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REVIEW ARTICLE

Epigenetic Regulation of Memory-Therapeutic Potential for Disorders

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Abstract: ***Background*:** Memory is a vital function which declines in different physiological and pathological conditions such as aging and neurodegenerative diseases. Research in the past has reported that memory formation and consolidation require the precise expression of synaptic plasticity genes. However, little is known about the regulation of these genes. Epigenetic modification is now a well established mechanism that regulates synaptic plasticity genes and neuronal functions including memory. Therefore, we have reviewed the epigenetic regulation of memory and its therapeutic potential for memory dysfunction during aging and neurological disorders.

***Method*:** Research reports and online contents relevant to epigenetic regulation of memory during physiological and pathological conditions have been compiled and discussed.

***Results*:** Epigenetic modifications include mainly DNA methylation and hydroxymethylation, histone acetylation and methylation which involve chromatin modifying enzymes. These epigenetic marks change during memory formation and impairment due to dementia, aging and neuro-degeneration. As the epigenetic modifications are reversible, they can be modulated by enzyme inhibitors leading to the recovery of memory.

***Conclusion*:** Epigenetic modifications could be exploited as a potential therapeutic target to recover memory disorders during aging and pathological conditions.

Keywords: Memory, gene expression, DNA methylation, histone acetylation, histone methylation, enzyme inhibitors.

1. INTRODUCTION

Memory is a higher order brain function which can store and recall the previously learnt information. It is initially formed as short term memory which is later stabilized in the form of synaptic connections. Such stabilization of long term memory is called memory consolidation which requires the expression of synaptic plasticity genes and protein synthesis [1]. Memory is tightly associated with neuroplasticity events which involve the modulation of synaptic molecules and neural networks. Specifically, the activation of neuronal plasticity genes is considered to be a key mechanism for the modification of neural networks and formation of memory. These synaptic plasticity genes include growth/neurotrophic factors, vesicular transporters, microtubule structures, transcription factors, kinases and receptors. After neuronal stimulation, these synaptic plasticity genes get activated and remodel synaptic structures by increasing the neuronal branching which further forms new connections to stabilize the memory. Thus, transcription of these synaptic plasticity genes is crucial for memory formation and stabilization [2]. The expression of synaptic plasticity genes is altered during memory formation and loss in different animal models and human subjects. Transcription of many synaptic plasticity genes such as brain derived neurotrophic factor (BDNF), activity-regulated cytoskeletal-associated protein (ARC), early growth response 1 (EGR1), glutamate receptor (GluR) and cAMP response element binding (CREB) protein is upregulated during spatial, fear and recognition memory formation and stabilization [3-6]. However, due to alteration in the expression of these synaptic plasticity genes, the long term memory tends to lose during physiological aging and different pathological conditions like dementia, depression, neurodegenerative diseases and neuropsychiatric problems [7-12].

The molecular mechanism regulating decline in the expression of synaptic plasticity genes is not clearly understood. However, research in the last decade reveals that expression of these synaptic plasticity genes is tightly regulated at transcriptional level by epigenetic mechanisms. Research in the past decade unveiled the role of epigenetic modifications including DNA methylation, histone acetylation and methylation in the regulation of synaptic plasticity genes and memory consolidation. Gene expression at trans-

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criptional level is regulated negatively by DNA methylation and positively by histone acetylation. Remarkably, the use of epigenetic modifiers, like enzyme inhibitors, rescues the epigenetic change and improves memory consolidation [7, 12, 13]. Thus epigenetic regulation of memory has a great therapeutic potential for treating memory disorders during aging and pathological conditions.

2. CHROMATIN MODIFICATIONS AND REGULATION OF MEMORY

Chromatin refers to a complex interaction of DNA, histone and nonhistone proteins, which in turn packs large DNA in the nucleus. Nucleosome is the fundamental unit of chromatin consisting of 147 bp DNA wrapped around histone octamer (two copies of each H2A, H2B, H3 and H4). Apart from this core histone, a linker histone called H1 is present between two nucleosomes. Chromatin is usually present in condensed state, which does not allow the binding of transcription factors and thus inhibits gene transcription. When chromatin is relaxed, transcription factors bind to the DNA easily and activate gene transcription. Thus, condensation and relaxation of chromatin regulate the expression of genes. The change in the chromatin state due to covalent modifications of DNA and histone influences the expression of associated genes and this phenomenon is known as epigenetic regulation. Thus, epigenetic regulation is defined as change in gene expression due to covalent modifications of DNA *i.e*. DNA methylation and histone post-translational modifications *i.e*. acetylation, methylation and phosphorylation without change in DNA sequence. DNA methylation and histone modifications change the interaction between DNA and histone and thus positively or negatively regulate gene expression at transcriptional level. Research in the past decade revealed that change in chromatin structure regulates synaptic plasticity genes and thereby many brain functions including memory.

2.1. DNA Modifications

DNA modifications include DNA methylation and hydroxymethylation which occur at the cytosine followed by guanine residues known as CpG islands. These modifications regulate the expression of genes involved in memory.

2.1.1. DNA Methylation

DNA methylation involves the transfer of methyl group from S-adenosyl methionine to cytosine residues. This process is catalyzed by a group of enzymes known as DNA methyltransferases (DNMTs) which further regulate memory processes.

2.1.2. DNA Methyltransferases

DNMTs are broadly categorized into *de novo* DNMTs and maintenance DNMTs. The *de novo* DNMTs, DNMT3a and DNMT3b, establish initial methylation patterns on unmethlyated DNA. On the other hand, the maintenance of DNMT, DNMT1 establishes methylation patterns on hemimethylated replicating DNA.

For the first time, Goto *et al*. [14] identified the presence of DNMTs in neurons. Furthermore, Feng *et al*. [15] demonstrated the differential expression of DNMT3a and DNMT3b in CNS precursor cells and post mitotic neuronal cells. Since learning and memory is the key function of brain, understanding their regulation is crucial to elucidate the mechanism of memory formation and maintenance. In this context, Levenson *et al*. [16] identified the role of DNMTs in regulating synaptic plasticity and showed the association of DNMT3a expression in hippocampus with induction of long term potentiation (LTP) and modulation of neuronal functions. Similarly, Miller and Sweatt [17] also reported the involvement of DNMTs in memory formation. They found that animals exposed to associative context-plus-shock training exhibit increased DNMT3a and DNMT3b expression in the cornu ammonis (CA) 1 region of hippocampus. Double knock out (KO) of DNMT1 and 3a showed impaired fear memory and spatial memory consolidation [18]. Thus, DNA methylation is an important regulator of various neuronal functions like memory acquisition and consolidation.

After observing decline in memory consolidation during aging, the underlying involvement of DNMTs was studied and Liu *et al*. [19] reported that DNMT1 deficiency impairs learning and memory in an age-dependent manner. Total DNA methylation level also decreased in the cerebral cortex and hippocampus of heterozygous DNMT1 KO mice. Such decline in DNA methylation level was associated with impaired spatial memory consolidation in older people. Surprisingly, DNMT1 heterozygous KO mice exhibited normal working memory but impaired memory consolidation. Similarly, Elsner *et al*. [20] also reported decline in the expression of DNMT1 in the hippocampus of old rats which had lower memory consolidation as compared to young. We also observed decline in the expression of DNMT1 in the cerebral cortex and hippocampus of old mice as compared to young and adult. Such decline in DNMT1 is positively correlated with reduction in recognition memory consolidation during aging [21].

The involvement of DNA methylation has also been studied during different neuropathological conditions. Mastroeni *et al*. [22] have shown that cytosine methylation level decreases with decline in DNMT1 expression in Alzheimer's disease (AD) patients as compared to healthy individuals of similar age. Also, DNMT1 mutation in cerebral cortex and hippocampus of mice leads to neurodegeneration which further results in the reduction of memory consolidation [23]. Similarly, Klein *et al*. [24] demonstrated that DNMT1 mutation causes aberrant change in DNA methylation which is responsible for dementia, hearing loss and neuro-degeneration in human. Oliveira *et al*. [25] found decline in the expression of DNMT3a2 in hippocampus and cortex during age associated decline in memory consolidation. Recently, we observed enhanced expression of DNMT1 in the hippocampus of scopolamine-induced amnesic mice and its association with impaired recognition memory consolidation [12]. Similarly, the expression of DNMT3a and DNMT3b was increased in sevoflurane-induced cognitive impairment [26]. Thus, DNA methylation is an important mechanism for regulation of memory.

2.1.3. DNA Methylation and Gene Expression

CpG methylation within promoter and intragenic regions has been extensively studied during learning and memory.

Cytosine methylation at the promoter prevents the binding of transcription factors either directly or through recruitment of methyl-binding proteins and formation of repressor complex [27, 28]. Consequently, the gene expression is suppressed (Fig. **1**). Several studies have shown that transcription repression through DNA methylation of particular genes is involved in physiological and pathological conditions. Levenson *et al*. [16] reported altered methylation pattern at the promoter of synaptic plasticity genes reelin and BDNF in the hippocampus. They provided the first evidence of DNA methylation in dynamic signaling in adult nervous system and showed that DNMT activity is required for normal hippocampal synaptic plasticity. A follow-up study by Miller and Sweatt [17] found that fear conditioning increased the methylation at promoter and thereby reduced the expression of memory suppressor gene protein phosphatase 1 (PP1). On the other hand, contextual fear conditioning decreased methylation at the promoter and thereby increased the expression of synaptic plasticity gene reelin. Thus, DNA methylation and demethylation at the promoter region of genes are crucial for fear memory consolidation. In a similar study, Lubin *et al*. [29] have shown the effect of context exposure and contextual fear conditioning on BDNF methylation in the hippocampus. They found decrease in BDNF methylation level at exon I and IV but increase at exon VI in CA1 region of hippocampus 2 h after contextual fear conditioning. Further, Siegmund *et al*. [30] studied the methylation status of 50 selected genes in the human cerebral cortex during aging and found increased methylation of 8 genes during aging, 18 genes during initial years after birth and 2 genes during AD. They concluded that changes in DNA methylation might alter the neuronal gene expression and thereby memory disorders associated with AD and schizophrenia.

In DNMT1 and DNMT3a double KO mice, Feng *et al*. [18] reported DNA demethylation of gene promoter resulting in the upregulation of immune genes such as Class I MHC and Stat1 which lead to decline in learning and memory. Munoz *et al*. [31] identified the putative role of DNA methylation in BDNF expression which regulates encoding of recognition memory in medial temporal lobe. They further found that expression of BDNF in hippocampus is regulated by DNA methylation which helps in object recognition memory consolidation. To study the long-lasting memory, Miller *et al*. [32] identified the cortical DNA methylation status of three memory-associated genes EGR1, reelin and calcineurin. They observed demethylation of EGR1 after 1 h and hypermethylation of reelin and calcineurin after 1day of training. Taken together, they showed that persistent, gene specific cortical hypermethylation gets induced in rats by hippocampus-dependent associative learning experience. They also proposed that the adult brain utilizes DNA methylation to store long-lasting memories. Ma *et al*. [33] identified an active neuronal demethylase Gadd45b in the mature hippocampus as a result of neuronal activity. They showed that Gadd45b is required for electroconvulsive therapy-induced demethylation of BDNF promoter and Fgf-1, leading to the recovery of memory. Sultan *et al*. [34] have further shown that genetic deletion of Gadd45b enhanced long term memory and synaptic plasticity, suggesting

