



King Saud University  
College of Medicine  
1<sup>st</sup> Year, 2<sup>nd</sup> Block

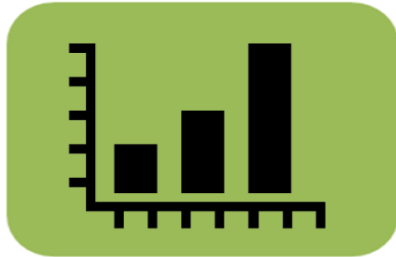
# Direct Acting Cholinergic Drugs 3



MUSCULOSKELETAL BLOCK



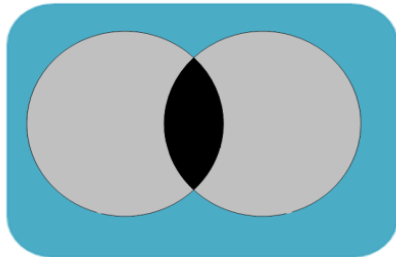
Classification of nervous system & Classify cholinomimetic drugs.



Describe the various steps in cholinergic transmission.



Mention the different types, locations and actions of cholinergic receptors.



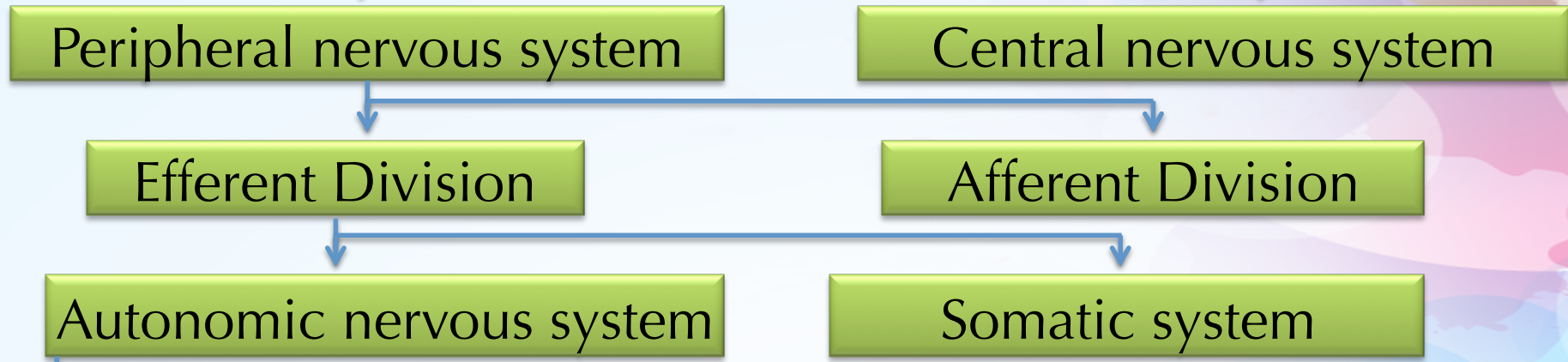
Describe the effects of acetylcholine on major organs



Describe the kinetics, actions and uses of direct acting cholinomimetic drugs.

