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Pharmacology

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Sheet ○ Slides

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We're still in sympathomimetic drugs ☹ And we'll talk in this sheet about other examples, as well as their therapeutic uses. Have fun *wink*

Catechol reuptake inhibitors:

-Another example of indirect-acting sympathomimetics.

-It is basically inhibiting transporters that get NE and serotonin back to the neuron, thus increasing their concentration in the synaptic cleft and having longer action.

-As we all know, serotonin is the hormone of happiness ☺ So, increasing its concentration may be associated with treating depression. This is exactly how many antidepressants, particularly tricyclic antidepressants, work (in treatment of depression and other problems as well). Such reuptake inhibitors include:

Atomoxetine: A selective inhibitor of the NE reuptake transporter used in the treatment of attention deficit disorders.

Sibutramine: A serotonin and NE reuptake inhibitor and was used as appetite suppressant for long-term treatment of obesity. However, it was banned in 2010 because it caused stroke in many patients.

Cocaine: -A local anesthetic with a sympathomimetic action that results from inhibition of NE reuptake. (The first local anesthetic to be discovered actually)

-Readily enters CNS causing an amphetamine-like psychological effect that is shorter lasting and more intense than amphetamine.

-Its major action in the CNS is to inhibit dopamine reuptake into neurons in the pleasure centers.

-It's easy to take (can be smoked, snorted into the nose, or injected). That's why it is a heavily abused drug.

-It does not have many clinical uses. However, it can be used as a vasoconstrictor to prevent bleeding in certain surgeries.

Fun Fact:
'Coca' in Coca Cola name refers to coca leaves which are a source of cocaine.

Dopamine Agonists:

Levodopa: -It is converted to dopamine in the body.

-It is valuable in the treatment of Parkinson's disease (No.1 drug), used along with **carbidopa** which inhibits peripheral metabolism of levodopa.

Fenoldopam: A D1-receptor agonist that selectively leads to peripheral vasodilation in some vascular beds, leading to a decrease in peripheral resistance. So, the primary indication for fenoldopam is in the IV treatment of severe hypertension.

Now we'll take again about Therapeutic uses of sympathomimetics.

Cardiovascular Applications:

-NE, phenylephrine, and methoxamine are direct-acting α agonists used in a **hypotensive emergency** to preserve cerebral and coronary blood flow. However, NE is not used much because It can cause gangrene in the periphery due to strong vasoconstriction. This treatment is of short duration while the intravenous fluid or blood is being administered.

-Cardiogenic shock is usually due to massive myocardial infarction. In this case, the heart is very weak and can't pump blood properly, so cardiac output is so low, and shock happens. Positive inotropic agents such as dopamine or dobutamine increase contractility (and cardiac output) and provide short-term relief of heart failure symptoms in patients with advanced ventricular dysfunction. These have to be taken carefully and in moderate doses, so they don't cause strong vasoconstriction.

-Chronic Orthostatic Hypotension again 😉 is caused by Impairment of autonomic reflexes that regulate BP. This can be due to medications that can interfere with autonomic function, diabetes and other diseases causing peripheral autonomic neuropathies. **Midodrine**, which is and orally active α 1 agonist, is frequently used. Other sympathomimetics, such as oral ephedrine or phenylephrine, can be tried.

-Isoproterenol and epinephrine used in the temporary emergency management of **complete heart block and cardiac arrest**. Complete heart block is the block of AV node, so no impulses are transmitted to the ventricles. On the other hand, in partial heart block, some impulses are transmitted (e.g. 3:1. Every 3 impulses, 1 is transmitted). **Isoproterenol**, a β agonist, is given to prevent complete heart block. Cardiac injections of **epinephrine** are used with patients having cardiac arrest.

Inducing Local Vasoconstriction:

-**Epinephrine** applied topically for epistaxis or for gingivectomy (removal of diseased gum tissue).

-**Cocaine** used for nasopharyngeal surgery because it combines a hemostatic effect with local anesthesia. It also acts as a vasoconstrictor so no need to use other drugs with it.

-Combining α agonists with local anesthetics (L.A.) greatly prolongs the duration of local anesthesia as well as the total dose & reduce toxicity of L.A. Why is that? Local anesthetics work as long as they're present in the site of action. So, combining it with α agonists (vasoconstrictors) reduces the absorption of anesthetic to the blood, resulting in longer duration of action without the need of using high doses (reduced toxicity). Epinephrine 1:200,000, is the favored agent for this application, but norepinephrine, phenylephrine, & other α agonists have also been used.

