Medical Committee
The University of Jordan

PHARMACOLOGY

Lecture No.: 20

Doctor Name: Yacoub Irsheid

Written By: Ola Atif

SHEET ■

SLIDES □

DONE BY: ISSA KHASHAN

PHARMACODYNAMICS OF SYMPATHOMIMETICS

-Note :

most of this information in this lecture is repeated , and we talked about it previously ☺

Effects of sympathomimetics

Effects on blood vessels :

vascular smooth muscle is under sympathetic control , and blood vessels are innervated by sympathetic nervous system , so the effect of sympathomimetics on blood vessels depends on their content of receptors .

what receptors do we have ?

α receptors , β2 receptors on vascular smooth muscles

as we said before , skin contains predominantly α1 receptors , and blood vessels to skeletal muscles contain predominantly β2 receptors . so sympathomimetics are going to **vasoconstrict blood vessels in the skin** , and **vasodilate blood vessels in skeletal muscles** .

When we talk about blood vessels we talk about blood vessesls , we have both artries and veins , both are constricted or dilated by sympathomimetics .

veins that contain α1 receptors will be constricted

veins that contain β2 receptors will be dilated

> **REMEMBER :**
> the consequence of arterial constriction is increasing diastolic blood pressure

what are the consequences of venoconstruction (construction of veins) ?

1- venous return to the heart increases.

2- the capacity of veins will be less (because it becomes smaller in diameter and size so the blood goes back to the heart)

when venous return to the heart increases the cardiac output will increase

(more blood to the heart means more contraction)

(less blood to the heart means less contraction)

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fource of contraction will increase by increasing the venous return

Venous retun :
the volume of the blood returning to the heart

increasing of the volume of the blood in the heart will increase the contractility of the heart.
So, venoconstriction increases the return of blood to the heart and that will increase the cardiac output , means **it will increase the systolic blood pressure**
(increase in the heart contractility will increase the systolic blood pressure)

stimulation of α receptors ⟶ vasoconstriction
stimulation of β receptors ⟶ vasodilation

Peripheral vascular resistance : resistance of blood vessels to the pumping action of the heart
we have resistance against pumping which increases with arterial constriction.
The peripheral vascular resistant has increased because of venoconstriction , while arterial dilation by β2 receptors will reduce the resistance . The heart will pump more calmly (freely) because the road is open.
vasodilation cause a reduction in peripheral vascular resistance and that will reduce the diastolic blood pressure.

going back to blood flow:
if the heart contraction remains the same and you dilate arteries , the blood flow will increase
if you increase contractility of the heart and dilate arteries , the blood flow will increase
if you reduce contractility of the heart and dilate arteries , the blood flow will decrease

(imagine that there is a village with 4 houses , then we build more houses and end up with 10 houses (as vasodilation) but the water pipe in this village is still the same (the pump is the same) so the water which reaches each house is less)

SO reduction in pumping action of the heart with arterial dilation reduces blood flow.
blood flow doesn't depend on condition of blood vessel alone (constricted or dilated) , but it depends also on the contractility of the heart.

for α and β2 receptors we say "predominant" , in skin we found α receptors predominantly and it dosen't mean that we don't have β2 receptors but the common one is α receptors and vica versa for blood vessels in skeletal muscles .

Dopamine D1 receptors promote vasodilation of renal blood vessels and other areas , but mainly renal because kidney is vulnerable to ischemia , if the renal blood flow decreases the kidney will be necrotic (damaged) . The kidney receives 1/4 of the cardiac output , if that is compromised , renal damage will happen . and that is why we care about renal vasodilation more than splanchnic and others . Renal is important than other places.

Effects on the heart :

mainly β1 receptors , we have β2 receptors but less than β1 receptors , and their function (β2) is same as β1 in the heart, which is to increase the contractility of the heart .

β1 and β2 receptors in myocardium increase the contractility , no differences in function, but predominantly we have β1 receptors in the heart.

we have β1 receptors predominantly in the heart and that increases the contractility and the cardiac output and also the heart rate
pacemaker activity (normal and abnormal) are increased by sympathomimetics in general because the heart rate will be increased by sympathomimetics
conduction of artioventricular (AV) node is increased by sympathomimetics

sympathomimetics effect by β1 receptors causes :

positive chronotropic effect ⟶ heart rate increased

positive ionotropic effect ⟶ increase in contractility

positive dromotropic effect ⟶ increase in conduction of AV node

Effects on blood pressure :

we talked about it previously , we have :**systolic** and **diastolic**
systolic blood pressure reflects cardiac outputs which reflects cardiac contractility

diastolic blood pressure the peripheral vascular resistance
we add to cardiac output the venous return . Drugs which stimulate α1 receptors **increase the venous return** and that **will increase contractility**

β2 receptors stimulation causes reduction in peripheral vascular resistance because of vasodilation

To sum up :

the effect on blood vessels depends on receptors present there
α1 receptors cause vasoconstriction
β2 receptors cause vasodilation
β1 receptors in the heart increases the contractility , also venous return(because of venoconstrucion) increases the contractility
vasoconstriction increases the resistance and diastolic pressure
vasodilation almost arterial dilation decreases the resistance and diastolic pressure

"it is simple if you know the two tables at the end of the second lecture"

Effects on the eye :

1-radial muscle of the iris has α1 receptors , when it contracts, it stretches to the outside causing dilation of the pupil (mydriasis)

2-reduce the formation of aqueous humor by α agonist
so we can use sympathomimetics that have α1 receptor stimulating action or agonist action to treat glaucoma.

