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Pharmacology

Doctor 2018 | Medicine | JU

◉ Sheet ○ Slides

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Doctor

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Last lecture we started talking about **α-blockers,** in this lecture we will continue talking about **α-blockers** as well as **β- blockers.**

Note: the red colored notes are the ones colored in the slides.

Yohimbine

- an indole alkaloid, **α2-selective antagonist**.
- It Blocks other receptors: **5HT receptor** (serotonin receptor), and **dopamine receptor**.
- Increases **ADH** release.
- Enhances sexual activity (aphrodisiac effect).
- Sometimes (rarely) used in the treatment of **orthostatic hypotension** because it **promotes NE release** through **blockade of presynaptic α2 receptors**.

Remember that orthostatic hypotension is the decreased blood pressure after standing following supine position, when there is no enough vasoconstriction to retain the blood in the circulation, blood goes down and central blood volume disappears, less blood reach the brain, which results in falling down.

Presynaptic α2 receptors act as normal feedback inhibition mechanism to decrease the release of NE. when Yohimbine blocks these receptors, more NE will be released, so it causes vasoconstriction and solves the problem.

- Was widely used to improve male **erectile dysfunction** but has been superseded by phosphodiesterase-5 inhibitors like sildenafil (viagra).

❖ Uses of the Alpha-Receptor–Blocking Drugs

1) Pheochromocytoma

A tumor in adrenal gland that results in production of excessive secretion of catecholamines Epinephrine and Norepinephrine, Causes intermittent or sustained hypertension, tachycardia, headaches, palpitations and increased sweating.

Treatment: It is treated surgically if possible. **Phenoxybenzamine** given orally **preoperative to control hypertension** and prevent stroke and heart failure. It is also used for the **chronic treatment of inoperable or metastatic pheochromocytoma** which can't be removed surgically so it's treated symptomatically.

To prevent cardiac stimulation, we use **β-blockers** (reverse the cardiac effects), but it **Should not be used prior to establishing effective α-receptor blockade** (it should be given after α -receptor blockers) because the inhibition of cardiac output caused by beta

blockers followed by vasodilation caused by α-blockers will cause the blood pressure to drop severely and might lead to death.

Metyrosine (α -methyltyrosine) is a competitive inhibitor of tyrosine hydroxylase which catalyzes the RLS in the synthesis of catechol amines, thus inhibiting the whole synthetic pathway, so this drug is used in **inoperable or metastatic pheochromocytoma**.

It has side effects because it causes **extrapyramidal effects** due to reduced dopamine levels, extrapyramidal effects are characterized by Parkinson like symptoms such as muscle rigidity, difficulty to initiate movement, difficulty in swallowing, mask like face, etc.

2) Reduce Hypertensive Emergencies

Labetalol (**α and β blocker**) is used in **Hypertensive Emergencies**, its action is immediate, it causes **vasodilation** by alpha blockade producing a decrease in peripheral resistance, and **inhibits cardiac stimulation** by beta blockade, which result in immediate **reduction in the blood pressure**.

3) Treatment of overdose of α1 agonist

Phentolamine is quick and short acting drug (half-life 19 min). Sometimes patients with low blood pressure in operating theatres are given **α1 agonist** to increase the blood pressure, if the dose is high and we want to **reverse the effect** quickly we give Phentolamine.

4) Chronic Hypertension

α1-selective antagonists are used in mild to moderate systemic hypertension. Not recommended as monotherapy rather they are used as **additive drugs** (combined with other drugs), because other drugs are more effective in preventing heart failure such as **ACE (angiotensin converting enzyme) inhibitors**.

Although, their main use is to treat patients with **hypertrophic prostate** (enlarged prostate with difficulty in urination).

The major adverse effect is **orthostatic hypotension**, which happens after the first dose.

5) Peripheral Vascular Diseases

Raynaud's phenomenon is caused by excessive reversible vasospasm in the peripheral circulation especially in the hands (white hands).

Prazosin or **phenoxybenzamine** are used for treatment, but **calcium channel blockers** are preferable for most patients because they have less side effects.

6) **Urinary Obstruction Benign prostatic hyperplasia (BPH),** common in elderly men, accompanied with difficulty in urination.

Block α1A-receptor → reduced contraction of smooth muscle in the bladder neck and prostatic capsule → Reduce urinary urgency and improves urine flow.

Prazosin, Doxazosin, and Terazosin are selective α1 blockers that are effective as treatment.

Tamsulosin is selective α1A-receptor antagonist preferred in patients who have **orthostatic hypotension** with other α1-receptor antagonists.

❖ β- Adrenoceptor Antagonists

The doctor mentioned some history regarding the discovery of β-blockers that is not mentioned in the slides ☻
β-blockers are discovered after the discovery of alpha blockers, when two scientists were working on isoproterenol and they substituted the two OH present on catechol nucleus by two chlorine atoms, so the compound became **dichloroisoproterenol** which is nonselective β-blocker, so it's the first developed β-blocker with high intrinsic activity (partial agonist activity) and low beta blocking activity. The second developed beta blocker is **pronethalol** and is stopped because of carcinogenic activity on rats. The third is **propranolol** which has low intrinsic activity and high beta blocking activity, still used until now.

