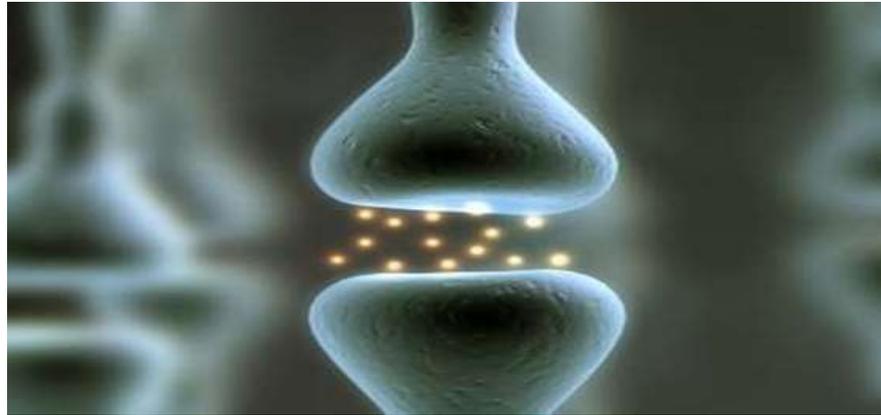


# NEUROTRANSMITTERS



**DR/ HEBA M. KAREEM**

# INTRODUCTION

**Neurotransmitters** are chemical messengers that transmit signals from a neuron to a target cell across a **synapse**.

Target cell may be a neuron or some other kind of cell like a muscle or gland cell.

Necessary for rapid communication in synapse.  
Neurotransmitters are packaged into **synaptic vesicles** - presynaptic side of a synapse.



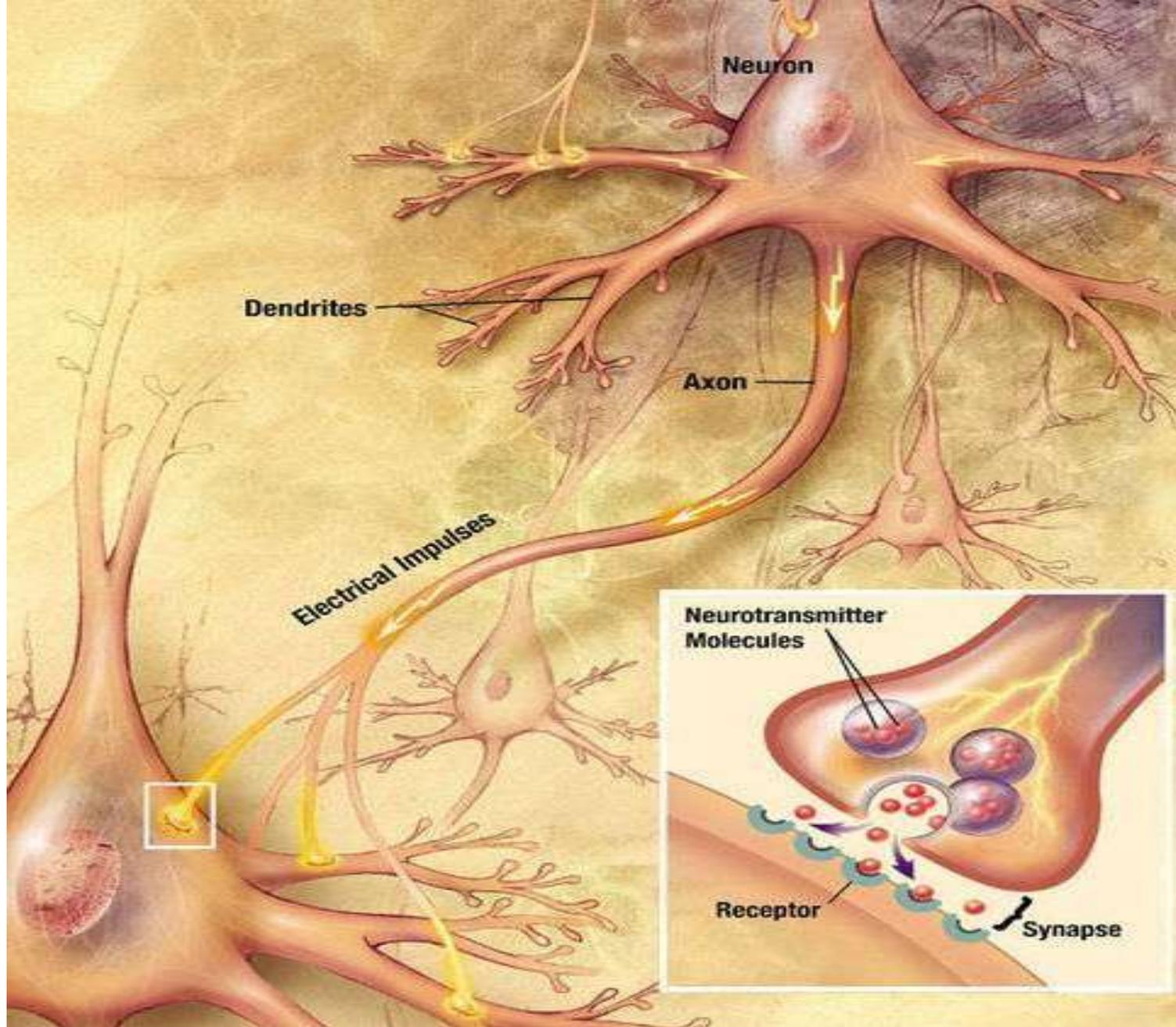
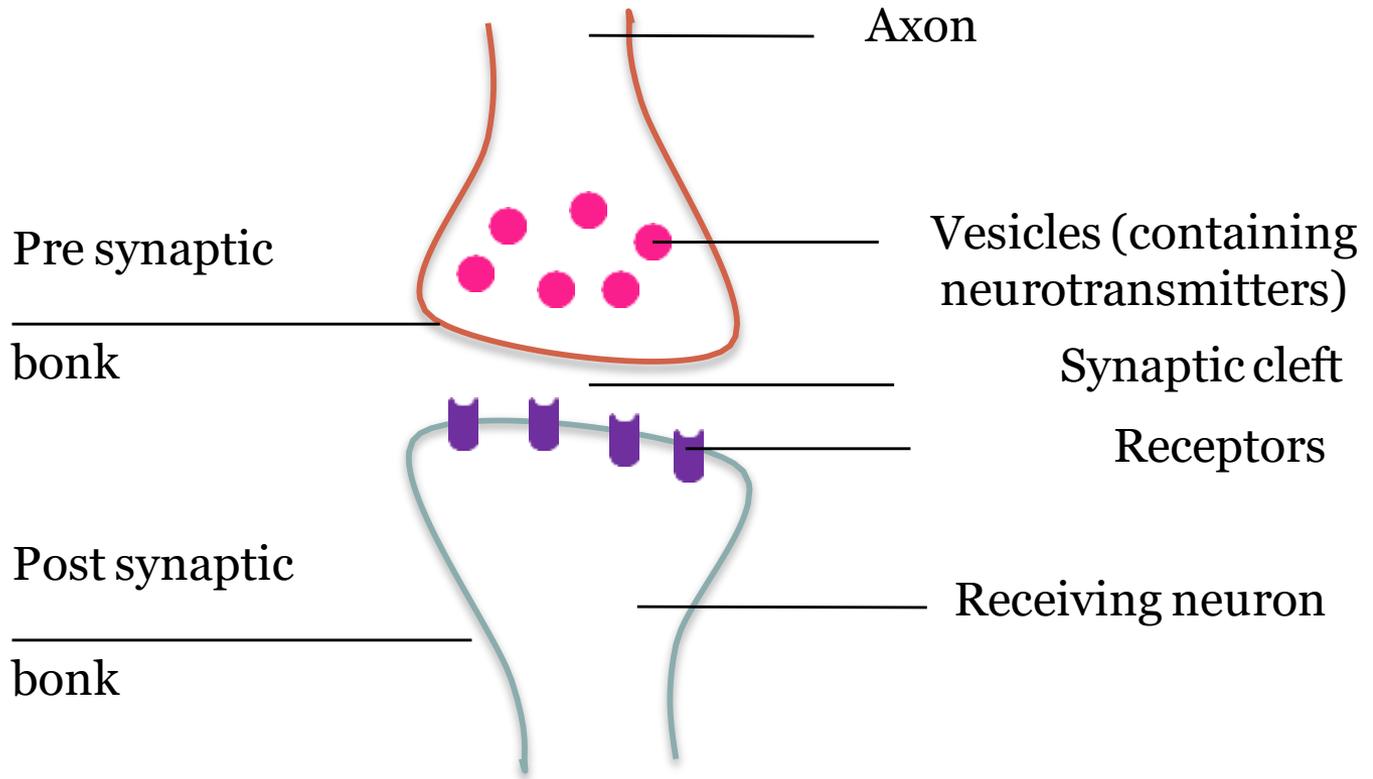


