Autonomic Nervous System

Introduction

2020

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Presynaptic receptors

They have negative feedback

presynaptic receptors and their mediators

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

Autoreceptors

Stimulated by the same transmitter released by the same neuron, increasing / decreasing the release of further amount of that transmitter

Hetero-receptors

present on the outer membrane of neuron (A)

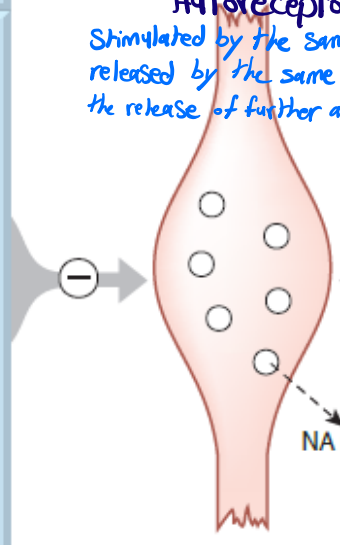
But stimulated with a transmitter released by another neuron increasing or decreasing release of a transmitter released by neuron (A)

Receptor type	Mediator
β_2	A
AT_1	Angiotensin II

positive feedback

ex. releasing NE from neuron B to inhibit Ach release from neuron A

"NE binds to receptors on neuron A, the hetero receptors."



Heteroreceptors respond to neurotransmitters, neuromodulators, or neurohormones released from adjacent neurons or cells; they are opposite to autoreceptors, which are sensitive only to neurotransmitters or hormones released by the cell in whose wall they are embedded.

● Heteroreceptors

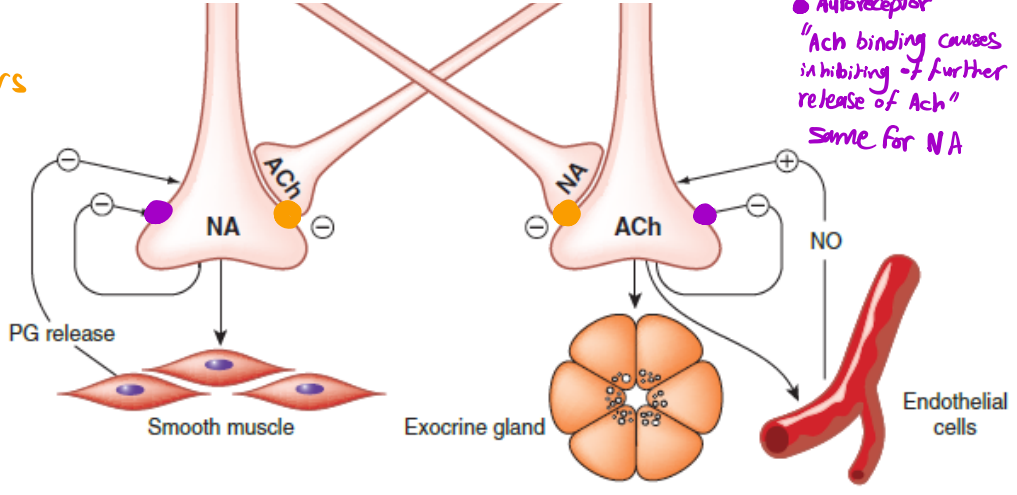
"Ach binding to receptors on the other neuron causes inhibiting of further release of NA"

Same for NA

● Autoreceptor

"Ach binding causes inhibiting of further release of Ach"

