Experimental Neurology 268 (2015) 30–36

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Review

The role of epigenetic regulation in learning and memory

Ji-Song Guan *, Hong Xie, XinLu Ding

Tsinghua-Peking Center for Life Sciences, MOE Key Laboratory of Protein Sciences, Center for Epigenetics and Chromatin Biology, School of Life Sciences, Tsinghua University, Beijing 100084, China

ARTICLE INFO

Article history:
Received 26 February 2014
Revised 26 April 2014
Accepted 2 May 2014
Available online 14 May 2014

Keywords:
Epigenetics
Synaptic plasticity
Memory formation
Memory maintenance

ABSTRACT

The formation of long-term memory involves a series of molecular and cellular changes, including gene transcription, protein synthesis and synaptic plasticity dynamics. Some of these changes arise during learning and are subsequently retained throughout life. 'Epigenetic' regulation, which involves DNA methylation and histone modifications, plays a critical role in retaining long-term changes in post-mitotic cells. Accumulating evidence suggests that the epigenetic machinery might regulate the formation and stabilization of long-term memory in two ways: a 'gating' role of the chromatin state to regulate activity-triggered gene expression; and a 'stabilizing' role of the chromatin state to maintain molecular and cellular changes induced by the memory-related event. The neuronal activation regulates the dynamics of the chromatin status under precise timing, with subsequent alterations in the gene expression profile. This review summarizes the existing literature, focusing on the involvement of epigenetic regulation in learning and memory. We propose that the identification of different epigenetic regulators and signaling pathways involved in memory-related epigenetic regulations will provide mechanistic insights into the formation of long-term memory.

Contents

Introduction

Learning and the formation of new memories require the structural and functional remodeling of synapses (Martin et al., 2000; Lamprecht and LeDoux, 2004) through tightly regulated cellular and molecular regulation machines. In response to a specific pattern of neuronal activity, synaptic strength undergoes long-lasting reduction or enhancement, known as long-term depression (LTD) and long-term potentiation (LTP), underlying the cellular mechanism of memory formation (Martin et al., 2000; Cooper, 2005; Bliss and Collingridge, 1993). At the molecular level, the neuronal activation triggers modification, trafficking and new protein synthesis of memory-related molecules through intracellular signaling cascades (Dash et al., 2007), gene transcription and protein synthesis (Davis and Squire, 1984; Barondes and Jarvik, 1964). However, it is still unclear how these changes in memory-related molecules are maintained in the long term in supporting various cellular events during memory formation, consolidation and retrieval.

What is the molecular mechanism involved in regulating memory formation and maintenance? In this review, we discuss the role of epigenetic modifications in regulating the cellular processes involved in neuronal memories. Epigenetic regulation has been widely recognized as a mechanism for making stable changes in the cellular status during development and for some heritable phenomena that require cellular memory (Ringrose and Paro, 2004; Levenson and Sweatt, 2005; Lipsky, 2013). Recent studies revealed the critical role of epigenetic

* Corresponding author at: Medical School Building D206, School of Life Sciences, Tsinghua University, Beijing 100084, China.
E-mail address: jsguan@mail.tsinghua.edu.cn (J.-S. Guan).

http://dx.doi.org/10.1016/j.expneurol.2014.05.006
0014-4886/

regulation in synaptic plasticity and memory (Kaas et al., 2013; Liu et al., 2009; Lubin et al., 2008; Rudenko et al., 2013; Stefanko et al., 2009; Sui et al., 2012; Yu et al., 2011; Guan et al., 2009). The types of epigenetic modifiers and their metabolic dynamics are specifically regulated in particular brain regions (Baker-Andresen et al., 2013; Gupta-Agarwal et al., 2012; Levenson et al., 2004, 2006; Mori et al., 2013; Miller et al., 2008; Bousiges et al., 2013; Chwang et al., 2006). During learning, different epigenetic regulators work in concert to converge the upstream cascade signaling and manipulate downstream gene transcription with precise timing. We propose that epigenetic regulation has two functions in learning and memory formation: as a 'gating' mechanism that enables gene expression changes that are important for learning, and a 'stabilizing' mechanism, which enables the maintenance of gene expression changes that is important for memory consolidation. We hypothesize that such dual roles of epigenetic regulation allow cellular memory to form the basis of circuitry memory, where information regarding different properties is stored in discrete neuronal cells (Xie et al., 2014).

Epigenetic modifications in memory formation

Nucleosomes, the basic units used by eukaryotic chromatin to pack huge genomes into the cell nucleus, contain an octamer of histone proteins, which are two pairs of the core histones H2A, H2B, H3 and H4 surrounded by 147 bp of DNA. The protruding N-terminal tails of the histone proteins, which are known to interact with nucleosomal DNA, undergo post-translational modifications (Jiang et al., 2008). As summarized in Fig. 1, various epigenetic modifications change the status of chromatin, thereby affecting gene transcription. Histone acetylation usually enhances transcription, because the acetyl group on lysine releases compacted DNA to be accessible to the transcription machinery, facilitating transcriptional initiation and elongation (Shahbazian and Grunstein, 2007). The addition of the acetyl group is catalyzed by histone acetyltransferases (HATs). The removal of the acetyl group is mediated by histone deacetylases (HDACs). Histone phosphorylation, which is tightly associated with histone acetylation, affects transcription in a histone microenvironment-dependent manner (Chwang et al., 2006; Banerjee and Chakravarti, 2011). The histone tail is usually phosphorylated by nuclear kinase and dephosphorylated by protein phosphatase (Brami-Cherrier et al., 2009; Koshibu et al., 2009). Another important histone modification is histone methylation, which is related to either transcription activation or repression (Kouzarides, 2007). The histone methylation is catalyzed by the SET domain of histone methyltransferases (HMTs) and removed by histone demethylases (HDMs), such as LSD1 and JMJD2 (Fuke et al., 2004; Shin and Janknecht, 2007). In addition to post-translational modifications on histones, other epigenetic processes include DNA methylation, non-coding RNAs, prions and prion-like phenomena, chromosomal position effects and Polycomb mechanisms. DNA methylation preferentially occurs on cytosine nucleotides adjacent to guanine nucleotides by adding a methyl group to the five prime positions of the cytosine base via DNA methyltransferases (DNMTs) (Turker, 1999; Bird, 2002; Goll and Bestor, 2005), including DNMT3a and DNMT3b for de novo synthesis, and DNMT1 for maintenance. Although the mechanism of DNA demethylation is still unclear, the recent discovery of ten-eleven translocation (TET) family enzymes suggests the existence of a demethylation pathway through oxidizing 5-methylcytosine to 5-hydroxymethylcytosine, followed by thymine DNA glycosylase (TDG)-mediated base excision repair or passive excision by DNA repair (Kohli and Zhang, 2013). These epigenetic modifications are critical for transcriptional regulation, as well as long-lasting cellular status changes in development and heritable phenomena.

