4

Doctor 2021 - رَوْح - medicine - MU

Pharmacology sheet

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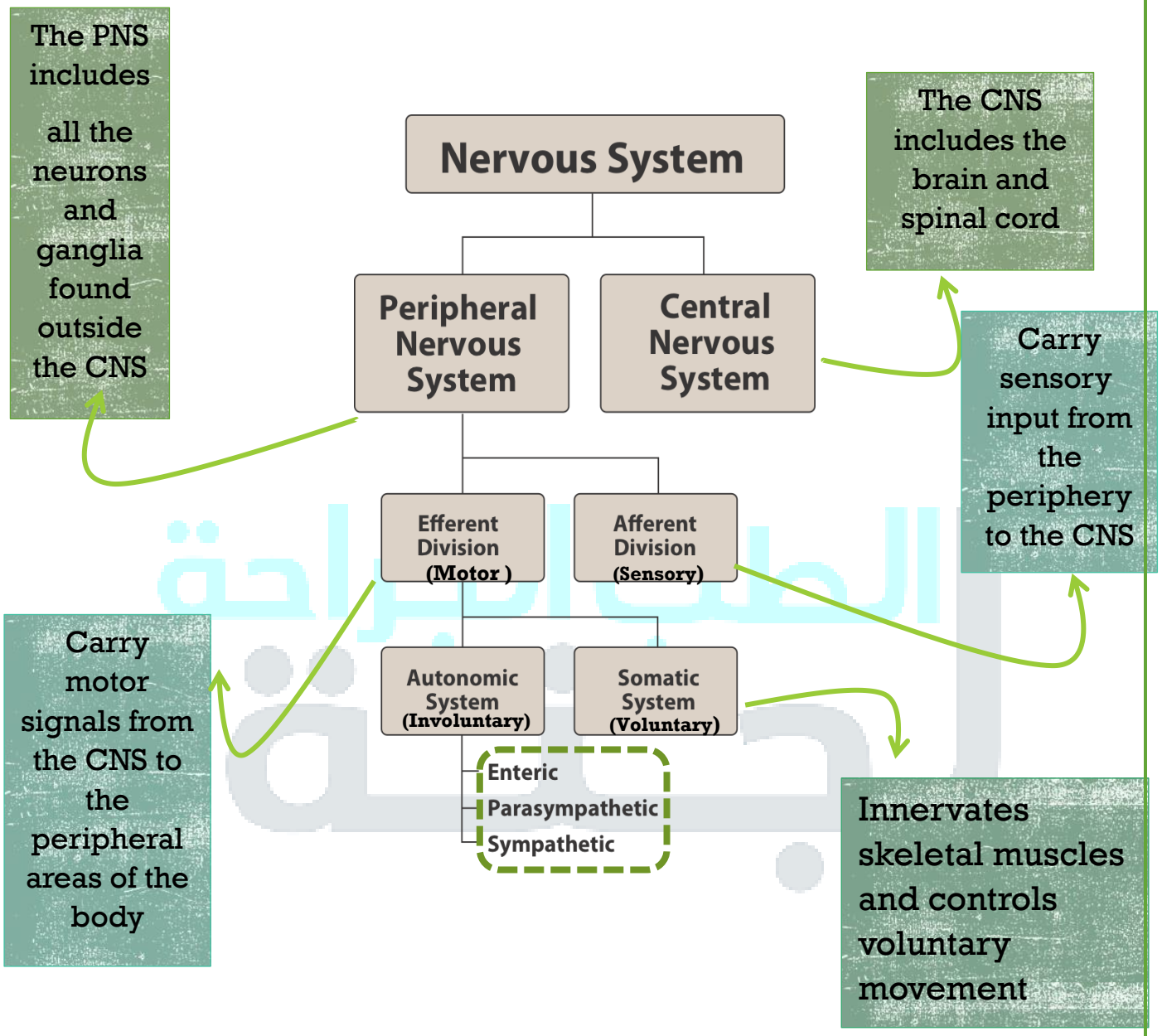
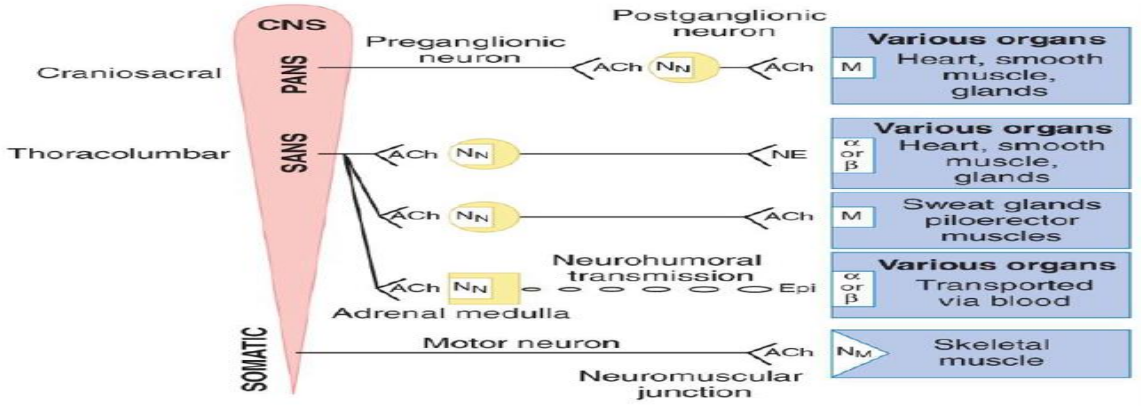
Introduction to Autonomic Nervous System Pharmacology





Divisions of nervous system

- **Preganglionic neuron in PANS longer than SANS one**
- **The opposite for the postganglionic neuron**
- **All autonomic ganglia on both sympathetic and parasympathetic are stimulated by Ach on Nn receptors**
- **Exception is sweat glands it is a sympathetic adrenergic but it has muscarinic receptors and Ach as a neurotransmitter**
- **Adrenal medulla is a modified autonomic ganglion (works as ganglia + endocrine gland). Normally ,it is secrete both E (more) and NE**
- **And with sympathatic adrenergic receptors**
- **When the adrenal medulla has benign tumor it starts secrete norepinephrine "NE' more than epinephrine"E" leads to VC and may lead to myocardial infarction**

Autonomic nervous system (ANS):

-The autonomic nervous system (ANS) carries the output of the central nervous system (CNS) to all peripheral organs except voluntary muscle.

