PHARMACOLOGY

بسم الله الرحمن الرحيم

FINAL – Lecture 5

Adrenergic Receptors Pt. 2 & Cholinergic Drugs

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

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Recall from the previous lecture...

...that β-adrenergic receptor antagonists are not all the same. Some are hydrophilic, while others are hydrophobic. **Hydrophobic** (lipid-soluble) drugs can cross the blood brain barrier (BBB) and induce effects on the CNS. While **hydrophilic** (water-soluble) drugs cannot cross the BBB, therefore, are inhibited from inducing any effects on the CNS. **Hydrophilic** (water-soluble) drugs are excreted by the kidney via filtration, while **lipophilic** (lipid-soluble) drugs are eliminated via metabolism.

Moving forward, there are lots of β-adrenergic blockers, or β-blockers. We're required to know the 9 β-blockers mentioned in the lectures.

إذا ما صليت لسا قوم صلي، وادعي لأهلنا المستضعفين ومش غلط تدعيلنا كمان

سم بالله ويلا بينا :)

Pay attention to the suffix **-ol** at the end of these drugs.

β-Adrenoceptor Antagonists

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

Non-selective β-blockers equally blocks β_1 & β_2 receptors. **Propranolol** is the **first discovered** β-blocker (a prototype). **Timolol** is used as eyedrops for treating **glaucoma** (an eye condition where fluids accumulate in the eye, building up pressure and damaging the optic nerve, which connects the eye to the brain. This condition can cause loss of vision). **Sotalol** is a β-blocker used via IV (parenteral), not orally.
Non-selectivity can be disadvantageous at times. For instance, in cases with ischemic heart disease (IHD), β_1 receptors must be blocked. Using a non-selective β-blocker would also block β_2 receptors present in the bronchial tree, which is **not** necessary and can cause adverse (undesirable) effects.

Pay attention to the suffix **-ol** at the end of these drugs.

β-Adrenoceptor Antagonists

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

This group of non-selective β-blockers blocks **both β-receptors equally**, as well as α_1 **&** α_2 **receptors- majorly non-selective. Labetalol** is used as an emergency hypertensive treatment, administered intravenously. Hypertension can cause organ damage, such as the eye, kidneys, heart, etc., therefore, it is crucial that high blood pressure is lowered ASAP.

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

Cardio selective: selectivity for β_1 receptors; used for cardiovascular diseases (CVD).
β_1 receptors are present in the heart, and the juxtaglomerular apparatus cells where renin is secreted. Renin produces angiotensin II, which stimulates aldosterone secretion (recall the RAAS from physiology, look at the 1st extra reference).

β-Adrenoceptor Antagonists

- Propranolol undergoes extensive hepatic first-pass metabolism → low bioavailability → oral dose is much larger than IV dose.

For example, a **40 mg** dose of propranolol is given **orally** every 6 hours, while an **IV** dose would be **2 mg (5%)**. If 40 mg were to be administered intravenously, the patient would suffer cardiac arrest, and then death.

- Metoprolol and carvedilol are metabolized.
- Atenolol is mainly excreted unchanged in urine. Its half-life is prolonged in renal failure.

Considering its excretion is via urine, a patient with kidney failure must have an adjusted dose of atenolol (smaller dose).

- Bisoprolol is partly exceted unchanged and partly metabolized.

β-Adrenoceptor Antagonists

Pharmacodynamics:

A. Effects on the cardiovascular system:

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

لَا إِلَهَ إِلَّا أَنْتَ سُبْحَانَكَ إِنِّي كُنْتُ مِنَ الظَّالِمِينَ

β-Adrenoceptor Antagonists

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

Inotropic effect refers to the strength of the heart's contraction. **Negative inotropic effect decreases** the **force** of contraction. Less force = less blood pumped = less cardiac output. Cardiac output = HR * Stroke volume.

