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Cell Subtype Specific Role of *Nab2* in Cocaine Seeking Behavior

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The nucleus accumbens (NAc) plays a role in drug seeking and addiction related behaviors in response to drug exposure. Studies have shown that exposure to psychostimulants, such as cocaine, is associated with molecular and functional imbalance in the two medium spiny neuron subtypes (MSNs) in the NAc, the dopamine receptor 1 and 2 enriched MSNs (D1-MSNs and D2-MSNs). We have previously reported the down regulated expression of a transcription factor, early growth response 3 (Egr3), in D2-MSNs in the NAc with exposure to cocaine. In this study, we show that the NGFI-A binding protein 2 (Nab2), a corepressor of Egr3, is altered in bidirectional manner to Egr3 expression in D2-MSNs of mice repeatedly exposed to cocaine. Furthermore, we show that Nab2 overexpression leads to decreased levels of Egr3, and Nab2 inhibition leads to increased levels of Egr3. A2A-Cre mice with D2-MSN specific knock-down of Nab2 in the NAc showed decreased cocaine-induced locomotion. We then tested if Nab2 perturbation in D2-MSNs has a behavioral impact in cocaine self-administration. A2A-Cre mice with D2-MSN specific knockdown of Nab2 in the NAc showed reduced cocaine intake during the 10 days of 2hr cocaine self-administration sessions compared to the control mice. These mice also made significantly reduced cocaine-paired active nose pokes during cocaine seeking test after 10 days of cocaine self-administration. Collectively, our studies identify distinct cell type specific molecular mechanisms of Nab2 in behavioral responses to cocaine including drug seeking behavior.