-Mucous membrane decongestants are α 1 agonists, such as **phenylephrine**. A longer duration of action at the cost of greater potential for cardiac and CNS effects can be achieved by the oral administration of **ephedrine** or **pseudoephedrine**. Long-acting topical decongestants include xylometazoline and oxymetazoline. Most of these decongestants are available as over-the-counter products.

Rebound congestion may follow the use of decongestants, How?
-Continuous vasoconstriction might eventually lead to local hypoxia, which in turn results in formation of strong vasodilators, and we're back to congestion :)

Pulmonary Applications:

-β 2-selective agents are used in the therapy of **bronchial asthma**. **Albuterol (Salbutamol), metaproterenol, terbutaline** are all available for this indication. Sympathomimetics other than the β 2–selective drugs are now rarely used because they are likely to have more adverse effects (such as cardiac arrest) than the selective drugs. **Treatment of asthma involves steroids as well.**

-**Anaphylaxis** which is the syndrome of bronchospasm, mucous membrane congestion, angioedema, and severe hypotension usually responds rapidly to the parenteral administration of epinephrine.

Epinephrine is effective because:

1- β1: increases cardiac output.

2- β2: relaxes constricted bronchioles.

3- α1: constricts capillaries (prevents leakage of fluids).

Glucocorticoids and antihistamines may be useful as secondary therapy in anaphylaxis

Ophthalmic Applications:

-**Phenylephrine** is an effective **mydriatic agent** used to facilitate examination of the retina. It is also a useful decongestant for minor allergic hyperemia (eye redness) and itching of the conjunctival membranes.

-**Glaucoma:** Epinephrine and α agonists now rarely used, but β -blocking agents are among the most important therapies. **Apraclonidine** is an α2-selective agonist that also lowers intraocular pressure and used in glaucoma. The mechanism of action of these drugs in treating glaucoma is still uncertain.

Genitourinary Applications:

-β 2 selective agents relax the pregnant uterus. **Ritodrine, terbutaline**, and similar drugs have been used to **suppress premature labor.**

-Oral sympathomimetic therapy is useful in the treatment of **urinary stress incontinence** (loss of small amounts of urine associated with coughing, laughing, sneezing, exercising or other movements that increase intra-abdominal pressure and thus increase pressure on the bladder.). **Ephedrine** or **pseudoephedrine** may be tried.

CNS Applications:

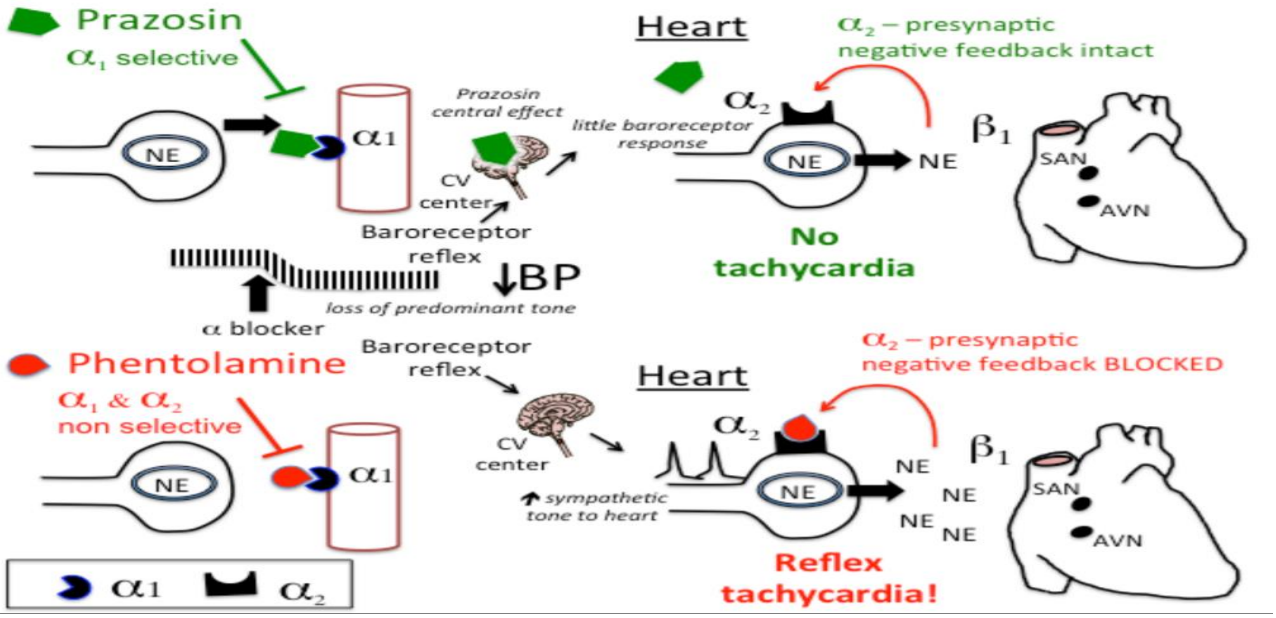
-**Modafinil** is used to treat **narcolepsy.**

-**Methylphenidate, clonidine,** and sometime **modafinil** can be used to treat **Attention-deficit hyperactivity disorder (ADHD).**

We'll start now the second part of our lecture, α-adrenergic receptor antagonists.

