◉ Sheet ○ Slides

number : 1

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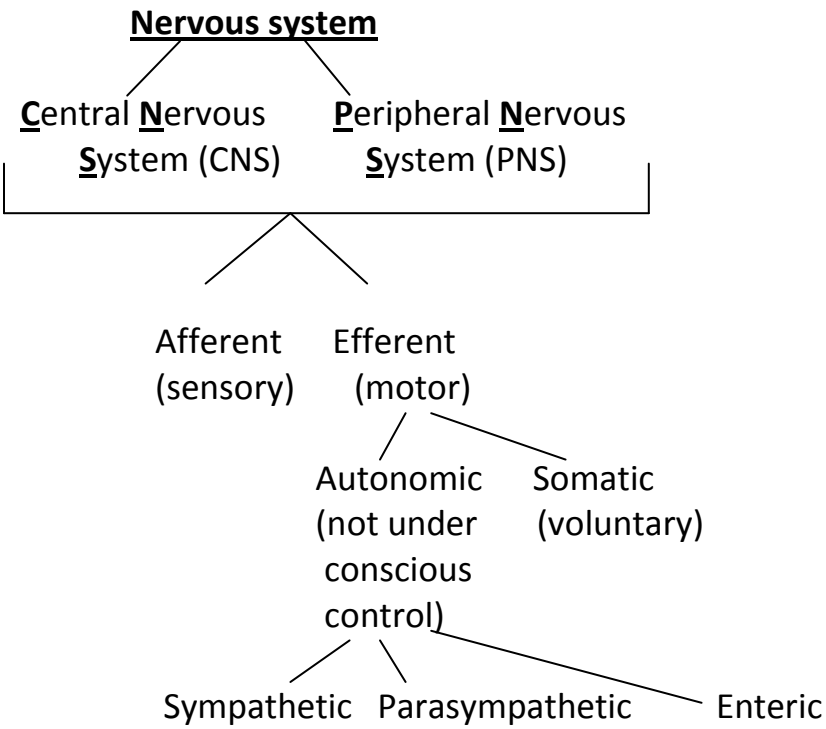
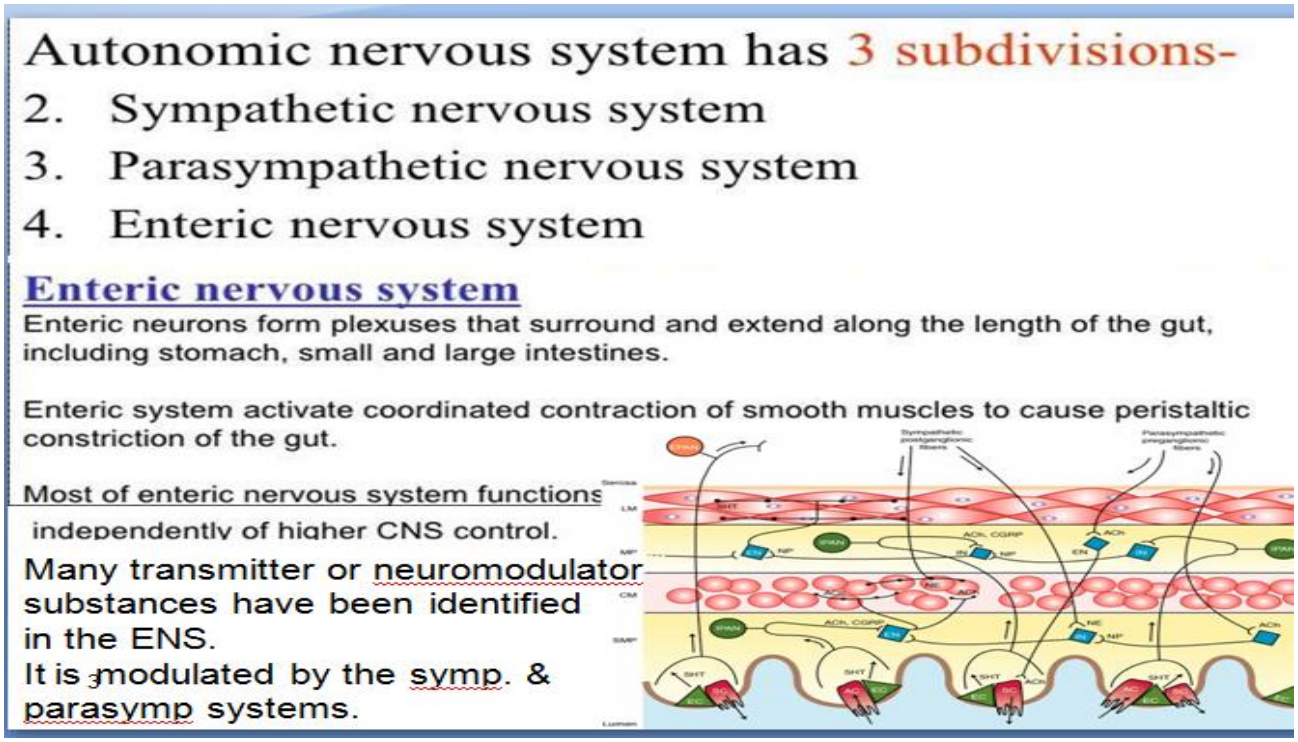
Autonomic Nervous System (ANS)

The autonomic nervous system is part of the nervous system.



