# Biochemistry of CNS Neurotransmitters

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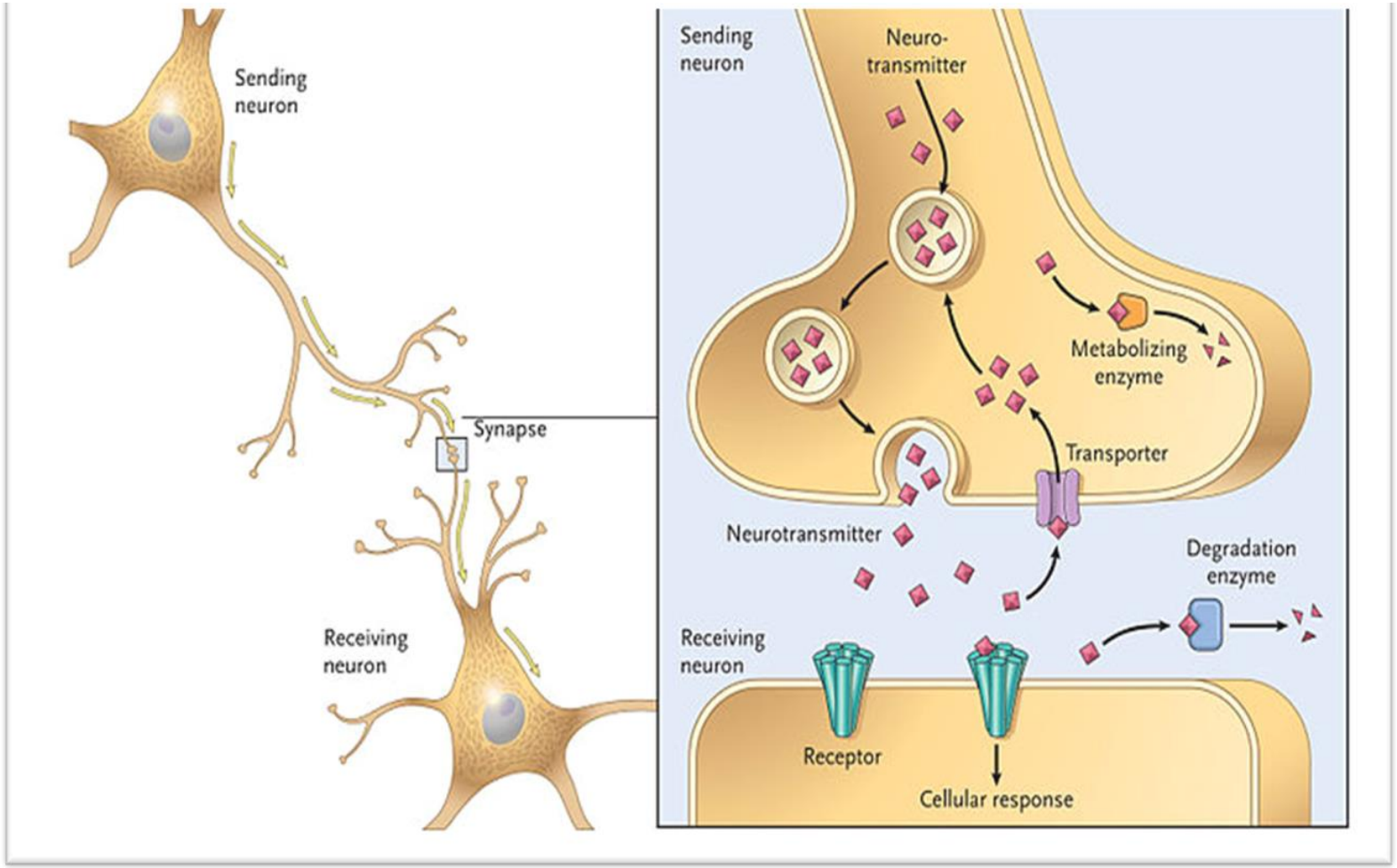
# Overview

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




- 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.

# Classification of neurotransmitters

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

1. Small nitrogen-containing molecules
2. Neuropeptides

The major small nitrogen-containing molecule neurotransmitters include ***glutamate***, ***GABA***, ***glycine***, ***acetylcholine, dopamine, norepinephrine***, ***serotonin***, and ***histamine***.

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

# Action of Neurotransmitters

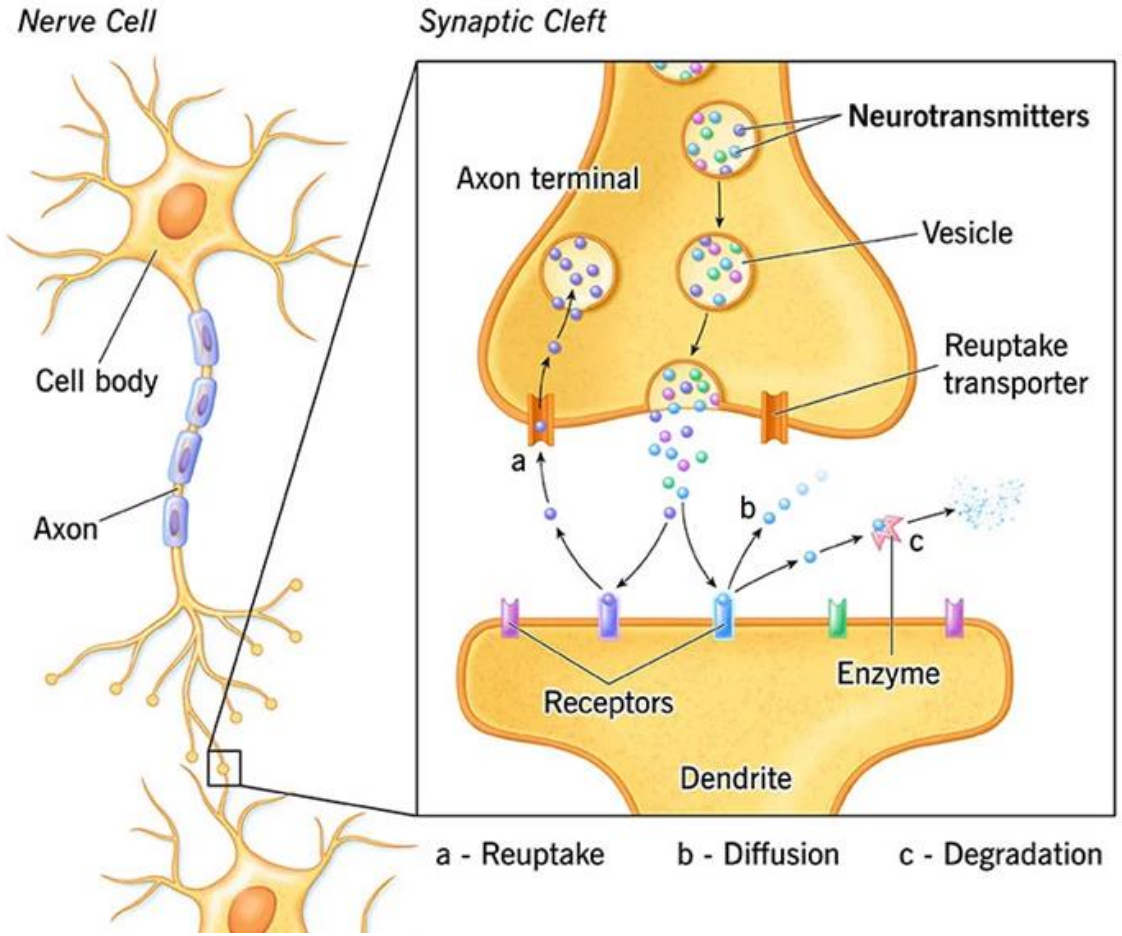
1. Most of these neurotransmitters are **synthesized from amino acids**, in the cytoplasm of the presynaptic terminal.
2. Once they are synthesized, the neurotransmitters are **transported** into storage vesicles by an ATP-requiring pump linked with the proton gradient.
3. **Release from the storage vesicle** is triggered by the nerve impulse that depolarizes the postsynaptic membrane and causes an influx of Ca2+ ions through voltage-gated calcium channels.

