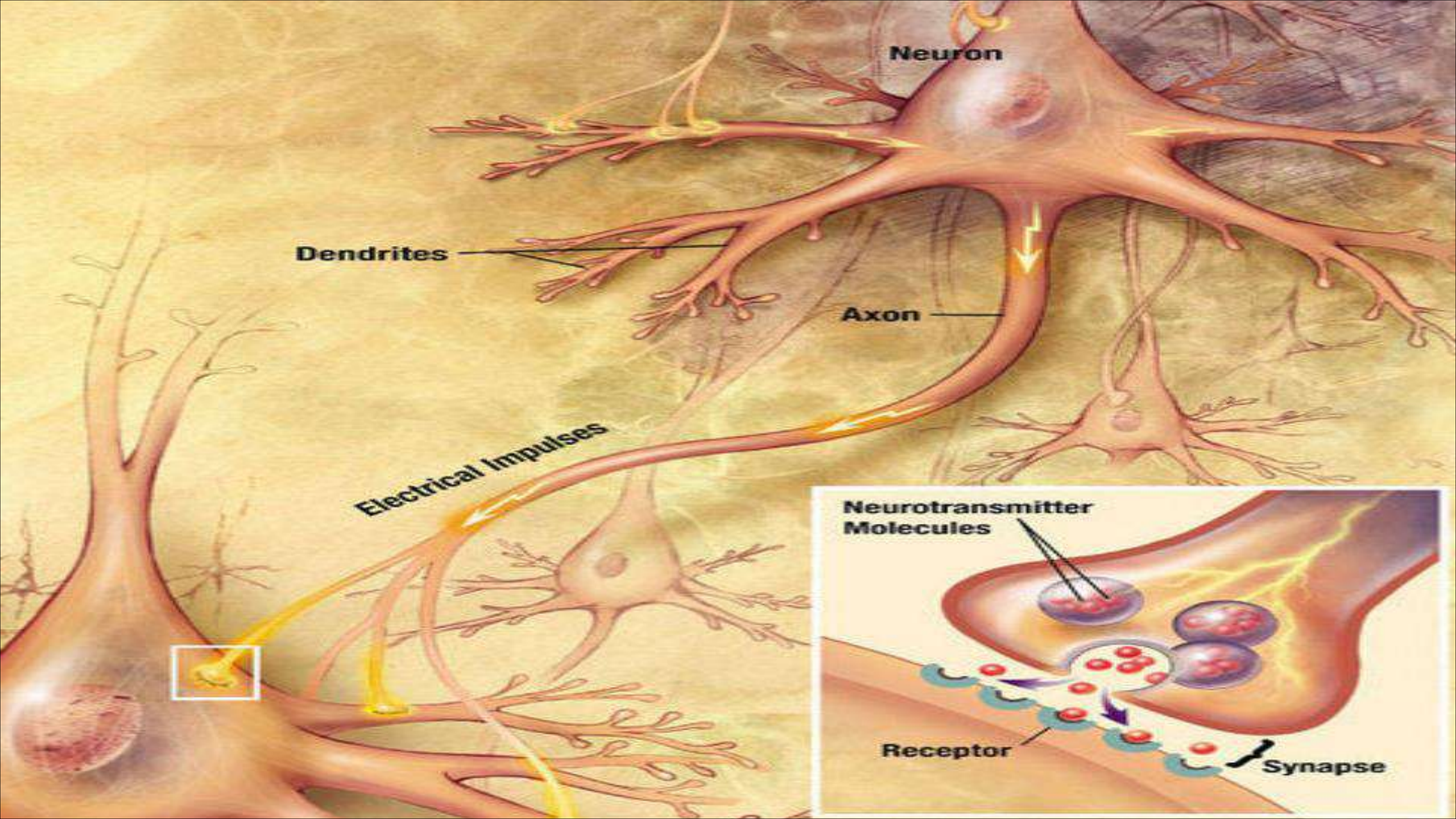
Amino Acid Neurotransmitters

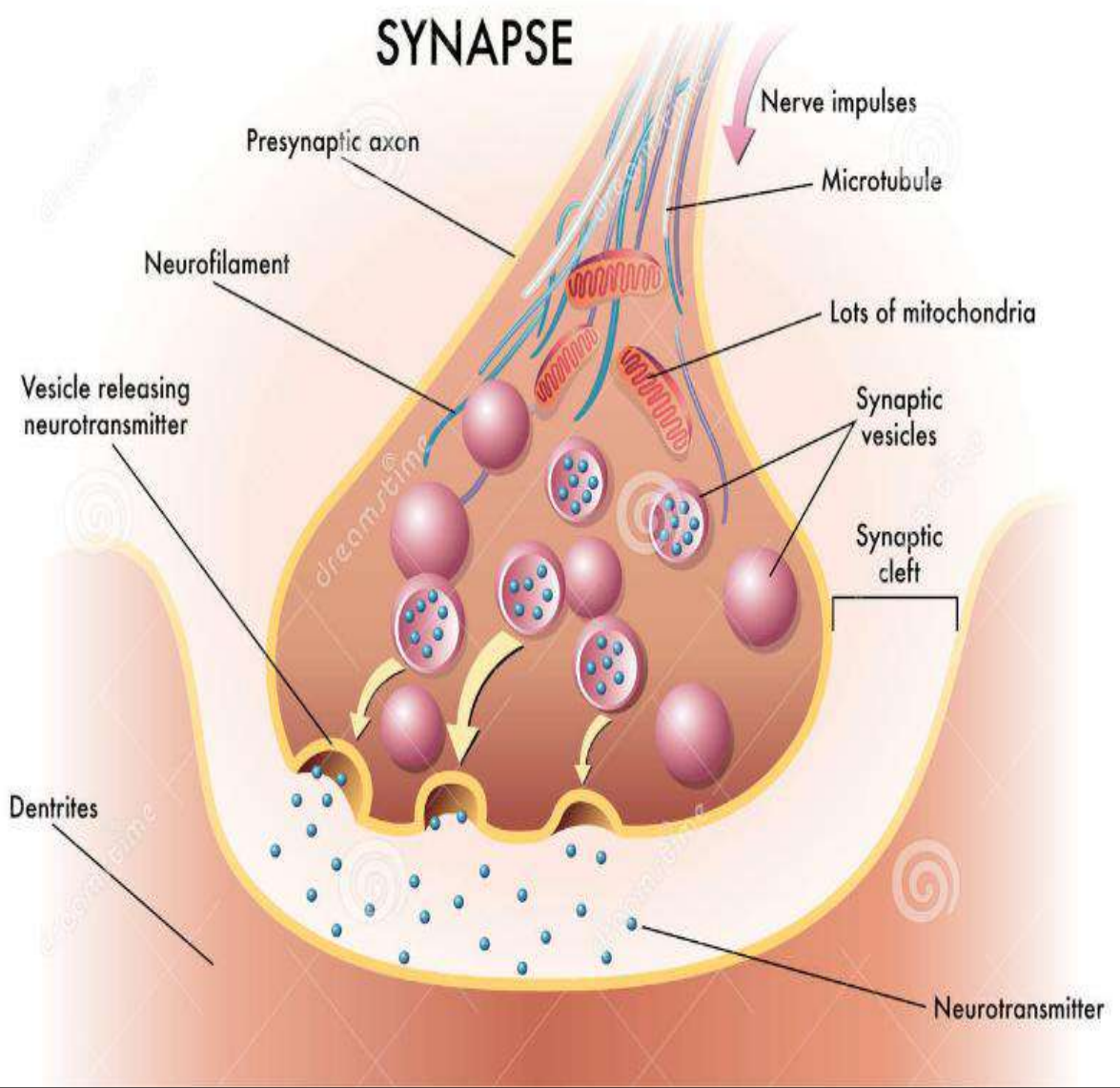
Neurotransmitters

- NEUROTRANSMITTERS are the brain chemicals that communicate information throughout our brain and body.
- They relay signals between nerve cells, called “neurons.”
- 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.

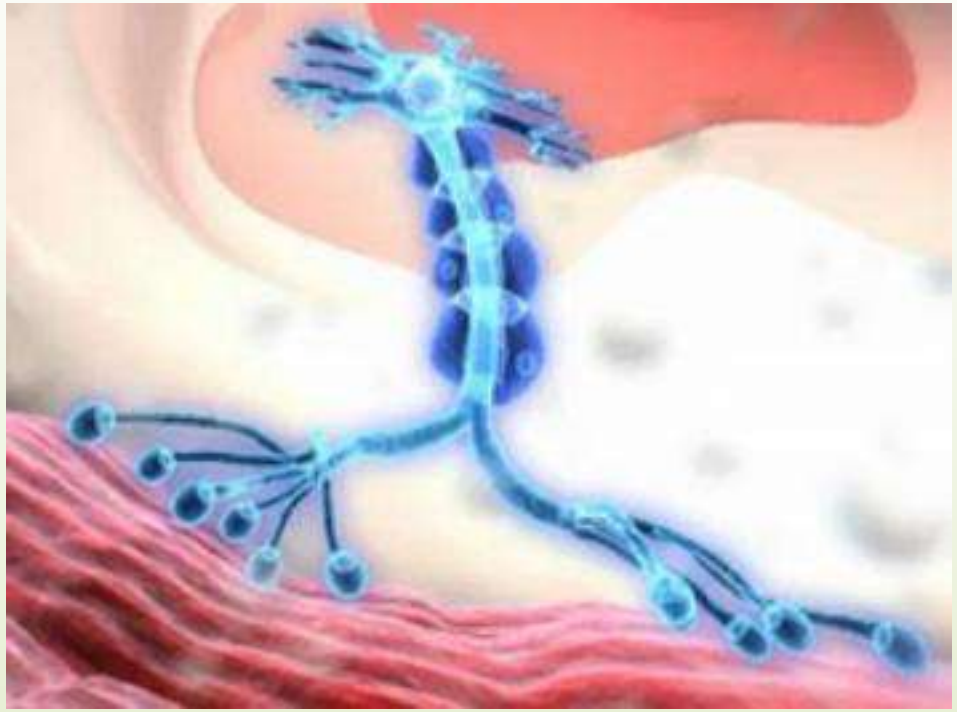

Neuron
Dendrites
Axon
Electrical Impulses
Neurotransmitter Molecules
Receptor
Synapse

Neurotransmitters (cont..)

