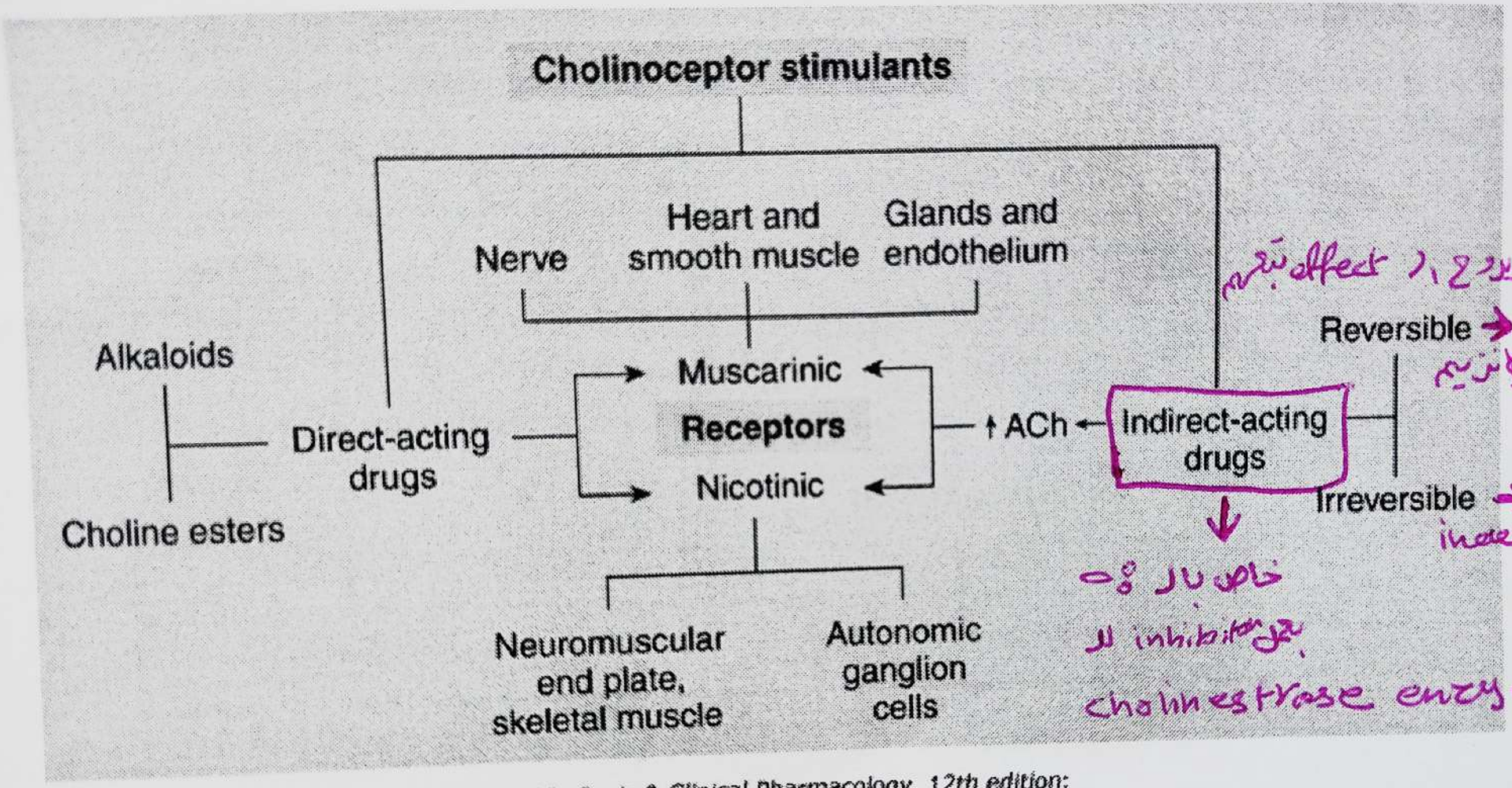
Artery Academy

Done by Mariam

Indirect-acting Cholinomimitic Drugs

2)



