Medical Committee
The University of Jordan

PHARMACOLOGY

Lecture No.: 15

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SHEET

SLIDES

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Autonomic Nervous System (ANS)

Refer to slides 1-14 for this lecture.

Lecture Outline

- Definition of the ANS
- Origin and Divisions of The ANS: Sympathetic and Parasympathetic
- Neurotransmittors of The Sympathetic and Parasympathetic Neurons
- Key Features of NTs as Potential Targets For Pharmacologic Agents.
- Detailed example on cholinergic neurons.
- Detailed example on adrenergic neurons.
- Metabolism of the 3 NTs (Dopamine, epinephrine and norepinephrine).

-What is the ANS? –Definition-

Involuntary nervous system, automatic (the processes go on by themselves), they're not under direct conscious voluntary control, and it's primarily concerned with visceral functions that are important to life.

Visceral: referring to the viscera الأحشاء, the internal organs of the body, within the chest (heart or lungs) or the abdomen (liver, pancreas or intestines).

Examples of visceral functions: heart beat, blood flow, breathing while sleeping, whereas actions like walking and talking are actions we proceed with and stop (control) at our will and so they are not under the ANS control.

-Origin and Divisions of The ANS:

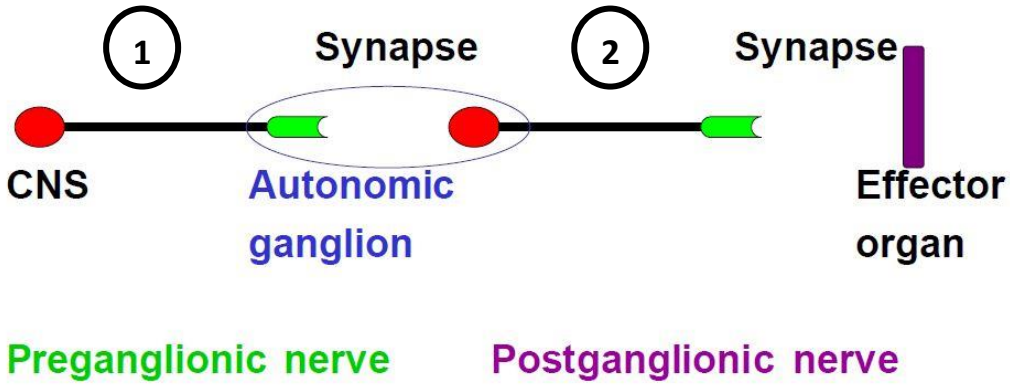
1) Sympathetic 2)Parasympathetic

These are **not antagonistic** systems, they work together to control our functions, (although sometimes they function oppositely, so if one stimulates the other blocks) but still they're not considered antagonistic to each other.

The ANS -both divisions- originate from the Central Nervous System (CNS), which consists of the spinal cord and the brain stem which in turn consists of pons and medulla.

Written by Reem Hamasha

The sympathetic division originates from the **thoracolumbar** part of the spinal cord while the **parasympathetic** division originates from the **craniosacral** part.



To explain the figure:

- Both divisions originate from the CNS and end on effector organs.
- Effector Organ: the organ affected by the function of the neuron.
- Neuron1 comes from the CNS and synapses with neuron2, neuron2 goes to the effector organ and synapses with it.
- Synapse: the space between the 2 neurons (neuron1 terminus and neuron2), or the space between a neuron's terminus and an effector organ.
- Notice the Autonomic Ganglion العقدة العصبية.
- Preganglionic nerve because it comes before the autonomic ganglion.
- Postganglionic nerve because it comes after the autonomic ganglion.