Same for NA



Adrenergic Transmission

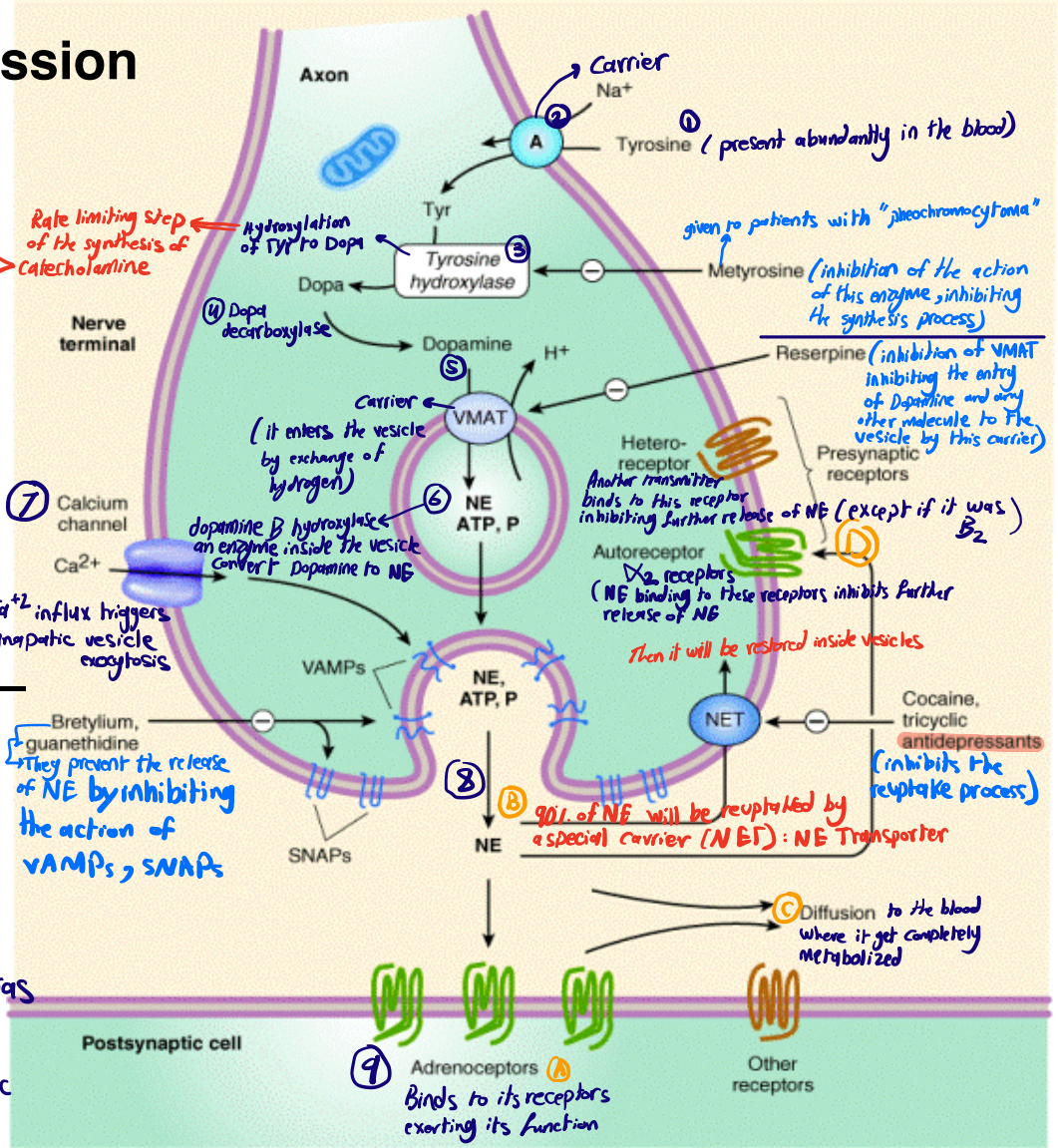
Synthesis, storage, release
↳ of catecholamines
(NA, A)
[the synthesis of NE, E is more complex]

VMAT

~~VAT~~; vesicular
Mono Amine
Transporter

SNAPs: synaptosome –
Associated proteins.

- Reserpine & Drug used to reduce high blood pressure, It also causes severe depression.
- Bretylium & used for cardiac arrythmias
- guanethidine & used for hypertension, But it has severe side effects involving sympathetic system effects



