GLUTAMATE

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INTRODUCTION

- For over 50 years biogenic amines have dominated thinking about the role of neurotransmitters in the pathophysiology of psychiatric disorders.

- However over the last decade evidence from brain imaging, genetic studies shows that amino acid neurotransmitters in particular GLUTAMATE & GABA play an important role in psychiatric disorders including Schizophrenia, Alzheimers and Anxiety.

Amino acid neurotransmitter

- **GABA**
- **Glycine**
- Inhibitory neurotransmitter
- At 15-20% of synapses

- **Glutamate**
- **Aspartate**
- Excitatory neurotransmitter
- At 75—80% of synapses

Glutamic Acid (or) Glutamate

- Acidic nonessential amino acid.
- Important as the building block of protein synthesis.
- As a neurotransmitter in CNS.
- Major excitatory neurotransmitter.
- Called king of neurotransmitters
- Also called master switch of brain
- Concentration in brain is 10mM, the highest of all aminoacids and of all NT.

Synthesis of Glutamate

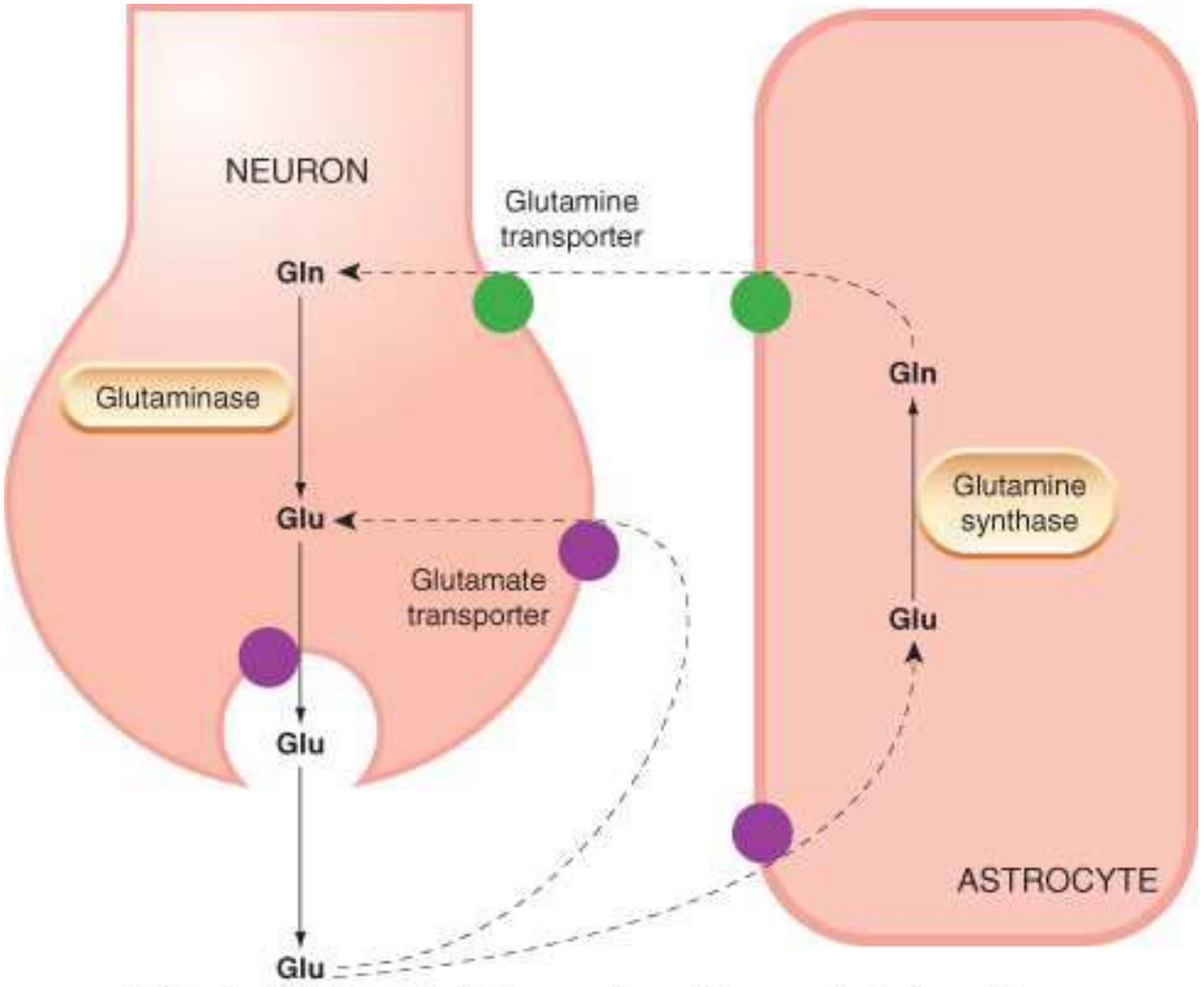
- Given the excitatory effects of glutamate, it is excluded from the brain by BBB i.e, Blood Brain Barrier is impermeable to Glutamate.