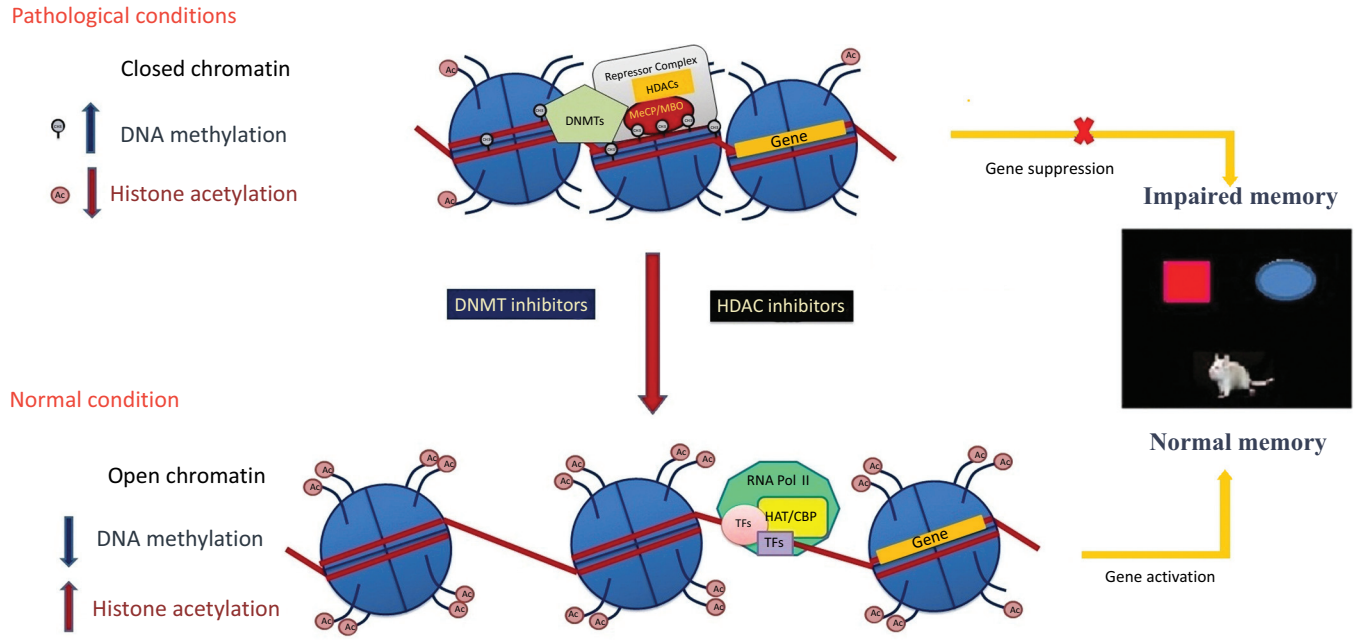

Fig. (1). This schematic diagram illustrates a mechanism for regulation of memory through chromatin modifications. In physiological condition, DNA methylation level is low and histone acetylation level is high at the promoter of synaptic plasticity genes resulting in relaxed chromatin, normal gene expression and memory. On the other hand, in pathological condition, DNA methylation is increased at the promoter of synaptic plasticity genes resulting in recruitment of repressor complex along with HDAC2 which in turn deacetylates histones. This leads to chromatin condensation, gene suppression and impairment of memory. Further, treatment with epigenetic modifiers (DNMTs and HDACs inhibitors) decreases DNA methylation, prevents binding of repressor complex and increases histone acetylation. This allows chromatin relaxation, gene activation and memory similar to normal physiological condition.

the memory-associated expression of Gadd45b in the hippocampus. They concluded that Gadd45b is a learning-induced gene which actively demethylates DNA and acts as a regulator of memory.

Penner *et al*. [8] reported association of age-dependent decrease in the transcription of ARC gene in the rat hippocampus with reduced spatial memory consolidation. They further studied the methylation pattern at the intragenic and promoter region of ARC gene and found altered methylation pattern in the CA1 and dentate gyrus (DG) region during resting and spatial learning. Therefore, they suggested that methylation of ARC gene is dynamically regulated by spatial behavior and changes in region and age specific manner. Similarly, Haberman *et al*. [35] identified that age-dependent DNA methylation changes in the promoter region of cognitively relevant genes like Gabra5, Hspa5 and Syn1 and suggested that methylation at single CpG is more relevant to individual cognitive performances. Oliveira *et al*. [25] showed increased DNA methylation of c-FOS, ARC and BDNF in the hippocampus, resulting in downregulation of synaptic plasticity genes during aging. We also reported hypermethylation of BDNF and ARC promoter during reduced memory consolidation in the hippocampus of scopolamine-induced amnesic mice [12]. A seminal study by Penner *et al*. [36] reported the CpG site-specific change in DNA methylation at the promoter region of EGR1 gene and age-related reduction in EGR1 transcription in DG and CA1 region during aging following spatial learning. Alteration in DNA methylation is associated with change in transcription of EGR1 gene and consequently decline in memory consolidation. Futher, Ju *et al*. [26] observed an association of sevoflurane-induced cognitive impairment with hypermethylation of BDNF and reelin gene resulting in their decreased expression. Zinc deficiency induced cognitive impairment is also associated with altered BDNF methylation in the hippocampus [37]. Recently, decreased memory consolidation during scopolamine-induced amnesia was found to be associated with increased promoter methylation and decreased expression of neuronal immediate early genes EGR1, Homer1 and NARP [38]. Animal model of prenatal stress (restraint stress in pregnant mice) showed upregulation in the expression of DNMT1 in the frontal cortex and hippocampus but no change in histone deacetylases (HDACs), histone methyltransferases (HMTs) and histone demethylases (HDMs) or methyl CpG binding protein 2 (MeCP2) [39]. The level of DNA methylation is lowered at the promoter region of peptidyl argininedeiminase 2 and its expression is increased in the white matter of patients with multiple sclerosis [40]. The expression of DNMT1 was upregulated and associated with hypermethylation of synaptic plasticity genes GAD1 and reelin in postmortem brain samples of Schizophrenia patients [41-45]. Thus gene specific promoter methylation is an important mechanism to regulate the expression of memory related genes during physiological and pathological conditions.

2.1.4. DNA Hydroxymethylation

DNA 5 methyl cytosine (5mC) is converted to DNA 5 hydoxymethyl cytosine (5hmC) by ten-eleven-translocation (TET) family of enzymes. Such DNA hydroxymethylation serves as a stable epigenetic mark and is enriched in gene coding regions, promoters and transcription factor binding sites which regulate gene expression. It positively regulates gene expression and its dysregulation may lead to impaired gene expression resulting in neurodevelopmental and neurodegenerative diseases [46-49]. Global 5hmC level decreases in AD patients as compared to age-matched control [50], while global 5hmC level increases during aging in mouse hippocampus [51]. TET1 is regulated by neuronal activity and TET1 hydroxylase positively regulates several genes implicated in learning and memory by their demethylation [52]. Further, overexpression of TET1 impairs hippocampus-dependent long term associative memory. Similarly, Rudenko *et al*. [53] reported that TET1 KO downregulated the expression of neuronal activity-regulated genes NPAS4, c-FOS and ARC with abnormal long term depression and impaired memory extinction in mice. They showed that neuronal TET1 maintains normal DNA methylation and thereby regulates the expression of activity regulated genes, synaptic plasticity and memory extinction. Biergans *et al*. [54] have also shown that memory consolidation in *Apis mellifera* requires a temporally controlled DNA methylation and demethylation pattern involving different enzymes like DNMT1b, TET1 and DNMT3 at different time points. TET1 KO mice exhibit active demethylation resulting in altered expression pattern of neuronal activity-regulated genes [55] and enhanced cued and contextual fear memory consolidation and object location memory. Similar to DNMT1, Dong *et al*. [39] observed upregulation in the expression of TET1 in the frontal cortex and hippocampus of animal model of prenatal stress. Thus, TET1 inhibition might be targeted as a therapeutic potential for memory decline in neurodegenerative disorders and aging.

2.2. Histone Modifications

Amino acid residues present at the N-terminal of histones undergo several post-translational modifications (PTMs), namely acetylation at lysine, methylation at lysine and arginine, and phosphorylation at serine. These PTMs alter the chromatin organization at the local level and regulate the expression of associated genes. They are catalyzed by several chromatin modifying enzymes which either add or remove small molecule from the histone tail. These chromatin modifying enzymes have been found to alter in different physiological and pathological conditions and thereby regulate the genes and associated functions.

2.2.1. Histone Acetylation

Histone acetylation is associated with active gene expression, while deacetylation is correlated with gene repression. Acetylation of histones is catalyzed by histone acetyl transferases (HATs) which add acetyl group from acetyl CoA onto lysine residues at N terminal tail of histones. This reduces affinity between histone and DNA resulting in relaxed chromatin which is easily accessible for the binding of transcription factors and active transcription. On the other hand, HDACs remove acetyl groups from lysine residues resulting in condensed chromatin and suppression of gene transcription. Thus, these chromatin modifying enzymes tightly regulate the histone acetylation mark and gene expression.

2.2.2. Histone Acetyltransferases

HATs are transcriptional activators. They are divided into five families: 1) GNAT family, 2) p300/CBP family, 3) MYST family, 4) transcription factor related HATs, and 5) nuclear receptor associated HATs [56]. p300/CBP family is lysine acetyl transferase (KAT3) and very important due to its involvement in many processes including regulation of transcription, cell cycle, development, neuronal differentiation, neurogenesis and memory consolidation [57-59]. CBP (CREB binding protein) acetylates many sites on histone H2B, H3 and H4 and helps in long term memory formation [60-62]. CBP conditional KO mice showed impaired long term memory as well as short term associative and recognition memory. Treatment with HDAC inhibitor trichostatin-A (TSA) rescued lower histone acetylation level but it was unable to recover short as well as long term memory, suggesting that memory impairment is not directly associated with lowering of HAT activity. Microarray study showed that large number of synaptic plasticity genes including CaMKs, NMDARs, AMPARs, PSD95 and glutamate receptors were downregulated in CBP conditional KO mice [63]. Postnatal forebrain specific CBP mutant mice showed strong reduction of acetylation level on H2A, H2B, H3 and H4, and impaired long term recognition memory [64]. Medial prefrontal cortex specific CBP mutant mice showed normal short term but impaired long term fear conditioning, Morris water maze and object location memory [65, 66]. These mice also exhibited decrease in the expression of synaptic plasticity genes EGR1 and BDNF and impairment of contextual fear conditioning and novel object recognition [67, 68]. Similarly, sleep deprivation induced memory impairment is associated with decline in expression of CBP, H3K9 and H4K12 acetylation level in the hippocampus [69]. CBP overexpression increased BDNF expression and restored the impairment of spatial memory in AD mouse model [70]. On the other hand, Giralt *et al*. [71] reported lowered CBP expression, H3 acetylation level and impaired memory in mouse model of Huntington's disease (HD). Further, CBP regulated synaptic plasticity genes ARC, c-FOS and NR4A2 were downregulated in HD mouse model. CBP is also involved in environmental enrichment mediated increase in neurogenesis and memory consolidation [72]. Stilling *et al*. [73] have shown the involvement of K-lysine acetyltransferase (Kat)2a in hippocamapal dependent fear, recognition and spatial memory consolidation. They observed that Kat2a conditional KO mice have impaired memory consolidation and decreased histone H4K12, H3K18 and H3K14 acetylation at the promoter region of synaptic plasticity genes Nbpwr1 and Hcrtr2. Inhibition of p300/CBP by C646 decreased histone pan-acetylation and impaired object recognition memory consolidation [6].

2.2.3. Histone Deacetylases

HDACs are transcriptional repressors. They are divided into four groups: class I, II, III and IV. Among these, class I HDACs comprise of HDAC1, 2, 3 and 8, which are found in the nucleus and regulate the expression of memory genes at transcriptional level [74]. HDAC2 negatively regulates memory and synaptic plasticity gene expression. Guan *et al*. [5] first showed that HDAC2 but not HDAC1 regulates the expression of synaptic plasticity genes and memory consolidation. HDAC2 regulates the expression of synaptic plasticity genes involved in different stages of memory. Its overexpression shows downregulation of synaptic plasticity gene BDNF, EGR1, Homer and GluR, and impairment of spatial and fear memory consolidation. Similarly, HDAC2 conditional KO mice showed enhanced contextual fear memory consolidation, attentional set-shifting task and LTP [75]. HDAC2 expression was upregulated in the hippocampus of neurodegenerative mouse model as well as in the brain of AD human subject [6]. This mouse model also showed decline in the expression of synaptic plasticity genes including BDNF, ARC and EGR1. We have also observed that HDAC2 expression was upregulated in the hippocampus of old as compared to young and adult mice and negatively correlated with decline in novel object recognition memory during aging [21]. Further, we noted that HDAC2 was upregulated in the hippocampus of scopolamine-induced amnesic mice and this upregulation was associated with decline in the expression of BDNF and ARC [12].

