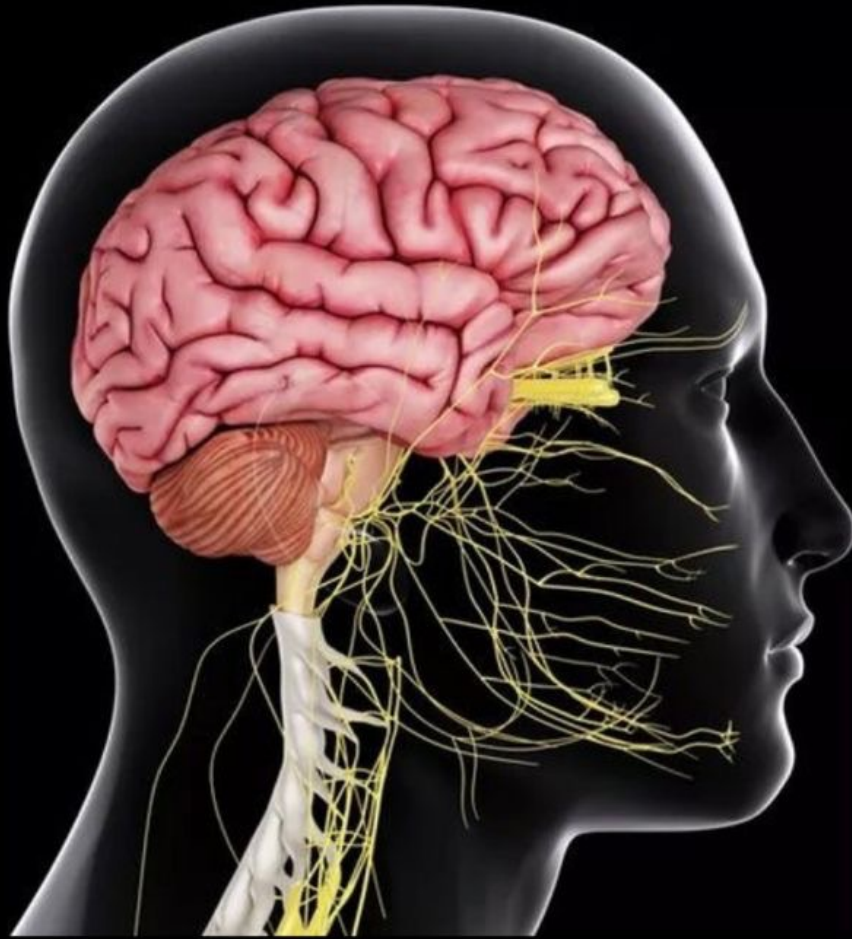




CENTRAL NERVOUS SYSTEM



SUBJECT : Biochemistry

LEC NO. : 1

DONE BY : Batool ALzubaidi

وَقُلْ رَبِّ زِدْنِي عِلْمًا

Biochemistry of CNS Neurotransmitters

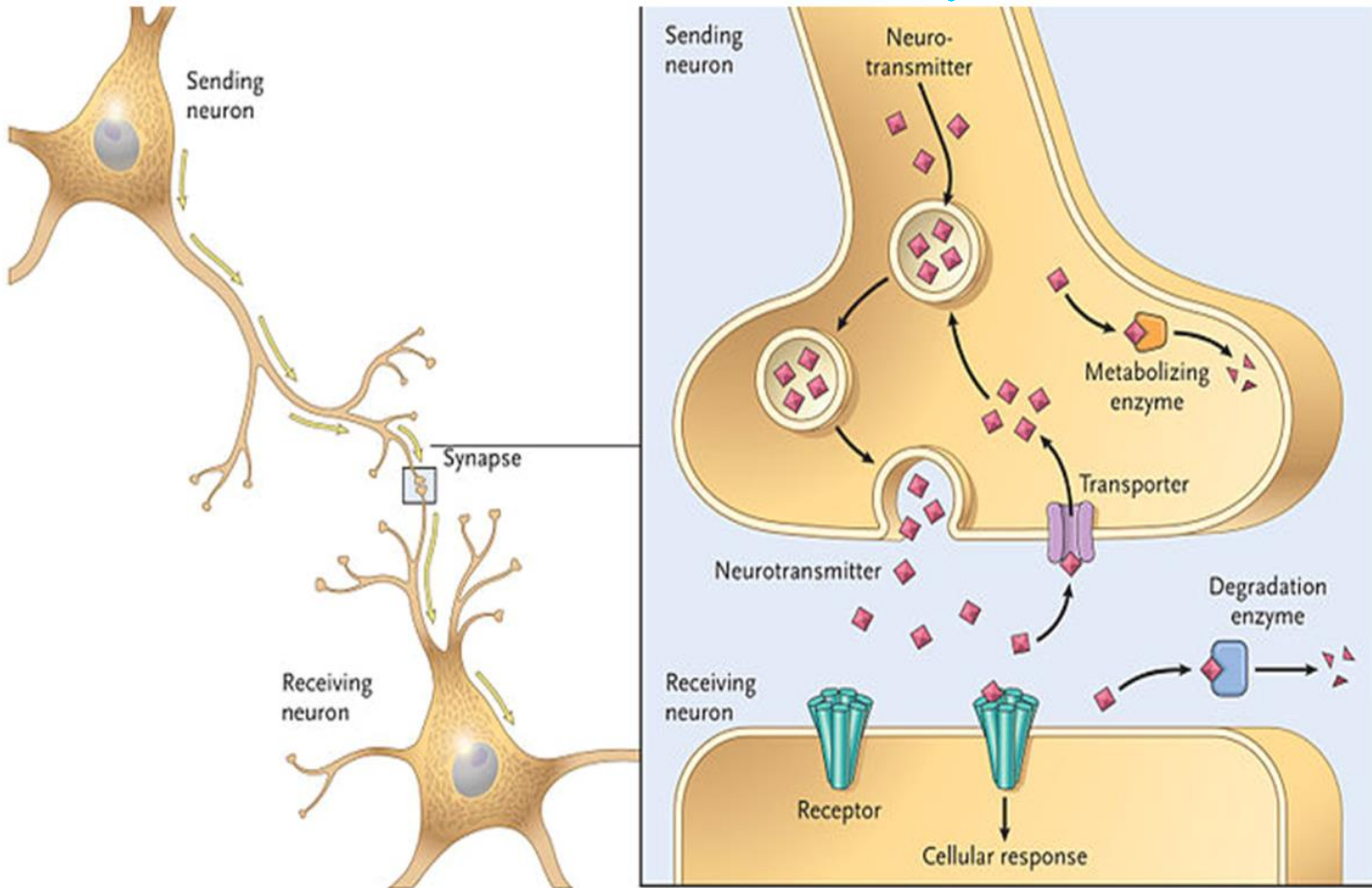
Nebras Melhem

Overview

1. Define neurotransmitters
2. Classify neurotransmitters
3. Illustrate steps of catecholamines synthesis and catabolism
4. Illustrate steps of histamine and serotonin synthesis and inactivation

Introduction

نطلع على الرسمة الي عنا
presynaptic neuron via sodium carrier
neurotransmitters
جوا ال presynaptic neuron عشان يتحولوا ل



Allow neurons to communicate with each other and with effector organ / target

- ❑ Neurotransmitters are endogenous chemicals that allow neurons to communicate with each other throughout the body.
- ❑ These endogenous chemicals are integral in shaping everyday life and functions.

