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Histone acetyltransferase KAT2A is a critical epigenetic regulator of cocaine responses in the nucleus accumbens

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Substance use disorder is characterized by cycles of drug-use, abstinence, drug-seeking, and relapse. The neural basis of these long-lasting drug-associated behaviors have been linked to neural circuit function through changes in neurotransmission and receptor-based changes across the reward circuitry of the brain. However, the underlying molecular mechanisms which contribute the persistence of these drug-induced changes to neural function remain relatively poorly understood. Previous work from our lab and others has identified cocaine-induced changes to transcriptional and proteomic profiles within the nucleus accumbens (NAc). To understand how drugs of abuse, such as cocaine, generate long-lasting behavioral changes, it is critical to link between neuronal activity and changes in gene expression. One potential avenue are epigenetic adaptations, where DNA-protein interactions are modified to alter accessibility and likelihood of targeted gene expression. We identified temporally specific changes in Histone H3 post-translational modifications and identify a key regulator in these changes – KAT2A. KAT2A is a histone acetyltransferase known to regulate activity-dependent transcription. We find that KAT2A-regulated phosphoacetylation of H3 is increased following chronic cocaine self-administration. Moreover, we demonstrate that loss of KAT2A function in D1-MSNs alters sensitivity and motivation for cocaine. Lastly, we generate a cocaine self-administration activity profile of D1-MSNs that is subsequently altered by alterations in KAT2A function. The results of these studies contribute evidence for persistent cocaine-induced epigenetic adaptations and are the first step in generating a mechanistic link between epigenetic adaptations and changes in neuronal firing. In addition, we provide data linking these changes in epigenetic state to cocaine-seeking behavior.