PHARMACOLOG

◉ Sheets ○ Slides

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Done by: Hashim Amer

Corrected by: Jawad Masarweh

Subject: Autonomic nervous system

Doctor: Hamzeh

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Autonomic nervous system

Nervous system is divided into:

1. Central nervous system →CNS: brain and spinal cord.
2. Peripheral nervous system →PNS: neuronal tissues outside the CNS.

Peripheral nervous system is devided into:

1. Somatic nervous system (for skeletal muscles).
2. Autonomic nervous system: called autonomic, because it's independent of conscious thoughts, as we can't change the functions that are controlled by the autonomic nervous system.(its self-controlled but can be activated by indirect way e.g. thinking about food increase salivation).

First, autonomic nervous system was divided into two subdivisions:

1. Sympathetic nervous system
2. Parasympathetic nervous system

but, recently, a third subdivision was added:

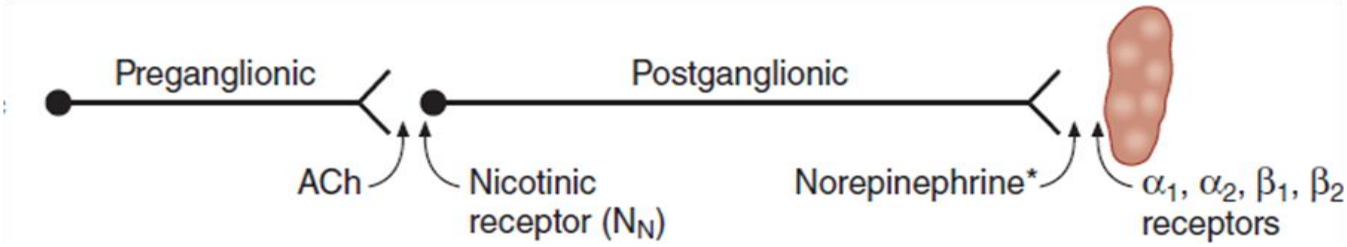
3. Enteric nervous system: that controls the movement in the gut and the activity of the gastrointestinal tract.
   Enteric neurons are affected by the parasympathetic nervous system (increases the activity of the enteric neurons→increase gastrointestential functions.and the sympathetic nervous system (decreases the activity of the enteric neurons).

All those three systems are almost independent of the CNS.

Back to the sympathetic and parasympathetic nervous systems, their neurons are classified according to the neurotransmitter they release, **Adrenergic neurons** and **Cholinergic neurons.**

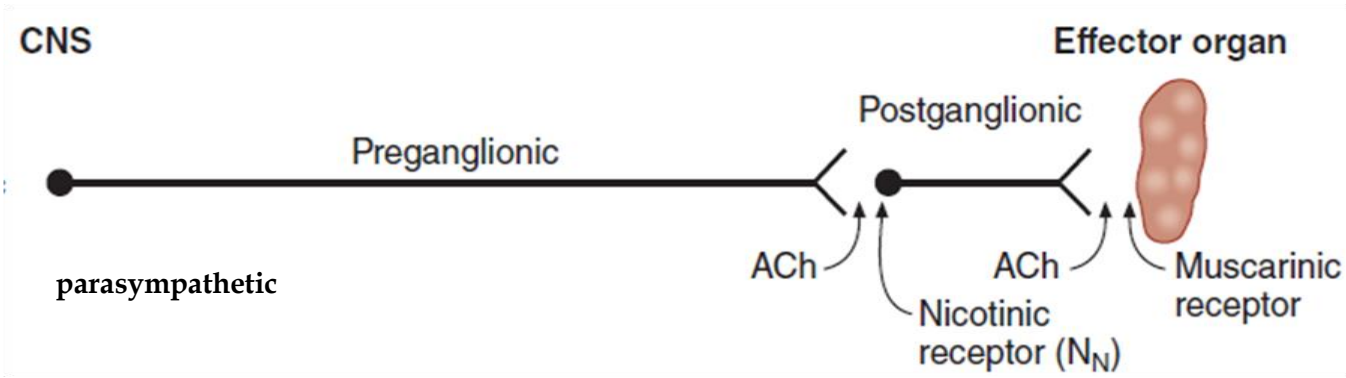
1. **Adrenergic neurons**: <u>release Norepinephrine</u>, called adrenergic because, in the twentieth century, scientists examined the sympathetic nervous system and found that the neurotransmitter released is **Adrenaline**, later on it turned out to be norepinephrine (noradrenalin) not adrenaline, however, the name stuck to it.
   Each neuron is actually composed of two neurons, the first one, comes out from the spinal cord and synapses at the autonomic ganglia, called **Preganglionic neuron**.
   As for the second neuron, its cell body is inside the autonomic ganglion, while its axon synapses with a certain tissue, called

