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REVIEW ARTICLE

Epigenetic Landscape of Methamphetamine Use Disorder

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Abstract: The persistence of the addiction phenotype in methamphetamine use disorder (MUD) suggests the potential presence of epigenetic changes and potential structural adaptations that may drive the manifestations of MUD in humans. In the present review, we discuss the evidence that documents the fact that methamphetamine exposure can cause changes in epigenetic modifications, including histone acetylation and methylation, as well as DNA methylation and hydroxymethylation in a complex manner that need to be fully dissected. Nevertheless, our work has demonstrated the existence of correlations between behavioral changes and epigenetic alterations during methamphetamine self-administration. We found that prolonged methamphetamine self-administration and contingent footshocks resulted in rats with compulsive drug-taking and abstinent phenotypes. In addition, rats that reduce their methamphetamine intake in the presence of punishment showed increased DNA hydroxymethylation in genes encoding potassium channels in their nucleus accumbens. Moreover, altered DNA hydroxymethylation in those genes led to an increase in their mRNA expression. Additional studies revealed decreased mRNA expression of histone deacetylases associated with increased histone acetylation and induced gene expression in the dorsal striatum. These changes were associated with a reduction in methamphetamine intake in response to contingent footshocks. More research is necessary in order to further dissect how pharmacological or genetic manipulations of identified epigenetic alterations and expression of potassium channels can impact methamphetamine-taking behaviors or relapse to methamphetamine-taking after long periods of abstinence. Investigations that use discovery approaches, such as whole-genome sequencing after chromatin immunoprecipitation, should accelerate our efforts to develop epigenetic therapeutic approaches against MUD.

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1. INTRODUCTION

The abuse of methamphetamine (METH) is widespread; nearly 37 million individuals use METH or amphetamine-type stimulants worldwide [1]. In the United States, methamphetamine use reported during drug-related treatment admissions increased by more than 50% between 2008 and 2017. This increase was observed among almost all demographic groups and all census regions [2]. Repeated exposure to methamphetamine can lead to the development of an addictive diathesis characterized by excessive drug-taking, compulsion to take the drug, drug-taking behavior in the presence of adverse social and medical consequences and repeated relapses even during active treatment of the psychiatric disease [3]. Methamphetamine use disorder (MUD) is a biopsychosocial disorder that is probably the result of molecular, cellular, and bio-pathological neuroadaptations consequent to repeated methamphetamine exposure [4]. Current investigations have begun to elucidate some of the mechanisms that serve as substrates for these neuroadaptations with the hope that they might help explain the transition from recreational methamphetamine use to MUD in humans [5]. Because methamphetamine impacts neurotransmission through the facilitation of the release of dopamine, norepinephrine, and serotonin in brain regions where monoaminergic terminals are located [6-8], therefore, the focus of biochemical and molecular studies has been on these brain areas. Some of these brain regions consist of nodal points in the so-called brain reward pathways that include the ventral tegmental area (VTA), the nucleus accumbens (NAc), the dorsal striatum, the hippocampus, and the prefrontal cortex (PFC) [9-12]. In the present review, we discuss data specific to the influences of methamphetamine on epigenetic markers in several brain regions.

Methamphetamine causes neurotransmitter release by reversing monoamine transport [13-15] subsequently increasing the levels of norepinephrine and dopamine in the synaptic cleft, as measured by microdialysis [16, 17]. Alt-

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hough ideas about methamphetamine use disorder have mostly focused on the transient increase in monoamine levels in the synaptic cleft, these acute changes cannot obviously account for the clinical course of methamphetamine and the repeated relapses observed when patients are participating in treatment programs during which they may or may not be exposed to the drug [18, 19]. This line of reason suggests that methamphetamine-induced epigenetic alterations and consequent changes in the expression of genes and proteins might be the relevant factors in promoting neurostructural modifications that might serve as the substrates for compulsive drug use and craving [3, 4].

A few laboratories have been investigating the epigenetic and transcriptional effects of methamphetamine on the brain. Herein, we provide a summary of the evidence that methamphetamine exposure causes epigenetic consequences in various brain regions. The review includes investigations of the effects of methamphetamine on histone acetyltransferases (HATs/KATs), deacetylases (HDACs), methyltransferases (HMTs/KMTs) [20] demethylases (HDMs/KDMs) [21], DNA methyltransferases (DNMTs) [22], and ten-eleven translocation methylcytosine dioxygenases (TETs) [23, 24].