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

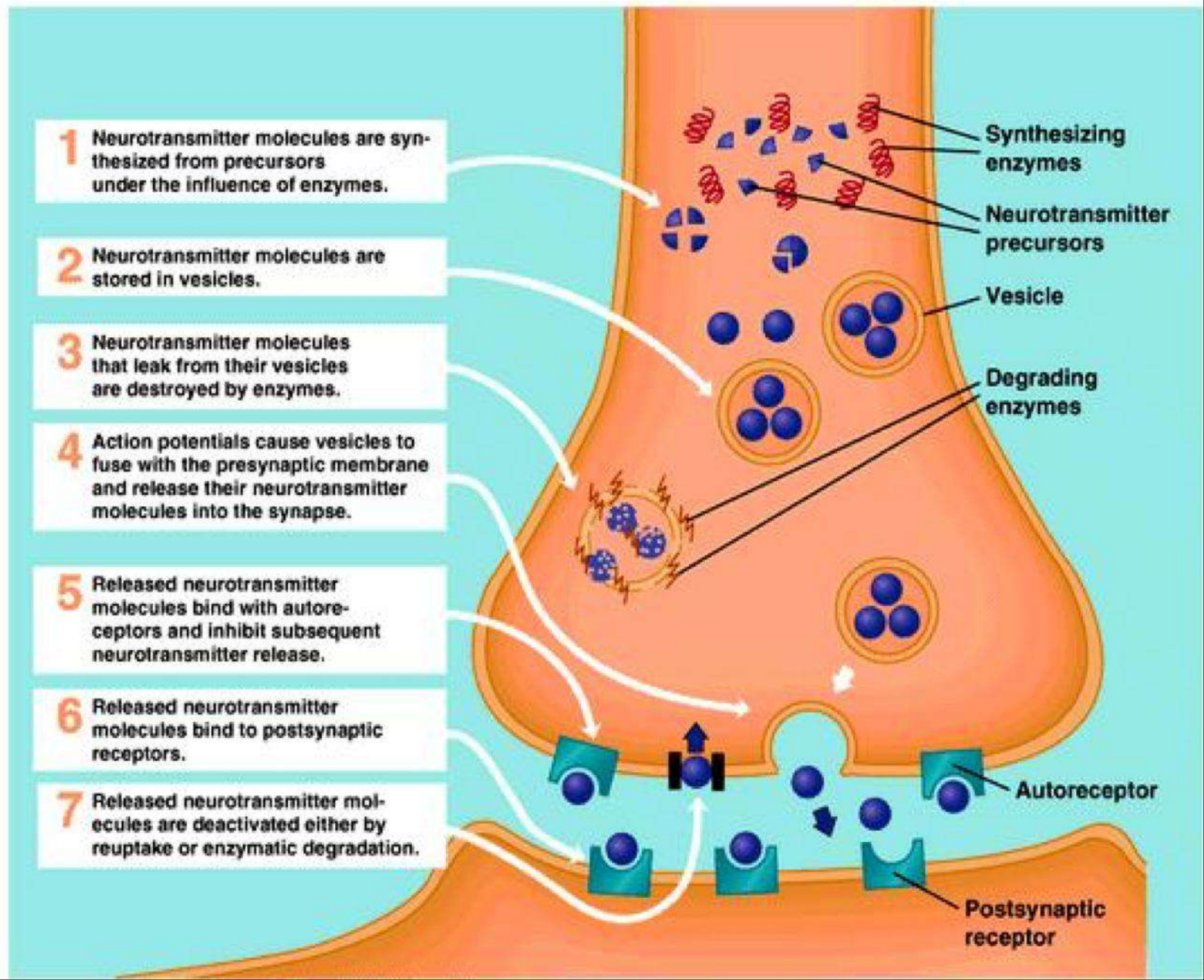


Mode Of Action



5 Stages

- Synthesis
- Storage
- Release
- Binding
- Inactivation

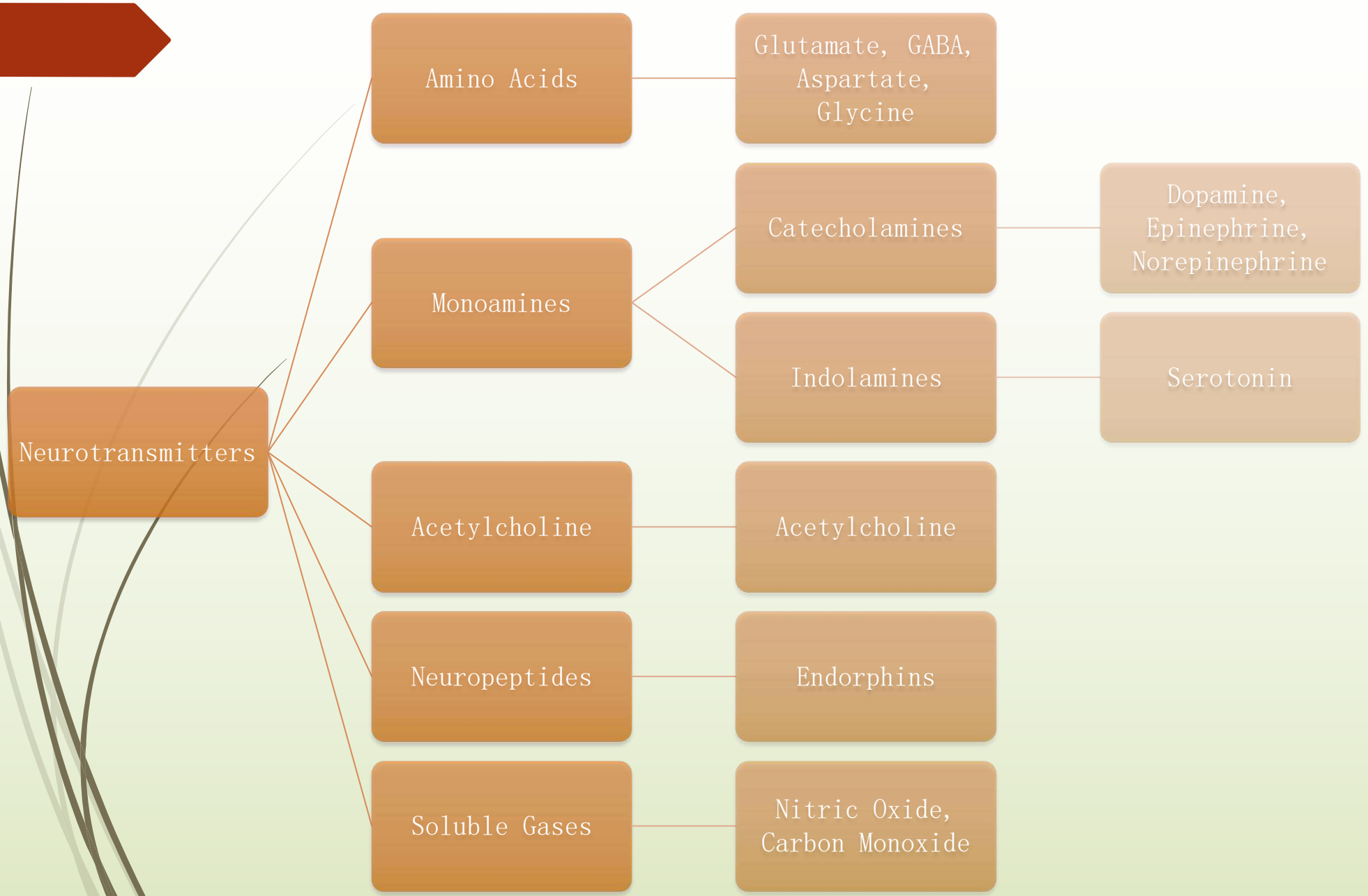


TYPES OF NEUROTRANSMITTERS

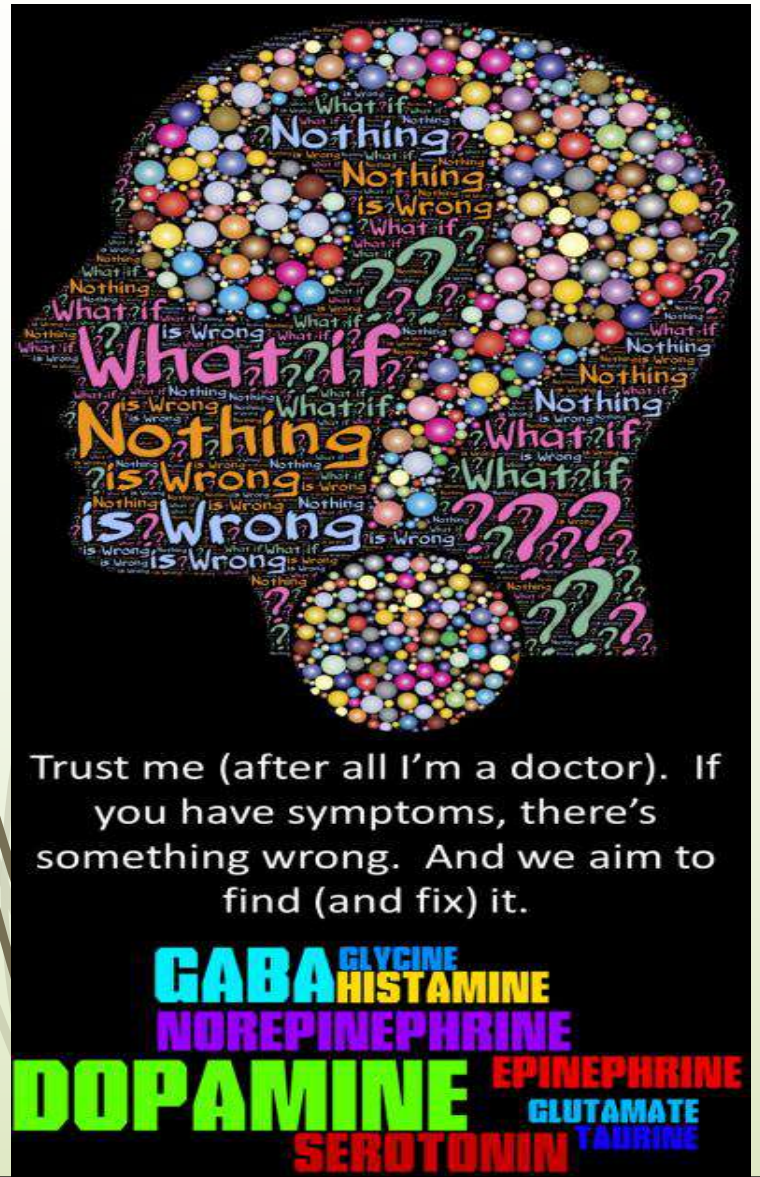
Two types

EXCITATORY	INHIBITORY	BOTH
Glutamate	Glycine	Acetylcholine
Aspartate	GABA	Nor epinephrine
Nitric oxide	Serotonin	
	Dopamine	