- Indir
drug
- Thus
acety
trans

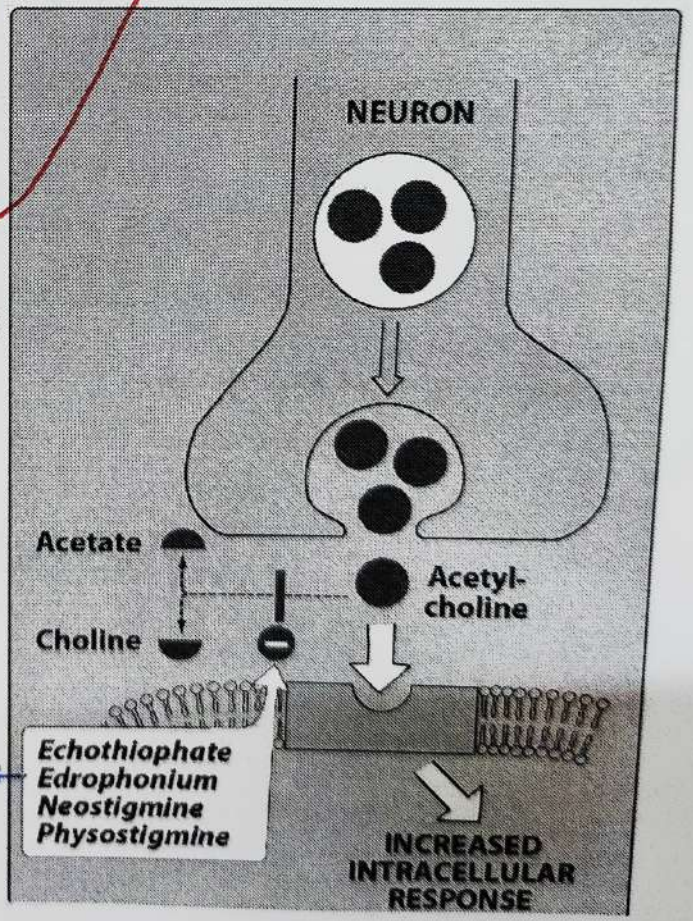
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th edition:*
www.accessmedicine.com

action of acetyl cholin لـ amplifing هاي الأدوية رح تعمل
يعني إنه الأستيل كولين هون هو إلي رح يشتغل ورح تزيد
شغلته وتحفيزه بال synaps ومثل ما حكينا سابقًا إنه هاي
الأستيل كولين الموجودة بال synaps رح تضل تترتبط بالـ effector وتحفزين
الإنزيمات تبعه

2) Indirect acting cholinomimitic drugs

(بشتغل على إنزيم نفسه (بترتبط عليه).

- Indirect acting cholinomimitics drugs inhibit acetylcholinesterase
- Thus, these drugs **amplify** acetylcholine effects wherever the transmitter is released.



fast acting ←

2) Indirect acting cholinomimitic drugs

Classification

chemical
duration ← الأساس في اختلاف هاي الأدوية

- The chief differences between members of this group are chemical and pharmacokinetic (their pharmacodynamic properties are almost identical)
- Based on their chemical structure:
  - **Edrophonium** (short acting; minutes)
    Simple alcohol bearing a quaternary group.
  - **Carbamates** (intermediate to long acting; hours)
    Carbamic acid esters.
  - **Organophosphates** (very long acting; days)
    Phosphoric acid esters.

هاي أدوية محكى نستغل الأكشن تبعها ونستخدمها على الكيوان تحمان مش بس الإنسان

- The duration of action depends on how strongly these agents interact with cholinesterase.

agents بناءً على مدى ارتباط هاي الـ duration بالـ acetyl cholinesterase. كل ما كان الـ binding قوي يكون الـ duration أطول.

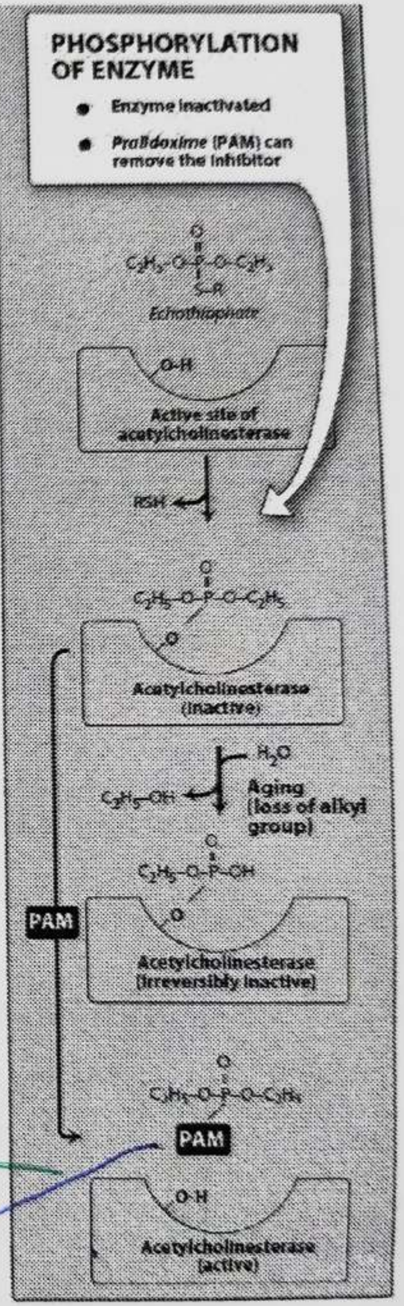
2) Indirect acting cholinomimitic drugs

Pharmacodynamics
Mechanism of Action

- Both carbamate and organophosphate bind to cholinesterase and undergo prompt hydrolysis. The alcohol portion of the molecule is then released. The acidic portion (carbamate ion or phosphate ion) is released much more slowly, preventing the binding and hydrolysis of endogenous acetylcholine. As a result, these drugs **amplify** acetylcholine effects wherever the transmitter is released.

