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Commentary

GABA fluctuations driven by astrocytic Glu/GABA exchange explain synaptic acuity

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Abbreviations: Bestrophin 1: Homopentameric Ca^{2+}-activated Cl^- channel; EAAT2 (SLC1A2, GLT-1): Excitatory Amino Acid Transporter type 2 to Glu uptake in astrocytes by electrogenic $3Na^+$/Glu symport; $GABA_A$ receptor: Heteropentameric Cl^- channel opened by GABA; GAT-3 (SLC6A11): GABA Transporter type 3 to astrocytic GABA uptake/release; GS: Gln Synthesize; MAOB: Key enzyme to astrocytic GABA production; SNAT3 (SLC38A3): Na^+-coupled Neutral Amino acid Transporter type 3.

Commentary

Gliocentric paradigms showcase functional association of neurons with astrocytes, as in tripartite glutamat*ergic* synapses. Astrocytes, activated by Glu:3Na(+) symport apply GABA*ergic* inhibitory feedback on synaptic excitation *via* GABA efflux by GAT-3 reversal and subsequent $GABA_A$ activation (astrocytic Glu/GABA exchange [1-3]). Mechanistic models of astrocytic Glu/GABA exchange predict fluctuations of extrasynaptic GABA and tonic inhibitory feedback on synaptic signaling, integration, and hyperexcitability [4,5].

In tripartite glutamat*ergic* synapses, extrasynaptic Glu activates astrocytic leaflet by Glu influx through EAAT2 Glu transporters [6]. Supported by Na^+/K^+-ATPase activity [7], EAAT2 performs electrogenic influx of 3 Na^+ with 1 Glu in each transport sequence ($3Na^+$:Glu symport). Spatiotemporal Na^+ dynamics in the leaflet enable the reverse operation of nearby GABA transporter GAT-3, resulting in astrocytic efflux of $2Na^+$:GABA. The molecular mechanism, first described in 2009 by Héja and co-workers [1], allows for opening of extrasynaptic $GABA_A$ receptors, thus increasing tonic inhibitory feedback [2,3]. This astrocytic Glu/GABA exchange generates intrinsic fluctuations of Na^+ and GABA along with GABA tone, contributing to synaptic plasticity [8].

Tonic inhibitory feedback on synaptic excitability, regulated by astrocytic Glu/GABA exchange is coupled to energy-dependent metabolic processes (**Figure 1**). Explicit molecular mechanism of astrocytic Glu/GABA exchange may relate gradients of extrasynaptic/cytosolic Na^+, [Glu], [Gln], [GABA] and mitochondrial/cytosolic [GABA] to Na^+:neurotransmitter transport rates ($3Na^+$:Glu uptake, $2Na^+$:GABA release, $1Na^+$:Gln release/uptake). Emergent dynamics, described by partial differential-equations, determine the resulting oscillatory phase-transition. Also, model calculations correlating synaptic strength and astrocytic Glu/GABA exchange predict fluctuations of extracellular [GABA] [27]. We assume that alternating [GABA] brings about fluctuations of inhibitory feedback on input excitation, shaping spatiotemporal accuracy of synaptic signaling (acuity). The hypothesis may serve as a basis for diverse brain functions, for example sensory acuity [30] or cognitive-integration [33].