2. HISTONE ACETYLATION AND METHAMPHETAMINE USE DISORDER

Histone acetylation is one of the most investigated chromatin modifications in rodent models of substance use disorders [25-27]. The accumulated evidence supports a role for histone acetylation in methamphetamine use disorder. Specifically, animals that underwent methamphetamine conditioned place preference (CPP) were reported to show increased H3 but not H4 acetylation in the brain [28]. In a model of methamphetamine-induced behavioral sensitization, mice were treated with methamphetamine for 10 days in conjunction with saline or the HDAC inhibitor, sodium butyrate (NaB) [29]. The authors reported that NaB increased the locomotor responses to methamphetamine acutely in sensitized animals [29]. They also found that acute NaB and methamphetamine increased histone H4 acetylation in the mouse dorsal striatum. Repeated methamphetamine also increased histone H3 acetylation but not the chronic drug combination [29]. However, the changes in behaviors did not show any direct patterns to changes in histone acetylation. More studies are needed to assess the specific role of HATs/KATs and HDACs in methamphetamine-induced locomotor sensitization by using viral vectors to increase or decrease the expression of specific KAT or HDAC to assess their role in this behavioral adaptation. This idea is relevant to the observations that methamphetamine injection can result in the decrease in histone H3 acetylated at lysine 9 (H3K9ac) and lysine 18 (H3K18ac) in nuclear sub-fractions but time-dependent increase in the acetylated H4K5 and H4K8 [30]. In addition to altered histone acetylation, injections of methamphetamine decreased HDAC1 protein expression but increased HDAC2 protein expression levels in the nucleus accumbens (NAc) [30]. These results were extended further by measuring the effects of chronic methamphetamine on gene expression and histone modifications in the dorsal striatum of rats [31]. Chronic methamphetamine was associated with decreased mRNA and protein levels of GluA1 and GluA2 alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) and GluN1 N-methyl-D-aspartate receptor (NMDAR) subunits. Chromatin immunoprecipitation-polymerase chain reaction (ChIP-PCR) revealed that chronic methamphetamine caused decreased enrichment of acetylated histone H4 at GluA1, GluA2, and GluN1 promoters. In addition, methamphetamine increased repressor element-1 silencing transcription factor (REST) corepressor 1 and histone deacetylase 2 enrichment onto GluA1 and GluA2 gene sequences. Furthermore, valproic acid, a histone deacetylase inhibitor, attenuated methamphetamine-induced decreased expression of AMPAR and N-methyl-D-aspartate receptor subunits in the dorsal striatum, and METH-induced decreased H4K16Ac recruitment on AMPAR gene sequences. Because of the multitude of changes that methamphetamine exposure can cause, it will be important to use vectors that influence specific HAT or HDAC instead of using non-specific HDAC inhibitors when assessing the role of histone acetylation/deacetylation in animal models of methamphetamine use disorders.

Class I, HDAC1 and HDAC2, and class II, HDAC4 and HDAC5, may also play differential roles in methamphetamine use disorder [32]. Specifically, Li *et al*. in 2014 reported that acute injection of methamphetamine decreased HDAC1 and HDAC2 mRNA levels but not HDAC4 and HDAC5 in the PFC, whereas chronic methamphetamine affected HDAC2, HDAC4 but not HDAC1 and HDAC5 in that structure [32]. After seven days of withdrawal from methamphetamine, there were significant decreases in HDAC4 and HDAC5 in the PFC. These results indicate that HDACs respond differentially during chronic methamphetamine administration and that their roles in various aspects of the development and maintenance of addiction need to be very carefully examined before making specific recommendation about the use of epigenetic drugs in the treatment of addiction in humans.

A genome-wide analysis using a ChIP-Sequencing approach was able to identify the role of a specific histone modification in the regulation of gene expression [26]. The authors reported that an acute METH injection caused changes in H4K5 acetylation around the transcription start sites (TSSs) of several genes in the dorsal striatum. Chronic methamphetamine injections also caused increased H4K5 acetylation marks at the TSS and changes in gene expression even though the patterns of gene expression were different between acute and chronic methamphetamine treatment [26]. Interestingly, microarray analysis revealed that chronic METH administration caused a global decrease in gene expression that appeared to be independent of changes in H4K5 abundance at these genes [26]. That study also identified putative proteins that, together with HDACs, might serve to modify the complex regulation of chromatin structure during methamphetamine administration. In addition to repeated injections of methamphetamine, it is essential to use drug self-administration paradigms to identify epigenetic modifications that might be more relevant to methamphetamine use disorders in humans. By using these paradigms, it has been reported that the expression of genes that code for proteins interacting with HDAC complexes was significantly impacted [3]. These genes included brain abundant signal protein 1 (basp1) mRNA levels. BASP1 is a corepressor of WT1 targets *via* interaction with HDAC1 [33]. Another gene of in-

terest was the protein product of Kruppel-like factor 10 (klf10) gene that contains an R1 domain through which it interacts with the HDAC corepressor, mSin3A [34]. Future studies will assess the role of these genes and proteins in mediating the molecular adaptations that might underlie transitions of recreational methamphetamine use during early stages of drug-taking behaviors to compulsive use during stages when criteria for addiction are met.

