بسم الله الرحمن الرحيم

Drugs modifying noradrenergic transmission (part 1): Catecholamines

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⇒ Adrenalin and noradrenalin act on them.

ADRENOCEPTORS :-

α_1

- Vasoconstriction ... smooth muscle
- Increased peripheral resistance
- Increased blood pressure
- Mydriasis
- Increased closure of internal sphincter of the bladder

α_2

- Inhibition of norepinephrine release
- Inhibition of acetylcholine release
- Inhibition of insulin release → ↑ blood glucose.

β_1

- Tachycardia
- Increased lipolysis
- Increased myocardial contractility
- Increased release of renin

β_2

- Vasodilation
- Decreased peripheral resistance
- Bronchodilation
- Increased muscle and liver glycogenolysis → ↑ B glucose
- Increased release of glucagon
- Relaxed uterine smooth muscle

β_3-adrenergic receptors ✓

- Adipose tissues increasing lipolysis due to activation of triglyceride lipase.
  → release of free fat acid
- Detrusor muscle of the bladder (relaxation). These β-3 receptors are selectively stimulated by mirabegron and used for treating overactive bladder
  ← مهم في الامتحانات .
  → selective to B3 relaxation of bladder
  → due to perment contracted bladder

1-what's the function of dopamin ?

2-what's the type of selective drug ?

Peripheral dopamine receptors

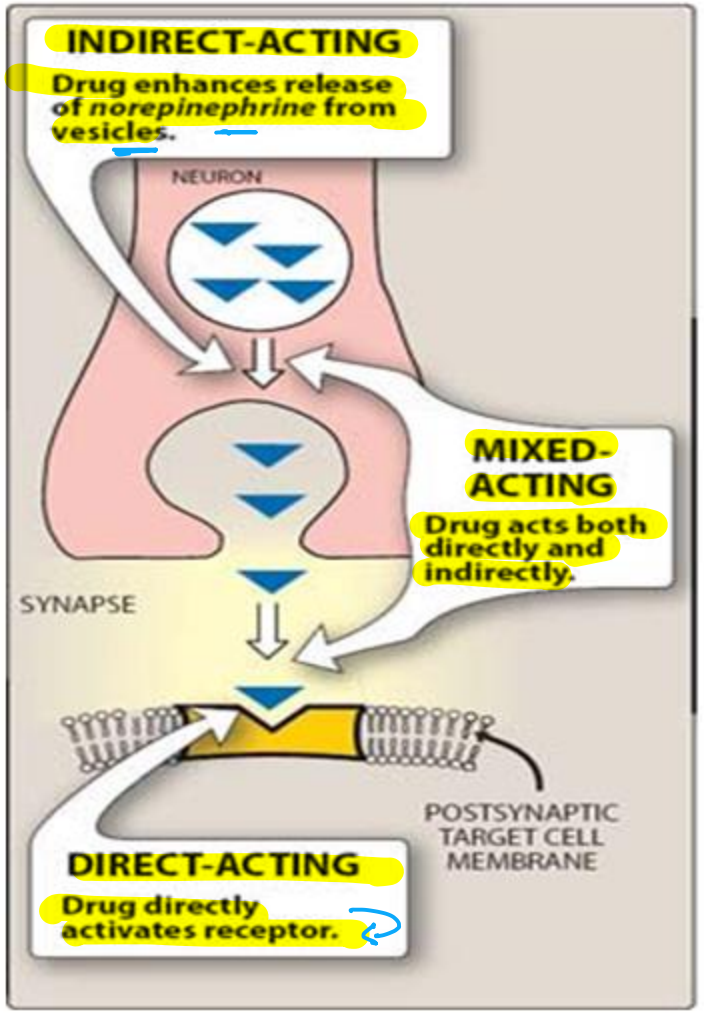
The stimulation of these receptors by Dopamine causes relaxation of renal blood vessels → increase renal blood flow.

Fenoldopam is a selective D1 agonist causing vasodilatation and can be used for treatment of hypertension. ✓

Sympathomimetics (adrenergic agonists)

According to mechanism of action; sympathomimetics are classified into:

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



1-what're the chemical classification?

benzin ring + 2 OH group + NH_2

Classifications of sympathomimetics According to chemical structure

(1) Catecholamines :-

a) **Endogenous (natural):** **Epinephrine**, **Norepinephrine** and dopamine.

a- b- c

b) **Non-endogenous or synthetic** (β-agonists)

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

مشكوك في أمينة

(2) Non-catecholamines :-

a) Selective β_2-agonists

b) Selective α1-agonists

c) Selective α2-agonists

d) Indirect acting sympathomimetics.

1- Describe the chemicle structure of it?

2- why the BioValability = zero ?

3- what's the result from changing chemical structure ?

