

CNS

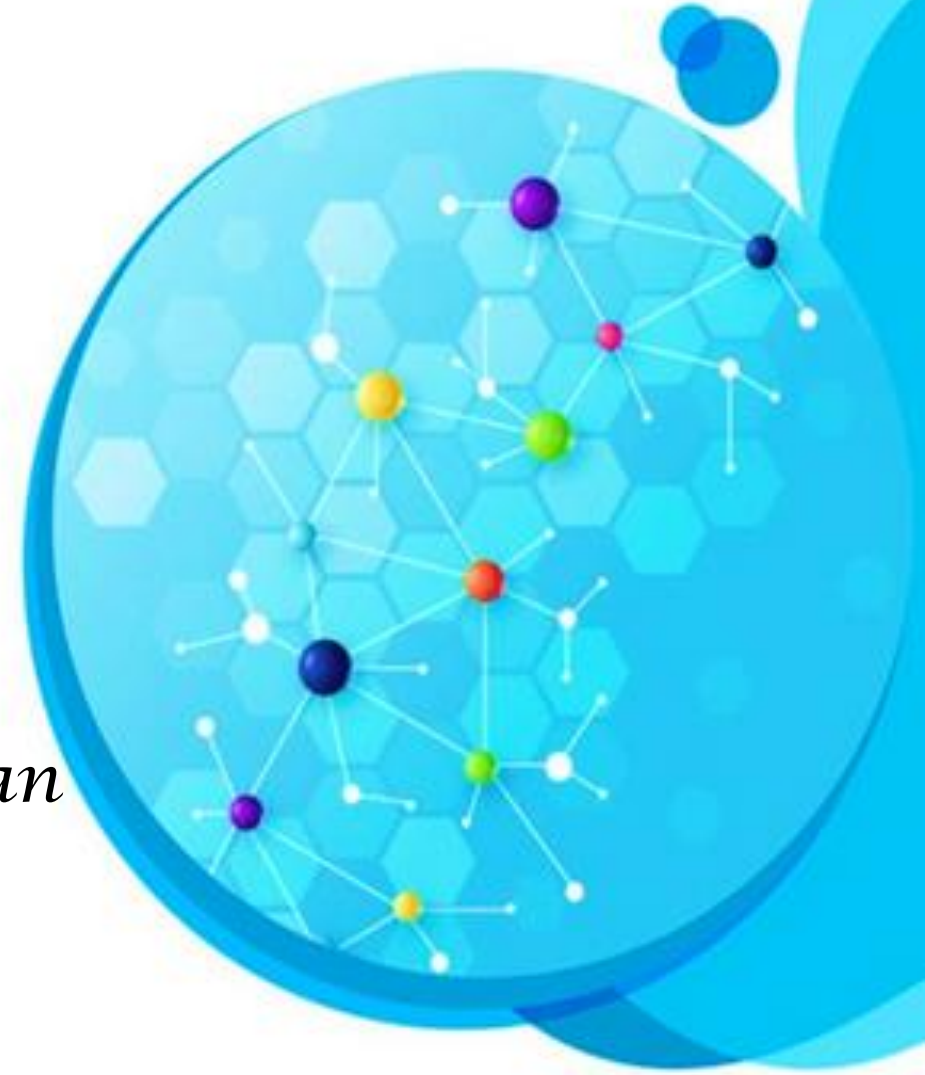
Medical Biochemistry

*Biochemistry of
neurotransmitters*

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Neurotransmitters

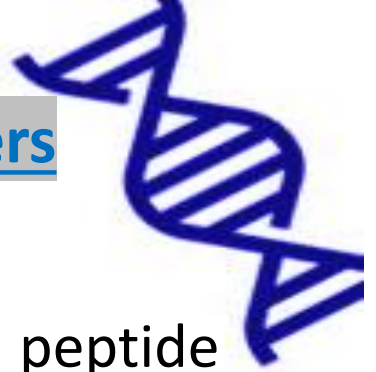
Small-molecule neurotransmitters



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Overview of biosynthesis of small-molecule neurotransmitters



