Doctor 021

PHARMACOLOGY

Sheet no.12

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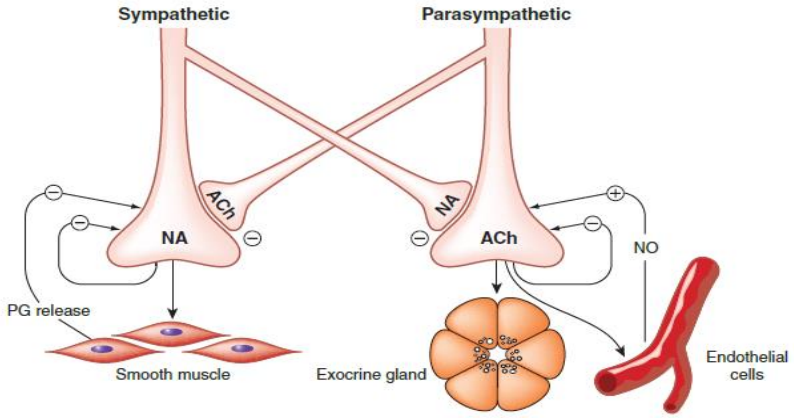
PRESYAPTIC RECEPTORS

There are 2 different types of receptors that located on the outer surface of presynaptic neurons:

1- Auto-receptors: are stimulated by the same neurotransmitter which is released from the neuron, the binding inhibits the release of further amount of the neurotransmitter (negative feedback)

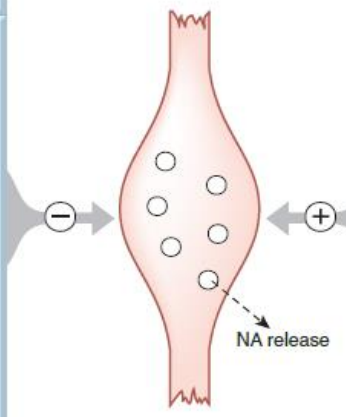
2- Heteroreceptors: are stimulated by other neurotransmitters, not the released ones.

There are sites where the sympathetic and parasympathetic neurons are close of each other, the main idea is that the sympathetic neuron can inhibit the release of Ach from the parasympathetic neuron by the binding of NE with the heteroreceptors which are on the surface of the parasympathetic neuron.



Moreover, there are receptors that inhibit the release of neurotransmitters (negative feedback) and there are other receptors which increase the release of neurotransmitters (positive feedback) such as β_2 receptors that are located on the heart.

