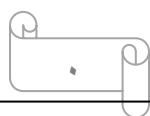


# pharmacology



By:.

Team of pharmacology





## **\*CHOLINOMIMETIC AGENTS:**

How should we study the cholinomimetic agents?

To study these agents we should understand the mechanism of Ach action and how the action is differing according to the type of the receptor it acts upon.

The Cholinomimetic agents are drug that either work by itself on the Muscarinic receptor (Direct) or they facilitate the chance for Ach to work upon both receptors (Indirect).

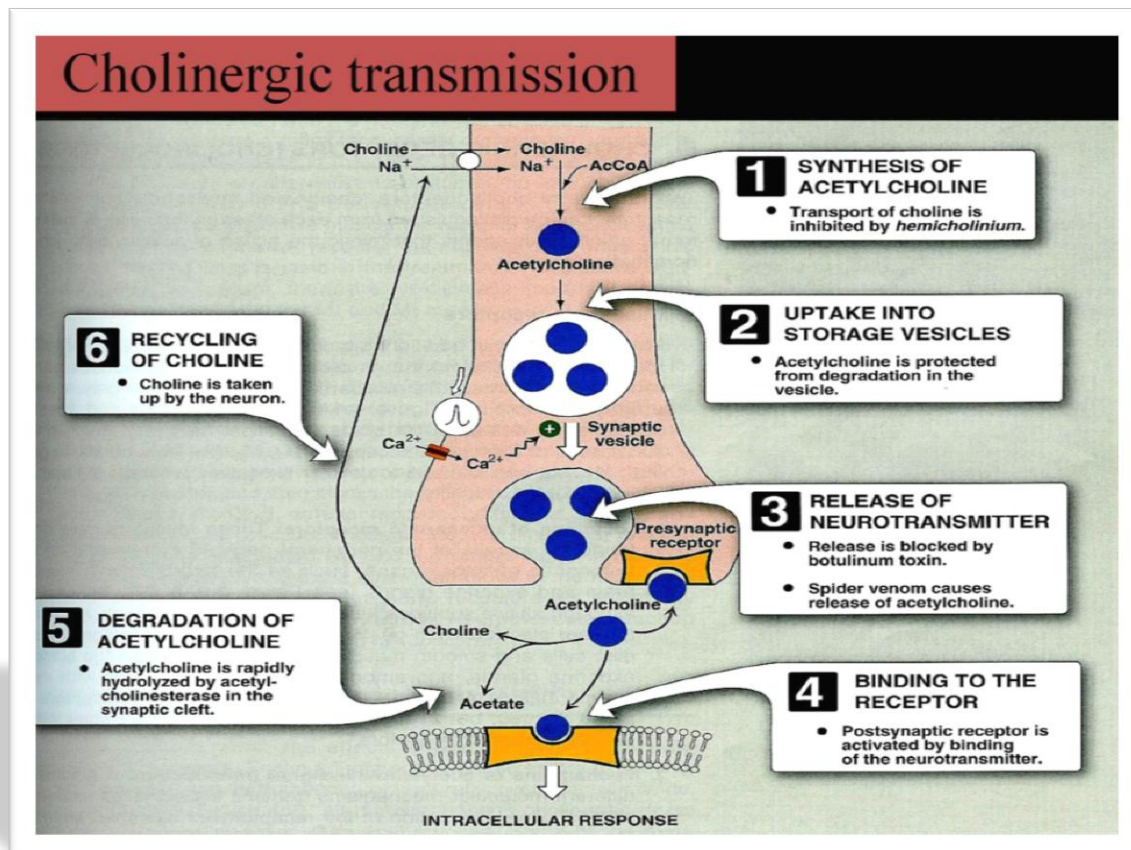
Both are doing the same action through the similarity between the direct acting and Ach or by action of Ach itself by the indirect acting.

### **\*\*\* Important note:**

1-The Direct acting drugs all are working on Muscarinic receptors by doing the same action of Ach on these receptors.

2-The Indirect acting drugs all are allowing Ach to work on both receptors (Nicotinic; Muscarinic).

