
In The Name Of
GOD

Excitotoxicity

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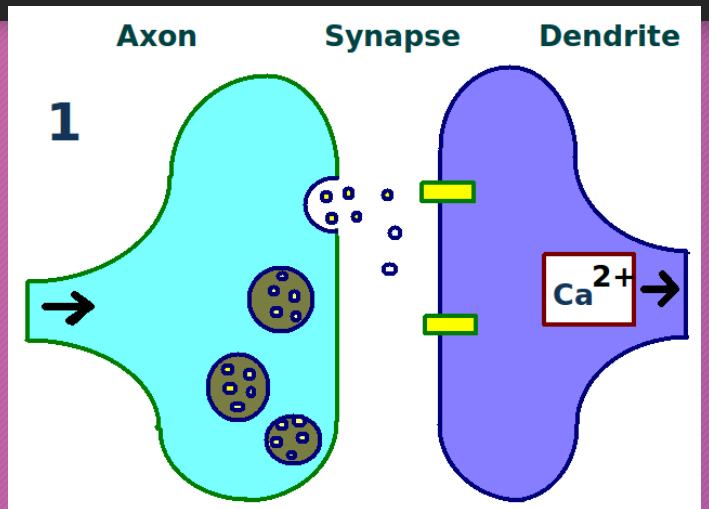
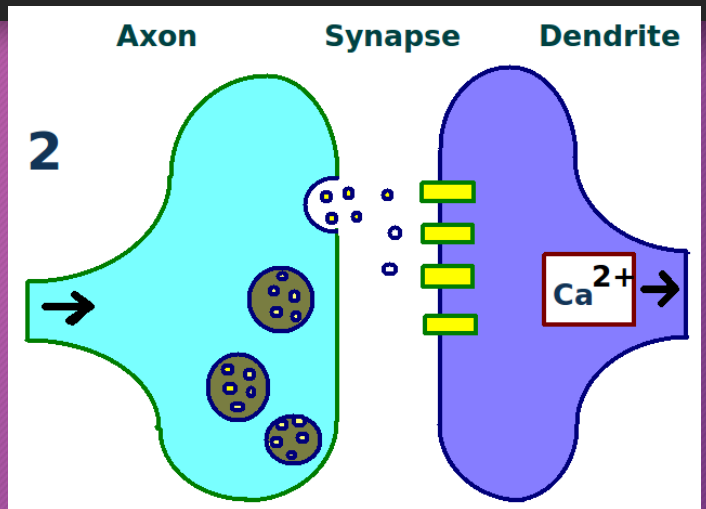
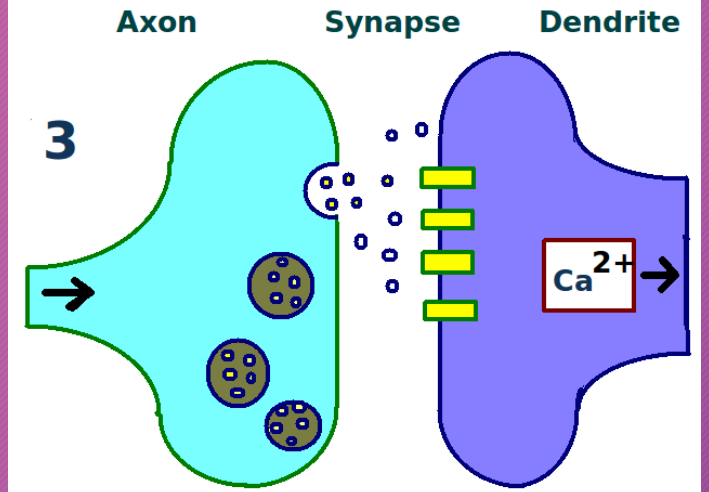
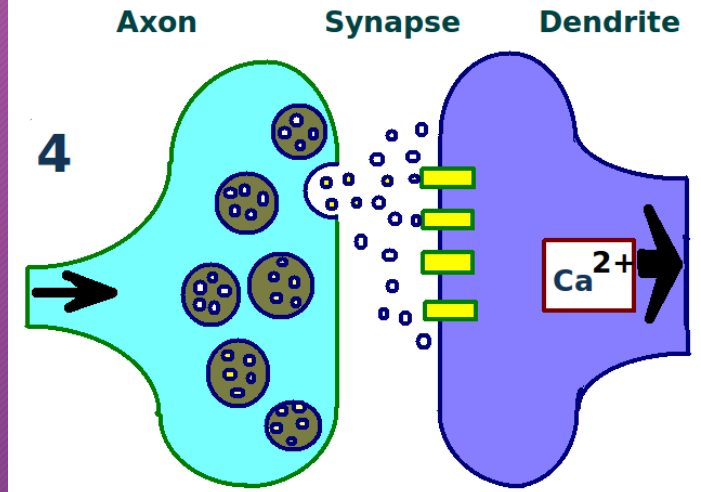
Long Term Potentiation