Neurotransmitters are made of amino acids

Classification of neurotransmitters

Molecules that serve as neurotransmitters fall into **two basic structural categories**:

1. **Small nitrogen-containing molecules** → **Small neurotransmitters**

2. **Neuropeptides** → **Large neurotransmitters**

The major **small nitrogen-containing molecule neurotransmitters** include **glutamate, GABA, glycine, acetylcholine, dopamine, norepinephrine, serotonin,** and **histamine**. **These are monoamines » contain an amino group that's bound to 2 carbons and the carbons are bound to aromatic ring**

Additional neurotransmitters that fall into this category include **epinephrine,** **aspartate,** and **nitric oxide**.

سالت طيب هدول شو بختلّفوا عن الي قبلهم؟ حكت مش كل التقسيمات راح تلاقوهم بناءً على
ال size of the neurotransmitter ممكن يكون حسب هل هو amino acid او اشني تاني

Action of Neurotransmitters

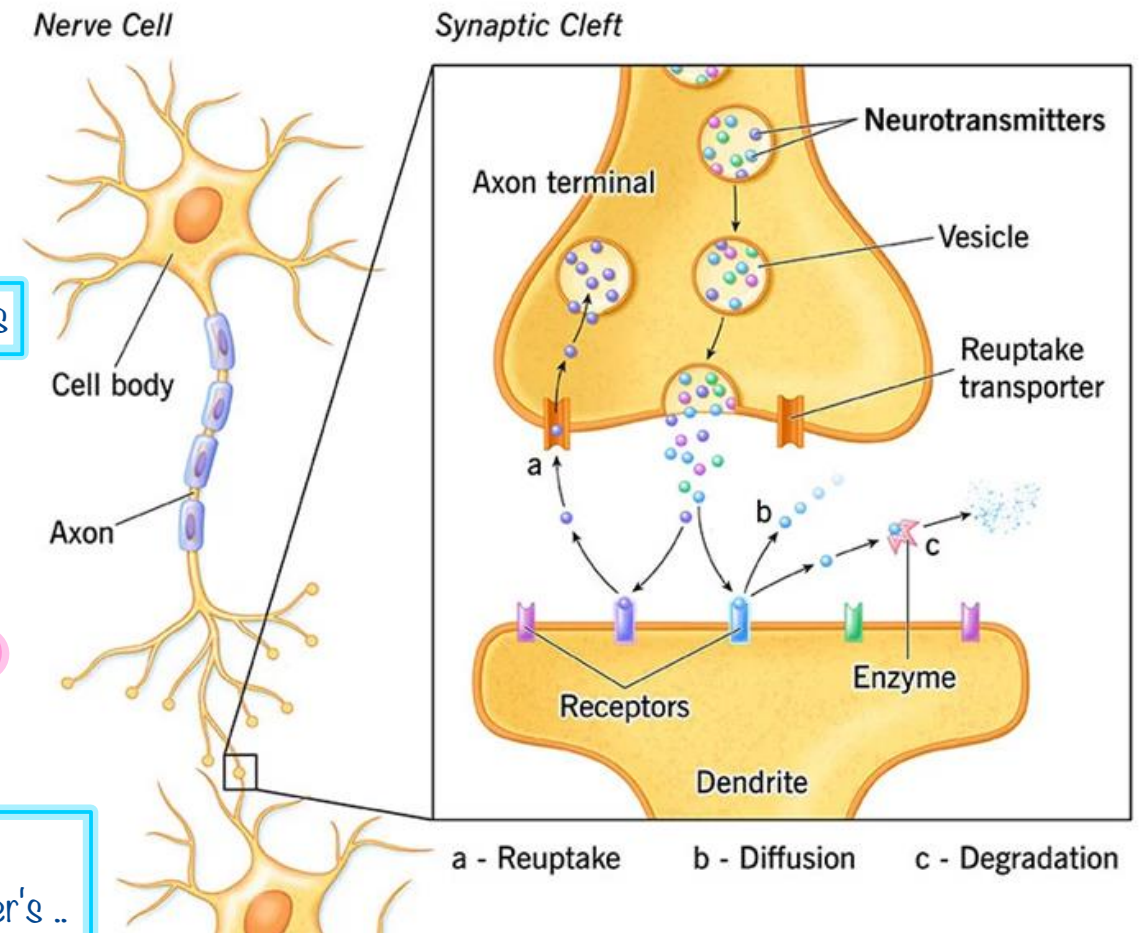
They're transported there through sodium carrier

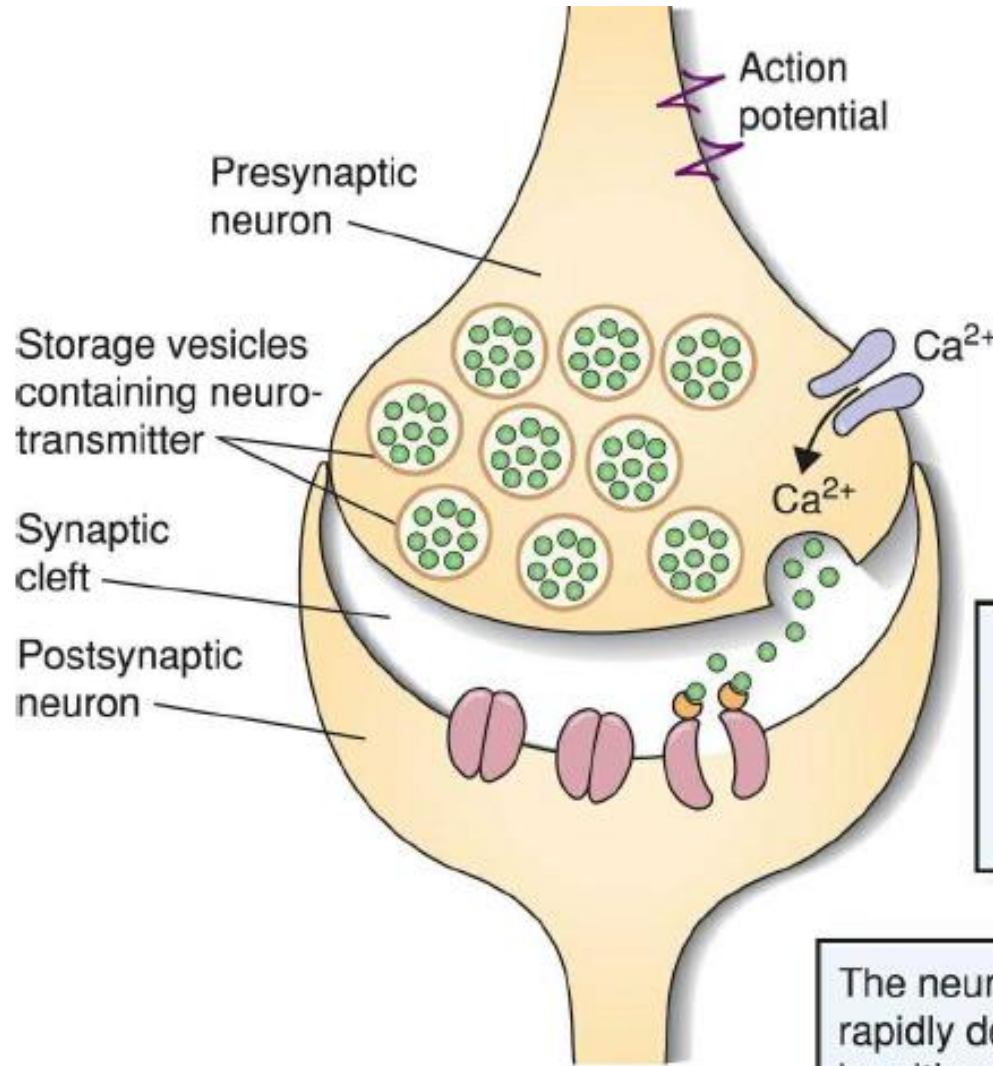
1. Most of these neurotransmitters are **synthesized from amino acids**, in the **cytoplasm of the presynaptic terminal**.
Importance of vesicles » storage of neurotransmitters so they're utilized when needed, facilitate their release
2. Once they are synthesized, the neurotransmitters are **transported into storage vesicles** by an **ATP-requiring pump** linked with the **proton gradient**.
Neurotransmitters aren't floating they're inside vesicles this is facilitated by vesicle-monoamine transporter
3. **Release from the storage vesicle** is triggered by the **nerve impulse** that **depolarizes the postsynaptic membrane** and **causes an influx of Ca^{2+} ions** through **voltage-gated calcium channels**.