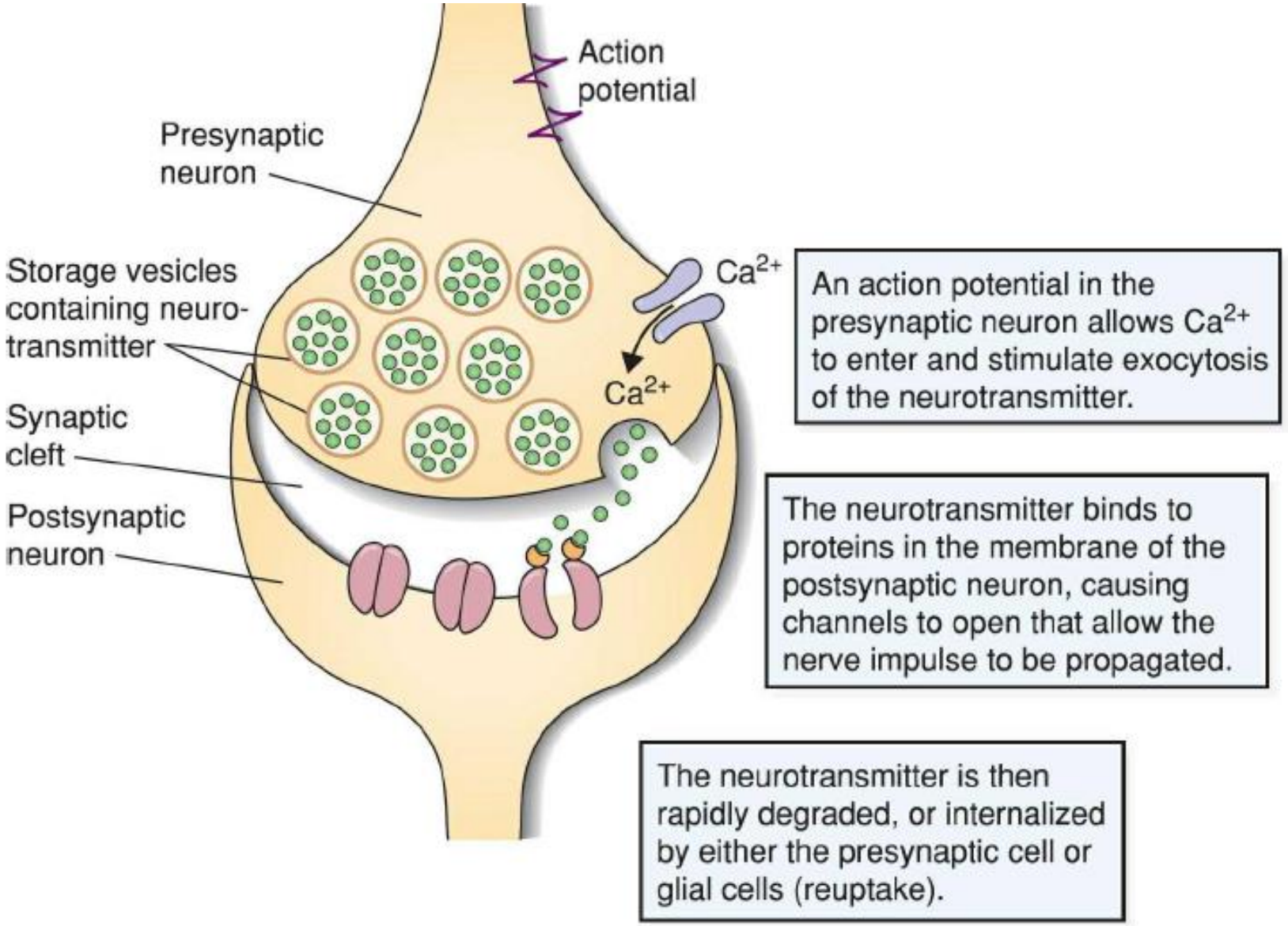
# Action of Neurotransmitters

4. The influx of Ca2+ promotes **fusion of the vesicle with the synaptic membrane** and release of the neurotransmitter into the synaptic cleft.

5. The transmission across the synapse is completed by binding of the neurotransmitter to a receptor on the postsynaptic membrane.

6. 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.



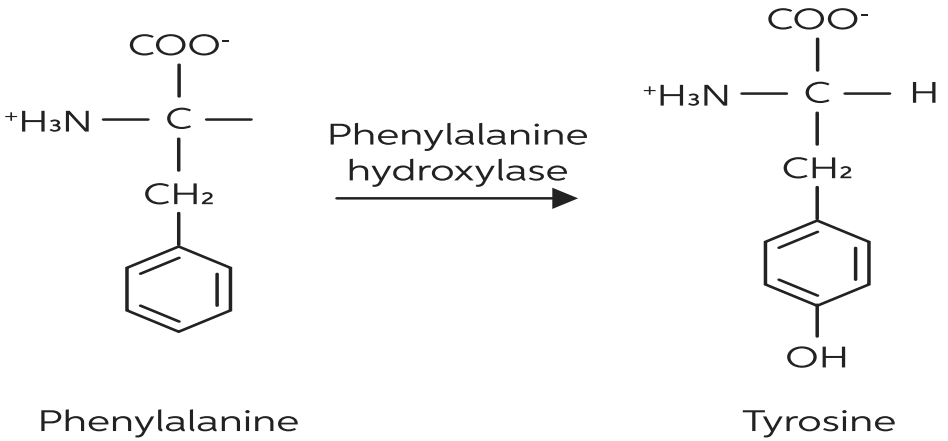

Action potential
Presynaptic neuron
Storage vesicles containing neuro-transmitter
Synaptic cleft
Postsynaptic neuron
$Ca^{2+}$
$Ca^{2+}$
An action potential in the presynaptic neuron allows $Ca^{2+}$ to enter and stimulate exocytosis of the neurotransmitter.
The neurotransmitter binds to proteins in 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).