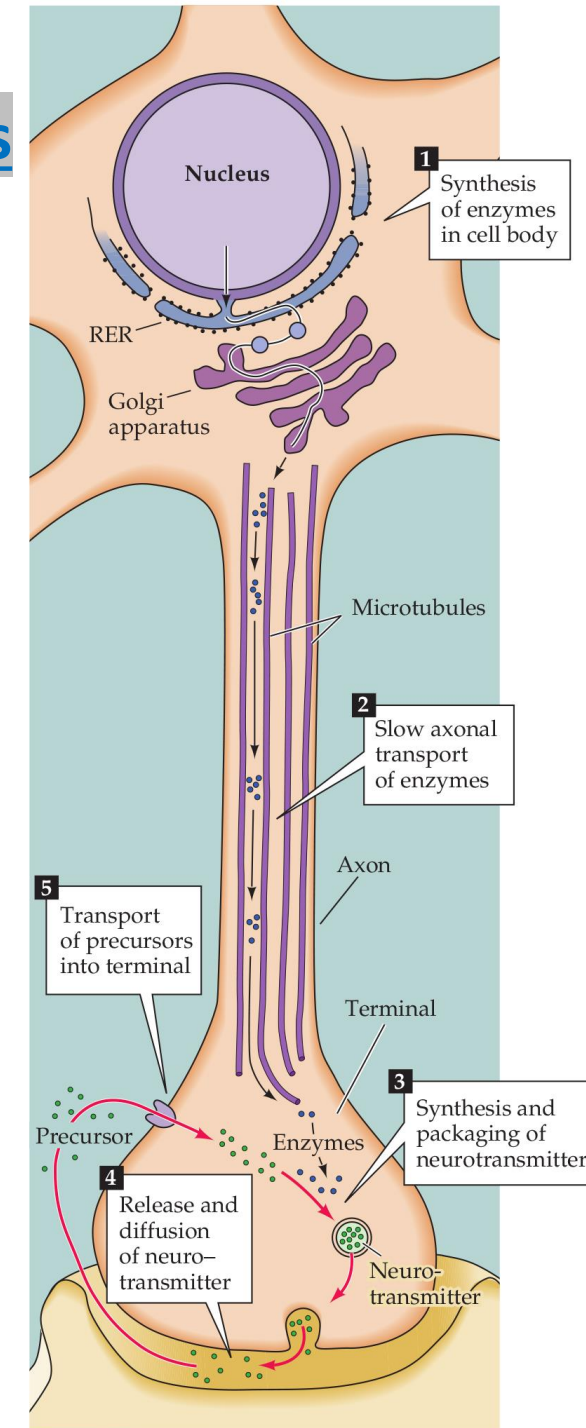
- The mechanisms responsible for the synthesis and packaging of peptide transmitters are fundamentally **different** from those used for the small molecule neurotransmitters.
- Peptide-secreting neurons generally synthesize polypeptides in their **cell bodies** [**Fast Axonal Transport** (~200–400 mm/day)].
- The synthesis of small-molecule neurotransmitters occurs within **presynaptic terminals**. The **enzymes** needed for **transmitter synthesis** are synthesized in the neuronal **cell body** and transported to the nerve terminal cytoplasm at 0.5–5 millimeters a day by a mechanism called **slow axonal transport**.





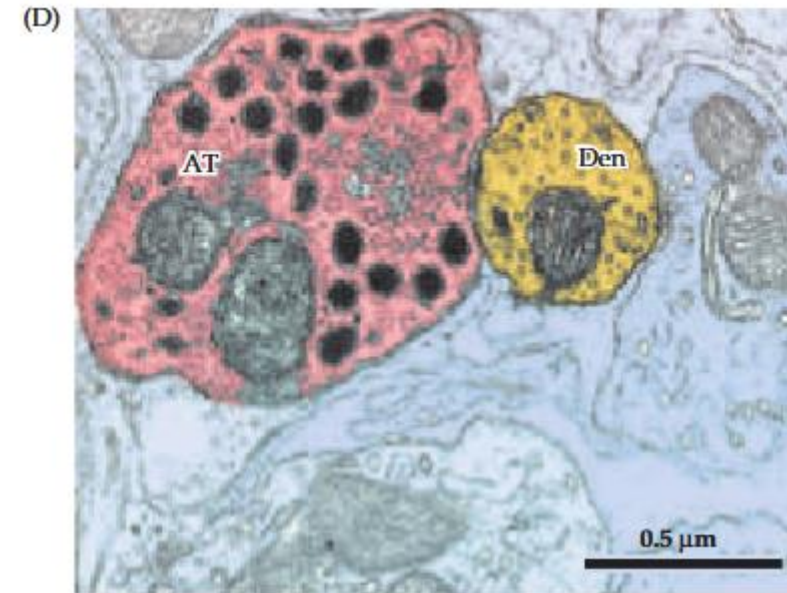
Synthesis of Small-Molecule Neurotransmitters

- The enzymes required for neurotransmitter synthesis are produced in RER and transported to the axon terminal cytoplasm via slow axonal transport.
- The precursors for neurotransmitter synthesis (e.g., amino acids, choline) are taken up from the extracellular fluid or derived from metabolic pathways.
- The transported enzymes catalyze the conversion of these precursors into neurotransmitters.
- Once synthesized, neurotransmitters must be stored in synaptic vesicles to prevent degradation and allow for rapid release upon stimulation.
- Vesicular transporters (e.g., VMAT for monoamines, VACHT for ACh, VGAT for GABA) actively transport neurotransmitters into vesicles.
- Release and they have a short action.
- Termination by Reuptake, Enzymatic degradation, or diffusion



