

The histone methyltransferase G9a in the nucleus accumbens bidirectionally controls cocaine self-administration, stress-induced reinstatement, and anxiety-like behaviors

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Repeated exposure to drugs of abuse induces lasting epigenetic changes in neurons that can promote addiction. Following chronic cocaine or opioid use, dimethylated lysine 9 on histone 3 (H3K9me2) – a enzymatic process mediated by the histone methyltransferase, G9a – is reduced in nucleus accumbens neurons. Consistent with this observation, chronic drug exposure also produces a decrease in G9a levels; however, the relevance of this reduction to addiction-relevant behaviors in the drug self-administration (SA) model is unknown. We show here that viral-mediated overexpression of G9a in the NAc increased sensitivity to the reinforcing effects of cocaine and enhanced the motivation to work for drug in the progressive ratio test. In addition, G9a overexpression led to a selective enhancement of stress-induced reinstatement of cocaine seeking and increased anxiety-like behavior in the elevated plus maze (EPM). Conversely, we found that viral-mediated knockdown of G9a levels in the NAc had the opposite effects on cocaine sensitivity and motivation for drug. G9a knockdown in the NAc also decreased context-, cocaine-, and stress-induced reinstatement of drug seeking, and it reduced anxiety-like behavior in the EPM. Together, these data show that G9a has bidirectional control over cocaine sensitivity, motivation, drug-seeking, and anxiety-like behaviors. These data also suggest that the reductions in G9a protein and H3K9me2 observed after chronic drug administration are counter-adaptations that limit addiction-related behaviors, and suggest that therapeutics that reduce G9a activity in the NAc might have value for the treatment of drug addiction and co-morbid anxiety observed in many substance use disorder patients.