Excitotoxicity

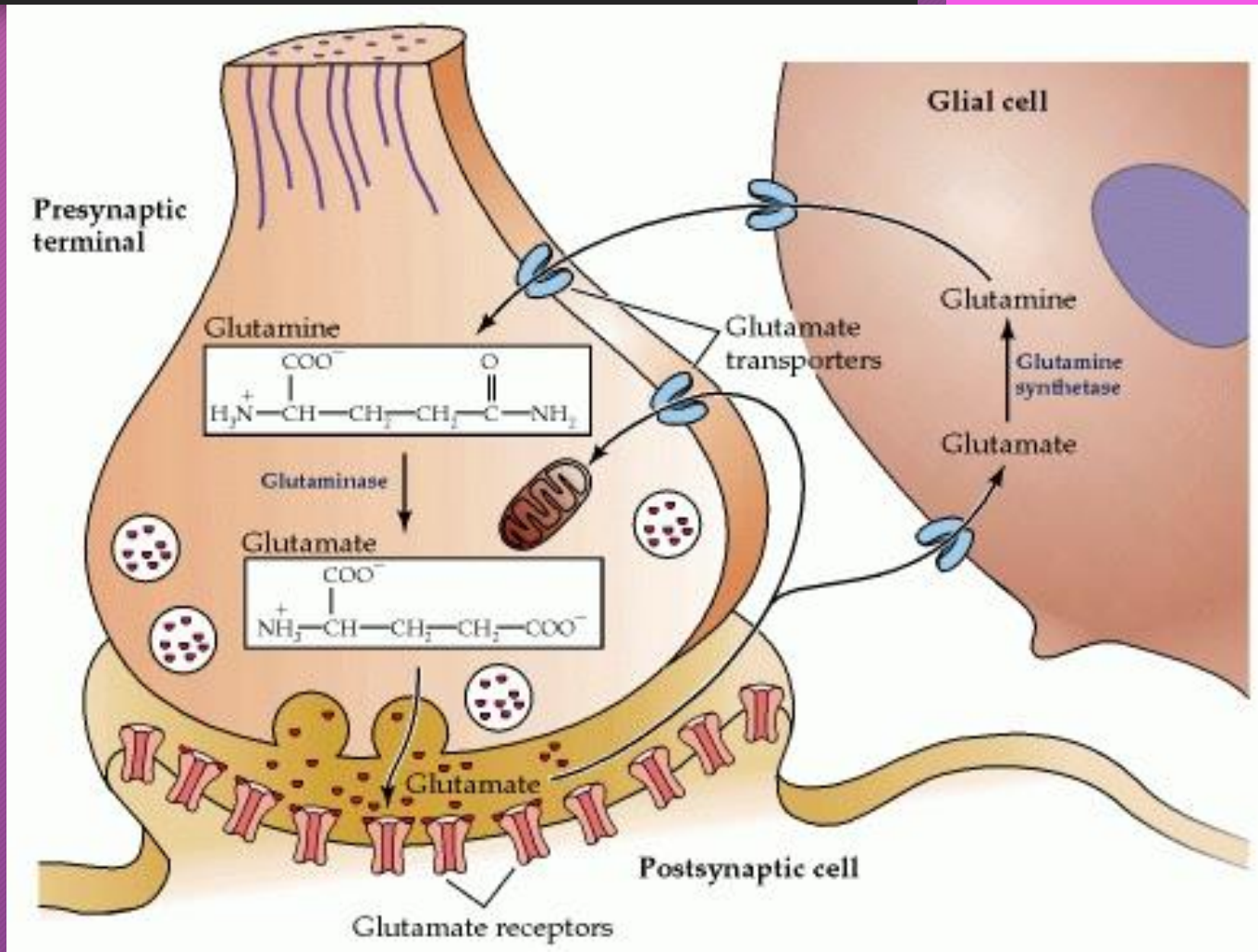
- **Excitotoxicity** is the pathological process by which nerve cells are damaged or killed by excessive stimulation by neurotransmitters such as glutamate and similar substances.
- Neuronal excitotoxicity usually refers to the injury and death of neurons arising from prolonged exposure to ***glutamate*** and the associated excessive influx of ions into the cell.
- The resulting **calcium** overload is particularly neurotoxic, leading to the activation of enzymes that degrade proteins, membranes and nucleic acids
- Excitotoxicity is considered to be a major mechanism of cell death in a number of central nervous system diseases including stroke, brain trauma, epilepsy and chronic neurodegenerative disorders.

