

Astrocytic NMDA receptors in the regulation of synaptic function and addiction behavior

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Neuroadaptations produced by drugs of abuse are responsible for the long-term maintenance of memory. Recent studies suggest that astrocytes may contribute to these neuroadaptations, however the potential mechanisms are not fully understood. We and others have found that astrocytes express NMDA receptors with unique subunit composition and biophysical properties. These include lack of Mg^{2+} block at resting membrane potentials, lack of desensitization and high agonist affinity. Synaptic and spillover glutamate can therefore activate these receptors and engage a feedback mechanism. The contribution of astrocytic NMDA receptors to drug-induced neuroadaptations and behavioral responses is not known.

Methods: Expression of NMDA receptors in astrocytes in the nucleus accumbens and prefrontal cortex was examined using electrophysiological techniques and the stoichiometry was resolved using pharmacological tools and genetic models. The role of astrocytic NMDA receptors in cocaine induced conditioned place preference paradigm was tested using conditional astrocytic NMDA receptor KO models and the underlying mechanism was explored using imaging and molecular techniques. The potential global effect of astrocytic NMDA receptors was examined using bulk RNAseq and biochemistry techniques.

Results: We found that astrocytes in the nucleus accumbens express NMDA receptors with GluN1/2A/2C stoichiometry. Similar stoichiometry of NMDA receptors was also observed in astrocytes in the dorsal striatum and medial prefrontal cortex. Ablation of GluN2C led to a switch in stoichiometry to primarily GluN1/2B. Loss of astrocytic NMDA receptors in the nucleus accumbens or GluN2C KO mice showed faster extinction of cocaine place preference memory. Glypican 4 mediated AMPA receptor recruitment underlies astrocytic NMDAR mediated plasticity that strengthens preference memory. Global analysis using RNAseq suggests that astrocytic NMDA receptors may play important roles in regulating synaptogenic factors and metabolic factors.

Discussion: Our studies demonstrate robust and widespread expression of NMDA receptors in astrocytes in brain regions that show drug-induced neuroadaptations and that are relevant to neuropsychiatric disorders. Thus, future studies should consider tripartite (presynaptic, postsynaptic and astrocytic) expression of NMDA receptors in synaptic regulation and behavioral control.

This work was supported by grants from NSF1456818 (to S.M.D.), NIH NS104705 (to S.M.D.), NIH NS118731 (to S.M.D.), and NIH MH116003 (to S.M.D.)