هاد، بسبب بأنه عنده short duration

- Edrophonium, though not an ester, has sufficient affinity for the enzyme active site to similarly prevent access of acetylcholine for 5–15 min.



رح يخليه active عن طريق انه يعالج ال linkage.

وجود ال PAM رح يمنع ارتباط ال substrate بال active site.

إنزيم

حكينا سابقًا إنه الأستيل كولين استريز عبارة عن بروتين وحكينا هاي الإنزيمات لأنها ما بتدخل بال reaction وإنما فقط بتعمل excitation or inhibition of reaction

وصدول الإنزيمات بكون active site بيرتبط فيه substrate وبيشتغل active site عشان يصير تأثيره على الـ reaction.

هيك الـ active site الموجود على الأستيل كولين بحمل OH group وهاي الـ OH بتلزم الأستيل كولين كمان بيرتبط فيه الـ substrate وبصير له Hydrolysis.

2) Indirect acting cholinomimitic drugs

Edrophonium

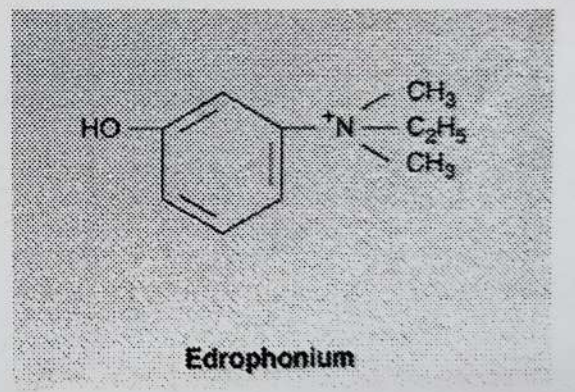
- Edrophonium

  Simple alcohol bearing a quaternary group.

absorbtion and distribution أقل

يبجي على active site للإنزيم
ومنع ارتباط الأسيتيل كولين عليه

"inhibition"



Edrophonium

2) Indirect acting cholinomimitic drugs

Carbamates

- Edrophonium
- Carbamates
  - Quaternary amines: neostigmine and pyridostigmine.
  - Tertiary amines: physostigmine and carbaryl.

absorption أكثر في Tertiary من
and distribution

Quaternary أقل في

Quaternary vs. tertiary amines regarding absorption and distribution?

2) Indirect acting cholinomimitic drugs

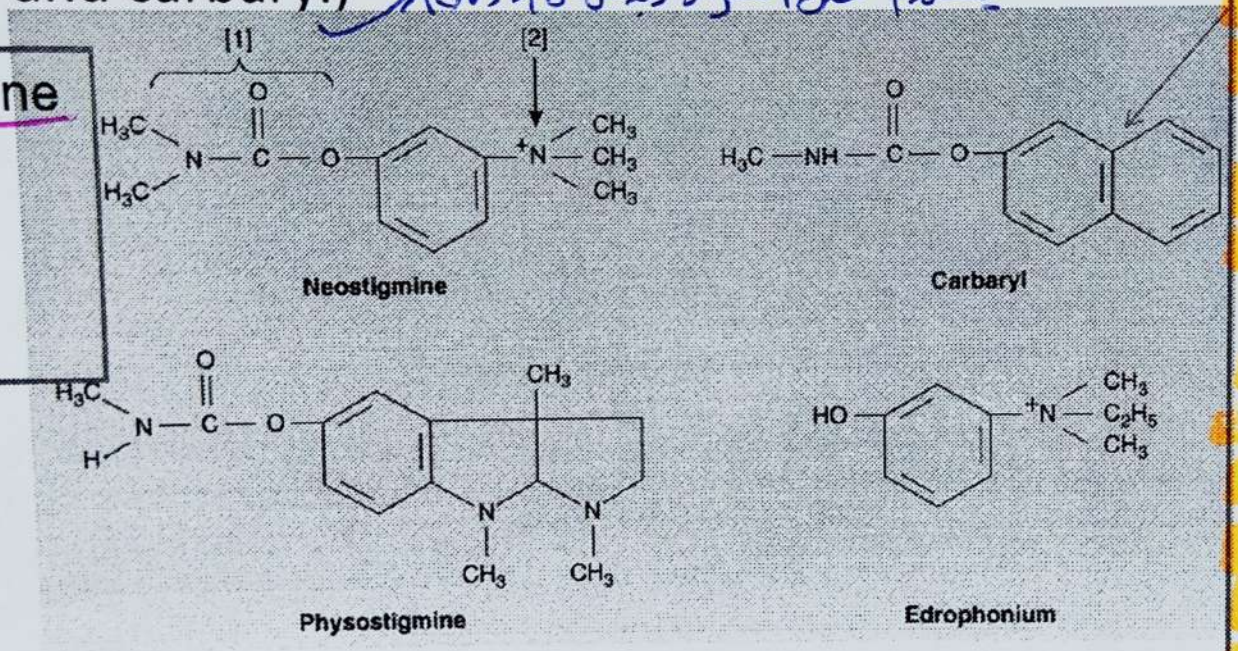
Carbamates

- Edrophonium
- Carbamates (Neostigmine, pyridostigmine, physostigmine and carbaryl)