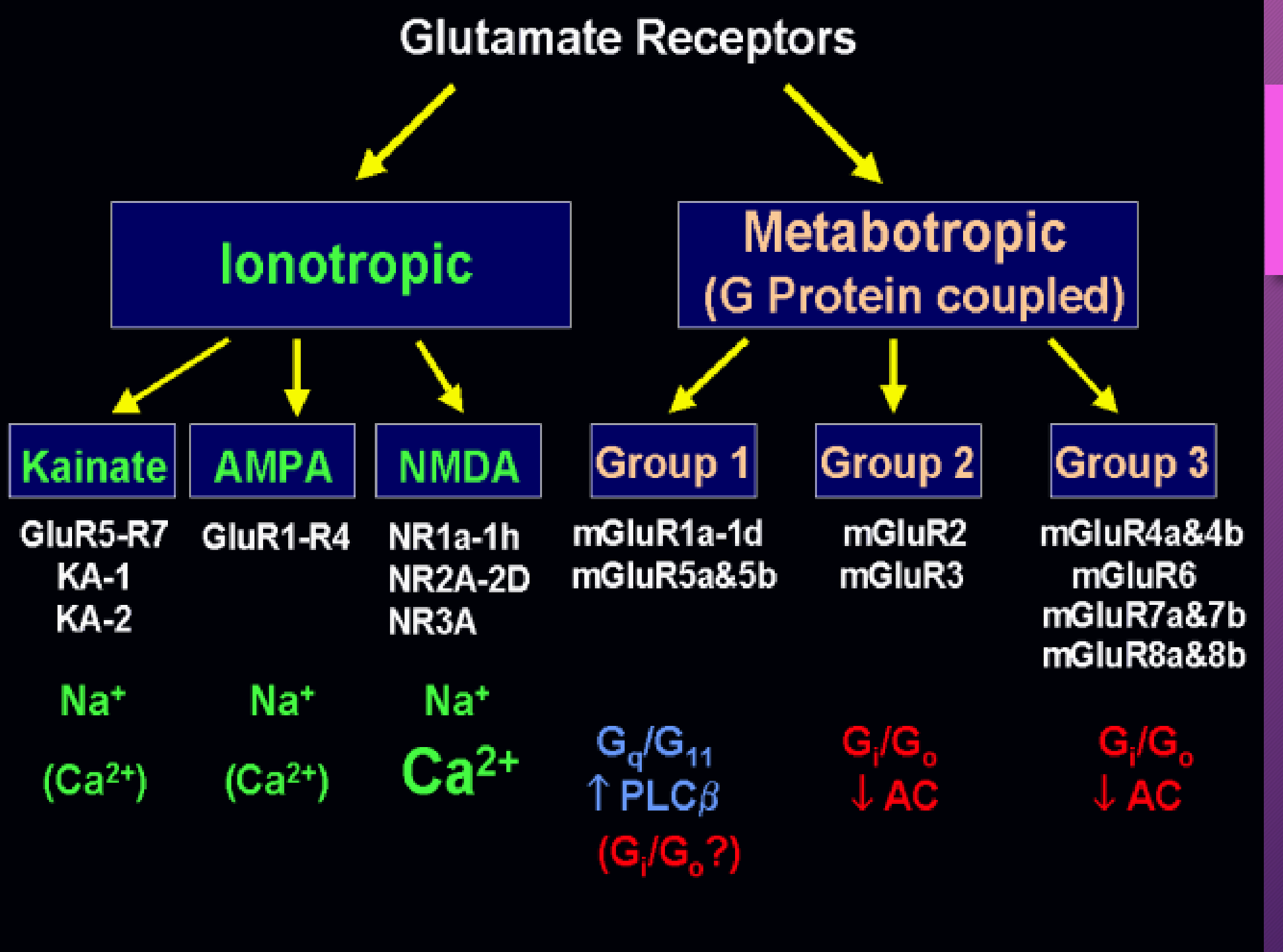
Glutamate

- **Excitatory Amino Acid**
- An important neurotransmitter for neural development, synaptic plasticity, and learning and memory under physiological conditions.
- This response is generated following an interaction of glutamate with ***receptors*** composing cation channels.
- Excessive activation of glutamate receptors can result in neuronal dysfunction and death, a process called excitotoxicity.

Glutamate synthesis

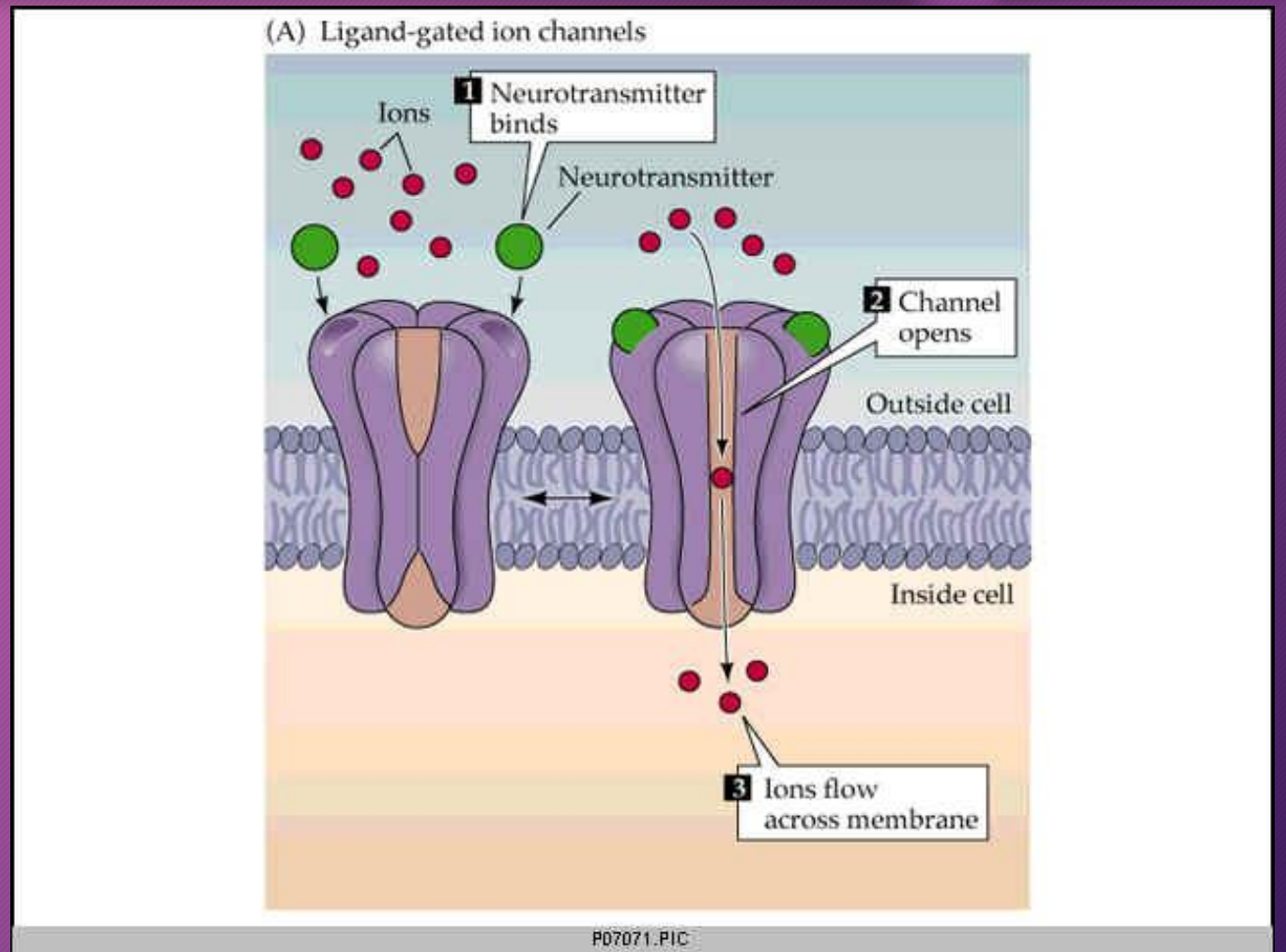
- Glutamate is a nonessential amino acid that does not cross the blood-brain barrier and must be synthesized in neurons from local precursors
- The most prevalent glutamate precursor in synaptic terminals is glutamine. Glutamine is released by glial cells and, once within presynaptic terminals, is metabolized to glutamate by the mitochondrial enzyme glutaminase
- Glutamate can also be synthesized by transamination of 2-oxoglutarate, an intermediate of the tricarboxylic acid (TCA) cycle. Hence, some of the glucose metabolized by neurons can also be used for glutamate synthesis.




