

The Class II Histone Deacetylase Hypothesis of Addiction

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Drug addiction is a brain disease that results in the compulsive pursuit and use of a drug despite negative consequences. The development of addiction is insidious, evolving over time from voluntary to involuntary use, followed by relapses even after extended periods of voluntary or forced abstinence. The brain regions that mediate reward-based learning and memory have been found, in both human and animal studies, to be central to the onset and maintenance of addiction (1). When exposed to an illicit drug like methamphetamine, neuroadaptations in these brain regions reinforce both the environmental cues and the procedures that promote seeking and taking of the drug, while extended drug use further reinforces the structural changes to promote compulsivity and cue-induced relapse. Delineation of the molecular steps by which drugs of abuse alter brain structure and function has been the holy grail of addiction research.

The changes in brain structure and function associated with addiction require gene transcription and the formation of new proteins that promote synaptic remodeling. While the inheritance of genes involved in this process is a key component of drug addiction, covalent modifications of these genes or posttranslational modifications of their chromatin structure (initiated by environmental factors, including early illicit drug use) can render the genes differentially responsive to subsequent activation by drug use (or drug cues) and serve as a critical component both of the vulnerability and the persistence of drug addiction. Chromatin-modulating enzymes such as histone deacetylases (HDACs) and histone acetyltransferases have been found to integrate a diverse array of molecular responses to drugs of abuse, including stimulants such as cocaine and methamphetamine (2). The HDACs are subdivided into several classes based on structure and function. The class IIa HDACs, including HDAC4 and HDAC5, share the unique property of shuttling between the cytoplasm and nucleus in an activity-dependent manner. Once in the nucleus, HDAC4 and HDAC5 promote deacetylation of target genes by forming a multiprotein complex with the class I HDAC, HDAC3 (3), and they also regulate transcription by binding transcription factors, such as myocyte enhancer factor 2 (4). While HDAC4 and HDAC5 are highly abundant in the brain, most studies on their role in drug addiction have focused on the nucleus accumbens, leaving the following question open: are the functions of these class II HDACs similar or divergent across various regions of the reward circuitry? In addition, research on epigenetics and psychostimulants have focused primarily on indirect measures of drug reward (e.g., conditioned place preference), and only recently have these studies been performed using rodent models of addiction-like behavior (e.g., self-

administration followed by relapse tests). Thus, a second and equally pressing question pertains to behavior: what role do the class II HDACs have in these self-administration paradigms that better model addiction in humans?

In this issue of *Biological Psychiatry*, Li *et al.* (5) directly address both issues by testing the effect of HDAC5 overexpression and knockdown in the dorsal striatum, using a rodent model of addiction and relapse: incubation of methamphetamine craving. In this model of relapse, pioneered by Grimm *et al.* (6), rodents that are given extended access to drugs, such as cocaine or methamphetamine, have enhanced drug-seeking behavior after an extended period of abstinence. Li *et al.* (5) found that after prolonged abstinence from self-administered methamphetamine, HDAC5 modulates cue-induced methamphetamine craving. Specifically, they found that knockdown of HDAC5 decreased the number of cue-induced lever presses for methamphetamine, whereas overexpression of HDAC5 increased cue-induced seeking of methamphetamine. Importantly, these effects were present after a month, but not after a brief period (i.e., 2 days) of abstinence.

In the context of the epigenetic literature on addiction, these data are surprising. Previous studies have found that class II HDACs, particularly HDAC4 and HDAC5, repress addiction-related behaviors. For instance, both we and others have found that increased nuclear accumulation of HDAC4 and HDAC5 in the nucleus accumbens decreases the rewarding effects of cocaine (7,8). Similar findings have also been reported for the sensitizing effects of methamphetamine (9). What then could account for the surprising finding that HDAC5 in the dorsal striatum positively regulates incubation of methamphetamine craving?

The molecular mechanisms that mediate drug-induced neuroadaptations in the dorsal striatum may be different from the corresponding adaptations in the nucleus accumbens. Few addiction-related studies have investigated HDAC mechanisms of neuroadaptation in the dorsal striatum, which is surprising, as the dorsal striatum has been found to have a unique role in addiction (1). Indeed, the three stages of the addiction cycle—binge/intoxication, withdrawal/negative affect, and craving/anticipation—are mediated by discrete brain circuits (1). Whereas the ventral striatum is critical during the (acute) drug intoxication stage, the dorsal striatum has a central role in the craving stage (1). The craving stage, which can persist for months or even years, is particularly important from a therapeutic point of view, since it represents the risk period for drug relapse in individuals who are trying to achieve abstinence. The authors' finding that epigenetic processes in the dorsal striatum regulate incubation of methamphetamine craving (5)

represents an important contribution to this body of literature and introduces intriguing questions regarding the potential targets of HDAC5 in this brain region.

However, before we conclude that HDAC5 has opposite effects in different regions of the striatum, it is important to consider the finding by Li *et al.* (5) that knockdown of HDAC5 led to an increase in messenger RNA levels of HDAC4 (5). While HDAC4 and HDAC5 are highly homologous, HDAC4 has some special characteristics that may be relevant here. For example, whereas HDAC5 is uniformly expressed throughout the brain during development, HDAC4 is upregulated during early postnatal stages when enhanced synaptogenesis occurs, and loss of HDAC4 causes neurodegeneration (10). In addition, in the striatum, the protein levels of HDAC4 seem to be higher than those of HDAC5 (e.g., see the Human Protein Atlas), and HDAC4 knockout mice are not viable, whereas HDAC5 knockouts are (suggesting that HDAC4 may effectively compensate for HDAC5 loss, but not vice versa). Finally, HDAC4 (but not HDAC5) has been found to interact with the FosB locus, which gives rise to Δ FosB that is critical for the development of addiction (7).

If the observed increase in levels of HDAC4 after knockdown of HDAC5 in the dorsal striatum happens to act as a compensatory (and possibly overriding) HDAC mechanism, then the findings of Li *et al.* (5) would be in line with previous drug-related HDAC4 studies of the nucleus accumbens (7). Thus, understanding the different roles of HDAC4 and HDAC5 and their possible compensatory actions will be essential for future designs of pharmacological agents to treat addiction.

Finally, the intracellular regulation of class II HDAC proteins is highly complex and dynamic. For instance, HDAC4 and HDAC5 shuttle back and forth between the nucleus and cytoplasm in an activity-dependent manner, and class II HDACs are modulated by posttranslational processes, including sumoylation, ubiquitination, and proteolysis (7). Thus, overexpression and knockdown of HDAC5 may not result in predictable increases and decreases in HDAC5 function, respectively, and these potential alterations of HDAC5 function in the dorsal striatum need to be addressed in future studies.

Taken as a whole, this study presents a series of experiments that demonstrate a causal role of dorsal striatum HDAC5 in regulating the incubation of methamphetamine craving during drug abstinence. This work contributes greatly to our understanding of the role of epigenetic regulation in the dorsal striatum during a critical stage of the drug addiction cycle and introduces the exciting potential for identifying new targets for pharmacological interventions.

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Article Information

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