## **Neurotransmitter in parasympathetic or cholinergic system is acetylcholine and nerves are cholinergic**



Cholinomimetics Parasympathomimetics

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

Direct acting **CHOLINOMIMETIC AGENTS:**

Alkaloid Family

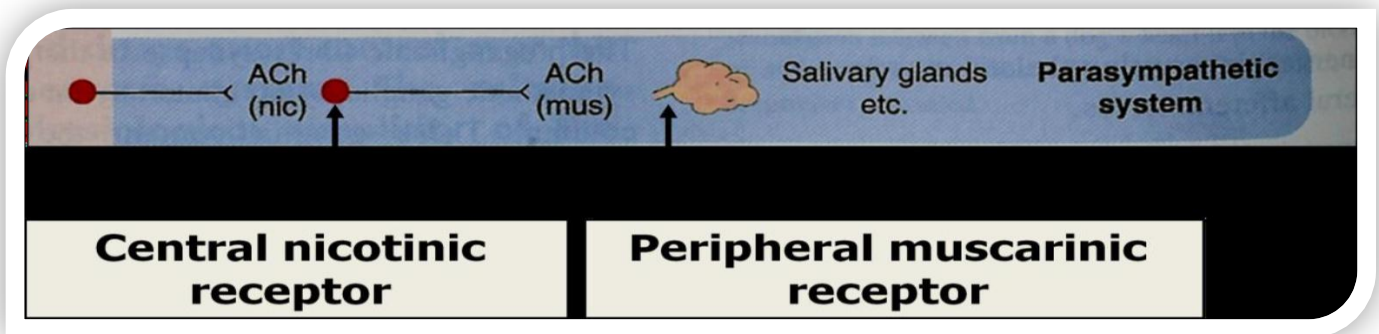
Choline ester Family

Choline ester

Alkaloid Family

### Cholinergic or parasympathetic receptors

- **Nicotinic** (N, central cholinergic ) receptors.
- **Muscarinic** (M, peripheral cholinergic) receptors.



#### ❖ **Nicotinic receptors**

*Type I receptors* : ion channel linked receptors

1. Autonomic ganglia (Nn).
2. Adrenal medulla (Nn).
3. CNS (Nn)
4. Neuromuscular junction (Nm)

#### ❖ **Muscarinic receptors**

*Type II receptors* : G-protein linked receptors

1. Five subclasses ; M1 - M5
2. M1, M3, M5 are excitatory in function (stimulation).
3. M2, M4 are inhibitory in function (inhibition).



- ✓ They are group of drugs acting on Muscarinic receptors to perform the same function of Ach but with **longer duration and more selective to muscarinic receptors.**

**\*Muscarinic Receptors:**

Muscarinic Receptors are G-Protein Coupled Receptors.

Increase Ca amount in the cell

M1 & M3 Ach receptors couple to Gq to stimulate PLC.

M2 & M4 Ach receptors couple to Gi to inhibit AC.

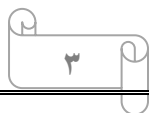
Decrease cAMP so decrease ATP so no more contracton in the ceel and opening for

Increase Ca amount in the cell

Decrease cAMP so decrease ATP so no more contracton in the ceel and opening for

**Muscarinic receptors**

<b>Receptor</b>	<b>Locations</b>	<b>Pharmacological actions</b>
<b>M1 (Neural)</b> Excitatory	<b>CNS</b> gastric parietal cells	<b>CNS excitation</b> <b>Gastric acid secretion</b>
<b>M2 (Cardiac)</b> Inhibitory	<b>Heart</b>	<b>Cardiac inhibition</b>
<b>M3</b> <b>Glandular</b> <b>Excitatory</b>	<b>Exocrine glands</b> <b>Smooth muscles</b> <b>Vascular endothelium</b>	<ul style="list-style-type: none"> <li>• Secretion of glands</li> <li>• Smooth muscle contraction</li> <li>• <b>Vasodilatation (via nitric oxide)</b></li> </ul>



**\*\* Comparison between Nicotinic (central) and Muscarinic (peripheral):**

<b>Nicotinic receptors</b> <b>Central cholinceptor</b>	<b>Muscarinic receptors</b> <b>Peripheral cholinceptor</b>
<b>Ion channel linked receptors</b>	<b>G protein linked receptors</b>
<b>Autonomic ganglia</b> <b>(sympathetic &amp; parasympathetic) stimulation</b> <b>( Nn )</b>	<b>On all peripheral organs that receive postganglionic parasympathetic fibers</b>
<b>Adrenal medulla (Nn)</b> <b>release of catecholamines</b> <b>(Adrenaline &amp; Noradrenaline)</b>	<b>Heart (M2) inhibition</b> <b>exocrine glands (M3) contraction</b>
<b>Skeletal muscle</b> <b>(Neuromuscular junction)</b> <b>(Nm) Contraction</b>	<b>Smooth muscles (GIT, urinary tract, bronchial muscles)</b> <b>(M3) contraction</b>
<b>Almost excitatory</b>	<b>Excitatory or</b>

