15

Pharmacology

Doctor 2018 | Medicine | JU

Sheet Slides

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Hi again, we're still talking about sympathomimetics here, some of the things discussed here have already been discussed in previous sheets so I'll refer you back to them.

◆ Effects of dopamine-Receptor activation:

- ❖ **low IV infusion** of dopamine[1] → **it activates D1 receptors, causing Vasodilation**, in renal, splanchnic, coronary and cerebral vessels.

- D1 receptors have an important role in the excretion of sodium, their activation (accomplished by **low doses of dopamine**) causes something called natriuresis, -the process of natrium's (sodium) increased excretion-
- This effect is required in a case called **oliguria** (few urine).

In **oliguria** there's **low urine output**. To stimulates the kidney to increase urine volume, we give an **infusion of dopamine**.

- ❖ In **moderate concentrations**[2], activation of β1 receptors leads to increasing the force of contraction without increasing heart rate much.

Dopamine is useful for people with heart failure.

How? Increasing heart rate would **require a higher consumption of O2**.

In heart failure patients, we want to increase the cardiac output **without** tiring the muscle further by increasing the heart rate.

Dopamine increases the **contractility** without causing a large increase in heart rate, thus increases cardiac output without increasing oxygen consumption.

Epinephrine → causes immediate death in heart failure patients, because it leads the heart to feel even more suffocated.

- ❖ In **high infusion concentrations**[3] (above enough for β1 activation), α1 receptors will be stimulated. Consequently, **arrythmias** and **vasoconstriction** will occur, increasing the peripheral resistance. This could kill the heart failure patient.
  That's why determining infusion rate is very important (we start with very low concentrations and we increase them slowly)
- ❖ In high concentrations dopamine basically does what epinephrine does.

❄ Non cardiac effects of sympathomimetics:

- In the respiratory system: **Activation of β 2** receptors in bronchial smooth muscle leads to bronchodilation. → β 2 agonists are important in the treatment of asthma.
- In the eye: **α receptors**; activation by drugs such as **phenylephrine** causes **mydriasis**.
  Glaucoma treatment (reduce intraocular pressure): **α agonists** also **increase the outflow** of **aqueous humor** from the eye and can be used clinically to **reduce intraocular pressure**. **β agonists** have little effect, but **β antagonists** reduce the production of aqueous humor.

- GUS: The bladder base, urethral sphincter, and prostate contain **α receptors** (70% are α 1A) **mediate contraction and control urination**.
  Alpha-receptor activation in the ductus deferens, seminal vesicles, and prostate plays a role in **normal ejaculation**.

- Hormone secretion:
  In pancreatic islets, **β receptors increase** insulin secretion and **α 2 receptors decrease** insulin secretion, but the major regulator of insulin release is the plasma concentration of glucose. Sympathomemitics effect isn't major.

  Stimulation of **β1 receptors** in the (**juxtaglomerular apparatus**) of the kidney **increases secretion of renin**. Secretion is **inhibited** by **α 2 receptors**.
  [Renin → angiotensin → angiotensin 2 → aldosterone (BP regulation)]
- Central nervous system:

- ALL catecholamines are almost completely excluded by blood-brain barrier.
- If we give an injection of **epinephrine,** we'll observe manifestations similar to **somatic manifestations of anxiety**: tremor, and things that indicate central stimulation. In reality they're due to certain metabolic effects.
- Noncatecholamines (like amphetamines): are **highly lipid soluble**, they readily enter the CNS producing CNS effects. The effect depends on the dose:
  At a low dose there's a nice feeling of alertness, but still, due to the pharmacological catastrophe, the CNS will shut down after that amphetaminic stimulation. *every stimulation is followed by inhibition*
- On high dose, it causes **full-blown psychotic behavior** (hallucinations, screams)

- May also cause: elevation of mood, insomnia, euphoria (happiness, confidence) & anorexia (appetite loss)

❖ Effects on metabolism:

- **β3 activation** Increases lipolysis with enhanced release of free fatty acids and glycerol into the blood.
- **β2 activation** increases Glycogenolysis in the liver, **increasing blood glucose**.
  - It also Promotes uptake of K^+ into cells, leading to a fall in extracellular potassium. It's a **Protective mechanism** during exercise, or fight or flight situations, because cells excrete potassium madly. It protects against K^+ plasma concentration increase.

Potassium level is very important because it controls stability of the heart

Specific Sympathomimetic Drugs:

❄ Endogenous Catecholamines (originally produced in the body)

Three: **epinephrine, norepinephrine, dopamine**

Epinephrine:

Agonist at both **α and β receptors**.

Very potent **vasoconstrictor** and **cardiac stimulant**.

