Pharmacology
team 436

MEDICINE
KING SAUD UNIVERSITY

# DIRECT ACTING CHOLINRTGIC DRUGS

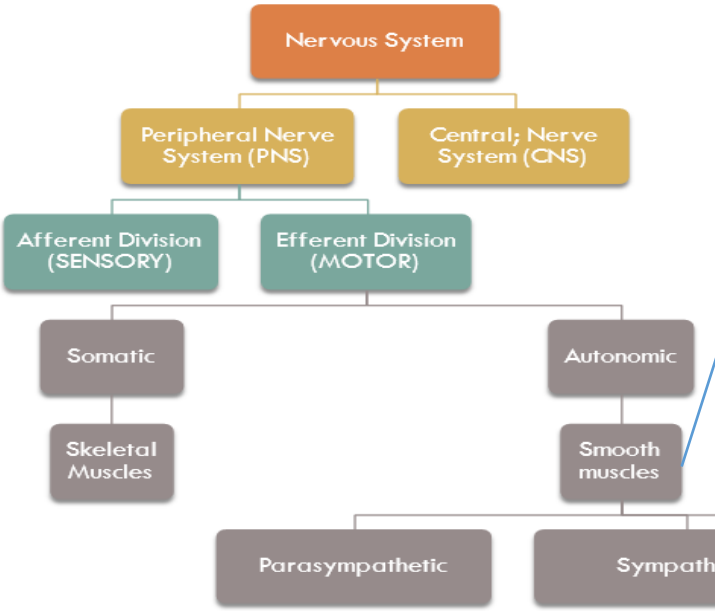
Objectives:

- 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.

Don’t say I’m having a bad day, say I have a character building day.

- Titles
- Very important
- Extra information
- Doctor’s note

# Organization of The Nervous System:



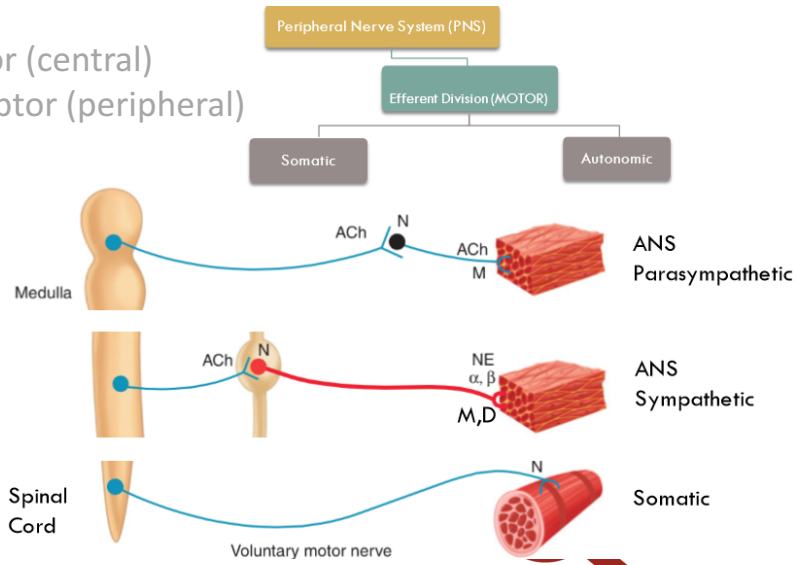

Parasympathetic is also called cholinergic while the sympathetic is adrenergic.

In this lecture we will study the cholinergic agonist drugs. Which means they increase the parasympathetic action.

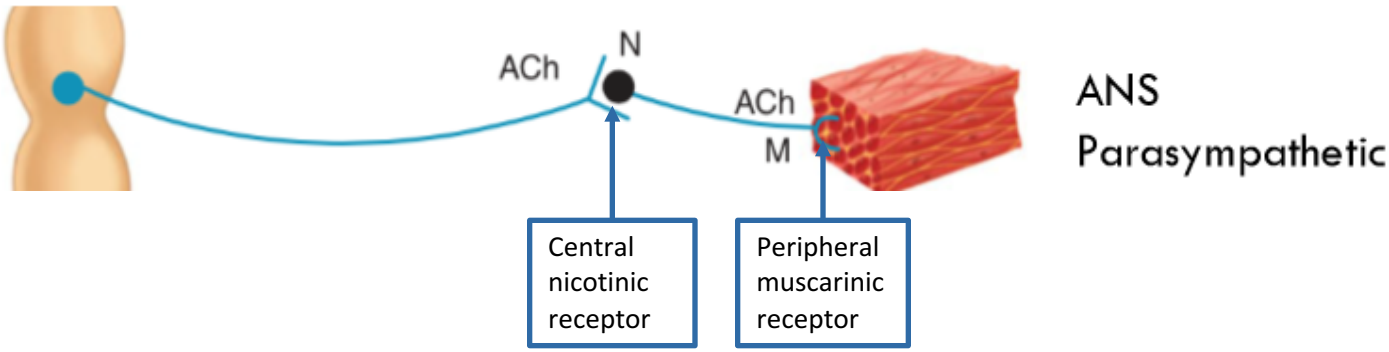
For GIT

## **ANS**, Efferent division of the PNS:

N: Nicotinic Receptor (central)
M: Muscarinic Receptor (peripheral)
ACh: acetylcholine



