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Glutathione in astrocytes as a target of neuroprotection

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Recent studies showed that dysfunction of astrocytes is involved in susceptibility of neuronal cells in several neurological disorders. Glutathione (GSH) is the most abundant intrinsic antioxidant in the central nervous system, and its substrate cysteine is easily oxidized to cystine. Since neurons lack the transport system for cystine, GSH synthesis in neurons is dependent on the cystine up-take via cystine/glutamate exchange transporter (xCT), synthesis and release of GSH in/from surrounding astrocytes. We previously demonstrated that zonisamide and levetiracetam increased the expression of xCT and GSH levels and release of S100b in/from the striatal astrocytes and showed neuroprotective effects against dopaminergic neurodegeneration in parkinsonian models. Also, we studied on neuroprotective properties of astrocytes, and found three target astroglial systems for neuroprotection: (1) cystine transporter xCT-GSH synthesis system, (2) serotonin 5-HT1A receptor-transcription factor Nrf2-strong anti-oxidant zinc-binding protein metallothionein system, and (3) glutamate transporter GLT1 system (Miyazaki and Asanuma, 2016, 2017), and vulnerability of neurons depend on the region-specific profiles of astrocytes. In this symposium, possible neuroprotective strategy targeting antioxidative molecules in astrocytes will be reviewed.