Gliotransmission and Plasticity

In light of the fact that many studies indicate a calcium-dependent release of neuroactive molecules from astrocytes, much attention was given to the role of astrocytic gliotransmission in synaptic transmission. The implications of findings that gliotransmission may occur under physiological conditions and via a calcium-dependent mechanism are profound, with astrocytes representing a potential third component of the synapse. The tripartite synapse, an illustration of which we feature on our main project page, is now a very popular concept. However, both calcium-dependent gliotransmission (as explored in the previous section) and subsequent modulation of neuronal synaptic activity are controversial and have not yet been demonstrated in vivo.

Effect of Gliotransmission on the Presynaptic Terminal

By uncaging IP3 or calcium in a single astrocyte, a number of laboratories were able to detect either an increase or a decrease in glutamate release from SC-CA1 synapses (Agulhon et al. 2008). Uncaging IP3 or calcium causes a global intracellular calcium elevation that triggers an increase in the frequency of sEPSCs of CA1 neurons. This global intracellular calcium elevation is thought to lead to the release of astrocytic glutamate, which then acts on presynaptic SC mGluRs to elevate presynaptic calcium and increase the probability of neurotransmitter release (Pr) (Agulhon et al. 2008).

Interestingly, other groups reported at the same synapse that electrical stimulation of SC evoked an increased in astrocytic calcium and triggered the release of ATP, which was then converted into adenosine extracellularly. Adenosine then suppressed glutamate release from presynaptic terminals via activating inhibitory presynaptic adenosine receptors (A1Rs) (Agulhon et al. 2008). Taken together with what was discussed in the previous paragraph, these results suggest that different methods of stimulation (uncaging vs. SC stimulation) may preferentially release one transmitter over the other from the same astrocytes.

To complicate matters further, studies using genetic models to selectively activate astrocytic Gq GPCR signaling or abolish astrocyte calcium activity (as Agulhon et al. had done in the 2010 paper we discuss in detail) found that astrocytic calcium does not affect glutamate release at the SC-CA1 synapse. (Fiacco et al. 2007) Fiacco et al.’s results suggest that astrocytic calcium increases may not be involved in modulation of neuronal activity.

Overall, these results indicate that gliotransmission is not a result of simple global elevation in calcium levels. Depending on the experimental protocol used to elevate internal calcium levels, transmitter release may or may not occur, and even when it occurs, its effect on synaptic transmission is variable. It is clear that further study is required to shed light on these conflicting results.

Effect of Gliotransmission on the Postsynaptic Terminal

The debate regarding the effect of gliotransmitters (mainly glutamate) on the postsynaptic terminal is just as controversial as that regarding the presynaptic terminal. Some groups, including Fellin et al. whose 2004 paper we read in class, reported that increases in calcium in a subpopulation of astrocytes leads to the release of glutamate that activates postsynaptic neuronal glutamatergic receptors (Agulhon et al. 2008). These glutamatergic receptors are mostly the NMDAR of the NR2B subtype, and activation of these extrasynaptic receptors induced slow inward currents (SICs) in a population of CA1 pyramidal neurons to synchronize their activity. However, many other groups, including Agulhon et al., have failed to observe any SICs following astrocytic calcium elevations. These conflicting results indicate that an increase in astrocytic calcium is not sufficient to induce glutamate release from astrocytes to affect neuronal postsynaptic glutamatergic receptors in situ (Fellin 2009).

Interestingly, investigators who observed SICs following astrocytic calcium elevations have all reported the occurrence of spontaneous SICs in basal conditions independent of astrocytic activity. In contrast, those investigators who did not observe SICs following stimulation to increase astrocytic calcium have not recorded any spontaneous SICs in basal conditions, either. This raises the possibility, argues Agulhon et al., that there are variables in the acute slice preparations that are primarily responsible for the occurrence of SICs. In particular, SICs seem to be sensitive to the osmolarity of the recording buffer because when it is reduced, SICs have been reported to occur 100% of the time. In fact, a 2006 paper by Kozlov et al. reported that perfusion with hypotonic buffer leads to a significant increase in SIC frequency in olfactory bulb neurons. This suggests that spontaneous and/or evoked glutamate release from astrocytes might be due certain nonphysiological states of the tissue and not calcium elevations in astrocytes.

Sources

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<td>2008</td>
<td>What is the Role of Astrocyte Calcium in Neurophysiology?</td>
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<td>Fellin</td>
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