



- Red : important
- Black : in male / female slides
- Pink : in female's slides only
- Blue : in male's slides only
- Green : Dr's notes
- Grey: Extra information, explanation

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# LECTURE 3: DIRECT ACTING CHOLINERGIC DRUGS

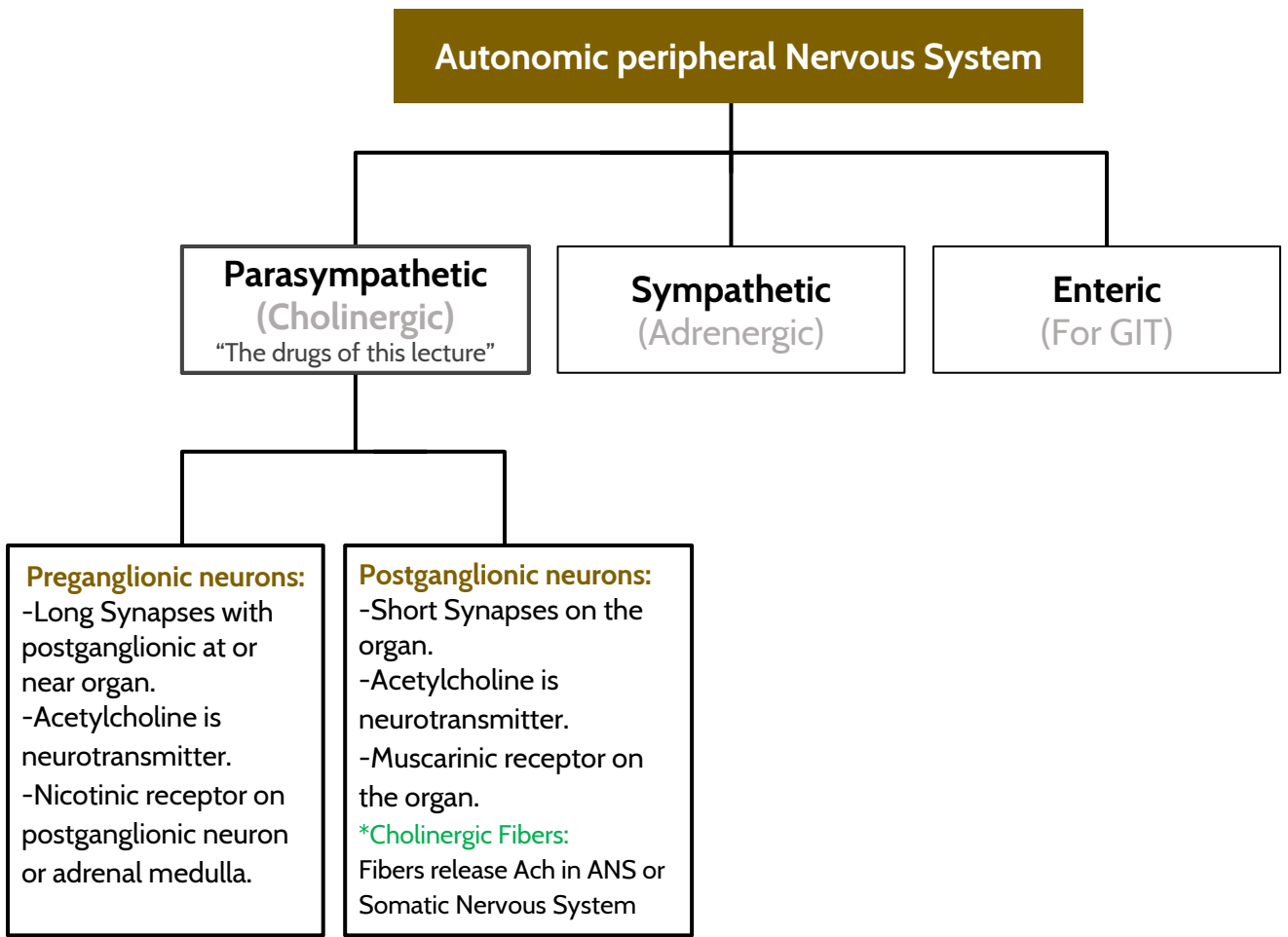
# OBJECTIVES:

