Adrenergic drugs

PharmPill team

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اللهم طهر قلبي من النفاق وعملي من الرياء ولساني من الكذب وعيني من الخيانة فأنت تعلم خائنة الأعين وما تخفي الصدور

اللهم اهدني لأحسن الأعمال والأخلاق ..

اخواني الطلاب .. اخواتي الطالبات دفعة 426

نحن فارم بل تيم قمنا بجمع مذكرات البنات مع الأولاد في هذه المذكرة

مع إضافة نوتات هذا العام

في هذه المذكرة .. تعبنا وقمنا بإنجاز رائع .. فلا تحرمونا من دعواتكم ..

عسا تنفعنا واياكم ... وتعود بالنفع لغيرنا

ان اصبنا فمن الله وان اخطانا فمنا ومن الشيطان

اوجة شكر خالص الى الاخت دعاء البلوي دفعة 424 ""

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باقي الاعضاء:

ابويســـرا

Blue eye

Dr.Cool

Adrenergic drugs

sympathetic nervous system

Outline :

Θ origin : throacolumber
Θ transmitter : norepinerphine
Θ receptor : adrenergic
Θ sympathomemtic drug
Θ sympathetic antagonists

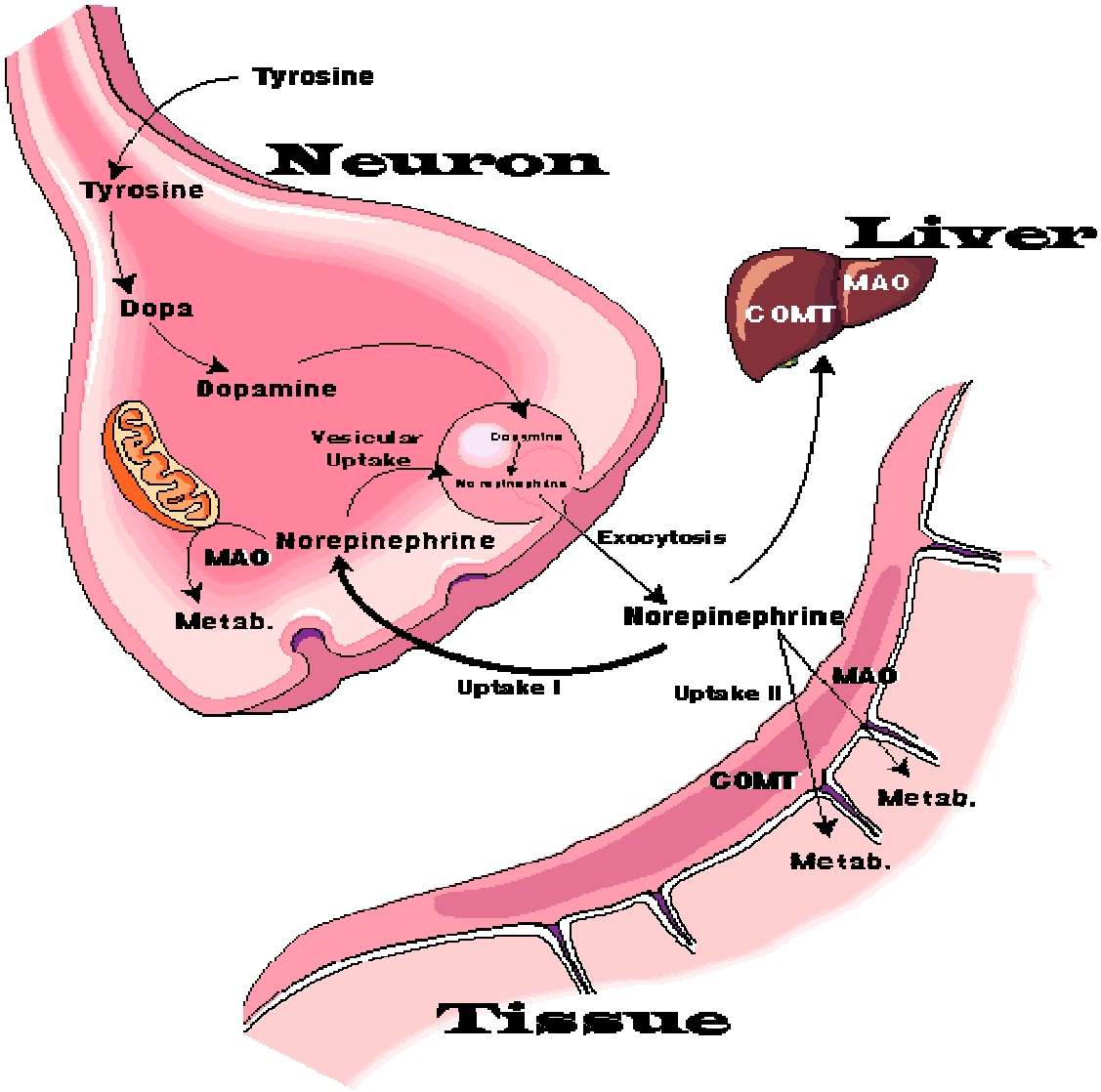
-The origin is from thoracolumbar segments "all thoracic + lumbers L1, L2, L3 and L4 " .
-They have short preganglionic fibers, and it relays in sympathetic chain ganglia & release Ach in these ganglia .
-They have long postganglionic fibers that innervate their body organs & release Norepinephrine as a neurotransmitter there .

