Doctor 021

# PHARMACOLOGY

Doctor :Dr.Hamza

# Sympathomimetic 2

❖ 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.

**Anaphylaxis**

❖ **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. Glucocorticoids and antihistamines may be useful as secondary therapy in anaphylaxis.**

**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.

**NE and direct-acting α agonists are used in a hypotensive emergency to preserve cerebral and coronary blood flow.**

**The treatment is of short duration while the IV fluid or blood is being administered**

## 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.

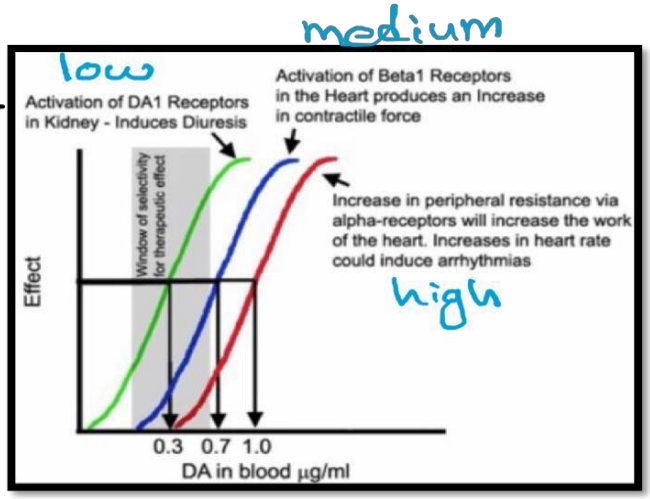
-Dopamine given to the patient intravenously due to its short half life→so The effect of Dopamine depands on level of prefusion.

**-Stimulates: Low dose only stimulate D1 & D2 receptors activated**

**-Medium dose→ β receptors activated/ High dose→ α receptors activated.**

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].

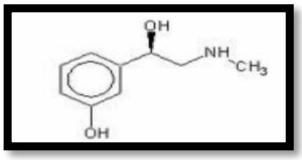
**-Dopamine antagonists are antipsychotic drugs.** Why? Because high dopamine amount is related to psychosis (hallucinations, screams)

**-Dopamine provides a short-term relief of heart failure symptoms in patients with advanced ventricular dysfunction.**

# 2)Direct-Acting Sympathomimetics

***not required to memorize the structures***

A) Phenylephrine

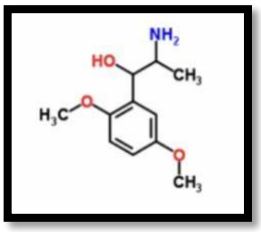



❖ **A relatively pure α 1 agonist**, make a vasoconstriction of all blood vessels.