# Parasympathetic




**Preganglionic neurons:**

- Long.
- Synapses with postganglionic at or near organ.
- Acetylcholine is neurotransmitter.
- Nicotinic receptor on postganglionic.

**Postganglionic:**

- Short.
- Synapses on the organ.
- acetylcholine is neurotransmitter.
- Muscarinic receptor on the organ.

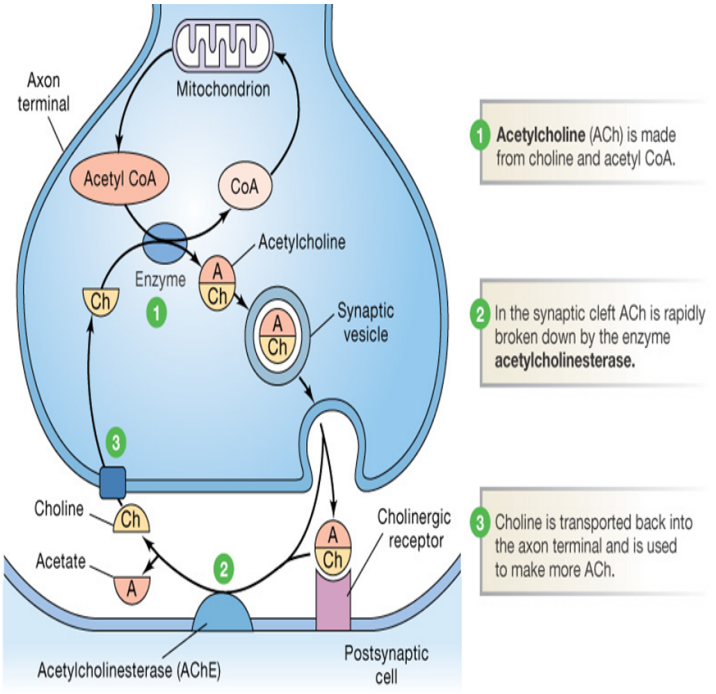
Cholinergic fibers(Enteric): group of fibers act by releasing acetylcholine.

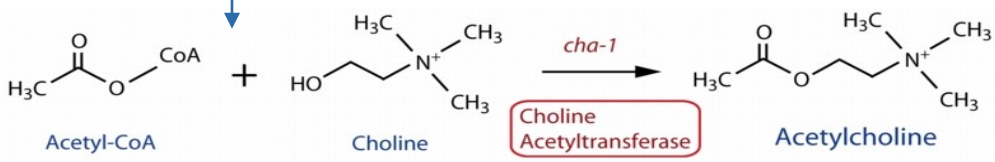
# Cholinergic Transmission:

- Half-life of Ach is very short.
- Targets for pharmacologic therapy (interventions):

1. Synthesis.
2. Storage.
3. Release.
4. Termination of action of the transmitter.
5. Receptor.

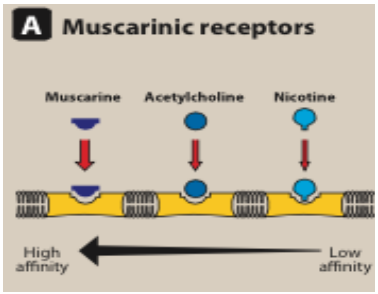
- Choline Transportation
- AcCoA (Acetyl CoA) Synthesis

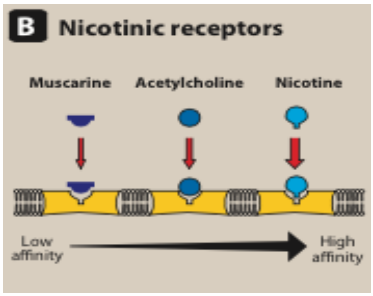


## Autonomic Receptors:

- Cholinergic R
  - Muscarinic R (mAChR)
    - $M_1$, $M_3$, $M_5$ (Gq coupled)
    - $M_2$, $M_4$ (Gi coupled)
  - Nicotinic R (nAChR)
    - $N_M$ (neuromuscular, or muscle type)
    - $N_N$ (neuronal, or ganglion type)




Classes of G proteins according to their α subunit:
$G_s$ :stimulates Adenyl cyclase.
$G_i$ :inhibits Adenyl cyclase.
$G_q$ :activates Phospholipase C.
For further info go back to "Receptors families" in the foundation block.

