SHEET NO. 17

PHARMACOLOGY

DOCTOR 2019 | MEDICINE | JU

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SCIENTIFIC CORRECTION :

GRAMMATICAL CORRECTION :

DOCTOR : Hamza

Sympathomimetic drugs are **agents** which in general mimic responses due to stimulation of sympathetic nerves.

1)Endogenous Catecholamines, we have three types of it in our body:

A) Epinephrine (adrenaline).

B) Norepinephrine (noradrenaline).

C) Dopamine.

A) Epinephrine (adrenaline)

→ It is a powerful **agonist of all adrenoceptors** → stimulate all type of alpha and beta receptors(**alpha**-1, **alpha**-2, **beta-1**, beta2 and beta-3 receptors). So because of over powerful stimulation of alphareceptor it is a Very potent **vasoconstrictor** and **cardiac stimulant** due to stimulation of beta-1 receptor in the heart. And this causes **a rise in systolic BP** by its positive **inotropic** and **chronotropic** effects and the **vasoconstriction** iduced in many vascular beds[alpha].

** **Positive intropic** (used in reference to various drugs that **affect** the myocardial contractility) effect increase the strength of muscular contraction >> inject a higher blood volume >> increase the stroke volume (volume of blood pumped to the arteries in one stroke (contraction) of the ventricle).

** **positive chronotropic** effect → increase heart rate.

Conclusion: Stimulation of the Beta1-adrenergic receptors in the heart results in positive **inotropic** (increases contractility), chronotropic (increases heart rate) effects. And together there is a vasoconstriction induced in many vascular beds due to stimulation of (α-receptor).

-At the same time **Epinephrine** also activates β-2 receptors in **skeletal muscle blood vessels**→leading to their **dilation** (more blood [increase blood flow] can perfuse the skeletal muscle) that's what the body need in emergency situation and exercise.

****Peripheral resistance(PR):** is the resistance of arteries to blood flow, when arteries **constrict** → the **resistance** increases and,
as they **dilate** → **resistance** decreases.

****Total peripheral resistance(TPR): the outcome of BV are resistant and other that not resistant[** refers to the amount of force affecting **resistance** to blood flow throughout the circulatory system, some blood vessels have high (R) and other have low (R)].
The TPR may fall → prevent baroreceptor from activated [baroreceptor increase when TPR increase.]
→ the **Epinephrine** here can increase the HR without interference from baroreceptor…..but in case of **NE** does not dilate BV → that means increase of TPR which lead to activated baroreceptor .

-**β 2** activate glycogenolysis in the liver.

-**β 3** stimulation → lipolysis (break down of lipids and increase in FFA) → ↑ free fatty acids.

Both **glucose and FFA** are fuel for body in emergency situations and exercise.

B) Norepinephrine (noradrenaline).

-**Agonist at α1, α 2 and β 1 receptors** with **similar** potency as epinephrine, but has relatively little effect on **β 2** receptors[weak potency at beta 2 receptor]. -Causes a **vasoconstriction** in all blood vessels include BV of the skeletal muscles >> increases peripheral resistance and both **diastolic** and **systolic** blood pressure.

****diastolic blood pressure**: the blood pressure when the heart is relaxed.

**systolic blood pressure: the blood pressure during the contraction of the ventricular muscle.

-**Compensatory baroreflex activation** overcome the direct positive chronotropic effects of NE on beta-1 receptor (increase the heart rate) producing **bradycardia** (decrease heart rate).

-The **positive inotropic effects** on the heart are maintained because of no parasympathetic intervention in the **ventricles** (no baroreflex effect) means that NE increase the force of contraction and stroke volume.

C) Dopamine

-neurotransmitter that plays several important roles in the brain and body. -Acts on many receptors but the most Sensitive one is the Dopamine receptors (D1 & D2).

- immediate precursor in the synthesis of NE.