❖ **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

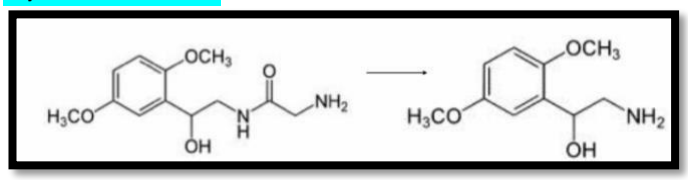



❖ **A direct-acting α 1 receptor agonist.**

❖ 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 to raise BP.**

C)Midodrine




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

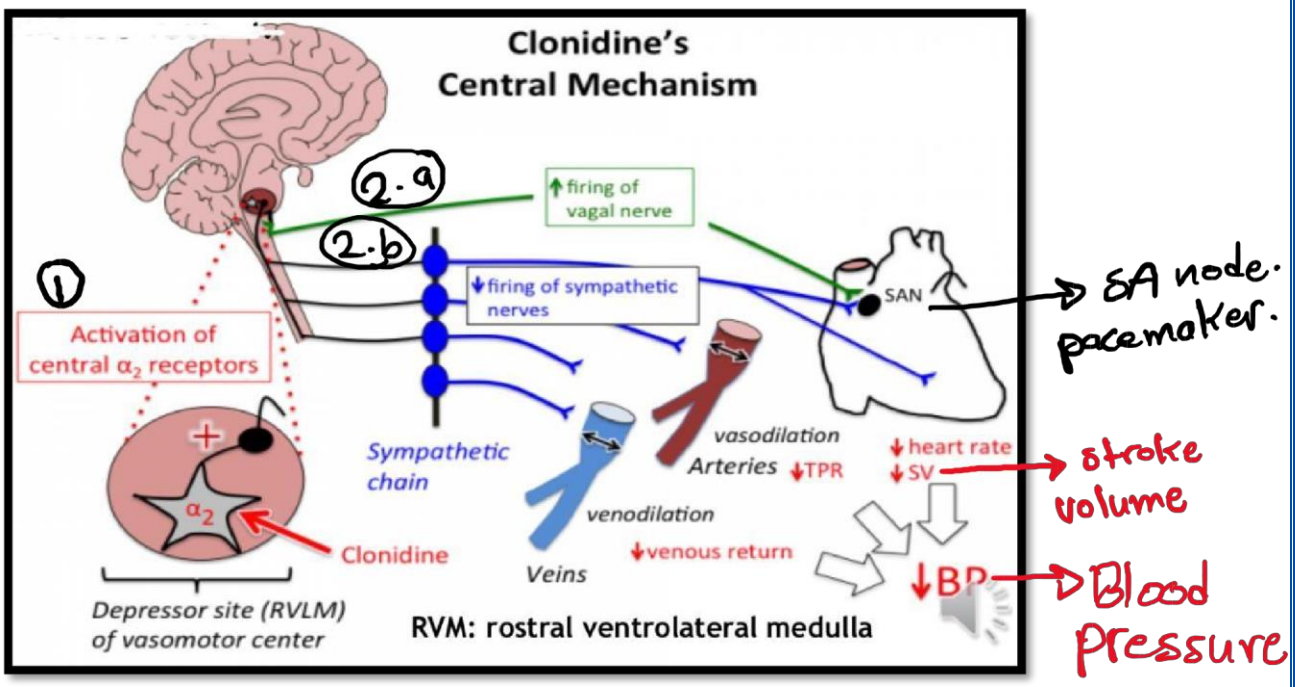
❖ **The primary indication for midodrine is the treatment of orthostatic hypotension** (Decreases in blood pressure when you standing up), **due to impaired autonomic nervous system function.**

❖ 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

❖ **Clonidine Stimulates α2A adrenoceptors in the vasomotor centre in brainstem causing a decrease in BP and cardiac output.**

❖ **High dose activates peripheral presynaptic autoreceptors on adrenergic nerve ending mediating negative feedback suppression of NE release**

❖ **Overdose stimulates peripheral postsynaptic α1 receptors & cause hypertension by vasoconstriction.**

❖ **Clonidine has a sedative, analgesic, antishivering 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.**

❖ **In the heart, Clonidin↓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**
- **Also used in treatment of attentiondeficit/hyperactivity disorder (ADHD) in children six to 17 years of age.**
- **May help manage behavioral symptoms, such as aggression and self-injurious behavior, associated with Prader-Willi syndrome (PWS) caused by a genetic change on chromosome number 15.**

## 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).**

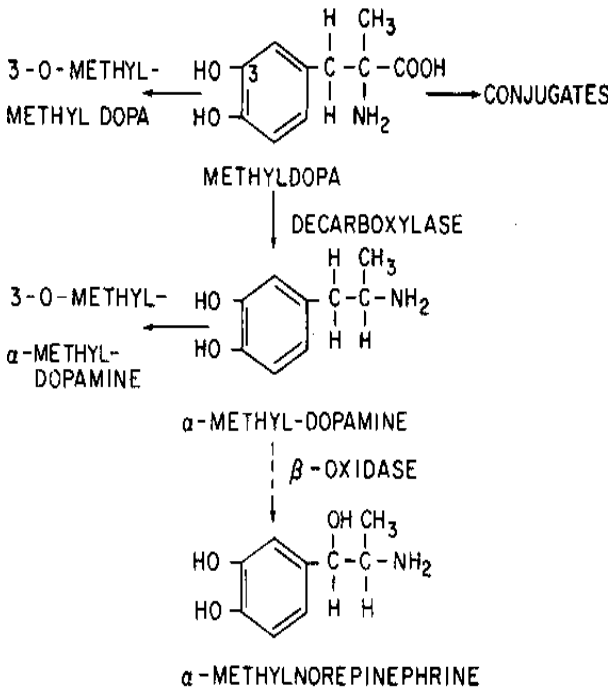
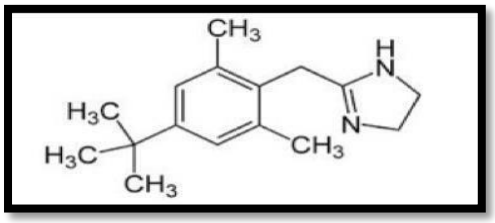



Figure 5

- 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.

