11

Pharmacology

Doctor 2017 | Medicine | JU

◉ Sheet ○ Slides

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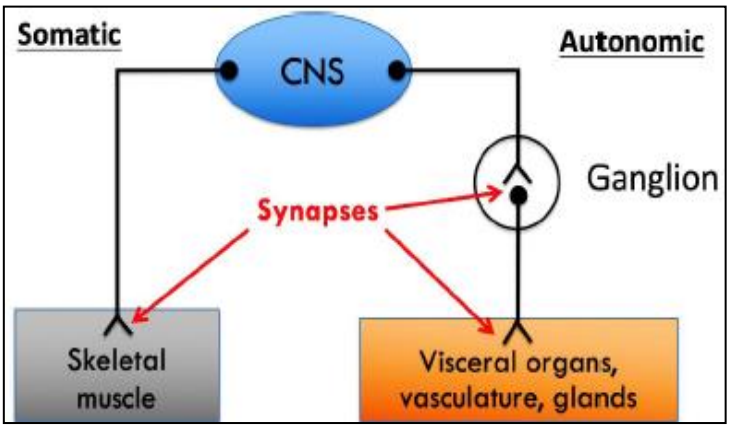
The Autonomic Nervous System (ANS)

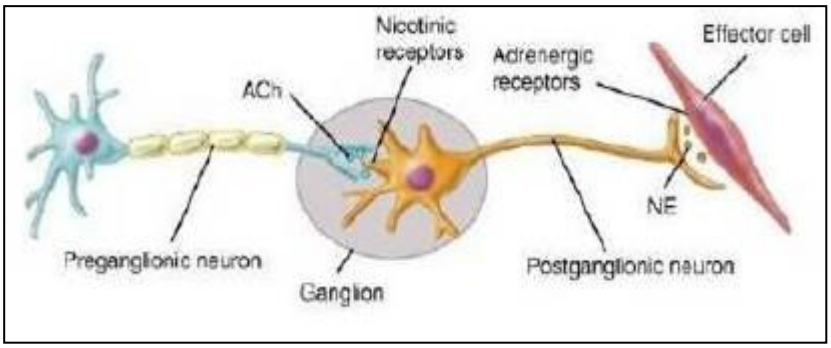
The nervous system is divided into two anatomical divisions:



1- The central nervous system (CNS); which is composed of the brain and the spinal cord

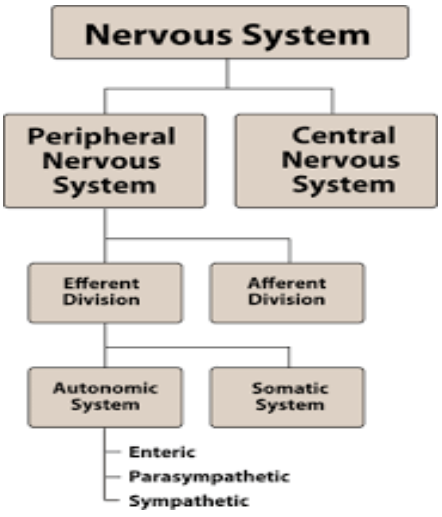
2- The peripheral nervous system(PNS); which includes neurons located outside the brain and spinal cord. Furthermore, the (PNS) is also subdivided into efferent (motor; that innervate the skeletal muscles) and afferent (sensor) divisions. However, the efferent (motor) portion can be divided into somatic & autonomic.

- The word (Autonomous) means self-control. So we can understand that the Autonomic Nervous System (ANS) does NOT function under a direct conscious control. In other words, we can NOT control its activity and function. *(Take your heart rate as an example. Can you control it? Of course not, as long as it is involuntary muscle in your body, thus, it is controlled by ANS).*



- In the **peripheral nervous system**, we have something called **Ganglia**(or Ganglion) which is meant to be 2 neurons; the 1st emerges from afferent nerves (input nerve fibers) and the 2nd emerges from efferent nerves (output or motor nerve fibers).

- PNS is important and necessary in keeping the internal environment of the organs stable and survived. It maintains homeostasis so that the body functions properly.