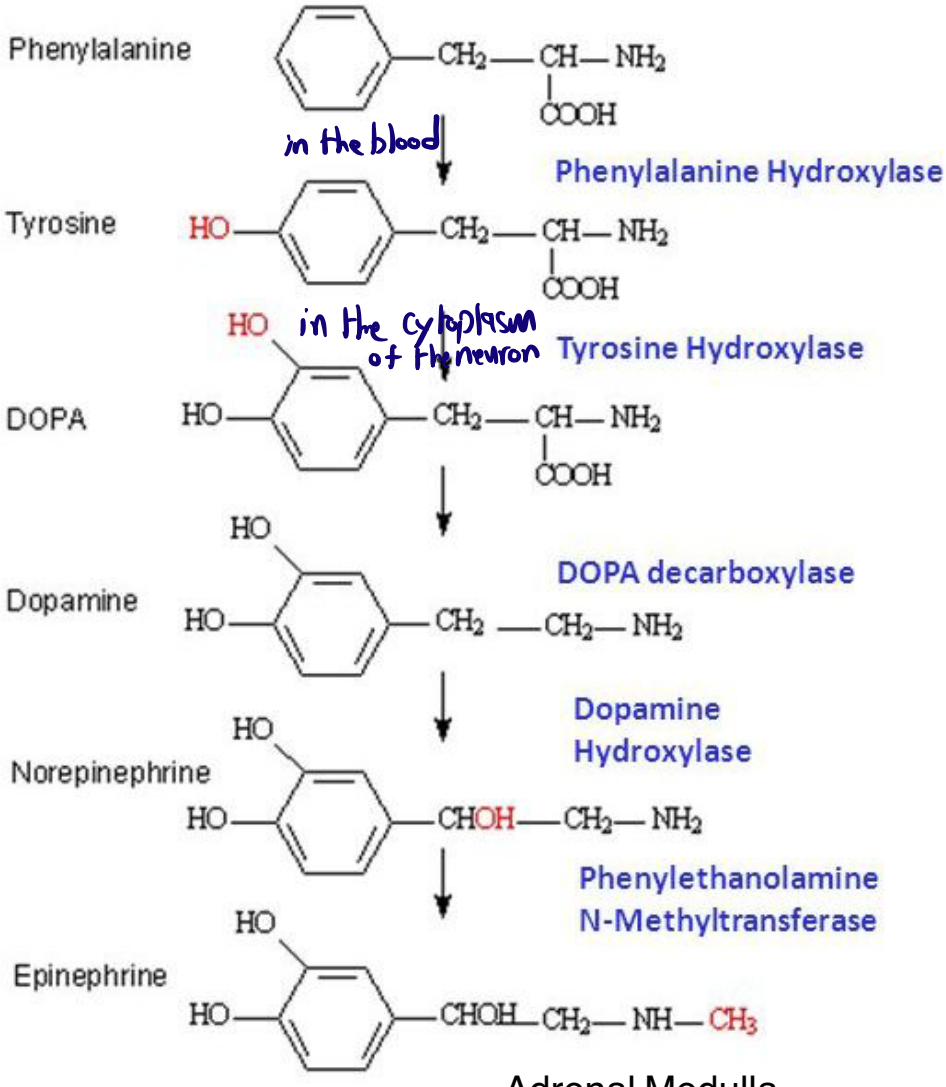
Synthesis of Norepinephrine

Tyrosine uptake by NET (carrier A)
Tyrosine Hydroxylase is
The rate-limiting enzyme,
Subject to end product inhibition

DA is transported into
Storage vesicle by VMAT
(vesicular monoamine transporter)
and converted to NE

Reserpine inhibits VMAT causing Depletion of CA.

Cocaine & Tricyclic antidepressants
Inhibit NET.



Storage:

NE is stored in vesicles bound to cAMP (4:1) + protein

Release: → when the action potential reaches the nerve terminal, voltage dependent Ca^{+2} channels open and Ca^{+2} rushes into the neuron terminal due to a greater extracellular concentration

1- Calcium dependent exocytosis.

NE + cAMP + protein + Dopamine-β- hydroxylaes are released.

Release can be blocked by guanethidine and pretylium. (1) (2)

ω–Conotoxin GVIA, (3) Toxin of marine snails blocks Ca channels & reduce NE & Ach release. → preventing Ca^{+2} influx