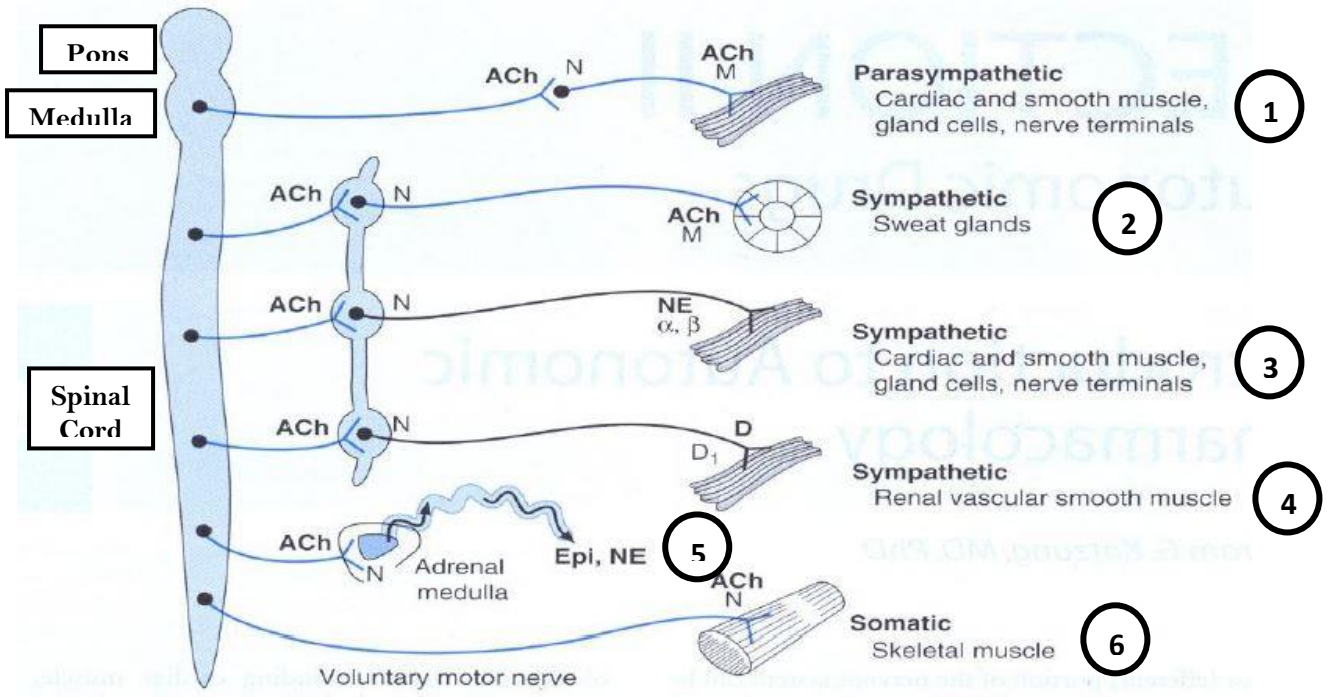
-How Do Neurons Function? –Neurotransmittors-

Neurons release chemicals into synapses, chemicals released from the terminus of the first neuron travel through the synapse, stimulate or activate or change the function of the 2nd neural cell body, then certain processes happen, another substance is released from the terminus of the 2ed neuron, travels through the synapse, goes to the effector organ, stimulate receptors there and produces the visceral functions.

These chemicals are called **neurotransmitters (NT),** there are lots of neurotransmitters in the nervous system, but when talking about the ANS, we are mainly concerned with 2 or few more NTs.

Neurons that release acetylcholine as a NT → cholinergic neurons.
Neurons that release norepinephrine (noradrenaline) as a NT → adrenergic neurons

(norepinephrine= noradrenaline) (epinephrine= adrenaline), both are scientific names, and which is used depends on the origin of the source (book).



- Notice the components of the CNS –in boxes- (from which the ANS originates) and recall the following, the medulla for example is in the cranial or cerebral region. Craniosacral (parasympathetic), thoracolumbar (sympathetic).
- When dissecting the thorax region, and reaching the vertebral column, located paravertebral (to the two sides) are 2 chains of sympathetic ganglia (called the sympathetic chain), it's an identified anatomical structure, you see it with your naked eyes when you dissect.
- Notice the 2 neurons before (originating from the CNS) and after (attached or synapsed to the effector organ) the ganglia, they synapse at the ganglia.
- In the case of sympathetic neurons: the presynaptic neuron is shorter than the postsynaptic neuron.
- In the case of parasympathetic neurons: the preganglionic is longer than the postsynaptic neuron.
- The parasympathetic ganglia don't form chains like in the sympathetic ganglia, instead, they are located near the effector organ or even within the wall of the organ.

