بسم الله الرحمن الرحيم

Drugs modifying noradrenergic transmission (part 1)

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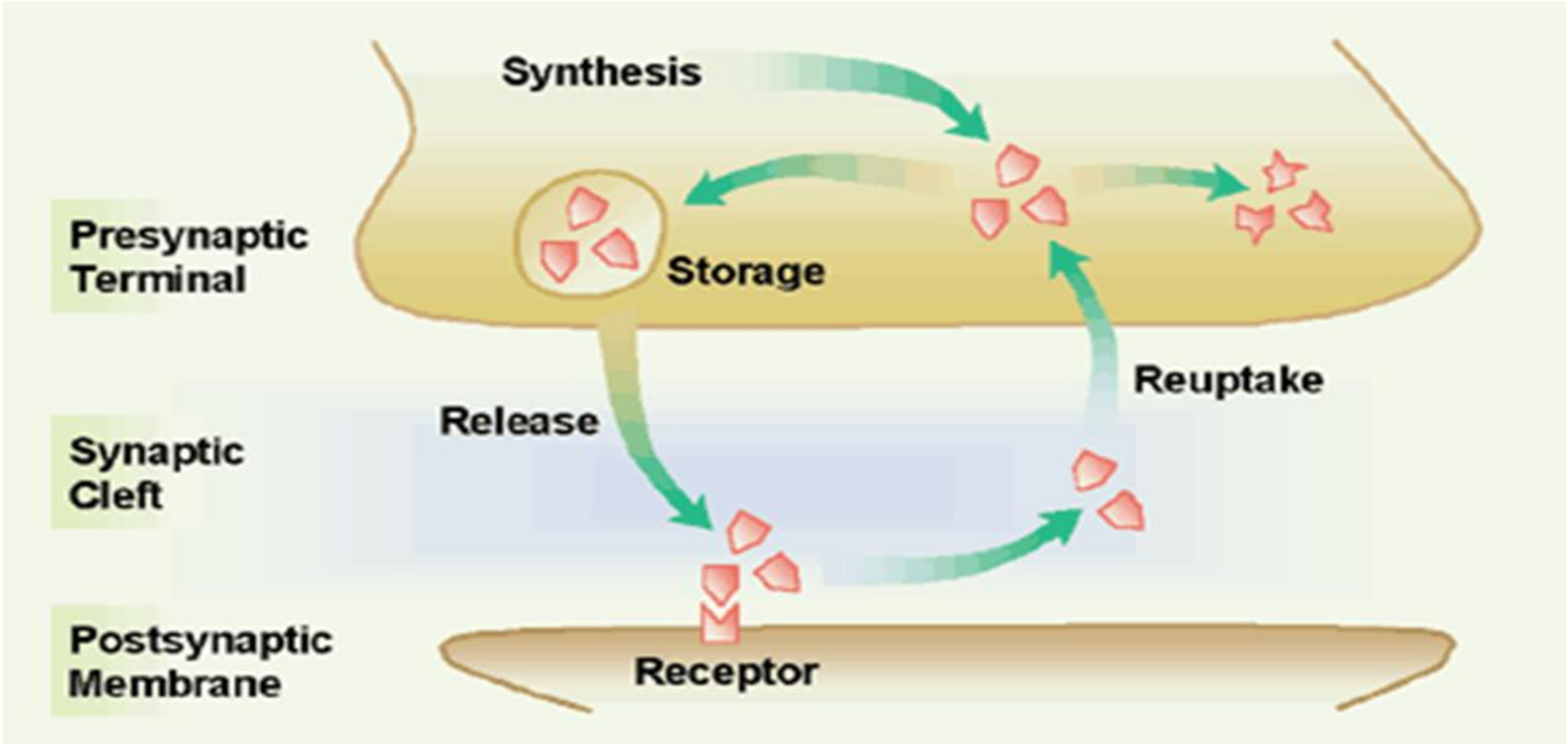
Noradrenergic transmission



