Medical Committee
The University of Jordan

PHARMACOLOGY

Lecture No.: 22

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SHEET

SLIDES

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ADRENOCEPTOR BLOCKERS

(α RECEPTORS)

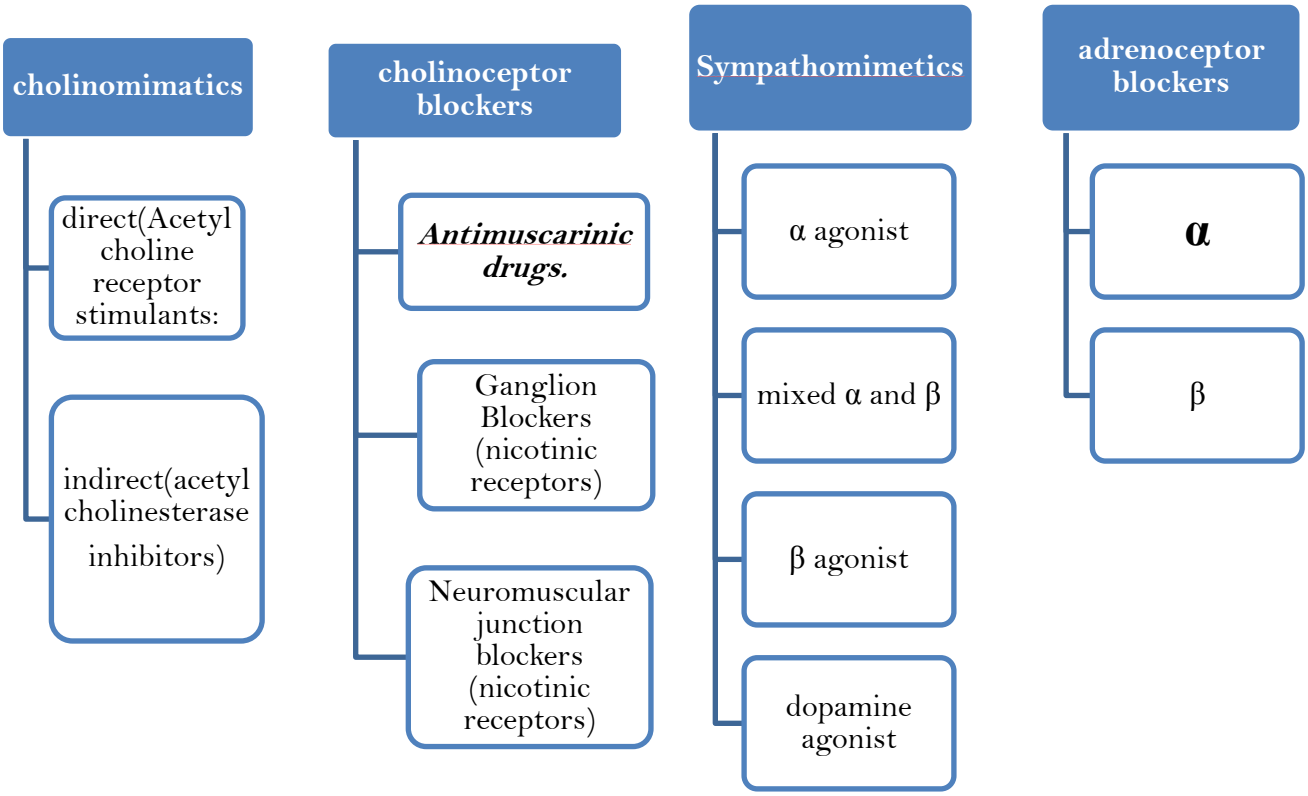
بسم الله الرحمن الرحيم...أدعو أن تكون الشيت جميلة ..فلنبدأ

Quick revision

We talked about sympathetic and parasympathetic systems and their receptors' locations in our bodies (studying the tables helps a lot) and the neurotransmitters that bind to these receptors and the actions they do.

Then we talked about drugs (and sometimes toxins) that work as inhibitors or stimulators of these receptors.

****Drugs or Toxins :**



Today's sheet is about blocking α receptors :D

****Things to keep in mind before starting !**

1-When we say **blockers** of adrenoreceptors we mean (most of the time) **competative** blockers so these substances will compete with catecholamines at alpha

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receptors (**both** alpha 1 and alpha 2) and you should remember the functions of each.

2-**vasodilators** in general produce **reflex sympathatic stimulation** (if you vasodilate your vessels whethere they are arteries or veins, the sympathatic nervous system will be activated and that will lead to this reflex manefisted by **increase in heart rate** , increase in **cardiac output** and **realease of catecholamines** from their terminals .