I- Catecholamines

- They are called catecholamines as they contain catechol ring (aromatic nucleus " benzene" and 2 OH groups). + NH_2
- All catecholamines are ineffective orally due to metabolism in GIT by MAO-A enzyme and in the liver by COMT enzyme.

↳ degraded it and Bioavailability = zero

Structure-activity relationship of catecholamines and related compounds

تبديل

Substitution on the aromatic nucleus

↳ don't degraded by COMT, central activity ✓

↳ No Cat-echol nucleus ↳ controle the dynamics

Substitution on the α-carbon atom

MAO, uptake-1, NE release

Substitution on the amino group ↳ controle the kinetices. ↳ control the affinity of binding.

sensitivity to the subunits of receptors

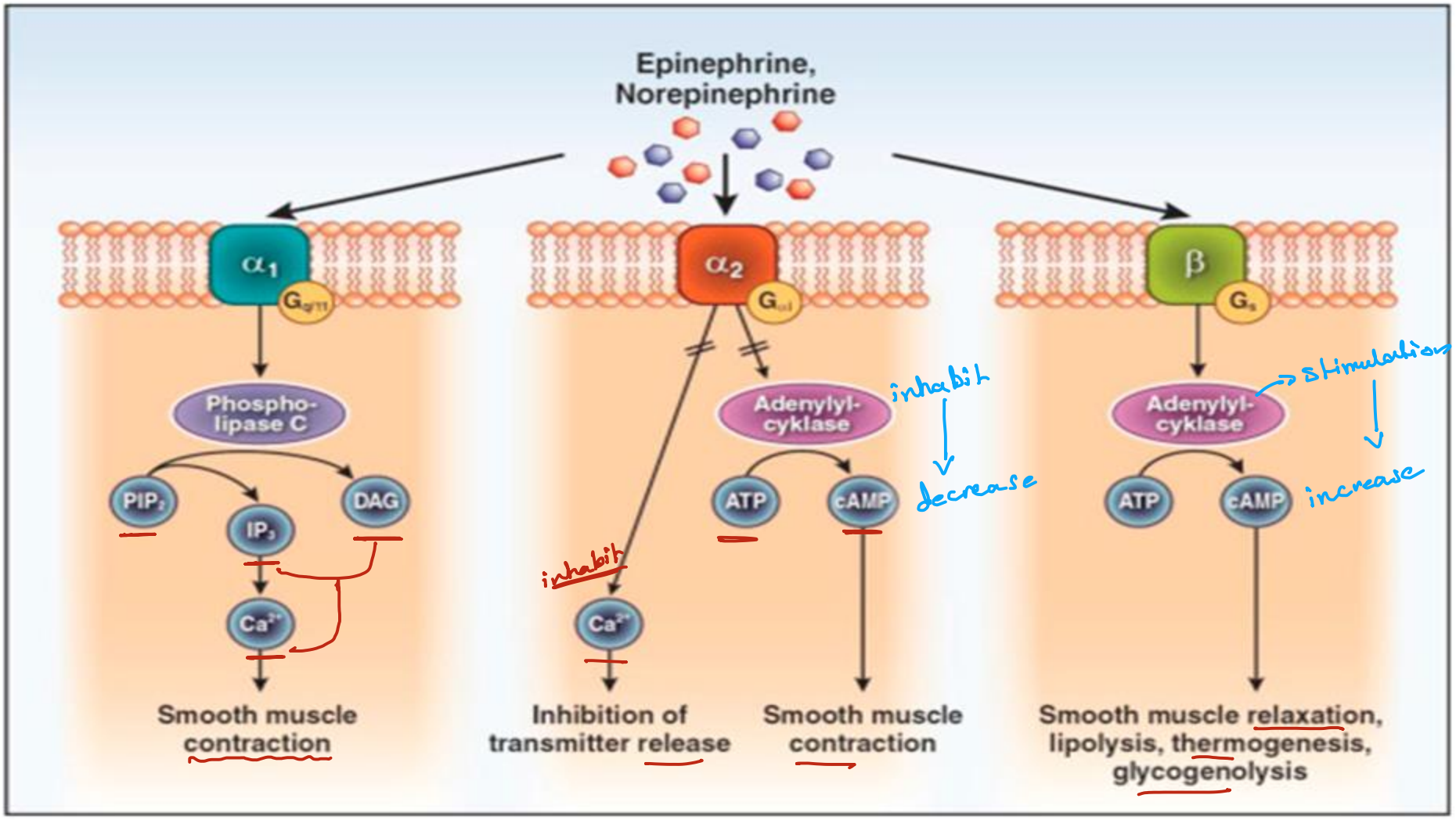
1- what's the machanism of action ?

endogenous

(1) Epinephrine (EP)= Adrenaline

Mechanism of action: acts by direct stimulation (Agonist) to all types of adrenergic receptors (mainly α, β)

+ dopamin.



1- what's the action of Ep in heart? what's the benefit of it?