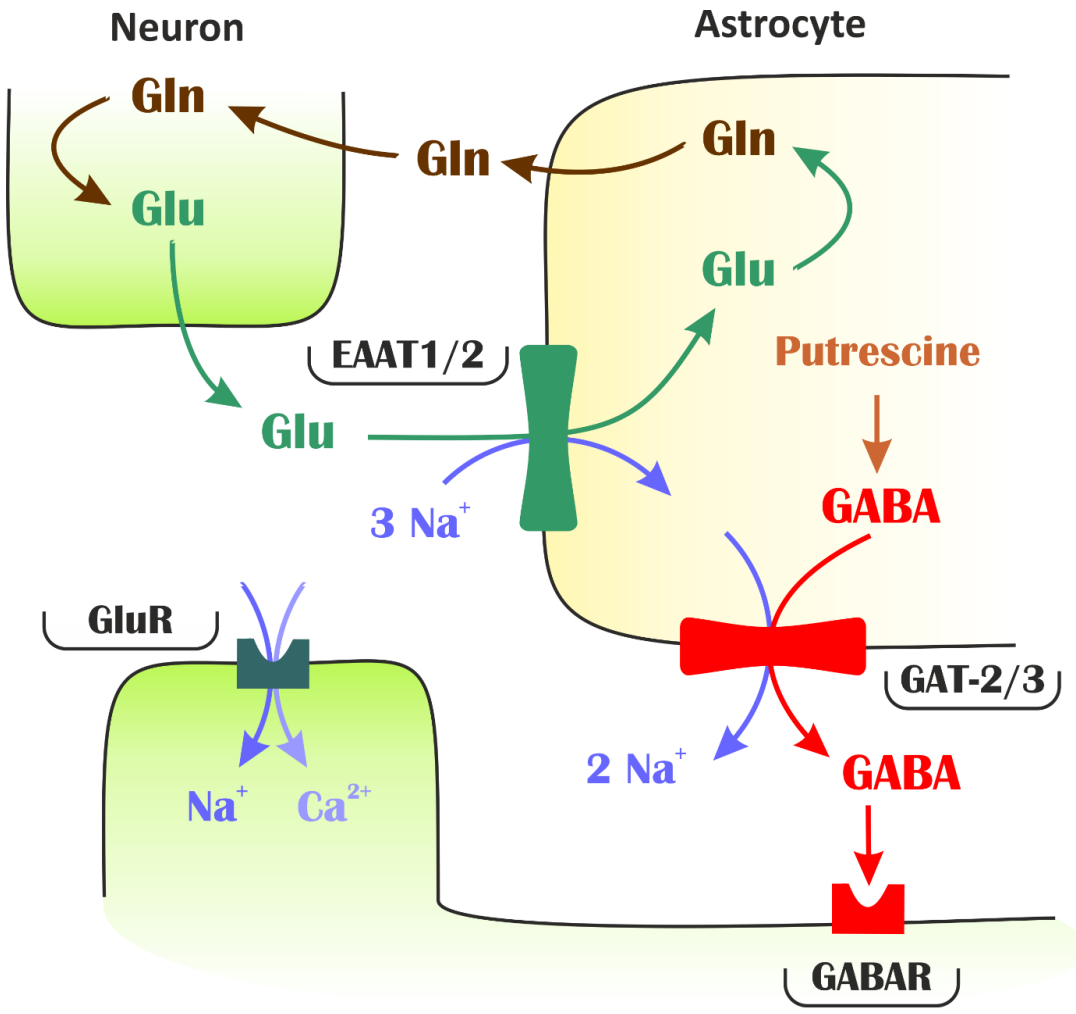

Figure 1. Scheme of tripartite glutamat*ergic* synapse, presenting major players of astrocytic Glu/GABA exchange. Action potential activates presynaptic release of Glu and binding to postsynaptic Glu receptors. Extrasynaptic Glu is taken up by $3Na^+$:Glu symporter EAAT2 [6]. The enhancement of astrocytic Na^+ reverses closest GABA transporter GAT-3 releasing $2Na^+$:GABA [3,9]. Released GABA activates extrasynaptic $GABA_A$ receptor, implementing tonic inhibitory feedback on synaptic excitation [1,2,10-28]. The astrocytic Glu/GABA exchange mechanism is coupled with key metabolic processes, including polyamine→GABA catabolism requiring MAOB [29-33], Glu metabolism to Gln by GS, and Glu-Gln recycling by Gln transporter SNAT3 [3,34-40].

Astrocytic release of GABA through inversed GAT-3 [41-43], but not Bestrophin-1 channel in brain areas such as cerebellum and hippocampus [44] suggests the emergence of astrocytic Glu/GABA exchange in these projection systems (**Figure 2A** vs. **Figure 2B**).

Recognizing glutamat*ergic* projection systems in cerebellar (**Figure 2A**) and hippocampal (**Figure 2B**) areas, we searched astrocytic Glu/GABA exchange using network approach [49]. Closely associated Glu-Gln recycling (Figure 1) data allege likely emergence of astrocytic Glu/GABA exchange [50-53].

Astrocytic Glu/GABA exchange is capable of affecting strength of hippocampal seizure-like activity, gamma-band oscillation [2], cognitive-integration [33] or cerebellar sensory acuity [30]. In addition, actual roles of astrocytic Glu/GABA exchange in neuroprotection [54], reward signaling-behavior [55], stroke [56], juvenile stress [40], epilepsy [57,58], Huntington's chorea [17,59] and Tourette-syndrome [22] have also been described. Broad and extensive participation of astrocytic Glu/GABA exchange characterizes the mechanism rather normal than unusual.

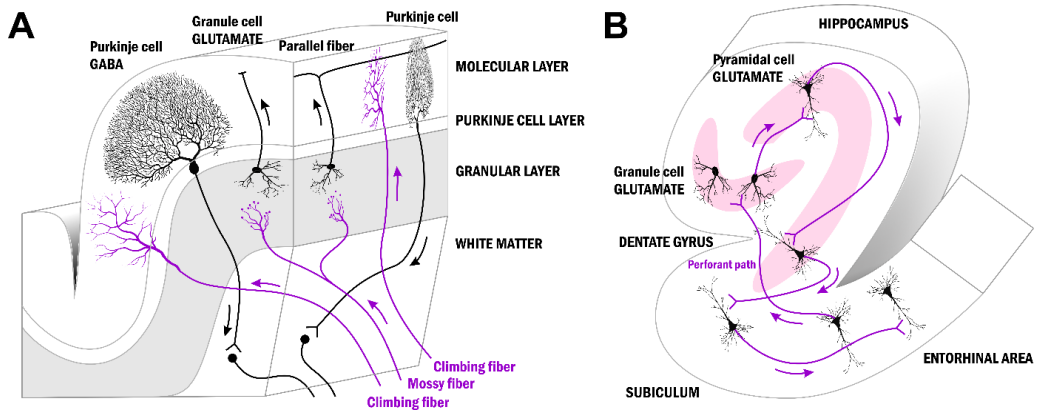

Figure 2. Comparison of glutamat*ergic* synapses in cerebellar [45] and hippocampal [46-48] projection systems with signaling and integrating functions, respectively. (**A**) Scheme of olivo-cerebellar climbing fibers in the inferior olive–dentate nucleus region. Note synapses formed between mossy fibers and granule cells (granular layer: grey). (**B**) Hippocampal section comprising entorhinal-perforant path system. Recurrent projection system featured by synapses between i) entorhinal pyramidal cells (pyramids) and dentate gyrus granule cells (granules); ii) granules and CA3 hippocampal area pyramids; iii) pyramids of CA1 hippocampal area and ventral subiculum; iv) pyramids of ventral subiculum and entorhinal area.

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Author Contribution

JK and LH wrote the manuscript, LH designed the figures.

Conflicts of Interest

The authors declare no competing interests.

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