# I. Catecholamine Neurotransmitters

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

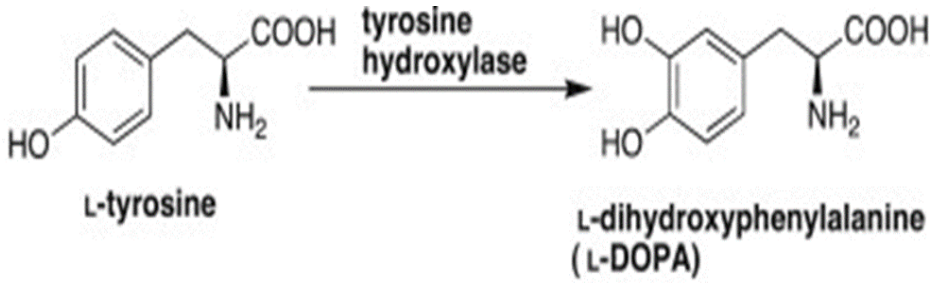
Tyrosine is supplied in the diet or is synthesized in the liver from the essential amino acid phenylalanine by *phenylalanine hydroxylase*.

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



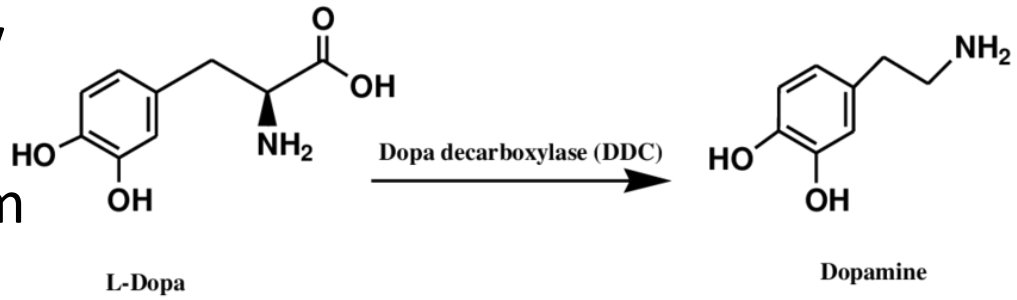
# Synthesis of Dopamine

- **<u>The first</u>** 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**).



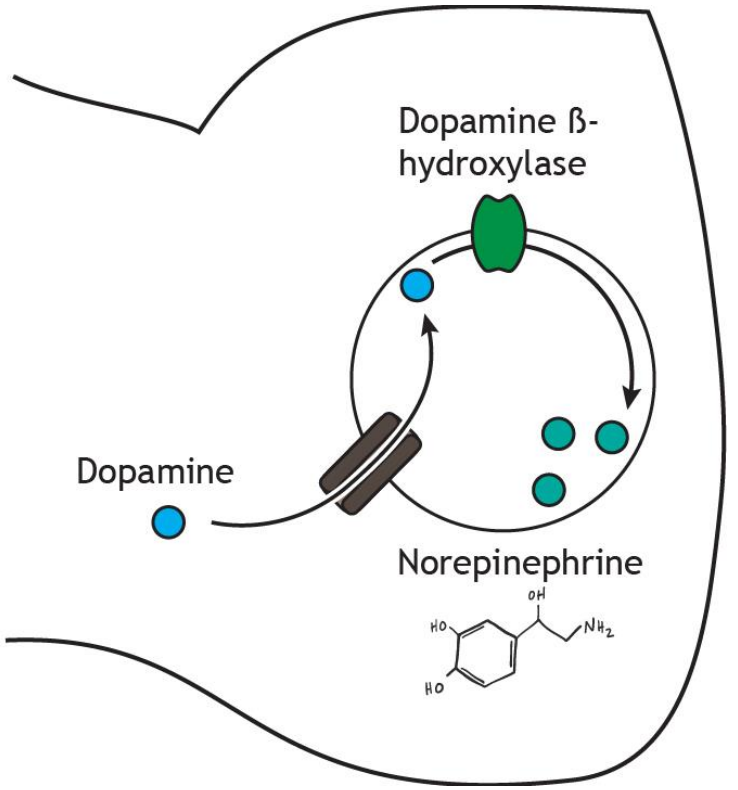
# Synthesis of Dopamine

- **<u>The second step</u>** 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).