How we treat Glucoma ?
parasympathomimetics (cholinomimetics) facilitate the outflow of the humor , they reduce the volume by **increasing its drainage**
sympathomimetics reduce the volume by **inhibiting the formation** of aqueous humor
(here , in this case , we can notice that sympathetic and parasympathetic are not antagonistic for each other)

REMEMBER :
sympathetic and parasympathetic are not antagonisms , even if they have opposite actions

so , sympathomimetics are going to **reduce the formation** of aqueous humor which presents in the eye , throw α receptor stimulation and that will reduce intraocular pressure

Effects on respiratory track :

1- β2 receptors cause bronchodilation. last lecture we talked about selective β2 agoists which are the drug of choice for bronchial asthma , first , we start with them to bronchodilate , there are other groups of drugs but " β2 agoists" are the main stay of therapy of bronchial asthma.

For flu and congestion we give α agonist such as: phenylephrine, meoxamine psudoephedrine . they do vasoconstriction in nose and Mucosa , and that will allow you to breath better because of vasoconstriction

vasoconstriction also reduces secretions (secretions mainly come from the circulation , blood)

2- blood vessels of upper respiratory track mucosa constrict in response to α receptor stimulation (decongestion)

Be careful : these drugs **elevate blood pressure** , so people more than 40 years shouldn't take decongestants (vasoconstrictors), also it causes **rebound** which means after the effect of the drug goes away , congestion becomes worse than before (imagine we have a boll , when you hit it to the ground the goes back higher than before , which represents rebound) so if keep using these drugs (abuse them) you become hypertensive , and may have complications of hypertension from the excessive use of the decongestants

Effects on gastrointestinal track :

1- β2 receptors relax the smooth muscles of GI track (in general : β2 receptors relaxes smooth muscles in GI track , respiratory track , blood vessels) so the movement decreases.

2- α2 selective agonist decrease muscle activity indirectly by presynaptically reducing the release of acetylcholine (works on heteroreceptors)

REMEMBER :
inhibition of Ach → heteroreceptors
inhibition of NE → autoreceptors

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acetylcholine secretometer , increases the contractility and secreations, so it inhibits the secreations and contractility indirectly by inhibiting Ach release . This is more important for relaxation than β receptors

3- α2 receptors stimulation decrease salt and water flux into the lumen of the intestine. Means it reduces secretions in the intestine
these receptors are not presynaptic , they are in the smooth muscles , but they are similar to α2 receptors that are presynaptic . its function in smooth muscles is to reduce secretions of GI tract
So , sympathomimetics generally reduce motility(throw β receptors) and secretions(throw α2 receptors) of GI tract

Effects on genitourinary track :

1-relaxation of pregnant human uterus , and we use them to prevent premature labor (we said that before and it is very important) it is the safest drug for inhibition for premature labor , other drugs can be used

2- The urinary bladder base, urethral sphincter and prostate contain α receptors that mediate contraction. The sphincter is an area (the urinary bladder has a body, base , urethra, and prostate . The base, urethra and prostate has α receptors that contract and cause urinary retention).

3- The β2 receptors of the bladder wall mediate relaxation . increasing of relaxation will increase the capacity of the bladder so it can have more urine(it is like a ballon, when it is contracted it has small capacity and when it is relaxed its capacity will increase)

4- ejaculation in sex organs , it is α receptor function , and erection is parasympathetic function . detumescence of erectile tissue that follows ejaculation is brought about by norepinephrine but it is less important than ejaculation and erection.

#**tumescence** :, mass
#**detumescence** is opposite to tumescence and means reduction of mass/size

Effects on exocrine glands :

exocrine glands : have a channel throw which secretions can pass.
slivary glands : produce saliva which wets the mouth and digest carbohydrates

(complex carbohydrates or starch). In salivary glands, adrenoceptors regulate secretion of amylase and water

What are the differences between apocrine glands and thermoregulatory glands?

#They are both sympathetic, but thermoregulatory is cholinergic

#They are both exocrine

They differ in the method of secretions.
#we call thermoregulatory glands " ecrine glands" , it doesn't lose part of cell while the secretions get out and , it is found all over the body (more than the apocrine)

apocrine glands form a vesicles which contains parts of its cell when the secretions gets out such in rest milk, so the apical region of that cell will get out with milk by sucking by the infant
Also , appocrine means sweating under stress conditions , so they are found in the palm of the hand

apocrine are stimulated by sympathomimetics , but ecrine (sweat glands) need acetylcholine , muscarinic receptors will not be stimulate by sympathomimetics , even it is sympathetic , but it has acetylcholine and muscarinic receptors which will not be stimulated by sympathomimetics in a case of ecrine . apocrine sweat gland will respond during stress , they don't operate by acetyl choline .