-Automatically react to changes in the internal and external environments

-The ANS, without conscious thought or effort, controls involuntary activities in the visceral organs of the body (such as the heart, breathing, digestion, blood vessels), contraction and relaxation of smooth muscle, and secretory glands

-The ANS is regulated by centers in the CNS, including the hypothalamus, brain stem, and spinal cord.

-It is organised anatomically and functionally into sympathetic and parasympathetic divisions.

- N_N Nicotinic receptors are located on cell bodies in ganglia of both PANS and SANS and in the adrenal medulla.
- N_M Nicotinic receptors are located on the skeletal muscle motor end plate innervated by somatic motor nerves.
- M_{1-3} Muscarinic receptors are located on all organs and tissues innervated by postganglionic nerves of the PANS and on thermoregulatory sweat glands innervated by the SANS.

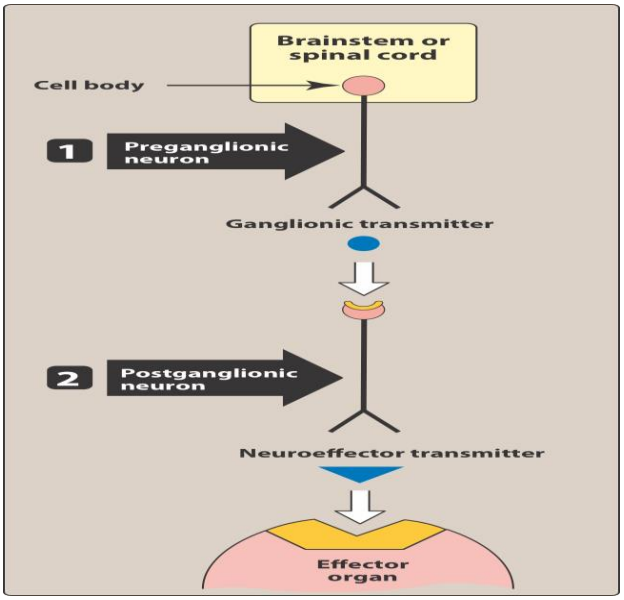
❖ Organization of ANS:

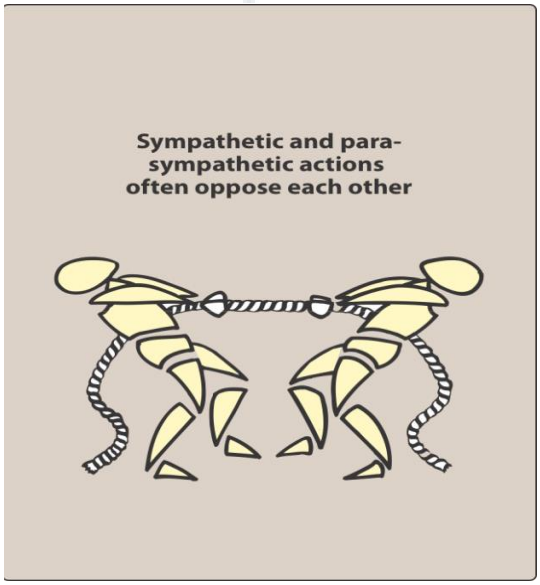
-Autonomic nerve impulses are carried through preganglionic fibers, ganglia, and postganglionic fibers

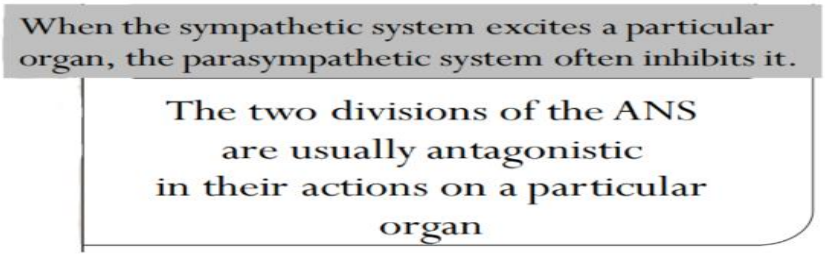
-Preganglionic impulses travel from the CNS along the preganglionic nerves to ganglia. Ganglia are composed of the terminal end of the preganglionic nerve and clusters of postganglionic cell bodies.

-A neurotransmitter is released from the terminal end of the preganglionic nerve allowing the nervous impulse to bridge the synapse between the preganglionic and postganglionic nerve.

-The postganglionic impulses travel from ganglia to effector tissues of the heart, blood vessels, glands, other visceral organs, and smooth muscle







- **Both sympathetic and parasympathetic are antagonists to each other but some organs one of them have the power →**
  - heart under the effect of parasympathetic to control heart rate (so that the heart doesn't undergo arrest)
  - blood vessels under the effect of sympathetic to control the pressure
- **When the sympathetic system excites a particular organ, the parasympathetic system often inhibits it.**
- **The two divisions of the ANS are usually antagonistic in their actions on a particular organ**

-Acetylcholine (ACh) is the neurotransmitter at both nicotinic and muscarinic receptors in tissues that are innervated.

-Note that all direct transmission from the CNS (preganglionic and motor) uses ACh, but postganglionic transmission in the SANS system may use one of the organ-specific transmitters described below:

-Norepinephrine (NE) is the neurotransmitter at most adrenoceptors in organs, as well as in cardiac and smooth muscle.

-Dopamine (DA) activates D1 receptors, causing vasodilation in renal and mesenteric vascular beds.

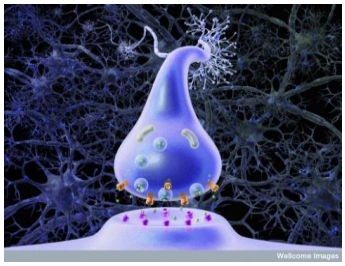
-Epinephrine (E), from adrenal medulla) activates most adrenoceptors and is transported in the blood.

❖ Neurotransmitters: chemical signal

-Communication between nerve cells and between nerve cells and effector organs occurs through the release of specific chemical signals, called neurotransmitters, from the nerve terminals.

-The neurotransmitters rapidly diffuse across the synaptic cleft or space (synapse) between neurons and combine with specific receptors on the postsynaptic (target) cell

-The **main neurotransmitters** of the ANS are acetylcholine and norepinephrine



-The nerve fibers that secrete acetylcholine are called cholinergic fibers

-Nerve fibers secreting norepinephrine are called adrenergic fibers.