-NTs of The Sympathetic and Parasympathetic Neurons:

Refer to the numbers on the previous figure

-Neurons that secrete acetylcholine: (cholinergic neurons)

In all ganglia, whether sympathetic or parasympathetic, the NT is **acetylcholine**, because all preganglionic neurons whether sympathetic or parasympathetic release acetylcholine. **Cholinergic preganglionic neurons (1-5)pre**

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, **cholinergic parasympathetic post ganglionic neurons 1post**

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)

In case of fear, people develop tachycardia and start sweating, you think of 2 things fight or flight, both cases tachycardia helps pump more blood to reach the skeletal muscles (they need the nutrients in the blood because they are going to work more). The body reduces heat by sweating otherwise your body temperature will increase.

So the neuron that innervates sweat glands is called **Cholinergic sympathetic postganglionic neuron 2post**.

-Neurons that secrete norepinephrine: (adrenergic neurons)

Norepiniphrine is the NT released by the post ganglionic sympathetic neurons. **Adrenergic post ganglionic sympathetic neurons. 3post**

Neurons innervating the **renal** vascular bed or the renal blood supply release Dopamine as a NT. **Dopaminergic post ganglionic sympathetic. 4post.**

Dopamenergic= release dopamine

Medical Application: dopamine mainly works in the CNS but it has functions in the peripheral nervous system especially in the renal blood supply:

The kidneys take approximately 1/4 of the cardiac output and they are very sensitive to ischemia (restriction in blood supply to tissues), if kidneys receive less blood than 1/4 of the cardiac output, they can be damaged, so in cases of shock ,for example, the kidneys must be protected. So in order to not destroy the kidneys immediately in cases of shock and to provide protection, dopamine is released from the post

ganglionic sympathetic neurons innervating the kidneys works to vasodilate renal blood vessels (dopamine affects the arterioles not the venules) and thus pump more blood to the kidneys on the expense of blood going to other organs. (This mechanism could happen in other parts of the body but it's most important in kidneys).

Remember: Diseases occur due to lots of imbalance between different things in the body, and the body usually tries to fight some diseases and restore the balance, when it fails, disease manifestation will start to occur.

Notice #5: this is also part of the ANS –the adrenal medulla-. On top of each kidney there is an adrenal gland that consists of the adrenal cortex القشرة (from outside) and the adrenal medulla (in the center, has the neuronal cells). The adrenal cortex secretes steroids like cortisol and cortisone, while the adrenal medulla releases epinephrine and norepinephrine (adrenaline and noradrenaline).

The adrenal medulla is considered an autonomic ganglion, just like 2,3,4 above it in the figure. The difference between 2,3,4 and 5: in 5 there is a preganglionic neuron that releases acetylcholine like in 2,3,4, but there is no post ganglionic neuron in 5, the gland releases epinephrine and norepinephrine directly into the body fluids and the circulation and not through another neuron, as if it is an endocrine gland. Note the tumors that affect 2,3,4, also affect 5.

Notice (6): this is not autonomic, but the neuron still releases acetylcholine and is therefore said to be cholinergic. For example while walking; a neuron comes from the CNS to the muscle and secretes acetylcholine allowing the muscle to contract, (1 neuron not 2). This is just to show that cholinergic neurons could be non autonomic.

Question:

On the adrenal medulla, do we consider epinephrine and norepinephrine hormones in this case? Not NTs?

Yes, they are hormones. NTs can be hormones as well, but this doesn't apply to all NTs. For example, acetylcholine is going to be hydrolyzed in the plasma within seconds.

Question:

Is norepinephrine secreted in sympathetic neurons innervating the kidneys and the sweat glands (along with dopamine and acetylcholine)?

No, only dopamine is secreted by the neurons innervating the renal vascular bed of the kidneys and only acetylcholine is secreted in the neurons innervating sweat glands.

-Cholinergic and Adrenergic Neurons (in short):

*Fibers in the slides refers to the axons of neurons.