Glutamate Receptors
Ionotropic
Metabotropic
(G Protein coupled)
Kainate
AMPA
NMDA
Group 1
Group 2
Group 3
GluR5-R7
KA-1
KA-2
GluR1-R4
NR1a-1h
NR2A-2D
NR3A
mGluR1a-1d
mGluR5a&5b
mGluR2
mGluR3
mGluR4a&4b
mGluR6
mGluR7a&7b
mGluR8a&8b
Na+
(Ca2+)
Na+
(Ca2+)
Na+
Ca2+
Gq/G11
↑ PLCβ
(Gi/Go?)
Gi/Go
↓ AC
Gi/Go
↓ AC

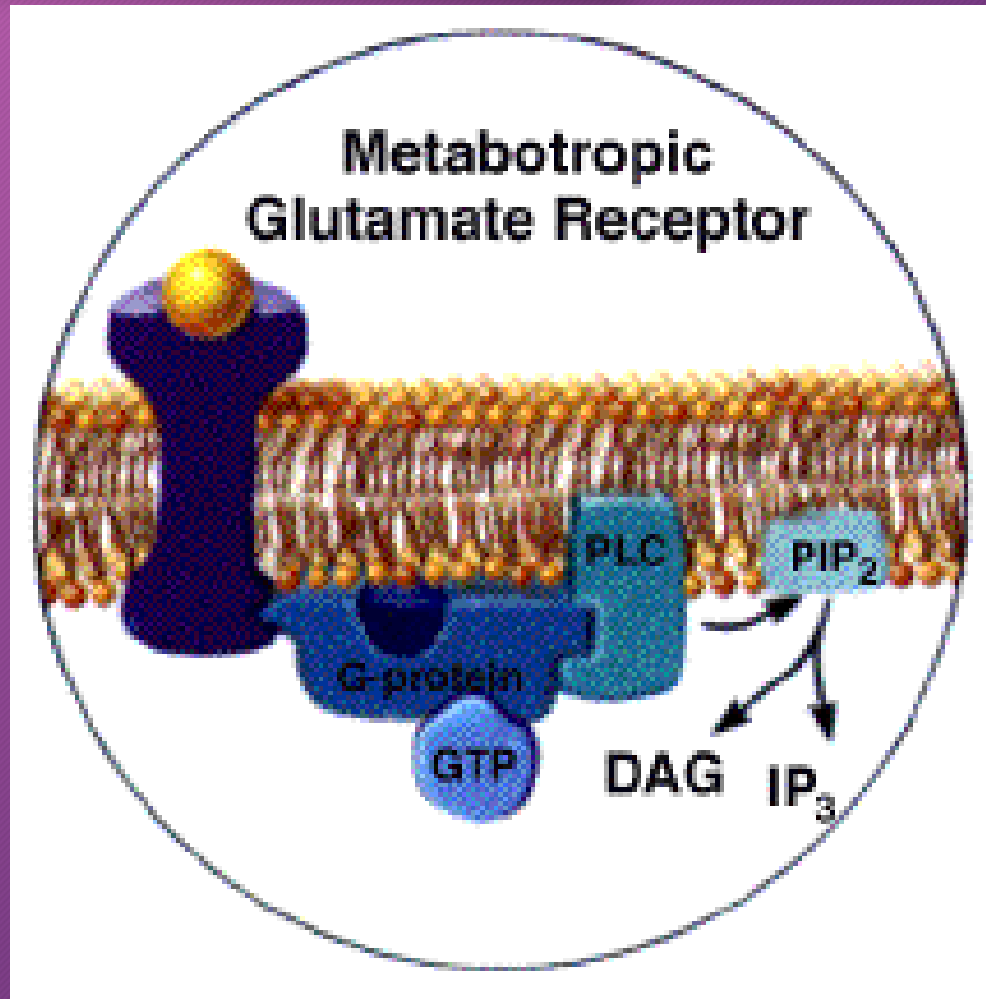
Ionotropic receptors

- Ligand gated non-selective cation channels.
- Allows flow of K^+, Na^+ and sometimes Ca^+ in response to glutamate binding.



