بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pharmacology | FINAL 1

Introduction to ANS pt.1

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وَلِلَّهِ الْأَسْمَاءُ الْحُسْنَى فَادْعُوهُ بِهَا

المعنى: الأول: الذي ليس قبله شيء، وكل ما سواه كائن بعد أن لم يكن، و(الآخِر): الباقي، الذي لا انتهاء لوجوده، وليس بعده شيء.

الورود: ورد الاسمان مرة واحدة في القرآن الكريم.

الشاهد: ﴿هُوَ ٱلْأَوَّلُ وَٱلْآخِرُ وَٱلظَّٰهِرُ وَٱلْبَاطِنُ ۖ وَهُوَ بِكُلِّ شَىْءٍ عَلِيمٌ﴾ [الحديد:٣].

اضغط هنا لشرحٍ أكثر تفصيلًا

Introduction to Autonomic Nervous System (ANS) Pharmacology

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1. Overview

- The autonomic nervous system is not under voluntary control.
- Although there are sites in the CNS that regulates the autonomic system rather than initiating voluntary control over it.

2. Voluntary vs. Involuntary Control

Voluntary Movements

- You can walk and then stop walking.
- You can talk and then stop talking.
- In these actions, you tell the brain to stop, and the brain signals the muscles to stop acting.
- This means voluntary actions are under conscious control.

Involuntary Functions

- The brain cannot tell the heart to stop beating.
- You cannot voluntarily stop the heart from working.
- Similarly, you cannot tell the breathing center to permanently stop breathing.

3. Autonomic Activities

- Breathing is autonomic: it continues 24 hours a day for the rest of your life, even when you are unconscious.
- The beating of the heart is also autonomic and independent of voluntary control.

4. Origin of the ANS

- The ANS originates from the CNS (it comes from there), but it is not under voluntary control.

5. Conscious vs. Unconscious Actions

- Conscious = voluntary actions (such as walking or talking).
- Breathing: although it is autonomic, you can temporarily modify it consciously, but its basic function continues involuntarily.

Introduction to ANS Pharmacology

- **The autonomic nervous system activities are NOT under direct conscious control.**
- **It is concerned primarily with visceral functions such as cardiac output, blood flow and digestion, ..etc .**

Autonomic Nervous System

It consists of 2 major divisions:

1. **Sympathetic (thoracolumbar outflow)**
2. **Parasympathetic (craniosacral outflow)**

- **Both divisions originate in nuclei within the central nervous system, giving rise to preganglionic efferent fibers that exit from brain stem or spinal cord and terminate in autonomic ganglia.**

1. Sympathetic vs. Parasympathetic Functions

- The sympathetic and parasympathetic divisions have opposing effects on many visceral (internal organ) functions, but they are not true antagonists.
- Why not? Because each division performs a specific set of functions, and each division can work independently (isolated from the other).
- Most of the time their effects are opposite, but not always.

2. Anatomical Origin

- Sympathetic division originates from the thoracolumbar region of the CNS.
- Parasympathetic division originates from the craniosacral region of the CNS.

3. ANS Neuron Pathway

Both sympathetic and parasympathetic systems use a two-neuron pathway:

(1) Preganglionic Neuron

- Originates inside the CNS
- Travels outward until it synapses with a second neuron
- This synapse occurs in a ganglion (plural: ganglia)
- We may have more than one synapse depending on the pathway

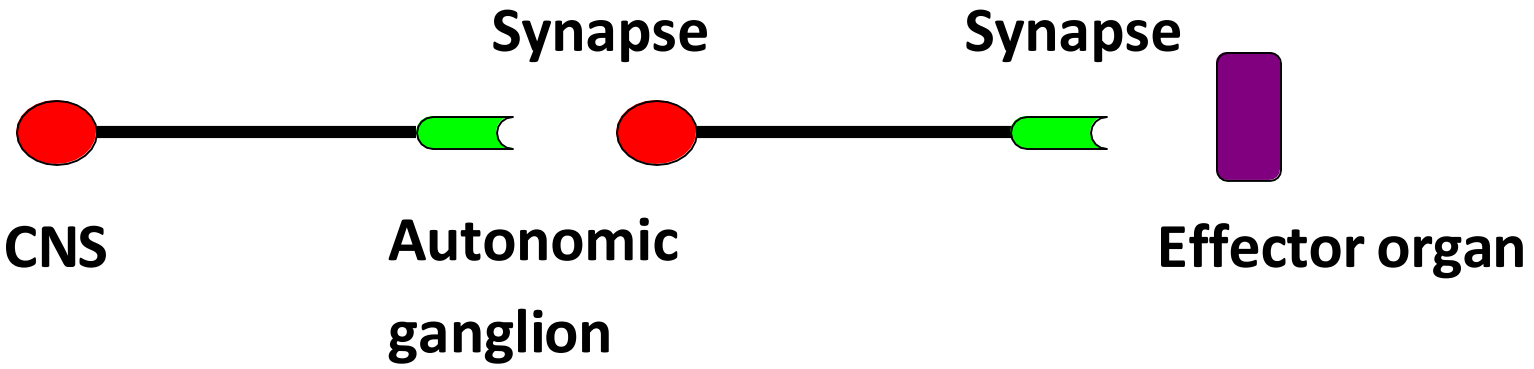
(2) Postganglionic Neuron

- The second neuron, after the ganglion, is called the postganglionic nerve
- It travels from the ganglion to the peripheral target organ

Autonomic Nervous System

- **From the autonomic ganglia, postganglionic fibers run to the tissues involved.**

