Medical Committee
The University of Jordan

PHARMACOLOGY

Lecture No.: 21

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Specific Sympathomimetics

-All the lectures we took until now are based on lecture 16, so they will not be that much difficult =)

-Note ; I change a bit the arrangement of information =P so don't get confused if you hear the record =P

-According to **chemical structure**, Sympathomimetics are divided into two types :

1-Catecholamines

-They contain catechol nucleus (catechol ring) which has two hydroxyl groups near to each other which means that the ring has the ortho configuration.

-Examples

Epinephrine, Norepinephrine, Isoproterenol, Dopamine, Doputamine, , Fenoldopam.

2-Noncatecholamines

-They don't contain the catechol nucleus (catechol ring).

-Examples

Phenylephrine, Methoxamine, Midodrine, Ephedrine, Amphetamine, Methamphetamine, Oxymetazoline, Phenmetrazine & Methylphenidate.

Note→Methylphenidate is similar to some extent to Amphetamine.

→Now, We are going to talk about the effect of each of them ☺

->Catecholamines

Epinephrine

-Receptors affected : All adrenergic receptors (α1,α2,β1,β2,β3).

-Action : JUST Revision

1-Increasement in the rate (Positive chronotropy) & the Contractility (Positive Inotropy) of the heart through β1 receptors.

2-Vasodilation in skeletal muscle blood vessels through β2 receptors.

3-Vasoconstriction in many vascular beds through α1 receptors.

-Therapeutic uses :

1. t's given intravenously in the ICU or subcutaneously in the emergency room under monitoring to treat **Anaphylaxis** (**severe** allergic reaction), because it's the physiological antidote (antagonist) for Histamine. And remember, histamine causes vasodilatation & depression of the heart, whereas epinephrine causes vasoconstriction & stimulation of the heart. BUT they are NOT anti-histamines, because anti-histamines only inhibit further action of histamine. So you give epinephrine to reverse the action of histamine, & then you give anti-histamine to prevent further action of histamine in severe allergic rxns.

-Epinephrine : REVERSE the action of Histamine.

-Anti-histamine : PREVENT further action of Histamine.

So both are part of treatment for SEVERE allergic reaction (anaphylactic shock – which causes heart depression, vasodilatation, low blood pressure and can be fatal), while people with some mild rash due to an allergic reaction are treated with anti-histamines only.

Norepinephrine:

-Receptors affected : All adrenergic receptors (α1,α2,β1,β2 (little or no effect) ,β3).

-Action :

Similar to epinephrine but it has little effect on β2 receptors, which means that all the smooth muscles that will be relaxed under β2 stimulation will not be

affected by norepinephrine. And these muscles are ; Bronchial smooth muscle, Vascular smooth muscle, GIT & UT smooth muscles. (Extract all β2 actions.)

Isoproterenol [β Agonist]:

-Receptors affected : β receptors (Significant effect) , α receptors (little - non significant effect).

-Action :

-For β receptors, it will work just like Epinephrine:

1-Vasodilation & relaxation of all smooth muscles we talked about through stimulation of β2 receptors).

2-Positive Inotropy & chronotropy through stimulation of β1 receptors).

3-Glycogenolysis,Gluconeogenesis

4-Bronchodilation…etc. All the actions produced through β receptors. (I just give the examples that the Dr talked about them in the lecture, back to lecture 16 to the table to see all of them).

-For α receptors, since it has no significant effect on them:

1- It will not cause Vasoconstriction & contraction of Sphincters which is caused by stimulation of α1 receptors.

2-It will not inhibit the release of acetylcholine which is caused by stimulation of α2 receptors**.**

VERY IMPORTANT NOTE

Just remember that the smooth muscles of the wall of UT & GIT are contracted under the effect of the parasympathetic nervous system so their contraction will not be affected & inhibited by Isoproterenol.

Dopamine

-Intermediate Precursor of norepinephrine.

-Receptors affected : D1,D2, β1,α.

-Therapeutic Uses : Cardiogenic shock and heart failure (which is associated with problems in the heart muscle.)

Note that heart failure can be caused by other factors like fluid overload but that doesn't affect the heart muscle, in that cause, dopamine isn't used.

