SHEET NO. 12

PHARMACOLOGY

DOCTOR 2019 | MEDICINE | JU

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SCIENTIFIC CORRECTION :

GRAMMATICAL CORRECTION :

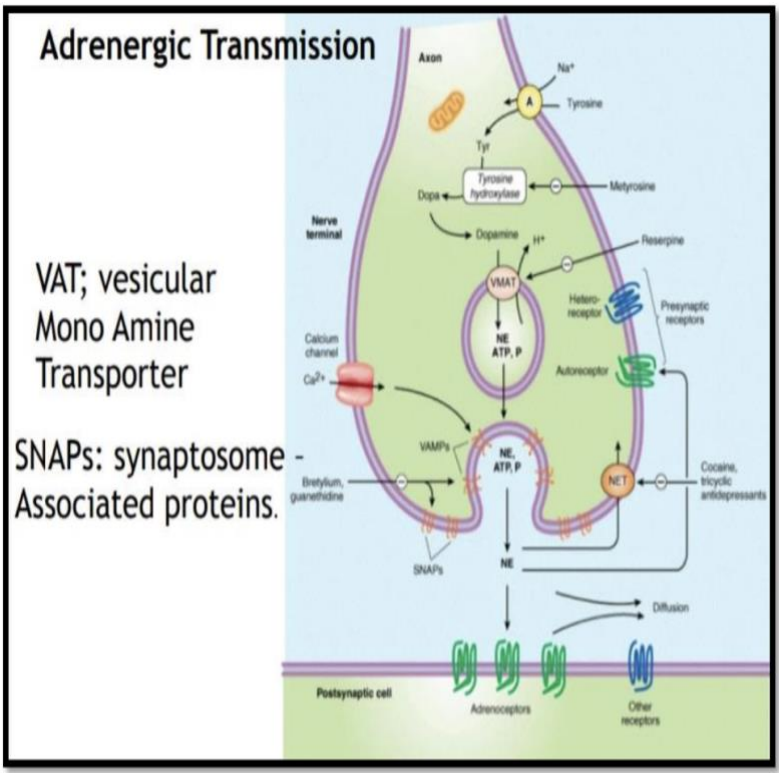
DOCTOR : Dr.Hamzeh

In the previous lecture we talked about cholinergic transmission , now we are going to discuss Adrenergic transmission :

Adrenergic Transmission :

Adrenergic transmission involves the following steps :

1) Synthesis
2) Storage
3) Release
4) The fate of norepinephrine (the neurotransmitter)



1) Synthesis :

1) Synthesis starts when the amino acid **tyrosine** is taken up by a special carrier in exchange with sodium ion into the neuron .
2) Then the **tyrosine hydroxylase enzyme** adds OH group to tyrosine ring forming dopa, then the **enzyme dopa decarboxylase** removes a carboxylic group from dopa forming dopamine.
3) Dopamine goes inside a storage vesicle via **VMAT (vesicular mono amine transporter)** in exchange with hydrogen ion .
4) Inside the vesicle an enzyme called **dopamine beta hydroxylase** converts dopamine to norepinephrine which will be sorted inside the vesicle bound to a ATP and a special protein .

The rate limiting step in synthesis is : The step involving the enzyme Tyrosine hydroxylase , because when it is activated, synthesis starts and when inhibited synthesis stop . Hence it's the most important enzyme .

Drugs as inhibitors :

A. **Metyrosine** : is a drug that inhibits tyrosine hydroxylase enzyme , thus inhibiting the synthesis of norepinephrine & it was used in patients who

have **pheochromocytoma** which is a cancer in adrenal medulla gland , that produces large amounts of Epi and NE .

B. **Reserpine** : which is a drug was used to decrease blood pressure for patients who have hypertension, and It completely inhibits VMAT, preventing dopamine from interning the vesicle, causing depletion of all **catecholamines**(norepinephrine, epinephrine, and also dopamine) completely , peripherally and centrally ; because if it isn't being stored in the vesicle it will be metabolized by mono amine oxidase enzyme .

▪ It is no longer used because it causes mental depression .

2) Release :

1. An action potential causes the opening of calcium ion channels
2. Entry of calcium ions to the neuron
3. Binding of calcium to special receptors (VAMPs, SNAPs) that sure about the proper position and the fusion of the vesicle with the membrane
4. Moving of the vesicle toward the membrane of the neuron .
5. Expulsion of all the content of the vesicle to the synaptic cleft.
6. Then norepinephrine reacts with adrenergic receptors present on the effector cell .