Illustration of the major elements in chemical synaptic transmission.

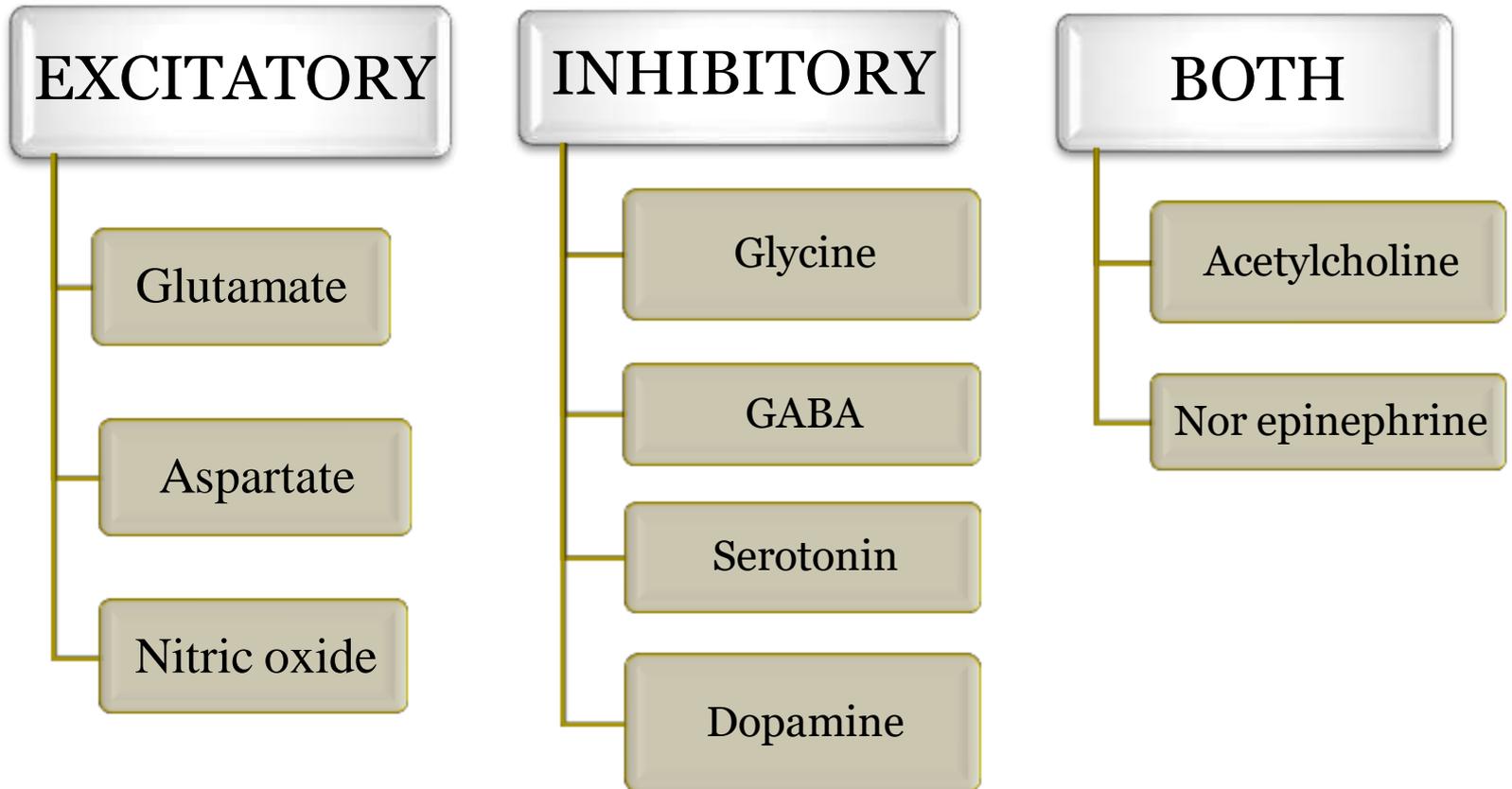
# *A schematic representation of a chemical synapse*