# OBJECTIVES

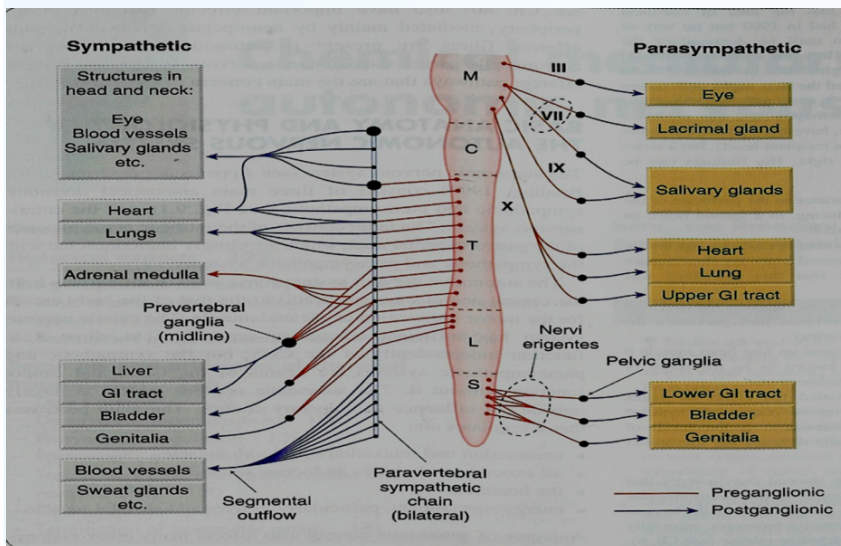
# Nervous System



The differences between the somatic and the autonomic N.S

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

**Parasympathetic Nervous System  
Is a craniosacral outflow**





# Neurotransmitters

Neurotransmitter in parasympathetic nervous system or cholinergic system is acetylcholine and nerves are called cholinergic nerves

## Cholinergic transmission

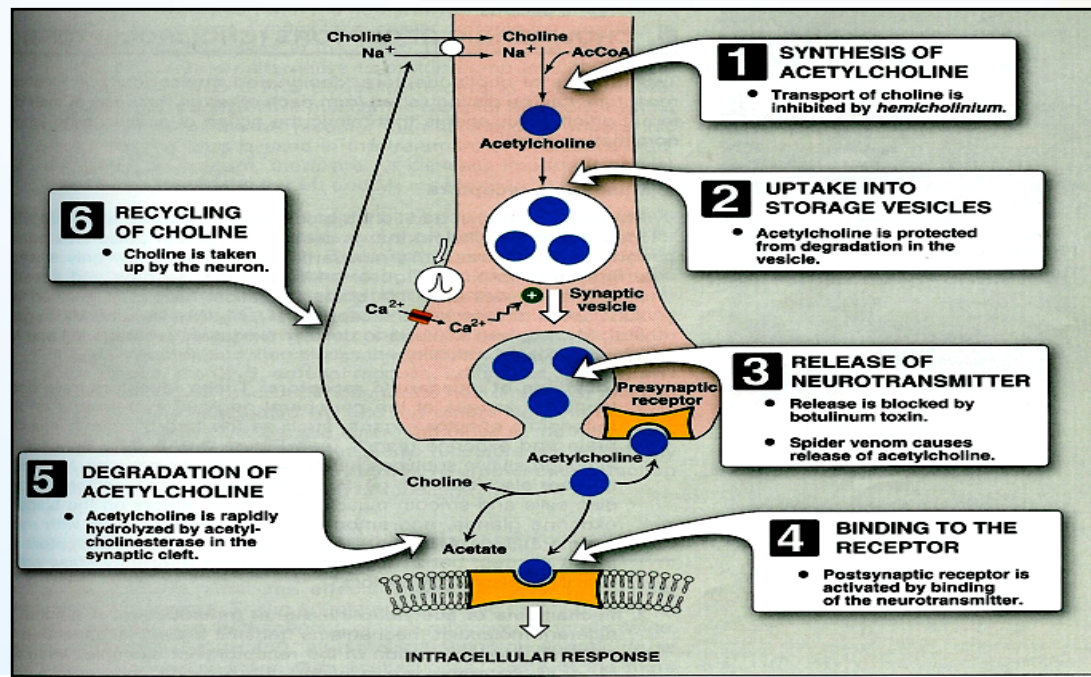
The release of neurotransmitter Ach from cholinergic nerves include the following steps:

- Synthesis of Ach.
- Storage of Ach in storage vesicles.
- Release of Ach.