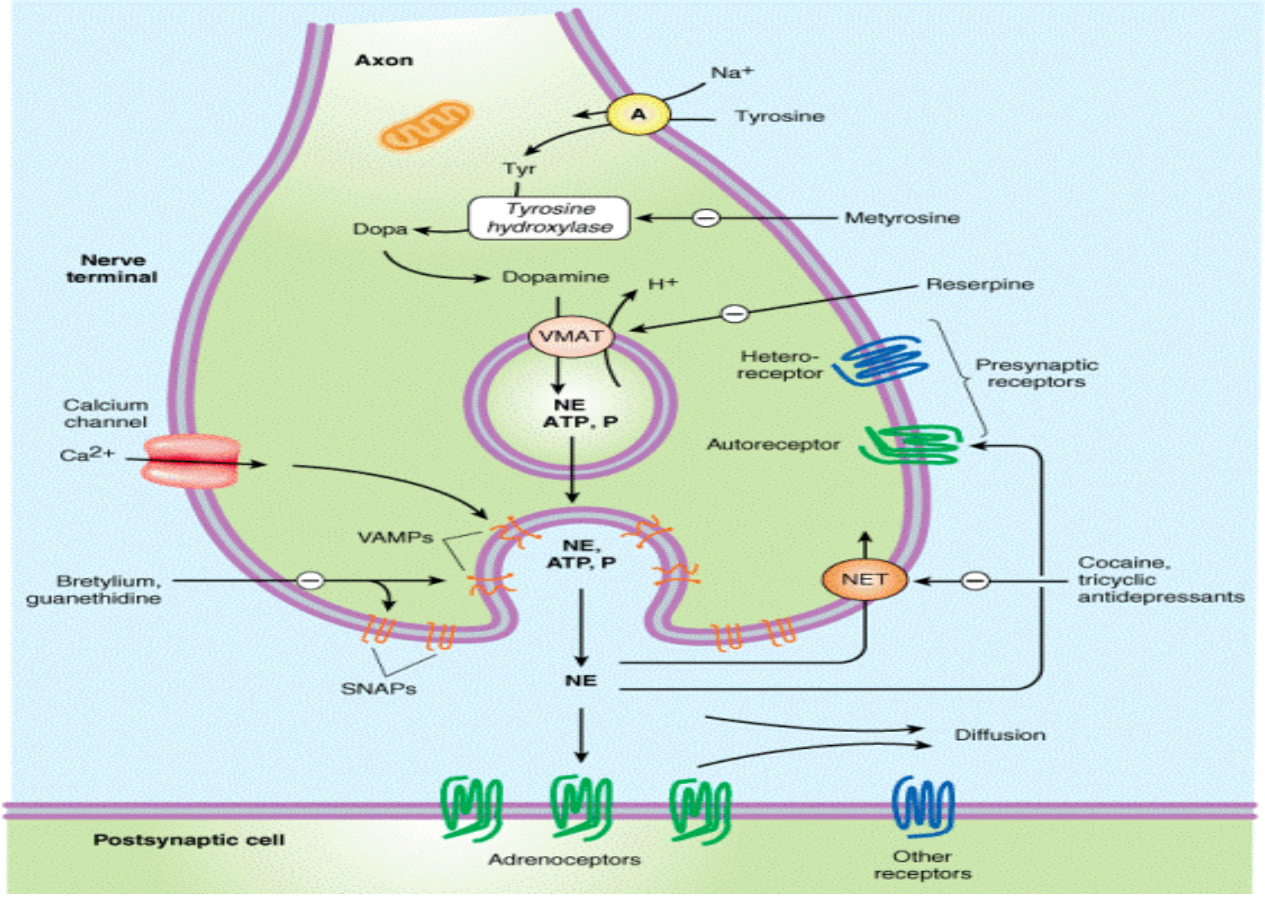
Mediator	Receptor type
ACh	Musc.
NA/A	α_2
5-HT	5-HT_1
Adenosine	A_1
PGE	EP
Histamine	H_2
Enkephalin	μ, δ
Dopamine	D_2
ATP	P2X / P2Y
Endocannabinoids	CB_1



Receptor type	Mediator
β_2	A
AT_1	Angiotensin II

ADRENERGIC TRANSMITION

Firstly, we are gonna talk about **the synthesis of NE.** **Tyrosine**, which is abundant in the blood, enters the neuron with Na^+ via a symport carrier, then it's hydroxylated by Tyrosine Hydroxylase to form **Dopa**.



SNAPs: synaptosome – Associated proteins

Tyrosine Hydroxylase is the most important enzyme **because it's the rate-limiting enzyme, subject to end product.**

- The drug Metyrosine, which is given to people who suffer pheochromocytoma, inhibits Tyrosine Hydroxylase, what causes the inhibition of Dopa synthesis. (therefore stops the synthesis of Dopamine, EP and NE)

Now, Dopa is decarboxylated in the cytosol by Dopa Decarboxylase to form **Dopamine**, which enters a vesicle to prevent its metabolization by monoaminoxidase, the antiport carrier which uptake the Dopamine inside the vesicle by exchanging it with H^+ called **VMAT (vesicular monoamine transporter).**

Note that VMAT carrier isn't specific for Dopamine, it's for all mono amines like Serotonin and others.

After that, there is an enzyme called Dopamine-β-hydroxylase converts Dopamine to **NE**, **NE is stored in vesicles bound to cAMP (4:1) + protein** (4 molecules of NE to 1 molecule of cAMP). And it's kept in the vesicle until the exocytosis begins.

Reserpine inhibits VMAT causing Depletion of CA, so dopamine can't enter the vesicle what causes the inhibition of NE synthesis.