## Pharmacological actions of cholinergic drugs

**cholinergic drugs** have Actions that are similar to the effects of parasympathetic system activation.

- nicotinic actions
- muscarinic actions

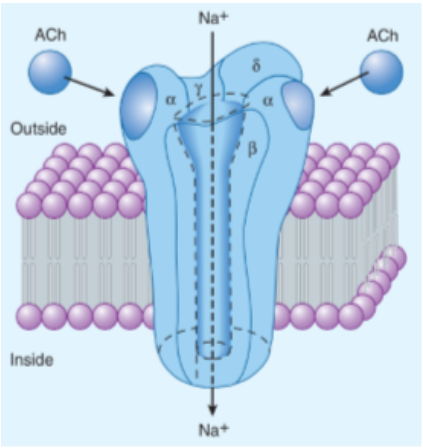
**Cholinergic drugs** acts upon two types of receptors

- nicotinic receptors
- muscarinic receptors

## 1-Autonomic Receptors (Nicotinic):

ligand is usually a molecule which produces a signal by binding to a site on a target protein.

- Ion channel linked receptors
- Similar to those induce by nicotine.




- Locations:

1. At neuromuscular junctions of skeletal muscle ($N_M$).
2. On Adrenal medulla ($N_N$).
3. In CNS ($N_N$).
4. Ganglionic neurons in the autonomic ganglia ($N_N$).

- Type:

1. Ligand-gated ion (Na+) channel.
2. Acetylcholine binds to the α subunits.
3. 2 acetylcholine molecules must be attached.
4. Structurally and functionally similar to the Na+ Channel.

| Receptor | Location | Pharmacological action |
|---|---|---|
| $N_N$ | Autonomic ganglia | sympathetic & parasympathetic stimulation. |
| $N_N$ | Adrenal medulla | release of catecholamines (adrenaline & noradrenaline) |
| $N_M$ | Skeletal muscles | ↓concentration of the drug or ACh → muscle contraction<br>↑concentrationof the drug or ACh → persistent depolarization & relaxation (depolarization block).(anesthetic effect) |

## 2-Muscarinic receptors

Muscarinic receptors belong to class of G protein-coupled receptors. These receptors, in addition to binding Ach, also recognize muscarine which is an alkaloid that is present in certain poisonous mushrooms. By contrast, muscarinic receptors show only a weak affinity for nicotine.

### Types and location of muscarinic receptors:

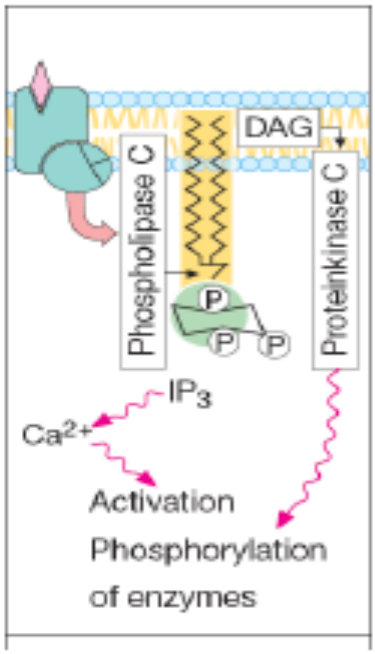
| Receptor | Locations | Pharmacological actions |
|---|---|---|
| M1 (Excitatory) | 1. CNS<br>2. gastric parietal cells | • CNS excitation<br>• Gastric acid secretion |
| M2 (Inhibitory) | 1. Heart | • Cardiac inhibition (Bradycardia) |
| M3 (Excitatory) | 1. Exocrine glands.<br>2. Smooth muscles (GIT, urinary tract, bronchial muscles).<br>3. Vascular endothelium. | • Secretion of glands.<br>• Smooth muscle contraction<br>• Vasodilatation (via nitric oxide) |
| M4 & M5 | 1. CNS | • memory, arousal, attention and analgesia |

Remember:
M1 in the 1st important organ *brain*.
M2 in the 2nd important organ *heart*.
M3 in other internal organs.

