Doctor 021

PHARMACOLOGY

Sheet no.11

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AUTONOMIC NERVOUS SYSTEM

-The nervous system is divided into:

1- CNS; the brain and spinal cord

2- The peripheral nervous system

There are 2 types of neurons:

- afferent(sensory neurons): transducing signals from the sensory receptors to CNS,

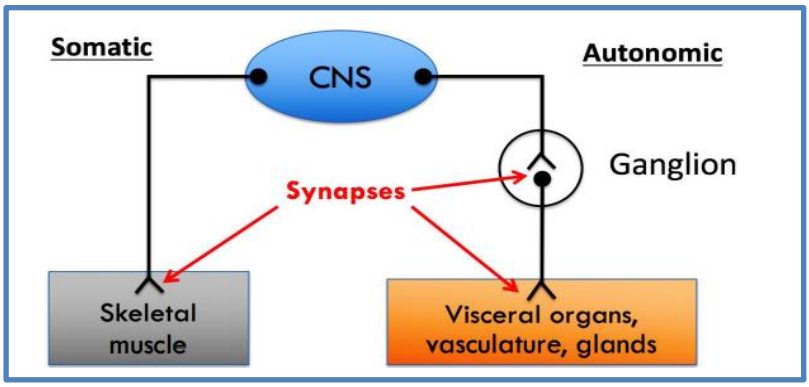
- efferent(motor): transducing signals from the brain to organs for processing

-The motor (efferent) portion of CNS can be divided into Autonomic and Somatic.

-autonomic deals with unconscious or involuntary processes, while somatic neurons deal with conscious actions.

-The autonomic nervous system (ANS) is largely independent(autonomous)and its activities are not under direct conscious control

which means it regulates certain body processes such as sweating, blood pressure, heart rate, and salivation without a person's conscious effort.



-The Autonomic nervous system has 3 subdivisions:

1. The sympathetic nervous system

2. The parasympathetic nervous system

3. The enteric nervous system.

***The enteric nervous system (ENS) is one of the main divisions of the autonomic nervous system (ANS) and consists of a mesh-like system of neurons that governs the function of the gastrointestinal tract.**

-Many transmitter & neuromodulator substances have been identified in the ENS.

-It is modulated by the sympathetic & parasympathetic Systems:

*parasympathetic: activates ENS, while the sympathetic: inhibits the ENS,

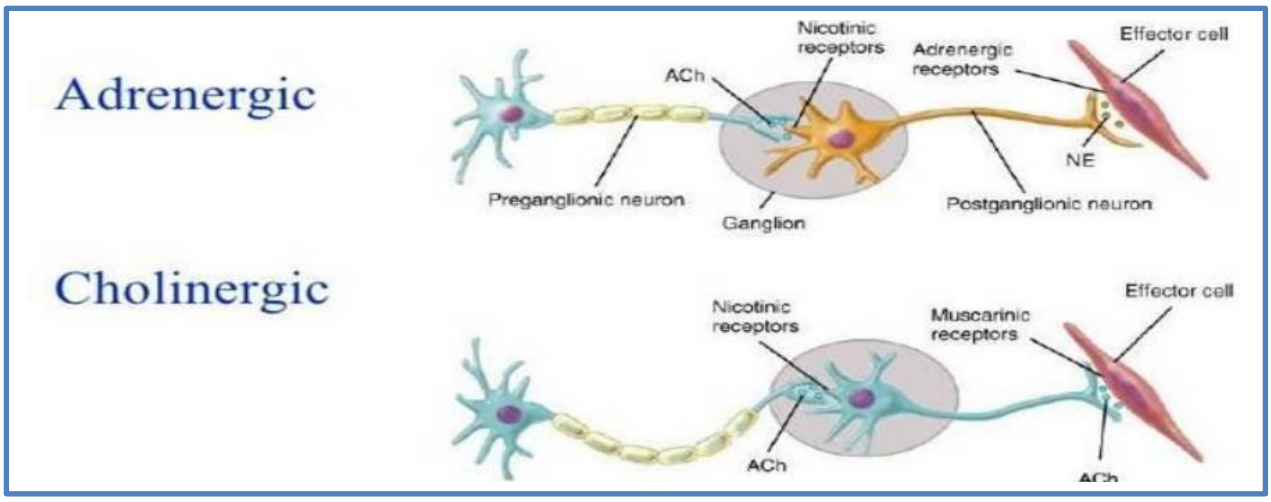
And that makes sense because ENS controls the GI tract so we are talking about rest and digest, which is activated by the parasympathetic system.