Action of Neurotransmitters

- The influx of Ca^{2+} promotes **fusion of the vesicle with the synaptic membrane** and release of the neurotransmitter into the synaptic cleft. **Through exocytosis**
- The transmission across the synapse is completed by **binding of the neurotransmitter to a receptor on the postsynaptic membrane.**
- The action of the neurotransmitter is **terminated** through **reuptake** into the presynaptic terminal, **uptake** into glial cells, **diffusion** away from the synapse, or **enzymatic inactivation.**

Glutamate is an excitatory neurotransmitter, if it keeps its bond to the receptor this will lead to overexpression that might lead to cell death like Parkinson disease and Alzheimer's... The reuptake cancels the signal when needed and allows to reuse the neurotransmitter





An action potential in the presynaptic neuron allows Ca²⁺ to enter and stimulate exocytosis of the neurotransmitter.

The neurotransmitter binds to proteins in the membrane of the postsynaptic neuron, causing channels to open that allow the nerve impulse to be propagated.

The neurotransmitter is then rapidly degraded, or internalized by either the presynaptic cell or glial cells (reuptake).

Catecho » aromatic ring bound to 2 hydroxyl groups

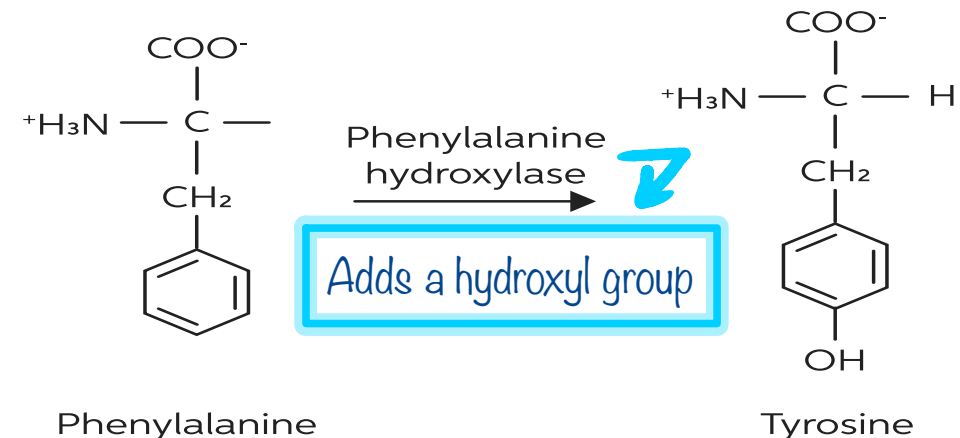
I. Catecholamine Neurotransmitters

The three neurotransmitters **dopamine**, **norepinephrine**, and **epinephrine** are synthesized in a common pathway from the amino acid **L-tyrosine**.

Tyrosine is supplied in the diet or is synthesized in the liver from the essential amino acid **phenylalanine** by **phenylalanine hydroxylase**.

Tyrosine is then transported to catecholamine secreting neurons via a **Na⁺ dependent carrier**.

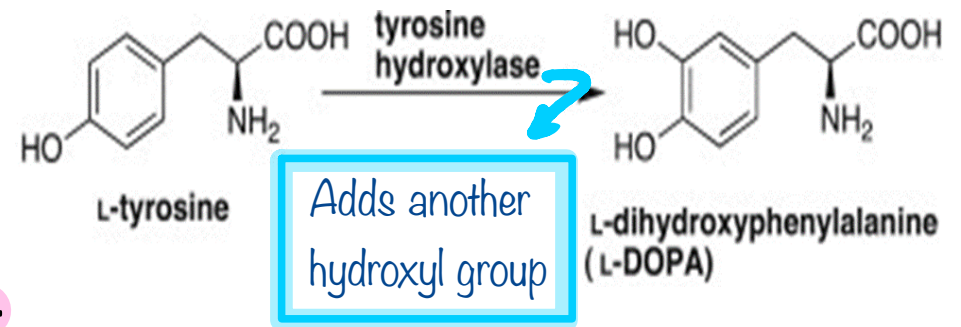
Question: phenylalanine gets converted to tyrosine in presynaptic neuron, is it true or false?! It's incorrect because in presynaptic neuron there's tyrosine



Synthesis of Dopamine

- **The first** and rate-limiting step in the **synthesis of these neurotransmitters from tyrosine**, is the **hydroxylation of the tyrosine ring by tyrosine hydroxylase**, in the cytoplasm of the cells.
- The product formed is **dihydroxyphenylalanine (L-DOPA)**.

L-DOPA is used as a dopamine replacement in parkinson disease treatment

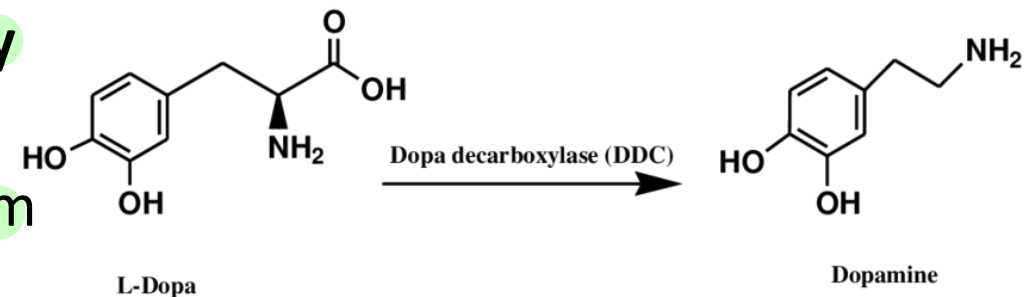


Synthesis of Dopamine

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This step requires pyridoxal phosphate which is vitamin B6

- **The second step** in catecholamine synthesis is the **decarboxylation of L-DOPA** to form **dopamine** by **dopa decarboxylase**.
- Dopamine is then **transported from the cytoplasm into the vesicle** by the **vesicular monoamine transporter (VMAT)**.