Classes of Neurotransmitters



Problems Due To Neurotransmitters

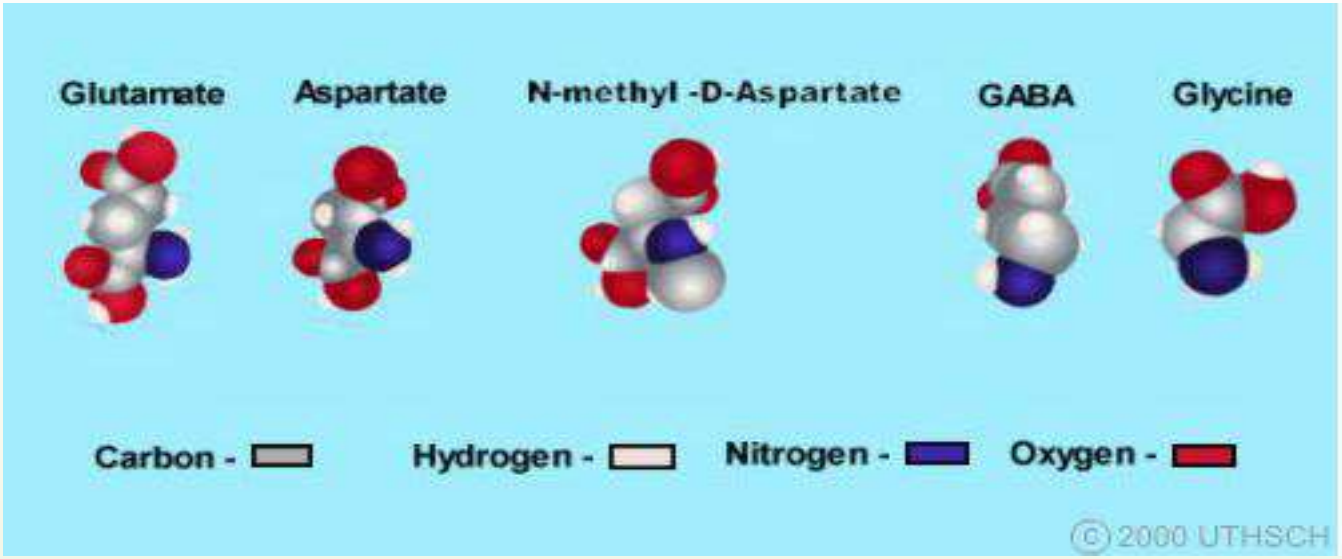


- **Brain fog** – loss of mental focus, ADD, ADHD, impaired memory, poor decision making
- **Fatigue**
- **Insomnia** – difficulty falling asleep, staying asleep, or both
- **Pain** – migraines, fibromyalgia
- **Obesity** – metabolic syndrome, insulin resistance, and diabetes
- **Mood disorders** – depression, mood swings, irritability
- **Anxiety** – panic, obsessions, PTSD
- **Behavioral disturbances** – addictions, binge eating, compulsions impulsivity, gambling, autism
- **Hormonal imbalances** – PMS, estrogen dominance, low testosterone, hypothyroidism

Amino Acid Neurotransmitters

- Unlike acetylcholine and biogenic amine, these are universal parts of cells.
- Glycine and Glutamate are common parts of proteins.
- Can Elicit an Excitatory or Inhibitory Response.
- The concentrations of synaptic GABA and glutamate are in the millimolar range whereas biogenic amine and peptide neurotransmitters are in the micromolar range or lower.
- Amino acid neurotransmitters are all products of intermediary metabolism with the exception of GABA

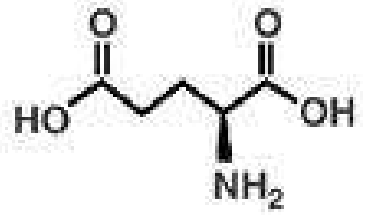
The structure of four key amino acid neurotransmitters



The excitatory amino acids carry two negative charges from the two carboxylate groups (COO-) as opposed to one for the inhibitory amino acids.

Recognize that N-methyl-D-Aspartate (NMDA) is a synthetic compound not found in the brain and is technically not a neurotransmitter. It is a highly useful agonist that can mimic the actions of glutamate on a particular subset of glutamate receptors.

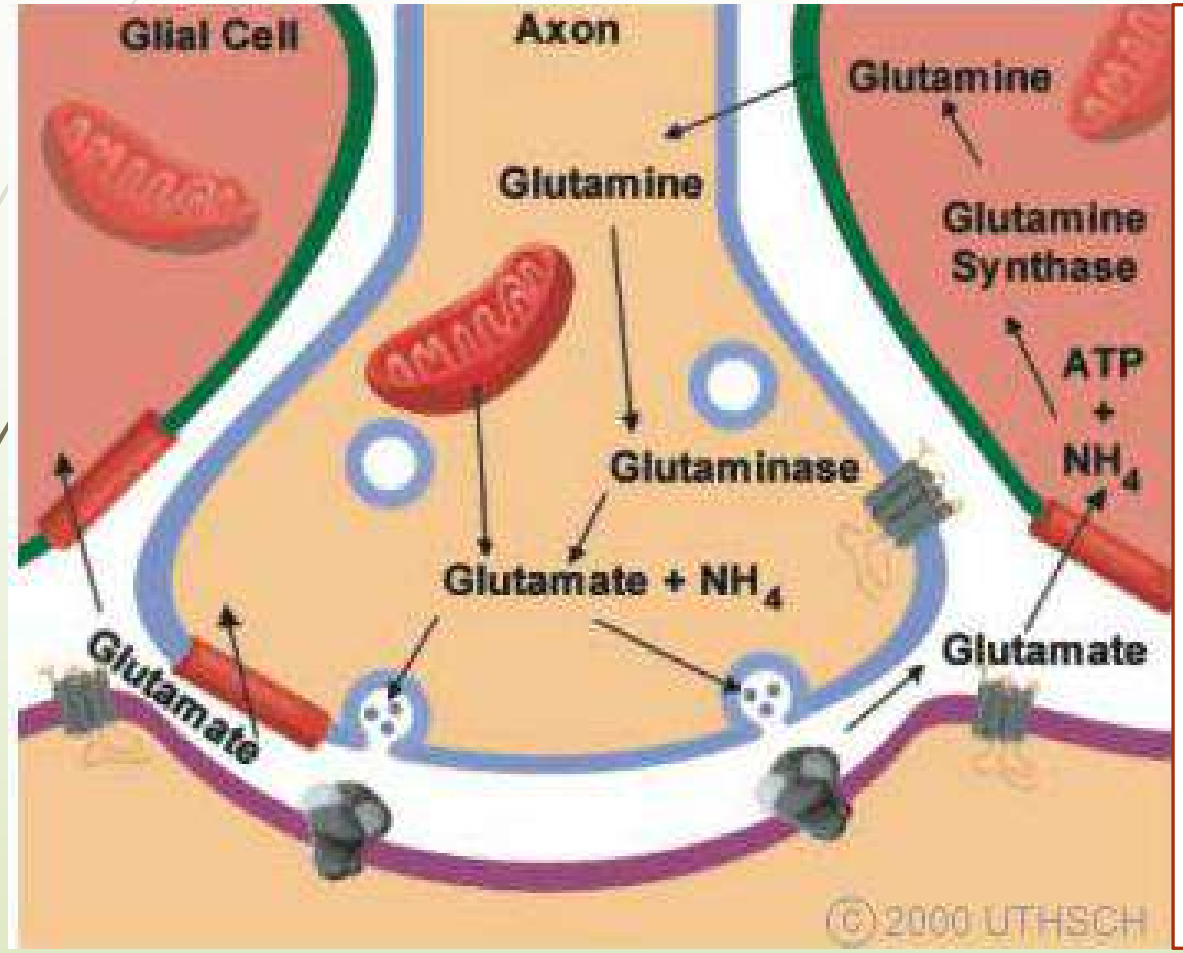
GLUTAMATE



L- Glutamic Acid

- Glutamate was discovered by Kikunae Ikeda who was able to extract an acid from seaweed
- It 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 α - ketoglutarate, an intermediate of Kreb's cycle
- They are produced in the mitochondria, transported into the cytoplasm, and packaged into synaptic vesicles

GLUTAMATE - Mechanism Of Action



- The actions of Glutamate are terminated by high-affinity uptake systems in neurons and glia
- Synthesis Process is done by the glutamine synthase produces glutamine from glutamate
- Breaking Proccess is done by Glutaminase Producing Glutamate From glutamine.
- Then be packaged into synaptic vesicles for another round of release