Metabolic effects :

"they are very important"

1- β2 and β3 receptors are both in metabolism , β3 receptors responsible for lipolysis to produce glycerol and fatty acids
#**Note :** when we say just β receptors(in general) , it is either unknown which one , or both of them are there

2- α2 receptors inhibit lipolysis (α2 receptors in fat cells are found on the cell surface or cell membrane not presynaptic)
Note : receptors can be found in the cells without being in direct contact with nerves

β3 receptors	⟶	stimulate lipolysis
α2 receptors	⟶	inhibit lipolysis

3- β receptor stimulation enhances glycogenolysis in the liver , breaking down of glycogen gives glucose .

4- β2 receptor stimulation promote uptake of potassium into skeletal muscles and other cells thet cotain β2 receptors that allows the uptake of potassium_. we use β2 agonist to treat hyperkalemia , to prevent the presence of potassium in the circulation because it affects the heart. So potassium will get out the circulation and get into the cells . " this is an important point"

A student asked : if we have a regulation between stimulation and inhibition , how does lipogysis happen ?
The doctor answered : it depends on the agonist you give it to the patient , if you give an agent that stimulates β3 receptors it will cause lipolysis , but if you give α agonist that will inhibit lipolysis , and if you gave a mix they may be balanced according to the number of the receptors . But if we give epinephrine it will affect both receptors

#Note : we have specific sympathomimetics for each type of receptors (α , β2 , β3, ..) so the effect depends on the receptor . for example : Phenylephrine is not going to stimulate lipolysis , instead it is going to inhibit it . Clonidine inhibits it more because it is α2 agonist . BUT Isobutanol , which affects β3 receptors , stimulates lipolysis .

#Note :feedback inhibion is not a term used here , it is used in release of neurotransmitter and how you stop the release from sympathetic nerves not for sympathomimetics

"BE CREFUL : in the exam , all the choices will be sympathomimetics but they don't do the same function so you should know the receptors , its distribution and agonists "

even if you don't stimulate norepinephrine release (no release for norepinephrine) and stimulate α2 receptors in adrenergic neurons , you are going to inhibit the release of

norepinephrine . because the agonist reaches the terminal

#lets start from the beginning to be clear :

we have **sympathetic** and **parasympathetic** nervous system , and we took in the previous lectures their receptors and functions . then we moved to talk about **muscarinic agonist** and **muscarinic antagonist** , and now we are talking about **sympathomimetics** (drugs stimulate receptors NOT a nerve stimulation). As we took parasympathetic , we have in blood vessels muscarinic receptors but they are not stimulated by parasympathetic nervous system.

Effects on endocrine functions :

1- β receptor stimulation increases insulin release by pancreas, it also increases the glucose by stimulating glycogenolysis

2- α2 receptor stimulation inhibits insulin release

β receptors	⟶	stimulate insulin release (because they do glycogenolysis)
α2 receptors	⟶	inhibit insulin release

in penceriatic β cells **inhibition** is more important than stimulation, the overwhelming thing is inhibition of insulin secretions by α2 receptors

-suppose you give a drug has no α1 or α2 receptors stimulation , you give β receptors stimulation , that is going to increase insulin secretion.

3- β1 receptor stimulation increases renin secretion . rennin activates angiotensin – aldosterone system to give functioning angutensin 2 , and aldosterone secretion . these receptors found in juxtaglomerular apparatus of the kidney

4- α2 receptor stimulation inhibits renin secretion

" the predominant is β1 receptors "

clonidine is going to inhibit rennin and insulin secretion , because it is selective to α2 agonist

Effects on central nervous system:

catecholamine do not cross blood brain barrier (BBB) , epinephnrine and norepinephrine are water-soluble (polar) compounds , if you inject them intravenously (IV) you will not see CNS effects.

Amphetamines release catecholamines and replace them in vesicles taken by nerve terminals.

Actions of amphetamines :

mild alerting effect with improved attention at small doses , if you take small dose, you become more alert and you have more attention, if you increase the dose further you will have boring tasks throw elevation of mood , insomnia الأرق , euphoria النشوة , and anorexia (loss of appetite) فقدان الشهية

side effects of using amphetamines as slimming drug : دواء للتنحيف

1- pulmonary hypertension : increase pressure in pulmonary circulation
up to 50% of people who take amphetamine and have pulmonary hypertension die in 5 years
2- valvular heart disease: valves of the heart will be abnormal , and will cause heart failure and congestion
so amphetamine is prevented , anorexia drugs are not legal

also amphetamines will cause **psychotic** behavior (psychosis) مريض نفسي

Done by : Ola Atif
" و تحسب أنك جرم صغير ... و فيك انطوى العالم الأكبر "