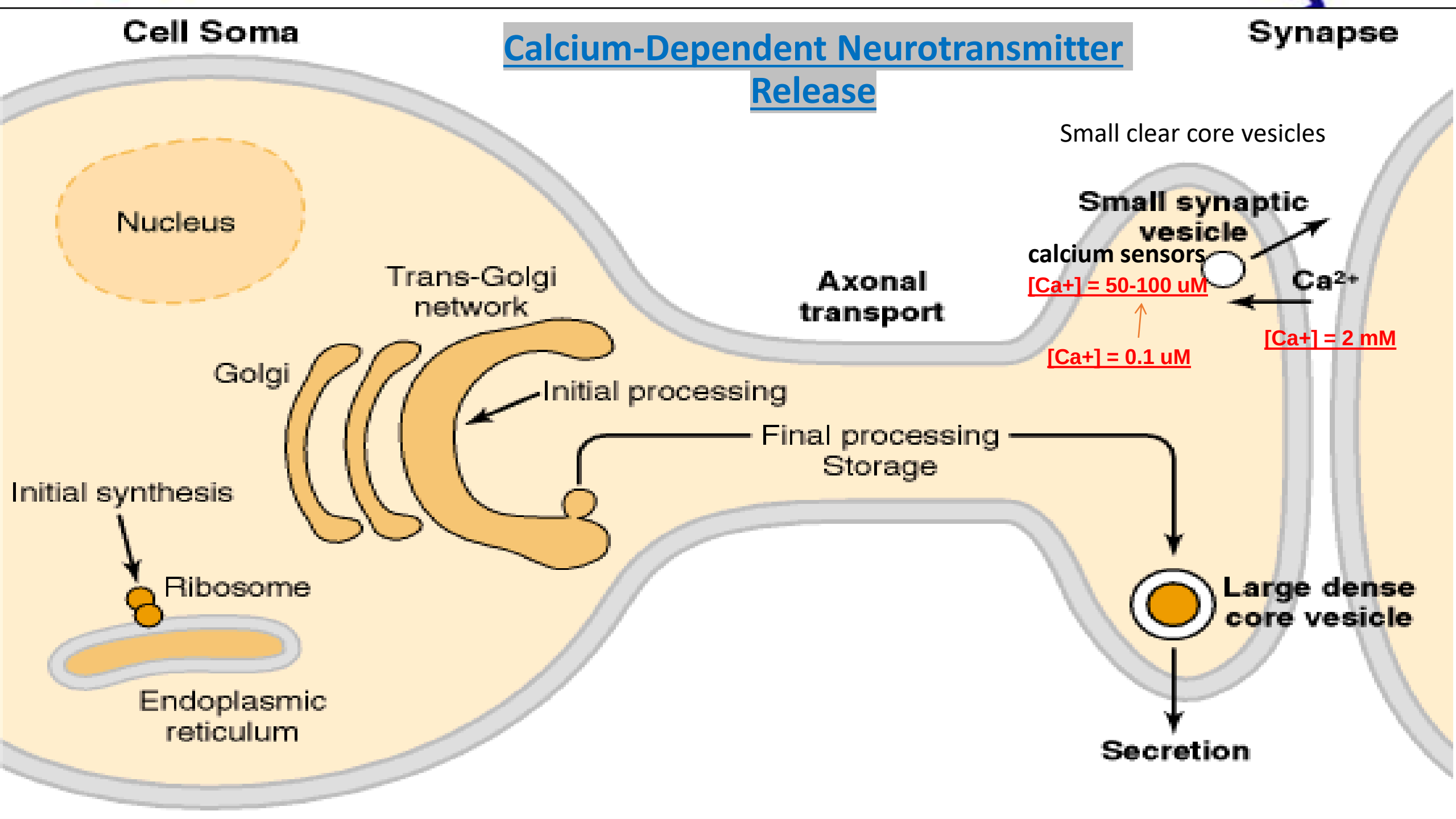


Small clear core vesicles



Most small-molecule neurotransmitters are packaged in vesicles 40 to 60 nm in diameter, the centers of which appear clear in electron micrographs; accordingly, these vesicles are referred to as small clear core vesicles







Small-Molecule Neurotransmitters

Specific examples of neurotransmitter synthesis

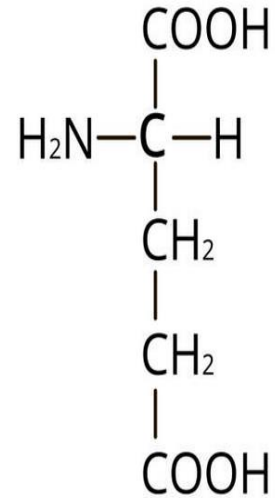


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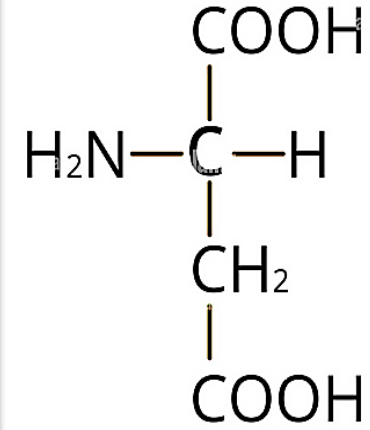




Glutamic Acid



Aspartic Acid



Both are excitatory neurotransmitters.