Nerve fiber that releases Ach→ cholinergic mainly (parasympathetic)

Sympathetic is the one that releases

1) **Norepinephrine/epinephrine →adrenergic**
2) **dopamine → dopanergic**

❖ Sympathetic Nervous System:

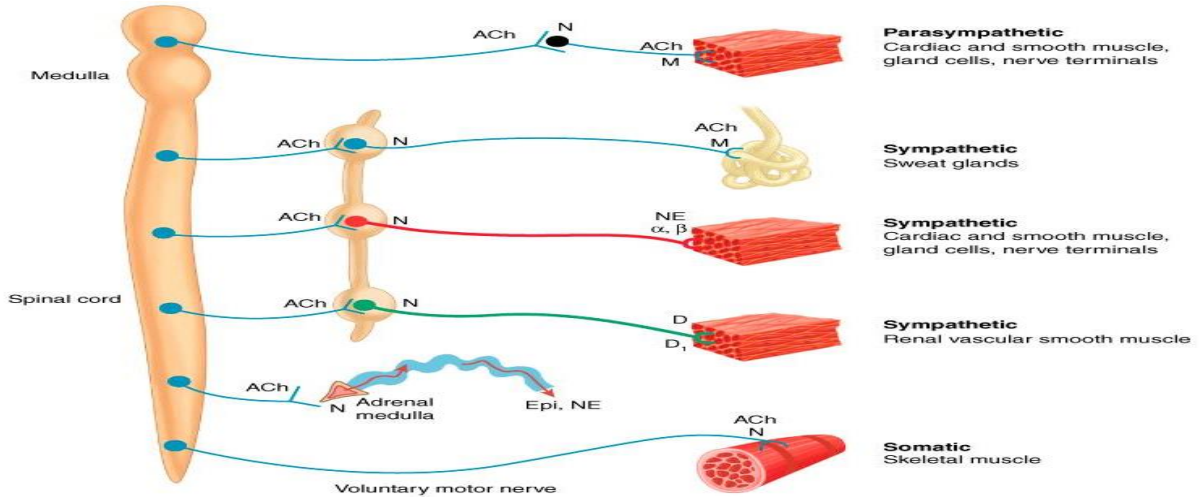
-The preganglionic neurons of the sympathetic system come from **thoracic and lumbar** regions of the spinal cord (Thoracolumbar)

-The preganglionic neurons are **short** in comparison to the postganglionic ones.

-**Axons** of the postganglionic neuron extend from these ganglia to the tissues that they innervate and regulate

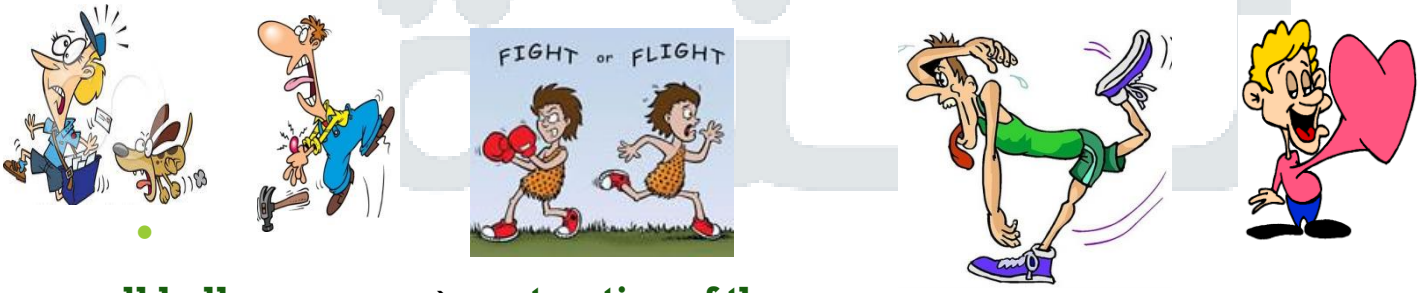
-**Lacking axons**, the adrenal medulla, in response to stimulation by the ganglionic neurotransmitter acetylcholine, influences other organs by secreting the hormone epinephrine (adrenaline), and lesser amounts of norepinephrine (noradrenaline) into the blood

-Norepinephrine is released at most postganglionic fibers of the sympathetic nervous system.



❖ Function of sympathetic neurons:

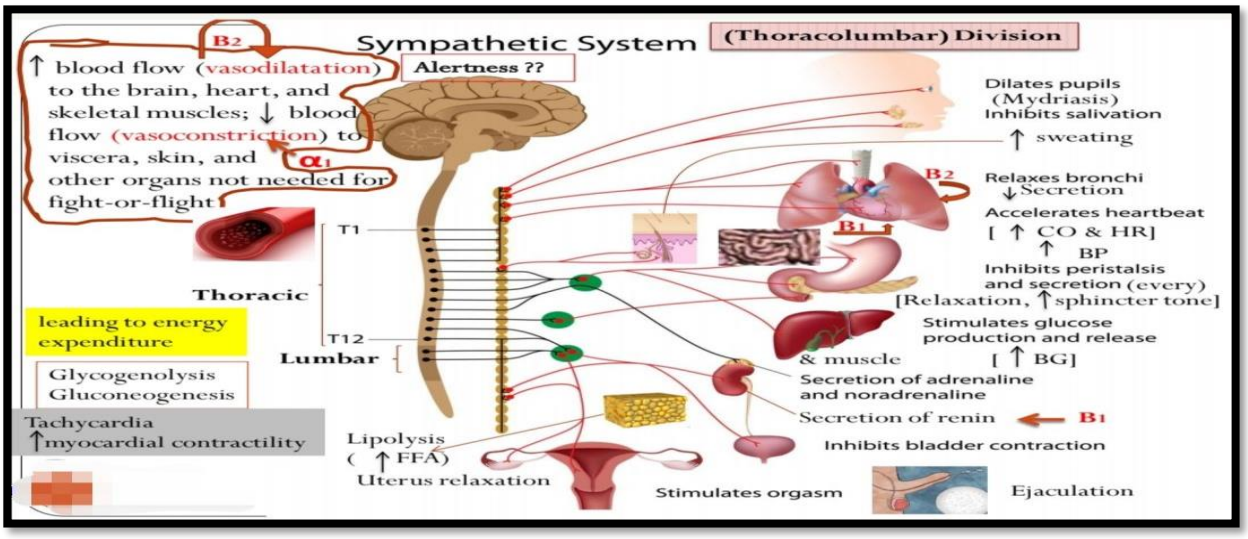
-Although continually active to some degree (for example, in maintaining the tone of vascular beds), the sympathetic division has the property of adjusting in response to stressful situations, such as trauma, fear, pain, hemorrhage, hypoglycemia, cold, or extraneous exercise or work (Fight or flight response)