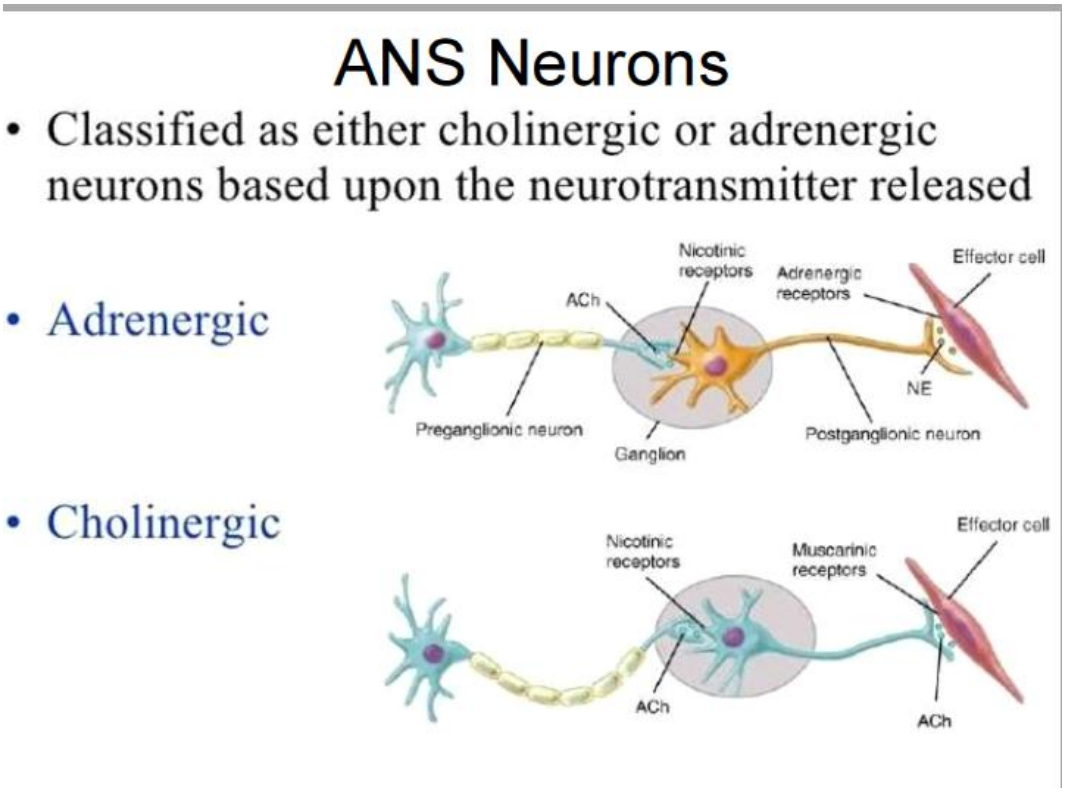
Note : The word autonomic implies that this system is independent of conscious control, meaning that it "controls itself".

Note: The autonomic nervous system is the main reason behind homeostasis.



Based on the diagram above, we may already be familiar with sympathetic and parasympathetic nervous system, and we will discuss it in more detail later. As for the enteric nervous system (ENS), it is the system that controls the activity (secretion, peristalsis, movement) of the gastrointestinal tract.

This system has many neurons, and is modulated by sympathetic and parasympathetic neurons, where sympathetic inhibits it and parasympathetic activates it.



ANS neurons are classified based on the neurotransmitter released from them. There are two types of ANS neurons:

1. Cholinergic: they release acetylcholine as a neurotransmitter.

2. Adrenergic: they release noradrenaline/norepinephrine as a neurotransmitter .

- In all ganglia, whether sympathetic or parasympathetic, the NT is acetylcholine, because all preganglionic neurons whether sympathetic or parasympathetic release acetylcholine.

-Now we come to the post ganglionic secretions, these vary depending on whether the postganglionic neuron is sympathetic or parasympathetic:
1) parasympathetic postganglionic neurons release acetylcholine.

2) sympathetic post ganglionic neurons innervaying sweat glands also release acetylcholine (this is an exception because usually norepiniphrine is the NT released by the post ganglionic sympathetic neurons).

Note: In the ganglion, acetyl choline is released, which causes action potentials in the next neuron (postganglionic neuron), activating it. The signal finally reaches the adrenergic receptors on the effector cell via norepinephrine release so we called this neuron Adrenergic neuron .