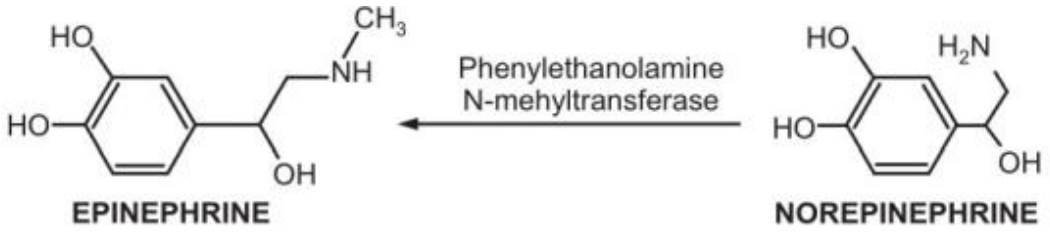
# Synthesis of the Norepinephrine

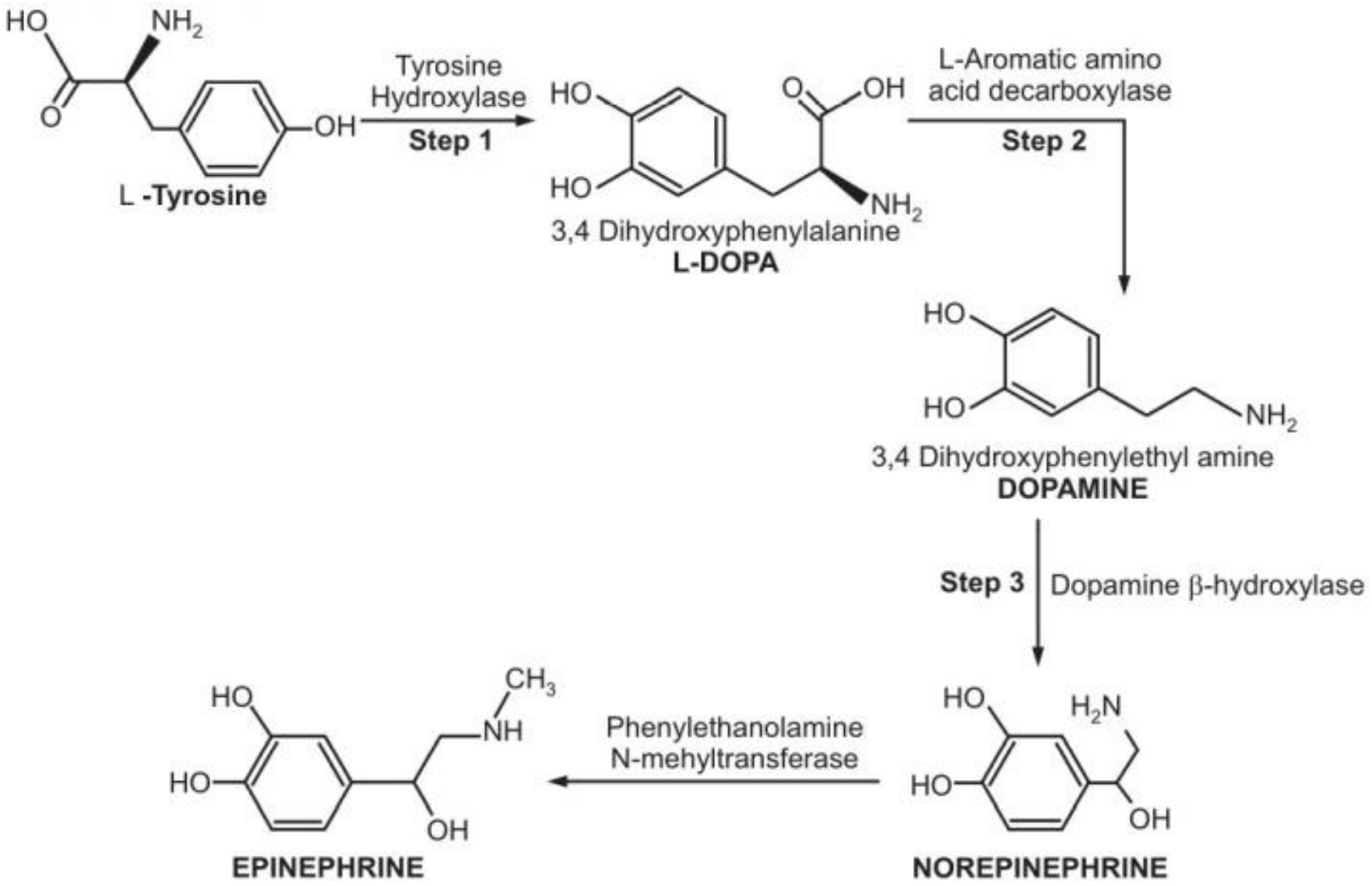
- Neurons that secrete norepinephrine synthesize it from dopamine in a hydroxylation reaction catalyzed by dopamine β-hydroxylase (DBH).
- ***This enzyme is present only within the storage vesicles of these cells.***



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



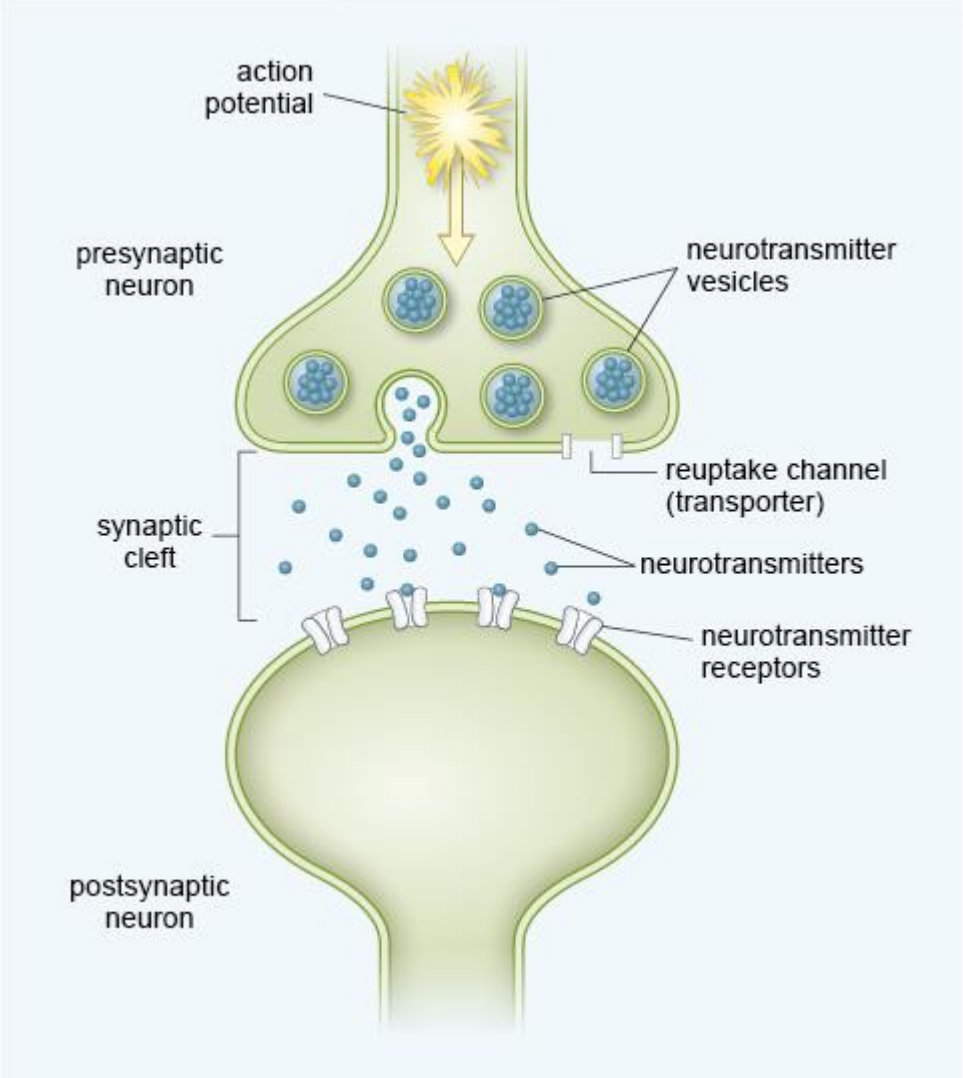

HO
NH2
O
OH
L -Tyrosine
Tyrosine
Hydroxylase
Step 1
HO
HO
O
OH
NH2
3,4 Dihydroxyphenylalanine
L-DOPA
L-Aromatic amino
acid decarboxylase
Step 2
HO
HO
NH2
3,4 Dihydroxyphenylethyl amine
DOPAMINE
Step 3
Dopamine β-hydroxylase
HO
H2N
HO
OH
NOREPINEPHRINE
Phenylethanolamine
N-mehyltransferase
HO
CH3
NH
HO
OH
EPINEPHRINE