Glutamate Receptors

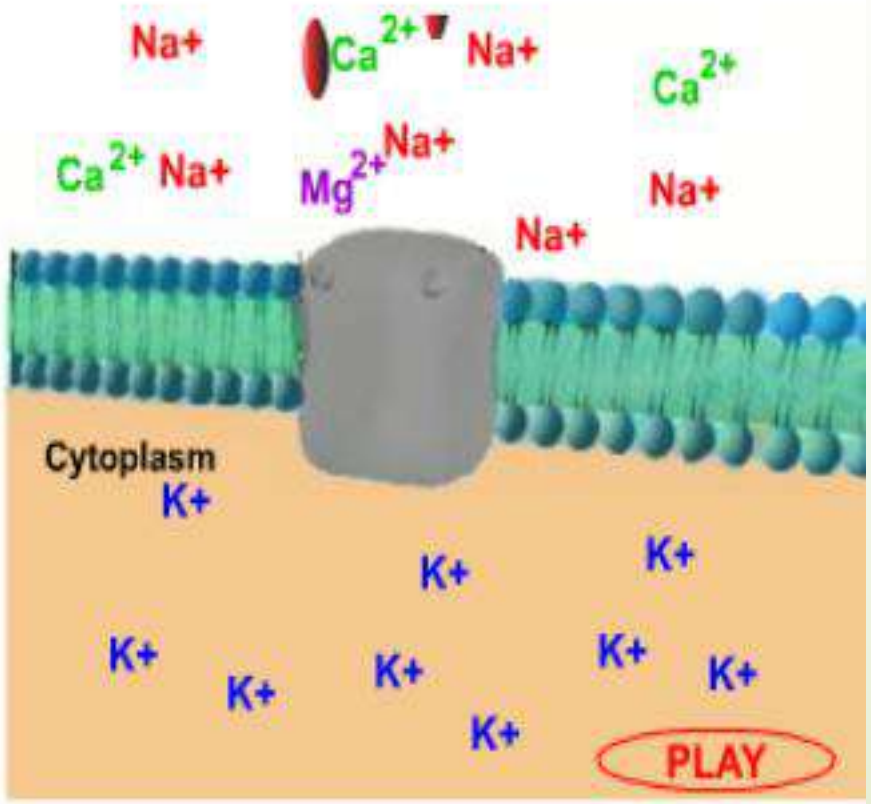
Three distinct types of glutamate receptors :-

1. Ionotropic Receptors: Glutamate binding directly opens an ion channel

    1. NMDA (N-methyl-D-aspartate) Receptor
    2. Non-NMDA (also known as kainate/AMPA receptors)

2. G-protein coupled glutamate receptor.

Glutamate Receptors (cont.)

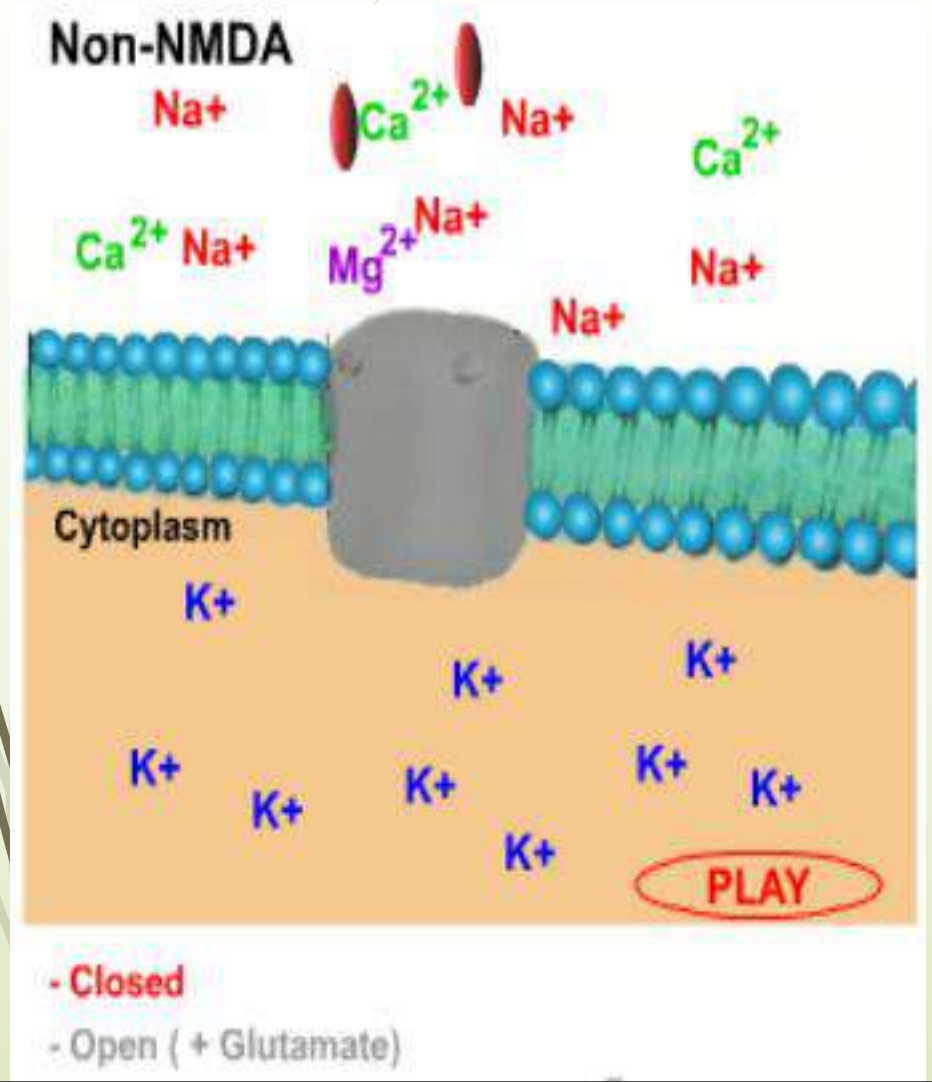


- Closed
- Blocked (+ Glutamate)
- Open (+ Glutamate + Depolorization)

NMDA receptors are unique in the nervous system and exhibit two important characteristics.

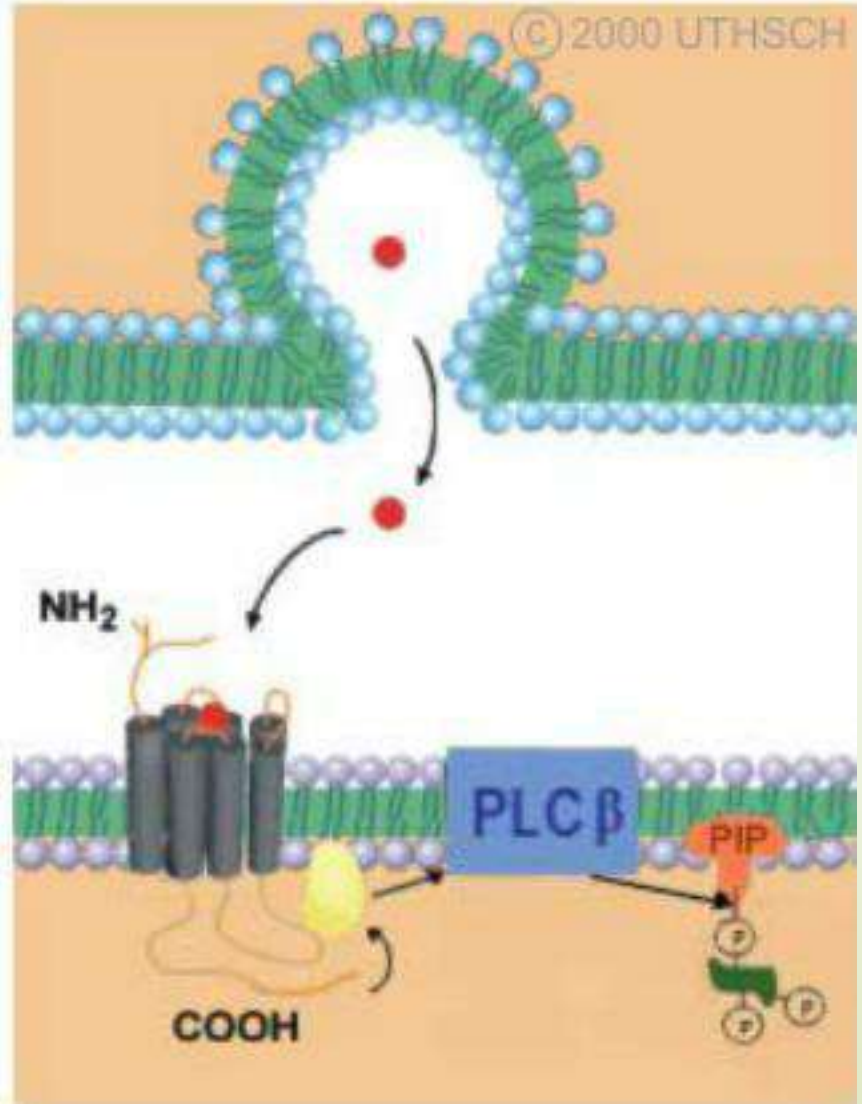
1. High permeability to Ca^{2+} (also permeable to Na^{+} and K^{+}), when they open, Ca^{2+} - can be detected in the neuron - alter both the short- and long-term response of the neurons
2. Require both ligand binding (Mg^{2+}) and membrane depolarization to open. Mg^{2+} stops ions from flowing through the channel. Mg^{2+} can be displaced from the channel by depolarizing the membrane. Due to this, the receptor is able to sense membrane potential and opens only when the neuron is depolarized.

Glutamate Receptors (cont.)



