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RESEARCH HIGHLIGHT

Anxiety, the chicken or the egg of addiction: targeting G9a for the treatment of comorbid anxiety and cocaine addiction

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Treating cocaine addiction is a major challenge and currently no FDA approved pharmacotherapies exist. One complicating factor is a high rate of comorbidity between cocaine and neuropsychiatric conditions such as anxiety. The relationship between anxiety symptoms and cocaine addiction is complicated; anxiety can be both a predisposing factor and a consequence of cocaine use as anxiety symptoms often emerge during drug use and withdrawal. Identifying and understanding the shared biological mechanisms that lead to comorbid anxiety and cocaine addiction, irrespective of which comes first, is critical for the identification of new treatments.

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One potential mechanism and therapeutic avenue is epigenetic regulation (including histone modifications and chromatin remodeling), which has emerged as a key contributor to the persistent changes in behavior following exposure to cocaine or anxiety-promoting factors such as stress [1]. One such epigenetic factor is the histone dimethyltransferase G9a (also known as EHMT2 and KMT1C), the focus of the study by Anderson et al. [2]. Previous studies have found an increase in G9a within the nucleus accumbens (NAc) following both cocaine self-administration and chronic non-contingent cocaine exposure, and G9a has been implicated in anxiety-like responses in rodent models [3, 4].

In this study, the authors aimed to determine the effect of reducing G9a expression within the NAc shell (NAcSh) on comorbid addiction- and anxiety-related behaviors. They generated a small hairpin RNA (shRNA) against G9a, which was then injected into NAcSh to reduce G9a expression, which reduced H3K9me2, a suppressive epigenetic histone mark and a target of G9a. Next, the authors assessed the effect of NAcSh knockdown of G9a on different measures of cocaine taking and seeking. They found that G9a knockdown shifted the cocaine dose-responses to the right and decreased progressive ratio responding, indicating a decrease in cocaine's reinforcing effects. They also tested the effect of G9a knockdown on different measures of relapse to cocaine seeking, including extinction responding and reinstatement of cocaine seeking after exposure to drug cues, drug priming, and footshock stress. G9a knockdown decreased extinction responding, drug priming- and stress-induced reinstatement, but not cue-induced reinstatement. Together, NAcSh knockdown of G9a decreased both ongoing cocaine self-administration and relapse/reinstatement during abstinence.

To address the role of G9a on basal versus cocaine-induced anxiety-like behavior, the authors tested the effect of G9a NAcSh knockdown in drug-naïve and cocaine-experienced rats. In drug-naïve rats tested in the elevated plus maze (EPM) and marble burying tasks, two measures of innate anxiety-like behaviors, NAcSh G9a knockdown reduced anxiety-like phenotypes, an effect that was also observed after cocaine self-administration. As this anti-anxiety phenotype was observed in drug-naïve rats, these data suggest that reduced anxiety-like behaviors in G9a knockdown rats might precede and predict the reduced addiction-related behaviors. In tentative support of this hypothesis, the authors reported that anxiety-like behavior in the EPM test correlated with progressive ratio responding.

The findings of this study are consistent with the authors' previous report showing that overexpression of G9a within the NAcSh enhances cocaine self-administration and reinstatement, as well as anxiety-like behavior [5]. The current study adds to these previous findings by demonstrating that G9a can bidirectionally modulate these comorbid phenotypes. Interestingly, the findings in this study regarding the role of NAc G9a in cocaine reward in rats are opposite to those previously reported by Maze et al. [6] using the conditioned place preference (CPP) model in mice who reported that G9a knockdown increased cocaine CPP while G9a overexpression decreased CPP.