First generation: non selective β-blockers, they block β1 and β2 equally.

Second generation: Cardioselective β1, the first one is practolol but it's stopped because of its side effects (toxic) .

Third generation: Vasodilator β blockers (**Extra**: third-generation beta blockers can cause vasodilation through blockade of alpha-adrenergic receptors), and at the same time they decrease cardiac output, contractility and heart rate by blockade of β receptors in the heart. After vasodilation, compensatory vasoconstriction might develop (by reflex increase of sympathetic tone over blood vessels).

Notes:

- ✓ all the benefits in the treatment with β-blockers come from blocking β1 receptors, blocking β2 is responsible for the side effects.

- ✓ The selectivity of β blockers to β1 or β2 is dose-related, and the selectivity tends to diminish at higher drug doses. For instance, low doses of β1 blockers are not supposed to cause bronchoconstriction.

Other major differences relate to their **lipid solubility**. Highly lipid soluble drugs have better absorption, fast metabolism and shorter half-life, can cross the BBB and have central side effects (they might cause depression and nightmares ☹).

Most drugs are well absorbed after oral administration, peak concentrations 1–3 hours after ingestion.

Another variation is the **local anesthetic (membrane-stabilizing) effects,** these effects are present in some β blockers such as propranolol, however, whatever the dose is high it will never achieve a concentration that causes local anesthesia, so this action is not important.

Lipophilic β blockers	Hydrophilic β blockers
• Propranolol, metoprolol, oxprenolol, carvedilol. • readily absorbed from GI, metabolized in liver. • hepatic failure prolongs their t1/2. • large volume of distribution, and penetrate BBB well.	• acebutolol, atenolol, bisoprolol, nadolol, sotalol. • less readily absorbed, not extensively metabolized. • long plasma half-lives which are prolonged in renal failure.

❖ Pharmacodynamics of β blockers:

➢ Effects on the Cardiovascular System

Very valuable in **hypertension, angina** and **chronic heart failure** and **following myocardial infarction (MI).**

Heart: ↓ Heart rate, ↓Stroke volume (the volume of blood ejected by one contraction), ↓ Cardiac output, ↓ AV conduction velocity, ↓ O2 consumption.

- ✓ cardiac output = stroke volume X heart rate
- ✓ the mechanism of action for patients with ischemia is to decrease O2 consumption by decreasing cardiac output.

Blood vessels: ↓BP both diastolic and systolic after continuous treatment.

So they decrease the peripheral resistance, and this effect can result from:

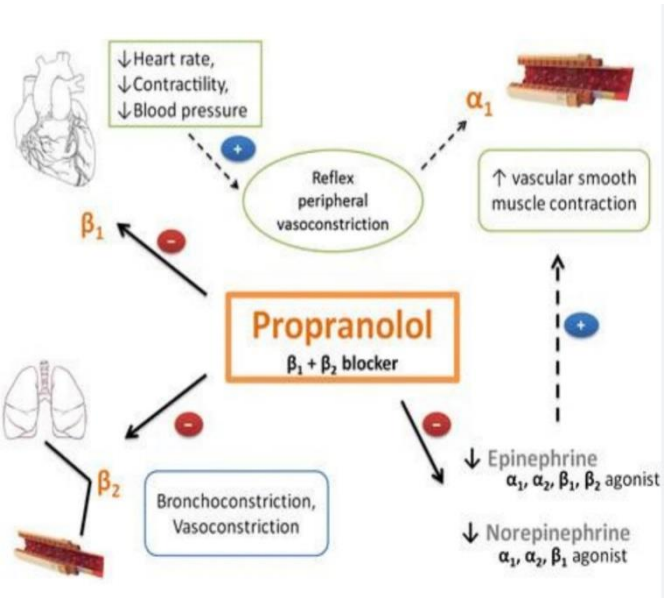
1) Blockade of presynaptic β2 receptors in the heart and decrease NE release.

2) nonselective and β1 selective blockers inhibit the mechanism of release of renin (which leads to decrease angiotensin 2 that is considered vasoconstrictor).

Notice that there are two types of presynaptic receptors in the heart:

α2 receptors ➡ Inhibit NE release **β2 receptors** ➡ Increase NE release

Note: At first, the decrease in cardiac output evokes reflex peripheral vasoconstriction, so they don't cause immediate hypotension in healthy individuals with normal BP, but <u>continuous treatment</u> may cause decreased BP.



➢ **Effects on the Respiratory Tract**

β2 blockade in lungs can produce bronchoconstriction and **increase in airway resistance, particularly in patients with asthma** (not noticed in normal people).