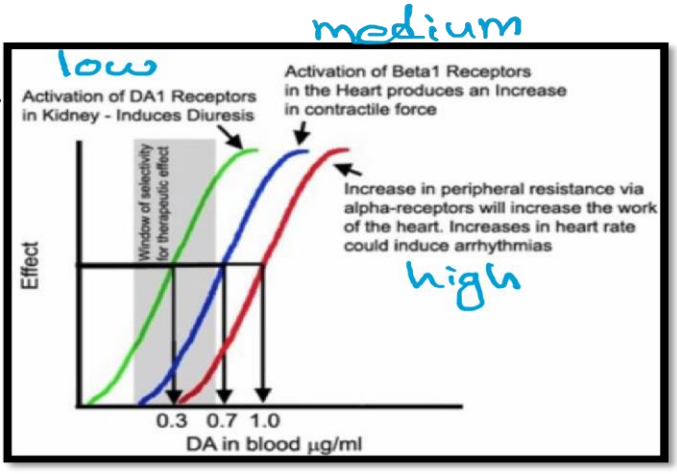
-Dopamine given to the patient intravenously due to its short half life→so The effect of Dopamine depands on level of prefusion.

-Stimulates: **Low** dose only stimulate D1 & D2 receptors activated **Medium** dose→ β receptors activated/ **High** dose→ α receptors activated.

// Be attention to the picture 👇 //

Diuresis: increase the urine output.

Arrhythmia: irregular heart beats.



-**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**, Can't give dopamine directly to people with Parkinson's because dopamine can't penetrate the blood brain barrier, so give levodopa [convert to dopamine in brain].

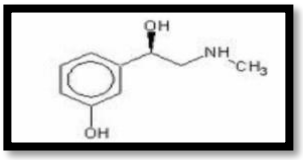
-Dopamine antagonists are antipsychotic drugs. Why?

Because high dopamine amount is related to psychosis (hallucinations, screams)

2)Direct-Acting Sympathomimetics

not required to memorize the structures

A) Phenylephrine

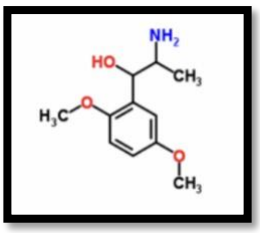


-A relatively **pure α 1 agonist**, make a vasoconstriction of all blood vessels.

- Not a catecholamine (CA), it is not inactivated by COMT & has a longer duration of action than the CA.

-Uses: **in the eye** >> it is effective mydriatic (agent that induces dilation of the pupil), in the **nose**>> it is effective decongestant in conditions such as colds and flu, also can be used to **raise the blood pressure.**

B) Methoxamine

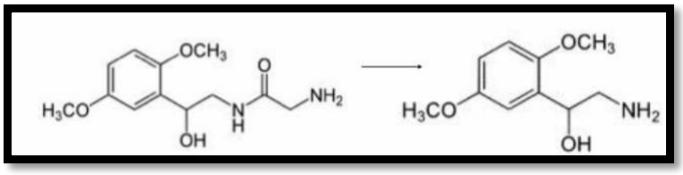


-**A direct-acting α 1 receptor agonist**.

-has long duration of action than **phenylephrine** because phenylephrine is inactivated by MAO but methoxamine **is not affected by COMT or MAO .**

-Causes a prolonged **increase in BP due to vasoconstriction & a vagally mediated bradycardia. Clinical uses** are rare and limited to hypotensive states.

C)Midodrine



-A **prodrug** (A precursor (forerunner) of a drug), enzymatically hydrolyzed to a **selective α 1receptor agonist.**