-all hollow organs → contraction of the sphincters and relaxation of it's walls

- **if both contraction rupture would occur**
- **if both relaxation this is paralysis**
- **digestion and secretions are paused**
- **renin→ controls blood pressure**
- **ladies that have threaten abortion are given uterus inhibitor → no contraction no abortion**

- **this system needs energy so we must got energy from glycogenolysis which leads to gluconeogenesis which gives us power.**



-hydroxylation of the tyrosine stage is the one that controls the amount of NE in the body, so if we have enough amount of it, it stops

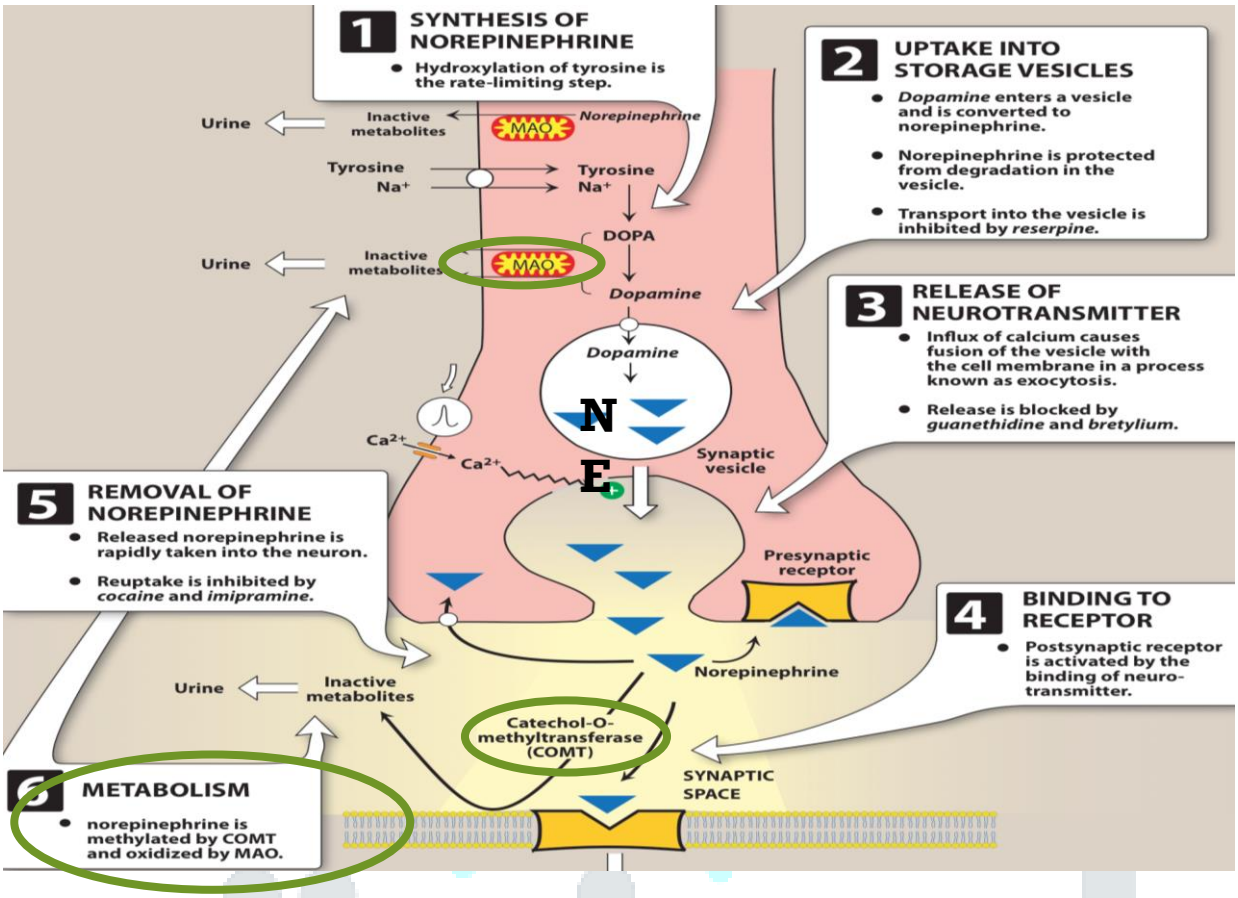
-reserpin is for hypertintion it privent moving of dopamine to a vesicle

-Ca+2 is very important for releasing the secretions

-Coacine inhibts the reuptake of adrenaline that's why people that use this drug feel hyper and energetic

-Withradwl symptomes antagonise the effect of the drug, as soon as we stop taking the drug and its low amount inside body , the person that was under effect of coacine goes to sleep and totally the opposite with morphine

-impramine → anti-depressent (DANGEROUS cuz it inhibits the adrenaline uptake)


1 SYNTHESIS OF NOREPINEPHRINE
Hydroxylation of tyrosine is the rate-limiting step.
2 UPTAKE INTO STORAGE VESICLES
Dopamine enters a vesicle and is converted to norepinephrine.
Norepinephrine is protected from degradation in the vesicle.
Transport into the vesicle is inhibited by reserpine.
3 RELEASE OF NEUROTRANSMITTER
Influx of calcium causes fusion of the vesicle with the cell membrane in a process known as exocytosis.
Release is blocked by guanethidine and bretylium.
4 BINDING TO RECEPTOR
Postsynaptic receptor is activated by the binding of neuro-transmitter.
5 REMOVAL OF NOREPINEPHRINE
Released norepinephrine is rapidly taken into the neuron.
Reuptake is inhibited by cocaine and imipramine.
6 METABOLISM
norepinephrine is methylated by COMT and oxidized by MAO.
Urine
Inactive metabolites
MAO
Norepinephrine
Tyrosine
Na+
DOPA
Dopamine
Ca2+
N
E
Synaptic vesicle
Presynaptic receptor
Catechol-O-methyltransferase (COMT)
SYNAPTIC SPACE

