بسم الله الرحمن الرحيم

PHARMACOLOGY

Final – Lecture 4

Sympathomimetics (Pt.2) & Adrenoceptor Antagonists (Pt.1)

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

Written by:

- **Lubna Alhourani**
- **Maria Alrawi**

Sympathomimetics

2. Respiratory tract:

A. Bronchial smooth muscles relax in response to β_2-receptor stimulation → bronchodilation.

B. Blood vessels of upper respiratory tract mucosa constrict in response to α-receptor stimulation → decongestion.

In cases of congestion or flu, decongestant drugs are given as $\alpha 1$ -agonists, such as **phenylephrine** and others. However, if you overuse it ; the congestion may become **rebound congestion**, meaning it is worse than before. So those drugs provides only temporary relief.

Sympathomimetics

3. Genitourinary tract:

- **β_2-receptors mediate relaxation of the pregnant human uterus.**
- **The urinary bladder[1] base, urethral sphincter[2] and prostate[3] contain α-receptors that mediate contraction and urinary retention.**

- When α-agonists stimulate these three structures, they contract, causing urine retention. People with **prostate enlargement** are given **α -blockers** to relax the sphincter, reducing the urine retention, and lowering the risk of infection due to urine stasis.

- **The thermoregulatory eccrine sweat glands are sympathetic cholinergic (muscarinic).**

- As the sympathomimetics are drugs that mimic the action of epinephrine and norepinephrine ; they will not stimulate the eccrine sweat glands that are only stimulated by the sympathetic nervous stimulation (specifically , Ach on cholinergic muscarinic receptors) .

Sympathomimetics

4. Exocrine glands:

- **The apocrine sweat glands located in the palms of the hands respond to adrenoceptor stimulants with increased sweat production. This is non-thermoregulatory sweating associated with psychologic stress.**

✓ Remember : secretions from glands other than sweat glands, such as those in the GI tract, are regulated by the parasympathetic nervous system. Therefore, sympathomimetics do not influence the secretion activity of these glands.

✓ Here , we're just talking about the sweat gland in the palms of the hands that are controlled by the sympathetic nervous system.

Sympathomimetics

5. Metabolic effects:

- **β_3-receptor stimulation increases lipolysis with release of fatty acids and glycerol.**
- **α_2-receptor stimulation inhibits lipolysis.** By reuptake mechanism of NE.
- **β-receptor stimulation enhances glycogenolysis in the liver leading to increased glucose release into the circulation.**
- **β_2-receptor stimulation promote uptake of potassium into cells.**

The body experiences two types of **hypokalemia**:

- The first occurs when potassium is taken up into cells, which does not lead to an overall reduction in the body's total potassium levels.
- The second occurs when potassium is lost through urine or diarrhea, resulting in a total reduction of potassium levels in the body.

Sympathomimetics

6. Effects on endocrine function:

- **β-receptor stimulation increases insulin release by pancreas.**
- **α_2-receptor stimulation inhibits insulin release.**
- **β_1-receptor stimulation increases renin secretion.**
- **$\alpha\alpha_2$-receptor stimulation inhibits renin secretion.**

- The effect of the ß-receptors stimulation on insulin release is **minor** , because insulin is normally released when the glucose level increases.

- The effect of α2-receptors stimulation is **predominant**, inhibiting the release of insulin and the uptake of glucose , maintaining the glucose levels in the case of hypoglycemia.

Specific Sympathomimetics

1. **Catecholamines:**

   Epinephrine, norepinephrine, dopamine, fenoldopam & dobutamine.

2. **Noncatecholamines:**

   Phenylephrine, amphetamine, methamphetamine, methylphenidate & others.

Epinephrine → It mediates negative feedback of its own release.

