

# Epigenetic Regulation of Memory by Acetylation and Methylation of Chromatin: Implications in Neurological Disorders, Aging, and Addiction

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**Abstract** Synaptic plasticity is one of the most fundamental properties of neurons that underlie the formation of the memory in brain. In recent years, epigenetic modification of both DNA and histones such as DNA methylation and histone acetylation and methylation emerges as a potential regulatory mechanism that governs the transcription of several genes responsible for memory formation and behavior. Furthermore, the recent identification of nitrosylation of proteins has shown to either activate or repress gene transcription by modulating histone methylation or acetylation status in mature neuron. Recent studies suggest that the use of major substrates of abuse, e.g., cocaine, induces alterations in molecular and cellular mechanisms of epigenetics that underlie long-term memories in the striatum and prefrontal cortex. Moreover, downregulation of genes due to alterations in epigenetics leads to cognitive deficiencies associated with neurological disorders such as Alzheimer's disease, Huntington's disease, psychiatric disorder such as Rett's syndrome and aging. In this review, I will discuss the evidence for several epigenetic mechanisms in the coordination of complex memory formation and storage. In addition, I will address the current literature highlighting the role of acetylation and methylation of chromatin in memory impairment associated with several neurological disorders, aging, and addiction.

**Keywords** Histone acetylation · Histone methylation · DNA methylation · Addiction · Nitrosylation

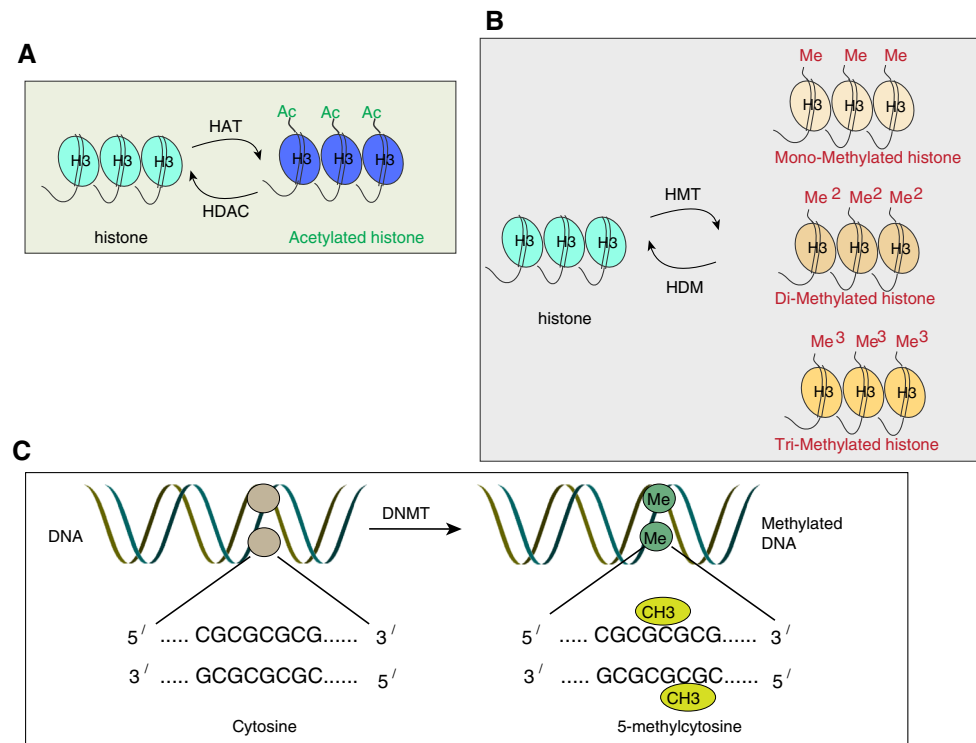
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## Chromatin: The Basis of Epigenetics

The formation, consolidation, and storage of memory largely depend on alterations in protein synthesis, gene expression, and structural properties of both neurons and synapses (Sultan and Day 2011; Abel and Lattal 2001). Synaptic depolarization in neurons leads to the activation of complex molecular signaling cascades that cause acute activation of several transcription factors such as CREB. This event ultimately leads to memory formation by influencing the structure of the postsynaptic dendritic spines that form the basis of the synaptic plasticity in brain (Alberini 2009; Stevens 1994). The transcriptional efficiency of these factors depends on stable alterations in chromatin, which consists of DNA and various core histone proteins such as H2A, H2B, H3, and H4 (Borrelli et al. 2008; Berger 2007).

Epigenetics is a dynamic process that can change gene expression without alterations in the DNA sequence and promote stable changes in the chromatin structure allowing for the regulation of gene transcriptional states (Jaenisch and Bird 2003; Goldberg et al. 2007). Recent studies have established that functional changes in epigenetic mechanisms such as posttranslational modifications of histones and covalent modification of DNA acting on chromatin (Fig. 1) form the fundamental basis of memory formation in brain. Histone modifications influence local gene expression through modifications of chromatin that recruit transcription factors that can either activate or repress gene transcription (Berger 2007; Borrelli et al. 2008; Jenuwein and Allis 2001). Histones contain a large number of amino acid residues in the N-terminal tail that are subject to covalent modifications such as acetylation, phosphorylation, methylation, ubiquitination, sumoylation, and ADP-ribosylation (Jenuwein and Allis 2001). Previously, it was



**Fig. 1** Schematic representation of epigenetic modifications. **a** Histone acetyltransferases (HATs) such as CBP, p300, and PCAF are known to catalyze addition of acetyl moieties to lysine residues of histones and convert them to acetylated histones. Histone deacetylases (HDAC) remove acetyl moieties from histone in a reversible manner. **b** Histone methyltransferases (HMT) are histone-modifying enzymes that catalyze the transfer of one, two, or three methyl groups

to lysine and arginine residues of histone proteins and convert them to either monomethylated, di-methylated or tri-methylated histones. Histone demethylases (HDM) are known to remove methyl groups from histones. **c** Methylation of DNA involves covalent addition of a methyl group to the 5/position of cytosine by DNA methyl transferases (DNMT)

demonstrated that an increase in poly-ADP ribosylation at the histone linker protein H1 is associated with novel object recognition. Moreover, PARP1, a key enzyme for poly-ADP-ribosylation, was shown to be important for hippocampal LTP and memory-related functions, including novel object recognition (Fontan-Lozano et al. 2010). However, due to space limitations, we will only discuss the influence of acetylation and methylation of histones on memory formation.