Metabotropic receptors

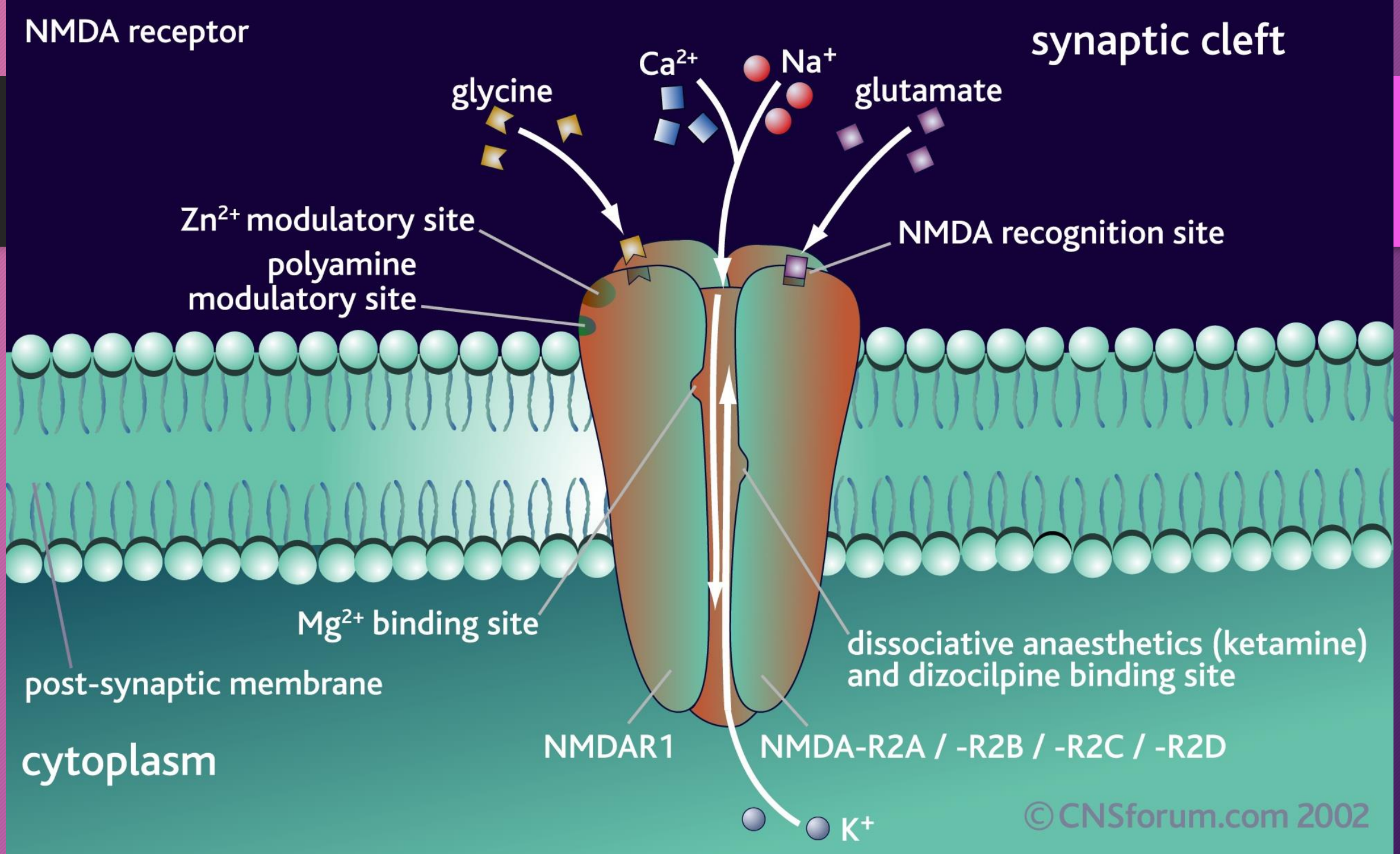
- Metabotropic receptors belong to the G-protein coupled receptor superfamily. Activation of metabotropic receptors leads to changes in cAMP levels and release of Ca2 from intracellular stores



NMDA Receptor

- NMDA receptors are glutamate-gated cation channels with high calcium permeability that play important roles in the processes underlying learning, memory, and neuroplasticity.

- Abnormal expression levels and altered NMDAR function have been implicated in numerous neurological disorders and pathological conditions.
- NMDAR hypofunction can result in cognitive defects, whereas overstimulation causes ***excitotoxicity*** and subsequent neurodegeneration.