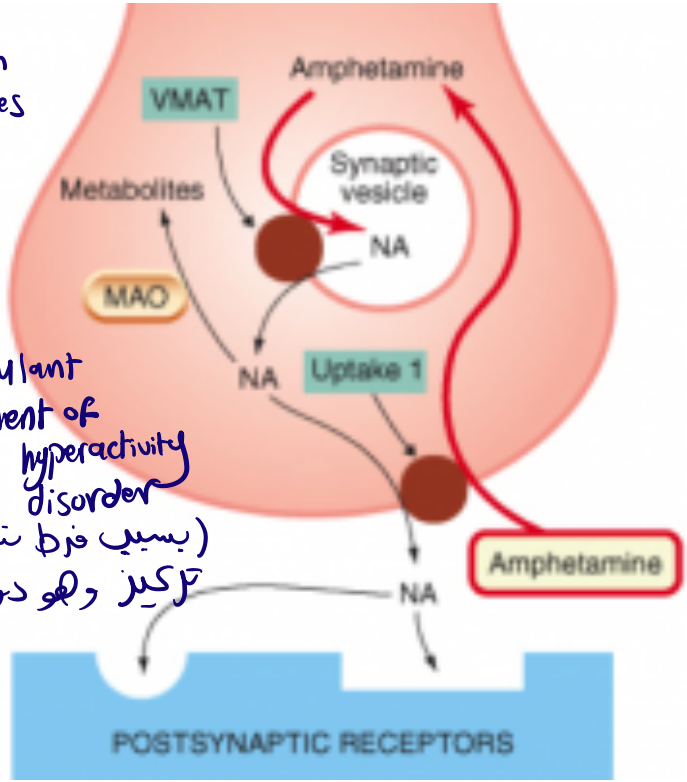
α–Latrotoxin (Black widow spider venom) acts on vesicles causing explosive release of NE & Ach. → increases neuron depolarization, increases Ca^{+2} influx, resulting in stimulating uncontrolled exocytosis of neurotransmitters from nerve terminals

→ Tyramine is an amino acid found in certain foods like cheese, jams. It's usually metabolized by monoamine oxidase enzymes in the liver or inteshines So it doesn't reach circulation. In cases of monoamine oxidase inhibition by certain drugs, metabolism of Tyramine won't occur, instead it reaches circulation and enters the neuron by NET, then it enters the vesicle.

2- Calcium independent relea

Tyramine, amphetamine are transported by NET (NE Transporter) into the neuron then transported by VMAT into the vesicles.

→ Strong CNS stimulant used in the treatment of attention deficit hyperactivity disorder (بسبب فرط نشاط وزيادة تركيز وهو دواء عنز قاوي عادة)



They displaces NE from the vesicular stores, into the cytoplasm.

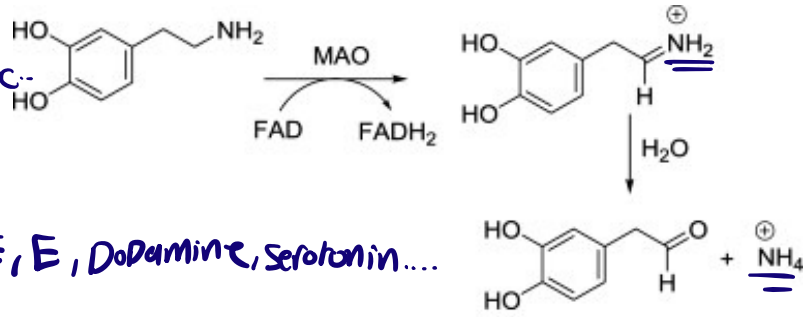
Ne is transported into the synaptic cleft by reverse transport via NET.

They **produce an indirect sympathomimetic effect**

→ They don't have direct effect on sympathetic system, but they force NE to bind its receptors.

Metabolism of Catecholamines:

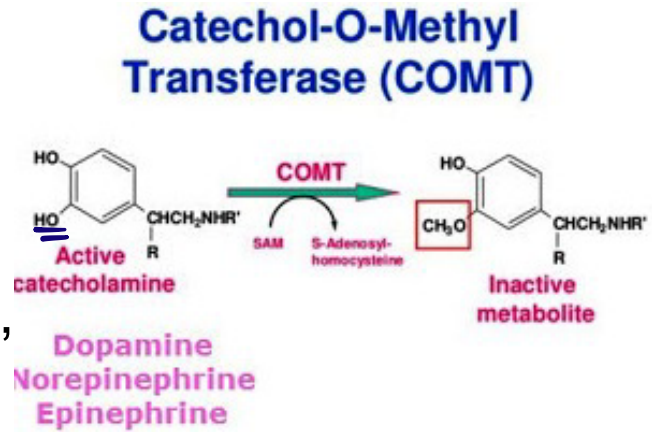
NE effects are terminated by neuronal reuptake (uptake1). 80% of the released NE are transported into the neuron by MAT (Mono amine Transporter).



