Astrocytes target presynaptic NMDA receptors to give synapses a boost

Rheinallt Parri & Vincenzo Crunelli

Astrocytes modulate synaptic strength. This effect occurs, reports a new paper, because ATP-dependent vesicular release of astrocytic glutamate acts on presynaptic neuronal NMDA receptors to increase synaptic efficacy.

Synaptic signaling between neurons is the basis of information transfer, and the modification of synaptic processes underlies learning and memory. Astrocytes possess many of the same molecules involved in the neuronal synaptic machinery and can influence both synaptic strengthening and depression. In this issue, Jourdain et al. elucidate a pathway behind this astrocytic modulation of synapses by showing that ATP-dependent vesicular release of glutamate from astrocyte terminals acts on neuronal presynaptic NMDA receptors to increase synaptic efficacy. Defining for the first time the entire sequence of an astrocyte-neuron signaling pathway at a single synapse, this finding has fundamental implications for our understanding of the basic physiological principles of synaptic transmission, and drastically enlarges the potential astrocytic and neuronal targets for its modulation.

In neuronal and astrocytic cocultures, elevating intracellular calcium concentration ([Ca^{2+}]_i) in astrocytes increases the frequency of miniature excitatory postsynaptic currents (mEPSCs) in neurons by acting on the NMDA subtype of glutamate receptors. However, in hippocampal slices, this astrocyte-dependent strengthening requires metabotropic glutamate receptor activation. Astrocytic glutamate release potentiates GABAergic transmission as well, and astrocytic ATP and its derivatives are also implicated in synaptic depression. Jourdain et al. built upon these findings to directly study astrocyte-neuron signaling in the hippocampal perforant path–to–granule cell (PP-GC) synapse. They chose this synapse because of its well defined anatomical elements and its accessibility for electrophysiological and imaging analysis. The authors were able to simultaneously patch clamp a single granule cell and a neighboring astrocyte in the dentate gyrus molecular layer of hippocampal slices and to directly depolarize the astrocyte to induce [Ca^{2+}]_i elevations. This astrocytic excitation increased the occurrence of spontaneous AMPA receptor–mediated excitatory postsynaptic currents in granule cells. Crucially, when the astrocyte was activated in the presence of tetrodotoxin, they recorded an increase in the frequency, but not the amplitude, of mEPSCs, indicating that the locus of this modulation was presynaptic.

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In further support of this pathway, the authors then localized the anatomical elements of the presynaptic perforant-pathway terminal and postsynaptic granule-cell spine together with the ensheathing astrocyte using electron microscopy. About 40% of these astrocytic processes had cytoplasmic vesicles, a high proportion of which were within 60 nm of the cytoplasmic membrane. Using immunogold labeling, the authors then demonstrated that these astrocytic vesicles contained glutamate and were positioned directly opposite the NMDA receptors of the perforant-pathway presynaptic terminals.

The astrocytes were also densely labeled for P2Y1 receptors, which are activated by ATP. Stimulation of the perforant pathway caused elevation of astrocytic [Ca^{2+}], that was inhibited by antagonists of the G protein–coupled P2Y1 receptors or metabotropic glutamate receptors. Moreover, even without perforant-pathway stimulation, inhibition of P2Y1 receptors decreased spontaneous astrocytic [Ca^{2+}], elevation, indicating that under basal conditions ATP is released and excites neighboring astrocytes in hippocampal slices.

The authors also confirmed the involvement of P2Y1 receptors in synaptic strengthening by directly activating these receptors with a specific agonist (2MeSADP). This drug caused an increase in spontaneous excitatory postsynaptic current frequency, which was inhibited by bath-applied ifenprodil or by blocking astrocytic [Ca^{2+}], elevation with the addition of the Ca^{2+} chelator BAPTA in the astrocyte recording electrode. The mEPSC analysis corroborated the presynaptic locus of these effects. Finally, the authors used a paired-pulse stimulation protocol to confirm that P2Y1 and NR2B receptor activation functionally strengthened PP-CG synapses. Collectively, therefore, these results indicate that ATP activates astrocytic P2Y1 receptors, resulting in an astrocytic [Ca^{2+}], elevation and associated vesicular release of glutamate, which in turn activates presynaptic NR2B-containing NMDA receptors to increase transmitter release (Fig. 1). Crucially, this pathway seems to be operative under basal conditions, at least in vitro. Although earlier studies had shown that inhibition of astrocytic glutamate release affects neuronal signaling, this is the first study to demonstrate in such an unequivocal way that specifically inhibiting the vesicular release of astrocytic glutamate with an acute and targeted approach does affect the synaptic responses of a single neuron in situ.

