Pharmacology team 436

MEDICINE 436 KING SAUD UNIVERSITY

INDIRECT ACTING CHOLINRTGIC DRUGS

Objectives:

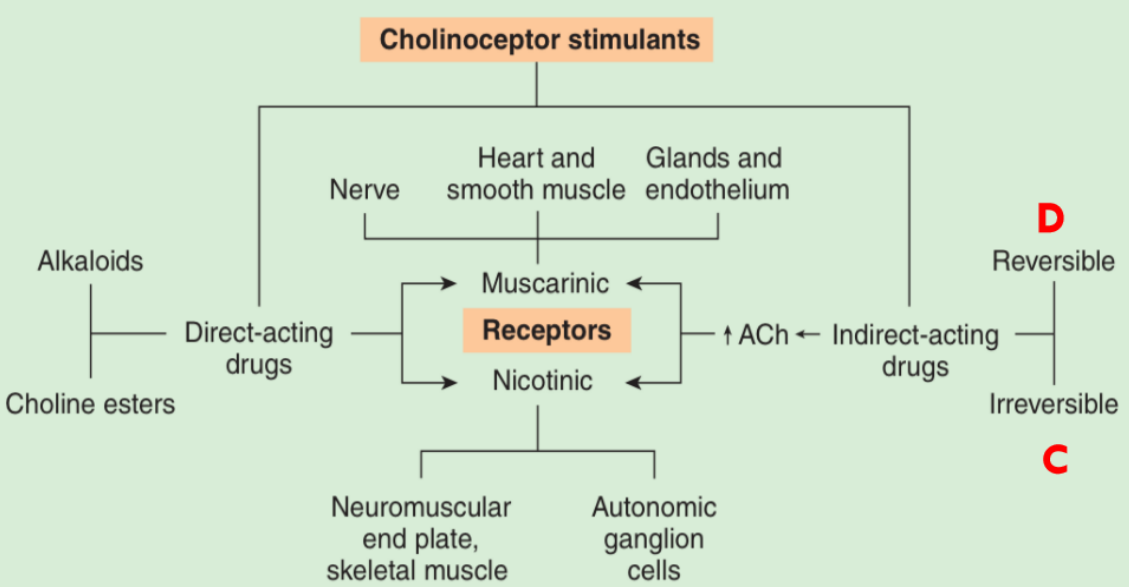
- Classification of indirect acting cholinomimetics
- Mechanism of action, kinetics, dynamics and uses of anticholinesterases
- Adverse effects & contraindications of anticholinesterases
- Symptoms and treatment of organophosphates toxicity

لا تكن هشا, أي ضربة تسقطك, وأي صدمة تضعفك, وأي فشل يعقدك, وأي خطأ يقتلك, كن قويا, فلا مكان للضعفاء بين الأطباء.

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

INDIRECT ACTING CHOLINRTGIC DRUGS

Also called indirect cholinomimetics:



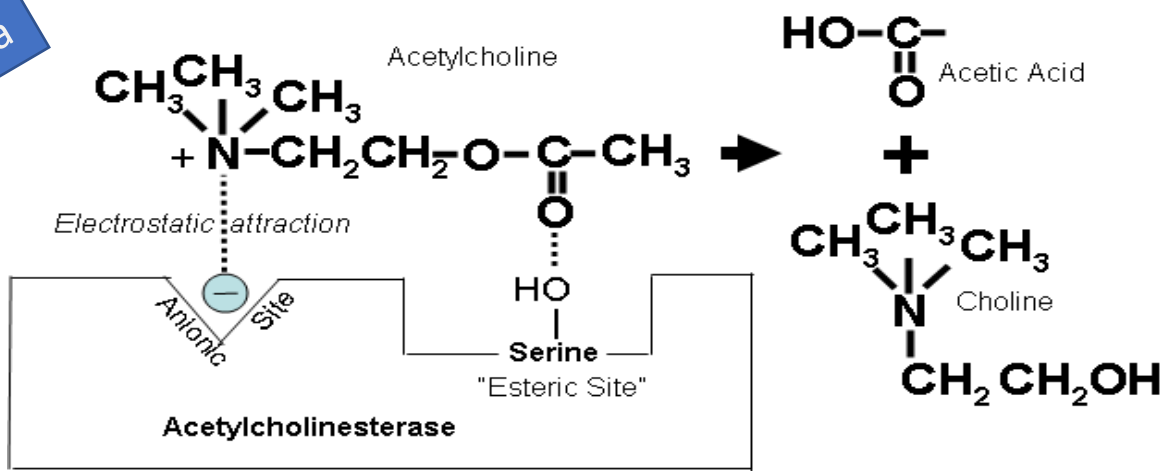
Mechanism of action: Anticholinesterases prevent hydrolysis of Ach by inhibiting acetyl cholinesterase thus, increase Ach concentrations and actions at the cholinergic receptors (both nicotinic and muscarinic).