Causes a rise in systolic BP by its:

1) positive inotropic (related to the force of contraction) and chronotropic (related to heart rate) actions on the heart by β1 activation

2) vasoconstriction induced in many vascular beds by α activation.

- Epinephrine also **activates β 2** receptors in **skeletal muscle blood vessels**, leading to their **dilation**. Consequently, **total peripheral resistance** may **fall**. (muscles need more perfusion during Fight or Flight)
- When we say **β 2** we mean ALL **β 2** in the body. Activation of β 2 receptors in skeletal muscle increases blood flow during exercise. But also, β 2 activation activates glycogenolysis in the liver.
- **β 3 stimulation** increases lipolysis, **increasing free fatty acids**. (hydrolyze sources in the body to fuel the fight or flight situation)

Norepinephrine:

Agonist at α1, α 2 and **β 1 receptors** with similar potency as epinephrine but has relatively little effect on β 2 receptors.

- **Increases:** peripheral resistance[1] and both diastolic and systolic blood pressure[2].

Because it causes vasoconstriction in all BVs including skeletal muscles BVs, this will trigger the baroreflex causing **brady cardia**.

Force of contraction isn't affected, because ventricles aren't affected by the parasympathetic nerve reflex

Dopamine:

- Immediate precursor in the synthesis of NE Stimulates

  Low dose activates D1 & D2 rec. Medium dose activates β rec. High dose activates α receptors

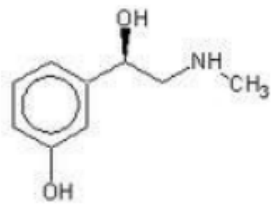
  Endogenous DA regulates sodium excretion and renal function.
- Its deficiency in the basal ganglia leads to Parkinson's disease, which is treated with its precursor levodopa.
- High dopamine amount is related to psychosis and other psychotic abnormalities. Thus, Dopamine antagonists are antipsychotic drugs (neuroleptics).

❄ Direct-Acting Sympathomimetics:

They work by <u>stimulating receptors directly.</u>

Phenylephrine:

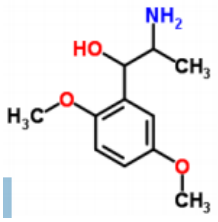
Relatively **pure α1 agonist**.



- Not a catecholamine. So, it is **not inactivated** by COMT (catechol-O-methyltransferase) & has a longer duration of action than the Catecholamines.
- Effective **mydriatic** and **decongestant** (for people with cold nose) and can be used to **raise the blood pressure**.

Methoxamine:

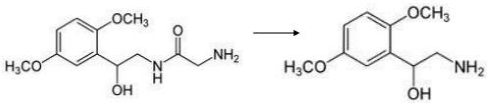
α 1 receptor agonist.



- It has a longer duration of action.
- Causes a prolonged increase in BP due to vasoconstriction. And causes a vagally mediated bradycardia against that increase in BP.
- Clinical uses are rare and limited to **hypotensive states.**

  Why would we increase pressure? To maintain a sufficient brain perfusion.

Midodrine:



A **prodrug**, that's enzymatically hydrolyzed to a **selective α 1-receptor agonist**.

- Causes **vasoconstriction.**
- It's used for **orthostatic hypotension** (explained before in sheet 14.1) caused by an impaired autonomic nervous system function, caused by something like diabetes.
- It's useful for someone who's **constantly moving and standing**, but if he's always in a supine position, it could cause dangerous hypertension.
  Q: then, Would you prescribe it for a hypotensive comatose patient?

❄ Alpha2-selective agonists:

Clonidine:

α 2 agonist

- **α 2A** are Present in the **vasomotor center** in the brain.
  When stimulated, they **increase firing of vagal nerve**, making the heart **bradycardiac** and they decrease the firing rate of the sympathetic nerves
- SA node firing decreases, rate of depolarization decreases, heart rate decreases, stroke volume decreases.
  Vessel will be dilated because the tone decreases. Thus, venous return decreases → final effect on BP? Definite Decrease!
- In high doses clonidine activates peripheral **presynaptic autoreceptors** causing decreased release of norepinephrine.
- **Overdose** stimulates peripheral postsynaptic **α1 adrenoceptors** & cause **hypertension** by vasoconstriction.
- **Clonidine has a sedative**, **analgesic**, **anti-shivering** and **diuretic** actions.
  The site for the sedative action is in the **locus ceruleus of the brain stem**.
  The site for the analgesic action is in the **spinal cord.**
  The mechanism for the anti-shivering and diuretic actions are **unknown**.
- In the heart, clonidine decreases HR by two things: decreasing NE release and a vago-mimetic action.

uses and indications:

- ADHD (attention deficit hyperactivity disorder) in children to help them focus for the good of their education. opioid withdrawal, restless legs syndrome, hypertension, alcohol withdrawal.