3) Fate :

a. **Neuronal uptake**: when the cleft is full with norepinephrine, it is taken up by NET (norepinephrine transporter), then norepinephrine re-enters the vesicles for storage by VMAT .

b. There are **auto receptors** and **hetero-receptors** that affect the release of Norepinephrine :

▪ **Auto receptors** : are alpha 2 receptors that when activated by norepinephrine inhibits further release of norepinephrine from the neuron (negative feedback mechanism), they are called auto receptors because they are activated by the same neurotransmitter that is released from the same neuron .

▪ **Hetero-receptors** for example cholinergic receptors; when a parasympathetic neuron is activated part of the acetylcholine will activate these receptors so inhibiting the release of norepinephrine .

Drugs that effect the release of norepinephrine :

1) **Bretylium & Guanethidine** : which are drugs that inhibit the release of

norepinephrine, their mechanism of action isn't known yet .

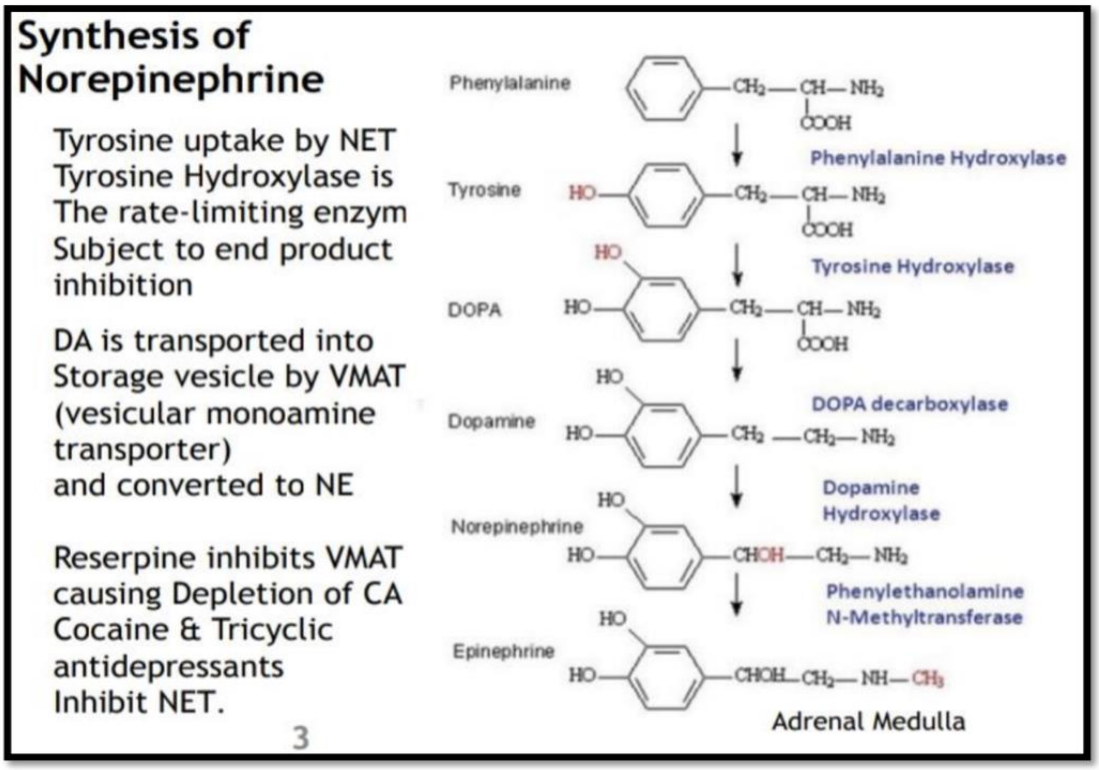
• Guanethidine was used in past to treat hypertension & Bretylium was used as anti-arrhythmia drug .

Both of them are no longer used for medical purposes

2) **Metyrosine & Reserpine** (discussed before)
3) **Cocaine, tricyclic antidepressants** : block NET so increasing the concentration of norepinephrine in the synaptic cleft .

*** keep in mind that 80% of norepinephrine is taken up by NET , the other 20 %** will diffuse into the tissues and get metabolized there .

