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Dysregulation of Acetylation Enzymes in Animal Models of Psychostimulant use Disorders: Evolving Stories

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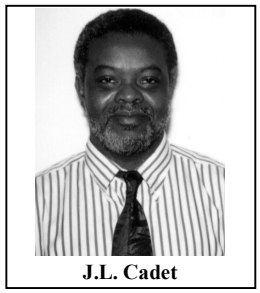

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Abstract: Substance use disorders are neuropsychiatric illnesses that have substantial negative biopsychosocial impact. These diseases are defined as compulsive abuse of licit or illicit substances despite adverse medicolegal consequences. Although much research has been conducted to elucidate the pathobiological bases of these disorders, much remains to be done to develop an overarching neurobiological understanding that might be translatable to beneficial pharmacological therapies. Recent advances in epigenetics promise to lead to such an elucidation. Here I provide a brief overview of observations obtained using some models of psychostimulant administration in rodents. The review identifies CREB binding protein (CBP), HDAC1, HDAC2, HADC3, HDAC4, and HDAC5 as important players in the acetylation and deacetylation processes that occur after contingent or non-contingent administration of psychostimulants. These observations are discussed within a framework that suggests a need for better animal models of addiction in order to bring these epigenetic advances to bear on the pharmacological treatment of human addicts.

Keywords: Acetylation, addiction, cocaine, dorsal striatum, epigenetics, gene expression, methamphetamine, nucleus accumbens.

INTRODUCTION

Substance use disorders (SUDs) are complex neuropsychiatric diseases of compulsive habits that permeate an individual's life despite disastrous medicolegal consequences. These disorders are highly prevalent throughout the world [1]. They are leading causes of morbidity and mortality due to medical and other legal and psychosocial complications [2]. For example, addiction to cocaine is associated with increased risks of cardiovascular and neurological complications including headaches and strokes, as well as multiple psychiatric symptoms including anxiety and cognitive impairments [3-8]. In the case of methamphetamine, complications include agitation, anxiety, cardiac arrhythmias, cognitive impairments, hyperthermia, psychosis, motor dysfunctions, strokes, and numerous pathological changes including gliosis in the brain [4, 9, 10]. These neurological and psychiatric complications suggest that therapeutic approaches that focus only on attenuating or suppressing drug taking behaviors may fail to address the complexity inherent in these multisystem disorders. Over several decades, attempts have been made by several groups of investigators who have provided simple and progressively more complex neurobiological explanations for the compulsive nature of drug taking behaviors. Some investigators have focused on single neurotransmitter hypotheses while others have documented the activation or inhibition of specific gene networks using approaches that have tested the involvement of single or multiple genes in the development, manifestations, and maintenance of SUDs [11-13]. Indeed, changes of gene expression have been reported with several classes of drugs including cocaine [13], methamphetamine [11], and opioids [12].

Gene transcription is regulated by complex epigenetic changes that include post-translational histone modifications and DNA methylation [14]. The N-tails of histones possess lysine residues that can be reversibly acetylated by histone acetyltransferases (HATs) or deacetylated by several histone deacetylases (HDACs) [15-17]. HATs can be grouped into type A nuclear HATs and type B cytoplasmic HATs. Classically, nuclear HATs can be grouped into CBP/p300, GNAT (GCN5/PCAF, and ELP3), and MYST (MOZ, Ybf2, Sas2, and Tip60) subfamilies [17-20]. Type B HATs are HAT1 and HAT2 [21, 22]. Other HATs of interest include ATF2, Clock, SRC-1 (NCOA1), SRC-2 (GRIP1, NCOA2, and TIF2), and SRC-3 (ACTR, NCOA3, and RAC3) [23-26], whose functions in the brain need to be investigated further.

HDACs remove acetyl groups from lysine residues on histones and stimulate the recruitment of several repressor complexes that mediate transcriptional changes [27]. HDACs are divided into four classes based on sequence similarities [28]. These include class I (HDAC1, HDAC2, HDAC3, and HDAC8), class IIA (HDAC4, HDAC5, HDAC7, HDAC9), class IIB (HDAC6, HDAC10), class III (Sirtuins1-7) and Class IV (HDAC11) HDACs [28]. Class I, II and IV HDACs are referred to as "classical" HDACs and are Zn^{2+}-dependent enzymes [29] whereas the sirtuins

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require NAD^+ as a cofactor [30]. Several of these HDACs regulate processes involved in development, differentiation, learning and memory, and neurodegeneration [31, 32].