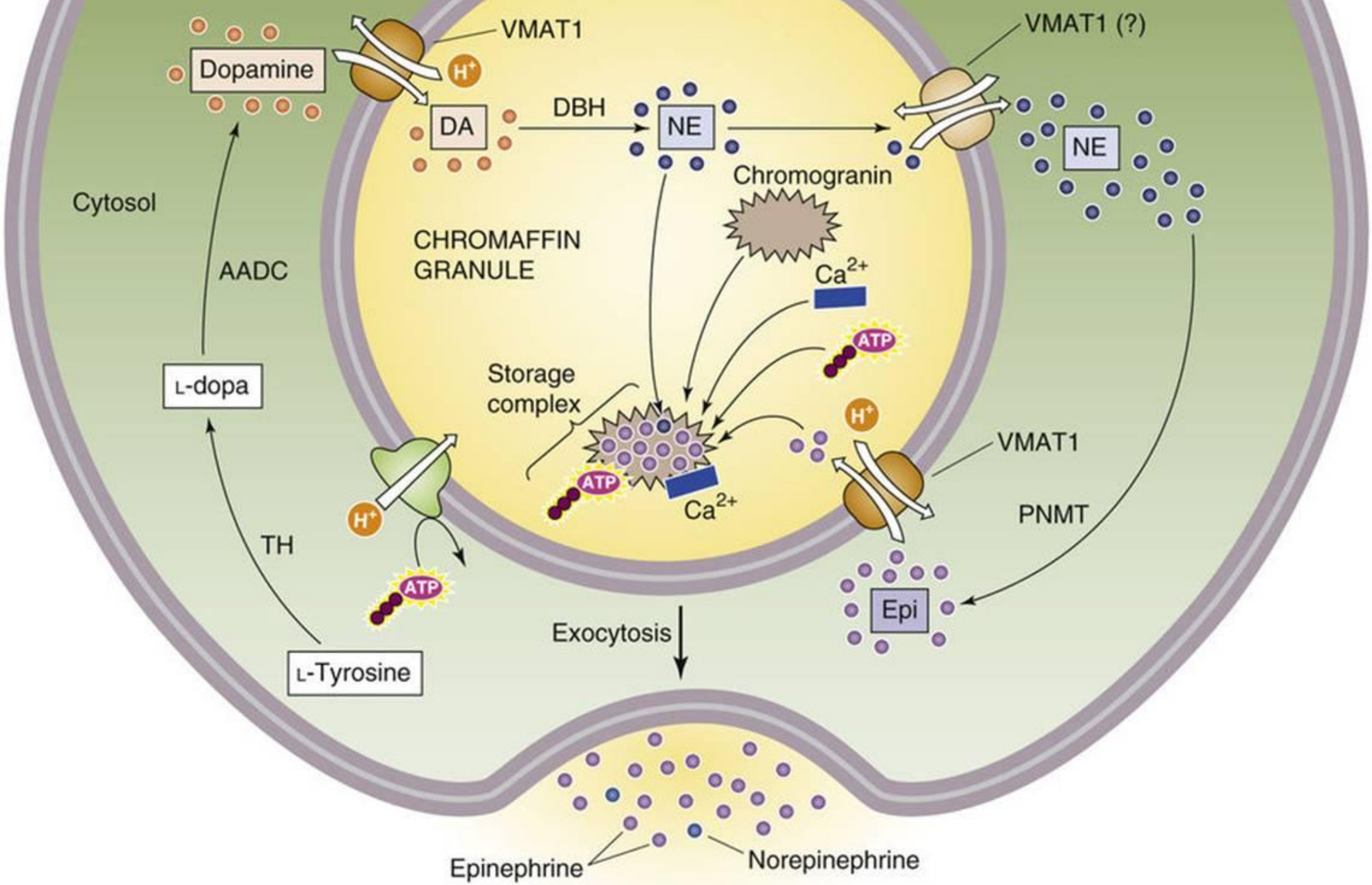
# Storage of Catecholamines

- 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**.

# 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.

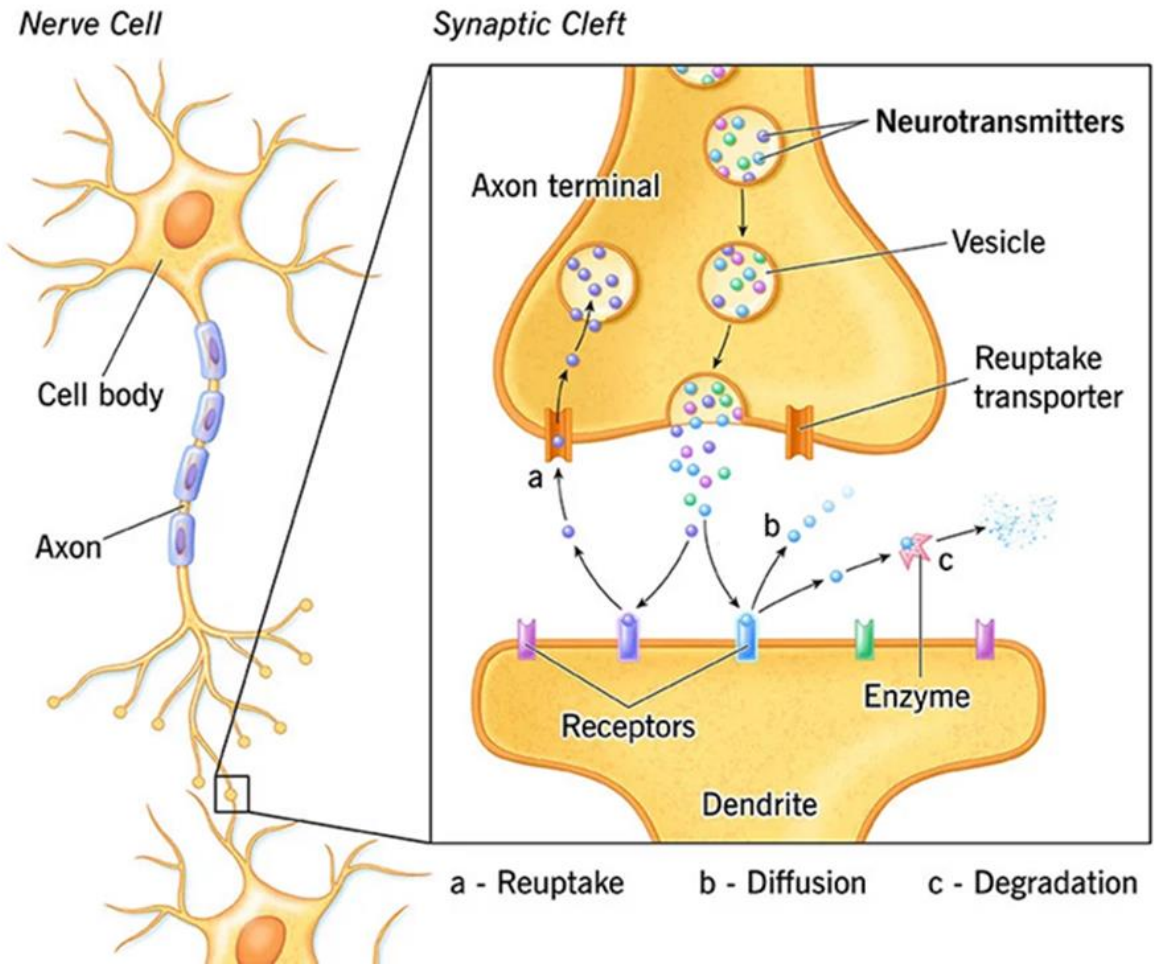



VMAT1
VMAT1 (?)
Dopamine
H+
DA
DBH
NE
NE
Chromogranin
Cytosol
CHROMAFFIN
GRANULE
AADC
Ca2+
ATP
L-dopa
Storage
complex
H+
VMAT1
ATP
Ca2+
PNMT
TH
ATP
Epi
Exocytosis
L-Tyrosine
Epinephrine
Norepinephrine

# 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).

- MAO is present on the **outer mitochondrial membrane** of many cells.