-ENS is called a small brain because it has so many neurons and interconnections!

- Sympathetic and parasympathetic can't function without the brain but the ENS can.

ANS NEURONS

- Classified as either cholinergic or adrenergic neurons based upon the neurotransmitter released.



-There are 2 classifications of neurons in ANS: cholinergic and adrenergic (or nor adrenergic) depending on the type of receptors they affect.

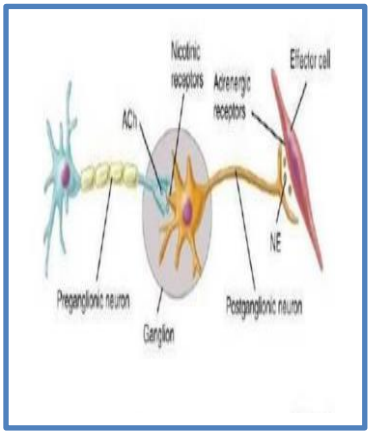
- when the adrenergic receptor was discovered, they thought that epinephrine & adrenaline were the chemical transmitters released from this neuron later on it was found that it isn't adrenaline it is noradrenaline or norepinephrine.

-ANS has 2 types of neurons depending on the location around the synapse(ganglia) (an aggregation of nerve cell bodies located in the peripheral nervous system):

***Preganglionic neuron**: comes out from the spinal cord and makes synapses inside the autonomic ganglia. (the neuron before the synapse, toward the synapse, the 1st neuron, presynaptic neuron)

***Postganglionic neuron**: the 2nd neuron, away from the synapse, post synaptic, the cell body is inside the ganglia.

ADRENERGIC (OR NORADRENERGIC NEURONS)

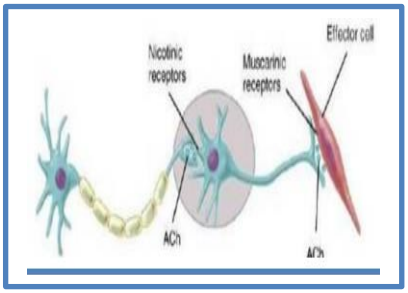


-**The preganglionic neuron releases acetylcholine at the ganglion**, which acts on **nicotinic receptors** of postganglionic neurons.

- The postganglionic neuron then releases norepinephrine to stimulate the adrenergic receptors of the target organ.

-it is a sympathetic neuron!

CHOLINERGIC NEURONS



-It is the same as adrenergic neurons, but the **postganglionic neurons of cholinergic neurons release acetylcholine instead of norepinephrine.**

