

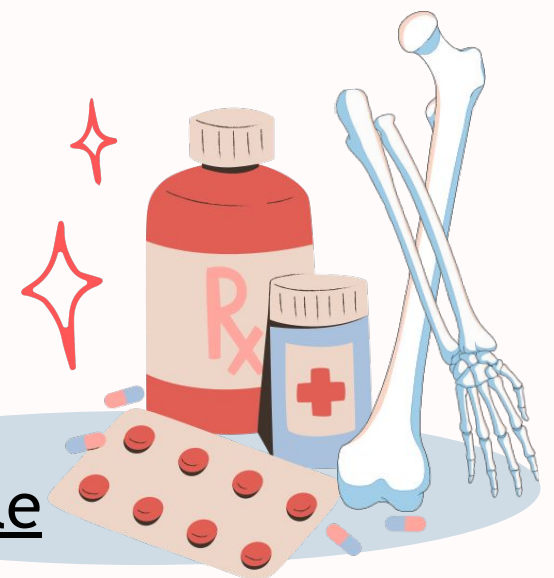
Direct-Acting Cholinergic Drugs

Lecture no.1

Color Index:

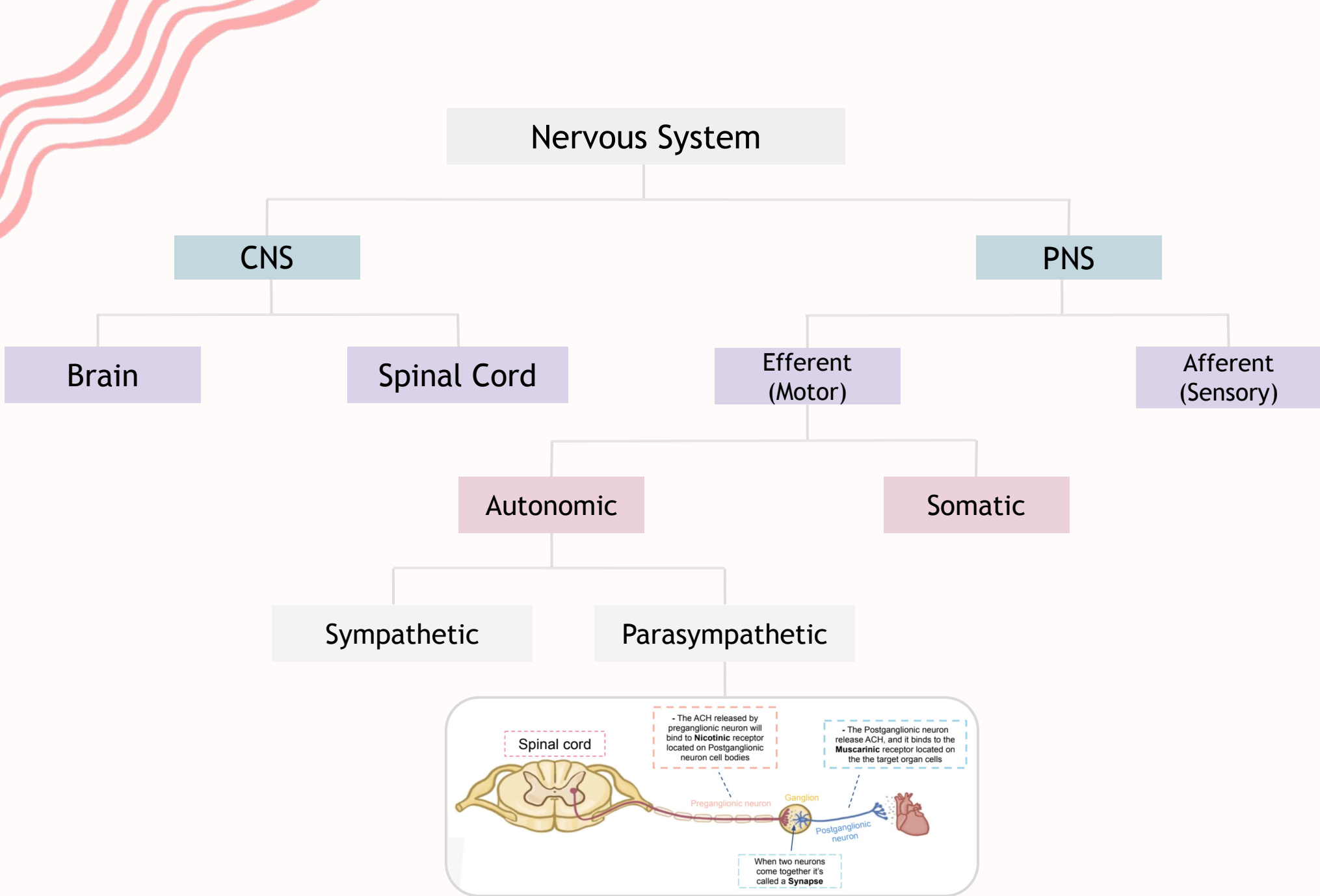
- Main Text
- **Important**
- Females' Slides
- Males' Slides
- Drs' Notes
- Extra info.