-Action :

1-Vasodilation in the renal vascular bed through stimulation of D1 receptors, so it increases renal blood flow & that will protect the kidney from damage in cases of shock.

2-Suppression (Inhibition) of norepinephrine release through stimulation of presynaptic D2 receptors, which are **AUTOreceptors** NOT heteroreceptors because as we took in the first lecture, dopamine is taken into the vesicle & converted in the vesicle to norepinephrine.

So D2 receptors for the sympathetic nervous system are autoreceptors.

However, the action of dopamine will be affected by the amount of dose you give;

-**Small doses (Renal doses)** will cause vasodilation of renal blood vessels through stimulation of D1 receptors.

-**Intermediate doses** which are a bit higher than the small ones will cause stimulation of the heart through stimulation of β1 receptors.

-**Large doses** which are much higher will cause vasoconstriction including the renal vascular bed through stimulation of α receptors.

-To explain this ;

In cases of shock, If you give this drug by IV infusion not by IV injection (Bolus injection), you give small doses to dilate the

renal blood vessels, If you increase the dose a little bit,

you will stimulate β1 receptors, & if you increase it

*IV infusion : supply of fluids via the insertion of specialized needle into a vein.

*IV injection (Bollus injection): syringe is connected to the IV access device & medication is injected directly & slowly.

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further, you will stimulate α receptors & when you reach this level (stimulation of α receptors), you are NOT serving your purpose because you are causing vasoconstriction of the renal blood vessels & that will damage the kidney, but stimulation the heart through β1 receptors is not bad in this case because it will increase the blood flow & with the vasodilation which occured at the first, you will have a better result.

-To sum up

->In cases of shock :

-we need Small doses & Intermediate doses.

-we don't need the large doses (they are bad).

Note that the specific concentrations of the small, intermediate and large doses are determined and can be found in books.

-BUT in **real clinical practice**, there is an overlap between these concentrations! Which means that if you give a renal (small dose), it may stimulate the heart also, or if you give an intermediate dose, it may be toxic and stimulates α receptors & causes vasoconstriction.

-How to solve this problem? How to know if this dose is dangerous or not?

These drugs are only given in the intensive care unit (ICU) under monitoring. There is a monitor, according to the data on the monitor, you will observe the blood pressure, if the blood pressure increases, you will conclude that the dose caused vasoconstriction, so you must decrease it. (Titration)

Douputamine

-In vitro (lab) It has two isomers ((+) isomer, (-) isomer)

-Receptors :

-β1 : Agonised by by the (+) isomer.

-α1: Antagonised by the (+) isomer, Agonised by the (-) isomer.

-In vivo (body), the opposite actions (Antagonism & Agonism of α1 receptors cancel each other because they are equal) & as a result it's a selective β1 agonist only.

-Action:

Increasment of the cardiac output (positive inotropy) through stimulation of β1 receptors.

-Therapeutic uses : Cardiogenic shock with heart failure affecting the heart muscle (like dopamine).

-It's given under monitoring with dopamine, because sometimes, the heart is weak & it's not enough to give dopamine to dilate the renal blood vessels, so you give with it doputamine to stimulate & strengthen the heart.

-However, these drugs can develop **tolerance** after repetitive doses, because of **down regulation of receptors** (less receptors→lower action→Tolerance).

Fenoldopam

-Derivative of dopamine.

-Receptors affected :D1 selectively.

-Action :

-It will cause vasodilation in renal blood vessels & other vessels through stimulation of D1 recepetors.

-Therapeutic uses : It's used intravenously to treat severe hypertension.

->Noncatecholamines

Phenylephrine, Methoxamine, Midodrine [α Agonists]

-They will be inactivated by Monoamine oxidase (MAO).

-But since they're noncatecholamines, they're not going to be metabolized (inactivated) by catechol-O-methyl transferase (COMT), thus they have a longer duration of action than catecholamines.

->Remember

Two enzymes are involved in the metabolism of catecholamines :

1-Catechol-O-Methyl transferase (COMT).

2- Monoamine oxidase (MAO).

-If the drug is released by the neurons, It will be metabolized by MAO first.

-If the drug administerd exogenously (by injection for example), It will go to the liver & be metabolized by COMT first.

At the end they're both going to act on the drug and produce the same product.