To sum up :

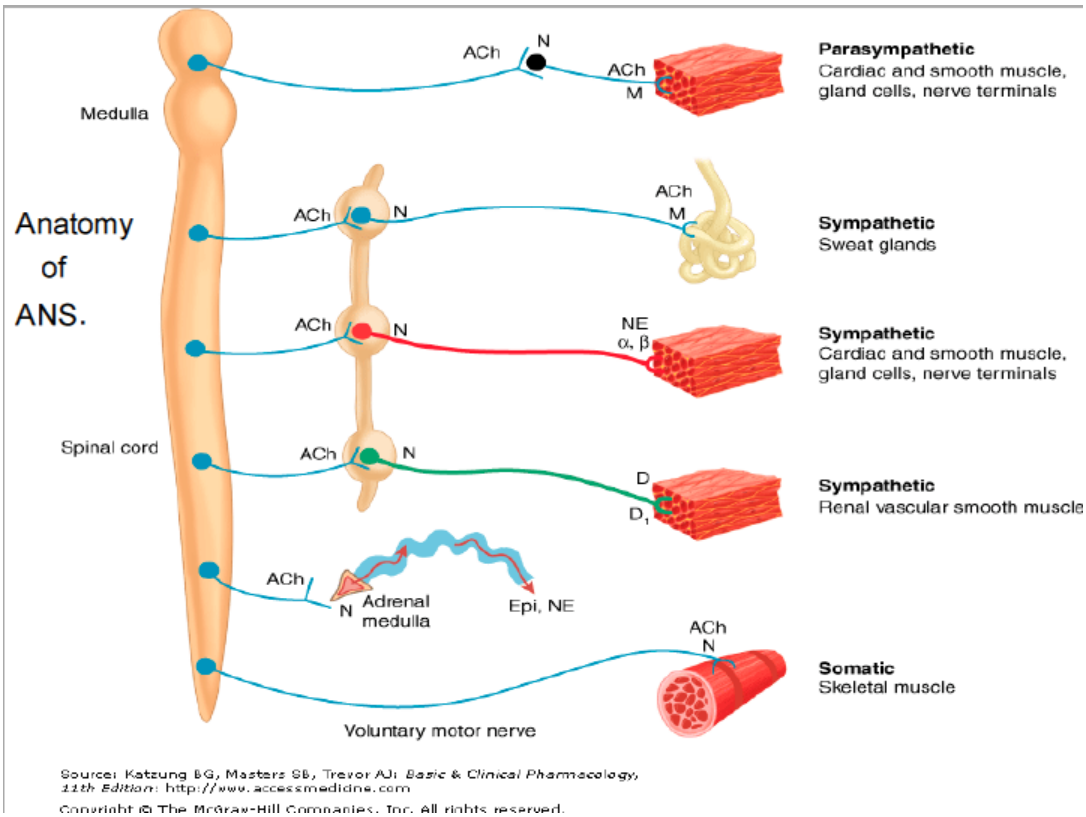
***Cholinergic neuron include**:
1. Autonomic preganglionic fibers.
2. Parasympathetic postganglionic fibers.
3. Few sympathetic postganglionic fibers (sweat gland).

***Adrenergic fibers include:** Norepiniphrine is the NT released by the post ganglionic sympathetic neurons.**:**
1. Most sympathetic postganglionic fibers.
2. Adrenal medulla releases a mixture of epinephrine (adrenaline) and norepinephrine (noradrenaline).

Note: Some sympathetic postganglionic fiber release dopamine (Dopaminergic post ganglionic sympathetic).

Q: Why do we give nicotinic and muscarinic receptors different names even though they're both activated by acetyl choline?

Simply to differentiate the position of receptors . In ANS ,nicotinic receptor on ganglionic postsynaptic membrane , whereas muscarinic receptors on effector cells membrane that innervated by Parasympathetic system & sweat gland .



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

Somatic nervous system is innervated by the voluntary motor nerve that emerges from the spinal cord uninterrupted (one single neuron from the spinal cord until it synapses with the effector muscle). When it's stimulated, it releases acetyl choline which binds to nicotinic receptors causing muscle contraction.

Sympathetic nervous system: (refer to above diagram for labeling)

a) In sweat glands, although it's sympathetic innervation, the neurotransmitter released is acetyl choline not norepinephrine. The neuron is cholinergic sympathetic neuron, therefore, the receptors are muscarinic. Note that parasympathetic innervation is similar to this.
b) Adrenergic neurons, norepinephrine is released stimulating alpha and beta to produce an action. (adrenergic neuron→adrenergic receptor)
c) Dopaminergic neurons, dopamine is released instead of acetyl choline or norepinephrine. They innervate the renal vascular smooth muscles. When activated, the blood vessels vasodilate, enhancing the diffusion of the kidney.

