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Methamphetamine Self-administration Alters Cell Type-specific Gene Expression in the Rat Nucleus Accumbens

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Methamphetamine (METH) is a highly addictive psychostimulant, neurotoxic at high doses. There is no FDA-approved medication for METH use disorder, warranting more studies on the underlying molecular mechanisms. The nucleus accumbens (NAc) is a crucial brain region in reward processing and addiction. METH use leads to profound neuroadaptive changes within the NAc; however, the responses of different cell types to METH in this area are not well characterized. Here, we investigated how self-administration of high METH doses impacts cell type-specific gene expression profiles within the rat NAc during withdrawal. Using cutting-edge RNA sequencing techniques, we assessed gene expression changes in specific cell types, including medium spiny neurons (MSNs), interneurons, and glia, at 10 days following METH exposure. We hypothesized that differentially expressed genes in the NAc will include genes associated with stress response and biological repair pathways. Here, we demonstrate that 10 days after the last operant session, NAc oligodendrocytes upregulate stress response pathways, RNA processing, and energy production. These findings suggest that self-administration of high METH doses is toxic to rat oligodendrocytes in rat NAc. Our findings may provide novel insights into the neurobiology of METH addiction and offer potential targets for therapeutic intervention for severe form METH use disorder. This study underscores the importance of considering cell type-specific responses in elucidating the molecular basis of drug addiction. Further, it highlights the potential of transcriptomic approaches in uncovering novel therapeutic avenues for treating substance use disorders.