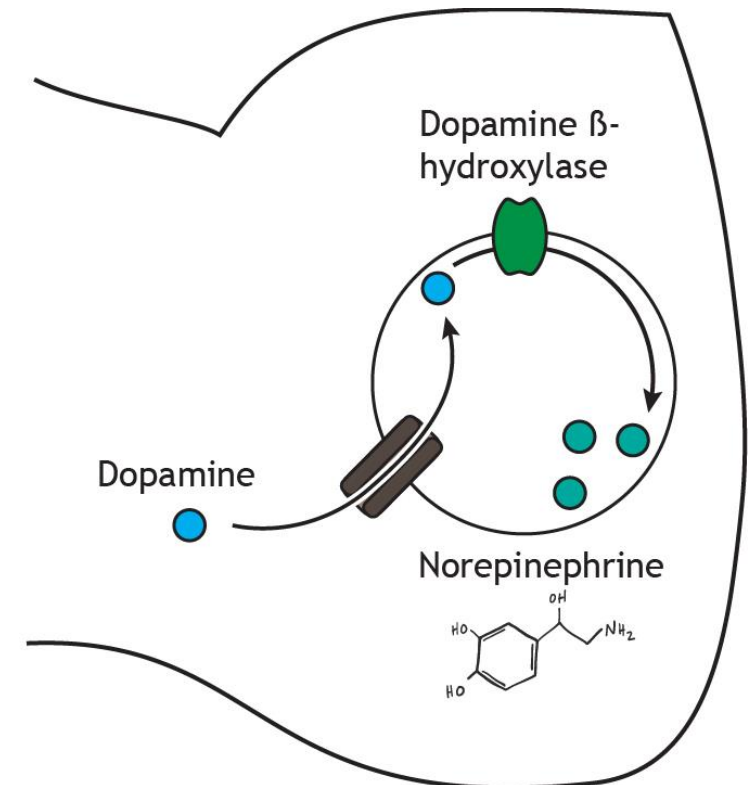


Synthesis of the Norepinephrine

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This reaction requires copper and ascorbate

- Neurons that secrete norepinephrine synthesize it from dopamine in a hydroxylation reaction catalyzed by dopamine β -hydroxylase (DBH).
- **This enzyme is present only within the storage vesicles of these cells.**



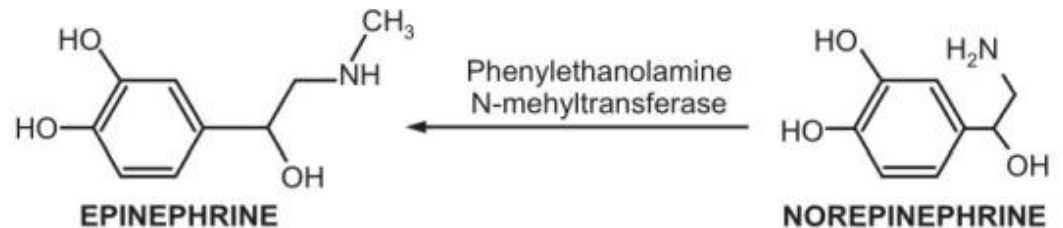
Synthesis of the Catecholamine Neurotransmitters

- Although the adrenal medulla is the major site of epinephrine synthesis, epinephrine is also synthesized in a few neurons that use it as a neurotransmitter.

حكمت اعرفوا الاختصار تاعه

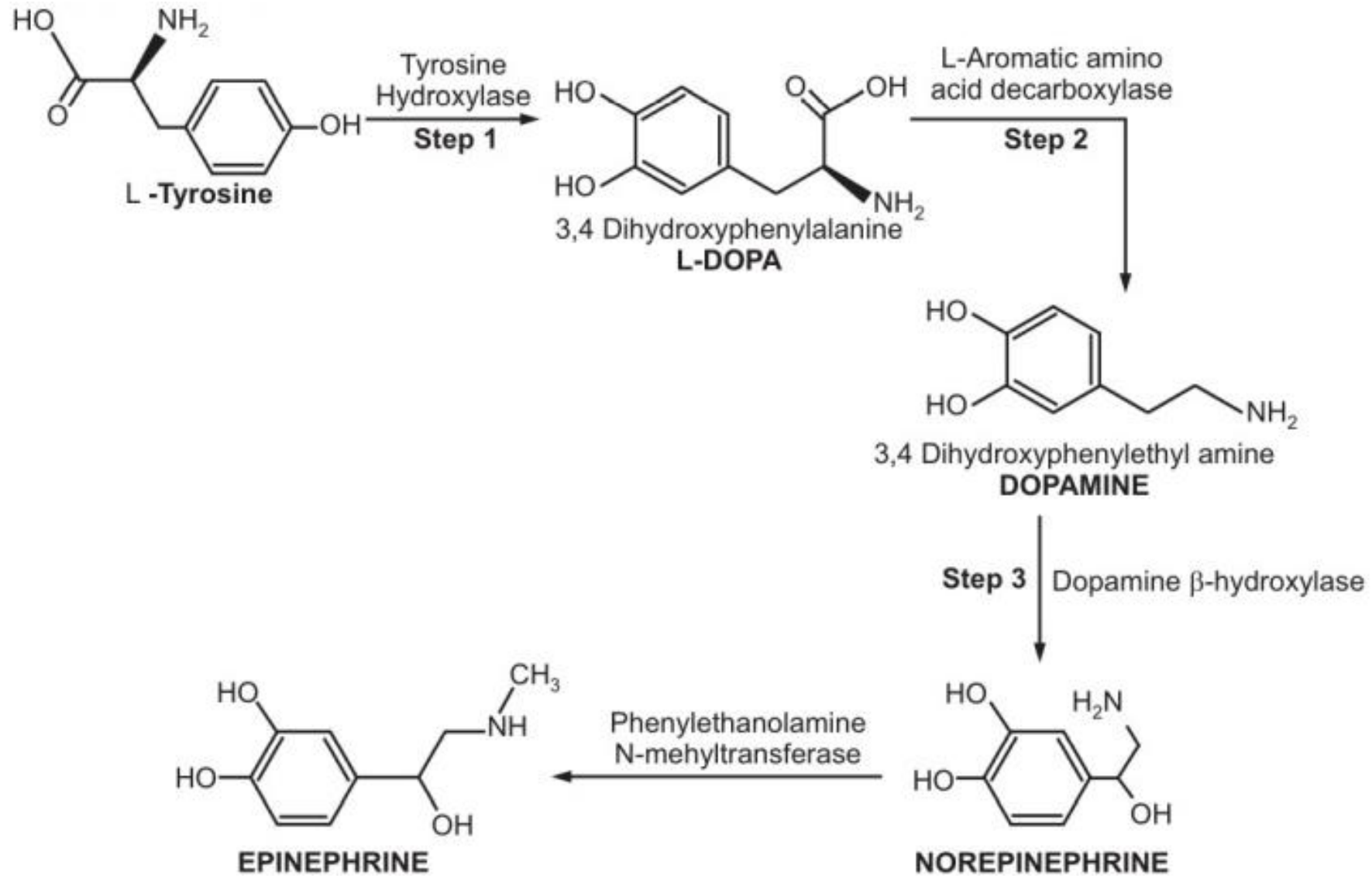
- The cytoplasmic enzyme phenylethanolamine-N-methyltransferase (PNMT), catalyzes the conversion of norepinephrine (after their release from vesicles) to epinephrine, in cytoplasm.

It differs from norepinephrine by having methyl group



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من وين بجيب ال methyl group هاي من SAM الي هو S adenosylmethionine

