بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pharmacology | FINAL 8

Adrenergic antagonist

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Adrenoeceptor Antagonists

(Adrenergic Antagonists)

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α - Adrenoreceptor Blockade

Pharmacodynamics:

Blood pressure is determined by two main factors: cardiac output and vascular resistance. Cardiac output reflects the amount of blood pumped by the heart per minute, while vascular resistance depends on the degree of constriction or dilation of blood vessels. Increased vascular resistance—due to vasoconstriction—leads to higher blood pressure, whereas decreased resistance results in lower blood pressure.

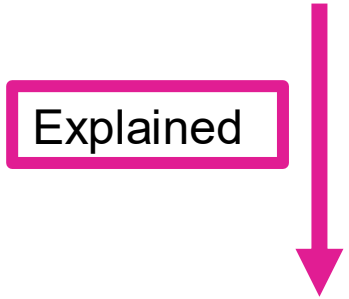
A. Cardiovascular system:

used to treat hypertension

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

α - Adrenoreceptor Blockade

- **Block of α_1-receptors in venules leads to venodilation, postural hypotension and reflex tachycardia.**
- **Tachycardia is more marked with nonselective α-blockers (α_1, α_2) because of increased release of norepinephrine (why?).**



Block of α_1-receptors in venules leads to venodilation, postural hypotension and reflex tachycardia.

Why do α_1-antagonists cause reflex tachycardia?

When blood pressure decreases, this change is detected by baroreceptors, which activate compensatory mechanisms. These mechanisms involve stimulation of the sympathetic nervous system, leading to increased release of norepinephrine. As a result, heart rate and blood pressure increase, producing reflex tachycardia in an attempt to restore blood pressure to normal levels.

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

When the drug is non-selective and also antagonizes α_2 receptors, the inhibitory feedback mechanism on sympathetic nerve endings is removed. Normally, α_2 receptors limit the release of norepinephrine. Blocking these receptors leads to increased norepinephrine release, which further stimulates the heart, resulting in a more pronounced tachycardia.

α - Adrenoreceptor Blockade

B. Other effects:

- **Miosis (α_1 receptors in dilator pupillae).**

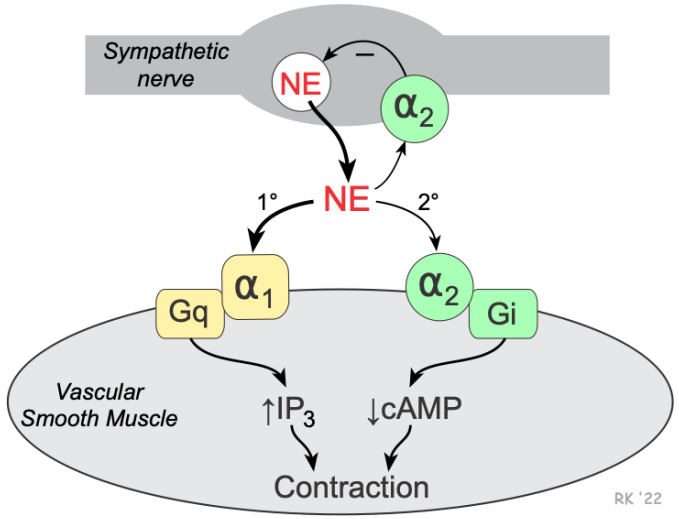
Nasal congestion

- **Nasal stuffiness (α_1 receptors in blood vessels)**
- **Decreased resistance to the outflow of urine (α_{1A} and α_{1B} receptors in the base of urinary bladder and the prostate).**

facilitates urination by relaxing the bladder neck and urethral sphincter, reducing resistance to urine flow.

α - Adrenoreceptor Blockade non-selective

- Non-selective α-antagonists have limited beneficial effects on blood pressure reduction, due to associated α2 block which increases norepinephrine effects (remember, block of the negative feedback
  α2 receptor will increase NE release).
- This may cause increased β1 stimulation with tachycardia



Alpha-2 receptors are located in multiple sites, including presynaptic sympathetic nerve terminals and the central nervous system, where they play a key role in regulating sympathetic activity. Activation of central α_2 receptors suppresses sympathetic outflow, leading to reduced release of norepinephrine and decreased sympathetic tone. Presynaptically, α_2 receptors act as inhibitory autoreceptors that limit norepinephrine release. In addition, a small number(neglectable)of α_2 receptors are present in blood vessels.