By the end of this lecture students should be able to:

- ✓ Mention 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

**this slide is just for good understanding  
Nervous System:**

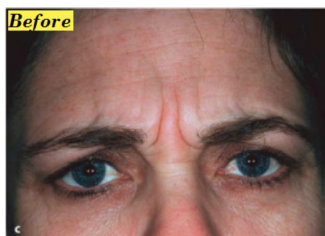
Central Nervous System	peripheral Nervous System	
<ul style="list-style-type: none"> <li>Brain</li> <li>Spinal cord</li> </ul>	<ul style="list-style-type: none"> <li>Afferent (Sensory)</li> </ul>	<ul style="list-style-type: none"> <li><b>Efferent (Motor):</b> Somatic; skeletal muscles Autonomic; Smooth muscles: Sympathetic Parasympathetic Enteric</li> </ul>



\* ANS: Autonomic Nervous System

**Found in Male's slides only**

Botox is Botulinum toxin that's produced by clostridium botulinum.



# Cholinomimetics

<b>M.O.A</b>	Drugs that produce actions similar to stimulation of parasympathetic system or similar to Acetylcholine.	
<b>Class</b>	<b>Direct Cholinomimetics</b>	<b>Indirect Cholinomimetics</b>
<b>Action</b>	Cause direct stimulation of cholinergic receptors. Each receptor will give different effect depending on the receptor and the drug/neurotransmitter.	Acts indirectly by inhibiting <b>Acetyl cholinesterase</b> thus preventing the hydrolysis of Ach. They are called <b>Cholinesterase inhibitors or anticholinesterases</b>
<b>Site of Action</b>	Cholinergic drugs act upon two types of receptors: <ul style="list-style-type: none"> <li>Nicotinic receptors</li> <li>Muscarinic receptors</li> </ul>	

## Cholinergic or Parasympathetic receptors

Nicotinic receptors (N) "Central Receptors"	Muscarinic receptors (M) "Peripheral Receptors"
<p><b>Type I receptors:</b> *when stimulation happens, channels open.  <b>Ion channel linked receptors</b> (Ligand gated ion channels)  <b>Located in:</b></p> <ul style="list-style-type: none"> <li>Skeletal muscles (Neuromuscular junction) (Nm)</li> <li>Autonomic ganglia (Sympathetic and parasympathetic ganglia) (Nn)</li> <li>Adrenal Medulla (Nn)</li> <li>CNS (Nn)</li> </ul> <p><b>Subclasses:</b></p> <ul style="list-style-type: none"> <li><b>Nm:</b> A class of nicotinic receptors found in skeletal muscles.</li> <li><b>Nn:</b> A class of nicotinic receptors found in autonomic ganglia (sympathetic and parasympathetic), CNS, and adrenal medulla.                      Nn → nerve to nerve    Nm → Nerve to muscle</li> </ul>	<p><b>Type II receptors:</b>                      G-protein linked receptors  <b>Located at:</b></p> <ul style="list-style-type: none"> <li>All target organs that are innervated by parasympathetic fibers (Heart, CVS, Eye, Bladder, etc). <b>Internal organs except ventricles</b></li> </ul> <p><b>Subclasses:</b></p> <ul style="list-style-type: none"> <li><b>M1, M3, M5</b> are excitatory or stimulatory in function. الأعداد الفردية</li> <li><b>M2, M4</b> are inhibitory in function. الأعداد الزوجية</li> </ul>

## Nicotinic Receptors VS Muscarinic

Nicotinic receptors "Central cholinceptors"	Muscarinic receptors "Peripheral cholinceptors"
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)

## Direct Acting cholinergic drugs:

Pharmacological Action

Actions that are similar to the effects of parasympathetic system activation. And are classified according to the type of receptor acting on into

### Nicotinic Action

### Muscarinic Action

Skeletal muscle

- . **Low concentration (Therapeutic dose) of Nicotine :**  
Muscle Contraction
- . **High concentration (Toxic dose) of Nicotine:**  
Persistent depolarization and relaxation (Blocking of depolarization). Constant contraction of muscle means there is no repolarization which is essential for muscle relaxation leading to muscle paralysis. Succinylcholine has similar effect.