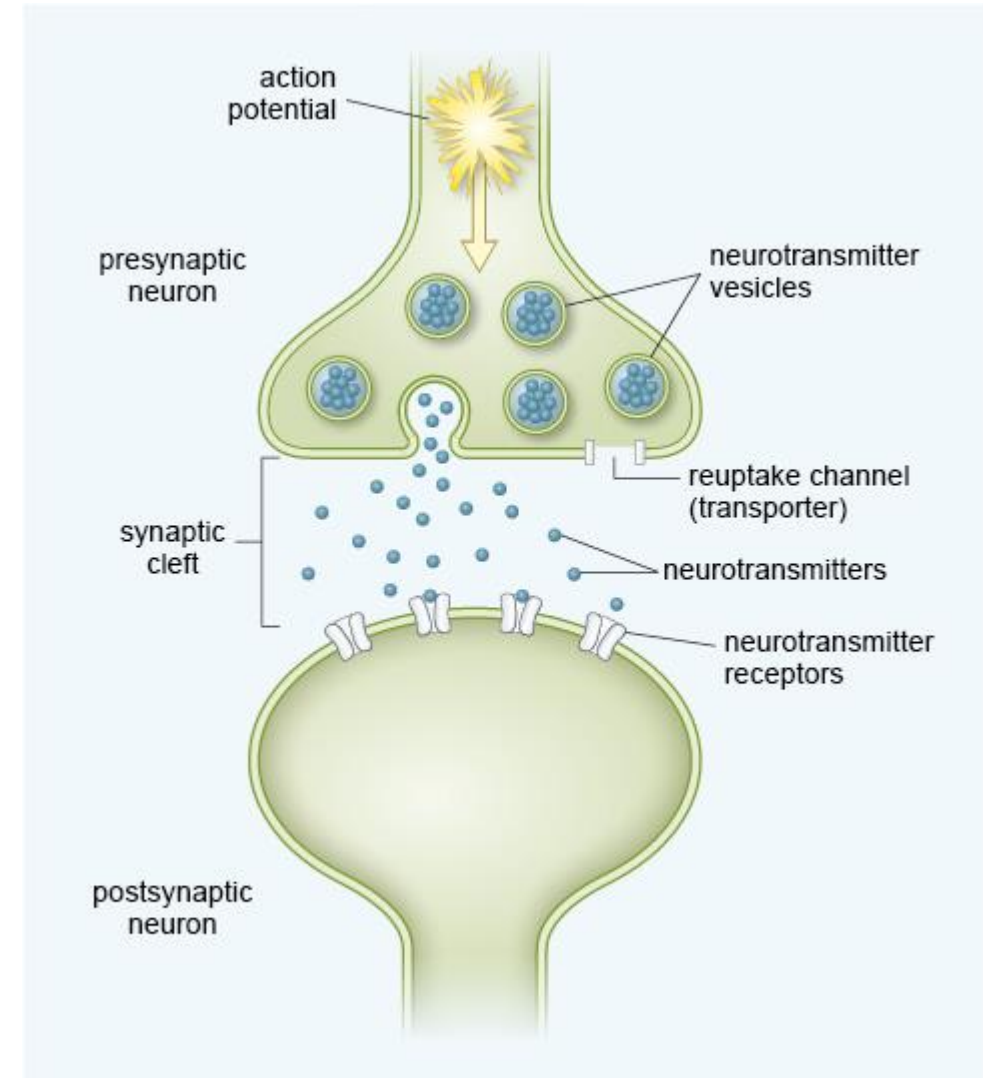


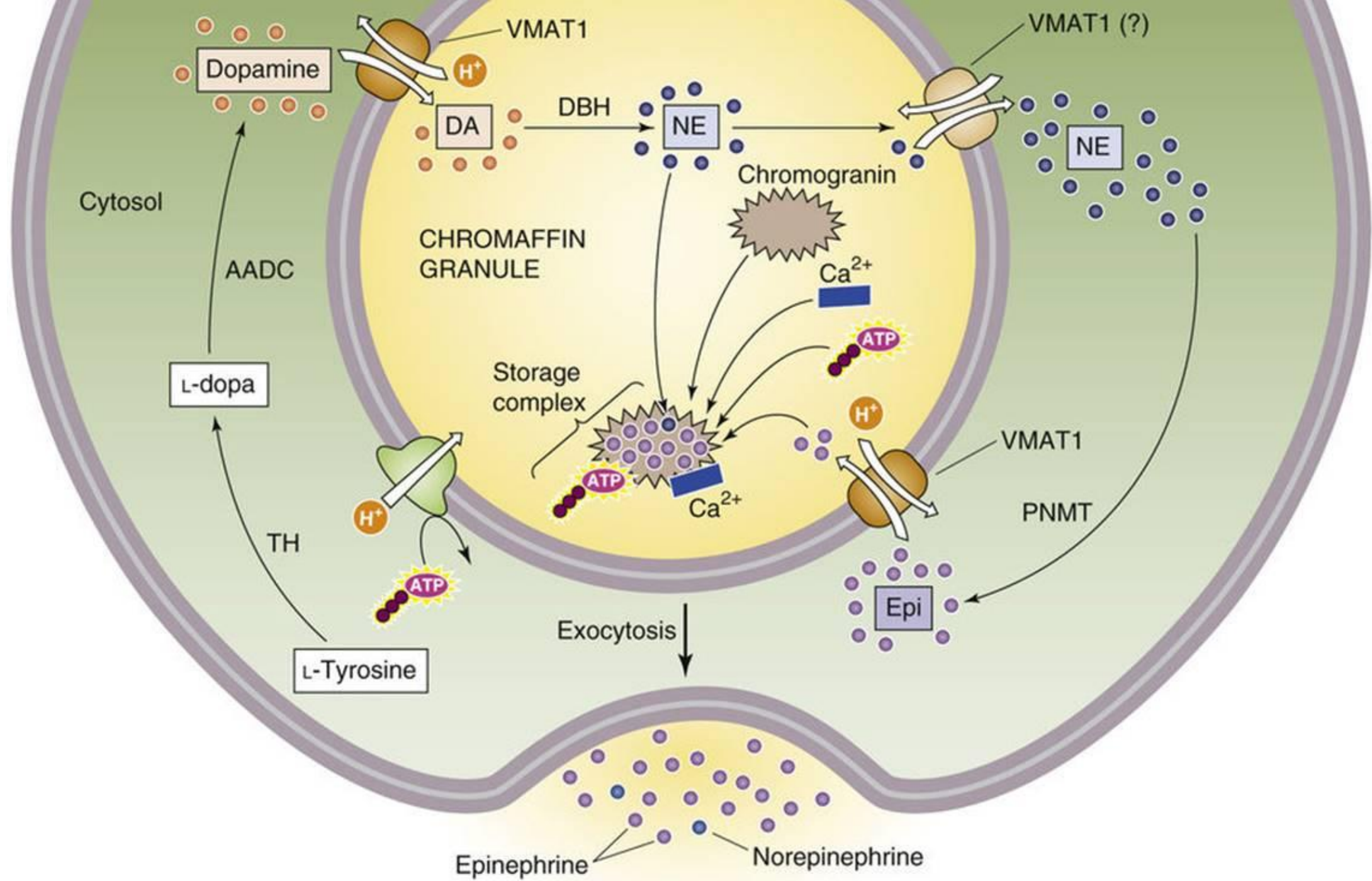
Storage of Catecholamines

- Ordinarily, only low concentrations of catecholamines are free in the cytosol, whereas high concentrations are found within the storage vesicles.
- The catecholamines are transported into vesicles by the protein **VMAT** (**vesicle monoamine transporter**).
- In the vesicles, the catecholamines exist in a complex with **ATP** and **acidic proteins** known as **chromogranins**.
1.
2.
3. Calcium
↳ v.I