Pharmacological actions of epinephrine

2- Describe the state of epinephrin in blood vessels?

(1) Cardiovascular effects

3- what's the result from small dose of Ep?
4- Describe the biphasic action?
5- Describe the Ep reversal?

a) Heart (β1)

EP is a powerful cardiac stimulant. **Tachycardia** occurs, the **cardiac contractility & output is increased**. ↑ O_2 intake ..... used in cardic arrest.

b) Systemic blood vessels and blood pressure:

The blood vessels contain 2 types of receptors **α and β_2**. → response by contraction → response by relaxation

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.

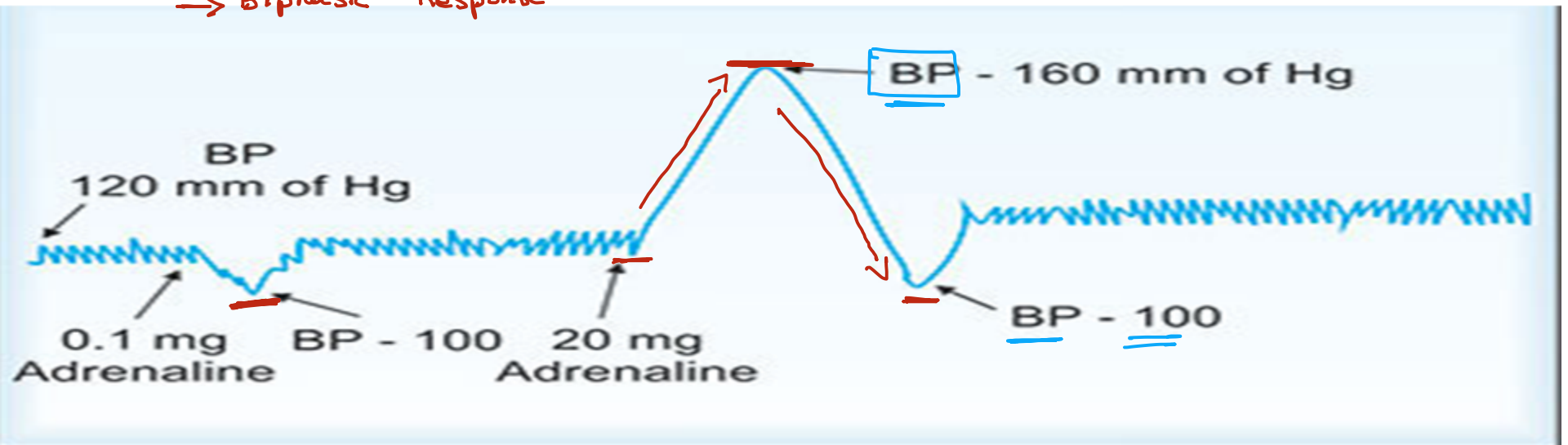
- **Both α_1** and **α_2** stimulation causes vasoconstriction and increases in the blood pressure.
- The stimulation of β_2-receptors causes **vasodilatation** (blood vessels of skeletal muscles) and **decrease blood pressure.**

Small dose of EP selectively activates β_2-receptors (higher affinity) 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 greater than β_2-receptors, the large dose of EP causes **vasoconstriction and increase in the** BP due to the α-action.

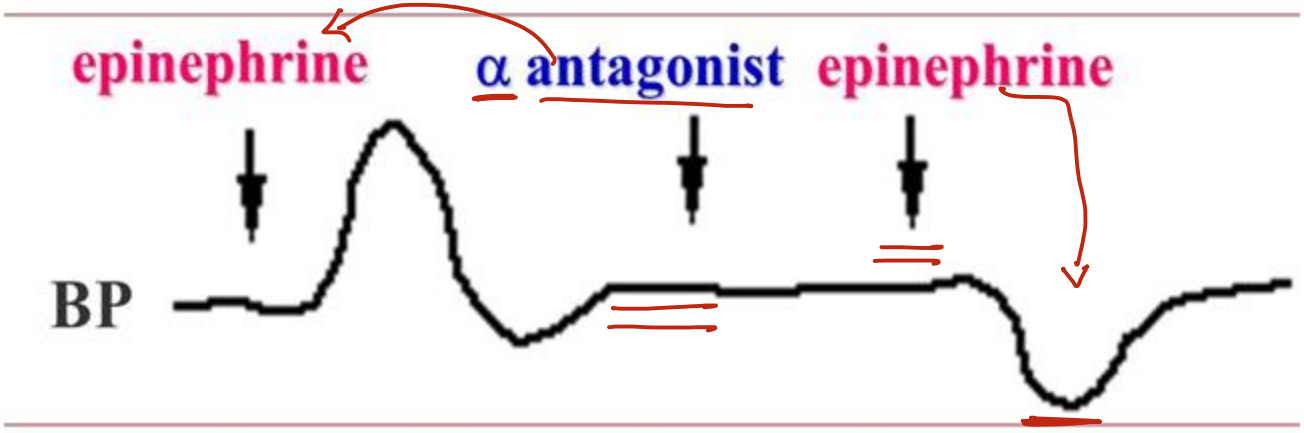
At the end of the action where the concentration of EP is decreased in the blood, EP acts on β_2-receptors causing decrease in the BP at the end of the effect, so large dose of EP causes **biphasic effect on the BP.**

→ Biphasic Response.