Compelling evidence from pharmacological and genetic studies has revealed that various epigenetic regulators may be involved in learning and memory (Table 1). One of the most well-demonstrated epigenetic modifications is histone acetylation. The administration of trichostatin A and sodium butyrate as global HDAC inhibitors (HDACi) enhanced long-term memory but not short-term memory, whereas genetic disruption of HATs impaired the formation of long-term memory

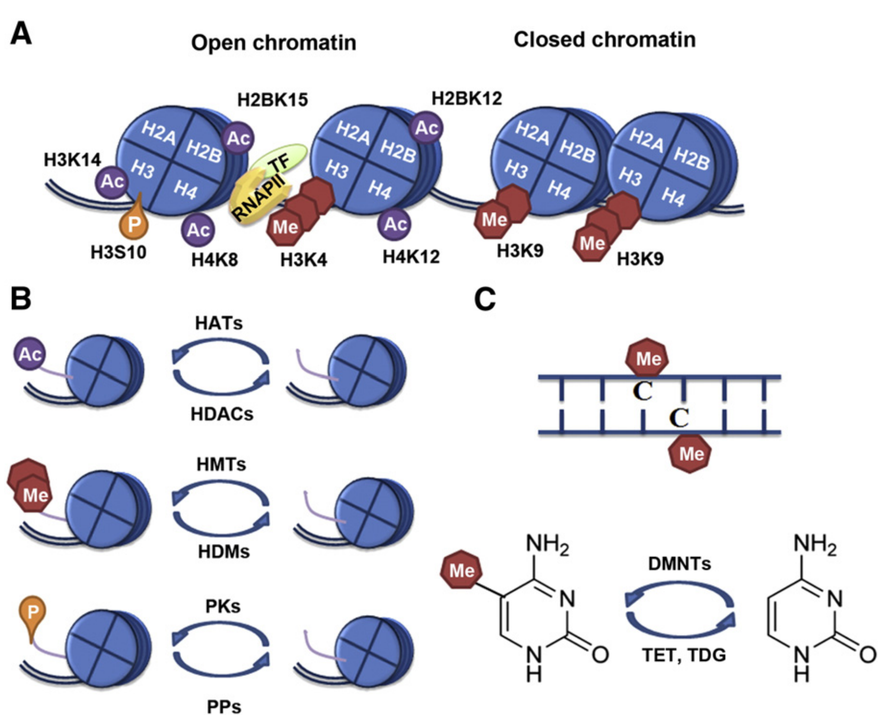

Fig. 1. Illustration of epigenetic modification involved in learning and memory. (A) 146 bp of DNA coiled around histone octamers forms chromatin, which can be turned in to open state or closed state by different combinations of histone modifications. In an open state, transcriptional machinery is accessible to the chromatin, while in a closed state, the machinery is prevented from binding to the gene region. (B) (C) Epigenetic modification enzymes catalyze the addition and removal of modification groups. HATs catalyze the addition of acetyl group and HDACs remove it. HMTs and HDMs are responsible for the addition and removal of methyl group, respectively. The histone tail is phosphorylated by PPs and dephosphorylated by PKs. Finally, the DNMTs add a methyl group to the cytosine base while the active DNA demethylation is conducted by TETs or through TDG-mediated base excision repair. CH3, methyl group; Ac, acetyl group; P, phosphoryl group; RNAPII, RNA polymerase II; TF, transcription factor.

Table 1
The implication of epigenetic regulators in learning and memory.

Classification	Regulator	Effect	Refs.
HATs	CBP/P300	Knockout of CBP in dorsal CA1 or p300 in superficial layers of the cortex and CA1 impairs long-term potentiation and long-term memory for contextual fear and object recognition. Intra-LA inhibition of CBP/P300 activity impairs fear memory consolidation and reconsolidation in the LA.	Barrett et al. (2011), Maddox et al. (2013) and Oliveira et al. (2011)
	PCAF	PCAF-KO mice show impaired learning and memory.	Maurice et al. (2008)
HDACs	HDAC1	Overexpression of HDAC1 in the hippocampus affects the extinction of contextual fear memories.	Bahari-Javan et al. (2012)
	HDAC2	Neuron-specific overexpression of HDAC2 decreased dendritic spine density, synapse number, synaptic plasticity and memory formation; loss of HDAC2 increases synapse number, improves associative learning and extinction rate of conditioned fear responses.	Guan et al. (2009) and Morris et al. (2013)
	HDAC3	Genetic deletions and pharmacologic inhibition of Hdac3 in area CA1 of the dorsal hippocampus enhanced long-term memory; Hdac3 deletion in nucleus accumbens enhance CPP acquisition; generally pharmacologic inhibition of Hdac3 enhances extinction of an established CPP.	Rogge et al. (2013), Malvaez et al. (2013) and McQuown et al. (2011)
	HDAC4	Selective deletion of Hdac4 in brain impairs long-term synaptic plasticity and hippocampal-dependent learning and memory.	Kim et al. (2012)
	SIRT1	Loss of function of SIRT1 impairs memory and synaptic plasticity; Knockout of SIRT1 affects in both short and long-term hippocampus-dependent memory.	Michan et al. (2010) and Gao et al. (2010)
HMTs	EHMT	Both short- and long-term courtship memories are impaired in EHMT mutant flies.	Kramer et al. (2011)
	G9a/GLP	Inhibition of G9a/GLP in the EC enhances contextual fear conditioning.	Gupta-Agarwal et al. (2012)
	Mll	Knockout of mll2/kmt2b gene in forebrain impairs hippocampus-dependent memory formation.	Kerimoglu et al. (2013)
DNMTs	DNMT1/DNMT3a	Dnmt1 and Dnmt3a double knockout mice show abnormal long-term plasticity in CA1 region and impaired learning and memory.	Feng et al. (2010)
PPs	PP1	Genetical inhibition of PP1 or nuclear pool of PP1 in hippocampal neurons enhances learning and memory.	Graff et al. (2010) and Genoux et al. (2002)
Others	TET1	Expression of TET1 catalytically inactive mutant impairs contextual fear memory; Tet1KO mice exhibited abnormal hippocampal long-term depression and impaired memory extinction.	Kaas et al. (2013) and Rudenko et al. (2013)
	Gadd45b	Gadd45bKO mice show selective enhancements in hippocampal-dependent memory and synaptic plasticity	Sultan et al. (2012)

(Vecsey et al., 2007; Yeh et al., 2004; Alarcon et al., 2004; Barrett et al., 2011). It has been found that HDAC2 is one of the major regulators involved in the regulation of long-term memory. Specifically, mice over-expressing HDAC2 showed impaired LTP and memory, while HDAC2-knockout mice showed enhanced synaptic plasticity (Guan et al., 2009). Other HDACs might also be involved in this process. The inhibition of HDAC3 enhanced behavior performance in fear memory formation and the extinction of drug-seeking behavior (Rogge et al., 2013; Malvaez et al., 2013; McQuown et al., 2011). In contrast to HDAC2- and HDAC3-deficient mice, mice with brain-specific knockout of HDAC4 showed significant memory deficits (Kim et al., 2012). The inhibition or knockout of SIRT1, the class III HDAC, led to the deficits in both short-term memory and long-term memory (Michan et al., 2010; Gao et al., 2010). Therefore, the HDAC regulation on memory is type-specific, suggesting that the specificity of epigenetic processes on different genomic loci resulting from various regulatory processes might have different impacts. In addition to HDACs, HATs such as the CREB-binding protein (CBP) and E1A-binding protein (p300) are also known to regulate long-term memory. Importantly, the disruptions of those epigenetic regulators have been associated with the pathogenesis of Alzheimer's disease (Caccamo et al., 2010; Duclot et al., 2010; Maddox et al., 2013).

