بسم الله الرحمن الرحيم

Drugs modifying noradrenergic transmission (part 1)

By
Dr. Mohammad Salem Hareedy

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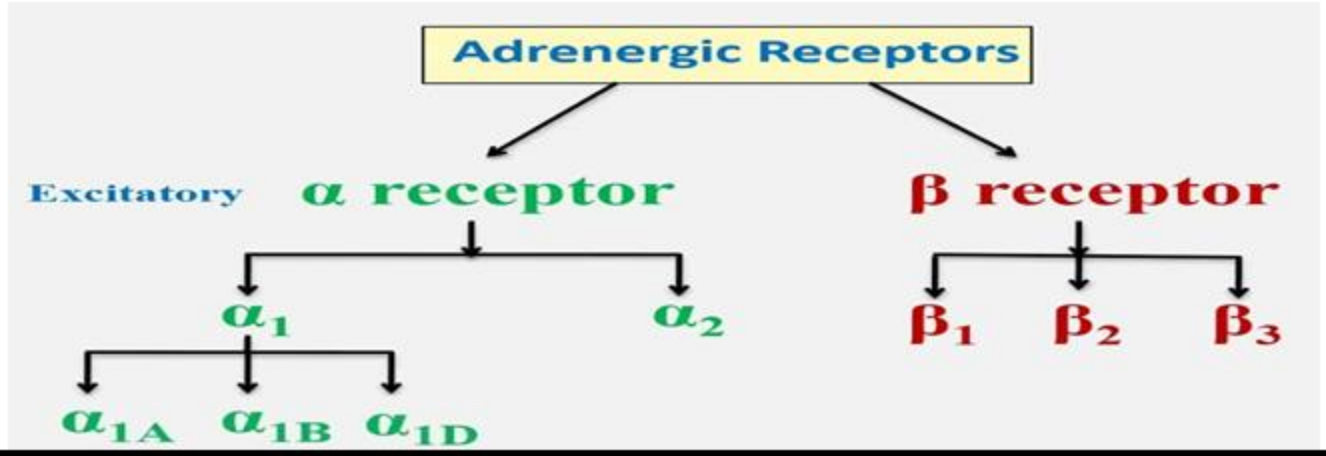
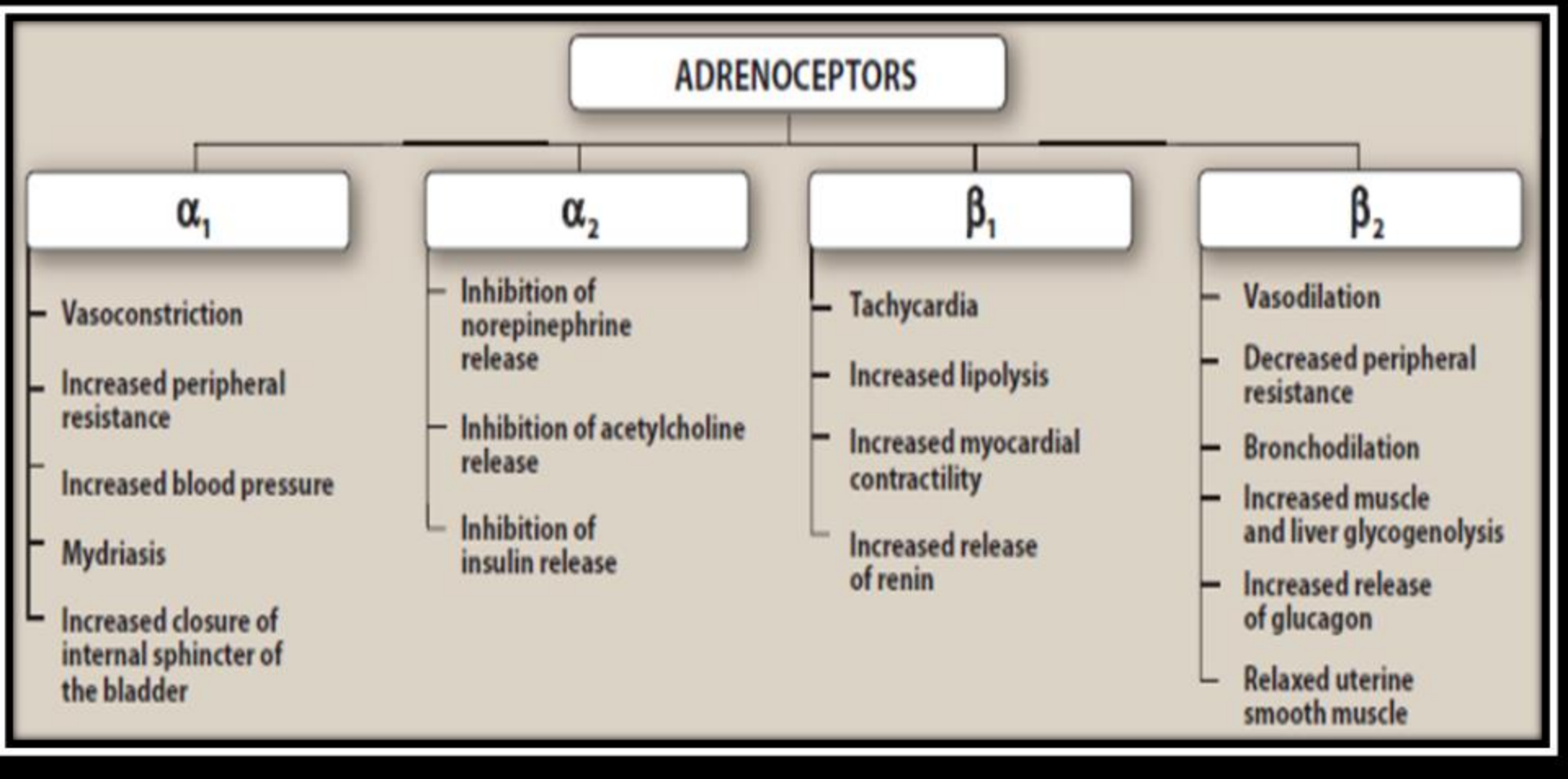

