Medical Committee
The University of Jordan

PHARMACOLOGY

Lecture No.: 17

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SHEET ■

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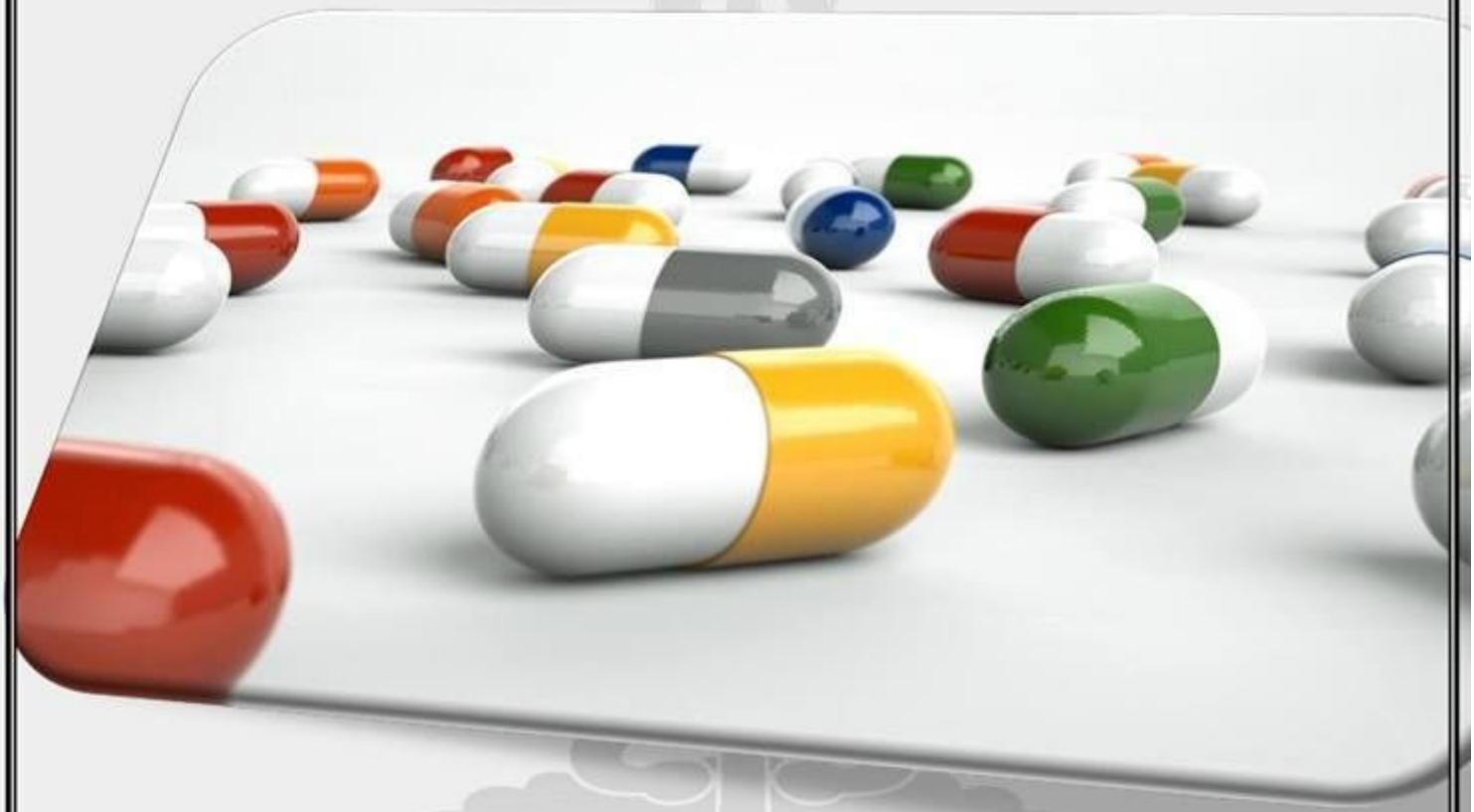

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بسم الله☺

We lastly talked about the synaptic regulation; the post-synaptic regulation for sympathetic and parasympathetic systems.

We also discussed the up regulation and the down regulation mechanisms too, we clarify the significance of the up regulation, and now let's ask about the importance and significance of down regulation, what is it? Why should we know if this certain drug that we'll be given to a patient would down regulate the receptors or not?

