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Altered Microglial Transcriptomic Changes and Signaling in the Nucleus Accumbens during Nicotine Withdrawal

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Microglia are innate immune cells that are highly responsive to homeostatic perturbations within the brain's microenvironment; however, their mechanistic role in nicotine withdrawal-related anxiety, which directly impacts relapse to smoking, is unknown. Here, we present data showing that withdrawal from chronic nicotine provokes striatal microglial activation, resulting in pro-inflammatory (TNFα and IL1β mRNA) responses being detected specifically in the nucleus accumbens, a sub-region of the striatum important in motivation as well as in affective responses. Concurrent with these changes, we also observe increased production of reactive oxygen species in the nucleus accumbens during nicotine withdrawal, but not during chronic saline or nicotine treatment. Utilizing n-acetylcysteine (NAC) as an antioxidant tool, we found that NAC could ameliorate ROS production and anxiogenic behaviors during withdrawal, but not prevent microglial activation in the nucleus accumbens. Cell-type specific sequencing of microglia and astrocytes within this region following chronic treatment shows concerted pro-inflammatory transcriptomic changes specifically within microglia, suggesting these cells as mediators of ROS production. To determine whether microglial signaling directly underlies the biochemical and behavioral responses during nicotine withdrawal, animals undergoing nicotine withdrawal were treated with the CSFR1 antagonist, PLX5622, which selectively depletes microglia in the brain. This resulted in reduced anxiogenic behavior during withdrawal as well as reduced levels of TNFα, IL1β, and ROS. Altogether, our data suggest that altered microglial signaling in the nucleus accumbens contribute to anxiogenic behavior during nicotine withdrawal in mice. Therefore, therapeutics targeting microglial signaling may be promising compounds for smoking cessation therapeutics.