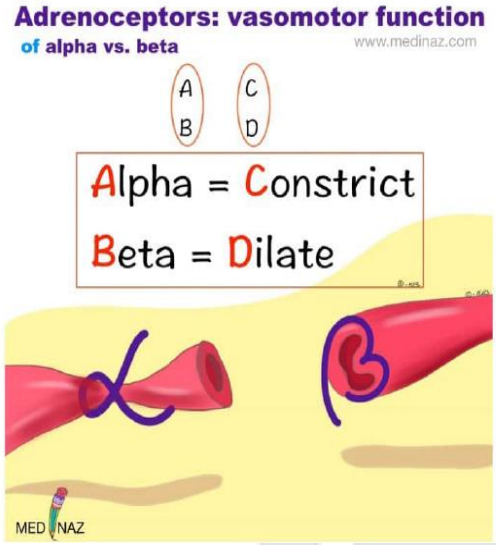
❖ Adrenergic receptors:

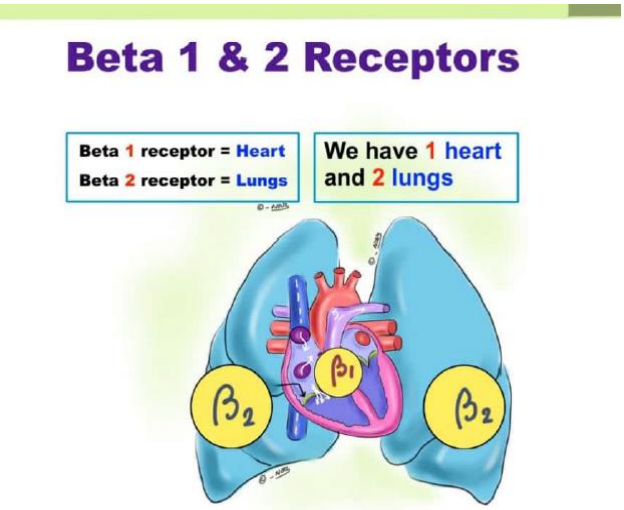
Receptor	Response
α_1	
Eye: radial (dilator) muscle	Contraction: mydriasis
Arterioles (skin, viscera)	Contraction: ↑ TPR, ↑ diastolic pressure, ↑ afterload
Veins	Contraction: ↑ venous return, ↑ preload
Bladder trigone and sphincter and prostatic urethra	Contraction: urinary retention
Male sex organs	Vas deferens: ejaculation
Liver	↑ glycogenolysis
Kidney	↓ renin release
α_2	
Prejunctional nerve terminals	↓ transmitter release and NE synthesis
Platelets	Aggregation
Pancreas	↓ insulin secretion
β_1	
Heart SA node	↑ HR (positive chronotropy)
AV node	↑ conduction velocity (positive dromotropy)
Atrial and ventricular muscle	↑ force of contraction (positive inotropy), conduction velocity, CO and oxygen consumption
His-Purkinje	↑ automaticity and conduction velocity
Kidney	↑ renin release
β_2 (mostly not innervated)	
Blood vessels (all)	Vasodilation: ↓ TPR: ↓ diastolic pressure, ↓ afterload
Uterus	Relaxation
Bronchioles	Dilation
Skeletal muscle	↑ glycogenolysis: contractility (tremor)
Liver	↑ glycogenolysis
Pancreas	↑ insulin secretion

D_1 (peripheral)	
Renal, mesenteric, coronary vasculature	Vasodilation: in kidney ↑ RBF, ↑ GFR, ↑ Na^+ secretion

Table II-3-1. Adrenergic Receptor Activation

- **Renin alpha1 → inhibits Renin beta1→ stimulate**
- **Insuline alpha2 □ inhibits insuline beta 2□ stimulate**





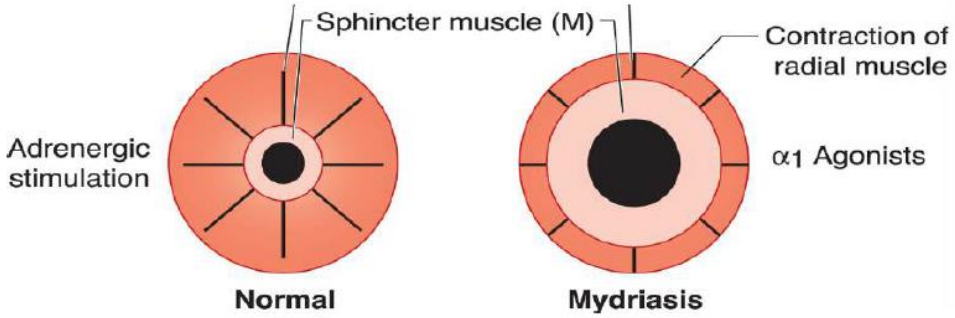


Figure II-1-5. Effect of ANS Drugs on the Eye

α_1	G_q coupled	↑ phospholipase C →↑ IP_3, DAG, Ca^{2+}
α_2	G_i coupled	↓ adenylyl cyclase → ↓ cAMP
$\beta_1\beta_2 D_1$	G_s coupled	↑ adenylyl cyclase → ↑ cAMP

Table II-3-2. Mechanisms Used by Adrenergic Receptors

- **Gi is inhibitory**
- **Gs is stimulatory**
- **When you stimulate adrenergic receptors? / what sequence of events that happen in the cell for the alpha and beta to be stimulated**