يستخدم لقتل الحشرات (ليس له تأثير على الـ CNS)

- Ph
- Qu

•Neostigmine also has a direct nicotinic activity



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th edition*: www.accessmedicine.com

Carbaryl is a carbamate insecticides designed for very high lipid solubility, so that absorption into the insect and distribution to its central nervous system are very rapid.

Carbaryl هو insecticide مصمم very high lipid soluble وبالتالي

• CNS ← Penetration يسهل

2) Indirect acting cholinomimitic drugs

Carbamates

Pharmacokinetics: → (neostigmine and pyridostigmine).

Quaternary carbamates and edrophonium:

- Absorbtion from the conjunctiva, skin, gut and lungs is predictably poor, since their permanent charge renders them relatively insoluble in lipids. Thus, much larger doses are required for oral administration than for parenteral injection.
- Distribution into the central nervous system is negligible. (ضئيلة أو معدومة)

هدول كمعدل امتصاصهم في هاي الأماكن :-
conjunctiva, skin, gut, lungs
كيس قليل، ليش؟ لأنهم insoluble in lipids
لهيك وقت العلاج oral بنعطي جرعات جدًا عالية مقارنة بال Parenteral inj.

2) Indirect acting cholinomimitic drugs

Carbamates

- Pharmacokinetics:
- **Physostigmine (tertiary amine),** in contrast,
  - is well absorbed from all sites and can be used topically in the eye.
  - It is distributed into the central nervous system and is more toxic than the more polar quaternary carbamates.
- The duration of carbamates effect is determined chiefly by the stability of the inhibitor-enzyme complex, (not by metabolism or excretion.)

2) Indirect acting cholinomimitic drugs

Classification

- The chief differences between members of this group are chemical and pharmacokinetic (their pharmacodynamic properties are almost identical)
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    Simple alcohol bearing a quaternary group.
  - Carbamates (intermediate to long acting)

    Carbamic acid esters.
  - **Organophosphates (very long acting)**

    Phosphoric acid esters.

ماضي إشي جديد

كله حكيناه

2) Indirect acting cholinomimitic drugs

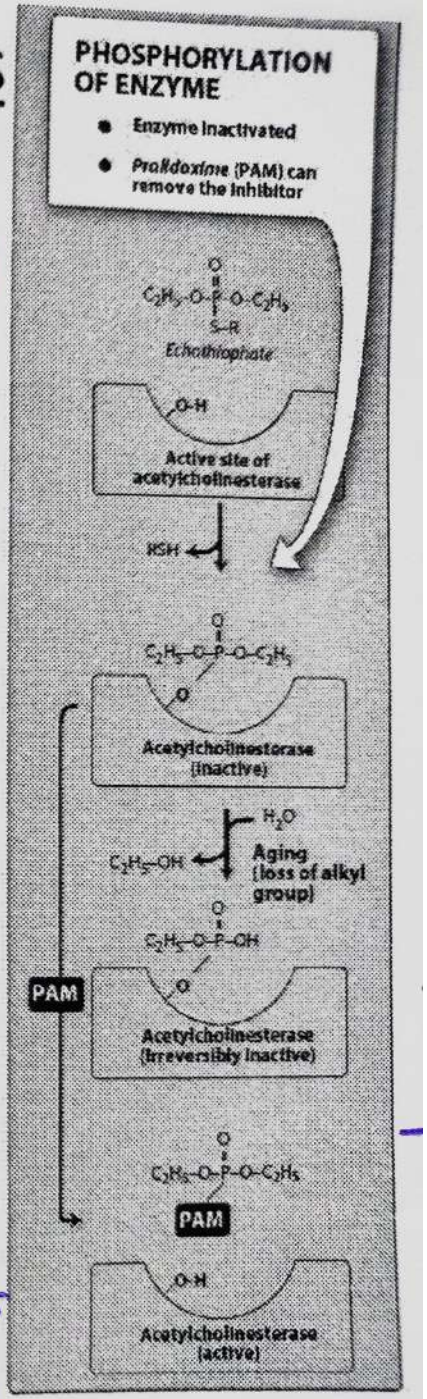
Organophosphates (irreversible)

- Organophosphates are long-acting drugs; they form an extremely stable phosphate complex with the enzyme. After initial hydrolysis, the phosphoric acid residue is released over periods of days to weeks. Recovery is due in part to synthesis of new enzyme.

antidot يعتبر for organo...