Autonomic Nervous System



Preganglionic nerve **Postganglionic nerve**

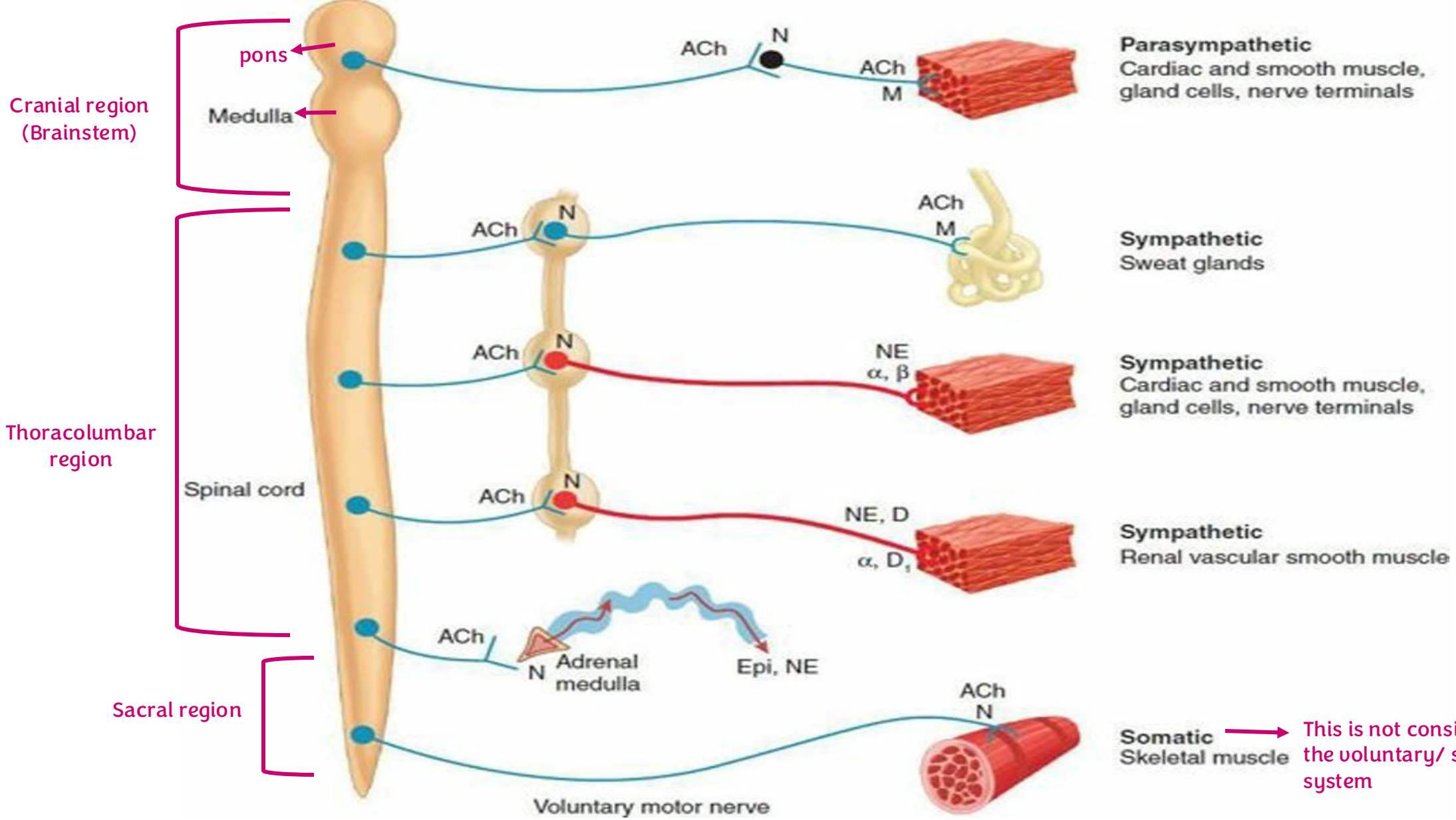
Autonomic ganglia may include more than one synapse

ANS Neurotransmitters

A synapse is the small gap between neurons, and there is also a synapse between the postganglionic neuron and the effector organ. Since there is a gap, the message cannot jump directly from one cell to another, so communication happens through neurotransmitters, which are chemicals secreted by neuron

- **Neurons of the ANS release neurotransmitters into the synapse, which carry information to/or activate the next cells.**
- **These chemicals may be:**

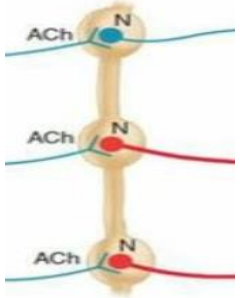
1. **Acetylcholine and the nerves that release it are called cholinergic neurones.**
2. **Norepinephrine (noradrenaline) and the nerves that release it are called adrenergic neurones.**



This is not considered ANS, it's part of the voluntary/ somatic nervous system

FIGURE 6–1 Schematic diagram comparing some anatomic and neurotransmitter features of autonomic and somatic motor nerves. Only the primary transmitter substances are shown. Parasympathetic ganglia are not shown because most are in or near the wall of the organ innervated. Cholinergic nerves are shown in blue, noradrenergic in red. Note that some sympathetic postganglionic fibers release acetylcholine rather than norepinephrine. Sympathetic nerves to the renal vasculature and kidney may release dopamine as well as norepinephrine during stress. The adrenal medulla, a modified sympathetic ganglion, receives sympathetic preganglionic fibers and releases epinephrine and norepinephrine into the blood. ACh, acetylcholine; D, dopamine; Epi, epinephrine; M, muscarinic receptors; N, nicotinic receptors; NE, norepinephrine.

1. Sympathetic Ganglia



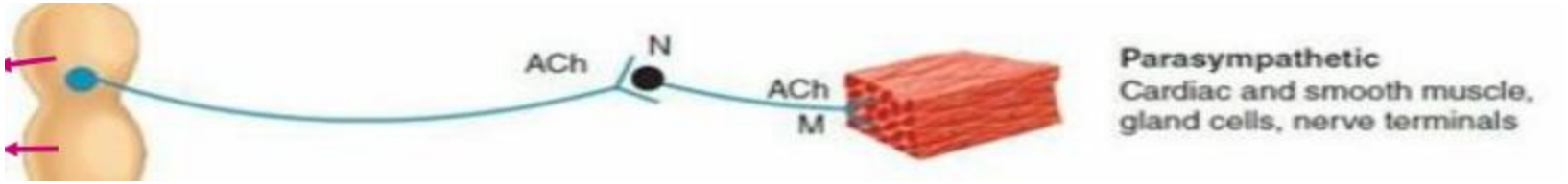
- Sympathetic ganglia are large enough to be seen clearly by the naked eye.
- If you attend an intra-abdominal surgery, you will notice a series of paravertebral sympathetic ganglia located on both the right and left sides of the spinal cord.
- These ganglia are arranged in a well-organized pattern throughout the sympathetic nervous system, making their anatomical position easy to identify.