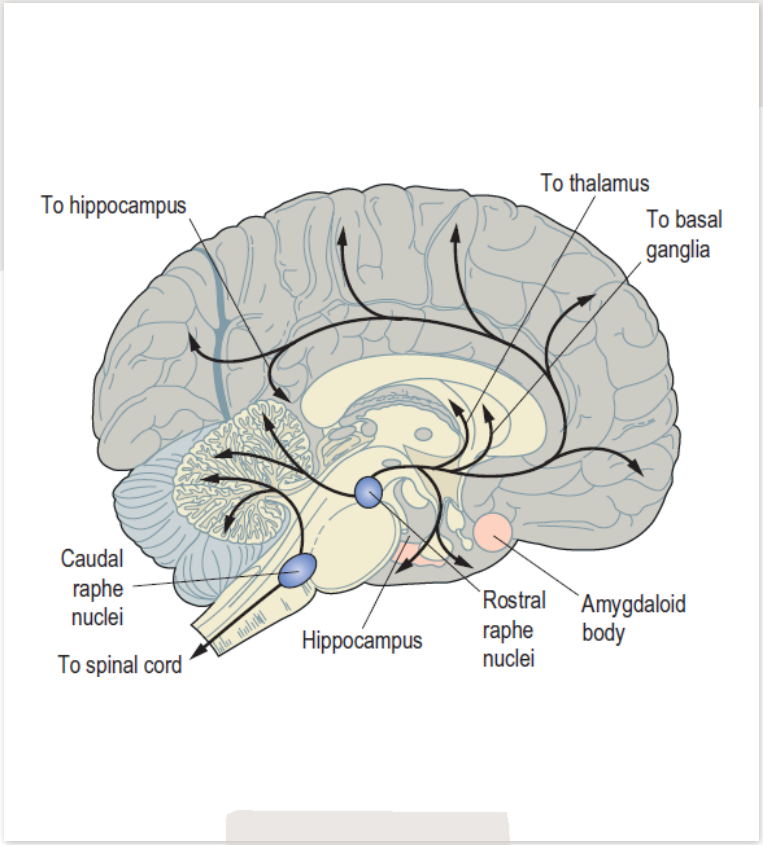
  In the presynaptic terminal, MAO inactivates catecholamines that are not protected in storage vesicles.

- 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.
- **Homovanillylmandelic acid** (**HVA**) is an indicator of dopamine degradation.
- The end product of epinephrine and norepinephrine is **vanillylmandelic acid** (**VMA**).

# II. Serotonin




Synthesized in serotoninergic neurons 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.

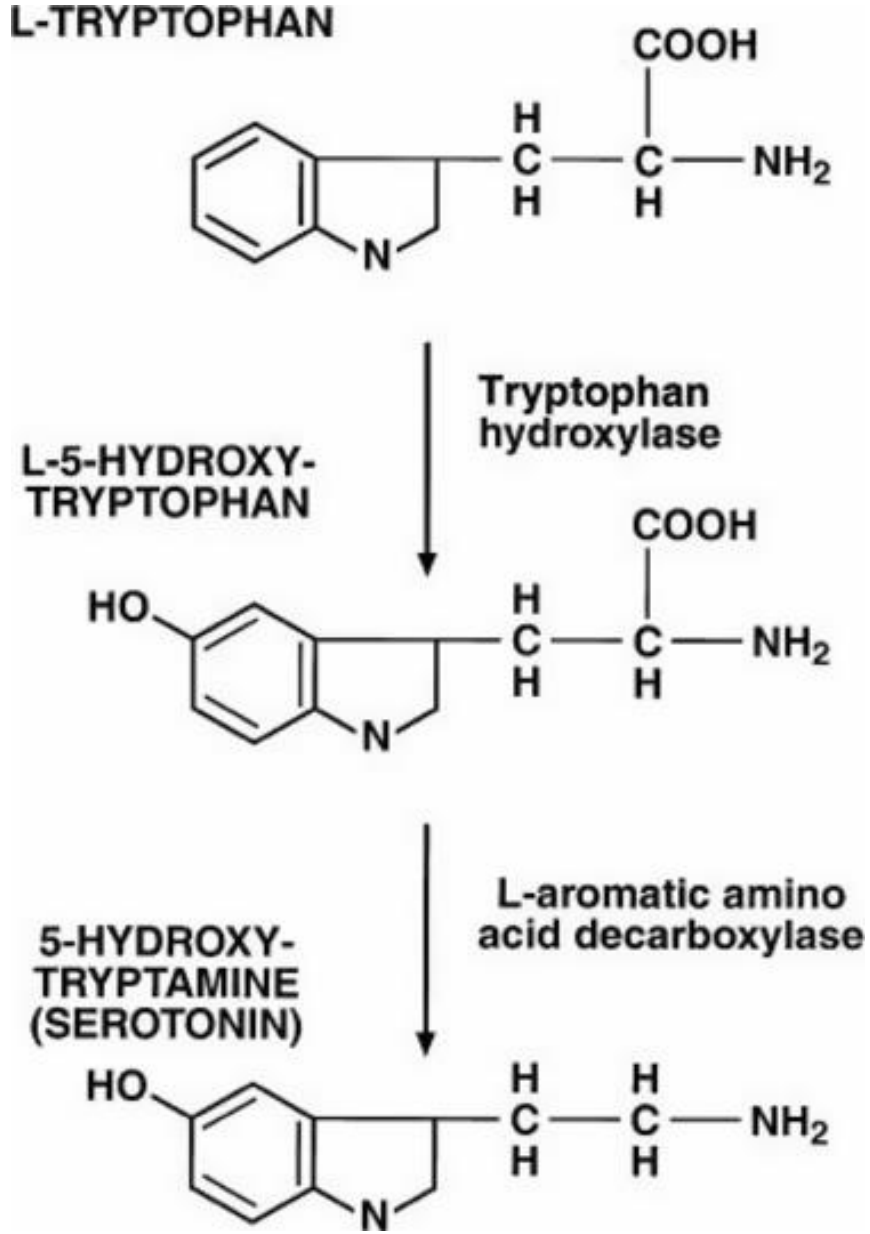
Serotonin is synthesized from the essential amino acid tryptophan.

# Metabolism of Serotonin

1. The first enzyme of the pathway, tryptophan hydroxylase. The rate limiting step is the conversion of tryptophan to 5-hydroxytryptophan.