Histone acetylation is one of the most studied transcriptionally permissive marks that occur on the amino group nitrogen on lysine residues. Acetylation of histones causes neutralization of the positive charge associated with lysine residue that results in detachment of histones from negatively charged DNA in chromatin (Jenuwein and Allis 2001). This process leads to unraveling of nucleosome contacts and places chromatin in a permissive state. Histone acetyltransferases (HATs) such as CBP, p300, and PCAF, are known to catalyze addition of acetyl moieties to lysine residues of histones, although these vary in their target specificity (Borrelli et al. 2008; Liu et al. 2008). Moreover, proteins containing bromodomains (Dhalluin et al. 1999) bind to acetyl lysine residues and facilitate transcription directly or indirectly by recruiting

other transcriptional co-activators on the promoter region of the genes responsible for memory formation (Yang 2004; Lee and Workman 2007; Roth et al. 2001; Sterner and Berger 2000).

Removal of the acetyl marks by histone deacetylases (HDACs) governs cellular transcriptional mechanisms that underlie the cellular proliferation, differentiation, and homeostasis related with synaptic plasticity and memory in adult brain (Morris et al. 2010; Gregoretti et al. 2004; Yang and Seto 2008). In general, HDACs execute transcriptional inhibition either by increasing their catalytic activity or by recruiting a co-repressor to the promoter of memory-related genes (Yang and Seto 2008). Mammalian HDACs are divided into four classes on the basis of their amino acid sequence and structure. Class I HDACs are expressed ubiquitously and are mostly localized in the nucleus. HDAC1 and 2 have similar structures and are found together in transcriptional repressor complexes such as SIN3A, NuRD, and CoREST (Afsari et al. 2003; Haberland et al. 2009). The localization of class IIa HDACs is not exclusive to nucleus. Upon stimulation, they enter into the nucleus from cytoplasm although deacetylase activity of class IIa HDACs is much less than class I HDACs. Class IIb HDACs are exclusively

cytosolic deacetylases and are responsible for deacetylation of cytosolic proteins such as tubulin. HDAC2 is the only member in the Class IV HDACs, and it does not share any homology to other group of deacetylases. Sirtuins are NAD<sup>+</sup> deacetylases and are found in all subcellular compartments (Michan and Sinclair 2007). All class I, II, and IV HDAC isoforms are expressed in neurons in brain (Broide et al. 2007). However, the expression of class I HDACs is higher than other classes of HDACs in memory-related areas of brain such as hippocampus, amygdala, and cortex. HDAC2–5 and HDAC11 are also expressed in oligodendrocytes, whereas the expression of all HDACs in astrocytes is low (Broide et al. 2007). The expression of HDACs also varies with neuronal development. HDAC1 is exclusively expressed in neural stem cells and glia, whereas HDAC2 is expressed in neuroblasts and differentiated neurons (MacDonald and Roskams 2008).

On the other hand, histone methylation has been identified as another reversible modification of histones that can play either a permissive or repressive function in gene expression (Peters and Schubeler 2005; Greer and Shi 2012; Zhang and Reinberg 2001). Histone methyltransferases (HMT) (including histone-lysine *N*-methyltransferase and histone-arginine *N*-methyltransferase) are histone-modifying enzymes that catalyze the transfer of one, two, or three methyl groups to lysine and arginine residues of histone proteins. The attachment of methyl groups occurs predominantly at specific lysine or arginine residues on histones H3 and H4 (Trievel 2004). A number of HMTs and demethylases (HDMs) have been identified that can methylate histone either on lysine or on arginine residues. Thus far, multiple residues (e.g., K4, K9, K27, and K36 on histone H3) were identified that can be modified with one, two, or three methyl moieties, which results in the regulation of the efficiency of transcription (Zhang and Reinberg 2001; Rice et al. 2003).

DNA methylation is one of the most prominent covalent modification of DNA that involves conversion of cytosines at CpG dinucleotides to 5-methylcytosine. The increase in the level of DNA methylation by DNA methyltransferases (DNMT1, 2 and 3) results in transcriptional silencing either due to inhibition of transcription factor binding or through recruitment of proteins containing methyl-binding domains (MBDs) (Chahrour et al. 2008; Wu and Zhang 2010). These events influence transcriptional efficiency either directly or indirectly by recruiting HDACs and affecting chromatin structure (Jones et al. 1998).