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

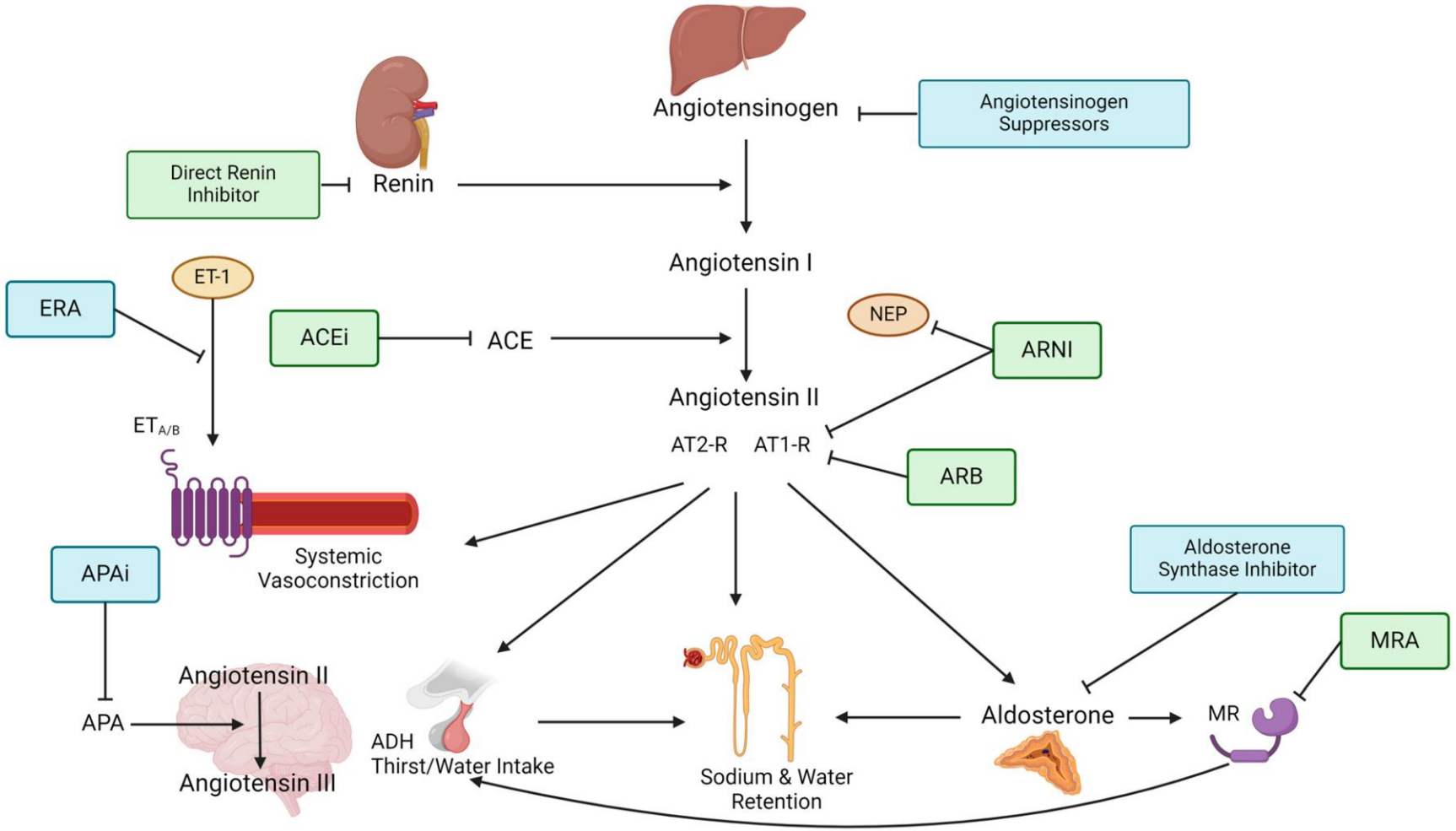
Coming up in the next two slides.

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

Reduces both systolic and diastolic pressure. This mechanism is reserved only for lipophilic drugs, because they posses the ability to cross the BBB and induce effects on the CNS.

RAAS

This is an **additional** picture; **you are not required to memorize this pathway.** However, steps of the RAAS will be discussed in the next slide(s). Look at this pathway and watch the extra reference video if you feel like you've forgotten RAAS and its functionality.