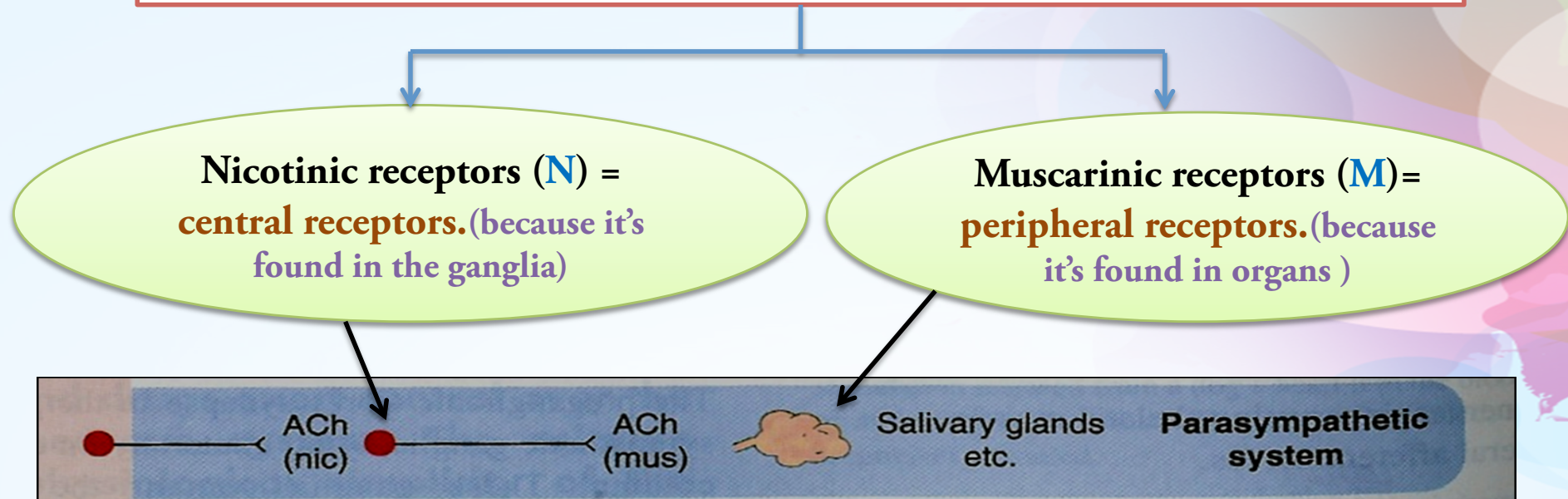
- \* Binding of Ach to postsynaptic receptors to give action.
- \* Metabolism by **acetyl cholinesterase** in synaptic cleft to give choline and acetate.



- \* Recycling of choline.



# Cholinergic or parasympathetic receptors



## Nicotinic receptors:

- \*Type I receptors : **ion channel linked receptors.**
- \***Almost excitatory**
- \***Located in:**
  - Skeletal muscles (neuromuscular junction) → **contraction.**
  - Autonomic ganglia (sympathetic and parasympathetic ganglia) → **stimulation.**
  - Adrenal medulla → **release of catecholamines (Adrenaline & Noradrenaline).**
  - CNS (Nn).

## Muscarinic receptors:

- \*Type II receptors : **G-protein linked receptors**
- \***Five subclasses** : M1, M2, M3, M4 and M5
- \***M1, M3, M5** are **excitatory** or **stimulatory** in function → stimulation. (that's why it's found in muscles and glands)
- \***M2, M4** are inhibitory in function → inhibition. (If these receptors stimulated in the heart it causes decrease heart rate)
- \*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 (Neural)  Excitatory	CNS Autonomic ganglia gastric parietal cells	CNS excitation Gastric acid secretion Activation of phospholipase C $\uparrow$ IP3 & DAG $\rightarrow$ $\uparrow$ Ca
M2 (Cardiac)  Inhibitory	Heart Presynaptic cholinergic fibers	Cardiac inhibition (Bradycardia) Presynaptic inhibition • Inhibition of adenyl cyclase ( $\downarrow$ cAMP) • Opening of K channels
M3 (Glandular)  Excitatory	Exocrine glands Smooth muscles Vascular endothelium	• Secretion of glands • Smooth muscle contraction • Vasodilatation (via nitric oxide) • Activation of phospholipase C $\uparrow$ IP3 & DAG.
M4 & M5	CNS	memory, arousal, attention and analgesia

## Nicotinic actions of Ach

\*Skeletal muscles :

-Low conc. of Ach  $\rightarrow$  muscle contraction.

-High conc. of Ach  $\rightarrow$  persistent depolarization & excessive relaxation that leads to paralysis.

\*Stimulation of Autonomic ganglia : stimulation of sympathetic & parasympathetic ganglia.