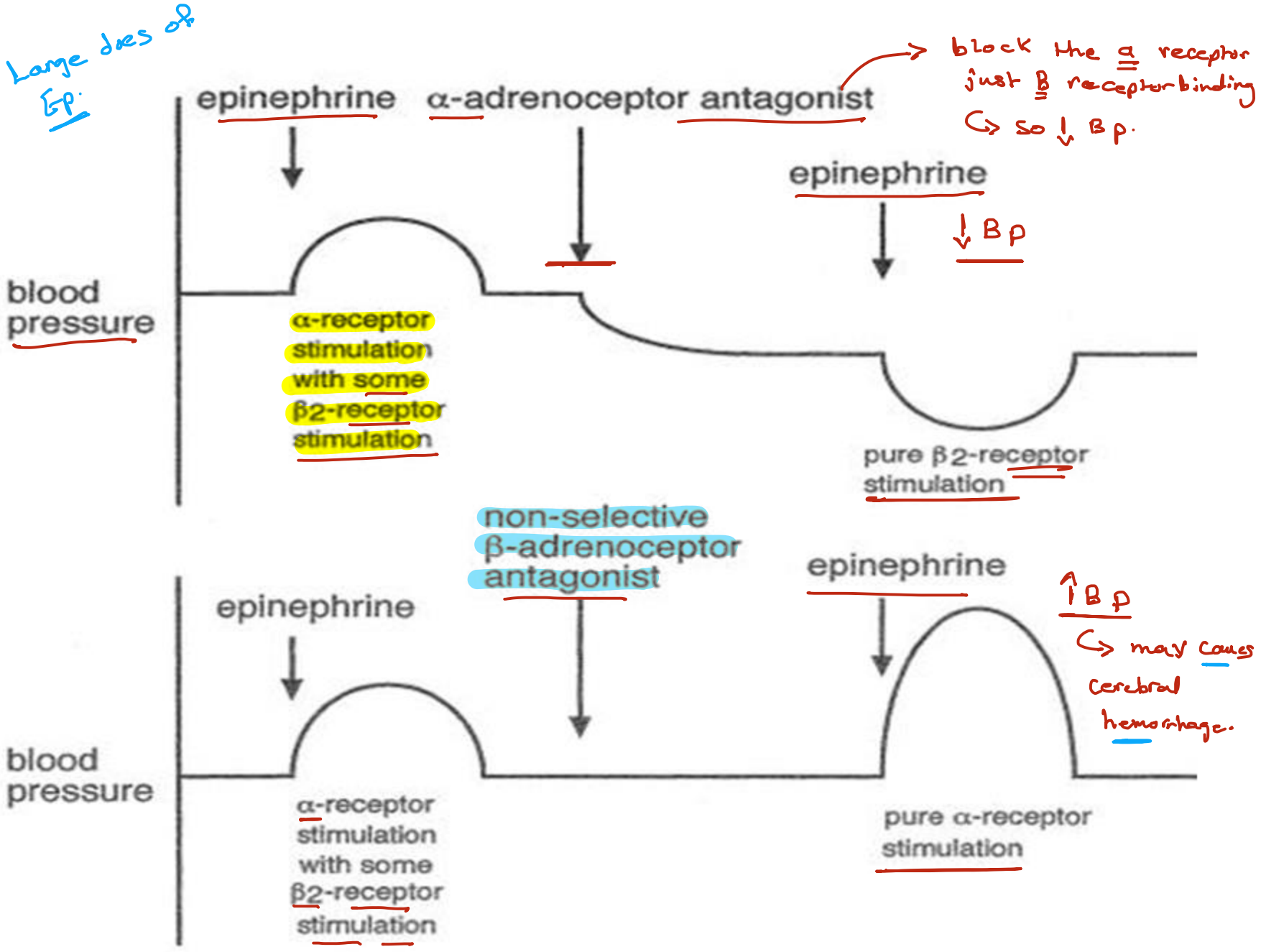
Epinephrine reversal:

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*)


Large dose of Ep.
epinephrine
α-adrenoceptor antagonist
block the α receptor just β receptor binding
so ↓ Bp.
epinephrine
↓ Bp
blood pressure
α-receptor stimulation with some β2-receptor stimulation
pure β2-receptor stimulation
non-selective β-adrenoceptor antagonist
epinephrine
epinephrine
↑ Bp
may causes cerebral hemorrhage.
blood pressure
α-receptor stimulation with some β2-receptor stimulation
pure α-receptor stimulation