HDACs form a repressor complex by interacting with methyl CpG binding proteins at the promoter region of genes [76]. This repressor complex removes acetyl group from histone and thereby suppresses the expression of gene [77]. Upregulation of HDAC2 expression in neurodegenerative mouse model is associated with increase in the binding of HDAC2 at the promoter region of synaptic plasticity genes like BDNF, ARC, EGR1 and Homer [6]. HDAC2 removes important acetyl mark from histone H3K9, H3K14 and H4K12 at the promoter region of synaptic plasticity genes and thereby suppresses gene expression [5, 6]. However, intrahippocampal silencing of HDAC2 by antisense oligonucleotide recovered recognition memory consolidation and histone H3K9/14 acetylation level at the promoter region of synaptic plasticity genes BDNF and ARC [12]. HDAC2 is also associated with different physiological and disease conditions including social isolation, depression, mood disorder, anxiety, schizophrenia, bipolar disorder and HD [78-82]. Liang and Fang [83] observed that isoflurane-induced memory impairment is associated with increase in the activity of HDAC2 but not HDAC4 in the hippocampus. Sleep deprivation induced cognitive impairment is associated with upregulation in the expression of HDAC2 and reduction in H3K9 and H4K12 acetylation level at the promoter region of BDNF gene in the hippocampus [69]. Similar to HDAC2, McQuown *et al*. [84] have reported that another member of class I family HDAC3 is a negative regulator of memory. HDAC3–FLOX mice showed increase in H4K8 acetylation level, synaptic plasticity genes c-FOS and NR4A2 and memory consolidation for object relocation and novel object recognition test. Recent report showed that anxiety like behavior due to social isolation is associated with increased CBP and decreased HDAC2 expression in the cerebral cortex of female mice [82]. Sharma *et al*. [85] observed that the expression of HDAC1 upregulated in the prefrontal cortex of schizophrenia subjects. Alcoholism is a complex psychiatric disorder and leads to anxiety like behavior [86]. Animals preferring alcohol showed higher level of HDAC2 expression and lower H3K9 acetylation at the promoter of synaptic plasticity genes BDNF and ARC in central and medial

nucleus of amygdala as compared to alcohol nonpreferred animals [86]. Uchida *et al*. [87] reported that the expression and binding of HDAC2 at the promoter of GDNF increased in the nucleus accumbens of stress and depressed mice. Exposure to general anesthesia during pregnancy harms the nervous system of the developing fetus and may cause memory impairment in the young [88]. Offspring of pregnant rat exposed with isoflurane anesthesia showed impaired spatial memory with increase in HDAC2 and decrease in CREB and NR2B expression in the hippocampus. Further, treatment with HDAC inhibitor Suberoylanilide hydroxamic acid (SAHA) ameliorated the effect of isoflurane and recovered memory in offspring [89]. Maternal separation is an early life stress which has adverse effect on nervous system of the young and impaired cognitive functions including learning and memory. Recently, Albuquerque *et al*. [90] reported that early life maternal deprivation in rats showed higher HDAC activity and lower H3 acetylation level which further impaired recognition memory.

Apart from class I HDAC2, recent reports have revealed the role of class II HDAC in learning and memory and comprises of HDAC4, 5, 6, 7, 9 and 10. Kim *et al*. [91] observed that conditional KO of HDAC4 impaired associative fear and spatial memory, but conditional KO of HDAC5 showed normal memory as compared to wild type in associative fear memory test. Similarly, conditional KO of HDAC4 or 5 showed normal basal synaptic transmission. However, they observed that LTP and paired-pulse facilitation decreased in HDAC4 KO mice. In a different report, Fitzsimons *et al*. [92] found that HDAC4 overexpression or inhibition in adult Drosophila impaired LTM, suggesting that basal level of HDAC4 is required for LTM. Govindarajan *et al*. [93] reported that HDAC6 KO enhanced spatial memory in wild type mice and recovered spatial and fear memory in mouse model of AD. Similarly, inhibition of HDAC6 recovered spatial and fear memory in mouse model of tau pathology [94]. These results are in contrast with the earlier results where inhibition of HDAC by class II inhibitors recovered memory.

Class III HDAC sirtuins comprise of sirtuin 1-7 and are known for their role in life span modulation. Kakefuda *et al*. [95] have observed that overexpression of sirtuin 1 impaired reference memory in mice. In contrast to the previous report, Michan *et al*. [96] showed that sirtuin 1 KO mice have impaired short term memory, associative fear memory, spatial memory but normal recognition memory similar to wild type. Several reports have shown that sirtuin plays an important role in calorie restriction mediated increase in lifespan [97, 98]. Heyward *et al*. [99] observed that diet induced obesity in mice showed lower sirtuin1 expression and impaired object location memory. Further, environmental enrichment increased the expression of sirtuin 2 and 6, and improved spatial and recognition memory in senescence accelerated mouse P8 [100]. On the other hand, Yin *et al*. [101] have reported that expression of sirtuin 6 is downregulated in the CA1 region following contextual fear conditioning. Further, they observed that overexpression of sirtuin 6 in CA1 region impaired fear memory. Thus, the role of sirtuins in learning and memory is still elusive and warrants further research to unveil its exact role in memory.

2.2.4. Histone Acetylation and Gene Expression

Previous studies have shown that specific histone acetylation marks are essential for the expression of synaptic plasticity genes and long term memory formation. These acetylation marks change in different physiological conditions and thereby affect gene expression and memory. Levenson *et al*. [3] first showed that hippocampal histone H3 acetylation is crucial for contextual fear memory formation. Similar study by Fischer *et al*. [102] has shown that environmental enrichment enhanced histone H3K9/14 and H4K5/8/12 acetylation in hippocampus as well as H3K9 and H3K5 in cortex of neurodegenerative mouse model. Such increase in histone acetylation is associated with enhanced spatial and associative memory consolidation in neuro-degenerative mouse model. Histone acetylation mark also changes in animals exposed to a specific learning task. Federman *et al*. [103] found that H3 histone acetylation level increased in the brain of adult male crabs (*Chasmagnathus granulates*) during memory consolidation. Similarly, Bousiges *et al*. [104] have observed that spatial and fear memory consolidation is associated with acetylation at H2B and H4 as compared to naive animals. Further, Intlekofer *et al*. [105] have shown an association between histone H4K8 acetylation and enhanced object location memory consolidation due to exercise. Histone acetylation marks are different in hippocampus and cortex; they are rapidly and transiently changed in the hippocampus but delayed and stable in the cortex. Graff *et al*. [6] have observed that acetylation level at histone H3K14 and H4K5 increased within 24 h and decreased after 24 h of novel object recognition test in the hippocampus. On the other hand, acetylation at H3K14 and H4K5 increased after 24 h and persisted till 7 days. The differential pattern of histone acetylation mark is due to differences in the function of hippocampus and cortex during memory formation and storage. Intrahippocampal estradiol treatment also recovered recognition memory consolidation, decreased HDAC2 expression and increased histone acetylation at H3K9 and H3K14 in the hippocampus of ovariectomized mice [106, 107]. Further, swimming exercise enhanced memory and H3K9, H4K5 and H4K12 acetylation levels in the hippocampus and recovered memory impairment resulting from isoflurane injection [108].

Histone acetylation activates the expression of synaptic plasticity genes and thereby memory consolidation. Guan *et al*. [5] have shown that HDAC2 overexpressed mice showed decrease in histone H3 and H4 acetylation level at the promoter region of synaptic plasticity genes CREB, EGR1, GluR1 and c-FOS. Neurodegenerative mouse model showed decreased level of H4K12 at the promoter region of synaptic plasticity genes BDNF, ARC, EGR1, Homer1 and GluR1 [6]. Bousiges *et al*. [109] have observed that spatial memory consolidation increased histone H2B and H4 acetylation level at the promoter region of BDNF, EGR1 and c-FOS. Similarly, contextual fear conditioning increased histone H3 acetylation level at the promoter region of BDNF [110]. Intlekofer *et al*. [105] have observed that histone H4K8 acetylation level increased at the promoter region of BDNF during exercise mediated enhanced object location memory consolidation. Similarly, fear condition increased histone H3 acetylation level at the promoter region of BDNF as

compared to naïve animal [111]. As histone acetylation pattern is different in hippocampus and cortex, histone acetylation at the promoter of EGR1 also showed similar change in these two regions [6]. Amyloid precursor protein (APP) mutant mice showed increase in histone H3 and H4 acetylation level at the promoter region of synaptic plasticity gene EGR1, indicating the role of APP in regulation of gene expression through chromatin modification [112]. Isoflurane-induced cognitive impairment models showed decrease in H3 and H4 acetylation at the promoter of GLT1 and mGLUR1/5 [83]. Further, we reported that lower histone H3K9 and H3K14 acetylation level at the promoter of synaptic plasticity genes BDNF, ARC, EGR1, Homer1 and NARP decreased their expression leading to reduced memory consolidation in scopolamine-induced amnesic mice [12, 38].

2.2.5. Histone Methylation

Methylation occurs at lysine and arginine residues on N terminal tail of histones and involves three different possible variations-monomethylation, dimethylation and trimethylation. These different forms of methylation influence chromatin organization differentially and regulate gene expression either positively or negatively [113-115]. Histone methylation is catalyzed by histone HMTs which add methyl group while HDMs remove methyl group from specific arginine or lysine in histones H3 and H4. HMTs have a conserved SET domain and are divided into seven families SUV39, SET1, SET2, EZ, RIZ, SMYD and SUV4-20 [116]. HDMs are divided into two classes: amine-oxidase type lysine specific demethylases (LSD) and JumonjiC domain-containing histone demethylases (JMJC).

Histone methylation is implicated in memory and CNS function. Gupta *et al*. [117] for the first time investigated the role of histone methylation in hippocampus-dependent memory. They reported that histone H3K4me3 (active mark for transcription activation) is crucial for the contextual fear memory consolidation and increased in the hippocampus of rats 1 h after contextual fear conditioning. Therefore, they suggested that expression of HMT regulates these methylation patterns at the promoter of synaptic plasticity genes during fear memory. Kerimoglu *et al*. [118] reported that H3K4 methylation through HMT myeloid/lymphoid or mixed-lineage leukemia 2 (Mll2/Kmt2b) is crucial for hippocampus-dependent memory function. Further, they found that Kmt2b critically regulated hippocampal memory consolidation by altered expression of synaptic plasticity genes *via* H3K4 di- and trimethylation linked with H3K9 acetylation. Enhancer of zeste homolog2 (Ezh2) is subunit of polycomb repressive complex 2 and silences gene expression by methylating H3K27 at the promoter of genes. Conditional KO of Ezh2 showed impairment in spatial and contextual fear memory in mice [119]. Jakovcevski *et al*. [120] suggested that H3K4 methylation at the promoter of synaptic plasticity genes through Mll1 enzyme is crucial for cognition and emotion in prefrontal cortex. Akbarian *et al*. [121] showed increase in H3 methylation (Arg17) of schizophrenic patients as compared to controls. Chronic social defeat stress, a method to induce depression in animals, increased dimethylation at H3K27 and thereby decreased the expression of BDNF [122]. Thus, histone methylation plays an important role in memory.

3. EPIGENETIC MODIFIERS AND RECOVERY OF MEMORY

3.1. DNMT Inhibitors

As DNMTs are mainly identified as negative regulator of memory, their inhibition could be targeted to recover memory impairment during aging and pathological conditions [123]. 5-Azacytidine (5-Aza) and Zebularine are well studied DNMT inhibitors which block the activity of DNMTs. Levenson *et al*. [16] pharmacologically inhibited DNMTs by the administration of 5-Aza and Zebularine and noted decreased methylation of synaptic plasticity related gene reelin and region specific effect of DNMT inhibition at the BDNF promoter. They suggested that inhibiting DNMTs activity blocks LTP and is crucial for information processing and storage in the hippocampus. Further, Miller and Sweatt [17] infused DNMTs inhibitors 5-Aza and Zebularine into the CA1 region of hippocampus immediately after contextual-fear conditioning and found decline in memory consolidation. They suggested that DNMTs activity is crucial for memory consolidation. Miller *et al*. [124] also found that pharmacological inhibition of DNMT immediately after fear conditioning decreases PP1 methylation resulting in aberrant transcription of gene and impairment of memory consolidation. Munoz *et al*. [31] incubated the rat hippocampal slices with methylation inhibitor agent 5-Aza and observed reduced methylation of BDNF gene as compared to untreated slices. Similarly, Miller *et al*. [32] infused DNMT inhibitors 5-Aza, Zebularine and RG-108 in the anterior cingulated cortex region of trained rats and found decreased methylation of calcineurin genes 30 days after fear conditioning which impaired long term memory. Zhao *et al*. [106] have reported that estradiol improved recognition memory consolidation through upregulation of DNMT3a and 3b in ovariectomized mice. They further showed that intrahippocampal infusion of 5-Aza after training improved recognition memory consolidation. We also demonstrated that intrahippocampal administration of 5-Aza decreased DNA methylation of ARC and BDNF promoter and restored recognition memory consolidation in scopolamine-induced amnesic mice [12]. Similarly, Ju *et al*. [26] showed that 5-Aza treatment rescued the sevoflurane-induced cognitive impairment by affecting DNA methylation.