2. Parasympathetic Ganglia

- Parasympathetic ganglia are not as obvious or as easy to see compared to sympathetic ganglia.
- They are located near the effector organ or within the wall of the effector organ, so they do not have a large, organized external pattern.
- Although some may be seen by the naked eye, they are not as distinct or as well positioned as sympathetic ganglia, so they do not stand out visually.

3. General Ganglion Function (Sympathetic or Parasympathetic)

- In both divisions, the preganglionic neuron releases acetylcholine (ACh) at the level of the ganglion.
- This ACh stimulates the postganglionic neuron, which then continues the signal and activates the effector organ by releasing another neurotransmitter.
- Therefore, the ganglion is the site of communication between the first neuron and the second neuron before the signal reaches the target tissue.



Parasympathetic Division

In the parasympathetic division, the postganglionic neuron releases acetylcholine (ACh), which then acts on the effector organ. There are multiple ACh receptors, known as nicotinic receptors and muscarinic receptors. Recent research has shown that each of these receptor types has different subtypes, similar to how certain enzymes can have isoenzymes. For receptors, these are called subtypes.

- Nicotinic receptors are located in the ganglion (between preganglionic and postganglionic neurons).
- Muscarinic receptors are located at the effector organ, where the postganglionic neuron exerts its action.

To understand their names:

- Nicotine (found in cigarettes) stimulates nicotinic receptors.
- Muscarine is a toxin found in certain mushrooms and stimulates muscarinic receptors when it binds to them. This is how muscarinic receptors were originally identified in pharmacology.

Generally,

- In the sympathetic division, the preganglionic neuron releases acetylcholine (ACh).
- This ACh binds to nicotinic receptors in the sympathetic ganglion, activating the postganglionic neuron.

1) "Normal" sympathetic pathway

Target: Cardiac muscle, smooth muscle, gland cells, nerve terminals

- The postganglionic neuron releases norepinephrine (NE) at the effector organ.
- NE acts on adrenergic receptors:
  - α (alpha) receptors
  - β (beta) receptors
- Each group has subtypes (α_1, α_2, β_1, β_2, β_3).
- These subtypes are important because different drugs can selectively bind to specific adrenergic receptors, giving specific therapeutic effects.

2) Renal vascular smooth muscle (renal vascular bed)

- Here, some postganglionic sympathetic fibers can release both NE and dopamine (DA).
- Dopamine is normally known as a central neurotransmitter in the brain, but in this case, it is also released in the renal vascular bed (the blood vessels of the kidney).

Dopamine receptors

- There are five dopamine receptors: D_1, D_2, D_3, D_4, D_5.
- All five are found in the brain.
- One of them (especially D_1) is also found in the renal vascular bed, and this is the one that matters for renal sympathetic regulation.

So, in this variation:

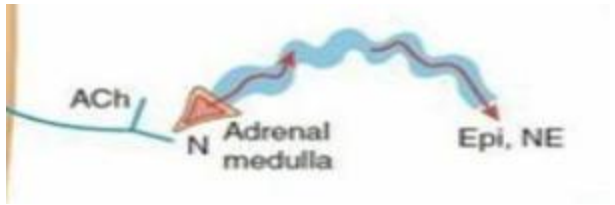
- Neurotransmitters: NE and dopamine
- Special point: one dopamine receptor subtype is shared between brain and renal vasculature and is important for kidney function.

3) Sweat glands (sympathetic but cholinergic)

- Sweat glands are a special exception in the sympathetic system.
- The postganglionic sympathetic neuron releases ACh, not NE.
- This ACh binds to muscarinic receptors on sweat glands resulting in sweating.

4) Adrenal medulla (modified sympathetic ganglion)

- The adrenal medulla acts like a modified sympathetic ganglion.
- A preganglionic cholinergic neuron from the CNS releases ACh onto nicotinic receptors in the adrenal medulla.
- There is no postganglionic neuron here.
- Instead, the adrenal medulla secretes epinephrine (Epi) and norepinephrine (NE) directly into the bloodstream just like endocrine glands (Epi is released more).
- These hormones then act on adrenergic receptors throughout the body, producing systemic sympathetic (“fight or flight”) effects.



ANS Neurotransmitters

- Cholinergic neurons = cholinergic fibers
- Adrenergic neurons = adrenergic fibers

Cholinergic fibers include:

1. All autonomic preganglionic fibers.
2. Most parasympathetic postganglionic fibers.
3. Few sympathetic postganglionic fibers (sweat gland).

ANS Neurotransmitters

Adrenergic fibers include:

1. Most sympathetic postganglionic fibers.
2. Some sympathetic postganglionic fiber release dopamine. In the renal vascular bed
3. Adrenal medulla releases a mixture of epinephrine and norepinephrine. (adrenaline & noradrenaline)

- Most autonomic nerves also release co- transmitters in addition.

In the autonomic nervous system (ANS), neurotransmitters are not usually released alone. They are often released together with additional substances, which are collectively called co-transmitters. We will discuss these co-transmitters in more detail later.

ANS Neurotransmitters

Key features of neurotransmitters as potential targets for pharmacologic agents:

1. **Synthesis.**
2. **Storage.**
3. **Release.**
4. **Mechanism of termination of action.**
5. **Action on receptors.**

For a chemical substance to be recognized as a neurotransmitter in the ANS (such as norepinephrine), all five conditions must be met. If even one condition is missing, then the substance is not considered a true neurotransmitter.