3- **postural hypotention** (انخفاض ضغط الدم الوضعي) –also called Orthostatic hypotension, so what does it mean and why we are talking about it here?!

It's the **reduction** in blood pressure due to change in body posture (when you acquire the upright posture) -
how ? if you are lying then you sit down or if you're sitting then you stand up meaning if you are moving to **a more vertical position (aquirement of the upright posture)** >>normally your autonomic nerous system will -in mele seconds- be activated to get things back to normal ,your heart rate increases and vasoconstriction occurs ..this is called (reflexes)therefore normal people should not face any problem …but if you have something wrong , you will have postural hypotention. So your blood pressure will drop (which we don't like)

Why are we talking about it ? because

4-using **venodilators** (α blockers) will make your postural hypotension worse due to failure to veinocostrict veins.

NOTE :you should distinguish between arteries (resistant vessels) and veins (capacitance vessel).

Veins **ARE** the capacitance vessels ?!?!

Dilating the veins will cause more blood to go in (يعني الوريد يتسع و تتجمع فيه الدم بشكل اكبر كسعة) these veins (specifically more blood will be in the lower limbs veins than other parts of your body by gravity)therefore less blood will go to the heart.

This video will make it clear ☺
http://www.youtube.com/watch?v=6LcX7fGaUe0

α-Adrenoceptor Antagonists types :

1- reversible 2-irreversible

note that all receptors interactions are REVERSIBLE meaning the binding of the drug to the receptor is not by covalent bonds,it's by attractive bonds like (hydrogen bonds,hydrophpbic and so on…) but in some –special- cases we'll have irreversable.

1-reversible antagonists

They are competing with the endogenous catecolamines released by sympathatic neurons. In competetion; the stronger will win scinetifically we mean concentration so the higher the conc. of the agonist the less the action of the antagonist (and vice versa) therefore you can overcome the blockage by increasing the conc. of the agonist.

e. g: Prazosin, Tamsulosin, Phentolamine. (and even more)

2-Irreversible antagonists

One example only .. they will bind covelantly to the receptors (it's not competetive with the endogenous agonist; because once these antagonists bind to the receptor NOWAY the agonist will interact even with increasing the conc. of the agonist **Because** the receptor is occupide and not available anymore) then the function is lost .. you lost the receptors … the solution ? is to wait until **NEW** receptors are synthesized .

Because synthesis of a receptor needs protien synthesis , processeing and insertion into the membrane IT'LL REQUIRE A LOT OF TIME (days to recover).

e. g: phenoxybenzamine.

A Student's Question :

if it's Irreversible why would we risk using it ??

There is one use (we'll discuss it in a moment) and it's not because of its feature as an irr. inhibitors …that's why we don't use such drugs routinly , it's not found in pharmacies, therfore not commonly available for everybody .

Pharmacodynamic effects of the ALPHA antagonist

1-CVS

No direct effect because α receptors are not present in the heart in SIGNIFICANT AMOUNT .. what will happen ?! The effect will be on blood vessels:

When you block α receptors, you'll have vasodilation (it's the reverse to its normal action "vasoconstriction").

In arteries (vasodilation) → lowering of peripheral vascular resistance and blood pressure.

In veins (veinodilation) → postural hypotension (you know it already ☺)

IN BOTH → reflex tachycardia

NOTE : any vasodilator in this world will cause reflex sympathatic stimulation.

As we said the sympathatic reflexes :

increase heart rate due to increased contractility ,

vasoconstriction, all in all result in increasing BP.

- Reduction in BP can lead to reflex sodium and water retention (an extrareflex method):

Your body won't wait you to do things…it moves in its own making reflexes to get things back on its track… if it feels your BP is droping ,it will stimulate the sympathatic reflexes (to elevate BP) like retention of water and Na→which increases your blood volume (NOT your blood cells but its fluids) → venus return → correction of the hypotension (reduction in BP).
سبحان الله

- Reflex sympathatic stimulation is the **4th mecanism of Tolerance !!** because your body in sympathtic reflexes is antagonising the action of the these drugs ! so with time …their action of theses compounds will be DECREASING. : example : you give a drug to a patient ..initially it will reduce the BP but after 4-5 days the BP will rise a little and in severe cases it may cause hypertintion again "the drug is not working" because of tolereance .