1-what's the action of Ep in each :-

(2) Effects on Smooth muscles

a) GIT:

EP causes **relaxation** of the smooth muscles of the GIT. No Therapuic use.

b) Bronchial muscles:

- **bronchodilation** (β_2 action). → Treat sever asthema.
- **vasoconstriction of pulmonary blood vessels** (α-action), so it decreases the pulmonary congestion and bronchial secretion. → Decongested → Treat the state of dilation which cause rhinorrhea.
- ↓ the release of inflammatory mediators from mast cell (β_2 action).

c) Urinary muscles:

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

d) Eye

The radial (Pupillary **dilator**) muscle of the **iris** is Contracted (α_1-action) causing **active mydriasis**.

(+) deconjested effect

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

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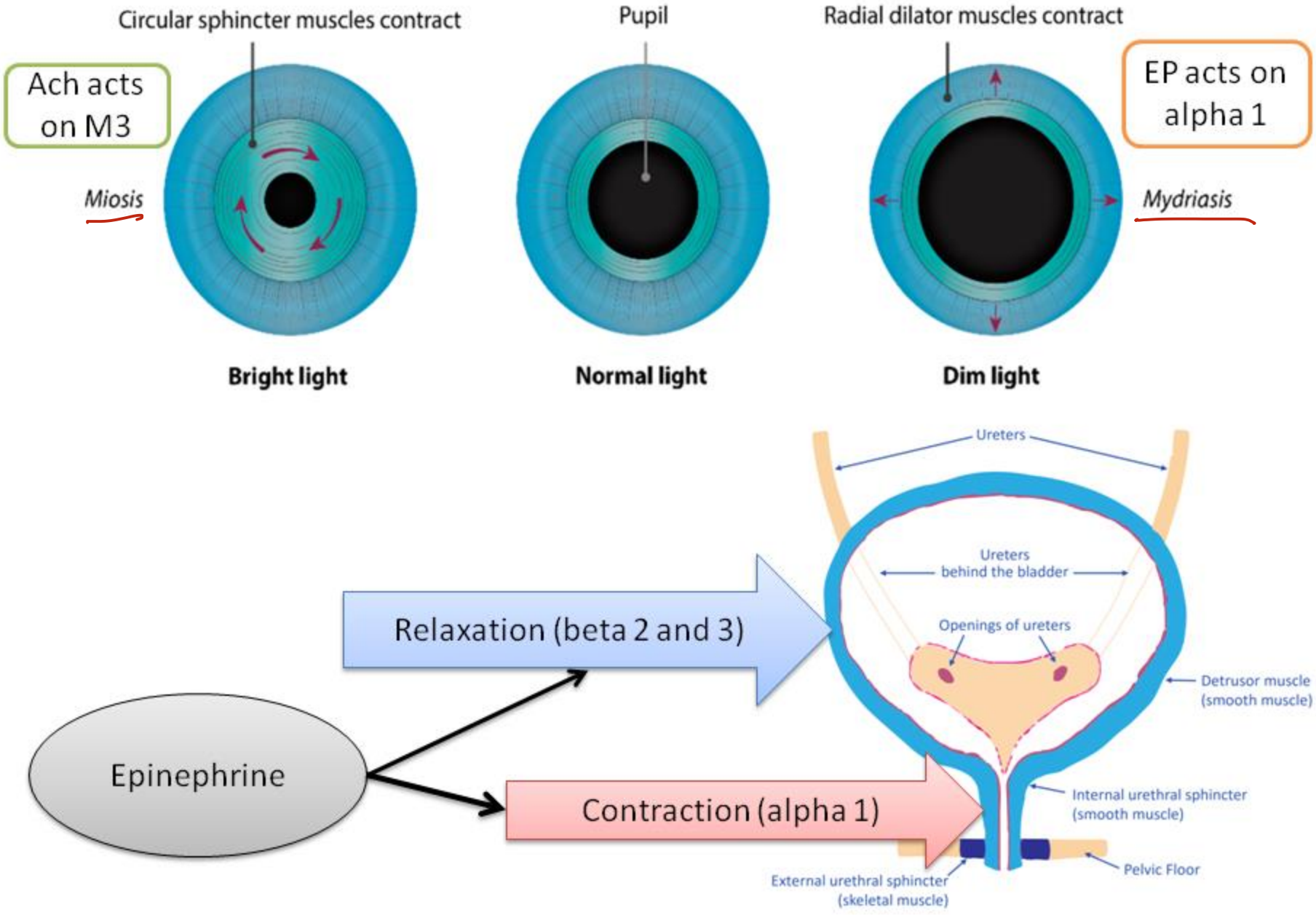
e) Pilomotor smooth muscles:

