SHEET NO. 18

PHARMACOLOGY

DOCTOR 2019 | MEDICINE | JU

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Sympathomimetics 3

*كلام الدكتور بين أقواس.
*الصور الي عيهم 🌸هذول خارجيات مش من السلايدات.
*شرح مقترح (انسخ الرابط):
https://www.youtube.com/watch?v=qS_wgYel4qE&list=PLiccn5I1-F3LRSatuFWZYbMNvEHbSU0QU&index=6
*موفقين.

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*As we know that sympathomimetics drugs could act directly (by directly activating α or β receptors as we study before) or indirectly or by mix of both ways.

-> in this lecture we will talk about indirectly acting sympathomimetics..
have fun 😊

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

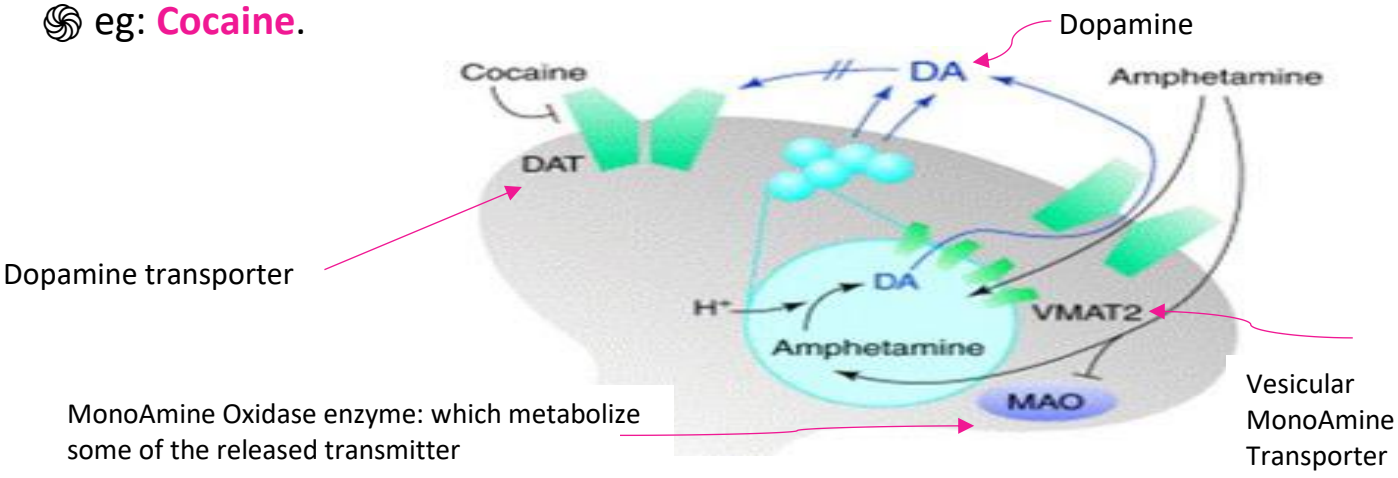
1} Entering the sympathetic nerve ending and displaces stored catecholamine transmitter (which trigger the release of catecholamine).

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

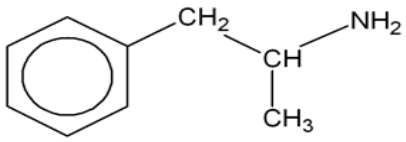
Catecholamine = epinephrine, nor epinephrine & dopamine

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.

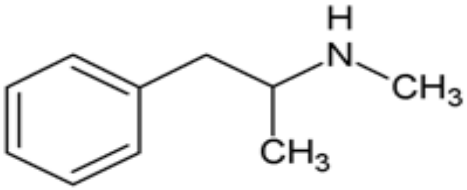
It readily enters the CNS (as it could go through BBB), where it has marked stimulant effects on mood and alertness and a depressant effect on appetite (it was used in the past as appetite suppressant سادّ للشهية, and it cause sudden death for lots of people because it highly stimulate the heart)

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) and dopamine (in the brain).

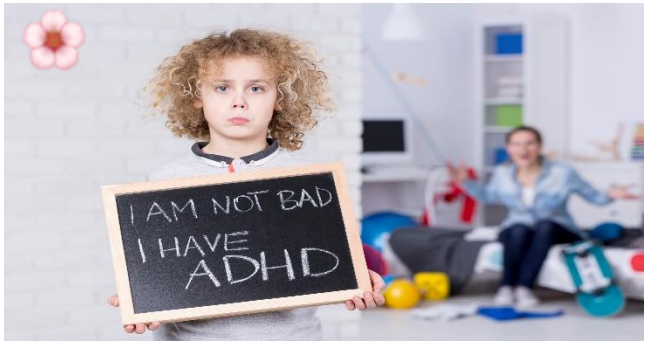
methamphetamine

(*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] مرض فرط النشاط وعدم التركيز عند الأطفال.

