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Epigenomic editing of nucleus accumbens neuron subtypes using the CRISPR-Cas12f derived system

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The nucleus accumbens (NAc) is a major hub in the reward circuit. Previously, our lab used CRISPR epigenome editing tools to target a transcriptional program altered in dopamine receptor 1 and 2 NAc medium spiny neurons (MSNs) by repeated cocaine exposure. We are currently targeting genes disrupted in NAc MSN subtypes in mice abstinent to fentanyl exposure. Existing methods pose a limitation in the use of higher molecular weight CRISPR-Cas system that limits the utility in delivering these vectors to the brain using commonly used adeno-associated viruses (AAVs). Recent advances in CRISPR demonstrate efficient and consistent manipulation of gene targets using Cas12f derived system. Cas12f is approximately half the size of the conventional Cas9 obtained from either S. aureus or S. pyogenes and is, therefore, easier to deliver via viral vector delivery. We utilized a Cas12f- derived system called CasMINI and modified it to work as CRISPRa (activation) and CRISPRi (inhibition) to modify gene transcription. We are testing this system to alter the transcription of genes regulated in NAc D1- or D2-MSNs in fentanyl-abstinent mice. Our results demonstrate the promising utility of CasMINI in Neuro2A cells and the potential application of these CRISPR tools into selective cell subtypes in the brain in opioid-abstinent paradigms.