- **pralidoxime (2-PAM)**, if used before the aging process, is able to break the phosphorus-enzyme bond and can be used as "cholinesterase regenerator" drugs for organophosphate insecticide poisoning

reactivation for acetylcholin esterase.

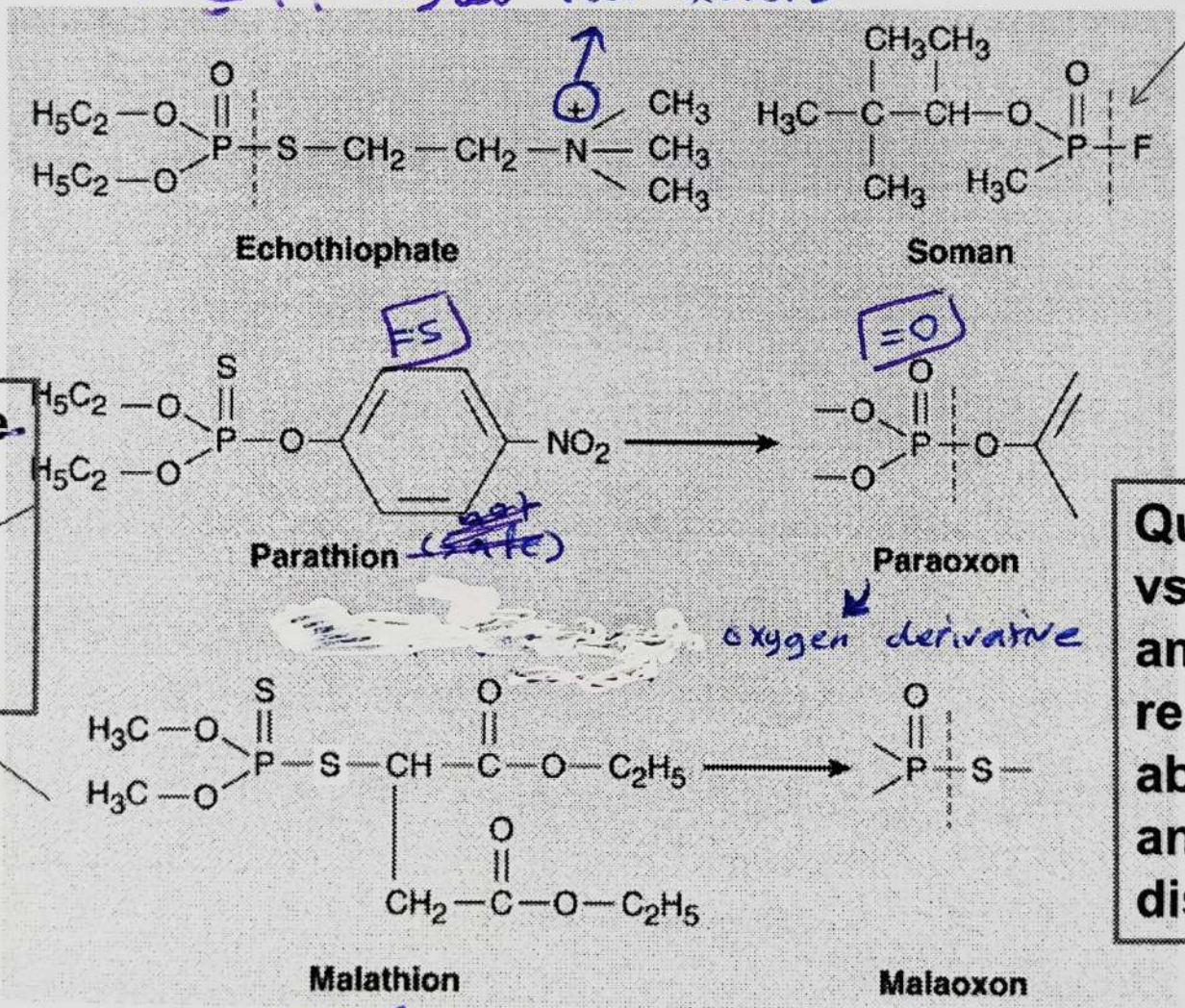


* وجود ارتباط ال organophosphate بإنزيم كليه inactive.
* أو أشخاص إلي بتتعرض لـ ، ما ح يصير لهم recovery غير لما يصير تكوين إنزيم جديد.

2) Indirect acting cholinomimitic drugs

Organophosphates

Nerve gas



thiophosphate (sulfur-containing phosphate) prodrugs

Quaternary vs. tertiary amines regarding absorption and distribution?