Eye (M3)

- \*Contraction of circular muscle of iris (also called iris sphincter muscle or constrictor pupillae)(**miosis**)
- \*Contraction of ciliary muscles for near vision  
When these 2 contractions happen , a decrease in intraocular pressure happens. (IOP) **So we use drugs that have muscarinic actions to treat glaucoma.**

Heart endothelium

- Bradycardia (decrease in heart rate) **M2**
- Release of Nitric oxide(NO) (EDRF) which causes Vasodilation **M3**

Lung (M3)

Constriction of bronchial smooth muscles and increase bronchial secretion. **Contraindication: Asthma**

Autonomic ganglia

By stimulating it. This happens by both sympathetic and parasympathetic stimulation.  
Secretion of Neurotransmitters

GIT

- Increase in motility(peristalsis) **over stimulation leads to diarrhea.**
- Gastric acid secretion **M1**
- Relaxation of sphincter causing defecation **M3**

Smooth muscles (M3)

**Urinary bladder:**  
Contraction of muscles  
Relaxation of sphincter leading to urination.  
**Smooth muscle:**  
Contraction. **Uterus is not sensitive to muscarinic agonists**

Adrenal medulla

release of Catecholamine (Adrenaline and Noradrenaline). Over stimulation leads Adrenergic crisis

Exocrine glands (M3)

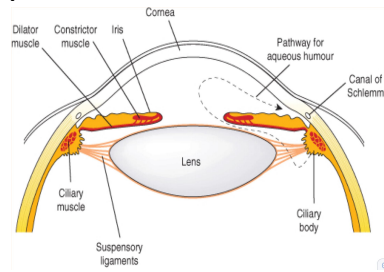
Increase in exocrine glands secretions (exocrine glands are glands that secretes through ducts) which are:  
Sweat, Saliva, Lacrimal, Bronchial, intestinal secretion.

CNS

- CNS excitation **M1**
- Memory, arousal, attention and analgesia **M4+M5**

## Parasympathetic Actions on Eye

- It innervates the **constrictor pupillae** (circular muscle of iris) which is important for adjusting the pupil in response to change in light intensity and regulating the intraocular pressure.
- Aqueous humor secreted by ciliary body is removed continuously by drainage into the **canal of schlemm**.
- Normal intraocular pressure: 10-15 mmHg above atmospheric pressure. Abnormal raised pressure (glaucoma) leads to **retinal detachment**.
- **Cholinergic drugs** leads to Miosis which **decreases** the intraocular pressure in glaucoma by **increasing the filtration angle**.
- When the ciliary muscle contracts, the lens **bulges** more. This parasympathetic reflex is essential to accommodate for near vision.



if the ciliary body is contracted the canal of schlemm will open allowing the drainage of fluid  
 Ciliary muscle is contracted  
 Suspensory ligament is relaxed.  
 (Opposite action)