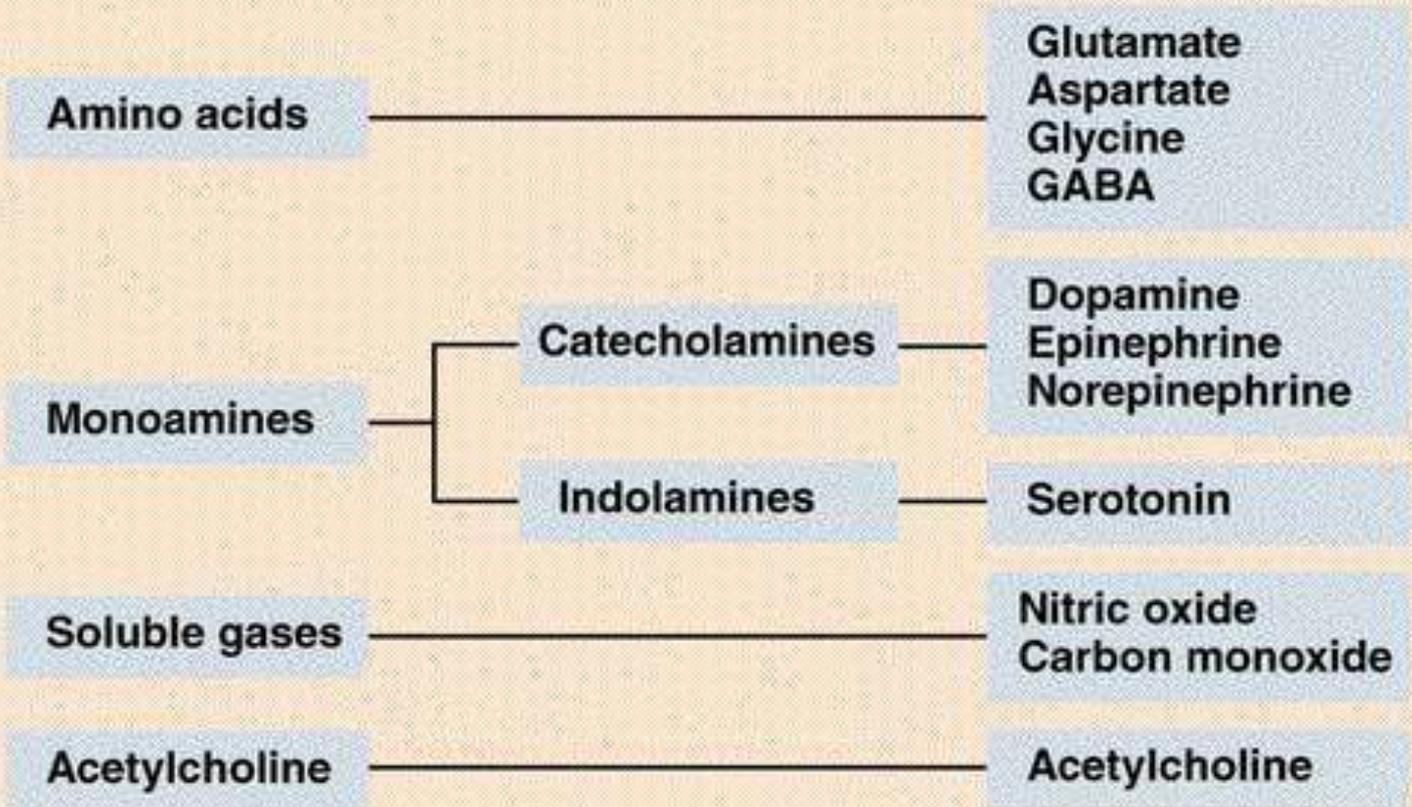
# PROPERTIES OF NEUROTRANSMITTERS

- 1) Synthesized in the presynaptic neuron
- 2) Localized to vesicles in the presynaptic neuron
- 3) Released from the presynaptic neuron under physiological condition
- 4) Rapidly removed from the synaptic cleft by uptake or degradation
- 5) Presence of receptor on the post-synaptic neuron.
- 6) Binding to the receptor elicits a biological response