3.2. HDAC Inhibitors

HDACs mainly deacetylate histones and regulate gene expression and memory consolidation. Hence, the inhibition or silencing of HDAC could be a promising approach to recover memory decline during aging and diseases [125, 126] (Fig. **1**). HDAC inhibitors inhibit the activity of HDACs and recovers histone acetylation level at the promoter of synaptic plasticity genes. Fischer *et al*. [102] have shown that nonspecific HDAC inhibitor sodium butyrate (NaB) significantly enhances spatial and associative memory consolidation in neurodegenerative mouse model. Similarly, intrahippocampal administration of NaB enhanced associative fear conditioning memory and histone H4K12 acetylation

level at the promoter of synaptic plasticity genes [7]. NaB treatment recovered hippocampal object location memory consolidation in CBP mutant mice [127]. NaB treatment after training enhanced recognition and object location memory consolidation, and histone H4K8 acetylation level at the promoter region of synaptic plasticity gene BDNF in old rats as compared to control [13, 105]. Kilgore *et al*. [74] have shown the recovery of freezing memory deficit by NaB in APP/PS1 AD mouse model. We also found that NaB treatment improved memory consolidation, increased acetylation of total histone H3K9 and H3K14 as well as the promoter region of synaptic plasticity genes BDNF and ARC in scopolamine-induced amnesic mice [12]. NaB treatment improved short as well as long term object recognition memory in mice treated with kainic acid, a convulsant agent which induces neuronal cell death and thereby induces neurodegeneration [128]. NaB treatment also enhanced behavioral performance with increased histone H3, H4 acetylation level and BDNF expression in depressed mice [129]. Recently, Villain *et al*. [130] reported that intrahippocampal infusion of NaB immediately after a weak training increased histone acetylation level and improved long term memory retention with normal short term memory. Further, NaB not only improved consolidation but also facilitated reconsolidation of spatial memory. It restored H3 acetylation, BDNF expression and recognition memory in cognitively impaired maternally deprived rats [90].

SAHA is also widely used as HDAC inhibitor to restore learning and memory. Alarcon *et al*. [60] have shown that intraventricular administration of SAHA restored fear memory consolidation and increased histone H2B acetylation level and late phase LTP in CBP mutant mice. Intraperitoneal treatment of SAHA increased fear memory consolidation in HDAC2 overexpressing mice [5]. SAHA also increased H4 acetylation level and recovered freezing memory deficit in mouse model of AD [74]. Peleg *et al*. [7] have shown that intrahippocampal administration of SAHA improved fear memory consolidation and H4K12 acetylation at the promoter of synaptic plasticity genes. SAHA also recovered the spatial memory deficit in sevoflurane-induced learning and memory impaired mice through hippocampal upregulation of synaptic plasticity genes CREB, CBP, EGR1 and Homer1 [131]. SAHA and a new HDAC inhibitor [N-(2-aminophenyl)-4-[N-(pyridine-3-ylmethoxy-carbonyl)aminomethyl]benzamide (MS-275)] showed antidepressant like effects in mouse model of social defeat and improved social interaction antidepressant like effects in this mouse model [78].

Another HDAC inhibitor, TSA treatment increased histone H3 acetylation, fear memory consolidation and LTP in CBP mutant mice [66]. TSA recovered recognition memory consolidation and histone acetylation at H3K14 and H4K12 in ovariectomized mice [106]. Post training transfusion of TSA in CA1 region of hippocampus increased H4 acetylation level and enhanced spatial memory consolidation in mice [132]. TSA treatment increased H3 and H4 acetylation level at the promoter region of synaptic plasticity genes NR4A1 and NR4A2 [133]. Intrahippocampal administration of TSA after training recovered H4 acetylation in CA1 region of old mice [134]. TSA also enhanced memory consolidation, H3K9 and H4K12 acetylation level at the promoter of BDNF and upregulated its expression in sleep deprived cognitively impaired rats [69]. TSA treatment also improved object recognition memory in kainic acid induced neurodengerative mice model [128]. TSA treatment recovered H3 acetylation level, expression of synaptic plasticity genes ARC, c-FOS and long term memory impairment in HD mouse model [71].

Thus, HDAC inhibition rescues spatial, fear and recognition memory in amnesia, neurodegenerative and mutant mice model as well as enhances memory in normal and aging mice. Hence, HDAC inhibitors can be used for the treatment of memory dysfunction *i.e*. restoration of memory to normal level in memory deficit model and as a memory enhancer to boost memory from normal level in healthy individual [135]. HDAC inhibitor can also be used as antidepressant and might prove beneficial for other neuropsychiatric disorders. However, due to the nonspecific nature of HDAC inhibitors, they inhibit the activity of more than one HDAC enzyme which leads to several side effects such as metabolic dysfunctions, fatigue, gastrointestinal, confusion, cardiac and hematological problem in animal and human studies [135-137]. Therefore, further research is required to find out specific HDAC inhibitors.

3.3. HMT Inhibitors

Unlike DNMT and HDAC inhibitor, little is known about the HMT inhibitor and its role in learning and memory. G9a/G9a-like protein (GLP) lysine dimethyltransferase controls H3K9 dimethylation and silences the expression of gene. Inhibition of G9a/GLP through specific inhibitor BIX-01294 (diazepin quinazolinamine derivative) increased the expression of synaptic plasticity genes EGR1 and cFOS, and enhanced fear memory consolidation [138]. Snigdha *et al*. [139] first time used HMT inhibitor ETP69, an analog of epidithiodiketopiperazine alkaloid chaetocin A, which inhibits SUV39H1. They observed that ETP69 treatment enhanced object location memory and contextual fear memory in old mice as compared to control group. Further, ETP69 decreased repressive histone mark H3K9 trimethylation at the promoter of synaptic plasticity genes BDNF and upregulated its expression in aged mice. It also promotes spine formation in aged hippocampus.

CONCLUSION AND FUTURE DIRECTION

The present review article focuses on the role of chromatin modifying enzymes, DNA methylation and hydroxymethylation, histone acetylation and methylation in the regulation of synaptic plasticity genes, memory and therapeutic approaches using epigenetic modifiers. Studies on animal models and human subjects revealed the role of chromatin modification in transcriptional regulation of gene expression and memory. Involvement of different DNMTs, HATs, HMTs and HDACs in the alteration of memory due to aging, disease and neurodegenerative pathologies makes it a more complex process of gene regulation. Distinct patterns of DNA methylation and histone acetylation have been observed during memory consolidation, memory impairment and different physiological conditions. Such specific marks have been associated with specific sets of synaptic plasticity genes in a particular condition. Remarkably, restoration of specific epigenetic marks by inhibition of these enzymes recovered

Table 1. List of enzyme inhibitors, their targets and effect on memory.

Enzyme Inhibitor	Target	Effect on memory	Refs.
5-Azacytidine	DNMTs	Rescues recogntion memory in ovariectomized mice, object recognition memory in scopolamine induced amnesic mice, cognition in sevoflurane exposure induced cognitively impaired rats	[12, 26, 100]
Sodium butyrate	Class I HDAC	Rescues spatial and contextual fear memory in CK-p25 neurodegenerative mice, fear memory in APP/PS1 AD mice, object location memory in CBP mutant mice, object recognition memory in scopolamine induced amnesic mice,	[12, 74, 102, 127]
		Enhances fear memory and object recognition memory in old mice, Improves long term memory retention with normal short term memory and improves recognition memory in cognitively impaired maternally deprived rats	[7, 13, 90, 130]
		Improves short as well as long term object recognition memory in kainic acid induced neurodegenerative mice model	[128]
		Enhance behavioral performance in depressed mice	[129]
Suberoylanilide hydroxamic acid (SAHA)	Class I and II HDACs	Rescues fear memory in CBP mutant mice, APP/PS1 AD mice, spatial memory in sevoflurane-induced memory impaired mice	[60, 74, 131]
		Enhances fear memory in old mice	[7]
		Antidepressant like effects in mouse model of social defeat and improves social interaction	[78]
MS-275	HDAC	Improves social interaction and acts as antidepressant in mouse model of social defeat	[78]
Trichostatin-A (TSA)	Class I and II HDACs	Rescue fear memory in CBP mutant mice, recogntion memory in ovariectomized mice	[66, 106]
		Improves object recognition memory in kainic acid treated neurodegenerative mice model	[128]
		Recovers long term memory impairment in HD mouse model	[71]
BIX-01294	G9a/GLP HMTs	Rescues fear memory consolidation	[138]
ETP 69	SUV39H1 HMTs	Rescues fear memory and object location memory	[139]

the expression of synaptic plasticity genes and memory in human subjects and animal models of neurodegenerative diseases and pathologies (Fig. **1**). DNMT, HDAC and HMT inhibitors which are being used currently have broad activity and inhibit more than one enzyme (Table **1**). Therefore, the use of specific inhibitor could be a promising way to recover memory. Further, identification of other modifications like DNA hydroxymethylation and histone phosphorylation in the regulation of learning and memory may add to the complexity of this process. Epigenetic research with respect to cognition and memory is still in infancy and needs to be explored in more depth.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

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

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REFERENCES

[1] Hernandez, P.J.; Abel, T. The role of protein synthesis in memory consolidation: progress amid decades of debate. *Neurobiol. Learn. Mem.,* **2008**, *89*(3), 293-311. [http://dx.doi.org/10.1016/j.nlm.2007.09.010] [PMID: 18053752]

[2] Cortés-Mendoza, J.; Díaz de León-Guerrero, S.; Pedraza-Alva, G.; Pérez-Martínez, L. Shaping synaptic plasticity: the role of activity-mediated epigenetic regulation on gene transcription. *Int. J. Dev. Neurosci.,* **2013**, *31*(6), 359-369. [http://dx.doi.org/10.1016/j.ijdevneu.2013.04.003] [PMID: 23665156]

[3] Levenson, J.M.; O'Riordan, K.J.; Brown, K.D.; Trinh, M.A.; Molfese, D.L.; Sweatt, J.D. Regulation of histone acetylation during memory formation in the hippocampus. *J. Biol. Chem.,* **2004**, *279*(39), 40545-40559. [http://dx.doi.org/10.1074/jbc.M402229200] [PMID: 15273246]

[4] Levenson, J.M.; Qiu, S.; Weeber, E.J. The role of reelin in adult synaptic function and the genetic and epigenetic regulation of the reelin gene. *Biochim. Biophys. Acta,* **2008**, *1779*(8), 422-431. [http://dx.doi.org/10.1016/j.bbagrm.2008.01.001] [PMID: 18237558]

[5] Guan, J.S.; Haggarty, S.J.; Giacometti, E.; Dannenberg, J.H.; Joseph, N.; Gao, J.; Nieland, T.J.; Zhou, Y.; Wang, X.; Mazitschek, R.; Bradner, J.E.; DePinho, R.A.; Jaenisch, R.; Tsai, L.H. HDAC2 negatively regulates memory formation and synaptic plasticity. *Nature,* **2009**, *459*(7243), 55-60. [http://dx.doi.org/10.1038/nature 07925] [PMID: 19424149]

[6] Gräff, J.; Rei, D.; Guan, J.S.; Wang, W.Y.; Seo, J.; Hennig, K.M.; Nieland, T.J.; Fass, D.M.; Kao, P.F.; Kahn, M.; Su, S.C.; Samiei, A.; Joseph, N.; Haggarty, S.J.; Delalle, I.; Tsai, L.H. An epigenetic blockade of cognitive functions in the neurodegenerating brain. *Nature,* **2012**, *483*(7388), 222-226. [http://dx.doi.org/10.1038/ nature10849] [PMID: 22388814]

[7] Peleg, S.; Sananbenesi, F.; Zovoilis, A.; Burkhardt, S.; Bahari-Javan, S.; Agis-Balboa, R.C.; Cota, P.; Wittnam, J.L.; Gogol-Doering, A.; Opitz, L.; Salinas-Riester, G.; Dettenhofer, M.; Kang, H.; Farinelli, L.; Chen, W.; Fischer, A. Altered histone acetylation is associated with age-dependent memory impairment in mice. *Science,* **2010**, *328*(5979), 753-756. [http://dx.doi.org/10.1126/ science.1186088] [PMID: 20448184]

[8] Penner, M.R.; Roth, T.L.; Chawla, M.K.; Hoang, L.T.; Roth, E.D.; Lubin, F.D.; Sweatt, J.D.; Worley, P.F.; Barnes, C.A. Age-related changes in Arc transcription and DNA methylation within the hippocampus. *Neurobiol. Aging,* **2011**, *32*(12), 2198-2210. [http:// dx.doi.org/10.1016/j.neurobiolaging.2010.01.009] [PMID: 20189687]

[9] Konar, A.; Shah, N.; Singh, R.; Saxena, N.; Kaul, S.C.; Wadhwa, R.; Thakur, M.K. Protective role of Ashwagandha leaf extract and its component withanone on scopolamine-induced changes in the brain and brain-derived cells. *PLoS One,* **2011**, *6*(11), e27265. [http://dx.doi.org/10.1371/journal.pone.0027265] [PMID: 22096544]

[10] Kumar, D.; Thakur, M.K. Age-related expression of Neurexin1 and Neuroligin3 is correlated with presynaptic density in the cerebral cortex and hippocampus of male mice. *Age (Dordr.),* **2015**, *37*(2), 17. [http://dx.doi.org/10.1007/s11357-015-9752-6] [PMID: 25693924]

[11] Kumari, A.; Thakur, M.K. Age-dependent decline of nogo-a protein in the mouse cerebrum. *Cell. Mol. Neurobiol.,* **2014**, *34*(8), 1131-1141. [http://dx.doi.org/10.1007/s10571-014-0088-z] [PMID: 25078756]