Alpha Adrenergic Antagonists

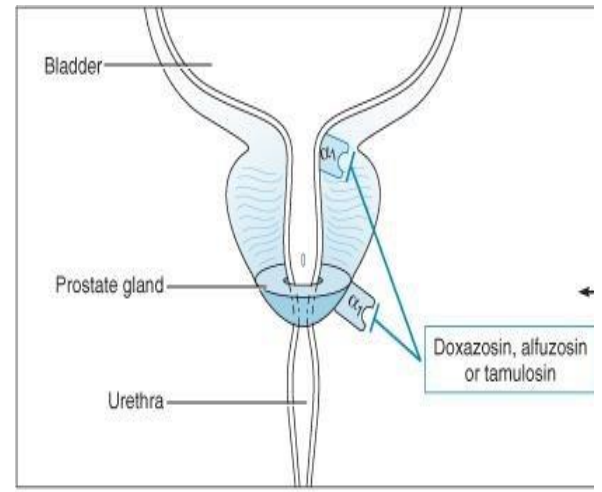
PHENOXYBENZAMINE

- Covalent, irreversible blockade
  - *may require days to recover*
- Nonselective (slight preference for alpha-1)
- Primary use (treat): pheochromocytoma

(explained in next slide)

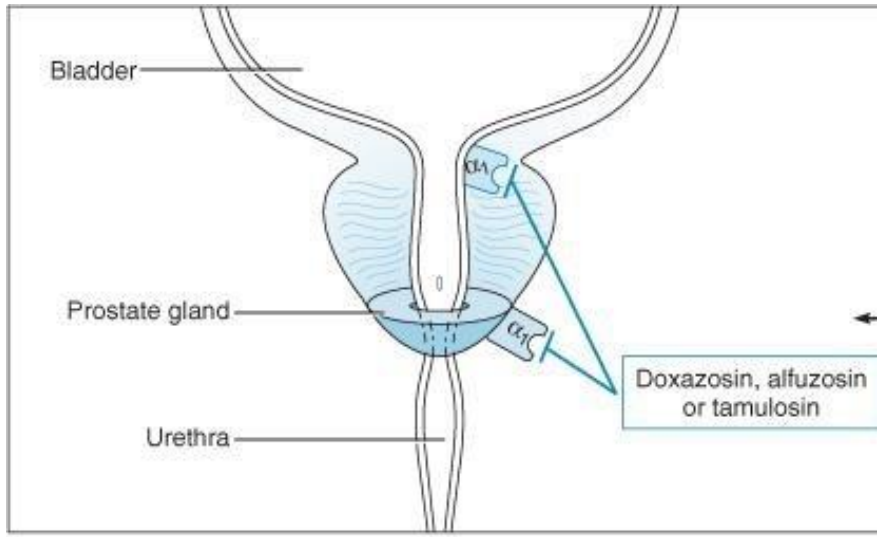
انسداد في مجرى البول

- Urinary obstruction (BPH)
- Side effects
  - *orthostatic hypotension*
  - *nasal congestion*



Explained in next slide

Benign prostatic hyperplasia (BPH) is a condition in which the prostate becomes enlarged. This enlargement can compress the urethra, making it difficult for patients to urinate and potentially leading to urinary retention. Alpha-1 blockers, which relax smooth muscles, can help relieve these urinary symptoms. Alpha-1 receptors are present both in the urethral sphincter and in the smooth muscle of the prostate, so blocking them helps relax both structures, improving urine flow. These drugs do not cure BPH itself, but they effectively relieve the symptoms associated with the condition.



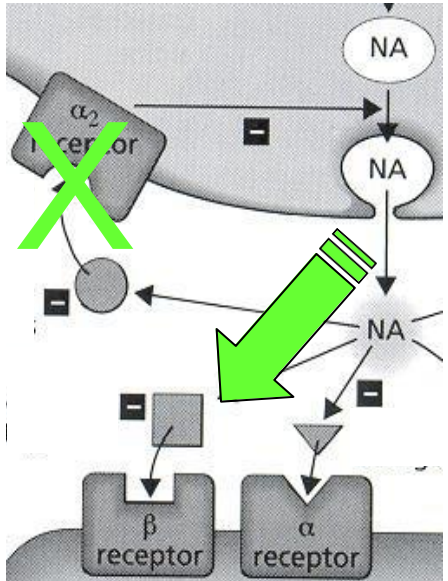
Pheochromocytoma

- A neuroendocrine tumor of the medulla of the adrenal glands that secretes excessive amounts of catecholamines norepinephrine and epinephrine
- Signs and Symptoms:
  - Elevated heart rate
  - Elevated blood pressure
  - Headaches
  - Weight loss
  - Elevated blood glucose

