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Epigenetic mechanisms in the medial habenula control reinstatement

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Propensity to relapse following long-periods of abstinence is a key feature of substance use disorders. Drugs of abuse, such as cocaine, cause long-term changes in the neural circuitry regulating reward, motivation, and memory processes through dysregulation of various molecular mechanisms, including epigenetic regulation of activity-dependent gene expression. Underlying drug-induced changes to neural circuit function are the molecular mechanisms regulating activity-dependent gene expression. Of note, histone acetyltransferases and histone deacetylases (HDACs), powerful epigenetic regulators of gene expression, are dysregulated following both acute and chronic cocaine exposure and are linked to cocaine-induced changes in neural circuit function. To better understand the effect of drug-induced changes on epigenetic function and behavior, we investigated HDAC3-mediated regulation of *Nr4a2/Nurr1* in the medial habenula (MHb), an understudied brain region with regard to cocaine-associated behaviors. Using DREADDs, we demonstrate that activating ChAT neurons in the ventral MhB induces reinstatement behavior in the absence of cocaine. To understand the epigenetic mechanisms underlying MHb-dependent reinstatement, we examined *Nr4a2*, an HDAC3 target gene and transcription factor with enriched expression in the cholinergic cell-population of the ventral MHb. We found that HDAC3 disengages from *Nr4a2* in the MHb in response to cocaine-primed reinstatement, suggesting that expression of *Nr4a2* is important for reinstatement. Indeed, overexpressing an endogenously occurring dominant negative splice variant of *Nr4a2*, called *Nurr2c*, in the MHb significantly impairs reinstatement. Together, these findings demonstrate that HDAC3-dependent regulation of *Nr4a2* in the ventral MHb is critical for relapse-like behaviors.