Glutamate, GABA and Aspartate

Since glutamate and aspartate cannot enter the brain (**Do not cross BBB**) from the bloodstream, **neurons and glial cells must synthesize them locally (nonessential).**



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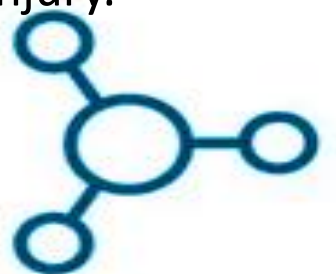




Physiological and Clinical Implications of Glutamate and Aspartate

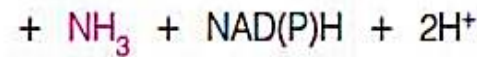
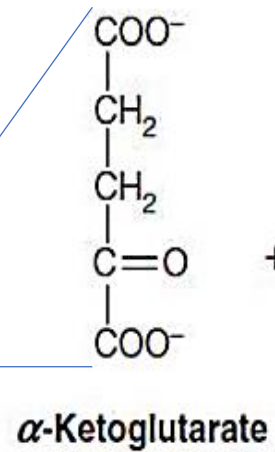
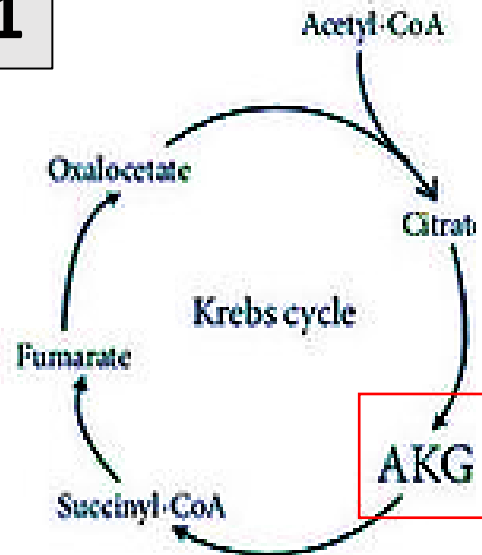


- Glutamate and aspartate are key players in **long-term potentiation (LTP)**, a process that strengthens synaptic connections and is essential for **learning and memory**.
- Deficits in glutamatergic signaling are linked to **cognitive impairments**, such as those seen in Alzheimer's disease.
- **Glutamate-mediated signaling** in the motor cortex and spinal cord is vital for **coordinated muscle movement**.
- Dysfunction in glutamatergic pathways leads to **motor disorders**, such as amyotrophic lateral sclerosis [ALS].
- Prolonged stimulation of neurons by excitatory amino acids results in neuronal death or injury.
- Overexcitatory effects result in Alzheimer's disease.