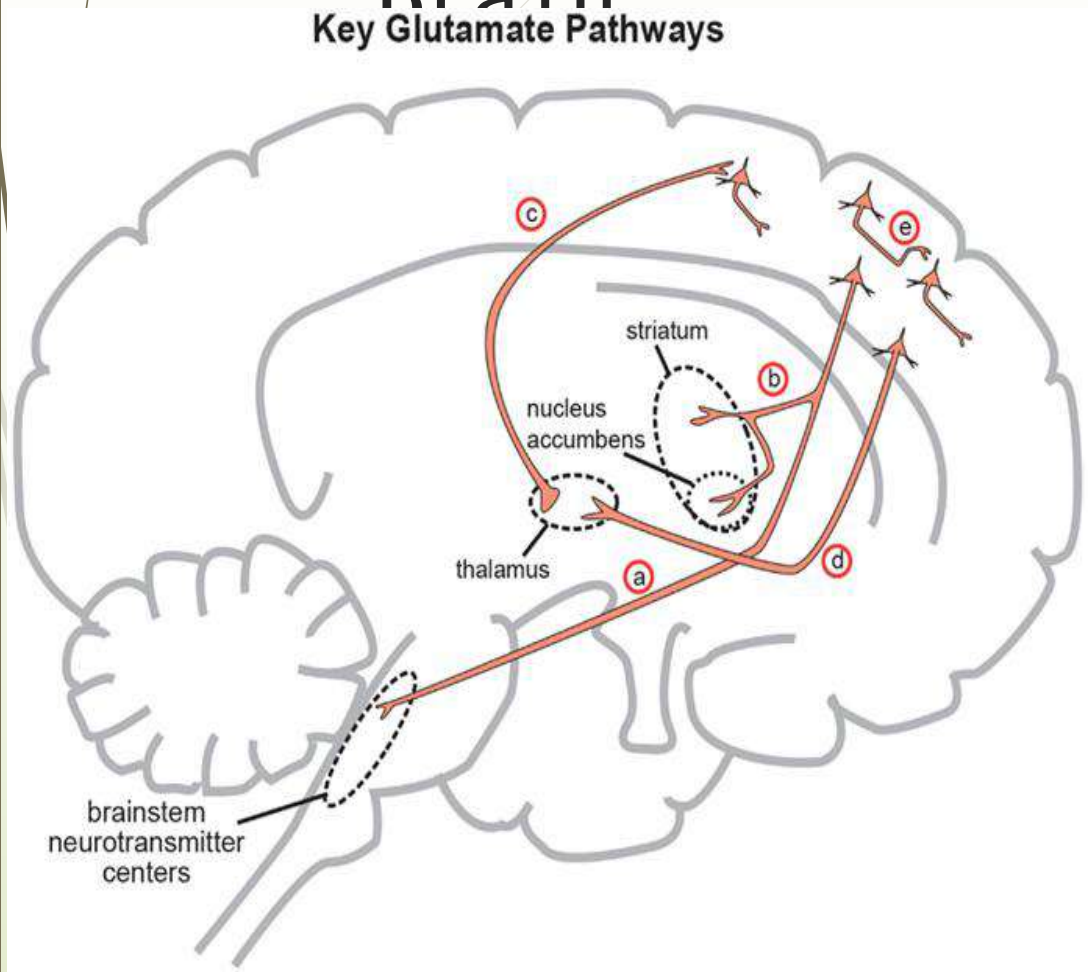
- Also Known as **Kainate/AMPA receptors** (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor).
- Opening of Non-NMDA receptors causes the majority of the excitatory postsynaptic potentials (EPSPs) in the nervous system.
- This receptor is mainly permeable to Na^+ and K^+
- Resembles the nicotinic ACh receptor, although glutamate receptors have some unique features. Four subunits, each having only three membrane spanning segments (as opposed to four for the nicotinic ACh receptor)

Glutamate Receptors (cont.)



- G-protein Coupled Glutamate receptors
- The glutamate GPCR's best known effects are the activation of phospholipase C which generates IP_3 and DAG from the precursor lipid phosphatidylinositol bisphosphate.
- Inositol-trisphosphate binds to receptors on intracellular organelles causing the release of Ca^{2+}.
- Increased Ca^{2+} along with diacylglycerol lead to the activation of protein kinase C which produces a variety of alterations in the enzymatic machinery of the cell including the regulation of ion channels that affect the electrical properties of the neuron.

Major Glutamatergic Pathways in the Brain

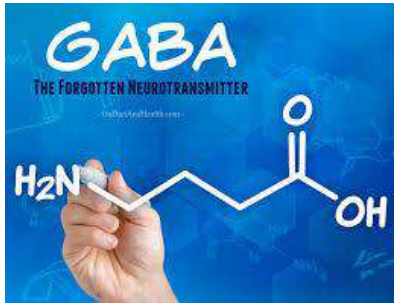


- Primary sensory afferent systems like retinal ganglion cells, cochlear cells, trigeminal nerve and spinal afferents
- Thalamocortical projections that distribute afferent information broadly to the cortex
- Pyramidal neurons of the cortico limbic regions - major source of intrinsic, associational, and efferent excitatory projections from the cortex
- Temporal lobe circuit - development of new memories.

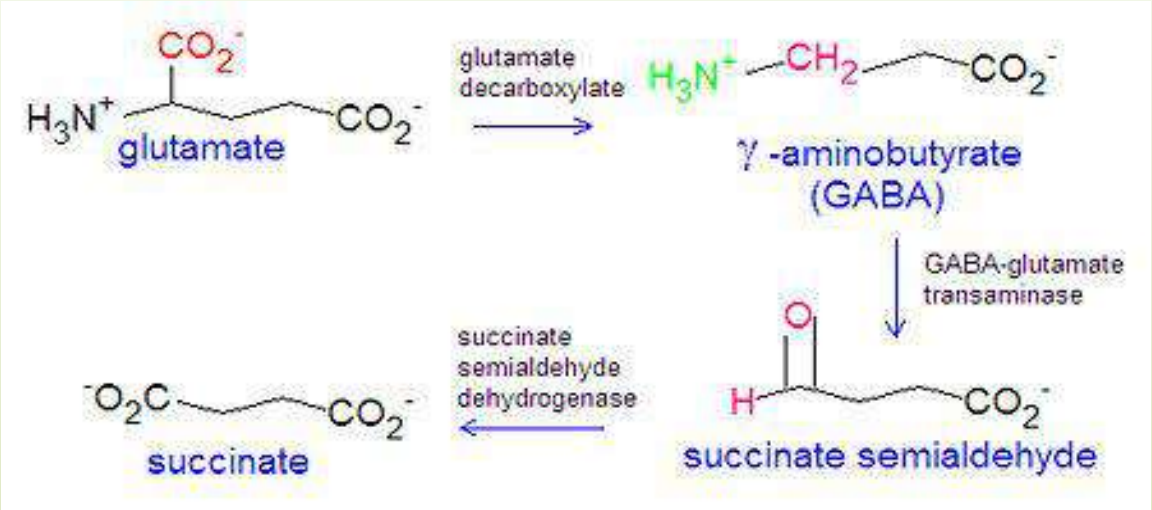
Glutamate And Psychiatric Disorders

- Decreased glutamatergic function at NMDA receptors - Psychotic symptoms
- Drugs acting at the Glycine site on the NMDA receptors - t/t of some symptoms in schizophrenia
- NMDA receptor hypofunction - implicated in the genesis of depressive symptoms.
- Changes in metabotropic glutamate receptor function - anxiety symptoms
- The glutamatergic system is a possible therapeutic target in the treatment of neurocognitive disorder

γ-AMINO BUTYRIC ACID (GABA)

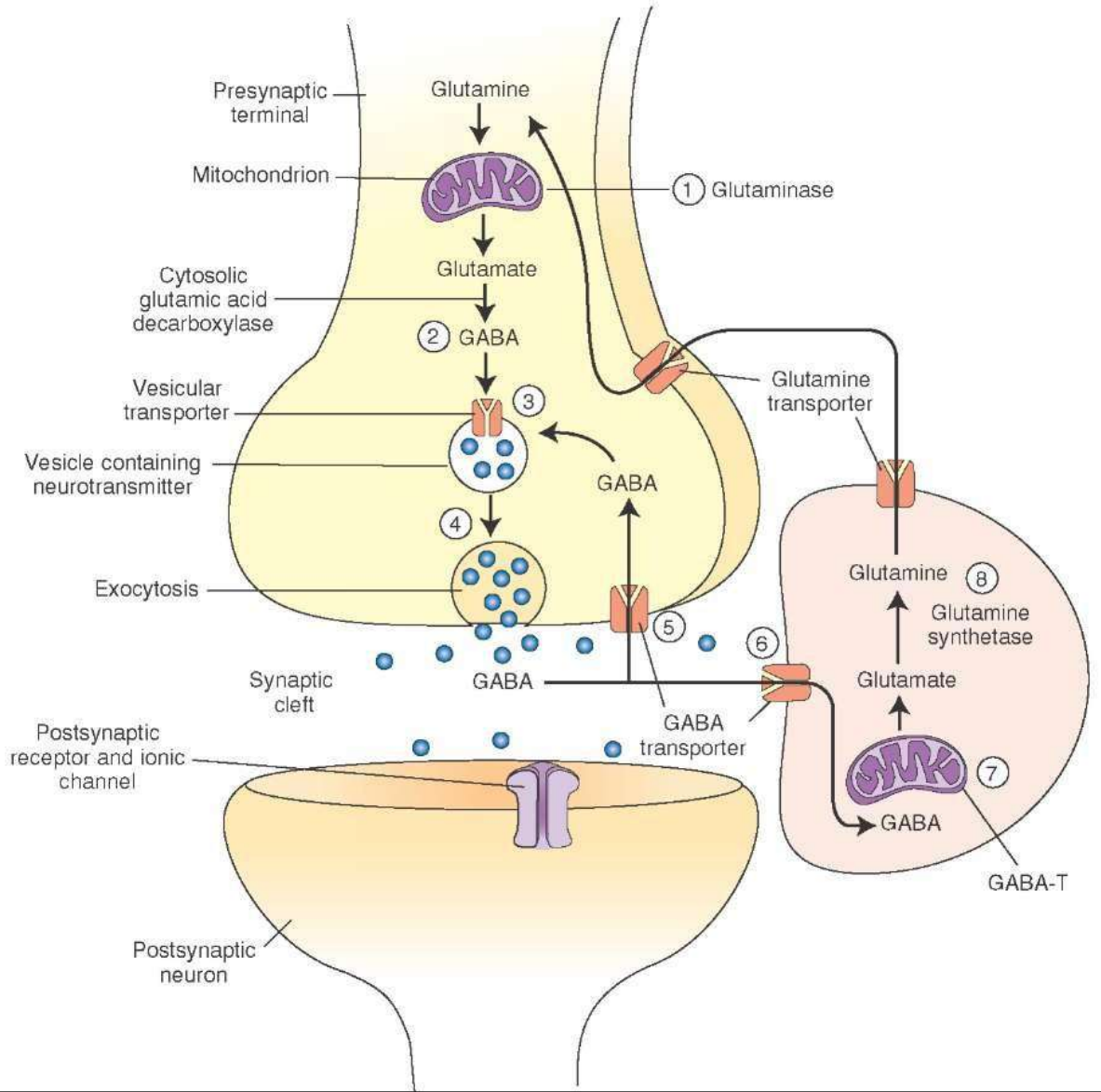


- 1950 – Eugene Roberts and J. Awapara discovered GABA
- Most commonly found inhibitory neurotransmitter in the brain.
- Present in high concentrations in the CNS – prevents the brain from becoming overexcited.
- Zwitter ion with deprotonated carboxy group and protonated amino group.



