Amino acid & amino acid derivatives neurotransmitters

(Glutamate, Aspartate, Glycine, Histamine & GABA)

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Glutamate: an excitatory amino acid neurotransmitter

- **The main excitatory neurotransmitter in the nervous system**
- **Neurons responding to glutamate are glutamatergic neurons**
- **Glutamate receptors:**

  - found throughout brain and spinal cord in neurons & glia.

  - ~ 25 subtypes of 3 ionotropic & 3 metabotropic receptor types
- **Three prescription medications specifically target glutamate or its receptors (memantine, ketamine, and D-cylcoserine). The side effects from these medications is extremely high which limit their use.**

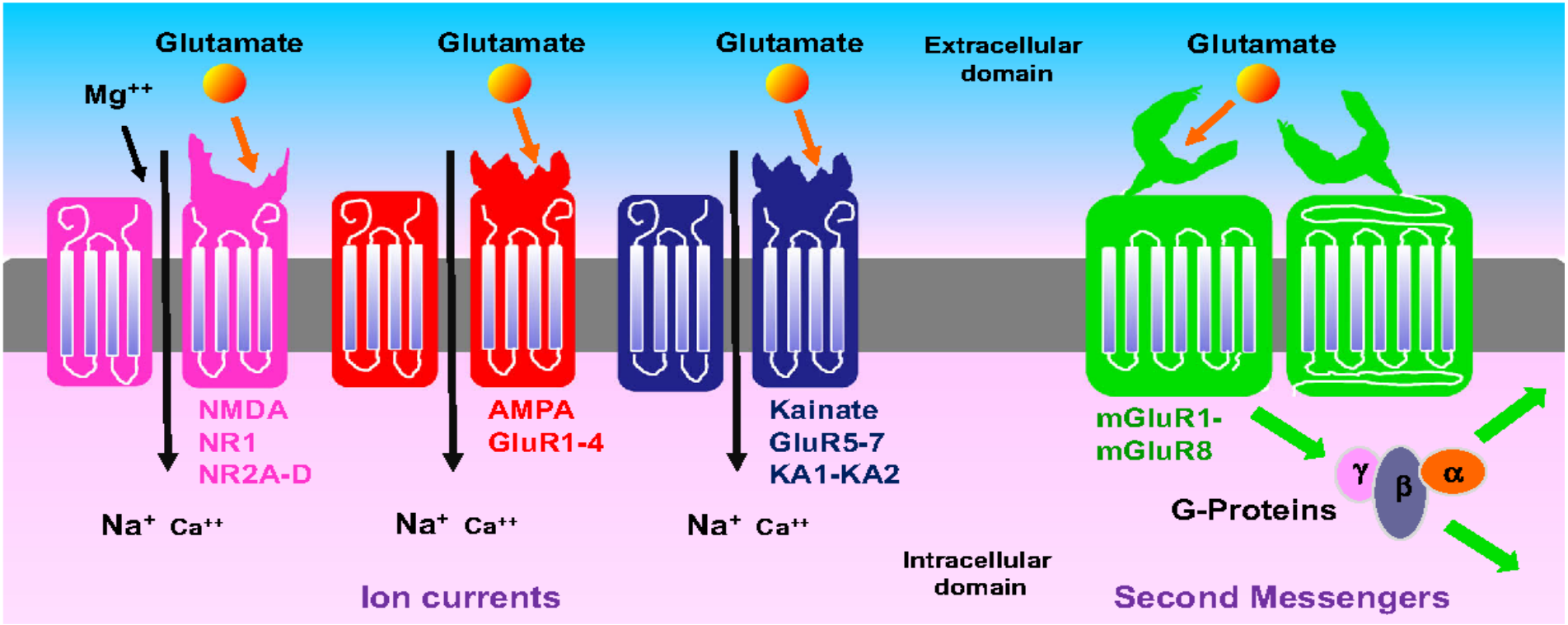
Glutamate receptors:

Ionotropic glutamate receptors (iGluR), which are ion channel receptors

NMDA	AMPA	Kainate
NR1 NR2A,B,C,D NR3A,B	GluR1 GluR2 GluR3 GluR4	KA1,2 GluR5 GluR6 GluR7

Metabotropic glutamate receptors (mGluR), which are G-protein coupled receptors

Group I	Group II	Group III
mGluR1 mGluR5	mGluR2 mGluR3	mGluR4 mGluR6 mGluR7 mGluR8



NMDA: *N*-methyl-D-aspartate, AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

Glutamate-glutamine cycle in the brain:

- It is the an interaction between the cerebral blood flow, neurons, and the protective astrocytes that regulates the metabolism of glutamate, glutamine, and ammonia.

