Doctor 021

PHARMACOLOGY

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Sympathomimetic Drugs 1

➢ The drugs that produce effects similar to the effect of sympathetic nervous system stimulation.

➢ These drugs act directly on alpha or beta receptors, and we have drugs act indirectly, and we have drugs that act both ways; directly and indirectly on alpha or beta receptors.

Now, in order to understand the effect of these drugs we have to know the Relative receptor affinity's of these drugs.

1) **Alpha agonists**: —> synthetic drugs

➢ drugs Mainly act on alpha1 receptors —> **phenylephrine, methoxamine** These drugs' effect on **alpha 1 receptors is bigger than alpha 2 but they have no effect on beta receptors** : so the are considered selective for alpha1 stimulant.

➢ drugs Mainly act on alpha 2 receptors—> **clonidine, methylnorepinephrine** While these drugs **have bigger effect on alpha2 receptors than the effect on alpha 1, and no effect on beta receptors** : so selective for alpha 2 receptor .

2) **Mixed alpha and beta agonists**:

➢ **Norepinephrine** : **has the same effect on @1 and @2 receptors. But its effect on B1 is bigger than on beta 2 receptors**.[very little effect on B2 receptor]

➢ **Epinephrine(adrenaline)** : **has the same effect on @1 and @2 receptors. And equally effect on B1 and B2 receptors**

** So epinephrine acts perfectly on all adrenoceptors or adrenergic receptor.B2 receptors are affected by epinephrine and not by norepinephrine

3)Beta agonist:

➢ B1 selective agonist: **dobutamine [effect on B1 more than effect on B2 ,and there in no effect on alpha receptors].**

➢ Both B1 and B2 agonist: **isoproterenol.[and has no effect on alpha receptors].**

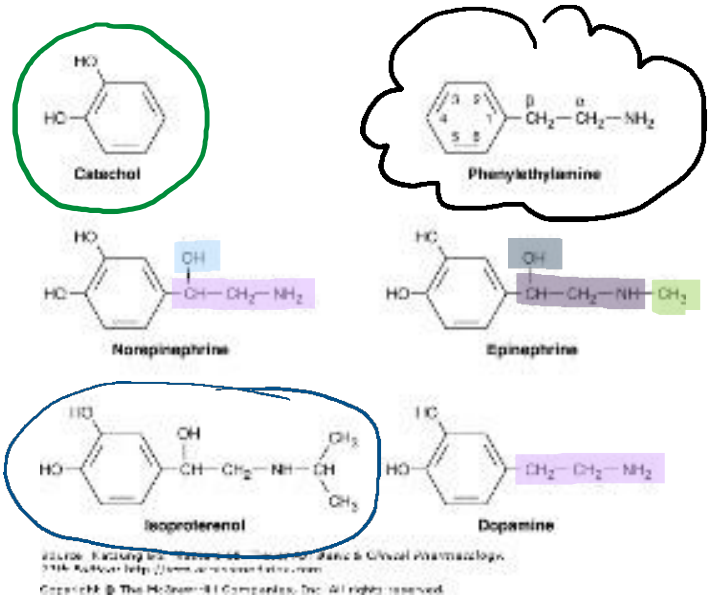
➢ B2 selective agonists: **albuterol (Salbutamol) /terbutaline**/**ritodrine** ➢ drugs used for those with bronchial asthma (bronchiodilators) **.[Very little effect on B1 receptors [in fact, given doses in usual concentration have no effect on B1 receptor], no effect on alpha receptors]**

Medicinal Chemistry of Sympathomimetic Drugs

1) catecholamines: catechol + amine

➢ ***NOTES:***

1-Phenylethylamine: It is the skeleton of all sympathomimetics.
2-The presence of two adjacent OH groups on the ring makes it a catechol ring 3-Norepinephrine, epinephrine and dopamine are natural catecholamines alkaloids
4-Isoproterenol: a synthetic drug it has isopropyl group on the amine portion, it's a powerful beta agonist that acts equally on both B1+ B2 receptors

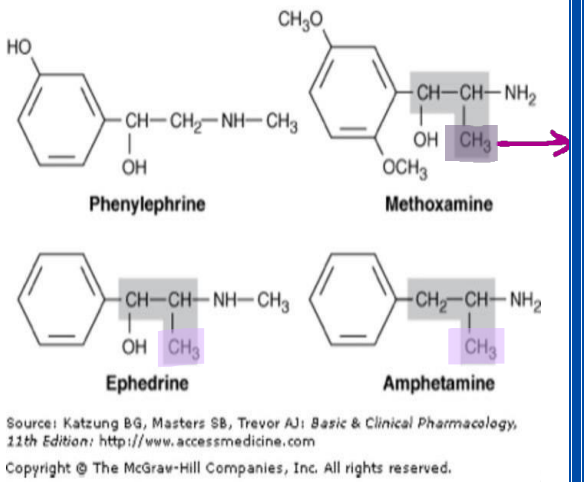


➢ ***Note*** ;- that catecholamines have two OH groups (on the catechol ring), and more oxygen in a compound makes it less soluble in lipids so it can't cross the brain blood barrier so it doesn't have a true effect on the central nervous system