- **Stimulates all adrenoceptors (α_1, α_2, β_1, β_2).**
- **Very potent vasoconstrictor and cardiac stimulant.**
- **Positive inotropic and chronotropic actions on the heart (β_1).**
- **Vasoconstrictor in many vascular beds (α_1), and vasodilator in skeletal muscle blood vessels (β_2) → increase blood flow during exercise.**

Norepinephrine

- **Similar to epinephrine except it has no significant effect on β_2 receptors.**

Dopamine

- **Activates D_1 receptors and produce vasodilation, which is specially clinically important in renal vascular bed → increase renal blood flow.**
  - Less selectivity compared to **dobutamine** on the heart.
  - Not very functional to stimulate the heart.
- **Activates β_1 receptors in the heart.**
- **At high concentration, it activates vascular α receptors leading to vasoconstriction including the renal vascular bed.**

Fenoldopam

- **Is a selective D_1 receptor agonist causing peripheral vasodilation.** More effective than dopamine on the D1 receptors.
- **Very useful intravenously in treating severe hypertension.**

Dobutamine

- **Is a selective β_1 agonist.**
- **It increases cardiac output (positive inotropic action).**
  - By increasing the contractility of the heart.

β_2-Selective Agents

The same **albuterol**.

- **Important in treatment of bronchial asthma (salbutamol, terbutaline, salmetrol, metaproterenol).**
- **Uterine relaxation in premature labor (Ritodrine).**

Derivative of **salbutamol** with longer action (longer half life).

Phenylephrine

- **It is a relatively pure α_1 agonist.**
- **Causes contraction of smooth muscle of blood vessels and others.**

Can be used as:

- Decongestant.
- To treat shock and increase the blood pressure.

Tyramine

Almost 16 types of food contain tyramine

- **Found in high concentration in wine, fermented food such as cheese.**
- **It is readily metabolized by MAO in the liver, and is inactive when taken orally.**
- **It produces indirect sympathomimetic action by releasing catecholamines from sympathetic nerve terminals → hypertension.**

Depression patients are prescribed with MAO inhibitors, because it is thought that depression is due to relative deficiency in biogenic amines (catecholamines, serotonin)

- **Patients taking MAO inhibitors should avoid tyramine-rich food to avoid hypertensive crisis.**

If this enzyme is inhibited, Tyramine accumulates & it will be taken by nerve terminals instead of catecholamines which causes hypertensive crisis(very high blood pressure),other drugs might contain MAO inhibitors (some antibiotics).Hypertensive crisis persists until catecholamines in nerve synapses are eliminated & consuming of Tyramine containing food is stopped.

Adrenoceptor Antagonists

- Yacoub Irshaid MD, PhD, ABCP

Department of Pharmacology

Adrenoceptor Antagonists

1. **α-Adrenoceptor Antagonists.**
2. **β-Adrenoceptor Antagonists.**

They are not as commonly used as B-Adrenoceptor Antagonist.

B adrenoceptor antagonist are widely used in medicine (we are going to talk about commonly used ones)

Both are Competitive inhibitors
If you increase the concentration of one you reduce the binding of the other.

α-Adrenoceptor Antagonists

-sin & -sine : alpha blockers

Prazosin: $\alpha_1 >>>> \alpha_2$ Mainly blocks a1 but can block a2 if high concentrations are consumed.

Terazosine: $\alpha_1 >>>> \alpha_2$ Same as Prazosin

Tamsulosin: α_{1A} and α_{1B} Affects a1 subtypes: in prostate gland (does not work on all a1 receptors), a1 receptors are responsible for contraction & retention, blocking them relieves obstruction.

Phentolamine: $\alpha_1 = \alpha_2$

Old drugs:

1. Phenoxybenzamine: irreversible inactivation-kills the receptor.
2. phentolamine: Father of them (originator- drugs are compared to it even in new drug development)

α-Adrenoceptor Antagonists

Pharmacodynamics:

A. Cardiovascular system:

Block of α_1-receptors in arterioles leads to vasodilation, lowering of peripheral vascular resistance and blood pressure.

Vasodilation:
1.reduce vascular resistance.
2.reduce blood pressure.
3.increase blood flow.

α-Adrenoceptor Antagonists

What is postural hypotension?
When you change your position from laying down to sitting blood is pulled down due to gravity thus lowering bp.