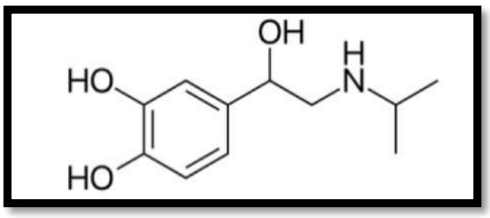
# E) Oxymetazoline




❖ **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

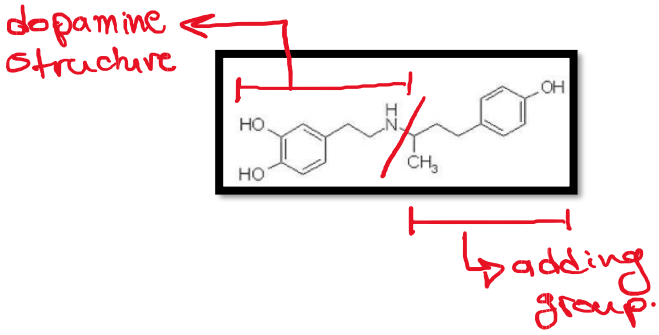
❖ **A fall in diastolic and mean arterial pressure due to vasodilator action(beta-2).**

❖ **Slight decrease or increase in systolic pressure,** why it is slightly? Because chronotropic and inotropic actions of isoproterenol.

- **Isoproterenol is used in the temporary emergency management of complete heart block**

# 4)Beta1-Selective agent

## 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.

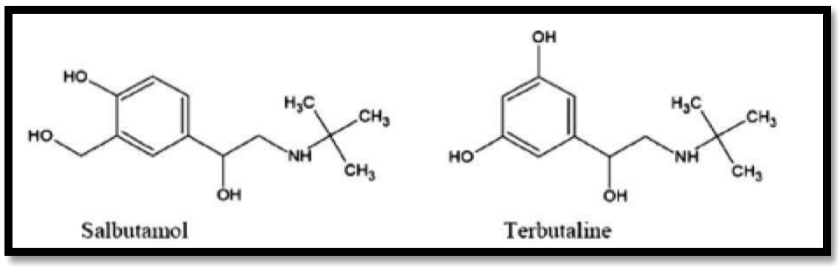
**-Used to provide a short-term relief of heart failure symptoms**

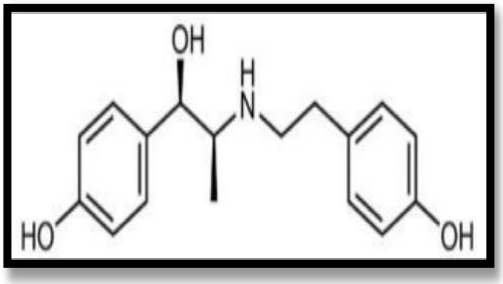
**So both dopamine and Dobutamine are used to stabilize patient with congestive heart failure.