- Thus, glutamate in the brain must be synthesised de novo from Glucose,

TCA ⟶ Alpha Ketoglutarate ⟶ Glutamic acid
(via transamination)

- Reuptake to storage vessels, 20% of glutamate turnover through 'glutamate transporter' & 40% through 'glutamine cycle'.

GLUTAMATE SYNTHESIS



Synthesis of glutamate cotransmitters (Glycine, D-serine)

- One of the key receptors for glutamate (NMDA) requires a cotransmitter in addition to glutamate to function.
- Glycine synthesized either from glycine neurons or from glia.
- Type 2 glycine transporter (GlyT2) present on glycine neurons.* (on glycine neurons)
- Type 1 glycine transporter (GlyT1) and glial SNAT (specific neutral amino acid transporter) present on glia. *
- Glycine synthesized in glia from amino acid L-serine with an enzyme called SHMT.

- This enzyme works in both directions, Thus
- Glycine converted to L-serine in glia with an enzyme SHMT (serine hydroxymethyl transferase) which in turn converted to D-serine.
- L-serine to D-serine conversion occurred in glia with an enzyme called D-serine racemase.
- Thus D-serine can be derived either from glycine or from L-serine.
- Reuptake of D-serine is by glial D-serine transporter (D-SER-T).

Transporters

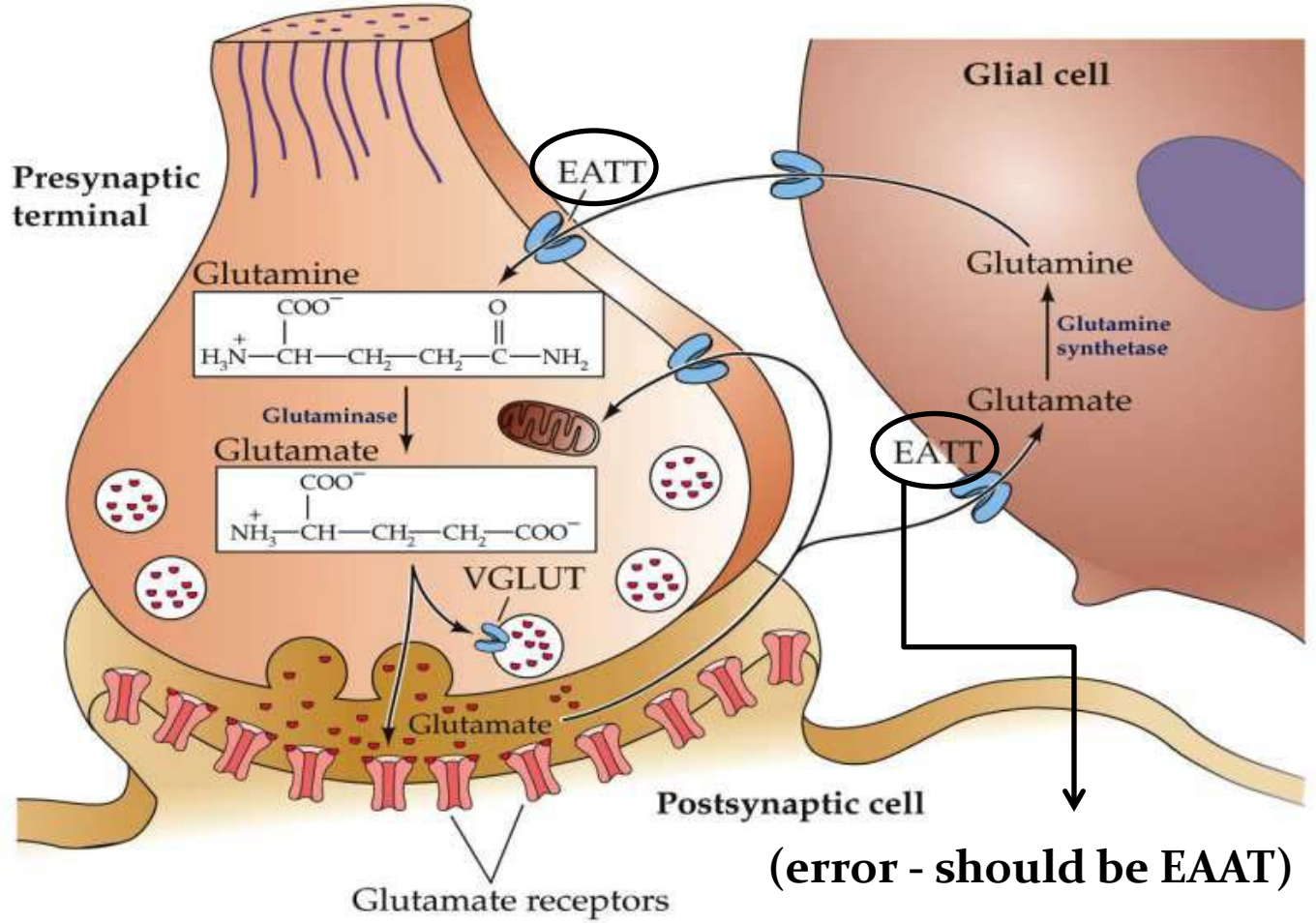
- The neuronal presynaptic reuptake pump (EAAT or excitatory amino acid transporter), Glutamate is transported across membranes of synapse by these Na++ dependent transporters.

- These are 5 types
- EAAT1 -Astrocyte
- EAAT2 -Astrocytes, Forebrain
- EAAT3 -Upper motor neurons
- EAAT4 -Cerebellar purkinje cells
- EAAT5 -Retina

- Of these EAAT1 & 2 are involved in the reuptake and release of glutamate during glutamine cycle
- The vesicular transporter for glutamate into synaptic vesicles (vGluT)