Postganglionic neuron. Inside the autonomic ganglia, a preganglionic neuron will release Acetylcholine.
<u>note:</u> Acetylcholine **is always released in the autonomic ganglia.**



The cell body of the postganglionic neuron has receptors for
sympathetic oline, these receptors called **Nicotinic receptors**(because also stimulated by Nicotine), when activated, Norepinephrine is released at the end of the postganglionic neuron, activating Adrenergic receptors(α and β receptors) on the target tissue. This type is found at <u>sympathetic</u>.

2. **Cholinergic Neurons:** <u>release Acetylcholine</u> .
a preganglionic neuron, when exited, will release Acetylcholine, which will bind to the Nicotinic receptors on the postganglionic neuron (same as Adrenergic neurons), once these receptors are activated, the postganglionic neuron will release Acetylcholine, which will bind to the Muscarinic receptors on the target tissue(because they are activated by muscarine. Muscarine can be obtained from wild poisonous mushrooms).-→this type is found at <u>parasympathetic</u>



• in case of voluntary motor nerve that innervates the somatic skeletal muscle, Acetylcholine is released, then It binds the nicotinic receptors on the skeletal muscle, causing skeletal muscle contraction.

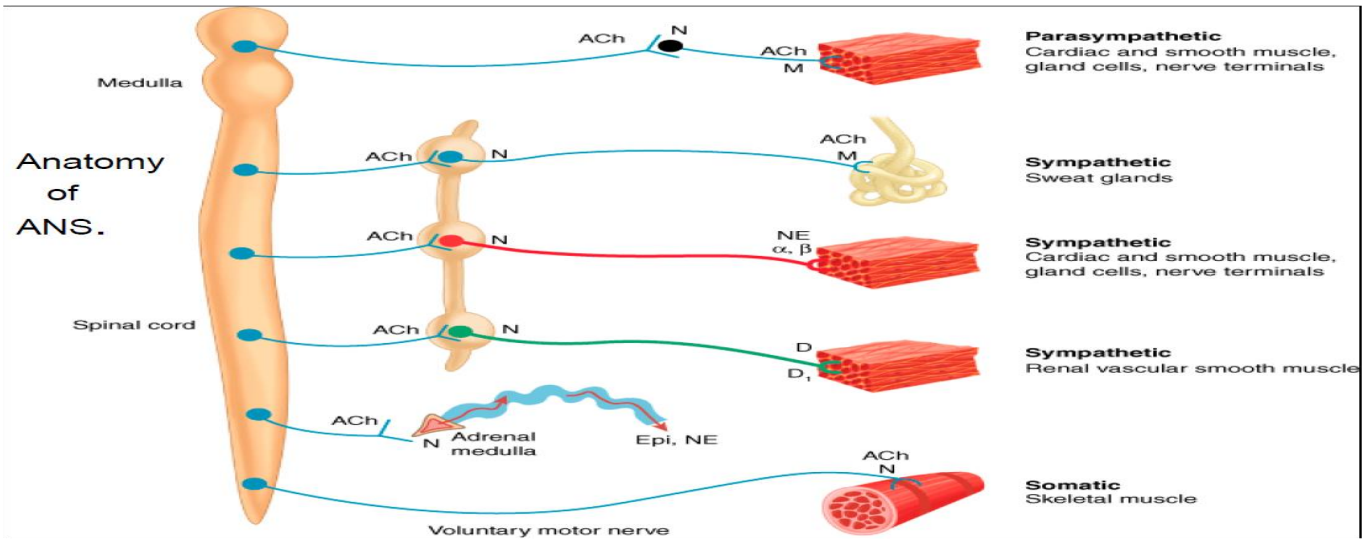
• **Sweat glands:** (innervated by special type of neurons)
Although they are innervated by the sympathetic nervous system, the neurotransmitter that is released from the postganglionic neuron is **NOT** norepinephrine, its Acetylcholine, which binds the Muscarinic receptors.