An important finding of the new work is that astrocytic glutamate activates presynaptic NR2B-containing NMDA receptors to affect strengthening. Presynaptic NMDA receptors are emerging as key modulators of synaptic transmission, and their activation is usually believed to be by the ‘spillover’ of presynaptically released glutamate. Spillover may occur either when the increased glutamate release that follows high-frequency stimulation overwhelms the uptake capacity of glial transporters or when synapses lack glial coverage. These results, therefore, uncover an additional mechanism of spillover, which could also be subject to controlling influences more reminiscent of a classical synapse than those implied by the term spillover. It would, therefore, be interesting to know whether the same mechanism operates at other synapses where the presence of presynaptic NMDA receptors and their effects on synaptic efficacy are well documented.

One of the most common forms of astrocyte-neuron signaling involves activation of glutamate or GABA receptors on the postsynaptic element of a synapse, with the gliotransmitter eliciting characteristic large and long-lasting inward or outward currents, respectively, even in the presence of tetrodotoxin. This type of glutamate signaling, which was proposed to lead to the synchronization of hippocampal neuronal ensembles, was not observed at the PP-GC synapses investigated by Jourdain et al. Does this mean that the manifestation of either pre- or postsynaptic effects by astrocytes is synapse-specific, region-specific or both? Or does it critically depend on the firing features of the presynaptic fibers? In this context, it will be important to know the
Young and excitable: new neurons in memory networks

Josef Bischofberger

In the adult hippocampus, a brain region that is important for memory, new neurons are generated continuously. A study now shows that these newly generated neurons are preferentially activated during learning and recall of new memories.

The hippocampal formation within the medial temporal lobe of the cerebral cortex is essential for our conscious memory of facts and events. The hippocampus is also one of the few regions in the central nervous system of adult mammals, including humans, where new neurons are continuously generated throughout life. Thus it is tempting to speculate that the new neurons are somehow involved in learning and formation of new memories. However, until now, little was known about the synaptic activation of newly generated hippocampal neurons in vivo. Do they form ‘meaningful’ synapses in a context- and information-specific manner? Are they reactivated during memory recall? Finally, is there a specific property of newly generated cells that might lead to a specific role in learning and memory processing? A paper in this issue by Kee and colleagues provides exciting new data to answer some of these questions.

Recent technical progress has allowed the unequivocal identification and functional characterization of newly generated granule cells in the adult hippocampus. Neuronal precursor cells are generated from neural stem cells in the subgranular zone of the dentate gyrus and continue to divide for a few more days. After the last cell cycle, the axon rapidly grows toward the hippocampal CA3 region, whereas the dendrites extend toward the ‘primary’ molecule, may have a general role in synaptic strengthening, because, in the hypothalamus, activation of glial α1 receptors by noradrenaline causes ATP release that causes synaptic strengthening through the insertion of AMPA receptors on the postsynaptic element. In contrast, glia-derived adenosine, also in the hippocampal CA1 region, leads to inhibition and heterosynaptic depression. Therefore, in the same brain area, strengthening or depression might occur following ATP release, depending on the activity of the ectonucleosidase-determined ATP degradation cascade.

In this regard, a crucial question arising from the Jourdain et al. study is the precise source of ATP. Is it co-released with glutamate from the perforant-pathway terminals? Or is it released from the astrocytes in response to glutamate released from the perforant pathway? The latter question could be addressed by testing whether inhibition of metabotropic glutamate receptors reduces or occludes the effect of P2Y1 receptor antagonists in preventing the ifenprodil effect. Whether glutamate or ATP is the signal which due to their spatial and biochemical autonomy might be able to act on a shorter time scale. Such issues will determine the latency to, and duration of, synaptic strengthening and hence its relevance in longer-term network activity or in rapid synaptic signaling.

Unfortunately, these answers will only come with additional detailed electrophysiological and imaging investigation.

This study also highlights a distinct role for ATP. ATP is degraded extracellularly first to ADP and finally to adenosine, and all these molecules have different selectivity for various purinergic receptors. ADP is a potent agonist at P2Y1 receptors and is further degraded to adenosine by the action of ectonucleosidases. Glial ATP, the ‘primary’ molecule, may have a general role in synaptic strengthening, because, in the hypothalamus, activation of glial α1 receptors by noradrenaline causes ATP release that causes synaptic strengthening through the insertion of AMPA receptors on the postsynaptic element. In contrast, glia-derived adenosine, also in the hippocampal CA1 region, leads to inhibition and heterosynaptic depression. Therefore, in the same brain area, strengthening or depression might occur following ATP release, depending on the activity of the ectonucleosidase-determined ATP degradation cascade.

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