synthesis and release of neurotransmitter :

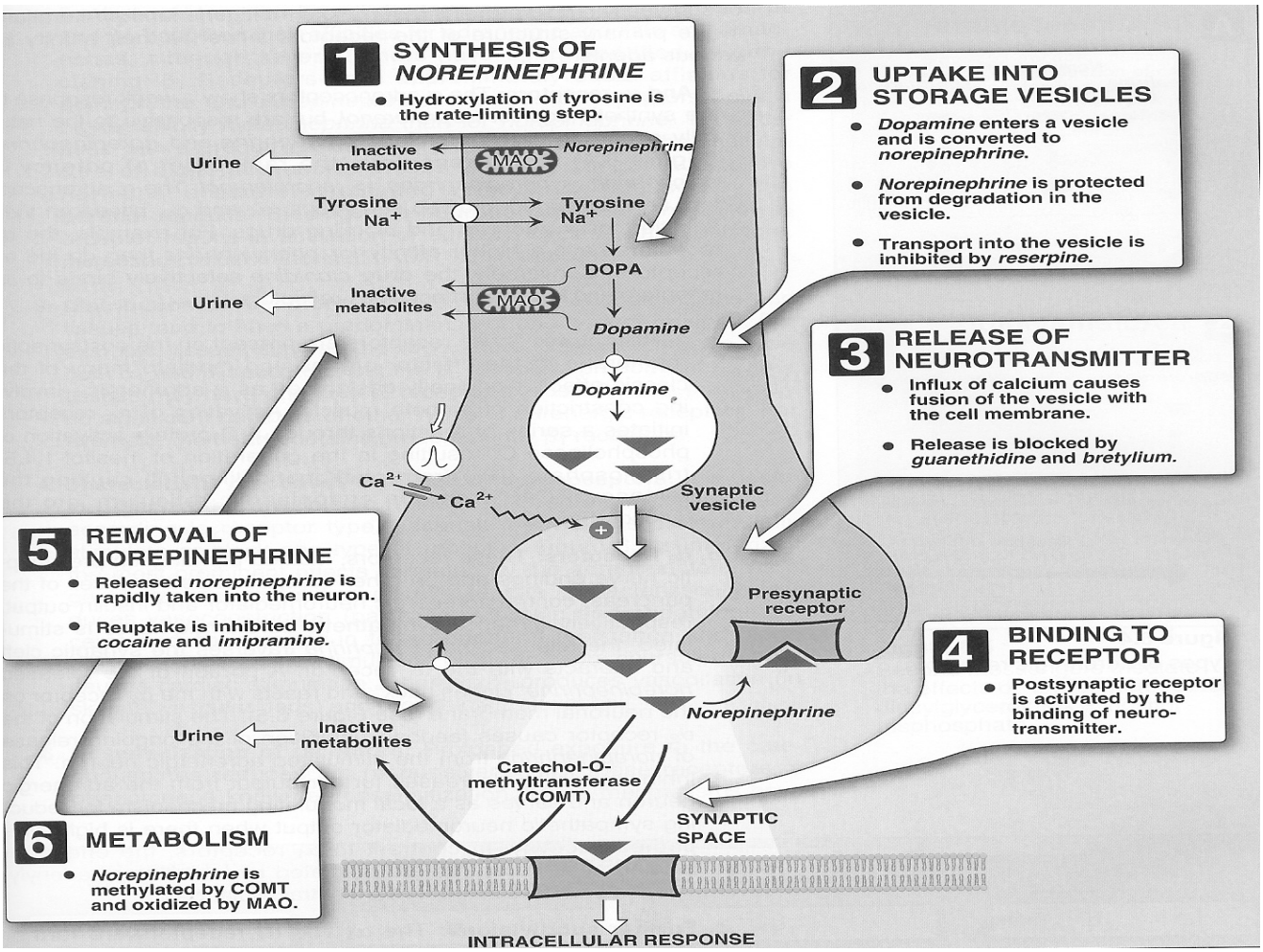
- Synthesis of NE .
- Storage of DA and NE in vesicles .
- Release of NE .
- Metabolism (COMT 20% + MAO 80%) .
- Binding to receptors .
- Uptake mechanism .