### Direct Acting Cholinergic Drugs

Drug Type	Natural Alkaloids	Synthetic Choline Esters
Features	<ul style="list-style-type: none"> <li>● Are lipid soluble nitrogen nonpolar compound found in nature</li> <li>● Tertiary amines</li> <li>● Common suffix (-ine) which means natural and basic</li> </ul>	<ul style="list-style-type: none"> <li>● Polar (contains N ion) quaternary ammonium compounds</li> <li>● muscarinic quaternary amine less completely absorbed from the GIT but still toxic when ingested in mushroom.</li> </ul>
Examples	<ul style="list-style-type: none"> <li>● Pilocarpine</li> <li>● Nicotine</li> <li>● Lobeline</li> </ul> <p>Nicotine &amp; lobeline has an alerting action on the CNS and high levels of nicotine leads to convulsions and coma</p>	<ul style="list-style-type: none"> <li>● Acetylcholine</li> <li>● Carbachol</li> <li>● Bethanechol</li> <li>● Cevimeline</li> <li>● Methacholine 3X more resistant to hydrolysis</li> </ul> <p><b>Mnemonic:</b>  <b>A</b>lways <b>C</b>are <b>B</b>efore <b>C</b>alling</p>
Pharmacokinetics	<ul style="list-style-type: none"> <li>● Non-polar, lipid soluble</li> <li>● Well absorbed by the skin.</li> </ul>	<ul style="list-style-type: none"> <li>● Poor distribution</li> <li>● Cannot cross BBB so <b>no CNS effects</b></li> <li>● <b>Not metabolized by cholinesterase EXCEPT Ach</b></li> <li>● all of them have longer duration of action than Ach</li> <li>● Never given I.V. or I.M. BUT S.C.</li> </ul>
Contra-indications	<ul style="list-style-type: none"> <li>● <b>Bronchial asthma</b> (because asthmatics are already hyperresponsive to cholinergic agonist, giving cholinergic drugs may cause unwanted bronchoconstriction which leads to increased narrowing of airways).</li> <li>● <b>Peptic ulcer</b> (M1 muscarinic agonists can stimulate gastric acid secretion from gastric parietal cells, thus intensifying the acidity and ulceration)</li> <li>● <b>Angina pectoris</b> (Chest pain, mostly related to a coronary artery disease, muscarinic receptors are found on the SA node of the heart and slows heart rate when activated which can decrease the heart flow further than it already is)</li> <li>● <b>Urinary incontinence</b> (inability to hold in urine, spontaneous urination)</li> <li>● <b>Intestinal obstruction</b> (the treatment for intestinal obstruction is providing rest for its activities, muscarinic agonist increase its GIT motility and irritate the GIT even more in this case)</li> </ul>	