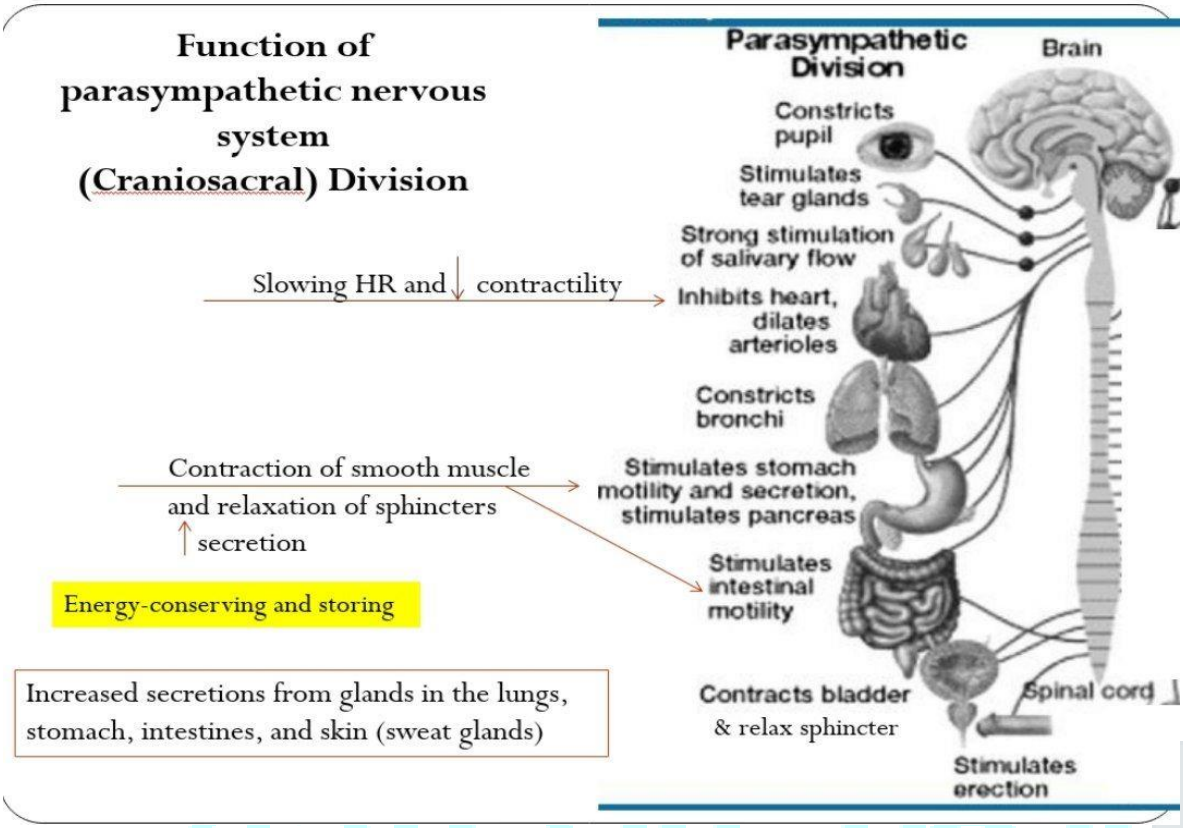
❖ Parasympathetic Nervous System:

-The parasympathetic pre-ganglionic motor fibers originate in cranial nerve and in sacral segments of the spinal cord

-Parasympathetic ganglia usually lie close to or within the target organ (preganglionic fibers are longer and postganglionic fibers are short)

-The parasympathetic division maintains essential bodily functions, and dominant over the sympathetic system in "rest and digest" situations (digestive processes and elimination of wastes) ... [Rest ... Relax .... Repair ...Renew]

-Acetylcholine (ACh) is the primary transmitter in the synapses between parasympathetic postganglionic neurons and their effector cells (also in brain and neuromuscular jun.)



- Erection done by nitric oxide mediator lead to VD

-All smooth muscle fibers → m3

-Parasympathetic stimulates secretions without any exception

-Atropine inhibit the parasympathetic so inhibit secretion and rise dryness especially in eye

-Stimulatory of the salivary glands and also tears

-Drugs that are muscarinic agonist → we can't give them to patients that suffer from asthma, because they already have bronchoconstriction and it's going to double their agony if we give them drugs that stimulates further bronchoconstriction

-Ventricle and contractile system → no muscarinic receptors, so that no arrest happens

-M2 → found SA node and responsible for rest and digest, lowers contractility

-Blood vessels has muscarinic receptors but they r not innervated, and works through exogenous such drugs

-In this system the sphincters relax and the walls contract

❖ Synthesis of acetylcholine:

-In mitochondria:

-CO A + ATP + Acetate → Acetyl thiokinase

Acetyl CO A+H2O+ADP

-In plasma:

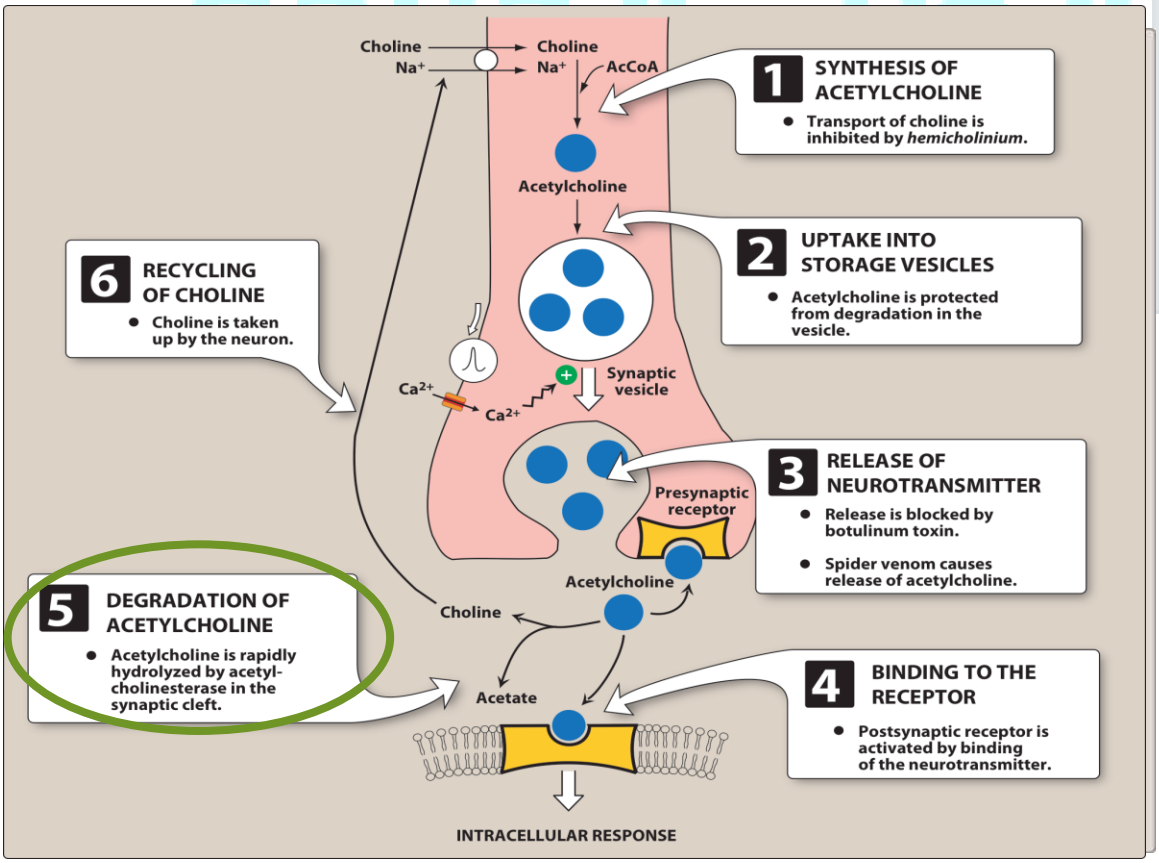
-Acetyl COA+ Choline → Choline transferase Acetyl choline +COA