Adrenergic Receptors
Excitatory
α receptor
β receptor
α1
α2
β1
β2
β3
α1A
α1B
α1D


ADRENOCEPTORS
α1
Vasoconstriction
Increased peripheral resistance
Increased blood pressure
Mydriasis
Increased closure of internal sphincter of the bladder
α2
Inhibition of norepinephrine release
Inhibition of acetylcholine release
Inhibition of insulin release
β1
Tachycardia
Increased lipolysis
Increased myocardial contractility
Increased release of renin
β2
Vasodilation
Decreased peripheral resistance
Bronchodilation
Increased muscle and liver glycogenolysis
Increased release of glucagon
Relaxed uterine smooth muscle

β $_3$-adrenergic receptors

Adipose tissues increasing lipolysis due to activation of triglyceride lipase.

Detrusor muscle of the bladder (relaxation) and used to prevent urinary urgency. There receptors are selectively stimulated by mirabegron and used for treating overactive bladder.

Peripheral dopamine receptors

Dopamine at small conc., selectively activate these receptors.
The stimulation of these receptors cause relaxation of renal blood vessels → increase renal blood flow.

Fenoldopam is a selective D1 agonist at blood vessels and used for treatment of hypertension.

Sympathomimetics (adrenergic agonists)

Classifications of sympathomimetics

1) Catecholamines

a) Natural (endogenous)

b) Synthetic (non endogenous)

2) Non-catecholamines

a) Selective $Beta_2$-agonists

b) Selective α1-agonists

c) Selective α2-agonists

d) Indirect acting sympathomimetics (releasers and uptake inhibitors)

e) Mixed Direct & indirect action.