GABA is synthesized from glutamic acid by glutamic acid decarboxylase (GAD), which catalyzes the removal of the α-carboxyl group.

GABA - Mechanism Of Action



- The actions of GABA are terminated by high-affinity uptake systems in neurons and glia
- Synthesis Process is done by the glutamate Decarboxylase produces gaba from glutamate
- Breaking Proccess is done by GABA transaminase Producing Glutamate From Gaba.
- Then be packaged into synaptic vesicles for another round of release

GABA Receptors

- Two distinct types of gaba receptors :-
- One is ionotropic While the other is Metabotropic

$GABA_A$ - Ionotropic

$GABA_B$ - Metabotropic

- GABA receptors are channel receptors.

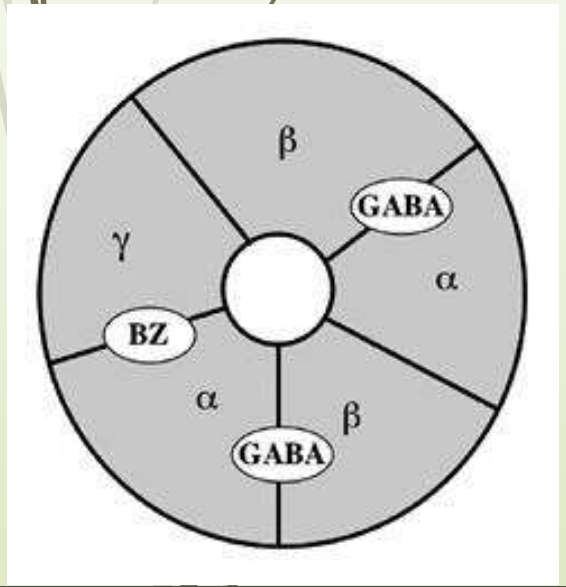
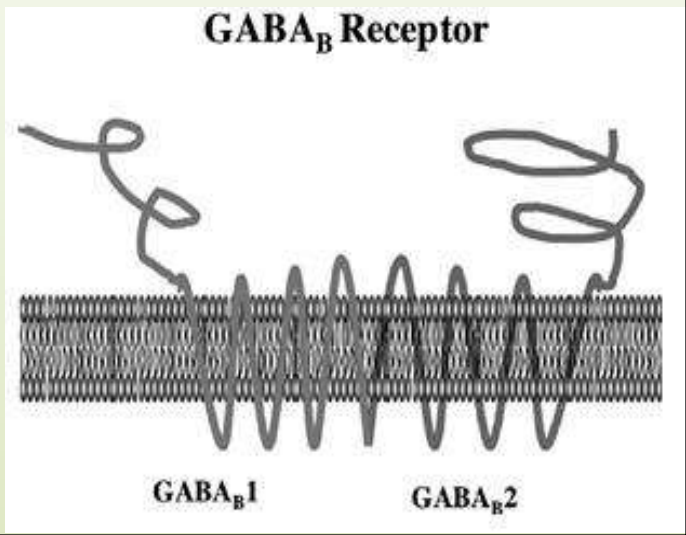
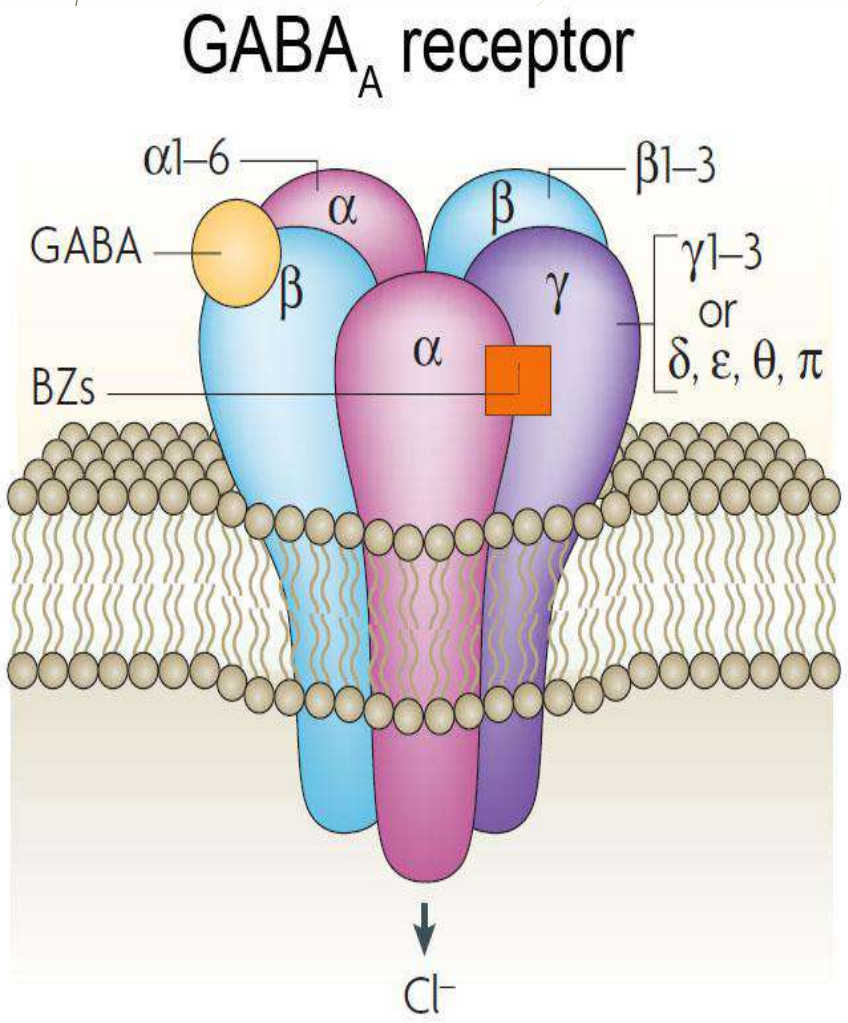


Table I GABA Receptors	
$GABA_A$	**$GABA_B$**
Largely Postsynaptic	Largely Presynaptic
Opens a Cl^- Channel	Alters Second Messengers
Rapid Response (15 msec)	Slow Response (300-500 msec and longer)
Multisubunit, Binds Modulators	Single Subunit



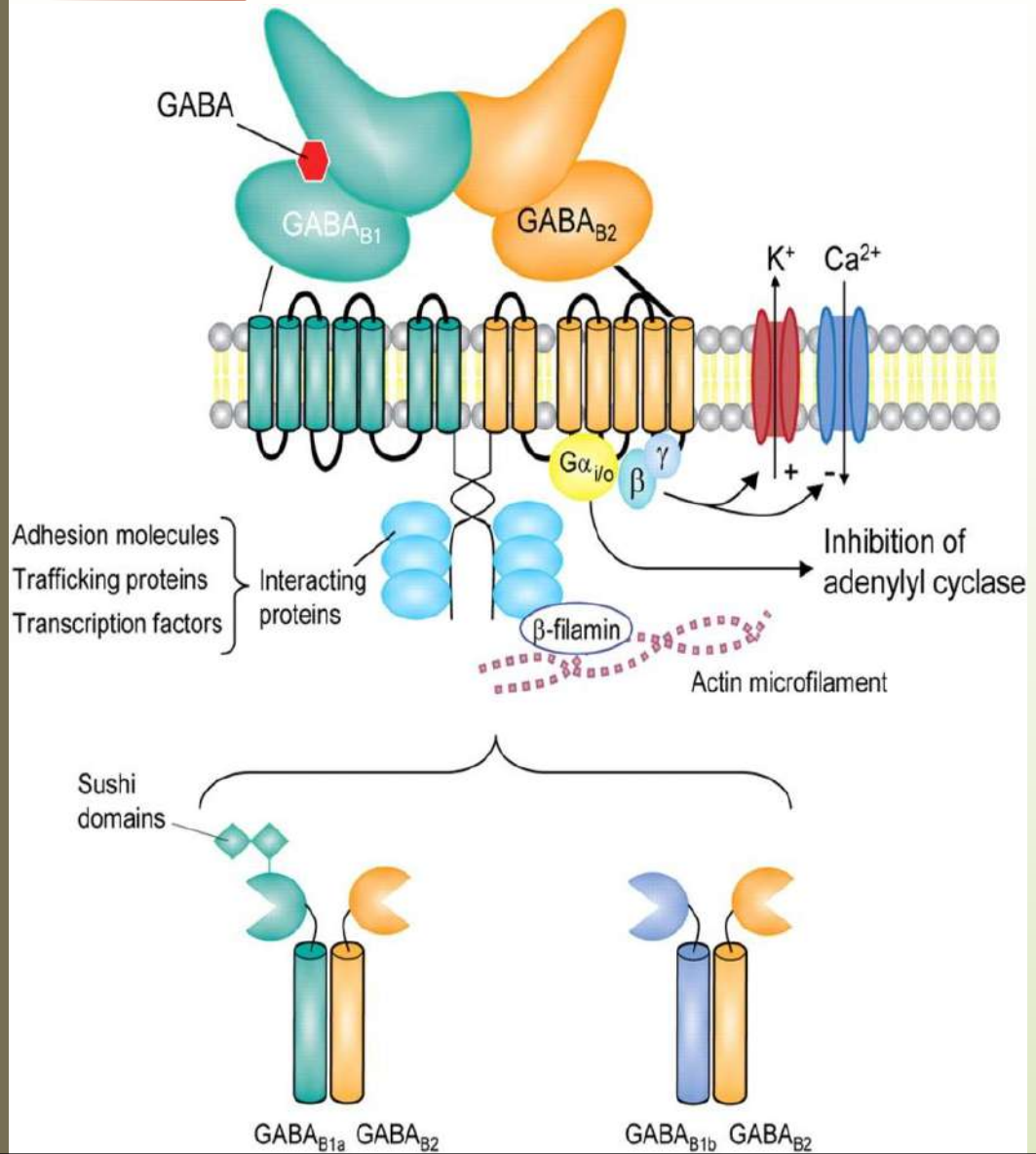
GABA Receptors (cont.)