Synthesis of Norepinepherine :



The previous picture summarizes the steps of norepinephrine's synthesis (Recall ☺) :

1) Phenylalanine is converted into tyrosine by the addition of a hydroxyl group by (phenylalanine hydroxylase) enzyme . -shown in red-
2) Then tyrosine enters the neuron and is converted into Dopa by the addition of another OH group by the enzyme(tyrosine hydroxylase) .

• **Parkinson disease and cell deficiency of dopamine is treated with dopa**

3) Dopa is converted into dopamine by the removal of a carboxylic group by (dopa decarboxylase) .

• **Dopa decarboxylase is sometimes called: L aromatic acid decarboxylase because it is not specific for dopa .**

4) Dopamine is converted into norepinephrine by the addition of a hydroxylic group to the β carbon in the hydrocarbon chain by (dopamine β hydroxylase) .

• **Any excess of norepinephrine will inhibit tyrosine hydroxylase so the synthetic pathway will stop (end product inhibition)**

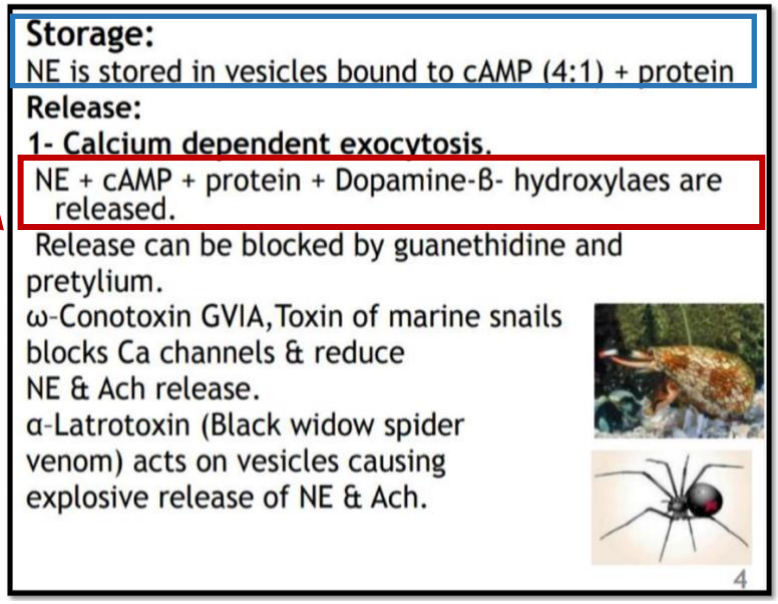
5) This step doesn't happen in the neuron it happens in the chromaffin cells of the adrenal medulla by the enzyme (Phenylethanolamine N-methyltransferase) that transfer a methyl group from S-adenosyl methionine to the amino end of the hydrocarbon chain in the norepinephrine , so it becomes epinephrine .

Storage & Release of Norepinephrine:

The release can either be calcium dependent or independent

1) The most common type of release is **calcium dependent** exocytosis and it requires action potential .

Action potential opens calcium ion channels , then movement of the vesicles towards the membrane , followed by rapture of the membrane and release of :



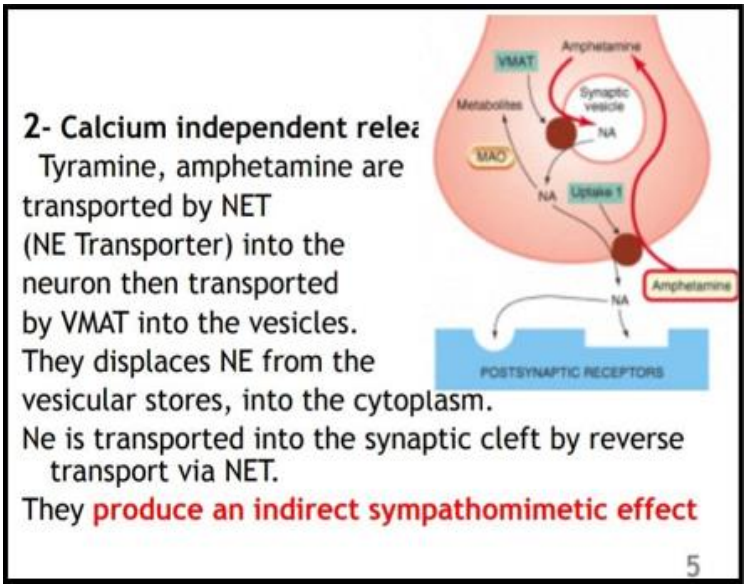
As you see from the pic : - another 2 inhibitors of the pathway are :

1) ω- Conotoxin : which is a toxin produced by marine snails , that block calcium channels , thus reducing calcium influx , and reducing NE and Ach release . " working on both cholinergic and adrenergic nerves " .
2) A very deadly venom called α-Latrotoxin (produced by black widow spider) , it's very poisonous as it binds on vesicles causing the release of NE and Ach explosively , so all content of all vesicles are thrown out into the synaptic cleft causing death .