اللهم اغفر لي ذنبي كله، دقه وجله، وأوله وآخره، وعلانيته وسره

[]s = concentrations

Propranolol

When a patient is administered propranolol, it lowers blood pressure by reducing contractility of the heart which, in turn, reduces cardiac output **(reduced systolic pressure)**. Propranolol inhibits vasodilation of skeletal muscles by blocking β_2 receptors (remember propranolol has no effect on **α** receptors). This increases the vasoconstrictor tone in the body, causing an **increase of diastolic pressure** during the first 1-3 days of treatment. By the 5th day, **both diastolic and systolic pressures drop**. The drop in diastolic pressure occurs due to the suppression of RAAS, look back at the first two mechanisms mentioned in slide #8. Angiotensin II is one of the **most potent vasoconstrictors;** it induces vasoconstriction in [small]. Aldosterone is released by angiotensin II, and it is responsible for Na+/water retention and H+/K+ excretion. Na+/water retention increases the blood volume, which increases both the venous return to the heart and the cardiac output (blood pressure as well). Therefore, suppression of angiotensin II → suppression of aldosterone release → no Na+/water retention → decreases blood volume → decreases venous return to the heart → decreased cardiac output → reduced systolic pressure.

اللهم أصلح لي ديني الذي هو عصمة أمري، وأصلح لي دنياي التي فيها معاشي، وأصلح لي آخرتي التي فيها معادي، واجعل الحياة زيادة لي في كل خير، واجعل الموت راحة لي من كل شر

β-Adrenoceptor Antagonists

2. Negative chronotropic effect → bradycardia.

Chronotropic effect refers to the heart rate. **Negative chronotropic effect** refers to the **reduction of beats per minute.** Excessive pathologic heart rate reduction is **bradycardia.**

3. Slowing of AV nodal conduction and prolonging its refractory period. This is useful for treating supraventricular arrhythmias.

Impulse pathway: Atria → through the AV node → ventricles.
Refractory period: a period following action potential where the heart muscle can**not** be re-stimulated.
Impulses from the atria take longer to be delivered to the ventricles. Prolonging the refractory period temporarily inactivates the ventricles. Therefore, if an atrial impulse arrives at the AV node during a refractory period, the impulse will be blocked from being transmitted to the ventricles. This prevents any premature contractions and helps block the progression of supraventricular tachycardia to ventricular tachycardia, which is a much more dangerous condition.

β-Adrenoceptor 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).

Aqueous humor: fluids accumulating in the eye.
Intraocular pressure is **not** due to hypertension, but rather because of fluid buildup in the eye.
Timolol, like mentioned previously, is given as eye drops to reduce the formation of aqueous humor and therefore decrease intraocular pressure. The production of aqueous humor is under β-receptor stimulation.

β-Adrenoceptor 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.**

β-Adrenoceptor Antagonists

D. Metabolic and endocrine effects:

3. Impair recovery from hypoglycemia in insulin-dependent diabetic patients.

Inhibition of glycogenolysis decreases blood sugar. Diabetic patients take insulin, which reduces [glucose] in the blood, inducing hypoglycemia. Non-selective β_2-blockers enhance the hypoglycemic effect of insulin. Hypoglycemia is far more dangerous than hyperglycemia. The brain depends on glucose solely for its function. Low [glucose] are endured for no more than 15 minutes. Repetitive hypoglycemic attacks and accumulative brain damage are observed in hypoglycemic patients. Hypoglycemic patients should **not** be given carbohydrates, only free sugar to reverse hypoglycemia(on a time crunch, can't wait for carb metabolism) . β-blockers reduce tachycardia, a symptom of hypoglycemia, therefore, diabetic patients can**not** detect hypoglycemia early on due to the masking of its symptoms.

β-Adrenoceptor Antagonists

D. Metabolic and endocrine effects:

4. Chronic use increase plasma concentrations of VLDL and decreased concentration of HDL→ atherosclerosis → increased risk of coronary artery disease. Increases the risk of ischemia in the heart.