Cholinergic Neurons:

1) Autonomic preganglionic fibers, all preganglionic neurons whether sympathetic or parasympathetic.

2) Parasympathetic post ganglionic neurons.

3) Few sympathetic post ganglionic neurons, the ones that innervate sweat glands. (this is an exception for sympathetic neurons)

Adrenergic Neurons:

1) Most sympathetic postganglionic neurons (most, because sweat glands are an exception, they're cholinergic).

2) Some sympathetic postganglionic fibers release dopamine (dopaminergic).

3) The adrenal medulla releases epinephrine and norepinephrine.

Note: When NTs are released, they're not released alone, but with other substances, these substances are called **co-transmitters**, we're going to see examples shortly.

-Key Features of NTs as Potential Targets For Pharmacologic Agents:

To affect the function of a certain NT in the ANS, the substance (drug, toxin, pharmacologic agent) must target one of the following:

1) The synthesis of the NT.

2) The storage of the NT.

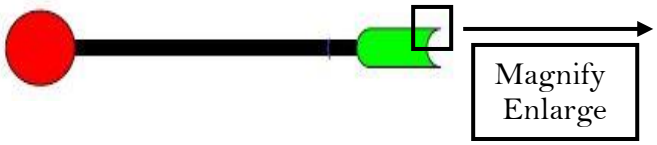
3) The release of the NT (control of the NT release).

4) The receptors which the NT binds to.

5) The termination of the action of NT.

The cell should not keep working. Meaning when the NT is released, it should not keep stimulating the cell, the cell will get fatigued which in turn leads to paralysis, loss of function and destruction. The action of NTs at their receptors looks something like this→ switch the light on, the lights turn on, but when you switch the light off, the light will stay on for some time and not turn off right away, the same is true for the action of a NT when it binds to its receptor, it will last for a specific time then it will be terminated, so the cell will rest. You allow time for receptors to rest (Post-receptor phenomena), which is the process that occurs in the cell after stimulation of the receptor by an agonist.

-Detailed Examples on Acetylcholine and Norepinephrine Effect Control:



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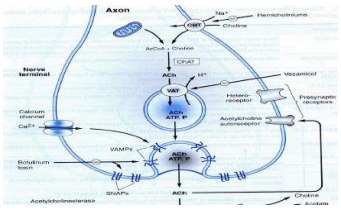
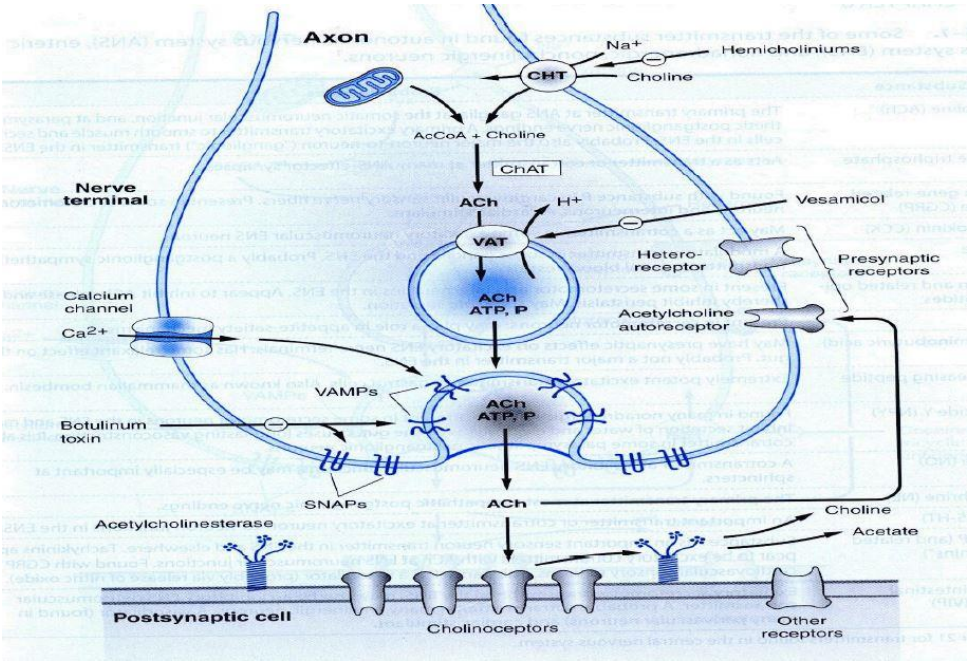


cholinergic terminal -for example-

Terminals which we're going to be explaining in a moment are not the entire tail of the arrow in the structure above, they're tuberosities or points located somewhere there, but magnified.