REMEMBER : Mechanisms of tolerance are "continuation of the previous lec. "

1-autoinduction (Refers to a drug that induces its own metabolism. like: Carbamazepine)

2-Down regulation of receptors. (drug antagonism)

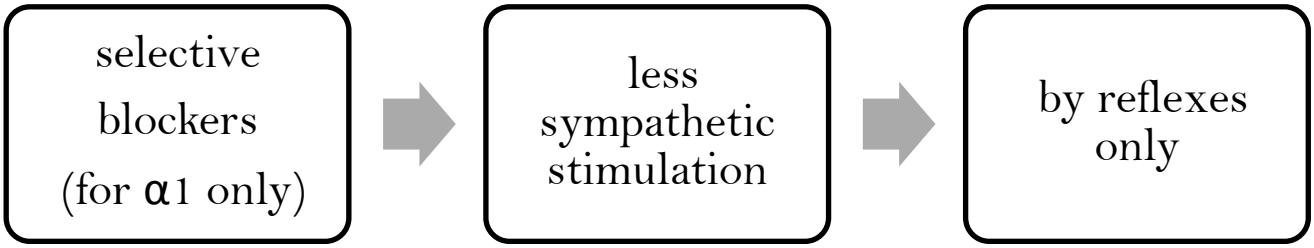
3-Depletion of neurotransmitters from their stores when the drug has actions upon their release.

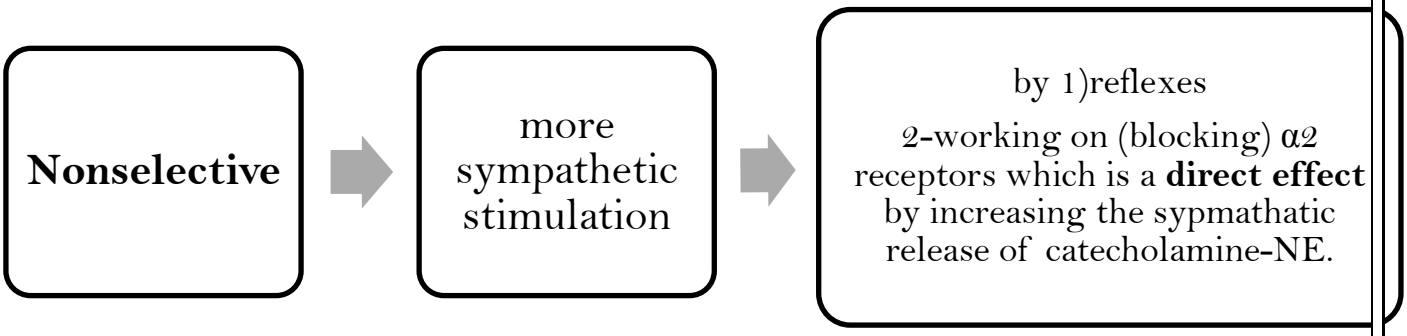
4-Sympathatic REFLEXES.

****Tachycardia is more marked with nonselective α-blockers (α_1, α_2) because of increased release of norepinephrine (why?)**

α 2 receptors are **autoreceptors** ,their effect is negative feed-back inhibition, decrease of norepnphrine release from it's terminals …so blocking them results in:

blocking the autoreceptors →blocking the negative feeb-back →increese the release on NE →so stimulating β1 receptors on the heart →causing tachycardia and stimulate α1 causing vasoconstriction ☺ ☺





2-EYE

In the radial muscle of the iris …we do have α1 receptors; when activated → the muscle contracts → mydriasis (dilation of the pupil)

So blocking these receptors will cause →relaxation of the muscle→miosis (constriction of the pupil)

**Note : eye muscles are skeletal voluntary "which move the eye up, down, right and left" but here we talk about involuntary "smooth muscle" .

3-GIT sphincters = relaxation

4-Urinary Tract

α_1 receptors in the base **of urinary bladder "sphincter"** and **the prostate gland** → stimulating alpha receptors → contraction of smooth muscles → they block urine outflow .

Blocking these receptors → relaxation → reduce urinary obstruction (retention).

As a matter of fact we use "α1 blockers" to **treat hyper plastic prostate** " a condition which the prostate is enlarged and presses the urethra and the outflow of urine ". So blockage by α1 blockers → relaxation of the prostate → treated ☺ .