2) noncatecholeamines: no catechol ring

➢***NOTES:***

1-Phenylephrine: a synthetic drug
a phenol has one OH group on the benzene ring so it's not catecholamines +has the same side chain of epinephrine.
2- Methoxamine: two methoxy groups on the ring it's not catecholamines.
3- Ephedrine: an alkaloid present in a plant native to china, no substituents on the ring, act both ways CNS stimulant + no substituents on the ring it's not catecholamines.



4- Methyl groups on: methoxamine, ephedrine and amphetamine make the compounds not affected by monoamine oxidase enzymes[MOA] so long duration reactions.
5- phenylephrine can be affected by MAO .
6-The four drugs are no affected by COMT enzyme(Catechol-Omethyltransferase)

Organ System Effects of sympathomimetics

CARDIOVASCULAR SYSTEM

The net effect of a Sympathomimetic drug depends on:

➢ **its relative selectivity for α or β adrenoceptors**
If we know that a drug is acting on alpha receptors we can predict its effect. If it acts on beta1 and beta2 receptors, we can also predict its effect knowing the different effects of alpha or beta stimulation

➢ -**the compensatory baroreflex mechanisms aimed at restoring homeostasis** Drugs that act on alpha receptors cause vasoconstriction of BVs, so increase vascular resistance(the resistance of blood flow in the vessel),this increase in resistance(increase blood pressure) is sensed by baroreceptors, which reflex (baroreflex) effect on the heart and decrease heart rate .

Effects of Alpha1-Receptor Activation

1)Effects on CVS

A pure α agonist (action on alpha 1 more that the action on alpha 2 receptors +no effect on beta receptors) **e.g. phenylephrine causes: arterial and venoconstriction that lead to**

❁ ↑ **peripheral arterial resistance** [due to the narrowing of these arteriols then increase BP

❁ ↓ **venous capacitance**: the amount of blood in the veins.[when the vein is dilated has more blood in it].

❁ ↑ **arterial resistance** (vessels are narrwo) **leads to a rise in blood pressure (BP).**

Now BP is high so we have to reduce this effect, so **the rise in BP elicits a baroreceptor-mediated increase in vagal tone** (vagal—> parasympathetic nerve innervating the heart is activated), slowing of the heart rate [to decrease the effect of raise BP].

Note: Some of us have stronger vagus activity, which means these bodies can relax faster after a stress.

If baroreflex function is removed by pretreatment with the ganglionic blocker (like trimethaphan which blocks nicotinic receptors in the autonomic ganglia the impulse that firing the parasympathetic nerve innervating

the heart will not pass the ganglia because it's blocked now by trimethaphan)**, the pressor effect of phenylephrine is increased approximately ten fold, and bradycardia is no longer observed.**

2)The skin vessels & the splanchnic vessels
***have predominantly α1 receptors.**
***constrict in response to epinephrine and norepinephrine.**

3)Vessels in skeletal muscle:
***have both alpha1 or beta2 receptors**
***may constrict or dilate depending on whether alpha or beta 2 receptors are activated.**

*in physiological condition, when epinephrine is released in response to emergencies for fight or flight situations, level of physiological concentration of epinephrine activates this beta receptors without activiating alpha receptors because beta receptors are more sensitive to epinephrine than alpha receptors

*more sensitive: means they are stimulated at a lower concentration than the needed to stimulate Alpha receptors.

*so in the case of fight or flight situation:

- the epinephrine released from the adrenal glands activities B2 receptors so it increases the blood flow to the muscles because we need our muscles in order to fight or to run away.

- at the same time, epinephrine vasoconstricts other blood vessels: skin vessels, splanchnic vessels, renal vessels… all constricted, so the blood is shifted actually to the organs that need to overcome this emergency situation so more blood goes to the muscles .

- also there is an increase or dilation in the coronary blood vessels supplying the heart with blood oxygen,

- so more blood goes through the skin, more oxygen goes to the heart and to the brain at the expense of other organs which are not important in cases of fight or flight situation.