- **Block of α_1-receptors in venules leads to venodilation, postural hypotension and reflex tachycardia.** Venodilation:
  Veins have higher capacity to accommodate blood---
  >veinous return is reduced ---> cardiac output is reduced ---> systolic bp is reduced. result? Pulling of blood(postural hypotension)

Postural hypotension leads to reflex sympathetic stimulation tachycardia by releasing catecholamines (norepinephrine)---> vasoconstriction to antagonize postural hypotension.
Those are the consequences of any vasodilator that causes postural hypotension

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

Bec. A2 receptors are responsible of inhibiting catecholamines release, blocking them results in less inhibition of their release.

α-Adrenoceptor Antagonists

Miosis: narrowing of pupil
Stimulation of radial muscle (contraction): dilation
Inhibition: constriction(miosis)

Diagnosis of pupil is really important in emergency room especially for comatized patients.

B. Other effects:

- **Miosis (α_1 receptors in dilator pupillae** radial muscle**).**
- **Nasal stuffiness** congestion **(α_1 receptors in blood vessels).** Vasodilation(release of fluids from nasal mucosa) --> ECF accumulation
- **Decreased resistance to the outflow of urine (α_{1A} and α_{1B} receptors in the base of urinary bladder and the prostate).** Is used to treat urine retention in patients with prostate enlargement (prostate hyperplasia).

Review, uses of a antagonists:
Anti-hypertensive vasodilation
Prostate enlargement

β-Adrenoceptor Antagonists

Always competitive

If you reduce the concentration of catecholamines you increase the inhibition & if you increase the concentration of catecholamines you reduce the inhibition.

- **These drugs occupy β receptors and competitively inhibit occupation of these receptors by catecholamines.**

Classifications:

- **β-Adrenoceptor antagonists are not the same, regarding their antagonism of receptors and lipophilicity.**
- **Lipophilic antagonists cross the blood brain barrier and affect the central nervous system in addition** have effects on the brain.

Drugs are weak acids and bases they differ in their lipophilicity depending on physiological PH, lipophilic drugs cross the BBB & are eliminated by metabolism but hydrophilic drugs cannot cross BBB and are eliminated by urinary & biliary excretion.

β-Adrenoceptor Antagonists

1. **Non-selective ($\beta_1 = \beta_2$): Propranolol, Timolol, Sotalol.** Propranolol Prototype/originator :used in pulmonary hypertension & portal hypertension(in people with liver cirrhosis due to shunting of blood from the portal to the systemic circulation) specifically, it could be used for systemic hypertension.
   *normally portal circulation pressure is less than systemic circulation pressure.
2. **Non-selective ($\beta_1 = \beta_2 \geq \alpha_1 > \alpha_2$): Carvedilol, Labetalol. They have alpha blocking activity also.** They are not bad, they have specific usage.

   Mixed antagonist: blocks a & b receptors but beta more
3. **β_1- selective or cardioselective ($\beta_1 >>> \beta_2$): Atenolol, Bisoprolol, Metoprolol, Esmolol.**

   Cardioselective : Because it works mainly on B1 receptors

β-Adrenoceptor Antagonists

- **Propranolol undergoes extensive hepatic first-pass metabolism** (highly lipophilic) **→ low bioavailability**
- **→ oral dose is much larger than IV dose.**
- **Metoprolol and carvedilol are metabolized.** = lipophilic, but not as much as propranolol
- **Atenolol is mainly excreted unchanged in urine. Its half-life is prolonged in renal failure.** patients with liver cirrhosis can use it (it is also selective B1)
- **Bisoprolol is partly exceted unchanged and partly metabolized.**
  Partially ionized (kidney) & partially unionized (metabolism)

*Sotalol & Esmolol are injected drugs

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	Slide 11 Slide 14	-	Additional sentence on both slides
V1 → V2	Slide 2	Rebound congestion occurs when the administration of decongestant is stopped	It occur when it's overused

Additional Resources:

رسالة من الفريق العلمي:

تذكّروا...
ما خابَ عبدٌ مُؤمِنٌ توَكَّلَ على الله