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Synthetic transcription factors, delivered to mouse nucleus accumbens, dysregulate drug- specific transcription and behaviors

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Earlier work has identified the Zfp189 gene as highly cocaine-responsive within the nucleus accumbens (NAc), with NAc Zfp189 activation solely regulating behavioral responses to stimulant, but not opioid, drugs. This points to the NAc Zfp189 gene product, ZFP189: a transcription factor (TF) of unknown function, as contributing to the worsening of cocaine addiction specifically. Here, to uncover the molecular basis of this seemingly drug-specific TF function, we created synthetic ZFP189 TFs by replacing the endogenous repressive KRAB moiety of ZFP189-WT with the transcriptional activator VP64-p65-Rta (ZFP189-VPR). We observe that synthetic ZFP189-VPR up-regulates, and ZFP189-WT down-regulates, the expression of a luciferase gene in vitro. In packaging these synthetic TFs in herpes simplex viral vectors and delivering to mouse NAc, we see that ZFP189-VPR potentiates, and ZFP189-WT diminishes, behavioral sensitivity to cocaine in locomotor, conditioned place preference, and intravenous drug self-administration procedures. These opposing behavioral outcomes driven by ZFP189 TFs of opposing function hints that the ZFP189-driven behavioral adaptations to cocaine are bi-directional and can be reversed by inversion of endogenous NAc ZFP189 function with ZFP189- VPR. Strikingly, our synthetic ZFP189 TFs did not impact behavioral responses to morphine or saline. Finally, in performing RNA-sequencing of manipulated NAc tissues, we see that our synthetic ZFP189 TFs are only capable of regulating transcription in the brains of mice with a history of cocaine exposure, hinting hint that cocaine induces a NAc molecular state amenable to ZFP189 TF function, whereas morphine or saline do not. This work illuminates potential targets for drug-specific, anti- addiction medications.