### **Influence of Histone Acetylation/Deacetylation on Memory**

The influence of histone acetylation on memory formation was shown to be associated with an increase in H3

acetylation (on K14) in hippocampal area CA1 within 1 h after contextual fear conditioning, whereas no change was observed in overall H4 acetylation (Levenson et al. 2004). This study suggests that acetylation of histones leads to structural changes in chromatin which in turn influences memory formation. Furthermore, the increase in H4 acetylation following latent inhibition but not following contextual fear conditioning suggests that different learning paradigms are likely to elicit distinct epigenetic signatures in the brain. The concept of alterations in histone acetylation status with contextual fear conditioning was confirmed in other areas of brain including prefrontal cortex (Bredy et al. 2007) and amygdala (Maddox and Schafe 2011; Monsey et al. 2011), which are important for other memory-related tasks including condition and novel object recognition (Lattal et al. 2007; Lesburgueres et al. 2011; Monsey et al. 2011; Maddox and Schafe 2011). Recent studies have suggested that changes associated with histone acetylation do not occur independently throughout the chromatin but instead occur in a gene-specific manner (Vecsey et al. 2007). Chromatin immunoprecipitation (ChIP) studies revealed that an increase in acetylation of histones near promoter region of genes (e.g., CREB) which are responsible for learning and memory facilitates gene expression programs (Lubin and Sweatt 2007; Bredy et al. 2007; Koshibu et al. 2009; Lubin et al. 2008). The influence of HATs such as CREB-binding protein (CBP) to the regulation of memory-related number of tasks was confirmed in mice where *cbp* was heterogeneously depleted (*cbp*<sup>+/-</sup>) (Chen et al. 2010a). In this model, impairment in long-term memory in fear conditioning and novel object recognition tasks suggest that the decrease in histone acetylation status in both hippocampus and amygdala contributes to this emotional behavior in mice (Wood et al. 2005). Interestingly, several other studies suggest that the importance of CBP in neuronal functions cannot be compensated by other acetyltransferase such as p300/PCAF, although all these acetyltransferases share high degree of sequence similarity among them (Oliveira et al. 2007; Kalkhoven 2004). Unlike CBP, mutations in the p300-HAT domain lead to selective long-term deficits in spatial and contextual fear memory in mice. Thus, differential association with transcriptional regulators and differences in target substrates may explain distinct roles of acetyltransferases in memory formation (Kalkhoven 2004; Ramos et al. 2010).

Consistent with the influence of histone acetylation in memory formation, several studies have convincingly demonstrated that HDACs also contribute to manipulate memory traces that form the basis of robust, persistent memories in brain. Several studies have shown that HDACs augment the consolidation of memory related to object recognition in mice (Haggarty and Tsai 2011; Lee and Silva 2009). Administration of HDAC inhibitor in mice enhances

cognitive function and reduces fear-object memory (Korzus et al. 2004). The rescue of HDAC inhibition by expressing CBP causes a decrease in memory deficits in mice. Consistent with the fact that the behavioral and synaptic functions of CBP are dependent on intact CREB function, another study has shown that CREB mutants exhibiting fear memory and LTP deficits were resistant to rescue by HDAC inhibition (Vecsey et al. 2007). Furthermore, it was also shown that HDAC1, 2, and 3 play a major role in memory formation. The overexpression of HDAC1 was unable to rescue the deficiencies mediated by lack of HDAC2. These data suggest that, at least in adult neurons, HDAC1 and HDAC2 have non-redundant and specifically regulated functions. Other studies have shown that HDAC2 specifically regulates associative and spatial memory compared with HDAC1 (Guan et al. 2009). This study was further confirmed by the fact that overexpressing HDAC2 in mice causes impairment in memory performance, whereas depletion of HDAC2 leads to better memory performance. Depletion of HDAC3 also leads to the augmentation of *c-fos* and other memory-related genes in vivo (McQuown et al. 2011). HDAC8 has been shown to have no influence on memory, and in fact, other classes of HDACs also did not have any involvement in mammalian cognition (Bahari-Javan et al. 2012; Fischer et al. 2010). In contrast to these studies, class IIa HDACs (HDAC4 and HDAC5) have shown to regulate learning and memory in *C. elegans* (W. H. Wang et al. 2011). Recently, it was shown that in a mouse model of schizophrenia, memory deficits in object-recognition tests are associated with an increase in the level of HDAC5 (Guan et al. 2002). Depletion of HDAC6 by HDACiWt-161 has no effect on behaviors related with memory (Guan et al. 2009). All together, these data suggest that acetylation of histones leads to an increase in the expression of several memory-related genes that can directly manipulate performance of memory. However, it is not clearly demonstrated how HDAC2 and HDAC3 maintain their specificity toward memory-related behaviors. More studies related to HDAC4 and HDAC5 will further establish their importance in learning and memory.

The influence of memory impairments due to imbalance in histone acetylation/deacetylation is associated with several neurodevelopmental, neuropsychiatric, and neurodegenerative diseases including Rubinstein–Taybi syndrome (RTS) and Alzheimer’s disease (AD). In most cases, memory impairments were accompanied by decreased histone acetylation either due to impairment of acetyltransferases or activation of HDACs (Graff et al. 2011; Graff and Mansuy 2009).

#### Neurodevelopmental Disorder

RTS, a rare autosomal-dominant neurodevelopmental disorder, (Roelfsema and Peters 2007) is caused by mutations

in the transcriptional coactivators p300 and CBP (Petrij et al. 1995; Roelfsema et al. 2005). Depletion of either partial or full length CBP/p300 protein in mice display cognitive deficits at different intervals following contextual and cued fear conditioning, as well as object recognition tasks, suggesting that p300/CBP-mediated histone acetylation is essential for memory formation (Alarcon et al. 2004). The identification of decreased histone acetylation on H2A and H2B in RTS-patient-derived lymphoblastoid cell lines (Lopez-Atalaya et al. 2012), further validate the importance of histone acetylation in RTS. However, our lack of understanding of the role of histone deacetylases restricts us in determining the importance of histone acetylation/deacetylation in memory impairment associated with RTS.