3. PARTICIPATION OF HISTONE METHYLATION IN MODELS OF METHAMPHETAMINE USE DISORDER

In addition to histone acetylation, there have been reports that methamphetamine use may also be associated with histone methylation. Behavioral sensitization after repeated injections of methamphetamine is associated with increased trimethylation of histone H3 at lysine 4 (H3K4me3) at the promoter of the chemokine, CCR2, in the NAc of mice [35]. Similarly, Aguilar-Valles *et al*. in 2014 used conditioned place preference (CPP) to assess how epigenetic changes in the NAc might support methamphetamine-associated memories [36]. Towards that end, they measured the expression of several modified epigenetic proteins and found an increased abundance of H3K4me2 and H3K4me4 in the NAc of animals that expressed methamphetamine CPP. They also reported changes in the expression of many genes that were upregulated by METH-associated contextual learning [36], with these genes belonging to classes associated with synaptic growth, memory, transcription, and chromatin modification. The authors found that the histone-lysine *N*-methyltransferase 2A (KMT2A), also called myeloid/ lymphoid or mixed-lineage leukemia 1 (MLL1), an enzyme involved in histone H3 trimethylation at K4, was upregulated in the NAc of the methamphetamine CPP animals. Using a small interfering RNA (siRNA) delivery approach, they showed that they could decrease KMT2A and H3K4me3 abundance as well as reduce methamphetamine CPP [36]. Interestingly, METH self-administration was not associated with increased H3K4me3 abundance on the promoters of c-fos and fosB in the dorsal striatum [37]. These different results can be explained by the models used in the two sets of experiments, the differential role of the ventral and dorsal striatum in behavioral responses to the drug, and the different species of rats vs. mice used by the investigators.

4. ROLES OF DNA METHYLATION AND DNA HYDROXYMETHYLATION IN METHAMPHETAMINE USE DISORDER

Recent studies have begun to pay attention to the role that DNA methylation and hydroxymethylation might play in the models of methamphetamine use disorders; the DNA methylation enzymes are expressed in the brain [38]. The establishment of DNA methylation patterns occurs during embryonic development *via* the actions of the de novo DNA methyltransferases (DNMTs), DNMT3A, and DNMT3B, with the maintenance of DNMT, DNMT1, preserving methylation early during development [39]. Numachi *et al*. in 2007, reported that repeated injection of methamphetamine for 21 days caused differential changes in DNMT1 expression in the NAc and dorsal striatum of two strains of rats [40]. Specifically, they reported that Fisher 344 rats exhibited increased striatal DNMT1 expression after both acute and repeated injections of methamphetamine, whereas Lewis rats showed reduced DNMT1 expression [40]. They also reported increased DNMT1 expression in the NAc of Fisher rats but not in the Lewis rats. Jayanthi *et al*. in 2014, also reported that chronic methamphetamine led to increased interactions of REST corepressor-1 and methylated CpG binding protein 2 with histone deacetylase 2 associated with decreased expression of glutamate AMPA receptors in the dorsal striatum [31]. Methylated DNA immunoprecipitation and hydroxymethylated DNA immunoprecipitation-polymerase chain reaction also revealed that chronic methamphetamine was associated with decreased enrichment of 5-methylcytosine and 5-hydroxymethylcytosine at GluA1 and GluA2 promoter sequences. These results indicate that comparable changes in DNA methylation and hydroxymethylation can occur in the model of methamphetamine use disorder. The relevance of these changes in behavioral responses to the drug will require specific genetic manipulations of the enzymes involved in catalyzing each reaction in the brain.

Jayanthi *et al*. in 2017, also reported the effect of methamphetamine on DNA hydroxymethylation in the rat NAc [41]. They found that methamphetamine caused DNA hypomethylation at sites near the corticotropin-releasing hormone (Crh/Crf) TSS and intragenic arginine vasopressin (Avp) sequences; these changes were accompanied by time-dependent increase in the expression of Crh and Avp in that structure. Methamphetamine also increased DNA hydroxymethylation at the Crh TSS and intragenic Avp sites. These methamphetamine-induced changes in DNA hydroxymethylation were accompanied by increased protein expression of ten-eleven-translocation (TET) enzymes that catalyze DNA hydroxymethylation. Moreover, administration of methamphetamine increased the binding of TET1 at the Crh promoter and of TET3 at Avp intragenic regions [41]. In order to further test the role of DNA hydroxymethylation in methamphetamine use disorder, Cadet *et al.* in 2017, used a behavioral paradigm in which rats that had already escalated methamphetamine intake were segregated into rats that reduce or stop their drug intake (non-addicted/resilient, non-compulsive,) from those that continue to take the drug compulsively (addicted, compulsive) in the presence of adverse consequences represented by contingent footshocks [42]. We used those divergent groups of rats to investigate potential alterations in global DNA hydroxymethylation in the NAc. Resilient rats were found to exhibit substantial differential DNA hydroxymethylation in comparison with both control and compulsive rats. Moreover, differential DNA hydroxymethylation was observed mainly at intergenic sites located on long and short interspersed elements. Cadet *et al*. in 2017, also reported that there were differentially hydroxymethylated regions in genes encoding voltage (Kv1.1, Kv1.2, Kvb1, and Kv2.2)- and calcium (Kcnma1, Kcnn1, and Kcnn2)-gated potassium channels observed in the NAc of resilient rats, with these changes being associated with increased mRNA levels of these potassium channels in comparison to compulsive and control rats [42]. Thus, changes in differentially hydroxymethylated regions and increased expression of specific potassium channels in the brain may suppress methamphetamine-taking behaviors in the presence