1. Synthesis
- The neurotransmitter must be synthesized inside the neuron, not supplied from outside sources.

2. Storage
- There must be a mechanism for storing the neurotransmitter within the neuron, and it must be stored in synaptic vesicles until stimulation occurs.

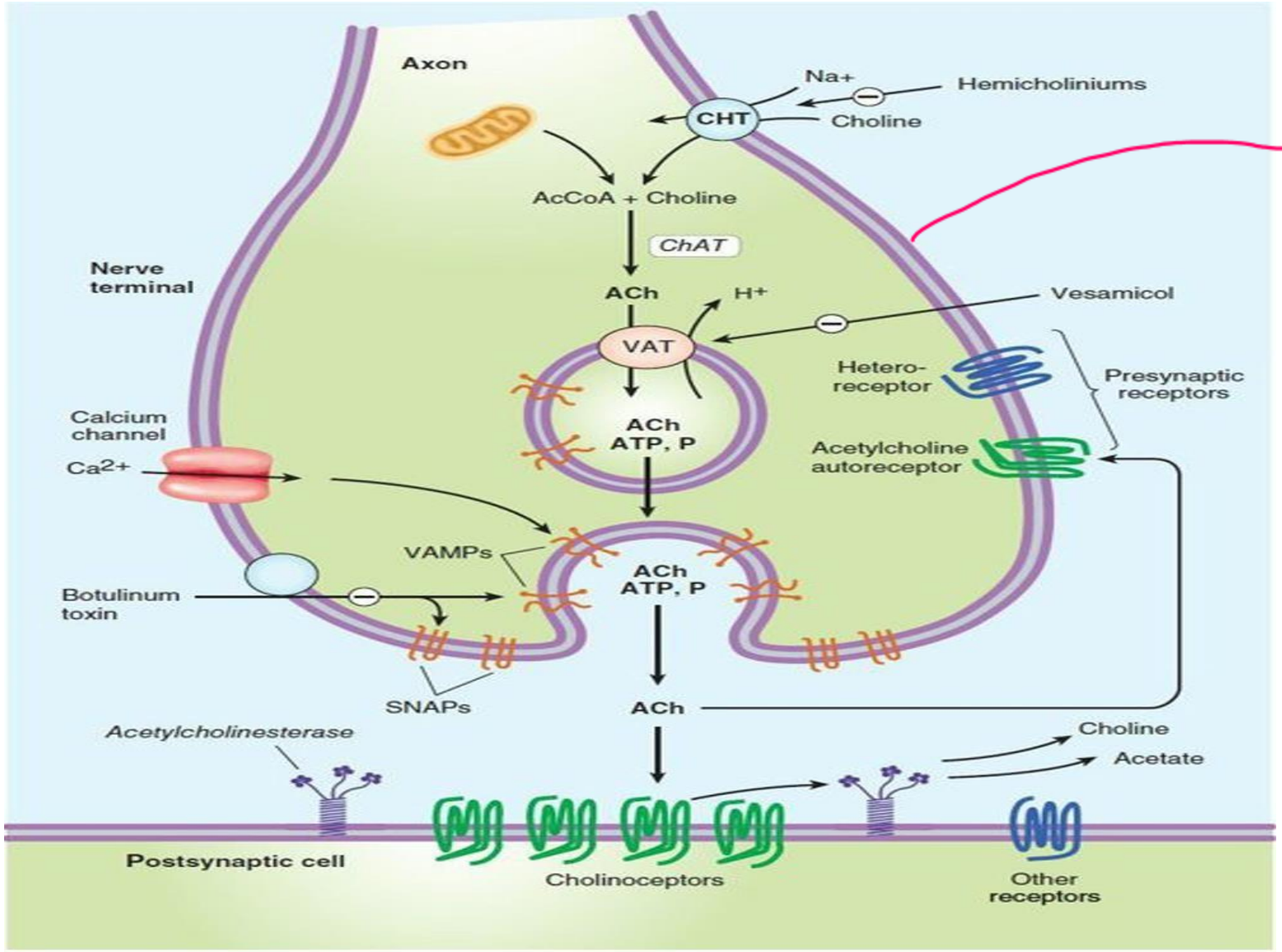
3. Release
- The stored neurotransmitter must be released from the neuron upon nerve stimulation.

4. Mechanism of Termination
- There must be a mechanism to terminate the neurotransmitter's action after release.
- If termination does not occur, continuous stimulation would cause:
  - fatigue in the postganglionic neuron
  - fatigue of the effector organ
  - loss of function or even paralysis (paralysis: fatigue to the level that the organ stops working)
- Therefore, we do not want the neurotransmitter to remain continuously active.
- This is why the body has post-receptor mechanisms (also called post-receptor phenomena) in the postganglionic neurons: they ensure that the neurotransmitter's effect stops so that the system remains functional and responsive.

5. Receptor Interaction
- The released neurotransmitter must act on specific receptors at the effector organ to produce its physiological response.

Parasympathetic nervous system (Cholinergic nervous system)

These tuberosities consist of structures involved in the synthesis mechanism: acetylcholine is produced from choline and acetyl-CoA through the action of the enzyme choline acetyltransferase. This explanation relates to the parasympathetic nervous system (the cholinergic nervous system).



this is a tuberosity on a terminal of the neuron

FIGURE 6–3 Schematic ilustration of a generalized cholinergic junction (not to scale).

Choline is transported into the presynaptic nerve terminal by a sodium-dependent choline transporter (CHT). This transporter can be inhibited by hemicholinium drugs. In the cytoplasm, acetylcholine is synthesized from choline and acetyl-CoA (AcCoA) by the enzyme choline acetyltransferase (ChAT). Acetylcholine (ACh) is then transported into the storage vesicle by a vesicle-associated transporter (VAT), which can be inhibited by vesamicol. Peptides (P), adenosine triphosphate (ATP), and proteoglycan are also stored in the vesicle. Release of transmitters occurs when voltage-sensitive calcium channels in the terminal membrane are opened, allowing an influx of calcium. The resulting increase in intracelular calcium causes fusion of vesicles with the surface membrane and exocytotic expulsion of acetylcholine and cotransmitters into the junctional cleft (see text). This step can be blocked by botulinum toxin. Acetylcholine's action is terminated by metabolism by the enzyme acetylcholinesterase. Receptors on the presynaptic nerve ending modulate transmitter release.