• **Dopaminergic Nerve:** present only in renal vascular smooth muscle, releases dopamine when stimulated by the sympathetic nervous system, dopamine will activate dopamine receptors D1, which promotes vasodilatation of renal vessels and increase in renal blood flow.

• As for the neurons that innervate **adrenal gland**, they are cholinergic, they release Acetylcholine, binding of Acetylcholine to the Nicotinic receptors of the Adrenal medulla will stimulate it to release Epinephrine(80%) and Norepinephrine (20%).

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

REMEMBER!
Adrenergic fibers include:
1. Most sympathetic postganglionic fibers.
2. Some sympathetic postganglionic fiber that release dopamine.
3. Adrenal medulla releases a mixture of epinephrine (adrenaline) and norepinephrine (noradrenaline).



● **Parasympathetic** cell bodies are located in brainstem cranial and sacral portion of the spinal cord, usually called **craniosacral outflow.** **post**ganglionic neurons are **short** (parasympathetic ganglia are located near the organ or sometimes even inside it), one preganglionic neuron give rise to one postganglionic neuron.

● **Sympathetic** cell bodies are located at T1-L2 levels, usually called **thoracolumbar outflow.**One sympathetic preganglionic neuron may have many branches and may synapse with 60+ 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.

These two systems are controlled by the hypothalamus.

● Some organs have only sympathetic innervation:

- Sweat glands.
- Adrenal medulla.
- Arrector pili mm and many blood vessels.

They are regulated by the "tone" of the sympathetic nervous system.
(High tone ___high firing rate ___ highly stimulated organ)

● Most of the organs receive dual innervations by both, sympathetic and parasympathetic nervous systems.

●the body is in a balanced situation between these systems, there are antagonistic effects between these two systems (one of them will stimulate, while the other one will inhibit).

● Hypothalamus regulates the tone between the parasympathetic and sympathetic systems

● the **parasympathetic** nervous system is sometimes called "rest and digest" system, it conserves energy, its responsible for the "business as usual" metabolic pathways that are not really necessary for survival (basic survival functions) like Salivation, Lacrimation, Urination and Defecation.

●the **sympathetic** nervous system is responsible for your body's "fight or flight" reactions, it increases blood sugar, lipolysis to provide free fatty acids, heart rate and blood flow, it also decreases non-survival activities to overcome the critical situation. Note that nervous people have high tone all the tone thus inactive non-survival are not active. So they will have stomach problems most of the time.

● Antagonistic control: a great example is heart rate, an increase in sympathetic stimulation causes heart rate to increase whereas an increase in parasympathetic stimulation causes heart rate to decrease.
At normal situation, the heart is under the control of the parasympathetic nervous system, unless there are some activities (exercises).

- In older people, sympathetic tone is dominant. (high heart rate)
- In children, sympathetic tone is dominant. (high heart rate)

● Exception to the antagonistic control: sometimes sympathetic and parasympathetic nervous systems work **together**, as in the male and the parasympathetic is responsible for erection, while the sympathetic is responsible for ejaculation.