Additional information about neurotransmitter at adrenergic neurons :

- NE and E have more half-life than does the Ach Because the Ach Has more toxic effects on the body.
- Also, NE is protected from MAO in a transport vesicles to protect it from the intra-cellular degradation by MAO.
- Ach. Is never uptaken by the cells while NE may be uptaken.
- The idea behind epinephrin/ NE uptaking inhibitors (e.g. imipramine) is to maintain as much concentration Of NE/ E as possible in the nerve terminals casuing their hyper-activation and the subsequent alleviation of depression that is caused by decrease neurotransmitter.



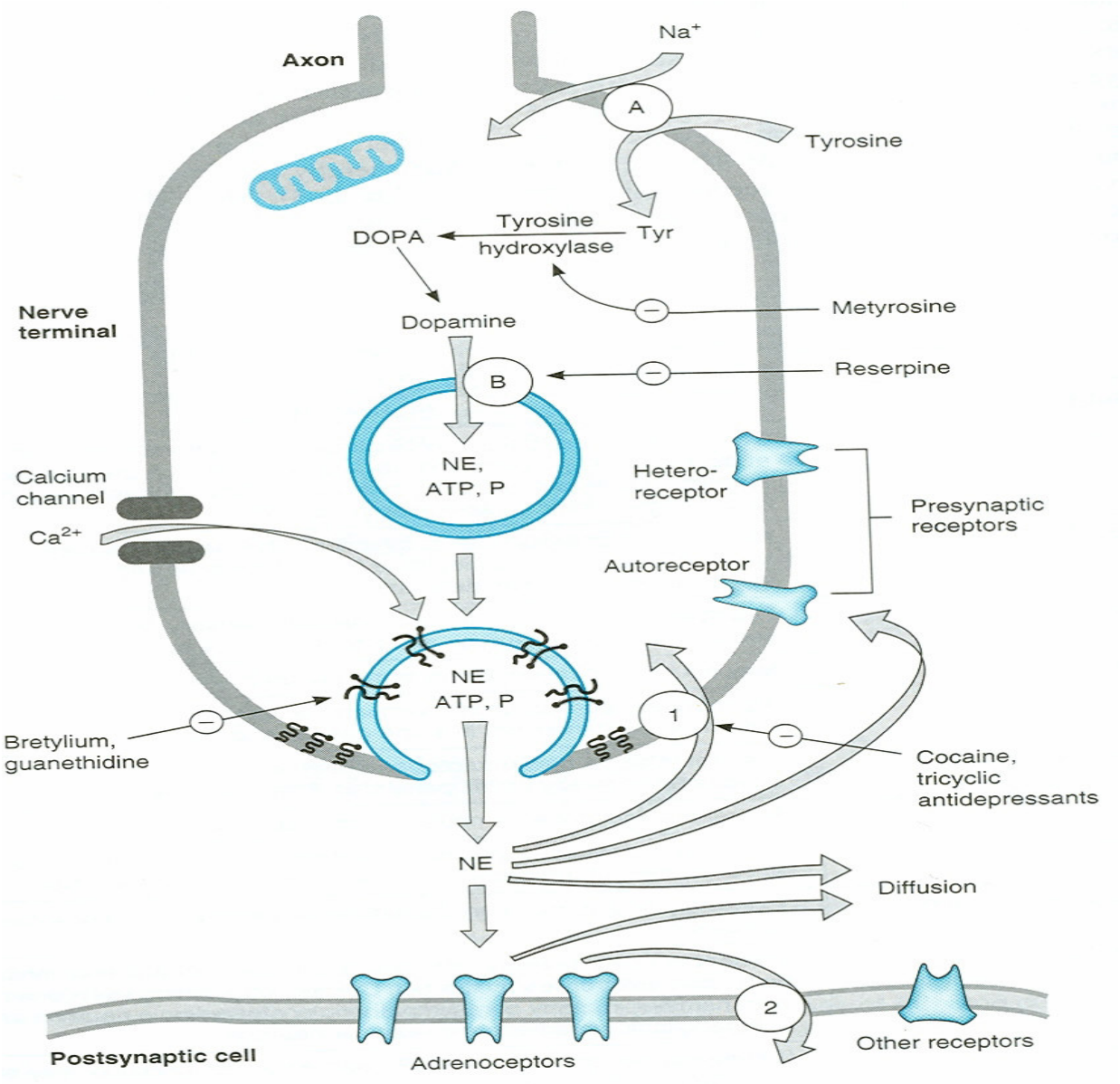
this figure I add it myself (0.o) . it will be benefit at the end of this chapter