Histone methylation is another modification tightly associated with learning and memory. Forebrain-specific knockout of the histone methyltransferase myeloid/lymphoid or mixed-lineage leukemia 2 (mll2/kmt2b) gene, which specifically regulates H3K4 di- and tri-methylation, led to impaired learning function (Kerimoglu et al., 2013). Another methyltransferase, Ehmt, which catalyzes H3K9 dimethylation, has been reported to regulate courtship memory in *Drosophila* (Kramer et al., 2011). Additionally, the inhibition of the G9a/GLP complex in the hippocampus affected long-term memory formation in mice, while the inhibition of G9a in the entorhinal cortex (EC) interfered with memory consolidation (Gupta-Agarwal et al., 2012). Therefore, both histone methylation and acetylation are critical regulators of memory formation.

In addition to histone modifications, DNA methylation has also been associated with memory formation and maintenance. The inhibition of DNA methyltransferases resulted in memory suppression and impaired memory consolidation (Lubin et al., 2008; Miller et al., 2008; Miller and Sweatt, 2007). Additionally, Dnmt1 and Dnmt3a double-knockout mice had deficits in synaptic plasticity, learning and memory (Feng et al., 2010). Importantly, it has been found that DNA methylation underwent activity-dependent dynamics in the hippocampi of adult mouse brains, which are critical for the proper encoding of external stimuli in the brain (Guo et al., 2011). The overexpression of the DNA methylation regulator TET1 in the hippocampus impaired memory formation (Kaas et al., 2013), whereas TET1 knockout mice only showed abnormal memory extinction, with no memory formation defects (Rudenko et al., 2013).

Taken together, the accumulating evidence has revealed not only the critical role of epigenetic regulators in learning and memory but also a complicated and specific epigenetic regulatory machine, which encodes and maintains a molecular network to achieve accurate and stable transcriptional regulation for functional alterations.

Furthermore, the cellular memory events within neuronal cells during memory formation might be related to and even constitute the circuit memory by which sensory information is stored within the brain circuit. Although it has been reported that neuronal activation triggers general changes in epigenetic markers, the modified markers are different during various memory tasks and at different time points of the same task, suggesting the specificity of epigenetic regulation in various processes of memory formation. For example, acetylation of histone H3 is generally enhanced after several hippocampus-dependent behavioral paradigms, such as contextual fear conditioning and the water maze (Levenson et al., 2004; Bousiges et al., 2013; Alarcon et al., 2004; Korzus et al., 2004). By contrast, histone H4 but not H3 shows significant enhancement in acetylation during latent inhibition tasks (Levenson et al., 2004). Therefore, epigenetic regulations during the processes of memory formation and consolidation might be specific according to the specific neuronal process. Additionally, different brain circuits commonly share the same epigenetic regulation mechanism for the same task and time point. The increase in H3K4me3 and H3K9me2 has been observed not only in the CA1 region of the hippocampus but also in EC (Gupta-Agarwal et al., 2012; Chwang et al., 2006; Gupta et al., 2010), implying that epigenetic regulation is commonly used in different brain areas. Therefore, the epigenetic modifications were observed in different states of memory processing in animals, underlying different molecular events to achieve specific and enduring memories within the brain circuit.

'Gating' mechanism of epigenetic regulation in memory formation

It has been known for decades that new protein synthesis is required for new memory formation (Davis and Squire, 1984). During memory formation, epigenetic regulation might act as a 'Gating' mechanism to allow for downstream gene expression changes in response to the environmental stimuli. Sensory stimuli trigger well-defined signal cascades, starting with the activation of the N-methyl-D-aspartate acid (NMDA) receptor. Several signaling pathways, such as the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) and the PKA pathway, transmit the activation signal transduction to the nucleus. In the nucleus, the signal-dependent phosphorylation of the CRE binding protein (CREB) activates the transcription of essential memory genes (Loebrich and Nedivi, 2009). This process produces new synaptic proteins and associated functional proteins, which allows long-lasting synaptic remodeling for memory circuit formation (Fig. 2). Evidence shows that the status of chromatin conformation before and during the stimuli is critical for the activity-triggered gene expression (Guan et al., 2009). Thus, specific epigenetic regulations, which increase or dampen the activity-dependent gene expression, modulate the amount of protein expression essential for neuronal circuit modification to facilitate or block the sensory stimulus-induced changes in the epigenetically regulated neuron, resembling the 'Gating' of memory formation in neurons or neuron ensembles.

Memory-related chromatin regulation is enriched for specific genes, especially the promoter area of synaptic plasticity-related genes. For instance, HDAC2 is significantly enriched at the promoters of genes related to synaptic plasticity. HDAC2KO mice showed increased acetylation of histones H3 and H4 at the promoter regions of BDNF, zif268, fos and GLUR1 (Guan et al., 2009). Tet1 knockout mice have robust decreases in the expression levels of neuronal activity-regulated genes, such as Npas4, Arc and c-fos (Rudenko et al., 2013). A lack of HDAC3 prolongs the learning-induced expression of c-fos and Nr4a2 (McQuown et al., 2011). Both HDAC2- and HDAC3-deficient mice showed alternations in memory formation. Thus, epigenetic regulators target specific memory-related genes.

Furthermore, the stimuli-induced neuronal activation triggered the modification on some epigenetic markers. For example, the contextual fear conditioned learning induced histone H3 acetylation and phosphorylation on BDNF promoters. Evidence showed that such activity-dependent epigenetic remodeling is induced by upstream classic signal cascades, as NMDA receptor inhibitor or ERK inhibitor, which impaired the formation of new memory, prevented the learning induced epigenetic changes (Levenson et al., 2004). Similar to the histone acetylation, learning also induced the expression of DNMT3a, the DNA methylation regulator. The learning induced expression of DNMT3a is suppressed by inhibition of NMDA receptor and ERK (Monsey et al., 2011). In addition to the NMDA–ERK pathway, other memory-related signaling pathways are also involved in epigenetic regulation: In response to learning, the CREB co-activator CBP/P300, a histone acetyltransferase, was phosphorylated through the Ca^{2+}/calmodulin-dependent kinase-IV (CamKIV), ribosomal protein S6 kinase-2 (RSK2) and mitogen-activated protein kinase (MAPK) pathways (Impey et al., 2002; Wang et al., 2003; Gusterson et al., 2002); the learning-induced activation of L-type Ca^{2+} channels and cAMP-dependent protein kinase A is sufficient to induce acetylation in histone 3 (Li et al., 2004).

In addition, the coupling between epigenetic changes and activity-triggered signaling pathway activation may amplify the initial signal. For instance, BDNF is a well-known neurotrophin that is involved in neuroplasticity and learning and memory (Choi et al., 2010; Psotta et al., 2013; Park and Poo, 2012). It has been reported that the promoter of BDNF undergoes dynamic chromatin remodeling. Interestingly, the activation of the Trk receptor by BDNF depolarizes the neuron and increases the phosphorylation of NMDAR (Figurov et al., 1996). At the same time, BDNF activation leads to the dissociation of HDAC2 from the chromatin by nitrosylation on cysteines 262 and 274 of HDAC2 (Nott et al., 2008). Both of the effects result in the increased histone acetylation of the promoter regions of the BDNF gene and other plasticity-related genes to largely increase gene expression by forming a positive feedback loop, maximizing the circuit changes during memory formation.

