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Histone demethylase JMJD3 mediates opioid-induced cellular and behavioral plasticity

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Opioid use disorder is a chronic and debilitating disease that is marked by relapse after periods of abstinence. A multitude of drug-elicited neuroadaptations in brain regions governing reward such as the Nucleus Accumbens, mediate maladaptive craving behaviors leading to relapse. One of the persistent changes underlying neuroadaptive mechanisms during abstinence from drugs of abuse is epigenetic modifications of DNA and histones. Here we show that following prolonged abstinence (AD 14) from heroin self-administration, histone demethylase, JMJD3 is increased in the NAc. Further, we demonstrate that this increase is specific to D2+ MSNs, demonstrating a cell-type specific regulation. To demonstrate a functional significance of these changes, we employed both a pharmacological and viral mediated approaches to modulate JMJD3 expression in the NAc, which demonstrated that JMJD3 levels/activity are sufficient to regulate cue-induced heroin seeking. Finally, we present data that the epigenetic factors are themselves regulated through the TGF-β super-family which we have previously demonstrated to be essential for drug seeking behaviors. Together these data highlight that JMJD3 is essential in mediating persistent cellular and behavioral adaptations following heroin exposure.