Due to TOLERANCE effect.
(we mentioned it in the first lecture and now will discuss further)
* what are the mechanisms of tolerance?

1- Auto-induction of metabolism
2- Down regulation of receptors

This was a quick revision, and you now have good background, now we'll start with the main topic for today's lecture which is : **Cholenirgic drugs.**

CHOLENIRGIC DRUGS
Or (CholinoMimetics: Drugs acting like Acetyl Choline)
They are divided into two main types:
1- DIRECT acting : work on receptors of Ach.
2- INDIRECT acting : work on Ach-esterase (INHIBIT it)
so will be an accumulation of Ach in the synapse

Now we'll talk in details;

1- DIRECT acting cholinemimetics:
-Cholin-esters, Derivatives of Ach, modified Ach , Methacholine, Carbachol and Methinchol
-Naturally occurring Alkaloids (Muscarin , that binds to muscarinic receptors), Pilocarpine (important in clinical use)

➔ Pharmacokinetics :
1- Choline-esters are quaternary ammonium compounds (like the Ach , it has a +ve charge) and this means that:
- they can't cross membranes, won't cross the blood-brain barrier. (highly water

soluble , and insoluble in lipids)
- can't be used orally because they won't be absorbed well.
- poorly absorbed and distributed also because the distribution needs passage through membranes so they can't distribute very well.
- they are hydrolyzed in the gut and inactive by oral route, in addition of not being absorbed, they are metabolized by the gut wall, they differ in their susceptibility to be hydrolyzed by the cholinesterase.

** Regarding the susceptibility;

The Acetyl Choline (Ach) is the most susceptible (will be eliminated faster (half-life in seconds)).

Methacholine is susceptible a little bit.
Bethanechol and carbachol cloride has negligible susceptibility , that means it has longer duration of action, and won't be eliminated very fast.
* you have benefits here, you have more prolonged action, and selectivity to the muscarinic and nicotinic receptors (but not absolute selectivity, for example: methylcholine and methinchol are selective but carbachol is not selective) .

Now:

2- Pilocarpine, The tertiary natural compound
- It's a tertiary amine, (tertiary amine: is not charged and have 3 groups/atoms bonded to the nitrogen atom).
- These can pass through membranes because they have some sort of lipid solubility, so they can be absorbed from everywhere and also distributed in the body.

3- Alkaloids Muscarinic (actually it's not used in the therapeutic process , because it's quaternary amine – not absorbed well-
- It's found in the poisonous mushroom and causes toxicity if eaten.
- it's quaternary amine, and even though it's toxic when injected . maybe because high amounts of this muscarine are in certain toxic mushroom kinds.
- Extra information for you: the toxic mushroom is not one type , there are 6 to 7 types that differs depending on the species and on the toxin they produce.

➔ Pharmacodynamics:

Similar to Ach, they stimulate muscarinic receptors mainly.

And now let's go in details about what we've discussed in the last lecture; (the effect of the cholinemimetics on specific organs) :

1- EYE :

- Contracts the smooth muscle of the iris sphincter (the circular muscle of eye or we call it sphincter pupilly), and this contraction leads to MIOSIS which is narrowing of the pupil .
- We use this in diagnosing the toxicity by Muscarine-containing mushroom, the patient will have miosis in his pupil. (miosis is very important sign in toxicology).
- He may have miosis due to other reasons other than Mushroom toxicity.
- We said before that the radial muscle is under sympathetic control (not parasympathetic). Now the ciliary muscle contracts to accommodate for near vision (for example when reading a book, parasympathetic) so ciliary muscle contacts under the influence of cholinomimetics to accommodate for near vision.
- Facilitation of aqueous humor outflow into the canal of Schlemm. (I once told you that glaucoma is a disease that happens as a result to increased intra ocular pressure that leads to increased pressure on the optic nerve (nerves are susceptible to pressure) so we won't be able to see efficiently and blindness may occur.
- It has to be treated, and one of the drugs that may be used is pilocarpine, it facilitates aqueous up flow (reduces the fluids in the eye and reduces the pressure on the optic nerve) .
- The pressure in the eye is due to the fluids in the anterior chamber.