- **Choline + acetate → happens in the cholinergic nerve fibers**
- **Choline + CoA + acetylcholine → kept in the vesicle**

-Acetyl choline hydrolysis:

-In tissues by cholinesterase enzyme which has 2 types

-True cholineesterase, Pseudo-cholineesterase



-Botulinum toxin causes flaccid paralysis by blocking ACH the respiratory muscle is gonna get paralyzed and cause death, anyways to remove its effect we get botulinum antidote

-When the release of ACH is high causes convulsions by the persistent stimulation

-So to wrap everything up, the blocking of ACH and the over release of it may cause death due to respiratory failuer

-Ps: remember parasympathetic don't affect the cardiac contractile system so will not lead to heart failure

❖ Drugs affecting acetylcholine:

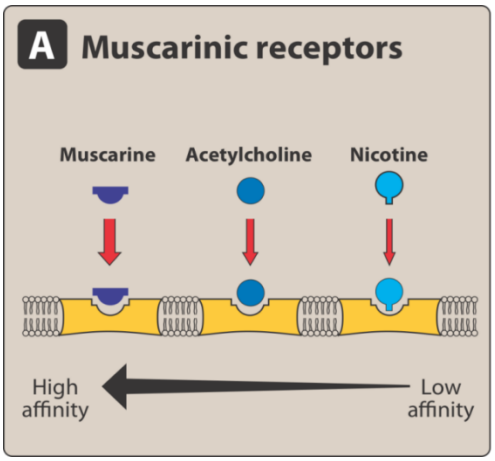
1 Hemicholinium
2 Botulinum toxin
3 Acetylcholinesterase (AChE) inhibitors
4 Receptor agonists and antagonists

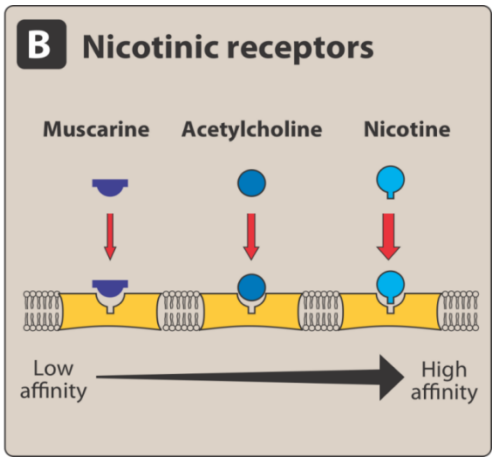
❖ Cholinergic receptors:

-The receptors for acetylcholine and related drugs is (*cholinoreceptors).*
They are 2 types:

-Muscarinic acetylchline receptors (M1-M5) and
-Nicotinic cholinoreceptors (or nicotinic receptor of acetylcholine)

- **Nicotinic n= located on autonomic ganglia and the adrenal medulla**
- **Nicotinic m = *located at neuromuscular* junctions in skeletal muscle.**



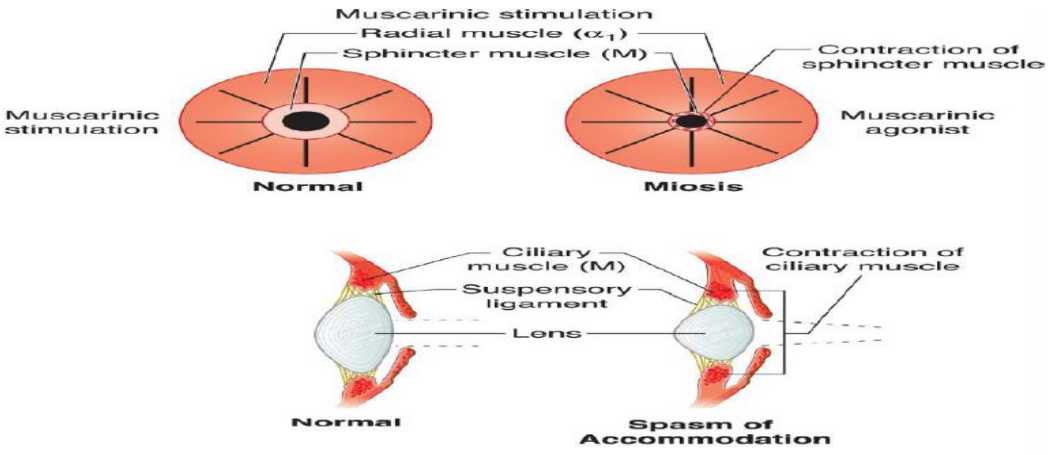


Target		Receptor	Response
Eye	Sphincter Ciliary muscle	M_3 M_3	Contraction—miosis Contraction—accommodation for near vision
Heart	SA node AV node	M_2 M_2	↓Heart rate (HR)—negative chronotropy ↓ Conduction velocity—negative dromotropy No effects on ventricles, Purkinje system
Lungs	Bronchioles Glands	M_3 M_3	Contraction—bronchospasm ↑ Secretion
GI tract	Stomach Glands Intestine	M_3 M_1 M_3	↑ Motility—cramps ↑ Secretion Contraction—diarrhea, involuntary defecation
Bladder		M_3	Contraction (detrusor), relaxation (trigone/sphincter), voiding, urinary incontinence
Sphincters		M_3	Relaxation, except lower esophageal, which contracts
Glands		M_3	↑ Secretion—sweat (thermoregulatory), salivation, and lacrimation
Blood vessels (endothelium)		M_3	Dilation (via NO/endothelium-derived relaxing factor)—no innervation, no effects of indirect agonists

