Astrocyte Regulation of Neural Circuit Activity During Opioid Relapse

A. Angelis, B. Kuhn, D. Neuhofer, M. Marini, D. Labate, A. Kruyer

Background: Decades of research have expanded our understanding of the neural basis of relapse to drug use, but have yielded few effective treatments that restore top-down control over drug seeking in active and former users. Relapse to drug use is driven by glutamatergic signaling in the nucleus accumbens core (NAcore) that drives GABA release at terminals in the dorsolateral ventral pallidum (dlVP). Our previous work reflects an important homeostatic role for astroglia in regulating glutamatergic and GABAergic signaling in basal ganglia structures to modify drug seeking behavior. Astrocytes are the most abundant glial type in the brain, and they play fundamental roles in synapse regulation through dynamic motility of their perisynaptic processes and expression of neurotransmitter receptors and transporters, but whether astrocyte fine process motility is targeted to distinct synapse types in the basal ganglia to tune motivated behavior is unknown.

Methods: Here we applied super-resolution imaging to determine whether astrocytes in the NAcore and dlVP exhibit circuit-selectivity in their structural rearrangements following 10-days of heroin self-administration, and during cue-induced heroin seeking. We used whole cell patch clamp electrophysiology to assess the effects of astrocyte-synapse adjacency on activity of the two main neural subtypes in the basal ganglia that serve to either drive or oppose reward seeking.

Results: We found that astrocytes exhibit *circuit selectivity* at baseline, and are more closely associated with D2-receptor expressing dendrites in the NAcore. We also found that the neural circuit bias exhibited by astrocytes is dynamic, and that astrocytes alter their adjacency to D1- and D2-neurons after withdrawal from addictive drug use and during relapse to dampen or increase drug seeking depending on drug availability. Extinction of heroin self-administration was associated with an increase in astrocyte adjacency to D1 receptor-expressing dendrites in the NAcore and terminals from these cells in the dlVP. Using mRNA-targeted antisense inhibition of ezrin, an actin-binding protein selectively expressed in perisynaptic astrocyte processes, we found that astrocyte-synapse adjacency increased short-term depression of synapses, regardless of neural subtype, and reduced glutamate release probability onto D1 neurons.

Discussion: We show that astrocyte-synapse adjacency has a strong impact on synapse plasticity and neural output, and can causally drive or suppress reward-associated behaviors, including relapse to addictive drug use, depending on circuit selectivity. These studies reveal that astrocyte-synapse association is highly plastic and functionally meaningful, highlighting astrocytes as a principle cellular regulator of motivated behavior. Given these new findings, essential questions remain regarding the signaling mechanisms that govern astrocyte-synapse adjacency, and the molecular cues that trigger astrocyte motility toward and away from synapse subtypes within the basal ganglia.

Acknowledgements: This work was supported by the National Institutes of Health (K01 DA054339).