SHEET NO.

PHARMACOLOGY

DOCTOR 2019 | MEDICINE | JU

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Cholinoceptor - Activating & Cholinesterase-Inhibiting Drugs -2

Review : Mechanism of action:

1) **Increase** in concentration of endogenous **acetylcholine** at cholinocepters .
2) **Edrophonium** :is a quaternary alcohol, which bind electrostatically and by hydrogen bonds to the active site ,thus preventing access of acetylcholine
3) The enzyme-inhibitor complex does not involve a covalent bond and and that is why short-lived (on the order of 2-10 minutes)
4) Carbamate esters, e.g., **neostigmine** and **physostigmine**. undergo a two-step hydrolysis sequence similar to acetylcholine.
5) The covalent bond of the carbamoylated enzyme is more resistant to the second (hydration) process, and this step is correspondingly prolonged (30 minutes – 6 hours)
6) The **organophosphates**. undergo initial binding and hydrolysis by the enzyme, resulting in a phosphorylated active site.
7) The covalent phosphorus -enzyme bond is extremely stable and hydrolyzes in water at a very slow rate (hundreds of hours).
8) After the initial binding-hydrolysis step, the phosphorylated enzyme complex may undergo a process called **aging**"
9) **Pralidoxime** If given before aging has occurred, is able to break the phosphorus-enzyme bond and can be used as "**cholinesterase regenerator**" drugs for organophosphate insecticide poisoning.

Organ System Effects due to indirectly inhibiting drugs

Central Nervous System

"for drugs that can penetrate BBB like Physostigmine and Organophosphates"

1. In **low** concentrations, the lipid-soluble cholinesterase inhibitors cause a subjective alerting response.
2. In **higher** concentrations, they cause generalized convulsions, which may be followed by coma and respiratory arrest and death.

-Eye**,** Respiratory Tract, GIT, Urinary Tract**: The effects are qualitatively similar to the effects of the direct-acting cholinomimetics.**

"eye:miosis , RT: Bronchoconstriction + increase bronchial secretion , GIT: Peristaltic activity is increased +diarrhea, UT :avoiding urine , urinary contrast"

-Cardiovascular System

Mimic the effects of vagal nerve activation on the heart. So, produce **Negative chronotropic**[HR goes down]**, dromotropic**[conduction velocity decreases]**, and inotropic**[contraction strength decreases] effects and **cardiac output falls**.

The fall in cardiac output is due to bradycardia, decreased atrial contractility, and some reduction in ventricular contractility[because ventricle not innervated by parasympathetic neurons],only the tissues that have cholinergic nerves innervating them that are affected.

The latter effect occurs as a result of **prejunctional inhibition of NE release**.

"that we know the NE or the neuron that release the EN has cholinergic heteroreceptor that will stimulated by Ach→ can decrease NE release then decrease the contractility of the ventricle a little bit."

Minimal effects by direct action on vascular smooth muscle ; because most vascular beds lack cholinergic innervations.

The net cardiovascular effects of moderate doses of cholinesterase inhibitors consist of:

1. modest bradycardia 2. a fall in cardiac output
3. an increased vascular resistance: which is due to **(sympathetic ganglion stimulation)** that results in a rise in blood pressure.

-Neuromuscular Junction

1. **Low** concentrations prolong and intensify the actions of Ach. This increases the strength of contraction, especially in muscles weakened by **curare-like neuromuscular blockers** or by **myasthenia gravis**.

Curare: used in surgery mostly, it's a heavy **relaxant** for muscles[muscles paralysis]+a neurovascular blocker of a competitive type , which competes with Ach on nicotinic receptor in the muscles→ leads to muscles paralysis .

myasthenia gravis: a disease that produces weak muscles contractions.

2. **higher** concentrations fibrillation of muscle fibers. **Antidromic firing** (nerve impulses in a direction opposite to normal) of the motor neuron may also occur, resulting in **fasciculations**[irregular muscles or fibers contraction] that involve an entire motor unit.

3. With marked inhibition of acetylcholinesterase, **depolarizing neuromuscular blockade occurs followed by a phase of nondepolarizing blockade** as seen with **succinylcholine** [a depolarizing neuromuscular blocker of a sustained type(no muscle contraction)].
4. Some quaternary carbamate cholinesterase inhibitors, e.g., neostigmine, have an additional direct nicotinic agonist effect at the neuromuscular junction[this quaternary atom is present also in ACh "due to the similarity with ACh"], which is an additive effect to the inhibition of metabolism of ACh . This may contribute to the effectiveness of these agents as therapy for myasthenia gravis [weakness of the muscles].

