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Commentary

Synergistic Interactions between Histone Deacetylase Inhibitors and Drugs of Abuse

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Drug addiction is a psychiatric condition that involves the progression of acute drug use to compulsive drug-seeking behavior, and the vulnerability to relapse after abstinence. Several recent studies have suggested that epigenetic processes, heritable changes in gene expression that do not involve changes in the DNA sequence, may underlie cellular mechanisms of drug-induced behaviors (Renthal and Nestler, 2008b). The epigenetic process could integrate environmental stimuli into prolonged changes in gene expression through chromatin remodeling, leading to structural and functional modification in the central nervous system and ultimately to altered neuroplasticity.

Recent data has shown that psychomotor stimulants, such as cocaine, increase histone acetylation thereby impacting the chromatin structure (Renthal and Nestler, 2009). Generally speaking, histone acetylation is associated with the activation of gene transcription while deacetylation is associated with transcriptional repression. A recent study showed that acute injection of cocaine induces immediate early gene expression, such as *c-Fos* and *FosB* in nucleus accumbens, which parallels a transient increase in acetylation at histone H4 in these genes' proximal promoters (Kumar *et al*, 2005; Levine *et al*, 2005; Renthal *et al*, 2008a; Renthal *et al*, 2007). In contrast, chronic administration of cocaine leads to stable induction of a distinct subset of genes, including *Bdnf, Cdk5,* and *Npy*, which remain elevated for a long period of time even after withdrawal of cocaine (Freeman *et al*, 2008). Similar to the time course of the stable gene expression, potent and long-lasting increases in histone H3 acetylation in these gene promoters have been observed upon repeated exposure to cocaine.

Another histone post-translational modification that can impact the chromatin structure is phosphorylation. Histone phosphorylation at the serine 10 residue of H3, a typical marker for transcriptional activation, is another covalent and transient modification that occurs globally in response to acute cocaine exposure (Brami-Cherrier *et al*, 2005; Kumar *et al*, 2005). Histone H3 phosphorylation is mediated through activation of the mitogen and stress-activated protein kinase-1 (MSK1) signaling cascade (Brami-Cherrier *et al*, 2005). These transient histone modifications following acute administration of drugs of abuse might be a prerequisite to shift the epigenetic signatures at specific loci to establish a chromatin environment that triggers an addicted state. Such dynamic epigenetic regulation might contribute to the persistence of behavioral abnormalities caused by drugs of abuse, including symptoms of withdrawal, tolerance, and relapse.

In this issue, Sanchis-Segura *et al* (2009) investigated the ability of sodium butyrate, a non-selective histone deacetylase (HDAC) inhibitor, in combination with drugs of abuse to trigger behavioral and biochemical alterations. The authors replicate earlier findings that sodium butyrate potentiates cocaine-induced locomotor sensitization and then go on to show that sodium butyrate also potentiates alcohol and morphine-induced locomotor sensitization. The ability of sodium butyrate to potentiate locomotor sensitization with three different classes of drugs, namely a psychomotor stimulant, a sedative, and an opiate, suggest that the HDAC inhibitor taps a common mechanism to induce the behavioral effect. Interestingly, despite the robust and potent enhancement of drug-induced locomotor sensitization by sodium butyrate, this treatment had no effects on other behavioral measures of addiction including the development of tolerance or withdrawal. They further show that a challenge injection of the drug of abuse to animals that received repeated co-administration of sodium butyrate and an abused drug following withdrawal resulted in a potent enhancement of locomotion compared with the response in animals that had not been co-administered the HDAC inhibitor. This suggests that HDAC inhibition in conjunction with drugs of abuse impacts long-term behavior and that the HDAC inhibitor mediated certain long-lasting cellular changes to alter the behavioral phenotype.

To gain insight into the molecular mechanisms mediating the enhanced drug-induced locomotor sensitization induced by sodium butyrate, the authors examined bulk

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chromatin acetylation as well as histone phosphorylation. They show that sodium butyrate in a dose-dependent manner increases histone acetylation, however, the doses used in this study did not elicit any changes. Surprisingly, the drugs of abuse themselves also had no effect on global histone acetylation, although this result does not rule out possible changes in histone acetylation at specific gene promoters as has recently been demonstrated (Kumar *et al*, 2005). In contrast, acute exposure to cocaine and morphine produced a significant increase in histone H3 phosphorylation in striatum in agreement with previous studies, which had suggested that the increased H3 phosphorylation by cocaine might occur through activation of the MSK1-signaling pathway. Interestingly, ethanol had no effect on histone H3 phosphorylation suggesting a potential difference in the effect of this drug on epigenetic processes.

In the final set of experiments, the authors analyzed gene expression profiling from the striatum of animals administered morphine alone or in conjunction with sodium butyrate. Although many genes were upregulated in response to morphine, only $\sim$13% of these genes were further augmented in animals given the combination of morphine and sodium butyrate. The genes regulated in conjunction with both treatments included *FosB* as well as the circadian-related genes, *Per1* and *Rev-erbα*, all of which may be relevant to the development of addiction-related behaviors and explain the synergistic behavioral effects that were observed.

This study adds to our growing knowledge that HDAC inhibitors, such as sodium butyrate, enhance specific behavioral responses to different classes of drugs of abuse. The biochemical data shows that drugs of abuse do not alter global acetylation but do not rule out specific changes in histone acetylation at distinctive promoters. Moreover, the alterations in histone H3 phosphorylation by cocaine and morphine are intriguing but the lack of an effect by ethanol suggests that other as yet identified epigenetic changes, or perhaps even non-histone-specific effects, may also impact the response to drugs of abuse. Future experiments will be necessary to examine the biochemical effects of co-administration of drugs of abuse with sodium butyrate to elucidate the combined action of the drugs that were observed at the behavioral level.

Efforts to understand the behavioral and biochemical changes mediated by drugs of abuse may provide important information on the disease process as well as novel therapeutic approaches. The augmentation of behavioral responses to drugs of abuse by HDAC inhibitors provides a novel and exciting manner in which epigenetic changes may mediate the long-lasting changes associated with aspects of addiction. Although much work is still needed, a better understanding of the involvement of epigenetic processes may provide an important insight for more effective treatments of addiction.

See related article by Sanchis-Segura *et al* on page 2642.

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DISCLOSURE

The authors declare no conflict of interest.

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