14.2

Pharmacology

Doctor 2018 | Medicine | JU

Sheet ○ Slides

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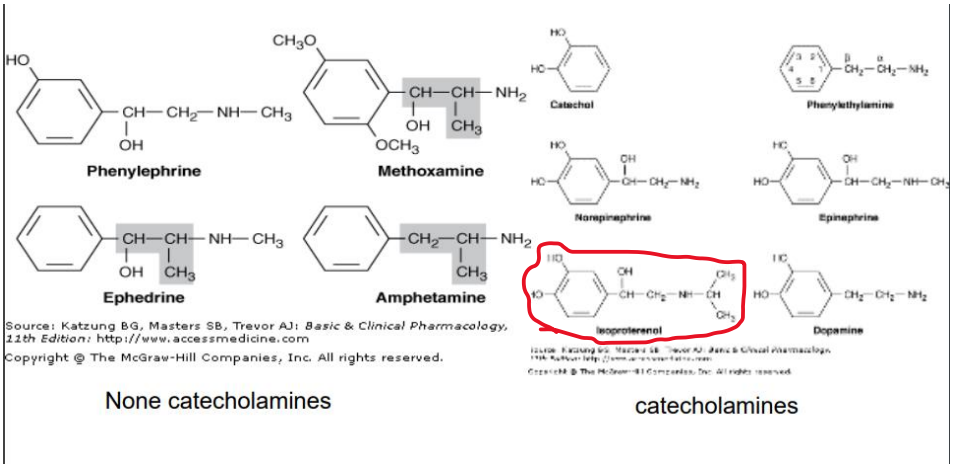
This is the second half of the 14th sheet. This one **will not** be included in the midterm exam but **WILL be** in the final**.** Also, I try to make my sheets integrated with slides.

Adrenoceptor Agonists & Sympathomimetic Drugs:

We have few types of **sympathetic receptors**, α and β types of receptors. Some drugs **only** activate alpha, some others only activate beta, and some can activate both.

pharmacological actions of drugs depend on what types of receptors they're working on.

Type of action Example drugs	Relative receptor affinities
Alpha agonists	
Phenylephrine, methoxamine	**$\alpha_1 > \alpha_2 >>>>> \beta$** **(selective α_1 agonists,** weak effect on **α_2** and nearly none on **β**)
Clonidine, methyl norepinephrine	**$\alpha_2 > \alpha_1 >>>>> \beta$** **(action on α_2** more than on **α_1**, nearly none on **β)**
Mixed alpha and beta agonists	
Norepinephrine	**$\alpha_1 = \alpha_2 = \beta_1 >> \beta_2$** **(acts equally on α_1, α_2, β_1** and much less on β_2**)**
Epinephrine	**$\alpha_1 = \alpha_2 = \beta 1 = \beta_2$** **(acts on ALL types of adrenoreceptors equally)**
Beta agonists	
Dobutamine	**$\beta_1 > \beta_2 >>>> \alpha$** **(selective β1 agonist, less effect on β_2 and nearly no α effect)**
Isoproterenol	**$\beta_1 = \beta_2 >>>> \alpha$** **(affects β_1 and β_2 equally, has no effect on α)**
Albuterol (Salbutamol), terbutaline, ritodrine (used for bronchial asthma)	**$\beta_2 >> \beta_1 >>>> \alpha$** **($\beta_2$ selective agonist, very poorly affects β_1 and has no effect on α)**



Isoproterenol, a **synthetic catecholamine**. Very powerful **beta agonist**, acts equally on both β_1 and β_2, has no effect on α.

Notice the badly circled molecule.

We have **two types of sympathomimetics based on their chemical structures**, catecholamines and non-catecholamines.

All Catecholamines are similar, with small differences. All have benzene rings with 2 hydroxyl groups (catechol), and short carbon chain with an amine attached (members: phenylethylamine, epinephrine, norepinephrine, dopamine and isoproterenol).

Non catecholamines don't have the **dihydroxyl ring feature**, even if their ring contain an OH, it's a phenol not a catechol. (members: phenylephrine, methoxamine, ephedrine,

Sympathomimetics' effects on organ system:

Cardiovascular system:

The net effect of a Sympathomimetic drug on the sympathetic system depends on:
-Its relative **selectivity for α or β adrenoceptors** (the receptor they affect).
-The **compensatory baroreflex mechanisms** aimed at restoring homeostasis.

Effects of Alpha1-Receptor Activation:

They generally **increase vascular pressure**, causing **baroreflex** that lowers heart rate.

A pure α_1 agonist e.g. phenylephrine causes:
- Arterial constriction and venoconstriction.

-Increase in **peripheral arterial resistance.** (blood passing through vessels creates resistance. When resistance increases, the pressure inside arteries increases. The less the diameter, the more the **resistance** and **pressure**)

-Decrease in venous capacitance.

→**Increase** in arterial resistance leads to a rise in blood pressure (BP).

→The rise in BP causes stretching, eliciting a **baroreceptor - mediated** increase in vagal tone (**stimulation of vagal nerve),** which results in **slowing of the heart rate (brady cardia)**.

Blood pressure depends on **cardiac output**[1] and **peripheral resistance**[2]. If peripheral resistance increases, cardiac output has to be decreased to counteract this effect and maintain the blood pressure.

Cardiac output depends on stroke volume and heart rate. **Stroke volume** is the volume of blood pumped from the heart in one contraction. Multiplied by number of contractions (heart rate) it gives us the **cardiac output**.

Cardiac output = stroke volume X heart rate

→ If we want to **block baroreflex function** to view actual effect of phenylephrine without baroreflex, we give a drug that blocks autonomic ganglia. An example of such drugs is the drug trimethaphan (a short acting ganglion blocker).

