

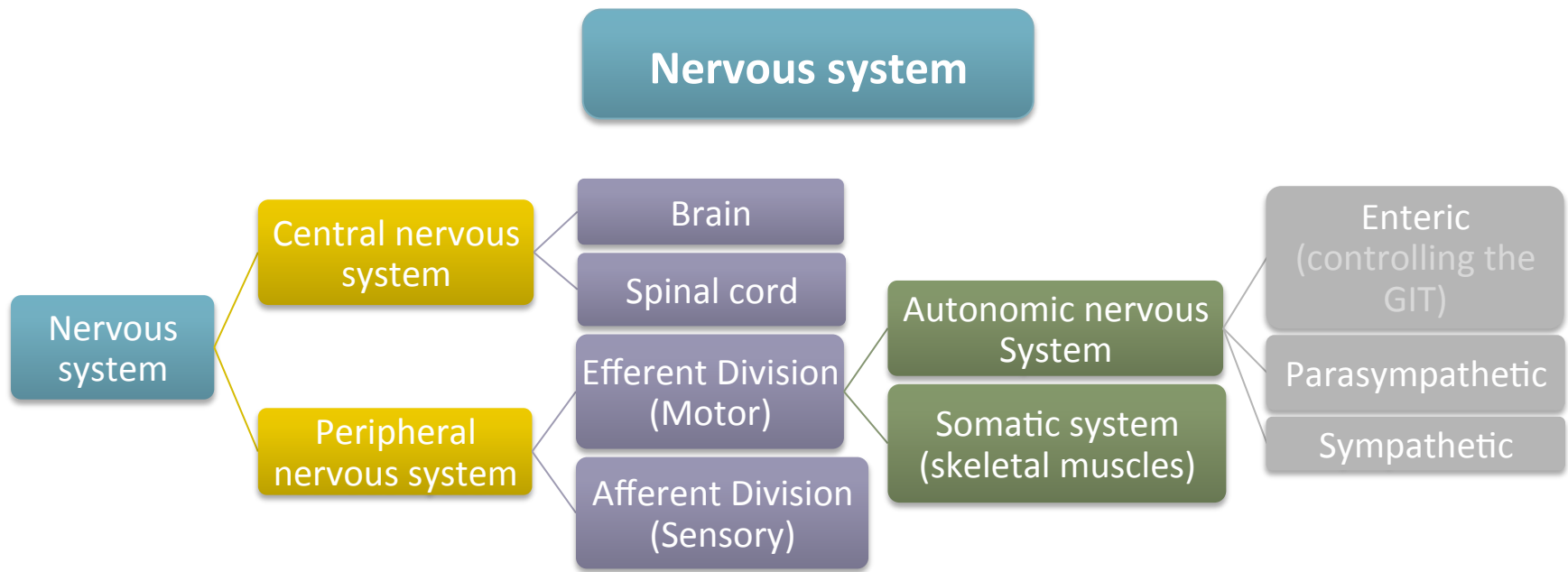


Lecture 5

Direct cholinergic drugs

Objectives:

1. Classification of nervous system.
 2. Describe the various steps in cholinergic transmission.
 3. Mention the different types, locations and actions of cholinergic receptors.
 4. Describe the effects of acetylcholine on major organs.
 5. Classify cholinomimetic drugs.
 6. Describe the kinetics, actions and uses of direct and indirect-acting cholinomimetic drugs
- Additional Notes
 - Important
 - Explanation –Extra-