2) calcium independent release .

This mechanism doesn't require action potential , and it doesn't use the norepinephrine stored in the neuron .

It uses other pools of norepinephrine .



A) A certain pool of norepinephrine is able to be released by this mechanism , this is done by certain materials like:
   1) **Tyramine :** that is present in cheese, some kinds of jam, and certain types of wine.
   2) **Amphetamine :** which is a powerful CNS stimulant .

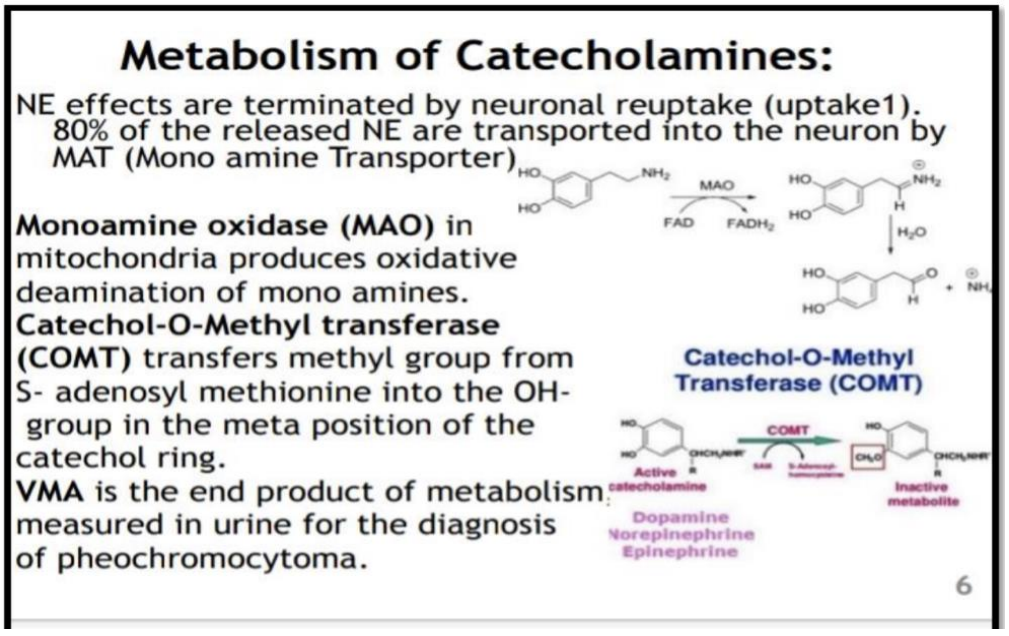
The mechanism :

1. Amphetamine is taken up into the neuron by NE transporter (that same one that releases NE normally) , then it gets inside the vesicle , thus displacing norepinephrine in the vesicles , so norepinephrine gets out , which doesn't require action potential .
2. Once Norepinephrine become outside the vesicle, it is not protected from MAO (mono amine oxidase) present on the surface of the mitochondria , so some of the norepinephrine will be metabolized. However , most of it will be released into the synaptic cleft to activate postsynaptic receptors and produce an effect .

Applications :

a) If we inject tyramine intravenously, the blood pressure will increase, because it causes the release of norepinephrine which binds to alpha1 receptors causing vasoconstriction .
b) The body has **rapid tolerance with tyramine and amphetamine**, so if we give them frequently, we will see that the response will decrease gradually until no response will result at all; a phenomena called **tachyphylaxis** (rapidly diminishing response to successive doses of a drug, rendering it less effective) .
c) **Remember :** that the neuron's stimulation by action potential is not subjected to tolerance , that is why the pool of tyramine and amphetamine is considered small and exhaustible .
d) Tyramine that is present in food stuff is not dangerous because it is metabolized by MAO in the intestine and liver .
e) But if a patient is taking **MAO inhibitors** , specially patients with depression then eats cheese for example, this will be dangerous because it causes severe elevation in blood pressure that might be fatal.
f) **Cheese reaction** is a well-documented reaction of that occurs in patients taking MAO inhibitors after they consume food with high tyramine content such as aged cheese, soy sauce, fava beans, and large amount of red wine.

