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The function of the ZFP189 transcription factor in the nucleus accumbens facilitates cocaine-specific transcriptional and behavioral adaptations

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Distinguishing the brain pathogenic mechanisms affected by distinct drugs of abuse may inform targeted therapies against specific substance use disorders (SUDs). Here, we explore the function of a drug-associated transcription factor (TF), ZFP189, whose expression in the nucleus accumbens (NAc) has previously been demonstrated to facilitate cocaine-induced molecular and behavioral adaptations. To uncover the molecular action of ZFP189, we created synthetic ZFP189 TFs of distinct transcriptional function, including ZFP189^{VPR}, which activates the expression of target genes and exerts opposite transcriptional control to the endogenously repressive ZFP189. By virally delivering these synthetic ZFP189 TFs to the NAc of mice, we discover that the molecular control exerted by synthetic or endogenous ZFP189 solely alters behavioral and transcriptional adaptations to cocaine, but not morphine, saline, or palatable food. We demonstrate that NAc ZFP189 function drives the brain plasticity necessary to facilitate an increase in cocaine self-administration behaviors, whereas NAc ZFP189^{VPR} impedes this worsening of cocaine taking behaviors. Collectively, this research illuminates the brain biological mechanisms through which a drug-associated TF specifically coordinates the brain adaptations necessary for the worsening of cocaine use.