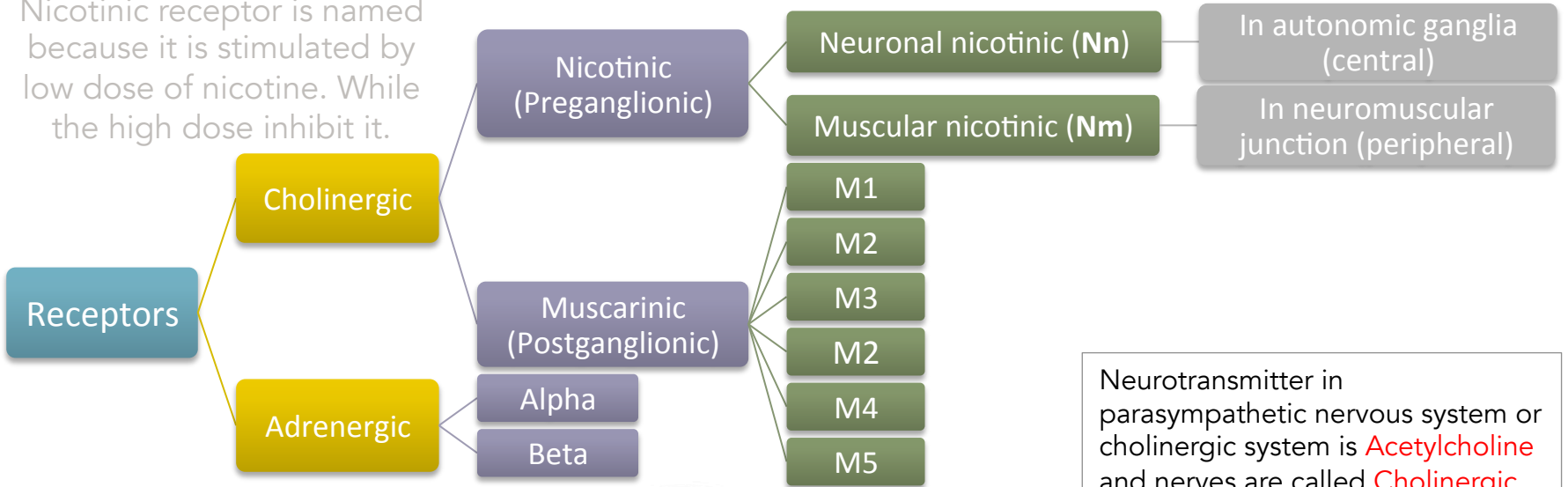


What are the differences between the somatic and the autonomic nervous system?

Somatic N.S	Autonomic N.S
Controls skeletal muscles	Controls internal viscera
Voluntary	Involuntary
Somatic nerve is one fiber	autonomic nerve is two fibers (Preganglionic & Postganglionic)

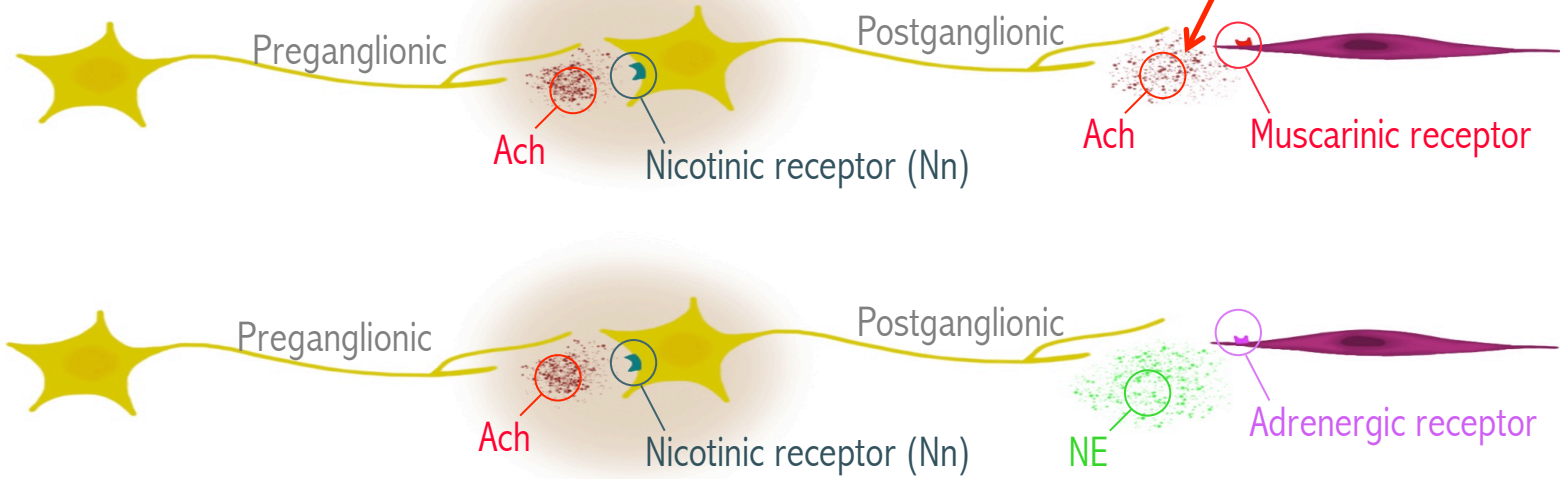
In this lecture we will focus more on Parasympathetic System, because we are discussing Cholinemimetics drugs "Acetylcholine function"