Editing File

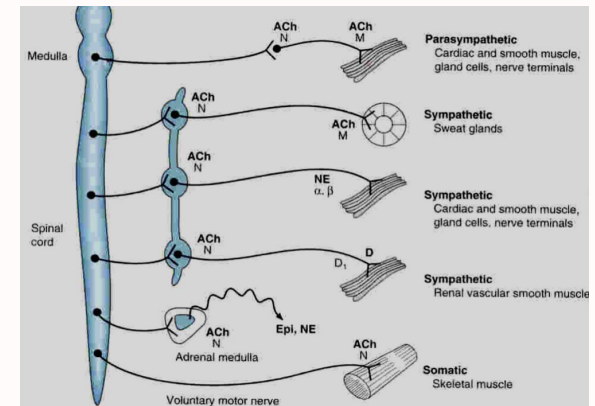
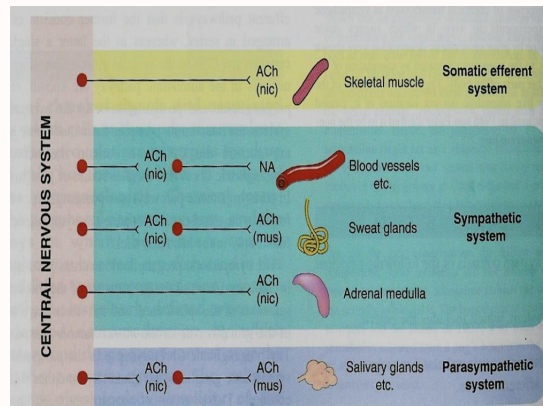
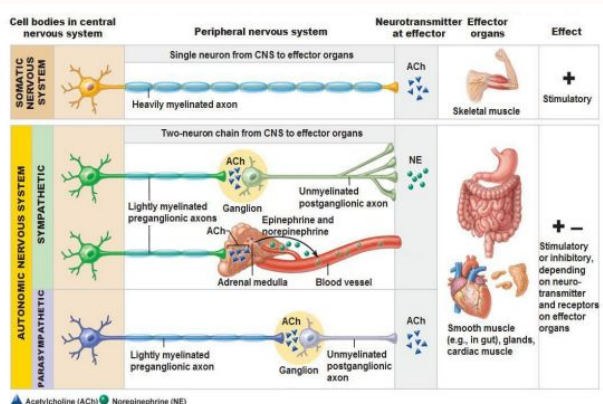


