Targeting glial glutamate transport and neuroinflammation to inhibit nicotine relapse

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Nicotine self-administration is associated with decreased constitutive expression of the glial glutamate transporter (GLT-1) within the nucleus accumbens core (NAcore; Knackstedt et al., 2009; Gipson et al., 2013). Additionally, we have previously found a rapid increase in GLT-1 expression during the initiation of cue-reinstated nicotine seeking (within 15 min), illustrating a highly dynamic role of this transporter that may be cue dependent. Nicotine exposure leads to alterations in brain homeostasis, including increased oxidative stress and increased extracellular glutamate during nicotine seeking (Barr et al., 2007; Gipson et al., 2013). *N*-Acetylcysteine (NAC) is a glutamatergic agent and antioxidant used in clinical studies in the treatment of various substance use disorders, including tobacco (Berk et al., 2013). NAC restores key glutamatergic proteins associated with increased drug relapse vulnerability. However, the specific molecular mechanisms driving its inhibitory effects on cued nicotine relapse are unknown.

Methods: Rats were trained to self-administer nicotine (0.02 mg/kg/infusion) and underwent extinction training, where they received chronic NAC (100 mg/kg) and an antisense (AS) vivo-morpholino designed to selectively suppress GLT-1 expression in the NAcore. Following extinction, rats were tested for cue-induced nicotine reinstatement. NAcore GLT-1, CD40 (a marker for reactive microglia), and pro-inflammatory tumor necrosis factor alpha (TNF-α) protein expression was then assessed using Western blot.

Results: Chronic NAC treatment significantly attenuated cue-induced nicotine seeking. As well, GLT-1 AS vivo-morpholino significantly suppressed GLT-1 in the NAcore, which blocked the attenuating effect of NAC on reinstatement. Unlike what has been observed with cue- induced cocaine reinstatement, inhibition of GLT-1 expression and NAC administration did not augment reinstatement over and above control conditions. Intriguingly, chronic NAC treatment significantly reduced proinflammatory TNF-α expression in the NAcore and inhibiting GLT-1 with the AS morpholino increased CD40 in the NAcore regardless of NAC or vehicle treatment.

Discussion: These results suggest that while GLT-1 may be a conserved neurobiological substrate underlying relapse vulnerability across drugs of abuse, there may be neuroimmunological mechanisms that modulate nicotine relapse and associated glutamatergic plasticity. Following reinstated nicotine seeking there was a significant upregulation of CD40 in the NAcore when GLT-1 expression was held down. These results suggest that blocking both constitutive and transient alterations in GLT-1 expression via morpholino may elevate extracellular glutamate, which may in turn activate microglia in the synaptic periphery during reinstated nicotine seeking. These results potentially suggest a complex relationship between astrocytic glutamate uptake, neuronal signaling, and microglia in the neuroimmunological response to elevated glutamatergic signaling in cued nicotine relapse. Notably, NAC decreased expression of pro-inflammatory TNF-α, suggesting neuroimmunomodulation as a potential component to its efficacy in promoting nicotine use cessation.

References: Knackstedt, L. A. et al. Biol. Psychiatry 65:841–845 (2009); Gipson, C. D. et al. Proc. Natl. Acad. Sci. U. S. A. 110:9124–9 (2013); Barr, J. et al. Mol. Cell. Biochem. 297:93–9 (2007); Berk, M., Malhi, G. S., Gray, L. J. & Dean, O. M. Trends Pharmacol. Sci. 34:167–177 (2013).