\*\*Based on the receptor type, Acetylcholine has two main effects:

- 1) Cholinergic (cholinomimetics) action(muscarinic).
- 2) Nicotinic Action

**1-Nicotinic action:**

**Skeletal muscles:**

- Low conc. → muscle contraction
- High conc. → persistent depolarization & paralysis.  
Through continuous depolarization.

**Ganglia:** stimulation of sympathetic & parasympathetic ganglia.

**Adrenal medulla:** release of catecholamines

(Adrenaline & Nor Adrenaline).



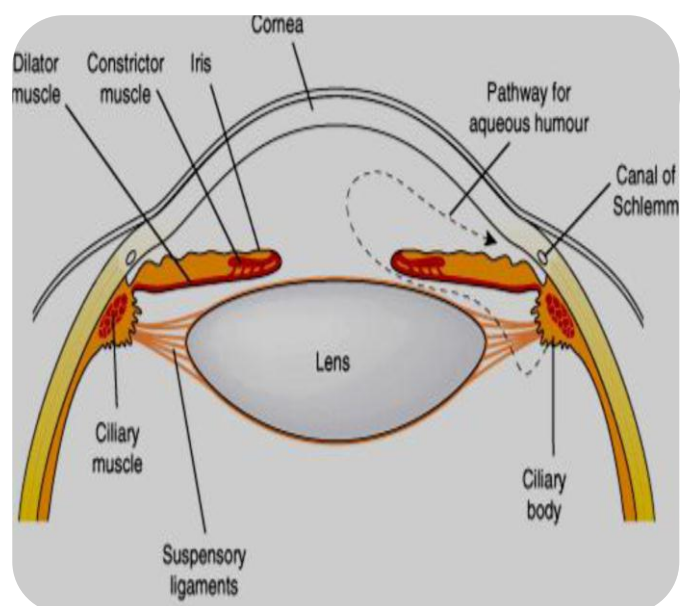
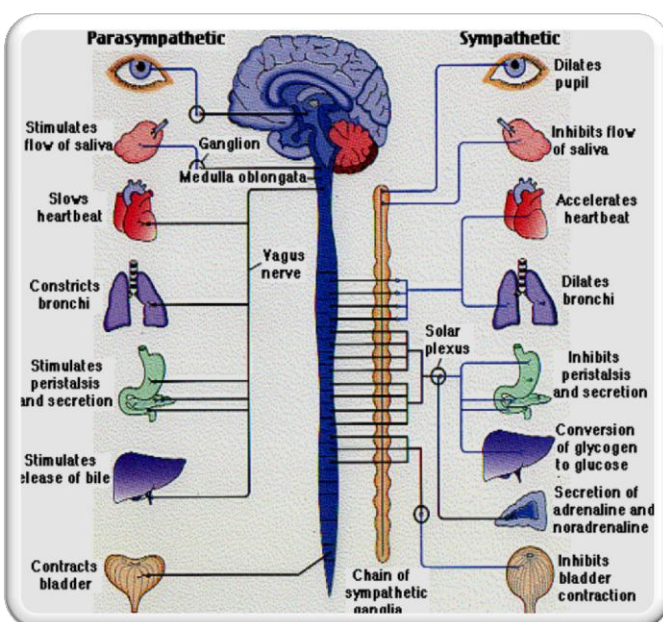




**Note: They are continuation of the physiological effects of ACh.**  
**muscarinic** المستقبل على Ach بفعل يحصل لما مشابه هو الأدوية هذه عمل