# Types of muscarinic receptors

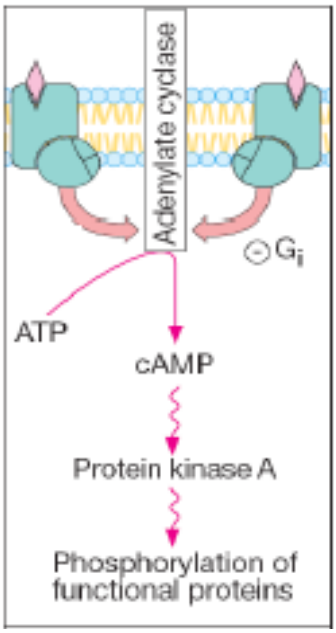
Muscarinic receptors

- Excitatory: M1,M2 and M5
- Inhibitory: M2, M4




Remember:

- Odd numbers are excitatory.
- Even numbers are inhibitory.




*الأعداد الزوجية"Inhibitory" الرجل لما يتزوج يتثبط وتقيد بتصرفاته (M2 & M4)*
*الأعداد الفردية "Stimulatory" الرجل لما يكون عازب يكون متحمس ويسوي اللي يبغي (M1 & M3 & M5)*

| Organs | muscarinic actions |
|---|---|
| Eye | Contraction of circular muscle of iris (miosis)(M3)<br>Contraction of ciliary muscles for near vision (M3)<br>Decrease in intraocular pressure (IOP) |
| Heart<br>endothelium | bradycardia ( decrease in heart rate ) (M2)<br>Release of Nitric Oxide (EDRF) |
| Lung | Constriction of bronchial smooth muscles<br>Increase in bronchial secretion M3 |
| GIT | Increase in motility (peristalsis)<br>Increase in secretion<br>Relaxation of sphincter -defecation M3 |
| Urinary bladder | Contraction of muscles<br>Relaxation of sphincter M3<br>Urination |
| Exocrine glands | Increase of secretions of exocrine glands<br>sweat, saliva, lacrimal, bronchial, intestinal secretions M3 |

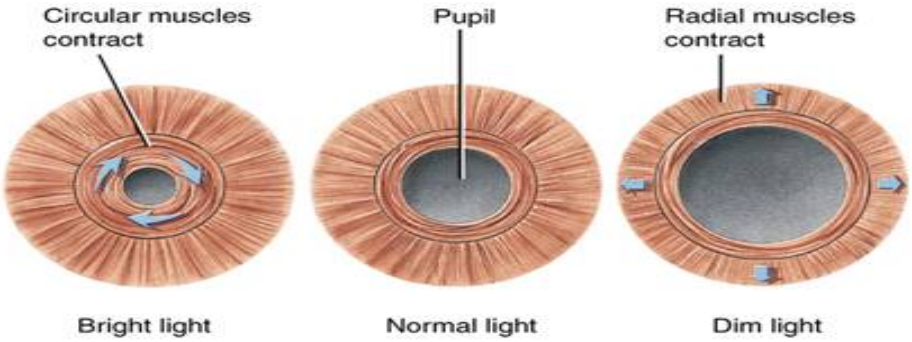
## Nicotinic vs Muscarinic receptors

| Nicotinic receptors<br>(Central cholinoceptors) | Muscarinic receptors<br>(Peripheral cholinoceptors) |
|---|---|
| Almost excitatory | Excitatory or inhibitory |
| Autonomic ganglia Nn<br>sympathetic & parasympathetic stimulation | On all peripheral organs innervated by postganglionic parasympathetic fibers |
| Adrenal medulla Nn<br>release of catecholamines (adrenaline & noradrenaline) | Heart (bradycardia, M2)<br>exocrine glands (secretion, M3) |
| Skeletal muscles Nm<br>contraction | Smooth muscles (contraction, M3)<br>(GIT, urinary tract, bronchial muscles, uterus) |

# Muscarinic effect on the eyes

## The iris has two muscles that control light intensity:

1. **Dilator pupillae,** a longitudinal radial muscle which **dilates** the pupil (mydriasis) in the dark, to allow as much as possible of light to enter the eye. It is innervated by **sympathetic** NS.
2. **Constrictor pupillae,** a circular muscle which **constricts** the pupil (miosis) in places with good lighting. It is innervated by **parasympathetic** NS.




هنا العضلات حقت العين حتنقبض و تنبسط حسب الضوء الداخل و الضغط جوا العين.

## Accommodating the ciliary muscle for near vision:

- Parasympathetic activation contracts **the ciliary muscle.** ( when ACh combines with muscarinic M3 receptor).
- Contraction of ciliary muscle pulls the **ciliary body** forward & inward , relaxing **the suspensory ligaments** of the lens (lens becomes spherical). (Contraction of ciliary body = relaxation of the suspensory ligaments , and vice versa).
- The lens bulges more (increased curvature) , this causes a decrease in focal length.
- This parasympathetic reflex is essential to accommodate for **near vision**.