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

# Muscarinic actions

Organs	Cholinergic actions
Eye	<p>Contraction of circular muscle of iris (<b>miosis</b>) → all drugs can produce this action leading to decrease in the intraocular pressure (<b>M3</b>)</p> <p>Contraction of ciliary muscles for near vision (<b>M3</b>)</p> <p>Decrease in intraocular pressure (IOP)</p>
Heart endothelium	<p>bradycardia (decrease in heart rate ) (<b>M2</b>) because it's an inhibitory action</p> <p>Release of nitric oxide (EDRF)</p>
Lung	<p>Constriction of bronchial smooth muscles</p> <p>Increase bronchial secretion <b>M3</b></p>
GIT	<p>Increase in motility (peristalsis)</p> <p>Increase in secretion</p> <p>Relaxation of sphincter (defecation ) <b>M3</b></p>
Urinary bladder	<p>Contraction of muscles</p> <p>Relaxation of sphincter <b>M3</b></p> <p>Urination</p>
Exocrine glands	<p>Increase of secretions : sweat, saliva, lacrimal, bronchial, intestinal secretions</p> <p><b>M3</b></p>



## Cholinomimetics (Parasympathomimetics) :

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

### Type of cholinomimetics

#### DIRECT CHOLINOMIMETICS:

cause direct stimulation of cholinergic receptors

#### INDIRECT CHOLINOMIMETICS:

Increase action of Ach indirectly by inhibiting acetylcholinesterase thus prevent the degradation of Ach.

#### DIRECT CHOLINOMIMETICS

##### 1) Synthetic cholinesters (Quaternary)

- ✓ Aetylcholine (M,N)
- ✓ Carbachol (M,N)
- ✓ Bethanechol (M)
- ✓ Cevimeline (M)

##### 2) Natural alkalioids (Tertiary)

- ✓ Pilocarpine

#### FEATURES OF GOOD DIRECTLY ACTING CHOLINERGIC DRUGS:

Since Ach is not specific and easily destroyed by cholinesterase, thus it is very essential to obtain cholinergic drug that has **low nicotinic activity, high muscarinic selectivity** BUT with **low susceptibility to cholinesterase**



## ACETYLCHOLINE (ACH)

Muscarinic and nicotinic agonist

Not used clinically because Ach:

- Is not selective (N,M)
- Has short duration of action, Due to rapid metabolism by acetylcholinesterase

**\*Only Ach is metabolized by cholinesterase**

## Synthetic cholineesters

e.g. Bethanechol, carbachol

F  
E  
A  
T  
U  
R  
E  
S

Quaternary ammonium compounds contain N<sup>+</sup>  
(polar)

Not metabolized by cholinesterase

can not cross BBB  
(No CNS effects)

Poor distribution

Only Given S.C  
(subcutaneously)

longer duration of action than Ach

	Ach	Carbachol	Bethanechol*	Pilocarpine*
Chemistry	Quaternary Polar	Quaternary Polar	Quaternary Polar	Natural alkaloids Tertiary amine <b>lipophilic</b> Non polar ( <b>Cross BBB</b> ) has central effect & not metabolized by cholinesterase
Administeration	Eye drops, I.V.	Oral, Eye drops, S.C.	Oral, S.C.	Oral, Eye drops
Absorption	NOT	better absorbed than Ach	better absorbed than Ach	Complete (Good distribution)
Duration	<b>Very short</b>	Longer	Longer	Longer
Receptors	Muscarinic Nicotinic	Nicotinic Muscarinic on ( Eye, GIT, U.T)	Muscarinic On (GIT, UT)	Direct Muscarinic On ( Eye, secretion)
Uses	No	- <u>Glaucoma</u> - Urinary retention, Paralytic ileus ( rarely used due to its nicotinic action )	Urinary retention (in <b>cases of post- operative atony**</b> , <b>neurogenic bladder</b> ), Paralytic ileus	Xerostomia جفاف الفم Drug of choice in emergency glaucoma <b>Adverse effects:</b> Profuse sweating Salivation Bronchoconstriction Diarrhea CNS effects