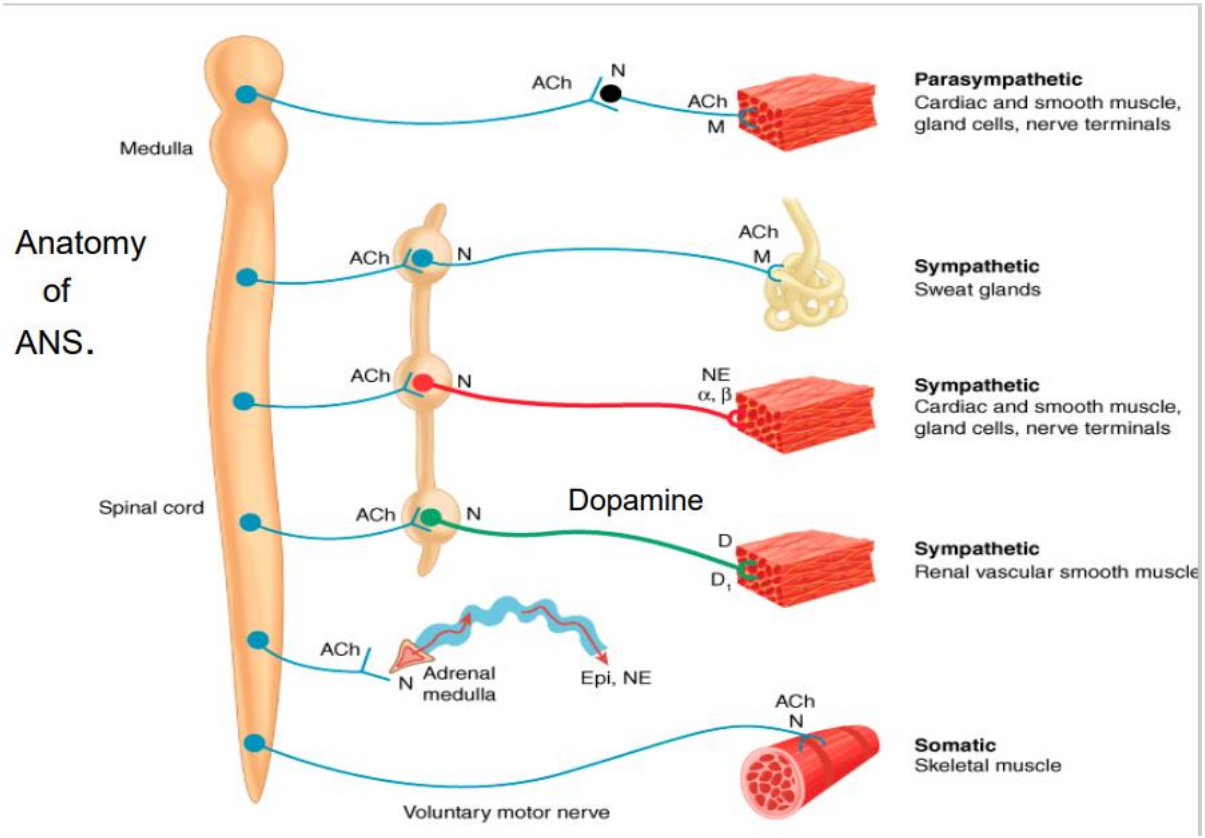
-Acetylcholine of postganglionic neurons will stimulate **muscarinic receptors on target organs**.

-it is a parasympathetic neuron! OR a sympathetic neuron for the sweat gland!

** Why do we call them muscarinic & nicotinic receptors when both are activated by Ach?

-Nicotine can stimulate the receptors inside the ganglion but cannot stimulate receptors on the target organ, while muscarine can stimulate the receptors on the target organs only without affecting receptors inside the ganglion.

ANATOMY OF ANS.



*Here we can see different types of neurons :

-Parasympathetic(cholinergic neuron):

-The parasympathetic preganglionic fibers arise from the brainstem and the sacral region of the spinal cord.

-Both preganglionic &postganglionic neurons release Ach.

-Ach from preganglionic neurons acts on nicotinic receptors while Ach from postganglionic neurons acts on muscarinic receptors.

-Sympathetic:

-The pre-ganglionic neurons of the sympathetic system come from the thoracic and lumbar regions of the spinal cord, and they make synapses in the chain of ganglia.

-"paravertebral ganglia on both sides of the spinal cord "

-Preganglionic neurons of the sympathetic system release Ach which acts on nicotinic receptors.

-so, what about the postganglionic? It is a long story:

1) Sympathetic neurons which innervate sweat glands (cholinergic neurons)

It is an exception that it releases Ach from postganglionic neuron -not norepinephrine – which acts on muscarinic receptors, when you are nervous or afraid you sweat because the sympathetic system gets activated

2)Typical sympathetic neurons release NE from postganglionic neurons which acts on α and β adrenergic receptors

3)Sympathetic dopaminergic neurons release dopamine from postganglionic neurons which acts on dopamine receptors D1&D2 (innervate renal vascular smooth muscles cause vasodilation, increase the flow of urine, and increase sodium excretion).

4) Sympathetic neurons which innervate the adrenal medulla gland

, when a preganglionic neuron is activated, it releases Ach which acts on nicotinic receptors in the adrenal medulla causing the secretion of 80% adrenaline and 20% norepinephrine.