SNAPs, synaptosomal nerve associated proteins; VAMPs, vesicle-associated membrane proteins.

Acetylcholine:
Is produced from acetyl-CoA and choline under the action of the enzyme choline acetyltransferase.

Acetyl-CoA:
Is obtained from the mitochondria inside the neuron.

Choline:
Is taken up from the circulation, it comes from the digestion of food and enters the neuron through a sodium-choline cotransporter, where sodium and choline move together into the cell.
(Sodium-choline cotransporter is saturable and can be inhibited.)

Vesicular Storage and Release Mechanism of Acetylcholine:

- After acetylcholine is formed in the cytoplasm of the nerve terminal (tuberosity), it is transported into synaptic vesicles by the vesicular acetylcholine transporter. This process occurs in exchange for hydrogen ions, and the vesicle stores acetylcholine together with ATP and phosphate.

- These stored contents are released into the synapse when the nerve is stimulated. Nerve stimulation causes depolarization, which opens voltage-dependent calcium channels, leading to an influx of calcium. The rise in intracellular calcium triggers vesicle fusion with the cell membrane and exocytosis of acetylcholine and the other stored substances. Calcium is essential for secretion in all cells since it mediates vesicle-membrane fusion.

- Once released into the synaptic cleft, acetylcholine diffuses in all directions. It does not necessarily bind only to the nearest postsynaptic receptors. These postsynaptic cholinoceptors are G-protein-coupled receptors (serpentine receptors).

شكله مثل الثعبان المتعرج

Termination of Acetylcholine Action (Postsynaptic Mechanism):

To terminate its action, acetylcholine is rapidly hydrolyzed by acetylcholinesterase, an enzyme located on the postsynaptic membrane. The enzyme breaks acetylcholine into choline and acetate. Acetate diffuses into tissues, enters the circulation, and participates in intermediary metabolism. Choline is partly taken back into the neuron through reuptake, while another portion diffuses away into the circulation. The reuptaken choline returns to the presynaptic terminal to be reused for acetylcholine synthesis.

Presynaptic Control of Neurotransmitter Release (Autoreceptors & Heteroreceptors):

In addition to acting on postsynaptic receptors, acetylcholine can bind to presynaptic autoreceptors. Activation of these autoreceptors inhibits further acetylcholine release, acting like a feedback signal that says: “stop releasing me.” This is called a presynaptic inhibitory autoreceptor, and it is another mechanism for terminating acetylcholine action.

There are also presynaptic excitatory (stimulatory) autoreceptors, which are not involved in terminating the signal but instead help regulate neurotransmitter release. Moreover, the presynaptic membrane contains other receptors called heteroreceptors, which are not cholinergic (they may be adrenergic or other types). These heteroreceptors help regulate parasympathetic nervous system activity and can either stimulate or inhibit neurotransmitter release, but not through the same receptor type—there are inhibitory heteroreceptors and stimulatory heteroreceptors.

The order of acetylcholine binding
Cholinergic receptors VS Acetylcholinesterase

After acetylcholine diffuses into the synaptic cleft..

It first binds to the postsynaptic receptors because they are the closest and the most abundant.

Any acetylcholine that remains is quickly broken down by acetylcholinesterase, which has a very high affinity for ACh and a very rapid catalytic rate.

Sympathetic nervous system (Adrenergic nervous system)