SYNTHESIS AND RELEASE OF NOREPINEPHRINE FROM THE ADRENERGIC NEURON

1. SYNTHESIS OF NOREPINEPHRINE
- Hydroxylation of tyrosine is the rate-limiting step

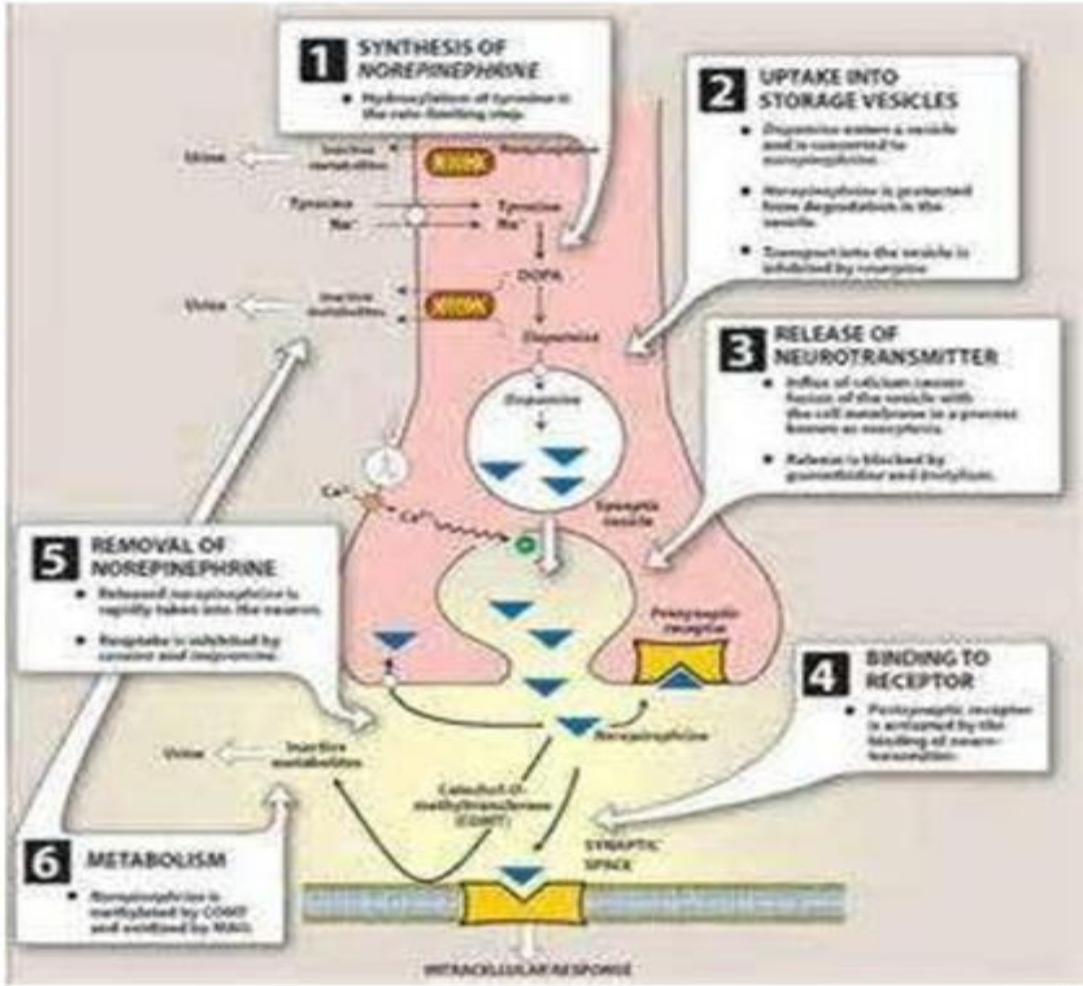
2. UPTAKE INTO STORAGE VESICLES
- Dopamine enters vesicle & is converted to norepinephrine
- Norepinephrine is protected from degradation in vesicle
- Transport into vesicle is inhibited by reserpine