-The adrenal medulla gland is considered a big ganglion

-Somatic neurons

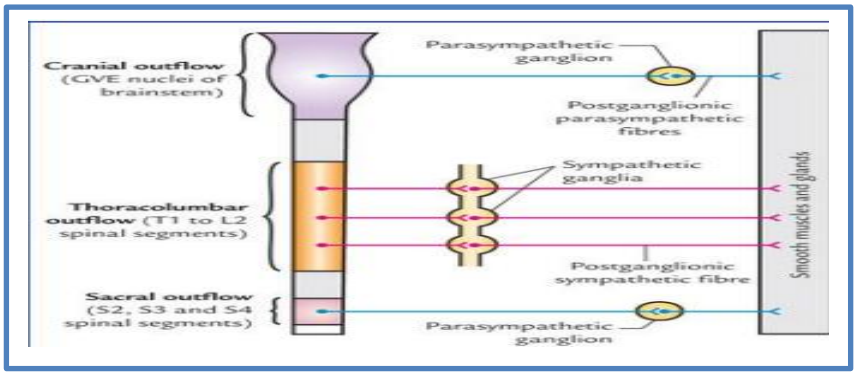
Only one neuron innervates skeletal muscles and releases Ach which also acts on nicotinic receptors

Let's recap:

The 1st neuron or even 1 neuron always secretes Ach on the nicotinic receptors

The second neuron may secrete Ach, NE, or dopamine depending if it is:

Sympathetic or parasympathetic(see the fig again)



-Parasympathetic cell bodies in brainstem & sacral spinal cord: craniosacral outflow.

-Parasympathetic: postganglionic neurons are short (ganglia located

near effectors) stimulation involves only one visceral effector (organ)

Preganglionic neurons are long while postganglionic neurons are short (ganglia located near the effector organ and sometimes inside it) stimulation involves only one visceral effector (organ). Usually, one preganglionic neuron makes a synapse with one postganglionic neuron which affects a certain organ (the ratio between pre to post is 1:1) means when the preganglionic neuron is activated only one postganglionic neuron will be activated and only a single effect is seen.

-Sympathetic cell bodies located T1-L2 levels: thoracolumbar outflow.

Preganglionic neurons are short while postganglionic neurons are long

-One sympathetic preganglionic neuron may have many branches and may synapse with 20+ postganglionic neurons.

-Projection of divergence explains why sympathetic responses can affect many effectors at once

(Widespread effect) and this is consistent with the function of the

The sympathetic nervous system which prepares the body for an emergency fight or flight situation that needs all the body's resources at the same time to maintain the survival of the beings.

THE PHYSIOLOGICAL EFFECT OF THE ANS:

-some organs have only sympathetic innervation like :

1. Sweat glands

2. Adrenal medulla

3. Arrector pili mm (smooth muscles of hair), responsible for goosebumps

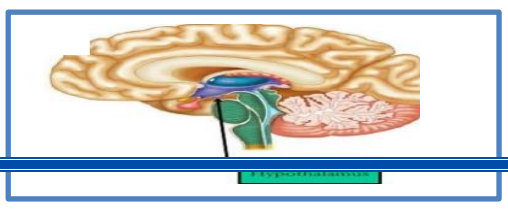
4. Many blood vessels

****The activity of this system is controlled by the regulation of the tone of the sympathetic system**

-The tone is the number of impulses passing in these neurons (-)

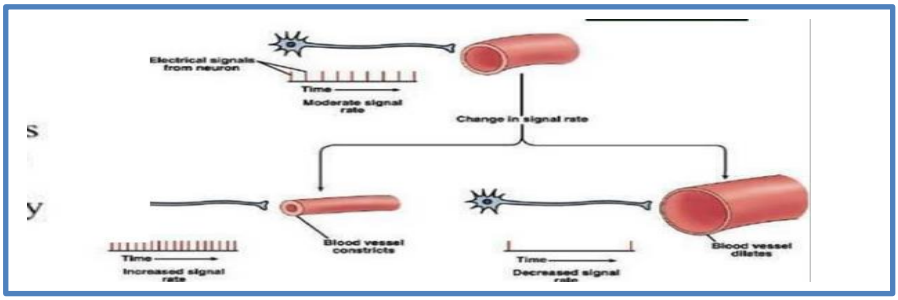
- Most body organs receive dual innervation (innervation by both sympathetic and parasympathetic)

****Hypothalamus regulates the balance (tone) between sympathetic & parasympathetic activity levels**



-Notice that there is a balance between these two systems because they usually have an opposite effect (antagonistic effect)- usually not always

-there is no zero effect of one of them, just that one of them has more effect in this condition(in other words,one of them is more active than the other)



This cartoon shows the concept of TONE, let's suppose that this is a vessel going to the skin in FIGHT OR FLIGHT, so vasoconstriction will happen, the rate of tones is much higher in constriction and lower in dilation.