- The Autonomic Nerve System (**ANS**) has three subdivisions:

1- **Sympathetic** nervous system.

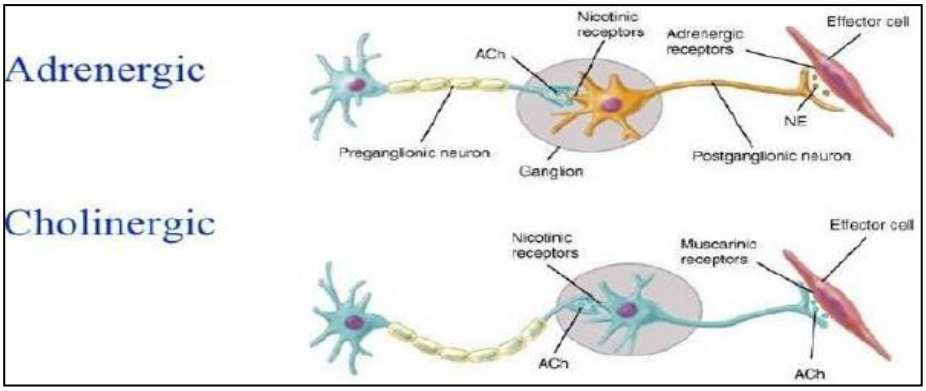
2- **Parasympathetic** nervous system.

3- **Enteric** nervous system(ENS).

- The Enteric Nervous System forms a collection of plexuses (networks) that surround and extend along the gut; including stomach, small and large intestine. Additionally, the (ENS) activates a coordinated function of the smooth muscles to cause peristaltic constriction of the gut in addition to that (ENS) can function independently of higher CNS and controls the motility, exocrine & endocrine secretions as well as the microcirculation of the GI tract. Not surprisingly, (**ENS**) has many **neurons** that are **called** The Second Brain or The Brain of the Gut.

- The Enteric Nervous System is modulated by sympathetic and parasympathetic systems. So we can say that the activation of sympathetic system inhibits the activity of the GI tract whereas parasympathetic system will stimulate the GI tract functions.

- Now, if we looked at the nerves, we would realize that the nerves themselves are classified according to the chemical transmitter released from them. Namely, we have **Adrenergic** nerves and **cholinergic** nerves.



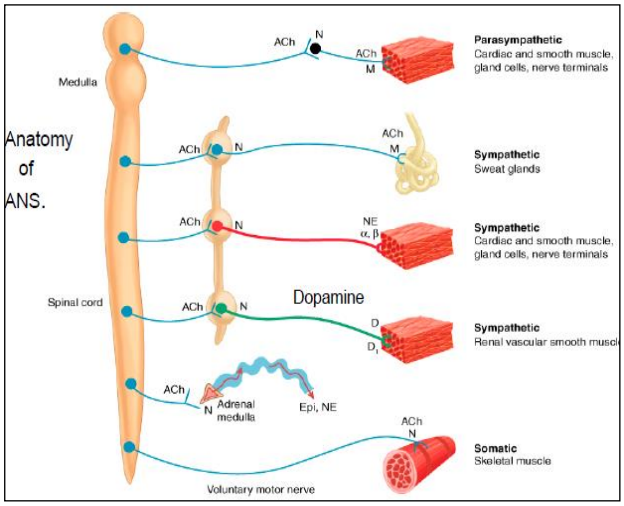
- An **adrenergic** nerve fiber is a neuron for which the neurotransmitter is adrenaline (epinephrine) and NOT Norepinephrine. That's what the DR in the lecture record said and he mentioned that the reason only adrenaline because NE is not actually a neurotransmitter; it is a hormone secreted from the adrenal medulla. (**5:50;** record of **section 2**). However, **both E** and **NE** can **act** on the **Adrenergic** receptors

- In terms of neurotransmitters, the neurotransmitter acetylcholine (Ach), for example, gets released from the pre-ganglionic neuron (Pre means before) and find its way to be attached to a receptor in another neuron which is obviously found inside the ganglia itself. Therefore, when there is an action potential approaching the first part of the pre-ganglionic nerve, the Ach then is released and activates its receptors as the action potential travels through the axon to, ultimately, reach the postganglionic neuron and release another neurotransmitter to produce the effect.