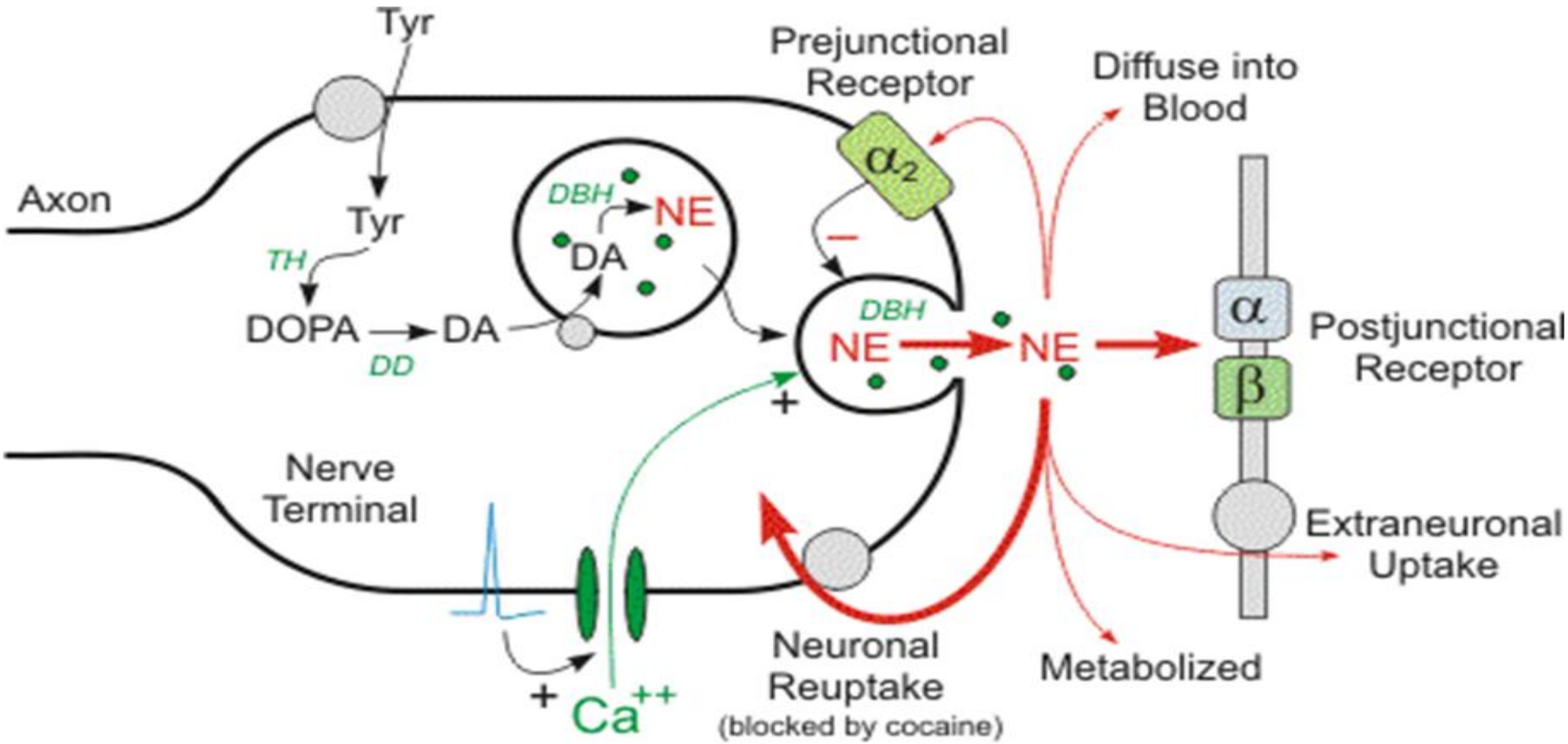
3. RELEASE OF NEUROTRANSMITTER
- Influx of calcium causes fusion of vesicle w/ cell membrane
- Release blocked by guanethidine & bretylium

4. BINDING TO RECEPTOR
- Postsynaptic receptor activated by binding of neurotransmitter

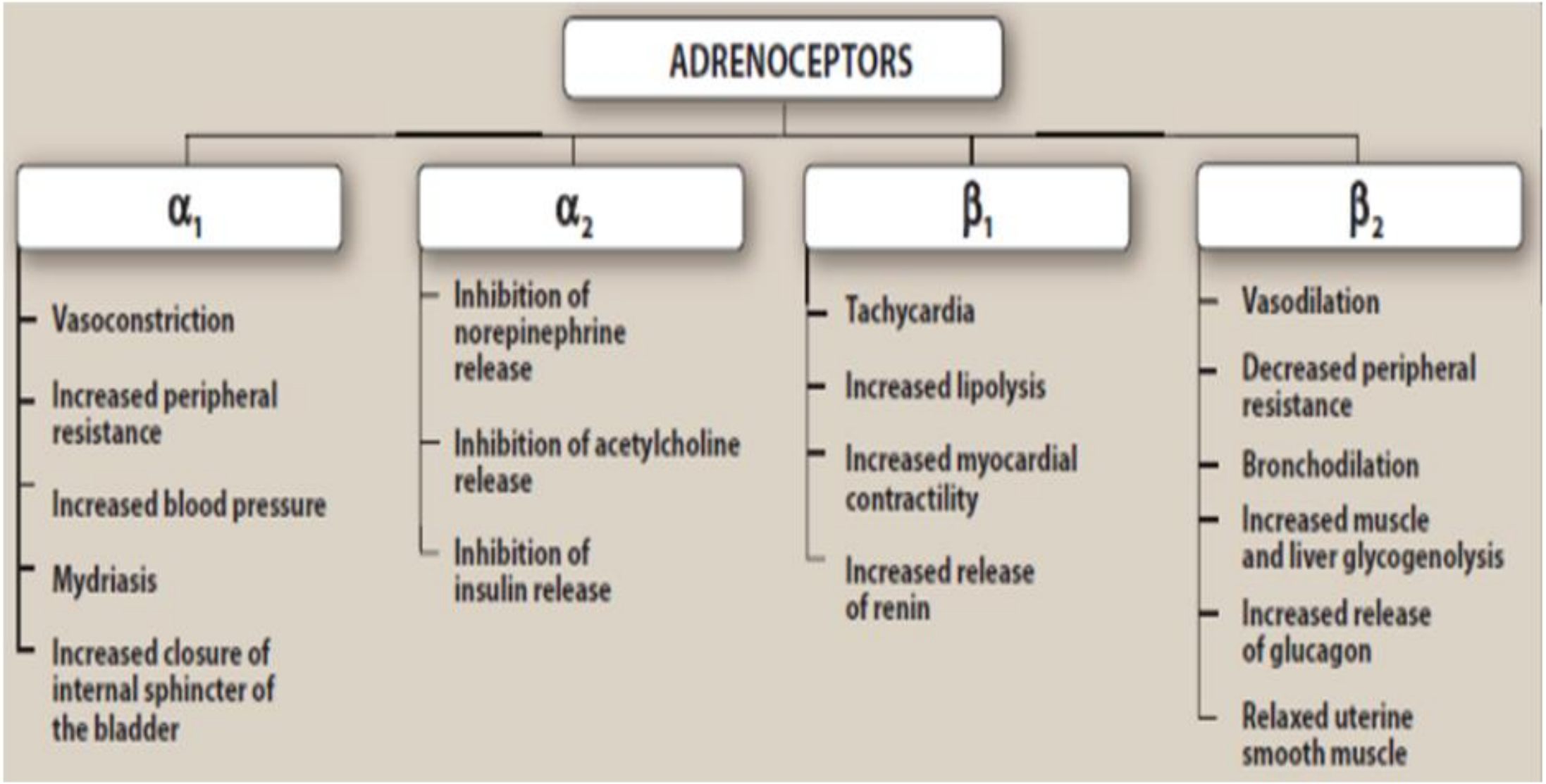
5. REMOVAL OF NOREPINEPHRINE
- Released norepinephrine is rapidly taken into neuron
- Uptake is inhibited by cocaine & imipramine