Catecholamines

- They are called catecholamines as they contain catechol ring.
- All catecholamines are ineffective orally due to metabolism in GIT by MAO-A enzyme and in the liver by COMT enzyme.

Types of catecholamines

Endogenous (naturally synthesized in neurons):

1. Epinephrine (Adrenaline): activates all types of adrenoceptors
2. Norepinephrine (noradrenalin)
3. Dopamine.

Non-endogenous (**synthetic**): all are only β-agonists

1. Non-selective β -agonist e.g., isoproterenol.
2. Selective β_1-agonist e.g., dobutamine.

Pharmacological actions of epinephrine

I-Cardiovascular effects

1- Heart (β1)

EP stimulates the contractility of the heart and ↑ heart rate (tachycardia) and ↑ conductivity, In high doses arrythmia occurs.

2- Blood vessels (BV) and blood pressure (BP)

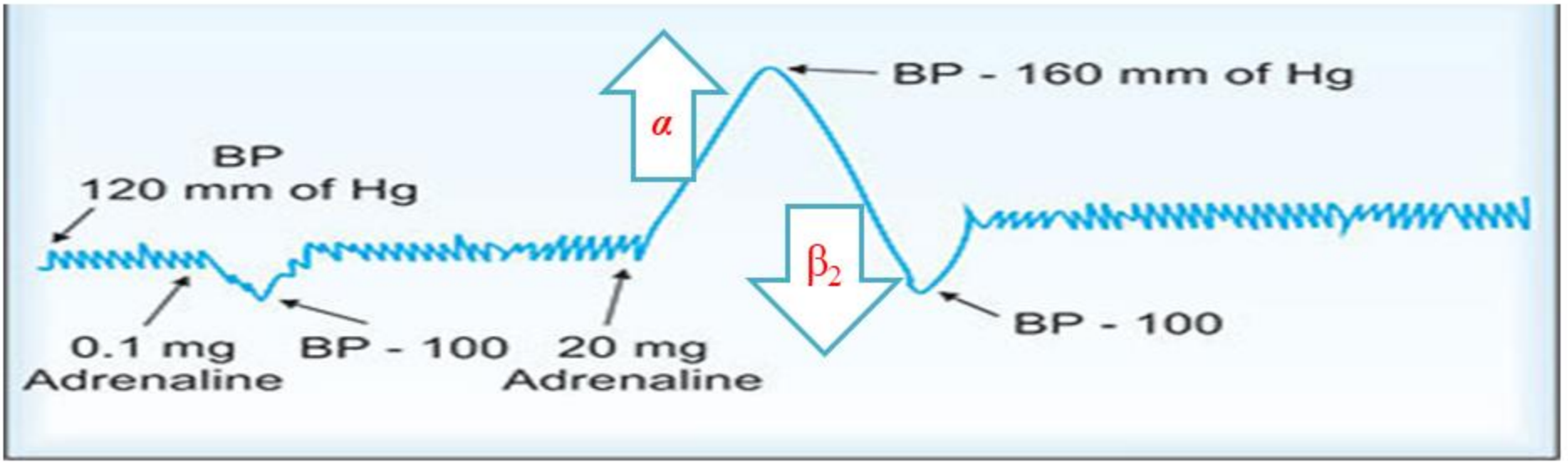
The blood vessels contain 2 types of receptors α and β.

Both α_1 & α_2 stimulation → vasoconstriction (in most BV) and ↑ BP.