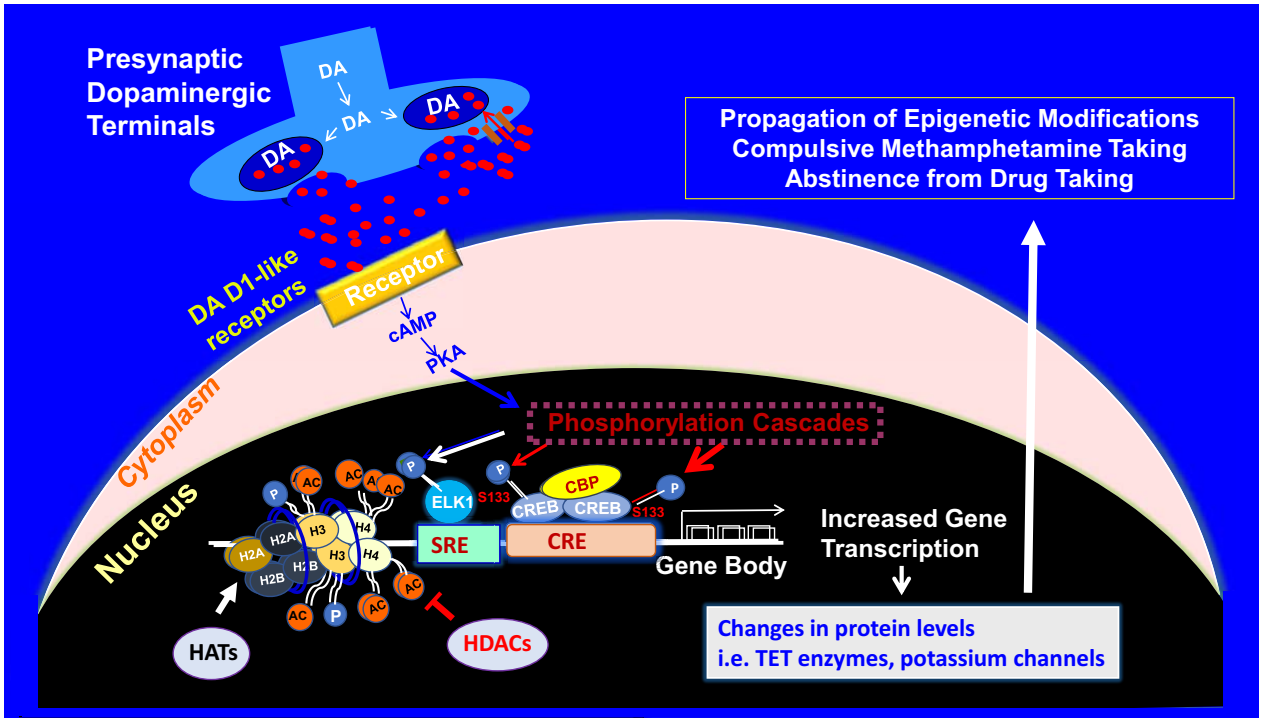

Fig. (1). This schema illustrates, in part, the potential role of histone acetylation and phosphorylation in methamphetamine use disorder. The figure shows the initial steps that may be involved after the release of dopamine (DA) and its interactions with DA D1-like receptors in various brain regions. Subsequent to DA-D1 interactions, there is an activation of protein kinase A and a subsequent cascade that leads to histone phosphorylation and the facilitation of histone acetylation. These biochemical events increase the transcription of immediate early genes and other genes involved in controlling epigenetic events. Together, these events may lead to persistent structural adaptations and associated behavioral changes that are labeled as methamphetamine use disorder. Further elucidation of these molecular events should help to develop a treatment against methamphetamine addiction. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

Table 1. Summary of data on chromatin modifications obtained from animal models of methamphetamine use disorder.

Chromatin Modification	Direction of Modification	Brain Region	Gene Identity	Refs.
Acetylation	H3 ↑	NAc	Nrxn, Syp, Dlg4, Gria1, Grin2a, Grin2b, Camk2a, Creb, Cdk5	[28]
-	H4K12 ↑	Dorsal striatum	-	[29]
-	H3K14 ↑	Dorsal striatum	-	[29]
-	H3K9 and H3K18 ↓	NAc	-	[30]
-	H4K5 and H4K8 ↑	NAc	-	[30]
-	H4K5; H4K12 and H4K16 ↓	Dorsal striatum	GluA1, GluA2 and GluN1	[31]
-	pan-AcK H2-3	NAc	-	[36]
Methylation	H3K4me3 ↑	NAc	CCR2	[35]
-	H3K4me2 and H3K4me3 ↑	NAc	-	[36]
-	H3K27me2 ↓	NAc	-	[36]
-	H3K4me3 ↑	Dorsal striatum	-	[37]
DNA hydroxymethylation	Increased	NAc	Crh, Avp	[41]

(Table 1) contd….