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). ✓


Circular sphincter muscles contract
Pupil
Radial dilator muscles contract
Ach acts on M3
EP acts on alpha 1
Miosis
Mydriasis
Bright light
Normal light
Dim light
Ureters
Ureters behind the bladder
Openings of ureters
Detrusor muscle (smooth muscle)
Relaxation (beta 2 and 3)
Epinephrine
Contraction (alpha 1)
Internal urethral sphincter (smooth muscle)
Pelvic Floor
External urethral sphincter (skeletal muscle)

(3) Metabolic effects ?!

a) EP ↑ the blood glucose (**hyperglycemia**) mainly due to:

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

b) **Increase in blood lactate** due to: ↑ lactic acid.

- ↑ glycogenolysis in the skeletal muscles.
-

c) **Increase in the free fatty acids** leading to hyperlipidemia due to action on β3-receptors in adipose tissue causing ↑ lipolysis.

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.

1- what's the action of it in CNS?

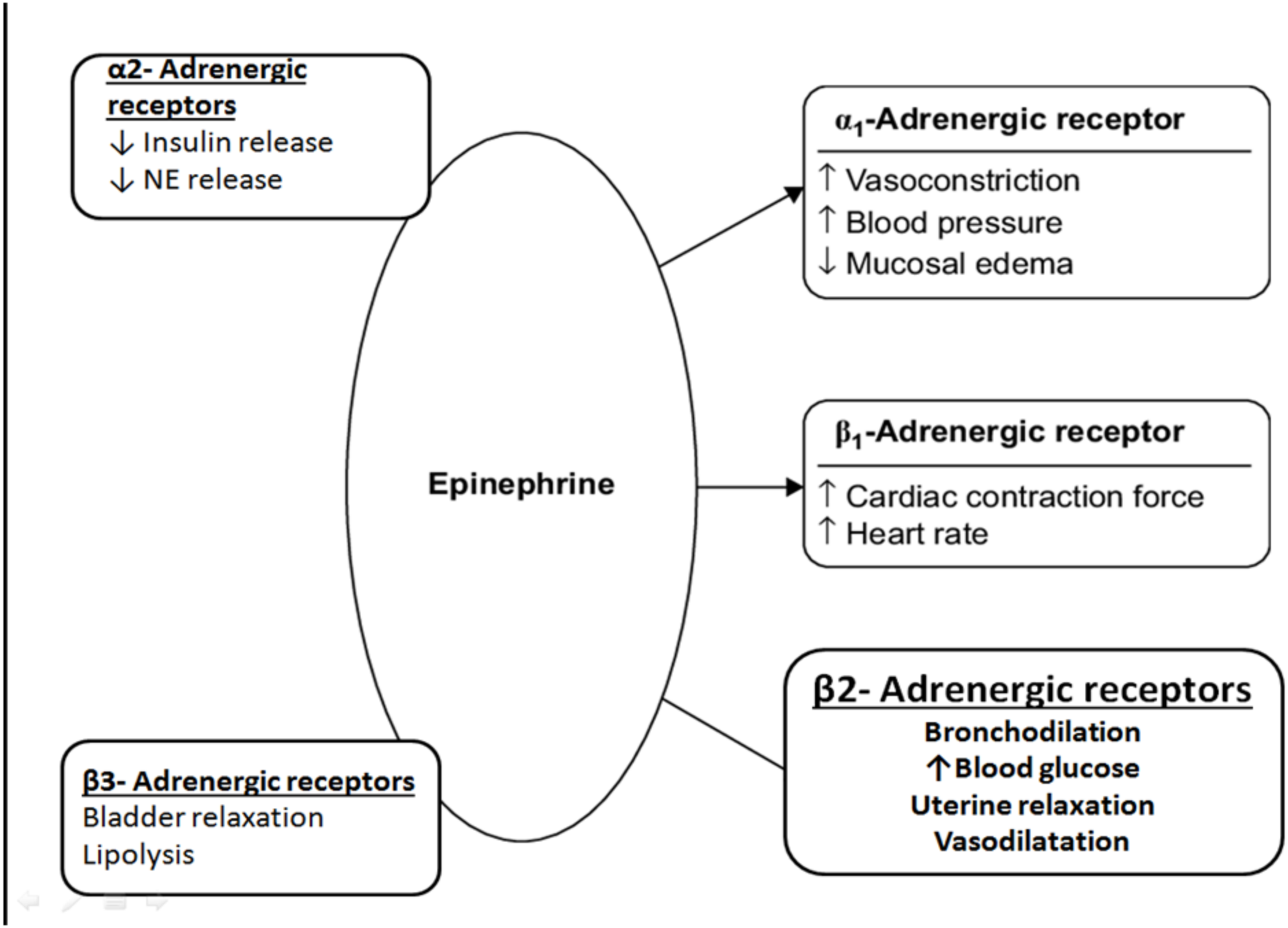
(4) CNS

EP is not significantly cross the BBB, due to catchol nucleus

It may cause tremors (secondary to cardiac and metabolic effects).