6. METABOLISM
- Norepinephrine is methylated by COMT & oxidized by monoamine oxidase





Tyr = tyrosine; TH = tyrosine hydroxylase; DD = DOPA decarboxylase;
DA = dopamine; DBH = dopamine β-hydroxylase; NE = norepinephrine


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 (D1)

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
According to chemical structure

(1) Catecholamines

a) Natural (endogenous) ***b) synthetic***

(2) Non-catecholamines

a) Selective B_2-agonists

b) Selective α1-agonists

i) Direct acting drugs

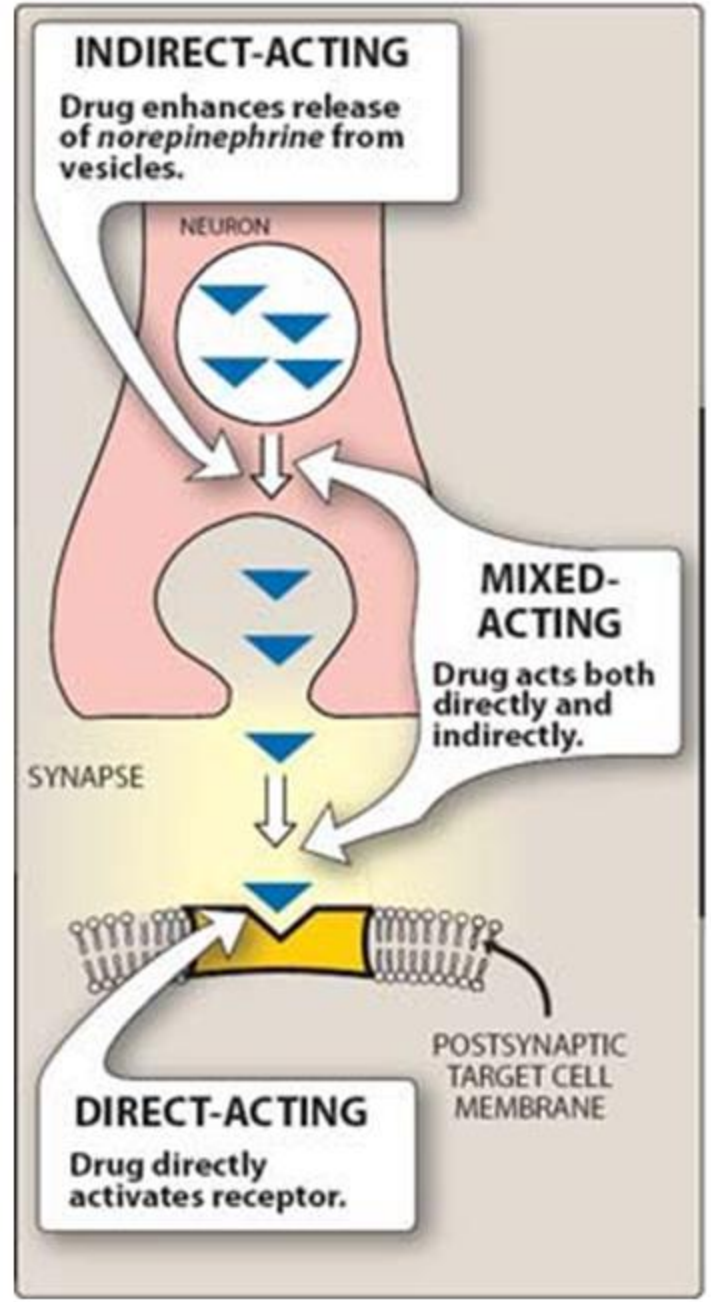
ii) Indirect acting drugs

c) Selective α2-agonists

d) Indirect acting sympathomimetics.