Chromatin Modification	Direction of Modification	Brain Region	Gene Identity	Refs.
-	Increased	NAc	Voltage (Kv1.1, Kv1.2, Kvb1 and Kv2.2)- and calcium (Kcnma1, Kcnn1, and Kcnn2)- gated potassium channels	[42]
DNA methylation	Increased	Hippocampus	Adora1, Aimp1, Akap5, Atg2b, Atp5s, B4galnt2, Bcl7c, Cacna1g, Cdc23, Chrm4, Cnga3, Cnst, Cpz, Dhx16, Elk3, Eme2, Exosc6, F11r, Fuca1, Gatad2a, Gdap1l1, Ggct, Glyr1, Gm266, Gnb1l, Gpatch3, Grinl1a, Hrk, Hspb8, Ilk, Kcnab2, L2hgdh, Mir762, Mrps34, Mst1, Nphp4, Nudt16l1, Pcdhgc3, Pcf11, Pgam1, Rrp8, Six6, Snx7, Sorbs1, Srsf5, Tatdn2, Tbck, Tex261, Tfb2m, Tia1, Tsen34, Txnrd3, Ube1y1, Ubn1, Vbp1, Zc3h7a, Zic3	[45]
-	Decreased	Hippocampus	Accn4, Aldh3b1, Allc, Ankrd23, Armc7, Atp2c1, Bex1, C1ql4, Camkk2, Car9, Cldn19, Crhr2, Cyp4f15, Ddhd2, Dlgap2, Dpp6, Fam100a, Gas2l3, Lsp1, Mpped2, Mysm1, Nell1, Pdia5, Pnck, Ppp2r3c, Rarg, Rusc2, Smurf1, Socs1, Timm13, Trpm4, Wdr12	[45]

of adverse consequences. These observations support the idea of using potassium channel activators to treat methamphetamine use disorder in humans [43]. A recent study by You *et al*. in 2019, have also reported that the two-pore potassium channel, KCNK13, is a potentially novel alcohol-sensitive molecular target [44]. These observations suggest that this channel needs to be included in the therapeutic arsenal against alcohol use disorder.

The effects of methamphetamine exposure on DNA methylation have also been investigated in the brains of offsprings of chronically drug-treated male and female mice [45]. Male and female C57Bl/6J mice were given methamphetamine in escalating doses or saline from adolescence through adulthood. After they had mated, female mice were still treated with either drug or saline throughout gestation. Interestingly, hippocampal DNA methylation studies revealed that there were significant differentially methylated regions consequent to *in utero* methamphetamine exposure. These data are consistent with the idea that methamphetamine-taking during pregnancy may cause substantial alterations in epigenetic markers during brain development [46, 47].

CONCLUDING REMARKS

Animal models of methamphetamine use disorder have indicated that this neuropsychiatric disease might be secondary to complex epigenetic and transcriptional changes that occur in the brain (Fig. **1**). Some of these epigenetic neuroadaptations consist of histone acetylation and methylation as well as DNA methylation and hydroxymethylation (Table **1**). It is highly likely that methamphetamine-induced changes in chromatin structures might be responsible, in part, for a cascade of transcriptional changes that lead to altered protein expression and secondary structural changes in the brain of some individuals that continue to compulsively take methamphetamine even in the presence of adverse consequences. It is also to be noted that delayed gene and protein expression might also serve in generating more epigenetic cascades to maintain the behaviors associated with substance use disorders. Further work is necessary to clarify the initial epigenetic and transcriptional steps that are involved in the transition of recreational methamphetamine use to methamphetamine use disorder. Understanding the molecular substrates of this transition should help develop epigenetic anti-addiction drugs to be used by the individuals who are at risk of transitioning to uncontrollable methamphetamine use. Similar studies to elucidate the molecular bases of craving should also be helpful to patients who fail treatment because of unsurmountable cravings.

LIST OF ABBREVIATIONS

AMPAR = Alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor

Avp = Arginine Vasopressin

Crh = Corticotropin-releasing hormone

ChIP-PCR = Chromatin Immunoprecipitation-Polymerase Chain Reaction

CPP = Conditioned Place Preference

H3K9ac = Histone H3 Acetylated at Lysine 9)

HAT = Histone Acetyltransferases

HDAC = Histone Deacetylases

HDM = Histone Demethylases

HMT = Histone Methyltransferases

MUD = Methamphetamine Use Disorder

NAc = Nucleus Accumbens

NaB = Sodium Butyrate

NMDAR = N-methyl-D-aspartate Receptor

PFC: = Prefrontal Cortex

REST = Repressor Element-1 Silencing Transcription Factor

TET = Ten-Eleven-Translocation

TSS = Transcription Start Site

VTA = Ventral Tegmental Area

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] UNODC, World Drug Report 2017. *United Nations Publication.,* **2017**.

[2] Jones, C.M.; Olsen, E.O.; O'Donnell, J.; Mustaquim, D. Resurgent methamphetamine use at treatment admission in the United States, 2008-2017. *Am. J. Public Health,* **2020**, *110*(4), 509-516. http://dx.doi.org/10.2105/AJPH.2019.305527 PMID: 32078347

[3] Cadet, J.L.; Brannock, C.; Jayanthi, S.; Krasnova, I.N. Transcriptional and epigenetic substrates of methamphetamine addiction and withdrawal: Evidence from a long-access self-administration model in the rat. *Mol. Neurobiol.,* **2015**, *51*(2), 696-717. http://dx.doi.org/10.1007/s12035-014-8776-8 PMID: 24939695

[4] Cadet, J.L.; Bisagno, V.; Milroy, C.M. Neuropathology of substance use disorders. *Acta Neuropathol.,* **2014**, *127*(1), 91-107. http://dx.doi.org/10.1007/s00401-013-1221-7 PMID: 24292887