2- Cardio Vascular System (CVS)

- before talking about its effects, we need to know that there are reflexes in the body that can counteract the effects of the parasympathetic nervous system.
*e.g: sometimes you may give the cholinemimetic to a patient and you won't see the effects that I'll tell you about it now, because reflexes within the heart are very good and efficient. So not every drug with every dose will affect the functions of the heart.
- now put reflexes aside, let's talk about the usual effects on the heart: **large doses of Ach produce bradycardia** (**lower heart pumping rate** to an abnormal level/range) → **negative chronotropic effect.**

- decreased AV node conduction:

Note: the SA node fires , the impulse travel through the atrial muscle then to the AV node, AV node conduct it to the ventricle.

- Cholinomimetics : affect the parasympathetic nervous system, slows down the conduction of AV node (decreased conduction) → **negative dromotropy.**
- Increases the refractory period , it's the period through which the heart is unable to response to new stimulus, it will be prolonged, because of the parasympathetic system effect and the cholinomimetics.

-Reduced contractility of the atrial muscle.

- (not the ventricles because there is no parasympathetic innervation to the ventricles, the parasympathetic is only for the atrial cells so it reduces the contractility of them) →
negative inotropy.

** so : cholinemimetics work on the parasympathetic nervous system then:

1- **Negative chronotropy : reduced rate**
2- **Negtine dromotropy : reduced conduction (AV node)**
3- **Negatibe inotropy : reduced contractility (atrail muscles)**

Now pilocarpine has few different effects.
pilocarpine initially reduces the blood pressure (also Ach can reduce blood pressure because of vasodilation).
* Now pilocarpine when given intravenously by fusion, it will reduce the blood pressure then HYPERTENSION occurs. So How does that happen unlike the other cholinomimetics which reduce the blood pressure?
Due to sympathetic ganglionic discharge, caused by activation of post ganglionic m1 receptors. But What does this mean? How can cholinemimetics make sympathetic discharge?
By presynaptic heteroreceptors that stimulate norepinephrine release, and this norepinephrine will cause increase in blood pressure due to vasoconstriction → Hypertension.

→Another question is: why does this occur in the sympathetic ganglion, why it's not in the terminals?
Actually It's a complex interaction , it starts with postganglionic neuron, it has autoreceptors that interact with other things to cause discharge of the sympathetic ganglion. It's not as simple as what heretreceptors do to stimulate norepinephrine releasing.

To sum up: pilocarpine increases the norepinephrine release at the end from sympathetic neurons and this leads to increasing in blood pressure.

3- Respiratory system :

-Contraction of smooth muscle (Bronchoconstriction)
- It's a stimulation of secretions of glands in the tract bronchial tree.

** we talked about that in the GI tract as a "secreto-motor" , also in the urinary tract in the parasympathetic innervation , the CHOLINOMIMETICS have similar effects → bronchial tree : contraction, narrowing, increased secretions (more narrowing) .

* in BRONCHAL ASTHMA, we should not give cholinomimetics, we need to block the activity of cholinomimetics because they make it worse and lead to more contraction in the bronchi with increasing in secretions of the bronchial tree, these secretions will reduce the free spaces because the will fill parts of the lumens of bronchi.

4- GI tract:

- increased secretions of gut
- **strong** stimulation of salivary and gastric glands , while pancreatic and small intestine glands will be **less** stimulated.
- increased motor activity in the gut & relaxation of sphincters . (part of the defecation reflex)
** the parasympathetic system and the cholinomimetics do the same things : increase motility , increase secretions, and relax sphincters.

5- Urogenital system
- stimulation of the **detrusor** muscle of the urinary bladder , it's the muscle of the wall of bladder, it Contracts.
- relaxation of sphincter occurs , so these may lead to urination (voiding).
- human uterus is not very sensitive to muscarinic agonists.

6- Glands
- many glands can be stimulated by cholinomimetics like other secretory and exocrine glands : nasopharyngeal glands , salivary glands .. etc.

2- INDIRECT acting Drugs (Ach-esterase inhibitors)

- when we inhibit Ach-esterase, Ach will accumulate and we'll have excessive function of it.

- we have 3 groups of drugs ..
1- **Edrophonium** : one single drug.
- (quaternary ammonium group) * remember the characteristics of an quaternary ammonium drug *
- short half life , so it's used in diagnosing certain conditions.