→ in mitochondria of neurons, liver, intestines, etc...

Monoamine oxidase (MAO) in mitochondria, produces oxidative deamination of mono amines. → NE, E, Dopamine, Serotonin....

Catechol-O-Methyl transferase (COMT) transfers methyl group from S- adenosyl methionine (SAM) into the OH-group in the meta position of the catechol ring. inactivating this catecholamine



VMA is the end product of metabolism, measured in urine for the diagnosis of pheochromocytoma. → Tumor in adrenal medulla gland (high level of VMA in the urine indicates this kind of tumor)

↳ Causes increase in catecholamines levels

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.

- cholinoceptors oR cholinergic receptors

They are present on the cell surface and they get activated by a neurotransmitter called Acetylcholine.

They have two types depending on the drug that affects them

- → muscrinic receptors (affected by muscrine)
  (M1, M2, M3, M4, M5)
- → Nicotinic receptors (affected by Nicotin)
  (NN, NM)

Activation of M2 : Causes decrease in heart rate and a reduction in heart Contraction force.

M3 : - on Smooth muscle → induce Contraction
- on blood vessels → vasodilation by the release of Nitric oxide
- it also regulates glands secretion, except that of the stomach that is regulated by M1

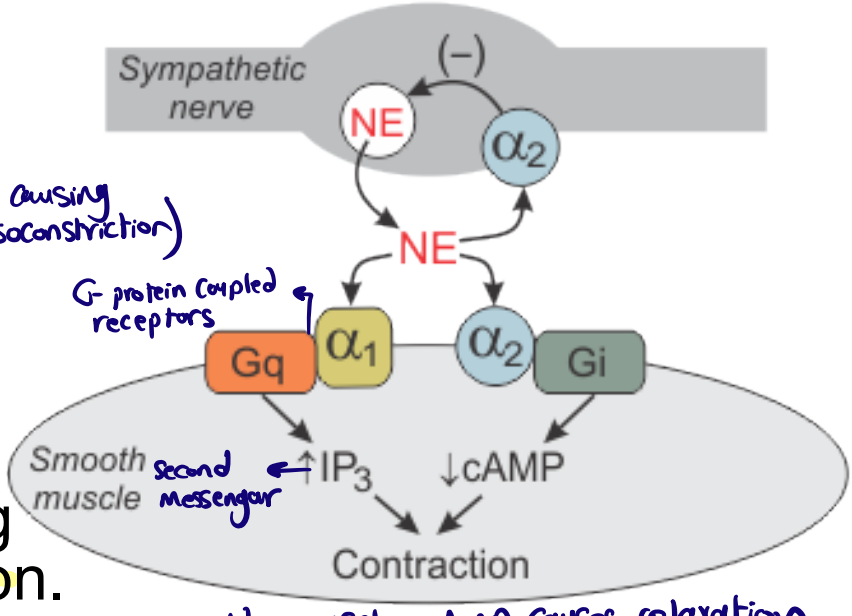
They are activated by NE, E and they exert their function by a second messengar

Adrenoceptors

Alpha1 (α)1 (Present on blood vessels causing vasoconstriction)

Postsynaptic, especially smooth muscle.

Formation of IP3 and DAG, causing increased intracellular Ca producing smooth muscle contraction.



- in smooth muscle cAMP causes relaxation while in cardiac muscles it causes contraction

Alpha2 (α)

Presynaptic adrenergic nerve terminals, platelets, lipocytes, smooth muscle.

Inhibits NE release.