In addition to targeting genes, the epigenetic regulators might also work by modifying non-histone proteins. The NF-κB pathway is known to be associated with memory formation (Kaltschmidt et al., 2006; Freudenthal et al., 2005; Kassed et al., 2002). The P65/RelA subunit of NF-κB can be either methylated by Set9 at K37 and K314/315, or acetylated by CBP at K310 and K314/315, regulating the DNA binding abilities of NF-κB (Ea and Baltimore, 2009; Yang et al., 2009, 2010; Rothgiesser et al., 2010). Moreover, HDAC2 showed nitrosylation on cysteines 262 and 274, which was triggered by neuronal activation

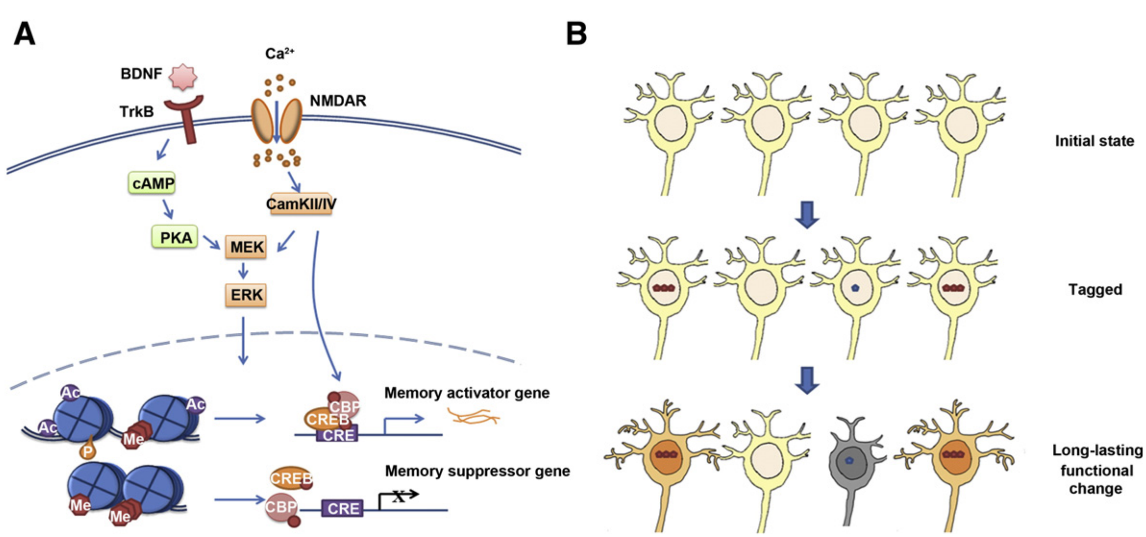

Fig. 2. (A) A model for epigenetic 'gating' of neuronal activity induced transcription in learning and memory. Task induced activation of specific post-synaptic receptor activates downstream signal cascades, which lead to the epigenetic modification changes in memory-related gene region. The open epigenetic status allows the neuronal activity to trigger long-term potentiation (LTP), synaptic and structural plasticity. (B) A model for 'stabilization' shows that specific neuron population is activated by environmental stimuli, transformed from the 'initial state' to 'tagged state', with different epigenetic markers on plasticity-related genes. The 'tagged' neurons showed different cellular properties from the 'initial state', such as the potential of plastic changes, protecting the intact circuit of specific memory traces from disruption by subsequent events. These long-lasting epigenetic modifications maintain the stabilization of long-term memory.

and led to a hyperacetylation-related increase of gene expression in cultured neurons (Nott et al., 2008). Therefore, neuronal activation, as the trigger of new memory formation, is tightly associated with gene transcription and post-transcriptional regulation on epigenetic regulators. Preventing such changes in the epigenetic markers and gene expression leads to the failure of circuit modification and memory formation.

Importantly, such epigenetic regulation in memory is precisely regulated in a time-sensitive window. Histone H3 only showed increased acetylation 1 h after contextual fear conditioning, and not 24 h later. A similar phenomenon was reported for H3K9me2 (Gupta-Agarwal et al., 2012; Levenson et al., 2004). Such precise timing of epigenetic regulation during learning appears to be critical for memory formation. The inhibition of DMNT impaired fear memory only if infused immediately after training. The HDACi only improves memory retrieval at day 30 if applied during early exposure (Lubin et al., 2008; Miller et al., 2008; Lesburgueres et al., 2011). Similarly, the effect of DNMT inhibition and HDACi on memory consolidation is observed only if infusion is conducted 60 min after memory reactivation, but not 6 h after the reactivation (Maddox and Schafe, 2011). In general, epigenetic changes are required at specific time points to encode or modify the memory traces.

The 'stabilization' mechanism of epigenetic regulation for long-term memory

Learning-induced protein synthesis is transient, while memories stored in our brain usually last for months or years, or even a lifetime. Owing to the rapid turnover of proteins, the newly synthesized proteins might not underlie the long-lasting character of long-term memory. In fact, epigenetic regulation might also take on the role of 'stabilization' for long-term memory, in which specific epigenetic markers might maintain the important gene expression changes for memory consolidation. These markers that achieve the role of 'stabilization' are different from those that perform the role of 'gating'. Different epigenetic regulatory machines and marker dynamics are employed in those two conditions. Recent work showed that contextual fear conditioning induced rapid and transient increases in DNMT expression in the hippocampus within 24 h (Miller et al., 2008; Gupta et al., 2010). Surprisingly, a long-lasting increase of DNA methylation in the specific gene promoter region in the medial prefrontal cortex (mPFC) was observed 30 days after fear conditioning, while the administration of a DNMT inhibitor on day 30 in the mPFC impaired memory recall (Miller et al., 2010). Additionally, DNA demethylation is required for memory extinction. TET1 knockout mice showed impaired memory extinction, and the lack of TET1 in the hippocampus blocked memory recall (Rudenko et al., 2013). These results implicated that keeping the marker of DNA methylation changes could be essential for the proper recall of long-term memory. However, those reports need to be further validated by other research groups, and the cellular mechanism by which DNA methylation regulates long-term memory is still waiting to be revealed.

In addition to DNA methylation, histone modifications might also be involved in the maintenance of long-term memory. DNA methylation and histone markers showed intensive cross-talk to maintain memory status. The administration of a DNMT inhibitor, which prevented the reinstatement of old memories before extinction (Maddox and Schafe, 2011; Wang et al., 2010; Lattal et al., 2007), affects not only DNA methylation but also the decrease of H3 and H4 acetylation (Sui et al., 2012). Similarly, HDACis could also prevent the reinstatement of past memories when administered before extinction. HDACis not only increases the histone acetylation, but also reduces DNMT1 expression through the suppression of the ERK pathway (Sarkar et al., 2011). Consistently, HDACis rescued the impairment of memory reconsolidation and the retrieval-induced H3 acetylation by inhibiting the expression of DNMT (Maddox and Schafe, 2011). The various modifications on the histone tail showed intensive cross-talk as well. The administration of HDACi in the hippocampus leads to an increase in H3K4me3 but a decrease in H3K9me2 (Gupta et al., 2010). Such crosstalk between various epigenetic modifications suggested that the epigenetic machinery might require different enzymes working in concert to achieve memory consolidation and maintenance.