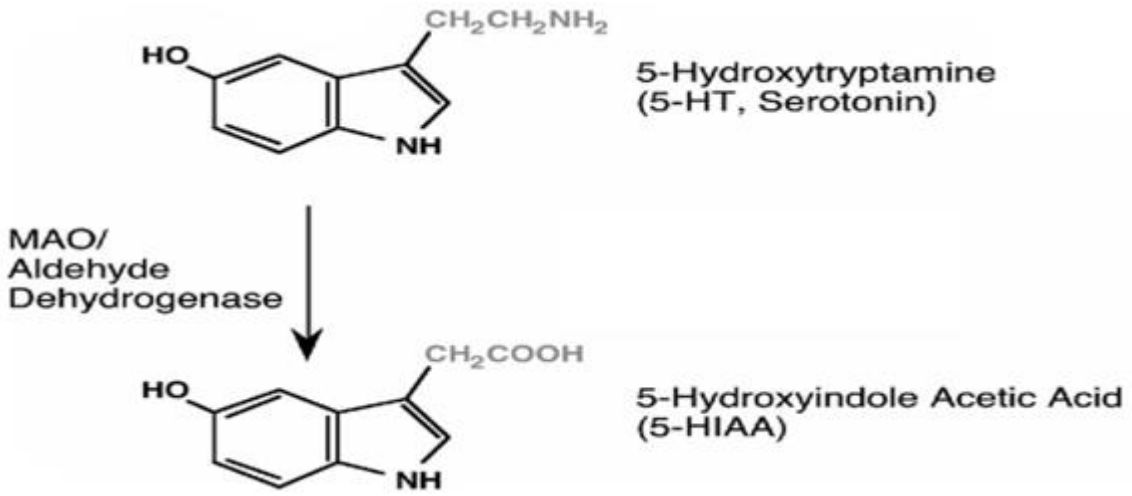
2. The second step is conversion to serotonin by the aromatic L-amino acid decarboxylase.

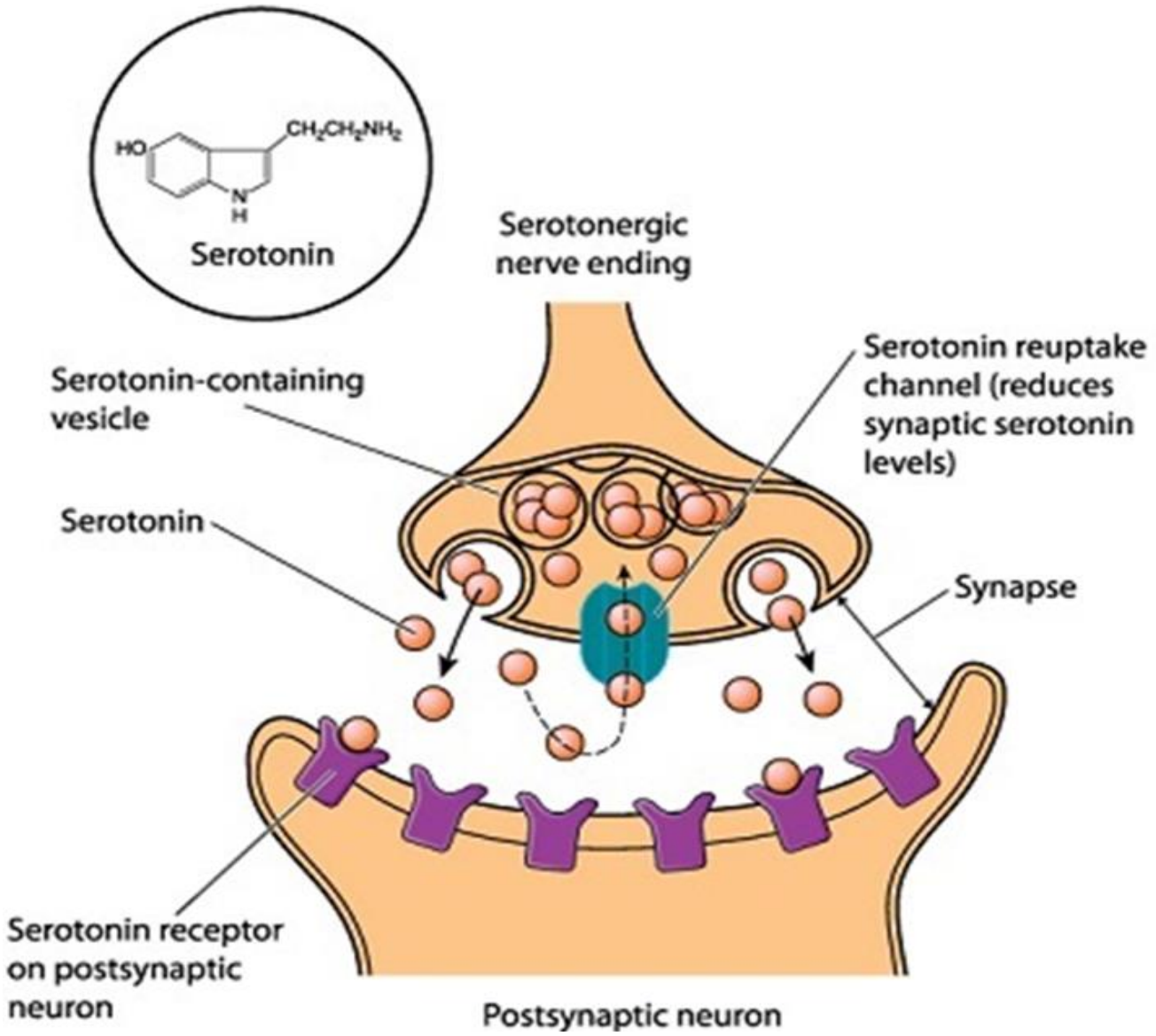
- Serotonin, like the catecholamine neurotransmitters, can be ***inactivated by MAO***.