- Low dose of Clonidine is used in migraine prophylaxis, menopausal flushing (hot flushes in menopausal ladies) and chorea (abnormal involuntary movement disorder).
- **Abrupt withdrawal** causes **rebound hypertension** → very dangerous, and fatal. Once clonidine is absent the sympathetic firing will be amplified greatly, which in turn would crazily increase the BP.
- **Side effects:** Sedation, dry mouth, dizziness (related to BV dilation) and constipation.

Guanfacine:

- Very similar to clonidine and used in treatment of hypertension.

Dexmedetomidine:

A centrally acting **α 2-selective agonist**.

used for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. It also reduces the requirements for opioids in pain control (with it we use less morphine for the same effect)

Methyldopa:

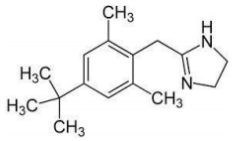
Metabolized to **α-methyl norepinephrine**, which then **lowers arterial pressure** by activation of **presynaptic α2 receptors** in the brainstem which reduce sympathetic outflow.
Lowers blood pressure (similar to clonidine) & a reduces plasma renin activity.

Used for: treatment of hypertension during pregnancy as a replacement for ACE (angiotensin converting enzyme, NOT acetylcholinesterase) inhibitors & angiotensin II receptor blockers (which are more efficacious but are strongly **contraindicated in pregnancy**).

Oxymetazoline:

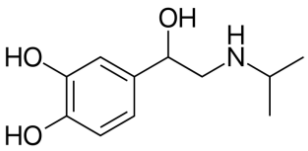
Direct-acting α1 agonist with significant **affinity for α 2A receptors**.

Used as topical decongestant because of promoting constriction of the nasal mucosa.



When taken in **large doses**, oxymetazoline may cause **hypotension** (alpha 2 A activation), because of a central clonidine-like effect.

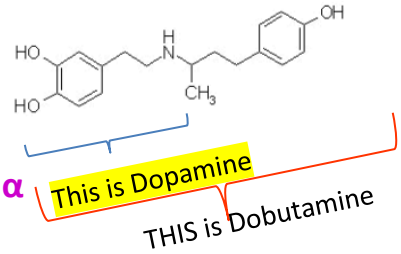
Isoproterenol (isoprenaline):



Explained in the last subject of the previous sheet (14.2)

❄ Beta1-selective agents:

Dobutamine:



- it's like dopamine's brother, BUT it has no effect on D receptors.
- Racemic mixture of (–) and (+) isomers.
  - The (+) isomer is a potent β 1 agonist and an **α 1 receptor antagonist.**
  - The (–) isomer is a potent **α 1 agonist**
  - The resultant effects of dobutamine is **β 1 stimulation.**
- So it's effect is like dopamine, it **increases heart contraction** more than heart rate. Positive inotropic effect **caused by the + (D) isomer on B1**
- Inotropic effect > chronotropic effect

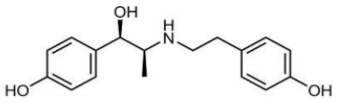
❄ Beta2-selective agents:

They're important in the talk about respiratory system.

Salbutamol, terbutaline are **Bronchodilators, used in the treatment of asthma.**

Ritodrine:

Used to achieve **uterine relaxation in premature labor.**



❄ Mixed-Acting Sympathomimetics:

They work in both ways: releasing NE[1] and Direct stimulation of sympathetic receptors[2].

Ephedrine:

- The plant Ephedra sinica, has been used in traditional Chinese medicine for 5,000 years for the treatment of asthma, hay fever & the common cold and allergy.
- Has a **high bioavailability** & a relatively **long duration of action**.

Mechanism:

It's taken up by the NET (norepinephrine transporter) and it gets stored in the vesicles, displacing NE which gets out and makes its effect.

It also **stimulates β2 receptors** directly, it has same effect as epinephrine but a longer duration. Because it's not a catecholamine, it doesn't get affected by COMT. It is not affected by MAO either, thanks to the N-methyl group. Still, it's weaker than epinephrine

Indications: Bronchodilator, Decongestant and also used as a pressor agent during spinal anesthesia

Pseudoephedrine:

One of four ephedrine enantiomers. Available over the counter as a component of many decongestant mixtures.