Clinical use :

➡ *The Eye*

Glaucoma was treated with pilocarpine, methacholine, carbachol or ChEIs; physostigmine, demecarium, echothiophate, isoflurophate).

"**Glaucoma**: is a condition that occurs when the production of aqueous humor exceeds the outflow of it → build up pressure inside the eye , also drugs that cause miosis of the eye that pull the iris toward the center→ that helps to open the filtration angle and facilitate the out flow of aqueous humor "

-These drugs have been replaced by topical -**βblockers** and **prostaglandin** derivatives as we noticed they perform the same functions with very less side effects." These drugs Produce the same lowering effect of the pressure inside the eye ,but not interfere with vision and have less side effects."

- **Acute angle-closure glaucoma** is a medical emergency that usually requires surgery. Before surgery : Initial therapy consists of a combination of a direct muscarinic agonist and a cholinesterase inhibitor (e.g., pilocarpine plus physostigmine) → to prepare the patient to lower intraocular pressure then can the surgeon operate to open the closed angle.

➡ *GI and Urinary Tracts*

- **Postoperative ileus** (atony or paralysis of the stomach or bowel following surgical manipulation to speed up or restore the peristaltic movement) and **congenital megacolon** (lack of cholinergic nerves in end of the colon) – the stimulation of those receptors can help solve the problem .

- **Urinary retention** postoperatively or postpartum or **secondary to spinal cord** injury or disease (neurogenic bladder). Usually due to atropine given in surgery. [we are discussing the uses of all cholinergic drugs]
- - **Bethanechol and Neostigmine** are the most widely used, but it must be certain that there is no **mechanical obstruction to outflow before using the cholinomimetic agents.**
- - **Pilocarpine** Has long been used to increase salivary secretion[in.
- - **Cevimeline** A new direct-acting muscarinic agonist used for the treatment of dry mouth associated with **Sjogren's syndrome** (a systemic autoimmune disease) and that was caused by radiation damage of the salivary glands .

Neuromuscular Junction

ptosis: can't open both eyes fully

Myasthenia gravis is an autoimmune disease affecting skeletal muscle neuromuscular junctions. Antibodies are detected in 85% of myasthenic patients. The antibodies reduce nicotinic receptor function.

Frequent findings are:

1-ptosis(pic)- ptosis: can't open both eyes fully-

2-diplopia: double vision

3- difficulty in speaking & swallowing

4- extremity weakness.

Severe disease may affect all the muscles, including those necessary for respiration and therefore severe cases might lead to death .

The disease resembles the neuromuscular paralysis produced **by d-tubocurarine(a curare drug** that competes with acetylcholine and block nicotinic receptors **).**

Patients with myasthenia are very sensitive to the action of neuromuscular blockers , like **d-tubocurarine** and other drugs that interfere with neuromuscular transmission, e.g., **aminoglycoside antibiotics** (oligomycin , gentamycin , etc).

Patients with **ocular myasthenia** **may be treated with cholinesterase inhibitors alone.** Patients having more widespread muscle weakness are also treated with **immunosuppressant drugs (steroids, cyclosporine, and azathioprine) to lessen the ABs produced**{ immune system Produce Antibodies that attack nicotinic receptors in the muscles.} In some patients, the **thymus gland is removed**.

Edrophonium :is used as a diagnostic test for myasthenia for its short acting time(2-10 min) so it is not used to treat myasthenia but use for diagnosis .
• A 2 mg dose is injected by IV. If the patient has myasthenia gravis**,** an immediate improvement in muscle strength that lasts 5 minutes can be observed , its important that it is short acting , so patients won't suffer for long.
• **Edrophonium** is also used to assess the adequacy of treatment with the longer-acting cholinesterase **inhibitors** in patients with myasthenia gravis.
➔ If somebody has been treated with other drugs and we don't know if the dose enough or not , we inject the edrophonium to see of we need a higher dose if there was room for improvement.

• Clinical situations in which **severe myasthenia** (**myasthenic crisis** for patient who do not take the proper dose and has low muscle strength) must be distinguished from excessive drug therapy (**cholinergic crisis**)→ we inject the edrophonium.

➔Myasthenic is usually AI so he must improve and cholinergic is usually due to the overdose of drugs so if there's a blockade and he got worse we would know.