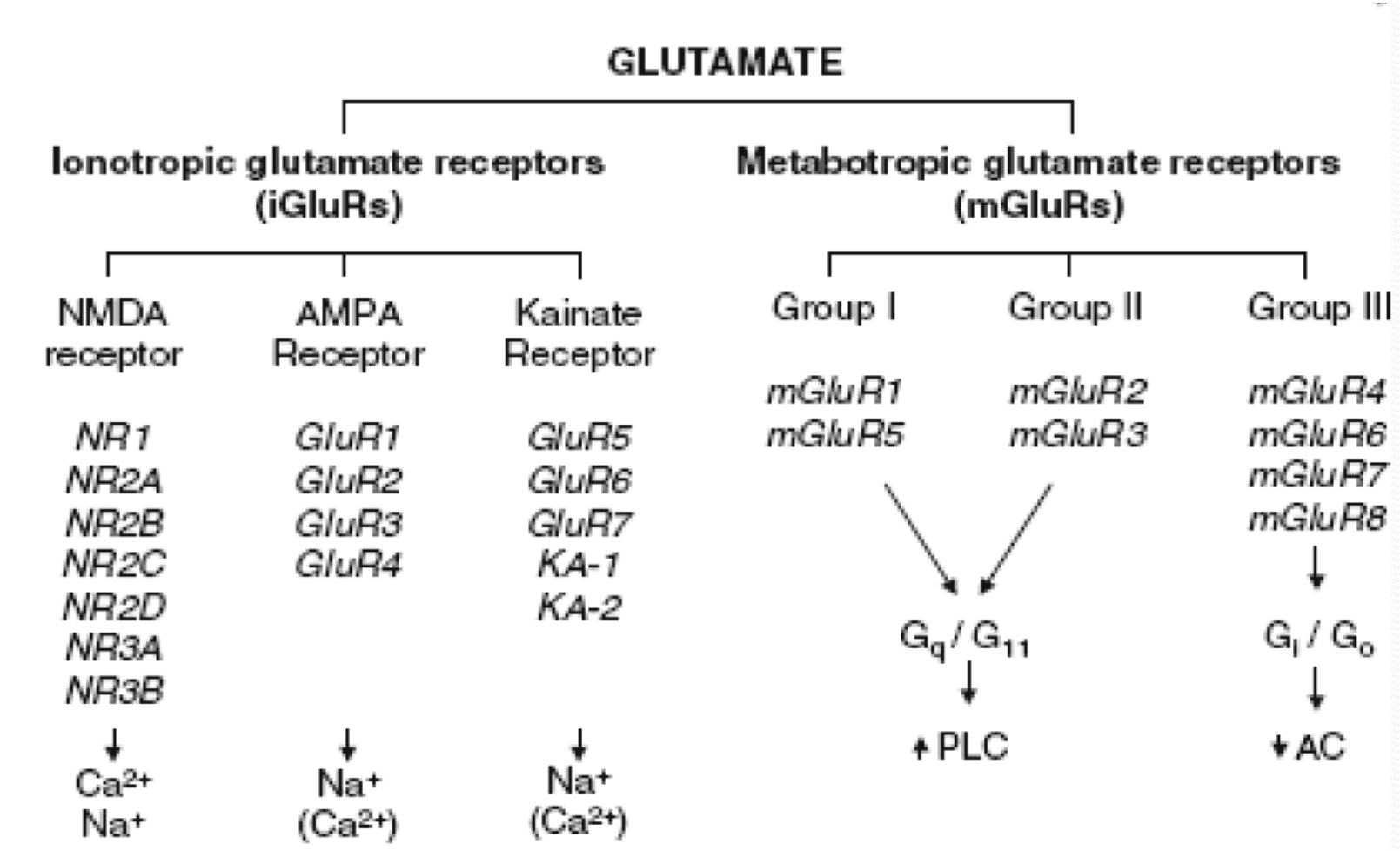
Glutamate fast neurotransmission

- Synthesis, packaging, reuptake, degradation

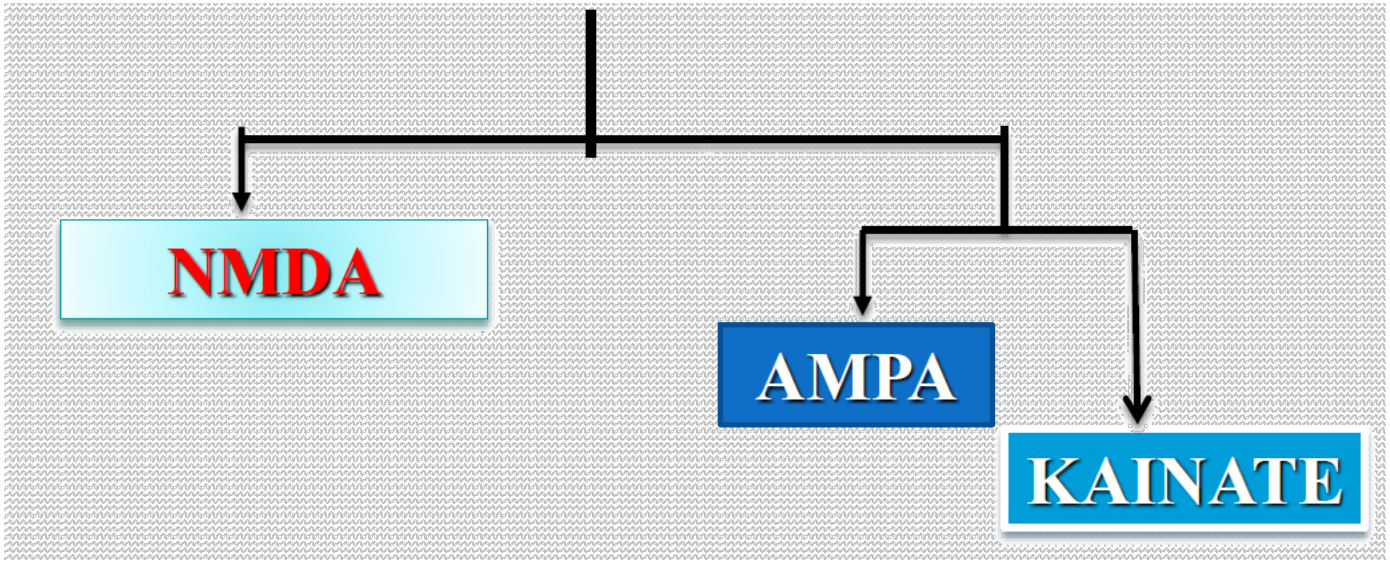


NEUROSCIENCE, Fourth Edition, Figure 6.6