Release of Catecholamines

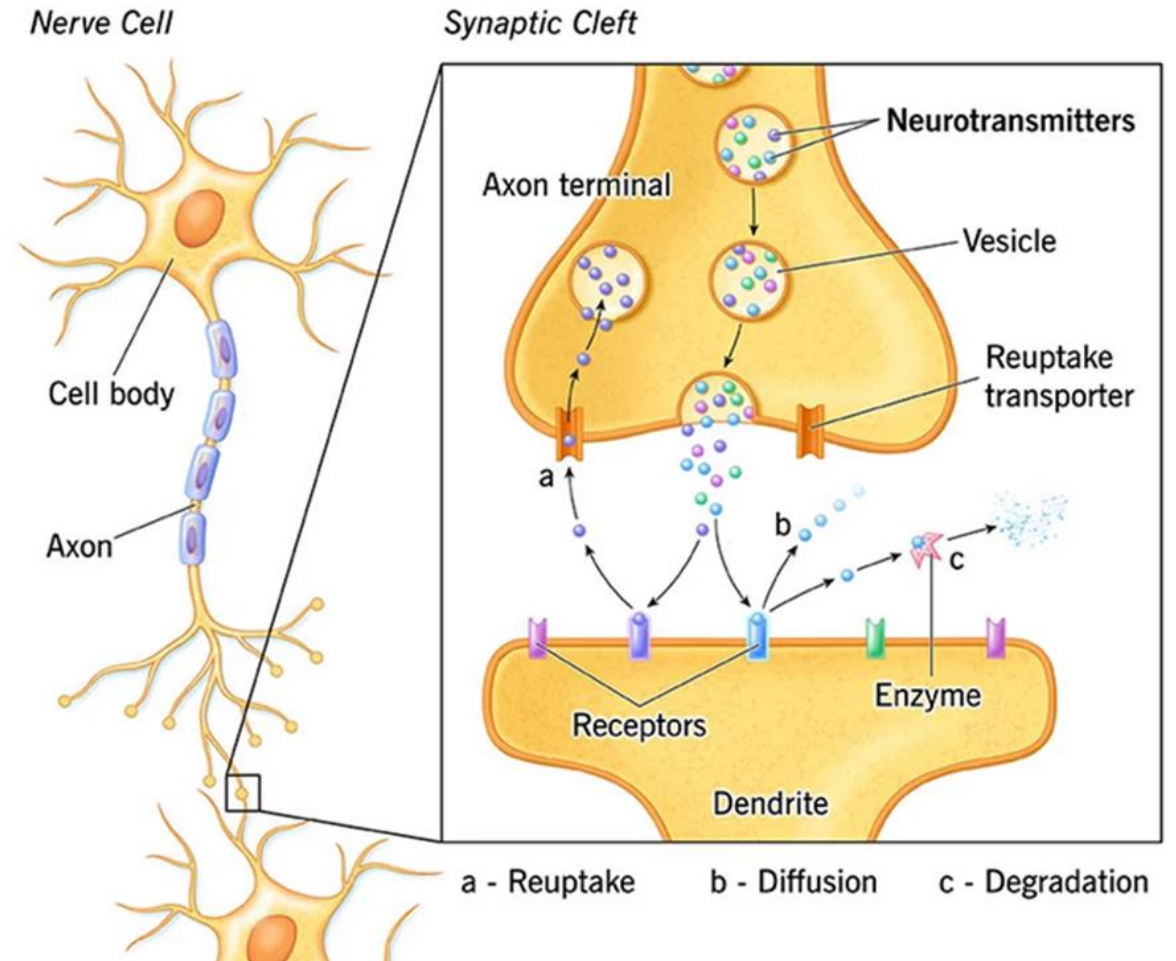
- The vesicles play a dual role: They maintain a ready supply of catecholamines at the nerve terminal that is available for immediate release, and they mediate the process of release.
- When an action potential reaches the nerve terminal, Ca^{2+} channels open, allowing an influx of Ca^{2+} , which promotes the fusion of vesicles with the neuronal membrane.
- The vesicles then discharge their soluble contents, into the extraneuronal space by the process of exocytosis.





Degradation of Catecholamines

- The action of catecholamines is terminated through reuptake into the presynaptic terminal and diffusion away from the synapse.
- Degradative enzymes are present in the presynaptic terminal, and in adjacent cells, including glial cells and endothelial cells.



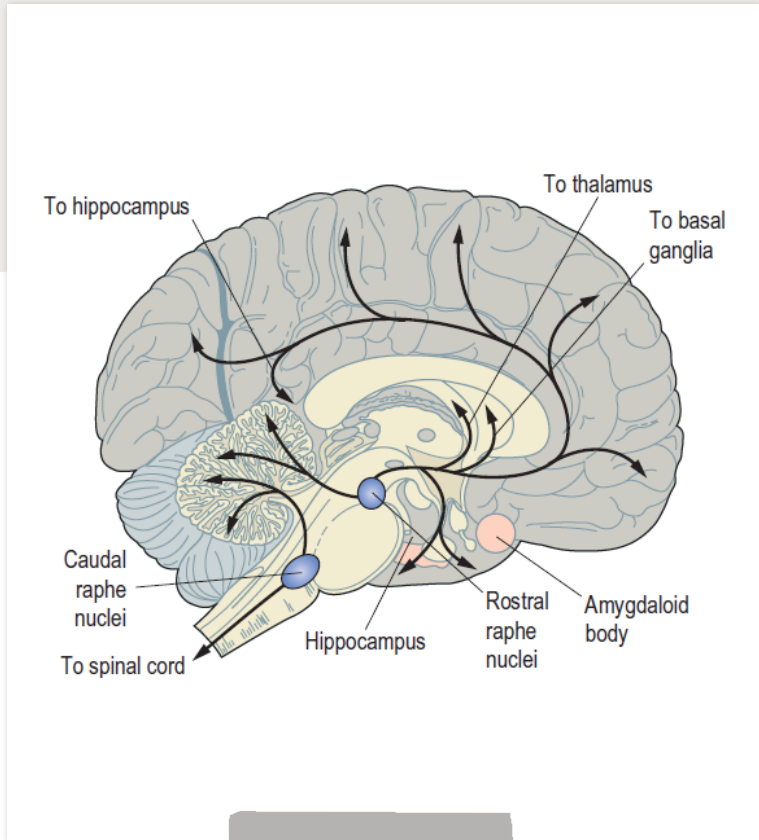
Degradation of Catecholamines

- Two of the major reactions in the process of inactivation and degradation of catecholamines are catalyzed by **monoamine oxidase (MAO)** and **catechol-O-methyltransferase (COMT)**.
- I ■ **MAO** is present on the **outer mitochondrial membrane** of many cells.
In the **presynaptic terminal**, MAO **inactivates catecholamines** that **are not protected in storage vesicles**.
- I ■ **COMT** is present in the **synaptic cleft and cytosol of the cell**.

Degradation of Catecholamines

- The action of MAO and COMT can occur in almost any order, resulting in a large number of degradation products and intermediates, many of which appear in the urine.
 - I • **Homovanillylmandelic acid (HVA)** is an indicator of dopamine degradation.
 - I • The end product of epinephrine and norepinephrine is **vanillylmandelic acid (VMA)**.
-

II. Serotonin



Synthesized in serotonergic neurons **I** which are concentrated in the **raphe nuclei** in the upper brain stem but project up to the cerebral cortex and down to the spinal cord.

Serotonin is synthesized from the essential amino acid tryptophan.

Metabolism of Serotonin

حکت ما بدھا ایانا
نعرف structures

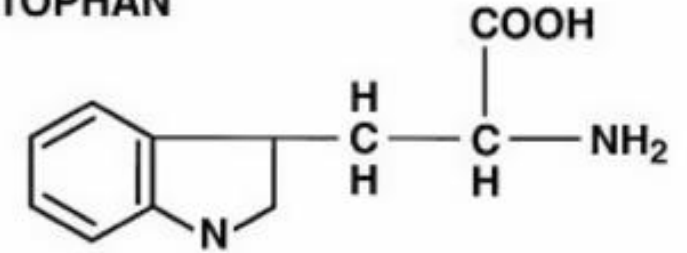
1. The first enzyme of the pathway, **tryptophan hydroxylase**. The **rate limiting** step is the conversion of **tryptophan to 5-hydroxytryptophan**.
2. The second step is **conversion to serotonin by the aromatic L-amino acid decarboxylase**.