Steps:

1. NH_4^+ in blood or from brain metabolic processes is taken up by astrocytes and incorporated into glutamate via glutamine synthetase.
2. Glutamine then is transported to presynaptic neurons via sodium-coupled neutral amino acid transporter 7 (SNAT7).
3. Within the presynaptic neuron glutamate is formed from the glutamine via the action of glutaminase.
4. Glutamate is released from secretory vesicles in presynaptic neurons to the synaptic cleft in response to propagation of nerve impulse along axons. Its release is Ca^{+2} dependent.

Glutamate-glutamine cycle in the brain:

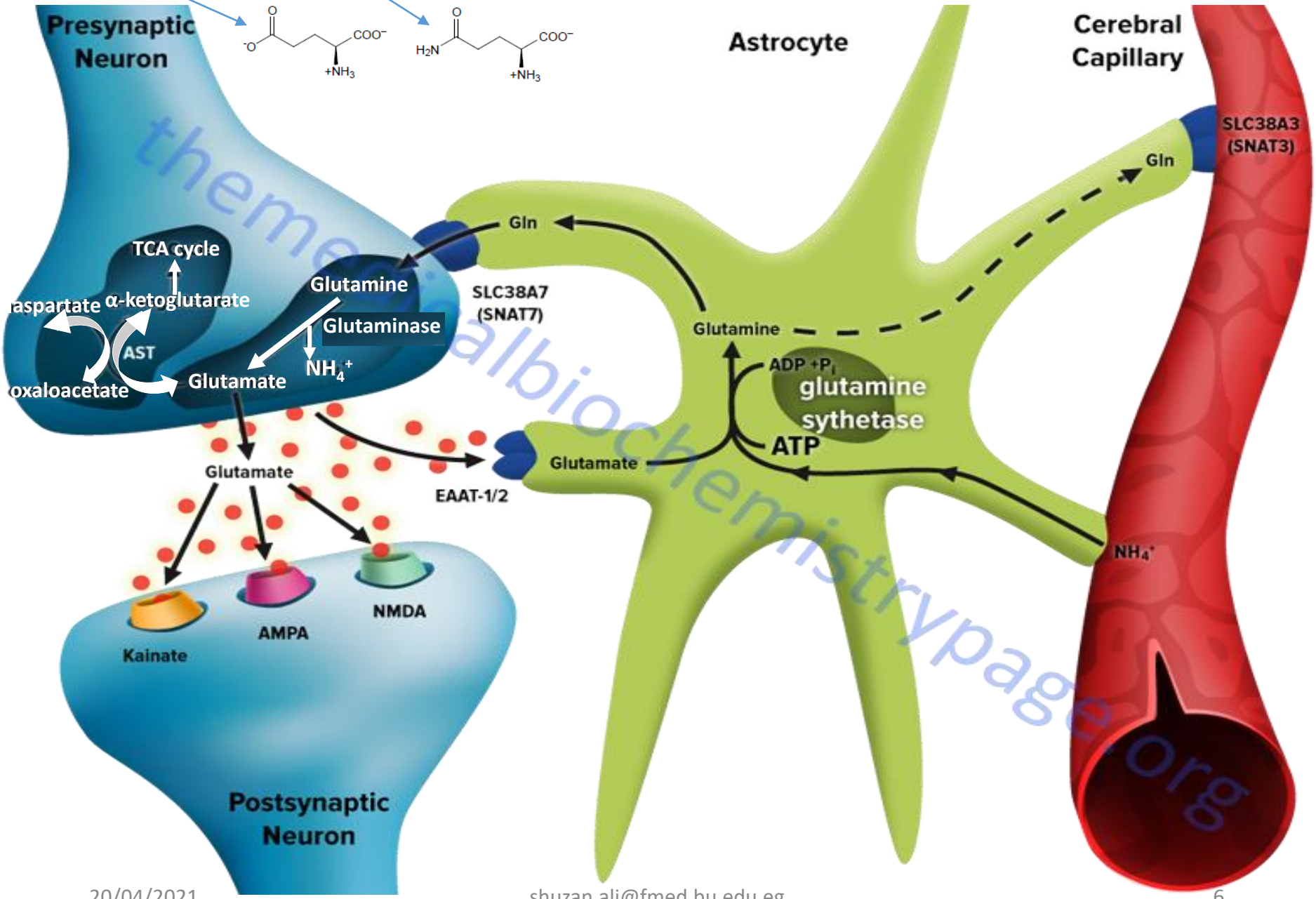
Steps:

5. **After making its action, it is rapidly removed to prevent over excitation of postsynaptic neurons. It is removed by three ways:**
   - **a. Uptake by postsynaptic neurons**
   - **b. Reuptake by presynaptic neurons**
   - **c. Uptake up by astrocytes (both Na^+-dependent & independent).**
     Na^+-dependent is predominant and it occurs via excitatory amino acid transporters 1 & 2 (EAAT1 & EAAT2).

6. **Within astrocytes, glutamate is converted back to glutamine. Some of astrocyte glutamine can be transported into blood via called sodium-coupled neutral amino acid transporter 3 (SNAT3).**

Aspartate: stimulates NMDA receptor but not as strong as glutamate

Glutamate-glutamine cycle in the brain:

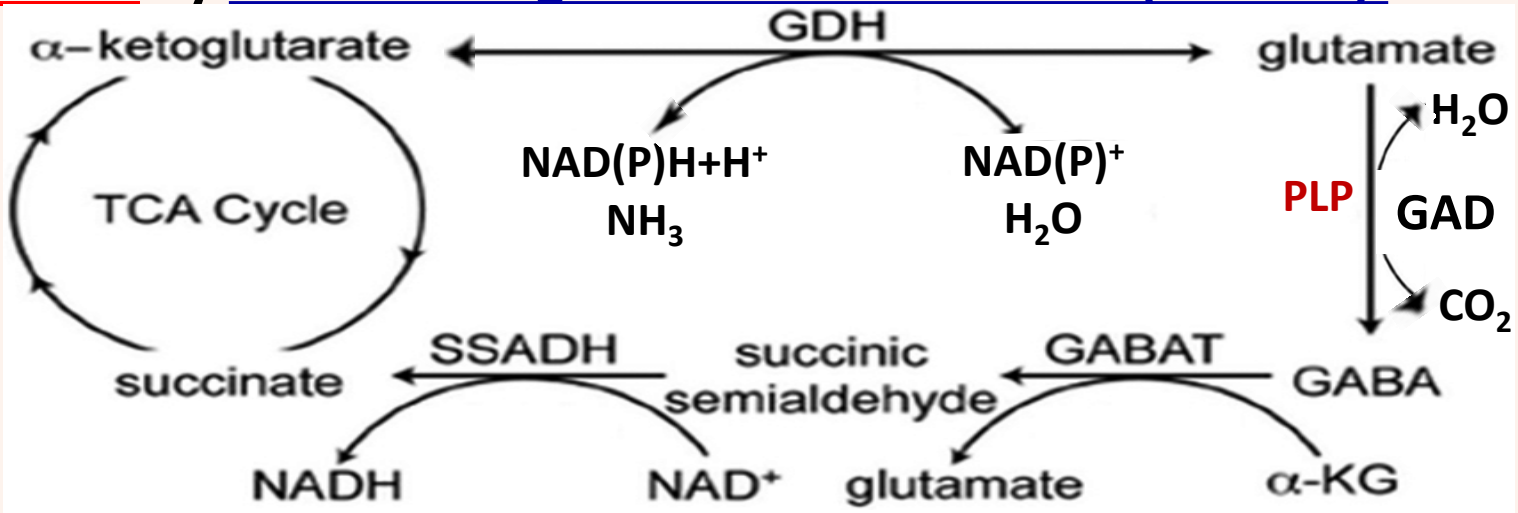


Gamma (γ) amino butyric acid (GABA): (an inhibitory amino acid derivative neurotransmitter)

- GABA is the chief inhibitory neurotransmitter in brain.
- It is a major inhibitor of presynaptic transmission in CNS & retina.
- Neurons that secrete GABA are termed GABAergic.