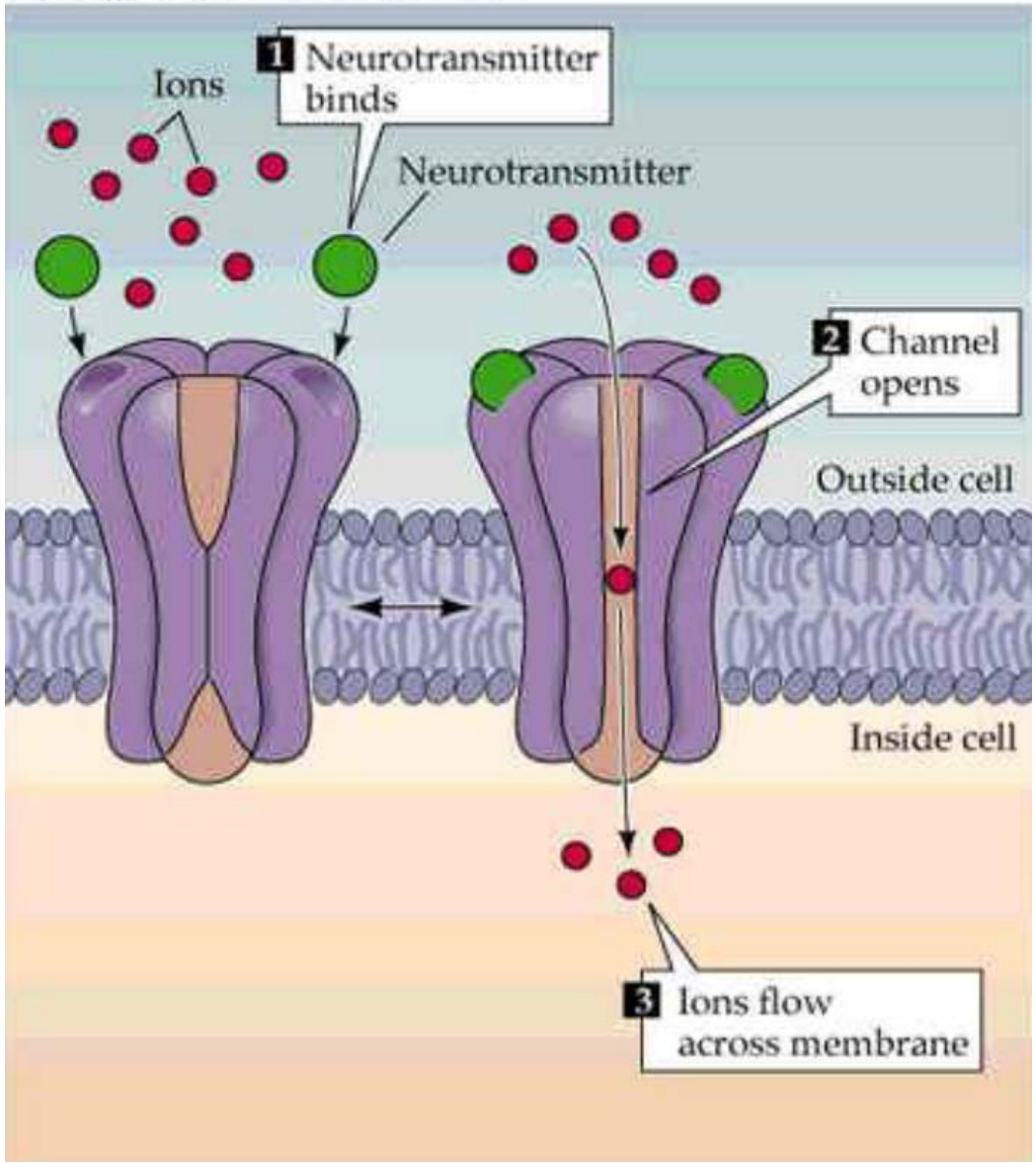
Glutamate receptors



IONOTROPIC GLUTAMATE RECEPTORS



(A) Ligand-gated ion channels

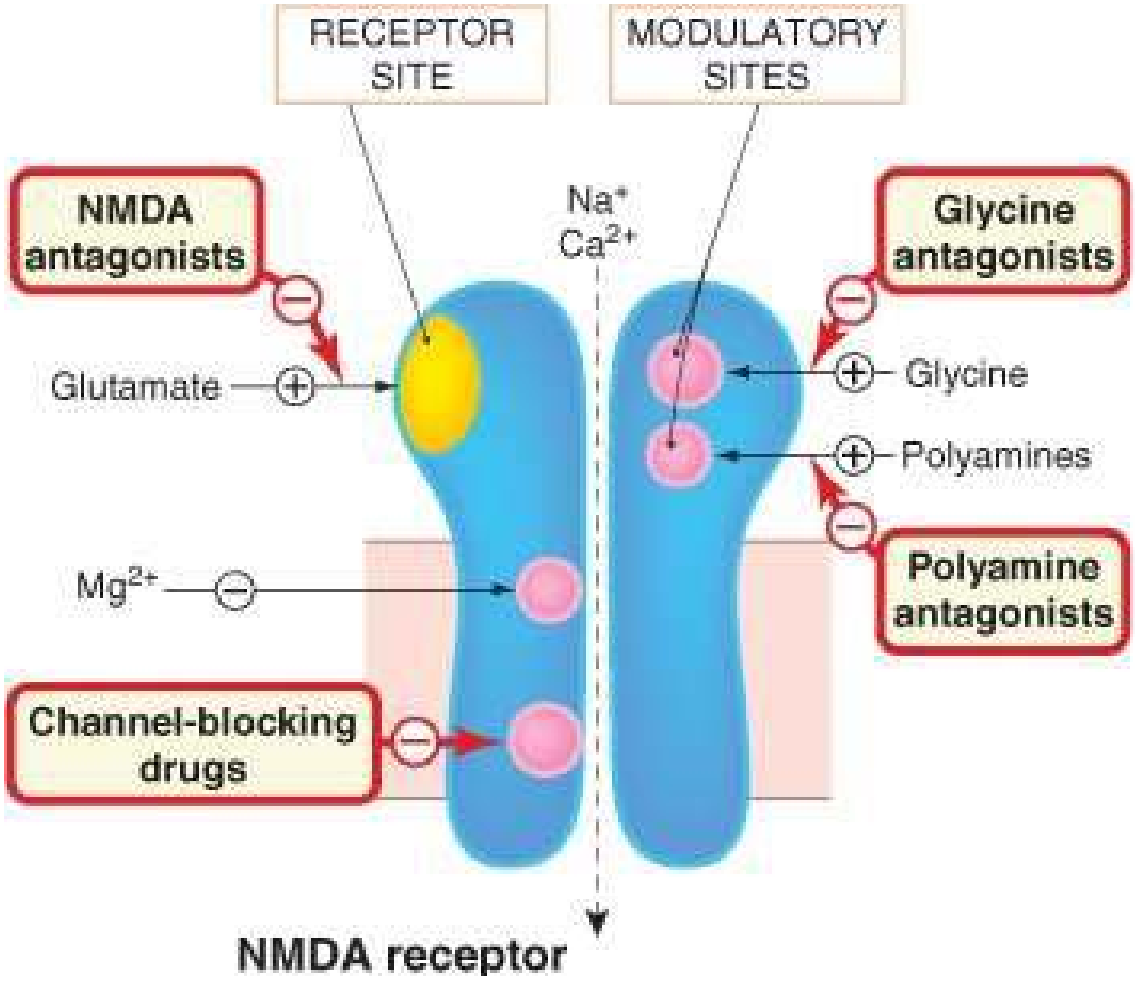


NMDA

- N–Methyl–D–Aspartic acid receptor.