5-hydroxy-tryptamine

I

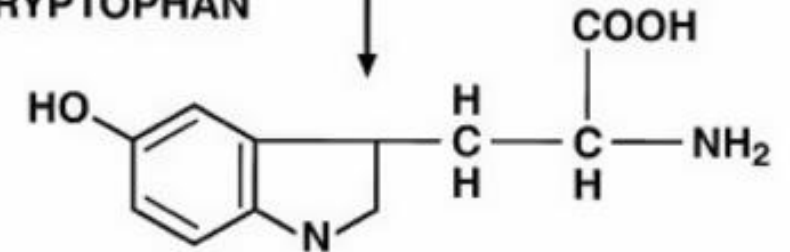
- Serotonin, like the catecholamine neurotransmitters, can be **inactivated by MAO**.

L-TRYPTOPHAN



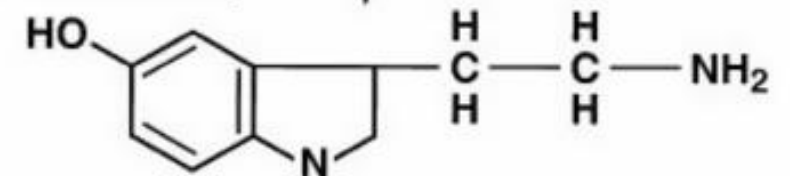
Tryptophan hydroxylase

L-5-HYDROXY-TRYPTOPHAN



L-aromatic amino acid decarboxylase

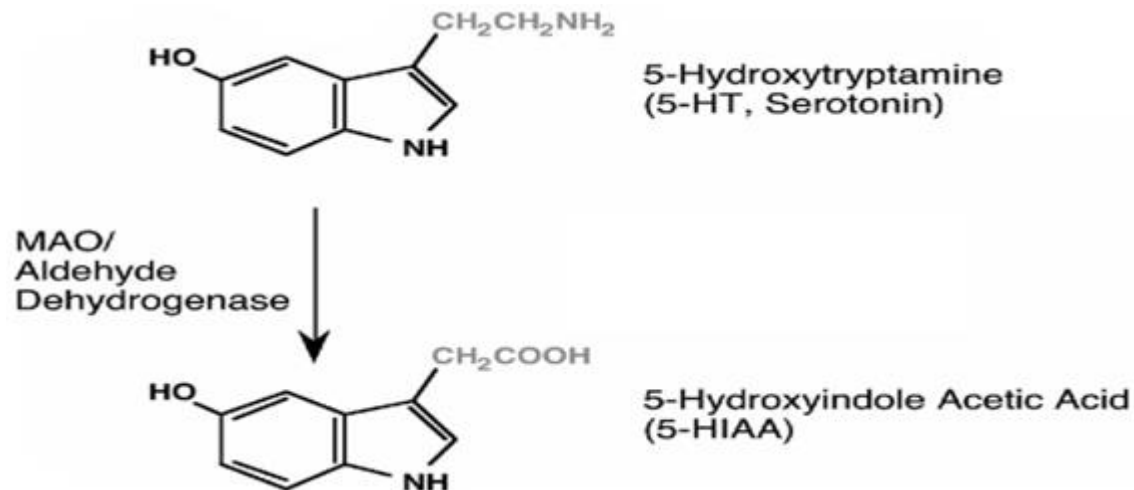
5-HYDROXY-TRYPTAMINE (SEROTONIN)

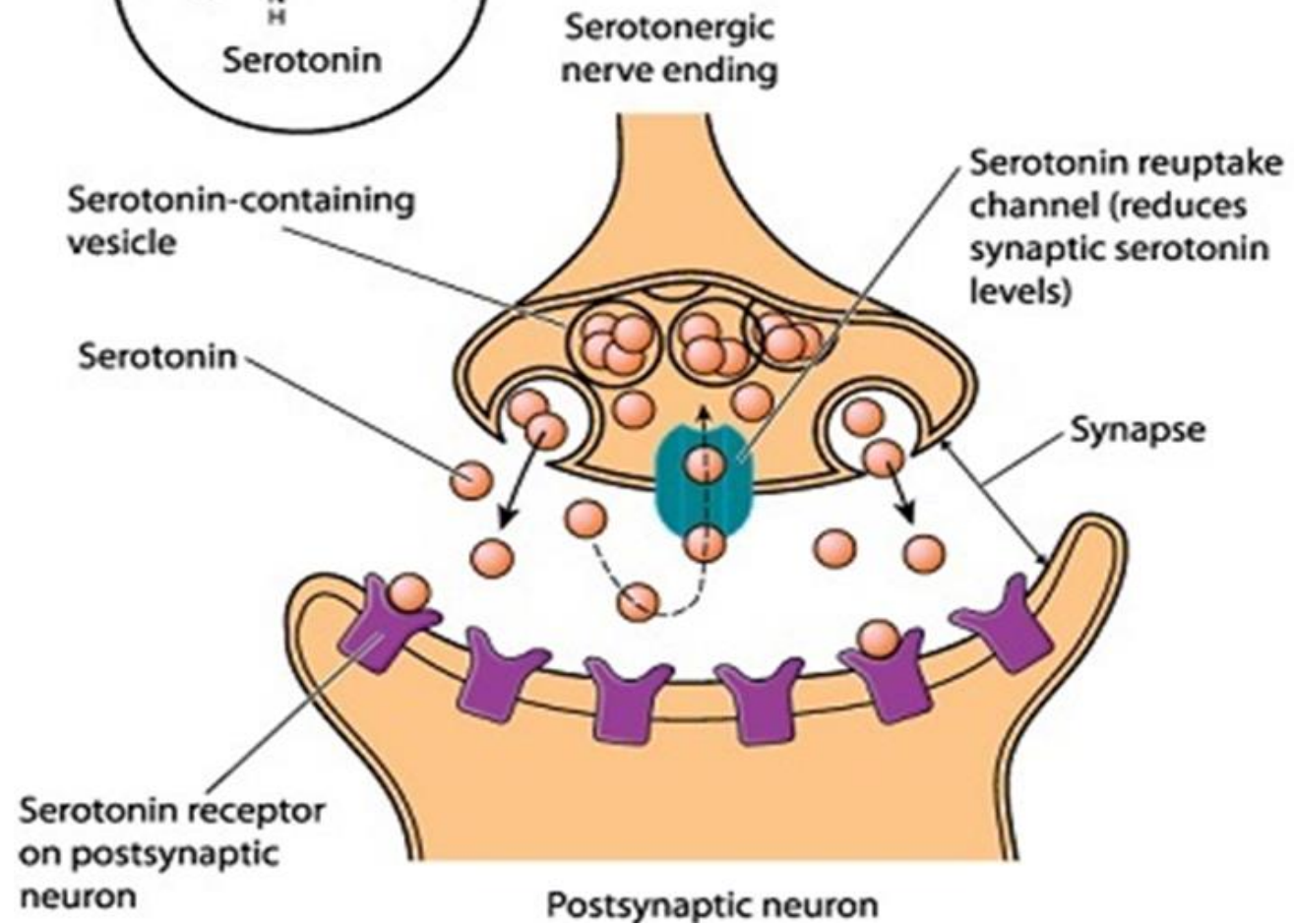
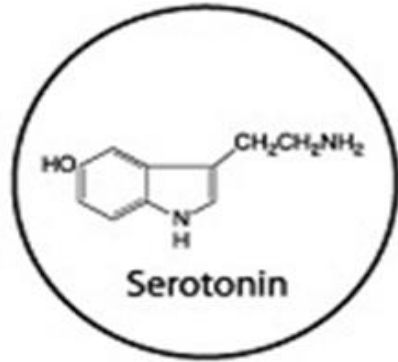


Metabolism of Serotonin

- Serotonin is transported into the vesicles by the VMAT.
- Once serotonin is returned to the nerve terminal, it is either taken back into the vesicles or is inactivated by MAO to form 5-hydroxyindoleacetic acid (5-HIAA).
- This substance is the principal urinary metabolite of serotonin.