However, cholinergic receptors are activated by (Ach) at the post-synaptic ganglia. (**REMEMBER** that **adrenergic** receptors are stimulated by **E** or **NE**). Also, if you look at the picture shown above, you will notice that (**Ach**) is a **common** neurotransmitter between the **Nicotinic** receptors (inside the ganglia) and the

Muscarinic receptors (at the effector cell; e.g. muscle). Furthermore, the muscarinic receptors are selectively stimulated by Muscarine (which is a poisonous substance produced by mushrooms as it's 100 times more potent than Ach), while the nicotinic receptors are stimulated by nicotine found in tobacco and cigarettes.

- Considering the figure below, the somatic neuron innervates skeletal muscle as is also releases (Ach) and then Ach will activate the Nicotinic receptors to produce muscle contraction. However, there is one of the cranial nerves coming from the mid brain which is cholinergic as it releases (Ach) in the per-ganglionic region and stimulates the Nicotinic receptors which, then, will the activates the Muscarinic receptors in the post- ganglionic region release (Ach) producing a parasympathetic effect (e.g. contractions of cardiac & smooth muscle).



According to the figure, notice the 2nd sympathetic pathway (i.e. the third line in the picture) which involves a release of (Ach) activating Nicotinic receptors in the ganglia and then continues to finally emerge a **sympathetic** effect by releasing **NE** through the α and β **adrenergic** receptors.

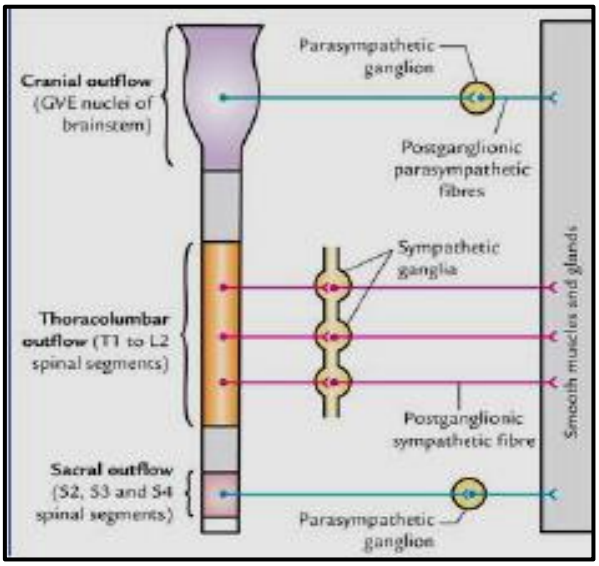
- There is an **exception** in the **sweat gland,** with the Muscarinic receptors, that is stimulated by (**Ach**) instead of NE, although it's under the **sympathetic control**. *(Please don't forget that exception ☺)*

- **Remember** also that the **desired effect** on our body has nothing to do with the type of neurotransmitter itself ! , BUT it **depends on the location of that receptor** in the organ which will bind to the released neurotransmitter.

- Renal vascular smooth muscles, from the picture above, are stimulated by Dopamine (through Dopaminergic neurons) which acts on D1 and D2 receptors causing a relaxation of smooth muscle and an increase of blood flow to the kidney.

After understating the previous illustrated figure, try to ask yourself about each type of these nervous pathways in order to easily recall each receptor and its neurotransmitters.