✓ β1 blockers are safer than nonselective β-blockers. However, **β1-selective blockers are not sufficiently specific to completely avoid interactions with β2 receptors.** Consequently, these drugs should generally be **avoided in patients with asthma**. Many patients with chronic obstructive pulmonary disease (which involves asthma) may tolerate these drugs because the benefits exceed the risk, e.g. in patients with concomitant **ischemic heart disease**, may outweigh the risks.

➢ **Effects on the Eye**

Reduce intraocular pressure in glaucoma by **decreasing aqueous humor production.** Glaucoma is treated by:

1) reduction of aqueous humor secretion.

2) enhancement of aqueous out-flow.

Drugs useful in reducing intraocular pressure: **Cholinomimetics** (pilocarpine, physostigmine, demecarium, etc), **α agonists** (epinephrine), **β blockers**, **prostaglandin F2 analogs**, **diuretics**.

Prostaglandin analogs and β blockers are the most popular (effective with minimal side effects).

➢ **Metabolic and Endocrine Effects**

- β-receptor antagonists increase LDL (the bad cholesterol) and triglycerides, and decrease HDL (the good cholesterol) by inhibiting **lipolysis**. Long term treatment of β-blockers might expose the patient to type 2 diabetes.
- **Glycogenolysis** in the liver is inhibited after β2-receptor blockade.

✓ So β–blockers should be used with caution in type 1 **insulin-dependent diabetic patients**, these patients suffer from hypoglycemia and associated symptoms (tremors, sweating and tachycardia), if they are given beta blockers the recovery of hypoglycemia will be delayed (no glycogenolysis), also no symptoms will appear which will worsen the condition.

❖ Specific Agents

Propranolol

- Prototype of β-blocking drug, High lipid solubility (very good absorption and reach the brain).
- Has low and dose-dependent bioavailability (bioavailability increases with increasing the dose).
- First-pass effect varies among individuals.
- A long-acting form of propranolol is available, prolonged absorption of the drug may occur over a 24-hour period. Short-acting form is given twice daily.

  Note: All beta blockers give duration of action that exceeds the expected duration according to their half-life.
- No effect on α and M receptors but may block some serotonin receptors in the brain, though the clinical significance is unclear.
- It has no partial agonist action at β receptors, strong local anesthetic effect.

Nadolol

Has a **very long duration of action (24 hours)**, completely excreted unchanged in kidneys.

Timolol

Has no local anesthetic activity, used topically to treat glaucoma and other therapies.

Note: We can't use propranolol to treat glaucoma because it causes local anesthesia in the eyes.

Sotalol

Nonselective that also exhibits Class II and Class III antiarrhythmic properties.

Extra: Antiarrhythmic agents are a group of pharmaceuticals that are used to suppress abnormal rhythms of the heart (cardiac arrhythmias), such as atrial fibrillation, atrial flutter, ventricular tachycardia, and ventricular fibrillation.

- There are four classes of antiarrhythmics:

Class 1 → Na^+ channel blockers.

Class 2 → β-blockers.

Class 3 → K^+ channels blockers.

Class 4 → Ca^{+2} channels blockers.

- ✓ Class 3 is used to treat ventricular arrythmia, while others are used to treat super ventricular arrhythmia.

❖ Cardioselective β Blockers (β1-selective antagonists)

- less effects on bronchioles, carbohydrate metabolism, lipids.
- Lower incidences of Cold hands and feet (one of the major side effects of propranolol and other nonselective beta blockers).

Note: This side effect happens due to blockade of β receptors in the blood vessels of muscles which results in restriction of blood flow. **(remember that there are inhibitory β2 receptors in the smooth muscles of blood vessels of skeletal muscles, these receptors when activated cause relaxation)**

- Less liable to impair exercise tolerance.

If someone takes nonselective beta blockers and then performs exercise he will feel tired after shorter period than usual, because exercise needs high cardiac output. Impairment of exercise tolerance is **less in β1 selective blockers**, because the blood vessels of skeletal muscles can still be activated by epinephrine and dilate.

- **Safer in patients who experience bronchoconstriction in response to propranolol,** but their β1 selectivity is modest, so they should be used with great caution in patients with asthma.
  However, the benefits may exceed the risks, e.g. in patients with myocardial infarction.

- Beta1-selective antagonists are preferred in patients with **diabetes or peripheral vascular disease** since β2 receptors are important in liver (recovery from hypoglycemia) and blood vessels (vasodilation).

Metoprolol

- High lipid solubility.
- Less likely to worsen asthma (cardioselective).
- used to treat angina and hypertension and also used to treat or prevent Myocardial Infarction (AMI) without bradycardia.

Atenolol

- Low lipid solubility.
- Longer duration action, One dose/day.
- Side effects related to CNS are less prominent, No effect on bronchus, carbohydrate metabolism, lipids.
- Most commonly used in Hypertension and angina.

NO MATTER WHAT, JUST KEEP GOING

BEST OF LUCK ツ