Acetylcholine –Cholinergic Terminal-



Synthesis:

Acetylcholine is synthesized by conjugating a donated acetyl group from Acetyl co enzyme A (AcCoA) and choline by the action of the enzyme choline acetyltransferase (ChAT). {remember acetyl transferase in the conjugation rxns, this is the same but specific to choline }. AcCoA comes from mitochondria**,** and choline comes from the outside, it's taken up by co-transport which is Na dependant, choline uptake mechanism.

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). Hemicholinium inhibits the uptake of choline, and thus decreases the synthesis of acetylcholine.

Storage:

Aacetyl choline enters vesicles called synaptic vesicles, VAT (vesicle- associated transporter), lets in acetylcholine in exchange with protons. The inhibitor of this process is vesamicol, a drug that inhibits acetylcholine uptake into the synaptic vesicles.

> Note: Acetylcholine is not stored alone in the vesicles, it's stored along with ATP and P (P is not a phosphate group, we already have phosphate in ATP molecules, P stands for proteins and peptides)

Release:

Action potential generation from the cell body down to the axon opens Ca++ channels, Ca++ enters the cell, it allows the fusion of the synaptic vesicle with the presynaptic membrane, when fusion occurs under the influence of Ca++, the vesicles open and release substances into the synapse (Acetylcholine+peptides+proteins).

The release could be inhibited by Botulinum toxin – prevents the release of acetylcholine into the synapse-. Some bacteria secrete this toxin, it can be fatal because preventing the release of acetylcholine leads to paralysis, ganglia will stop functioning, no ANS working means no visceral functions means death!

Note: When talking about cells in general, we refer to the membrane as plasma membrane, but when talking about neural cells we refer to the membrane as an axonal membrane (related to the axon of the neuron). We also say cytoplasm when talking about cells in general, but here we're concerned with the axon of a neural cell so we refer to the cytoplasm as axoplasm.

Receptors for Acetylcholine: (1+2) Only

1) Acetylcholine binds to its receptors (**acetylcholine receptors/ cholinoceptors**) located on the effector organ, if those receptors are stimulated, certain functions occur which we'll discuss later.

2) Acetylcholine binds to **presynaptic autoreceptors**, auto because they are receptors for acetycholine itself. When acetylcholine binds to those receptors, they tell the cell to stop releasing acetylcholine. (negative feedback inhibition of acetylcholine release), negative= stop the release.

3) **Other ligands bind to presynaptic heteroreceptors affect/ control the release of acetylcholine from the cell terminal,** (receptors regulating the release of mediators other than their own ligands)) meaning receptors that are **not** for acetylcholine but for something else. Hetero receptors don't terminate the action of acetylcholine but control the neuron, they influence increase or decrease in the release of acetylcholine.

**2+3 affect the release of acetylcholine **

Termination of Action:

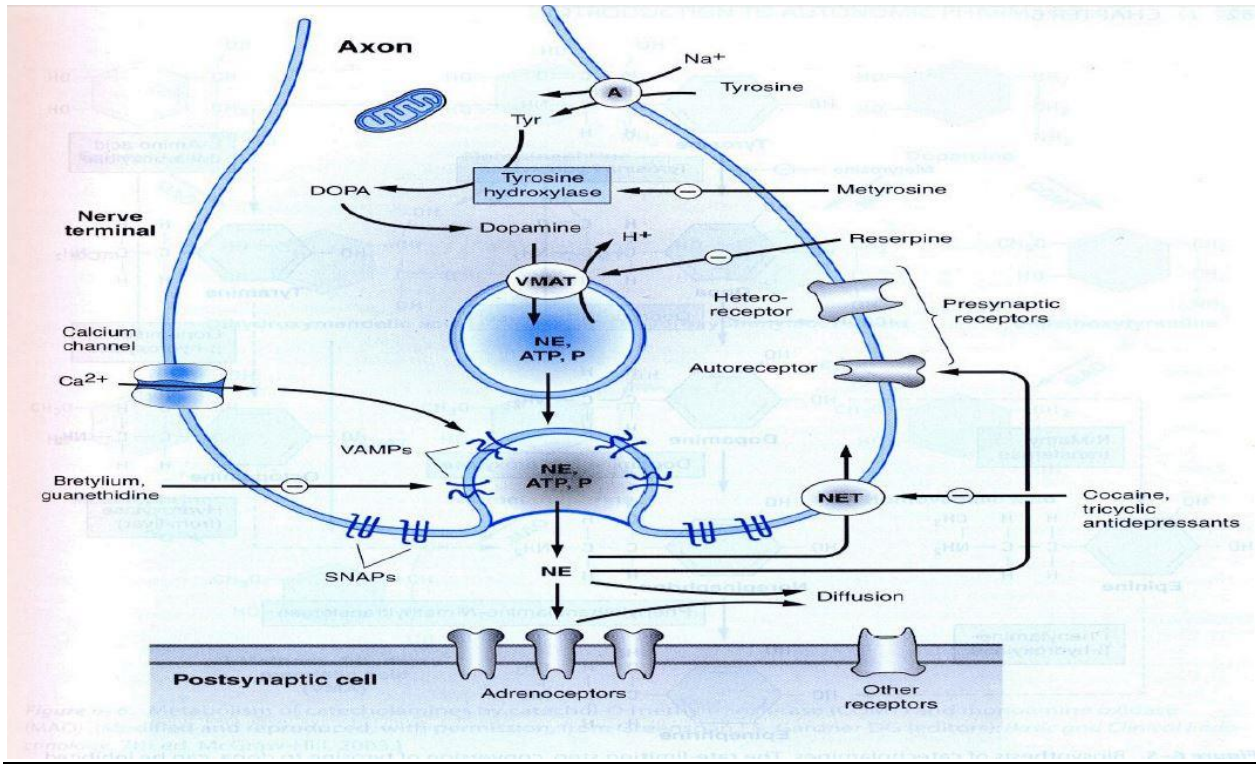
Acetylcholine undergoes hydrolosis by the enzyme acetylcholinesterase, this enzyme binds acetylcholine and breaks it down to acetate and choline (note: not AcetylCoA but acetate), both defuse, acetate enters Krebs cycle and body metabolism, and choline is reuptaken by the neural cells. Does the cell reuptake all the choline

defused? No, only about 50% of the defused choline re-enters the cell and is re-used again. Which is the most important mechanism to terminate the action of acetylcholine? Hydrolosis by acetylcholinesterase.

Nerve gas used in chemical warfare inhibits the enzyme acetylcholinesterase, this causes build up of acetylcholine in the synapse and excessive cell stimulation which in turn causes paralysis.

Inhibitor/ what it inhibits	The Result
Hemicholinium inhibits the uptake of choline	decreases the synthesis of acetylcholine
Vesamicol inhibits VAT	Reduced acetylcholine uptake into the synaptic vesicles.
Botulinum toxin inhibits the fusion of the vesicle with the presynaptic membrane	prevents the release of acetylcholine into the synapse, could be lethal.
Nerve gas inhibits acetylcholinesterase	Acetylcholine build up in synapse Excessive stimulation and paralysis.

Norepinephrine –Adrenergic Terminal-



Synthesis and Storage:

Tyrosine enters the cell by Na+ dependant co-transport, then tyrosine hydroxylase converts tyrosine to DOPA (dihydroxyphenylalanine), then DOPA is converted to dopamine, dopamine enters the vesicle and there (inside the vesicle) it's converted to norepinephrine. Dopamine is an active NT in certain places and norepinephrine is active in certain places as well, note that norepinephrine can be converted to epinephrine.