Parasympathetic cell bodies in brainstem and sacral spinal cord: ***craniosacral outflow.***

Parasympathetic Division: postganglionic neurons are short (ganglia located near effectors), stimulation involves only one visceral effector (organ)

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

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

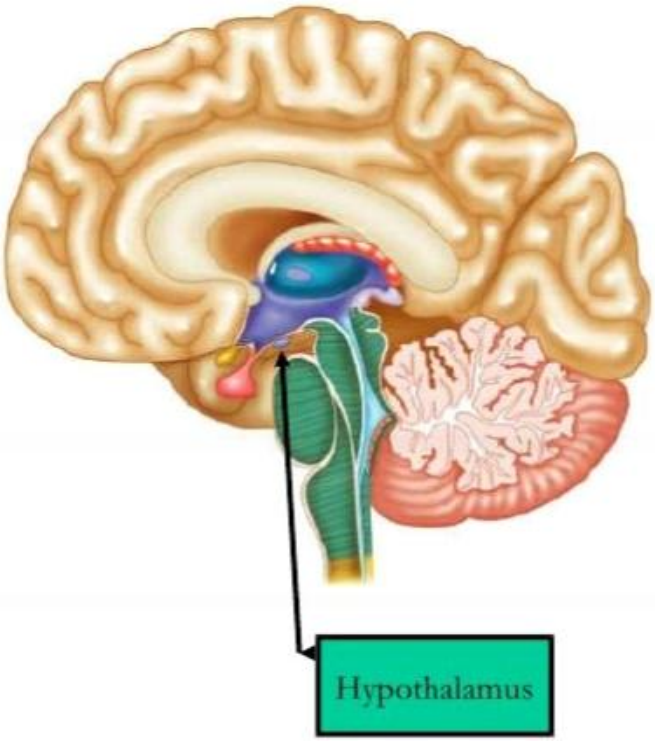
Projection of divergence explains why sympathetic responses can affect many effectors at once

Parasympathetic neurons (cell bodies) are located in the brainstem cranial and sacral portion of the spinal cord, known as the **craniosacral outflow.**
Sympathetic neurons (cell bodies) are located at T1-L2 levels and create what is known as **thoracolumbar outflow.**

-- Parasympathetic preganglionic fiber is very long. Its action is isolated, and discrete, and involves only one organ at a time. Unlike sympathetic innervation, which causes **divergence (**can affect many effectors at once). One sympathetic preganglionic neuron may have many branches and may synapse with 20+ postganglionic neurons(the action is widely spread), and when norepinephrine is released in the circulation, it can activates all the receptors on its way. (for example in case of danger). In case of sympathetic, the preganglionic is short while the postganglionic is long. Hence, sympathetic branching is consistent with its function of **fight or flight.** In case of emergency, the blood vessels of non-vital organs (such as the skin and digestive system) are constricted, to ensure that the vital survival organs are getting as much blood supply as possible.

Physiological Effects of the ANS

- Some organs have only sympathetic innervation
  - sweat glands, adrenal medulla, arrector pili mm & many blood vessels
  - controlled by regulation of the "tone" of the sympathetic system
- Most body organs receive dual innervation
  - innervation by both sympathetic & parasympathetic
- Hypothalamus regulates balance (tone) between sympathetic and parasympathetic activity levels



- Hypothalamus controls sympathetic and parasympathetic activity levels. (High tone —high firing rate — highly stimulated organ)
- Most organs have dual (both sympathetic and parasympathetic) innervations, while some organs have only sympathetic innervation.
- Organs with dual innervation have opposite effects for each type of innervation. (i.e. sympathetic does one thing, parasympathetic does its opposite)