-How is the blood controlled when we only have sympathetic innervation to blood vessels? By controlling the tone

-NOTE: In each transmission (of any system sympathetic or parasympathetic- dopamine receptor or whatever), we are concerned with: the synthesis, storage, release, disposal, or end effect of

neurotransmitter

-Parasympathetic nervous system

*** Rest and digest, basic survival functions:**

during rest, when you have no worries, you are enjoying your time, etc. Parasympathetic tone is the dominant tone in the body and heart.

*** Metabolic (business as usual)**

*** S(alivation), L(acrimation), U(rination), D(efecation)**

-Sympathetic

*** fight or flight = "survival" :**

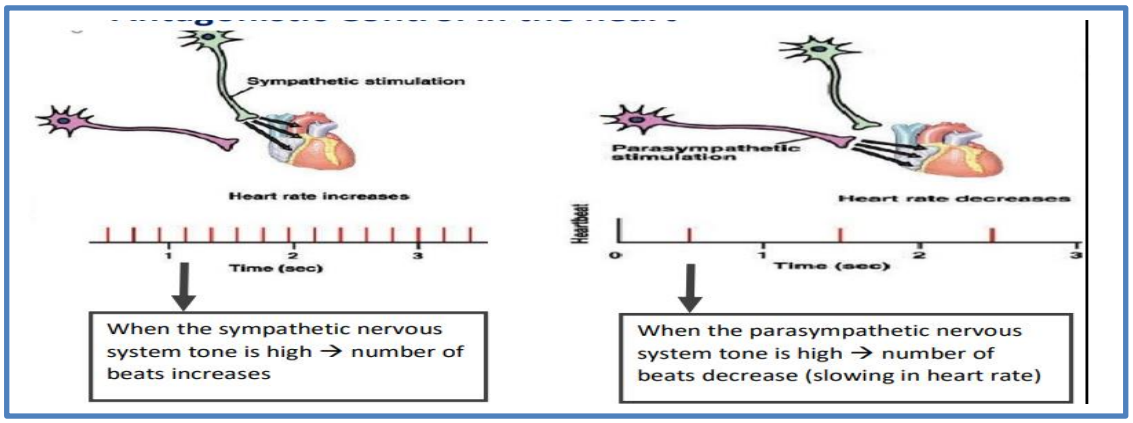
(this system is used in emergencies so that all body resources are activated to face a danger).

*** any increase in skeletal muscular activity (running & gym for these activities :increase *heart rate, *blood flow, *breathing**

Decrease: *non-survival activities, *food digestion, etc.

Sympathetic and parasympathetic systems have an antagonistic effect

ANTAGONISTIC CONTROL IN THE HEART



- Most internal organs are innervated by both branches of the ANS which exhibit antagonistic control

-at any time, the heart rate is determined by the balance between the sympathetic& parasympathetic nervous systems

-Based on the age (not duration):

*** For young people at rest, the parasympathetic system is dominant in the heart**

*** For babies usually the sympathetic system is the dominant one (the heartbeat is very high)**

EXCEPTION TO THE DUAL INNERVATION RULE (ONLY HAVE ONE INNERVATION)

Sweat glands and blood vessel smooth muscle are only innervated by sympathetic and rely strictly on up-down control.

Other examples: Adrenal glands, Piloerector muscles of hair

EXCEPTION TO THE ANTAGONISM RULE

sympathetic and parasympathetic work cooperatively

- to achieve male sexual function. parasympathetic is responsible for erection while sympathetic is responsible for ejaculation.

- There's similar ANS cooperation in the female sexual response

ACETYL CHOLINE(ACH) SYNTHESIS

Cholinergic transmission

1-Synthesis: choline uptake.

Choline + acetylCo -A +

Choline acetyltransferase.

2-transported to vesicles, by vesicle associated transporter

Stored quantas (up to 50000)

