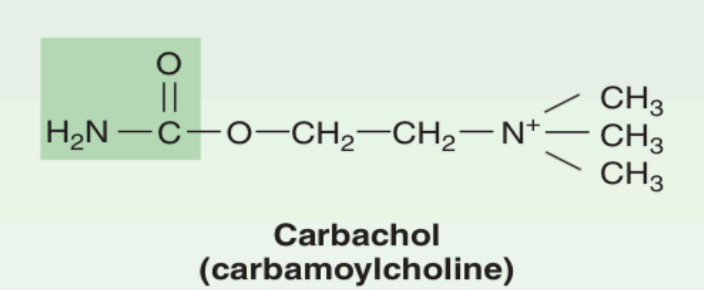
- Acetylcholine (Ach)
  - Muscarinic and nicotinic agonist
  - Not used clinically because Ach
    - Is not selective as it acts on both nicotinic and muscarinic receptors
    - Has short duration of action. Why?
    - Due to rapid metabolism by acetycholinesterase



Acetylcholine

Drugs direct-acting on Ach receptors (CHOLINOCEPTORS)

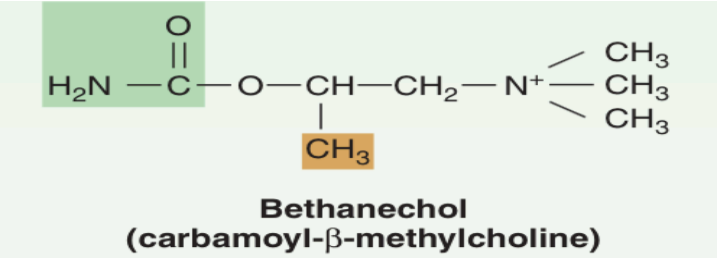
- **Carbachol**
  - Muscarinic actions on Eye, GIT, UT.
  - Has nicotinic actions (side effects).
  - Resistant to hydrolysis by acetyl cholinesterase
  - Longer duration than Ach.
  - Used for treatment of glaucoma



Carbachol
(carbamoylcholine)

Drugs direct-acting on Ach receptors (CHOLINOCEPTORS)

Bethanechol



Bethanechol
(carbamoyl-β-methylcholine)

- 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

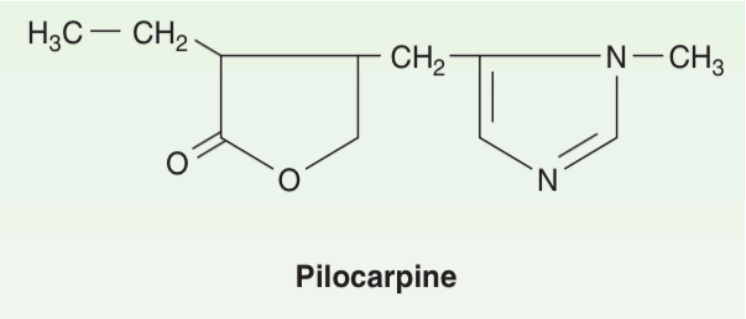
Drugs direct-acting on Ach receptors (CHOLINOCEPTORS)

- **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).

Drugs direct-acting on Ach receptors (CHOLINOCEPTORS)

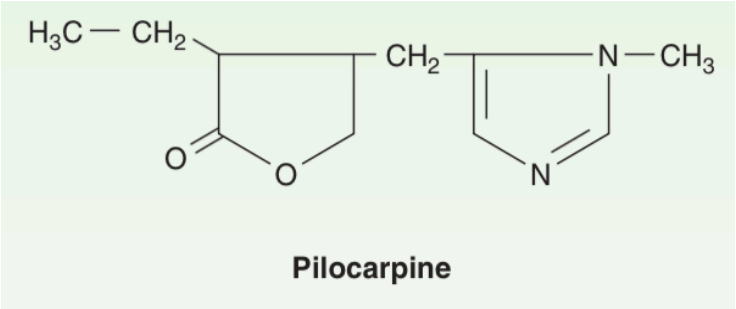
- **Pilocarpine**
  - well absorbed, good distribution
  - Cross BBB (has central effects).
  - Not metabolized by cholinesterase
  - Long duration of action
  - Excretion is enhanced by acidification of urine
  - Direct muscarinic agonist(mainly on eye & secretion).



Pilocarpine

Drugs direct-acting on Ach receptors (CHOLINOCEPTORS)

- **Pilocarpine**
- Uses:
  - Xerostomia (*dry mouth*).
  - Drug of choice in emergency glaucoma
    applied as eye drops.
- Adverse effects:
  - Profuse sweating
  - Salivation
  - Bronchoconstriction
  - Diarrhea
  - CNS effects



Pilocarpine

Drugs direct-acting on Ach receptors (CHOLINOCEPTORS)

	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

Drugs direct-acting on Ach receptors (CHOLINOCEPTORS)

	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**

Drugs direct-acting on Ach receptors (CHOLINOCEPTORS)

Contraindications

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

End