الـAnticholinesterases تمنع تكسير الAch عبر تثبيط ال acetyl cholinesterase
وبالتالي يزيد تركيز الAch ويكمل يعطي تأثيره على الreceptors.

As mentioned before Ach act on both nicotinic and muscarinic receptors. Thus, increasing in its concentration will increase its affinity and then produces both nicotinic and muscarinic actions.

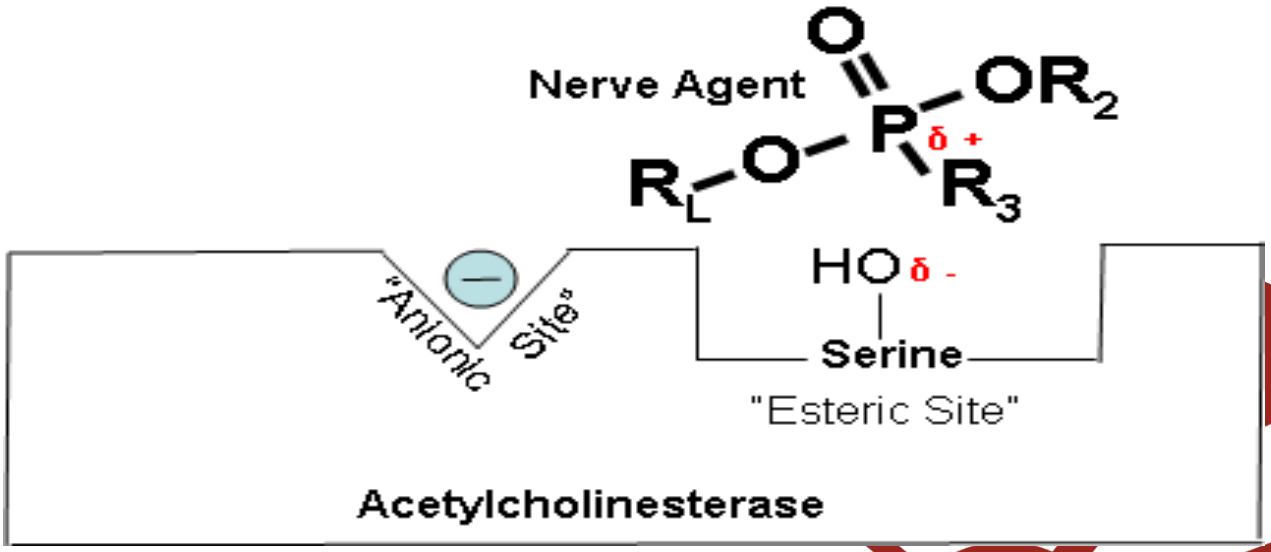
Structure and function of acetylcholinesterase

extra



Normally, acetylcholine binds to acetylcholinesterase at two sites, anionic site and esteric site, then the enzyme somehow breakdown the acetylcholine into acetic acid and choline.

In order to inhibit this enzyme we need to create a substance that is similar to acetylcholine either in both sites or even one site.



Indirect acting on Ach receptors

Reversible anticholinesterases		Irreversible anticholinesterases
Short acting (Alcohols) **e.g. edrophonium.**	Intermediate acting (Carbamates esters) **e.g. Physostigmine, Neostigmine, Pyridostigmine.**	Long acting Phosphates esters **e.g. insecticides, gas war e.g. Ecothiophate & Isoflurophate.**

Structure: (Reversible anticholinesterases)

Short acting:

simple alcohols . **e.g. Edrophonium**

- Forms weak hydrogen bond with acetylcholinesterase enzyme.

Intermediate acting:

Carbamic acid esters.

e.g. Physostigmine, Pyridostigmine and Neostigmine.