Indole » benzene ring + pyrrole ring





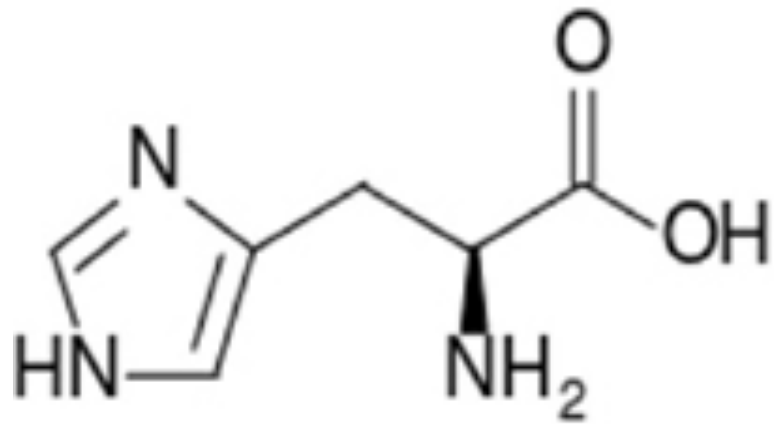
III. Histamine

- Within the brain, histamine is produced both by **mast cells and by certain neuronal fibers.**
- Involved in **local immune responses**, as well as **regulating physiological function in the gut** and acting as a **neurotransmitter for the brain, spinal cord, and uterus.**
- **Histamine is synthesized from decarboxylation of histidine, by histidine decarboxylase.**

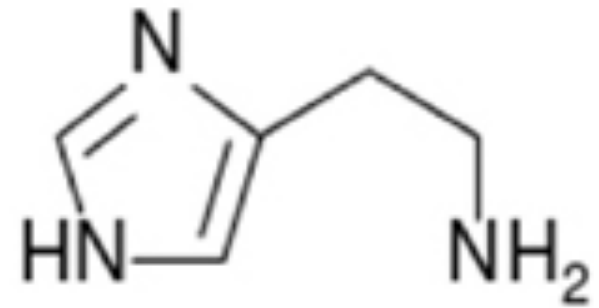


This step requires pyridoxal phosphate which is vitamin B6

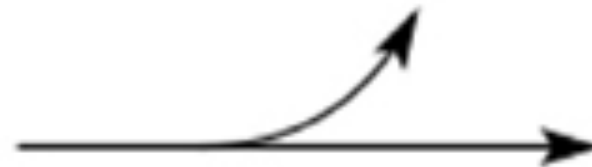
Histidine



Histamine



CO₂



Histidine decarboxylase

Metabolism of Histamine

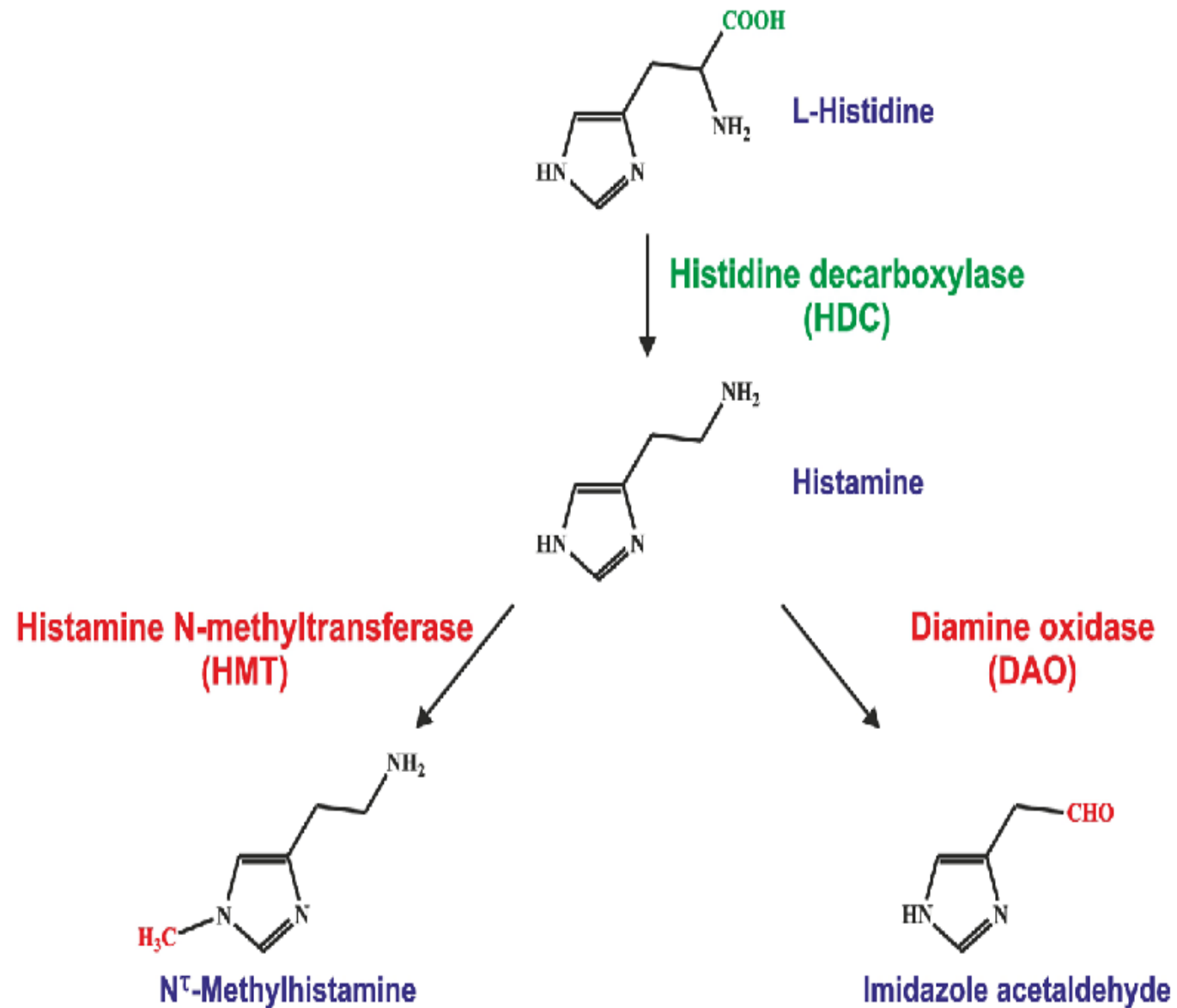
Unlike other neurotransmitters, histamine **does not appear to be recycled into the presynaptic terminal to any great extent.**

1. The first step in the inactivation of histamine **in the brain** is methylation.

The enzyme **histamine methyltransferase (HMT)** transfers a methyl group to a ring nitrogen of histamine to form **methylhistamine**.

2. The second step is **oxidation by MAO.**

- In **peripheral tissues**, histamine undergoes **deamination by diamine oxidase**, followed by **oxidation to a carboxylic acid**.



Questions

A patient with a tumor of the adrenal medulla experienced palpitations, excessive sweating, and hypertensive headaches. His urine contained increased amounts of vanillylmandelic acid. His symptoms are probably caused by an overproduction of which of the following?

- A. Acetylcholine
- B. Norepinephrine and epinephrine
- C. Dopa and serotonin
- D. Histamine
- E. Melatonin

Answer is B