[12] Singh, P.; Konar, A.; Kumar, A.; Srivas, S.; Thakur, M.K. Hippocampal chromatin-modifying enzymes are pivotal for scopolamine-induced synaptic plasticity gene expression changes and memory impairment. *J. Neurochem.,* **2015**, *134*(4), 642-651. [http://dx.doi.org/10.1111/jnc.13171] [PMID: 25982413]

[13] Reolon, G.K.; Maurmann, N.; Werenicz, A.; Garcia, V.A.; Schröder, N.; Wood, M.A.; Roesler, R. Posttraining systemic administration of the histone deacetylase inhibitor sodium butyrate ameliorates aging-related memory decline in rats. *Behav. Brain Res.,* **2011**, *221*(1), 329-332. [http://dx.doi.org/10.1016/j.bbr.2011. 03.033] [PMID: 21421011]

[14] Goto, K.; Numata, M.; Komura, J.I.; Ono, T.; Bestor, T.H.; Kondo, H. Expression of DNA methyltransferase gene in mature and immature neurons as well as proliferating cells in mice. *Differentiation,* **1994**, *56*(1-2), 39-44. [http://dx.doi.org/10.1046/ j.1432-0436.1994.56120039.x] [PMID: 8026645]

[15] Feng, J.; Chang, H.; Li, E.; Fan, G. Dynamic expression of de novo DNA methyltransferases Dnmt3a and Dnmt3b in the central nervous system. *J. Neurosci. Res.,* **2005**, *79*(6), 734-746. [http://dx.doi.org/ 10.1002/jnr.20404] [PMID: 15672446]

[16] Levenson, J.M.; Roth, T.L.; Lubin, F.D.; Miller, C.A.; Huang, I.C.; Desai, P.; Malone, L.M.; Sweatt, J.D. Evidence that DNA (cytosine-5) methyltransferase regulates synaptic plasticity in the hippocampus. *J. Biol. Chem.,* **2006**, *281*(23), 15763-15773. [http://dx.doi.org/10.1074/jbc.M511767200] [PMID: 16606618]

[17] Miller, C.A.; Sweatt, J.D. Covalent modification of DNA regulates memory formation. *Neuron,* **2007**, *53*(6), 857-869. [http://dx.doi. org/10.1016/j.neuron.2007.02.022] [PMID: 17359920]

[18] Feng, J.; Zhou, Y.; Campbell, S.L.; Le, T.; Li, E.; Sweatt, J.D.; Silva, A.J.; Fan, G. Dnmt1 and Dnmt3a maintain DNA methylation and regulate synaptic function in adult forebrain neurons. *Nat. Neurosci.,* **2010**, *13*(4), 423-430. [http://dx.doi.org/10.1038/nn.2514] [PMID: 20228804]

[19] Liu, L.; van Groen, T.; Kadish, I.; Li, Y.; Wang, D.; James, S.R.; Karpf, A.R.; Tollefsbol, T.O. Insufficient DNA methylation affects healthy aging and promotes age-related health problems. *Clin. Epigenetics,* **2011**, *2*(2), 349-360. [http://dx.doi.org/10.1007/ s13148-011-0042-6] [PMID: 22704347]

[20] Elsner, V.R.; Lovatel, G.A.; Moysés, F.; Bertoldi, K.; Spindler, C.; Cechinel, L.R.; Muotri, A.R.; Siqueira, I.R. Exercise induces age-dependent changes on epigenetic parameters in rat hippocampus: a preliminary study. *Exp. Gerontol.,* **2013**, *48*(2), 136-139. [http:// dx.doi.org/10.1016/j.exger.2012.11.011] [PMID: 23201423]

[21] Singh, P.; Thakur, M.K. Reduced recognition memory is correlated with decrease in DNA methyltransferase1 and increase in histone deacetylase2 protein expression in old male mice. *Biogerontology,* **2014**, *15*(4), 339-346. [http://dx.doi.org/10.1007/s10522-014-9504-5] [PMID: 24924148]

[22] Mastroeni, D.; Grover, A.; Delvaux, E.; Whiteside, C.; Coleman, P.D.; Rogers, J. Epigenetic mechanisms in Alzheimer's disease. *Neurobiol. Aging,* **2011**, *32*(7), 1161-1180. [http://dx.doi.org/10. 1016/j.neurobiolaging.2010.08.017] [PMID: 21482442]

[23] Golshani, P.; Hutnick, L.; Schweizer, F.; Fan, G. Conditional Dnmt1 deletion in dorsal forebrain disrupts development of somatosensory barrel cortex and thalamocortical long-term potentiation. *Thalamus Relat. Syst.,* **2005**, *3*(3), 227-233. [http://dx. doi.org/10.1017/S1472928807000222] [PMID: 17710197]

[24] Klein, C.J.; Botuyan, M.V.; Wu, Y.; Ward, C.J.; Nicholson, G.A.; Hammans, S.; Hojo, K.; Yamanishi, H.; Karpf, A.R.; Wallace, D.C.; Simon, M.; Lander, C.; Boardman, L.A.; Cunningham, J.M.; Smith, G.E.; Litchy, W.J.; Boes, B.; Atkinson, E.J.; Middha, S.; B Dyck, P.J.; Parisi, J.E.; Mer, G.; Smith, D.I.; Dyck, P.J. Mutations in DNMT1 cause hereditary sensory neuropathy with dementia and hearing loss. *Nat. Genet.,* **2011**, *43*(6), 595-600. [http://dx.doi.org/ 10.1038/ng.830] [PMID: 21532572]

[25] Oliveira, A.M.; Hemstedt, T.J.; Bading, H. Rescue of aging-associated decline in Dnmt3a2 expression restores cognitive abilities. *Nat. Neurosci.,* **2012**, *15*(8), 1111-1113. [http://dx.doi.org/10.1038/ nn.3151] [PMID: 22751036]

[26] Ju, L.S.; Jia, M.; Sun, J.; Sun, X.R.; Zhang, H.; Ji, M.H.; Yang, J.J.; Wang, Z.Y. Hypermethylation of hippocampal synaptic plasticity-related genes is involved in neonatal sevoflurane exposure-induced cognitive impairments in rats. *Neurotox. Res.,* **2016**, *29*(2), 243-255. [http://dx.doi.org/10.1007/s12640-015-9585-1] [PMID: 26678494]

[27] Moore, L.D.; Le, T.; Fan, G. DNA methylation and its basic function. *Neuropsychopharmacology,* **2013**, *38*(1), 23-38. [http:// dx.doi.org/10.1038/npp.2012.112] [PMID: 22781841]

[28] Lu, H.; Liu, X.; Deng, Y.; Qing, H. DNA methylation, a hand behind neurodegenerative diseases. *Front. Aging Neurosci.,* **2013**, *5*, 85. [http://dx.doi.org/10.3389/fnagi.2013.00085] [PMID: 24367332]

[29] Lubin, F.D.; Roth, T.L.; Sweatt, J.D. Epigenetic regulation of BDNF gene transcription in the consolidation of fear memory. *J. Neurosci.,* **2008**, *28*(42), 10576-10586. [http://dx.doi.org/10.1523/ JNEUROSCI.1786-08.2008] [PMID: 18923034]

[30] Siegmund, K.D.; Connor, C.M.; Campan, M.; Long, T.I.; Weisenberger, D.J.; Biniszkiewicz, D.; Jaenisch, R.; Laird, P.W.; Akbarian, S. DNA methylation in the human cerebral cortex is dynamically regulated throughout the life span and involves differentiated neurons. *PLoS One,* **2007**, *2*(9), e895. [http://dx.doi. org/10.1371/journal.pone.0000895] [PMID: 17878930]

[31] Muñoz, P.C.; Aspé, M.A.; Contreras, L.S.; Palacios, A.G. Correlations of recognition memory performance with expression and methylation of brain-derived neurotrophic factor in rats. *Biol. Res.,* **2010**, *43*(2), 251-258. [http://dx.doi.org/10.4067/S0716-97602010000200013] [PMID: 21031270]

[32] Miller, C.A.; Gavin, C.F.; White, J.A.; Parrish, R.R.; Honasoge, A.; Yancey, C.R.; Rivera, I.M.; Rubio, M.D.; Rumbaugh, G.; Sweatt, J.D. Cortical DNA methylation maintains remote memory. *Nat. Neurosci.,* **2010**, *13*(6), 664-666. [http://dx.doi.org/10.1038/nn.2560] [PMID: 20495557]

[33] Ma, D.K.; Jang, M.H.; Guo, J.U.; Kitabatake, Y.; Chang, M.L.; Pow-Anpongkul, N.; Flavell, R.A.; Lu, B.; Ming, G.L.; Song, H. Neuronal activity-induced Gadd45b promotes epigenetic DNA demethylation and adult neurogenesis. *Science,* **2009**, *323*(5917), 1074-1077. [http://dx.doi.org/10.1126/science.1166859] [PMID: 19119186]

[34] Sultan, F.A.; Wang, J.; Tront, J.; Liebermann, D.A.; Sweatt, J.D. Genetic deletion of Gadd45b, a regulator of active DNA demethylation, enhances long-term memory and synaptic plasticity. *J. Neurosci.,* **2012**, *32*(48), 17059-17066. [http://dx.doi.org/10. 1523/JNEUROSCI.1747-12.2012] [PMID: 23197699]

[35] Haberman, R.P.; Quigley, C.K.; Gallagher, M. Characterization of CpG island DNA methylation of impairment-related genes in a rat model of cognitive aging. *Epigenetics,* **2012**, *7*(9), 1008-1019. [http://dx.doi.org/10.4161/epi.21291] [PMID: 22869088]

[36] Penner, M.R.; Parrish, R.R.; Hoang, L.T.; Roth, T.L.; Lubin, F.D.; Barnes, C.A. Age-related changes in Egr1 transcription and DNA methylation within the hippocampus. *Hippocampus.,* **2016**, *26*(18), 1008-1020.

[37] Hu, Y.D.; Pang, W.; He, C.C.; Lu, H.; Liu, W.; Wang, Z.Y.; Liu, Y.Q.; Huang, C.Y.; Jiang, Y.G. The role of protein synthesis in memory consolidation: progress amid decades of debate. *Neurobiol. Learn. Mem.,* **2008**, *89*(3), 293-311.

[38] Srivas, S.; Thakur, M.K. Epigenetic regulation of neuronal immediate early genes is associated with decline in their expression and memory consolidation in scopolamine-induced amnesic mice. *Mol. Neurobiol.,* **2016**, *54*(7), 5107-5119. [http://dx.doi.org/10.1007/s12035-016-0047-4] [PMID: 27553230]

[39] Dong, E.; Dzitoyeva, S.G.; Matrisciano, F.; Tueting, P.; Grayson, D.R.; Guidotti, A. Brain-derived neurotrophic factor epigenetic modifications associated with schizophrenia-like phenotype induced by prenatal stress in mice. *Biol. Psychiatry,* **2015**, *77*(6), 589-596. [http://dx.doi.org/10.1016/j.biopsych.2014.08.012] [PMID: 25444166]

[40] Mastronardi, F.G.; Noor, A.; Wood, D.D.; Paton, T.; Moscarello, M.A. Peptidyl argininedeiminase 2 CpG island in multiple sclerosis white matter is hypomethylated. *J. Neurosci. Res.,* **2007**, *85*(9), 2006-2016. [http://dx.doi.org/10.1002/jnr.21329] [PMID: 17469138]

[41] Veldic, M.; Guidotti, A.; Maloku, E.; Davis, J.M.; Costa, E. In psychosis, cortical interneurons overexpress DNA-methyltransferase 1. *Proc. Natl. Acad. Sci. USA,* **2005**, *102*(6), 2152-2157. [http://dx.doi.org/10.1073/pnas.0409665102] [PMID: 15684088]

[42] Abdolmaleky, H.M.; Cheng, K.H.; Russo, A.; Smith, C.L.; Faraone, S.V.; Wilcox, M.; Shafa, R.; Glatt, S.J.; Nguyen, G.; Ponte, J.F.; Thiagalingam, S.; Tsuang, M.T. Hypermethylation of the reelin (RELN) promoter in the brain of schizophrenic patients: a preliminary report. *Am. J. Med. Genet. B. Neuropsychiatr. Genet.,* **2005**, *134B*(1), 60-66. [http://dx.doi.org/10.1002/ajmg.b.30140] [PMID: 15717292]

[43] Costa, E.; Chen, Y.; Dong, E.; Grayson, D.R.; Kundakovic, M.; Maloku, E.; Ruzicka, W.; Satta, R.; Veldic, M.; Zhubi, A.; Guidotti, A. GABAergic promoter hypermethylation as a model to study the neurochemistry of schizophrenia vulnerability. *Expert Rev. Neurother.,* **2009**, *9*(1), 87-98. [http://dx.doi.org/10.1586/14737175.9.1.87] [PMID: 19102671]

[44] Huang, H.S.; Akbarian, S. GAD1 mRNA expression and DNA methylation in prefrontal cortex of subjects with schizophrenia. *PLoS One,* **2007**, *2*(8), e809. [http://dx.doi.org/10.1371/journal.pone.0000809] [PMID: 17726539]

[45] Grayson, D.R.; Guidotti, A. The dynamics of DNA methylation in schizophrenia and related psychiatric disorders. *Neuropsychopharmacology,* **2013**, *38*(1), 138-166. [http://dx.doi.org/10.1038/npp.2012.125] [PMID: 22948975]

[46] Wang, T.; Pan, Q.; Lin, L.; Szulwach, K.E.; Song, C.X.; He, C.; Wu, H.; Warren, S.T.; Jin, P.; Duan, R.; Li, X. Genome-wide DNA hydroxymethylation changes are associated with neurodevelopmental genes in the developing human cerebellum. *Hum. Mol. Gen.,* **2012**, *21*(26), 5500-5510.