Stimulation of **β2-receptors** → **vasodilatation** (in BV of skeletal muscles) and ↓ **BP.**

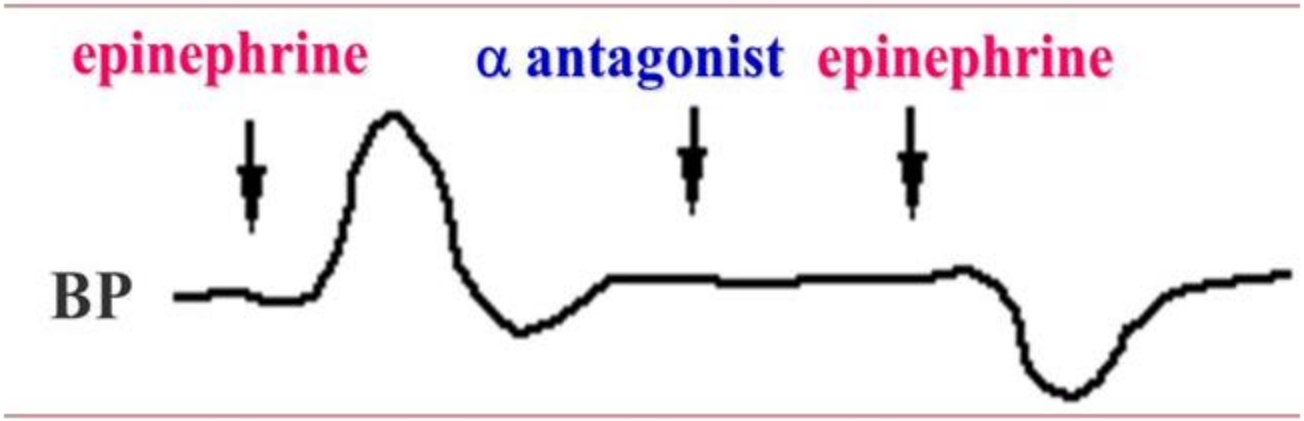
The **affinity** of epinephrine is **higher** for **β_2-receptors** than α-receptors. So, the actions of epinephrine on **β_2** receptors are more persistent. However, the **α-receptors are more abundant** than the β_2-receptors.

- **Small dose of EP** activates β_2-receptors only as the sensitivity of EP is higher to **β2-receptors** causing **vasodilation** and ↓ **BP** before returning to normal BP.
- **Large dose of EP** acts on β_2 and ***α*-receptors** but as the number of α-receptors is more than the number of β_2-receptors, so, the large dose of EP causes **vasoconstriction** & ↑ BP due to the α-actions. At the end, when the concentration of EP is decreased in the blood, EP persist to act on β_2-receptors only causing a final decrease in the BP before returning to normal BP **(biphasic effect on the BP).**



Epinephrine reversal:

Large dose of EP after the administration of α-blockers like prazosin acts only on β2-receptors causing vasodilatation and decreases in BP.



Epinephrine reversal

(*adrenaline reversal*)

II-Effects of EP on Smooth muscles

1-GIT (α1 and β 2):

EP causes **relaxation** of the smooth muscles of the GIT.

2- Bronchial muscles:

- EP causes **bronchodilation** (β_2 action).
- **EP** ↓ release of inflammatory mediators from mast cell (β_2 action).
- **EP** causes **vasoconstriction of pulmonary vessels** (α-action), so it decreases the pulmonary congestion, and bronchial secretion.

3- Urinary muscles:

EP causes **relaxation** of the detrusor muscle (β_2, β_3-actions) with **contraction of the sphincter**, **prostate** and trigone (α_1-action) that may cause **retention of urine.**

4- Pupillary dilator muscle of the eye:

EP causes contraction of the pupillary dilator muscle (α_1-action) causing **active mydriasis**.

It ↓ **the intraocular pressure (I.O.P)** due to vasoconstriction of blood vessels (α-action) with reduction in aqueous humor formation. It is useful in patients with glaucoma (high IOP).

5- Pilomotor smooth muscles:

EP causes contraction (α_1-action) leading to **erection of hairs** (goose flesh). EP causes also increase in the sweating with pallor of skin.

6- Uterus:

EP causes **relaxation of the pregnant uterus** near term (β_2-action) but it causes contraction of non-pregnant uterus (α_1-action).

III- Metabolic effects of EP

1-Hyperglycemia due to:

- ↑ glycogenolysis and gluconeogenesis (mainly β_2 action) in liver.
- ↓ in insulin secretion (α_2-action).
- ↑ in the release of glucagon (β2-action).