In fact, some mechanistic studies have revealed the importance of the crosstalk between various epigenetic regulators. One case is PP1, which is reported to be a memory suppressor gene (Koshibu et al., 2010). PP1 is responsible for histone 3 S10 dephosphorylation. It interacts with and regulates the activities of other epigenetic regulators, such as HDACs and histone demethylases (Koshibu et al., 2009). HDACi abolishes the interaction between PP1 and HDACs (Brush et al., 2004). However, the inhibition of DNMT by inhibitors increased PP1 expression (Miller and Sweatt, 2007), thus demonstrating the interplay between those epigenetic regulators.

Furthermore, recent studies suggested that long-term memory could require epigenetic tagging, a form of the 'stabilization' role of epigenetic regulation, in the cortical circuit. Such neuron tagging is observed in the hippocampus only at an early stage, but showed persistency in the cortex (Lesburgueres et al., 2011). Interestingly, the delivery of HDACi in the cortex during the early but not the late phase of memory consolidation improved remote memory, suggesting that epigenetic modification may be associated with the initial cortical neuron tagging. Most recently, S-nitrosylation of HDAC2 and histone acetylation are found during recent memory recall, which enables the expression of c-fos and neuronal plasticity-related genes; however, this expression is absent in remote memory recall. Further intervention of the epigenetic tagging by HDACi during the reconsolidation phase allows for the attenuation of the remote memory (Graff et al., 2014). In addition to fear-conditioned learning, the administration of HDACi converts short-term memory into long-term memory in object recognition tasks (Stefanko et al., 2009). The HDAC inhibitor also stabilized the extinction memory to eliminate the spontaneous recovery of fear memories (Lattal et al., 2007). Therefore, although the circuit and molecular mechanisms underlying the maintenance of long-term memory are still far from clear, accumulating evidence supports the role of epigenetic regulation in the 'stabilization' of long-term memory.

Taken together, in the same neuron, the 'gating' mechanism of epigenetic regulation might facilitate storage of the most relevant stimuli in the cell, while the 'stabilization' mechanism might protect the stored information from disruption by unrelated events to maintain the integrity of long-term memory within the brain circuit. In a population of neurons, such dual role of epigenetic regulation might facilitate learning in the early period of life under the 'gating' mechanism and secure the learned information in adults under the 'stabilization' mechanism. The inter-connections between the transition from the 'gating' mechanism to the 'stabilization' mechanism still need to be discovered. Such specific epigenetic markers as tags for neurons in a developmentally identical population might participate in an important circuit mechanism for preserving various long-term memory traces by suppressing gene expression and plasticity within specific cell ensembles (Fig. 2B).

Summary and outlook

Accumulating evidence has revealed the important role of epigenetic regulation in learning and memory. However, until now, most of the evidence supporting the role of epigenetic regulation in long-term memory is still associative. To validate the attractive hypothesis that epigenetic regulation underlies the molecular mechanisms of long-term memory, two essential points need to be addressed. Firstly, the mechanisms underlying the neuronal activation-triggered changes of chromatin status and its role in the formation and maintenance of memory traces are poorly understood. Secondly, by assessing the chromatin status in a mixture of various neurons and non-neuronal cells from the brain regions, current studies cannot determine whether and how neuronal activation triggers specific epigenetic regulations within the memory-related neuronal circuit. Regardless, recent studies of epigenetic events in the central nervous system have had a promising impact on our understanding of long-term memory and related diseases.

Acknowledgments

The work is supported by National Basic Research Program of China grant 2013CB835100, National Natural Science Foundation of China (NSFC) grant 31171008, and Tsinghua University grant 2011Z02143.

References

Alarcon, J.M., et al., 2004. Chromatin acetylation, memory, and LTP are impaired in CBP+/− mice: a model for the cognitive deficit in Rubinstein–Taybi syndrome and its amelioration. Neuron 42, 947–959. http://dx.doi.org/10.1016/j.neuron.2004.05.021 (S0896627304003022 [pii]).

Bahari-Javan, S., et al., 2012. HDAC1 regulates fear extinction in mice. J. Neurosci. 32, 5062–5073. http://dx.doi.org/10.1523/JNEUROSCI.0079-12.2012 (doi:32/15/5062 [pii]).

Baker-Andresen, D., Ratnu, V.S., Bredy, T.W., 2013. Dynamic DNA methylation: a prime candidate for genomic metaplasticity and behavioral adaptation. Trends Neurosci. 36, 3–13. http://dx.doi.org/10.1016/j.tins.2012.09.003 doi:S0166-2236(12)00167-1 [pii]).

Banerjee, T., Chakravarti, D., 2011. A peek into the complex realm of histone phosphorylation. Mol. Cell. Biol. 31, 4858–4873. http://dx.doi.org/10.1128/MCB.05631-11 (doi: MCB.05631-11 [pii]).

Barondes, S.H., Jarvik, M.E., 1964. The influence of actinomycin-D on brain RNA synthesis and on memory. J. Neurochem. 11, 187–195.

Barrett, R.M., et al., 2011. Hippocampal focal knockout of CBP affects specific histone modifications, long-term potentiation, and long-term memory. Neuropsychopharmacology 36, 1545–1556. http://dx.doi.org/10.1038/npp.2011.61 (doi:npp201161 [pii]).

Bird, A., 2002. DNA methylation patterns and epigenetic memory. Genes Dev. 16, 6–21. http://dx.doi.org/10.1101/gad.947102.

Bliss, T.V., Collingridge, G.L., 1993. A synaptic model of memory: long-term potentiation in the hippocampus. Nature 361, 31–39. http://dx.doi.org/10.1038/361031a0.

Bousiges, O., et al., 2013. 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 8, e57816. http://dx.doi.org/10.1371/journal.pone.0057816 (PONE-D-12-28173 [pii]).

Brami-Cherrier, K., Roze, E., Girault, J.A., Betuing, S., Caboche, J., 2009. Role of the ERK/MSK1 signalling pathway in chromatin remodelling and brain responses to drugs of abuse. J. Neurochem. 108, 1323–1335. http://dx.doi.org/10.1111/j.1471-4159.2009.05879.x (doi:JNC5879 [pii]).

Brush, M.H., Guardiola, A., Connor, J.H., Yao, T.P., Shenolikar, S., 2004. Deactylase inhibitors disrupt cellular complexes containing protein phosphatases and deacetylases. J. Biol. Chem. 279, 7685–7691. http://dx.doi.org/10.1074/jbc.M310997200 (M310997200 [pii]).

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

Choi, D.C., et al., 2010. Prelimbic cortical BDNF is required for memory of learned fear but not extinction or innate fear. Proc. Natl. Acad. Sci. U. S. A. 107, 2675–2680. http://dx.doi.org/10.1073/pnas.0909359107 (doi:0909359107 [pii]).

Chwang, W.B., O'Riordan, K.J., Levenson, J.M., Sweatt, J.D., 2006. ERK/MAPK regulates hippocampal histone phosphorylation following contextual fear conditioning. Learn. Mem. 13, 322–328. http://dx.doi.org/10.1101/lm.152906 (doi:13/3/322 [pii]).

Cooper, S.J. Donald O., 2005. Hebb's synapse and learning rule: a history and commentary. Neurosci. Biobehav. Rev. 28, 851–874. http://dx.doi.org/10.1016/j.neubiorev.2004.09.009 (doi:S0149-7634(04)00099-5 [pii]).

