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PERSPECTIVES

Astrocytic glutamate targets NMDA receptors

So-Young Lee and Philip G. Haydon
 Department of Neuroscience, University
 of Pennsylvania School of Medicine,
 Philadelphia, PA 19104, USA

Email: pghaydon@mail.med.upenn.edu

Glutamate plays essential roles in the control of neuronal function: it is an essential signal for mediating excitatory synaptic transmission, by acting on *N*-methyl-D-aspartate (NMDA) receptors it can induce synaptic plasticity and, if its levels go unchecked, it can stimulate excitotoxicity. Consequently, extracellular levels of this transmitter are tightly regulated. Astrocytes, the predominant glial cell type of the CNS, are synaptically associated (Araque *et al.* 1999) where they take up glutamate to hold the levels of this excitatory chemical in check. In what seems a counter-intuitive move, several studies have shown that astrocytes also release glutamate (Volterra & Meldolesi, 2005; Newman, 2003). What are the consequences of this process of gliotransmission? In this issue of *The Journal of Physiology* this problem is addressed by Lee *et al.* (2007), who used a receptor that is preferentially expressed in astrocytes: protease-activated receptor 1 (PAR1) is shown to selectively increase astrocytic Ca^{2+} , which causes the Ca^{2+} -dependent release of glial glutamate that in turn leads to an indirect enhancement of synaptic NMDA receptor activity. Although astrocytes release comparatively low levels of glutamate, the fine synaptic tuning provided by astrocytic glutamate provides the opportunity for glial cells to have a significant impact on on-going synaptic transmission.

PARs are a class of G protein-coupled receptors which are activated by proteolysis to reveal a new N-terminus which is responsible for auto-activation of the receptor. Working from the prior knowledge that PAR1 is preferentially expressed by astrocytes in area CA1 of the hippocampus, Lee *et al.* (2007) made use of these receptors to study roles for gliotransmission. They first worked with cultures where they demonstrated that PAR1 activates Ca^{2+}

signalling and glutamate release selectively in astrocytes, then moved back to acute slice preparations where they determined functional consequences of this signalling pathway on synaptic transmission.

In a beautiful series of experiments, glutamate sniffer cells were used to monitor gliotransmission in culture. Glutamate release from astrocytes was detected with HEK 293 cells transfected with the non-desensitizing GluR1 mutant receptors, which allowed sensitive detection of glial-derived glutamate. Activation of PAR1 elicited a glutamate-evoked current in the sniffer cells, which was estimated to result from about $1\ \mu\text{M}$ extracellular glutamate. Ca^{2+} signals in and glutamate release from neurons were not detected. When sniffer cells were replaced with cultured hippocampal neurons NMDA receptor-mediated actions were detected by neuronal recordings that were judged to be due to glial glutamate since this pathway was absent when the astrocytes were derived from PAR1^{-/-} and the neurons from wild-type mice.

After demonstrating that activation of PAR1 in cultured astrocytes evokes neuronal NMDA currents they used brain slice preparations to determine whether this signalling pathway is functional in more intact tissues. Activation of PAR1 depolarized CA1 hippocampal pyramidal neurons, increased noise levels of recordings and assisted in relieving the Mg^{2+} block of NMDA receptors, actions that were all attenuated by NMDA receptor antagonist. Since the NMDA receptor is expressed by hippocampal neurons, not by hippocampal astrocytes and because PAR1 is expressed in astrocytes where it causes the Ca^{2+} -dependent release of glutamate, these studies strongly suggest that PAR1-evoked gliotransmission regulates neuronal NMDA receptors in brain slice preparations.

One concern about these studies, which the authors acknowledge, is that no direct evidence is provided for the release of glutamate from astrocytes in slice preparations. However, Jourdain *et al.* (2007) have shown that astrocytic processes in dentate gyrus contain vesicles that are near to neuronal NMDA receptors. Additionally, and in agreement with the overall results of Lee *et al.* (2007) activation of astrocytic P2Y1 receptors

stimulates NMDA receptor mediated synaptic modulation that is blocked by the dialysis into astrocytes of the Ca^{2+} chelator BAPTA.

What are functional consequences for gliotransmission in area CA1? Activation of PAR1 changed the decay kinetics of slow rise time miniature excitatory postsynaptic currents (mEPSCs). Reasoning that slow rise time mEPSCs arise from remote, poorly voltage-clamped synapses, they turned to current clamp measurements to ask whether gliotransmission causes a membrane potential-dependent modulation of synaptic NMDA receptors that are known to control the decay of the synaptic potential. Neuronal recordings demonstrated a reliable PAR1-evoked, and presumably gliotransmission dependent, augmentation of the NMDA component of the synaptic potential. How does gliotransmission augment synaptic NMDA receptor function? The authors propose two scenarios (see Lee *et al.* Fig. 12): either glial activation of NMDA receptors depolarizes neurons and thereby assists in the relief of the Mg^{2+} block of synaptic NMDA receptors, or incoming synaptic activity relieves the Mg^{2+} block on perisynaptic NMDA receptors that are occupied by glial glutamate. In either approach, an NMDA component associated with the synaptic potential would be augmented.

Given that the target of gliotransmission is the NMDA receptors, which are crucial for synaptic plasticity, it will be intriguing to determine whether astrocytes contribute to or modulate synaptic plasticity. Although the average extracellular accumulation of glutamate provided by gliotransmission is only low micromolar (1000-fold less than synaptic glutamate), its ability to potentiate NMDA receptors activity has the potential for potent effects on synaptic plasticity. Indeed a recent study suggests that one role for gliotransmission is to regulate metaplasticity (Panatier *et al.* 2006). However, an understanding of the contribution of gliotransmission in brain function awaits the development of further astrocytic selective manipulations (Pascual *et al.* 2005) that will allow an unambiguous identification of putative roles of gliotransmitters. Nonetheless, once considered a bystander our view of

astrocytes is changing to one in which they are active players in neuronal network function.

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