2-High blood lactate due to ↑ glycogenolysis in the skeletal muscles.

3-Hyperlipidemia and ↑ free fatty acids due to ↑ in lipolysis (β_3 action)

Clinical note: The increased incidence of atherosclerosis and coronary artery disease that are associated with chronic stress may be partially due to the metabolic consequences of chronic sympathetic stimulation.

IV-Other effects

- It **increases** the blood coagulation by increasing the activity of factor V. Epinephrine also increases platelet aggregation.

- **Potent Anti-allergic effect** as Epinephrine is the physiological antagonist of histamine (which induces bronchoconstriction and vasodilation). Epinephrine produces bronchodilation, vasoconstriction and inhibit release of allergic inflammatory mediators from mast cells.

- Epinephrine **stimulates rennin release** from the kidney (beta 1 effect) leading to salt and water retention and vasoconstriction. This will lead to increased blood pressure.

- EP can't cross the Blood Brain Barrier significantly , so central effects are very limited.

Pharmacokinetics of epinephrine

1- Absorption & routes of administration:

- It is not taken orally due to extensive first pass metabolism
- There is slow absorption after S.C. use due to its vasoconstrictor effect and absorption can be enhanced by local hot fomentation and massage.
- There is rapid absorption after I.M. use.
- It can be taken by inhalation (in asthma).
- It is used intracardiac in cardiac arrest.
- It is rarely used I.V. due to its cardiovascular effects (tachycardia).

2- Metabolism: mainly in liver and the kidney by MAO and COMT to yield metabolites like dihydroxy mandelic acid & metanephrine.

3- Excretion: mainly in urine as metabolites, only 1% is excreted unchanged.

Therapeutic uses of Epinephrine

Vascular uses:

1-Local hemostatic to control bleeding in epistaxis and bleeding after tooth extraction or via endoscopy to stop GIT bleeding.

2-With local anesthetic: as it causes **vasoconstriction** that decreases systemic absorption of local anesthetic, increases the duration of anesthesia & decreases bleeding causing bloodless field of operation.

Cardiac uses:

3-Sudden cardiac arrest due to anesthesia or hypersensitive carotid sinus, as **EP intra-cardiac** can be used.

4-Complete heart block (Stokes Adams syndrome), but Isoproterenol is better.

Allergic uses:

5-Acute anaphylactic shock: S.C. EP is the ***drug of choice***.

It treats hypotension, bronchospasm and laryngeal edema (cortisol and antihistamine may be added). Also, EP can be used in other allergic conditions (angioedema, urticaria, etc....).

Ep. can ↓ release of allergic mediators from mast cells.

6-Acute bronchial asthma: EP is used S.C. or by inhalation as it causes bronchodilation (β_2-action) and ↓ pulmonary congestion and edema (α-action).

Ocular uses:

7-**Dipivefrin,** a pro-drug to EP, is used topically (eye drops) for treating **open angle glaucoma.**

Side effects of Epinephrine.

1) CVS stimulation: tachycardia, palpitation and hypertension.

- High doses may cause arrhythmia, angina pectoris.
- Cerebral hemorrhage and worsening of cardiac failure are dangerous adverse effects.

2) Nervousness, tremors and headache.

3) Hyperglycemia and lactic acidosis.

N.B. These adverse effects occur with most of sympathomimetic drugs

Contraindications and precautions:

1-Hypertension (to avoid cerebral hemorrhage)

2-Angina pectoris (EP may cause myocardial infarction).

3-Congestive heart failure (EP ↑ the cardiac work)

4-Hyperthyroidism (as the risk of cardiac arrhythmia is increased).

5-Diabetes mellitus (as EP causes hyperglycemia).

6-During anesthesia with halothane (arrhythmia)

7-Patients who use non-selective β-blockers as propranolol (as EP will act only on α-receptors causing marked increase in the BP that may cause cerebral hemorrhage).