According to mechanism of action; sympathomimetics are classified into:

1. Direct acting
2. Indirect acting
3. Mixed acting



I- 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

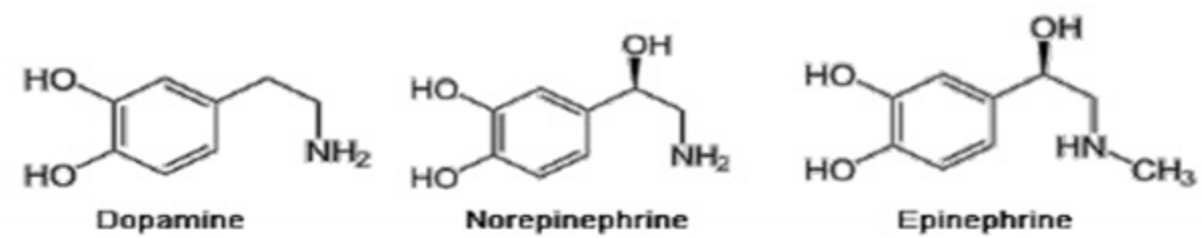
a) Endogenous: e.g., epinephrine, norepinephrine and dopamine.

b) Non-endogenous (β-agonists)

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

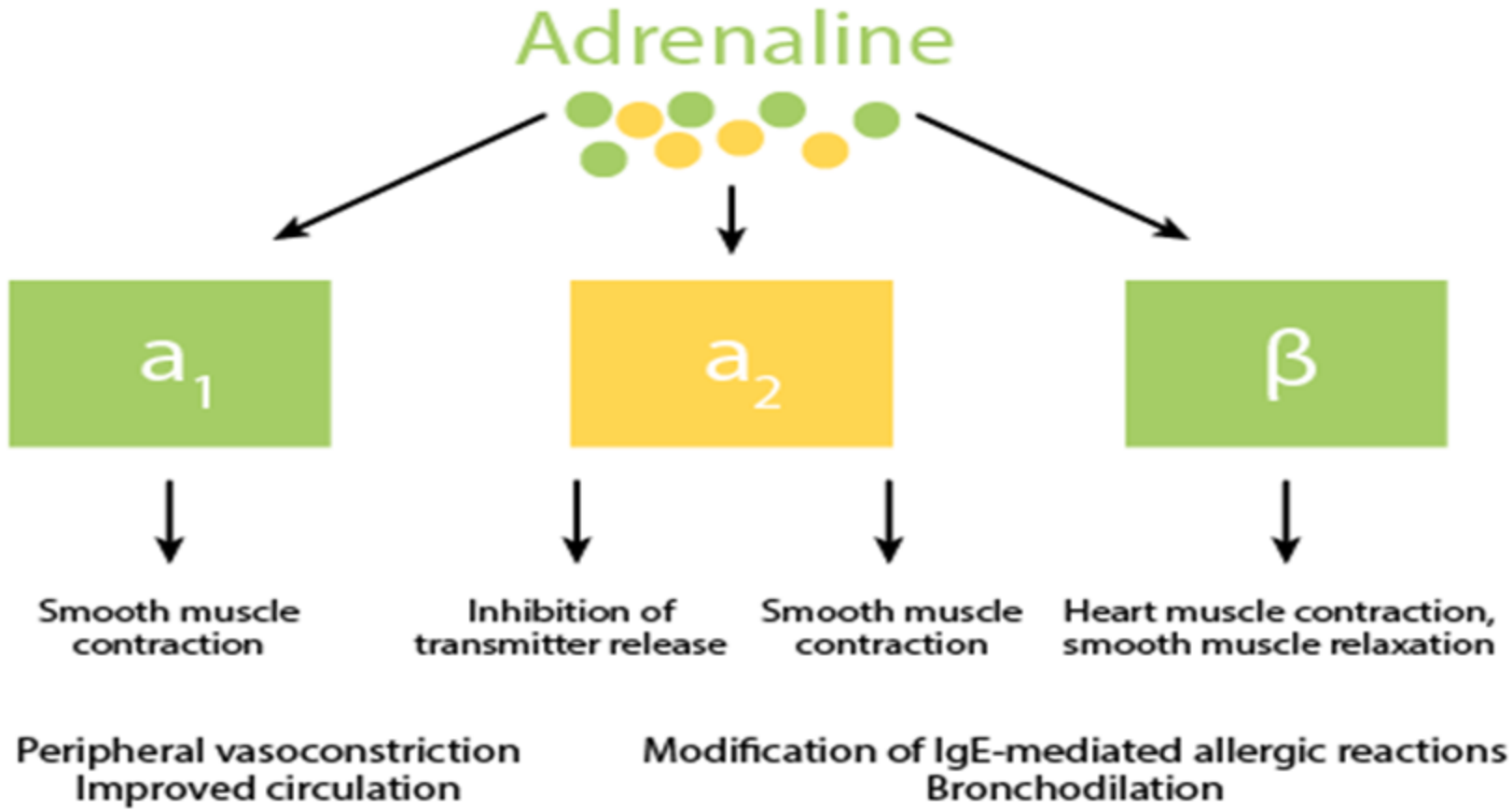