## Natural Alkaloids

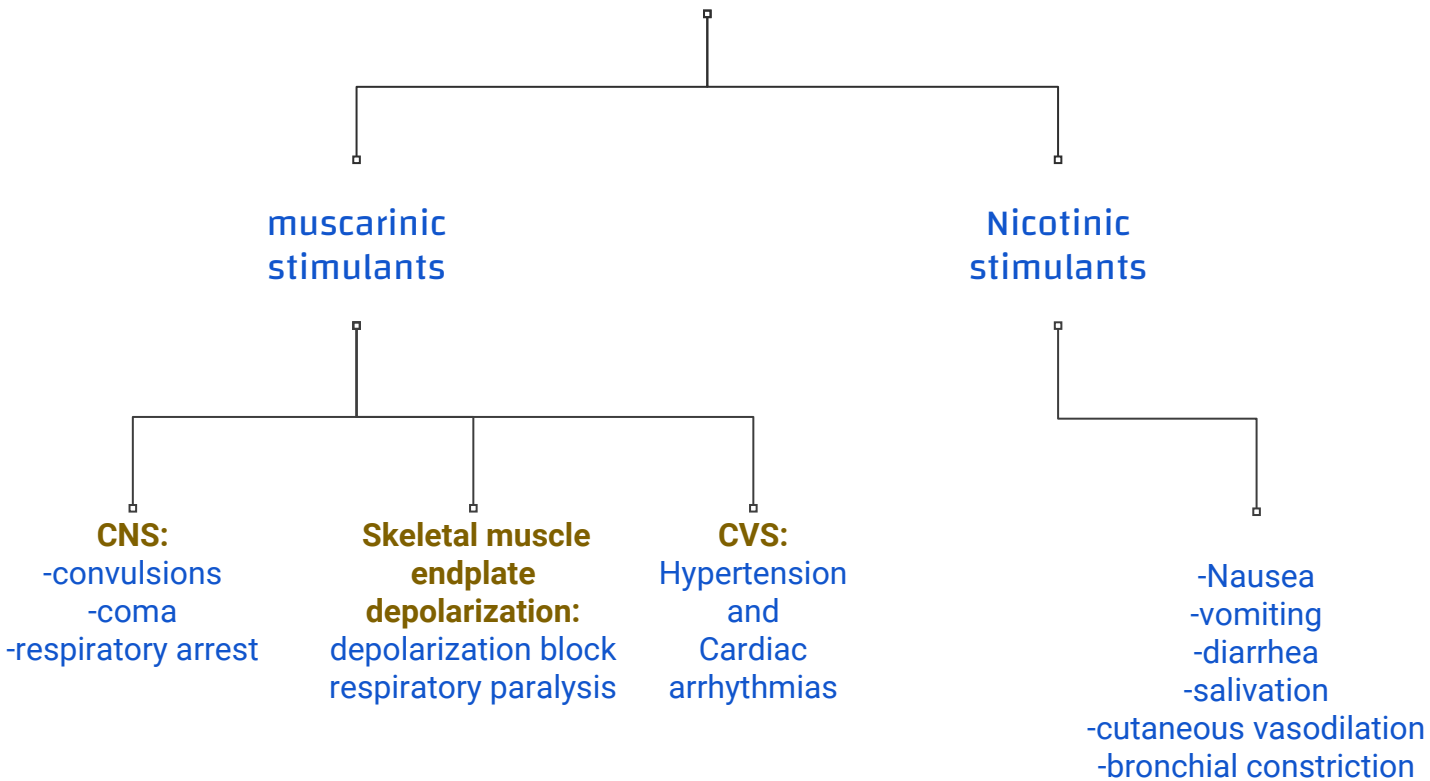
Drug	<b>Pilocarpine</b>	
M.O.A	<ul style="list-style-type: none"> <li>● <b>Direct muscarinic agonist</b></li> <li>● Acts mainly on eye and secretion</li> </ul>	
P.K	<ul style="list-style-type: none"> <li>● <b>Non-polar (lipophilic)</b> tertiary amine</li> <li>● Well absorbed, good distribution</li> <li>● Cross BBB, so has CNS effects</li> <li>● Cross placenta</li> <li>● <b>Not metabolized by cholinesterase</b></li> <li>● Long duration of action</li> <li>● Excretion is <b>enhanced</b> by acidification of urine</li> </ul> <div style="text-align: right; color: #ccc; font-size: small;">because basic drugs are best excreted in acidic medium</div>	
Uses	<ul style="list-style-type: none"> <li>● <b>Xerostomia (dry mouth)</b></li> <li>● <b>Drug of choice in emergency glaucoma (applied as eye drops)</b></li> </ul>	
Side Effects	<ul style="list-style-type: none"> <li>● Profuse sweating</li> <li>● Salivation</li> <li>● Bronchoconstriction</li> <li>● Diarrhea</li> <li>● CNS effects</li> </ul>	

## Synthetic Choline Esters

Drug	Acetylcholine	Carbachol (Carbamoylcholine)	Bethanechol (Carbamoyl-β-methylcholine)	Cevimeline
M.O.A	Muscarinic and nicotinic agonist	-Muscarinic action on the eyes, GIT, UT. -Has nicotinic actions (side effects)	- Prominent muscarinic actions on GI, UT. - No nicotinic actions <span style="color: #0070c0; font-size: small;">due to the presence of a methyl group which reduces its potency at nicotinic junctions.</span>	Direct acting muscarinic agonist (M3)
P.K	-	-Resistant to hydrolysis by acetylcholinesterase -Longer duration than Ach	-Resistant to hydrolysis by acetylcholinesterase -Longer duration than Acetylcholine	-
Uses	<b>Not used clinically. (Why?)</b> -not as selective as it acts on both muscarinic and nicotinic receptors. -Has short duration of action. <b>Why?</b> Due to rapid metabolism by <span style="color: #c00000;">acetylcholinesterase</span>	-Treatment of glaucoma as eye drops only	<span style="color: #008000;">Drug of choice in:</span> -Paralytic ileus <span style="font-size: small; color: #008000;">it's a post-operative side effect of the anesthesia</span> -Urinary retention in case of postoperative atony and neurogenic bladder.	treatment of the dry mouth symptom associated with Sjogren's syndrome <b>Sjogren's syndrome:</b> autoimmune disease characterized by formation of antibodies leading to dryness of mouth (xerostomia) and eye.
Side effects	-	Nicotinic side effects	-	-

Found in Male's slides only

## TOXICITY



## TREATMENT:

- Muscarinic excess → atropine
- CNS stimulation → central anticonvulsants e.g. Diazepam
- Neuromuscular block → mechanical respiration



## Chronic Nicotine toxicity:

- 30% of deaths due to cancer and coronary heart disease are due to smoking.
- Nicotine contributes to ↑ risk of vascular diseases, sudden coronary death and ulcers.





