PHARMACOLOGY

بسم الله الرحمن الرحيم

MID – Lecture 2

Intro to ANS (Pt.2)

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

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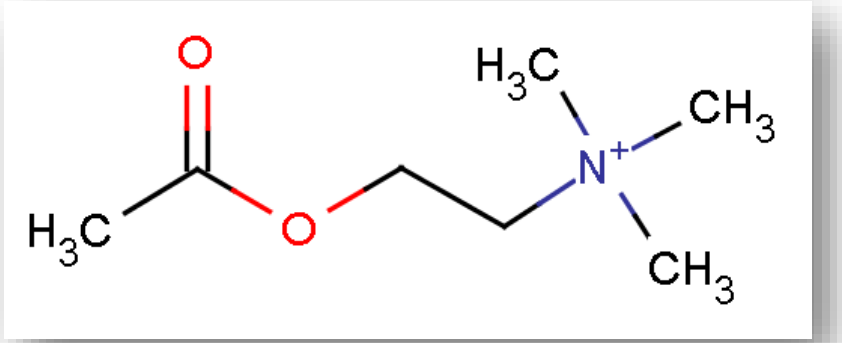
Quiz on the previous lecture!

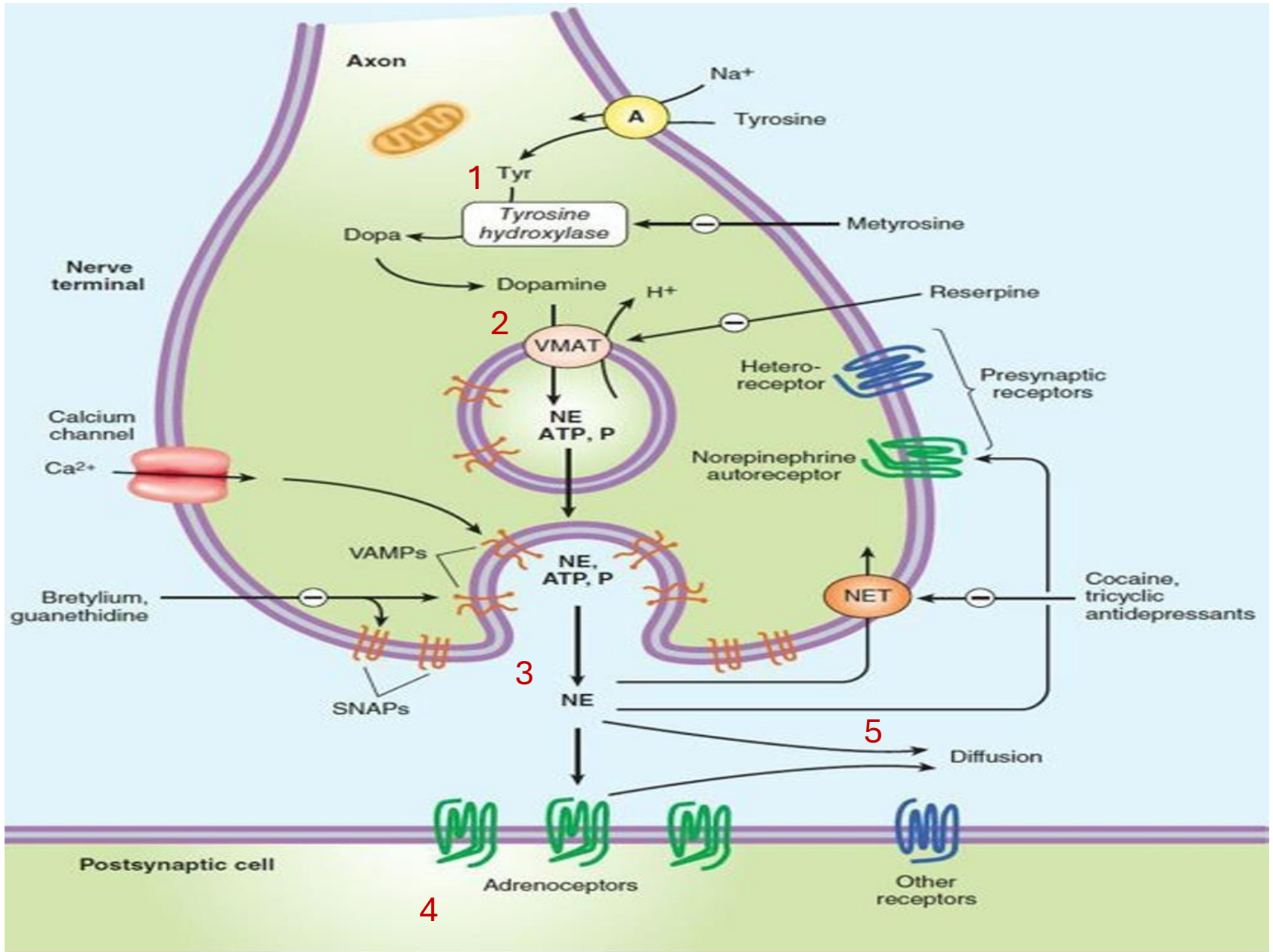


وَتَوَكَّلْ عَلَى الْحَيِّ الَّذِي لَا يَمُوتُ وَسَبِّحْ بِحَمْدِهِ ۚ وَكَفَىٰ بِهِ بِذُنُوبِ عِبَادِهِ خَبِيرًا

رسالة بسيطة منا: كلنا تعبانين ومنهلكين من الفترة الماضية، بس عمره ما كان طريق الطب سهل، اعرف انه لما تشوف دكتور ف انت شايف شخص جاهد نفسه وضحّى بوقته في سبيل هذا المنصب العظيم

انطلقوا بالتوفيق

Generalized NE junction scheme



Explanation next slide

1. *Synthesis*:
    - Tyrosine enters to the axon terminal by cotransport with sodium via a **sodium-dependent carrier** (A).
    - Following entry, **tyrosine** is converted to **Dopamine.** (see slides 7 & 8)

➢ Dopamine is a catecholamine and a monoamine that can work as a NT by itself.

2. *Storage*:
    - Dopamine is then transported into a **storage vesicle** in exchange of H^+ by **vesicular monoamine transporter** (VMAT).
    - In the vesicle, dopamine is converted to **Norepinephrine** (NE) by **dopamine-β hydroxylase.**
    - The vesicle contains ATP and some peptides or proteins.
3. *Release*:
    - Upon **stimulation**, NTs are released.
    - When the action potential reaches the terminal, **voltage-sensitive calcium** (Ca^{2+}) channels open.
    - Ca2+ **enters** the cell (influx).
    - Ca2+ causes the **fusion** of the vesicle with the presynaptic membrane → release by exocytosis.