- ❖ A nice story about this drug which is an alkaloid presents in a small shrub in India. It was being used in 50s and 60s as a tranquilizer and reduces the blood pressure for hypertension patients, then the doctors recognized a very high suicidal rates among those who took this drug. Because Reserpine clears all mono amines in the body, they have found that if the percentage of mono amines is low, the person will have a depression. So, all the drugs that treat the depression, increase the concentration of these mono amines.

Let's continue, when the action potential begins the membrane will be depolarized, and the entry of Ca^{+2} which causes the movement of the vesicle to the membrane to start exocytosis of NE.

- ❖ Bretylium and guanethidine prevent the release of NE, the first one was used for cardiac arrhythmia, and the last one for hypertension which inhibits the sympathetic nervous system that causes several side effects, so they are not used these days.

After the release of NE, there are 4 routes:

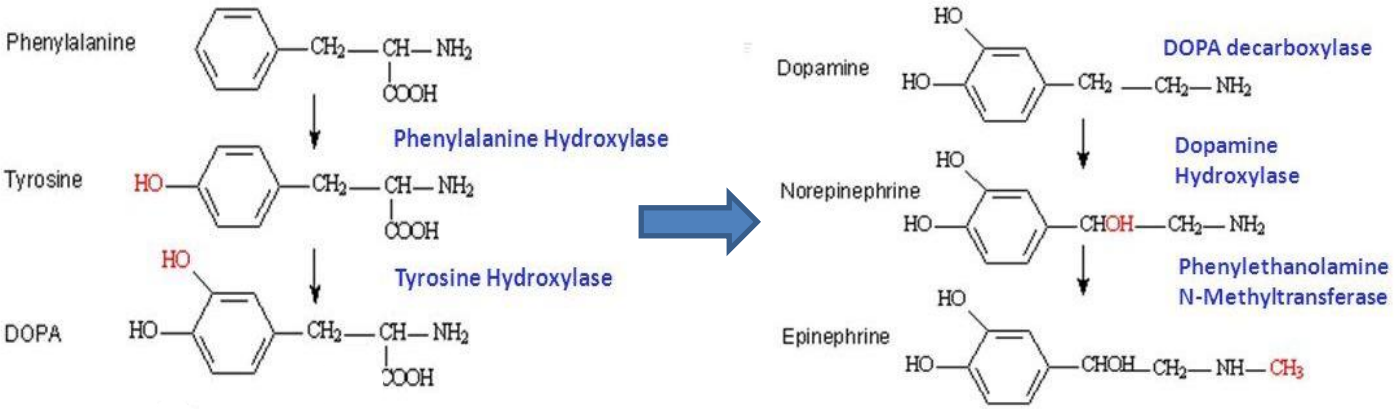
1- It activates the adrenergic receptors and gives the response.
2- The presynaptic will reuptake about 80% of it by NETs(norepinephrine transporters)
3- It diffuses into the blood to get metabolized in Liver.
4- When there are a lot of NE in the synaptic cleft, it will give negative feedback by auto-receptors, alpha 2 ones, that inhibit more release of NE as what we've discussed earlier.

- ❖ It re-enters the presynaptic neuron due to the difficult way of its synthesis not like Ach, and after that a small portion will be metabolized by mono amine oxidases and the rest will enter the vesicle via VMAT and stays until it's released again (with the presence of reserpine even this small amount can't re-enter the vesicle).

Cocaine & Tricyclic antidepressants Inhibit NET (norepinephrine transporter), so NE will not get back into the presynaptic neuron. As we've discussed earlier, to treat the depression we must increase the conc. of

mono amines, so by the mechanism of inhibiting NETs we will achieve our target. But these inhibitors will not give the response immediately it needs 3-4 weeks because the conc. of NE won't increase due to the presence of presynaptic receptors, but after a certain time the drugs will down-regulate these receptors and NE concentration will increase.