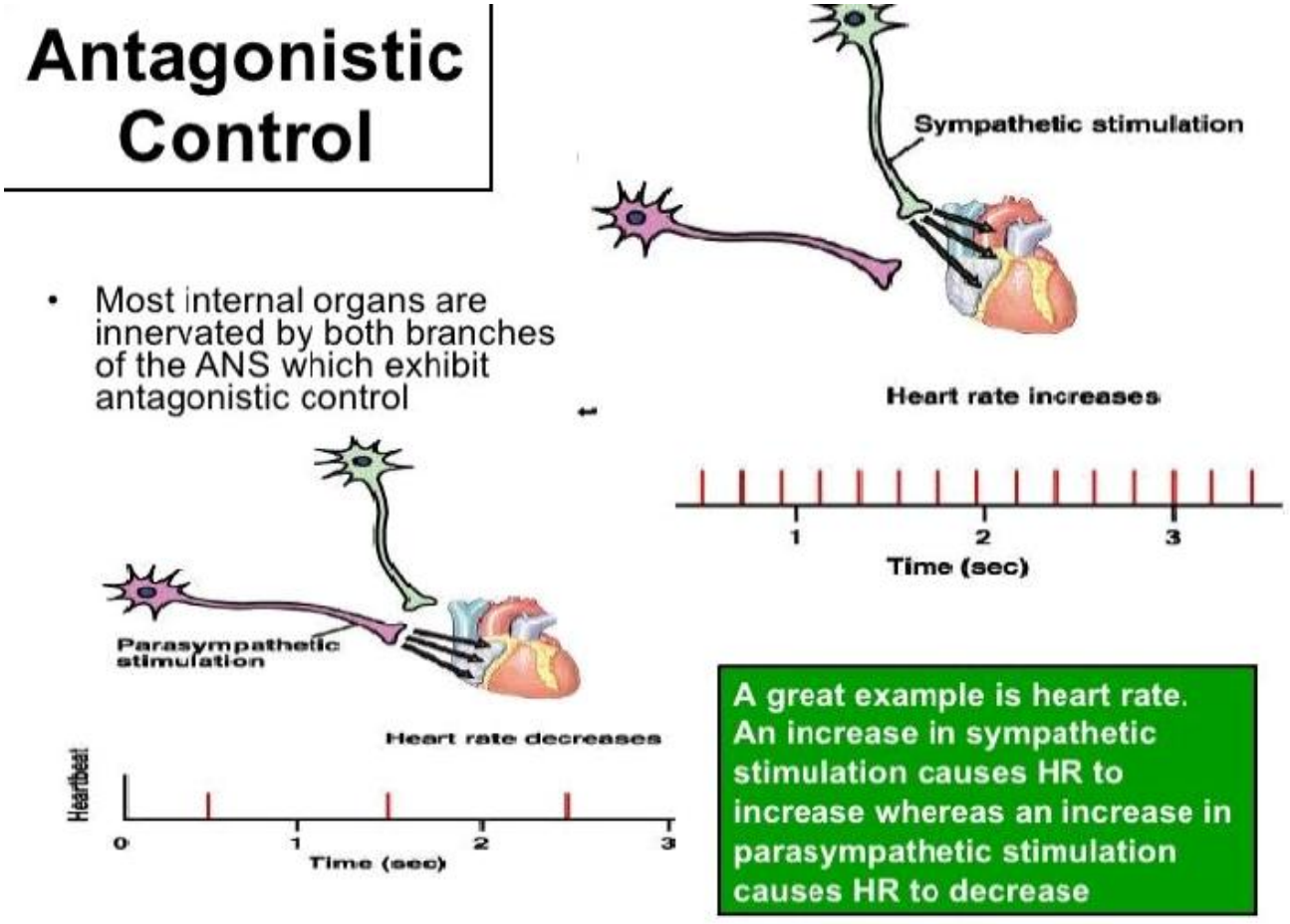
– Parasympathetic
  - S(alivation) L(acrimation) U(rination) D(efecation)
  - metabolic "business as usual"
  - rest and digest - basic survival functions
– Sympathetic
  - fight or flight = "survival"
  - any increase in skeletal muscular activity

for these activities - increase heart rate, blood flow, breathing

decrease non-survival activities - food digestion, etc.

Sympathetic and parasympathetic systems have antagonistic effects

- Parasympathetic: controls basic survival functions. (Not vital)
- Sympathetic: in case of emergency, decreases non-vital, non-survival activities.
- Sympathetic and parasympathetic are antagonistic in nature, but we have exceptions discussed later.



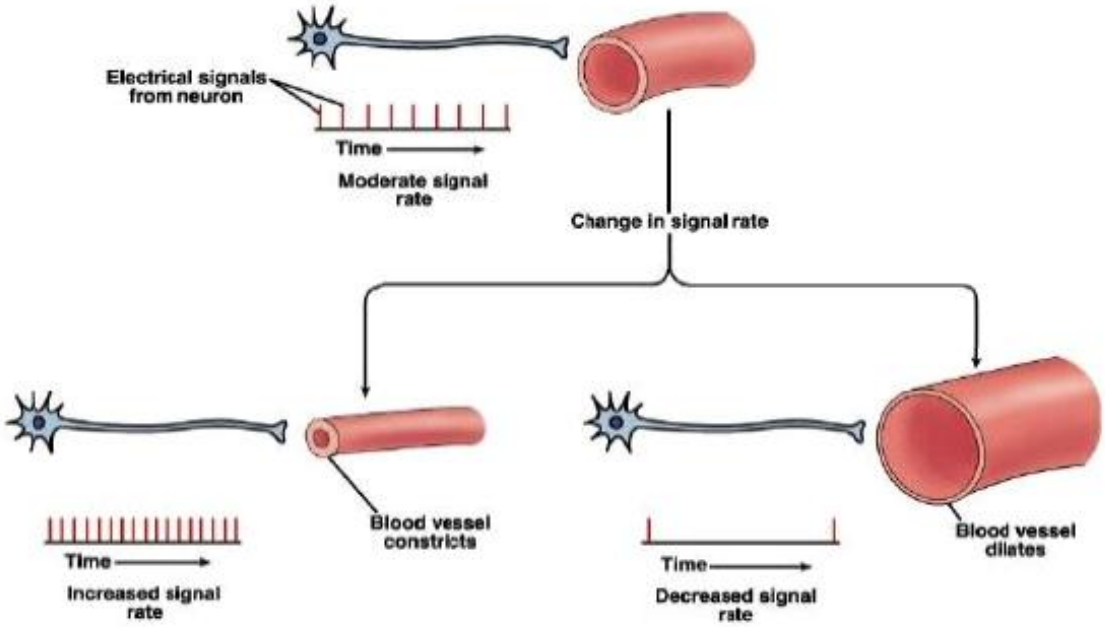
(This slide is self-explanatory; the doctor didn't mention anything more.)