That is why calcium independent pathways are said to produce indirect sympathetic effect .



Cholinoceptors

Muscarinic M1: CNS neurons, sympathetic postganglionic neurons, some presynaptic sites.

Muscarinic M2: Myocardium, smooth muscle, some presynaptic sites; CNS

Muscarinic M3: Exocrine glands, vessels (smooth muscle and endothelium); CNS

Muscarinic M4: CNS neurons.

Muscarinic M5: CNS neurons.

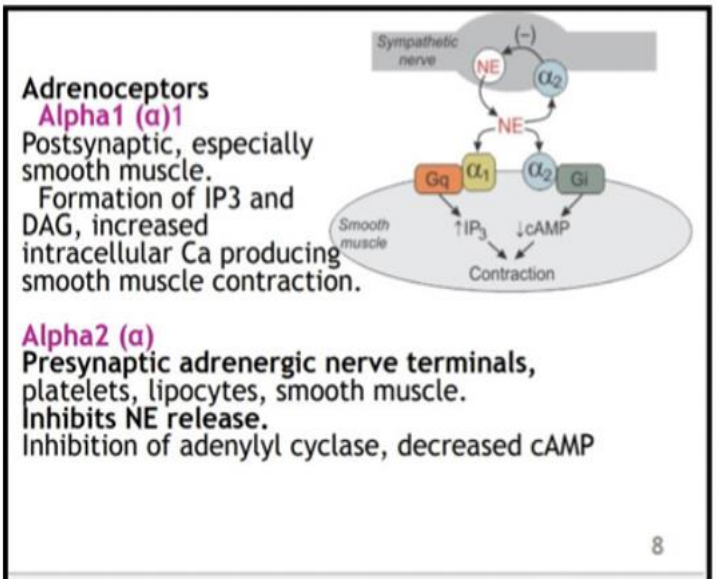
Nicotinic NN: Postganglionic neurons, some presynaptic cholinergic terminals.

Nicotinic NM: Skeletal muscle neuromuscular end plates.

There are two types of adrenoreceptors : alpha and beta .

Alpha receptors themselves are divided into alpha 1 and alpha 2 receptors .

And they recently found that each of alpha 1 and alpha 2 are subdivided into other subdivisions as well . ☺



1) **Alpha 1 receptors** : are **postsynaptic** , especially smooth muscles in which all smooth muscles of blood vessels have alpha 1 receptors in which they produce vasoconstriction upon stimulations .

   Then they form second messengers like IP3 and DAG , in which their increase causes the increase of intracellular Ca , producing smooth muscle contraction .

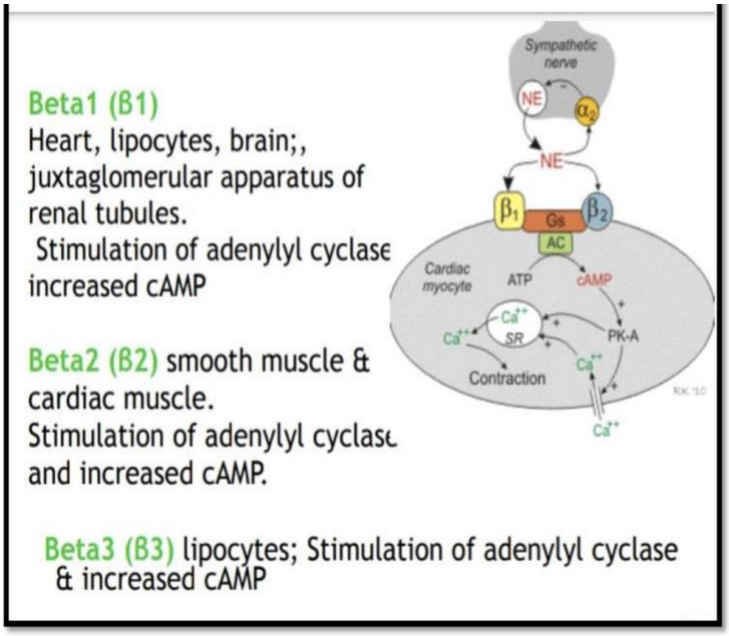
2) **Alpha 2 receptors** : are **presynaptic adrenergic nerve terminals** found in platelets , lipocytes , and smooth muscles . **T**hey inhibit the release of norepinephrine from the presynaptic neuron by inhibiting adenylyl cyclase , and thus decrease cAMP .