[47] Sun, W.; Zang, L.; Shu, Q.; Li, X. From development to diseases: the role of 5hmC in brain. *Genomics,* **2014**, *104*(5), 347-351. [http://dx.doi.org/10.1016/j.ygeno.2014.08.021] [PMID: 25205306]

[48] Coppieters, N.; Dieriks, B.V.; Lill, C.; Faull, R.L.; Curtis, M.A.; Dragunow, M. Global changes in DNA methylation and hydroxymethylation in Alzheimer's disease human brain. *Neurobiol. Aging,* **2014**, *35*(6), 1334-1344. [http://dx.doi.org/10.1016/j.neurobiolaging.2013.11.031] [PMID: 24387984]

[49] Wen, L.; Tang, F. Genomic distribution and possible functions of DNA hydroxymethylation in the brain. *Genomics,* **2014**, *104*(5), 341-346. [http://dx.doi.org/10.1016/j.ygeno.2014.08.020] [PMID: 25205307]

[50] Chouliaras, L.; Mastroeni, D.; Delvaux, E.; Grover, A.; Kenis, G.; Hof, P.R.; Steinbusch, H.W.; Coleman, P.D.; Rutten, B.P.; van den Hove, D.L. Consistent decrease in global DNA methylation and hydroxymethylation in the hippocampus of Alzheimer's disease patients. *Neurobiol. Aging,* **2013**, *34*(9), 2091-2099. [http://dx.doi.org/10.1016/j.neurobiolaging.2013.02.021] [PMID: 23582657]

[51] Chen, H.; Dzitoyeva, S.; Manev, H. Effect of aging on 5-hydroxymethylcytosine in the mouse hippocampus. *Restor. Neurol. Neurosci.,* **2012**, *30*(3), 237-245. [PMID: 22426040]

[52] Kaas, G.A.; Zhong, C.; Eason, D.E.; Ross, D.L.; Vachhani, R.V.; Ming, G.L.; King, J.R.; Song, H.; Sweatt, J.D. TET1 controls CNS 5-methylcytosine hydroxylation, active DNA demethylation, gene transcription, and memory formation. *Neuron,* **2013**, *79*(6), 1086-1093. [http://dx.doi.org/10.1016/j.neuron.2013.08.032] [PMID: 24050399]

[53] Rudenko, A.; Dawlaty, M.M.; Seo, J.; Cheng, A.W.; Meng, J.; Le, T.; Faull, K.F.; Jaenisch, R.; Tsai, L.H. Tet1 is critical for neuronal activity-regulated gene expression and memory extinction. *Neuron,* **2013**, *79*(6), 1109-1122. [http://dx.doi.org/10.1016/j.neuron.2013.08.003] [PMID: 24050401]

[54] Biergans, S.D.; Giovanni Galizia, C.; Reinhard, J.; Claudianos, C. Dnmts and Tet target memory-associated genes after appetitive olfactory training in honey bees. *Sci. Rep.,* **2015**, *5*, 16223. [http://dx.doi.org/10.1038/srep16223] [PMID: 26531238]

[55] Kumar, D.; Aggarwal, M.; Kaas, G.A.; Lewis, J.; Wang, J.; Ross, D.L.; Zhong, C.; Kennedy, A.; Song, H.; Sweatt, J.D. Tet1 oxidase regulates neuronal gene transcription, active DNA hydroxymethylation, object location memory, and threat recognition memory. *Neuroepigenetics,* **2015**, *4*, 12-27. [http://dx.doi.org/10.1016/j.nepig.2015.10.002] [PMID: 26644996]

[56] Selvi, B.R.; Cassel, J.C.; Kundu, T.K.; Boutillier, A.L. Tuning acetylation levels with HAT activators: therapeutic strategy in neurodegenerative diseases. *Biochim. Biophys. Acta,* **2010**, *1799* (10-12), 840-853. [http://dx.doi.org/10.1016/j.bbagrm.2010.08.012] [PMID: 20833281]

[57] Partanen, A.; Motoyama, J.; Hui, C.C. Developmentally regulated expression of the transcriptional cofactors/histone acetyltransferases CBP and p300 during mouse embryogenesis. *Int. J. Dev. Biol.,* **1999**, *43*(6), 487-494. [PMID: 10610021]

[58] Bedford, D.C.; Brindle, P.K. Is histone acetylation the most important physiological function for CBP and p300? *Aging (Albany NY),* **2012**, *4*(4), 247-255. [http://dx.doi.org/10.18632/aging.100453] [PMID: 22511639]

[59] Chatterjee, S.; Mizar, P.; Cassel, R.; Neidl, R.; Selvi, B.R.; Mohankrishna, D.V.; Vedamurthy, B.M.; Schneider, A.; Bousiges, O.; Mathis, C.; Cassel, J.C.; Eswaramoorthy, M.; Kundu, T.K.; Boutillier, A.L. A novel activator of CBP/p300 acetyltransferases promotes neurogenesis and extends memory duration in adult mice. *J. Neurosci.,* **2013**, *33*(26), 10698-10712. [http://dx.doi.org/10.1523/JNEUROSCI.5772-12.2013] [PMID: 23804093]

[60] Alarcón, J.M.; Malleret, G.; Touzani, K.; Vronskaya, S.; Ishii, S.; Kandel, E.R.; Barco, A. Chromatin acetylation, memory, and LTP are impaired in CBP+/- mice: a model for the cognitive deficit in Rubinstein-Taybi syndrome and its amelioration. *Neuron,* **2004**, *42*(6), 947-959. [http://dx.doi.org/10.1016/j.neuron.2004.05.021] [PMID: 15207239]

[61] Barrett, R.M.; Malvaez, M.; Kramar, E.; Matheos, D.P.; Arrizon, A.; Cabrera, S.M.; Lynch, G.; Greene, R.W.; Wood, M.A. Hippocampal focal knockout of CBP affects specific histone modifications, long-term potentiation, and long-term memory. *Neuropsychopharmacology,* **2011**, *36*(8), 1545-1556. [http://dx.doi.org/10.1038/npp.2011.61] [PMID: 21508930]

[62] Crump, N.T.; Hazzalin, C.A.; Bowers, E.M.; Alani, R.M.; Cole, P.A.; Mahadevan, L.C. Dynamic acetylation of all lysine-4 trimethylated histone H3 is evolutionarily conserved and mediated by p300/CBP. *Proc. Natl. Acad. Sci. USA,* **2011**, *108*(19), 7814-7819. [http://dx.doi.org/10.1073/pnas.1100099108] [PMID: 21518915]

[63] Chen, G.; Zou, X.; Watanabe, H.; van Deursen, J.M.; Shen, J. CREB binding protein is required for both short-term and long-term memory formation. *J. Neurosci.,* **2010**, *30*(39), 13066-13077. [http://dx.doi.org/10.1523/JNEUROSCI.2378-10.2010] [PMID: 20881124]

[64] Valor, L.M.; Pulopulos, M.M.; Jimenez-Minchan, M.; Olivares, R.; Lutz, B.; Barco, A. Ablation of CBP in forebrain principal neurons causes modest memory and transcriptional defects and a dramatic reduction of histone acetylation but does not affect cell viability. *J. Neurosci.,* **2011**, *31*(5), 1652-1663. [http://dx.doi.org/10.1523/JNEUROSCI.4737-10.2011] [PMID: 21289174]

[65] Vieira, P.A.; Korzus, E. CBP-Dependent memory consolidation in the prefrontal cortex supports object-location learning. *Hippocampus,*

2015, *25*(12), 1532-1540. [http://dx.doi.org/10.1002/hipo.22473] [PMID: 25941038]

[66] Korzus, E.; Rosenfeld, M.G.; Mayford, M. CBP histone acetyltransferase activity is a critical component of memory consolidation. *Neuron,* **2004**, *42*(6), 961-972. [http://dx.doi.org/10.1016/j.neuron.2004.06.002] [PMID: 15207240]

[67] Wood, M.A.; Kaplan, M.P.; Park, A.; Blanchard, E.J.; Oliveira, A.M.; Lombardi, T.L.; Abel, T. Transgenic mice expressing a truncated form of CREB-binding protein (CBP) exhibit deficits in hippocampal synaptic plasticity and memory storage. *Learn. Mem.,* **2005**, *12*(2), 111-119. [http://dx.doi.org/10.1101/lm.86605] [PMID: 15805310]

[68] Wood, M.A.; Attner, M.A.; Oliveira, A.M.; Brindle, P.K.; Abel, T. A transcription factor-binding domain of the coactivator CBP is essential for long-term memory and the expression of specific target genes. *Learn. Mem.,* **2006**, *13*(5), 609-617. [http://dx.doi.org/10.1101/lm.213906] [PMID: 16980541]

[69] Duan, R.; Liu, X.; Wang, T.; Wu, L.; Gao, X.; Zhang, Z. Histone acetylation regulation in sleep deprivation-induced spatial memory impairment. *Neurochem. Res.,* **2016**, *41*(9), 2223-2232. [http://dx.doi.org/10.1007/s11064-016-1937-6] [PMID: 27161370]

[70] Caccamo, A.; Maldonado, M.A.; Bokov, A.F.; Majumder, S.; Oddo, S. CBP gene transfer increases BDNF levels and ameliorates learning and memory deficits in a mouse model of Alzheimer's disease. *Proc. Natl. Acad. Sci. USA,* **2010**, *107*(52), 22687-22692. [http://dx.doi.org/10.1073/pnas.1012851108] [PMID: 21149712]

[71] Giralt, A.; Puigdellívol, M.; Carretón, O.; Paoletti, P.; Valero, J.; Parra-Damas, A.; Saura, C.A.; Alberch, J.; Ginés, S. Long-term memory deficits in Huntington's disease are associated with reduced CBP histone acetylase activity. *Hum. Mol. Genet.,* **2012**, *21*(6), 1203-1216. [http://dx.doi.org/10.1093/hmg/ddr552] [PMID: 22116937]

[72] Lopez-Atalaya, J.P.; Ciccarelli, A.; Viosca, J.; Valor, L.M.; Jimenez-Minchan, M.; Canals, S.; Giustetto, M.; Barco, A. CBP is required for environmental enrichment-induced neurogenesis and cognitive enhancement. *EMBO J.,* **2011**, *30*(20), 4287-4298. [http://dx.doi.org/10.1038/emboj.2011.299] [PMID: 21847097]

[73] Stilling, R.M.; Rönicke, R.; Benito, E.; Urbanke, H.; Capece, V.; Burkhardt, S.; Bahari-Javan, S.; Barth, J.; Sananbenesi, F.; Schütz, A.L.; Dyczkowski, J.; Martinez-Hernandez, A.; Kerimoglu, C.; Dent, S.Y.; Bonn, S.; Reymann, K.G.; Fischer, A. K-Lysine acetyltransferase 2a regulates a hippocampal gene expression network linked to memory formation. *EMBO J.,* **2014**, *33*(17), 1912-1927. [http://dx.doi.org/10.15252/embj.201487870] [PMID: 25024434]

[74] Kilgore, M.; Miller, C.A.; Fass, D.M.; Hennig, K.M.; Haggarty, S.J.; Sweatt, J.D.; Rumbaugh, G. Inhibitors of class 1 histone deacetylases reverse contextual memory deficits in a mouse model of Alzheimer's disease. *Neuropsychopharmacology,* **2010**, *35*(4), 870-880. [http://dx.doi.org/10.1038/npp.2009.197] [PMID: 20010553]

[75] Morris, M.J.; Mahgoub, M.; Na, E.S.; Pranav, H.; Monteggia, L.M. Loss of histone deacetylase 2 improves working memory and accelerates extinction learning. *J. Neurosci.,* **2013**, *33*(15), 6401-6411. [http://dx.doi.org/10.1523/JNEUROSCI.1001-12.2013] [PMID: 23575838]

[76] Robertson, K.D. DNA methylation and chromatin - unraveling the tangled web. *Oncogene,* **2002**, *21*(35), 5361-5379. [http://dx.doi.org/10.1038/sj.onc.1205609] [PMID: 12154399]

[77] Grzenda, A.; Lomberk, G.; Zhang, J.S.; Urrutia, R. Sin3: master scaffold and transcriptional corepressor. *Biochim. Biophys. Acta,* **2009**, *1789*(6-8), 443-450. [http://dx.doi.org/10.1016/j.bbagrm.2009.05.007] [PMID: 19505602]

[78] Covington, H.E., III; Maze, I.; LaPlant, Q.C.; Vialou, V.F.; Ohnishi, Y.N.; Berton, O.; Fass, D.M.; Renthal, W.; Rush, A.J., III; Wu, E.Y.; Ghose, S.; Krishnan, V.; Russo, S.J.; Tamminga, C.; Haggarty, S.J.; Nestler, E.J. Antidepressant actions of histone deacetylase inhibitors. *J. Neurosci.,* **2009**, *29*(37), 11451-11460. [http://dx.doi.org/10.1523/JNEUROSCI.1758-09.2009] [PMID: 19759294]

[79] Mielcarek, M.; Benn, C.L.; Franklin, S.A.; Smith, D.L.; Woodman, B.; Marks, P.A.; Bates, G.P. SAHA decreases HDAC 2 and 4 levels *in vivo* and improves molecular phenotypes in the R6/2 mouse model of Huntington's disease. *PLoS One.,* **2011**, *16*(11), e27746.

