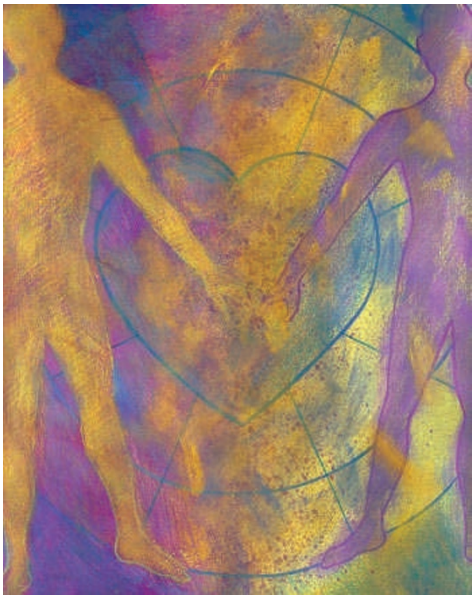
NEURON–GLIA INTERACTIONS

An intimate relationship



Astroglia ensheath central synapses and have a vital role in synaptic transmission. This is partly due to the cell surface expression of astroglial glutamate transporters (GLT1; also known as SLC1A2 and EAAT2) that mediate the uptake of extracellular glutamate and thereby modify the intensity of neurotransmission as well as prevent glutamate neurotoxicity. Although it is known that astroglia can regulate neuronal events, such as dendritic spine formation, little is known about the communication from neurons to astroglia. Previous studies have suggested that neuronal activity might regulate astroglial GLT1 expression, but the underlying mechanism was unknown. Publishing in *Neuron*, Rothstein and colleagues have now revealed that the expression of the transcription factor kappa-B motif-binding phosphoprotein (KBBP) in astrocytes is neuron-dependent and that KBBP regulates astroglial GLT1 expression.

The authors used an *in vitro* co-culture system that kept neurons and astrocytes in different chambers and only allowed axons to make direct contact with astrocytes. Monitoring GLT1 expression in co-cultured astrocytes by immunostaining for GLT1 itself or by using a fluorescent reporter that monitored GLT1 promotor activity revealed that the highest level of GLT1 expression or promotor activity was in astrocytes that were in direct contact with axons. Activation of GLT1 expression was inhibited by blocking neurotransmitter release with tetrodotoxin or glutamate receptor antagonists. These results show that astroglial GLT1 expression is dependent on synaptic interaction and that presynaptic activity has a role in transcriptional activation of GLT1.

To evaluate the transcriptional mechanism, the authors analysed the 2.5 kb upstream promoter region of GLT1 using deletion studies and site-directed mutagenesis. They identified 10 base pairs that were essential for GLT1 promotor activation *in vitro* and *in vivo*. Furthermore, they identified KBBP as the transcription factor that binds specifically to this region and demonstrated that KBBP expression correlates with GLT1 expression in mouse astrocytes during synaptogenesis (postnatal days 2–21). KBBP expression in co-cultured astrocytes was also induced by axonal contact and highly correlated with GLT1 expression. Silencing KBBP expression *in vitro* by using small interfering RNA or *in vivo* by using antisense oligonucleotides reduced GLT1 expression in astrocytes, supporting the notion that KBBP recruitment to the GLT1 promotor is required for GLT1 expression.

Next, the authors investigated KBBP and GLT1 expression in *in vivo* mouse models of denervation and neuronal degeneration. Corticospinal tract transection, neurotoxin-induced degeneration of spinal motor neurons and chronic degeneration in an amyotrophic lateral sclerosis mouse model all resulted in the loss of KBBP expression in the affected astroglia and concomitant loss of GLT1, indicating that the integrity of presynaptic terminals helps to maintain astrocyte function.

This study revealed part of the neuron-dependent transcriptional mechanism that leads to GLT1 expression in astrocytes. Further studies of transcriptional changes in astrocytes following synaptic disruption will lead to a more complete understanding of how astroglia contribute to normal and diseased brain function and to targets for glial therapy being identified.

Claudia Wiedemann

ORIGINAL RESEARCH PAPER Yang, Y. *et al.* Presynaptic regulation of astroglial excitatory neurotransmitter transporter GLT1. *Neuron* **61**, 880–894 (2009)