**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.

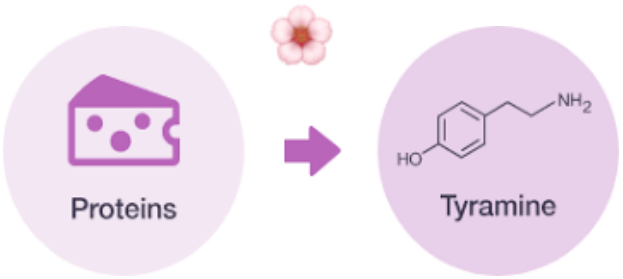
Narcolepsy is depression in CNS that causes sleepiness
وهي حالة بتخلي الشخص ينام بأي وقت وبأي مكان (لما تيجيه الحالة) فهذا الدوا بخليهم صاحيين

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

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 بالحقن, 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.



**We talked about drugs that activate SNS indirectly by the first mechanism {refer to page 1} ,, 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

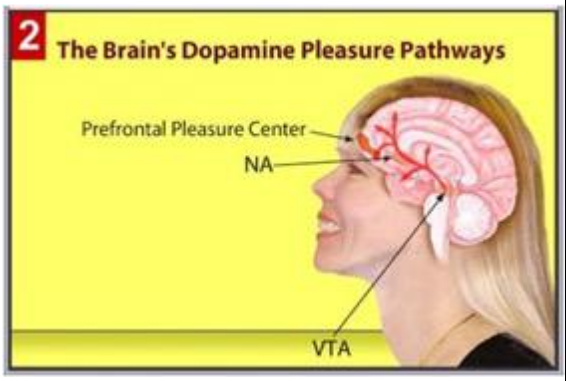
Sibutramine

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.

** 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).

Therapeutic Uses of Sympathomimetics

Cardiovascular Applications

Treatment of Acute Hypotension:

NE, phenylephrine, and methoxamine Direct-acting α agonists used in a hypotensive emergency to preserve cerebral and coronary blood flow.

The treatment is of short duration while the intravenous fluid or blood is being administered (its given to restore BP until the fluids reach and work).

Cardiogenic shock and acute heart failure:

*shock means decrease in BP (usually due to massive myocardial infraction), that can lead to death, so we need to increase the contractility of the heart to increase the output so the heart can pump enough blood to the organs.

Positive inotropic agents عوامل تزيد قوة الانقباضة such as dopamine or dobutamine through Intravenous perfusion to provide short-term relief of heart failure symptoms in patients with advanced ventricular dysfunction. =(we can't use epinephrine or isoproterenol because they cause sever cardiac stimulation and lead to tachycardia which might lead to death).

In low to moderate doses, these drugs (dopamine or dobutamine) increase cardiac output and cause relatively little peripheral vasoconstriction and they work more in the contractile force more than the heart rate so the HR doesn't increase much (because increase in HR means that the heart need more oxygen).

Chronic Orthostatic Hypotension:

⇨ Orthostatic Hypotension: is a decrease in blood pressure while standing up due to:

1. Impairment of autonomic reflexes that regulate blood pressure.
2. Or due to medications that can interfere with autonomic function.

3. Or due to diabetes and other diseases causing peripheral autonomic neuropathies.

in this case we use Midodrine drug, its orally active α 1 agonist. Also, we can try another sympathomimetic drugs such as ephedrine or phenylephrine.

Cardiac Applications

Epinephrine is the primary drug administered during cardiopulmonary resuscitation (CPR) الإنعاش القلبي الرئوي to reverse cardiac arrest توقف القلب.

Epinephrine increases arterial blood pressure and coronary perfusion during CPR via alpha-1-adrenoceptor agonist effects.

⇨ When the heart stop, stimulation of β1 receptors make the heart start beating again.

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

**Complete heart block:

= we know that atrioventricular nodes (AV) is the gate for the impulses to go from the atrial to the ventricles, and heart block means that this gate is closed so no impulse can go through it.

= this close could be partial or complete, so when a person got complete block, the ventricles stop contracting → blood pressure drop suddenly -> there's no blood going to the brain → so he falls down.

= this could happen in any time so isoproterenol because of its action on β1 receptors, increase the conduction velocity, solving the problem temporarily.

Inducing Local Vasoconstriction:

Epinephrine applied topically for epistaxis الرعاف or for gingivectomy (removal of diseased gum tissue that could case bleeding).

= so epinephrine strops the bleeding.

Cocaine used for nasopharyngeal surgery because it has two properties:

1- homeostatic effect (because it releases NE which cause vasoconstriction).
2- Its also a local anaesthesia.