# 5) Beta2-selecive 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.



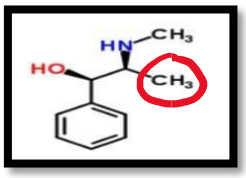
**C) Ritodrine**

**-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



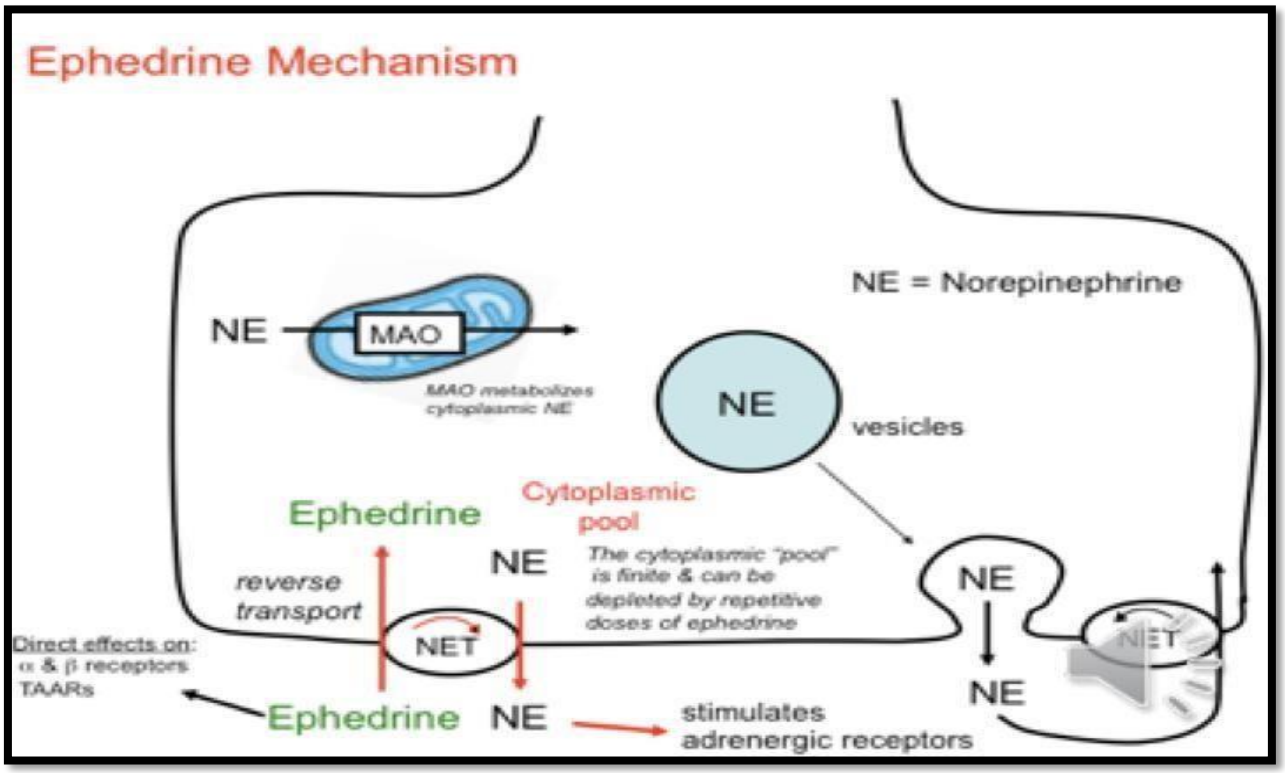

-Vasoconstrictor

**-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.

❖ **Oral ephedrine or pseudoephedrine are useful in the treatment of stress incontinence (loss of small amounts of urine associated with coughing, laughing, sneezing, exercising or other movements that increase intraabdominal pressure and thus increase pressure on the bladder).**

**(B) Pseudoephedrine**
**-One of four ephedrine enantiomers.**
**-Available over the counter as a component of many decongestant mixtures.**

# Indirect – Acting Sympathomimetics

**Indirectly acting drugs works mainly by one of the two mechanisms:**

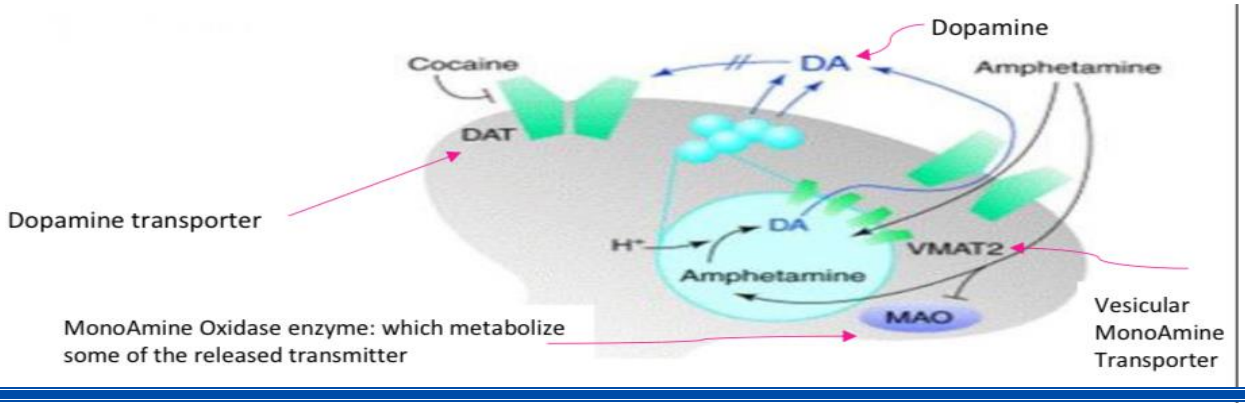
1} **Entering the sympathetic nerve ending and displaces stored catecholamine transmitter** (which trigger the release of catecholamine).

🌀 **such drugs are called amphetamine-like or displacers.**

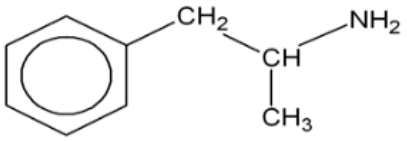
*Catecholamine = epinephrine, nor epinephrine & dopamine*

**2} Inhibiting the reuptake of released NE by interfering (or inhibiting) with the action of the NE transporter (NET).**

🌀 **eg: Cocaine**.



# Amphetamine-like & amphetamine




Amphetamine like is a displacer, it displaces NE from the vesicles. While Amphetamine is **a racemic mixture** (meaning that it has levo- and dextro- isomers) **that is important because of its use and misuse as a CNS stimulant**.