Exception to the dual innervation rule:

Sweat glands and blood vessel smooth muscle are only innervated by symp and rely strictly on up-down control. Other examples :Adrenal glands, Piloerector muscles of hair

Exception to the antagonism rule:

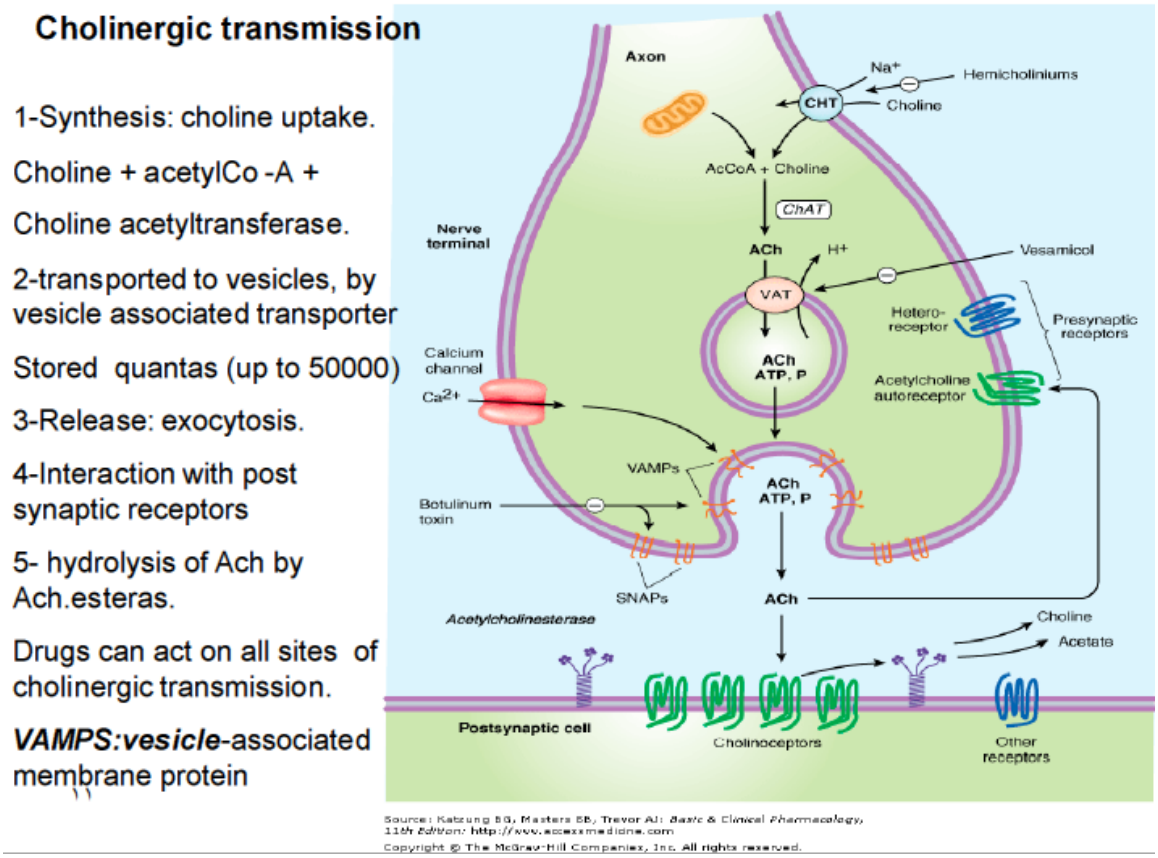
Symp and parasymp work cooperatively to achieve male sexual function. Parasymp is responsible for erection while symp is responsible to ejaculation. There's similar ANS cooperation in the female sexual response.



- Exception to dual innervation. (innervated by sympathetic only).

- Exception to antagonism. (sometimes parasympathetic and sympathetic work together cooperatively) .

	Effect of			
	Sympathetic Activity		Parasympathetic Activity	
Organ	Action[1]	Receptor[2]	Action	Receptor[2]
Penis, seminal vesicles	Ejaculation	α	Erection	M



Cholinergic transmission involves the following steps:

1. Synthesis (of Acetylcholine): starts with choline uptaking, since its needed to synthesize acetylcholine.

Choline + acetyl CoA + (Choline acetyltransferase) → Acetylcholine.

Choline is present abundantly in the body, it's transported into the neuron by choline transporters (it's taken up by co-transport which is Na dependant), whereas acetyl coA is obtained from the mitochondria . The uptake of choline is the rate limiting step in the synthesis of acetylcholine so if this step is inhibited the synthesis of acetylcholine will be affected (decreased). When formed, acetylcholine is located outside the storage vesicle.

- *Hemicholinium* (drug): inhibits choline transporters, which stops the influx of choline into the neuron, thus the transmission stops.

2.Storage Aacetyl choline enters vesicles called synaptic vesicles, VAT (vesicle- associated transporter), lets in acetylcholine in exchange with protons. Acetylcholine is stored as quantas (up to 50000 molecule per quanta, bundled together by a specific protein).