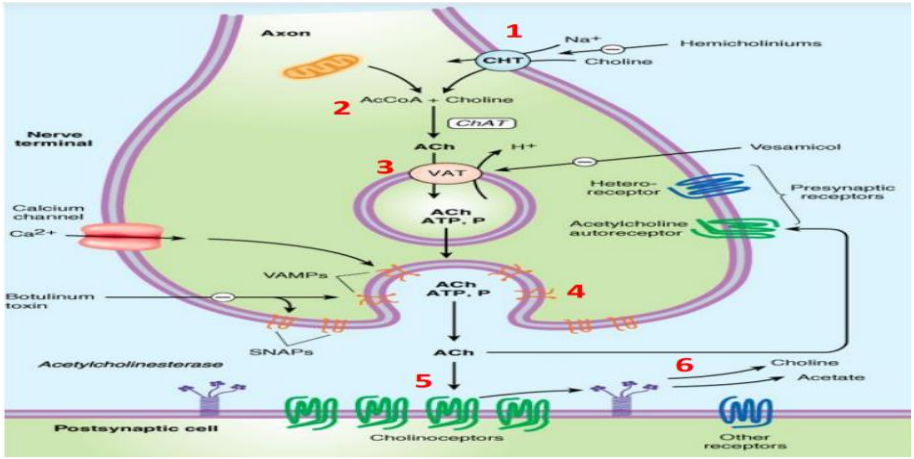
3-Release: exocytosis.

4-Interaction with post synaptic receptors

5- hydrolysis of Ach by Ach.esteras.

Drugs can act on all sites of cholinergic transmission.

VAMPS:vesicle detaicossa-nietorp enarbmem



-<u>Choline is the starting material for the synthesis of acetyl-choline and it is abundant in blood:</u>

1- Synthesis of Ach starts with choline uptake, it is taken up by secondary active transport (symport)with Na+, so choline enters the neuron

2- Inside the neuron, there is choline that needs an acetate group derived from acetyl CoA to form acetylcholine, so acetyl coA comes out from the mitochondria then an enzyme called choline acetyltransferase transfers the acetate group from acetyl CoA to choline forming acetylcholine (this process is very fast and efficient).

* Acetylcholine esterase is present outside in the synaptic cleft & breaks down ester linkage in Ach forming acetate+ choline and also it is present inside the neuron, that's why Ach has to enter the vesicle:

3- When Ach is formed, to protect it from degradation by Ach esterase, it must get inside a presynaptic vesicle called: <u>Vesicle Associated Transporter (VAT)</u>

<u>*VAT:</u> is a transporter that exchanges Ach with proton(antiport) and

once Ach gets inside the vesicle, it binds to ATP and a protein.

* Ach is stored in the vesicle as quantum (each quantum contains up to 50000 of Ach)

4- releasing of Ach by (exocytosis), (Ca2+ dependent):

For exocytosis, we need a Ca2+ channel (voltage-gated channel) so, when there is an action potential reaching the neuron, it causes depolarization so the Ca2+ channel opens and increases Ca2+ cytosolic concentration (influx), this stimulates the movement of the vesicle to the neuron membrane that

faces the effector cell and fuses with it and causes exocytosis of its contents into the synaptic cleft.

***The vesicle has to bind in the right place and then firmly(tight) to the neural membrane, how?**

By Docking, we have proteins on the vesicle membrane (VAMP: vesicular associated membrane protein) and the neural membrane (SNAPs: a complex form between VAMPs and SNAPs so, the vesicle becomes stable on the neural membrane which helps in exocytosis.

5)After Ach is released, it stimulates postsynaptic receptors(nicotinic or muscarinic receptors)

- it is released in huge amounts, most of Ach is being combined to receptors (not all) because some Ach is destroyed by Ach esterase before it reaches the receptor

6- Ach is hydrolyzed into choline and acetate by cleaving the ester bonds in Ach

- Recycling of choline: Choline is taken back into the presynaptic nerve by a sodium-dependent choline transporter (CHT) to be incorporated in the synthesis of Ach again. While acetate goes into the Krebs cycle

- When the synaptic cleft is full of Ach, it stimulates 2 types of presynaptic receptors and when they are activated, they inhibit the release of Ach:

REGULATORY RECEPTORS FOR ACH SYNTHASE

1- **Acetylcholine auto receptor**:
When acetylcholine is accumulated in the synaptic cleft, it goes to this receptor and activates it by giving signals to stop the release of more acetylcholine (negative feedback).
-they are called auto-receptors because acetylcholine is the neurotransmitter secreted from the neuron, it's also the inhibitor.
2-Heteroreceptor: -It is called heteroreceptor because it isn't stimulated by Ach, it's stimulated by other neurotransmitters from other neurons (e.g.: norepinephrine)
-Sympathetic and parasympathetic nervous systems close together, especially in the heart
so when there is an activation of sympathetic, NE(norepinephrine) will be released: increasing the heart rate & Some of this NE stimulates heteroreceptors noradrenergic receptors specially α2 on the