\*knowing the difference between these two drugs is so important

**\*\*Atony:** a muscle that has lost its strength

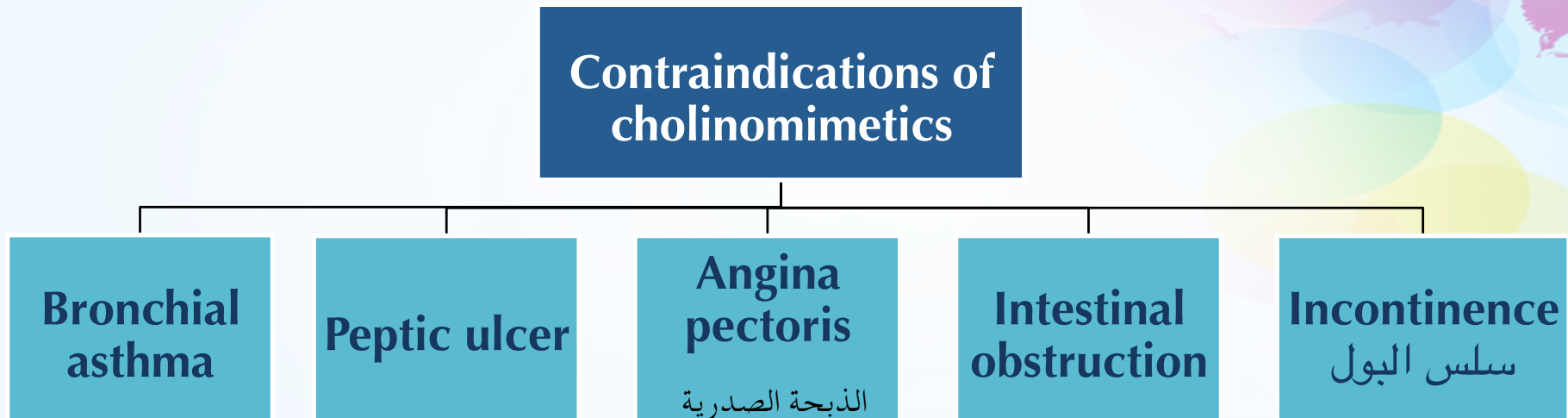
# Cevimeline

-Direct acting muscarinic agonist

-At glandular M3

-Used orally for treatment of dry mouth symptom associated with Sjogren's syndrome.

\*Sjogren's syndrome is a systemic autoimmune disease in which immune cells attack & destroy the exocrine glands that produce tears and saliva



\*To understand how it is contraindicated see the muscarinic and nicotinic action tables

# Summary

- Parasympathetic Nervous System **Is a craniosacral outflow.**



- Only **Ach** is metabolized by cholinesterase.

❖ **Cevimeline (Direct act):** treatment of dry mouth (**Sjogren's syndrome**)

Nicotinic receptors		Muscarinic receptors	Cholinomimetics	
ion channel		G-protein	Ach	not used
excitatory		Excitatory (M1,3,5) inhibitory (M2,4)	Carbachol	<u>Glaucoma</u>
General: Skeletal muscles ..etc		Specific: Heart, eye ..etc	Bethanechol <small>(post-operative atony)</small>	Urinary retention
			Pilocarpine	Xerostomia



# M.C.Q.s

1- Which one of the following is not a feature of nicotinic receptors:

- A- Ion channel linked receptors
- B- Almost excitatory
- C- G protein linked receptors
- D- centrally located.

2- ACH is rapidly degraded by:

- A- Amidase
- B- Lipase .
- C- Cholinesterase.
- D- Esterase.

3- which of the following is an inhibitory receptor:

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

4- High concentration of ACH in the skeletal muscles leads to :

- A- Repolarization.
- B- Paralysis.
- C- Muscle contraction.
- D- reverse RMP.

5- Which one of the following is considered as a muscarinic action o the heart:

- A- Tachycardia.
- B- Bradycardia.
- C- release of NO.
- D- B and C

5-D  
3-B 4-B  
1-C 2-C

# M.C.Q.s

6- Indirect cholinomimetics increases the action of ACH by:

- A- Activating ACH esterase
- B- Inhibiting ACH esterase
- C- Releasing of Na
- D- stimulate cholinergic receptors

7- Which one of the following drugs is non-polar

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

8- Which of the following drugs has no nicotinic action :

- A- Bethanechol
- B- ACh
- C- Carbachol
- D- All of them

9- Muscarinic receptors (M3) are found in

- A- CNS
- B- Endothelium
- C- Gastric cells
- D- Nerves

10- Which one of the following is the pharmacological action of M2:

- A- Open Na channels
- B- Open Na-K pump
- C- Open K channels
- D- None of them

	10-C
9-B	8-A
7-D	6-B



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**We hope that we made this lecture easier for you  
Good Luck !**