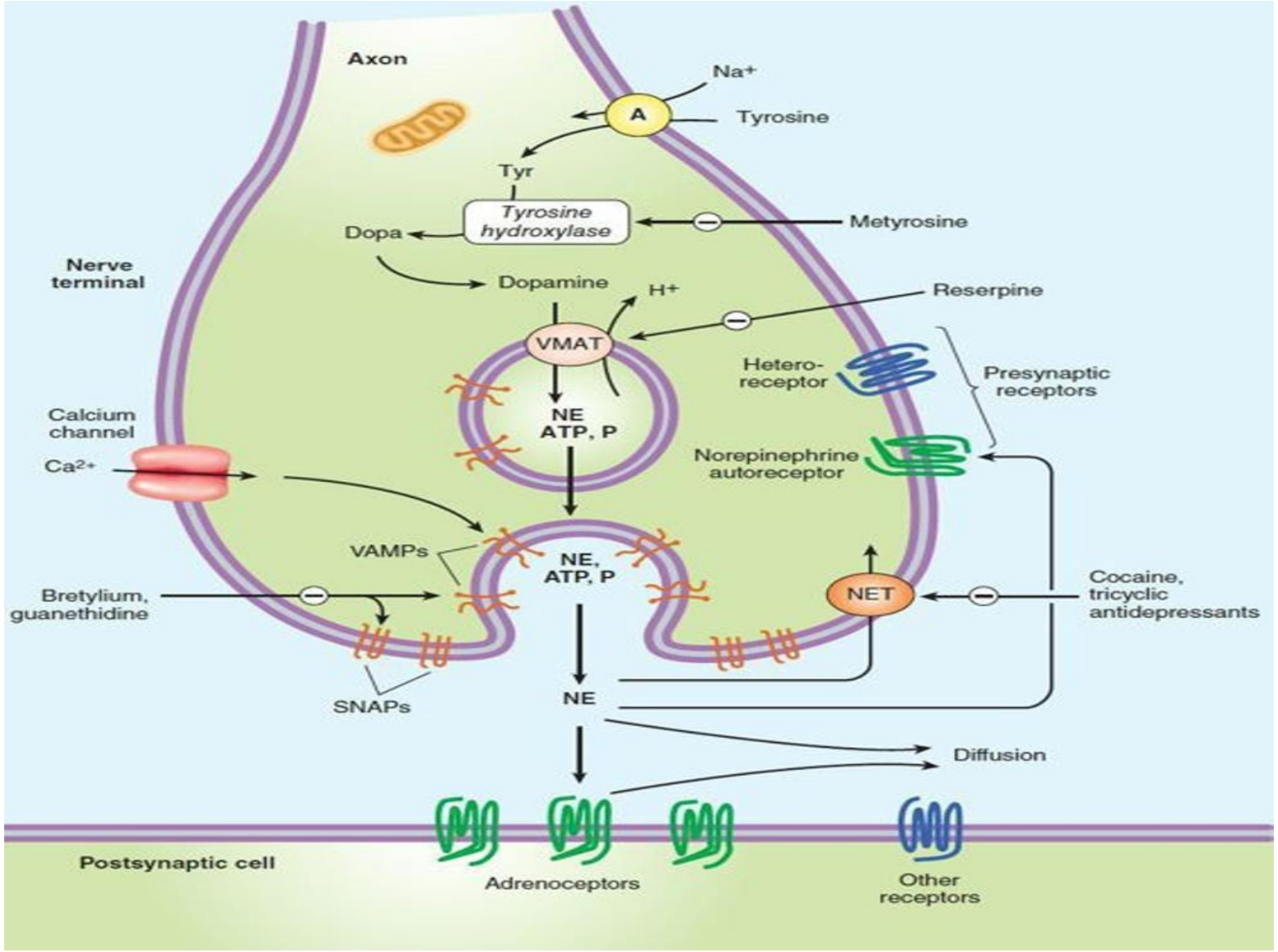


FIGURE 6–4 Schematic diagram of a generalized noradrenergic junction (not to scale).

Tyrosine is transported into the noradrenergic ending or varicosity by a sodium-dependent carrier (A). Tyrosine is converted to dopamine (see Figure 6–5 for details), and transported into the vesicle by the vesicular monoamine transporter (VMAT), which can be blocked by reserpine. The same carrier transports norepinephrine (NE) and several related amines into these vesicles. Dopamine is converted to NE in the vesicle by dopamine-β hydroxylase. Physiologic release of transmitter occurs when an action potential opens voltage-sensitive calcium channels and increases intracellular calcium. Fusion of vesicles with the surface membrane results in expulsion of norepinephrine, cotransmitters, and dopamine β-hydroxylase. Release can be blocked by drugs such as guanethidine and bretylium. After release, norepinephrine diffuses out of the cleft or is transported into the cytoplasm of the terminal by the norepinephrine transporter (NET), which can be blocked by cocaine and certain antidepressants, or into postjunctional or perijunctional cells. Regulatory receptors are present on the presynaptic terminal.

SNAPs, synaptosome-associated proteins; VAMPs, vesicle-associated membrane proteins.

Adrenergic Nervous System (Sympathetic):

The adrenergic nervous system is more complex than the cholinergic nervous system.

Unlike acetylcholine synthesis, which occurs in approximately one step, the synthesis of norepinephrine involves multiple steps. The precursor of catecholamines (epinephrine and norepinephrine) is tyrosine, which is taken up into the presynaptic neuron via a tyrosine-sodium co-transporter. Tyrosine then undergoes several enzymatic steps via tyrosine hydroxylase to form the sympathetic neurotransmitters: dopamine, norepinephrine, and epinephrine.

(details in the next slides ☺)

Vesicular Storage and Conversion:
Dopamine is stored in synaptic vesicles, entering via VMAT (vesicular monoamine transporter) in exchange for hydrogen ions (protons). Within the vesicle, dopamine is converted into norepinephrine. Neurons that secrete dopamine do not require this step.

Epinephrine is not released from vesicles in this way; instead, the adrenal medulla releases epinephrine directly into the bloodstream.

**The vesicles containing norepinephrine also include ATP and phosphate.

Neurotransmitter Release:
When the presynaptic neuron is stimulated:
1.The neuron depolarizes.
2.Calcium ions influx.
3.Vesicles fuse with the presynaptic membrane.
4.Norepinephrine is secreted and acts on postsynaptic adrenoceptors.

Key Differences Between Cholinergic and Adrenergic Transmission:
There is no enzyme that degrades norepinephrine; termination of its action occurs entirely via reuptake through the norepinephrine transporter (NET) back into the cytoplasm, where it can then be restored into vesicles.

Clinical Relevance:
Inhibitors of norepinephrine reuptake are important drugs. Tricyclic antidepressants are used to treat pathological depression, and cocaine also inhibits norepinephrine transport. These drugs increase norepinephrine levels in the synapse, enhancing its effect on effector organs. According to some theories, depression is associated with low levels of biogenic amines (catecholamines and serotonin) in the brain. These drugs prolong norepinephrine action at the synapse to compensate.