Table II-2-1. Muscarinic Receptor Activation

- **M1 found in gastric mucosa, rise the secretion ex: HCl so when peptic ulcer cases we don't give the patient m1 agonist**

- **so if we wanna help with ulcers we give the patients a m1 antagonist to stop m1 from working**



- **Glaucoma →high intracellular pressure because of blocking of some lacriminal tubes → more pressure on retina could cause blindness**
- **Contraction of ciliary muscle rise the drainage of aqueous humer so decrease the pressure**
- **The ciliary muscle controls the convexity of the eye → high convexity allows seeing anything near in sight**

Muscarinic stimulation

1. Miosis
2. Accommodation (near vision)

Muscarinic antagonism

1. Mydriasis
2. Accommodation to far vision, leading to cycloplegia (paralysis of accommodation)

α1-agonists

1. Mydriasis
2. No cycloplegia

❖ Autonomic effects on eye:

-Dilation of pupil has two types → active mydriasis -- sympathetic "contraction of dilator pupile"

→passive mydriasis ---------- parasympathetic "relaxation of ciliary muscle"

-When muscarinic antagonist , paralesis of ciliary muscle occurs called cycloplegia so we cannot accommodate near vision

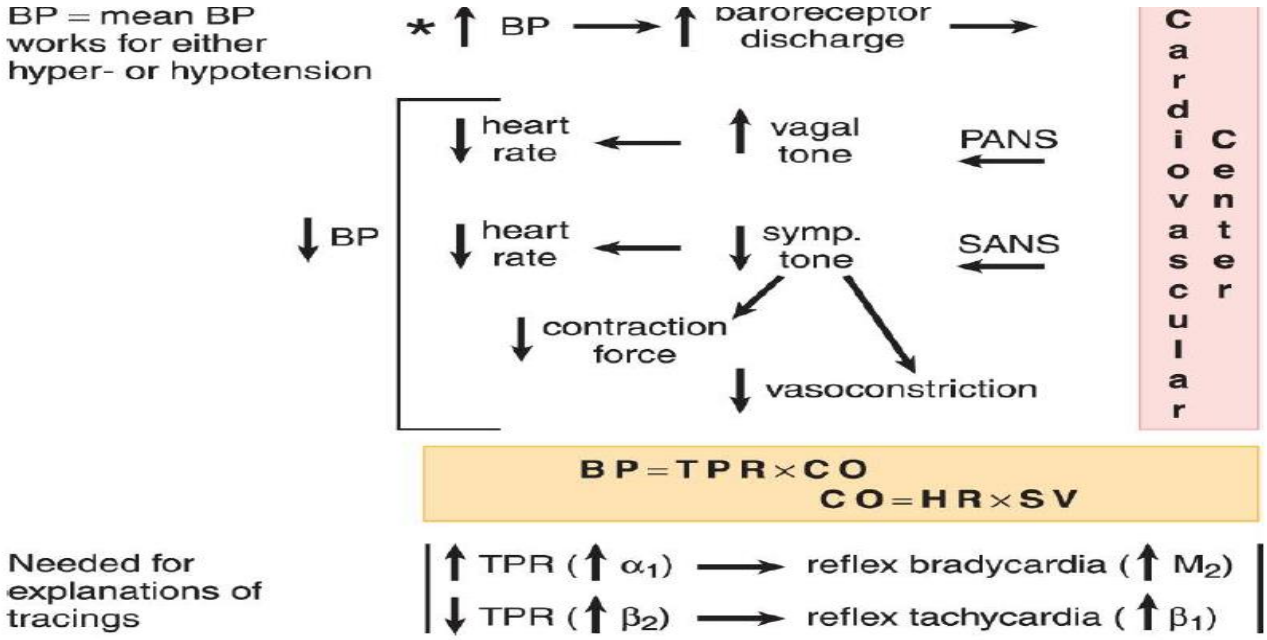


Figure II-1-2. Autonomic Feedback Loop

- **Angiotensin II is a strong vasoconstrictor**
- **Renin will cause hypertension**
- **People with high aldosterone have edema**
  When gives a1 agonist → VC → high TPR so body do reflex bradycardia
  When the opposite with b2 do reflex tackycardia "RISING HR TO ACCOMMODATE THE LOW TPR AND CONTROLL BP"

Activity:

- **Baroreceptor reflexes can be blocked at the ganglionic synapse with ……?**

- **Alternatively, a reflex bradycardia can be blocked with……?**
- **a reflex tachycardia can be blocked with ……?**

✓ **Answer:**

- **Baroreceptor reflexes can be blocked at the ganglionic synapse with <u>NN receptor Antagonists</u>**
- **a reflex bradycardia can be blocked with <u>muscarinic antagonists</u>**
- **a reflex tachycardia can be blocked with <u>β1 antagonists.</u>**

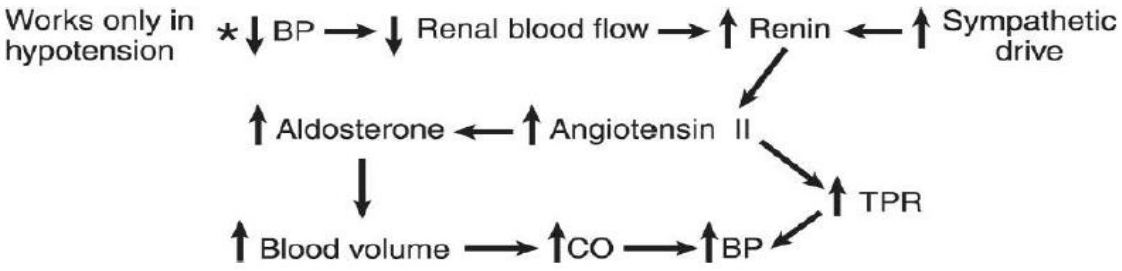


Figure II-1-3. Hormonal Feedback Loop

لطالما غلَب القليل المستمر ذاك الكثير المنقطع، لذا لا تقللوا من شأن خطواتكم مهما كانت صغيرة أو بطيئة، ما دامت موجّهة نحو الطريق الصحيح، ومهما تعثّرتم انهضوا وأكملوا مسيركم، فإن الأيام تمضي، والزمن يطوي نفسه؛ ويومًا ما ستفرحون بإنجازكم باسمًا بين أيديكم.

شروق القويعي.