Beta receptors are subdivided into 3 divisions :

1) Beta 1

2) Beta 2

3) Beta 3



1) When **beta1 receptors** are activated :

A. The heart rate, force of contraction and the conductive velocity of the heart **will increase**
B. And it will stimulate renin release which activates renin- angiotensin-aldosterone system that causes retention of sodium and water and vasoconstriction thus increase in blood pressure
C. It is found in the heart , lipocytes , brain , and juxtaglomerular apparatus of renal tubules .
D. They stimulate adenylyl cyclase , thus increases cAMP (second messengers).

2) **Beta2 receptors** : especially present in the smooth muscles of the bronchioles of the lungs, that when stimulated, it causes relaxation so we use beta2 agonist (bronchodilators) to treat patients with **bronchial asthma .**

• Beta2 also present as presynaptic receptors in cardiac muscle that when stimulated, they increase the release of norepinephrine , which happens by stimulation of adenylyl cyclase and increased cAMP .

3) **Beta3 receptors :** found in lipocytes , when stimulated, they produce lipolysis (breaking down of lipids into free fatty acids) so adds more fuel to the body

Also dopamine receptors consist of D1 and D2 , and each of these two are subdivided into other subdivisions .

Dopamine receptors

D1 (DA 1, D5)

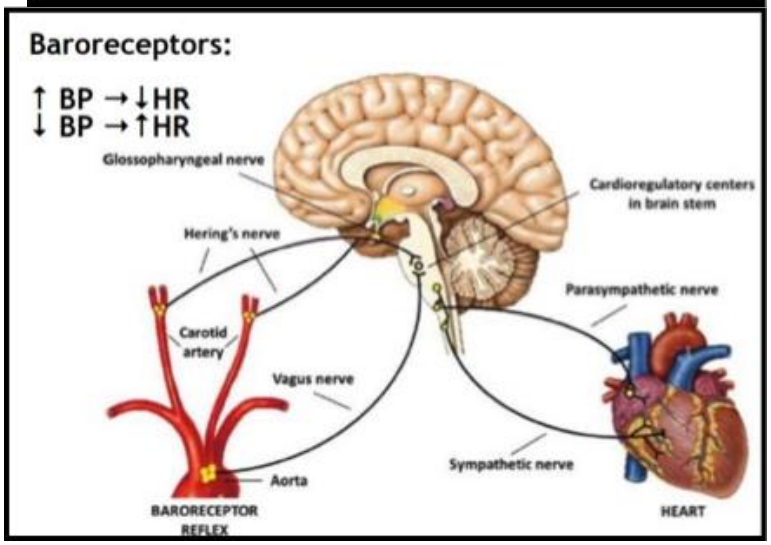
Brain, especially smooth muscle of the renal vascular bed.

Stimulation of adenylyl cyclase and increased cAMP.

D2 (DA 2, D3, D4) Brain, especially smooth muscle; presynaptic nerve terminals (D2).