Objectives

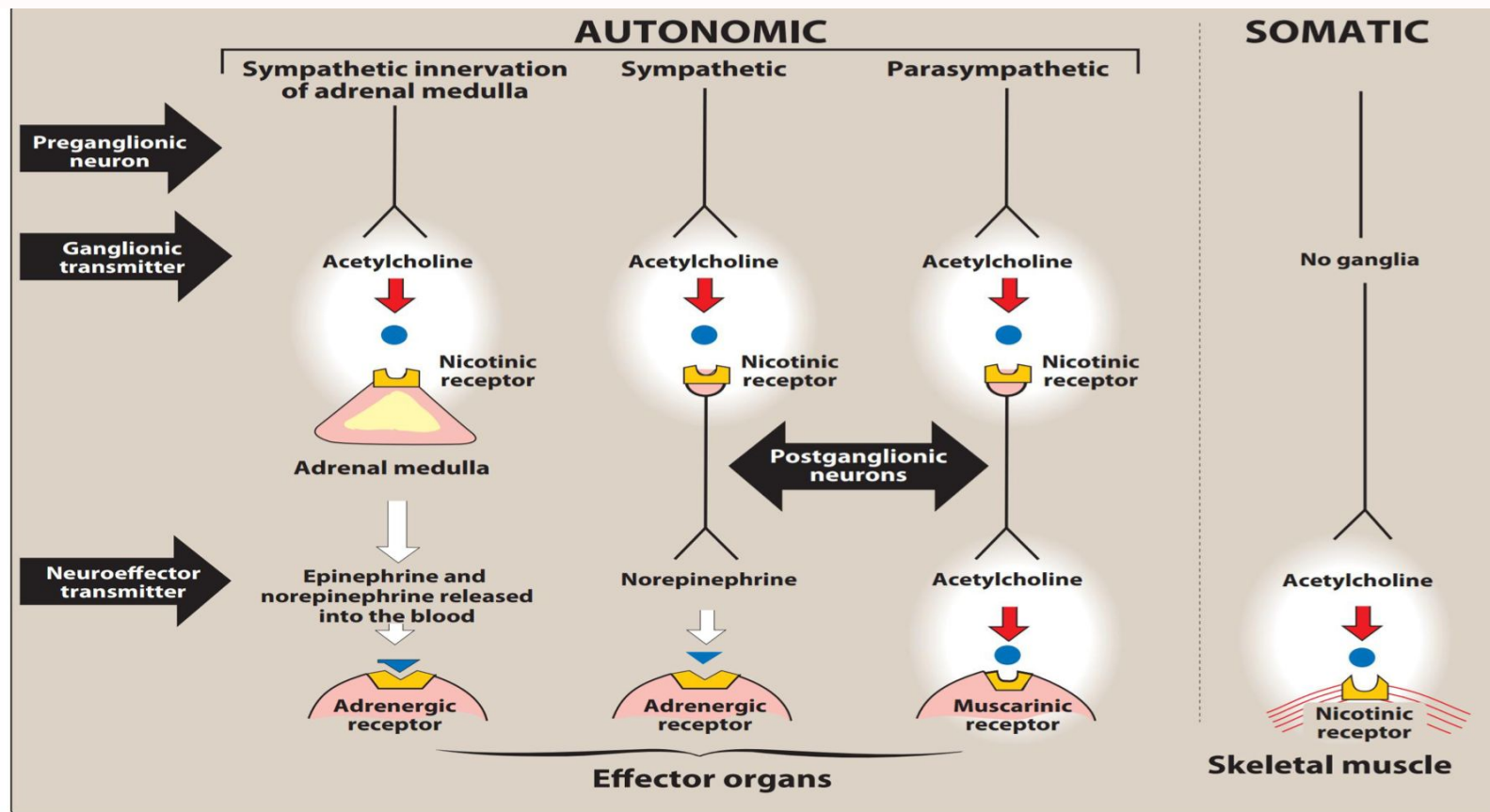
- Mention the different types, locations and actions of cholinergic receptors.
- Identify the mechanism of action of direct acting cholinomimetics.
- Describe the pharmacokinetics of cholinergic drugs.
- Identify pharmacological actions and uses of cholinomimetics.



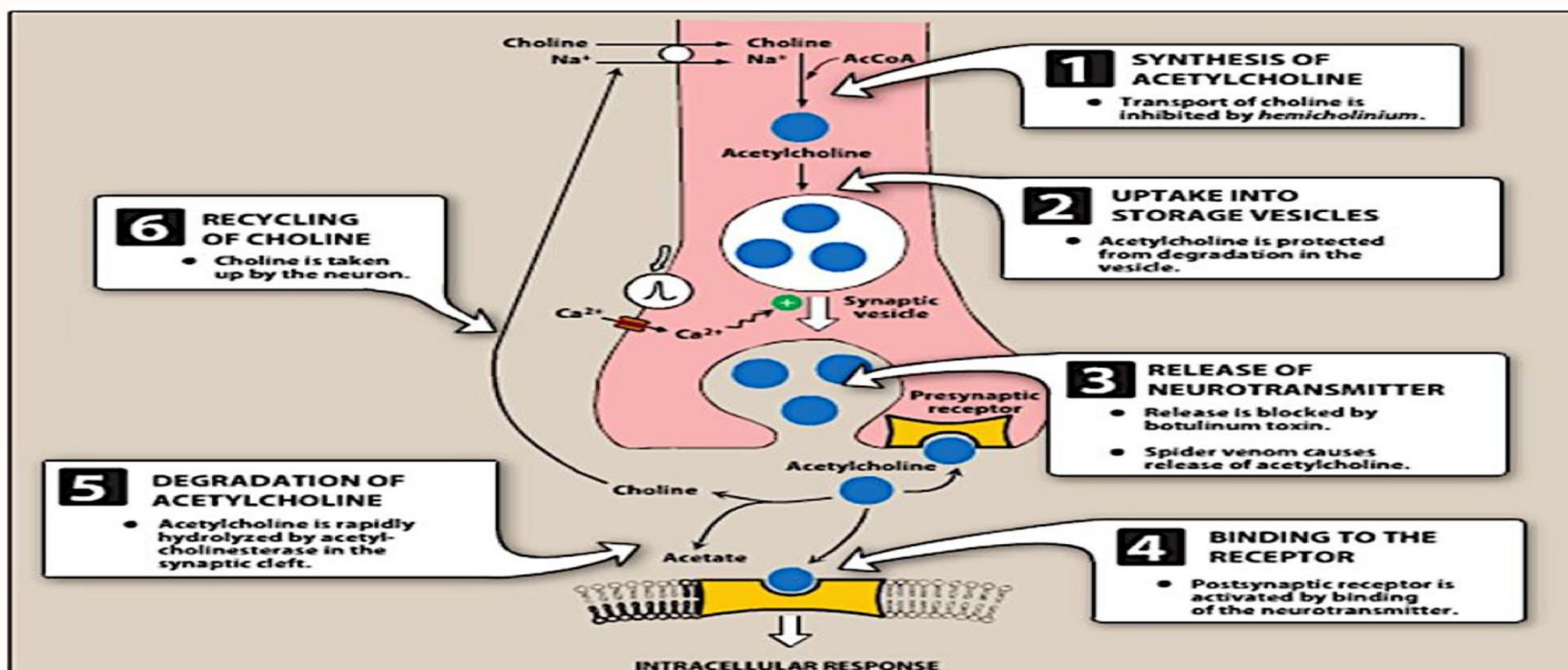
→ Comparisons between the Autonomic and Somatic Motor System