Alpha Adrenergic Antagonists

PHENTOLAMINE

- Nonselective (equal affinity for both)
- Competitive blockade
- Primary use: pheochromocytoma
- Not good general antihypertensive
  - *reflex tachycardia (α-2 block)*
- Side effects
  - *orthostatic hypotension*
  - *reflex cardiac stimulation*
  - *nasal congestion*



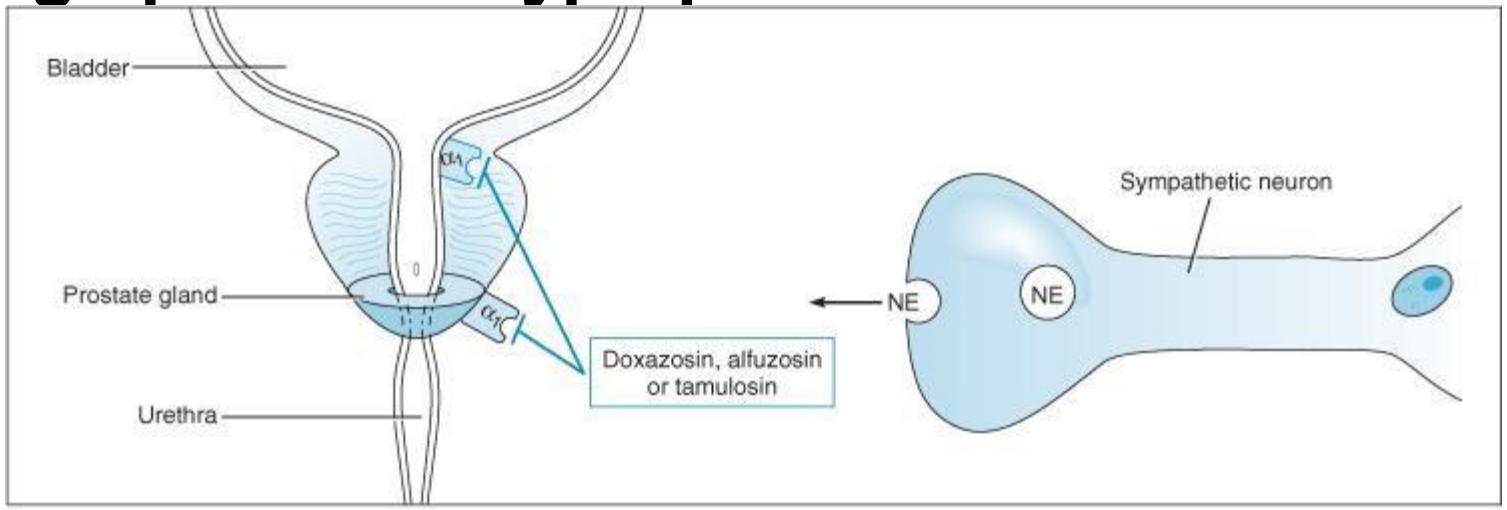
Selective α1-blockers

- **Selectively block α_1 receptors** Ends with "osin"

  -ie. Prazosin , Alfuzosin, Doxazosin,, Terazosin, Tamsulosin

  - Used in the treatment of chronic hypertension Because it's selective…. But clinically It's not our first choice of treating

- **Also used to treat urinary retention in men with benign prostatic hyperplasia**



Alpha Adrenergic Antagonists

PRAZOSIN

- **Selective alpha-1 antagonist**
- **Primary use: antihypertensive**
- **Little or no alpha-2 blockade**
  - ***limited reflex tachycardia***
- **Dilates arterial and venous beds**
  - Lower blood pressure by causing relaxation of both arterial and venous smooth muscle.
- **Improve urinary flow in BPH**
- ***"First-Dose Phenomenon"*** Explained ⬇⬇
  - ***give it at bedtime***

The “first-dose phenomenon” occurs with certain drugs, such as prazosin and other drugs in its class. These drugs can lower blood pressure, sometimes causing significant hypotension, especially postural (وضعية الجسم) hypotension. Postural hypotension refers to a drop in blood pressure when a person suddenly changes position, such as standing up, which can lead to dizziness or fainting. The body often responds with a faster heart rate (tachycardia) to compensate for this drop in blood pressure. To minimize this risk, the first dose is usually given at bedtime, when the patient is lying down and less likely to change posture. This effect is typically strongest with the first dose, and tolerance develops with continued use.

Beta Adrenergic Antagonists

- The drugs which block β-receptors are very widely used in therapeutics, mostly for their antihypertensive effect, and efficacy in the treatment of angina and some arrhythmias.

