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CREB-mediated activation of *Zfp189* and re-engineering ZFP189 within mouse accumbens reveal transcriptional mechanisms governing cocaine-induced neuroadaptations

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Research over the past three decades has demonstrated that transcription factors (TFs), such as CREB, functioning within brain reward regions, regulate changes in reward sensitivity across many classes of drugs. However, since the drug-induced function of a given TF directly regulates the expression of many genes simultaneously, it is challenging to elucidate the causal transcriptional events that drive these drug-responsive neuroadaptations. Here, we utilize a novel fusion construct consisting of an RNA-guided, nuclease-dead Cas9 (dCas9) tethered to CREB to directly target CREB binding to individual genes in mouse brain. We observe that localizing CREB to an informatically identified gene target, *Zfp189,* within mouse nucleus accumbens (NAc) results in physiological activation of *Zfp189* expression, potentiated cocaine self-administration, and heightened neuronal function in response to cocaine in a medium spiny neuron subtype-dependent manner. To interrogate the downstream targets of the *Zfp189* gene-product, a Krüppel associated box (KRAB) zinc finger TF of unknown function, we replaced the ZFP189 KRAB domain with a transcriptional activating VPR domain. These novel constructs robustly regulate expression of a targeted *luciferase* gene and divergently affect cocaine, but not morphine, related behaviors when delivered intra-NAc. These experiments indicate *Zfp189* is a gene target through which CREB manifests tolerance to cocaine, and that the downstream functions of ZFP189 are directly responsible for altering cocaine, but not morphine, related behaviors. This work is evidence that neuroepigenetic editing models a single drug-induced molecular interaction and identifies its causal contribution to the broader syndrome, which may reveal therapeutic targets for drug addiction.