#### Alzheimer’s Disease

On the other hand, AD is considered to be one of the most common forms of dementia and affects 1-in-8 of the world’s elderly. The hallmark of AD is a progressive deterioration of cognitive functions due to accumulation of amyloid plaque formation, neurofibrillary tangles, and neuronal loss in various areas of the brain. Processing of the amyloid precursor protein (APP) by presenilin 1 and 2 (PS1 and PS2) ultimately leads to amyloid plaque formation in brain (Holtzman et al. 2011; Huang and Mucke 2012; Walsh and Selkoe 2004). Several studies suggest that APP can directly modulate lysine acetylation of histones with progression of AD. This notion was further substantiated by the fact that overexpression of APP in mouse neuronal cultures led to a decrease in both H3 and H4 acetylation and CBP levels. Moreover, loss of PS1 in conditional knockout mice also reduced CBP levels and the expression of CBP target genes (Saura et al. 2004). In two other APP/PS1 mouse models of familial AD, both H3 and H4 acetylation was reduced significantly (Francis et al. 2009; Govindarajan et al. 2011). Alteration in HDAC activity has been implicated in the onset and progression of a host of human diseases, including neurodegenerative disorders, cardiovascular disease, and cancer (Kazantsev and Thompson 2008; Haberland et al. 2009). Most recently, it was shown that an increase in the level of HDAC2 specifically in different mouse model of AD such as 5XFAD and CK-p25 leads to a decrease in histone acetylation. This event leads to reduction in transcription of memory-related genes in hippocampus. Depletion of HDAC2 in CK-p25 mice restored histone acetylation, gene expression programs, and memory capacities. The increase in the level of HDAC2 in the hippocampus and entorhinal cortex of postmortem brain samples of AD patients validates data generated using the rodent models of AD. Taken together, it was substantiated that both gain-of-function and

loss-of-function of histone acetylation can contribute to cognitive deficiencies associated with AD. Thus, targeting a reduction in histone acetylation may provide a major breakthrough in the field of therapeutic intervention.

#### HDACi and AD

Considering the importance of HDACs in the cognitive decline in AD, HDACi treatment will provide a new avenue for treatment of the cognitive deficiencies associated with AD or other neurodegenerative diseases. It was observed that administration of a class I selective HDAC inhibitor, sodium butyrate in the CK-p25 mouse model of AD, rescued memory impairments and spatial memory tasks but did not rescue neuronal loss in the hippocampus (Fischer et al. 2007). Moreover, treatment with sodium butyrate rescued synaptic density and restored synaptic plasticity in the same mice model of AD. To characterize the molecular target of sodium butyrate, it was found that sodium butyrate mediates its neuroprotective actions through HDAC2 (Haggarty and Tsai 2011; Guan et al. 2009; Graff et al. 2012).

The influence of HDACi was also tested in the APP/PS1 mouse model of AD. It was observed that treatment of several HDAC inhibitors such as NaB, valproic acid, and SAHA rescued contextual fear memory in the *APP/PS1* mouse model of AD. Furthermore, the administration of TSA resulted in significant decrease in contextual fear conditioning and fear memory impairment in a similar mouse model of AD (Francis et al. 2009). Likewise, treatment with sodium butyrate has shown similar effects along with increase in histone acetylation (Govindarajan et al. 2011). Further evidence suggests that chronic administration of phenylbutyrate reversed the associative memory deficits in Tg2576 mice, which was accompanied by reversal of the loss of synaptic density (Ricobaraza et al. 2009). Taken together, the success of HDAC inhibition to rescue memory impairments and synaptic plasticity in various mouse models of AD provides more confidence to design novel therapeutic strategies based on HDAC, and more specifically, HDAC2.

#### Aging

Recently, it was reported that aging leads to a decrease in acetylation of histone H4 lysine 12 (H4K12) which results in disruption of memory-associated activities in mice due to loss in transcription of several memory-related genes, such as Formin 2, in the hippocampus. Administration of an inhibitor of HDACs such as hydroxamic acid in hippocampus rescued the memory-associated H4K12 acetylation level, restored transcriptional activation of several memory-related genes, and improved neurobehavioral

outcomes in aged mice (Peleg et al. 2010). These results provide important proof-of-principle studies to design novel therapeutic intervention strategies against cognitive deficiencies associated with aging. In other studies, it was shown that systemic administration of HDAC inhibitors to mouse model of aging reversed learning and consolidation deficits in mice (Fontan-Lozano et al. 2008). These results suggest that HDAC inhibitors can serve as candidate agents for potential treatment of learning and memory impairments during aging.

#### Addiction

Like AD and other age-related disorders, use of multiple drugs of abuse induces changes in histone acetylation in the brain that underlie some of the functional abnormalities found in addiction models (McQuown and Wood 2010; Renthal and Nestler 2008; Maze and Nestler 2011). After acute or chronic exposure to cocaine, the acetylation level of H3 and H4 was significantly increased in the nucleus accumbens (NAc); however, the specific histone acetyltransferase or HDAC was not identified yet (McQuown and Wood 2010; Kumar et al. 2005). Thus, identification of the intracellular signaling pathways that mediate this regulation in vivo will provide an intrinsic mechanism for how histone acetylation amplifies the effects of drug abuse in a region- and cell-type-specific manner in brain (Schroeder et al. 2008; Bertran-Gonzalez et al. 2008). Recent studies have shown that the administration of nonspecific HDAC inhibitors in NAc regulates place conditioning and locomotor responses in a dose- and time-dependent manner (McQuown and Wood 2010; Kumar et al. 2005; Renthal et al. 2007; Romieu et al. 2008; Kim et al. 2008). Interestingly, overexpression of HDAC4 or HDAC5 decreases behavioral responses to cocaine (Kumar et al. 2005; Renthal and Nestler 2008), whereas genetic deletion of HDAC5 hypersensitizes mice to the chronic effects (but not to the acute effects) of the drug (Renthal and Nestler 2008). However, more studies are needed to understand clearly how inter-regulation of various members of HDACs impacts overall neurobehavioral outcomes associated with cocaine. On the other hand, depletion of CBP causes a significant decrease in cocaine sensitivity (Levine et al. 2005). Other groups have shown that after chronic cocaine exposure in NAc causes upregulation of NAD-dependent deacetylases such as SIRT1 and SIRT2, which results in decrease in place preference and self-administration (Renthal et al. 2009). Mechanistically, induction of SIRT1 and SIRT2 causes an increase in H3 acetylation and subsequent  $\Delta$ FOSB binding at their gene promoters (Renthal et al. 2009). Although the importance of CBP has been demonstrated in cocaine sensitivity, the role of other HATs such as p300 or pCAF has not yet been elucidated. Since,