Release:

The same as what we mentioned before (action potential, Ca++ enters the cell, influences fusion of the synaptic vesicle with the presynaptic membrane, and release of norepinephrine into the synapse).

Receptors for Norepinephrine (NE): (1+2) only

1) NE binds to the **postsynaptic receptors or adrenoreceptros**, this gives off the function of the effector organ.

2) NE binds to **autoreceptors** on the presynaptic membrane, note that here these receptors have 2 types:

a) negative feedback (stops the release of NE).

b) positive feedback (increases the release of NE).

Note: the role of negative feedback receptor is more significant than that of positive feedback receptors.

3) Other ligands bind to heteroreceptor and affect/ control the release of NE from the terminal cell .

Termination of Action:

There is no enzyme that breaks down NE, no NEhydrolase for example, so how does termination occur? By reuptake of NE by the neural cells. Whether in cholinergic or adrenergic terminals, the free norepinephrine or acetylcholine can be reuptaken by neural cells, (can go back to the axoplasm by active reuptake), for NE it happens twice, 1st reuptake into the cytoplasm, 2ed reuptake into the synaptic vesicle, (in cholinergic terminals what is reuptaken is choline and not acetylcholine).

Once NE reupaken, does it go back to a tyrosine from? No, it goes straight to the synaptic vesicles ready to be used again, it doesn't need synethsis. **So this is how termination occurs in adrenergic terminals (not by hydrolosis but by reuptake)**

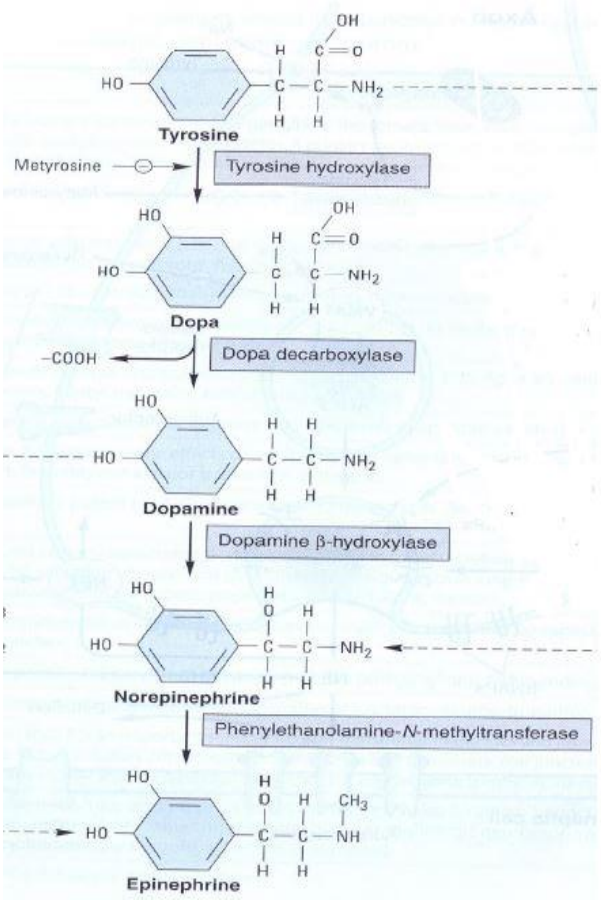
Binding to receptors is reversible, follows the law of mass action, meaning the drug-receptor complex is reversible, so free NT and bound NT coexist, part of the free NE goes back to the cell, the equilibrium in the synapse will shift towards the free NE, which causes dissociation of NE from its receptors, and the free NE enters the cell.

Inhibition of the reuptake of NE:
1) Cocaine inhibits the reuptake process, causes build up of NE in the synapse (in the CNS)
2) Tricyclic antidepressant inhibits the reuptake process, this drug is given to those with depressive illness to reduce depression.