    - Released NTs **diffuse** into the synaptic cleft.

❖ Diffusion leads the **NE** to

a) Reach the **Postsynaptic** membrane (postjunctional cells).
b) Diffuse to **other cells** (ex. Perijunctional cells.), reaching the liver causes metabolism of NE.
c) Reach the **presynaptic** membrane and regulate their release by Norepinephrine autoreceptors; by **feedback** inhibition or activation.

Recall the feedback receptors from the first lecture and how it can regulate this process.

4. *Action*:

NE reaches its **receptors** (i.e. **Adrenoceptors**) and binds to it and initiate action (postsynaptic potential).

➢ Adrenoceptors are the subtypes Alpha and Beta receptors.

5. *Termination*:

- **Only** by **reuptake**, NE will be reuptaken and transported again into the Axoplasm (axon's cytoplasm) by **Norepinephrine transporters** (NETs) (**active transport**).
- Once in the axoplasm, NE can get enzymatically degraded or transported back into storage vesicles by **VMAT** to be reused.

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.

A

Dopa, Dopamine, NE and EPI are all catecholamines; because they have a catechol ring (benzene ring with two adjacent OH groups in meta and para directions.)

B

Dopamine is an important NT in the brain, and remember for the kidneys as well.

D

Dopamine can by converted to other catecholamines in the brain, depending on the neuron type;

- **Dopaminergic:**

Don't have 3 so they release **dopamine** (and no NE & EPI).