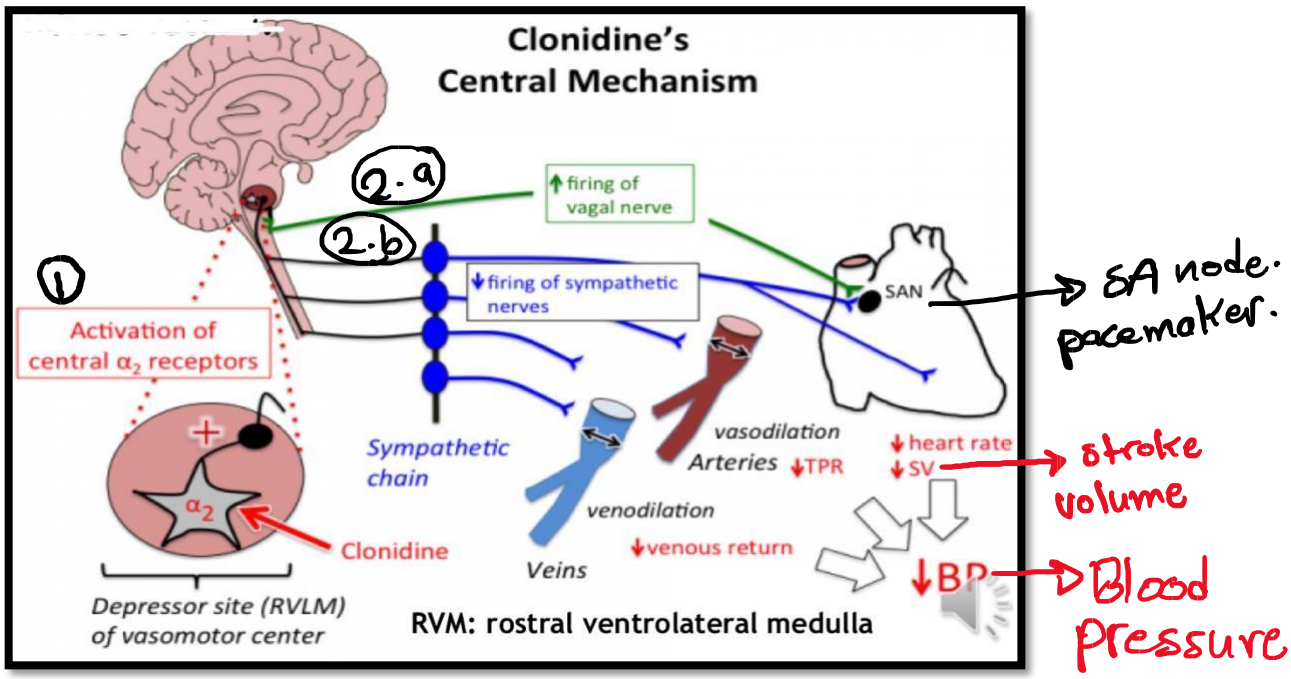
-The primary indication for midodrine is the treatment of **orthostatic hypotension** (Decreases in blood pressure when you standing up), due to impaired autonomic nervous system function.

EXPLAIN **orthostatic hypotension** →You supposed to have sympathetic reflexes increase sympathetic tone in the large veins of leg, so that vasoconstrictor prevents blood pooling but if these reflexes are impded. Then when standup the gravity will pull the blood down, so the blood volume decreases and you fall down.

-Although the drug has efficacy in diminishing the fall of blood pressure when the patient is standing, it may cause hypertension when the subject is supine.

3)Alpha2-selective agonists

-**Decrease BP** through actions in the CNS even though **direct** application to a blood vessel may cause vasoconstriction because blood vessels have some **alpha-2 receptor** that when stimulated produce the same effect of alpha-1 receptors.



Clonidine's central mechanism

How alpha-2 agonist work???

(1) Clonidine's **activate central alpha-2 receptors** in the depressor site of **vasomotor** center →this activation result in increasing the vagal tone → increase firing of the vagal nerve →causes a **Bradycardia** (decrease the heart rate) same as it decreases the firing of sympathetic nerves→ decrease heart rate and SV →decrease cardiac output →decrease BP→ decreases the firing of sympathetic nerves also means that:

1)the sympathetic tone of blood vessels become less and decrease>>vasodilation of arteries >>decreases TPR>>decrease BP

2)the sympathetic tone of the **veins** decreases >>**venodilation**>> decreases the veins return because the veins now can hold more blood so less blood is received by the heart which contribute to the decrease of cardiac output >> decrease BP.