- binds to two sites of cholinesterase enzyme.
- All polar and synthetic except physostigmine.

Indirect acting on Ach receptors

Structure: (Irreversible anticholinesterases):

Organic derivatives of phosphoric acid (Long Acting) **e.g. Ecothiophate & Isoflurophate.**

- used as insecticides(malathion) or nerve gases (sarin) .
- Form very stable covalent bond with cholinesterase .
- All phosphates are lipid soluble except Ecothiophate which is polar .

ممكن نقرأ اسم الدرق كذا .. أي (E) كنو (cno) ذايب (thiop) بالمويه , عشان تتذكر إنه هو الاستثناء هنا

Edrophonium

Pharmacological effects of anticholinesterases: (All anticholinesterase)

Action	Yes/No
muscarinic	Yes
nicotinic	Yes
CNS effects	Has BBB so only lipid soluble drugs

CNS actions:

(excitation leads to convulsion leads to respiratory failure leads to coma).

- only for lipid soluble anticholinesterases
- e.g. physostigmine & phosphate ester

Pharmacological effects of anticholinesterases

Nicotinic actions:

- Neuromuscular junction:

  Therapeutic dose leads to muscle contraction while the Toxic dose leads to relaxation or paralysis of skeletal muscles.

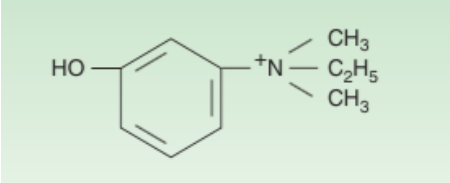
- Ganglia: stimulation of sympathetic and parasympathetic ganglia.
- Adrenal medulla: release of catecholamines (A & NA).

Muscarinic actions :

Organs	Cholinergic actions
eye	•Contraction of circular muscle of iris (miosis)**(M3)** •Contraction of ciliary muscles for near vision **(M3)** •Decrease in intraocular pressure
Heart endothelium	•Bradycardia (decrease heart rate) **(M2)** •Release of nitric oxide (EDRF)
Lung	•Constriction of bronchial smooth muscles •Increase bronchial secretion **(M3)**
GIT	•Increased motility (peristalsis) •Increased secretion •Relaxation of sphincter **(M3)**
Urinary bladder	•Contraction of muscles •Relaxation of sphincter (**M3)**
Exocrine glands	•Increase of sweat, saliva, lacrimal, bronchial, intestinal secretions **(M3)**

EDRF : Endothelium-derived relaxing factor

Edrophonium



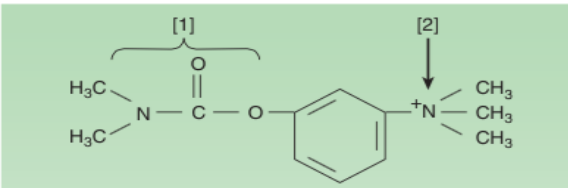
- Reversible anticholinesterase.
  Forms weak hydrogen bond.
- Alcohol so its Polar.
- NOT absorbed orally (given by injection). Because its polar so it can't be absorbed easily by oral root.
- Has short duration of action (5-15 min).
- Used only for the diagnosis of myasthenia gravis due to its limited duration of action.

Edrophonium

Eyelid drop → (E) (drop) honium ممكن نقرأ أول مقطعين من الدرق ك

ونعرف طبعا ان هذي العلامه تساعدنا عشان نشخص مرض myasthenia gravis ونفس الشيء هالدرق يستخدم للتشخيص فقط.

Neostigmine



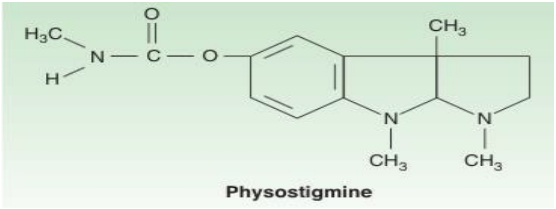
- Reversible anticholinesterase.
- Quaternary ammonium comp.
- Polar compound.
- Can be used orally.
- No CNS effect.
- Has muscarinic & nicotinic actions (prominent <u>on GIT & urinary tract</u>).

Uses :

- Treatment of myasthenia gravis.
- Paralytic ileus & Urinary retention.
- Competitive neuromuscular blockers intoxication by increasing the level of Ach. Thus prevent the action of NMBs (Neuromuscular Blocking Agents).