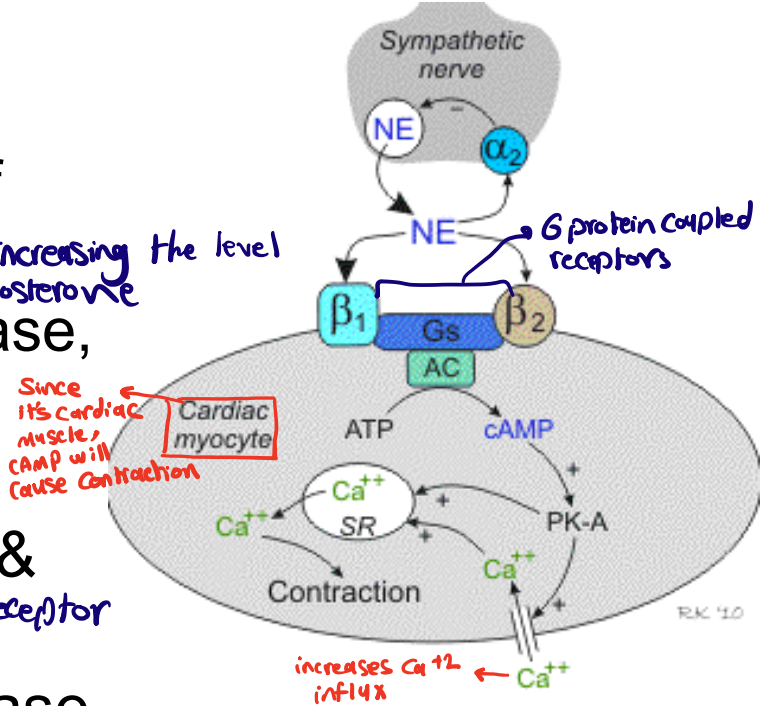
Inhibition of adenylyl cyclase, decreased cAMP → producing smooth muscle contraction

Beta1 (β1) Heart, lipocytes, brain;, juxtaglomerular apparatus of renal tubules. Stimulation of adenylyl cyclase, increased cAMP ⇒ Cardiac Muscle Contraction

increase heart rate

lipolysis

increase renin release, increasing the level of angiotensin II and aldosterone



Beta2 (β2) smooth muscle & cardiac muscle. Stimulation of adenylyl cyclase and increased cAMP. ⇒ Cardiac Muscle Contraction

presynaptic autoreceptor

Beta3 (β3) lipocytes; Stimulation of adenylyl cyclase & increased cAMP

They present in brown adipose tissue and they play role in lipolysis and thermogenesis in brown fat (They produce fatty acid)

Dopamine receptors

present mainly in the brain (CNS) and they are highly related to neurological diseases like schizophrenia

D1 (DA 1, D5) subtypes with almost the same effect

Brain, especially smooth muscle of the renal vascular bed.

Stimulation of adenylyl cyclase and increased cAMP.