[80] Chen, G.; Guan, F.; Lin, H.; Li, L.; Fu, D. Genetic analysis of common variants in the HDAC2 gene with schizophrenia susceptibility in Han Chinese. *J. Hum. Genet.,* **2015**, *60*(9), 479-484. [http://dx.doi.org/10.1038/jhg.2015.66] [PMID: 26063464]

[81] Volmar, C.H.; Wahlestedt, C. Histone deacetylases (HDACs) and brain function. *Neuroepigenetics,* **2015**, *1*, 20-27. [http://dx.doi.org/10.1016/j.nepig.2014.10.002]

[82] Kumari, A.; Singh, P.; Baghel, M.S.; Thakur, M.K. Social isolation mediated anxiety like behavior is associated with enhanced expression and regulation of BDNF in the female mouse brain. *Physiol. Behav.,* **2016**, *158*, 34-42. [http://dx.doi.org/10.1016/j.physbeh.2016.02.032] [PMID: 26921097]

[83] Liang, B.; Fang, J. Postnatal isoflurane exposure induces cognitive impairment and abnormal histone acetylation of glutamatergic systems in the hippocampus of adolescent rats. *J. Mol. Neurosci.,* **2016**, *60*(1), 11-20. [http://dx.doi.org/10.1007/s12031-016-0756-1] [PMID: 27307148]

[84] McQuown, S.C.; Barrett, R.M.; Matheos, D.P.; Post, R.J.; Rogge, G.A.; Alenghat, T.; Mullican, S.E.; Jones, S.; Rusche, J.R.; Lazar, M.A.; Wood, M.A. HDAC3 is a critical negative regulator of long-term memory formation. *J. Neurosci.,* **2011**, *31*(2), 764-774. [http://dx.doi.org/10.1523/JNEUROSCI.5052-10.2011] [PMID: 21228185]

[85] Sharma, R.P.; Grayson, D.R.; Gavin, D.P. Histone deactylase 1 expression is increased in the prefrontal cortex of schizophrenia subjects: analysis of the National Brain Databank microarray collection. *Schizophr. Res.,* **2008**, *98*(1-3), 111-117. [http://dx.doi.org/10.1016/j.schres.2007.09.020] [PMID: 17961987]

[86] Moonat, S.; Sakharkar, A.J.; Zhang, H.; Tang, L.; Pandey, S.C. Aberrant histone deacetylase2-mediated histone modifications and synaptic plasticity in the amygdala predisposes to anxiety and alcoholism. *Biol. Psychiatry,* **2013**, *73*(8), 763-773. [http://dx.doi.org/10.1016/j.biopsych.2013.01.012] [PMID: 23485013]

[87] Uchida, S.; Hara, K.; Kobayashi, A.; Otsuki, K.; Yamagata, H.; Hobara, T.; Suzuki, T.; Miyata, N.; Watanabe, Y. Epigenetic status of Gdnf in the ventral striatum determines susceptibility and adaptation to daily stressful events. *Neuron,* **2011**, *69*(2), 359-372. [http://dx.doi.org/10.1016/j.neuron.2010.12.023] [PMID: 21262472]

[88] Wang, S.; Peretich, K.; Zhao, Y.; Liang, G.; Meng, Q.; Wei, H. Anesthesia-induced neurodegeneration in fetal rat brains. *Pediatr. Res.,* **2009**, *66*(4), 435-440. [http://dx.doi.org/10.1203/PDR.0b013e3181b3381b] [PMID: 20016413]

[89] Luo, F.; Hu, Y.; Zhao, W.; Zuo, Z.; Yu, Q.; Liu, Z.; Lin, J.; Feng, Y.; Li, B.; Wu, L.; Xu, L. Maternal exposure of rats to isoflurane during late pregnancy impairs spatial learning and memory in the offspring by up-regulating the expression of histone deacetylase 2. *PLoS One,* **2016**, *11*(8), e0160826. [http://dx.doi.org/10.1371/journal.pone.0160826] [PMID: 27536989]

[90] Albuquerque Filho, M.O.; de Freitas, B.S.; Garcia, R.C.; Crivelaro, P.C.; Schröder, N.; de Lima, M.N. Dual influences of early-life maternal deprivation on histone deacetylase activity and recognition memory in rats. *Neuroscience,* **2017**, *344*, 360-370. [http://dx.doi.org/10.1016/j.neuroscience.2016.12.054] [PMID: 28089578]

[91] Kim, M.S.; Akhtar, M.W.; Adachi, M.; Mahgoub, M.; Bassel-Duby, R.; Kavalali, E.T.; Olson, E.N.; Monteggia, L.M. An essential role for histone deacetylase 4 in synaptic plasticity and memory formation. *J. Neurosci.,* **2012**, *32*(32), 10879-10886. [http://dx.doi.org/10.1523/JNEUROSCI.2089-12.2012] [PMID: 22875922]

[92] Fitzsimons, H.L.; Schwartz, S.; Given, F.M.; Scott, M.J. The histone deacetylase HDAC4 regulates long-term memory in Drosophila. *PLoS One,* **2013**, *8*(12), e83903. [http://dx.doi.org/10.1371/journal.pone.0083903] [PMID: 24349558]

[93] Govindarajan, N.; Rao, P.; Burkhardt, S.; Sananbenesi, F.; Schlüter, O.M.; Bradke, F.; Lu, J.; Fischer, A. Reducing HDAC6 ameliorates cognitive deficits in a mouse model for Alzheimer's disease. *EMBO Mol. Med.,* **2013**, *5*(1), 52-63. [http://dx.doi.org/10.1002/emmm.201201923] [PMID: 23184605]

[94] Selenica, M.L.; Benner, L.; Housley, S.B.; Manchec, B.; Lee, D.C.; Nash, K.R.; Kalin, J.; Bergman, J.A.; Kozikowski, A.; Gordon, M.N.; Morgan, D. Histone deacetylase 6 inhibition improves memory and reduces total tau levels in a mouse model of tau deposition. *Alzheimers Res. Ther.,* **2014**, *6*(1), 12. [http://dx.doi.org/10.1186/alzrt241] [PMID: 24576665]

[95] Kakefuda, K.; Fujita, Y.; Oyagi, A.; Hyakkoku, K.; Kojima, T.; Umemura, K.; Tsuruma, K.; Shimazawa, M.; Ito, M.; Nozawa, Y.; Hara, H. Sirtuin 1 overexpression mice show a reference memory deficit, but not neuroprotection. *Biochem. Biophys. Res. Commun.,* **2009**, *387*(4), 784-788. [http://dx.doi.org/10.1016/j.bbrc.2009.07.119] [PMID: 19643082]

[96] Michán, S.; Li, Y.; Chou, M.M.; Parrella, E.; Ge, H.; Long, J.M.; Allard, J.S.; Lewis, K.; Miller, M.; Xu, W.; Mervis, R.F.; Chen, J.; Guerin, K.I.; Smith, L.E.; McBurney, M.W.; Sinclair, D.A.; Baudry, M.; de Cabo, R.; Longo, V.D. SIRT1 is essential for normal cognitive function and synaptic plasticity. *J. Neurosci.,* **2010**, *30*(29), 9695-9707. [http://dx.doi.org/10.1523/JNEUROSCI.0027-10.2010] [PMID: 20660252]

[97] Corbi, G.; Conti, V.; Scapagnini, G.; Filippelli, A.; Ferrara, N. Role of sirtuins, calorie restriction and physical activity in aging. *Front. Biosci. (Elite Ed.),* **2012**, *4*, 768-778. [Elite Ed]. [http://dx.doi.org/10.2741/e417] [PMID: 22201912]

[98] Guarente, L. Calorie restriction and sirtuins revisited. *Genes Dev.,* **2013**, *27*(19), 2072-2085. [http://dx.doi.org/10.1101/gad.227439.113] [PMID: 24115767]

[99] Heyward, F.D.; Walton, R.G.; Carle, M.S.; Coleman, M.A.; Garvey, W.T.; Sweatt, J.D. Adult mice maintained on a high-fat diet exhibit object location memory deficits and reduced hippocampal SIRT1 gene expression. *Neurobiol. Learn. Mem.,* **2012**, *98*(1), 25-32. [http://dx.doi.org/10.1016/j.nlm.2012.04.005] [PMID: 22542746]

[100] Griñan-Ferré, C.; Pérez-Cáceres, D.; Gutiérrez-Zetina, S.M.; Camins, A.; Palomera-Avalos, V.; Ortuño-Sahagún, D.; Rodrigo, M.T.; Pallàs, M. Environmental enrichment improves behavior, cognition, and brain functional markers in young senescence-accelerated prone mice (SAMP8). *Mol. Neurobiol.,* **2016**, *53*(4), 2435-2450. [http://dx.doi.org/10.1007/s12035-015-9210-6] [PMID: 26014386]

[101] Yin, X.; Gao, Y.; Shi, H.S.; Song, L.; Wang, J.C.; Shao, J.; Geng, X.H.; Xue, G.; Li, J.L.; Hou, Y.N. Overexpression of SIRT6 in the hippocampal CA1 impairs the formation of long-term contextual fear memory. *Sci. Rep.,* **2016**, *6*, 18982. [http://dx.doi.org/10.1038/srep18982] [PMID: 26732053]

[102] Fischer, A.; Sananbenesi, F.; Wang, X.; Dobbin, M.; Tsai, L.H. Recovery of learning and memory is associated with chromatin remodelling. *Nature,* **2007**, *447*(7141), 178-182. [http://dx.doi.org/10.1038/nature05772] [PMID: 17468743]

[103] Federman, N.; Fustiñana, M.S.; Romano, A. Histone acetylation is recruited in consolidation as a molecular feature of stronger memories. *Learn. Mem.,* **2009**, *16*(10), 600-606. [http://dx.doi.org/10.1101/lm.1537009] [PMID: 19794185]

[104] Bousiges, O.; Neidl, R.; Majchrzak, M.; Muller, M.A.; Barbelivien, A. Detection of histone acetylation levels in the dorsal hippocampus reveals early tagging on specific residues of H2B and H4 histones in response to learning. *PLoS One.,* **2013**, *8*(3), e57816.