Dextro-isomer has more central action than peripheral action.
Levo-isomer has more peripheral action then central action.

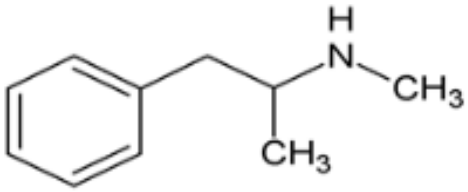
Amphetamine is a controlled drug just like heroine and morphine.

**It readily enters the CNS** (as it could go through BBB), **where it has marked stimulant effects on mood and alertness and a depressant effect on appetite** (it was used in the past as appetite suppressant, and it cause sudden death for lots of people because it highly stimulate the heart)

**-Its D-isomer is more potent than the L-isomer.**
**-Amphetamine's actions are mediated through the release of** NE (peripherally; which causes the cardiac stimulation and increase blood pressure) **an dopamine** (in the brain).

# Methamphetamine (N- methylamphetamine)

**-Very similar to amphetamine with an even higher ratio of central to peripheral actions.**
**--The same use ,misuse, abuse of amphetamine**




# Methylphenidate

**-Its major pharmacologic effects and abuse potential are similar to those of amphetamine.**
**-Methylphenidate may be effective in some children with attention deficit hyperactivity disorder** (keep moving , don't listen to teacher )

** although these drugs are activator but it make the child calm and listen and concentrate more in their classes (but we should be more care about the schedule; we have to give them certain times and stop them; because its affect the appetite so the growth of the children) .

# Modafinil

**-A psychostimulant** that work on many chemical transmitters.

-**It inhibits both NE & DA transporters, & increases interstitial concentrations of NE, DA , serotonin**[ important transmitter in the brain] **and glutamate** (the major excitatory neurotransmitter in the brain) **while decreasing GABA levels** (the major inhibitory neurotransmitter in the brain).

**-It is used primarily to improve wakefulness in narcolepsy.**

-Narcolepsy is depression in CNS that causes Sleepiness

**-It is often associated with mild increases in Blood Pressure & Heart Rate.**

**- Modafinil may also be useful in ADHD**

# Tyramine

**-Found in ↑ conc. in some fermented foods such as wine,cheese** and its harmful to eat as much as you like from the cheese because it **metabolized by MAO firstly in GIT (mainly the intestine) & secondly in the liver so it is inactive orally .**

-**If this therapy administered parenterally,it has an indirect sympathomimetic action caused by the release of stored catecholamines**. [the same as amphetamine]

- it doesn't have central action, just peripheral action stimulation of catecholamines receptor→increase BP.

**- In patients (with mental depression of example) that treated with MAO inhibitors, tyramine may cause marked increases in blood pressure which could lead to death, and this reaction called (Cheese reaction) because cheese is rich with tyramine.**

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***Now we will talk about drugs that use the second mechanism of activating SNS.***

## Catecholamine Reuptake Inhibitors:

**Many antidepressants, particularly tricyclic antidepressants inhibit NE & serotonin reuptake in the brain leading to orthostatic tachycardia as a side effect.**

orthostatic tachycardia is tachycardia that occurs while standing up as standing up evokes sympathetic reflexes so there's vasoconstriction in the veins in the leg so it prevent the pooling of blood into the legs so less amount of blood refer to the heart

❖ **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.**

❖ **Cocaine**

**A local anaesthetic with a sympathomimetic action that results from inhibition of NE** and Dopamine **reuptake** in the brain**.**

- it's the first local anaesthetic discovered and was used for long time by European people for pleasure until they discover that its addictive and cause sudden death.
- **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 centres.**
- as a sympathomimetic, it cause heart attack and can lead to death**. it can be smoked, snorted into the nose, or injected. It is a heavily abused drug more than heroine or morphine.**
- **Coca Cola name refers to kola nuts, a source of caffeine, and coca leaves a source of cocaine.**
- **In 1903 cocaine was removed from coca cola drink**
- **Cocaine is used for nasopharyngeal surgery because it combines a hemostatic effect with local anesthesia.**

# Dopamine Agonists:

❖ **Levodopa**

**This drug is converted to dopamine in the body** because dopamine can't pass the BBB while levodopa can.

**Valuable in the treatment of Parkinson's disease.**

❖ **Fenoldopam**

**A D1-receptor agonist** (works only on dopamine receptors) **that selectively leads to peripheral vasodilation in some vascular beds** (so it decreases blood pressure).

**The primary indication for fenoldopam is in the IV** (intra-venous) **treatment of severe hypertension** (it's safe and quickly acting).

GOOD LUCK

V1