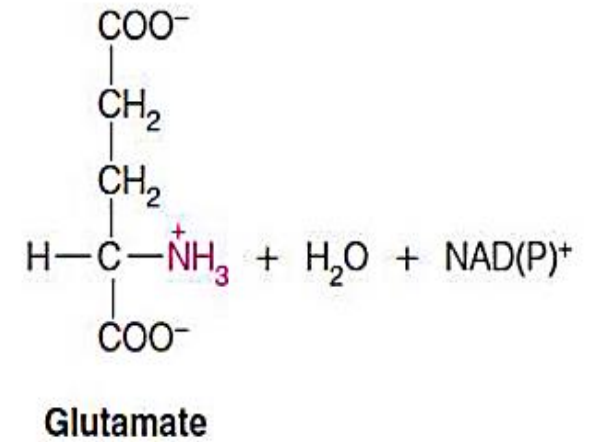


Synthesis of glutamate

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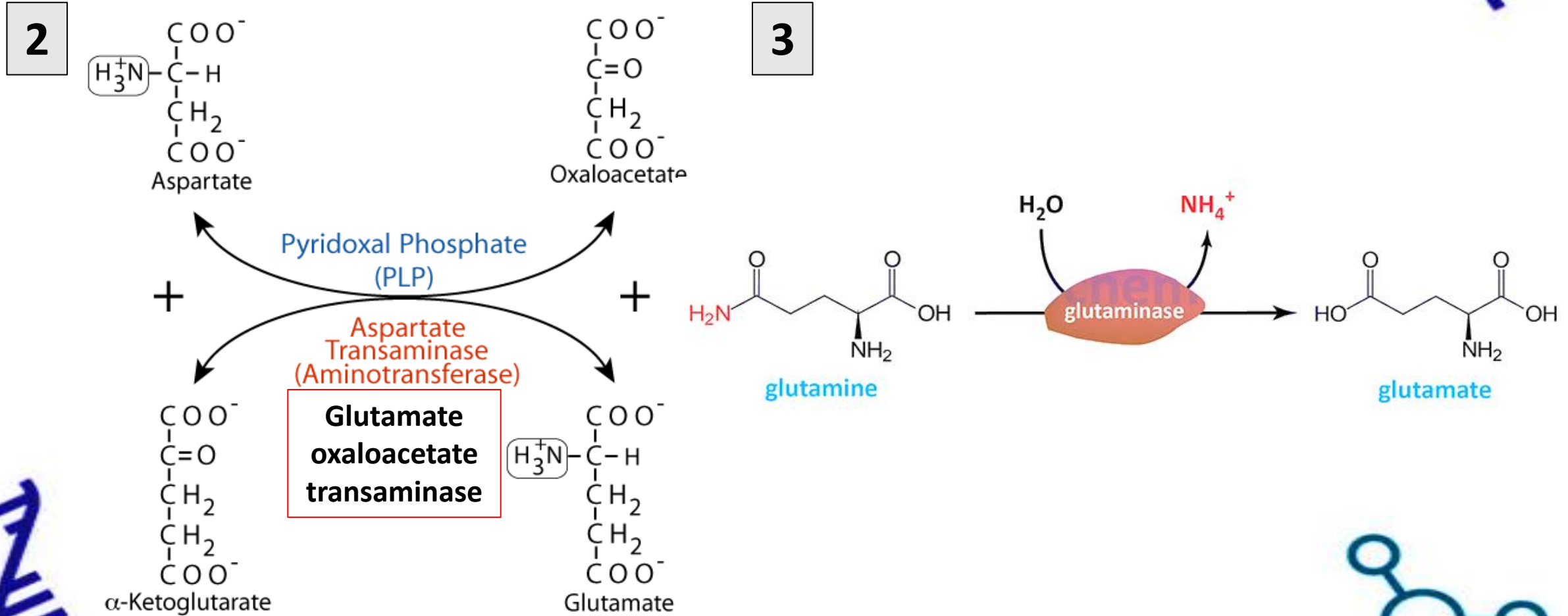


GDH

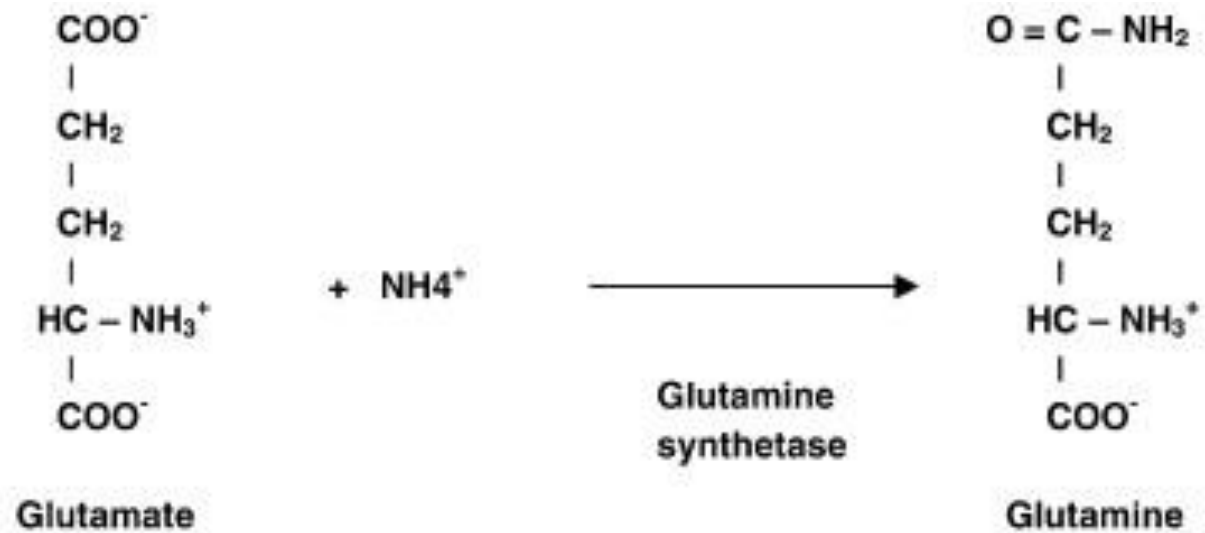


Glutamate dehydrogenase (GDH)