Nicotinic receptor is named because it is stimulated by low dose of nicotine. While the high dose inhibit it.



Neurotransmitter in parasympathetic nervous system or cholinergic system is **Acetylcholine** and nerves are called **Cholinergic nerves**

Autonomic NS

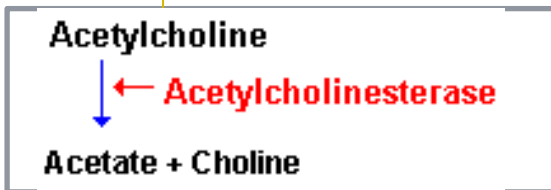
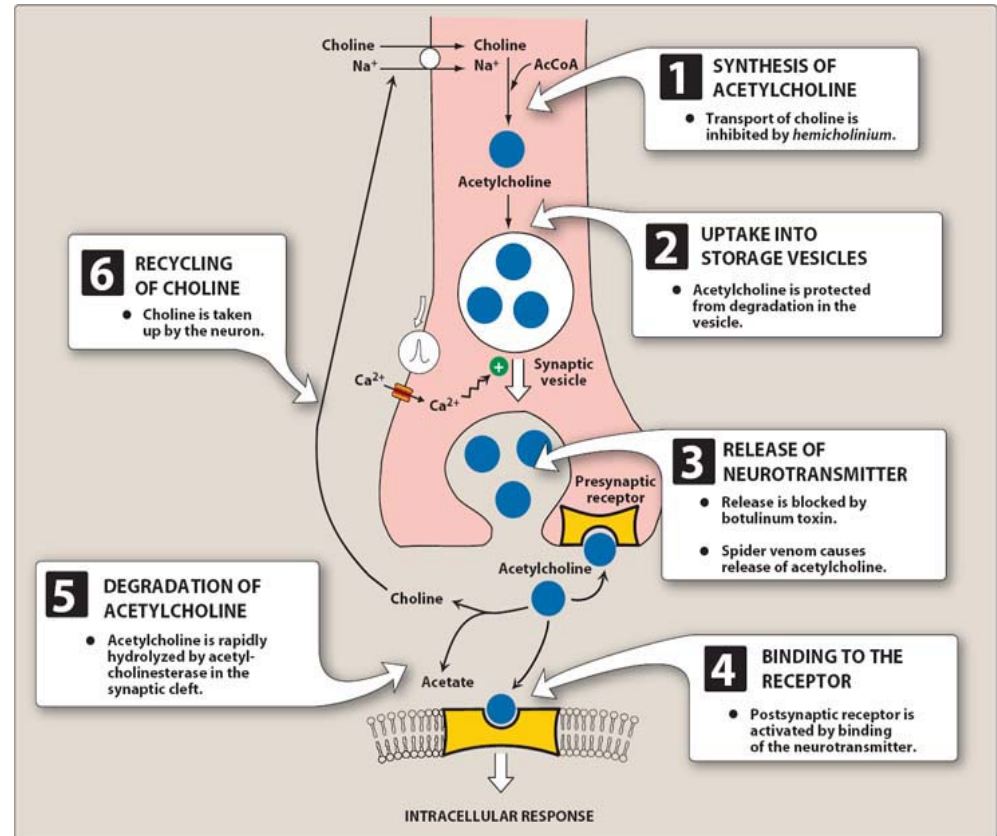
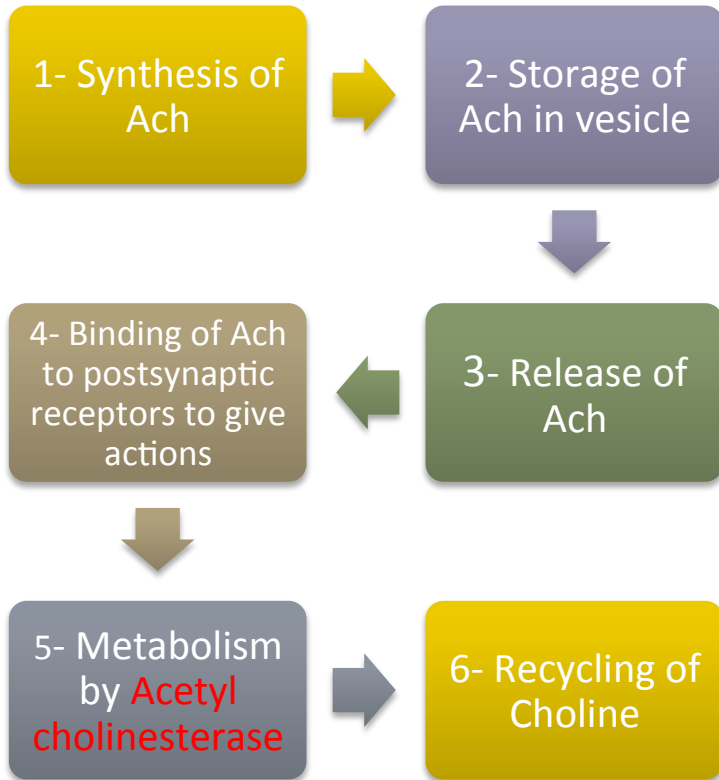