# TYPES OF NEUROTRANSMITTERS

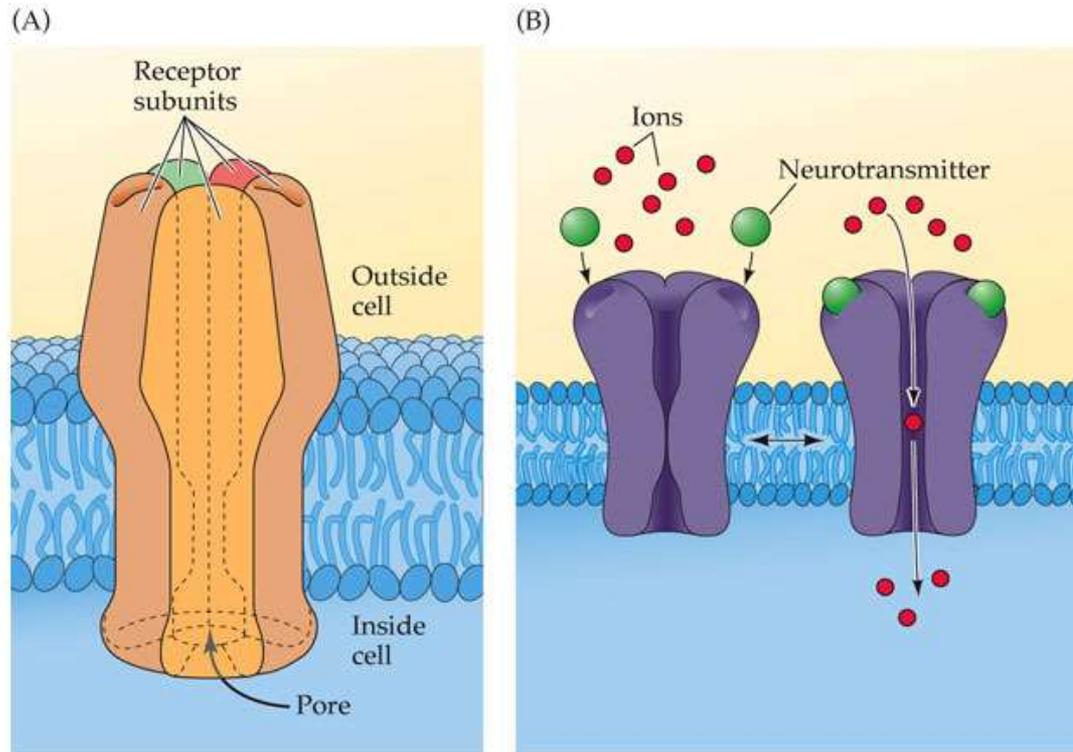


## ► Classes of Neurotransmitters



# Receptors of neurotransmitters

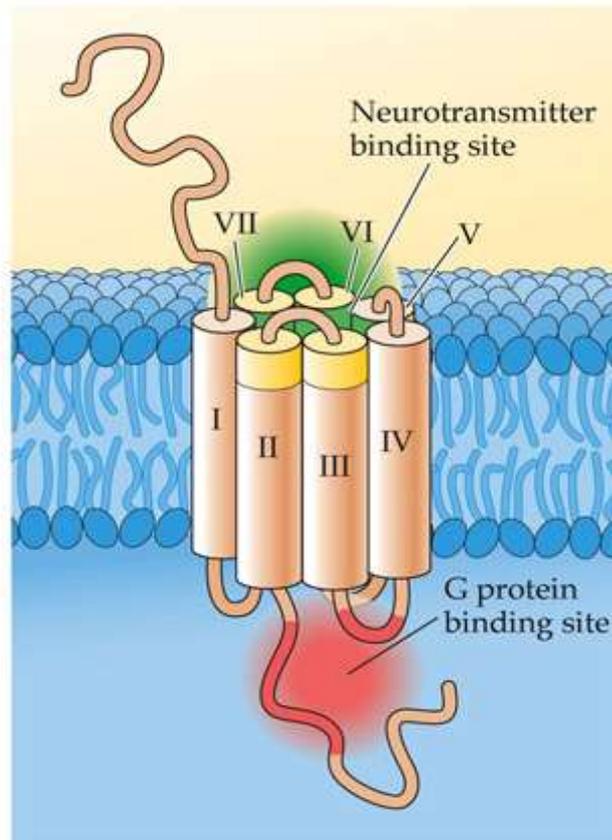
## A- Ionotropic Receptors



PSYCHOPHARMACOLOGY, Figure 3.9 © 2005 Strauer Associates, Inc.

1. Work very fast; important role in fast neurotransmission
2. Each is made of several subunits (together form the complete receptor)
3. At center of receptors is channel or pore to allow flow of neurotransmitter
4. At rest - receptor channels is closed
5. When neurotransmitter bind -- channel immediately opens
6. When ligand leaves binding site -- channel quickly closes

## B- Metabotropic Receptors



PSYCHOPHARMACC

1. Work more slowly than ionotropic receptors
2. Comprise a single protein subunit, winding cell membrane seven times (**transmembrane domains**)
3. They do not possess a channel or pore

# MODE OF ACTION



## ► Seven Processes in Neurotransmitter Action

1. Neurotransmitters are synthesized from precursors under the influence of enzymes

2. Stored in vesicles

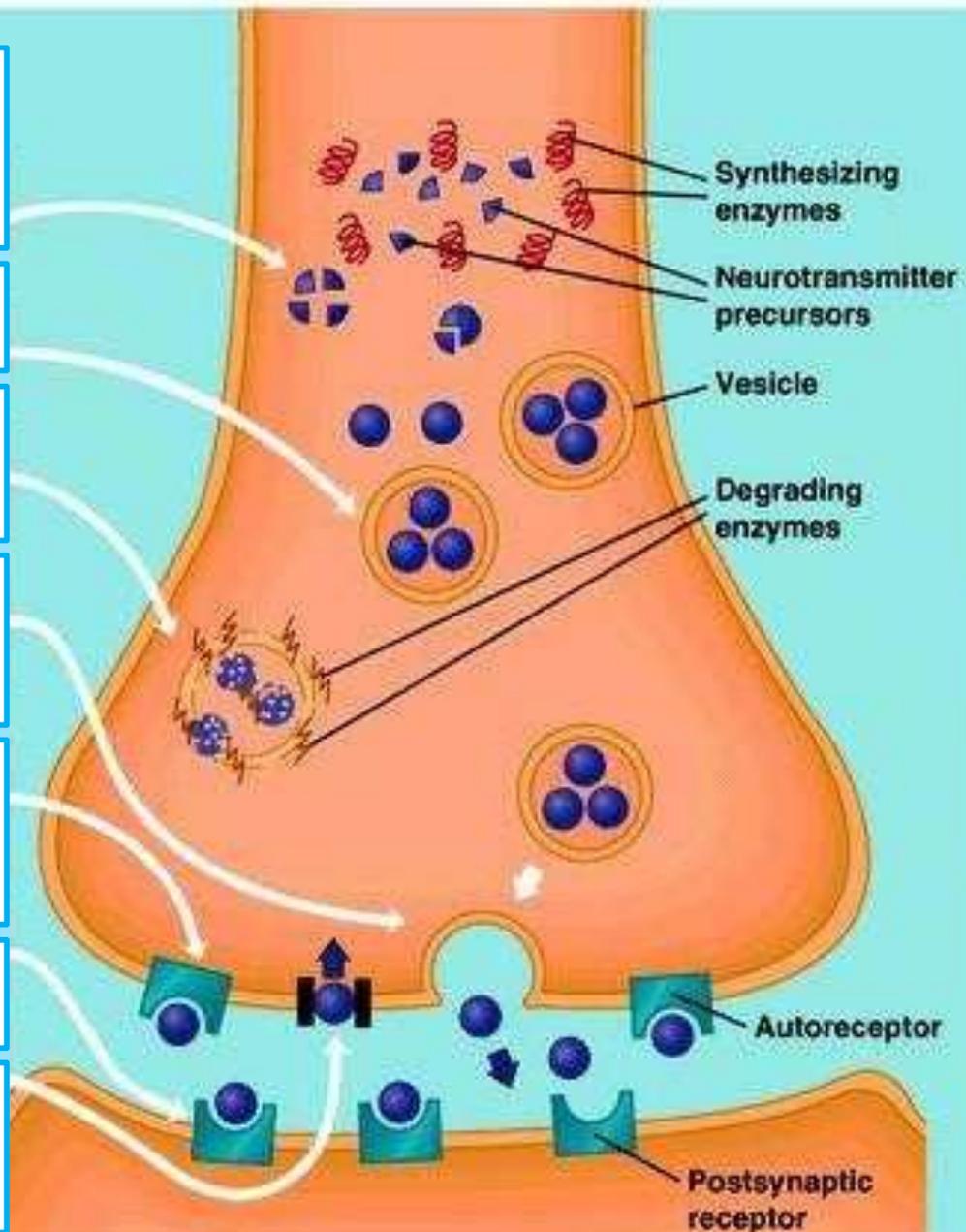
3. Neurotransmitter molecules that leak from their vesicles are destroyed by enzymes