- ➔ Combining α agonists with local anaesthetics (L.A.) greatly prolongs the duration of local anaesthesia & the total dose & reduce toxicity of L.A.
- ➔ Local anaesthetics are injected around the nerve, so they block conduction in the nerve (no action potential bc. sodium channels are blocked), they are called also membrane stabilizer effect.
- ➔ The problem of L.As (except cocaine) that they cause vasodilation, so the L.A is taken by the blood so after short time the patient feel pain because the conc. of L.A is below the amount needed to cause anaesthesia so the doctor need to give the patient more anaesthetic which expose the patient to side effects; so giving vasoconstrictor means little blood goes there so the L.A stays for long time and no need to give the patient mor doses, so we reduce the dose and the toxicity of the L.A
- ➔ Epinephrine (which used in conc. of 1:200,000), is the favoured agent for this application, but norepinephrine, phenylephrine, & other α agonists have also been used.
- ➔ Systemic effects on the heart and peripheral vasculature may occur but are usually minimal bc epinephrine is vasoconstrictor so it stays in the site of injection.

★ α1 agonist are also used as mucous membrane decongestant مضاد احتقان in common cold we use α1 agonist which cause vasoconstriction and remove the congestion, BUT continuing take of them causes rebound congestion يعود الاحتقان ,why? Because using vasoconstrictor for long time will make these tissue deprived of oxygen (hypoxia) so the metabolism reactions is go in the other way making vasodilator substances so the congestion becomes worse.

- ⇨ To avoid this situation we take oral vasoconstrictor, this will make the one face the systemic effect but its Ok if he doesn't have high blood pressure or heart problems.

★ Phenylephrine used in nasal decongestant sprays.

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.

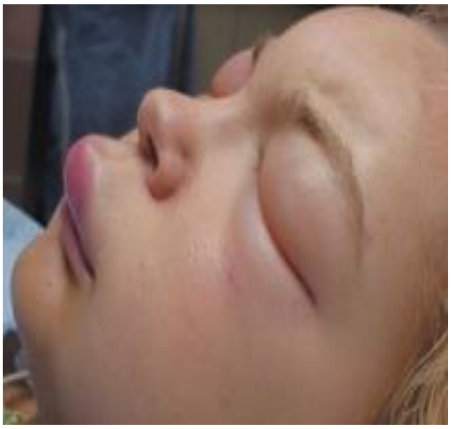
**Most of these decongestants are available as *over the counter* products.

Pulmonary Applications

β 2-selective agents are used in the therapy of bronchial asthma such as Albuterol (Salbutamol), metaproterenol, terbutaline all is 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 than the selective drugs.
= > before the discovery of these β2-selective drugs, patients used epinephrine and other beta agonists, but they suffer from cardiac stimulation.
*patients that were given isoproterenol to treat asthma shows higher death rate than those who are not treated and died by asthma 🙃

Anaphylaxis الحساسية المفرطة



The syndrome of bronchospasm, mucous membrane congestion, angioedema, and severe hypotension usually responds rapidly to the parenteral administration of epinephrine.
*if you have allergy to penicillin and you got injected with it you will have anaphylaxis.

Epinephrine is effective because:
1- β1 increases cardiac output.
2- β2 relaxes constricted bronchioles.
3- α1 constricts capillaries.

** after giving epinephrine we can use other drugs like Glucocorticoids (to stop the immune system) 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 hyperaemia احتقان الدم & itching حكة of the conjunctival membranes.

Glaucoma:

=glaucoma: is the intraocular pressure in the eye because the production of Aqueous humour exceeds the outflow of it.
Epinephrine is now rarely used, but β -blocking agents are among the most important therapies.
Apraclonidine which is alpha 2-selective agonist that also lower intraocular pressure is used in glaucoma.
= > The mechanism of action of these drugs in treating glaucoma is still uncertain.

Genitourinary Applications

β2 selective agents relax the pregnant uterus, Ritodrine, terbutaline, and similar drugs have been used to suppress premature labour.
*they inhibit the uterine contraction so they save pregnancy

Oral sympathomimetic therapy is useful in the treatment of stress incontinence سلس البول (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 and can pause the pass of the urine).
= Ephedrine or pseudoephedrine may be tried.

CNS Applications

Treatment of narcolepsy. حالة النوم الي حكينا عنها بصفحة 3

Modafinil, new *amphetamine substitute*, with fewer side effects than amphetamine is used in this condition.

Attention-deficit hyperactivity disorder (ADHD)

A behavioural syndrome of short attention span, hyperkinetic physical behaviour, and learning problems.
Some patients respond well to low doses of Methylphenidate & related agents (which serve as stimulant) or to Clonidine, Modafinil may also be useful in ADHD.

يعطيكم العافية

لا تنسوا والدة زميلنا جعفر من دعاءكم

واذكرونا بدعوة حلوة بظهر الغيب