Physostigmine

- Reversible anticholinesterase.
- Tertiary ammonium compound.
- Non polar (lipid soluble).
- Good lipid solubility.
- Good oral absorption.
- Has muscarinic, nicotinic action.
- Cross BBB (has CNS effects). Because it's lipid soluble.



Physostigmine

Uses :

- Glaucoma.
- Atropine toxicity (atropine is anticholinergic drug).

used in atropine toxicity because atropine has an effect on the CNS. Thus, we need a drug that can clean up atropine from all over the body.

Physostigmine

يذكرني هالدرق بمادة الفسيولوجي فعلى سبيل الربط فقط فقط نقدر نقول كذا
فسيولوجي (Physostigmine) يا نظر عيني (Glaucoma) بلا مياعه (lipid soluble)خلاص جاني اتروفي (Atropine toxicity) لعضلاتي من كثر الجلسة عليك

وين يستخدم هالدرق
نظر عيني "يعني مرض يصيب العين وهو الجلاكوما"
اتروفي لعضلاتي "يذكرني بانه يستخدم بعلاج Atropine toxicity
خاصية مميزه له
بلا مياعه " تذكرني بالدهون والزيوت"

Drugs	Chemical structure	Actions	Administration	Kinetics	Uses
Neostigmine	Quaternary ammonium compound	Nicotinic muscarinic M, N	Can be used orally	-0.5-2hr -polar	•Myasthenia gravis treatment •Paralytic ileus •Urinary retention •Curare toxicity
Physostigmine	Tertiary ammonium compound	Nicotinic muscarinic M, N, CNS	Good oral absorption, can be used topically in the eye	-0.5-2hr -nonpolar (lipid soluble)	•Glaucoma •Atropine toxicity
Pyridostigmine	Quaternary	Nicotinic muscarinic M, N		-3-6hr -polar	• Myasthenia gravis treatment
Ambenonium	Quaternary	Nicotinic muscarinic M, N		-4-8hr -polar	•Myasthenia gravis treatment
Edrophonium	Quaternary (Attach mainly to acetyl cholinesterase by weak hydrogen bond.)	Nicotinic muscarinic M, N	injection	-5-15 min -Polar	•Diagnosis of Myasthenia gravis, not for the treatment.

Organophosphorous compounds e.g. Ecothiophate

Mechanism:

-Irreversible anticholinesterase.
-Binds to cholinesterase by strong covalent bond.
-Have very long duration of action.
-Aging make bond extremely stable.
-All are highly lipid soluble except ecothiophate.
-Used for glaucoma.

Symptoms of organophosphates toxicity:

Heart:

Sever bradycardia and hypotension.

Lung:

bronchospasm.

GIT:

Increased GIT motility → cramps & diarrhea.

CNS:

CNS effects (lipid soluble) → convulsion, coma and respiratory failure.

Skeletal muscles :

Initial twitching of skeletal muscles → muscle weakness & paralysis.

Treatment of organophosphate toxicity

Support respiration → Cholinesterase reactivator → atropine

- Atropine to block muscarinic action and CNS effect.

OXIMES e.g. Pralidoxime (PAM)

-cholinesterase reactivator.
-Acts by regeneration of cholinesterase enzyme.
-reactivates recently inhibited enzymes before aging.
-Has poor BBB penetration.

Uses

-I.V. → over 15-30 min for organophosphate intoxication.

Pralidoxime used in treatment of organophosphate poisoning due to the ability of regeneration of cholinesterase enzyme

Donepezil

-it's centrally acting reversible to acetylcholinesterase inhibitor.
-Anticholinesterase drugs.
-Given orally.
-used for treatment of dementia of Alzheimer's disease.