4. Action potential cause vesicle to fuse with synapse and release neurotransmitters

5. Some of it binds with auto receptor and inhibit subsequent neurotransmitter release

6. Rest of it bind to post synaptic receptors.

7. Released neurotransmitters are deactivated either by re uptake or enzyme degradation.



# Steps in neurotransmitter processing are:

***Synthesis:*** Neurotransmitters are synthesized by the enzymatic transformation of precursors.

***Storage:*** They are packaged inside synaptic vesicles.

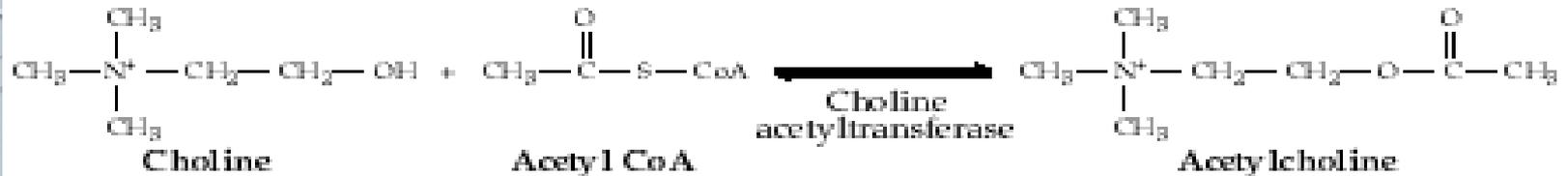
***Release:*** They are released from presynaptic terminal by exocytosis when calcium enters axon terminal during an action potential  
Diffuse across the synaptic cleft to the postsynaptic membrane.

***Binding:*** They bind to receptor proteins.

***Inactivation:*** The neurotransmitter is degraded either by being broken down enzymatically, or reused by active reuptake.

# ACETYLCHOLINE (ACH)

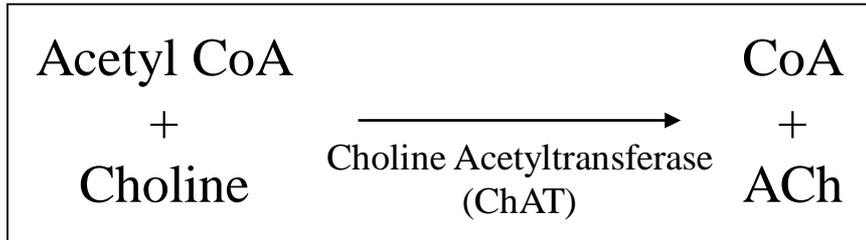
- Acetylcholine was the first neurotransmitter to be discovered.
- 1921 by a German biologist named **Otto Loewi**.



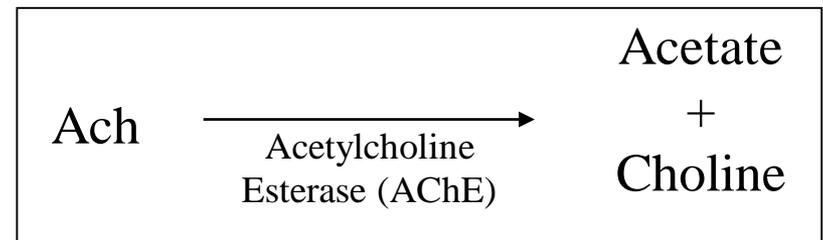
- -Uses *choline* as a precursor - **cholinergic** neurotransmitter.
- -Used by **the Autonomic Nervous System**, as an inhibitory neurotransmitter.
- -Responsible for stimulation of muscles, including the muscles of the gastro-intestinal system. -Used everywhere in the brain.
- -Related to **Alzheimer's Disease**. Acetylcholine is decreased in both concentration and function in patients with Alzheimer's disease.
- **Too much**: muscle contractions- e.g. organophosphorus (OP) poisoning
- **Too little**: paralysis: curarae and botulism toxin

# Acetylcholine

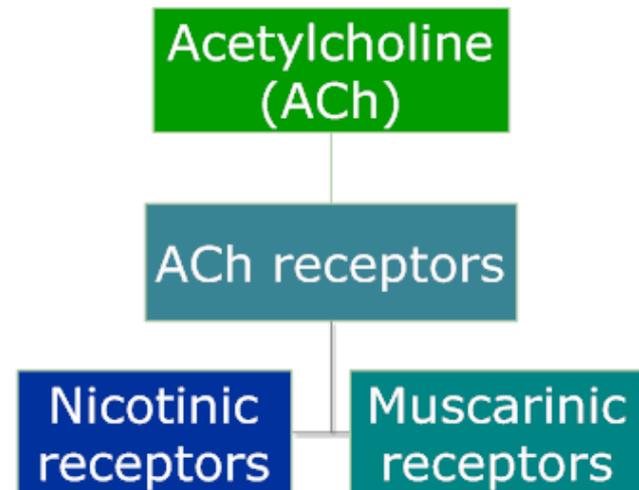
## Synthesis



## Removal



- 2 receptor types
  - Nicotinic (ionotropic): Excitatory; found predominately on neuromuscular junctions
  - Muscarinic (metabotropic): Both excitatory and Inhibitory; found predominately in brain



# Monoamines

They are neurotransmitters and neuromodulators that contain one amino group connected to an aromatic ring by a two-carbon chain (such as -CH<sub>2</sub>-CH<sub>2</sub>-).