Somatic NS



Cholinergic Transmission

- The release of neurotransmitter Ach from cholinergic nerves include the following steps:



Cholinergic Receptors

1- Muscarinic Receptors

- Type II receptors, **G-Proteins Linked Receptors**. (very fast receptor, open to influx Na when stimulated)
- 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 (Heart, CVS, eye, bladder, etc.).

2- Nicotinic Receptors

Type I receptors, Ion **Channel Linked Receptors**.

Located In:

1. Skeletal Muscles “Neuromuscular Junction”
2. Autonomic Ganglia “Sympathetic & Parasympathetic”
3. Adrenal Medulla
4. Central Nervous System

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 Inhibitory M5 Excitatory	CNS	Memory “Alzheimer's patients”, arousal, attention and analgesia

Pharmacological actions of parasympathetic N.S

Nicotinic actions

Almost excitatory

Skeletal muscles

Low conc. Of Ach → muscle contraction

High conc. of Ach → persistent depolarization & relaxation.

Autonomic System

Autonomic ganglia
(Sympathetic & Parasympathetic stimulation)

Adrenal medulla:
release of catecholamine
(**Adrenaline** & **Noradrenaline**)

Muscarinic Actions

(In all peripheral organs innervated by postganglionic parasympathetic fibers)

Excitatory "1,3,5" or Inhibitory "2,4"