(5) Other effects

- It increases the blood coagulation by increasing the activity of factor V. Epinephrine also increases platelet aggregation (alpha 2).
- 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.


α2- Adrenergic receptors
↓ Insulin release
↓ NE release
α1-Adrenergic receptor
↑ Vasoconstriction
↑ Blood pressure
↓ Mucosal edema
Epinephrine
β1-Adrenergic receptor
↑ Cardiac contraction force
↑ Heart rate
β2- Adrenergic receptors
Bronchodilation
↑Blood glucose
Uterine relaxation
Vasodilatation
β3- Adrenergic receptors
Bladder relaxation
Lipolysis

1- what're the route of absorbation? what's special about them? 2- Describe the metabolism effect? 3- Describe it excretion?

Pharmacokinetics of Epinephrine

1- Absorption and routes of administration:

→ Bio Validability = zero

- 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. short duration due to Lary vessels of muscle
- 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).

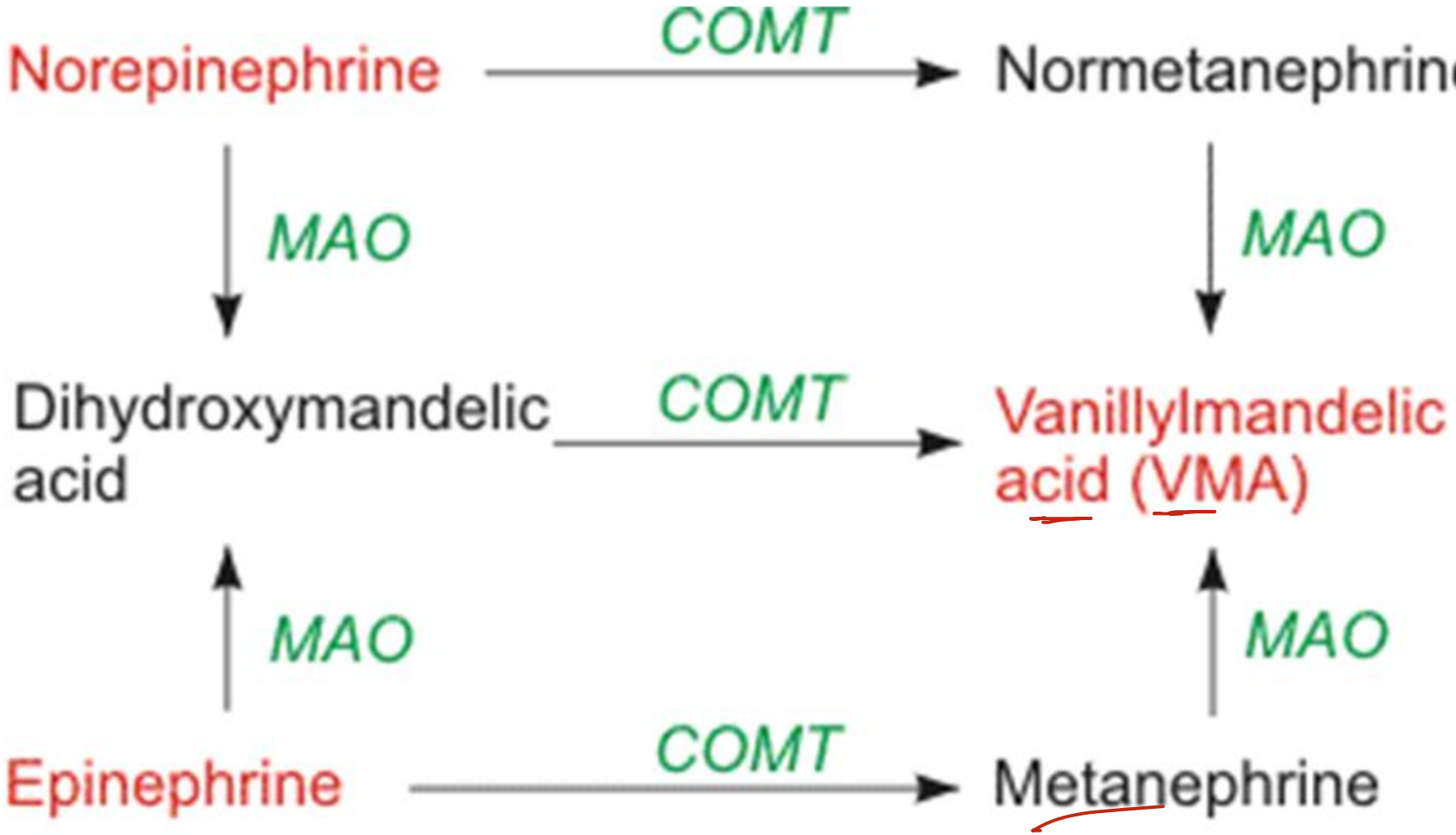
phase ① → oxidation, hydrolysis

2- Metabolism: by Monoamine oxidase (MAO) and Catechol-O-methyltransferase (COMT). ②

phase II → methyle conjugation.