ANS control of iris.

# Continue….

## Constrictor pupillae is important for:

- Adjusting the pupil in response to change in light intensity.
- Regulating the intraocular pressure.

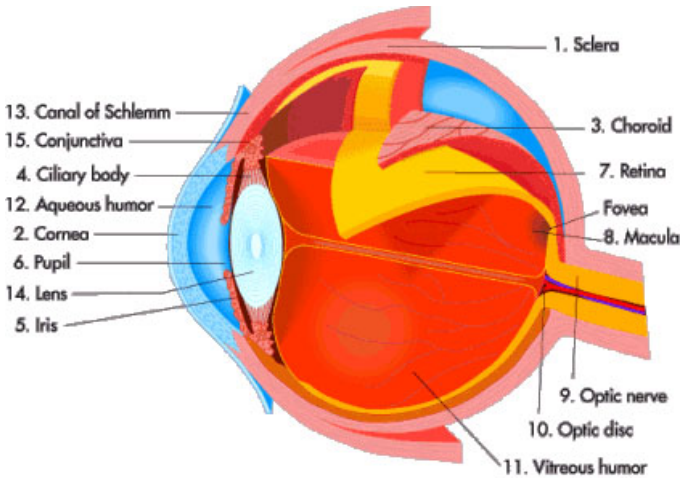
For better understanding you have to take a look at the anatomy of the eye and to be familiar with some terms.

- *Aqueous humour:* the clear fluid filling the space in the front of the eyeball between the lens and the cornea.
- *Ciliary body:* is the structure in the eye that releases a clear liquid in the eye.
- *Canal of Schlemm:* is a circular lymphatic-like vessel in the eye that collects aqueous humor from the anterior chamber and delivers it into the episcleral blood vessels via aqueous veins.

## Regulating the intraocular pressure:

**In the healthy eye:**

- Aqueous humour is secreted by the cells of the epithelium covering the ciliary body.
- Increased tension in the ciliary body removes the Aqueous humour continuously by drainage into the canal of Schlemm.
- Normal intraocular pressure is 10-15mmHg above atmospheric pressure.




**In some people:**

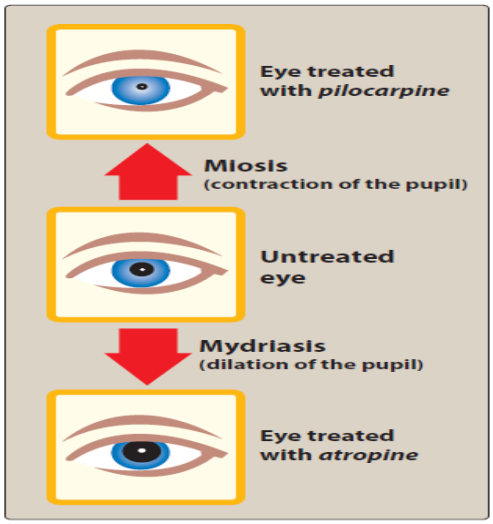
- Dilatation of their pupil will block canal of schlemm, therefore it impeds drainage of aqueous humour.
- The accumulation of aqueous humour leads to an increase in intraocular pressure.
- IOP may lead to glaucoma, and retinal detachment.

## The effects of parasympathetic nervous system of the eye:

| Eye | Parasympathetic Nervous System |
|---|---|
| **Iris**<br>**radial muscle**<br>**circular muscle** | No effect<br>Contraction (miosis) M3 |
| **Ciliary muscle** | Contraction M3 |
| **Accommodation** | for near vision |
| **Intraocular pressure(IOP)** | Decrease |

## Mechanism of treatment of glaucoma:

When using cholinergic drugs (e.g. pilocarpine), constrictor pupillae causes miosis, which contracts the pupil away from canal of schlemm, leading to increased filtration of Aqueous humour.
Thus, activation of constrictor pupillae decreases intraocular pressure in patients with glaucoma.