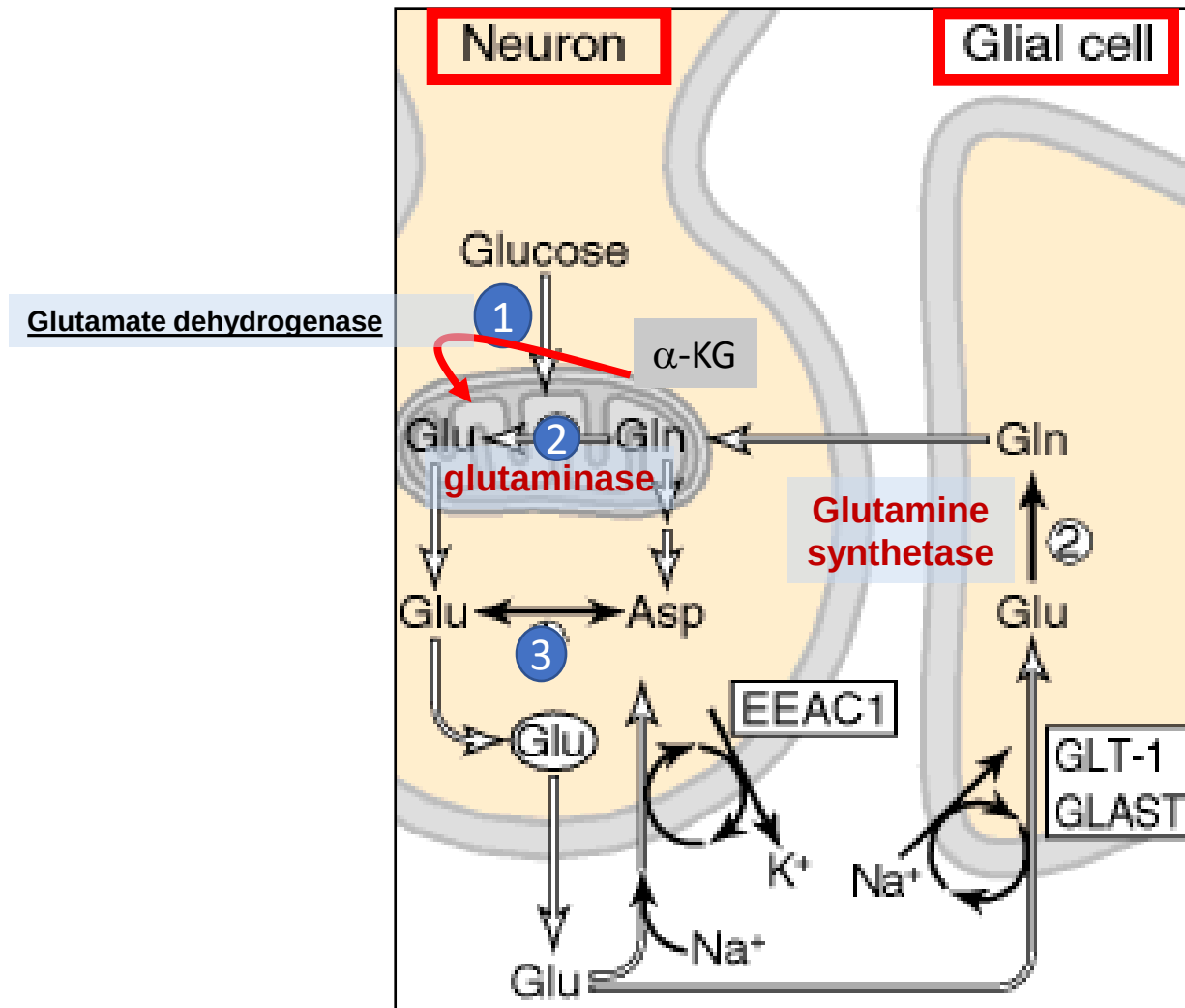
Synthesis of glutamate



Degradation of Glutamate



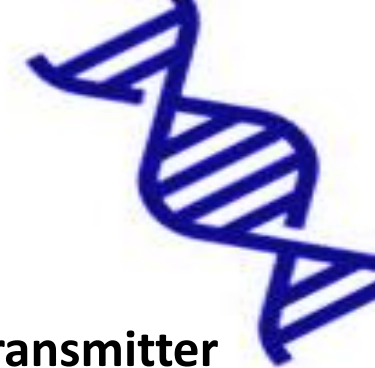
Glutamate is converted to **glutamine** by the enzyme **glutamine synthetase**.



- Glutamate is packaged into presynaptic vesicles by VGLUT
- proteins and synaptically released in a voltage-dependent manner.
- Synaptically-released Glutamate is recycled from the extracellular space by EAATs expressed predominantly on astroglia.
- In astrocytes, Glutamate is converted to Glutamine by Glutamine synthetase and exported extracellularly to be taken up again by neurons.
- Glutamate receptors are present on presynaptic and postsynaptic neurons as well as on glial cells



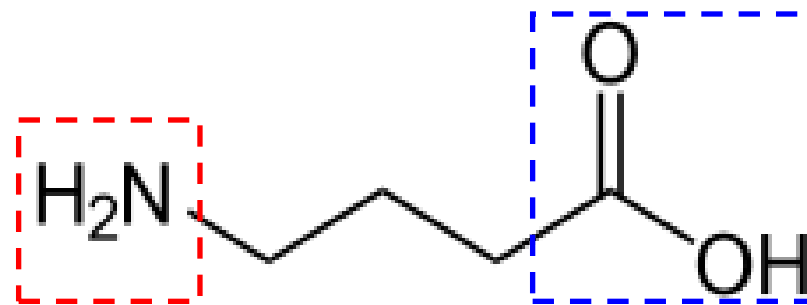
Gamma-Amino Butyric Acid (GABA)



GABA is a **non-proteinogenic amino acid** that functions as the **primary inhibitory neurotransmitter** in the **central nervous system (CNS)**.

GABA is found in the CNS at **millimolar** (mM) concentrations, which is significantly higher than the concentrations of classical monoamine neurotransmitters (e.g., dopamine, norepinephrine, serotonin; typically exist at **nanomolar** (nM) or **micromolar** (μM) concentrations in the synaptic cleft).