NMDA receptor
synaptic cleft
glycine
Ca^{2+}
Na^{+}
glutamate
Zn^{2+} modulatory site
polyamine modulatory site
NMDA recognition site
Mg^{2+} binding site
post-synaptic membrane
dissociative anaesthetics (ketamine) and dizocilpine binding site
cytoplasm
NMDAR1
NMDA-R2A / -R2B / -R2C / -R2D
K^{+}
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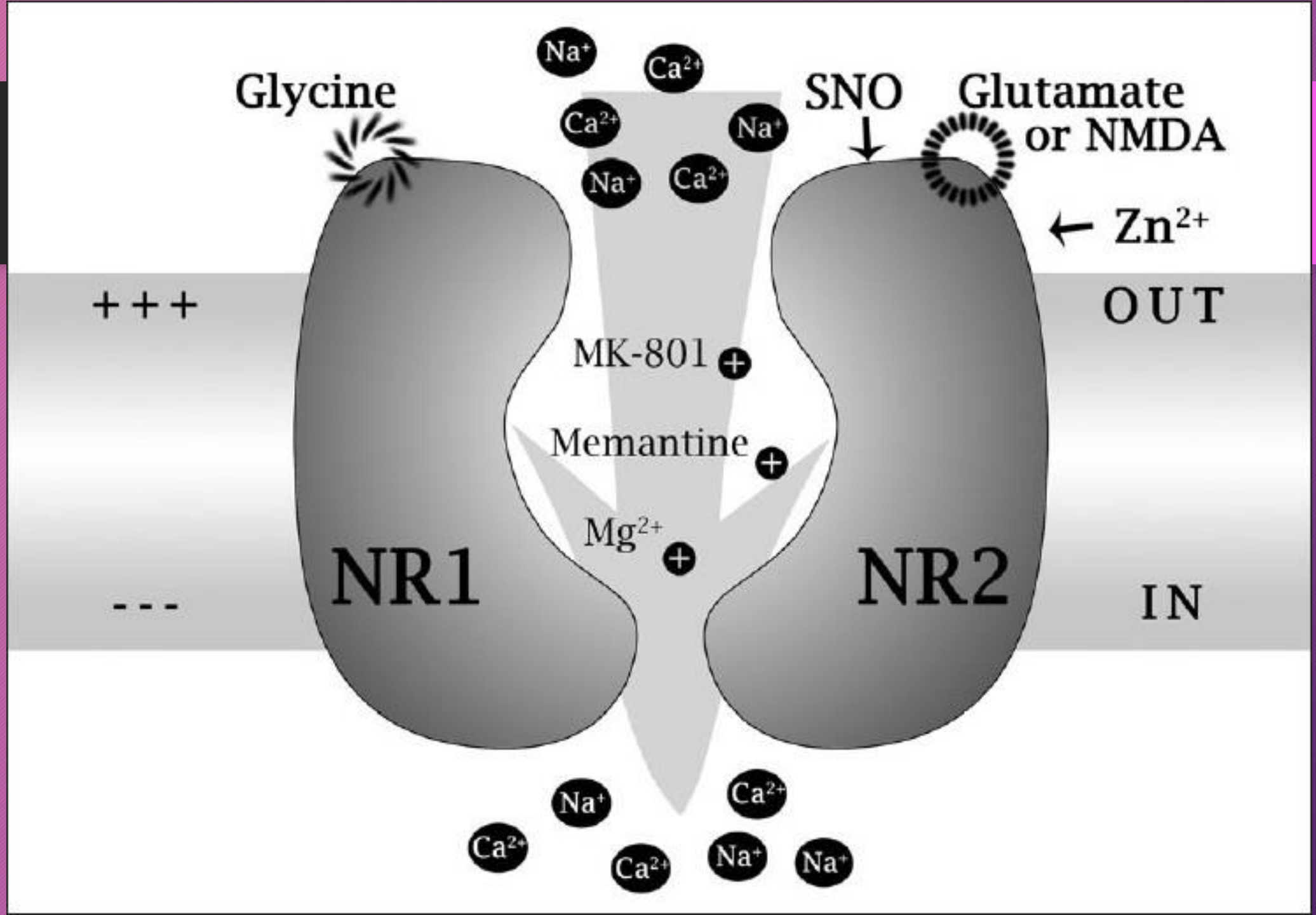
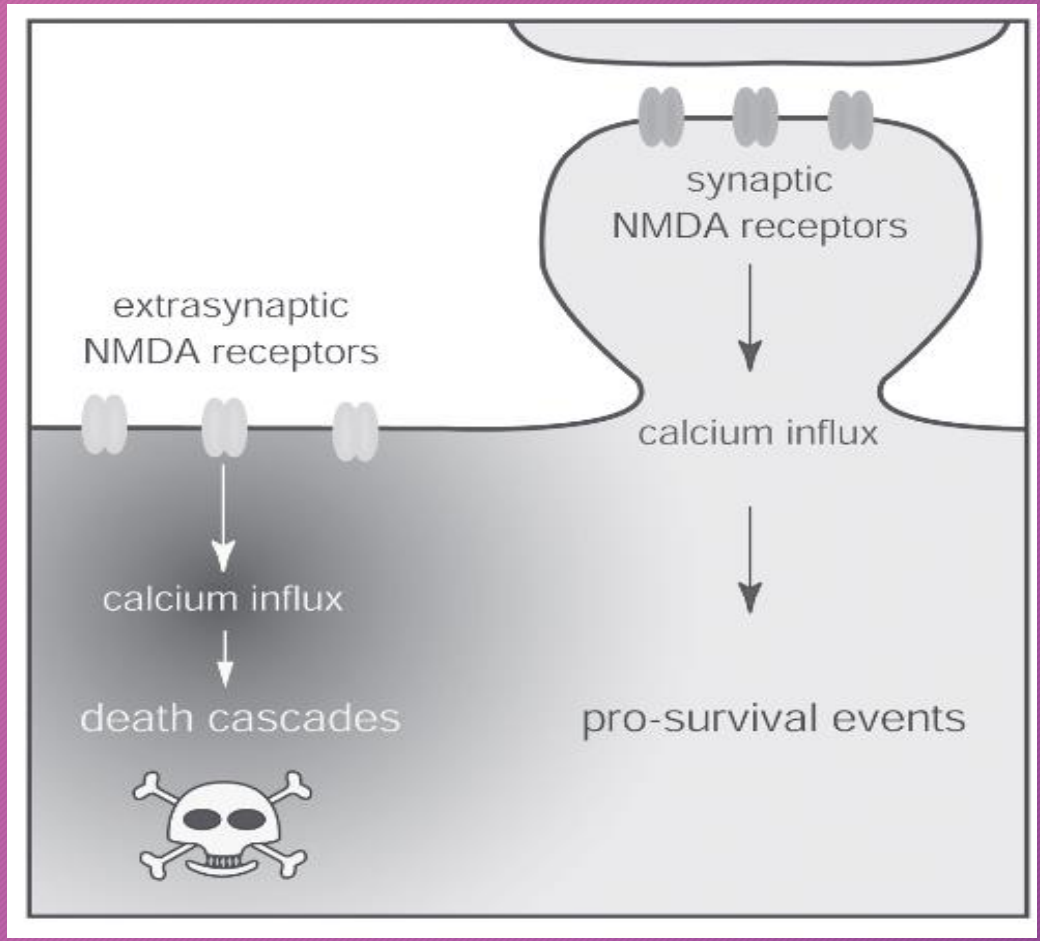
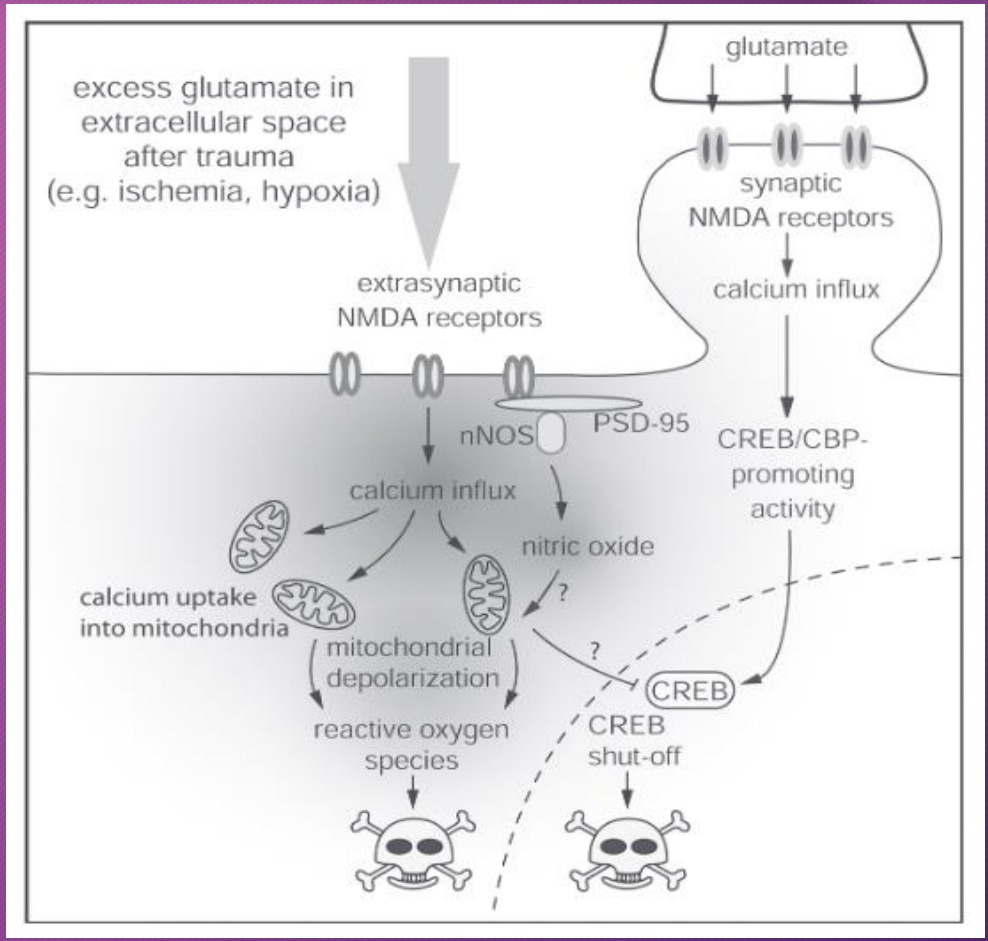