Several factors might contribute to these differences, including the opposing effects of G9a knockdown in dopamine D1R and D2R expressing cells of the NAc [7], as well as the anatomical heterogeneity of the NAc. The NAc is divided anatomically and functionally into the core and shell subregions that play different roles in cocaine self-administration and relapse. While the studies of Anderson and colleagues in rats focuses exclusively on the shell, the previous studies examining NAc G9a expression and function in cocaine CPP in mice did not distinguish between these subregions [6, 7]. Together, this discrepancy between results from mouse studies using CPP and rat studies using addiction models of drug self-administration and relapse emphasizes the importance of using these latter models to investigate epigenetic mechanisms of drug addiction.

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While the canonical target of G9a is H3K9me2, it is also highly plausible that reduced G9a is exerting its effects by mechanisms other than H3K9me2-mediated repression of gene expression. This possibility is supported by several non-canonical roles of G9a in other systems, such as methylating non-histone proteins, including other epigenetic and transcription factors known to be involved in cocaine's behavioral and physiological effects [1], and regulating protein–protein interactions that alter chromatin states that can impact gene expression and behavior in complex ways [3]. When thinking about G9a as a therapeutic target, it will be critical to better understand the downstream mechanisms leading to its beneficial effects on addiction-related and anxiety-like behaviors.

In sum, Anderson and colleagues establish several important findings that support G9a within the NAcSh as a common mechanism underlying comorbid anxiety-like and addiction-like phenotypes in rats. These data, along with both clinical and preclinical data, support the idea that treatment of comorbid anxiety could be beneficial for addiction treatment, and highlights the importance of further studying the connection between neuropsychiatric disorders and addiction. The study also raises several important questions for future exploration. For example, it will be interesting to determine if acute inhibition of G9a (either pharmacologically or genetically) will decrease cocaine-seeking behavior elicited by exposure to cocaine or stress. Designing experiments to tease out G9a mechanisms in cocaine addiction and anxiety will greatly advance our knowledge and the development of treatments. Importantly, this study establishes G9a knockdown as a model that can be utilized to address the above questions and to further interrogate epigenetic and gene expression changes that might underlie comorbid addiction and anxiety.

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ADDITIONAL INFORMATION

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REFERENCES

1. Pierce RC, Fant B, Swinford-Jackson SE, Heller EA, Berrettini WH, Wimmer ME. Environmental, genetic and epigenetic contributions to cocaine addiction. Neuropsychopharmacology. 2018;43:1471–80.
2. Anderson EM, Sun H, Guzman D, Taniguchi M, Cowan CW, Maze I et al. Knockdown of the histone di-methyltransferase G9a in nucleus accumbens shell decreases cocaine self-administration, stress-induced reinstatement, and anxiety. Neuropsychopharmacology. 2018. https://doi.org/10.1038/s41386-018-0305-4. [Epub ahead of print]
3. Anderson EM, Penrod RD, Barry SM, Hughes BW, Taniguchi M, and Cowan CW, It is a complex issue: emerging connections between epigenetic regulators in drug addiction. Eur J Neurosci. 2018. https://doi.org/10.1111/ejn.14170. [Epub ahead of print]
4. Wang DY, Kosowan J, Samsom J, Leung L, Zhang KL, Li YX et al. Inhibition of the G9a/GLP histone methyltransferase complex modulates anxiety-related behavior in mice. Acta Pharmacol Sin. 2018;39:866–74.
5. Anderson EM, Larson EB, Guzman D, Wissman AM, Neve RL, Nestler EJ et al. Overexpression of the histone dimethyltransferase G9a in nucleus accumbens shell increases cocaine self-administration, stress-induced reinstatement, and anxiety. J Neurosci. 2018;38:803–13. p
6. Maze I, Covington HE 3rd, Dietz DM, LaPlant Q, Renthal W, Russo SJ et al. Essential role of the histone methyltransferase G9a in cocaine-induced plasticity. Science. 2010;327:213–6.
7. Maze I, Chaudhury D, Dietz DM, Von Schimmelmann M, Kennedy PJ, Lobo MK et al. G9a influences neuronal subtype specification in striatum. Nat Neurosci. 2014;17:533–9.