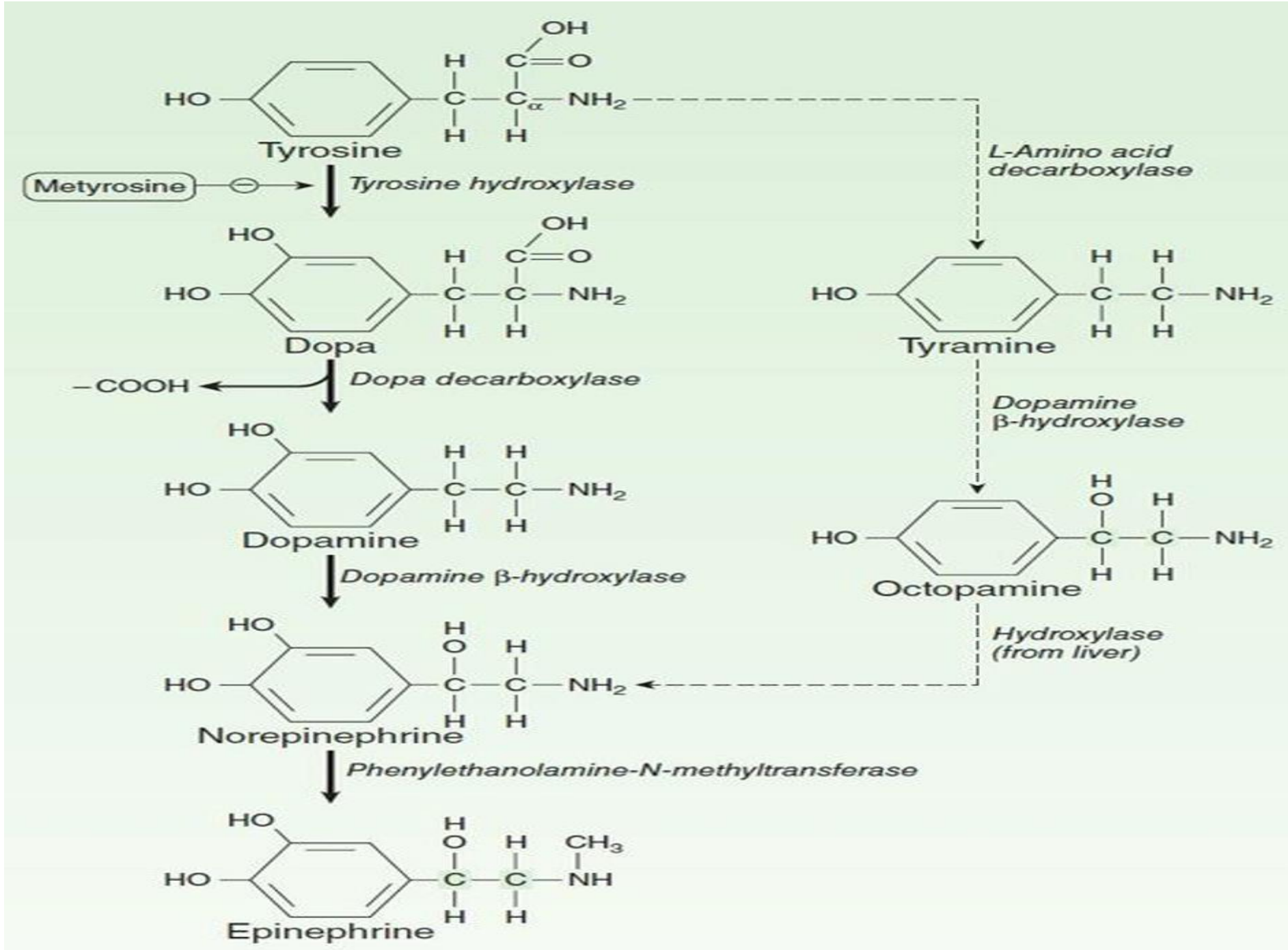
Reuptake Steps:
1.Back into the cytoplasm via NET.
2.Back into vesicles via VMAT.

Autoreceptors and Modulation:

Presynaptic norepinephrine autoreceptors mediate negative feedback inhibition of catecholamine release. Some adrenergic receptors may provide positive feedback, stimulating catecholamine release, although inhibition is more prominent. Additionally, heteroreceptors for other neurotransmitters can modulate norepinephrine action for regulatory purposes.

An advice for life from Dr. Yacoub:
If you feel down for any reason (reactive depression), avoid taking antidepressants, antidepressants are dangerous if used without a prescription due to a serious depression :)

& instead NST advises you to read رسالة الفريق العلمي..


Tyrosine
Metyrosine
Tyrosine hydroxylase
Dopa
–COOH
Dopa decarboxylase
Dopamine
Dopamine β-hydroxylase
Norepinephrine
Phenylethanolamine-N-methyltransferase
Epinephrine
L-Amino acid decarboxylase
Tyramine
Dopamine β-hydroxylase
Octopamine
Hydroxylase (from liver)

Neurons release different neurotransmitters: **most neurons secrete norepinephrine**, neurons that supply the renal vascular bed secrete dopamine, and the adrenal medulla contains the neurotransmitters epinephrine and norepinephrine.

