بسم الله الرحمن الرحيم

Drugs modifying noradrenergic transmission (Part 2)

By
Dr. Mohammad Salem Hareedy

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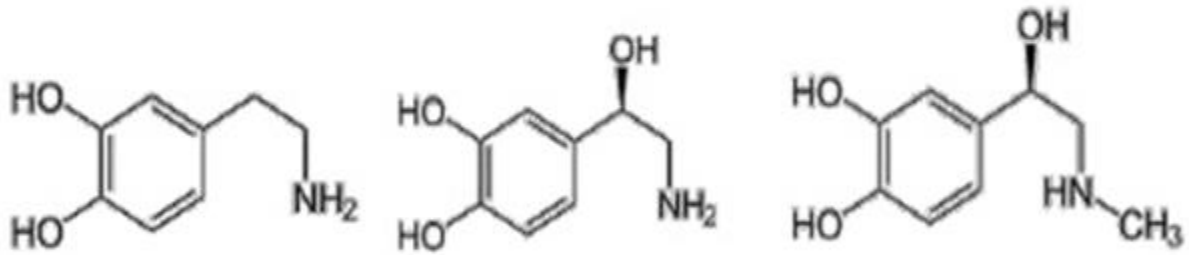
CATECHOLAMINES

- Norepinephrine – alpha agonist property
- Epinephrine – mixed acting (alpha & beta agonist)
- Isoproterenol – selective beta agonist
- Dopamine – immediate precursor of NE



Dopamine Norepinephrine Epinephrine

All catecholamines had a short half life

(2) Norepinephrine (NEP)

NEP differs from EP in:

It acts mainly on α and β_1-receptors in the heart with **little effect** on (β2 and β3) receptors.

It causes vasoconstriction and increases the peripheral resistance and blood pressure at any dose.

It may elicit a reflex bradycardia in high doses.

It has weaker metabolic action than EP.

Therapeutic uses:

-It is used in **treatment of hypotension** as in **shock**. It is used by I.V. infusion, its action disappears after 1-2 minutes of stopping infusion, so it has a controllable effect.

Side effects:

Palpitation, increase in the BP, headache and anxiety.

(3) Dopamine

Pharmacological characters:

- It is precursor of epinephrine and NE.
- It acts as central neurotransmitter, and its deficiency causes Parkinsonism.
- It is metabolized by MAO and COMT.
- It is ineffective orally and given by I.V. infusion with very short duration of action.
- It has no action on CNS when injected, as it does not cross the BBB.

CVS action:

a) At low concentration:

It acts on dopamine receptors type I (D_1) which are presented in the renal, mesenteric and coronary vessels causing vasodilation. It is useful in conditions with impaired renal function as **cardiogenic shock and hypovolemic shock.**

b) At somewhat higher concentration:

It stimulates **β_1 receptors** of heart causing positive inotropic effect

c) At high concentrations:

It stimulates vascular **α_1-receptors** causing vasoconstriction of vessels including renal blood vessels with reduction in the renal blood supply.

Therapeutic uses:

1. Shock (hypovolemic, cardiogenic and septic).
2. Refractory congestive heart failure.
3. After myocardial infarction and after cardiac surgery.

(4) Isoproterenol (isoprenaline)

It is **non-selective β-adrenergic agonist** and acts on β_1 and β_2 receptors without action on α-receptors.

It causes increase in heart rate and decrease in the blood pressure

Therapeutic uses:

It is used as in emergency to increase the heart rate in patients with **bradycardia and heart block.**

Now it is not used in bronchial asthma as the selective β_2-agonists is the best group.

II- Selective β_2-adrenergic agonists

Mechanism of action:

These drugs have relative specificity for β_2-receptors, thus **relax smooth muscle of bronchus, uterus and blood vessels**, with **little effect on the heart** but this selectivity is lost with large doses.

Advantages:

- Less stimulant effect on the heart which contain β_1-receptors.
- They have good oral bioavailability (they are not catechols and so not substrate for COMT).
- They have longer duration of action compared to catecholamines.
- They are given in small doses by inhalation in aerosol form, so they activate β_2 in the bronchi with very low systemic drug concentration (so they cause less activation of β_2 in skeletal muscles with less tremors)

Classifications:

1) Drugs used in asthma:

a) Short acting (duration 3-6 h.).

1. ***- Salbutamol (albuterol).***
2. ***- Terbutaline***
3. ***- Metaproterenol***

They are used **orally or by inhalation** in **acute asthma**, and by **injection in status asthmaticus**.

b) Long acting (duration 12 h.)

Salmeterol is used by inhalation, has slow onset, so used in chronic cases as maintenance treatment of asthma or for prophylaxis and it is ***not suitable in acute asthma***.

Formoterol **as salmeterol** but it has rapid onset.

2) Drugs used in gynecology:

Ritodrine has selective action on uterus, It is used as a tocolytic agent (relax the uterus in pregnant females). It can be used to delay or prevent premature delivery.

Side effects of beta agonists:

1-Tremors (due to stimulation od beta 2 receptors in skeletal muscle), it is the most common side effect. Inhalation route decreases this side effect.

2-Tolerance (receptor down regulation, with chronic use).