A summery of the journey:



RELEASE

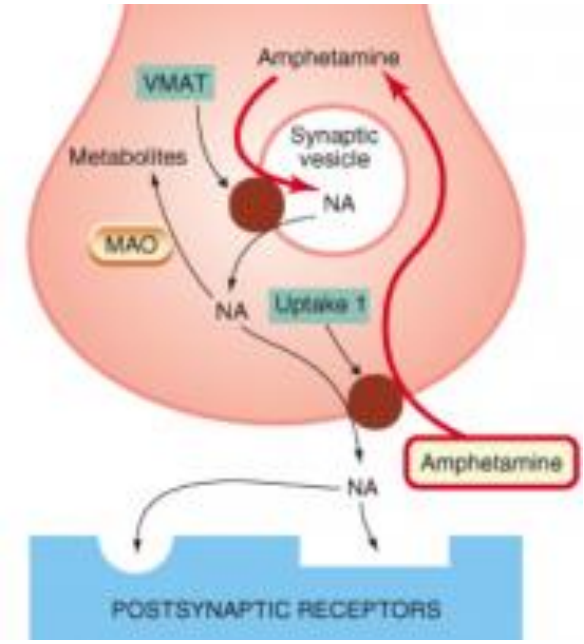
1- Calcium dependent exocytosis. That we've discussed

- **NE + cAMP + protein + Dopamine-β-hydroxylaes are released.**
- **Release can be blocked by guanethidine and pretylium.**

- **ω–Conotoxin GVIA, Toxin of marine snails blocks Ca channels & reduce NE & Ach release.**
- **α–Latrotoxin (Black widow spider venom) acts on vesicles causing explosive release of NE & Ach.**

2- Calcium independent release.

- **Tyramine, amphetamines are transported by NET (NE Transporter) into the neuron then transported by VMAT into the vesicles.**
- **They displace NE from the vesicular stores, into the cytoplasm.**
- **Ne is transported into the synaptic cleft by reverse transport via NET.**
- **They <u>produce an indirect sympathomimetic effect</u>**



Tyramine, which is found in cheese, wine and many jams, is going to be metabolized whether in Intestines or in Liver by mono amino oxidases so it won't diffuse into the circulation, but if the mono amino oxidases got inhibited, Tyramine will not be metabolized and it will diffuse into the circulation to the nerves and enters the presynaptic neuron by NET, then to the vesicle and displaces NE, in which the last one will stimulate the postsynaptic receptors causing hyper pressure and cardiac arrythmia (cheese reactions).

Amphetamine mimics Tyramine's action but it's a drug (not natural), who take it will remain energetic and it causes hallucination and many other side effects.

METABOLISM OF CATECHOLAMINES

As we said NE effects are terminated by neuronal reuptake (uptake1). 80% of the released NE are transported into the neuron by MAT (Mono amine Transporter).

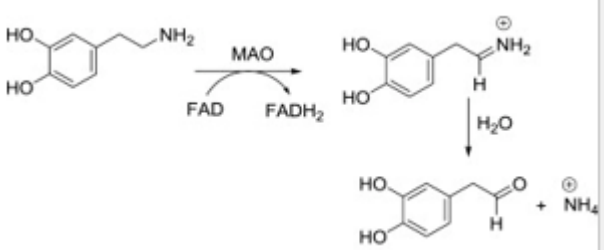
Two main enzymes:

1-Monoamine oxidase (MAO) in mitochondria produce oxidative deamination of mono amines.

This enzyme was found inside the neuron and outside it, in different important locations like liver, intestine.

Mono amines: Norepinephrine, epinephrine, dopamine, serotonin…

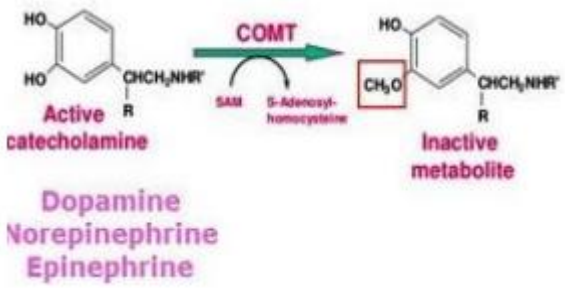
This enzyme produces oxidative deamination by removing the (NH2).



<u>focus in this pic</u>

2-Catechol-O-Methyl transferase(COMT)

This enzyme work on the catechol ring (benzene ring connected with two OH groups) **by transferring methyl group from S- adenosyl methionine** (methyl donor in our body known as SAM) **into the OH- group in the meta position of the catechol ring,** and the resulting molecule is inactive (have not pharmacological action).



