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Lysine acetyltransferase KAT2a is a novel cocaine-recruited epigenetic regulator in the nucleus accumbens

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Cocaine use disorder (CUD) imposes a large burden on public health, particularly because there are no FDA-approved pharmacotherapies for the disorder. The onset and maintenance of CUD is driven by physiological and transcriptional changes within the brain that lead to maladaptive cocaine taking and seeking; however, the precise molecular mechanisms remain opaque.

Epigenetic mechanisms, which typically take place at the level of the nucleosome - a nuclear complex of DNA wrapped around a protein octamer assembled from two subunits each of H2A, H2B, H3, and H4 - are emerging as a critical driver of cocaine-induced transcriptional adaptation. We have identified lysine acetyltransferase 2a (KAT2a) as a novel cocaine-recruited epigenetic regulator within the nucleus accumbens, a key brain region mediating the reinforcing effects of drugs. We initially identified KAT2a in silico as a computationally-predicted upstream regulator of the transcriptomic and proteomic regulation induced following cocaine

self-administration in both male and female mice. In vivo, cocaine increases a KAT2a-recruiting covalent mark on histone H3 (H3S10P), increases KAT2a:H3 associations, and increases KAT2a-associated acetylation of H3 (H3K9Ac and H3K14Ac), which are permissive to gene expression. Further, KAT2a and these KAT2a-associated histone marks, have increased occupancy at the key cocaine responsive genes CFos, Homer3, Oprk1, and Sigmar1. Finally, a cell type-specific KAT2a acetyltransferase domain dominant negative manipulation (E567Q) blunts cocaine self-administration and alters D1 medium spiny neuron activity. Together, these results highlight a novel cocaine-induced transcriptional regulator and a potential future therapeutic target to alleviate the devastating impact of CUD on public health.