As shown in the picture, we can remarkably notice that the parasympathetic neurons come out from two regions. The 1st is called Cranial and the 2nd one is sacral. Additionally, their post-ganglia are short and very close to the effectors, whereas their pre-ganglia are long. (If you still have the **Physiology** sheet no. 11, try to open page 7 & enjoy the comparison table of sympathetic and parasympathetic systems!!, not hard ☺). Moreover, you may realize that the **parasympathetic** system only works with **one post-ganglionic** nerve to produce a single effect and, therefore, its effect is meant to be **isolated.** On the other hand, the **sympathetic** comes from the **Thoracolumbar** region which start from the level of **T1 to L2**, as its pre-ganglionic nerves seem to be short in comparison to its long post-ganglionic ones. Not only this, but also some of these single pre-ganglionic neurons can have branches into more than one post-synaptic neurons which means if one pre-ganglionic neuron is stimulated, two or more post-ganglionic nerves would be stimulated at the same time; which explains the key significance of mobilizing the energy in our bodies to survive in fight & flight situations.



- Now, we have to understand that not all the organs in our bodies are supplied with sympathetic and parasympathetic nervous systems. For instance, the heart is innervated through both sympathetic and parasympathetic, whereas sweat glands and adrenal medulla, for instance, are only innervated by a parasympathetic stimulation. **So how can the body maintain their balance (Homeostasis) if they only function under the parasympathetic system !?**

Answer: Balance is adjusted and achieved by the Hypothalamus which controls what is called the (tune or spike) of their activities and functions. The tune, in regards to how the DR has already illustrated it, emits sound waves (spikes) indicating whether the nerve for example is active or not; the higher the tune is, the more active the neuron is and vice versa.

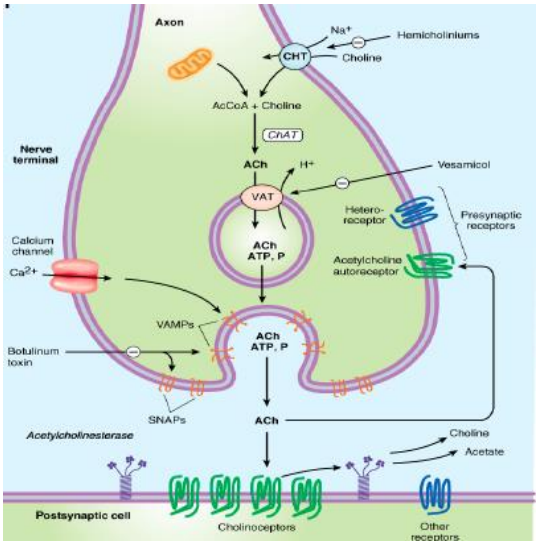
- Usually, parasympathetic system works when we are in a "rest and digest" status; away from fight and flight incidence. Thus, this system motivates lacrimation salivation, digestion, defecation and urination etc.. .In the contrary, the sympathetic system is ON when we need our body to function properly in order to survive.

To illustrate, imaging that you are fighting with Ahmed Olimat; you will need your eye's pupil to be more dilated (mydriasis) as well as your heart rate has to be increased (Tachycardia) to get as big blood flow as possible, whereas in unimportant areas such as skin; you do not need a huge blood supply during dangerous moments and that's why our skin looks yellow-faded. The same thing happens with the blood flow to the kidneys & GI tract where the blood supply is not really a big deal at that time.

- However, it is not always that sympathetic and parasympathetic systems are antagonistic to each other; sometimes they can work cooperatively in order to perform a certain task. For example, sympathetic & parasympathetic work together to achieve male sexual function. parasympathetic is responsible for erection while sympathetic is responsible for ejaculation. There's also a similar ANS cooperation in the female sexual response.

The Cholinergic Transmission

In order to understand the process of transmitting a neurotransmitter, we shall realize how the neurotransmitters themselves are synthesized, stored and released and what will happen to them after release. Always, any neurotransmitter is actually synthesized in the same neuron which will release it afterwards. Regarding the cholinergic receptors that release (Ach); **acetylcholine** is composed of **Choline** & **Acetate**.



So, how does the cholinergic transmission occur? Let's follow these steps:

1- Firstly, the process start with the synthesis of Choline; which is present in blood plasma.
2- Then it enters the neuron (Pre-synaptic) by ChT (Choline transporter) by active transport; as the transporter delivers it inside the neuron.