ROLE OF HATS IN ANIMAL MODELS OF DRUG ADMINISTRATION

HATs play important roles in gene regulation *via* acetylation of histones (Fig. **1**) [16, 17]. Although cocaine is known to cause major changes in gene expression, relatively few studies have investigated the role of HATs in cocaine-induced behaviors. Levine *et al*. (2005) [33] reported that cocaine caused increased fosB mRNA expression that was accompanied by increased binding of CBP and histone H4 on the fosB promoter. These cocaine-induced changes were attenuated in mice that were CBP haploinsufficient. The CBP mutant mice showed no differences in baseline locomotor activity in comparison to control mice but exhibit decreased locomotor responses and sensitization after chronic cocaine. Another group of investigators also reported that both acute and chronic cocaine administration caused increased acetylation of histone H3 at lysine 14 (H3K14Ac) and of histone H2B at lysine 12 (H2BK12Ac) in the nucleus accumbens (NAc) of wild-type mice [34]. These cocaine-induced acetylation effects were attenuated in mice with CBP deletion in the NAc. Moreover, acute cocaine increased c-fos expression and binding of CBP at the c-fos promoter in wild-type mice, with attenuation of these responses in CBP knockout mice. CBP deletion was also associated with decreased locomotor response to cocaine. Furthermore, bilateral deletion of CBP in the NAc also attenuated cocaine conditioned place preference (CPP). Altogether, these data demonstrated the importance of CBP in cocaine-induced histone acetylation in the brain and behavioral responses. In contrast, Madsen *et al*. (2012) [35] showed that deletion of CBP in the mouse striatum produced increased sensitivity to cocaine and amphetamine. These contradictory data suggest that the specific brain region where CBP is deleted might impact behavioral responses to psychostimulant. It remains to be determined if methamphetamine might activate histone acetylation and regulate behaviors through CBP activation in a fashion similar to cocaine. The fact that some of the transcriptional effects of methamphetamine self-administration (SA) are mediated *via* CREB phosphorylation [36] suggests that this is a possibility because phosphorylated CREB recruits CBP to gene promoters in order to increase their transcription [18, 37, 38].

ROLE OF HDACS IN ANIMAL MODELS OF DRUG ADMINISTRATION

Class I HDACs

Class I HDACs are known to be involved in the regulation of gene expression (Fig. **1**) [39]. Some studies have now provided evidence that class I HDACs are regulated in animal models of drug administration (Table **1**). For example, Schroeder *et al*., (2008) [40] showed that pretreatment of mice with sodium butyrate, a class I and II HDAC inhibitor, in conjunction with a dopamine D1 agonist caused increased cocaine-induced locomotion and increased TH and BDNF mRNA expression in the ventral midbrain. They found, in addition, that this treatment was associated with H3 hypoacetylation at the promoters of these genes, findings that are counterintuitive since increased gene expression is more often associated with increased histone acetylation. In a subsequent elegant study, Kennedy *et al*., (2013) [41] showed that local knockdown of HDAC1 caused reduction of cocaine-induced locomotor sensitization, with knockdown of HDAC2 and HDAC3 having no significant effects. Interestingly, HDAC1 knockdown decreased HDAC2 expression. Another group of investigators used the cocaine SA model to assess epigenetic responses [42]. They reported that cocaine SA produced increased HDAC2 expression. Increased HDAC2 may have inhibitory or stimulatory effects on the expression of its target genes [43]. Of related interest, Deschatrettes *et al*., (2012) [44] reported that increased expression of the cyclic GMP-dependent protein kinase was able to reduce HDAC2 expression in cocaine-treated rats. Moreover, induction of cyclic GMP was shown to reduce cocaine SA by a process that involved reduced HDAC2 expression [45]. Recently, the involvement of another class I HDAC, HDAC3, was also demonstrated in cocaine-related behaviors [46, 47]. Using a selective HDAC3 inhibitor called RGFP966, Malvaez *et al*., (2013) [46] showed that systemic administration of the drug facilitated extinction of cocaine CPP. They also showed that RGFP966 blocked reinstatement of cocaine-seeking behavior. The RGFP-induced behavioral changes were associated with increased acetylation of histone H4 at lysine 8 (H4K8Ac) in the infra-limbic cortex but not in the nucleus accumbens and hippocampus. In addition, the authors reported increased H3K14Ac in all 3 brain regions. The RGFP966 treatment also produced decreased HDAC3 binding but increased H4K8Ac binding at the c-fos promoter [46]. Importantly, focal deletion of HDAC3 in the mouse NAc also facilitated cocaine CPP [47]. Moreover, there were increased c-fos and Nr4a2 mRNA levels and increased H4K8Ac abundance at the promoters of these genes in these mice. Taken together, these observations suggest that cocaine-mediated behaviors might regulate gene expression by diverse class I HDAC-regulated events. This suggestion will need to be investigated further by using genome-wide approaches such as RNA sequencing in animals in which the expression of specific class I HDACs is either increased or suppressed.