CATECHOLAMINES

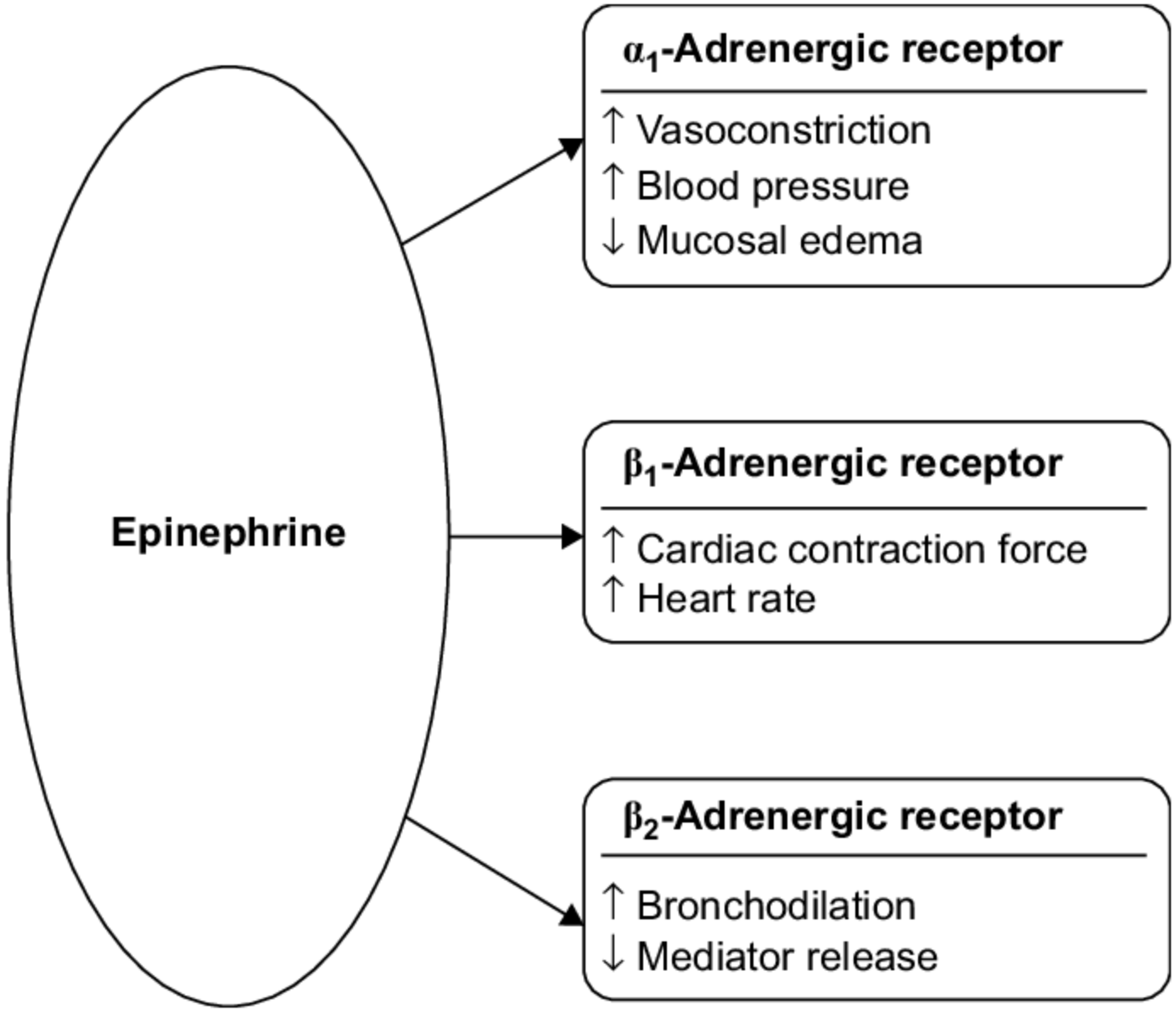
- Norepinephrine – alpha agonist property
- Epinephrine – mixed acting (alpha & beta agonist)
- Isoproterenol – selective beta agonist
- Dopamine – immediate precursor of NE



(1) Epinephrine (EP) or adrenaline

Mechanism of action: It is a direct adrenergic agonist "acts by direct stimulation of all types of adrenergic receptors (α, β and D)".