# Metabolism of Serotonin

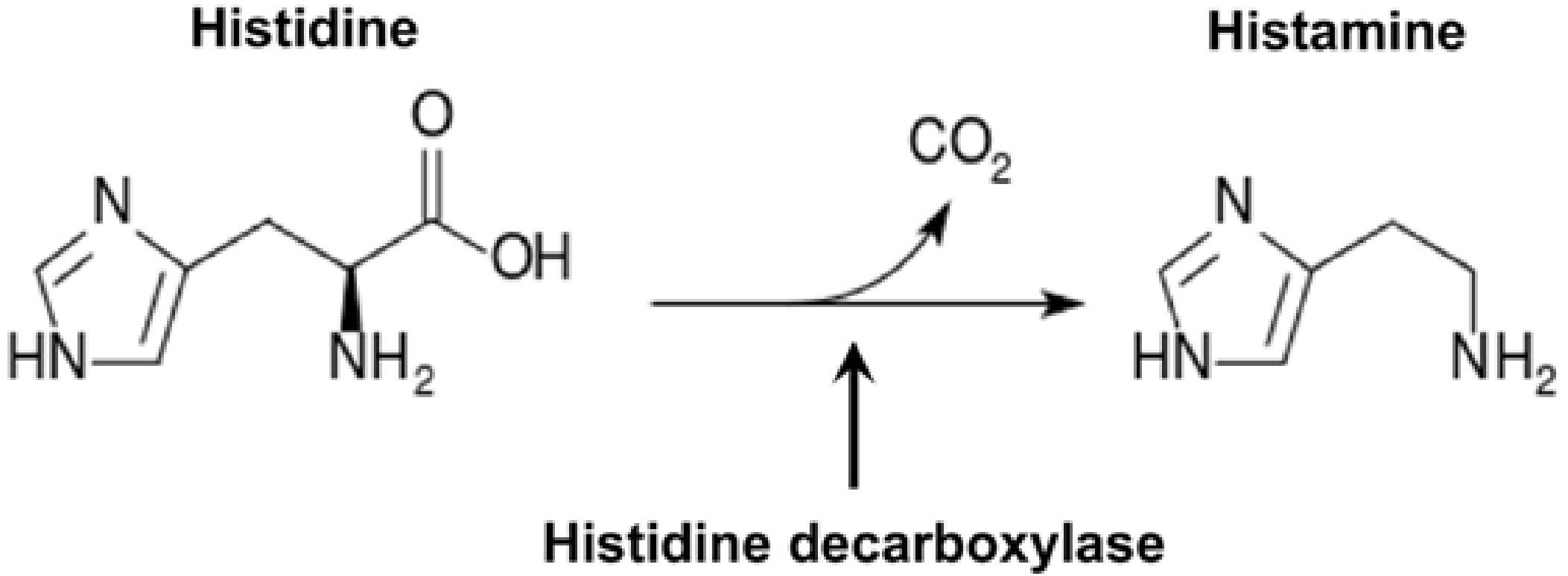
- Serotonin is transported into the vesicles by the VMAT.
- Once serotonin is returned to the nerve terminal, it is either taken back into the vesicles or is inactivated by MAO to form 5-hydroxyindoleacetic acid (5-HIAA).
- This substance is the principal urinary metabolite of serotonin.




HO
CH2CH2NH2
N
H
Serotonin
Serotonergic nerve ending
Serotonin-containing vesicle
Serotonin reuptake channel (reduces synaptic serotonin levels)
Serotonin
Synapse
Serotonin receptor on postsynaptic neuron
Postsynaptic neuron

# 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.**


Histidine
Histamine
O
N
OH
HN
NH2
CO2
N
HN
NH2
Histidine decarboxylase

# Metabolism of Histamine

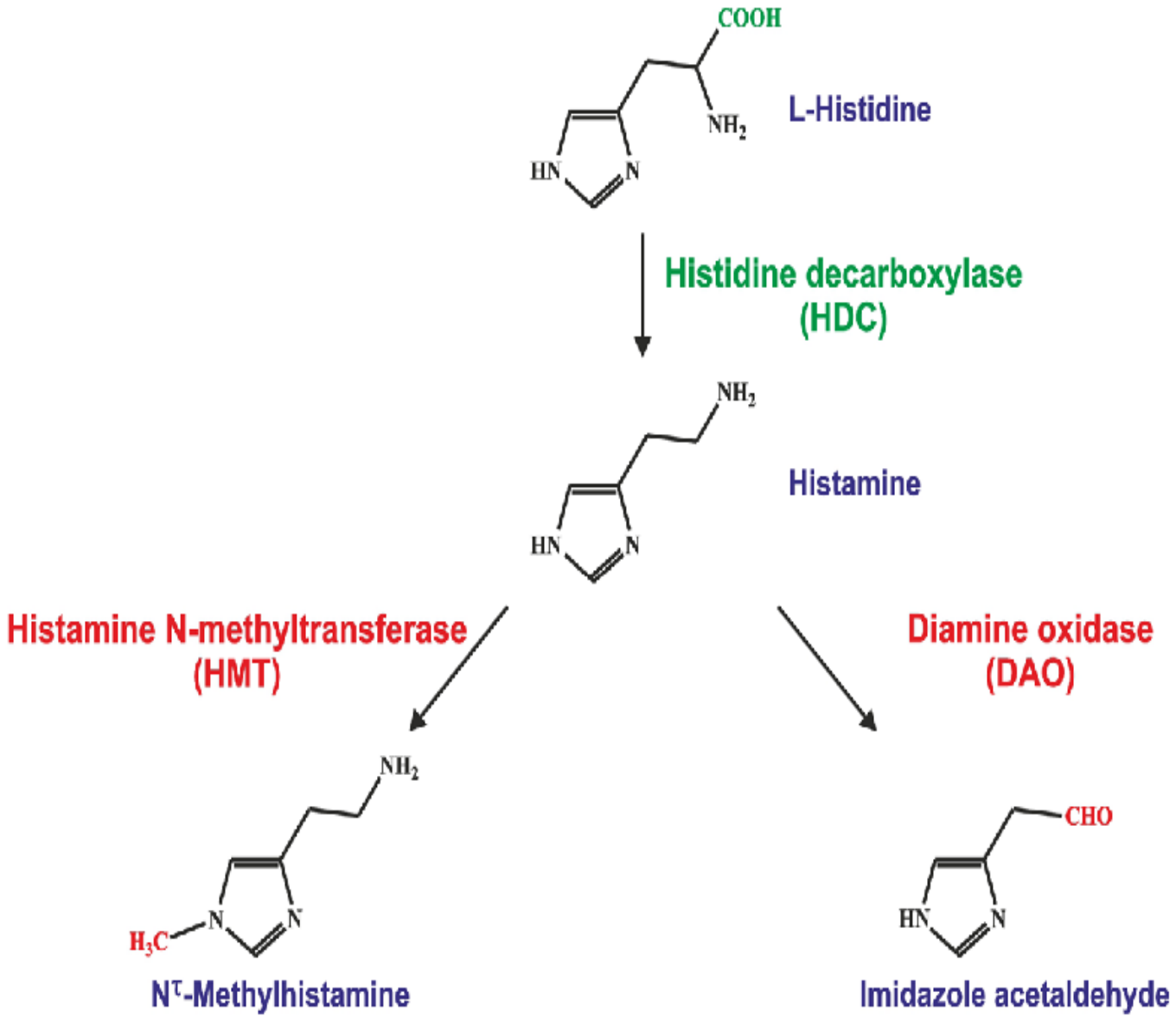
Unlike other neurotransmitters, histamine **does not appear to be recycled into the presynaptic terminal to any great extent**.

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.


COOH
NH2
HN
N
L-Histidine
Histidine decarboxylase
(HDC)
NH2
HN
N
Histamine
Histamine N-methyltransferase
(HMT)
Diamine oxidase
(DAO)
NH2
H3C
N
N
Nτ-Methylhistamine
CHO
HN
N
Imidazole acetaldehyde

# 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