2) Indirect acting cholinomimitic drugs

Organophosphates

- Pharmacokinetics:
- **Organophosphates** (except for echothiophate) are:
  - well absorbed from the skin, lung, gut, and conjunctiva—thereby making them dangerous to humans and highly effective as insecticides. Toxic for humans

① ②

- **Echothiophate** is highly polar and more stable than most other organophosphates. When prepared in aqueous solution for ophthalmic use, it retains activity for weeks. ③

④ Poor absorb

2) Indirect acting cholinomimitic drugs

Organophosphates

- **Soman** is an extremely potent "nerve gas."
- The thiophosphate insecticides (**parathion**, **malathion**, and related compounds) are:
  - quite lipid-soluble (1) and are rapidly absorbed (2) by all routes.
  - They are prodrugs (3) that are inactive as such, they must be activated in the body by conversion to the oxygen analogs (malaoxon from malathion, paraoxon from parathion).

Prodrug يتحول من thiophosphate insecticides الى

active في الجسم

2) Indirect acting cholinomimitic drugs

Organophosphates

- Malathion and a few other organophosphate insecticides are also rapidly metabolized by other pathways to inactive products in birds and mammals but not in insects; these agents are therefore considered safe enough for sale to the general public.

- Parathion is not detoxified effectively in vertebrates; thus, it is considerably more dangerous than malathion to humans and domestic animals and is not available for general public use in the USA.

* Malathion → safe for general Puplic use
* Parathion → more dangerous " " " "

هاي السكاشن حكيناها بداية التفويخ .

2) Indirect acting cholinomimitic drugs

Organ system effects

- By inhibiting cholinesterase, indirect acting cholinomimitics cause an increase in the concentration, half-life, and actions of acetylcholine in synapses where acetylcholine is released physiologically. Therefore, the indirect agents have muscarinic or nicotinic effects depending on which organ system is under consideration.

- Cholinesterase inhibitors do not have significant actions at uninnervated sites where acetylcholine is not normally released (eg, vascular endothelial cells).

Indirect acting cholinomimitics

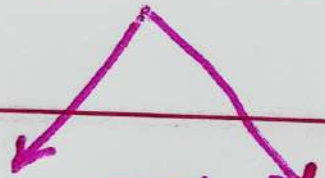
↓

inhibiting cholinesterase

↓

increase in the concentration and half-life and actions of acetyl choline in synapses

يعني الـ indirect agents have:



muscarinic effect [or] nicotinic effect.

اعتمادًا على الـ which organ system is under consideration.

2) Indirect acting cholinomimitic drugs

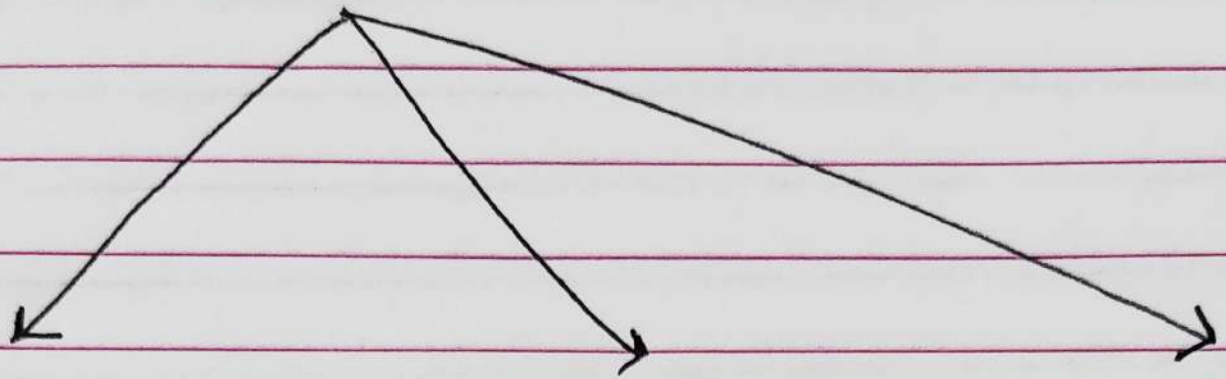
Organ system effects

- Major effects of cholinesterase inhibitors:

1. Actions on the parasympathetic nervous system, may cause bradycardia, hypotension, hypersecretion, bronchoconstriction, GI tract hypermotility, and decrease intraocular pressure.
2. Action on sympathetic nervous system may cause an increase in systemic vascular resistance and blood pressure
3. Actions on the neuromuscular junction will result in prolonged muscle contraction.

عملت مخطط للسلايد يساعدكم بالحفظ

Major effects of cholinesterase inhibitor 8=



Parasympathetic Nervous system

- bradycardia
- Hypotension
- Hypersecretion
- bronchoconstriction
- GI tract hypermotility
- decrease intraocular pressure.

sympathetic Nervous system

- increase in systemic vascular resistance and blood pressure.

Neuromuscular Junction

- prolonged muscle contraction.

Cholinomimitics Toxicity

سواء كانت direct or indirect

- SLUDGE syndrome: → كل كلمة بتبشر إلى syndrome بحتين وإضافة عليهم حرف الـ M .
  - Salivation
  - Lacrimation
  - Urination
  - Defecation
  - Gastrointestinal upset
  - Emesis
- An extension is **SLUDGEM**, where the additional M indicates:
  - Miosis: stimulation of the pupillary constrictor muscles

  or
  - Muscle spasm: stimulation of skeletal muscle.