[5] Cadet, J.L.; Patel, R.; Jayanthi, S. Compulsive methamphetamine taking and abstinence in the presence of adverse consequences: Epigenetic and transcriptional consequences in the rat brain. *Pharmacol. Biochem. Behav.,* **2019**, *179*, 98-108. http://dx.doi.org/10.1016/j.pbb.2019.02.009 PMID: 30797763

[6] Howell, L.L.; Kimmel, H.L. Monoamine transporters and psychostimulant addiction. *Biochem. Pharmacol.,* **2008**, *75*(1), 196-217. http://dx.doi.org/10.1016/j.bcp.2007.08.003 PMID: 17825265

[7] Salomon, L.; Lanteri, C.; Glowinski, J.; Tassin, J.P. Behavioral sensitization to amphetamine results from an uncoupling between noradrenergic and serotonergic neurons. *Proc. Natl. Acad. Sci. USA,* **2006**, *103*(19), 7476-7481. http://dx.doi.org/10.1073/pnas.0600839103 PMID: 16648258

[8] Sora, I.; Li, B.; Fumushima, S.; Fukui, A.; Arime, Y.; Kasahara, Y.; Tomita, H.; Ikeda, K. Monoamine transporter as a target molecule for psychostimulants. *Int. Rev. Neurobiol.,* **2009**, *85*, 29-33. http://dx.doi.org/10.1016/S0074-7742(09)85003-4 PMID: 19607959

[9] Ikemoto, S.; Yang, C.; Tan, A. Basal ganglia circuit loops, dopamine and motivation: A review and enquiry. *Behav. Brain Res.,* **2015**, *290*, 17-31. http://dx.doi.org/10.1016/j.bbr.2015.04.018 PMID: 25907747

[10] Pessiglione, M.; Vinckier, F.; Bouret, S.; Daunizeau, J.; Le Bouc, R. Why not try harder? Computational approach to motivation deficits in neuro-psychiatric diseases. *Brain,* **2018**, *141*(3), 629-650. http://dx.doi.org/10.1093/brain/awx278 PMID: 29194534

[11] Schultz, W. Neuronal reward and decision signals: From theories to data. *Physiol. Rev.,* **2015**, *95*(3), 853-951. http://dx.doi.org/10.1152/physrev.00023.2014 PMID: 26109341

[12] Thibaut, F. Basal ganglia play a crucial role in decision making. *Dialogues Clin. Neurosci.,* **2016**, *18*(1), 3. http://dx.doi.org/10.31887/DCNS.2016.18.1/fthibaut PMID: 27069375

[13] Fleckenstein, A.E.; Volz, T.J.; Riddle, E.L.; Gibb, J.W.; Hanson, G.R. New insights into the mechanism of action of amphetamines. *Annu. Rev. Pharmacol. Toxicol.,* **2007**, *47*, 681-698. http://dx.doi.org/10.1146/annurev.pharmtox.47.120505.105140 PMID: 17209801

[14] Goodwin, J.S.; Larson, G.A.; Swant, J.; Sen, N.; Javitch, J.A.; Zahniser, N.R.; De Felice, L.J.; Khoshbouei, H. Amphetamine and methamphetamine differentially affect dopamine transporters *in vitro* and *in vivo*. *J. Biol. Chem.,* **2009**, *284*(5), 2978-2989. http://dx.doi.org/10.1074/jbc.M805298200 PMID: 19047053

[15] Reith, M.E.A.; Gnegy, M.E. Molecular mechanisms of amphetamines. *Handb. Exp. Pharmacol.,* **2020**, *258*, 265-297. http://dx.doi.org/10.1007/164_2019_251 PMID: 31286212

[16] Baumann, M.H.; Ayestas, M.A.; Sharpe, L.G.; Lewis, D.B.; Rice, K.C.; Rothman, R.B. Persistent antagonism of methamphetamine-induced dopamine release in rats pretreated with GBR12909 decanoate. *J. Pharmacol. Exp. Ther.,* **2002**, *301*(3), 1190-1197. http://dx.doi.org/10.1124/jpet.301.3.1190 PMID: 12023554

[17] Rothman, R.B.; Baumann, M.H.; Dersch, C.M.; Romero, D.V.; Rice, K.C.; Carroll, F.I.; Partilla, J.S. Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. *Synapse,* **2001**, *39*(1), 32-41. http://dx.doi.org/10.1002/1098-2396(20010101)39:1<32::AID-SYN5>3.0.CO;2-3 PMID: 11071707

[18] Ballester, J.; Valentine, G.; Sofuoglu, M. Pharmacological treatments for methamphetamine addiction: Current status and future directions. *Expert Rev. Clin. Pharmacol.,* **2017**, *10*(3), 305-314. PMID: 27927042

[19] Tiffany, S.T.; Wray, J.M. The clinical significance of drug craving. *Ann. N. Y. Acad. Sci.,* **2012**, *1248*, 1-17. http://dx.doi.org/10.1111/j.1749-6632.2011.06298.x PMID: 22172057

[20] Blackledge, N.P.; Klose, R.J. Histone lysine methylation: An epigenetic modification? *Epigenomics,* **2010**, *2*(1), 151-161. http://dx.doi.org/10.2217/epi.09.42 PMID: 22122751