3- As soon as Choline enters, it gets bound with acetyl-CoA (AcCoA). However, (AcCoA) is coming out from the mitochondria. *(**Note** that the rate limiting factor of the process of (Ach) synthesis is the (AcCoA) amounts that leave the mitochondria).*

4- Now, so far, the (Ach) has not been synthesized yet. In order to produce (Ach), an enzyme called Acetylcholine Transferase (AchT) should be presented. Therefore, the (AchT) facilitate the process of (Ach) production. Additionally, there is a **drug** called (**anticholinum**®) which is known to be a selective **inhibitor** of Acetylcholine Esterase(**AchE**) as it **inhibits** the **entry** of **Choline** to the cell and, consequently, **synthesis stops** & the neuron uses all the (Ach) stored in it.

5- Once the (Ach) has been already synthesized, it gets transported to the storage vesicle through vesicle associated transporter (VAT). The storage vesicle has ATP & certain proteins inside so that the (Ach) binds with them. *(**Note** that there are also some drugs that inhibits the transportation of (Ach) by affecting the function of (VAT), even if there were large amounts of Choline inside the neuron).*

6- (**Ach**) remains **inside** the vesicle **until** an **action potential** opens Ca++ channels so the Ca++ ions move vesicles towards the neuronal membrane to release (Ach) out of the Pre-synaptic neuron by **Exocytosis**, so that (Ach) can later act on the effector cell (Post-synaptic) and bind to its Cholinergic receptors.

7- After (Ach) has done with its function, it goes back to enter the Pre-synaptic neuron by Acetylcholine auto-receptor. *(**Note** that* Auto-receptors & Hetero-receptors, in the pre-synaptic neuron, control the amounts of (Ach) being released).

- **Remember** that the enzyme Acetylcholinesterase (AchE) inhibits the function of (Ach) by breaking its ester bonds, so no more synthesis and linking of Choline and AcCoA.
- We also have something called **Vesicle Associated Membrane Proteins (VAMPs)** which are special proteins present on the surface of each vesicle to **direct** the vesicle **fusion** & regulate the **Exocytosis** process.
- ***Botulinum toxin* (BTX)** is **a neurotoxic protein** that **prevents** the **release** of the (**Ach**) from the axon endings, because it destroys VAMPs, so no Exocytosis and no neurotransmission. Furthermore, it can also be used as an injection or **treatment**

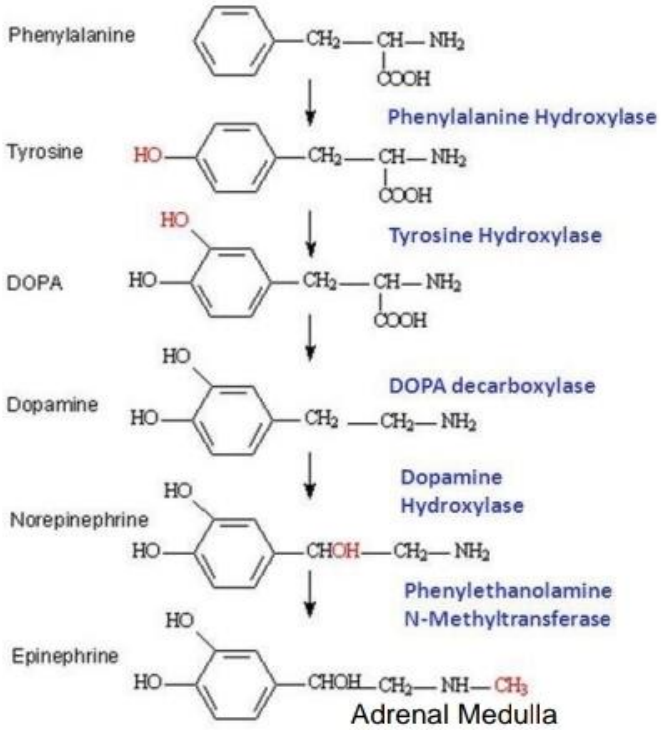
for **cosmetic** purposes as well as sever types of **muscular spasms and pain** around many different areas of the body such as bones and back.