cognitive deficiencies associated with CBP deficiency cannot be rescued by overexpression of p300, elucidation of the role of p300 in the addicted brain will provide further information about cocaine sensitivity and related neuro-behavioral outcomes.

### Influence of Histone Methylation in Memory

Histone methylation has been identified as another potential epigenetic mark in chromatin that can strongly affect transcription of several genes responsible for learning and memory. Unlike histone acetylation, the divergent effects of histone methylation on transcription depend on the methylation state. Tri-methylation on lysine 4 (K4) at H3 (H3K4Me3) facilitates transcriptional activation, whereas di- and tri-methylation on K9 at H3 (H3K9Me2 and H3K9Me3) repress transcription. Unlike H3K4Me3, monomethylation at H3 (H3K4Me) is associated with enhancer regions that are at a distance from the transcriptional start sites of the genes. Similarly, monomethylated marks at lysine 9 and 27 of histone H3 (H3K9Me and H3K27Me) and lysine 20 of histone H4 (H4K20Me) facilitate active gene transcription. Moreover, the recruitment of DNA methyltransferase (DNMT) enzymes to methylated histone lysine sites is a mechanism by which DNA methylation and histone methylation operate in tandem to regulate chromatin structure (Vecsey et al. 2007; Alarcon et al. 2004; Archibald et al. 1998).

### Huntington's Disease (HD)

Recently, it was observed that certain histone methylation patterns, including the histone H3 methylation marks H3K4me3 and H3K9me2, serve to activate and repress gene transcription, respectively, in the hippocampus during fear–memory consolidation (Fontan-Lozano et al. 2010; Gupta et al. 2010; Gupta-Agarwal et al. 2012). Specifically, H3K4me3 corresponds to an increase in the activity of mixed-lineage leukemia 1 (MLL1), while increase in the level of H3K9me2 due to the enhanced enzymatic action of the G9a dimethyltransferase represses the activity of MLL1 (Yeh et al. 2004; Putignano et al. 2007; Gupta-Agarwal et al. 2012). Furthermore, various levels of histone methylation have shown to play a role in polyglutamine aggregates and nuclear inclusions associated with HD. Excessive H3K9 methylation and increased expression of a variant histone, macroH2A1, have been observed in blood and brain tissues, including the striatum and frontal cortex from individuals with Huntington's disease (Portela and Esteller 2010). The increase in transcriptional repression leads to the decreased expression of the neurotrophic factor BDNF, dopamine receptors, MAP kinase

signaling components, and other transcriptional changes that have been observed in the striata of people with HD. It was shown recently that gene-specific changes in histone H3 lysine 4 tri-methylation (H3K4me3) occur at transcriptionally repressed promoters in R6/2 mouse and human HD brain. Genome-wide analysis showed a chromatin signature for this mark. Reducing the levels of the H3K4 demethylase SMCX/Jarid1c in primary neurons reversed downregulation of key neuronal genes caused by mutant Huntington's expression. Thus, targeting this epigenetic signature may be an effective strategy to ameliorate the consequences of HD (Vashishtha et al. 2013). Taken together, targeting histone methylation enzymes may provide novel therapeutic targets to constitute potent avenues of HD treatment. However, their precise mechanism of action needs to be better understood to alleviate their undesired side effects and lack of specificity.

### Aging

Like HD, an increase in repressive chromatin marks such as di-methyl and tri-methyl histone H3K9 is also characteristic features of aging. Deficits in learning and memory in senescence-prone mice are associated with loss of monomethyl histone H4K20 and tri-methyl H3K36 (Hargreaves et al. 2009), which are known to facilitate transcriptions (Wang et al. 2010). On the other hand, it was also observed that aging leads to significant increase in another mark of transcriptional repressors such as H3K27me3. Taken together, alterations in histone methylation status impair neuronal (Fischer et al. 2010; Lu et al. 2004) and oligodendroglial (Coprav et al. 2009) gene expression, decline in signaling in nerve cells and defects in axon myelination that have been implicated both in aging (Yankner et al. 2008) and other neurodegenerative diseases (Tang et al. 2009). Thus far, the involvement of histone methylation in aging is established; however, whether preventing the activity of histone methyltransferases will restore the loss of memory functions associated with aging has not been well elucidated.