- ❖ It doesn't matter which of these enzymes (MAO or COMT) will start working on the catecholamines (they will work on the same catecholamines) and they will end with common product.
- ❖ The epinephrine and norepinephrine end with VMA **(vanillylmandelic acid),** The dopamine end with different product.
- ❖ VMA has diagnostic value for patients who have pheochromocytoma (tumor in adrenal medulla). The patients will have severe sympathetic activation, for diagnosis the VMA will be measured in the urine, if the patient has a high level of VMA then the patient will have pheochromocytoma.

CHOLINOCEPTORS (CHOLINERGIC RECEPTORS)

- ➢ **Muscarinic M1: CNS neurons, sympathetic postganglionic neurons** (as heteroreceptors)**, some presynaptic sites.**
- ➢ **Muscarinic M2: Myocardium(heart), smooth muscle, some presynaptic sites; CNS**
- ❖ all the effects of parasympathetic on the heart come from the M2.
- ➢ **Muscarinic M3: Exocrine glands**, **vessels (smooth muscle and endothelium); CNS**
- ❖ Although the parasympathetic nerves are rare in the blood vessels, but still M3 found there, because if we injected any substance that stimulate muscarinic receptors these receptors provide nitric oxide that works as vasodilator.
- ➢ **Muscarinic M4: CNS neurons.**
- ➢ **Muscarinic M5: CNS neurons.**
- ❖ the muscarinic receptors 4&5 found only in the brain, the rest receptors found in the brain and other tissues.

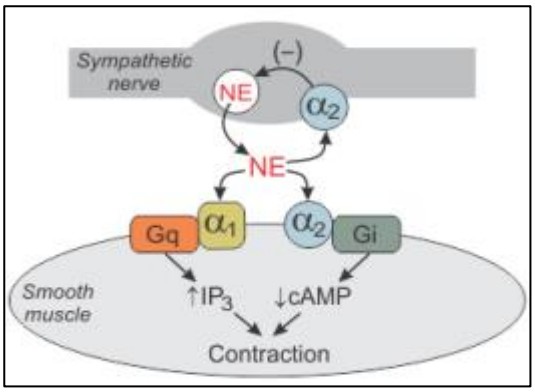
- ❖ in the stomach there are M1 receptors.

- ➢ **Nicotinic NN (nicotinic neuro): Postganglionic neurons, some presynaptic cholinergic terminals.**
- ➢ **Nicotinic NM (nicotinic muscular): Skeletal muscle neuromuscular end plates.**

ADRENOCEPTORS

- ➢ **Alpha1 (α)1**

They found in Postsynaptic, especially smooth muscle(blood vessels) and **they produce vasoconstriction upon stimulations Formation of IP3 and DAG, increased intracellular Ca producing smooth muscle contraction.**



- ❖ P3 and DAG are second messengers.

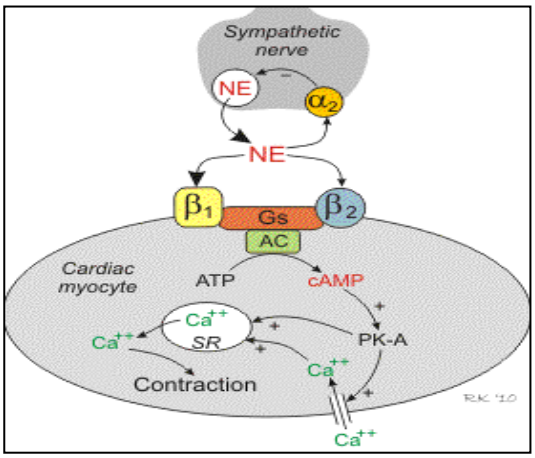
- ➢ **Alpha 2 (α)2**

Presynaptic adrenergic nerve terminals, platelets, lipocytes, smooth muscle. They Inhibit NE release, and Inhibition of adenylyl cyclase, decreased cAMP(because it is produced by adenylyl cyclase) **.**

cAMP is important for inhibiting the release of neurotransmitter (prevent releasing of norepinephrine).