- It is a hetero tetramer composed of NR1 sub unit that comprises channel and also has binding site *glycine modulatory site* & NR2 sub unit contains ligand binding site for agonist.
- At resting membrane potential channel blocked by Mg++
- It has been described as *coincidence detector* because 3 events must occur for the channel to open
- 1. A sufficient amount of glutamate has been released and binds to receptor
- 2. Glycine/D-serine release from astrocytes and binds to its site
- 3. The synaptic membrane sufficiently depolarized to remove the Mg++ blockade

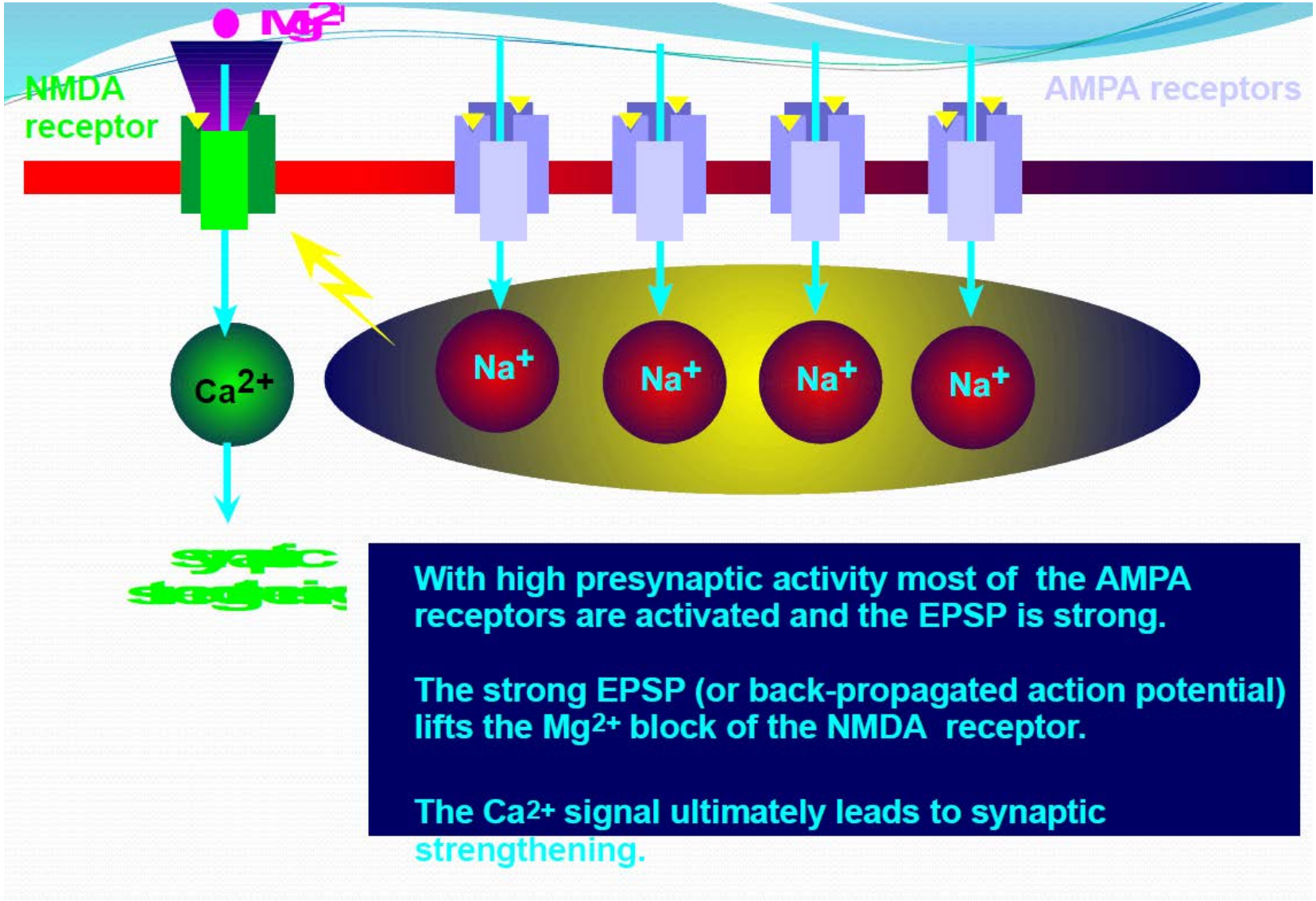
- NR2 sub unit further divided into 4 types, 2A-2D.