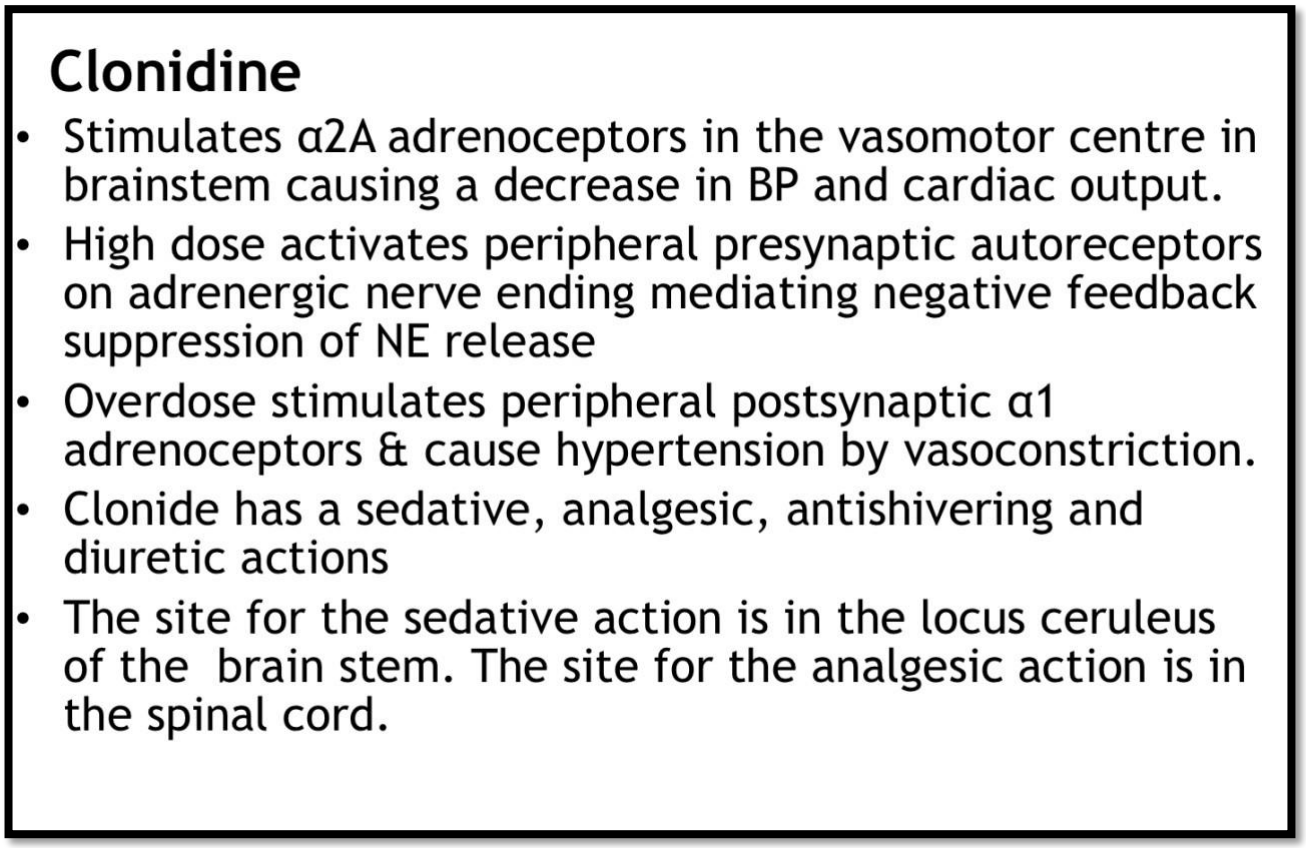
**Remember

-**cardiac output =heart rate * SV**

-all sympathetic nerve endings have **a presynaptic alpha-2 receptors** and when activated they inhibit the release of more norepinephrine.

-Alpha-1 receptor (A, B, D) // Alpha-2 receptor (A, B, C)

A)Clonidine



-In the **heart**, clonidine ↓HR (↓ NE release) and through a **vagomimetic** action because it is centrally stimulating the **vagus nerve**.

-The mechanism for the **antishivering** and **diuretic actions** are unknown.

→Uses:

- **ADHD** (attention deficit hyperactivity disorder) in children, now these children they are hyperactive and because they are hyperactive the attention span is very little, so they can't concentrate to learn, they have difficulty in school, also they have movement activities.