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

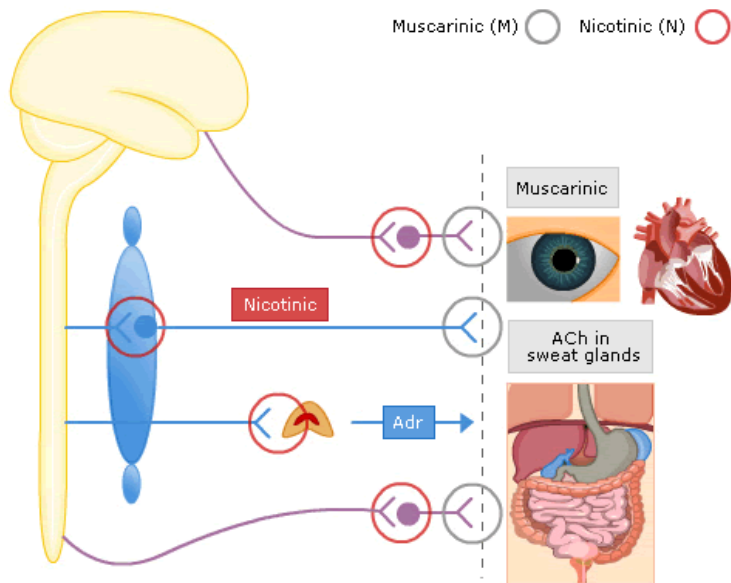
- Increase in motility (peristalsis)
- Increase in secretion
- Relaxation of sphincter defecation M3