- Catecholamines

Dopamine - DA

- Dopaminergic

Norepinephrine - NE

- Noradrenergic

Epinephrine - E

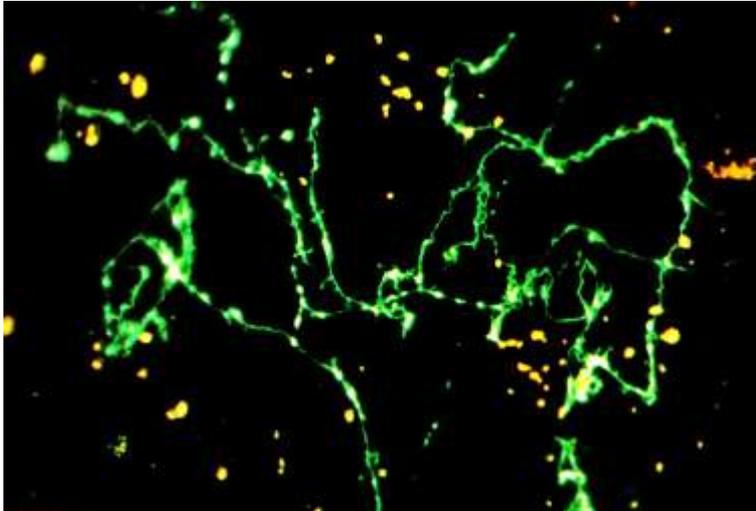
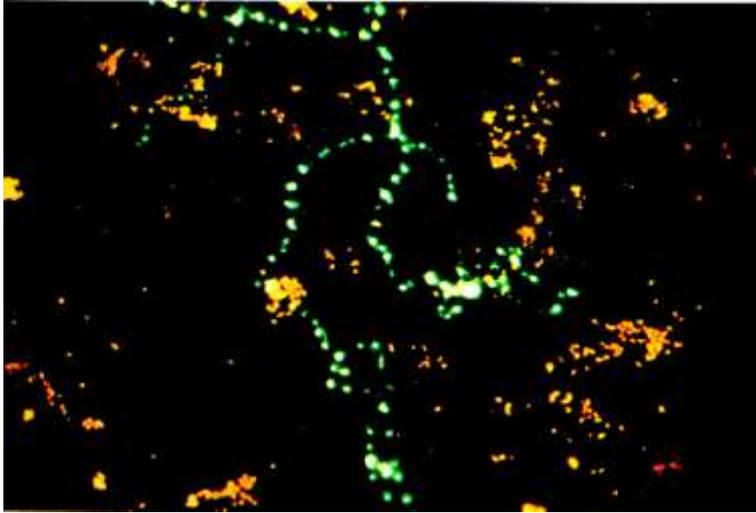
- Adrenergic ~