### Addiction

It was reported previously that chronic exposure of cocaine leads to a reduction in the level of H3K9Me2 due to a decrease in G9a and G9a-like protein (GLP), which catalyzes the demethylation of H3K9me2 in NAc (Maze et al. 2010; Aguilar-Valles et al. 2013). Further, genome-wide studies revealed that changes in the level of H3K9Me2 lead to increases and decreases in activity of several genes in brain that influence behaviors related to cocaine exposure (Renthal et al. 2009). Consistent with these studies, the same group has shown that either depletion of G9a or

pharmacological inhibition of G9a in NAc mimic behaviors associated with cocaine exposure (Maze et al. 2010). Previously, the same group has identified that the transcription factor,  $\Delta$ FOSB regulates synthesis of major sets of genes that stimulate behavior related with cocaine exposure (Kelz et al. 1999; Zachariou et al. 2006; Colby et al. 2003). Recent studies have identified that a functional feedback loop exists between G9a and  $\Delta$ FOSB (Maze et al. 2010). G9a binds to the Fosb promoter and suppresses the expression of  $\Delta$ FOSB. This was further evidenced by the fact that downregulation of G9a facilitates the accumulation of  $\Delta$ FOSB after chronic cocaine exposure. Other than influencing the transcriptional efficiency of  $\Delta$ FOSB directly by modulating the status of histones, studies have shown that cocaine-induced expression of CDK5 in the NAc leads to either an increase in the H3 acetylation or decrease in histone methylation that results in binding of  $\Delta$ FOSB to the Cdk5 gene promoter and the recruitment of specific chromatin remodeling factors, such as transcription activator BRG1 (Kumar et al. 2005). However, it is not very clear whether modification of histone methylation is only specific to cocaine or whether other drugs of abuse also have similar influences on histone modifications. Other than acetylation and methylation, histones are also known to undergo other epigenetic modifications such as poly-ADP ribosylation. Thus, it is not known whether cocaine or other drugs of abuse also have an influence on other histone modifications and if so, then it would be important to understand whether poly-ADP ribosylation of histones under the influence of cocaine follow the known effects that are substantiated in various models of cognitive functions.

### Influence of DNA Methylation on Memory

DNA methylation was considered for a long time to be a stable and irreversible modification that marks transcriptionally inactive genes. An increase or decrease in the level of DNA methylation directly regulates the expression of genes responsible for memory formation in brain (Gupta et al. 2010; Miller and Sweatt 2007; Lubin et al. 2008; Feng et al. 2010; Miller et al. 2010). Alterations in the level of DNA methylation are largely manipulated either by the activity of DNMTs or by the interaction between methyl-CpG-binding protein 2 (MeCP2) and CpG-methylated sequences (Chahrour et al. 2008). The dissociation of MeCP2 from CpG-methylated sequences facilitates synthesis of genes responsible for memory formation. Likewise, *mecp2* truncation mutants showed poor performance in hippocampus-dependent spatial, contextual, and social recognition memory paradigms (Moretti et al. 2006). These behavioral deficits are evidenced in Rett's syndrome

patients, suggesting a conserved function of MeCP2 in mammals. In various memory-related tasks such as contextual fear conditioning, the increase in DNMT1 mRNA in hippocampus affects memory paradigm significantly (Miller and Sweatt 2007; Miller et al. 2010). Furthermore, an increase in methylation of CpG sequences in the promoter region of one of the memory-related genes, protein phosphatase 1 (PP1), explains memory loss in mice (Miller and Sweatt 2007). Studies related with neural stem cells have shown that DNA methylation is not restricted to promoter regions of genes that are repressed during postnatal neurogenesis. In neural stem cells, DNMT3a was also associated with methylated non-proximal promoter regions of genes that are transcribed during neurogenesis. Moreover, the binding of DNMT3 to high levels of H3K4me3, which is considered as an epigenetic mark of transcription, further reinforces the idea of transcriptional silencing. Consistent with this study, another group has shown that a decrease in the interaction between DNMT3 to low levels of H3K27me, which is considered to be a transcriptional activator, potentiates transcription (Suzuki and Bird 2008). Other than directly influencing transcription, DNMT3 also regulates the activation of polycomb repression complex 2 (PRC2), a nuclear repressor complex that is recruited to chromatin by several mechanisms. When both *dnmt3a* and *dnmt1* were deleted in postnatal forebrain excitatory neurons, mutants displayed impaired long-term spatial and contextual memory (Feng et al. 2010). However, a mutation in either *dnmt3* or *dnmt1* in brain has no effects on hippocampal morphology or cell count, but only a minor reduction in volume was reported. These data suggest that DNMT1/3 has a specific role in adult brain function. Taken together, these studies strongly implicate DNMT function in adult memory consolidation.

In the hippocampus, neural activity raises intracellular Gadd45b, which has been shown to possess DNA demethylase activity *in vitro*. Mice that lack Gadd45b show a remarkable decrease in activity-dependent adult neurogenesis *in vivo* and their neurons show a marked reduction in dendritic growth *in vitro*. Importantly, exposure of newborn neurons to depolarizing conditions induced Gadd45b-dependent demethylation of the promoters for *Bdnf* and fibroblast growth factor-1 (*Fgf-1*) promoters (Ma et al. 2009).

### Alzheimer's Disease (AD)

A growing body of literature has suggested that aberrant DNA methylation is closely associated with neurological disorders such as AD. It was shown that limiting the substrate level of DNA methylation reactions such as SAM, epigenetically upregulate expression of PS1 and BACE in cell culture which are known to process APP and

subsequent release of amyloid beta (A $\beta$ ), a hallmark pathological feature of AD (Fuso et al. 2005).