-Receptors affected : ONLY α receptors**.**

-Action :

1-Raising blood pressure (vasoconstriction) through stimulation of α1 receptors.

2-Effective Mydriatic (dilation of the eye pupil) through α1 receptors (Phenylephrine).

3-Decongestion.

-Therapeutic uses : Hypotension (in the ICU under monitoring), Decongestion of nose in common cold.

-Phenylephrine is used as mydriatic & conjunctival decongestant/vasoconstrictor & this is when the eye is red due to an allergic reactions or infection of the eye since blood is suitable for bacterial growth (Congestion of the eye/Vasodilation of the eye), NOT bleeding of the eye.

* All These sympathomimetics if used to raise blood or cause renal dilation, it should be done under strict monitoring in ICU.

Ephedrine

-The first but not the only orally active sympathomimetic drug (in addition to β2).

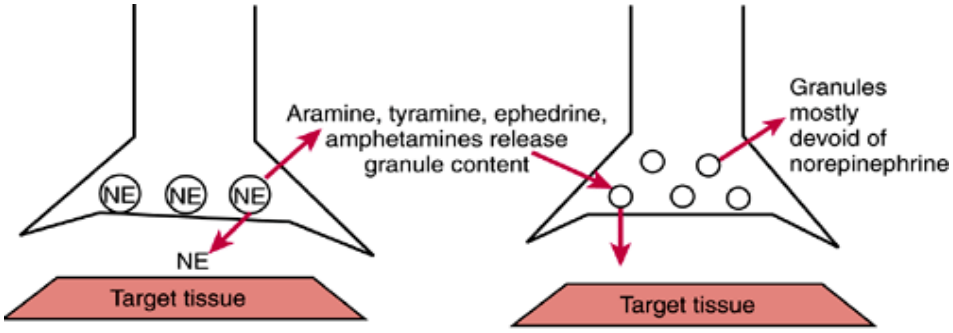
-Found in various plants, Ephedra sinica.

-Receptors affected : All adrenergic receptors (α1, α2, β1, β2, β3).

-Action :

1-Direct Stimulation of all adrenergic receptors & crossing the Blood brain barrier (BBB) -since it's lipid soluble- & causes CNS stimulation.

2-Indirect stimulation of adrenergic receptors by stimulation of the release of endogenous catecholamines from their stores. They displace them from the side of the vesicles so enhancing their release.



-Also, these drugs can develop **Tolerance** after repetitive doses.

-Lets explain how-

-Since this drug has two actions & one of them is stimulation of the release of catecholamines from their store, what will happen is at repetitive oral doses & continuous release of catecholamines, you will reach a level that their stores will be empty & that will lead to depletion of catecholamines, & thus you stop the action of releasing of catecholamines because they are already released & their stores are empty, & you will only have the action of direct stimulation of adrenergic receptors (one action not two).

-Two actions (direct stimulation of adrenoreceptors & Indirect stimulation of adrenoreceptors by the release of catecholamines→Repetitive doses (depletion of catecholamine)→One action (direct stimulation of adrenoreceptors)→Tolerance.

-As a result, we took three mechanisms of tolerance :

1-Autoinduction

2-Down regulation of receptors.

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

-β2 selective agents

-Action:

All the actions that will be produced by stimulation of β2 receptors. Go back to the table.

-Therapeutic uses

-Salbutamol, Terbutaline, Salmetrol, Metaproterenol→for treatment of bronchial asthma.

-Ritodrine→ Uterine relaxation in premature labor (suppression of premature labor).

You may think that , they are all β2 selective agents right? Then, why we choose Ritodrine for uterine relaxation & the others for bronchial asthma?

-What happens is ; during drug development, you have to test the drug on human being at one stage. Ritodrine was developed to relax the uterus & was

tested at the beginning to see if it relaxes the uterus or not, so the purpose was to relax the uterus & they can't write on the leaflet that this drug is for bronchial asthma, because it was NOT tested to see if it can treat bronchial asthma at that stage.

-Same story goes back to Salbutamol,Terbutaline..etc. Although they can relax the uterus, they cannot write that on the leaflet because they weren't tested on the uterus.

"The doctor commented here that if a Q comes in the exam about which drug can relax the uterus for example, we choose any drug of the above even if it was not tested on human being =) (all β2 agonists can relax the uterus)"

Tyramine

1-Is a by-product of tyrosine from the minor pathway, so we have very little Tyramine in our body.

