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KZFP Function Within Medium Spiny Neurons Enables Molecular and Behavioral Responses to Cocaine

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We have previously discovered that Zfp189, which encodes a Krüppel-associated box zinc finger protein (KZFP) transcription factor (TF), differentially accumulates in nucleus accumbens (NAc) Drd1+ and Drd2+ medium spiny neurons (MSNs) over the course of cocaine exposure and is causal in producing MSN functional and behavioral changes to cocaine. Here, we aimed to illuminate the brain cell-type specific molecular mechanisms through which this KZFP TF produces cocaine-related brain changes, with emphasis on investigating transposable elements (TEs), since KZFPs like ZFP189 are known regulators of TEs. To investigate this, we annotated TEs in existing single nuclei RNA-sequencing (snRNAseq) datasets of rodents that were exposed to either acute or repeated cocaine. We synthesized novel synthetic ZFP189 TFs, each capable of exerting distinct forms of transcriptional control at in vivo ZFP189 target genes, including TEs. These ZFP189 TFs were conditionally virally delivered to the NAc of Drd1- and Drd2-Cre+ mice and the subsequent effect on MSN dendritic spine morphology, cocaine-induced locomotion behaviors, and cell-type specific transcriptional response were characterized. We discover that cocaine exposure releases TEs within NAc MSNs – rapidly in Drd1+ MSNs and steadily in Drd2+ MSNs. By conditionally delivering ZFP189 TFs to the Drd1+ or Drd2+ MSNs of mouse NAc, we discover that opposite forms of KZFP-mediated transcriptional control in these opposing cell-types converge on producing behavioral and cell morphological adaptations to cocaine. We discover that normal KZFP function is critical to produce cocaine-induced transcription within NAc MSNs which can be impeded with the synthetic KZFP TF.