**Reducing Astrocyte Calcium Signaling in the Nucleus Accumbens Increases Cocaine Self-administration Behavior.**

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Accumulating evidence indicates meaningful roles for glial cells in drug use and substance use disorders. For example, rat cocaine self-administration is associated with long-lasting changes in astrocyte structure and activity within the nucleus accumbens (NAc). Moreover, pharmacological manipulation of astrocytes alters drug taking behaviors. A critical component of astrocyte function is signal transduction via Ca2+ signaling. How astrocyte signaling dynamics influence drug related behaviors is still unknown. Here, we aim to determine the effects of NAc astrocyte Ca2+ depletion on behavioral responses to cocaine, using both self-administration and behavioral sensitization models. Animals underwent 10 days of long-access cocaine self-administration after receiving viral infusion of either astrocyte-specific AAV5-GFaABC1D-hPMCA2, to deplete NAc astrocyte Ca2+, or AAV5 GfaABC1D-Lck-mCherry control. We found a significant increase in cocaine self-administration for hPMCA2 expressing rats. However, no differences in seeking behavior was observed following 45 days of abstinence. Together, these data suggest that astrocytes are critical to the on-demand neural signaling during cocaine taking. To determine if these effects extend to other drug related behaviors, a separate cohort of rats were infused with virus as above and underwent a 7-day, cocaine-induced behavioral sensitization procedure. Locomotor behavior was assessed on days 1 and 7, and we found no significant differences in locomotion between hPMCA2 and control treated rats. However, both treatment groups did show cocaine induced increases in locomotor activity on day 7, consistent with behavioral sensitization. Overall, our data demonstrate that the actions of astrocytes may be specific to different drug related behaviors.