Previously, it was shown that manipulating the level of DNA methylation may interfere with A $\beta$  load. In a mouse model of AD, vitamin B deficiency was associated with site-specific demethylation near the PS1 transcriptional start site, which ultimately led to an increase in APP processing. A recent study suggests that enhancing DNA methylation by treatment with folic acid partially suppresses neuronal toxicity in the same mouse model of AD (Chen et al. 2010b). Taken together, these studies suggest that systemic manipulation of methyl-donor levels promotes cognitive rescue through epigenetic regulation of a set of genes associated with disease. The recent finding of hypo-methylation in cortical postmortem tissue from patients, along with characterized hallmarks of AD, confirms the importance of DNA methylation in this disease. Further evidence of low systemic folate and high homocysteine, a metabolite of the DNA methylation reaction, suggests the importance of DNA methylation in AD (Fuso et al. 2005). A decrease in the level of DNA methylation can also explain several aspects of AD. For example, reduction in the level of catalytic activity of DNMT1 in cortex leads to an increase in APP mRNA expression. The importance of DNA hypomethylation was further evidenced in AD patients where a decrease in the methylation of DNA was associated with the PS1 promoter region compared with age-matched controls. Taken together, these data suggest that both increases and decreases in DNA methylation can occur in AD, but they occur in a gene-specific manner. Identification of these genes may further substantiate the importance of studying DNA methylation in AD research.

#### Addiction

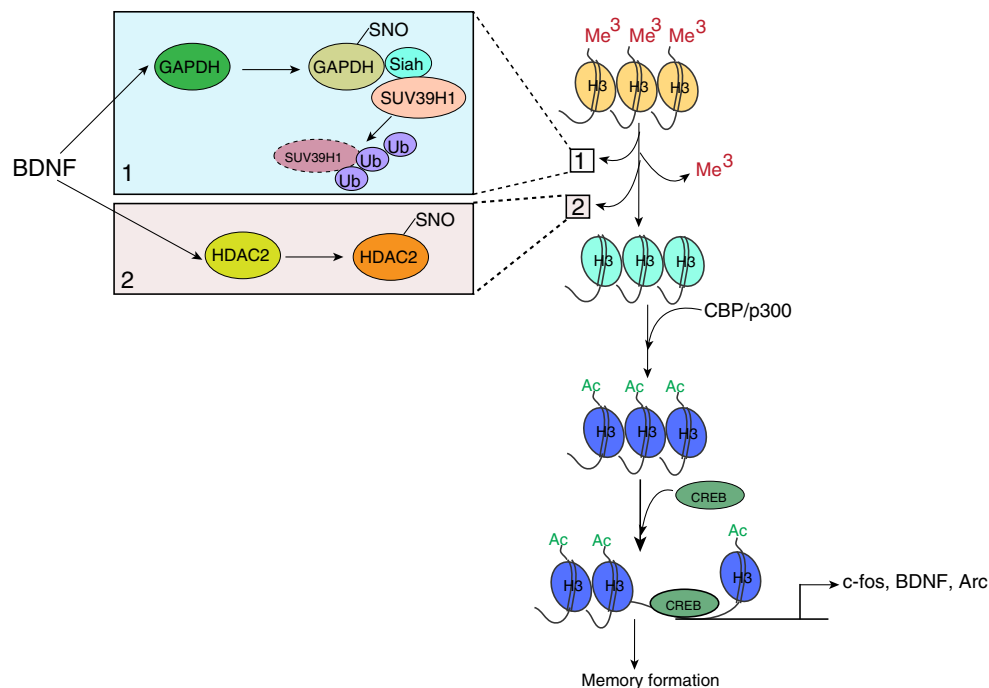
The importance of MeCP2 in the field of drug abuse was first documented by Cassel et al. where they have shown that self-administration of cocaine causes an increase in the expression of MeCP2 both in the NAc and in the striatum (Cassel et al. 2006; Host et al. 2011). Downregulation of MeCP2 in the striatum causes a decrease in drug intake under extended, but not limited, access conditions, which leads to a reduction in cocaine-induced hyperactivity and place conditioning (Im et al. 2010). However, depletion of MeCP2 in NAc causes the reversal of cocaine-induced behaviors in mice (Deng et al. 2010). Another independent study shows that MeCP2 regulates the expression of brain-derived neurotrophic factor (BDNF) by modulating the level of microRNA inside the brain (Im et al. 2010). Since, BDNF has been shown to have strong influence on behaviors related with cocaine exposure; regulation of BDNF by MeCP2 provides a mutually exclusive model to

study cocaine-induced reward behavior (Graham et al. 2007). Furthermore, it was shown that the administration of cocaine repeatedly causes a decrease in the level of DNMT3A expression in the mouse NAc during early but causes an increase in the level of DNMT3A expression at later time points (Kim et al. 2008; LaPlant et al. 2010). The influence of DNMT3A was further evidenced from the fact that depletion of DNMT3A causes an increase in behavioral responses to cocaine, whereas overexpression of DNMT3A causes a decrease in these responses (LaPlant et al. 2010). Thus, future research is needed to identify the specific genes that are regulated by changes in the level of DNMT3A after exposure to cocaine. Moreover, the cocaine-induced alteration in DNMT3a possesses the further possibility that changes in DNA methylation may occur in germ cells, which may be passed to the next generation and increase the risk of increased addictive neurobehavioral outcomes in those offspring.