Jacob et al., Nature Reviews Neuroscience, 2008

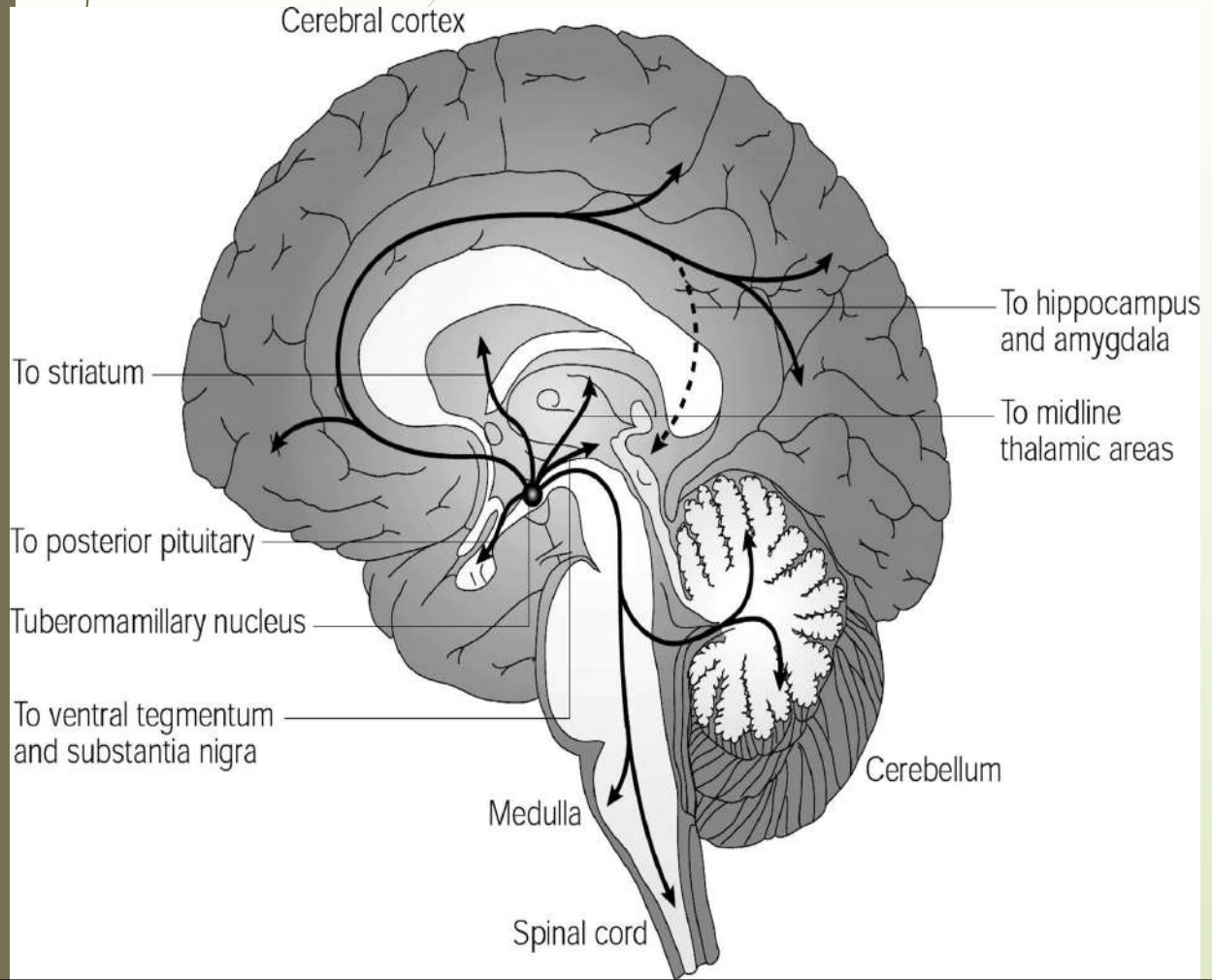
- It has pentameric structure.
- Each GABA $_A$ receptor contains two alpha subunit, two beta subunit & one gamma subunit.
- It has structural similarity & functional similarity with ligand-gated ion channels
- The $GABA_A$ complex, when activated, Produces RMP of -70 mV
- They produce a channel that permits the permeation of the negatively charged Cl^- ion.
  - GABA binds predominantly to the alpha subunit.
  - Benzodiazepines (like Lorazepam and Diazepam) bind to the gamma subunit.
  - Barbiturates (Phenobarbital and secobarbital) bind to both the alpha and beta subunits.
  - Picrotoxin blocks ion flow through the receptor

GABA Receptors (cont.)



- They are Hetrodimers of two seven-membrane-spanning GCPRs.
- Localized both pre- and postsynaptically.
- Postsynaptic $GABA_B$ receptors cause a long-lasting hyperpolarization by activating potassium channels.
- Presynaptically $GABA_B$, they act as auto- and heteroreceptors to inhibit neurotransmitter release.
- Two $GABA_B$ subunits have been cloned B_1 and B_2
- Produce Effects By :-
  - Include alterations (either increases or decreases) in cAMP levels
  - Increases in K^+-conductance
  - Decreases in Ca^{2+}-conductance

Major Gabanergic Pathways in the Brain

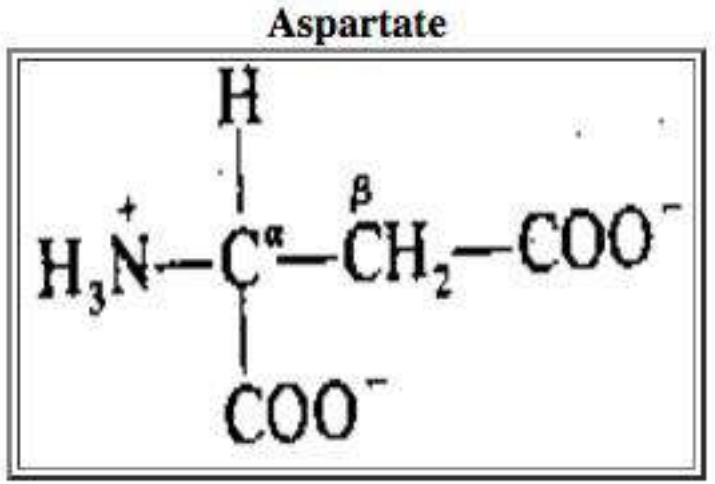


- In the corticolimbic regions – GABA is localized to the intrinsic (i.e local circuit) neurons.
- In the cerebral cortex, – outer boundaries of the column with inwardly directed axons.
- In the striatum, GABAergic neurons project directly to the *substantia nigra pars reticulata*, which regulates dopaminergic neuronal activity.
- GABAergic neurons that project to the *globus pallidus* to synapse on pallidal-subthalamic GABAergic neurons that regulate the excitatory output from the subthalamic nucleus.
- In the cerebellum, GABAergic Purkinje cells are its main efferent system.

GABA And Psychiatric Disorders

- GABAergic dysfunction has been associated with anxiety disorders, especially panic disorder, as well as with major depressive disorder.
- Disruption is GABA Neurotransmitter would result in Schizophrenia
- If GABA is lacking in certain parts of brain seizure disorders occurs.
- The GABA receptor effects may be associated with the anxiolytic effects of ethanol Producing a hyper excitable state characterized by delirium tremens

ASPARTATE



- It is an nonessential amino acid
- Aspartic acid was first discovered in 1827 by Auguste-Arthur Plisson and Étienne Ossian Henry, derived from asparagine, which had been isolated from asparagus juice in 1806, by boiling with a base
- It is an excitatory neurotransmitter in the brain.
- a selective NMDA receptor agonist, localized to the ventral spinal cord.

ASPARTATE - Mechanism Of Action

- Aspartate is non-essential in mammals, being produced from oxaloacetate by transamination. It can also be generated from ornithine and citrulline in the urea cycle.

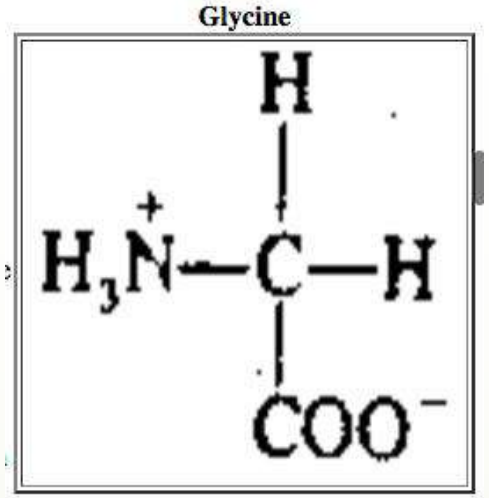
  Asparagine is derived from aspartate via transamidation.

- Aspartate opens an ion-channel by Acting on the NMDA receptor and is inactivated by reabsorption into the pre-synaptic membrane like in Glutamate.