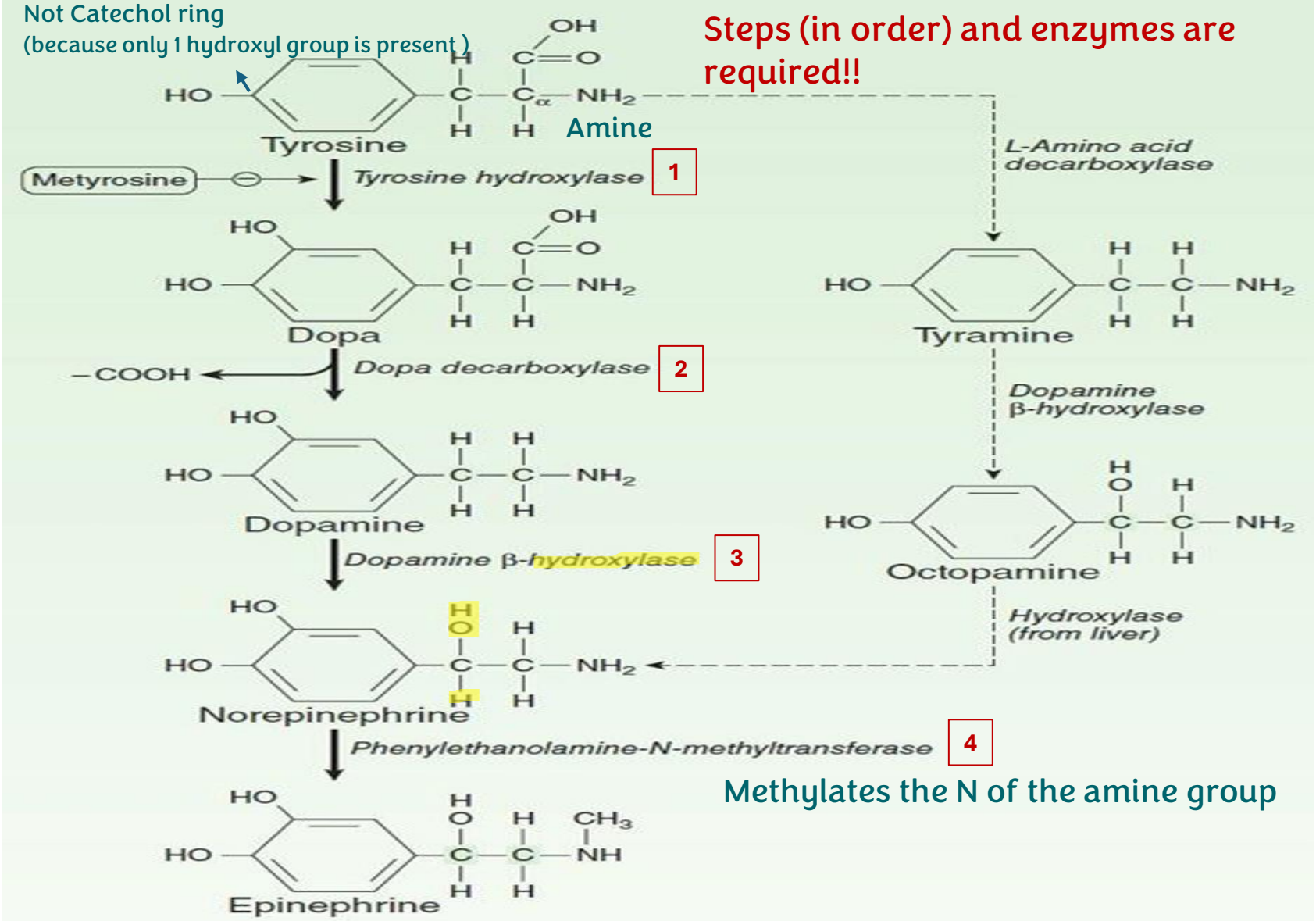
- **Adrenergic:**

Don't have 4; so they can release **NE** (and no EPI).

- **Adrenal medulla:**

Has 4; so it can release **EPI**.

READ FROM A → D



C

Notice that EPI has a larger group (- NHCH3) than NE (-NH2), thus change in affinity of subtypes of receptors.

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.

Metabolism of catecholamines.