- Chemical formula: **C₄H₉NO₂**



GABA





Functions of GABA

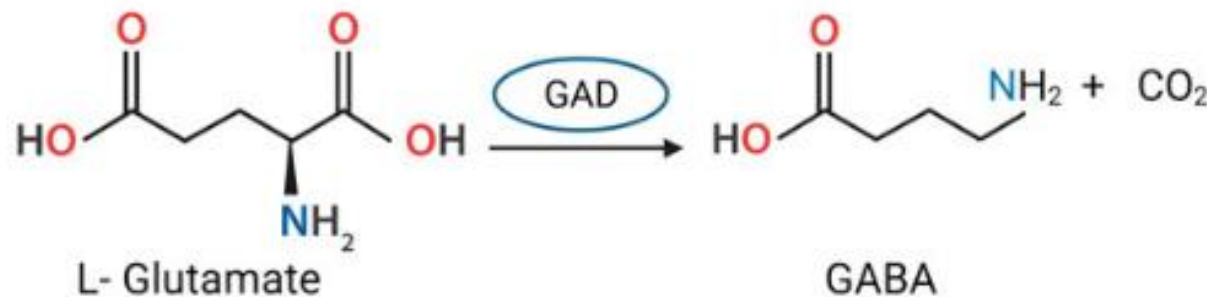


- **Inhibition of Neuronal Activity:** GABA is the main inhibitory neurotransmitter in the CNS, reducing neuronal excitability and preventing overstimulation.
- **Anxiety Relief:** By calming neuronal activity, GABA helps reduce anxiety and promote relaxation.
- **Seizure Control:** GABAergic drugs (e.g., benzodiazepines) are used to treat epilepsy by enhancing GABA's inhibitory effects.

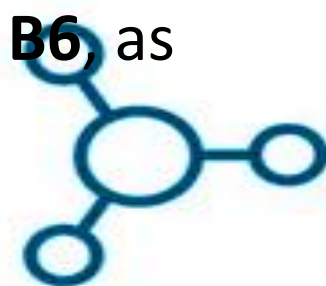




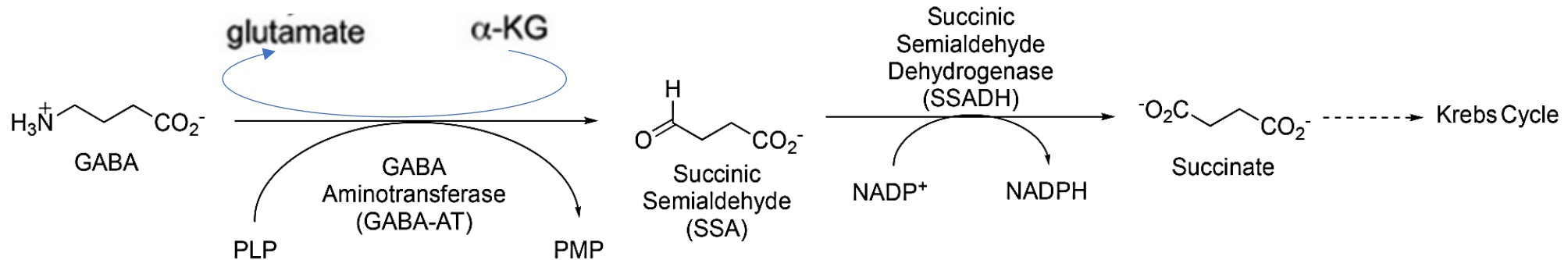
Synthesis of GABA



- GABA is synthesized by the GABAergic neurons from L-glutamic acid in presence of Glutamic acid decarboxylase (GAD).
- GAD present in neurons, pancreatic cells and in body fluid.
- GAD acts as a catalyst that removes carboxyl group from glutamate and produce GABA.
- GAD requires **pyridoxal phosphate (PLP)**, the active form of **vitamin B6**, as a cofactor.



Degradation of GABA



GABA Transaminase (GABA-T):

- GABA is converted to **succinic semialdehyde** by the enzyme **GABA transaminase (GABA-T)**.
- This reaction requires **α -ketoglutarate** as a co-substrate, which is converted to **glutamate**.