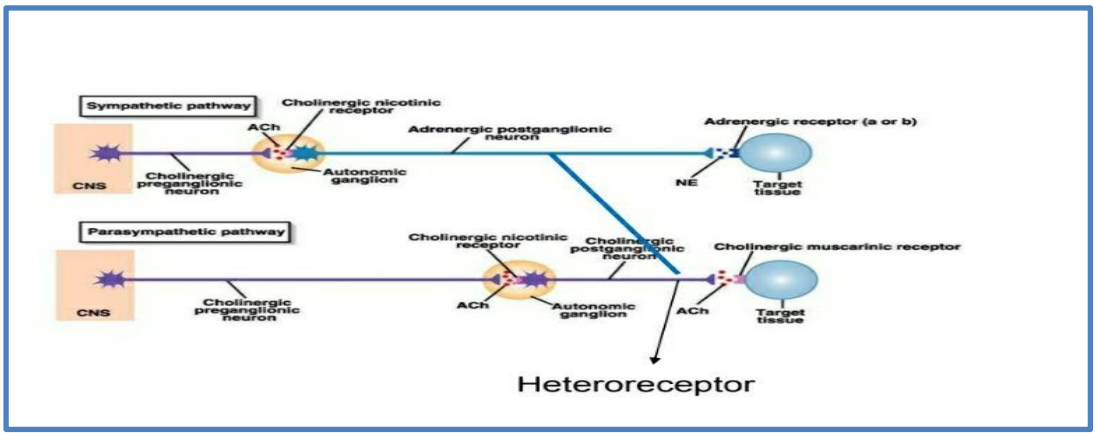
parasympathetic neuron, and cause the release of Ach to stop (so, the sympathetic nervous system is dominant)

More explanation about α2 receptors: (from Lippincott - pharmacology):α2 Receptors: These receptors are (noradrenergic receptors) located primarily on sympathetic, presynaptic nerve endings & control the release of norepinephrine, α2 receptors are also found on presynaptic parasympathetic neurons and control Ach release.

-When a sympathetic adrenergic nerve is stimulated, a portion of the released norepinephrine "circles back" and reacts with α2 receptors (sympathetic) on the presynaptic membrane.

-- Stimulation of α2 receptors causes feedback inhibition & inhibits further release of norepinephrine from the stimulated adrenergic neuron

--Norepinephrine released from a presynaptic sympathetic neuron can diffuse to & interact with α2 receptors on presynaptic parasympathetic neurons, inhibiting acetylcholine release



DRUGS INTERFERE WITH ACH SYNTHESIS

Drugs can act on all sites of cholinergic transmission: to interfere with the cholinergic transmission to achieve therapeutic effects or for experimental purposes

1)a drug called hemicholinium:

- inhibit the choline uptake process

- when it binds this means that neurons no longer can produce Ach: Ach decreases quicker

- it is not used clinically, it is used for experiments

2) vesamicol drugs:

-experimental drug not used clinically only used for research purposes

- it inhibits the uptake process of Ach by VAT so the synthesized Ach is broken down by Ach esterase and does not get inside the vesicle

-transmission fails because the only way for Ach to get outside to cholinergic receptors is by exocytosis (by vesicles)

3) botulinum toxin (important)

- can block exocytosis

-it destroys the protein that is needed for docking the vesicle to the neuron(VAMPs & SNAPs), there is no way for fusion between the vesicle and the neural membrane

-no Ach release → no transmission

- can be used clinically in case of severe back pain & severe muscle spasm, in which a microinjection of botulinum toxin causes the muscle to relax (by preventing Ach secretion, thus preventing muscle contraction), which relieves pain – sometimes used in bladder

-used in cosmetic surgeries "Botox"

PAST PAPER

1. botulinum toxin interferes with cholinergic transmission by :

A- inhibiting choline transporter .

B- inhibiting choline acetyl transferase enzyme .

C- inhibiting vesicle associated transporter

D- interfering with exocytosis .

E- interaction with post synaptic receptor

2. High IV infusion rate of dopamine may cause all the following effects; EXCEPT

A.Vasodilation of renal vessels

B. Vasoconstriction effect

C. Positive dromotropic effect

D. Positive chronotropic effect

E. Positive Inotropic effect

Good luck

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