Long-term therapy of myasthenia gravis is usually accomplished with **pyridostigmine, neostigmine or ambenonium.**
• **Muscarinic** side effects [salivation, diarrhea .etc…] is controlled by **atropine**. When the patient continues to take these drugs →Tolerance to the muscarinic effects develops, so atropine treatment is not required. Atropine: muscarinic blockers.

• Neuromuscular blockade is frequently produced as an adjunct to surgical anesthesia[during anesthesia the muscles need to be relaxed] the relaxation involve all the body like respiratory tract . After surgery, **neostigmine and edrophonium** are the drugs of choice used to **reverse this pharmacologic paralysis promptly** → normal respiration continuous then can take the patient out of the operating room.

Central Nervous System

•Tacrine is an anticholinesterase developed lately , used for the treatment of mild to moderate Alzheimer's disease. Since the old acetylcholinesterase don't penetrate the blood brain barrier .

Tacrine's efficacy is modest, and hepatic toxicity is significant.(physostigmine is highly toxic- on system- to be use)

Tacrine can penetrate the BBB , and can treat Alzheimer's disease , in Alzheimer's disease there is degeneration in cholinergic nerves in the brain that causes loss of memory .

• Donepezil is newer, more selective used in treatment of cognitive dysfunction in Alzheimer's patients. Given once daily because of its long half-life, and it lacks the hepatotoxic effect of tacrine.

Toxicity

• Varies markedly depending on their absorption, access to the CNS, and metabolism

Direct-Acting Muscarinic Stimulants

• Pilocarpine and the choline esters over dosage cause: **nausea, vomiting, diarrhea, urinary urgency, salivation, sweating, cutaneous vasodilation, and bronchial constriction**.

The effects are all blocked competitively by atropine

•Certain mushrooms contain muscarinic alkaloids. (**Amanita muscaria**, the first source of muscarine, contains very low concentrations of the alkaloid.) Ingestion of these mushrooms causes **typical signs of muscarinic excess within 15–30 minutes >>> (heart arrest) ..>> fatal(because receptor stimulated heart strongly >>> stop bleeding). Treatment is with atropine, 1–2 mg parenterally.**

Direct-Acting Nicotinic Stimulants

- Acute Toxicity

The fatal dose of nicotine is 40 mg, or 1 drop of the pure liquid (pure nicotine) – very toxic - . This is the amount of nicotine in two regular cigarettes. Fortunately, most of the nicotine in cigarettes is destroyed by burning or escapes via the "side stream" smoke.

Ingestion of nicotine insecticides or of tobacco by infants and children is usually followed by vomiting (to get rid of poisons), limiting the amount of the alkaloid absorbed.

Toxic Effects of large dose of nicotine :

1. central stimulant actions, which cause convulsions and may progress to coma and respiratory arrest

2. skeletal muscle end plate depolarization, which may lead to depolarization blockade and respiratory paralysis (**because resp. muscles are paralyzed)**

3. hypertension and cardiac arrhythmias(a dangerous Side effect). Treatment of acute poisoning is symptom directed.

- Muscarinic excess resulting from parasympathetic ganglion stimulation can be controlled with atropine.(All of the previous effects are blocked competitively by atropine)
- Central stimulation is treated with anticonvulsants such as diazepam. - Neuromuscular blockade is not responsive to treatment and requires mechanical respiration.((patient is placed on a ventilator)(to make sure patient is breathing , after a while this blockade disappears by itself)

Fortunately, nicotine is metabolized and excreted relatively rapidly. Patients who survive the first 4 hours usually recover completely if hypoxia and brain damage have not occurred.

Chronic Nicotine Toxicity (smoking)

• Nicotine contributes to the increased risk of vascular disease and sudden coronary death associated with smoking.

• Also, the high incidence of ulcer recurrences in smokers.(because nicotine increased acid in stomach)

• now you should encourage your patients to stop smoking but the response may be impossible in some cases so there are alternative ways

➡ Replacement therapy with nicotine in the form of **gum, transdermal patch, nasal spray, or inhaler** are used to help patients stop smoking.