Dash, P.K., Moore, A.N., Kobori, N., Runyan, J.D., 2007. Molecular activity underlying working memory. Learn. Mem. 14, 554–563. http://dx.doi.org/10.1101/lm.558707 (doi:14/8/554 [pii]).

Davis, H.P., Squire, L.R., 1984. Protein synthesis and memory: a review. Psychol. Bull. 96, 518–559.

Duclot, F., Meffre, J., Jacquet, C., Gongora, C., Maurice, T., 2010. Mice knock out for the histone acetyltransferase p300/CREB binding protein-associated factor develop a resistance to amyloid toxicity. Neuroscience 167, 850–863. http://dx.doi.org/10.1016/j.neuroscience.2010.02.055 (doi:S0306-4522(10)00283-6 [pii]).

Ea, C.K., Baltimore, D., 2009. Regulation of NF-kappaB activity through lysine monomethylation of p65. Proc. Natl. Acad. Sci. U. S. A. 106, 18972–18977. http://dx.doi.org/10.1073/pnas.0910439106 (doi:0910439106 [pii]).

Feng, J., et al., 2010. Dnmt1 and Dnmt3a maintain DNA methylation and regulate synaptic function in adult forebrain neurons. Nat. Neurosci. 13, 423–430. http://dx.doi.org/10.1038/nn.2514 (doi:nn.2514 [pii]).

Figurov, A., Pozzo-Miller, L.D., Olafsson, P., Wang, T., Lu, B., 1996. Regulation of synaptic responses to high-frequency stimulation and LTP by neurotrophins in the hippocampus. Nature 381, 706–709. http://dx.doi.org/10.1038/381706a0.

Freudenthal, R., et al., 2005. NF-kappaB transcription factor is required for inhibitory avoidance long-term memory in mice. Eur. J. Neurosci. 21, 2845–2852. http://dx.doi.org/10.1111/j.1460-9568.2005.04126.x (doi:EJN4126 [pii]).

Fuke, C., et al., 2004. Age related changes in 5-methylcytosine content in human peripheral leukocytes and placentas: an HPLC-based study. Ann. Hum. Genet. 68, 196–204. http://dx.doi.org/10.1046/j.1529-8817.2004.00081.x AHG081 (pii).

Gao, J., et al., 2010. A novel pathway regulates memory and plasticity via SIRT1 and miR-134. Nature 466, 1105–1109 (doi: nature 09271 [pii]).

Genoux, D., et al., 2002. Protein phosphatase 1 is a molecular constraint on learning and memory. Nature 418, 970–975. http://dx.doi.org/10.1038/nature00928 (nature00928 [pii]).

Goll, M.G., Bestor, T.H., 2005. Eukaryotic cytosine methyltransferases. Annu. Rev. Biochem. 74, 481–514. http://dx.doi.org/10.1146/annurev.biochem.74.010904.153721.

Graff, J., Koshibu, K., Jouvenceau, A., Dutar, P., Mansuy, I.M., 2010. Protein phosphatase 1-dependent transcriptional programs for long-term memory and plasticity. Learn. Mem. 17, 355–363. http://dx.doi.org/10.1101/lm.1766510 (doi:17/7/355 [pii]).

Graff, J., et al., 2014. Epigenetic priming of memory updating during reconsolidation to attenuate remote fear memories. Cell 156, 261–276. http://dx.doi.org/10.1016/j.cell.2013.12.020 (doi:S0092-8674(13)01589-4 [pii]).

Guan, J.S., et al., 2009. HDAC2 negatively regulates memory formation and synaptic plasticity. Nature 459, 55–60 (doi: nature 07925 [pii]).

Guo, J.U., Su, Y., Zhong, C., Ming, G.L., Song, H., 2011. Hydroxylation of 5-methylcytosine by TET1 promotes active DNA demethylation in the adult brain. Cell 145, 423–434. http://dx.doi.org/10.1016/j.cell.2011.03.022 (doi:S0092-8674(11)00299-6 [pii]).

Gupta, S., et al., 2010. Histone methylation regulates memory formation. J. Neurosci. 30, 3589–3599. http://dx.doi.org/10.1523/JNEUROSCI.3732-09.2010 (doi:30/10/3589 [pii]).

Gupta-Agarwal, S., et al., 2012. 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. 32, 5440–5453. http://dx.doi.org/10.1523/JNEUROSCI.0147-12.2012 (doi:32/16/5440 [pii]).

Gusterson, R., et al., 2002. The transcriptional co-activators CBP and p300 are activated via phenylephrine through the p42/p44 MAPK cascade. J. Biol. Chem. 277, 2517–2524. http://dx.doi.org/10.1074/jbc.M104626200 (M104626200 [pii]).

Impey, S., et al., 2002. Phosphorylation of CBP mediates transcriptional activation by neural activity and CaM kinase IV. Neuron 34, 235–244 (doi:S0896627302006542 [pii]).

Jiang, Y., et al., 2008. Epigenetics in the nervous system. J. Neurosci. 28, 11753–11759. http://dx.doi.org/10.1523/JNEUROSCI.3797-08.2008 (doi:28/46/11753 [pii]).

Kaas, G.A., et al., 2013. TET1 controls CNS 5-methylcytosine hydroxylation, active DNA demethylation, gene transcription, and memory formation. Neuron 79, 1086–1093. http://dx.doi.org/10.1016/j.neuron.2013.08.032 (doi:S0896-6273(13)00791-5 [pii]).

Kaltschmidt, B., et al., 2006. NF-kappaB regulates spatial memory formation and synaptic plasticity through protein kinase A/CREB signaling. Mol. Cell. Biol. 26, 2936–2946. http://dx.doi.org/10.1128/MCB.26.8.2936-2946.2006 (doi:26/8/2936 [pii]).

Kassed, C.A., Willing, A.E., Garbuzova-Davis, S., Sanberg, P.R., Pennypacker, K.R., 2002. Lack of NF-kappaB p50 exacerbates degeneration of hippocampal neurons after chemical exposure and impairs learning. Exp. Neurol. 176, 277–288 (doi:S0014488602979677 [pii]).

Kerimoglu, C., et al., 2013. Histone-methyltransferase MLL2 (KMT2B) is required for memory formation in mice. J. Neurosci. 33, 3452–3464. http://dx.doi.org/10.1523/JNEUROSCI.3356-12.2013 (doi:33/8/3452 [pii]).

Kim, M.S., et al., 2012. An essential role for histone deacetylase 4 in synaptic plasticity and memory formation. J. Neurosci. 32, 10879–10886. http://dx.doi.org/10.1523/JNEUROSCI.2089-12.2012 (doi:32/32/10879 [pii]).

Kohli, R.M., Zhang, Y., 2013. TET enzymes, TDG and the dynamics of DNA demethylation. Nature 502, 472–479 (doi: nature 12750 [pii]).

Korzus, E., Rosenfeld, M.G., Mayford, M., 2004. CBP histone acetyltransferase activity is a critical component of memory consolidation. Neuron 42, 961–972. http://dx.doi.org/10.1016/j. neuron .2004.06.002 (S0896627304003526 [pii]).

Koshibu, K., et al., 2009. Protein phosphatase 1 regulates the histone code for long-term memory. J. Neurosci. 29, 13079–13089. http://dx.doi.org/10.1523/JNEUROSCI.3610-09.2009 (doi:29/41/13079 [pii]).