- Indolamines

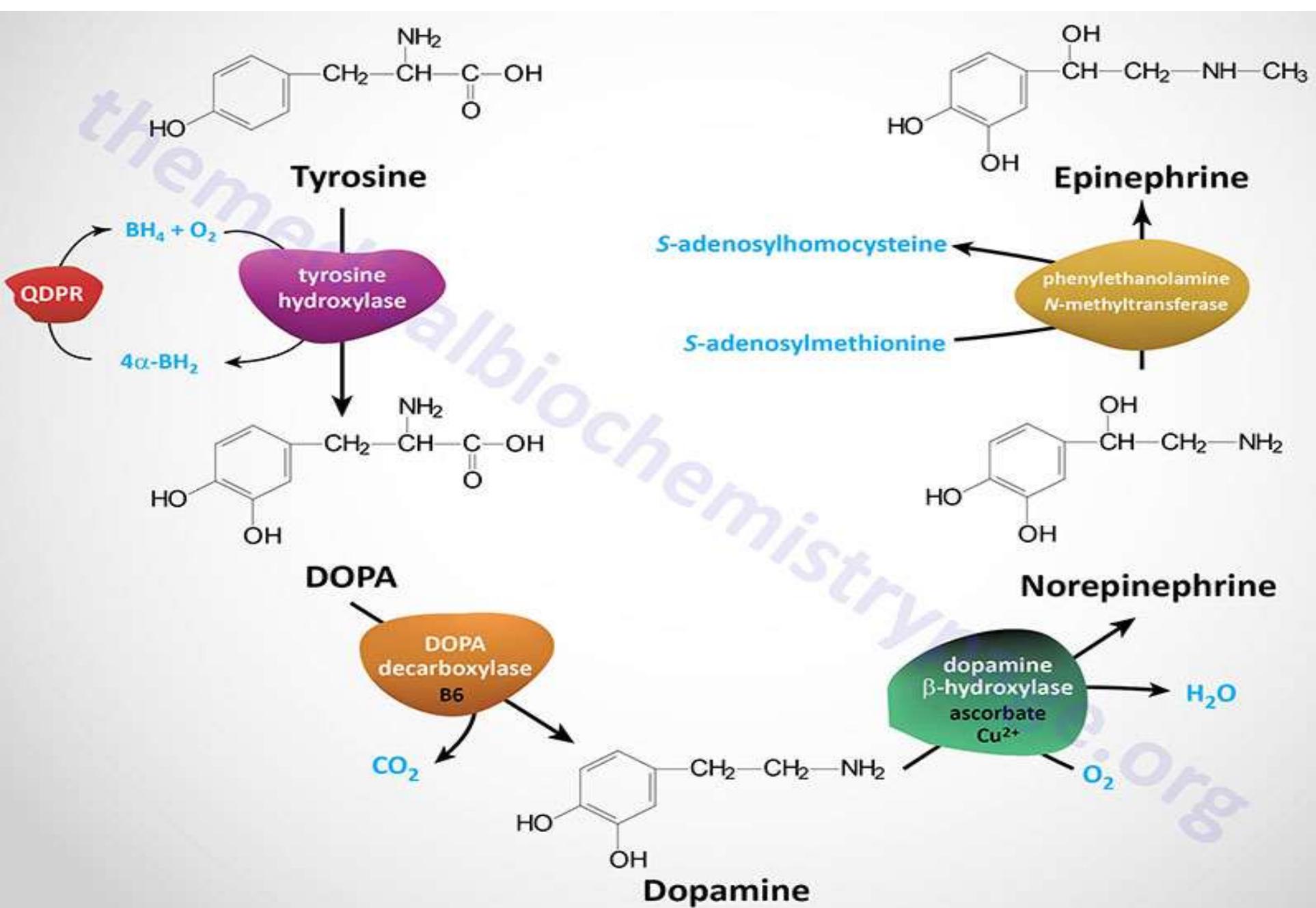
Serotonin - 5-HT

- Serotonergic

# Monoamines (DA, NE, 5-HT)

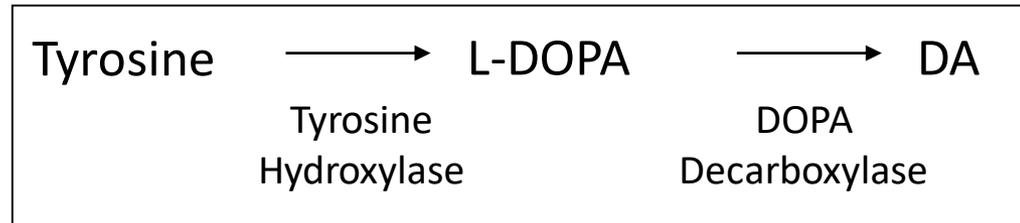


- Modulatory (can have both excitatory and inhibitory effects- varies by receptor)
- Recycled by reuptake transporter
- Excess NT in terminal broken down by
  - monoamine oxidase (MAO)
  - catechol-O-methyltransferase - COMT



# Dopamine (DA)

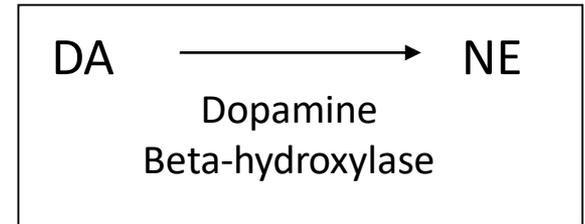
Biosynthesis:



- Dopamine reuptake transporter (DAT)
- 5 receptor types (D1–D5, all metabotropic)
- **Too little**: Parkinson's disease:
- Treatment: Increase available DA via L-Dopa
- **Too much**: schizophrenia
- Treatment: Reduce available DA via antidopaminergics/antipsychotics

# Norepinephrine

- Generally **excitatory** behavioral effects
- Biosynthesis:
- Many receptor types (**metabotropic**)
  - $\alpha_1$ ,  $\beta_{1-2}$  (postsynaptic, excitatory)     $\alpha_2$  (autoreceptor, inhibitory)
  - Norepinephrine is strongly associated with bringing our nervous systems into "high alert."
  - It increases heart rate and blood pressure.
  - It is also important for forming memories.

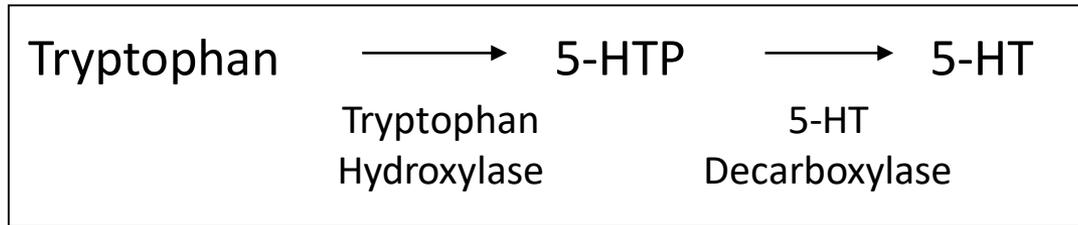


## Catabolism

- It occurs through the actions of catecholamine-O-methyltransferase, (COMT) and monoamine oxidase, (MAO). Both of these enzymes are widely distributed throughout the body. However, COMT is not found in nerve endings as is MAO.

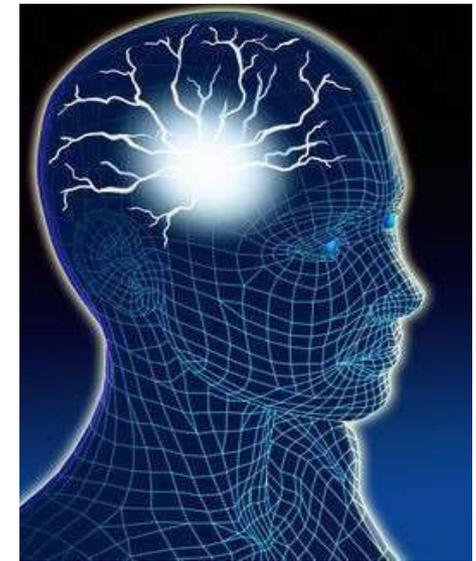
# Serotonin (5-HT)

- Varying excitatory and inhibitory behavioral effects
- Biosynthesis:



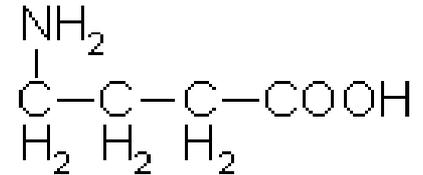
- At least 14 receptor types, all metabotropic and postsynaptic except:
  - 5-HT<sub>1A,B,D</sub> (autoreceptors) – found in CNS
  - 5-HT<sub>3</sub> (inhibitory, ionotropic) – found in the intestines
  - **Too little** is linked to depression and sleep disorders
  - **Too much**: Serotonin syndrome: confusion, twitching and trembling, dilated pupils, shivering, headache, sweating and diarrhea., irregular and fast heartbeat

# GLUTAMATE

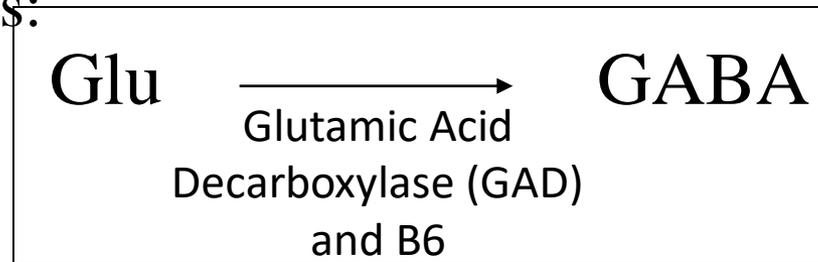


- It is an amino acid
- It is the most commonly found **excitatory** neurotransmitter in the brain.
- It is involved in most aspects of normal brain function including cognition, memory and learning.
- Glutamate is formed from  $\alpha$ -ketoglutarate, an intermediate of Krebs's cycle.