## Muscarinic actions

Organs	Cholinergic actions
Eye	<b>Contraction of circular muscle of iris (miosis)(M3)</b> <b>Contraction of ciliary muscles for near vision (M3)</b> <b>Decrease in intraocular pressure</b>
Heart endothelium	<b>bradycardia ( heart rate ) (M2)</b> <b>Release of NO (EDRF)</b>
Lung	<b>Constriction of bronchial smooth muscles</b> <b>Increase bronchial secretion M3</b>
GIT	<b>Increased motility (peristalsis)</b> <b>Increased secretion</b> <b>Relaxation of sphincter M3</b>
Urinary bladder	<b>Contraction of muscles</b> <b>Relaxation of sphincter M3</b>
Exocrine glands	<b>Increase of sweat, saliva, lacrimal, bronchial, intestinal secretions M3</b>



## Direct cholinomimetics

- Acetylcholine (M,N)
- Carbachol (M,N)
- Bethanechol (M)
- Pilocarpine (M)

### 1. Acetylcholine (Ach)

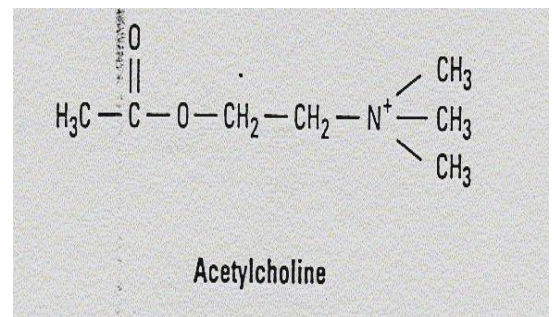
Muscarinic and nicotinic agonist

Not used clinically because Ach

Is not selective (N, M)

Has short duration of action. Why?

Degradation by *acetylcholinesterase*



### 2. Pilocarpine

Natural alkaloids

Tertiary amine *lipophilic*

*Pharmacokinetics*

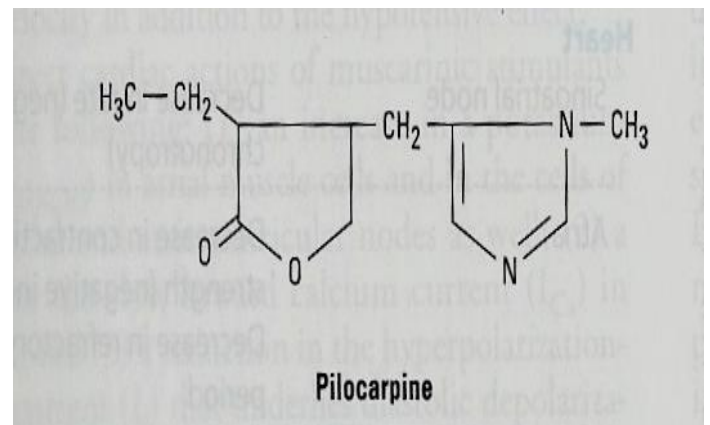
It is well absorbed

Good distribution

Can cross BBB (*has central effects*).

Long duration of action

Direct muscarinic agonist (*mainly on eye & secretion*)



