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Astrocytes convert network excitation to tonic inhibition of neurons

Laszlo Heja
Institute of Molecular Pharmacology, Hungary

Several studies demonstrated the ability of astrocytes to sense, respond to and regulate neuronal function. Importantly, astrocytes possess the complete set of membrane proteins to detect GABA the major inhibitory neurotransmitter of the brain. In addition to ionotropic and metabotropic GABA receptors, astrocytes also express GABA transporters the role of which has long remained uncertain.Here we present evidence that activation of the glial glutamate transporters by their endogenous substrates triggers the reversal of the closely localized glial GABA transporter subtypes GAT-2 or GAT-3 and subsequently increase the extracellular GABA level. In addition, we explore the potential physiological and pathophysiological role of the Glu/GABA exchange process in freshly isolated hippocampal slices and in the hippocampus *in vivo*. We demonstrate that the glutamate uptake-induced release of putrescine-derived GABA from astrocytes has a direct impact on the excitability of pyramidal neurons in the hippocampus. The released GABA significantly contributes to the tonic inhibition of neurons in a network activity-dependent manner providing a tuneable, *in situ* negative feedback.GABA release can be prevented by blocking glutamate uptake with the non-transportable inhibitor DHK, confirming that it is the glutamate transporter activity that directly initiates the reversal of GABA transporters by elevating the local intracellular Na^+ concentration in astrocytes and therefore turning out the driving force for the GABA transporters. We prove that the Glu/GABA exchange mechanism is functioning in the hippocampus under physiological conditions *in vivo*. Importantly, blockade of the mechanism increases the duration of seizure-like events in the low-$[Mg^{2+}]$ in vitro model of epilepsy, demonstrating that the negative feedback control of astrocytes on neuronal excitability offers significant neuroprotection in pathophysiologically overactivated states.

heja.laszlo@ttk.mta.hu