NOW Let's talk about Drugs a little !! 4 drugs to know

1-Phentolamine 2-Phenoxybenzamine 3-Prazosin 4-Terazosins

Phentolamine and phenoxybenzamine are old drugs and historical and used for **hypertension of pheochromocytoma "PCC"

What is PCC ?? a **neuroendocrine tumor** of the sympathetic chain or adrenal medulla → releasing **excessive** amount of epinephrine and norepinephrine →**severe hypertension** comes in **attacks** not persistent (when a **release** occurs , the BP is **elevated**) and this is associated with **panic** attacks (نوبات هلع و خوف) ..**example**: you see someone is sitting normally and peacefully but suddenly he is frightened and he's hearing his heart beats "tachycardia" and if you measure his BP ,it'll be very high.

Now you have to keep in mind that the **REAL** treatment of PCC is **SURGERY** "you will have to remove the tumor " but until you do that ,you need to treat this hypertension and even during surgery " when you are trying to remove the tumor you will move it here and there –manipulating it- to cut it off → causing a huge release of EP and NE "causing hypertension crisis مصيبه".

****hypertension crisis is bad why ?**

Damages the brain, kidney, retina , every vessel in the body..some of these vessels would explode and we DON'T want that …

That's why in preparation for surgery and during it we give α blockers .."around the surgery in general".

But hear this out ..you should give him beta blockers too. "mixed"

***you give these drugs temporary (during and around the opration) to get rid of the excess of catecholamine release but the ultimate treatment is surgical operation.

Extra info. From internet

A hypertensive emergency "crisis" exists when blood pressure reaches levels that are damaging to organs. Hypertensive emergencies generally occur at blood pressure levels exceeding 180 systolic OR 120 diastolic, but can occur at even lower levels in patients whom blood pressure had not been previously high.

Characteristics :

A) Nonselective (α1 and α2) ..reversible..competitive inhibition
And because it's nonselective the sympathetic reflex stimulation will be more "previously said-don't forget" and to **push it even further,**

- **Phentolamine blocks** muscarinic receptors and (H_1 , H_2) histamine receptors; which are vasodilators; so this drug isn't pure α agonist, that's the reason behind not using this drug routinely in treatment of hypertension.

B) IT'S NOT PURE alpha blockers !!

therefore we don't like it →we don't use it routinely in the treatment of hypertension but temporary in cases of PCC .

C) Not that lipid soluble → poor absorption .

Side effects :

A) **Heart**: related to stimulation of the heart ..(tachycardia ..arrhythmia .. myocardial ischemia ..damage to the heart muscle).

B)**Nose** "nasal congestion-sometimes called nasal stuffiness" الاحتقان ; two reasons :

i. M3 blockage → less secretions
ii. Alpha blockage →vasodilatation → more blood will go to your nasal mucosa → more intestinal fluids will be in it→the mucosa is swollen in your sinusesالجيوب الانفية → the spaces for air passage is reduced → patient finds it hard to take a breath "flow of air in and out " .

C) headache

- Note : all vasodilators (even direct vasodilators which are not related to the CNS) cause headache ..as an adverse effect not pharmacological effect..therefore it may happen to some people and others don't ..and in different degrees .

Your sinuses are hollow air spaces within the bones between your eyes, behind your cheekbone, and in the forehead. They produce mucus, which helps keep the inside of your nose moist. That, in turn, helps protect against dust, allergens, and pollutants.

-internet

****Student's question "dr. said it's a very good question"**

Q:"In vasodilatation, more blood is going to the brain meaning more oxygen so why do vasodilators cause headache" ??

A: because the dilated blood vessels will press on the neurons of the cerebral vessels as well as the neurons of skeletal muscles of the head, especially in the temporal region …it's called **Throbbing headache** → with each beat, more blood in the dilated vessels, more pressure on the sensory pain receptors (anywhere around the dilated vessels) **resulting in HEADACHE,** then the headache becomes milder (doesn't fade away) before the next beat and becomes severe again after the next heart beat **زي شخص ماسك شاكوش و بخبط فيك!!**

2-Phenoxybenzamine

A) Alpha (1 and 2) blocker..irreversible (covalent bonding)..nonselective (α1 and 2) ..

As Phentolamine; it works on alpha, histamine and muscarinic receptors but here we have an extra one …**SEOTONIN** receptors .!!

- **We dislike this drug ..why ?!** 1-irrversable binding 2-nonselectivity .

B) Bioavailability is low.

C) Lipid soluble →absorbed well and crosses brain blood barrier BBB : produces effects on the CNS "we are not concerned about it now " ..causing :

1-fatigue → وهن و ضعف feeling weak and can't perform any task.

2-sedation → تهدئة calmness -the first stage of sleeping- .

3-nausea→ you feel you want to vomit الغثيان و لعية المعدة.