★ Sites of actions of cholinergic agonists in the autonomic and somatic nervous system



★ Synthesis and release of Ach



Cholinomimetics / Parasympathomimetics

- Drugs that produce actions similar to stimulation of parasympathetic system or similar to Acetylcholine. They produce Nicotinic & Muscarinic actions.

Classification of Cholinomimetics

Direct

- It causes direct stimulation of cholinergic receptors (Nicotinic, Muscarinic receptors) by binding to it.
- Producing **Nicotinic** and **Muscarinic** actions.

Examples:

- Acetylcholine
- Methacholine
- Carbachol
- Bethanechol
- Pilocarpine

Indirect

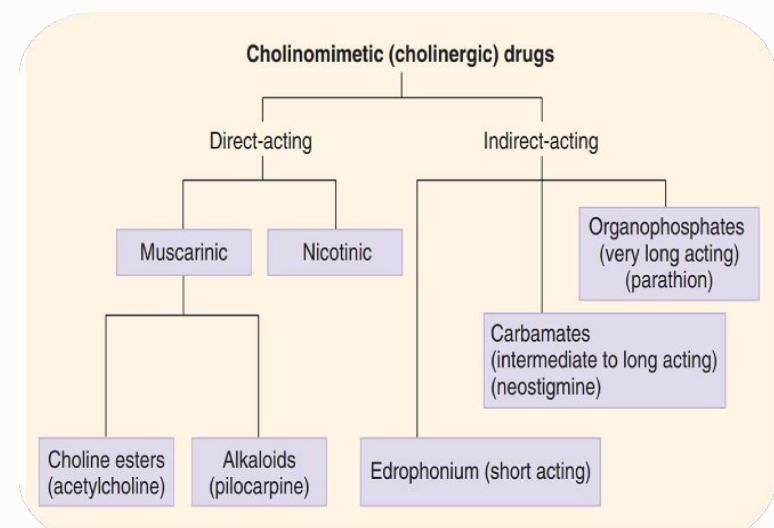
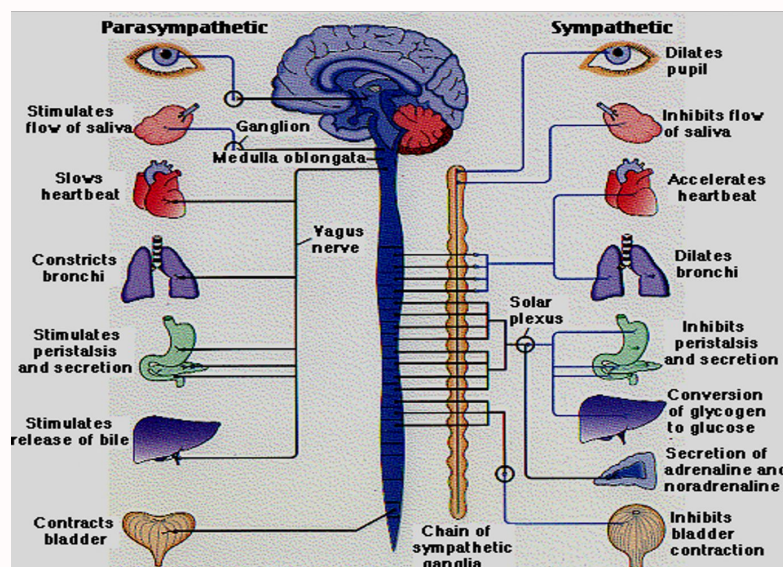
- Acts indirectly by **inhibiting acetylcholinesterase** thus prevent the hydrolysis of Ach.
- They are called cholinesterase inhibitors or anticholinesterases.