2- **Carbamates**.
- they carb-amelate enzymes (means that they put the carb-amyl group (chemical group) they have on the enzyme) and this inhibits the enzyme REVERSIBLY.
some examples:
* neostigmine: drug , ester of carbamic acid (quaternary ammonium)
*physostigmine: drug, natural product, tertiary amine
*carbaryl: an insecticides (not drug) , carbamyl compound, may cause toxicity to humans due to accumulation of Ach by inhibiting Ach esterase reversibly, it's very lipid soluble

3- **ORGANOPHOSPHATES**
- very strong IRREVERSIBL inhibitors of Ach-esterase. Ach-esterase activity won't come back unless you synthesize new enzymes.
-Organophosphates may be :
* drugs (ekothiophate) : thiocholine derivative, can be used for treatment of glaucoma.

* insecticides (parathion & malathion and their metabolites: paraoxon & malaoxon, respectively)
* nerve gases (soman & sarin)
→ all of them leads to accumulation of Ach and excessive stimulation, then nerve gases and insecticides lead to death!

These compounds (Antichlinesterases) have similar pharmacodynamics (same effects) , but differ in chemical structure and pharmacokinetics.

→Pharmacokinetics:
- Absorption of quaternary carbamates from the conjunctiva, skin and lungs is

poor. Oral doses are much higher than parenteral doses (because in the parenteral dose you inject the drug directly while oral doses will be metabolized in the body before reaching the circulation).
* Distribution into the central nervous system (CNS) differs and depends on the lipid solubility. (e.g: quaternary ammonium won't be distributed in the CNS , while tertiary amines will be distributed in it).
- physostegmine as we said it's a tertiary amine and is usually given to the soldiers if they inhale sarin or soman gases , it's injected into the sides of their thighs directly.
- Organophosphates are very lipid soluble, they are widely absorbed and distributed (except the ekothiophate).

NOW regarding the pharmacodynamics effect; Ach-esterase will be inhibited and loads of endogenous Ach will accumulate as we've said before, then :
1. Edrophonium produces a short-lived (2-10 minutes) and reversible inhibition of the enzymes. And we use it for diagnosing Myesthynia gravis disease.
2. Carbamates produce a prolonged (0.5- 6 hours) and reversible inhibition.

3. Organophosphates make irreversible inhibition by phosphorylation of the active site covalently and irreversibly.
- also, when they bind the enzyme the cause AGING of the enzyme (كهولة الإنزيم), during the aging process: one oxygen- phosphorus bonds is broken leading to strengthening of the phosphorus- enzyme bond.
so when the O-P bond is broken, the P-enzyme bond will become stronger and this action is irreversible.
- before aging (before this breaking of O-P bond) you can activate the enzyme by oximes.

* Oximes (Chemical groups), like : (pralidoxime) , they are nucleophiles and are able to break the phosphorus- enzyme bond **before aging** occurs. They weaken the bond between Phosphorus and enzyme and make it reversible inhibition. (they don't work after aging).

* Aging progresses with time, so the faster we give these drugs to patient, the faster we regenerate the enzyme.
- That's why Organophosphates are no longer used as insecticides (they are very dangerous).
legally, you may find carbamate-insecticidis but not organophosphates ones. But if they present, then they enter illegally and should be taken off from markets.
- Organophosphates only present as Ekothiophate drugs or nerve gases.

→ going back to oximes, we call them "Cholinesterase regenerators".

- They are part of the treatment of organophosphate but not carbamate poisoning , but WHY?
remember, we said that with organophosphates, oximes break the P-enzyme bonds , substitute it, and make it reversible which is better than being irreversible. BUT it's not the case with carpamate! Carpamate is reversible and if we apply another reversible inhibitory drug; this will lead to further inhibition.
- So oximes make carbamate poisoning worse (reversible inhibitor + reversible inhibitor = more inhibition for the enzyme), BUT oximes treat organophosphate poisoning **before aging only**.

To sum up: oximes regenerate the enzyme inhibited irreversibly by organophosphate_ before aging, but they make poising by carbamte worse, because oximes themselves are inhibitors of the Ach esterases

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The ORGAN SYSTEM EFFECT for indirect acting cholinemimetics , specially to those lipid soluble ones, are less specific than the directly acting cholinemimetics' effect. Because if they are lipid soluble and traverse membranes , they will lead to accumulation of Ach not only in the parasympathetic terminals, but also in skeletal muscles and in the brain. So the poisoning is going to be not only exaggerated by cholinomimitects effect (parasympathetic system effect), but also at the neuromuscular junction in our muscles and in our brain
So the indirect acting agents that are lipid soluble will affect the GI tract, Eyes, etc… (all what we said about the parasympathetic system) , also it will affect the CNS (nicotinic & muscarinic receptors).