#### Influence of Nitric Oxide on Neurotrophin-Mediated Epigenetic Regulation of Memory

The neurotrophins are known as a family of peptide growth factors that promote the growth and survival of neurons by activating the Trk family of receptor tyrosine kinases. Neurotrophic factors, such as nerve growth factor (NGF) and BDNF, act by turning on genetic programs, especially those associated with cAMP response element binding (CREB) (Walton and Dragunow 2000; Riccio 2010). Phosphorylation of CREB at serine-133 has been thought to be important in the actions of numerous growth factors, including the neurotrophins (Kornhauser et al. 2002; Carlezon et al. 2005; Shaywitz and Greenberg 1999). Neurotrophins can directly affect epigenetic events by inducing the accumulation of nuclear nitric oxide (NO) and S-nitrosylation of proteins by increasing intracellular calcium (Nott et al. 2008; Riccio 2010). The temporal and spatial level of NO in the nervous system is mostly regulated by nitric oxide synthase (nNOS) (Bredt and Snyder 1994). A signaling system initiated by NO mediates diverse physiologic and pathophysiologic events in blood vessels, inflammatory tissues, and in neuronal systems with notable behavioral alterations attendant upon deletion of nNOS (Tricoire and Vitalis 2012; Zhou and Zhu 2009). NO signaling occurs inside cells through a posttranslation modification of proteins known as S-nitrosylation where NO attach to the free cysteine residue of the protein and convert them to nitrosylated residues (Shahani and Sawa 2011; Hess et al. 2005). In general, nitrosylation of proteins can occur to a protein in a non-enzymatic process irrespective of the nature of the cells. S-nitrosylation is known to regulate the enzymatic activity, protein–protein interactions,





**Fig. 2** Schematic diagram of BDNF signaling leads to transcriptional upregulation of memory-related genes. Upon BDNF treatment, NO triggers S-nitrosylation of GAPDH and augments its binding to Siah, translocating the GAPDH–Siah protein complex to the nucleus. In the nucleus, Siah binds with SUV39H1, which is degraded via ubiquitination (Box 1). At the same time, BDNF S-nitrosylates HDAC2

(Box 2), which results in dissociation of nitrosylated HDAC2 from BDNF-regulated gene promoters. Both processes lead to an augmentation in histone acetylation by p300/CBP and facilitate transcriptional efficiency of CREB to synthesize memory-related genes such as Arc, BDNF, and c-fos

or subcellular localization in a context-dependent manner (Hess et al. 2005).

Recently, Riccio and associates (Nott et al. 2008) described a specific pathway that mediates stimulation of histone acetylation. In this model, S-nitrosylation of HDAC2 induces chromatin remodeling in neurons, indicating an important role for NO in this process. It was shown that BDNF induces S-nitrosylation of HDAC2 in cortical neurons. S-nitrosylation of HDAC2 induces its dissociation from BDNF-regulated gene promoters, thereby increasing histone acetylation and gene transcription at specific promoter regions (Fig. 2). However, S-nitrosylation of HDAC2 does not affect its deacetylase activity (Nott et al. 2008). Recently, the same group has shown that HDAC2 nitrosylation regulates neuronal radial migration during cortical development by regulating the expression of a subunit of the ATP-dependent chromatin-remodeling complex brahma (Brm). In the cortex, expression of a mutant form of HDAC2 that cannot be nitrosylated dramatically inhibits Brm expression. (Walton and Dragunow 2000). In contrast to this study, other group has shown that HDAC2 can be S-nitrosylated at the C152 residue and its catalytic activity compromised in a mouse model of muscular dystrophy (Colussi et al. 2008). The apparent discrepancy of HDAC2 nitrosylation in neuron and muscle

cells provides an example of the spatial regulation of HDAC2 in different tissues.

A novel cascade was established, which commences with activation of NO-elicited nitrosylation of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) with nuclear translocation of GAPDH, together with the ubiquitin E3 ligase Siah1 (Hara et al. 2005). With cytotoxic stresses, nuclear GAPDH activates the histone-acetylating enzymes p300/CBP leading to acetylation and activation of p53 and enhancement of cell death transcriptional targets such as PUMA and Bax (Sen et al. 2008) (Zhou and Zhu 2009). With physiologic stimuli, such as the neurotrophic factors BDNF and NGF, the nuclear complex of nitrosylated GAPDH, linked to Siah1 and the histone-methylating enzyme SUV39H1, triggers degradation of SUV39H1 via the ubiquitin E3 ligase activity of Siah1 (Sen and Snyder 2011). This facilitates acetylation of histone H3 leading to CREB binding to DNA with enhanced expression of CREB-regulated genes such as c-fos and BDNF and associated augmentation of nerve outgrowth (Fig. 2).

Recently, we have shown that modulation of the nitrosylation of GAPDH regulates behaviors associated with exposure of cocaine in mice. We have identified a novel signaling cascade wherein low, behavioral-stimulating doses of cocaine trigger the formation of the nitrosylated

GAPDH/Siah1 complex, leading to augmented expression of CREB genes, whereas higher, neurotoxic doses activate the NO/GAPDH/p53 system. CGP3466B, a very potent inhibitor of GAPDH nitrosylation and GAPDH-Siah binding, prevents both stimulant and neurotoxic actions of cocaine (Xu et al. 2013).

## Conclusion

In conclusion, epigenetic modifications of DNA and histones appear to have critical roles in many aspects of neural plasticity that directly influence the establishment of memory in brain. Although alterations in the level of histone/DNA modifications contribute largely to various neurological disorders, the precise mechanisms that can provide a novel clinical intervention strategy remain obscure. Clearly, the hypothesis that histone-modifying enzymes are involved in the pathophysiology of neurodegenerative diseases warrants further investigation. For example, it is possible that functions of CBP outside of the epigenetic regulation of chromatin may account for its additional role in short-term memory function. Since short-term memory depends more on cortical processing than hippocampal function, further studies are thus needed to address the role of CBP in anatomical analysis (Lamprecht et al. 1997). Moreover, the signaling mechanisms that link physiological synaptic activation with Gadd45b-dependent DNA demethylation remain unclear. DNA methylation recently emerges as a target of therapeutic intervention in AD and thus merits the use of isoform-specific knockdown with RNA interference in a region-specific manner in adult brain. Although much more work is needed, advances in neuroepigenetics research are now emerging as a potential field that promises to greatly contribute to the future of molecular medicine.

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**Conflict of interest** I would like to declare that I do not have any conflict of interest.

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