# Parasypathomimetics (cholinergic drugs)

## indirect

- Reversible
  (e.g. physostigmine, neostigmine, edrophoniom)
- Irreversible
  (e.g. organophosphorus, Echothiophate “used in glucoma”, War gases, parathion)

## Direct

(e.g. Ach, methacholine, carbachol, bethanechol, pilocarpine)

# Drugs direct-acting on Ach receptors (CHOLINOCEPTORS)

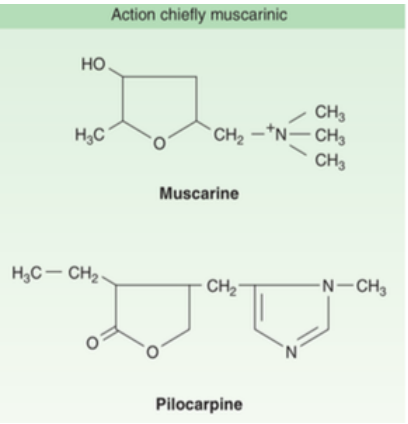
## A- Choline Esters

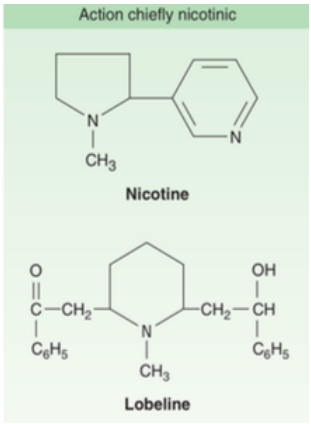
(Quaternary ammonium compounds)

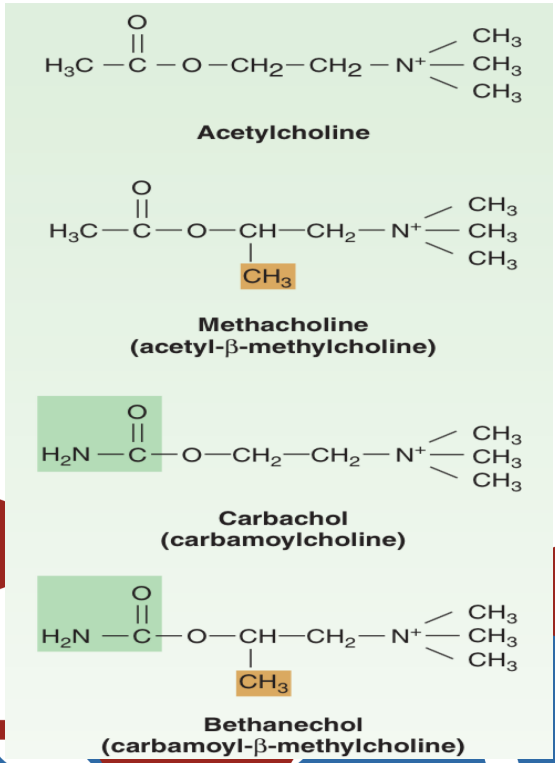
- Polar
- Poor distribution
- Do not cross BBB (no CNS effect)
- Not metabolized by cholinesterase.( except Ach)
- Have longer duration of action than Ach
- β-methyl group → Selectivity to M receptor
- Never given I.V. or I.M But S.C (to avoid side effects)
- Cevimeline

## B- Tertiary natural alkaloids

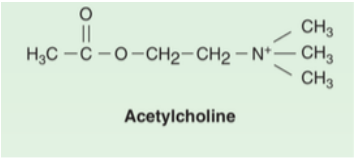
- Well absorbed except Muscarine , Excreted by the kidneys



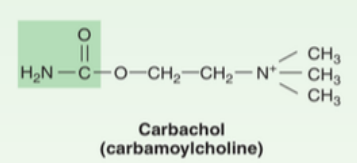



- Acetylcholine
  - Muscarinic and nicotinic agonist
  - Not used clinically because
    - not selective as it acts on both nicotinic and muscarinic receptors
    - Has short duration of action Due to rapid metabolism by acetycholinesterase.



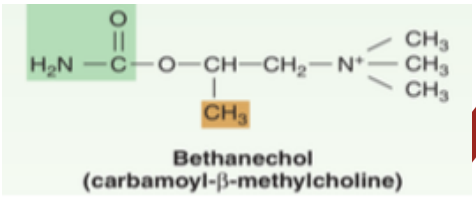
Acetylcholine

- Carbachol
  - Muscarinic actions on Eye, GIT, UT
  - Has nicotinic actions (side effects)
  - Resistant to hydrolysis by acetyl cholinesterase because of carbamoyl group
  - Longer duration than Ach (no breakdown)
  - Used for treatment of glaucoma



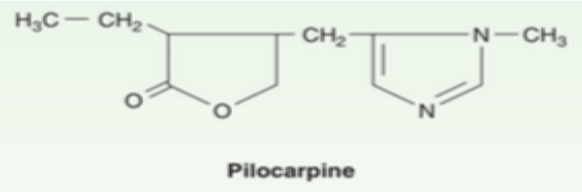
Carbachol
(carbamoylcholine)