ASPARTATE and Psychiatric Disorders

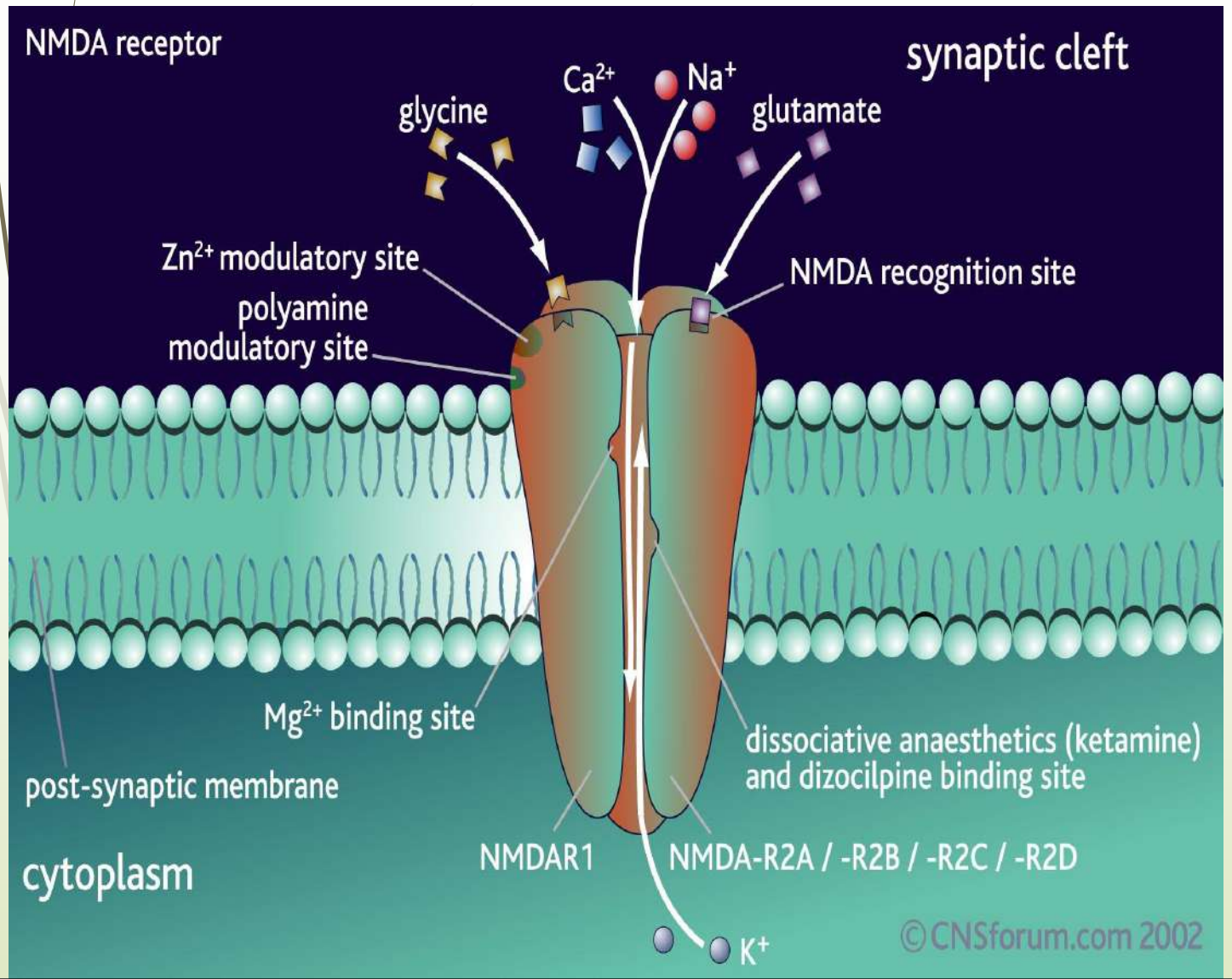
- Low levels of Aspartate in urine links to feelings of tiredness and depression.
- High levels of aspartate have been linked to anxiety and seizures.

GLYCINE



- It is an amino acid
- Glycine was discovered in 1820, by Henri Braconnot who boiled a gelatinous object with sulfuric acid.
- It is an Inhibitory neurotransmitter in the brain.
- Major neurotransmitter released from inhibitory interneurons in spinal cord and brainstem

GLYCINE - Mechanism Of Action



- The glycine receptor (GlyR), like the $GABA_A$ receptor also permits the influx of Cl^- into neurons and displays a reversal potential near -70 mV.
- GlyR is an ionotropic receptor that produces its effects through chloride current
- Strychnine is a glycine antagonist which can bind to the glycine receptor without opening the chloride ion-channel

GLYCINE ENCEPHALOPATHY

- **Glycine encephalopathy** (also known as **non-ketotic hyperglycinemia** or **NKH**) is a rare autosomal recessive disorder of glycine metabolism.
- The disease is caused by defects in the glycine cleavage system, an enzyme responsible for glycine catabolism.
- The symptoms are **exclusively neurological** in nature, and clinically this disorder is characterized by abnormally high levels of the amino acid glycine in bodily fluids and tissues, especially the cerebral spinal fluid.
- All forms of glycine encephalopathy present with only neurological symptoms,
- Mental retardation (IQ scores below 20 are common)
- Hypotonia
- Apneic seizures,
- Brain malformations.

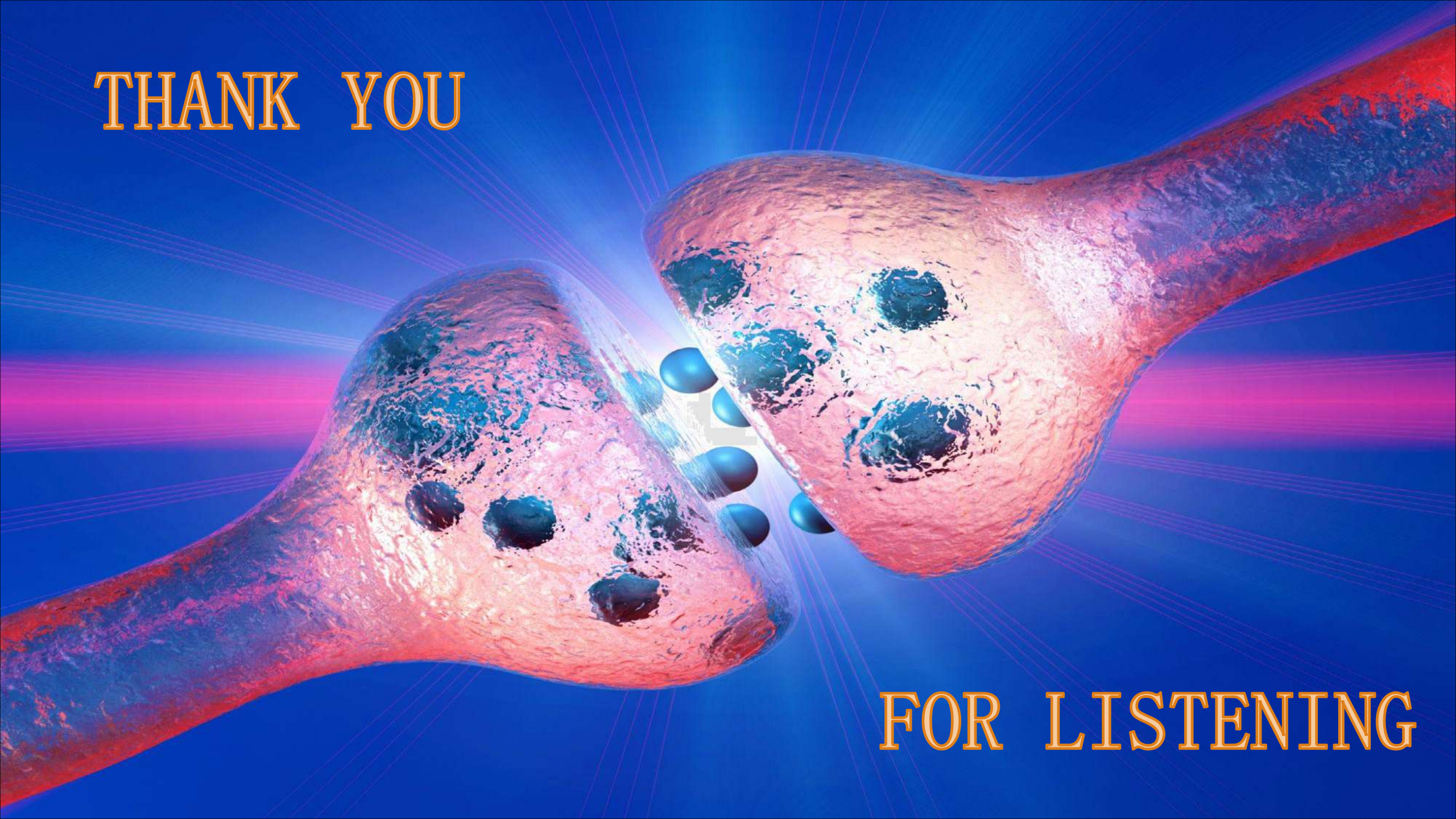
Summary

- The ability of nervous system to orchestrate complex behaviors, learn and remember depends on communication between vast numbers of neurons.
- Mediated by neurotransmitters which plays an important role in control and coordination of body.
- Glutamate neurotransmitter is an excitatory neurotransmitter involved in cognition, memory and learning.
  - Mediates effect by 3 receptors NMDA, Kainate, G-Protein
  - Impairment in this neurotransmitter will leads to Psychotic symptoms, schizophrenia, depressive symptoms, Anxiety symptoms, Neurocognitive disorder.
- GABA neurotransmitter is an inhibitory neurotransmitter involved in Various pathways in brain.
  - Mediates effect by 2 receptors $GABA_A$ (Ionotropic) $GABA_B$ (Metabotropic)
  - Impairment in this neurotransmitter will leads to Schizophrenia, depressive symptoms, Anxiety symptoms, Seizure disorders, Delirium tremens.

- Aspartate neurotransmitter is an excitatory neurotransmitter localized to the ventral spinal cord.
  - Mediates effect by 1 receptors i.e NMDA Receptors
- Glycine neurotransmitter is an inhibitory neurotransmitter localized to the ventral spinal cord.
  - Mediates effect by 1 receptors GlyR (ionotropic receptors)
  - Impairment in this neurotransmitter will leads to Glycine encephalopathy.

References

- Comprehensive textbook of psychiatry. Kaplan and Saddock. 10th edition
- Handbook Of Psychopharmacology - Amino Acid Neurotransmitters, Leslie Iversen edition 4
- http://neuroscience.uth.tmc.edu/s1/chapter13.html
- https://www.integrativepsychiatry.net/neurotransmitter.html
- https://psychology.columbia.edu/#/search/gaba%20receptor
- https://www.ncbi.nlm.nih.gov/books/NBK28252/
- http://www.benbest.com/science/anatmind/anatmd10.html#aspartate
- Google images


THANK YOU
FOR LISTENING