4)The blood vessels of the nasal mucosa:
***have α 1 receptors,**
***local vasoconstriction induced by sympathomimetics produces a decongestant action.**

*people who have common cold: they have vasocongestion + running nose —> they put drops or spray in the nose so it becomes clear —> because these drugs are alpha1 agonist, so they constrict blood vessels in the basal mucosa which stops the congestion.

Effects of Alpha2-Receptor Activation

Alpha2 adrenoceptors' main sites are:

1) CNS 2) presynaptic ganglia

But are also present in the vasculature, and their activation leads to vasoconstriction.

➢ **This effect is observed only when α 2 agonists are given by rapid IV injection or in very high oral doses. Otherwise we see vasodilation instead of constriction Because—>When given systemically, these vascular effects are by the central effects of α 2 receptors in brain which lead to inhibition of sympathetic tone and a decrease in BP+decrease in HR.**

Alpha 2 receptor simulation stimulates the presynaptic A2 receptor present on the membrane of the sympathetic neuron and this A2 receptors inhibit the release of norepinephrine.

Hence, α 2 agonists are used in the treatment of hypertension.

Effects of Beta-Receptor Activation

Stimulation of β1 receptors in the heart increases cardiac output by ;

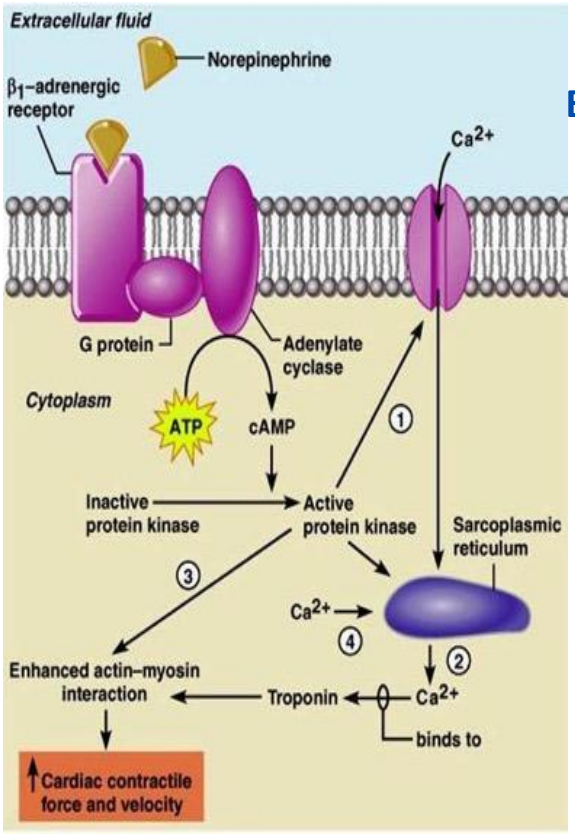
-stimulating contractility (force of contraction of the cardiac muscle): **so the heart muscle is able to eject more blood**

1- stroke volume —> the volume of blood ejected from the ventricle in one contraction or one stroke

-increasing the heart rate (number of beats or contractions in one minute)

2- if you multiplay the stroke volume by the heart rate you will get the cardiac output.

β agonists also decrease peripheral resistance by activating β 2 receptors, causing vasodilation in vascular beds of sk. Muscles



B1 car

Isoproterenol:

- **activates both β 1 and β 2 receptors equally**
- **The net effect is to maintain or slightly increase systolic pressure and to lower diastolic pressure, so that mean blood pressure is decreased**
- **Beta-receptor activation results in increased calcium influx in cardiac cells needed for the contraction**
- **Pacemaker activity is increased so it generates action potential at higher frequency (positive chronotropic effect).**

Conduction velocity in the AV node is increased so more action potential is going through from the atria to the ventricles **(positive dromotropic effect), and the refractory period is decreased.** Refractory period: is the period when AV node cannot allow any impulse to pass, so when this period is decreased, more impulses will pass to the ventricles.

- **intrinsic contractility is increased (positive inotropic effect),**
- **The direct effects on heart rate (HR) may be dominated by a reflex response to BP changes.** **[paroreflex to maintain homeostasis]**
- **Physiologic stimulation of the heart by catecholamines increases coronary blood flow** which provides more oxygen to the heart.[when heart working more=need more oxygen]

Effects of Dopamine-Receptor Activation

- dopamine is given by IV infusion instead of injection because it has very short half life, the effect of dopamine depends on the infusion rate (low, moderate) **low IV infusion of dopamine** [act on the most sensitive reseptors to dopamine=in dopamine receptors=D1] **promotes vasodilation of renal, splanchnic, coronary, and cerebral vessels** + **peripheral resistance may decrease via activation of D1 receptors**. this means that D1 receptors are very sensitive for dopamine because they can be affected even in low conc. of dopamine.
- **activation of the D1 receptors in the renal vasculature induce natriuresis (↑Na+ excretion in the urine).**
- **The renal effects of dopamine have been used clinically to improve perfusion to the kidney in situations of oliguria (abnormally low urinary output)** —> dopamine causes dilation to the renal blood vessels and this increases blood flow to the kidney and this so increases the urine volume.