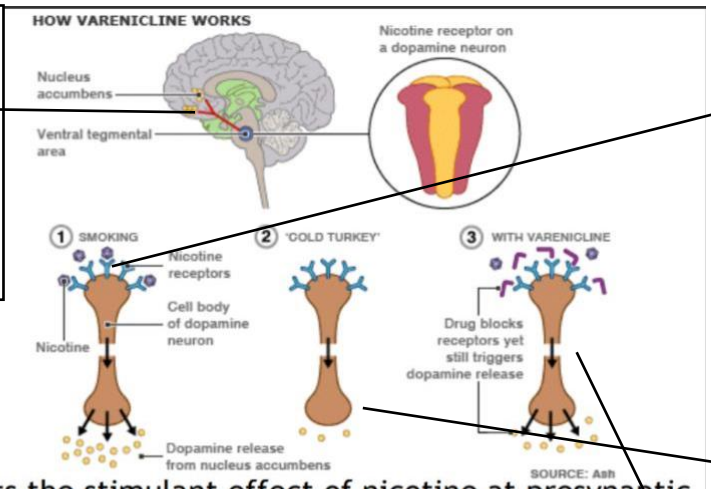
Varenicline

• Has partial agonist action at central nicotinic receptors.(partial agonist :block nicotinic receptors but in same time produce some stimulation)
• It also has antagonist properties that persist because of its long half-life

(المقصود من هذا الحكي انو هذا الدوا رح يساعد الاشخاص المدخنين (الي بدخنوا بكميات كبيرة للاقلاع عن التدخين على المدى الطويل

لانو ما رح يلغي كل النيكوتين الي بالجسم ف بهاي الحالة بكون قلل نسبة الى ادنى حد ممكن وبنفس الوقت ما تكون بحجم الكمية الي كانت بالجسم قبل العلاج

Nicotinic site function is pleasure center
لو ترجعوا للفيديو لانه بستفيدوا اكثر
(34:00 -37:42)



- It prevents the stimulant effect of nicotine at presynaptic nicotinic receptors that cause release of dopamine.
- its use is limited by nausea and insomnia and also by exacerbation of psychiatric illnesses, including anxiety and depression.

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dopamine will be release if patient takes morphine

The pleasure of smoking is achieved by the release of dopamine from the pleasure center , then binding to nicotinic receptor to produce an effect ,

2) With no smoking >>no nicotine will bind >>no dopamine will be release >>so will negatively affect the mood .

3) with varenicline >> partial agonist >>release dopamine (but less than that in smoking state)

Cholinesterase Inhibitors

• The major source of intoxications is pesticide.
• pesticides can cause symptoms which persist for days.
• chemical warfare agents (soman, sarin, VX) induce effects rapidly. . Miosis, salivation, sweating, bronchial constriction, vomiting, and diarrhea.

CNS involvement (cognitive disturbances, convulsions, followed by coma and death) usually follows rapidly, accompanied by peripheral nicotinic effects, especially depolarizing neuromuscular blockade , so patients stop breathing.

Therapy always includes:

1. **maintenance of vital signs—respiration in particular may be impaired.**
2. **decontamination to prevent further absorption**.(gastric lavage : if the patient has eaten something sprayed with such agents then gastric lavage will remove the unabsorbed part of it **,** also cleaning the surface of sprayed foods also helps)

3. **atropine given parenterally in large doses , given as often as required** to control muscarinic excess. Therapy often also includes treatment with pralidoxime (to regenerate enzyme), and benzodiazepines for seizures.

• **Preventive therapy for cholinesterase inhibitors warfare agents**(given to solders will go to battle ageist nerve gases) • Personnel are given auto injection syringes containing **pyridostigmine and atropine**.
• Chronic exposure to certain organophosphate compounds causes delayed neuropathy associated with demyelination of axons.

pyridostigmine Is reversible acetylcholine inhibitor . so when soldiers sense that the enemy is releasing nerve gases poisons (organophosphate) , each one of them auto inject himself with **pyridostigmine** , which attach to the active site of the enzyme
that inactivates the enzyme for few hours to prevent the formation of covalent bond with poisons (organophosphate) or nerve gas to prevent enzyme phosphorylation .

atropine Prevent muscarinic effects which Produce by pyridostigmine

• The effects are not caused by cholinesterase inhibition but rather by neuropathy target esterase (NTE) inhibition whose symptoms (weakness of upper and lower extremities, unsteady gait) appear 1–2 weeks after exposure.

• Another nerve toxicity called intermediate syndrome occurs 1–4 days after exposure to organophosphate insecticides. This syndrome is also characterized by muscle weakness; its origin is not known but it appears to be related to cholinesterase inhibition.

كن محسنا فما ضاع إحسان سدى

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