- *Vesamicol* (drug): inhibits VAT, preventing acetylcholine from entering the vesicle, which leads to a failure in the transmission. (The empty vesicle is still released from the neuron by exocytosis)

3.Release of acetylcholine vesicles. This process is calcium dependent, when the action potential reaches the end of the neuron it opens the calcium channels, calcium ions influx into the neuron, causing the movement of so many vesicles towards the synaptic region then to the synaptic cleft. (In resting potential, the calcium-ion channels are closed). On the synaptic region, there are certain docking proteins known as SNAPs and VAMPs.

- *SNAPs and VAMPs* (vesicular associated membrane protein), are in charge of aligning the vesicles in the correct orientation for successful exocytosis (fusion of the neuronal and vesicular membranes).

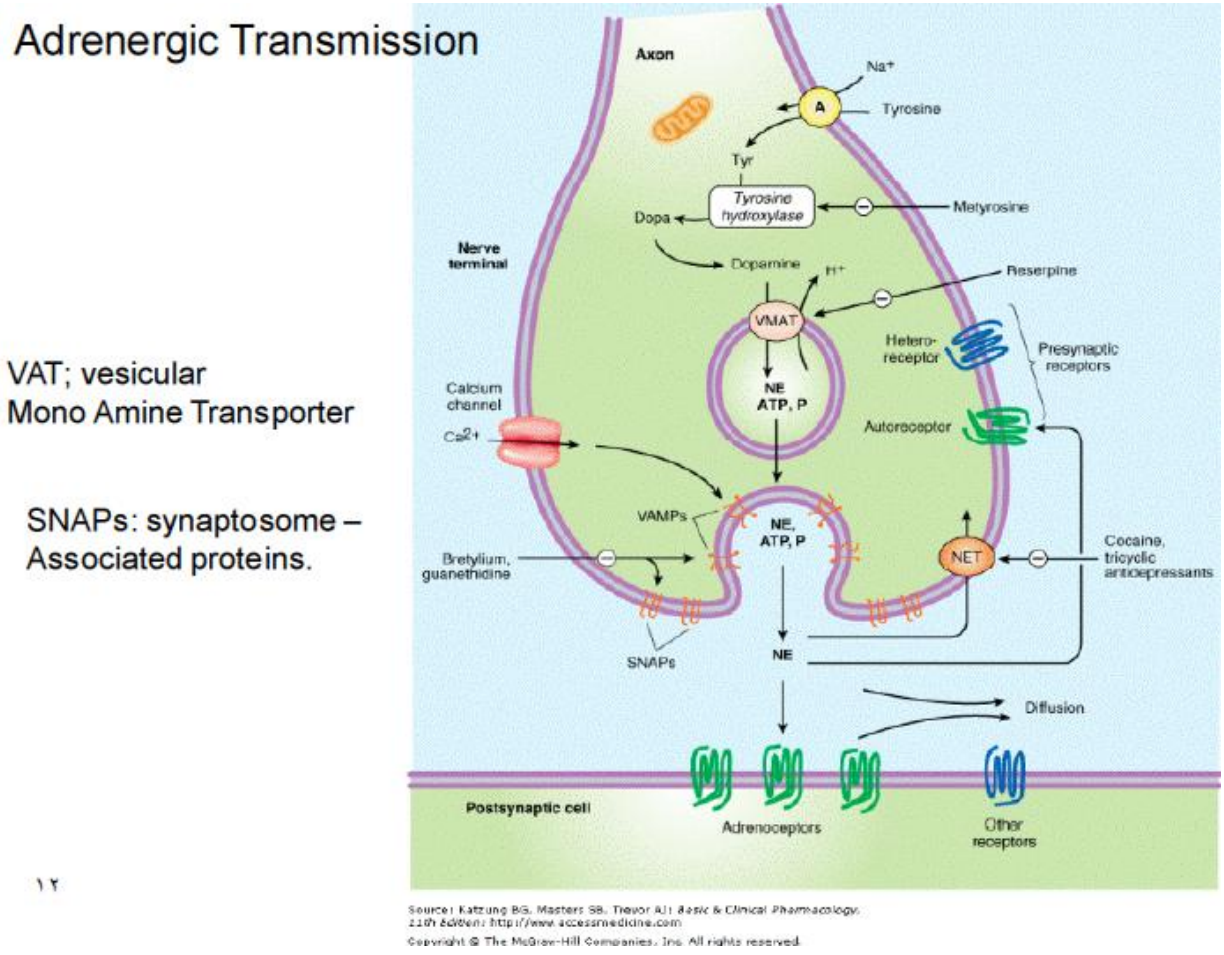
- *Botulinum toxin*: this toxin disables the docking proteins by cleaving SNAPs, so no acetylcholine will be released. It is used in cosmetic surgery, as its effect lasts many months.

1. **Interaction** of the acetylcholine with the post synaptic receptors.
2. **Hydrolysis** of acetylcholine by acetylcholine esterase, liberating choline + acetate. 80% of liberated choline will be retaken by the cholinergic neuron to be used again for acetylcholine synthesis.

- *Acetylcholine autoreceptors*: regulatory receptors found on the presynaptic neuron, they are used to control the amount of acetylcholine released. When acetylcholine esterase is cleaving acetylcholine, these receptors are

activated, preventing too much release of acetylcholine, they are regulated by negative feedback.