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

99%



MAO = monoamine oxidase
COMT = catechol-O-methyltransferase

Therapeutic uses of Epinephrine

Vascular uses:

صانع للنزوح / Vasoconstruction and stimulate platlet- aggregation.

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.

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2-With local anesthetic (especially for dental manipulations) as it causes vasoconstriction that decreases systemic absorption of anesthetic, 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, as EP intra-cardiac can be used.

↳ in ventricle.

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

↳ without ↑ BP.

Allergic uses:

5-Acute anaphylactic shock: S.C. or IM EP is the ***drug of choice***. It reverses hypotension, bronchospasm and laryngeal edema. Also, EP can be used in other allergic conditions (angioedema, urticaria, rash, etc....).

Ep. can decrease the degranulation of mast cells and decrease release of allergic mediators.

6-Acute bronchial asthma: EP is used a- S.C. or b- by inhalation as it causes bronchodilation due to β_2-action and decreases pulmonary congestion and edema due to α-action (but it has no role in prophylaxis).

Ocular uses:

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

→ prodrug .... enter the eye .... convert into EP ... ↓ IOP.

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**.

2) Nervousness, tremors and headache.

3) GIT: nausea & 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.

4-Hyperthyroidism (to avoid cardiac arrhythmia).

5-Diabetes mellitus .

6-General anesthesia with halothane (to avoid arrhythmia).

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

(2) Norepinephrine (NEP)

NEP differs from EP in:

- It acts mainly on α and β_1-receptors in the heart with **negligable effects** on (β2 and β3) receptors.
- It causes vasoconstriction and increases the peripheral resistance and blood pressure at any dose.
- in high doses; NE may elicit a reflex parasympathetic stimulation causing bradycardia in some individuals (NB: Atropine can block this reflex)
- It has weaker metabolic actions than EP.

Therapeutic uses:

-It is used in **treatment of hypotension** and **shock**. without tachycardia.

-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) Isoproterenol (isoprenaline)

↳ Synthetic.

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

Therapeutic uses: The main drug in treatment bradycardia and heart block.

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

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

Adverse effects: Tachycardia, and **hyperglycemia**.

Beta- carbon atom

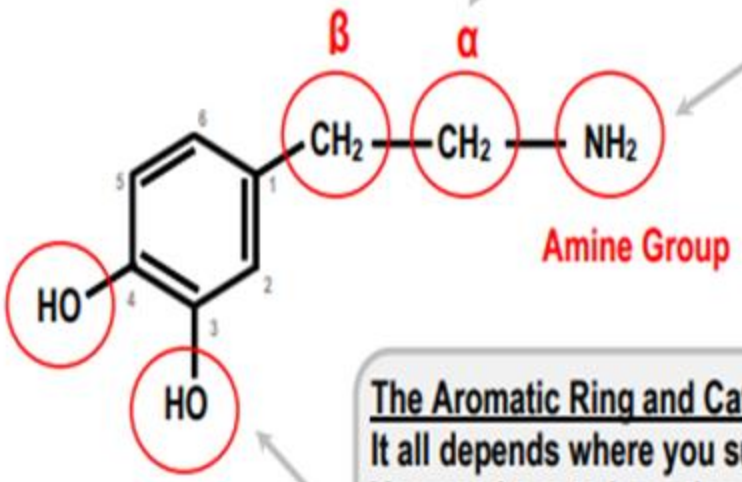
Hanging an extra hydroxyl group here tends to decrease lipid solubility, and thus decrease CNS penetration

ANY additional group here GREATLY increases alpha and beta receptor agonist activity.

Alpha- carbon atom

Any additional groups here block the action of MAO, and thus increase the half life.

Drugs with this structure dwell longer at the synapse, and **act as indirect sympathomimetics**



Amine group

A methyl group here confers alpha selectivity.

The smaller the group, the more alpha effect there is.

Increase of the alkyl substituent on the amine group increases the molecules preference for beta receptors instead of alpha

The bigger the alkyl substituent, the more beta effect there is.

The Aromatic Ring and Catechol hydroxyl groups

It all depends where you substitute the extra groups.

You need two to have the maximum receptor affinity.

However, having two polar hydroxyl groups decreases lipid solubility and keeps you out of the brain. Having no groups like phenylethylamine results in good CNS penetration.

Positions 3 and 5 = beta-2 selectivity in compounds with large amino substituents.

Supplementary material

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