Astroglial gliotransmitters released via Cx43 hemichannels regulate NMDAR-dependent transmission and short-term fear memory in the basolateral amygdala

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Abstract

Astrocytes release gliotransmitters via connexin 43 (Cx43) hemichannels into neighboring synapses, which can modulate synaptic activity and are necessary for fear memory consolidation. However, the gliotransmitters released, and their mechanisms of action remain elusive. Here, we report that fear conditioning training elevated Cx43 hemichannel activity in astrocytes from the basolateral amygdala (BLA). The selective blockade of Cx43 hemichannels by microinfusion of TAT-Cx43L2 peptide into the BLA induced memory deficits 1 and 24 h after training, without affecting learning. The memory impairments were prevented by the co-injection of glutamate and D-serine, but not by the injection of either alone, suggesting a role for NMDA receptors (NMDAR). The incubation with TAT-Cx43L2 decreased NMDAR-mediated currents in BLA slices, effect that was also prevented by the addition of glutamate and D-serine. NMDARs in primary neuronal cultures were unaffected by TAT-Cx43L2, ruling out direct effects of the peptide on NMDARs. Finally, we show that D-serine permeates through purified Cx43 hemichannels reconstituted in liposomes. We propose that the release of glutamate and D-serine from astrocytes through Cx43 hemichannels is necessary for the activation of post-synaptic NMDARs during training, to allow for the formation of short-term and subsequent long-term memory, but not for learning per se.