The risk factor for IHD is low levels of HDL, because it is the first step in the development of atherosclerosis. The oxidation of LDLs marks the beginning of atherosclerosis. Smokers face risks of atherosclerosis because they have high []s of free radical that can oxidize LDLs, which accelerates atherosclerosis. HDL is protective and prevents atherosclerosis (helps remove excess cholesterol from the bloodstream, preventing plaque buildup), whereas VLDL can be converted to LDL. Chronic use of beta-blockers can lead to an Increase in VLDL and a decrease in HDL. Therefore, patients are also prescribed medications to treat this dyslipidemia (abnormal lipid metabolism) and accordingly lower the risk of coronary artery disease/IHD.

β-Adrenoceptor Antagonists

- **Carvedilol is extensively metabolized in the liver.**
- **It attenuates oxygen free radical-initiated lipid peroxidation.**

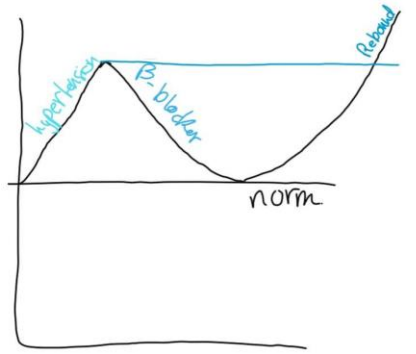
Increase []s but it won't considered harmful since it prevents its peroxidation and this independent β-blocker effect; of the additional function that doesn't affect the sympathetic nervous system.

- **It inhibits vascular smooth muscle mitogenesis(** inhibits hypertrophy/ hyperplasia-> requires cell division**). (the last 2 are important for its use in the <u>treatment</u> of chronic heart failure)->** the most serious adverse effect of β-adrenergic blockers in general is heart failure by reducing contractility and conduction except Carvedilol.

β-Adrenoceptor Antagonists

- **Esmolol is an ultra-short-acting β_1-selective adrenoceptor antagonist.**
- **It is rapidly inactivated by red blood cells esterases(** although it's rare, this is an example of drug metabolism by hydrolysis**). (t½ ~ 10 min)->** infective orally; acute IV delivery in to
- **It is useful in controlling supraventricular arrhythmias, arrhythmias associated with thyrotoxicosis** and prevents it from progressing into ventricular arrhythmias which could be fatal caused by AV node blockage-> by increasing the refractory period of the atrial impulses, it slows down the conduction through the AV node, preventing excessive transmission= arrhythmia.

β-Adrenoceptor Antagonists



- **Abrupt discontinuation of these drugs leads to <u>rebound effects</u> (exaggeration of the condition they were used to treat) because of upregulation (increased number) of receptors during treatment.** the body's natural response to blockers is to increase the no. Of receptors(upregulation), in cases of abrupt discontinuation catecholamine receptors will be free and able to bind to catecholamines in the circulation leading to adverse effects(rebound hypertension)
- **Therefore, when these drugs are to be discontinued, tapering of the dose (gradual reduction) rather than sudden withdrawal is recommended.** circulation if you a give a patient 40mg propranolol, the following week decrease the dosage to 20mg-> 10mg-> 5mg-> stop; to reverse the upregulation

Cholinergic Drugs

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Cholinergic Drugs

Cholinomimetics:

1. **Acetylcholine receptor stimulants**

- **Agonists that stimulate acetylcholine muscarinic and nicotinic receptors.**
- **Muscarinic receptors are located on smooth muscle, heart & exocrine glands**
- **Nicotinic receptors are located in autonomic ganglia.**

Cholinergic Drugs

2. Cholinesterase inhibitors:

- **Drugs which inhibit the hydrolysis of acetylcholine leading to its accumulation at its receptors.**
- **The excess acetylcholine stimulates cholinoceptors (not selective** CNS(if it crosses the BBB), ANS, and Skeletal muscles**) to evoke increased response.**

Direct-Acting Cholinomimetics

1) **Choline esters: Acetylcholine(**a NT, can't be given as a drug because of hydrolysis**),** **Methacholine(** a drug**).**
2) **Alkaloids (naturally occurring-** from plants and living organisms **):** **Muscarine(**like mushrooms= toxin not a drug**), Pilocarpine(**a drug**)**

Pharmacokinetics:

- **Choline esters are quaternary ammonium compounds-> charged, highly water soluble(** ionized**) and insoluble in lipids(** doesn't cross membranes, can't be distributed in the body, cant enter the brain, action is limited to the peripheries, and it's hydrolysable by choline estrase **).**
- **They are poorly absorbed and poorly distributed into most tissues.**