  Also used in **opioid withdrawal** (opioids are drugs used to treat pain including morphine and heroin, so stop taking them would result in an increased sympathetic)

  +restless legs syndrome **(people can't stop shaking their legs)**, **hypertension, alcohol withdrawal.**
- **Low dose of Clonidine** is used in migraine prophylaxis (it prevents the attack of migraine), menopausal flushing **(Most women will experience hot flushes when going through the menopause)**. and chorea (abnormal involuntary movement disorder).

-Abrupt withdrawal causes rebound hypertension (when you suddenly stopped taking clonidine)

→Side effects: Sedation, dry mouth, dizziness and constipation.

B) Guanfacine

-Centrally **acting α 2-selective agonist**, but have minor side effect than clonidine.

-used in the treatment of **hypertension**

C)Dexmedetomidine

-A centrally **acting α 2-selective agonist** used for sedation **(its sedative effect higher than clonidine, other effects are less)** of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. Now for those patient It also reduces the requirements for opioids in pain control which is good because high dose of opioids can produce side effects.

D)Methyldopa

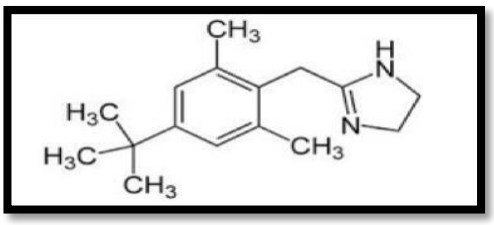
-Metabolized to α-methyl norepinephrine which then stored in sympathetic nerve ending and it is released instead **on norepinephrine as a neurotransmitter**.

- methyldopa converted to **alpha-methyl NE especially** in the brain which then lowers arterial pressure by activation of **presynaptic α2 receptors** in the brainstem which reduce sympathetic outflow, lowering blood pressure (similar to clonidine) & a reduction of plasma renin activity.

-Used for **treatment of hypertension** during **pregnancy** as a replacement for **ACE inhibitors** (angiotensin converting enzyme inhibitor) & angiotensin II receptor blockers (which are more efficacious than methyldopa, but are strongly contraindicated in pregnancy).

**You should be carful to give any drug during pregnancy because drugs can affect the fetus specially the new drug that we don’t know how it will affect the fetus.

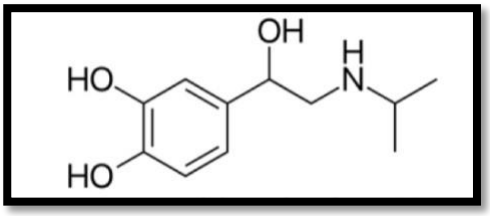
E) Oxymetazoline



-Direct-acting alpha-1agonist with significant affinity for alpha- 2A receptors.

-Used as topical decongestant because of promoting constriction of the **nasal mucosa, so it stops the mucus**. But if taken in large doses then the **alpha-2** receptors will take place and will may cause **hypotension** because of a central clonidine -like effect.

F) Isoproterenol (isoprenaline)



-It is a **Catecholamine** but it is a synthetic drug.

-Very potent β -receptor agonist and has **little effect on α receptors.**

-Has positive (because it stimulates all types of beta-receptors) chronotropic (increase the heart rate) and inotropic actions (β1) (increases the force of contraction in the heart).

-it is a potent vasodilator (β-2 receptor present in the blood vessels of the skeletal muscle>>decreases the PR" peripheral resistance")?

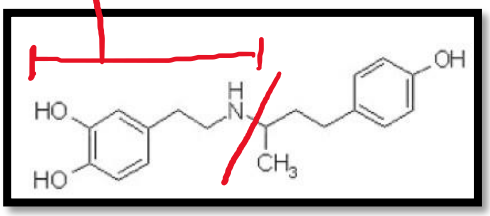
-These actions lead to:

- **A marked increase in cardiac output**, in this case there is no interference from baroreceptor because there is no increase in PR

- **A fall in diastolic and mean arterial pressure due to vasodilator action(beta-2).**
- **Slight decrease or increase in systolic pressure**, why it is slightly? Because chronotropic and inotropic actions of isoproterenol.