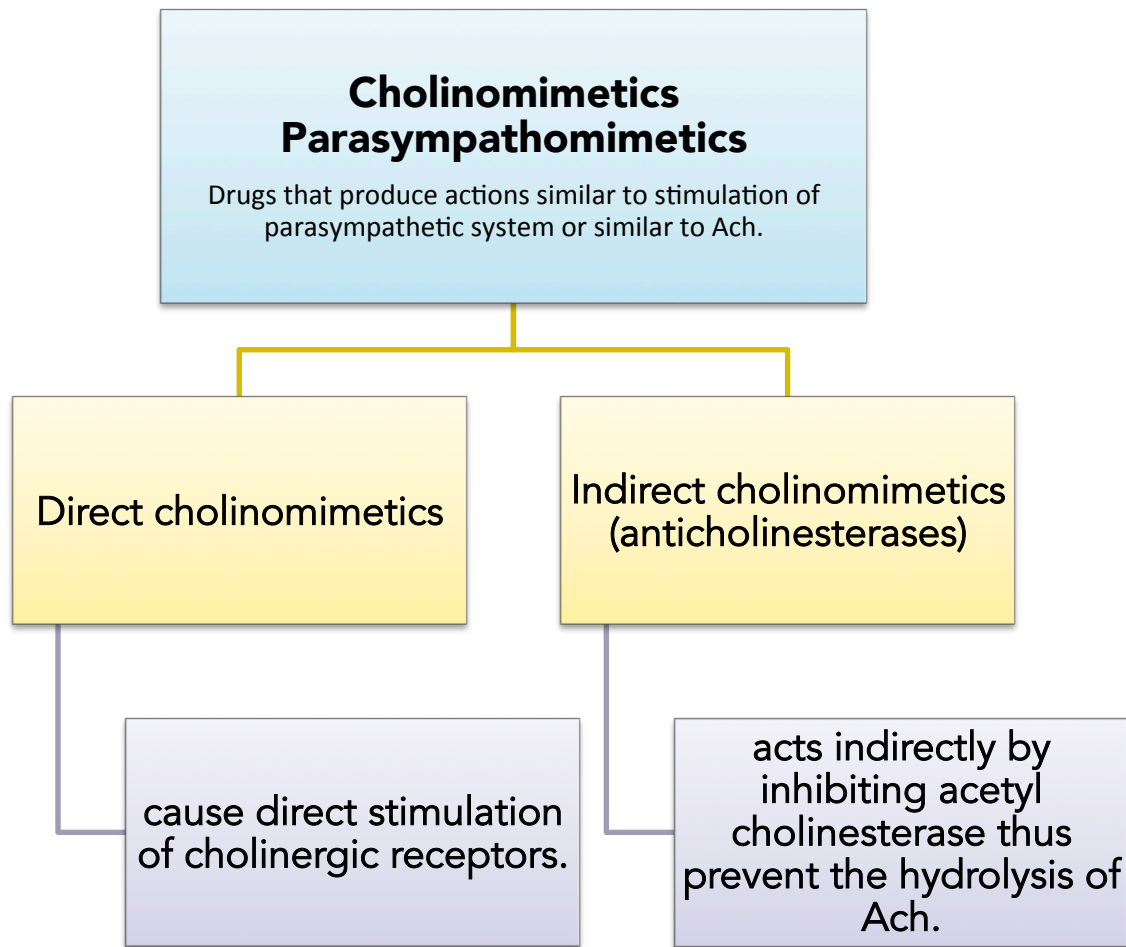
Urinary Bladder

- Contraction of muscles
- Relaxation of sphincter M3
- Urination

Exocrine glands

- Increase of secretions of exocrine glands, sweat, saliva, lacrimal, bronchial, intestinal secretions M3





Contraindications of direct cholinomimetics

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

Direct cholinomimetics

Drug	Acetylcholine	Carbachol	Bethanechol	Pilocarpine	Cevimeline
Receptors	(Muscarinic, Nicotinic)		Muscarinic		
Clinical Uses	Not used clinically because Ach is not selective as it acts on both nicotinic and muscarinic receptors	<ul style="list-style-type: none"> - treatment of glaucoma (given as eye drops to reduce side effects) - Urinary retention & paralytic ileus (rarely used due to its nicotinic actions) 	<ul style="list-style-type: none"> - Paralytic ileus (after abdominal surgery) - Urinary retention in cases of post-operative atony & neurogenic bladder 	<p>Xerostomia (<i>dry mouth</i>).</p> <p>Drug of choice in emergency glaucoma <i>applied as eye drops</i>.</p>	Used for treatment of dry mouth symptom associated with Sjogren's syndrome (autoimmune disease characterized by decreased salivation)
Chemistry		<ul style="list-style-type: none"> □ Synthetic choline esters. □ Quaternary ammonium compounds contain N⁺ (polar) 		natural alkaloids	-
Pharmacokinetics	Has a short duration of action due to rapid metabolism by acetylcholine esterase	<p>Longer duration of action</p> <ul style="list-style-type: none"> □ 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. 		<ul style="list-style-type: none"> • well absorbed, good distribution • Cross BBB (has central effects). • Not metabolized by cholinesterase • Long duration of action 	-
Side effects	-	Has nicotinic actions similar to Ach (side effects)	-	Profuse sweating, Salivation, Bronchoconstriction, Diarrhea, CNS effects	-
Selectivity	-	Muscarinic actions on Eye, GIT, UT.	Prominent muscarinic actions on GIT, UT.	Direct muscarinic agonist (mainly on eye & secretion).	-

Any drug ends with the suffix (-ine) means that it comes from a natural source (Morphine, Cevimeline)

★ Summary

Cholinomimetics –Parasympathomimetics- (Direct Cholinemimetics)

Drug	Acetylcholine	Carbachol	Bethanechol	Pilocarpine	Cevimeline
Chemistry	Polar Quaternary			Non-Polar Tertiary Amine	
Absorption	×	Better Absorbed than Ach	Better Absorbed than Ach	Well absorbed, good distribution	
Metabolism by cholinesterase	✓	×			
Duration	Short	Longer than Ach		Long	
Administration	I.V Eye Drops	S.C Oral, Eye Drops	S.C Oral	Oral, Eye Drops	
Receptors	Nicotinic + Muscarinic		Muscarinic		
Selectivity	×	Eye, GIT, UT	GIT, UT	Eye, Exocrine Glands	Exocrine Glands
Uses	×	Treatment of Glaucoma (Mainly)	Treatment of Paralytic ileus and urinary retention	Xerostomia Emergency Glaucoma	Sjogren's syndrome

★ MCQs

1. Which is not true about Nicotinic receptors?

- A) Located in Adrenal Medulla
- B) Ion channel linked receptors
- C) Peripheral receptors
- D) Located in Autonomic ganglia