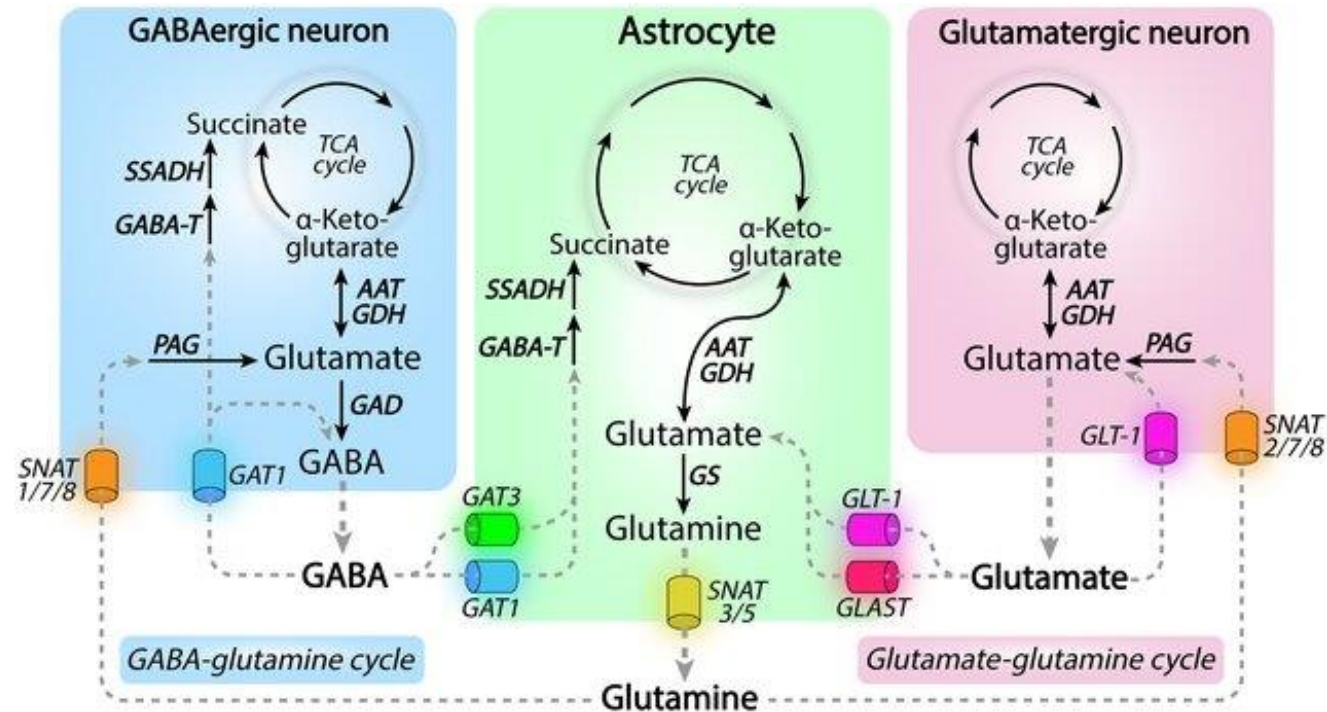
Succinic Semialdehyde Dehydrogenase (SSADH):

- Succinic semialdehyde is oxidized to **succinate** by the **succinic semialdehyde dehydrogenase (SSADH)**.
- Succinate then re-enters the **Krebs cycle**.

The glutamate/GABA-glutamine cycle

The majority of glutamate, and a substantial fraction of GABA, released from neurons is recovered from the synapse by uptake into astrocytes. Astrocytes express the glutamate transporters GLT-1 and GLAST and the GABA transporters GAT1 and GAT3, whereas glutamatergic and GABAergic neurons express GLT-1 and GAT1, respectively. In the astrocyte, glutamate and GABA are metabolized, which supports the synthesis of the non-neuroactive amino acid glutamine, which is subsequently released. The astrocyte-derived glutamine is taken up by neurons and is converted into glutamate by glutaminase (PAG) to replenish the neurotransmitter pools. Glutamine transfer is primarily mediated by the sodium-coupled neutral amino acid transporters (SNATs). Astrocytes express SNAT3 and SNAT5, whereas SNAT1, SNAT2, SNAT7, and SNAT8 are neuronal glutamine transporters.

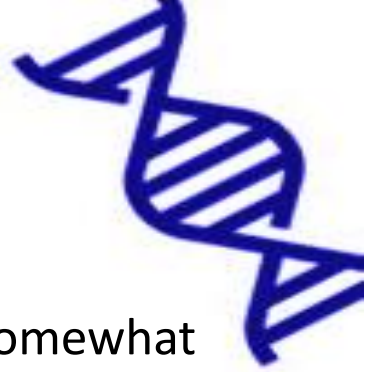
GLT-1: Glutamate Transporter 1; GLAST: Glutamate-Aspartate Transporter. GAT1: GABA Transporter 1; GAT3: GABA Transporter 3.



Abbreviations not explained above: GDH: glutamate dehydrogenase; AAT: aspartate aminotransferase; GAD: glutamate decarboxylase; GABA-T: GABA transaminase; SSADH: succinic semialdehyde dehydrogenase; glutamine synthetase: GS.



Aspartate



- A vesicular uptake mechanism for aspartate has not yet been demonstrated, somewhat weakening the case for considering aspartate to be a neurotransmitter.
- Unlike glutamate, which is loaded into synaptic vesicles by vesicular glutamate transporters (VGLUTs), no specific vesicular aspartate transporter has been conclusively identified.
- Some studies suggest that VGLUTs may transport aspartate to some extent, but this is not well-established.
- Precursor: oxaloacetate [Aspartate Aminotransferase (AAT)]
- $\text{Glutamate} + \text{Oxaloacetate} \leftrightarrow \text{Aspartate} + \alpha\text{-Ketoglutarate}$





Thanks Part 2



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