- NR2A- corticolimbic regions in mature brain
- NR2B- immature cortex
- NR2C- cerebellum
- NR2D- cerebellum, midbrain
- Have prominent role in learning, excito toxicity.
- Sub units also have binding sites for Zn++, H+ and a polyamine site.


RECEPTOR SITE
MODULATORY SITES
NMDA antagonists
Na+
Ca2+
Glycine antagonists
Glutamate
Glycine
Polyamines
Mg2+
Polyamine antagonists
Channel-blocking drugs
NMDA receptor

AMPA

- α-Amino 3–Hydroxy 5–Methyl 4-Isoxazole propionate (AMPA) receptors are broadly distributed in CNS.
- They are mediating most EPSPs in CNS.
- Contains 4 sub units, GluR1-4.
- Subunits 1,3,4 have Glutamine(Q) residue that results in high permeability to Ca++.
- Subunit 2 have Arginine(R) residue that restricts Ca++ passage and conducts only Na+.
- mRNA editing of GluR2 results in Arginine to Glutamine change and increases Ca++ conductance.


Mg^{2+}
NMDA receptor
AMPA receptors
Ca^{2+}
Na^+
Na^+
Na^+
Na^+
With high presynaptic activity most of the AMPA receptors are activated and the EPSP is strong.
The strong EPSP (or back-propagated action potential) lifts the Mg^{2+} block of the NMDA receptor.
The Ca^{2+} signal ultimately leads to synaptic strengthening.

- Ca++ acts as important second meesenger → Activates intracellular cascades.
- Ca++ binds to *calmodulin* protein → Activates protein kinases like CAM kinase.

CAM Kinase effects AMPA receptors in 2 ways :-

Phosphorylates AMPA receptors already present in dendritic spine membrane

↓

Increasing their conductance to sodium ions

&

Promotes intracellular AMPA receptors to move to the membrane

↓

Making more receptors available to stimulate the spine (Trafficking)

↓

LONG TERM POTENTIATION

Kainite receptors

- Consists of 5 sub units, GluR 5-7, KA1, KA2.
- These are less understood than AMPA, NMDA.
- GluR 5-7 sub units form glutamate gated cation channels.
- KA1, KA2 sub units aggregate with GluR 5-7 sub units to form high affinity kainite receptors.
- Their activation reduces glutamatergic neurotransmission because of presynaptic location.

- Eg:- GluR7 allelic variant associated with MDD.

Physiological or Pathological Roles

- **AMPA receptors**
- Mediate most fast EPSPs in the CNS

- **Kainite receptors**
- Regulation of neuronal excitability
- Epilepsy, Excitotoxicity and Pain

- **NMDA receptors**
- Mediate most fast EPSPs in the CNS
- Anaesthesia
- Learning and memory
- Developmental plasticity
- Epilepsy
- Excitotoxicity (eg :- Stroke)
- Schizophrenia

THANK YOU