Astrocyte-mediated mechanisms of cocaine seeking

Michael D. Scofield, Anze Testen, Kati L. Healey, Marian T. Sepulveda-Orengo, Ben Siemsen, Hao Li, Kathryn J. Reissner

Withdrawal from chronic cocaine self-administration leads to dysfunction in glutamate homeostasis and glutamatergic signaling within the nucleus accumbens (Scofield et al, 2016a; Wolf, 2016). Rectification of this dysfunction is known to reduce measures of cocaine craving and seeking in preclinical animal models of psychostimulant use disorders. As glutamate homeostasis is largely accomplished via the action of astrocyte-enriched systems including the cystine-glutamate antiporter and the high affinity glutamate transporter, EAAT2/GLT-1, it is reasonable to hypothesize that withdrawal from cocaine use leads to functionally significant adaptations in astrocytes within the reward circuitry of the brain.

Methods: Rats received surgical implantation of intra-jugular catheters, as well as microinjection of AAV5-GfaABC1D-Lck-GFP in various brain regions per experiment. Rats were trained in cocaine or saline self-administration on an FR1 schedule of reinforcement for 2h sessions for 10-12 days, followed by 15 days of extinction training. Deeply sedated rats were perfused with 4% paraformaldehyde, and brains were removed for analysis by immunohistochemistry for synaptic markers and fluorescent astrocyte imaging. High resolution imaging of astrocytes was performed on a Zeiss LSM800 confocal microscope, and deconvoluation and analysis was performed using Bitplane AutoQuant and Bitplane Imaris software.

Results: Extinction from cocaine self-administration leads to a reproducible reduction in morphometric properties of astrocytes within the nucleus accumbens core, which does not extend to the prelimbic region of the medial prefrontal cortex or the basolateral nucleus of the amygdala. Relatedly, a reproducible decrease in synaptic colocalization of astrocyte peripheral processes is observed using either a presynaptic marker (synapsin I) or a post-synaptic marker (PSD-95).

Discussion: Extinction from cocaine self-administration leads to an astrocyte phenotype reflective of atrophic astrocytes as described by Pekney and colleagues, observed within the nucleus accumbens but not other nuclei within the reward circuitry. Implications of this atrophic phenotype, specifically decreased synaptic colocalization, include impaired modulation of synaptic function by astrocytes. Ongoing studies are designed to determine specifically whether impaired astrocyte-derived D-serine co-agonism of accumbens NMDA receptors contributes to the mechanism of cocaine reinstatement. Ongoing studies are also designed to more fully characterize the effects of cocaine on astrocytes, including the effects of long-access cocaine self-administration and forced abstinence, as well as the effects of an active drug seeking event, on colocalization of peripheral processes with synapses.

References: Scofield et al *Pharmacol Rev*. 2016, 68(3):816-71. Scofield et al *Biological Psychiatry* 2016, 80(3):207-15. Wolf, ME. *Nat Rev Neurosci*. 2016, 17(6):351-65. Pekny, M., et al., *Acta Neuropathol*, 2016. 131(3): p. 323-45

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