❄ Indirect-Acting Sympathomimetics:

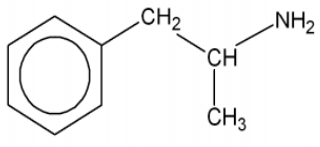
- These ones DON'T directly stimulate receptors, but they increase the concentration of norepinephrine or dopamine on the receptor sites.
- They use two mechanisms:
  - They get taken up by the nerve, then they displace the transmitter, sit in its place and they force it to do its job (displacers / amphetamine like)
  - By inhibiting reuptake of norepinephrine. (80% of it is taken up) blocking that causes it's concentration to remain high.

    e.g. Cocaine and Modafinil

Modafinil:

- Inhibits both NE & DA transporters, & increases interstitial concentrations of NE, DA, serotonin and glutamate (excitatory neurotransmitter) while decreasing GABA (inhibitory neurotransmitter) levels.
- It is used primarily to improve wakefulness in **Narcolepsy** (مرض النوم)
  It is often associated with mild increases in BP & HR.

Amphetamine likes:

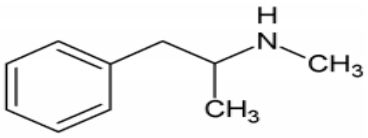


Amphetamine:

- it's a racemic mixture that is a high-power CNS stimulant.
  - important cause of its use and misuse.
- Highly lipid soluble, because it lacks oxygen. * look up there
- **Effects:** Readily enters the CNS, where it has **marked stimulant effects** on mood and alertness and **a depressant effect** on appetite.
- Its D-isomer is more potent than the L-isomer.
- Amphetamine's actions are mediated through the release of NE and dopamine.

Methamphetamine:

Similar to **amphetamine**. With a higher ratio of central to peripheral effects.



(N- methylamphetamine)
methamphitamine

Methylphenidate:

Methylphenidate may be effective in some children with **attention deficit hyperactivity disorder (ADHD).**

All these amphetamine likes are restricted, and you can't get them easily by a prescription. Because of their high abuse rate

Tyramine:

- Found in high concentrations in some fermented foods such as cheese, some jams.
- It gets metabolized by MAO in the GIT & the liver so it is **inactive** orally.
  we consume it in high amounts, but we don't observe effects.
- If administered parenterally, it has an indirect **sympathomimetic action** caused by the release of stored catecholamines.
- In patients treated with **MAO inhibitors** (like people with atypical depression), tyramine may cause marked increase in blood pressure **(Cheese reaction)**.

Drug	uses and indications	Notes
Direct acting sympathomimetics		
Phenylephrine	Mydriatic for tests, decongestant for common cold. used to raise the blood pressure.	
Methoxamine	Increasing pressure in Hypotensive states	
Midodrine	For orthostatic hypotension	Causes hypertension in patients who are constantly supine
Alpha 2 selective agonists		
Clonidine	Anti-hypertensive. (reduces hypertension) ADHD. opioid withdrawal. restless legs syndrome. alcohol withdrawal. **In low doses** used for: migraine prophylaxis menopausal flushing chorea	Clonidine is a sedative, analgesic, anti-shivering and diuretic drug.
Guanfacine	Treatment of hypertension.	
Dexmedetomidine	Sedation of intubated ICU resident patients, instead of high opioid doses.	
Methyldopa	treatment of **hypertension during pregnancy**	
Oxymetazoline	topical decongestant	In high doses it causes hypotension, by a central clonidine-like effect.
Beta 1 selective agents		
dobutamine	Increasing force of contraction, without increasing HR.	
Beta 2 selective agents		
Salbutamol, terbutaline	Bronchodilators, used in the treatment of asthma.	

Ritodrine	Uterine relaxant in case of premature labor.	
Non selective beta agonists		
Isoproterenol	Increase cardiac output without markedly affecting the BP.	
Mixed acting sympathomimetics		
Ephedrine	Bronchodilator Decongestant pressor agent during spinal anesthesia	Used in chinese medicine in: asthma, hay fever & the common cold and allergy
Pseudoephedrine	Used in decongestant mixtures.	
Indirect acting sympathomimetics		
cocaine	You give it to someone to ruin their life ☹	
Amphetamine	Mood elevator Depressor of appetite	
Methamphetamine	=	
Methylphenidate	attention deficit hyperactivity disorder (ADHD).	
Modafinil	Narcolepsy (sleeping -non parasitic- disease)	
Tyramine	Central nervous system effects.	**Unsafe for People taking MAO inhibitors** (like people with atypical depression), tyramine may cause marked increase in blood pressure **(Cheese reaction)**.

"One of the main pharmacological principles is that: after every great stimulation a great inhibition must take place. In order to have a permanent excitatory effect, continuous breaks must take place between continuous small stimulations"

remember that You're not an exception to this rule!