Reversible:

- Physostigmine
- Neostigmine
- Edrophonium

Irreversible:

- Organophosphorus Echothiophate (used in glaucoma)
- War gases and parathion



Cholinergic Parasympathetic Receptors

Nicotinic (N) Receptors

-Type I receptor: **Ion channel /Ligand Gated linked receptor.** (Effects are rapid & allow Na influx)

-Central Receptors

Stimulated by Nicotine and Ach

Locations and nicotinic Action:

- 1-Skeletal Muscles (Neuromuscular junction, **Nm**):
 - Low concentration (Therapeutic dose) → muscle **contraction**.
 - High concentration (Toxic dose) → Persistent **depolarization & relaxation** (Blocking of depolarization)
- 2-Autonomic ganglia (**Nn**) → Sympathetic and Parasympathetic **stimulation**.
- 3-Adrenal Medulla (**Nn**) → Release of Catecholamines (Adrenaline & noradrenaline)
- 4-CNS (**Nn**)

Action: almost excitatory

Nn: Nerve to Nerve (transmission of cholinergic signals)
Nm: Nerve to Muscle (muscle contraction)

Muscarinic (M) Receptors

-Type II receptor: **G-Protein linked/coupled receptor (GPCR)** (Effects are slower)

-Peripheral Receptors

Stimulated by Muscarine and Ach

Location:

- Located at **all target peripheral organs that are innervated by postganglionic parasympathetic fibers (e.g., Heart, CVS, Eye, Bladder, etc..)**

Muscarinic Action:

- Heart → Bradycardia (M2)
- Exocrine glands → Secretion (M3)
- Smooth muscle → Contraction (M3)

Five Subclasses: M1, M3, M5 (**Excitatory**) الأعداد الفردية
M2, M4 (**Inhibitory**) الأعداد الزوجية

Pharmacological Action: excitatory or inhibitory

- M1 & M3 → activate Gq→ increase intracellular calcium (contraction/secretion)
- M2 → Activate Gi → increase efflux of K (hyperpolarization, decrease heart rate)

Direct-acting nicotinic agonists

→ They are used in smoking cessation and to produce skeletal muscle paralysis.

Succinylcholine

- Is used to facilitate tracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

Varenicline

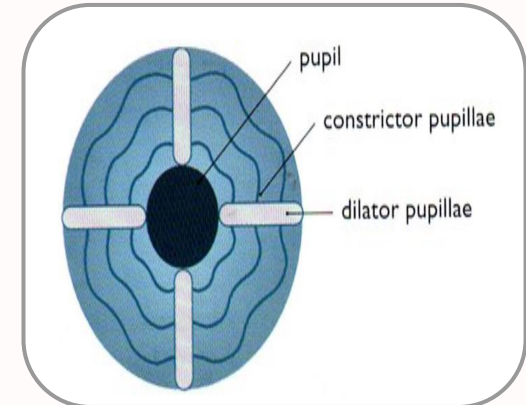
- Is a newer nicotinic agonist with partial agonist properties. It appears to reduce craving in persons addicted to nicotine through a nonautonomic action.

Muscarinic Receptor	Location	Muscarinic Action
M1 (Excitatory)	CNS (neurons)	-CNS excitation -Increase intracellular Ca2 (contraction/secretion)
	Gastric Parietal Cells	-Gastric Acid Secretion
M2 (inhibitory)	Heart (cardiac cells)	- Cardiac Inhibition (Bradycardia) (Decrease in the heart rate) - Increase intracellular k+ (hyperpolarization, decrease heart rate)
M3 (Excitatory)	Vascular Endothelium	- Vasodilation via release of NO (EDRF) (Endothelium Derived Relaxing Factor)
	Exocrine Gland	- Increased secretion of glands (sweat,saliva, lacrimal, bronchial, intestinal secretions)
	Smooth Muscle (GIT, urinary tract, bronchial muscles)	- Smooth Muscle Contraction
	GIT	- Increases Motility of GIT (Peristalsis)(May lead to diarrhea) - Increase in secretion - Relaxation of sphincter → defecation
	Lung	- Constriction of bronchial smooth muscle. (Cannot be prescribed for patients with asthma) - Increase bronchial secretion
	Eye	- Contraction of circular muscle iris (Miosis) - Contraction of ciliary muscles for near vision - When these two contractions happen, a decrease in intraocular pressure (IOP) happens. (Helps patients with glaucoma)
	Urinary Tract	- Contraction of muscles - Relaxation of sphincter - Urination
M4 and M5 (Excitatory and Inhibitory)	CNS	Memory, arousal, attention and analgesia.

The 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.