The effects of another illicit drug, methamphetamine, on class I HDACs have also been investigated. Martin *et al*., (2012) [48] first showed that a single injection of the drug could cause significant decreases in HDAC1 but increases in HDAC2 protein levels in nuclear fractions of the rat NAc. These changes were accompanied by decreased abundance of H3K9Ac and H3K18Ac but increased H4K5Ac and H4K8Ac. Acute effects of methamphetamine in the dorsal striatum appears to be regulated, in part, by increased H4K5Ac binding at the promoters of several immediate early genes, including *Arc, Crem, Egr2, c-fos,* and *Npas4* [49]. Jayanthi *et al*. (2014) [50] also tested the effects of chronic methamphetamine administration on HDAC1 and HDAC2 expression in the dorsal striatum and found significant increases in their expression. They also reported corresponding hypoacetylation of histone H4 acetylation at lysines 4, 8, 12 and 16, with these changes occurring at the promoters of glutamate receptors, *GluA1, GluA2,* and

GluN1, in the striatum [50]. Importantly, repeated injection of the HDAC inhibitor, valproic acid, was able to prevent the chronic effects of methamphetamine on histone H4 acetylation and on glutamate receptor expression [50]. It remains to be determined to what extent these mechanisms might also be involved in models of methamphetamine CPP and self-administration.

Class II HDACs

Class II HDACs are divided into classes IIA and IIB [28]. Class IIA HDACs shuttles between the cytosol and the nucleus [51, 52]. The effects of drugs of abuse on the expression of class II HDACs have recently been investigated. Wang *et al*. (2010) [53] reported that chronic bilateral injection of the HDAC inhibitor, TSA, in the rat NAc shell caused higher self-administration rates in rats that received 300 or 500 microgram/kg/infusion of cocaine. They also observed that the HDAC inhibitor potentiated cocaine SA-induced increases in H3 and H4 acetylation in the NAc. Some of the behavioral effects of cocaine appear to involve HDAC4 because HDAC4 overexpression was able to attenuate the motivation to self-administer cocaine. HDAC5, another class IIA HDAC, was also reported to show decreased expression in the NAc after chronic non-contingent injections of cocaine [54]. Interestingly, cocaine SA caused decreased nuclear localization of HDAC5 and of its phosphorylated form [42]. These observations are consistent with those of Dietrich *et al*. (2012) [55] who reported that repeated injections of cocaine to rats caused activation of the salt-inducible kinase, SIK1, and subsequent phosphorylation of HDAC5 in the nucleus, followed by moving of the phosphorylated HDAC5 form into the cytoplasm. Together, these results had suggested that cocaine SA might have produced HDAC5 export from the nucleus or cytoplasmic retention of HDAC5, with differential alterations in the expression of HDAC5 target genes. The idea is in contrast to the observations of Taniguchi *et al*. (2012) [56] who found that chronic cocaine injections caused HDAC5 dephosphorylation and increased HDAC5 nuclear accumulation in the mouse striatum. They also reported that HDAC5 dephosphorylation resulted in decreased cocaine CPP. The different results reported by these groups might be related to the specificity of the antibodies, the species of animals used, the route of cocaine administration, and/or the brain region being studied. More research is needed to clarify these points.