Epinephrine
α1-Adrenergic receptor
↑ Vasoconstriction
↑ Blood pressure
↓ Mucosal edema
β1-Adrenergic receptor
↑ Cardiac contraction force
↑ Heart rate
β2-Adrenergic receptor
↑ Bronchodilation
↓ Mediator release

Pharmacological actions of epinephrine

(1) Cardiovascular effects

a) Heart:

EP is a powerful cardiac stimulant (β_1-receptors). Ep. increases cardiac rate, cardiac output and oxygen consumption of the heart.

b) Systemic blood vessels and blood pressure:

The blood vessels contain 2 types of receptors α and β_2.

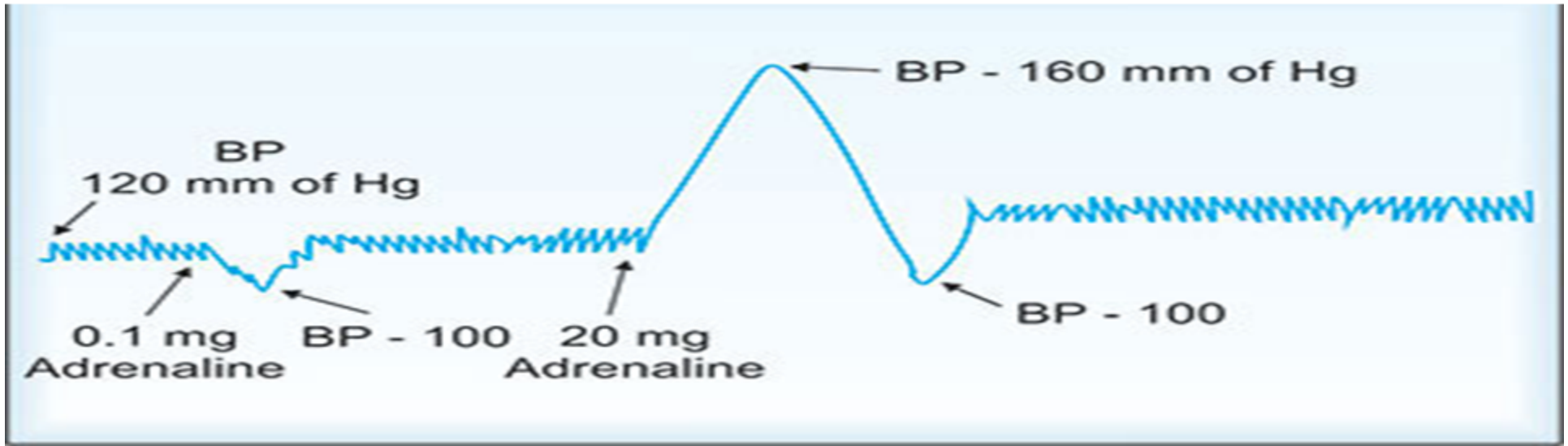
Both α_1 and **α_2** stimulation causes vasoconstriction and increases in the blood pressure.

The stimulation of β_2-receptors causes **vasodilatation** (blood vessels of skeletal muscles) **and decrease blood pressure.**

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 number of α-receptor is more than the number of β_2- receptors.

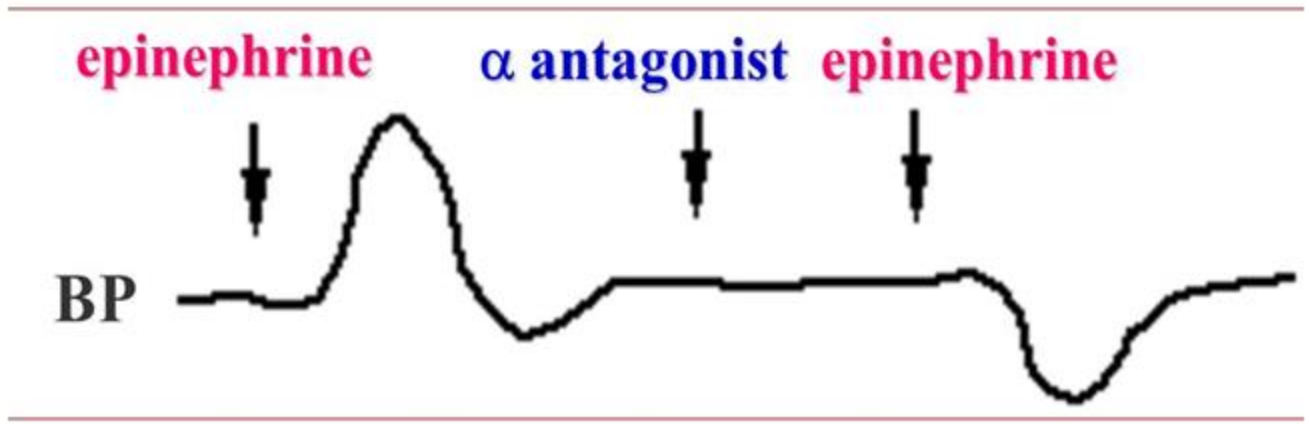
Small dose of EP acts on β_2-receptors only as the sensitivity of EP is higher to β_2-receptors causing **vasodilation** and **decrease in the blood pressure (BP)**.