❖ **moderate infusion rate of DA stimulate β1 receptors in the heart leading to increasing contractility & the HR increases slightly, so DA is used to treat congestive heart failure** [the situation when the heart can't pump blood to allbody, or short time management before swichting to other drugs in complicated cases.

❖ But high doses can KILL those patients because —> **At higher rates of infusion, dopamine activates vascular α receptors, leading to vasoconstriction of BV, including in the renal vascular bed (α receptor).**

❖ **Consequently, high rates of infusion of dopamine may mimic the actions of epinephrine**. Epinephrine can't be given to patients of congestive heart failure, also leads to death.

Non-cardiac Effects of Sympathomimetics

Activation of β2 receptors in bronchial smooth muscle leads to bronchodilation so β2 agonists are important in the treatment of asthma. The best bronchodilators are B2 agonists like: albuterol (Salbutamol) / terbutaline / ritodrine. But we also have to give patients steroids because bronchial asthma is an allergic disease.

❖ **In the eye:**

α receptors on the radial muscle of iris; activation by drugs such as phenylephrine causes mydriasis (pupil dilation):

--this is important for ophthalmologist: they want to examine the fundus of the eye, then they have to have a mydriasis (wide pupil) so they can look and see.

Now Alpha agonists also increases the outflow of aqueous humor from the eye, and can be used clinically to reduce intraocular pressure and treat glaucoma . we mentioned that before when we learnt about pilocarpine but the difference now is that some alpha agonists like epinephrine don't affect the vision.

In contrast, beta agonists have little effect, but beta antagonists decrease the production of aqueous humor —> The mechanism is still unknown but beta agonists are now mainly used rather than pilocarpine in **treating glaucoma** because they don't interfere with vision.

The bladder base, urethral sphincter, and prostate contain alpha receptors that mediate contraction and control urination. α1-A receptors play an important role

Alpha-receptor activation in the ductus deferens, seminal vesicles, and prostate plays a role in normal ejaculation.

Hormone secretion

In pancreatic islets, β receptors increase and α 2 receptors decrease insulin secretion, but this is not very important because the major regulator of insulin release is the plasma concentration of glucose.

❖ In kidney **renin secretion is stimulated by β 1**: this is important because renin causes the conversion of angiotensinogen to angiotensin 1 in the plasma then to angiotensin 2,

❖ Angiotensin 2: is a vasoconstrictor + dose lead to the release of aldosterone hormone that is needed for the retention of water and sodium

❖ **Renin secretion is inhibited by α 2 receptors** this inhibition stops the release of aldosterone hormone which is very dangerous so that we don't give alpha2 agonists (like epinephrine or high doses of dopamine) to patients with congestive heart failure

CNS

❖ **The catecholamines are almost completely excluded by blood-brain barrier.** [as we know catecholamines have OH groups that make it water soluble due to presence of oxygen(decrease lipid solubility)].

❖ **Peripheral effects of β- adrenoceptor agonists such as tachycardia and tremor are similar to the somatic manifestations of anxiety**: although catecholamines have no true effect on central nervous system but some beta agonist such as a epinephrine give effect similar to the effects of central nervous system stimulation

❖ Sometimes we give a beta blocker to remove the manifestations of anxiety

❖ **Noncatecholamines (amphetamines), which readily enter the CNS produce CNS effects.**

❖ **These actions vary from mild alerting, with improved attention to boring tasks to full-blown psychotic behavior.**

❖ The effect of amphetamines is very similar to the effect of cocaine

❖ **May also cause elevation of mood, insomnia, euphoria, & anorexia.**

Effects on Metabolism

❖ **(β3): respond to epinephrine much more than norepinephrine —> increase lipolysis with enhanced release of free fatty acids and glycerol into the blood.**

❖ **(β2): Glycogenolysis in the liver, increasing glucose release into the blood. (β2)**

❖ **Promotes uptake of K into cells, leading to a fall in extracellular potassium**

❖ **This may lead to a fall in the plasma potassium concentration during stress or protect against a rise in plasma potassium during exercise.**

❖ Potassium concentration in blood is critical and changes can induce cardio arrhythmias and when you exercise, potassium concentration in your blood will be high so your body releases epinephrine which affect beta2 receptor so increase the uptake of potassium .

GOOD LUCK

V1