Remember→Tyrosine is the precursor of all catecholamines (Epinephrine, Norepinephrine, Dopamine).

2-Is found in high concentration in fermented food such as cheese.

3-It is readily metabolized by monoamine oxidase (MAO) in the liver, & is inactive (has no effect) when taken orally because it is metablolized during the first pass effect.

-However, if you inhibit it's metabolism by taking monoamine oxidase (MAO) inhibitors such as antidepressants & food high with Tyramine are ingested, this Tyramine will displace catecholamines from pre-synaptic vesicles, so huge amounts are displaced & that will lead to hypertensive crisis.

-Hypertensive crisis can lead to damage to the brain, heart, kidney, retina of the eye in adults above than 40 years old.

-Other Therapeutic uses:

1- Vasoconstrictors mixed with local anesthetic (التخدير الموضعي).

-Local anesthetics are dangerous to the heart & the brain

1-They produce cardiac arrhythmias in the heart.

2-They produce convulsions in the brain when they cross the blood brain barrier.

-Lets explain this→Suppose you have to do an operation on the hand, you inject it distal to the region (infiltration anesthesia) then we have no sensation of the pain in that region. If there is a good blood supply to the area where we want to inject the local anesthetic, it's going to go to the circulation in huge amounts & that will lead to depression of the heart & crosses the BBB & causes convulsions.

- So we give a vasoconstrictor mixed with these local anasthetics & this vasoconstrictor serves two purposes:

1-It prevents this local anesthetic from entering with huge amounts into the circulation because when vessels are constricted, they have a small size so these local anesthetic will enter these vessels slowly & into small amounts. Not all at once.

2- It prolongs the action of the local anesthetics thus prevents continuous injection of this local anesthetic & as a result, it will go to the circulation slowly without complications on the heart or the CNS.

-**Note** : Cocaine (local anesthetic) inhibits the reuptake of catecholamines so it causes vasoconstriction & we can't give it with a vasoconstrictor, you will lose the hand.

2-α2 agonists (apraclonidine & brimonidine which are derivatives of clonidine) for treatment of Glaucoma.

-α agonists in general if we use them in glaucoma, they will reduce the formation of aqueous humor.

Definitions of aqueous humor & glaucoma from the internet just to understand

-Aqueous humor: the clear fluid filling the space in the front of the eyeball between the lens & the cornea.

-**Glaucoma:** a condition of increased pressure within the eyeball, causing gradual loss of sight.

Why do we selectively choose α2 agonists for treatment of Glaucoma, why we didn't choose phenylephrine which is both α1 & α2 agonist??

-Because we don't want the extra vasoconstriction which occurs by α1 agonist.

3- α2 agonists (Clonidine & Methyldopa) for treatment of hypertension.

Remember→

- Stimulation of α2 receptors inhibits the release of norepinephrine which will lead to decrease in the pressure, because there will be no vasoconstriction by α1 receptors, no increase in the cardiac output by β1 receptors.

- That's why we want to stimulate them by using α2 agonists in cases of hypertension to decrease the pressure.

Adverse Effects

- **Extension of pharmacological effects on Cardiovascular system (CVS) & central nervous system (CNS).**

1-Stimulation of the heart can lead to tachycardia.

2-Vasodilation can lead to hypotension.

3-Vasoconstriction can lead to hypertension.

4-Marked elevation of blood pressure, increased cardiac work, ischemia & arrhythmias.

5-Restlessness, tremor, insomnia, anorexia, anxiety, & paranoid state.

- **Those that cross the blood brain barrier such as Ephidrine & Amphetamine; they don't have the same degree of action.**

Amphetamine

1) Is more soluble.

2) It has no direct effect on receptors but has indirect effect on receptors which means it can release catecholamines.

3) It can cause drug addiction

-Ephidrine

1) Is less soluble.

2) It has direct & indirect effect on receptors.

3) It doesn't cause drug addiction.

There are other adverse effects on other systems in the body like constipation, etc.. but we're only focusing on the CNS.

SUCCESS IS LIKING YOURSELF, LIKING WHAT YOU DO, & LIKING HOW YOU DO IT

BY SIREEN AL-KHATIB =)