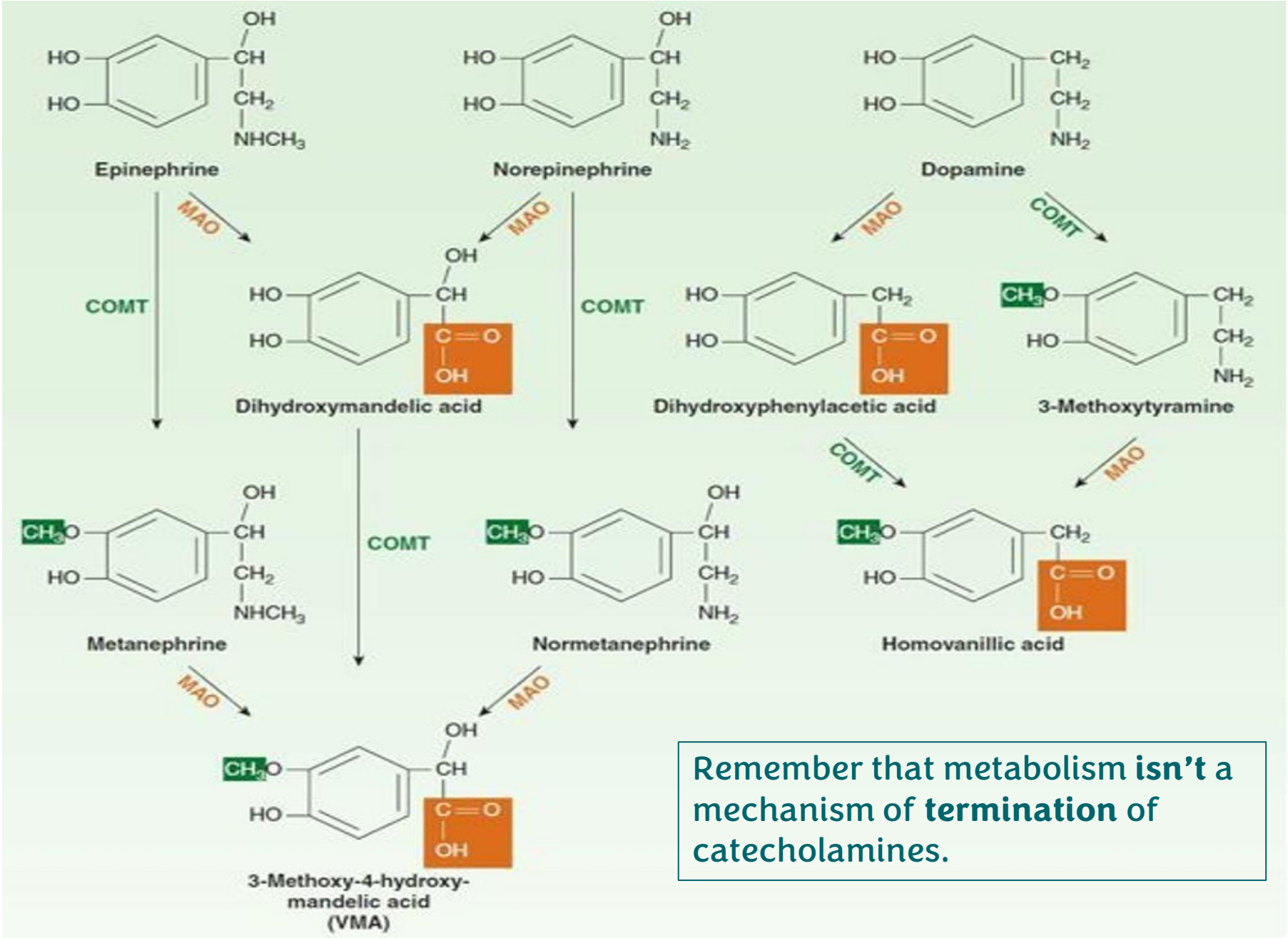


FIGURE 6–6 Metabolism of catecholamines by catechol-*O*-methyltransferase (COMT) and monoamine oxidase (MAO). (Reproduced,

Remember that metabolism **isn't** a mechanism of **termination** of catecholamines.

Don't memorize the figure.
See next slide...

❖ There are 2 enzymes related to catecholamines metabolism:

1) Oxidases;

Oxidation isn't by CYP450 but by **Monoamine oxidases** (MAO).

Instead of alkyl group with amine, it'll be carboxyl.

2) Transferases;

Conjugation with methyl groups by methyltransferases or alkyl transferases- named **Catecholamine-O-methyltransferases** (COMT).

To sum up,

- Catechol-hydroxyl group gets methylated by COMT.
- Oxidation of the amine group by MAO.
- The end result of metabolism is 3-Methoxy-4-hydroxy-mandelic acid (**VMA**)

Clinical correlation: VMA and pheochromocytoma

- Tumors secreting high levels of catecholamines can be diagnosed by **measuring VMA in urine.**
- This diagnostic test identifies tumors of the adrenal medulla or **sympathetic** chain.
- Such a tumor, called pheochromocytoma, leads to hypertensive episodes due to excessive catecholamine release.
- Catecholamines cause vasoconstriction and increased heart rate, elevating blood pressure.
- Treatment is surgical, but preparation is crucial to avoid a hypertensive crisis during surgery caused by catecholamine release from the adrenal glands.