→We'd observe that the pressor effect of phenylephrine has increased approximately ten times (because nothing is opposing it), and bradycardia would no longer be observed.

Alpha-1 receptor activation continued ..

The **skin vessels** & the **splanchnic vessels** have predominantly α_1 receptors and they **constrict** in response to epinephrine and norepinephrine.

Vessels in **skeletal muscles** may dilate upon β_2 stimulation or constrict **when alpha receptors** are activated because they have both. β_2 are a**ctivated by epinephrine in fight or flight** situations because they're less sensitive than α_1 (remember that in fight or flight situations the epi. concentration is higher so it activates the less sensitive β_2 receptors) and they **cause vasodilation to increase muscle perfusion**. However, if concentration of epinephrine is so high both would be activated. Upon increase in epinephrine there would be vasoconstriction, even in skeletal blood vessels, caused by α_1 activation (because they're MORE sensitive).

The **blood vessels** of the nasal mucosa have both, α_1 receptors and local **vasoconstriction** induced by sympathomimetics activating **α_1**, producing a **decongestant action**.

Effects of Alpha-2 receptor activation:

α_2 adrenoceptors are present in three sites:

1) post synaptic (but less than the abundance of α_1). When stimulated they produce the same effect as activation of α_1 receptors (**vasoconstriction**). This effect is observed **only** when α_2 agonists are given by **rapid IV injection** or in **very high oral doses.**

2) presynaptic neurons, auto receptors. When stimulated, they inhibit the release of norepinephrine.

3) in the brain (CNS). When stimulated they inhibit the sympathetic tone, reducing blood pressure.

Hence, α_2 agonists are used for **treatment of hypertension**.

Effects of Beta-Receptor Activation:

Stimulation of **β_1 receptors** in the heart increases cardiac output by: increasing the heart rate.

β agonists also **decrease peripheral resistance** by activating **β_2** receptors, causing vasodilation in vascular beds of skeletal Muscles.

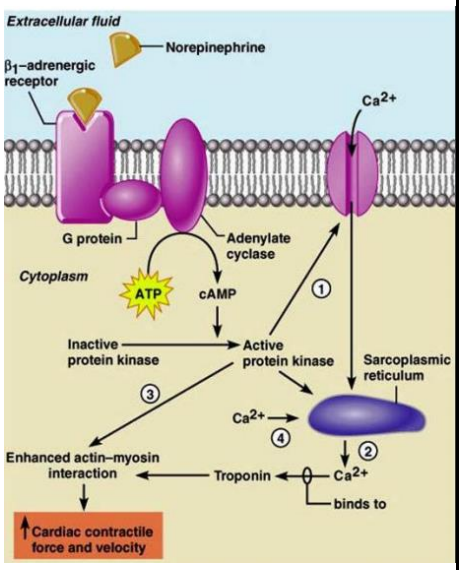
So, **β_1 → increases cardiac output**
β_2 → vasodilation.

Isoproterenol **activates both β_1 and β_2** receptors, as well as **β_3** receptors (Adipose tissue).

*Before we get into explanation let's have an idea of what are **systolic** and **diastolic blood pressures**:

Systolic BP: is pressure during systole (**contraction of the ventricle**) and stretch of blood vessels.
Diastolic BP: is pressure when the **heart relaxes** after that pump

This diastole reflects the diameter of the artery in its unstretched state:
Wide diameter → less resistance → lower diastolic pressure
Narrow diameter → more resistance → higher diastolic pressure



Notice how activation of **β_1** receptors by norepinephrine activates a G-protein linked cascade of events, where adenylate cyclase is activated releasing cAMP, which in turn activates protein kinase, which activates Ca^{2+} channels increasing Ca^{2+} influx. Ca^{2+} induces the sarcoplasmic reticulum to release more Ca^{2+}, which bind to troponin enhancing actin-myosin interaction and thus causing **a stronger contraction of the cardiac muscle**.

The net effect of isoproterenol is to maintain or just slightly increase systolic pressure and to lower diastolic pressure, so that the **mean blood pressure** is decreased.

Activation of **β** receptors, theoretically would cause:

(1) increase in the cardiac output by activation of β_1 receptors, which as we explained, results in **increased calcium influx** to cardiac cells, resulting in:
Pacemaker activity is increased (**positive chronotropic effect**).
Conduction velocity in the AV node is increased (**positive dromotropic effect**), and the **refractory period** is decreased (faster successive pumps of blood).
Intrinsic contractility is increased (**positive inotropic effect**)
these all result in more impulses and stronger force of contraction, which means a higher cardiac output (**result: higher systolic**).

(2) dilation in peripheral arteries by β_2 activation in blood vessels **(result: lower diastolic**)

what we actually observe is a **decrease in diastolic** as expected, but **no increase in systolic**, that's because if diastolic decreases, systolic decreases as well.
-think of how the diameter of the arteries would increase, accommodate more blood, and thus, the pressure of blood ejection on the arteries would decrease-

the effect of β_1 activation and increase of cardiac output were **opposed by the decrease in the diastolic pressure by β_2 activation** (increase in vascular diameter), so the increase in it doesn't show and the **mean Blood Pressure decreases.**

Normally, the direct effects on heart rate (HR) may be dominated by a reflex response to BP changes like **vagal nerve stimulation**.

In this case: no reflex bradycardia, because BP didn't increase.

Physiologic stimulation of the heart by catecholamines increases coronary blood flow. Because, in fight or flight situations, organs like heart, skeletal muscles, and brain need the most amount of perfusion to achieve an effective reflex. Other organs aren't important at that period.

GOOD LUCK