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Dominant negative of transcription factor NR4A2 in medial habenula attenuates reinstatement of cocaine self-administration in mice

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Substance use disorder is complicated by a lifelong risk of relapse. Relapse vulnerability is programed partly during drug use, when the action of drugs of abuse in the reward circuit enables the formation of abnormally strong context/reward memories. These memory processes underlie common relapse triggers such as exposure to drug-associated cues or environments and can be extremely long lasting. This persistence may be attributed to epigenetics, which has been shown to establish stable changes in cell function, and in turn changes in behavioral outcomes.

Recent studies have implicated the medial habenula (MHb) in cocaine-associated behaviors, yet the role of the MHb in regulating reinstatement of cocaine self-administration remains unknown. The lab recently identified the histone deacetylase 3 target gene, *Nr4a2*, as an important regulator of cocaine-associated behavior. NR4A2 is a transcription factor that regulates aspects of dopamine signaling during development, and is densely expressed in the MHb. **We hypothesized that reducing NR4A2 function in the MHb would reduce reinstatement of cocaine self-administration** and tested this by expressing the dominant negative form of NR4A2 (NURR2C) in MHb cholinergic neurons of ChAT-Cre mice trained to self-administer cocaine. To drive a robust reinstatement, we used an incubation of craving model wherein animals were extinguished and reinstated after 30 days homecage withdrawal. Control animals reinstated normally compared to NURR2C animals, which had reduced reinstatement. These findings identify the nuclear orphan receptor NR4A2 (with recently identified exogenous ligands) as a therapeutic target for medicinal chemistry to develop agonists/antagonists that may be relevant for addiction treatment.