◙ **Note :**

» tyrosin enters the nerve accompany the Na . in side the nerve it will hydroxylze by tyrosin hydroxylase to become Dopa . we get the dopamine which is an intermediate product by decarboxylation the Dopa . Dopamine will enter the vesicles. if there is a simulation → Ca ↑ and it will make exocytosis for the vesicles

» for the fate of the norepinephrin : it will inactivated or broken down by COMT and MAO , so if we want to treat so depressed person, we give'em MAO inhibitor



after these three pictures of adrenergic synthesis, I believed u will never forget it :p

classification of adrenoceptors :

• α-adrenoceptors
- subtype → α_1 and α_2
- α_1 and α_2 are further subdivided into A , B, C , and D
- important in treatment of disease ,e.g., tamsulosine is a selective α_1A antagonist is used to treat benign prostate hypertrophy

◙ **Note :**

that α_1 work on most postsynaptic receptor (on the effecter organ) ,whereas α_2 work mainly on presynaptic receptor , e.g., β cell of langerhans

• β adrenoceptors
- subtype → $\beta_{1, 2 , \text{and } 3}$

◙ **Note :**

β_1 → work mainly on the heart
β_2 → work mainly on the non-vascular smooth muscle
β_3 → work mainly on adipose tissue

all adrenoceptors are G-protein coupled *and work throught* second messengers

◦ α_1 adrenoceptors activate phospholipase C producing IP3 and DAG

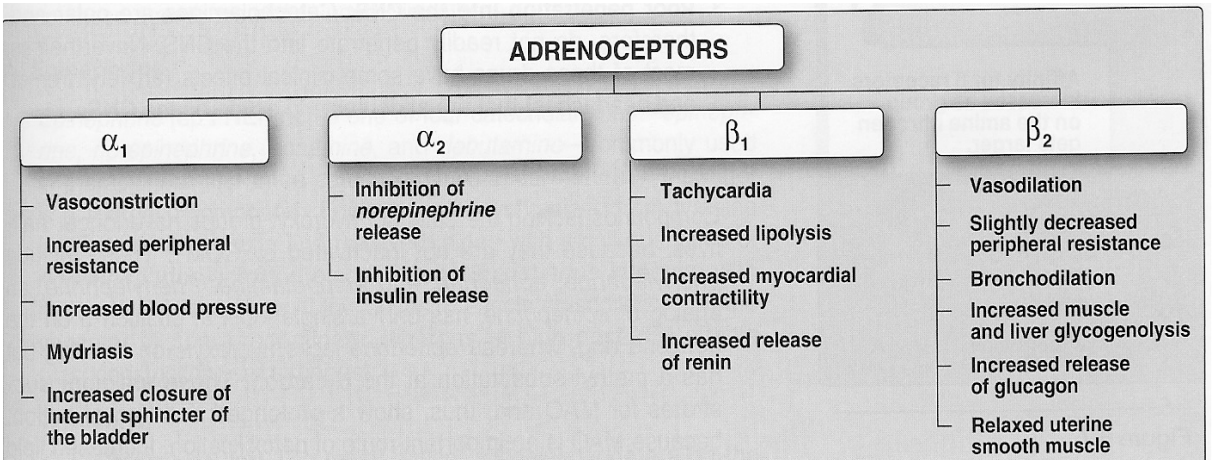
◦ α_2 adrecnoceptor inhibit adenylate cyclase → ↓ cAMP

◦ β adrenoceptor stimulate adenylate cyclase → ↑ intracellular cAMP

◙ **Note :**

- **α_1** (the only one that activates Gq not Gi or Gs molecules)
- **α_2** (only pre-synaptic receptor)
- **β_1** (has equal affinity for epinephrine & norepinephrine)
- **β_2** (has higher affinity for epinephrine than for nor epinephrine)

Note :
- **Gs** : the stimulatory G protien of adenylyl cyclase .
- **Gi** : the inhibitory G protien of adenylyl cyclase .
- **Gq** : the protein coupling α receptors to phospholipase C .