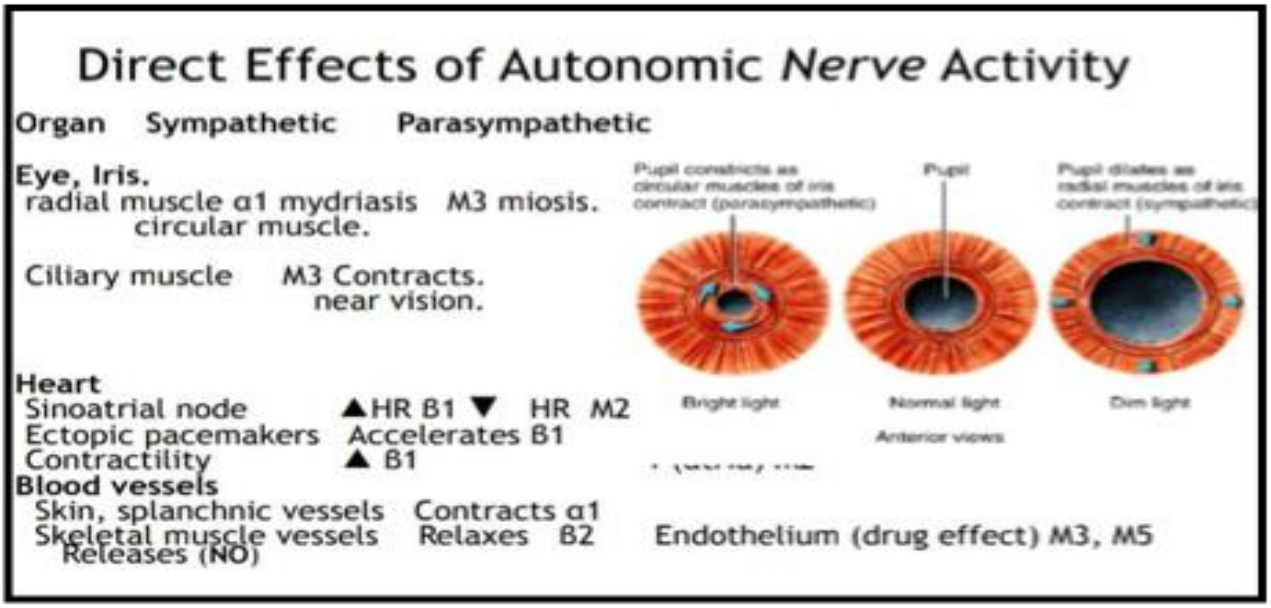
Inhibition of adenylyl cyclase; increased potassium conductance.

Baroreceptors are mechanical receptors that sense the increase in the stretch of great arteries like aorta and carotid artery



1) So when blood pressure increases, the arteries will be stretched, then these baroreceptors will sense this stretch and send a signal to the brain, then the brain immediately activates the vagus nerve which is parasympathetic nerve that causes bradycardia (decrease in heart rate) .
2) When blood pressure decrease, this will be sensed by the baroreceptors, then send signal to the brain to activate the sympathetic nerve that cause tachycardia (increase in heart rate) to keep the homeostasis of the body constant .
3) The cardio regulatory center in the brain stem coordinate this process .

Direct effects of Autonomic Nerve Activity : continue reading to understand more ☺



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 :

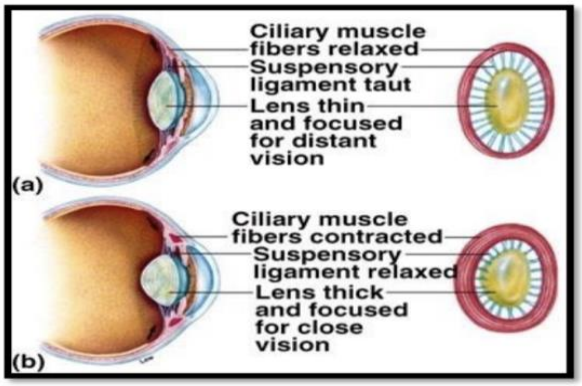
▪ **Radial muscle** has alpha1 receptors that when stimulated the radial muscle will contract, increasing the pupil size (mydriasis- pupil dilation) which is a sympathetic effect , in the case of dim light for ex .

▪ **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 .

• At any time the pupil size depends on 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 and have M3 receptor, that when activated the muscle will contracts so changing the accommodation of the eye to be suitable for near vision .

Ciliary muscles :



Heart

- **Sinoatrial node** has beta1 receptors that when stimulated, it increases the heart rate & 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 .
- Beta1 receptors when activated, it increase 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 .**

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

➢ It is important in **emergency situations** because skeletal muscles needs more blood to fight or flight, while non essential organs like skin don't need blood; so the person becomes yellow because small amount of blood flow to skin, also the renal blood flow decreases

➢ In emergency situations a dilation in the blood vessels of essential organs like coronary arteries, vessels of brain and skeletal muscles & constriction of blood vessels of the skin, kidney, etc.

• No innervation of the blood vessels by **parasympathetic** neurons but all blood vessels have 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 $\alpha 1$ receptors causes contraction .
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 its 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 results .
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

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
B. Gluconeogenesis: synthesis of glucose from non carbohydrate sources
C. When a person feels worried, his blood sugar rises because of activation of the sympathetic nervous system

Where there is no struggle , there is no strength

و قل رب زدني علما