The doctor said them all, but focus on the **general idea**, as he said: "I am not asking you in detail, but I want you to know why. Why am I talking about this? Because this is a diagnostic test for pheochromocytoma."

Autonomic Receptors

- Receptor subtypes have distinct functions, with some overlap.
- Specific functions depend on particular receptor subtypes, enabling selective drug actions.

❖ **Selective Pharmacology:**

·Selectivity in drug action is critical to avoid widespread stimulation of receptors, which can cause side effects.

❖ **Drug Metabolism:**

·Drugs like NE and dopamine are metabolized by enzymes (e.g., COMT in the liver/intestine, MAO in the brain) and the final metabolite of these pathways is VMA.

❖ **Adverse Reactions:**

·Non-selective drug actions can lead to adverse effects alongside therapeutic outcomes.

To sum up: Specificity ensures the drug is effective, reduces side effects, and avoids being broken down too quickly. It allows the drug to target the exact problem without causing harm to other parts of the body.

Added slide-further explanation

❖ Drug Metabolism:

When we try to directly administer dopamine, epinephrine (EPI), or norepinephrine (NE) as drugs, they are quickly metabolized by enzymes in the body, which reduce their effectiveness:

1. **In the intestines and circulation**: These molecules are broken down before they even reach their target.

2. **Through IV administration**: They are metabolized first in the liver by the enzyme **COMT (Catechol-O-Methyltransferase)**, followed by **MAO (Monoamine Oxidase)**.

3. **In the brain**: The process reverses — first **MAO** breaks them down, then **COMT**.

Because of this rapid breakdown, these compounds can't directly reach or act on their target tissues effectively. Therefore, scientists develop **autonomic drugs** that are more specific, stable, and resistant to metabolism, ensuring they can act where they are needed without being destroyed too quickly.

Autonomic Receptors

- Cholinoceptors (Cholinergic): Receptors stimulated by acetylcholine. Muscarinic and nicotinic receptors stimulated by the alkaloids muscarine and nicotine, respectively. (so we have 2 subtypes of Cholinoceptors)
- Adrenoceptors (Adrenergic): Receptors stimulated by catecholamines such as norepinephrine (noradrenaline) or epinephrine (adrenaline).
- Dopamine receptors (Dopaminergic): Receptors stimulated by dopamine. (Critical significance in the central nervous system (CNS).

Autonomic Receptors

TABLE 6–2 Major autonomic receptor types.

NOT REQUIRED

Receptor Name	Typical Locations	Result of Ligand Binding
Cholinoceptors		
Muscarinic M_1	CNS neurons, sympathetic postganglionic neurons, some presynaptic sites	Formation of IP_3 and DAG, increased intracellular calcium
Muscarinic M_2	Myocardium, smooth muscle, some presynaptic sites; CNS neurons	Opening of potassium channels, inhibition of adenylyl cyclase
Muscarinic M_3	Exocrine glands, vessels (smooth muscle and endothelium); CNS neurons	Like M_1 receptor-ligand binding
Muscarinic M_4	CNS neurons; possibly vagal nerve endings	Like M_2 receptor-ligand binding
Muscarinic M_5	Vascular endothelium, especially cerebral vessels; CNS neurons	Like M_1 receptor-ligand binding
Nicotinic N_N	Postganglionic neurons, some presynaptic cholinergic terminals; receptors typically contain two α3 and one β4 type subunits in addition to γ and δ subunits	Opening of Na^+, K^+ channels, depolarization
Nicotinic N_M	Skeletal muscle neuromuscular end plates; receptors typically contain two α1 and β1 type subunits in addition to γ and δ subunits	Opening of Na^+, K^+ channels, depolarization

In sweat glands only

Sweat glands and heteroreceptors in the neurons

Vagal nerve: sensory, parasympathetic neuron.