Glycine
SNO
Glutamate
or NMDA
← Zn2+
+++
OUT
MK-801
Memantine
Mg2+
NR1
NR2

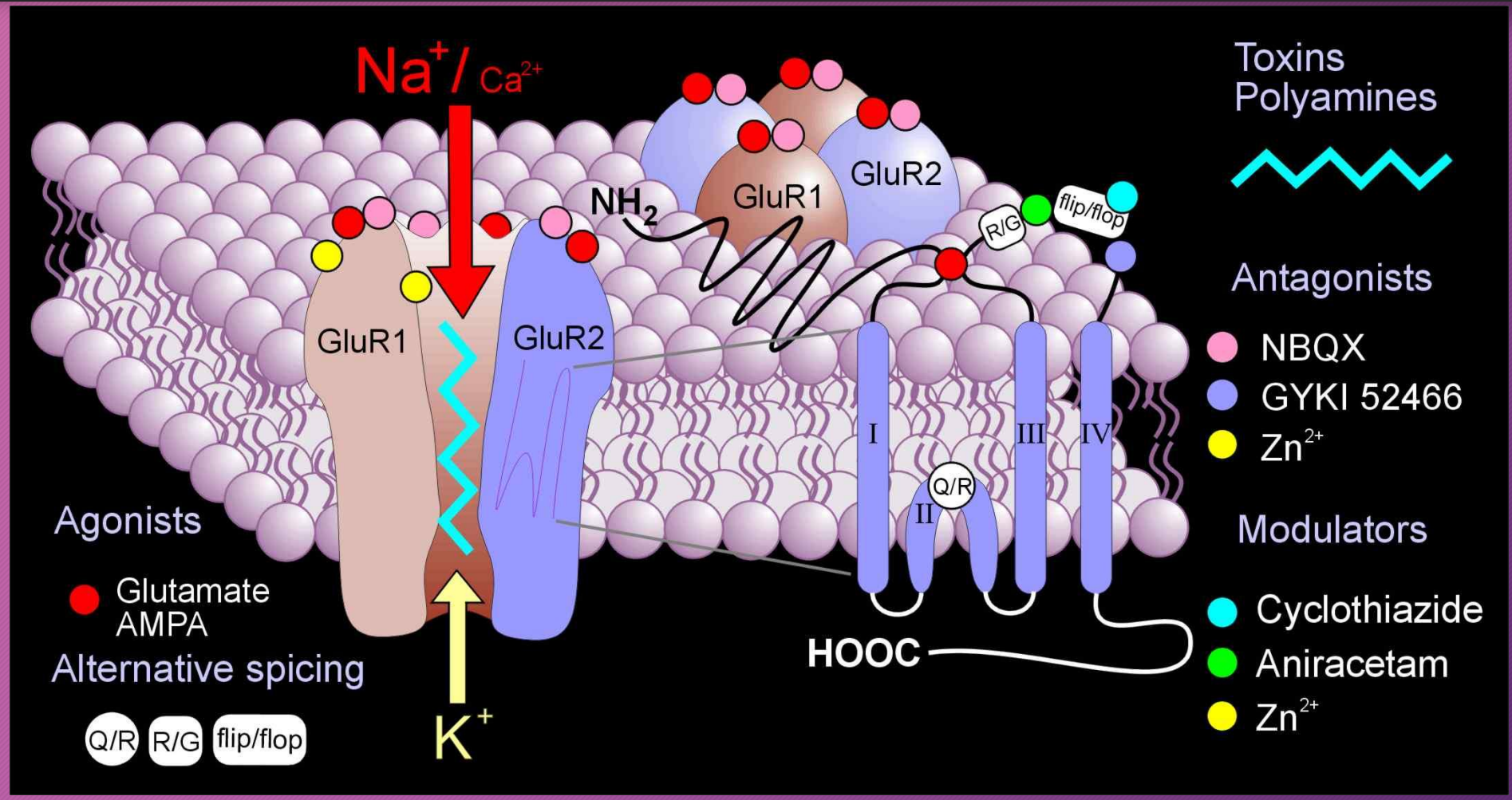
IN
Na+
Ca2+

Synaptic vs Extrasynaptic NMDAR





AMPA receptors



AMPA receptors

- AMPA-type glutamate receptors have also been implicated in excitotoxicity because assemblies of these receptors are highly permeable to Ca2.
- The Ca2+ permeability of the AMPA receptor is determined by the presence or absence of the GluR2 subunit in the receptor complex.
- Low expression of GluR2 permits the construction of AMPA receptors with high Ca2+ permeability.