# GABA (Gamma Aminobutyric Acid)



- Principal Inhibitory NT
- Biosynthesis:

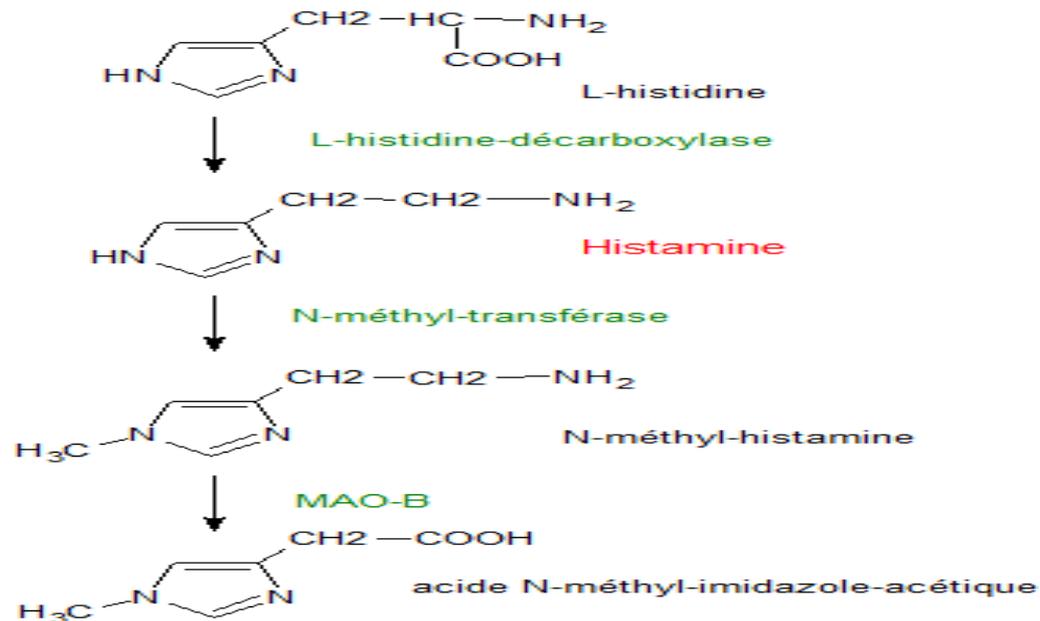


- Removed by reuptake
- 2 receptor types
  - GABA<sub>A</sub> GABA<sub>C</sub> (ionotropic; Cl<sup>-</sup> channel)
  - GABA<sub>B</sub> (metabotropic)

If GABA is lacking in certain parts of the brain, **epilepsy** results.

## 4- Histamine

- Histamine forming cells are in posterior hypothalamus also found in gastric mucosa and in mast cells.
- Formed by histidine decarboxylation using histidine decarboxylase, while, degraded by N-methyl transferase and histaminase (MAO-B).



- Four known types of histamine receptors are found.
- Its function in brain is not very clear.
- Its main function is that it is excitatory.
- It increases during inflammation (inflammatory states causes depletion of tryptophan and serotonin)

# Neuropeptides

- Low concentration in brain (picomolar)
- Large vesicles
- Co-localized with other transmitters
- Modulatory functions
- Mostly inhibitory
- Virtually all metabotropic
- Slow acting, long duration
- Examples: Enkephalins, Endorphins, Oxytocin, Vasopressin, Opioids

# *Endorphins*

- **Morphine** and **heroin** are agonists that bind to receptor sites, thereby increasing endorphin activity



Neurotransmitter	Function
Acetylcholine	Transmitter at muscles; in brain, involved in learning, etc.
<b>Monamines</b>	
Serotonin	Involved in mood, sleep, and arousal, and in aggression, depression, obsessive-compulsive disorder, and alcoholism.
Dopamine	Contributes to movement control and promotes reinforcing effects of abused drugs, food, and sex; involved in schizophrenia and Parkinson's disease.
Norepinephrine	A hormone released during stress. Functions as a neurotransmitter in the brain to increase arousal and attentiveness to events in the environment; involved in depression.
Epinephrine	A stress hormone related to norepinephrine; plays a minor role as a neurotransmitter in the brain.
<b>Amino Acids</b>	
Glutamate	The principal excitatory neurotransmitter in the brain and spinal cord. Vitaly involved in learning, and implicated in schizophrenia.
Gamma-aminobutyric acid (GABA)	The predominant inhibitory neurotransmitter. Its receptors respond to alcohol and the class of tranquilizers called benzodiazepines. Deficiency in GABA or receptors is one cause of epilepsy.
Glycine	Inhibitory transmitter in the spinal cord and lower brain. The poison strychnine causes convulsions and death by affecting glycine activity.
<b>Peptides</b>	
Endorphins	Neuromodulators that reduce pain and enhance reinforcement.
Substance P	Transmitter in neurons sensitive to pain.
Neuropeptide Y	Initiates eating and produces metabolic shifts.
<b>Gas</b>	
Nitric Oxide	One of two known gaseous transmitters, along with carbon monoxide. Can serve as a retrograde transmitter, influencing the presynaptic neuron's release of neurotransmitter. Viagra enhances male erections by increasing nitric oxide's ability to relax blood vessels and produce penile engorgement.

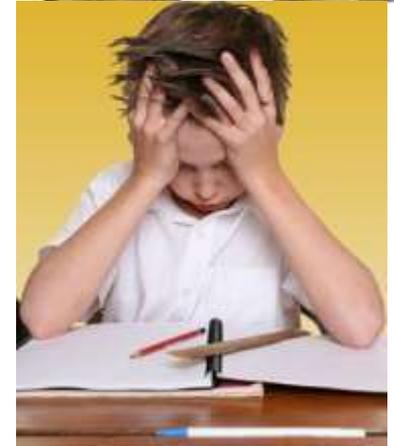
# DISEASES ASSOCIATED WITH NEUROTRANSMITTERS

## NEUROTRANSMITTER

- Acetylcholine
- Dopamine
- GABA
- Serotonin
- Glutamate

## DISEASE

- Alzheimer's
- Parkinson's disease
- Schizophrenia
- Epilepsy
- Migraines
- Depression
- Migraine
- stroke



# RECENT DEVELOPMENTS

- A team of scientists from **University of Barcelona** in 2011, has discovered *that D-aspartic acid (D-Asp)* is a novel neurotransmitter that could potentially be used in the **fight against** neurological diseases such as Parkinson's and schizophrenia.
- According to a new study by researchers at the **Ohio State University Comprehensive Cancer Center in 2011**, doses of a neurotransmitter dopamine might offer a way to boost the effectiveness of anticancer drugs and radiation therapy.



THANK U