- Bethanechol
  - Prominent muscarinic actions on GIT, UT. and No nicotinic action (methyl group)
  - Resistant to hydrolysis by acetyl cholinesterase
  - Longer duration than Ach
  - Used for
    - Paralytic ileus (failure of peristalsis)
    - Urinary retention in cases of post-operative atony & neurogenic bladder



Bethanechol
(carbamoyl-β-methylcholine)

- Cevimeline
  - Direct acting muscarinic agonist (M3)
  - Used for treatment of dry mouth symptom
  - associated with Sjogren's syndrome
    - (autoimmune disease characterized by Formation of antibodies leading to dryness of mouth and eye)
- Pilocarpine



Pilocarpine

  - Natural source
  - **Tertiary** (lipid soluble)
  - well absorbed, good distribution
  - Cross BBB (has central effects)
  - Not metabolized by cholinesterase
  - Long duration of action
  - Excretion is enhanced by acidification of urine
  - Direct muscarinic agonist(mainly on eye & secretion)
  - Uses:
    - Xerostomia (dry mouth).
    - Drug of choice in emergency (long duration of action) glaucoma
      - applied as eye drops.
  - Adverse effects: (exaggeration of effects)
    - Profuse sweating
    - Salivation
    - Diarrhea
    - CNS effects
    - Bronchoconstriction

Pilocarpine

* كيف احفظ اسمه ((بل (Pil) هو (o) كربون (Carpine)))

* اسمه قسمته ثلاث أقسام فخلاص نوع مجموعة الأمين( Tertiary Amine 3 )

* بعض الخصائص المميزة له ربطتها بالكربون Carbon=Carpine

*The carbon from natural source (so this drug from natural source)*

*The carbon is build up the organic compounds which are lipid soluble (so this drug is lipid soluble)*

| Drug | ACh | Carbachol | Bethanecol | Pilocarpine | Cevimeline |
|---|---|---|---|---|---|
| Chemistry | Quaternary Polar | Quaternary Polar | Quaternary Polar | Tertiary non polar | |
| Absorption | NOT | better absorbed than Ach | better absorbed than Ach | Complete | |
| Metabolism by cholinesterase | metabolized by cholinesterase | NOT metabolized by cholinesterase | | | |
| Duration | Very short | Longer (++) | Longer (++) | Longer (++) | |
| administration | I.V. ,eye drops (not actually used) | Oral, eye drops S.C. | Oral ,S.C. | oral, eye drops | |
| Receptors | Muscarinic Nicotinic | Muscarinic Nicotinic | Muscarinic | Muscarinic | Muscarinic |
| Muscarinic | +++ | +++ | +++ | +++ | +++ |
| Selectivity | NOT | Eye, GIT Urinary bladder | GIT, Urinary bladder | More on eye, exocrine glands | Exocrine glands |
| Nicotinic | +++ | +++ | NO | NO | NO |
| Uses | NO | Glaucoma | Paralytic ileus Urinary retention | Glaucoma Xerostomia | Sjogren's syndrome |

## Contraindications: (would make things worse)

- Bronchial asthma
- Peptic ulcer
- Angina pectoris (pain due to low blood flow to the heart)
- Urinary incontinence
- Intestinal obstruction

| | | |
|---|---|---|
| Use For eye (glaucoma) | Pilocarpine | كل الكلمتين فيهم مقطع (Carp/ Carb) ويذكرني بكلمة(الكربة) والهم اللي يحسون فيه من يفقد بصره وفعلا أي مرض بالعين زي (Glaucoma) فيه كربة ونتذكر يعقوب عليه السلام لما ابيضت عيناه من الحزن والهم. |
| | Carbachol | |

refer to increase the salivary secretion سعابيلك \ تفالك

| | | |
|---|---|---|
| Use exocrine gland ( dry mouth ) | Pilocarpine | فيها مقطع (Pilo) يذكرني بكلمه بللتنا بسعابيلك \ تفالك |
| | Cevimeline | فيها مقطع (meline) يذكرني بكلمه ملينا من سعابيلك \ تفالك |

تحت نتكلم بشكل عام ، بس فعليا ما نستخدم (Carbachol) نستخدمه فقط (For Glaucoma as eye drops) لأنه (non selective so to minimize its side effect)

| | | |
|---|---|---|
| Use GIT Urinary bladder | Carbachol | أخر مقطع بالكلمتين آكول (achol) والشخص الآكول ياكل كثير (GIT) ويشرب (Urinary bladder) كثير |
| | Bethanechol | |

شلون أتذكر أي واحد فيهم هو اللي يستخدم على وجه الخصوص هنا
بداية الكلمه (Betha) تذكرني بكلمة (Bathroom)

# SAQ

A dentist would like to reduce salivation in a patient in preparation for an oral surgical procedure.