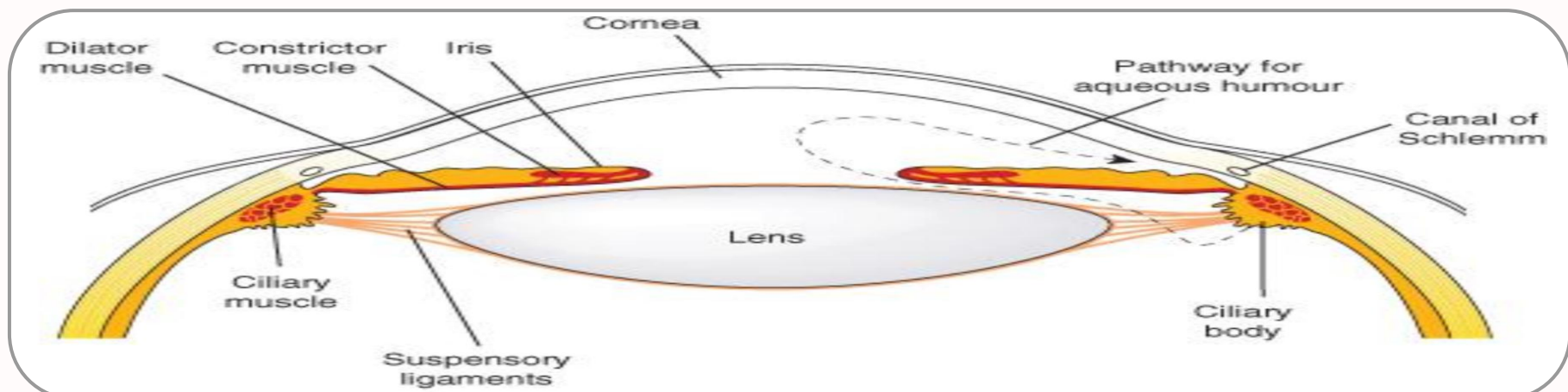
Intraocular Pressure

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 (Miosis) of iris thus pulling ciliary muscles away from the trabecular meshwork and Schlemm's canal thus facilitating drainage and reducing intraocular pressure.

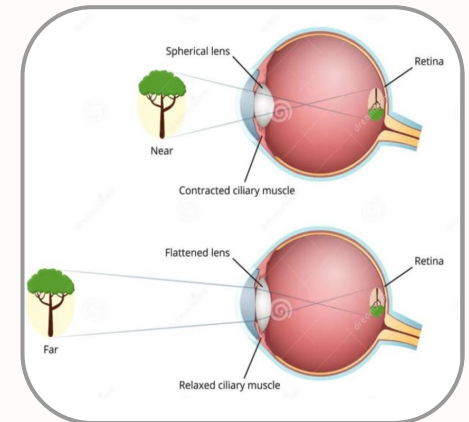
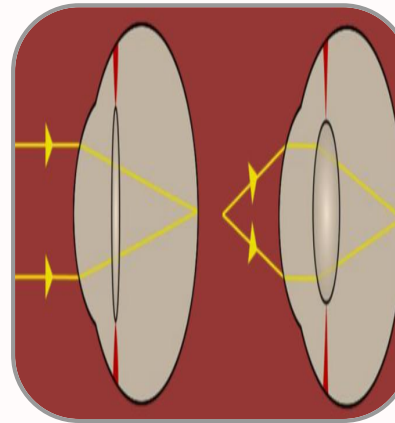
REGULATING THE IOP:

- It 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



Parasympathetic Actions on Eye

- Iris radial muscles (No effect)
- Iris Circular muscles (Contractions M_3)(miosis)
- Ciliary muscles (Contractions M_3)
- Accommodation (for near vision)
- Intraocular pressure (IOP) (decreased)

442

★ Dr's Note: There are two ways to decrease the IOP:

- 1- by drainage or outflow (M_3)
- 2- by decreasing the formation of aqueous humor.

442

★ Miosis (contraction of the pupil) will decrease the Intraocular Pressure (IOP) by the contraction of the circular muscle which leads to dilation of the schlemm's canal and this will lead to more drainage of fluid, resulting in a decrease in the IOP.



Direct Cholinomimetics

A drug that binds and activates cholinceptors;
the effects mimic those of acetylcholine

Naturally occurring alkaloids

(tertiary amines)

- pilocarpine
- nicotine

Synthetic choline esters

(Quaternary ammonium
compounds)

- Acetylcholine
- Carbachol
- Bethanechol
- Cevimeline



Contraindications of direct cholinomimetics:

Bronchial asthma - Peptic ulcer - Angina pectoris - Urinary
incontinence - Intestinal obstruction