Class III HDACs

The class III HDACs, Sirts, appear to also be involved in the effects of psychostimulants. Using a genome-wide approach, Renthal *et al*. (2009) [57] performed chromatin immunoprecipitation (ChIP) to investigate the effects of repeated injections of cocaine in the NAc of mice. They used antibodies against pan-acetylated histones H3 and H4 in the ChIP experiments. This cocaine injection schedule caused increased H3 and H4 acetylation at the promoters of a large number of genes, with 15% of genes showing overlap of both H3 and H4 acetylation. Some genes that showed cocaine-induced increased histone acetylation include *Arc, Atf1, Cart, Cdk5, Egr3, histone H4, Sirt1,* and *Sirt2* [57]. The role of sirtuins in the behavioral effects of cocaine was supported by the observations that an activator of sirtuins, resveratrol, enhanced cocaine CPP whereas a sirtuin inhibitor, sirtinol, attenuated this behavioral outcome. A more recent study has also investigated the role of Sirt1 in cocaine-induced behaviors using mice with selective deletion or overexpression of Sirt1 in the NAc [58]. This paper showed that increasing Sirt1 in the NAc increased cocaine CPP. Increased Sirt1 expression was also associated with increased expression of *BDNF, Creb1, CBP,* and *Cdk5*. In contrast, Sirt1 deletion caused decreased cocaine CPP. Increasing Sirt2 expression also increased cocaine CPP. It is, thus, of interest that chronic methamphetamine injections also increased Sirt1 and Sirt2 mRNA and protein levels in the rat dorsal striatum [50]. Together, these observations suggest the possibility that class III HDACs might also be involved in the regulation of genes involved in the development and manifestation of psychostimulant addiction. It is also possible that changes in sirtuin regulation might participate in neurologic and metabolic changes observed in addicted humans [9, 11].

Class IV HDAC

The class IV HDAC, HDAC11, was cloned and characterized by Gao *et al*. (2002) [59] and is presently the only member of that class. HDAC11 is highly expressed in the brain [60]. Related to addiction, Host *et al*. (2011) [42] recently reported that cocaine SA was accompanied by

Table 1. HDAC Inhibitors and psychostimulant-induced behavior and biochemistry.

Inhibitors	Psychostimulant	Behavior/Biochemistry	Reference
Resveratrol	Cocaine	Increased CPP	Renthal (2009)
Sirtinol	Cocaine	Decreased CPP	Renthal (2009)
Sodium butyrate	Amphetamine Cocaine	Increased locomotion Increased locomotion	Kalda (2007) Kumar (2005)
TSA	Cocaine	Reduced self-administration	Romieu (2008)
Valproic Acid	Amphetamine Methamphetamine	Increased locomotion Normalized Glu Rs	Jayanthi (2014)

CPP, condition place preference; TSA, trichostatin A.

increased HDAC11 expression. This of interest because HDAC11 contains residues shared by classes I and II HDACs [59] involved in the behavioral effects of cocaine (see above). Also of interest is the fact that HDAC11 is involved in the regulation of gene expression in maturing oligodendrocyte cultures that showed increased expression of the enzyme, as well as decreased abundance of histone H3 acetylated at lysine 9 (H3K9) and at lysine 14 (H3K14) [61]. These observations suggest that cocaine-induced increases in HDAC11 expression may be involved in producing white matter abnormalities reported in cocaine self-administering rodents [62].

RELATIONSHIP OF EPIGENETIC CHANGES TO ADDICTION AND POTENTIAL DRAWBACKS OF ADDICTION MODELS

Several groups have now suggested, based on some of the data reviewed above, that drug-induced epigenetic changes might serve as the molecular substrates of addiction. It has been suggested further that therapeutic approaches that involve epigenetic agents that can counter drug-induced epigenetic dysregulations should be important weapons in the anti-addiction armamentarium. Epigenetic observations in animal models of drug administration have indeed gone a long way to provide partial explanation for the molecular effects of drugs in various brain regions. However, it is important to mention some of the problems that have been raised regarding the models used in these studies.