subtypes with almost the same effect

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

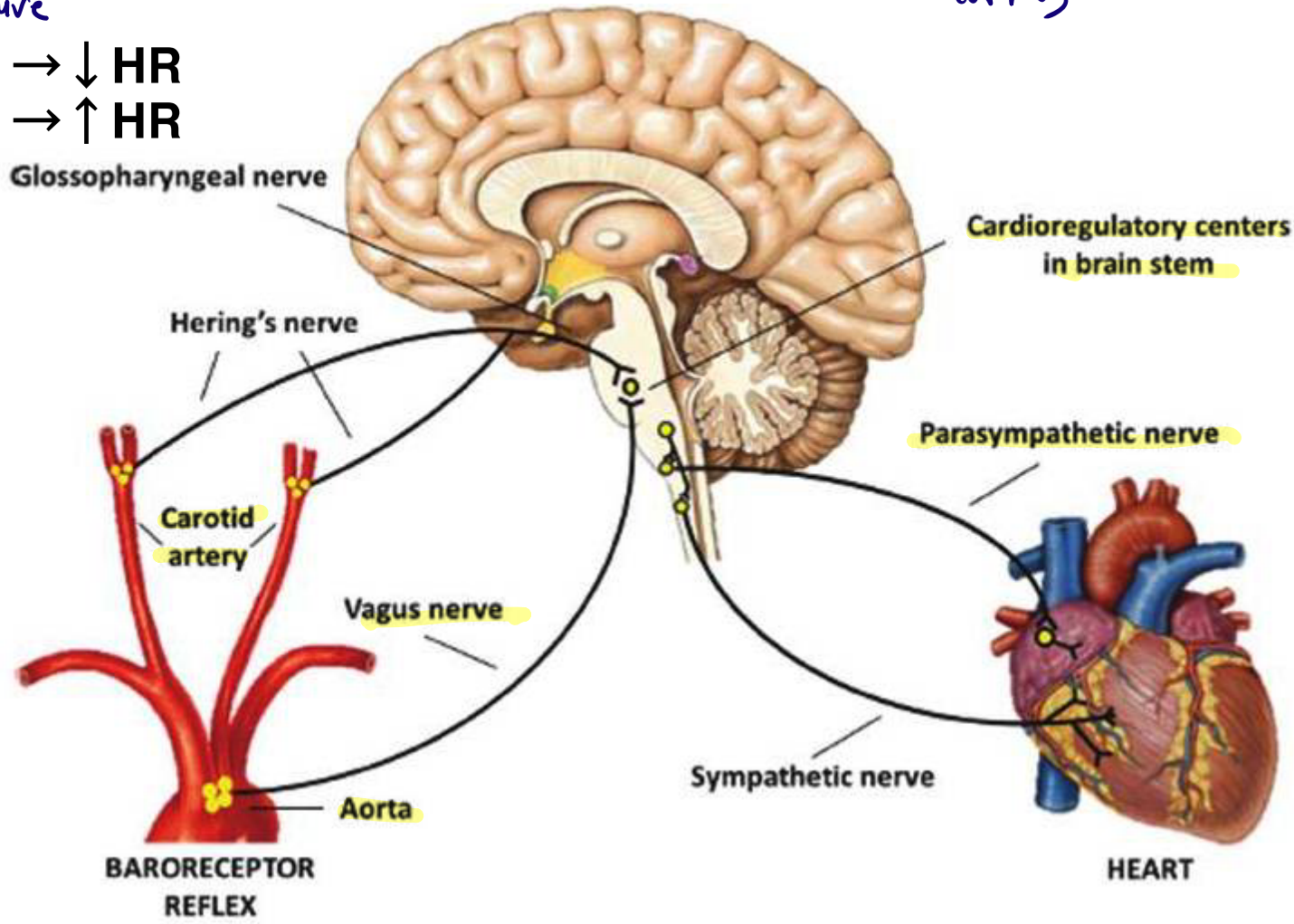
Inhibition of adenylyl cyclase; increased potassium conductance. → hyperkalemia

Baroreceptors: Receptors present in the carotid artery (a big artery in the aorta)

↑ pressure

↑ BP → ↓ HR

↓ BP → ↑ HR



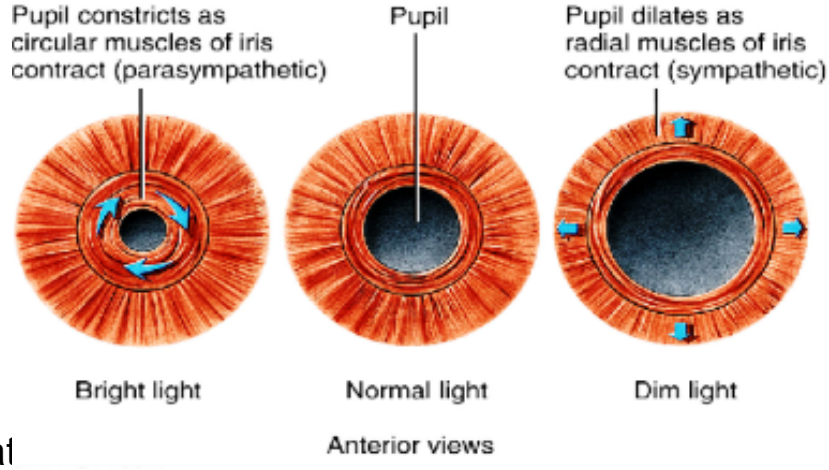
- Baroreceptors
  - Located in the carotid artery (one of the main branches of the aorta)
  - They function as sensors that sense any change in the blood pressure (Decreasing or increasing)
  - They are mechanoreceptors, so they will provide the brain with information about the blood pressure and volume by detecting the level of stretch on vascular walls
    As blood pressure increases, vessels are stretched, the firing rate of baroreceptors increases
  - They are connected with the brain through cardioregulatory center in the brain stem.
    ↳ part of the brain that controls heart rate, blood pressure, blood volume, etc.
  - High pressure baroreceptors causes increase in the activity of the vegal nerve stimulating parasympathetic system to decrease the blood pressure
  - Low pressure baroreceptors causes decrease of the baroreceptor output, stimulating sympathetic system to increase blood pressure

Direct Effects of Autonomic *Nerve* Activity

Organ Sympathetic Parasympathetic

Eye, Iris.
radial muscle α1 mydriasis M3 miosis.
circular muscle.