- ➢ **Beta1 (β1)**

They were found in the Heart (increase heart rate), lipocytes, brain.



juxtaglomerular apparatus of renal tubules (activates renin enzyme and that leads to formation of angiotensin 2 which activates releasing aldosterone enzyme that causes retention of sodium and water and vasoconstriction thus increase in blood pressure).

they act by Stimulation of adenylyl cyclase, increased cAMP

- ➢ **Beta2 (β2)**

smooth muscle & cardiac muscle

in the cardiac muscle it's found as presynaptic (auto-receptor)

Stimulation of adenylyl cyclase and increased cAMP.

- **Beta3 (β3)**

lipocytes; they act by Stimulation of adenylyl cyclase & increased cAMP

They found in adipose tissue and make lipolysis (degradation of lipids, so they increase fatty acids).

DOPAMINE RECEPTORS

- **D1 (DA 1, D5)**

D1 &D5 have the same effect but they are not exactly the same receptor.

They found in Brain, especially smooth muscle of the renal vascular bed.

They act by Stimulation of adenylyl cyclase and increased cAMP.

Some of these receptors have a connection with different Neurological diseases such as Psychosis and schizophrenia that might happen by accumulation of D4 receptors in certain area .

NOTE: all factors that cause psychosis or hallucinations affect dopamine in the brain.

- **D2 (DA 2, D3, D4)**

They have the same effect.

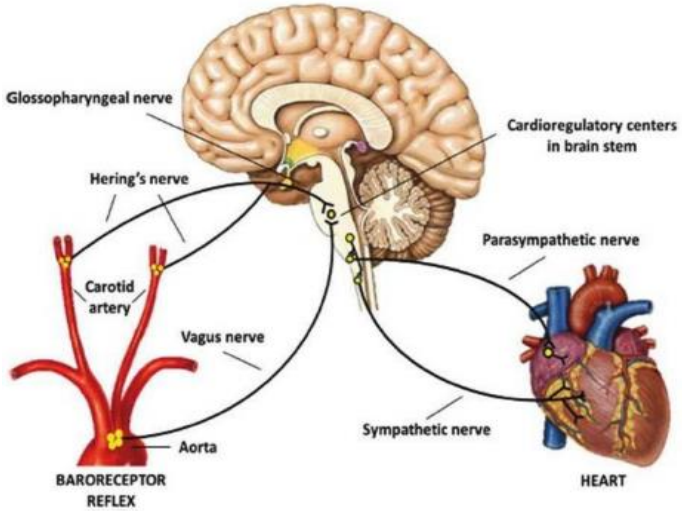
They were found in the Brain, especially smooth muscle; presynaptic nerve terminals (D2), D2 inhabits the release of neurotransmitters.

They act by Inhibition of adenylyl cyclase (decreased cAMP)**; increased potassium conductance.**

Increasing potassium conductance causes hyperpolarization which will lead to inhibition of action potentials by increasing the stimulus required to move the membrane potential to the action potential threshold.

BARORECEPTORS

The word (Baro) indicates pressure, Baroreceptors: receptors are located within the carotid sinuses and the aortic arch.