***Q1: List two Cholinergic drugs we can not use in this case for salivary gland and why?***

Pilocarpine / Cevimeline

Because they will the opposite by increasing the secretion of salivary gland.

***Q2:What is the mechanism of action of these drugs as Cholinergic drugs ?***

Produce primarily effect by binding directly to cholinergic receptors which is Muscarinic receptor in salivary gland, so act as Muscarinic Agonist and increase the secretion.

***Q3:Which subtype of Muscarinic receptor is the target here ? And where we can found it also in our bodies ?***

M3 / we can found it in ( Exocrine glands in general & Smooth muscles of GIT, urinary tract & bronchial muscles & Vascular endothelium & eyes )

***Q4: Why do they have long duration of action ? And how we can enhance their excretion from our bodies ?***

Because, they do not metabolized by cholinesterase. / by acidification of urine.

***Q5: Increasing the secretion is considered as one of their pharmacological effects, list other three of them ?***

- Increase in motility of GIT (peristalsis) / Vasodilatation via nitric oxide / Decrease in intraocular pressure via Contraction of circular & ciliary muscles of eyes.

***Q6: list other cases or diseases we can use these drugs to treat Xerostomia (dry mouth):***

Sjogren's syndrome / patient with anti-cancer drugs

# SAQ

**56 Female has Glaucoma . Her doctor prescribe Pilocarpine to decrease the intraocular pressure. Her past medical history includes no kidney or heart disease but she has asthma.**

***Q1: Which class or family of glaucoma drugs this drug is belong to ?***
Cholinergic drugs (cholinomimetics).

***Q2 : Which other drug can we use it also in this case ?***
Carbachol

***Q3:Which subtype of Muscarinic receptor is the target for this drug ?***
M1 which are found in eyes.

***Q4: Explain how does it decrease the intraocular pressure ?***
By producing actions similar to stimulation of parasympathetic system which innervate two muscle in eyes helping in (circular & ciliary ). The contraction of these muscles allow the aqueous humour is removed continuously by drainage into the canal of Schlemm.

***Q5: Is it recommended to give him this drug as I.V injection ? And what is the best route of adminstation ?***
*No , we have to avoid it because it may lead to bradycardia .*
*The best route is Subcutaneous (S.C)*

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**22 male has abdominal surgery. After his operation he has constipation , nausea and vomiting. The doctor gave him Bethanechol to treat these post-operative complication. Her past medical history includes Urinary incontinence.**

***Q1:*** **These post-operative complication such as constipation , nausea and vomiting are related to *which condition?***
The most likely is Paralytic ileus.

***Q2 : What is the mechanism of this drug in this case to treat the relaxation of this muscle ?***
It is act as cholinergic drug which act as Muscarinc agonist (M3) and increase the motility of GIT (peristalsis) and Relaxation of sphincter (defecation)

***Q3:The patient can not continue use these drug any more because he has Urinary incontinence which considered as one of contraindications, list two more?***
Bronchial asthma / Peptic ulcer / Intestinal obstruction.

# SAQ

***Q1:The Synthetic Acetylcholine is prototype but does not have clinical uses nowadays ,Why ?***

*It* is not selective as it acts on both nicotinic and muscarinic receptors → Has many side effect.

It has a rapid metabolism by acetycholinesterase → Has short duration of action.

***Q2 : Pilocarpine is Tertiary amine act as Muscarinic agonist , what can we expect about this drug ?***

Non-polar (lipid soluble) → well absorbed, good distribution ,Cross placenta & BBB and has central action.

***Q3:Why we can not use some Cholinergic drugs which act as Muscarinic agonist with patient with peptic ulcer?***

Because in the stomach we have subtype1 of Muscarinic receptor (M1) which is stimulating with these drugs to increase Gastric acid secretion by gastric parietal cells.

***Q4: What does miosis mean ?***

Miosis is the Constriction of the pupil that is excessive and relative to the amount of light the pupil receives. / Two muscles are involve in adjustment the amount of light in our eyes which are (constrictor & dilator pupillae) .

***Q5: By which system is innervated with ?***

The constrictor pupillae is responsible for this condition and it I nervated by parasympathatic system.

***Q6: List two drugs can induce miosis ?***

*Pilocarpine / Carbachol*

# QUIZ


| Boys | Girls |
|---|---|
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| عبدالعزيز رضوان | روان سعد القحطاني |
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| خالد العيسى | وتين الحمود |
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