Clinical pharmacology of cholinomimitics

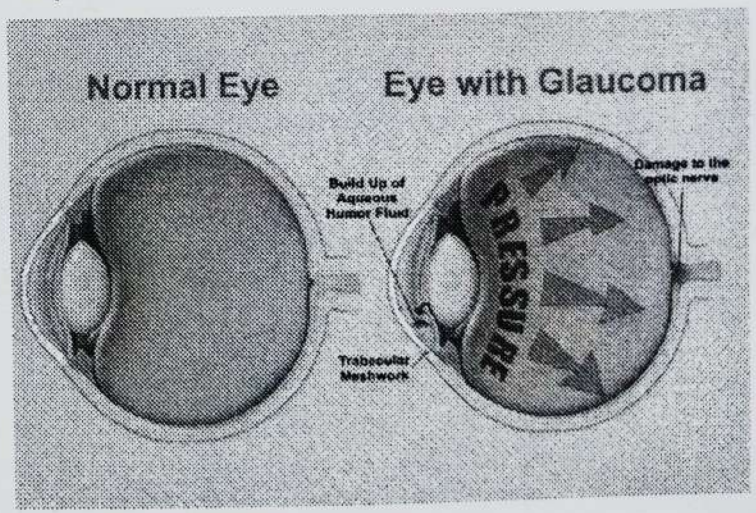
1. Glaucoma
2. Myasthenia gravis
3. Urinary retention
4. Sjogren's syndrome

رح نحكي عنهم بالتفصيل

شوغرين

1. Glaucoma المياه الزرقاء

- It is a group of ocular disorders united by a clinically characteristic increase in intraocular pressure (increase in fluid pressure in the eye (aqueous humor).
- Cholinomimitics work by contracting of the ciliary muscle and increasing the outflow of the aqueous humor.
- In the past, glaucoma was treated with either direct agonists (pilocarpine, methacholine, carbachol) or cholinesterase inhibitors (physostigmine).
- For chronic glaucoma, these drugs have been largely replaced by prostaglandin derivatives and topical β blockers.



2. Mysthenia gravis الوهن العضلى الوبيل

وصف المرض

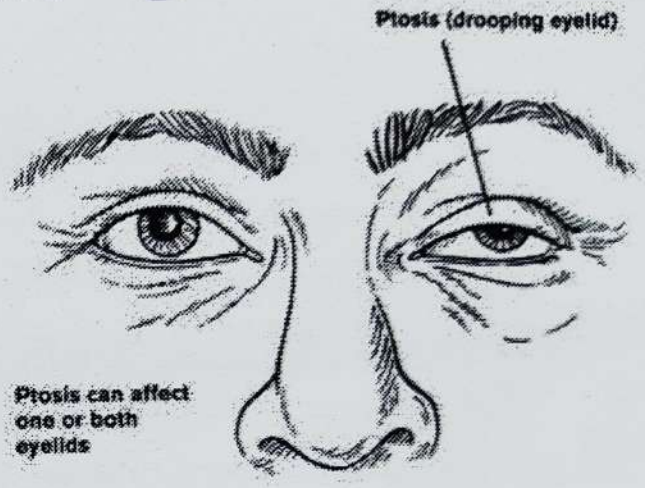
* Is an autoimmune neuromuscular disease leading to fluctuating muscle weakness and fatigue.

سببه

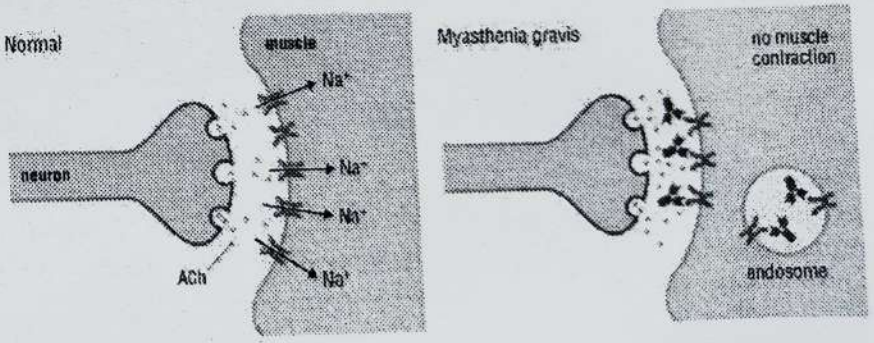
* Muscle weakness is caused by circulating antibodies that block acetylcholine receptors at neuromuscular junction.

دوا المرض

* Cholinesterase inhibitors (**neostigmine** and **pyridostigmine**) - but not direct-acting acetylcholine receptor agonists- are extremely valuable as therapy for myasthenia.