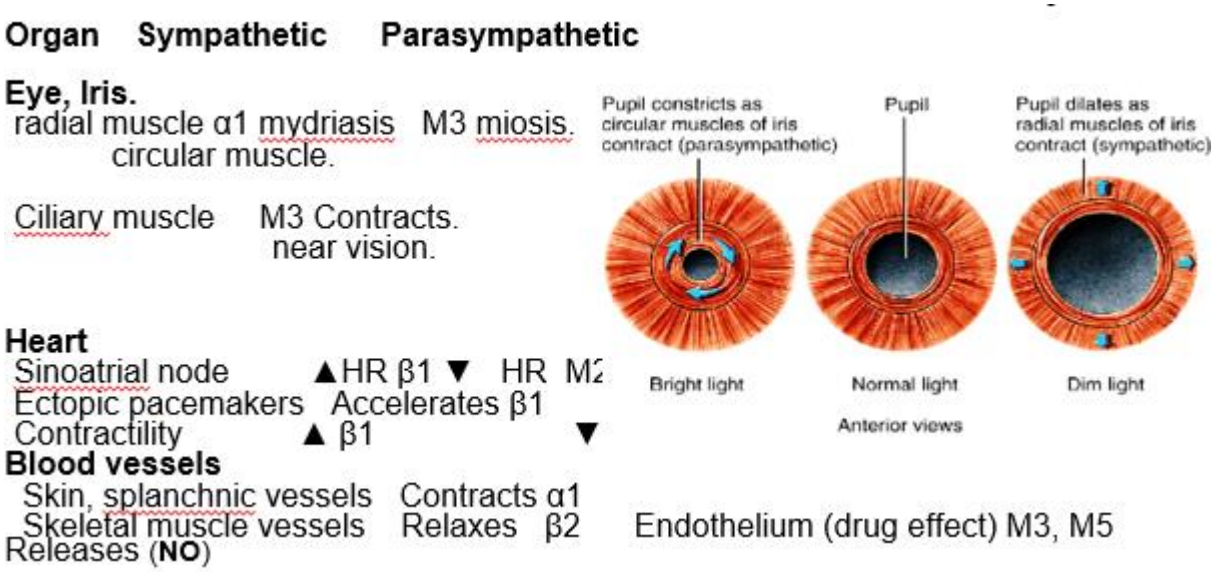
↑ BP →↓HR

-**The first case**: when blood pressure increases, the arteries will be stretched, then these baroreceptors will sense this stretch, in order to maintain homeostasis, they send a signal to the brain, especially cardio regulatory centers in the brain stem (Take a look at the image above) then the brain immediately activates the vagus nerve which is parasympathetic nerve that causes bradycardia (decrease in heart rate).

↓BP →↑HR

-**The second case**: When blood pressure decrease, this will be sensed by the baroreceptors, then send signal to the brain to activate the sympathetic nerve (Baroreceptors reflex) that cause tachycardia (increase in heart rate) to keep the homeostasis of the body constant.

DIRECT EFFECTS OF AUTONOMIC NERVE ACTIVITY



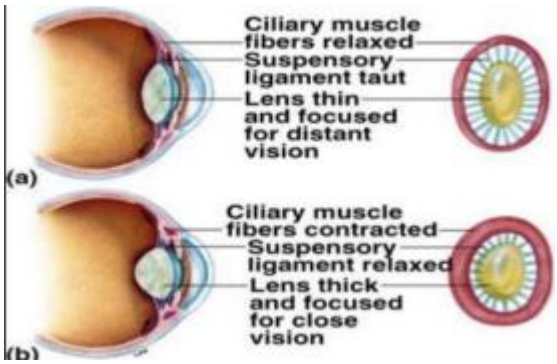
There are always sympathetic and parasympathetic effects on our organs:

1-Eye, iris: Radial muscle & circular muscle (seen in the pic above) control the pupil size, in the following ways:

- **Radial muscle** has alpha1 receptors that when stimulated the radial muscle will contract, increasing the pupil size (mydriasis- pupil dilation) which is a sympathetic effect, in the case of dim light for ex .
- **Circular muscle** has M3 receptors that when stimulated the circular muscle will contract, decreasing the pupil size (miosis- pupil constriction) which is a parasympathetic effect, like in bright light.

NOTE: at any time, the pupil size depends on the light of the environment, if there is bright light the pupils will constrict, if there is dim light the pupils will dilate.

▪ **Ciliary muscles** when contracts they affect the focus of the eye & they are only innervated by cholinergic nerve (parasympathetic nerve) and have M3 receptor, that when activated the muscle will contracts so changing the accommodation of the eye to be suitable for near vision.



The picture is not from the slides

2-Heart

• **Sinoatrial node** has beta1 receptors that when stimulated, increases the heart rate and has M2 receptors that when stimulated it decreases the heart rate .

• **Ectopic pacemaker** is not the normal pacemaker which is the SA node due to diseased heart or due to consumption of too much alcohol or caffeine, certain spots in the atrium starts to discharge high rate of action potential, and the heart always follows the higher rate which will lead to Arrhythmia ,so taking Beta1 stimulant that will result in ectopic pacemaker .