The Adrenergic Transmission

Now let's move to the adrenergic transmission which is a bit more complex than Cholinergic one. However, in the adrenergic transmission, we have the amino acid **Tyrosine** (Tyr) which represents the **starting** material for the **synthesis of Catecholamines** (epinephrine, norepinephrine and dopamine). Sometimes, (Tyr) comes from the amino acid **phenylalanine**.

Now, let's see how (Tyr) starts off the journey of Adrenergic transmission.

1- Tyrosine enters the pre-synaptic neuron by active transport, then it is converted to one of the Catecholamines by the enzyme **Tyrosine hydroxylase**. This enzyme represents the most important step in this pathway because it is the rate limiting step in the synthesis of Catecholamines. Additionally, the enzyme Tyrosine hydroxylase can be also inhibited by the amounts of the end product (i.e. E, NE or Dopamine) *(**Remember** that the rate limiting step in the Adrenergic transmission/synthesis was the amounts of (AcCoA) that are leaving the mitochondria).*

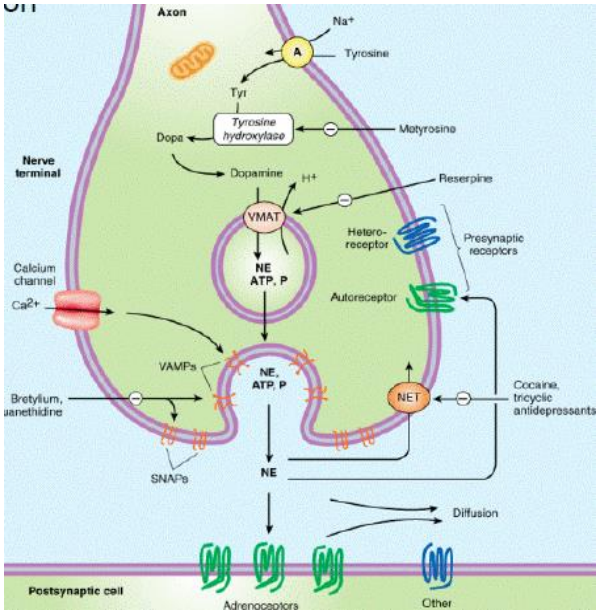


2- Tyrosine hydroxylase, **firstly** convert (**Tyr**) to **Dopa** and NOT dopamine.

3- After that, **Dopa** gets converted into **Dopamine** by the an enzyme known as ***DOPA* decarboxylase**. So, (Tyr) is not converted directly to Dopamine!

4- Dopamine is transported into storage vesicle by the vesicular Mono Amine Transporter (VMAT/VAT), which is the same (VAT) in the Adrenergic transmission,

and convert to (NE). In the vesicle itself, we have an enzyme called ***Dopamine β-hydroxylase*** that can hydroxylize dopamine to produce the neurotransmitter (NE)



5- (NE) is now stored in vesicles, each 4 molecules are bound to one cAMP molecule. It's ready to get released to the post-synaptic neuron where the cholinergic receptors exist.

6- A neuronal reuptake process also happens in which 90% of the (NE) released is taken back to the pre-synaptic neuron and stored inside the vesicles.

- Metyrosine is a drug that inhibits the function of the enzyme Tyrosine hydroxylase and, therefore, the synthesis of catecholamines would be stopped. Clinically, once someone has a tumor in the Adrenal medulla which releases a huge amounts of catecholamines, it is advised that we give him Metyrosine to minimize the catecholamines being released.

- Reserpine is also a drug that inhibits the vesicular Mono Amine Transporter (VMAT) causing a depletion of catecholamines inside the neuron and ,therefore, no more NE is synthesized. Also, Cocaine and Tricyclic antidepressants drugs inhibit the reuptake of (NE) by blocking the action of the norepinephrine transporter (NET), so the NE can have an extended action. Reserpine was used for hypertension.