## Summary

Drug	Acetylcholine	Carbachol (Carbamoylcholine)	Bethanechol (Carbamoyl- $\beta$ -methylcholine)	Pilocarpine
chemistry	quaternary Polar	quaternary Polar	quaternary Polar	tertiary non Polar
absorption	NOT	better absorbed than Ach		complete
metabolism	metabolised by cholinesterase	Not metabolised by cholinesterase		
duration	very short	longer (++)		
administration	I.V eye drops	oral, eye drops S.C	oral, S.C	oral, eye drops

## direct Cholinomimetic

Drug	Acetylcholine	Carbachol	Bethanechol	Pilocarpine	Cevimeline
receptors	muscarinic nicotinic	muscarinic nicotinic	muscarinic	muscarinic	muscarinic
muscarinic	+++				
selectivity	NOT	eyes, GIT, urinary bladder	GIT, urinary bladder	more on eyes, exocrine glands	exocrine glands
nicotinic	+++		NO		
uses	NO	Glaucoma	paralytic ileus, urinary retention	Glaucoma xerostomia	sjogren's syndrome

# QUIZ

## Quiz (MCQ) :

Q1. Which one of these is an G-protein linked receptors ?

A) Type I receptors    B) Type II receptors    C) Type III receptors

Q2. The Nicotinic action of low concentration of nicotine in the skeletal muscle?

A) Blocking of depolarization    B) Muscle Relaxation    C) Muscle Contraction

Q3. The normal ocular pressure is ?

A) 1-5 mmHg    B) 10-15 mmHg    C) 20-30 mmHg

Q4. All of these have no CNS effect except?

A) Pilocarpine    B) Bethanechol    C) Carbachol

Q5. Which one of these has the shortest duration of action ?

A) Acetylcholine    B) Carbachol    C) Bethanechol

ANSWER : 1)B - 2)C - 3)B - 4)A - 5)A

## Quiz (SAQ) :

Q1. In which receptors the Cholinergic drugs act on ?

Q2. What are the Muscarinic Actions in GIT ?

Q3. Why do the Synthetic Choline Esters drugs have longer duration of action than Ach?

4-5. A patient came to the emergency after he felt a gradual loss of his sight, after examinations the diagnosis was Glaucoma.

Q4. What is the suitable drug in this case?

Q5. What is the type of administration of this drug?

Q6. Why does the Acetylcholine drug not favor to use clinically ?

Q7. How many acetylcholine bind with ligand-gated ion (N<sup>+</sup>) channel?

Q8. What are the clinical uses of Cevimeline drug ?

9-11. A patient with urinary retention came to see a doctor. The doctor gave him a subcutaneous injection of a direct-acting cholinergic drug,

Q9. What was the drug?

Q10. Does the drug have central effect? Why?

Q11. What adverse effects would possibly happen to the patient after administering the drug?

# QUIZ

1. Nicotinic receptor - Muscarinic receptors

2. Increase in motility(peristalsis)-Increase in secretion Postsurgical  
-Relaxation of sphincter causes defecation.

3. Because they are not metabolized by Cholinesterase

4. Pilocarpine

5. eye drops

6. Is not selective as it acts on both nicotinic and muscarinic  
receptors-Has short duration of action.

7. 2 acetylcholine molecules

8. For dry mouth symptom associated with Sjogren's syndrome

9. Bethanechol

10. No, it has quaternary structure that makes it polar. Thus can't cross  
the BBB.

11. Diarrhea, Bradycardia, Sweating & Salivation, Broncho-constriction



# GOOD LUCK

## Team Leaders:

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### Sources:

Team 435

Team 437