### 3. Pilocarpine

#### Adverse effects:

*Profuse sweating*

*Salivation*

*CNS effects*

#### Uses:

*Xerostomia (dry mouth).*

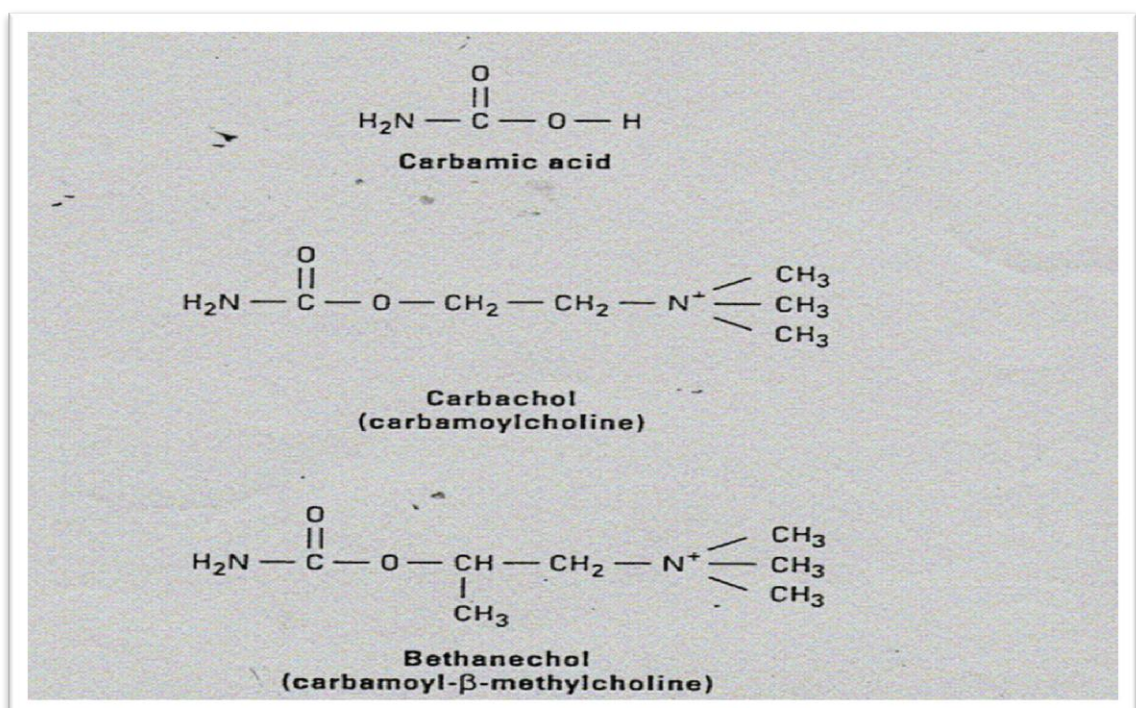
*Drug of choice in emergency glaucoma*

*( open-angle & closed-angle) applied as eye drops*

#### Synthetic choline esters

#### Bethanechol, Carbachol

- Quaternary ammonium compounds (polar)
- 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.





## Carbachol

- ✓ Orally-SC
- ✓ Not metabolized by cholinesterases.
- ✓ Longer duration of action than Ach
- ✓ Muscarinic actions on Eye, GIT, UT.
- ✓ Has nicotinic actions (*what are these actions?*).

## Used for

- ✓ Mainly in glaucoma
- ✓ Urinary retention & paralytic ileus (*rarely*)

## 5. Bethanechol

- ✓ Orally-SC
- ✓ Prominent muscarinic actions on GIT, UT.
- ✓ No nicotinic action
- ✓ Not metabolized by cholinesterases.
- ✓ Longer duration of action than Ach

## Used for

- ✓ In urinary retention (post-operative atony, neurogenic bladder, spinal cord injury)
- ✓ In paralytic ileus

## \*\*New Drugs:

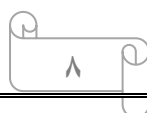
### Cevimeline:

- Direct acting cholinomimetics
- A muscarinic agonist, with particular effect on M3
- Used for treatment of dry mouth symptom associated with

### Sjogren's syndrome

#### receptors

- It is given orally.
- Increased salivation.
- Used for treatment of dry mouth symptom associated with Sjogren's syndrome.



### Contraindications of cholinomimetics

- **Bronchial asthma.**
- **Peptic ulcer.**
- **Angina pectoris**
- **Incontinence**
- **Intestinal obstruction**

### \*\*New Uses of Cholinergic Drugs:

- **Donepezil:** for improving memory (Cognitive Function) in Alzheimer disease. it is **(Indirect acting)**
- **Cevimeline:** dryness of the mouth caused by radiation therapy for head and neck cancer and also indicated for dry eye.

	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	Hydrolyzed by cholinesterase	NOT hydrolyzed by cholinesterase	NOT hydrolyzed by cholinesterase	NOT hydrolyzed cholinesterase
Duration	Very short	Longer (++)	Longer (++)	Longer ( ++)
Administ	I.v. eye drops	Oral, Eye drops s.c.	Oral, Eye drops s.c	Oral, eye drops

	Ach	Carbachol	Bethanechol	Pilocarpine
Receptors	Muscarinic Nicotinic	Muscarinic Nicotinic	Muscarinic	Muscarinic
Muscarinic	+++	+++	+++	+++
Selectiity	NOT	Eye, GIT Urinary bladder	GIT Urinary Bladder	More on eye, secretion
Nicotinic	+++	+++	NO	NO
Uses	NO	Glaucoma Paralytic ileus Urinary Retention	Paralytic ileus Urinary Retention	Glaucoma Xerostomia

### Some important notes:

- ✓ -ACH is important because it is controlling Norepinphrine
- ✓ -ACH is very dangerous while Norepinphrine not
- ✓ -All tertiary drug can go to barin while Quaternary drug not.