Cholinergic transmission, it involves the following steps:

1. **Synthesis** (of Acetylcholine): starts with Choline uptaking.
   Choline + acetyl CoA + (Choline acetyltransferase) → **Acetylcholine**.
   Choline is present abundantly in the body, it's transported into the neuron by choline transporters, whereas Acetyl CoA is obtained from the mitochondria.
   When formed, Acetylcholine is located **outside** the storage vesicle.
   - **Hemicholinium (drug):** inhibits choline transporters, which stops the influx of choline into the neuron, Thus transmission Stop.

2. **Transporting** Acetylcholine into vesicles by vessecular acetylcholine transporter(VAT), Acetylcholine is stored as quantas(up to 50000).
   - **Vesamicol**: inhibits **VAT**, preventing Acetylcholine from entering the vesicle, which leads to a failure in the transmission.

3. **Release**, it is calcium dependent, when action potential arrives to the end of the neuron it opens the calcium channels, calcium ions influx into the neuron, causing the movement of so many vesicles to the synaptic cleft.
    - SNAPs and VAMPs (vesicular associated membrane protein), are used to properly docking of the vesicle ,which ensures proper aligning and binding of acetylcholine. (Exocytosis)

4. **Interaction** of the Acetylcholine with the post synaptic receptors.

5. **Hydrolysis** of Acetylcholine by Acetylcholine esterase, liberating Choline + Acetate, choline will be re taken by the cholinergic neuron to be used again.

    - presynaptic receptors are located at the presynaptic neuron, they are **Acetylcholine autoreceptors**, regulatory receptors, they are used to control the amount of Acetylcholine, when Acetylcholine esterase is cleaving Acetylcholine, these receptors are activated, preventing further release of Acetylcholine, they are regulated by negative feedback.

    - There are other receptors on the presynaptic neuron, but they don't attach to Acetylcholine, called **Hetero receptors**.

    - **Botulinum toxin:** used in cosmetic surgeries, it cleaves SNAPs, so acetylcholine won't be release. Thus will remove wrinkles

Adrenergic transmission: starts **synthesis** from Tyrosine, its taken up by the neuron, by transporter A, when it gets inside, tyrosine hydroxylase will add a hydroxyl group to the tyrosine, the new compound is 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)
- **Dopa decarboxylase** doesn't only act on dopa, it acts on other monoamines (serotonin)

Dopa decarboxylase transforms dopa into dopamine, which has to get into the storage vesicle in order to form more epinephrine.

- Vesicular monoamine transporter(**VAT**) will transport dopamine inside the vesicle.
- **Dopamine β hydroxylase** will transform dopamine to norepinephrine inside the vesicle.
- **Reserpine** is a selective inhibitor, that inhibits VAT, no neurotransmitter
  can get inside the vesicle in the presence of reserpine.
- Taking **Reserpine (a TMAT drug trans monoamine transport)** will cause depletion of all of the monoamines(epinephrine, norepinephrine, serotonin and dopamine), almost has the same effect as if we cut off sympathetic nuerons.thus lead to relaxtion
- A person who is taking reserpine will suffer from severe depression. And eventually they will suicide so they stoped using this drug.
- Parkinsin pateint have low dopamine we give him DOPA not dopamine since dopamine cant cross BBB.

Releasing methods:

1. **Calcium dependent exocytosis:** when calcium ions influx, upon action potential, NE + protein + Dopamine-β- hydroxylaes are released.
   - **Pretylium, guanithidine** and **Botulinum toxin** prevent the releasing of Norepinephrine.
   - they were used in treating hypertension, but, they are not much used now due to their side effects(e.g. severe diarrhea).
   - Alpha2-autoreceptors are presynaptic receptors by which noradrenaline release is inhibited by noradrenaline itself. (regulatory)
   - Norepinephrine effects are not terminated by metabolism, but by neuronal reuptake, 80 % of the released Norepinephrine are transported into the neuron by NET (Norepinephrine Transporter).

   - Cocaine and Tricyclic are antidepressants Inhibit NET. So NE will stay longer.

2. **Calcium independent release.**

(Please refer to the slides)
Good luck