NOTE: people with Arrhythmias are given Beta Blockers.

• **Beta1 receptors** when activated, it increases the contractility for both the atria and the ventricles while M2 receptors when activated, it only decrease the contractility of the atria because the ventricles are not innervated by cholinergic parasympathetic nerves.

3- Blood vessels

• All blood vessels have **alpha1 receptors, (in the skin, splanchnic vessels, etc..),** that when stimulated, it causes **vasoconstriction** so increasing blood pressure.

• **Skeletal muscles vessels also have beta2 receptors** in addition to alpha1 receptors

• **Stimulation of beta2 receptors causes relaxation of the skeletal muscles blood vessels**

• No innervation of the blood vessels by parasympathetic neurons but all blood vessels have **endothelium M3 receptors** that **when stimulated by a drug** it causes vasodilation due to the release of **NO (nitric oxide)** a natural powerful vasodilator .

Bronchiolar smooth muscle	Relaxes	β2	Contracts	M3	
Gastrointestinal tract					
Smooth muscle Walls	Relaxes	β2, α2	Contracts	M3	
Sphincters	Contracts	α1	Relaxes	M3	
Secretion			Increases	M3	
Genitourinary smooth muscle					
Bladder wall	Relaxes	β2	Contracts	M3	
Sphincter	Contracts	α1	Relaxes	M3	
Uterus, pregnant	Relaxes	β2			
	Contracts	α	Contracts	M3	
Penis, seminal vesicles	Ejaculation	α	Erection	M	
Skin					
Pilomotor smooth muscle	Contracts	α			
Sweat glands	Increase	M			
Metabolic functions					
Liver	Glycogenolysis,	β2 α			
	Gluconeogenesis	β2 α			
Fat cells	Lipolysis	β3			
Kidney	Renin release	β1			

The previous pic explains the effects of sympathetic and parasympathetic nervous system by their receptors on different organs (so it's important , and below are some additional points):

- **Bronchial smooth muscles:** have β2 receptors that upon stimulation, cause relaxation of muscles which is of great value for patients with bronchial asthma. Why?

Normally those patients suffer from congested bronchioles, difficulty in breathing and wheezing, thus they are given β2 agonists (bronchodilators).

While the parasympathetic contains M3 receptors that upon stimulation cause contraction (bronchoconstriction).

- **GI tract**

A. In the smooth muscle cells, there are β2 (of greater importance) and α2 receptors, in which stimulation causes relaxation.

B. In the sphincters the stimulation of α1 receptors causes contraction (inhibition in activity).

C. So, when the intestine is relaxed and the sphincters are closed, this means there is no movement of the intestine which is caused by the inhibitory effect of the sympathetic nervous system, because it's not needed in emergency.

D. In contrast the parasympathetic neurons activate the GI system, by contraction of smooth muscle wall and relaxation of sphincter through M3 receptors, so when a patient is given a drug that stimulates cholinergic receptors of the GI tract, diarrhea will result.

E. Secretion is increased by parasympathetic stimulation (M3) but it is not affected by sympathetic neurons.

➢ Genitourinary

A. When the bladder body is relaxed ($\beta 2$) and the sphincters is constricted ($\alpha 1$) so the urination is inhibited which is a sympathetic effect while parasympathetic causes the opposite effect.

B. Stimulation of beta2 receptors causes relaxation of uterus, so sometimes beta2 agonists are given to save the pregnancy by preventing abnormal contractions of the uterus.

C. penis, seminal vesicles: ejaculation (α receptors), Erection (M receptos)

➢ Skin

A. Polio motor smooth muscle contract when alpha receptors is activated when there is fear or emergency situations causing erection of body hair

B. This is more important in animals because when their body hair rises, they look bigger

C. Sweat glands are sympathetic but also have muscarinic receptors that when stimulated it increases sweat secretion

➢ Metabolic activities

A. Glycogenolysis: breaking down of glycogen so increasing blood sugar which is important in emergency situations ($\beta 2$ α).

B. Gluconeogenesis: synthesis of glucose from non-carbohydrate sources ($\beta 2$ α).

C. When a person feels worried, his blood sugar rises because of activation of the sympathetic nervous system.

V1