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Cocaine-induced histone methylation on Egr3 and Nab2 promoters

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Epigenetic modifications underlie transcriptional adaptations in the nucleus accumbens (NAc) in cocaine addiction. However, there is little information about the role of histone demethylation in the NAc in response to cocaine. The NAc is primarily made up of medium spiny neurons (MSNs) that consist of two subtypes based on their enrichment of dopamine receptor 1 and 2. The two MSNs promote opposing reinforcing, rewarding, and psychostimulant sensitizing behaviors. However, there is limited knowledge of the epigenetic processes occurring in each MSN subtype in drug abuse. Recent studies demonstrate that repeated cocaine alters transcriptional regulation through altered histone methylation of genes via histone methyltransferase enzymes. Our previous work demonstrates that Egr3 transcriptionally regulates a histone lysine methylation enzyme in NAc after repeated cocaine exposure and we are currently investigating Egr3 binding on promoters of histone demethylase enzymes including lysine specific histone demethylase 1A, KDM1A, under these same conditions. In parallel we have examined mRNA levels of KDM1A in NAc D1-MSNs and D2-MSNs after repeated cocaine. The goal of the present study is to examine KDM1A binding and associated histone methylation marks at Egr3 and Nab2 promoters after repeated cocaine exposure. Using chromatin immunoprecipitation (ChIP) we observe altered KDM1A binding, as well as altered H3K4me3 and H3K9me2 on Egr3 and Nab2 promoters in NAc in the cocaine group compared to saline controls. Overall our studies are providing new information into the effects of cocaine on histone demethylation and its potential regulation of Egr3 and Nab2 transcription in MSN subtypes.