2. Which Muscarinic receptor subclass is inhibitory in function?

- A) M1
- B) M2
- C) M3
- D) M5

3. M2 provides which of the following pharmacological actions?

- A) Vasodilatation
- B) Analgesia
- C) Bradycardia
- D) Gastric acid secretion

4. Muscarinic actions of Ach include?

- A) Peristalsis
- B) Tachycardia
- C) Dilation of bronchial smooth muscles
- D) Increase in IOP

5. Which synthetic choline ester can cross BBB?

- A) Carbachol
- B) Bethanechol
- C) Pilocarpine
- D) Cevimeline

6. Which of drug is applied as eye drops in emergency glaucoma?

- A) Carbachol
- B) Bethanechol
- C) Pilocarpine
- D) Cevimeline

Answers:
1- C
2- B
3- C
4- A
5- C
6- C

Good luck!

Done by Pharmacology team 434

Moneera Aldraihem

Maha Al-Rabiah

Amal Afrah

Ahad alsubai

Noha AlGwaiz

Nora AlHelali

Lama alwallan

Sarah Mohammad aljasser

Manal alhamdan

Sara al bqami

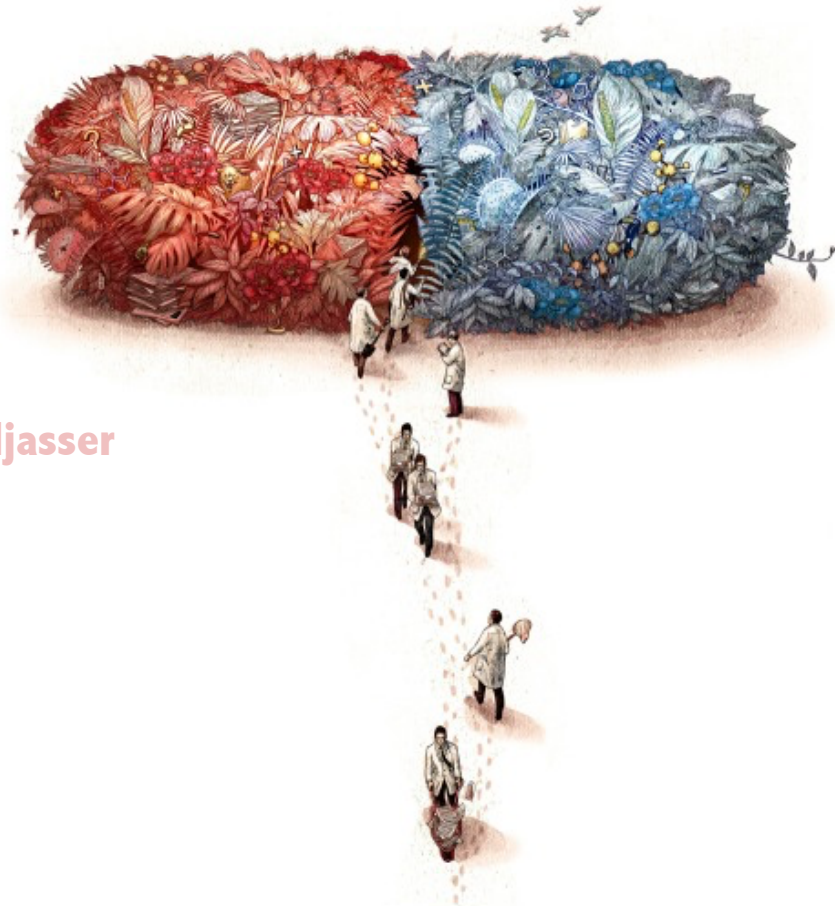
Rasha bassas

Lamyaa Althawadi

Dhahera aljohani

Sara alsalman

Razan alsubhi



For any correction, suggestion or any useful information do not
hesitate to contact us: Pharmacology434@gmail.com