Direct-Acting Cholinomimetics

- **They are hydrolyzed in the GIT and <u>not active by the oral route.</u>**
- **The tertiary(**lipid soluble **)natural cholinomimetic alkaloid pilocarpine is well absorbed from most sites of administration.**

- **The alkaloid muscarine is a quaternary amine and is less completely absorbed from GIT than tertiary amines but is toxic when ingested.**

a muscarine is natural alkaloid but quaternary, it enters the cell through aqaues pores causing toxicity **<u>after oral administration.</u>**

Direct-Acting Cholinomimetics

Pharmacodynamics:

- **Most of the direct organ-system effects of cholinomimetics can be predicted from knowledge of the effects of parasympathetic nerve stimulation and the distribution of muscarinic receptors.**

Direct-Acting Cholinomimetics

Organ	Response
Eye	
Sphincter muscle of iris	Contraction (miosis)
Ciliary muscle	Contraction for near vision
Heart	
Sinoatrial node	Decrease in rate (negative chronotropy)
Atria	Decrease in contractile strength (negative inotropy). Decrease in refractory period
Atrioventricular node	Decrease in conduction velocity (negative dromotropy). Increase in refractory period
Ventricles	Small decrease in contractile strength
Blood vessels	
Arteries, veins	Dilation (via EDRF). Constriction (high-dose direct effect)

Direct-Acting Cholinomimetics

Lung	
Bronchial muscle	Contraction (bronchoconstriction)
Bronchial glands	Stimulation
Gastrointestinal tract	
Motility	Increase
Sphincters	Relaxation
Secretion	Stimulation
Urinary bladder	
Detrusor	Contraction
Trigone and sphincter	Relaxation
Glands	
Sweat, salivary, lacrimal, nasopharyngeal	Secretion

EDRF, endothelium-derived relaxing factor.

*Only the direct effects are indicated; homeostatic responses to these direct actions may be important (see text).

Direct-Acting Cholinomimetics

Eye: Go back to the table- slide 24

1. **Contraction of the smooth muscle of the iris sphincter → miosis. M_3**
2. **Contraction of the ciliary muscle → accommodation for <u>near vision</u>** for far vision accommodation; relaxed muscles**. M_3**

1. **Facilitation of aqueous humor outflow(** glaucoma timolol reduces formation, **), which reduces intraocular pressure** cholinomimetics-> facilitate drainage/ outflow**. M_3**

Direct-Acting Cholinomimetics

Cardiovascular System (M_2 receptors):

1. **Reduction of heart rate → bradycardia (negative chronotropy**
2. **Decreased AV node conduction velocity (negative dromotropy)** important for supraventricular tachycardia prevents progression into ventricular
3. **Decreased contractility of atrial muscle (negative inotropy).**
4. **Effects on ventricles are much less than those on atria** because the parasympathetic supply/ innervation to the ventricle is scares, but it's directly affected when the atrial and AV node are affected.

Tachycardia originated from atrial and AV node is called supraventricular tachycardia, ventricular tachycardia we said it could be fatal because of the possibility of it stemming from ventricular fibrillation, it contracts rapidly and ineffectively, it doesn't have much time to fill with blood so it can't pump the blood effectively. Instead, the ventricles simply quiver or shake leading to loss of circulation(this is why it's fatal and click on this to see it in a time-lapse)

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			

Additional Resources:

Extra References for the Reader to Use:

1. RAAS

رسالة من الفريق العلمي:

أَنَّ رَسُولَ اللَّهِ -صَلَّى اللهُ عَلَيْهِ وَسَلَّمَ- كَانَ يَقُولُ عِنْدَ الكَرْبِ: لاَ إِلَهَ إِلَّا اللَّهُ العَظِيمُ الحَلِيمُ، لاَ إِلَهَ إِلَّا اللَّهُ رَبُّ العَرْشِ العَظِيمِ، لاَ إِلَهَ إِلَّا اللَّهُ رَبُّ السَّمَوَاتِ، وَرَبُّ الأَرْضِ، وَرَبُّ العَرْشِ الكَرِيمِ