Ciliary muscle M3 Contracts.
near vision.



Heart
Sinoatrial node ▲HR β1 ▼ HR M2
Ectopic pacemakers Accelerates β1
Contractility ▲β1 ▼(at

Blood vessels
Skin, splanchnic vessels Contracts α1
Skeletal muscle vessels Relaxes β2 Endothelium (drug effect) M3, M5
Releases (**NO**)

- Effects of sympathetic and parasympathetic systems on our organs

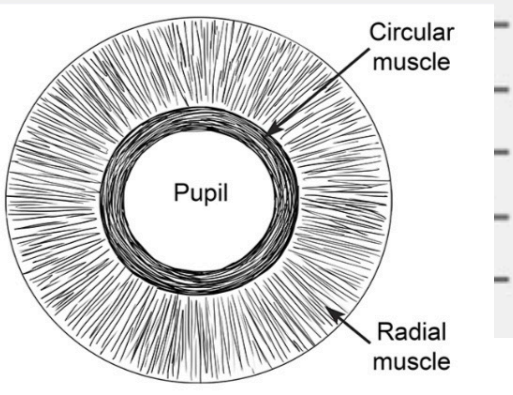
1. Eye, iris → Radial muscle (pupil dilator muscle)
→ Circular muscle (The sphincter muscle of the iris)
→ Ciliary muscle

- Radial muscle : affected by sympathetic system through α1 receptor
Causing mydriasis. (Contraction of radial muscle causes the pupil to dilate allowing more light to pass into the eyes)
- Circular muscle : affected by parasympathetic system through M3
Causing miosis (Contraction of Circular muscle causes the pupil to constrict allowing less light to pass into the eyes)

Pupil → Constriction (parasympathetic M3)
dilation (sympathetic α1)

- Ciliary muscle : it's connected with the lens through ligaments changing the shape of the lens when your eyes focus on a near object.

It's affected only by parasympathetic system through M3 receptor
Causes contraction of the muscle increasing its power to refract light for near vision.



2. Heart → Sinoatrial node (natural pacemaker of heart, controls HR)
→ Ectopic pacemaker
→ Contractility

- SA Node : affected by parasympathetic system through M2 decreasing HR
affected by sympathetic system through B1 increasing HR

- Ectopic pacemaker : An excitable group of cells that causes a premature heart beat outside the normally functioning SA node of the human heart.
affected by elevated sympathetic system input through B1
* In some cases ectopic pacemaker activity may take over the natural heart rhythm if it has higher intrinsic rate than the SA node, it may causes arrythmia in severe and chronic cases, and that's why such patients are given B blocker.

- Contractility : affected by sympathetic system through B1 increasing Contractility of the atria and the ventricles
affected by parasympathetic system through M2 decreasing Contractility of the atria only.

3. Blood vessels → Skin, splanchnic vessels (includes (gastric, small intestinal, colonic, pancreatic ....))
→ Skeletal muscle vessels
→ Endothelium

- Skin, splanchnic vessels : affected by Sympathetic system through α1 causing contraction leading to vasoconstriction.
- Skeletal muscle vessels : affected by sympathetic system through β2 causing relaxation leading to vasodilation.

Both are affected also by parasympathetic system causing opposite effects.

- Endothelium vessels : affected by parasympathetic system through M3, M5 but via a drug effect and not an endogenous neurotransmitter. resulting in the release of Nitric oxide leading to vasodilation.

	Sympathetic		parasympathetic	
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		

widening airway (easier breathing)

induces airway narrowing

moves the food when contracts

prevent the stomach content to go back into esophagus.

glycogen breaks down into glucose

glucose generation from non carb substrates

production of fatty acid

activating renin-angiotensin-aldosterone system

Men suffering from anxiety may have trouble having an erection.