The no.1 killing disease is cardiac disease

- In the 1960's β-blockers were developed, and the earliest prototype β-blocker was Propanolol, a non-specific β receptors antagonist, which is still widely used.

Beta receptors are present in heart ;
increasing heart rate,
and in bronchi, causing relaxation

And blood vessel supply in skeletal muscles and in skeletal muscles themselves
and in kidneys (beta 1) for renin release

Beta Adrenergic Antagonists

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

Classifications:

And prevent all the effects we talked about earlier

- β-Adrenoceptor antagonists are not the same, regarding their antagonism of receptors and lipophilicity.
- Lipophilic antagonists (Dissolve in lipids) cross the blood brain barrier and affect the central nervous system in addition.

Have mostly more CNS effect (either side effects or uses)

Beta Adrenergic Antagonists

(Ends with lol)

1. **Non-selective ($\beta_1 = \beta_2$): Propranolol, Timolol, Sotalol.**

Beta1 , beta2 and alpha 1

2. **Non-selective ($\beta_1 = \beta_2 \geq \alpha_1 > \alpha_2$): Carvedilol, Labetalol. They have alpha blocking activity also.**

Beta 1 only

Beta1 is present and heart

3. **β_1- selective or cardioselective ($\beta_1 >>> \beta_2$): Atenolol, Bisoprolol, Metoprolol, Esmolol.**

Beta receptors are different that one's activation cause contraction to the heart and the other cause relaxation to everything else

We neglect beta3 because it has no drugs available in the industry (it's present in adipose tissue)

Beta Adrenergic Antagonists

- Non-selective — We get an adverse action in the heart. We decrease heart rate and decrease contractility
  - ie Nadolol, pindolol, propranolol, tomilol
  - Block both β_1 receptors in cardiac tissue and β_2 in smooth muscle, liver and other tissues
- Blockade of β_1 reduces sympathetic stimulation of heart…Therefore, negative
  - chronotrope — Decrease in heart rate
  - Inotrope — Ino= strength, decrease ventricle and atrial myocide (decrease in contractility)
  - ++ Negative dromotropic effect (decrease conduction velocity)
- Blockade of β_2 may cause bronchoconstriction

That's why we're not supposed to give non selective beta blockers to patients who have asthma or COPD

- and limit glycogenlysis → Adverse effects

Beta2 Is present in liver and activates glycogenolysis , when blocked it will affect the concentration of glucose in plasma

Beta Adrenergic Antagonists

Pharmacodynamics:

A. Effects on the cardiovascular system:

.1Lowering of blood pressure in patients with hypertension. The mechanism is probably multifactorial and may involve:

Blood pressure depends on peripheral vascular resistance and cardiac output. Cardiac output is affected if I block beta1 receptor ;result in a negative inotropic effect.

Beta Adrenergic Antagonists

a) **Negative inotropic effect on the heart → reduction of cardiac output.**

b) **Suppression of renin-angiotensin system.**

c) **A centrally-mediated effect due to reduction of sympathetic outflow from the CNS.**

Beta1 in kidney is responsible for renin secretion,(renin – angiotensin system) which is responsible for blood pressure increase

Beta Adrenergic Antagonists

Lowering of heart rate

2. **Negative chronotropic effect → bradycardia.**

3. **Slowing of AV nodal conduction and prolonging its refractory period. This is useful for treating supraventricular arrhythmias.** عدم انتظام ضربات القلب

Dromotropic effect

In skeletal blood vessels it inhibits dilation

causes peripheral vascular resistance, even though we decrease blood pressure in general(we see resistance, but we don't see increase in blood pressure because we have different mechanisms)

The doctor said it is a complicated mechanism so just know it don't dive deep into it

Beta Adrenergic Antagonists

B. Effects on respiratory tract: Increased airway resistance (bronchoconstriction) due to block of β_2 receptors.

C. Effects on the eye: Reduce intraocular pressure (useful for glaucoma) due to reduction in aqueous humor production (timolol.(

intraocular pressure: Increased pressure in the eye due to the increase of the aqueous humor in the chamber of the eye
Beta receptors activation is responsible for its secretion

Beta Adrenergic Antagonists

D. Metabolic and endocrine effects:

1. **Inhibition of lipolysis (β_3)**
2. **Inhibition of glycogenolysis (β_2).**
3. **Impair recovery from hypoglycemia in insulin-dependent diabetic patients.**
4. **Chronic use increase plasma concentrations of VLDL and decreased concentration of HDL→ atherosclerosis → increased risk of coronary artery disease.**