[105] Intlekofer, K.A.; Berchtold, N.C.; Malvaez, M.; Carlos, A.J.; McQuown, S.C.; Cunningham, M.J.; Wood, M.A.; Cotman, C.W. Exercise and sodium butyrate transform a subthreshold learning event into long-term memory *via* a brain-derived neurotrophic factor-dependent mechanism. *Neuropsychopharmacology,* **2013**, *38*(10), 2027-2034. [http://dx.doi.org/10.1038/npp.2013.104] [PMID: 23615664]

[106] Zhao, Z.; Fan, L.; Frick, K.M. Epigenetic alterations regulate estradiol-induced enhancement of memory consolidation. *Proc. Natl. Acad. Sci. USA,* **2010**, *107*(12), 5605-5610. [http://dx.doi.org/10.1073/pnas.0910578107] [PMID: 20212170]

[107] Zhao, Z.; Fan, L.; Fortress, A.M.; Boulware, M.I.; Frick, K.M. Hippocampal histone acetylation regulates object recognition and the estradiol-induced enhancement of object recognition. *J. Neurosci.,* **2012**, *32*(7), 2344-2351. [http://dx.doi.org/10.1523/JNEUROSCI.5819-11.2012] [PMID: 22396409]

[108] Zhong, T.; Ren, F.; Huang, C.S.; Zou, W.Y.; Yang, Y.; Pan, Y.D.; Sun, B.; Wang, E.; Guo, Q.L. Swimming exercise ameliorates neurocognitive impairment induced by neonatal exposure to isoflurane and enhances hippocampal histone acetylation in mice. *Neuroscience,* **2016**, *316*, 378-388. [http://dx.doi.org/10.1016/j.neuroscience.2015.12.049] [PMID: 26748054]

[109] Bousiges, O.; Vasconcelos, A.P.; Neidl, R.; Cosquer, B.; Herbeaux, K.; Panteleeva, I.; Loeffler, J.P.; Cassel, J.C.; Boutillier, A.L. Spatial memory consolidation is associated with induction of several lysine-acetyltransferase (histone acetyltransferase) expression levels and H2B/H4 acetylation-dependent transcriptional events in the rat hippocampus. *Neuropsychopharmacology,* **2010**, *35*(13), 2521-2537. [http://dx.doi.org/10.1038/npp.2010.117] [PMID: 20811339]

[110] Lubin, F.D.; Sweatt, J.D. The IkappaB kinase regulates chromatin structure during reconsolidation of conditioned fear memories. *Neuron,* **2007**, *55*(6), 942-957. [http://dx.doi.org/10.1016/j.neuron.2007.07.039] [PMID: 17880897]

[111] Bredy, T.W.; Wu, H.; Crego, C.; Zellhoefer, J.; Sun, Y.E.; Barad, M. Histone modifications around individual BDNF gene promoters in prefrontal cortex are associated with extinction of conditioned fear. *Learn. Mem.,* **2007**, *14*(4), 268-276. [http://dx.doi.org/10.1101/lm.500907] [PMID: 17522015]

[112] Hendrickx, A.; Pierrot, N.; Tasiaux, B.; Schakman, O.; Brion, J.P.; Kienlen-Campard, P.; Smet, C.D.; Octave, J.N. Epigenetic induction of EGR-1 expression by the amyloid precursor protein during exposure to novelty. *PLoS One.,* **2013**, *8*(9), e74305. [http://dx.doi.org/10.1371/journal.pone.0074305]

[113] Berger, S.L. The complex language of chromatin regulation during transcription. *Nature,* **2007**, *447*(7143), 407-412. [http://dx.doi.org/10.1038/nature05915] [PMID: 17522673]

[114] Kirmizis, A.; Santos-Rosa, H.; Penkett, C.J.; Singer, M.A.; Vermeulen, M.; Mann, M.; Bähler, J.; Green, R.D.; Kouzarides, T. Arginine methylation at histone H3R2 controls deposition of H3K4 trimethylation. *Nature,* **2007**, *449*(7164), 928-932. [http://dx.doi.org/10.1038/nature06160] [PMID: 17898715]

[115] Ng, S.S.; Yue, W.W.; Oppermann, U.; Klose, R.J. Dynamic protein methylation in chromatin biology. *Cell. Mol. Life Sci.,* **2009**, *66*(3), 407-422. [http://dx.doi.org/10.1007/s00018-008-8303-z] [PMID: 18923809]

[116] Yi, S.H.; He, X.B.; Rhee, Y.H.; Park, C.H.; Takizawa, T.; Nakashima, K.; Lee, S.H. Foxa2 acts as a co-activator potentiating expression of the Nurr1-induced DA phenotype *via* epigenetic regulation. *Development,* **2014**, *141*(4), 761-772. [http://dx.doi.org/10.1242/dev.095802] [PMID: 24496614]

[117] Gupta, S.; Kim, S.Y.; Artis, S.; Molfese, D.L.; Schumacher, A.; Sweatt, J.D.; Paylor, R.E.; Lubin, F.D. Histone methylation regulates memory formation. *J. Neurosci.,* **2010**, *30*(10), 3589-3599. [http://dx.doi.org/10.1523/JNEUROSCI.3732-09.2010] [PMID: 20219993]

[118] Kerimoglu, C.; Agis-Balboa, R.C.; Kranz, A.; Stilling, R.; Bahari-Javan, S.; Benito-Garagorri, E.; Halder, R.; Burkhardt, S.; Stewart, A.F.; Fischer, A. Histone-methyltransferase MLL2 (KMT2B) is required for memory formation in mice. *J. Neurosci.,* **2013**, *33*(8), 3452-3464. [http://dx.doi.org/10.1523/JNEUROSCI.3356-12.2013] [PMID: 23426673]

[119] Zhang, J.; Ji, F.; Liu, Y.; Lei, X.; Li, H.; Ji, G.; Yuan, Z.; Jiao, J. Ezh2 regulates adult hippocampal neurogenesis and memory. *J. Neurosci.,* **2014**, *34*(15), 5184-5199. [http://dx.doi.org/10.1523/JNEUROSCI.4129-13.2014] [PMID: 24719098]

[120] Jakovcevski, M.; Ruan, H.; Shen, E.Y.; Dincer, A.; Javidfar, B.; Ma, Q.; Peter, C.J.; Cheung, I.; Mitchell, A.C.; Jiang, Y.; Lin, C.L.; Pothula, V.; Stewart, A.F.; Ernst, P.; Yao, W.D.; Akbarian, S. Neuronal Kmt2a/Mll1 histone methyltransferase is essential for prefrontal synaptic plasticity and working memory. *J. Neurosci.,* **2015**, *35*(13), 5097-5108. [http://dx.doi.org/10.1523/JNEUROSCI.3004-14.2015] [PMID: 25834037]

[121] Akbarian, S.; Ruehl, M.G.; Bliven, E.; Luiz, L.A.; Peranelli, A.C.; Baker, S.P.; Roberts, R.C.; Bunney, W.E., Jr; Conley, R.C.; Jones, E.G.; Tamminga, C.A.; Guo, Y. Chromatin alterations associated with down-regulated metabolic gene expression in the prefrontal cortex of subjects with schizophrenia. *Arch. Gen. Psychiatry,* **2005**, *62*(8), 829-840. [http://dx.doi.org/10.1001/archpsyc.62.8.829] [PMID: 16061760]

[122] Tsankova, N.M.; Berton, O.; Renthal, W.; Kumar, A.; Neve, R.L.; Nestler, E.J. Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. *Nat. Neurosci.,* **2006**, *9*(4), 519-525. [http://dx.doi.org/10.1038/nn1659] [PMID: 16501568]

[123] Kennedy, A.J.; Sweatt, J.D. Drugging the methylome: DNA methylation and memory. *Crit. Rev. Biochem. Mol. Biol.,* **2016**, *51*(3), 185-194. [http://dx.doi.org/10.3109/10409238.2016.1150958] [PMID: 26915423]

[124] Miller, C.A.; Campbell, S.L.; Sweatt, J.D. DNA methylation and histone acetylation work in concert to regulate memory formation

and synaptic plasticity. *Neurobiol. Learn. Mem.,* **2008**, *89*(4), 599-603. [http://dx.doi.org/10.1016/j.nlm.2007.07.016] [PMID: 17881251]

[125] Konar, A.; Singh, P.; Thakur, M.K. Age-associated cognitive decline: Insights into molecular switches and recovery avenues. *Aging Dis.,* **2016**, *7*(2), 121-129. [http://dx.doi.org/10.14336/AD.2015.1004] [PMID: 27114845]

[126] Thakur, M.K.; Konar, A.; Kumar, D.; Baghel, M.S.; Singh, P. Recovery of age-related memory loss: Hopes and challenges. *Top. Biomed. Gerontol.,* **2016**, , 267-278.

[127] Haettig, J.; Stefanko, D.P.; Multani, M.L.; Figueroa, D.X.; McQuown, S.C.; Wood, M.A. HDAC inhibition modulates hippocampus-dependent long-term memory for object location in a CBP-dependent manner. *Learn. Mem.,* **2011**, *18*(2), 71-79. [http://dx.doi.org/10.1101/lm.1986911] [PMID: 21224411]

[128] Fontán-Lozano, A.; Romero-Granados, R.; Troncoso, J.; Múnera, A.; Delgado-García, J.M.; Carrión, A.M. Histone deacetylase inhibitors improve learning consolidation in young and in KA-induced-neurodegeneration and SAMP-8-mutant mice. *Mol. Cell. Neurosci.,* **2008**, *39*(2), 193-201. [http://dx.doi.org/10.1016/j.mcn.2008.06.009] [PMID: 18638560]

[129] Schroeder, F.A.; Lin, C.L.; Crusio, W.E.; Akbarian, S. Antidepressant-like effects of the histone deacetylase inhibitor, sodium butyrate, in the mouse. *Biol. Psychiatry,* **2007**, *62*(1), 55-64. [http://dx.doi.org/10.1016/j.biopsych.2006.06.036] [PMID: 16945350]

[130] Villain, H.; Florian, C.; Roullet, P. HDAC inhibition promotes both initial consolidation and reconsolidation of spatial memory in mice. *Sci. Rep.,* **2016**, *6*, 27015. [http://dx.doi.org/10.1038/srep27015] [PMID: 27270584]

[131] Lin, X.F.; Han, Y.Q.; Li, H.L.; Zhao, Y.P.; Fei, X.J.; Sheng, J.X.; Lu, H.H.; Liu, S.; Zhang, L. SAHA attenuates sevoflurane-induced learning and memory impairments in fetal mice. *Genet. Mol. Res.,* **2014**, *13*(4), 10769-10778. [http://dx.doi.org/10.4238/2014.December.18.18] [PMID: 25526197]

[132] Dagnas, M.; Guillou, J.L.; Prévôt, T.; Mons, N. HDAC inhibition facilitates the switch between memory systems in young but not aged mice. *J. Neurosci.,* **2013**, *33*(5), 1954-1963. [http://dx.doi.org/10.1523/JNEUROSCI.3453-12.2013] [PMID: 23365234]

[133] Vecsey, C.G.; Hawk, J.D.; Lattal, K.M.; Stein, J.M.; Fabian, S.A.; Attner, M.A.; Cabrera, S.M.; McDonough, C.B.; Brindle, P.K.; Abel, T.; Wood, M.A. Histone deacetylase inhibitors enhance memory and synaptic plasticity *via* CREB:CBP-dependent transcriptional activation. *J. Neurosci.,* **2007**, *27*(23), 6128-6140. [http://dx.doi.org/10.1523/JNEUROSCI.0296-07.2007] [PMID: 17553985]

[134] Dagnas, M.; Micheau, J.; Decorte, L.; Beracochea, D.; Mons, N. Post-training, intrahippocampal HDAC inhibition differentially impacts neural circuits underlying spatial memory in adult and aged mice. *Hippocampus,* **2015**, *25*(7), 827-837. [http://dx.doi.org/10.1002/hipo.22406] [PMID: 25530477]

[135] Gräff, J.; Tsai, L.H. The potential of HDAC inhibitors as cognitive enhancers. *Annu. Rev. Pharmacol. Toxicol.,* **2013**, *53*, 311-330. [http://dx.doi.org/10.1146/annurev-pharmtox-011112-140216] [PMID: 23294310]

[136] Kwon, H.S.; Huang, B.; Ho Jeoung, N.; Wu, P.; Steussy, C.N.; Harris, R.A. Retinoic acids and trichostatin A (TSA), a histone deacetylase inhibitor, induce human pyruvate dehydrogenase kinase 4 (PDK4) gene expression. *Biochim. Biophys. Acta,* **2006**, *1759*(3-4), 141-151. [http://dx.doi.org/10.1016/j.bbaexp.2006.04.005] [PMID: 16757381]

[137] Subramanian, S.; Bates, S.E.; Wright, J.J.; Espinoza-Delgado, I.; Piekarz, R.L. Clinical toxicities of histone deacetylase inhibitors. *Pharmaceuticals (Basel),* **2010**, *3*(9), 2751-2767. [http://dx.doi.org/10.3390/ph3092751] [PMID: 27713375]

[138] Gupta-Agarwal, S.; Franklin, A.V.; Deramus, T.; Wheelock, M.; Davis, R.L.; McMahon, L.L.; Lubin, F.D. G9a/GLP histone lysine dimethyltransferase complex activity in the hippocampus and the entorhinal cortex is required for gene activation and silencing during memory consolidation. *J. Neurosci.,* **2012**, *32*(16), 5440-5453. [http://dx.doi.org/10.1523/JNEUROSCI.0147-12.2012] [PMID: 22514307]

[139] Snigdha, S.; Prieto, G.A.; Petrosyan, A.; Loertscher, B.M.; Dieskau, A.P.; Overman, L.E.; Cotman, C.W. H3K9me3 inhibition improves memory, promotes spine formation, and increases BDNF levels in the aged hippocampus. *J. Neurosci.,* **2016**, *36*(12), 3611-3622. [http://dx.doi.org/10.1523/JNEUROSCI.2693-15.2016] [PMID: 27013689]