Synthesis & catabolism:

- GABA cannot cross BBB, so must be synthesized within neurons
- Glucose is the principal precursor for GABA via conversion in TCA cycle to α-ketoglutarate. In GABA shunt α-ketoglutarate is trans-aminated to glutamate by GABA α-oxoglutarate transaminase (GABA-T).



GDH: glutamate dehydrogenase, GAD: glutamate decarboxylase, SSADH: Succinate semialdehyde dehydrogenase

Gamma (γ) amino butyric acid (GABA):

GABA exerts its effects by binding to 2 receptor subtypes:

1. **GABA-A (GABAA) ionotropic receptors:**

They are Cl^- channels increasing Cl^- influx into GABAergic neuron.

2. **GABA-B (GABAB) metabotropic G-protein coupled receptors:**

They activate K^+ channel leading to K^+ efflux from the cell.

Clinical implications:

1. Glutamate decarboxylase needs PLP, so in **vitamin B6 deficiency**, there is ↓ synthesis of GABA→ convulsions

2. **PLP** is generated from vit. B6 by pyridoxal kinase (requires zinc). **zinc deficiency or pyridoxal kinase defects** → seizures, as in pre-eclampsia

3. **Sedation by benzodiazepine & barbiturates** by binding GABA-A receptor. Benzodiazepine potentiates GABA-A receptors responses to GABA binding. Barbiturates can induce GABA-A channel opening in absence of GABA if administered at high dose so they can be lethal due to CNS suppression. Lethal toxicity of benzodiazepines requires a large dose. So barbiturates are not often used clinically any longer.

Glycine: an inhibitory amino acid neurotransmitter

- Glycine & GABA are the **major inhibitory** neurotransmitters in CNS
- Glycine can also function in an **excitatory capacity** as a co-agonist acting on the **NMDA** subtype of glutamate receptors.
- Glycinergic synapses mediate fast inhibitory neurotransmission within spinal cord, brainstem & caudal brain. It exerts control over a variety of motor & sensory functions, including vision and audition.

Glyine receptors (ionotropic ligand-gated ion channels):

- Glycine binding → opening of GlyR integral anion channel → **Cl^- influx** → **hyperpolarizes** postsynaptic cell, inhibiting neuronal firing.
- GlyR is formed of α & β subunits. (GlyRα and GlyRβ). These subunits are tightly bound to a cytosolic scaffolding protein **(Gephyrin).** Humans express four GlyR genes encoding α subunits (GLRA1–GLRA4) and a single GlyR gene for β subunit (GLRB).

Glycine: an inhibitory amino acid neurotransmitter

Glycine Transporters: (2 types)

a. GlyT1: predominantly expressed in glutamatergic neurons
it regulates glycine levels in NMDA-type glutamate receptors

b. GlyT2: predominantly expressed in glycinergic neurons
It regulates inhibitory glycinergic neurotransmission

Both terminates glycine action by reuptake into presynaptic terminals.

Hereditary hyperkplexia (HKPX)= startle syndrome:

- **Hyperekplexia** ("exaggerated surprise"): a neurologic disorder with exaggerated startle response (eye blinking or body spasms) to sudden unexpected noise, movement, or touch and hypertonia.

Forms:

a. HKPX1 (hereditary hyperekplexia type 1): Several mutations in glycine receptor **alpha 1** (GLRA1) gene

b. HKPX2: caused by mutations in glycine receptor **beta** (GLRB) gene.

c. HKPX3 (hereditary hyperekplexia type 3): inherited hyperekplexia, of presynaptic origin due to mutations in **GlyT2** gene.

d. Mutation of Gephyrin (GPHN)

Histamine: an excitatory amino acid derivative neurotransmitter

- Histamine is a **biogenic amine** which is a potent **excitatory** neurotransmitter that binds to specific **histamine receptors**.

Synthesis:

- Histamine is synthesized by decarboxylation of histidine by **L-histidine decarboxylase (HDC).**
- Within the GIT, bacteria also produce histamine by a similar reaction.
- The principal cells that synthesize and release histamine are:

a. **Mast cells and basophils** of immune system (>90%)

b. **Enterochromaffin-like cells** of the GIT

c. **Neurons in the brain**: tuberomammillary nucleus of hypothalamus.

Functions: - In the brain, it affects arousal & attention.

- In the periphery, it affects inflammation and vasodilatation

THANK YOU