[21] Trojer, P.; Reinberg, D. Histone lysine demethylases and their impact on epigenetics. *Cell,* **2006**, *125*(2), 213-217. http://dx.doi.org/10.1016/j.cell.2006.04.003 PMID: 16630806

[22] Lo, R.; Weksberg, R. Biological and biochemical modulation of DNA methylation. *Epigenomics,* **2014**, *6*(6), 593-602. http://dx.doi.org/10.2217/epi.14.49 PMID: 25531254

[23] Melamed, P.; Yosefzon, Y.; David, C.; Tsukerman, A.; Pnueli, L. Tet enzymes, variants, and differential effects on function. *Front. Cell Dev. Biol.,* **2018**, *6*, 22. http://dx.doi.org/10.3389/fcell.2018.00022 PMID: 29556496

[24] Wang, Z.; Tang, B.; He, Y.; Jin, P. DNA methylation dynamics in neurogenesis. *Epigenomics,* **2016**, *8*(3), 401-414. http://dx.doi.org/10.2217/epi.15.119 PMID: 26950681

[25] Browne, C.J.; Godino, A.; Salery, M.; Nestler, E.J. Epigenetic mechanisms of opioid addiction. *Biol. Psychiatry,* **2020**, *87*(1), 22-33. http://dx.doi.org/10.1016/j.biopsych.2019.06.027 PMID: 31477236

[26] Cadet, J.L.; Jayanthi, S.; McCoy, M.T.; Ladenheim, B.; Saint-Preux, F.; Lehrmann, E.; De, S.; Becker, K.G.; Brannock, C. Genome-wide profiling identifies a subset of methamphetamine (METH)-induced genes associated with METH-induced increased H4K5Ac binding in the rat striatum. *BMC Genomics,* **2013**, *14*, 545. http://dx.doi.org/10.1186/1471-2164-14-545 PMID: 23937714

[27] Walker, D.M.; Nestler, E.J. Neuroepigenetics and addiction. *Handb. Clin. Neurol.,* **2018**, *148*, 747-765. http://dx.doi.org/10.1016/B978-0-444-64076-5.00048-X PMID: 29478612

[28] Shibasaki, M.; Mizuno, K.; Kurokawa, K.; Ohkuma, S. L-type voltage-dependent calcium channels facilitate acetylation of histone H3 through PKCγ phosphorylation in mice with methamphetamine-induced place preference. *J. Neurochem.,* **2011**, *118*(6), 1056-1066. http://dx.doi.org/10.1111/j.1471-4159.2011.07387.x PMID: 21781114

[29] Harkness, J.H.; Hitzemann, R.J.; Edmunds, S.; Phillips, T.J. Effects of sodium butyrate on methamphetamine-sensitized locomotor activity. *Behav. Brain Res.,* **2013**, *239*, 139-147. http://dx.doi.org/10.1016/j.bbr.2012.10.046 PMID: 23137698

[30] Martin, T.A.; Jayanthi, S.; McCoy, M.T.; Brannock, C.; Ladenheim, B.; Garrett, T.; Lehrmann, E.; Becker, K.G.; Cadet, J.L.

Methamphetamine causes differential alterations in gene expression and patterns of histone acetylation/hypoacetylation in the rat nucleus accumbens. *PLoS One,* **2012**, *7*(3), e34236. http://dx.doi.org/10.1371/journal.pone.0034236 PMID: 22470541

[31] Jayanthi, S.; McCoy, M.T.; Chen, B.; Britt, J.P.; Kourrich, S.; Yau, H.J.; Ladenheim, B.; Krasnova, I.N.; Bonci, A.; Cadet, J.L. Methamphetamine downregulates striatal glutamate receptors *via* diverse epigenetic mechanisms. *Biol. Psychiatry,* **2014**, *76*(1), 47-56. http://dx.doi.org/10.1016/j.biopsych.2013.09.034 PMID: 24239129

[32] Li, H.; Li, F.; Wu, N.; Su, R.B.; Li, J. Methamphetamine induces dynamic changes of histone deacetylases in different phases of behavioral sensitization. *CNS Neurosci. Ther.,* **2014**, *20*(9), 874-876. http://dx.doi.org/10.1111/cns.12301 PMID: 24954603

[33] Toska, E.; Campbell, H.A.; Shandilya, J.; Goodfellow, S.J.; Shore, P.; Medler, K.F.; Roberts, S.G. Repression of transcription by WT1-BASP1 requires the myristoylation of BASP1 and the PIP2-dependent recruitment of histone deacetylase. *Cell Rep.,* **2012**, *2*(3), 462-469. http://dx.doi.org/10.1016/j.celrep.2012.08.005 PMID: 22939983

[34] Zhang, J.S.; Moncrieffe, M.C.; Kaczynski, J.; Ellenrieder, V.; Prendergast, F.G.; Urrutia, R. A conserved alpha-helical motif mediates the interaction of Sp1-like transcriptional repressors with the corepressor mSin3A. *Mol. Cell. Biol.,* **2001**, *21*(15), 5041-5049. http://dx.doi.org/10.1128/MCB.21.15.5041-5049.2001 PMID: 11438660