Direct Cholinomimetics	Natural alkaloids	Synthetic choline esters
Example	Tertiary amines: -Pilocarp <u>ine</u> -Nicot <u>ine</u>	Quaternary ammonium compounds: -Acetyl <u>choline</u> -Carbach <u>ol</u> -Bethane <u>chol</u> -Cevimeline
Features	<ul style="list-style-type: none"> - Natural alkaloids - Are lipid soluble nitrogen nonpolar compound found in nature - basic character - Tertiary amines - Common suffix (ine) which means natural and basic 	<ul style="list-style-type: none"> - Polar (contains N⁺ ion) - Synthetic choline esters (quaternary ammonium compounds) <p>Muscarinic quaternary amine not well absorbed in the GIT (orally) but still toxic when ingested in mushrooms</p>
Pharmacokinetics	-Non-polar, lipid soluble -Well absorbed by the skin	<ul style="list-style-type: none"> - Poor distribution - Cannot cross BBB so no CNS effects -Not metabolized by cholinesterase (except Ach) - All of them have longer duration of action than Ach - Never given I.V. or I.M. But S.C.

Pilocarpine

(natural alkaloids)

Mechanism of action

- Direct muscarinic agonist
- Secretagogue
- Acts mainly on eye and secretion

Pharmacokinetics

- Non-polar (lipophilic), tertiary amine
- Well absorbed, good distribution
- Cross BBB, so has central effects
- Not metabolized by cholinesterase
- Long duration of action
- Excretion is enhanced by acidification of urine

Uses

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

Side effects

- Profuse sweating (diaphoresis)
- Salivation
- Bronchoconstriction
- Increase GIT motility (diarrhea)
- spasm
- CNS effects

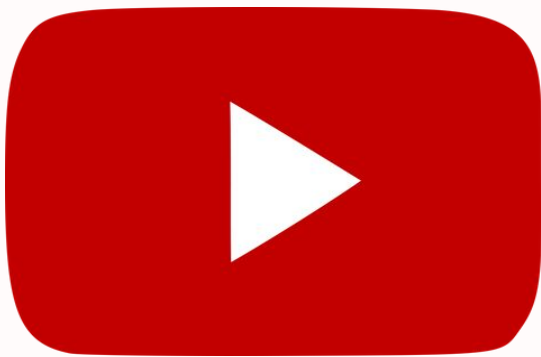
Synthetic Choline Esters	Mechanism of action	Pharmacokinetics	Uses	Side effects
Acetylcholine	Muscarinic & Nicotinic (not selective)	—————	Not used clinically, why? Because it's not selective (acts on both nicotinic & muscarinic receptors) and has a short duration of action due to rapid metabolism by acetylcholinesterase	—————
Carbachol	Muscarinic action on the eyes, GIT, UT Has nicotinic action (side effect)	Resistant to hydrolysis by acetylcholinesterase ↓ longer duration than Ach	Treatment of glaucoma as eye drops only	Nicotinic side effect
Bethanechol	Prominent muscarinic action on GI, UT <u>No</u> nicotinic actions		- Drug of choice in paralytic ileus (Which is a failure of intestinal motility) - Urinary retentions in case of postoperative atony and neurogenic bladder	—————
Cevimeline	Direct acting muscarinic agonist (M3)	—————	Treatment of the dry mouth symptom associated with radiation therapy & Sjogren's syndrome (an autoimmune disease characterized by Formation of antibodies leading to dryness of mouth and eye)	—————

	Ach	Carbachol	Bethanechol	Pilocarpine
Found in males' slides only				
Chemistry	Quaternary Chemistry Polar			Tertiary Non-Polar
Absorption	Not Absorbed	Better absorbed than Ach		Complete absorption
Metabolism by cholinesterase	Metabolized by cholinesterase	Not Metabolized by cholinesterase		
Duration	Very Short	Longer than Ach		
Administration	<ul style="list-style-type: none"> I.V. Eye drops 	<ul style="list-style-type: none"> Oral S.C Eye drops 	<ul style="list-style-type: none"> Oral S.C 	<ul style="list-style-type: none"> Oral Eye drops

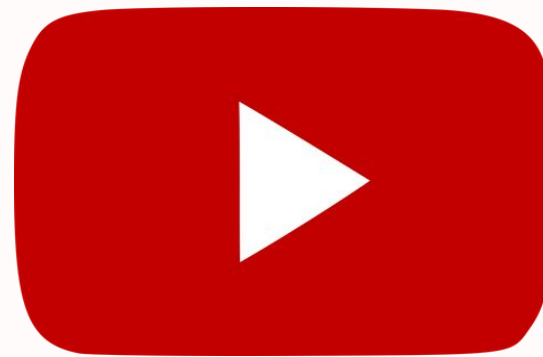
Found in males' slides only	Ach M&N	Carbachol M&N	Bethanechol M	Pilocarpine M	Cevimeline M
Receptors	Muscarinic & Nicotinic	Muscarinic & Nicotinic	Muscarinic	Muscarinic	Muscarinic
Muscarinic	Yes	Yes	Yes	Yes	Yes
Nicotinic	Yes	Yes	No	No	No
Selectivity	Not selective	Eye, GIT ,Urinary bladder	GIT, Urinary bladder	More on eye, Exocrine glands	Exocrine glands
Uses	Not used	Glaucoma	Paralytic ileus, urinary retention	Glaucoma, Xerostomia	Sjogren's Syndrome