Koshibu, K., Graff, J., Mansuy, I.M., 2010. Nuclear protein phosphatase-1: an epigenetic regulator of fear memory and amygdala long-term potentiation. Neuroscience 173, 30–36. http://dx.doi.org/10.1016/j.neuroscience.2010.11.023 (doi:S0306-4522(10)01514-9 [pii]).

Kouzarides, T., 2007. Chromatin modifications and their function. Cell 128, 693–705. http://dx.doi.org/10.1016/j.cell.2007.02.005 (doi:S0092-8674(07)00184-5 [pii]).

Kramer, J.M., et al., 2011. Epigenetic regulation of learning and memory by *Drosophila* EHMT/G9a. PLoS Biol. 9, e1000569. http://dx.doi.org/10.1371/journal.pbio.1000569.

Lamprecht, R., LeDoux, J., 2004. Structural plasticity and memory. Nat. Rev. Neurosci. 5, 45–54. http://dx.doi.org/10.1038/nrn1301 (nrn1301 [pii]).

Lattal, K.M., Barrett, R.M., Wood, M.A., 2007. Systemic or intrahippocampal delivery of histone deacetylase inhibitors facilitates fear extinction. Behav. Neurosci. 121, 1125–1131. http://dx.doi.org/10.1037/0735-7044.121.5.1125 (doi:2007-13974-032 [pii]).

Lesburgueres, E., et al., 2011. Early tagging of cortical networks is required for the formation of enduring associative memory. Science 331, 924–928. http://dx.doi.org/10.1126/science.1196164 (doi:331/6019/924 [pii]).

Levenson, J.M., Sweatt, J.D., 2005. Epigenetic mechanisms in memory formation. Nat. Rev. Neurosci. 6, 108–118. http://dx.doi.org/10.1038/nrn1604 (doi:nrn1604 [pii]).

Levenson, J.M., et al., 2004. Regulation of histone acetylation during memory formation in the hippocampus. J. Biol. Chem. 279, 40545–40559. http://dx.doi.org/10.1074/jbc.M402229200 (M402229200 [pii]).

Levenson, J.M., et al., 2006. Evidence that DNA (cytosine-5) methyltransferase regulates synaptic plasticity in the hippocampus. J. Biol. Chem. 281, 15763–15773. http://dx.doi.org/10.1074/jbc.M511767200 (doi:M511767200 [pii]).

Li, J., et al., 2004. Dopamine D2-like antagonists induce chromatin remodeling in striatal neurons through cyclic AMP-protein kinase A and NMDA receptor signaling. J.