Bad cholesterol

Good cholesterol

Imbalance in lipid profile and increase chance of the atherosclerosis; so we need to take extra care when you're prescribing this drug for patients that already have cholesterol problems

Beta Adrenergic Antagonists

Sudden

- **Abrupt discontinuation of these drugs leads to rebound effects (exaggeration of the condition they were used to treat) because of upregulation (increased number) of receptors during treatment.**

Causes pre-exposure for myocardial infarction or myocardial ischemic heart disease

- **Therefore, when these drugs are to be discontinued, tapering of the dose (gradual reduction) rather than sudden withdrawal is recommended.**

If we use a blocker for a long period of time ,the body doesn't like this change so it increases the number of receptors, and if we suddenly stop taking a blocker the neurotransmitter norepinephrine will bind to a huge number of receptors and causes more activation of the heart in this case.
(now imagine a patient that already have heart disease or a weak heart; will have an increased risk of ischemia)

Propranol

- **Therapuetic uses are wide and include:**
- Antihypertensive: the antihypertensive effect is still not clear. However, it inhibit the renal secretion of the renin, which may play a role.
- Prophylaxis of angina pectoris and ventricular and superventricular arrhythmia, long-term prophylaxis of myocardiac infarction (with a high risk of infarction and sudden death).
- It is also used as a prophylactic of migraine.
- In treatment of Hyperthyroidism, effective in blunting the widespread sympathetic stimulation that occur in acute hyperthyroidism.
- Propanolol and other β blocker may be lifesaving in protecting against serious cardiac arrhythmias

Propranol

- Contraindications:

  ✖ Asthmatic

  ✖ *Diabetic*

  a. Propanolol must never given to any individual with chronic obstruction pulmonary disease because it causes an immediate contraction of the bronchiolar smooth muscles, which may result in a serious and potential lethal side effect.

  b. Propanolol effect the carbohydrate metabolism, and may increase the action of insulin, so diabetics treated with insulin should use it with caution.

Selective Beta-1 Blockers

- Have greater affinity for β_1 than for β_2 receptors
  - ie: Acebutolol, Atenolol, Esmolol, Metoprolol

CARDIOSELECTIVE b-BLOCKERS

- Produce fewer adverse effects than non-selective, but their selectivity is not absolute

Beta Adrenergic Antagonists

ESMOLOL

- Esmolol is an ultra-short-acting β_1-selective adrenoceptor antagonist.

Used in cases of emergency (IV)

- It is rapidly inactivated by red blood cells esterases. (t½ ~ 10 min).
- It is useful in controlling supraventricular arrhythmias, arrhythmias associated with thyrotoxicosis.

Beta-1 Adrenergic Antagonists

METOPROLOL

- Selective beta-1 blocker
- Metoprolol has a significantly longer half-life
- (3-7 hours) compared to esmolol
- Primary uses: Used for chronic conditions
  - antihypertensive
  - ischemic heart disease (depress HR)
  - little effect on normal heart or BP at rest
- Less tendency for bronchoconstriction

Labetalol and carvedilol

Non-selective

Used for chromocytoma (tumor with large amounts of epinephrine and norepinephrine

- These two agents are reversible β blockers and α1 blocker (producing peripheral vasodilatation).
- Non-selective (β1 = β2 ≥ α1 > α2)They have alpha blocking activity also.
- **Carvedilol** is extensively metabolized in the liver.
- It attenuates oxygen free radical-initiated lipid peroxidation.
- It inhibits vascular smooth muscle mitogenesis.

It inhibit both receptors, but it inhibit more beta If we inhibit beta receptors the alpha receptors would take over.

- **Labetalol: Unique Feature – Does *not* significantly decrease uteroplacental blood flow**

  Inhibition causes blood vessel dilation (does not affect placental blood flow)

  - Important in **preeclampsia** and **pregnancy-induced hypertension**
  - Better maternal/fetal safety profile compared to some other agents
- Labetolol is also used to treat hypertensive emergencies because it can rapidly lower blood pressure.

Decrease the vasodilatory effect and heart rate

By inhibiting both alpha1 and beta1

Additional Resources:

رسالة من الفريق العلمي:

محاضرات الدكتور عبد الرحمن الفروخ:

https://youtu.be/wJwqWxYe17U?si=CEmFdK_ZkT949N5d

https://youtu.be/twyjRKmTY-8?si=QK45ym8r8UHDfDAL

https://youtu.be/Hh7NUD57ctg?si=KL4yYLu2nwbMyDeu

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			
V1 → V2			