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, the large dose of EP causes **vasoconstriction and increase in the** BP due to the α-action. At the end of the action where the concentration of EP is decreased in the blood, EP acts on β_2-receptors causing decrease in the BP at the end of the effect, so large dose of EP causes **biphasic effect on the BP.**



Epinephrine reversal:

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



Epinephrine reversal

(*adrenaline reversal*)

(2) Effects on Smooth muscles

a) GIT:

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

b) Bronchial muscles:

- EP causes **bronchodilation** (β_2 action) especially if there is constriction due to disease (asthma) or drug (histamine).
- It decreases the release of inflammatory mediators from mast cell (β_2 action).
- It causes **vasoconstriction of pulmonary vessels** (α-action), so it decreases the pulmonary congestion, edema and bronchial secretion.

c) 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.**

d) Pupillary dilator muscle of the eye:

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

It **decreases the I.O.P** due to vasoconstriction of blood vessels (α-action) with reduction in aqueous humor formation. It is useful in patients with wide (open) angle glaucoma.

e) 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.

f) Uterus:

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

(3) Metabolic effects

a) EP increases the blood glucose and causing **hyperglycemia** mainly due to:

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

b) **Increase in blood lactate** due to:

Increase in glycogenolysis in the skeletal muscles

c) **Increase in the free fatty acids** and causing hyperlipidemia due to action on β3-receptors in adipose tissue causing increase in lipolysis due to activation of triglyceride lipase enzyme.

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.

(4) CNS

EP is not significantly cross the BBB, so its central effect is very limited. It may cause mild stimulation if used I.V. as restlessness, excitement, headache and tremors (tremors may be secondary to its cardiovascular or metabolic effects).

(5) Other effects

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

- **Potent Anti-allergic effect** as it decreases the urticaria and angioneurotic edema.

- Epinephrine **stimulates rennin release** from the kidney (beta 1 effect) leading to salt and water retention and vasoconstriction.

Pharmacokinetics

1- Absorption and 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 to give dihydroxy mandelic acid (90 %) and by the COMT to give metanephrine (7 %).

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

Therapeutic uses of Epinephrine

Vascular uses:

1-Local hemostatic to control bleeding as packs soaked in 1 % EP is used to control epistaxis and bleeding after tooth extraction or via endoscopy to stop GIT bleeding.

2-With local anesthetics (especially for dental manipulations) as it causes vasoconstriction that decreases systemic absorption of local anesthetics, thereby increases the duration of anesthetic and decreases bleeding causing bloodless field of operation.

Cardiac uses:

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

4-Complete heart block (Stokes Adams syndrome), but isoproterenol is better as it causes less arrhythmias than EP.

Allergic uses:

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

It treats hypotension, bronchospasm and laryngeal edema induced by histamine. Also, EP can be used in other allergic conditions (angioedema, urticaria, etc....).

Ep. decreases the release of allergic mediators from mast cells.

Remember: Ep is the physiological antagonist of histamine

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

Ocular uses:

7-Locally in the eye in treatment of open angle glaucoma (***dipivefrin,*** which is a pro-drug to EP, is used in glaucoma).

Side effects of Epinephrine. (occurs with most of sympathomimetics)

1) CVS stimulation: tachycardia, palpitation and hypertension. High doses may cause arrhythmia, angina pectoris, cerebral hemorrhage and **worsening of cardiac failure**.

2) CNS: nervousness, tremors and headache.

3) GIT: nausea and vomiting may occur.

4) Hyperglycemia and lactic acidosis.

5) Pulmonary edema with toxic doses.

Contraindications and precautions:

1-Hypertension (to avoid cerebral hemorrhage)

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

3-Congestive heart failure (as EP increases the cardiac work and loads on the heart).

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

5-Diabetes mellitus (as EP causes hyperglycemia).

6-During anesthesia with halothane (as EP potentiates arrhythmia produced by halothane).

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).


Thank
you!!