Neurochem. 90, 1117–1131. http://dx.doi.org/10.1111/j.1471-4159.2004.02569.x (JNC2569 [pii]).
Lipsky, R.H., 2013. Epigenetic mechanisms regulating learning and long-term memory. Int. J. Dev. Neurosci. 31, 353–358. http://dx.doi.org/10.1016/j.ijdevneu.2012.10.110 (doi:S0736-5748(12)00583-7 [pii]).
Liu, L., van Groen, T., Kadish, I., Tollefsbol, T.O., 2009. DNA methylation impacts on learning and memory in aging. Neurobiol. Aging 30, 549–560. http://dx.doi.org/10.1016/j.neurobiolaging.2007.07.020 (doi:S0197-4580(07)00297-7 [pii]).
Loebrich, S., Nedivi, E., 2009. The function of activity-regulated genes in the nervous system. Physiol. Rev. 89, 1079–1103. http://dx.doi.org/10.1152/physrev.00013.2009 (doi:89/4/1079 [pii]).
Lubin, F.D., Roth, T.L., Sweatt, J.D., 2008. Epigenetic regulation of BDNF gene transcription in the consolidation of fear memory. J. Neurosci. 28, 10576–10586. http://dx.doi.org/10.1523/JNEUROSCI.1786-08.2008 (doi:28/42/10576 [pii]).
Maddox, S.A., Schafe, G.E., 2011. Epigenetic alterations in the lateral amygdala are required for reconsolidation of a Pavlovian fear memory. Learn. Mem. 18, 579–593. http://dx.doi.org/10.1101/lm.2243411 (doi:18/9/579 [pii]).
Maddox, S.A., Watts, C.S., Schafe, G.E., 2013. p300/CBP histone acetyltransferase activity is required for newly acquired and reactivated fear memories in the lateral amygdala. Learn. Mem. 20, 109–119. http://dx.doi.org/10.1101/lm.029157.112 (doi:20/2/109 [pii]).
Malvaez, M., et al., 2013. HDAC3-selective inhibitor enhances extinction of cocaine-seeking behavior in a persistent manner. Proc. Natl. Acad. Sci. U. S. A. 110, 2647–2652. http://dx.doi.org/10.1073/pnas.1213364110 (doi:1213364110 [pii]).
Martin, S.J., Grimwood, P.D., Morris, R.G., 2000. Synaptic plasticity and memory: an evaluation of the hypothesis. Annu. Rev. Neurosci. 23, 649–711. http://dx.doi.org/10.1146/annurev.neuro.23.1.649.
Maurice, T., et al., 2008. Altered memory capacities and response to stress in p300/CBP-associated factor (PCAF) histone acetylase knockout mice. Neuropsychopharmacology 33, 1584–1602. http://dx.doi.org/10.1038/sj.npp.1301551 (doi:1301551 [pii]).
McQuown, S.C., et al., 2011. HDAC3 is a critical negative regulator of long-term memory formation. J. Neurosci. 31, 764–774. http://dx.doi.org/10.1523/JNEUROSCI.5052-10.2011 (doi:31/2/764 [pii]).
Michan, S., et al., 2010. SIRT1 is essential for normal cognitive function and synaptic plasticity. J. Neurosci. 30, 9695–9707. http://dx.doi.org/10.1523/JNEUROSCI.0027-10.2010 (doi:30/29/9695 [pii]).
Miller, C.A., Sweatt, J.D., 2007. Covalent modification of DNA regulates memory formation. Neuron 53, 857–869. http://dx.doi.org/10.1016/j.neuron.2007.02.022 (doi:S0896-6273(07)00142-0 [pii]).
Miller, C.A., Campbell, S.L., Sweatt, J.D., 2008. DNA methylation and histone acetylation work in concert to regulate memory formation and synaptic plasticity. Neurobiol. Learn. Mem. 89, 599–603. http://dx.doi.org/10.1016/j.nlm.2007.07.016 (doi:S1074-7427(07)00110-4 [pii]).
Miller, C.A., et al., 2010. Cortical DNA methylation maintains remote memory. Nat. Neurosci. 13, 664–666. http://dx.doi.org/10.1038/nn.2560 (doi:nn.2560 [pii]).
Monsey, M.S., Ota, K.T., Akingbade, I.F., Hong, E.S., Schafe, G.E., 2011. Epigenetic alterations are critical for fear memory consolidation and synaptic plasticity in the lateral amygdala. PLoS One 6, e19958. http://dx.doi.org/10.1371/journal.pone.0019958 (PONE-D-11-06156 [pii]).
Mori, T., et al., 2013. Increased histone H3 phosphorylation in neurons in specific brain structures after induction of status epilepticus in mice. PLoS One 8, e77710. http://dx.doi.org/10.1371/journal.pone.0077710 (PONE-D-13-20684 [pii]).
Morris, M.J., Mahgoub, M., Na, E.S., Pranav, H., Monteggia, L.M., 2013. Loss of histone deacetylase 2 improves working memory and accelerates extinction learning. J. Neurosci. 33, 6401–6411. http://dx.doi.org/10.1523/JNEUROSCI.1001-12.2013 (doi:33/15/6401 [pii]).
Nott, A., Watson, P.M., Robinson, J.D., Crepaldi, L., Riccio, A., 2008. S-Nitrosylation of histone deacetylase 2 induces chromatin remodelling in neurons. Nature 455, 411–415 (doi: nature 07238 [pii]).
Oliveira, A.M., et al., 2011. Subregion-specific p300 conditional knock-out mice exhibit long-term memory impairments. Learn. Mem. 18, 161–169. http://dx.doi.org/10.1101/lm.1939811 (doi:18/3/161 [pii]).
Park, H., Poo, M.M., 2012. Neurotrophin regulation of neural circuit development and function. Nat. Rev. Neurosci. 14, 7–23. http://dx.doi.org/10.1038/nrn3379 (doi:nrn3379 [pii]).
Psotta, L., Lessmann, V., Endres, T., 2013. Impaired fear extinction learning in adult heterozygous BDNF knock-out mice. Neurobiol. Learn. Mem. 103, 34–38. http://dx.doi.org/10.1016/j.nlm.2013.03.003 (doi:S1074-7427(13)00040-3 [pii]).
Ringrose, L., Paro, R., 2004. Epigenetic regulation of cellular memory by the Polycomb and Trithorax group proteins. Annu. Rev. Genet. 38, 413–443. http://dx.doi.org/10.1146/annurev.genet.38.072902.091907.
Rogge, G.A., Singh, H., Dang, R., Wood, M.A., 2013. HDAC3 is a negative regulator of cocaine-context-associated memory formation. J. Neurosci. 33, 6623–6632. http://dx.doi.org/10.1523/JNEUROSCI.4472-12.2013 (doi:33/15/6623 [pii]).
Rothgiesser, K.M., Fey, M., Hottiger, M.O., 2010. Acetylation of p65 at lysine 314 is important for late NF-kappaB-dependent gene expression. BMC Genomics 11, 22. http://dx.doi.org/10.1186/1471-2164-11-22 (doi:1471-2164-11-22 [pii]).
Rudenko, A., et al., 2013. Tet1 is critical for neuronal activity-regulated gene expression and memory extinction. Neuron 79, 1109–1122. http://dx.doi.org/10.1016/j.neuron.2013.08.003 (doi:S0896-6273(13)00714-9 [pii]).
Sarkar, S., et al., 2011. Histone deacetylase inhibitors reverse CpG methylation by regulating DNMT1 through ERK signaling. Anticancer Res. 31, 2723–2732 (doi:31/9/2723 [pii]).
Shahbazian, M.D., Grunstein, M., 2007. Functions of site-specific histone acetylation and deacetylation. Annu. Rev. Biochem. 76, 75–100. http://dx.doi.org/10.1146/annurev.biochem.76.052705.162114.
Shin, S., Janknecht, R., 2007. Diversity within the JMJD2 histone demethylase family. Biochem. Biophys. Res. Commun. 353, 973–977. http://dx.doi.org/10.1016/j.bbrc.2006.12.147 (doi:S0006-291X(06)02790-2 [pii]).
Stefanko, D.P., Barrett, R.M., Ly, A.R., Reolon, G.K., Wood, M.A., 2009. Modulation of long-term memory for object recognition via HDAC inhibition. Proc. Natl. Acad. Sci. U. S. A. 106, 9447–9452. http://dx.doi.org/10.1073/pnas.0903964106 (doi:0903964106 [pii]).
Sui, L., Wang, Y., Ju, L.H., Chen, M., 2012. Epigenetic regulation of reelin and brain-derived neurotrophic factor genes in long-term potentiation in rat medial prefrontal cortex. Neurobiol. Learn. Mem. 97, 425–440. http://dx.doi.org/10.1016/j.nlm.2012.03.007 (doi:S1074-7427(12)00037-8 [pii]).
Sultan, F.A., Wang, J., Tront, J., Liebermann, D.A., Sweatt, J.D., 2012. Genetic deletion of Gadd45b, a regulator of active DNA demethylation, enhances long-term memory and synaptic plasticity. J. Neurosci. 32, 17059–17066. http://dx.doi.org/10.1523/JNEUROSCI.1747-12 (doi:32/48/17059 [pii]).
Turker, M.S., 1999. The establishment and maintenance of DNA methylation patterns in mouse somatic cells. Semin. Cancer Biol. 9, 329–337. http://dx.doi.org/10.1006/scbi.1999.0133 (S1044-579X(99)90133-5 [pii]).
Vecsey, C.G., et al., 2007. Histone deacetylase inhibitors enhance memory and synaptic plasticity via CREB:CBP-dependent transcriptional activation. J. Neurosci. 27, 6128–6140. http://dx.doi.org/10.1523/JNEUROSCI.0296-07.2007 (doi:27/23/6128 [pii]).
Wang, Z., Zhang, B., Wang, M., Carr, B.I., 2003. Persistent ERK phosphorylation negatively regulates cAMP response element-binding protein (CREB) activity via recruitment of CREB-binding protein to pp90RSK. J. Biol. Chem. 278, 11138–11144. http://dx.doi.org/10.1074/jbc.M209108200 (M209108200 [pii]).
Wang, L., et al., 2010. Chronic cocaine-induced H3 acetylation and transcriptional activation of CaMKIIalpha in the nucleus accumbens is critical for motivation for drug reinforcement. Neuropsychopharmacology 35, 913–928. http://dx.doi.org/10.1038/npp.2009.193 (doi:npp2009193 [pii]).
Xie, H., et al., 2014. In vivo imaging of immediate early gene expression reveals layer-specific memory traces in the mammalian brain. Proc. Natl. Acad. Sci. U. S. A. 111, 2788–2793. http://dx.doi.org/10.1073/pnas.1316808111 (doi:1316808111 [pii]).
Yang, X.D., et al., 2009. Negative regulation of NF-kappaB action by Set9-mediated lysine methylation of the RelA subunit. EMBO J. 28, 1055–1066. http://dx.doi.org/10.1038/emboj.2009.55 (doi:emboj200955 [pii]).
Yang, X.D., Tajkhorshid, E., Chen, L.F., 2010. Functional interplay between acetylation and methylation of the RelA subunit of NF-kappaB. Mol. Cell. Biol. 30, 2170–2180. http://dx.doi.org/10.1128/MCB.01343-09 (doi:MCB.01343-09 [pii]).
Yeh, S.H., Lin, C.H., Gean, P.W., 2004. Acetylation of nuclear factor-kappaB in rat amygdala improves long-term but not short-term retention of fear memory. Mol. Pharmacol. 65, 1286–1292. http://dx.doi.org/10.1124/mol.65.5.1286 65/5/1286 (pii).
Yu, N.K., Baek, S.H., Kaang, B.K., 2011. DNA methylation-mediated control of learning and memory. Mol. Brain 4, 5. http://dx.doi.org/10.1186/1756-6606-4-5 (doi:1756-6606-4-5 [pii]).