distribution of adrenoceptor

TYPE	TISSUE	ACTION
α_1	Most vascular smooth muscle (innervated)	Contraction
	Pupillary dilator muscle	Contraction (dilates pupil)
	Pilomotor smooth muscle	Erect hair
	Prostate	Contraction
	Heart	Increase force of contraction
α_2	Postsynaptic CNS adrenoceptor	Probably multiple
	Platelets	Aggregation
	Adrenergic & cholinergic nerve terminals	Inhibition of transmitter release
	Some vascular smooth muscle	Contraction
	Fat cells	Inhibition of lipolysis
β_1	Heart	Increase force & rate of contraction
β_2	Respiratory , uterine & vascular smooth muscle	Promotes smooth muscle relaxation
	Skeleton muscle	Promotes potassium uptake
	Human liver	Activates glycogenolysis
β_3	Fat cells	Activates lipolysis
D_1	Smooth muscle	Dilates renal blood vessels
D_2	Nerve ending	Modulates transmitter release

Table 6–3. Characteristics of some important adrenoceptors in the ANS.

Receptor	Location	G Protein	Second Messenger	Major Functions
α_1	Effector tissues: smooth muscle, glands	G_q	↑ IP_3, DAG	↑ Ca^{2+}, causes contraction, secretion
α_2	Nerve endings, some smooth muscle	G_i	↓ cAMP	↓ Transmitter release, causes contraction
β_1	Cardiac muscle, juxtaglomerular apparatus	G_s	↑ cAMP	↑ Heart rate, ↑ force; ↑ renin release
β_2	Smooth muscle, cardiac muscle	G_s	↑ cAMP	Relax smooth muscle; ↑ glycogenolysis; ↑ heart rate, force
β_3	Adipose cells	G_s	↑ cAMP	↑ Lipolysis
D_1	Smooth muscle	G_s	↑ cAMP	Relax renal vascular smooth muscle

Desensitization of Receptors:

- Prolong exposure to catecholamines reduces the responsiveness of these receptor.

- mechanisms :
  1- **sequestration** of the receptors (so, unavailable for interaction with transmitter).

  2- **Down regulation** of the receptors (disappearance of the receptor either by destruction or decrease synthesis).

  3- Inability to couple G-protein (because the receptors have been **phosphorylated** on the cytoplasmic side by either protein kinase or β-adrenoceptor kinase).

