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Transcription factor 4 coordinates gene expression and dopamine responses in the nucleus accumbens

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Substance use disorders are an increasingly common cause of morbidity and mortality, owing in part to an incomplete understanding of the molecular mechanisms that drive behavioral responses to drugs of abuse. Psychostimulants, such as cocaine, exert their effects through maladaptive enhancement of dopamine (DA) neurotransmission in the reward circuitry, particularly the nucleus accumbens (NAc). Within the NAc, these drugs promote DA-dependent transcriptional and epigenetic alterations in medium spiny neurons (MSNs) that are governed by master transcription factors (TFs). However, a comprehensive understanding of the epigenetic mechanisms that orchestrate drug-induced DA responses remains elusive. Our work has identified transcription factor 4 (TCF4) as a putative effector of DA-mediated transcriptional reprogramming in the NAc. TCF4 has been previously implicated in neurodevelopmental and neuropsychiatric disease, but its functions in the reward circuitry are unknown. Mechanistically, we hypothesize that TCF4 regulates a network of genes involved in striatal DA signaling and synaptic plasticity. In line with this, modulation of *Tcf4* in MSNs using a novel CRISPR-based strategy bidirectionally alters DA-induced gene expression and neuronal activation. Moreover, *Tcf4* exhibits differential expression patterns in the NAc in response to temporally distinct cocaine administration paradigms. Collectively, our results reveal a previously unknown function for TCF4 in coordinating DA signaling and gene expression in a key brain reward structure that is targeted by cocaine. These findings expand our knowledge of the epigenetic landscape of psychostimulant action and provide a foundation for examining the contributions of TCF4-mediated gene expression programs to addiction-related behaviors.