D) Treatment of hypertension PCC.

E) Adverse effects:

- The same as Phentolamine
- Inhibition of ejaculation, it's associated with all α-blockers, because ejaculation is a sympathetic α-adrenergic function.

**Student's Question : "we use Phentolamine to treat PCC; so why taking the risk of using phenoxybenzamine (an irreversible drug) ?

It's a STORAGE-AVAILABILITY issue …you work in a hospital that the Phentolamine is available -not phenoxybenzamine – so you are forced to use it and vice versa even if phenoxybenzamine is IRREVERSABLE…but don't forget you must give it (alpha blocker) **with a Beta Blocker** Drug too.

الدكتور يقول ان اختيار الدواء هذا او ذاك يعتمد على مكان العمل وعملية التزويد ! فلو كان الدكتور مسؤولا عن المستشفى فهو يحرص على توافر الPhentolamine .

****A Student question**

Q:"after we have done the surgery to PCC patient ..won't there be tolerance for these drugs?!

A: 2 -3 days after the surgery , We stop administrating them …it's a temporary use "don't forget this" not chronic .

3-Prazosin

A) highly **selective** for α_1 receptors and typically 1000-fold less potent at α_2 receptors.

Produces **less tachycardia in comparison with the previous two drugs..why ?!

It won't work on alpha 2 ..no antagonism to it (still functioning)>> YES to feed-back inhibition and catecholamine release .. "tachycardia is **only** caused by the reflex here "

B) **effects**: **Relaxes smooth muscles in arterioles, venules and prostate ,smooth radial iris muscle "eye", smooth muscle "sphincter" of the UT…etc …what we've already mentioned .**

C) has **first pass effect** ,expensively metabolized with a short half life =3hours.

D) management of chronic hypertension.

**problems when giving this drug alone ? reflex sympathetic stimulation , reflex water-Na retention and tolerance of its action.

4-Terazosin

is **similar** to prazosin but the half life is longer "**The t½ ~ 9-12 hours"** and it effects the frequency of administration .. instead of giving prazosin 4 times daily we can give terazosin once or twice daily as a treatment of hypertension or prostate enlargement.
e.g :Doxazosin, Tamsulosin, Alfuzosin, Indoramin.

****ADVERSE EFFECTS OF alpha ADRENORECEPTOR blockers :**

1-tachecardya …sympathetic stimulation
2-Na-water retention
3-headache
4- congestive nose

**Therapeutic cleverness : clever selection of drugs فن الثيرابتك:

The lesser number of drugs and the lesser the frequency of administration →the better the collaboration of the patient تعاون المريض مع وصف الدكتور
e.g if a patient comes to you "elderly" having a hypertension and prostate enlargement ..by only giving him alpha receptors blockers ..you're treating both problems " عصفورين بحجر واحد"

A student asked : if he doesn't have a prostate enlargement ..does it cause him any problems regard urination ?! no ,it won't hurt him ..because he's normal .

A student asked : giving alpha blockers to a pregnant lady would affect her uterus in a way that prolongs the delivery period ?!
Normally they are not used with pregnant ladies because they are contraindicated for other reasons, but if you presume they're indicated it won't have an effect on it because the beta 2 receptors in the uterus are much more than alpha receptors "with progression of pregnancy ,the beta receptors in the uterus increase and alpha decrease " .

* Therapeutic Effect :

1-PCC.. temporary use (around and during surgery). "
2- hypertension emergency; the hypertension of PPC comes in attacks (with each release) so it's considered as emergency hypertension.
3-chronic hypertension.
4-urinary retention.
5-prostate enlargement (causes urinary retention).
6- cause meiosis .
7-Antidote for local vasoconstrictor excess due to infiltration of α agonists.

Remember we said in previous lec. about using the alpha agonist with local anesthetics.. why ? to prolong the duration of the action by vasoconstriction and to reduce toxicity "reduction in the amounting reaching the blood " especially the heart and brain toxicity .

Now suppose that you have excessive amount of vasoconstrictors ? what will happen ?! well if you are doing this to a patient's hand or any organ or part of his body..he will lose it by gangrene .. excessive vasoconstriction >> ischemia >>necrosis "gangrene" ..IT's NOT TOO LATE ! if you notice the signs and symptoms "you're going to know them" of this quickly..what to do? inject **alpha blockers** at the same site to prevent the action of the vasoconstrictors on the blood vessels >> so you won't get any impairment "perfusion" of the organ due to this vasoconstrictor .

بالتوفيق

و ادعوا لنا بالخير :]