Classification of Adrenergic Agonist:

Θ according to the chemical structure :

A -Catecholamines:

❖ Contain 3,4 dihydroxybenzene group (catechol ring) . Such as:
Epinephrine, norepinephrine, isoproterenol, dopamine.

Its properties :

i- high potency on α , and β receptor

ii- rapid inactivation not only by COMT postsynaptic and by MAO intraneuronal, but also **inactivated within other tissue as in liver and gut wall .**

iii- brief period of action

iv- poor pentration into CNS

◙ **Note :**

These compounds share the following properties:

1- High potency drugs .
2- rapid in onset and have short duration of action because they are degraded by COMT and MAO
3- not effective orally because they are degraded by COMT in the gut.
4- Poor penetration in the CNS as they are polar.

B-Non-catecholamine:

- ❖ more specific, include: phenylepinephrine, epinephrine, amphetamine.
- ❖ They are compound lacking OH group.
- ❖ Have longer t 1/2 (half-life) , so given orally .
- ❖ Not inactivated by COMT and poor substrate for MAO.
- ❖ Lipophilic drug so better cross BBB.

Θ according to the mechanism of action :

***1- Direct acting*: -MCQ-**

- e.g.: epinephrine, nor-epinephrine, isoproternol, phenylephrine.
- Acts direct on α or β receptors.

2- Indirect acting agonists:

- e.g.: amphetamine + tyramine.
- They are taken up into presynaptic neuron and cause release of norepinephrine from the cytoplasmic pools or vesicles of adrenergic neuron.

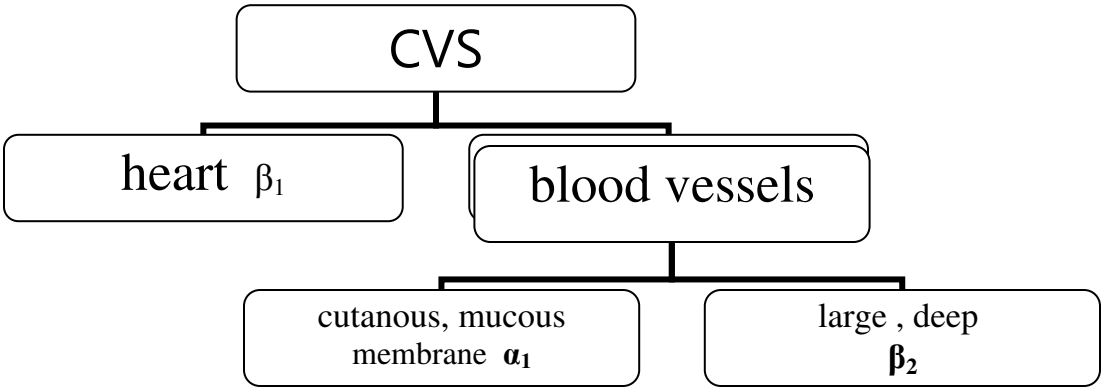
3- mixed action agonists:

- e.g.: ephedrine, metaraminol.
- Have capacity of both:
  1- direct acting.
  2- Indirect acting.

pharmacological actions of sympathomimetic drugs in general :

♣ ***On CVS :***

we divided the cardiovascular system into : heart , and blood vessels



• β_1 (heart) : positive iontropic (↑ myocardium contraction),
positive chronotropic (↑ heart rate),
↑ cardiac output,
↑ O_2 demands (needs) on the myochardium.

• β_2 : vasodilation on blood vessels in liver and skeletal muscle
↓ in renal blood flow
↑ diastolic pressure

• α_1 : vasoconstriction of blood vessels in the skin and mucous membrane
↑ in systolic blood pressure,
with slight ↓ in diastolic pressure

◙ **Note :** There are little or **no parasympathetics** innervating the vasculature

♣ ***On eye :***

• α_1-adrenoceptors activate radial papillary muscle → mydriasis

• in open angle glaucoma ↓ production of aqueous humor by vasoconstriction of the ciliary body blood vessels (β antagonist) and α agonist will ↑ the outflow of aqueous humor from the eye.