[35] Ikegami, D.; Narita, M.; Imai, S.; Miyashita, K.; Tamura, R.; Narita, M.; Takagi, S.; Yokomizo, A.; Takeshima, H.; Ando, T.; Igarashi, K.; Kanno, J.; Kuzumaki, N.; Ushijima, T.; Suzuki, T. Epigenetic modulation at the CCR2 gene correlates with the maintenance of behavioral sensitization to methamphetamine. *Addict. Biol.,* **2010**, *15*(3), 358-361. http://dx.doi.org/10.1111/j.1369-1600.2010.00219.x PMID: 20624155

[36] Aguilar-Valles, A.; Vaissière, T.; Griggs, E.M.; Mikaelsson, M.A.; Takács, I.F.; Young, E.J.; Rumbaugh, G.; Miller, C.A. Methamphetamine-associated memory is regulated by a writer and an eraser of permissive histone methylation. *Biol. Psychiatry,* **2014**, *76*(1), 57-65. http://dx.doi.org/10.1016/j.biopsych.2013.09.014 PMID: 24183790

[37] Krasnova, I.N.; Chiflikyan, M.; Justinova, Z.; McCoy, M.T.; Ladenheim, B.; Jayanthi, S.; Quintero, C.; Brannock, C.; Barnes, C.; Adair, J.E.; Lehrmann, E.; Kobeissy, F.H.; Gold, M.S.; Becker, K.G.; Goldberg, S.R.; Cadet, J.L. CREB phosphorylation regulates striatal transcriptional responses in the self-administration model of methamphetamine addiction in the rat. *Neurobiol. Dis.,* **2013**, *58*, 132-143. http://dx.doi.org/10.1016/j.nbd.2013.05.009 PMID: 23726845

[38] Bayraktar, G.; Kreutz, M.R.; Neuronal, D.N.A. Neuronal DNA methyltransferases: Epigenetic mediators between synaptic activity and gene expression? *Neuroscientist,* **2018**, *24*(2), 171-185. http://dx.doi.org/10.1177/1073858417707457 PMID: 28513272

[39] Li, E.; Zhang, Y. DNA methylation in mammals. *Cold Spring Harb. Perspect. Biol.,* **2014**, *6*(5), a019133. http://dx.doi.org/10.1101/cshperspect.a019133 PMID: 24789823

[40] Numachi, Y.; Shen, H.; Yoshida, S.; Fujiyama, K.; Toda, S.; Matsuoka, H.; Sora, I.; Sato, M. Methamphetamine alters expression of DNA methyltransferase 1 mRNA in rat brain. *Neurosci. Lett.,* **2007**, *414*(3), 213-217. http://dx.doi.org/10.1016/j.neulet.2006.12.052 PMID: 17254711

[41] Jayanthi, S.; Gonzalez, B.; McCoy, M.T.; Ladenheim, B.; Bisagno, V.; Cadet, J.L. Methamphetamine induces TET1- and TET3-dependent DNA hydroxymethylation of crh and avp genes in the rat nucleus accumbens. *Mol. Neurobiol.,* **2017**, *55*(6),5154-5166. PMID: 28842817

[42] Cadet, J.L.; Brannock, C.; Krasnova, I.N.; Jayanthi, S.; Ladenheim, B.; McCoy, M.T.; Walther, D.; Godino, A.; Pirooznia, M.; Lee, R.S. Genome-wide DNA hydroxymethylation identifies potassium channels in the nucleus accumbens as discriminators of methamphetamine addiction and abstinence. *Mol. Psychiatry,* **2017**, *22*(8), 1196-1204. http://dx.doi.org/10.1038/mp.2016.48 PMID: 27046646

[43] McCoy, M.T.; Jayanthi, S.; Cadet, J.L. Potassium channels and their potential roles in substance use disorders. *Int. J. Mol. Sci.,* **2021**, *22*(3), 1249. http://dx.doi.org/10.3390/ijms22031249 PMID: 33513859

[44] You, C.; Savarese, A.; Vandegrift, B.J.; He, D.; Pandey, S.C.; Lasek, A.W.; Brodie, M.S. Ethanol acts on KCNK13 potassium channels in the ventral tegmental area to increase firing rate and modulate binge-like drinking. *Neuropharmacology,* **2019**, *144*, 29-36. http://dx.doi.org/10.1016/j.neuropharm.2018.10.008 PMID: 30332606

[45] Itzhak, Y.; Ergui, I.; Young, J.I. Long-term parental methamphetamine exposure of mice influences behavior and hippocampal DNA methylation of the offspring. *Mol. Psychiatry,* **2014**, *20*(2), 232-9. PMID: 24535458

[46] Salinas, R.D.; Connolly, D.R.; Song, H. Invited review: Epigenetics in neurodevelopment. *Neuropathol. Appl. Neurobiol.,* **2020**, *46*(1), 6-27. http://dx.doi.org/10.1111/nan.12608 PMID: 32056273

[47] Vissers, C.; Sinha, A.; Ming, G.L.; Song, H. The epitranscriptome in stem cell biology and neural development. *Neurobiol. Dis.,* **2020**, *146*, 105139. http://dx.doi.org/10.1016/j.nbd.2020.105139 PMID: 33065280