One of these objections deals with the fact that drug administration paradigms used in several of these studies often involve non-contingent injections of amphetamine, cocaine or methamphetamine by experimenters [50, 63-65]. It has often been pointed out that this approach does not mimic the way that humans administer drugs. In addition, because some of the inhibitors used also impact several HDAC classes [50, 63-67], it is often not possible to specify which specific HDAC is involved in the drug-induced behavioral or biochemical changes. Drug self-administration approaches are thought to be more reminiscent of drug abuse by humans. Indeed, there are only a few self-administration

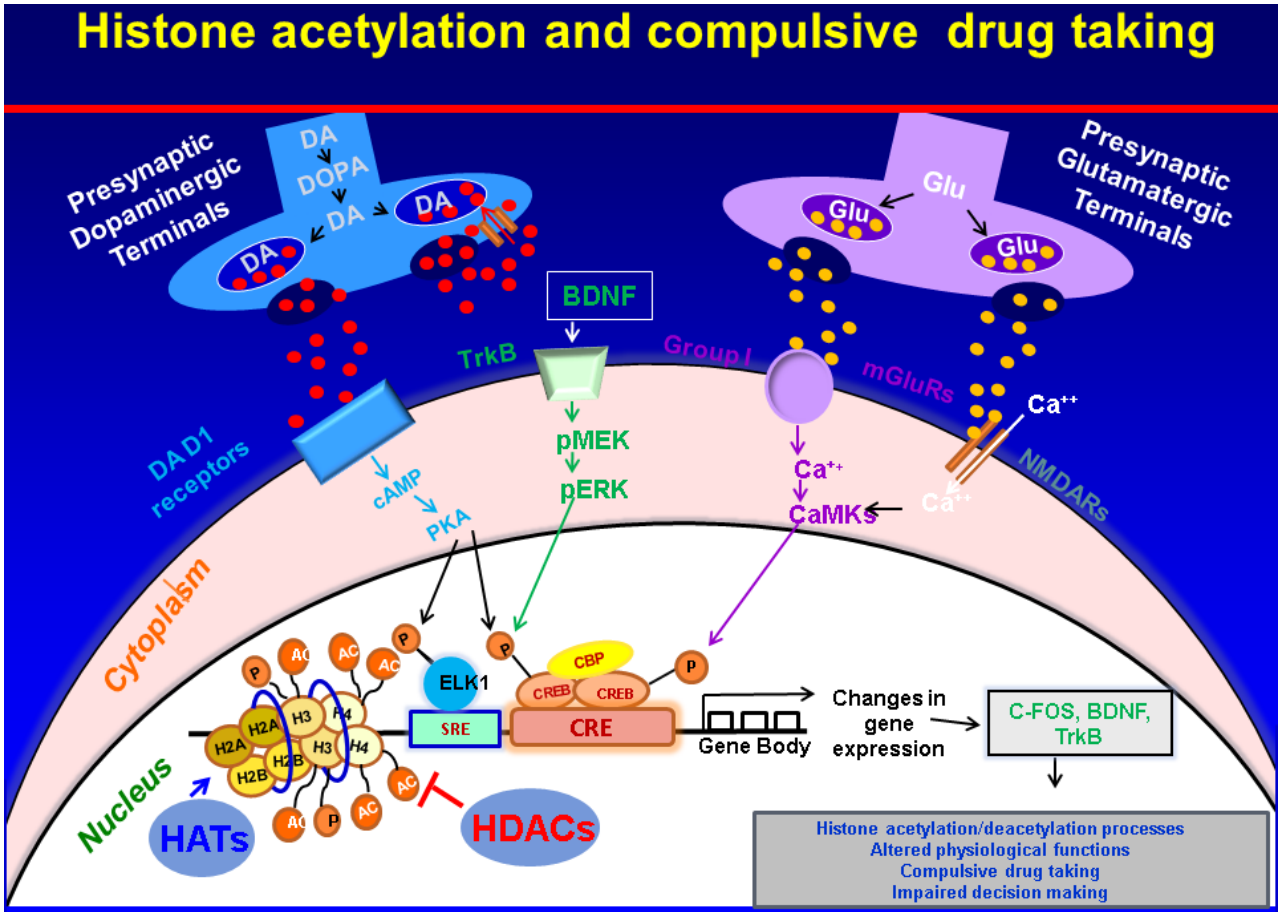

Fig. (1). Scheme showing the potential involvement of HATs and HDACs in the regulation of gene expression observed in animal models of drug abuse. This model takes into consideration the fact that psychostimulants such as cocaine and methamphetamine exert some of their effects through activation of dopamine and glutamate receptors followed by activation of the c-AMP-PKA/CREB phosphorylation cascade. Thus, drug-induced changes in epigenetic markers are thought to occur downstream to the stimulation of these receptors. Classically, HATs and HDACs are thought to drive or inhibit gene expression. However, both HATs and HDACs are been shown to bind to genes with either high level or low level of transcription. These observations also indicate that more in-depth reasoning is necessary to clarify the potential use of epigenetic agents in models of substance use disorders.