◙ **Note :**

α stimulant (agonist)	→ ↑ outflow of the aqueous humor	to treat open angle glaucoma, not narrow angle glaucoma
β antagonist	→ ↓ production of aqueous humor	

Refresh your memory :

- Ach. Activates circular muscles of cilliary muscle and causes miosis (constriction of the pupil and flattening of the lens) and opening the canal of schlem, therefore stimulating the flow of Aqueous humor through the channel and decreasing the intra-ocular pressure.
- Sympathetic effects through α_1 receptors is exactly the opposite to the previous statements.

♣ ***On respiratory tract :***

- β_2 receptor potent bronchodilator

- α_1 receptor (remember we said before that α_1 works on the effecter organs; postsynaptic tissue) causes vasoconstriction of blood vessels of the upper respiratory tract.

- mucosa → decongestion

◙ **Note :**

» nasal congestion due to vasodilation of mucosal blood vessels which causes oedema and will close the nose .so if we give the patient **Decongestants** like sympathomimetics, which exert their effect by vasoconstriction of the mucosal blood vessels. Thus reducing the oedema of the nasal mucosa.

» put in your mind that some sympathomimetics can rebound the congestion.

- α_1 – adrenoreceptorare the most determine of arteriolar tone. When their stimulated no others receptors have an affects on BP. So, hypertension may be treated by blocking α_1 .
- Vasoconstriction in the nasal blood vessels cause relief congestion
- So agonists to α_1 receptors may decongest the nose but will have the hypertension as a side effect.

♣ ***On GIT :***

relaxation of GIT smooth muscle through α_2 and β_2 stimulant agents (remember we said before that β_2 works on non-vascular smooth muscles).

♣ ***On exocrine glands :***

regulate secretion of amylase and H_2O from salivary gland, and ↑ sweat production from sweat glands

♣ ***On metabolic processes :***

mainly on α_2 and β_2
hyperglycemia due to ↑ glycogenolysis in the liver and muscle (β_2)
↑ release of glucagons (β_2 effect)
↓ insulin (α_2 effect)

lipolysis (β_2 receptor of adipose tissue)
↑ free fatty acid and glycerol in the blood
inhibit the production of leptin by adipose tissue through β_3 (important in treatment of obesity)
β_2 enhance up take of potassium K^+ into cells → ↓ extracellular potassium (protect against rise in potassium level during stress or exercise).

♣ ***On uterine smooth muscle :***

delay premature labour through relaxing uterine smooth muscles (β_2)

♣ ***<u>On genitourinary system :</u>***

α_1 receptor stimulate smooth muscles proliferation in various tissue ,e.g., blood vessels, and prostate.

◙ **Note :**
if we over stimulate α_1A, which is an adrenoceptor found in prostate . it will cause prostatic tumor (hypertrophy). the tumor will close the urethra cause urinary retention .

- So α_1 antagonists may be used to treat the urinary incontinence.

renin secretion is stimulated by β_1 and inhibited by α_2 receptors.

◙ **Note :**
remember that renin causes hypertension by vasoconstriction of blood vessels . So, if we want to treat the hypertension we give the patient β blockers.

♣ ***<u>In the seminal vesicles:</u>*** (with α_2)
α stimulation cause ejaculation. Thus, all α blockers inhibit ejaculation
That's why depressed people (low sympathetic activity) will have low sex drive.

♣ ***<u>skeletal muscle :</u>***

improve rate and force of contraction
clenbuteral is an anabolic drug used by sport's men to improve their performance (β_2 agonist)

♣ ***CNS :***

indirect catecholamines have a prominent effect :
alerting, improved attention, insomnia, euphoria, anxiety, tremors, anorexia.

Insomnia, is a sleeping disorder characterized by the inability to fall asleep and/or the inability to remain asleep for a reasonable amount of time.
Euphoria (emotion), a state of very intense happiness and feelings of well-being.
Anorexia, an eating disorder in which people do not eat correctly due to the obsessive fear of weight gain
Anxiety, is a normal reaction to stress. It helps one deal with a tense situation in the office, study harder for an exam, keep focused on an important speech

that was as general pharmacological actions of sympathomimetic drugs

to be continued →