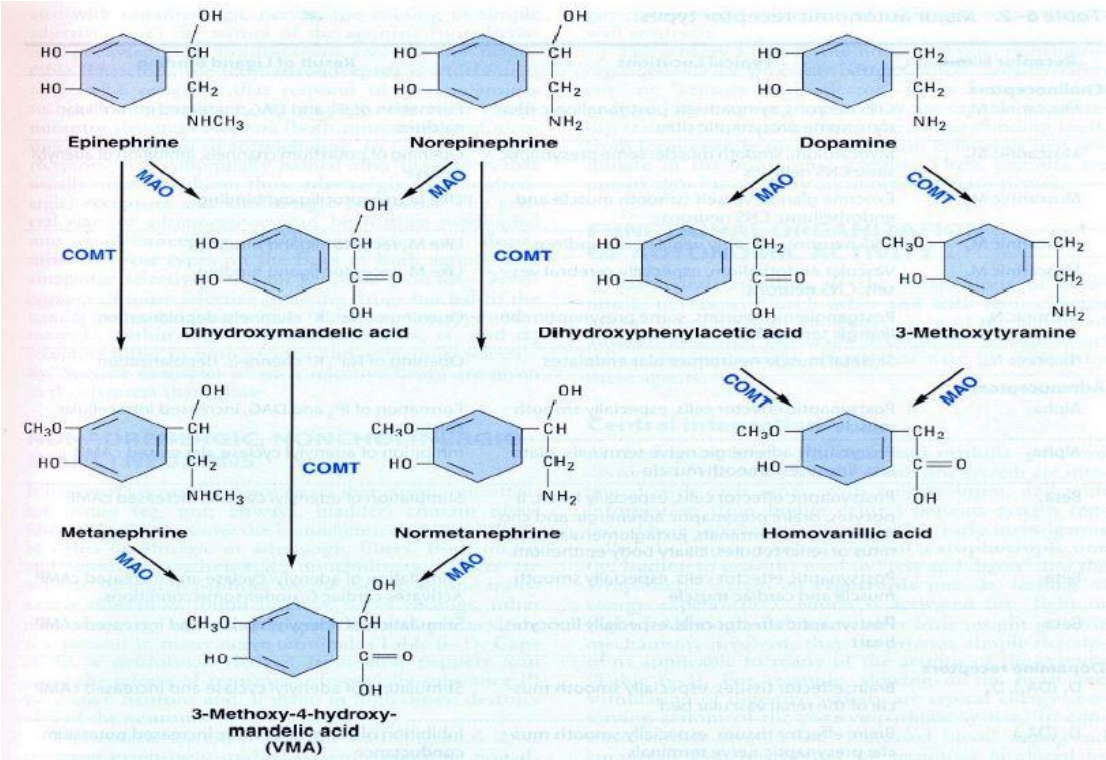
-From Tyrosine to Norepinephrine (Details):

Tyrosine→ DOPA → Dopamine → norepinephrine → epinephrine.

The last 3 are active, dopamine= dopaminergic neurons use this as a NT. Norepinephrine= used by the sympathetic post ganglionic neurons. Epinephrine= used in the adrenal medulla and in the CNS. Note: all of them are more important in the CNS than in the Peripheral nervous system.



-Metabolism of the 3 NTs (Dopamine, epinephrine and norepinephrine):



Epinephrine and Norepinephrine:

Epinephrine and norepinephrine give off one metabolite despite having 2 pathways for metabolism, the metabolite is Vanillylmandelic Acid VMA, (instead of methoxyhydroxy).

Medical Application:

VMA's concentration in blood or urine gives an idea about how much epinephrine and norepinephrine is in the body, high VMA levels indicate tumors in the sympathetic chains and the adrenal medulla, since these 2 secrete epinephrine and

norepinephrine, excessive secretion due to tumors would lead to excessive amounts of the metabolite VMA. (the tumor is called pheochromocytoma).

2 enzymes are involved in the metabolism of these 2 neurotransmittors:

1) Monoamine oxidase MAO, (causes oxidation)

2) Catechol-O-methyltransferase COMT, (causes conjugation of a methyl group)

It's not important which acts first, MAO or COMT, because at the end both pathways give off the same metabolite.

Dopamine:

it's metabolized by the same enzymes through 2 pathways but the product is homovanillic acid, we use this for diagnosis of excessive dopamine activity in the CNS not in the peripheral nervous system.

Good Luck!

ريم حماشا