Metabotropic receptors

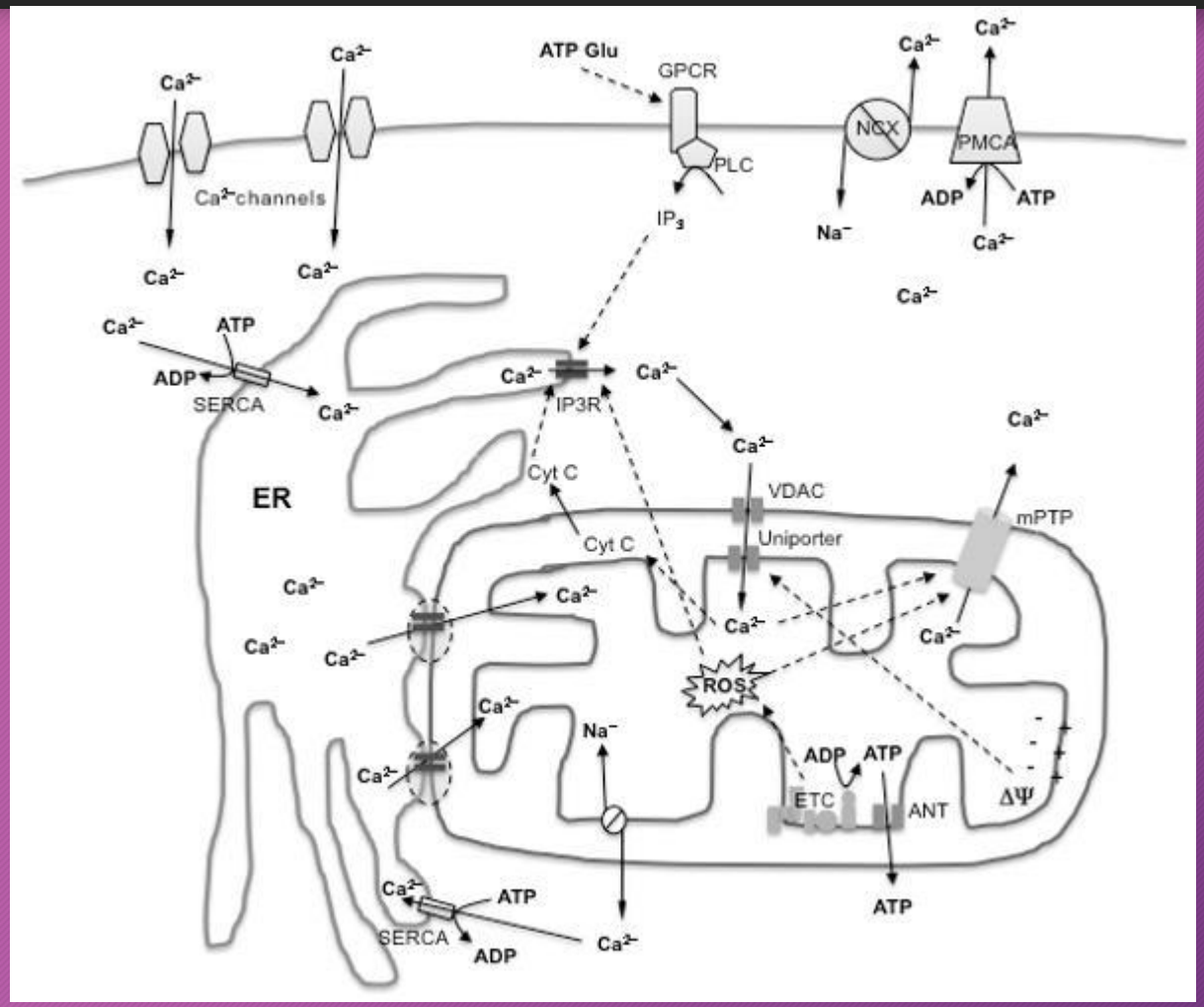
- Metabotropic (mGluR) receptors mediate slow synaptic responses, owing to their coupling with intracellular G-proteins
- mGluR1 and mGluR5 subunit subtypes are coupled to the inositol trisphosphate (IP3)/Ca2+ signal transduction pathway and can thus affect protein kinase activation and stimulation of Ca2+ release from neuronal stores, both of which can trigger delayed cell death processes.

Excitotoxicity and ions (Na+, Cl–, Ca2+)

- ***Acute*** excitotoxicity is thought to be mediated by excessive depolarization of the postsynaptic membrane.
- Numerous reports indicate that acute excitotoxicity following glutamate receptor activation is dependent on ***Na+ and Cl– entry***.
- Some studies suggest that cation-dependent Cl transport protein Na-K-Cl cotransporter type 1 (NKCC1) is involved in the initial stages of cell damage that depend on extracellular Na+ and Cl–.
- Inhibition of NKCC1 activity reduces NMDA-induced swelling and glutamate-mediated neurotoxicity

- Sustained Ca2+ influx through glutamate receptor channels is thought to represent a common pathway of neuronal cell death.
- Excess levels of glutamate in the CNS can result in elevated intracellular Ca2+ levels, which in turn cause a rise in the Ca2+ concentration in sensitive organelles such as mitochondria and the endoplasmic reticulum.

Calcium mediated excitotoxicity and mitochondrial dysfunction



- Mitochondrial calcium uptake regulates production and activation of three metabolic enzymes, the pyruvate, ketoglutarate and isocitrate dehydrogenases
- Under normal conditions, calcium induced depolarization activates mitochondrial dehydrogenases and mitochondrial ATP synthase
- Excessive calcium uptake into isolated mitochondria is known to result in increased formation of ROS, which in turn inhibits pyruvate dehydrogenase and tricarboxylic acid cycle enzymes as well as complex I of the respiratory chain. Further, mitochondrial dysfunction triggered by mild excitotoxic insult can lead to both caspase-dependent and independent apoptotic-like cell death

- The NMDA-mediated excessive Ca2+ entry into the cytosol activates ***calcineurin***, which induces apoptosis in both rat hippocampal neurons and stable cell lines such as HeLa cells
- A number of studies have shown that activation of ***calpain***, a calcium dependent apoptotic protease, also precedes cell death under various conditions of elevated cytosolic Ca2+

Excitotoxicity and oxidative stress

- It is evident that excitotoxicity is related to the generation of free radicals produced as a consequences of activation of calcium-dependent enzymes, such as phospholipase A2, nitric oxide synthase, and Xanthine oxidase and by oxidative dysfunction in mitochondria.
- Glutamate receptor over-stimulation is the main mediator to intracellular oxidative stress


Thank you!