- **<u>The release of (NE) is further divided into two types:</u>**

1- **Calcium dependent exocytosis:** *in which,* the vesicles are held in place by Ca2+-sensitive vesicle membrane proteins (VAMPs), which bind to the actin filaments & microtubules of the cytoskeleton. When an action potential reaches the terminal of a presynaptic neuron, voltage-dependent calcium (Ca2+) channels in the pre-synaptic membrane open and Ca2+ rushes in. This influx of calcium ions triggers a series of events which ultimately lead to

release of the neurotransmitter . This type of release can **be blocked by guanethidine and pretylium**. **ω–Conotoxin GVIA**, a toxin of marine snails that blocks Ca++ channels & reduce NE & Ach release. However**,, α–Latrotoxin** (Black widow spider venom) acts on vesicles causing explosive release of NE & Ach.

2- **Calcium independent release:** in which, Tyramine and amphetamine are transported by (NE) transporter (NET) into the neuron then transported by (VMAT) into the vesicles. They, in turn, displace the (NE) from the vesicular stores into the cytoplasm and then (NE) is finally transported into the synaptic cleft by reverse transport via (NETs).So, they produce an indirect sympathetic effect. *(For further information, please refer to the slides)*

Metabolism of Catecholamines

Finally, in terms of the metabolism of catecholamines, (**NE**) effects are terminated by neuronal **uptake** (Uptake 1). As **80%** of the released NE is transported **into the neuron by MAT (Mono Amine Transporter).**

- **Monoamine oxidase** (MAO) in mitochondria produces **oxidative deamination of mono amines**. *It's found outside the neurons and in liver*.

- **Catechol-O-Methyl Transferase** (COMT) transfers **methyl group** from S- adenosyl methionine **into the OH-group** in the meta position of the catechol ring. *It's found in the neurons, intestine walls, and liver.*

- **VMA** is the **end product** of metabolism, measured **in urine** for the diagnosis of pheochromocytoma (a tumor present in certain cells in medulla). The **normal concentration** of VMA for 24 hours in the urine **is 5-6 mg but in pheochromocytoma its concentration reaches 15-30 mg.**

GOOD LUCK ☺

Go ahead & test yourself a bit

1- **Which of the following is a systematic effect of a muscarinic agonist?**
   A. Reduced heart rate (bradychardia)
   B. Increased blood pressure
   C. Dilation of pupil (Mydriasis)
   D. Constipation

2- **Botulinum toxin blocks the release of (Ach) from cholinergic nerve terminals. Which of the following is a possible effect of Botulinum toxin?**
   A. Skeletal muscle paralysis
   B. Improvement of myasthenia gravis symptoms
   C. reduced heart rate
   D. Increased salivation

3- **Which of the following is correct regarding SOMATIC motor neurons?**
   A. The neurotransmitter at the somatic motor neuron ganglion is (Ach)
   B. The neurotransmitter at the somatic motor neuron ganglion is (NE)
   C. Somatic motor neurons do not have ganglia
   D. Responses in somatic motor neurons are slower than ANS

4- **Which of the following statements is correct regarding the sympathetic and parasympathetic systems?**
   A. Acetylcholine activates muscarinic receptors
   B. Acetylcholine activates adrenergic receptors
   C. Norepinephrine activates muscarinic receptors
   D. Activation of sympathetic system causes a drop in blood pressure

5- **Which of the following is correct regarding the autonomic nervous system (ANS)?**
   A. Afferent neurons carry signals from the CNS to the effector organs
   B. The neurotransmitter at the parasympathetic ganglion is (NE)
   C. The neurotransmitter at the sympathetic ganglion is (Ach)
   D. Parasympathetic neurons release (NE) in the effector organs

6- **An elderly man was brought to the emergency room after ingested a large amount of a drug that blocks α_1, $\beta 1$ and β_2 adrenergic receptors, which mainly mediate the cardiovascular effects of (E) & (NE) in the body. Which of the following symptoms would you expect in this patient?**
   A. Dilation of pupil (Mydriasis)
   B. Reduced heart rate (bradychardia)
   C. Increased blood pressure

Kindly, try to solve them by yourself first and the answers then will be uploaded soon !