Heteroreceptors: are another type of receptors found on the presynaptic membrane that stop excess acetyl choline release. Unlike autoreceptors, heteroreceptors don't bind to acetylcholine (another ligand used, thus they are not regulated by negative feedback). Hetero receptors don't terminate the action of acetylcholine but control the neuron, they influence increase or decrease in the release of acetylcholine.



Adrenergic transmission: starts synthesis from tyrosine (reminder: tyrosine is the starting material of all catecholamines, and can be extracted from phenylalanine). Tyrosine enters the cell by Na+ dependant co-transport. When it gets inside, tyrosine hydroxylase (rate-limiting enzyme) will add a hydroxyl group to the tyrosine forming a new compound called dopa.

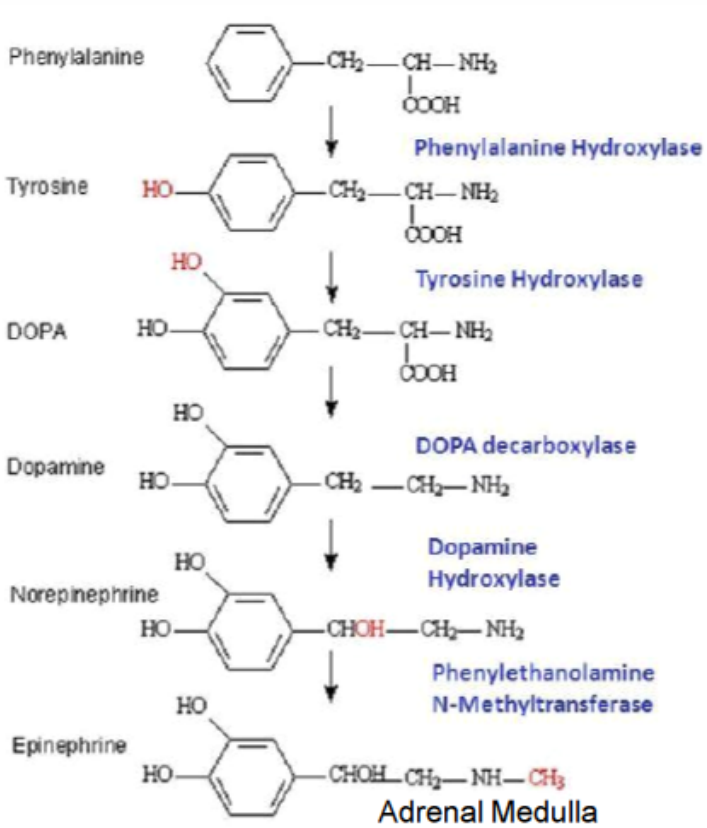
- *Metyrosine* inhibits tyrosine hydroxylase. Pheochromocytoma is a tumor in the adrenal gland, in such case, adrenaline's amount is high, so we treat the patient by giving him metyrosine. (less stimulation of adernal gland thus less NE & E produced)

Synthesis of Norepinephrine

Tyrosine uptake by NET
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.



1. **Dopa decarboxylase** transforms dopa into dopamine, which has to get into the storage vesicle in order to form more epinephrine. (Dopa decarboxylase doesn't only act on dopa, it can also act on other monoamines such as serotonin)
2. **Vesicular monoamine transporter(VMAT or VAT)** will transport dopamine inside the vesicle.
3. Inside the vesicle, dopamine β hydroxylase causes hydroxylation of the β carbon atom, converting dopamine into norepinephrine.

VMAT is inhibited by reserpine. How?

- *Reserpine* prevents any monoamine (neurotransmitter) from entering inside the vesicle. Thus resulting in depletion of catecholamines (epinephrine, norephrine, serotonin and dopamine.)

A person taking reserpine will suffer from severe depression.
(NET explained in next slide)

Storage:

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

Release:

1- Calcium dependent exocytosis.

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

Release can be blocked by guanethidine and pretylium.

–Conotoxin GVIA (Toxin of marine snails) blocks Ca ω channels and reduce NE & Ach release.

–Latrotoxin (Black widow spider venom) acts on α vesicles causing explosive release of NE & Ach.

As in cholinergic neurons, adrenergic neurons also release the vesicles by exocytosis.

1. **Calcium dependent exocytosis**: when calcium ions influx upon action potential, NE + protein + Dopamine-β- hydroxylases are released.

- *Pretylium*, *guanithidine* and *botulinum toxin* prevent the release of norepinephrine.

- SNAPs are also available for guidance of exocytosis.

-After norepinephrine is released, it stimulates interaction with the post synaptic adrenergic receptors.

80% of the released NE is taken up again by NET (NorEpinephrine Transporter), back into the neuron, where it's restored inside the vesicles.

- *Cocaine and tricyclic antidepressants* inhibit NET, so the 80% of NE that's supposed to be retaken by the neuron remain outside, causing further stimulation of the receptors, inducing the feeling of "happiness".