4)Beta1-selective agents

dopamine structure



adding group.

Dobutamine

-**Racemic** mixture; it has 50% in levo form (–) and 50% in dextro form (+) isomers so it **has two isomers** at the same time with different effect.

- **The (+) isomer is a potent β-1 agonist** and an α-1 receptor antagonist.
- **The (–) isomer is a potent α-1 agonist**, so it cancels the effects of the dextro isomer as alpha-1 receptor antagonist. So → The resultant effects of dobutamine is β-1 stimulation only.

-Has a positive inotropic action caused by the isomer with predominantly β1 receptor activity.

-Has relatively greater inotropic than chronotropic effect (like dopamine) compared with isoproterenol. **"Advantage"** → that the effect on the force of contraction is higher than his ability to increase heart rate, increasing heart rate is bad to people with congestive heart failure.

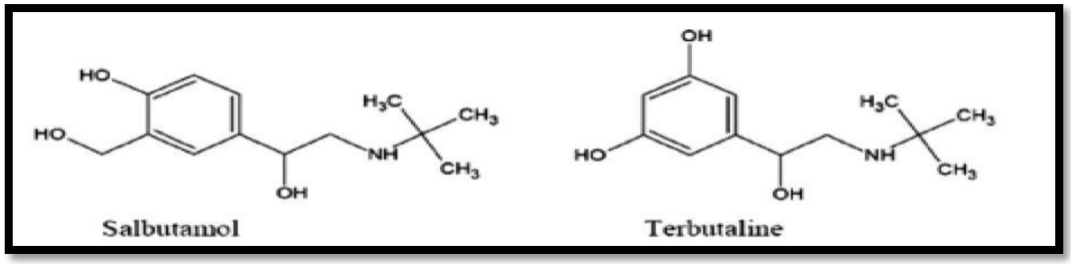
**So both dopamine and Dobutamine are used to stabilize patient with congestive heart failure.

5)Beta2-selective agents

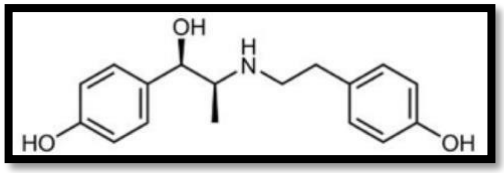
A) Salbutamol (most commonly used).

B) terbutaline

-Bronchodilators, used in the treatment of **asthma** because beta-2 receptors are present in the bronchioles which stimulated and they **promote relaxation of bronchial muscle.**



C)Ritodrine

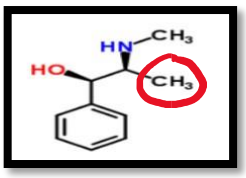


-**Used to achieve uterine relaxation in premature labor,** during pregnancy; stimulation of beta-2 receptor inhibits the contraction of the uterus, so if a pregnant woman had premature contraction and the threat to loose the baby we give Ritodrine in order to stop(inhibit) these contractions and stabilize pregnancy until the full term.

6)Mixed-Acting Sympathomimetics

Acts in both ways; directly stimulating adrenoreceptors and indirectly by causing the release of norepinephrine from the vesicles of the store in the adrenergic neuron endings.

