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The histone demethylase KDM6B in the medial prefrontal cortex epigenetically regulates cocaine reward memory

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Epigenetic remodeling contributes to synaptic plasticity via modification of gene expression, which underlies cocaine-induced long-term memory. A prevailing hypothesis in drug addiction is that drugs of abuse rejuvenate developmental machinery to render reward circuitry highly plastic and thus engender drug memories to be highly stable. Identification and reversal of these pathological pathways are therefore critical for cocaine abuse treatment. Previous studies revealed an interesting finding in which the mRNA of histone lysine demethylase, KDM6B, is upregulated in the medial prefrontal cortex (mPFC) during early cocaine withdrawal. However, whether and how it contributes to drug-seeking behavior remain unknown. Here we used a conditioned place preference paradigm to investigate the potential role of KDM6B in drug-associated memory. We found that KDM6B protein levels selectively increased in the mPFC during cocaine withdrawal. Notably, systemic injection of KDM6B inhibitor, GSK-J4, disrupted both reconsolidation of cocaine-conditioned memory and cocaine-primed reinstatement, suggesting dual effects of KDM6B in cocaine reward memory. In addition, we found that NMDAR expression and function were both enhanced during early cocaine withdrawal in mPFC. Injection of GSK-J4 selectively reversed this cocaine-induced increase of NR2A expression and synaptic function, suggesting that mal-adaptation of cocaine-induced synaptic plasticity in mPFC largely underlies KDM6B-mediated cocaine-associated memory. Altogether, these data suggest that KDM6B plays an essential role in cocaine-associated memory, which mainly acts through enhancing cocaine-induced synaptic plasticity in the mPFC. Our findings revealed a novel role of KDM6B in cocaine-associated memory and inhibition of KDM6B is a potential strategy to alleviate drug-seeking behavior.