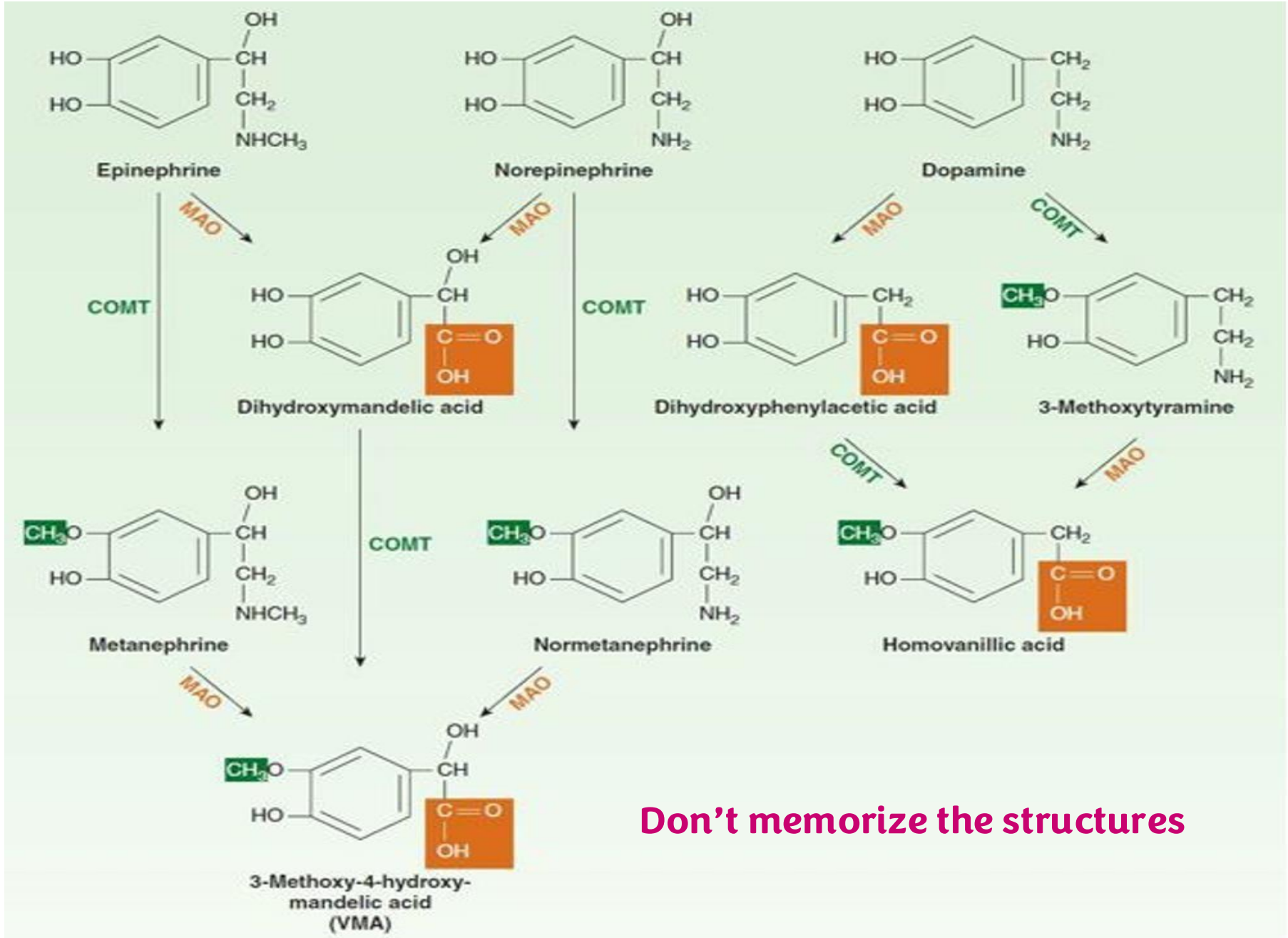
The synthesis pathway begins with tyrosine, which is converted by tyrosine hydroxylase into DOPA (dihydroxyphenylalanine). Then, DOPA decarboxylase removes a carboxyl group from DOPA, producing dopamine.

Catecholamines are named this way because they contain a catechol ring, which is a benzene ring with two hydroxyl groups in the meta and para positions, giving it its characteristic chemical structure.

Next, dopamine β-hydroxylase adds a hydroxyl group to the β-carbon of dopamine, resulting in the formation of norepinephrine. After that, phenylethanolamine-N-methyltransferase adds a methyl group to norepinephrine, converting it into epinephrine.

Thus, dopamine synthesis requires 2 steps, norepinephrine synthesis requires 3 steps, and epinephrine synthesis requires 4 steps.

FIGURE 6–5 Biosynthesis of catecholamines.
The rate-limiting step, conversion of tyrosine to dopa, can be inhibited by metyrosine (α methyltyrosine). The alternative pathway shown by the dashed arrows has not been found to be of physiologic significance in humans. However, tyramine and octopamine may accumulate in patients treated with monoamine oxidase inhibitors.
(Reproduced, with permission, from Gardner DG, Shoback D [editors]: Greenspan's Basic & Clinical Endocrinology, 9th ed. McGraw-Hil, 2011. Copyright © The McGraw-Hil Companies, Inc.)



Don't memorize the structures

FIGURE 6–6 Metabolism of catecholamines by catechol-*O*-methyltransferase (COMT) and monoamine oxidase (MAO). (Reproduced,

Metabolism of Epinephrine & Norepinephrine (by MAO & COMT):

It is important to know that two enzymes work together in the metabolism of catecholamines: monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT). The order in which these enzymes act does not matter because the final metabolic product will be the same.

If MAO acts first, it produces an intermediate that is then metabolized by COMT.
If COMT acts first, it produces a different intermediate, which is then metabolized by MAO.

In both pathways, the final product is the same:
3-methoxy-4-hydroxy-mandelic acid, also known as **vanillylmandelic acid (VMA)**.

VMA in Sympathetic Activity and Tumor Diagnosis:

VMA is excreted in the urine, and its measurement helps assess the activity of the sympathetic nervous system.
If you excrete a normal amount of VMA, this indicates normal sympathetic activity.
If you excrete an excessive amount of VMA, this indicates excessive sympathetic activity.

VMA measurement is used in the diagnosis of catecholamine-secreting tumors.
A tumor in the adrenal medulla (pheochromocytoma) or in the sympathetic chain (paraganglioma) causes hypersecretion of epinephrine and/or norepinephrine, leading to elevated VMA levels in urine or plasma.

رسالة من الفريق العلمي:

ما أصاب أحدًا قطُّ همٌّ ولا حَزَنٌ فقال اللهمَّ إني عبدُك ابنُ عبدِك ابنُ أمَتِك ناصيَتي بيدِك ماضٍ فيَّ حُكمُك عَدْلٌ فيَّ قضاؤُك أسألُك بكلِّ اسمٍ هو لك سميتَ به نفسَك أوْ علَّمْتَه أحدًا مِنْ خلقِك أو أنزلته في كتابِك أو استأثرتَ به في علمِ الغيبِ عندَك أنْ تجعلَ القرآنَ ربيعَ قلبي ونورَ صدري وجلاءَ حُزني وذهابَ هَمّي إلا أذهب اللهُ همَّه وحُزْنَه وأبدله مكانه فَرَجًا قال : فقيل : يا رسولَ اللهِ ألا نتعلمُها فقال : بلى ينبغي لِمَنْ سمِعها أنْ يتعلمَها.

وبلاش antidepressants ☺

لِمَن يعاني من ضياع وقته وقلّة البركة، اضغط هنا..

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	Slide #37	But this applies only to epinephrine and norepinephrine not dopamine	Deleted
V1 → V2			