3-Tachycardia (due to stimulation of beta 1 receptors in high doses).

4- Hyperglycemia: due to increased glucose production from the liver.

5- Hypokalemia.

- The regular use of these drugs for long time may cause **bronchial hyper-reactivity** with failure to control bronchial asthma (it can be avoided through using inhaled corticosteroids with them).

III- Selective α_1-adrenergic agonists

1) Methoxamine:

It acts directly on **α_1-receptors** causing **vasoconstriction** with marked increase in the B.P that may be associated with reflex bradycardia due to vagal stimulation.

It is used I.V. in treatment of hypotension.

2) Phenylephrine:

It is a selective α_1-agonist that increases the BP with reflex bradycardia. Higher doses can activate β-receptors.

It is used **orally** and has longer duration of action. It can be used topically.

Uses:

Treatment of **hypotension** as during spinal anesthesia.

It is used as **nasal decongestant.**

It is used as **eye decongestant**.

It is used as **mydriatic in the eye.**

3- Midodrine (selective alpha 1 agonist) is used orally for treatment of hypotension.

4-Oxymetazoline and Xylometazoline (selective alpha 1 agonists) are used **topically** as **decongestants**.

5- **Mephentermine and metaraminol.**

NB all oral anti-cold medications containing any sympathomimetics like alpha agonists should be avoided or given with cautions for patients suffering from hypertension

IV- Selective α_2-adrenergic agonists

(1) Clonidine

Mechanism of action:

It acts by direct stimulation of ***Presynaptic α_2-receptors:*** present in the cardiovascular control centers in the medulla and their stimulation suppress sympathetic outflow from the brain to the periphery causing vasodilation and decrease in the BP.

Clonidine may bind to central ***imidazoline*** receptors also to produce effects.

- It is Used to suppress narcotic and alcohol withdrawal manifestations and help in cessation of smoking.
- It is used to decrease the doses of general anesthesia and analgesia
- It is used by transdermal route to decrease the incidence of menopausal hot flashes.
- It is rarely used now for treatment of severe hypertension.
- Could be useful in prophylaxis against migraine

Side effects:

1-Dry mouth (xerostomia) and sedation.

2-Sexual dysfunction and bradycardia.

3-Withdrawal reactions in the form of hypertensive crisis on sudden withdrawal due to receptor down regulation.

2) α-methyl dopa

Mechanism of action:

It is metabolized in the neurons to α-methyl-dopamine then α -methyl NE which is a potent stimulator to the presynaptic α_2-receptors in the CNS, so it decreases the sympathetic outflow.

It is preferable in treatment of ***hypertension during pregnancy*** (pre-eclampsia) due to its effectiveness and previously known safety to the mother and the fetus.

Side Effects of alpha methyldopa:

1-Sedation, *decreased in mental acuity, headache* and psychic depression (due to decreased monoamines in CNS).
2- Iatrogenic parkinsonism (due to decreased dopamine in basal ganglia)
3-Hyperprolactinemia (due to decreased dopamine).
4-Dry mouth and bradycardia.
5-Postural hypotension (more with diuretics).
6-Edema due to salt and water retention (pseudo tolerance).
7-Hypersensitivity effects: fever, hemolytic anemia, leucopenia, thrombocytopenia and **hepatitis**.

V- Indirect acting agonists

(1) Amphetamine

It causes **psycho-stimulation of CNS.**

1- treatment of Narcolepsy: (attacks of sleep occur suddenly under unsuitable conditions).

2- Treatment of Obesity as it has anorectic effect ***(suppress appetite)***

3- Treatment of Attention deficit hyperactivity disorder (ADHD).

It occurs in children with excessive motor activity and difficulty in attention. Now, methamphetamine and dextroamphetamine (derivatives of amphetamine) can be used.

- Amphetamine produces CNS stimulation, Euphoria, and **addiction** could occur.
- Acute toxicity of amphetamine may cause Death due to CNS stimulation and convulsions or hypertension.

-Treatment of acute amphetamine toxicity:

a) Acidification of urine by NH_4C1 (as amphetamine is a weak base) to increase excretion.

b) Symptomatic treatment: as the use of sedative, anticonvulsive or antihypertensive drugs.

(2) Cocaine

- Cocaine is a local anesthetic (block Na channels) and an indirect sympathomimetic (increase the release of NE and inhibits its neuronal reuptake)
- it causes potent CNS stimulation, euphoria, and addiction.
- It causes increased sympathetic activity (tachycardia, vasoconstriction, hypertension and mydriasis).
- Not used therapeutically due to high risk of addiction.

(3) Tricyclic antidepressants:

They inhibit its neuronal reuptake of NE (cocaine-like effects). Tramadol has similar effect

(4) Ephedrine:

It acts indirect by releasing NE and directly on α and β-receptors (dual mechanism) but the primary action is the indirect one.

It causes CNS stimulation, euphoria, and addiction

it is used in treatment of hypotension due to spinal anesthesia (as treatment or prophylactic).

Ephedrine is a potent nasal decongestant in common cold. Now, **pseudoephedrine** is used in treatment of common cold instead of ephedrine to avoid addiction).


Thank
you!!