A) Ephedrine



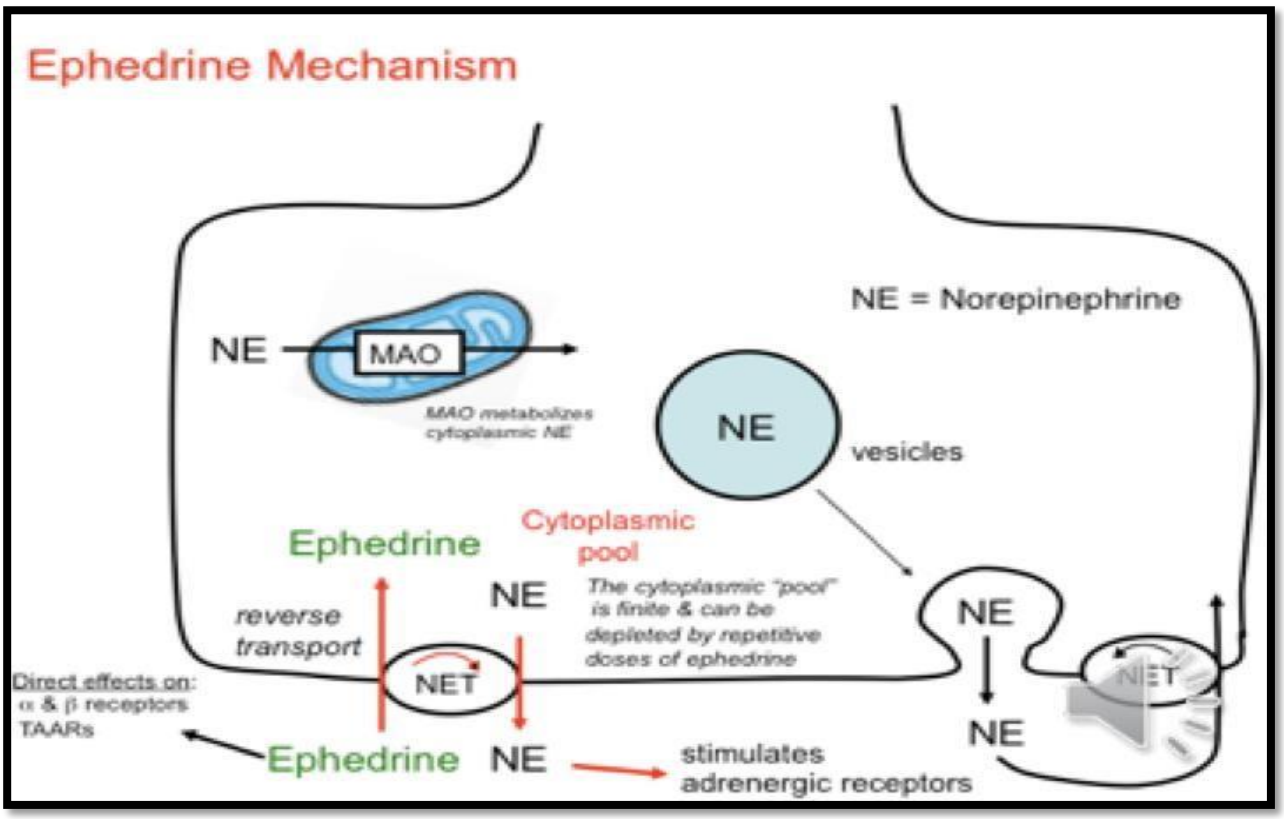
-Vasoconstrictor

-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 has high bioavailability (more lipid soluble than Catecholamines, and it can penetrate the blood brain barrier) & a relatively long duration (it is not affected by COMT enzyme).

-Not affected by mono-amino oxidase enzyme because of the present of methyl group (circular one).

-It **releases NE** & **activates** "**indirect effect**", β2 receptors "directly".

-it is a mild CNS stimulation effect.



-Note that Ephedrine is taken up NET (net ephedrine transporter) into the neuron which stimulate the release of NE from the vesicles that stimulate alpha and beta receptors

-Not affected by MAO enzymes, but some of NE release is metabolize by MAO before it gets outside the neuron.

****Indications**:

- **Bronchodilator** (people who have some pulmonary infection); a syrup is given to the patient to drink which contain Ephedrine, that is a bronchodilator in this case at the same time it causes a vasoconstriction and it decreases the secretion of **mucus** in the lung.
- **Decongestant**.
- **A pressor agent during spinal anesthesia** (injection of local anaesthetic into the subarachnoid space in the spinal cord produces block of conduction in all nerves in the area), so the patient can have

surgery without filling the pain but at the same time **the autonomic nerves** are
also blocked so it removes the sympathetic tone on the blood vessels and that is why there is a decrease in blood pressure during anesthesia, so we use like **Ephedrine** drug to **increase blood pressure in this case.**

B) Pseudoephedrine

-**One of four ephedrine enantiomers.**

-Available over the counter as a component of many **decongestant mixtures.**

Best wishes to you.

دعواتكم ، وبالتوفيق للجميع