Only memorize the underlined part + added information

Autonomic Receptors

Mediate smooth muscle **contraction**

Mediate smooth muscle **relaxation**

Causes vasodilation

Adrenoceptors		
$Alpha_1$	Postsynaptic effector cells, especially smooth muscle	Formation of IP_3 and DAG, increased intracellular calcium
$Alpha_2$	Presynaptic adrenergic nerve terminals, platelets, lipocytes, smooth muscle	Inhibition of adenylyl cyclase, decreased cAMP
$Beta_1$	Postsynaptic effector cells, especially heart, lipocytes, brain; presynaptic adrenergic and cholinergic nerve terminals, juxtaglomerular apparatus of renal tubules, ciliary body epithelium → Kidneys.	Stimulation of adenylyl cyclase, increased cAMP
$Beta_2$	Postsynaptic effector cells, especially smooth muscle and cardiac muscle Smooth muscles of blood vessels in skeletal muscles and bronchi	Stimulation of adenylyl cyclase and increased cAMP. Activates cardiac G_i under some conditions.
$Beta_3$	Postsynaptic effector cells, especially lipocytes; heart	Stimulation of adenylyl cyclase and increased cAMP[1]
Dopamine receptors → In the kidney		
D_1 (DA_1), D_5	Brain; effector tissues, especially smooth muscle of the renal vascular bed	Stimulation of adenylyl cyclase and increased cAMP
D_2 (DA_2)	Brain; effector tissues, especially smooth muscle; presynaptic nerve terminals	Inhibition of adenylyl cyclase; increased potassium conductance
D_3	Brain	Inhibition of adenylyl cyclase
D_4	Brain, cardiovascular system	Inhibition of adenylyl cyclase

[1] Cardiac β_3-receptor function is poorly understood, but activation does *not* appear to result in stimulation of rate or force.

Presynaptic Regulation

- **Negative feedback control is found at the presynaptic level of autonomic function, such as:**
- **Presynaptic α_2-adrenoceptors when activated by norepinephrine and similar substances lead to reduction of further norepinephrine release; negative feedback.**

Presynaptic Regulation

- **Conversely, Presynaptic β-adrenoceptors when activated by norepinephrine and similar substances facilitate further norepinephrine release; positive feedback.**
- **These receptors are called autoreceptors.**
- **Heteroreceptors may also be involved in presynaptic regulation. They are activated by substances released from other nerve terminals.**

Presynaptic Regulation

1. **Some vagal fibers in the myocardium synapse on sympathetic noradrenergic nerve terminals and inhibit norepinephrine release; feedback inhibition.**

When a parasympathetic fiber synapses on a sympathetic fiber terminal, the parasympathetic fiber inhibits the release of NE→ REGULATION.

2. **Alternatively, some substances move to these receptors from the blood or nearby tissues. (by NT diffused out of the synapse)**

Presynaptic Regulation

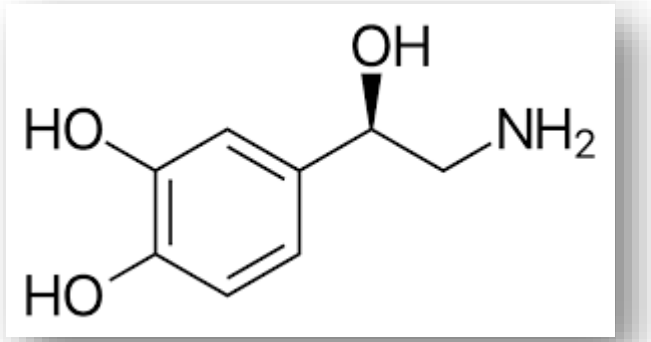
3. **Serotonin (5-HT) stimulation of its receptors at cholinergic preganglionic sites inhibits cholinergic transmission.**
4. **Adenosine and ATP stimulation of their receptors (P_1 and P_2 respectively) at adrenergic autonomic neurons inhibit adrenergic function.**
5. **Angiotensin II stimulates its receptor (AT_2-1) at adrenergic nerve terminals & stimulates adrenergic transmission.**

Don't memorize

Postsynaptic regulation

1. **Up-regulation of receptors: Increased number of receptors upon continued decreased receptor activation by antagonist.**
2. **Down regulation of receptors: Decreased number of receptors upon continued increased receptor activation by agonist.**

QUIZ ON THIS LECTURE



For any feedback, scan the code or click on

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	Slide 19	When a parasympathetic fiber binds to a sympathetic fiber terminal, the sympathetic fiber inhibits the release of NE	When a parasympathetic fiber synapses on a sympathetic fiber terminal, the parasympathetic fiber inhibits the release of NE
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي:

حكمة اليوم:
لا تصاحب الخُزعفل؛ لأنه كالأندويل النُعشر,
فيَردُنّك كالخَلزْلز...
لا تصاحب: أي لا ترافق.