studies that have investigated the effects of psychostimulants on epigenetic markers. These papers have found changes in the expression of HDACs, with some papers reporting that HDAC inhibitors can either block or enhance drug-induced behaviors depending on the paradigm or inhibitor used. In addition, some studies have investigated the behavioral impact of HDAC inhibitors without providing detailed analyses of the biochemical and epigenetic effects of these drugs in the specific model under study [63]. Importantly, genetic deletion of HDACs has also resulted in differential behavioral responses depending on the specific HDACs (see discussion above). In self-administration studies, investigators have almost always used all the rodents that self-administer the drug in question and have labeled these animals addicted. It is known, however, that not all humans who administer drugs are addicted to the drug of choice. This is because their usage may be only recreational, with such use not at all impacting on the individual's activities of daily living. Indeed, addiction is, by definition, a neuro-psychiatric disorder that is manifested by repeated, increasing, and compulsive abuse despite adverse medico-legal consequences. As a corollary, nobody would propose that everyone who shows paranoid tendencies should be diagnosed as a schizophrenic patient. This argument supports the idea that the self-administration animal model may need to be tweaked further in order to better reflect human addicted conditions.

Another model often used is the CPP. Several groups have tested the role of specific HDACs in psychostimulant-induced CPP after identifying changes in their expression after non-contingent drug administration. This is a very clever approach that documents the participation of these enzymes in the rewarding effects of drugs without necessarily meeting criteria for an addiction diagnosis. This is because a drug can be rewarding to an individual without necessarily being translated into the individual becoming addicted to that drug (*e.g.* large number of social drinkers). Thus, this discussion supports the need to separate the subacute pharmacological effects of a drug from its addictive consequences.

In neurology and psychiatry, there has been a successful longstanding approach to examine post-mortem tissues from patients who suffer from Alzheimer's disease, Huntington's disease, and schizophrenic diatheses. Additional post-mortem studies are often conducted using small animal models of these disorders. These lines of studies allow for greater comparison between human disorders and corresponding rodent models. These investigations promise to quicken the pace at which epigenetic discoveries will be made for these human diseases. This quickened pace will more than likely lead to advances that can be translated into treatment and prevention approaches. This argument suggests that the field of addiction medicine needs to venture where neurology and psychiatry are presently in order to conduct and support more molecular studies using post-mortem brains of human addicts.

CONCLUDING REMARKS

In summary, this paper has provided a brief overview of acetylation/deacetylation events that occur after administration of drugs to rodents. Although these studies have begun to identify the effects of these drugs on acetylation-related enzymes in the brain, more interesting observations remain to be made by using models that are more representative of addiction in humans. Models that take into consideration insensitivity or inattention to adverse consequences as a potential factor in the development of addiction promise to advance this field further. At this juncture, it is important to note that the epigenetic enzymes, discussed above, can modify non-histone cytoplasmic and mitochondrial proteins that play important roles in the regulation of metabolic activities [16, 68, 69]. These cellular processes need to be kept in mind when discussing the role of HATs and HDACs in addiction. Moreover, the combinatorial roles of histone modifications in regulating gene expression need to be considered [70, 71] because the addictive drugs in question may exert concomitant influences on the expression of diverse epigenetic enzymes [11, 41]. Furthermore, although HATs and HDACs were thought to mainly associate, respectively, with active and inactive genes, the role of these proteins in regulating transcription is now known to be even more dynamic [43]. This discussion thus indicates that more rigorous reasoning is needed in our thinking about the designing of epigenetic therapeutics for psychostimulant use disorders [72]. Hopefully, the present argument will serve as an impetus for the development of a scientific portfolio to support studies that investigate the potential generation of brain specific epigenetic agents. These compounds could obviate complications inherent in using drugs that impact the functions of HATs and HDACs in peripheral organs. Such an approach may revolutionize the treatment of drug addiction.

CONFLICT OF INTEREST

The authors confirms that this article content has no conflict of interest.

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