1- in CNS:
- briefly, low concentrations causes diffuse activation of CNS, and subjecting alerting response.
- if it's in high concentrations, then the patient will go into unconscious convulsions that may lead to coma and death.
- So it's an activation followed by depression, (this is very common in issues related to CNS), the doctor expressed the reason but we don't need to memorize it for the exam, the reason it that we have two types of neurons in our central nervous system; inhibitory & excitatory, if you stimulate an inhibitory neuron you cause inhibition, and if you stimulate the excitatory one you will cause stimulation. And that's what happen; stimulation at low concentrations and

inhibition at high concentrations.
-This depends on the suseptability of these neurons for inhibition and stimulation.
- It's easily recognized with farmers who بيرشّوا محصولهم ☺

2- in Cardio Vascular System (CVS):
Pay Attention please :)
here you as a doctor may be confused with some symptoms that opposite what we've said.
we said that organophosphate poisoning or anti Ach-esterase poisoning will lead to bradychardia. BUT actually it sometimes causes TCHYCARDIA, but why? Due to stimulation of sympathetic ganglia!

- so we need to look to all symptoms together, for example if the patient has secretions form mouth and in his lungs, urination, defecation, rapid movement in the intestine, constriction of the pupil but with unexpected TACHYCARDIA, he should be diagnosed as organophosphate poisoning patient. And we need to know that this tachycardia is due to the stimulation of sympathetic ganglia

3- Neuromuscular junction :
- contraction of muscles occur even though the patient might be lying and not moving. this contraction is due to excessive Ach accumulation.
- after a time, the muscle will have fatigue then become paralyzed.

Excessive stimulation leads to paralysis.

** SO all of these symptoms are important to diagnose organophosphate poisoning, insecticides poising, or exposure to nerve gases.

Therapeutic uses:

1- in Eyes: Glaucoma , esters (pilocarpine, methacholine, carbachol, physostigmine, echothiophate) : they facilitate the up flow of the fluids in eyes.

2- in Gastrointestinal and Urinary tracts , these drugs are no more used.

3- Neuromuscular junction.
- Firstly, with Myasthenia gravis : "weakening of muscles": a disease occurs due to reduced function of ACH, because of problems in receptors. We can overcome this problem by increasing the amount of Ach or its mimics. (you can give the

patient pyridostigmine, accumulation of ACh occurs and the muscle goes back to its normal state).
*we can use Edrophonium to diagnose myasthenia gravis patients (because it has short half-life). The patient will suddenly seems good for a short period of time and this is how we know that he suffers from myasthenia gravis, then we use a drug for treatment.
* we can use pyridostigmine (similar to neostigmine and physostegmine) to treat this patient.

- a second use: sometimes we use competitive neuro-muscular junction blockers for local anesthesia; doctors don't want the patient to move during surgeries so they relax the muscles by these blockers, then after finishing the antagonize the effect of these blockers by giving the patient an Ach esterase.

- third use: Antimuscarinic drug (atropine)
if poisoning happened due to antimuscarenic drug then we increase Ach (because they are competitive inhibitors).

Adverse Effects
→ ADVERSE EFFECTS exaggerate with pharmacological effects.
1- If secretions increased in the GI tract it will cause nausea and vomiting and diarrhea.
2- If secretions increased in the respiratory tract, it will cause bronchoconstriction and difficulties in breathing. (excessive secretion in the GI tract diarrhea happens).
3. Relaxation of the sphincter of the urinary bladder leads to urination
4. Salivation
5. Lacrimation
(SLUD) : Salivation, Lacrimation, Urination, and defecation → a sign of Anti-Cholino-esterase/organophosphate poisoning /cholinomimetics poisoning/carbamate poisoning .
6. Miosis
7. Sweating
8. Cutaneous(skin) vasodilation / flushing. (always when there is vasodilation in the skin blood vessels we have flushing, which is being a little bit reddish in color), due to excess Ach. (flushing is the symptom of cutaneous vasoldilation).
9. Bronchoconstriction.
10. CNS effects (toxic effects: alertness, convulsions, coma and death)

→ the treatment of organ poisoning generally and mainly is by antagonizing the Ach.
→ Antidote is atropine. (we will talk about this in the coming lectures)
→ Don't forget that we treat Organophosphate poisoning by pralidoxime (oximes) (before aging)
→ Don't foreget that carbamate poisoning will become worse by pralidoxime.