From **Immunity:The Immune Response in Infectious and Inflammatory Disease** by DeFranco, Locksley and Robertson



3. Urinary retention احتباس البول

مين نصيبه؟

* Urinary retention may occur postoperatively or postpartum or may be secondary to spinal cord injury or disease (neurogenic bladder).

① بعد الجراحة ② بعد الولادة ③

العلاج

* In patients with urinary retention, **bethanechol** can be given subcutaneously in a dose of 5 mg and repeated in 30 minutes if necessary.

بنعطي bethanechol حقن تحت الجلد
بمقدار 5mg منه مع إمكانية تكرار الجرعة
كل نصف ساعة عند اللزوم.

4. Sjogren's syndrome مرض متلازمة جوغرن

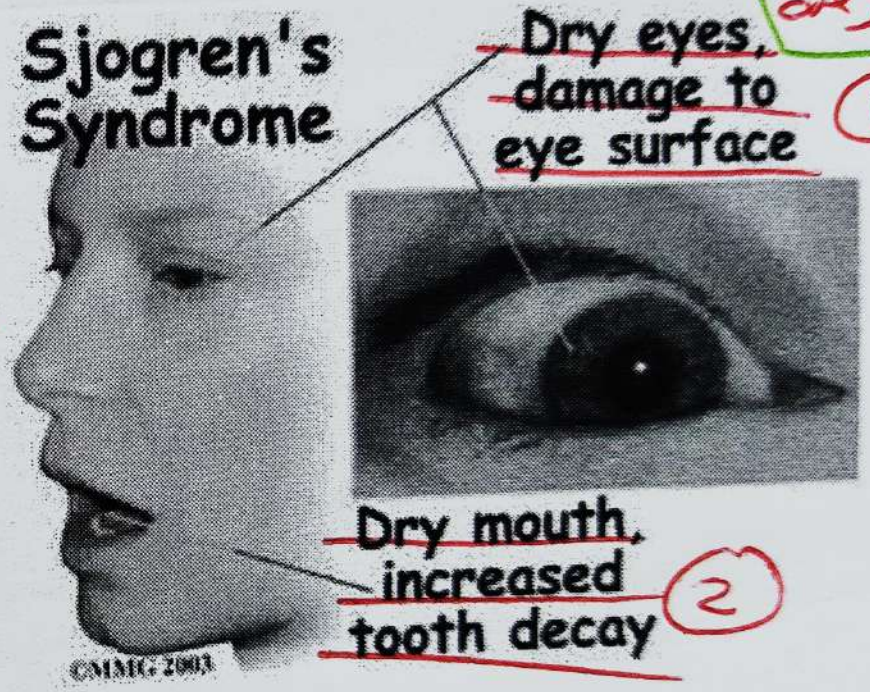
وصف المرض

* Is a systemic autoimmune disease in which immune cells attack and destroy the exocrine glands that produce tears and saliva.

ducts يكونوا إلى ← تفرز خارج الجسم

العلاج *

Pilocarpine is used to treat this syndrome.



أعراضه

مرض مناعي بتهاجم فيه الخلايا المناعية وتبدأ تدمّر الغدد الخارجية إلي بتنتج الدموع واللعاب (tears and saliva).

Case study

- In mid-afternoon, a coworker brings 43-year-old JM to the emergency department because he is unable to continue picking vegetables. His gait is unsteady and he walks with support from his colleague. JM has difficulty speaking and swallowing, his vision is blurred, and his eyes are filled with tears. His coworker notes that JM was working in a field that had been sprayed early in the morning with a material that had the odor of sulfur. Within 3 hours after starting his work, JM complained of tightness in his chest that made breathing difficult, and he called for help before becoming disoriented.
- How would you proceed to evaluate and treat JM? What should be done for his coworker?

← حليهم هايلايت اورغ ← الأعراض ← case بهمني بأي

← وال history of Patient ← حليهم هايلايت زهري .

← بعدين بنحدد العرض Poisoning by organophosphate cholinesterase inhibitors.

← وبناءً حليه العلاج ← حليه هايلايت اورغ بالسكيد اباي .

+ الإسعافات اللازمة

Questions???

- Decontaminate the Patient by removal of clothing and washing affected areas
- Ensure an open airway and ventilate with oxygen.

Case study answer

- The patient's presentation is characteristic of poisoning by organophosphate cholinesterase inhibitors. Ask the coworker if he can identify the agent used. Decontaminate the patient by removal of clothing and washing affected areas. Ensure an open airway and ventilate with oxygen. For muscarinic excess, administer atropine (0.5–5 mg) intravenously until signs of muscarinic excess (dyspnea, lacrimation, confusion) subside. To treat nicotinic excess, infuse 2-PAM (initially a 1–2% solution in 15–30 minutes) followed by infusion of 1% solution (200–500 mg/h) until muscle fasciculations cease. If needed, decontaminate the coworker and isolate all contaminated clothing.

→ muscarinic excess → atropine

→ nicotinic excess → 2-PAM