History:
α-blockers were discovered way before β-blockers,
perhaps because there's no β-blocker in nature.

*In general, α-blockers cause decrease in peripheral vascular resistance and blood pressure and may cause orthostatic hypotension. Surprisingly, selective and non-selective have different outcomes regarding heart rate after following this scenario.



-When using phentolamine (a non-selective α blocker), α1 receptors on bloods vessels are blocked thus promoting vasodilation and decreasing blood pressure. Baro-reflex takes place and the sympathetic tone to the heart increases, causing tachycardia. α2 auto receptors are blocked, so there's no going back :(

-When using Prazosin (a selective α1 blocker), α1 receptors on bloods vessels are blocked thus promoting vasodilation and decreasing blood pressure. Baro-reflex takes place but still, there is no tachycardia. This happens thanks to our soldiers (un-inhibited auto receptors) that were not blocked by Prazosin (remember it's α1 selective).

Other effects of α-blockers include:

Miosis: α1 receptors in the iris (which are responsible for mydriasis) are blocked, leaving the parasympathetic tone to work all alone.

Nasal stuffiness(congestion): α1 receptors in the nasal vessels are blocked, resulting in vasodilation and congestion (feels like you have cold although you don't)

Increasing urination: α1 receptors in the base of bladder are blocked, reducing the resistance to the flow of urine. α blockers are used for the treatment of urinary retention due to prostatic hyperplasia

Now we'll start taking examples, one by one.

Non-selective α blockers:

Phenoxybenzamine:

- Binds covalently to α receptors, causing irreversible blockade of long duration.

- Blocks α1& to less extent α2 receptors.

- Also inhibits reuptake of NE and blocks histamine (H1), ACh, and serotonin receptors.

- Causes little or no fall in BP in normal supine individuals (at that state the sympathetic tone is not that high), it reduces BP when sympathetic tone is high, e.g., as a result of upright posture.

- Absorbed poorly but usually given orally (It is not given by IV because these injections are very painful)

-Used to treat **pheochromocytoma**, which is a tumor in adrenal medulla leading to excessive production of catecholamines. It is used also to treat peripheral vascular diseases.

- Adverse effects includes orthostatic hypotension, tachycardia, Nasal stuffiness and inhibition of ejaculation.

Phentolamine:

- Rapidly acting α blocker with short half-life (19 mins)

- Acts equally on α1 and α2 receptors.

- Reduces peripheral resistance (due to blockade of α1) and causes cardiac stimulation (α2 receptors blockade enhances release of NE).

- It has minor inhibitory effects at 5HT (serotonin) receptors and agonist effects at muscarinic receptors increasing salivary, sweat, and lacrimal secretions. It also has agonist effect at H1 and H2 histamine receptor which increase acid secretion.

- It is used to diagnose **pheochromocytoma**, control **hypertension** due to clonidine withdrawal, and treat **cheese reaction** initiated by tyramine. It is also used to counteract vasoconstriction caused by alpha agonists.

- Adverse effects include severe tachycardia, arrhythmias, and myocardial ischemia.

Selective α1 blockers:

Prazosin:

- Highly selective α1 blocker and less potent at α 2 receptors.

- Relaxes both arterial and venous vascular smooth muscles and smooth muscle in the prostate, due to blockade of α1 receptors, with no or little tachycardia.

- Extensively metabolized, with short half-life (3 hours).

- Has a favorable effect on plasma lipids, so it increases HDL/LDL ratio.

- Used for **hypertension** and **benign prostatic hyperplasia (BPH).**

- Adverse effects include first dose phenomenon, a sudden hypotensive state when taking the first dose. **So, it's advised to take the very first dose at bedtime.**

Terazosin: same as above, but with longer half-life (9-12) hours.

Doxazosin: has the longest half-life (22 hours).

Tamsulosin: Uroselective α1A blocker (α1A are predominant in bladder base and prostate). So, it is the best option to treat BPH with no effect on blood pressure and heart rate. However, it can cause dizziness and retrograde ejaculation.

Good Luck!!