For better understanding watch these videos

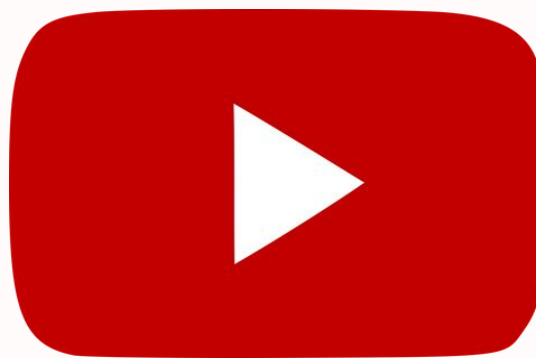
Click the icon



Ninja Nerd



Dr.Fouda



Osmosis

MCQs

Q1. Which one of these has the shortest duration of action?

- | | | | |
|--------------|----------------|------------------|----------------|
| a) Carbachol | b) Bethanechol | c) Acetylcholine | d) Pilocarpine |
|--------------|----------------|------------------|----------------|

Q2. Which one of the following can cross BBB (Blood Brain Barrier)?

- | | | | |
|----------------|----------------|---------------|------------------|
| a) Pilocarpine | b) Bethanechol | c) Cevimeline | d) Acetylcholine |
|----------------|----------------|---------------|------------------|

Q3. Which of the following cholinomimetics activates both muscarinic and nicotinic receptors?

- | | | | |
|--------------|-------------|----------------|-------------|
| a) Carbachol | b) Lobeline | c) Pilocarpine | d) Nicotine |
|--------------|-------------|----------------|-------------|

Q4. A 43 year-old patient is recovering from abdominal surgery and develops postoperative urinary retention. A drug that you could give orally to treat this condition is?

- | | | | |
|------------------|--------------|----------------|-------------|
| a) Acetylcholine | b) Clonidine | c) Bethanechol | d) Atropine |
|------------------|--------------|----------------|-------------|

Answers:
1) C
2) A
3) A
4) C

MCQs

Q5. Bethanechol is clinically indicated in the treatment of which one of the following conditions?

a) Glaucoma

b) Myasthenia gravis

c) GIT ulcer

d) Paralytic ileus

Q6. Which of the following drugs treats xerostomia(dry mouth)?

a) Donepezil

b) Neostigmine

c) Pilocarpine

d) Physostigmine

Q7. Which one of the following is inhibitory in function?

a) M_1

b) M_2

c) M_3

d) All of them

Q8. Which one of the following is used in Sjogren's syndrome?

a) Pilocarpine

b) Cevimeline

c) Carbachol

d) Bethanechol

Q9. Muscarinic receptors are found in ?

a) Eye

b) Heart

c) CNS

d) All of them

Answers:

5) D
6) C
7) B
8) B
9) D

SAQs

1

Define Cholinomimetic drugs ?

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

2

If we used a drug that acts on M3 receptor at the eye, what are the expected reactions?

Contraction of circular muscle iris (Miosis).
Contraction of ciliary muscles for near vision.
Decrease in intraocular pressure.

3

A dentist would like to reduce salivation in a patient in preparation for an oral surgical procedure, which receptor will he block to reduce salivation?

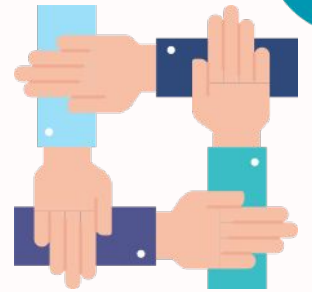
block muscarinic receptor (M3), located in the salivary gland.

4

Why we don't use Ach clinically?

- 1) Not selective (Act on Both Nicotinic & Muscarinic Receptor).
- 2) It has short duration of action due to it's metabolize by Acetylcholinesterase.

Team Leaders:



- Rakan Almutib
- Shoug Albattah

Team Members:

- Khalid Alkanhal
- Jenan Alsayari
- Omar Alattas
- Lama Alahmari
- Waleed Alanazi
- Wsaif Alotaibi
- Ali Al-Abdulazem
- Nora Alturki
- Saleh Alotaibi
- Sahar Alfallaj
- Fawaz Almadi
- Madaen Alarifi



Contact us at : pharmacology.444ksu@gmail.com