Team 435

Reversible anticholinesterases

Drug	Actions	Kinetics	Pharmacokinetics	
Alcohols (Short acting) (Weak H-bonds)				
Edrophonium	M, N	Very Short 5-15min polar	NOT absorbed orally, given by injection	• Diagnosis of myasthenia gravis
Carbamate esters (Intermediate acting) (Bind to two sites)				
Neostigmine Quaternary ammonium comp	M, N	Short 0.5-2hr polar	Can be used orally (polar) prominent on GIT & urinary tract.	•**Myasthenia gravis** treatment •Paralytic ileus •Urinary retention •Curare toxicity
Physostigmine Tertiary ammonium compound	M, N, CNS	Short 0.5-2hr non-polar (lipid soluble)	Good oral absorption	•**Glaucoma** (eye) •atropine toxicity
Pyridostigmine	M, N	Short 3-6 polar	-----	• **Myasthenia gravis** treatment
Ambenonium "not a stigmine derivative"	M, N	Short 4-8 polar	-----	• **Myasthenia gravis** treatment
Long acting				
Donepezil	M, N	Long	Given orally	• dementia of Alzheimer's disease

Irreversible anticholinesterases

Drug	Actions	Kinetics	Mechanism	Uses
Organophosphorus compounds (Long acting) (stable covalent bond)				
Isoflurophate	M, N, CNS	-----	-----	• dementia of Alzheimer's disease
Ecothiophate	M, N	Long 100hr, polar	Aging make bond extremely stable	• **Glaucoma**
pralidoxime (Oximes)	M, N, CNS	-----	reactivates recently inhibited enzymes before aging	• organophosphate intoxication

Summary for cholinomimetics & their uses:

Eye : treatment of glaucoma

- Pilocarpine / - Carbachol (direct muscarinic agonist).
- Physostigmine. (indirect cholinomimetics).
- Ecothiophate (indirect cholinomimetics).

Urinary retention and paralytic ileus

-Bethanechol (direct)
-Neostigmine (indirect)

Myasthenia gravis (only indirect cholinomimetics)

-Ambenonium.
-Pyridostigmine. (indirect cholinomimetics)
-Neostigmine. (indirect cholinomimetics)

فيه كثير أدوية تستخدم لعلاج Myasthenia gravis اكيد بس اللي أخذناهم ممكن نربطها بسالفة
امبيه نو (**Ambeno**nium) بردوا (**Pyrido**stigmine) اطرافك لما عرفت ان عندك (Myasthenia gravis) عادي فيه نيو درقز
تعالج هالمرض. (**Neo**stigmine)

Xerostomia

-Pilocarpine
-Cevimeline **(Used in treatment of Sjogren's syndrome).**

Alzheimer's disease

-Donepezil.

Sjogren's syndrome : is a long-term autoimmune disease in which the patient's white blood cells attack the saliva and tear glands, leading to dry mouth and eyes.

Adverse effects of cholinergic drugs:

- Bradycardia
- Sweating & Salivation
- Bronchoconstriction
- Diarrhea

(any action other than the main wanted action will be considered as an adverse effect.)

Contraindications of cholinergic drugs:

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

SAQ

32-year-old female came with short history of fatigue associated with ptosis. The patient also noticed that her symptoms increases with work.
The doctors expected that she has Myasthenia gravis.

1-What drug can help them in there diagnosis?
Edrophonium.

2-Explain the mechanism of action of this drug.
The drug binds to acetylcholinesterase by forming a weak hydrogen bond. Thus inhibit the action of acetylcholinesterase which leads to increase amount of Ach which then will release her symptoms.

3-Can we use this drug for treating her disease?
This drug can't be used for treating myasthenia gravis due to its extreme short duration of action.

4-list three drugs can be used in this condition?
1-neostigmine.
2-ambenonium.
3-pyridostigmine.

SAQ

A 56-year-old obese female just got out of a knee joint replacement surgery. Then, she experienced a urinary retention and constipation.
The general practitioner prescribed her a drug called Neostigmine.

1-Describe the mechanism of action of this drug.

The drug binds to acetylcholinesterase by forming a weak bond between the two binding sites of the enzyme. Thus, increase in Ach which then increases the peristaltic movement of the colon and initiate the movement of the muscle of the urinary bladder.

2-List three possible side effects could be seen in this case.

Bronchospasm.
Bradycardia.
Salivation.

3-Why cholinergic drugs are contraindicated in patient with peptic ulcer?

Because cholinergic drugs increases the secretion of gastric acid.

QUIZ

Boys	Girls
عبدالرحمن ذكري	اللولو الصليهم
عبدالعزيز رضوان	روان سعد القحطاني
مؤيد أحمد	أثير الرشيد
فيصل العباد	سما الحربي
فارس النفيسة	نوره الشبيب
خالد العيسى	وتين الحمود
عمر التركستاني	أمل القرني
عبدالرحمن الجريان	ابتسام المطيري
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