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Review article

The roles of class I histone deacetylases (HDACs) in memory, learning, and executive cognitive functions: A review

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ABSTRACT

Coordinated changes in gene expression are critical for synaptic plasticity supporting learning, memory, and optimal cognitive task performance. These gene expression changes are not only mediated by signaling pathways that activate transcription factors, but also by chromatin modifications that influence the accessibility of the transcriptional machinery to specific genomic regions. During the past decade, evidence accumulated that alterations in chromatin-based epigenetic regulation of gene expression are linked to cognitive dysfunctions in the ageing or neurodegenerating brain as well as to cognitive dysfunctions resulting from chronic stress exposure. This review summarizes the results of studies that unraveled a role of histone modifying enzymes and histone modifications in normal and impaired learning and memory, and in the disruption of executive cognitive task performance. It emphasizes the different roles of specific class I histone deacetylases (HDACs) in cognitive processes governed by the hippocampus and prefrontal cortex and discusses the potential therapeutic implications of targeting them to hold the progression of disease-related cognitive dysfunctions.

1. Overview

This review begins with a brief description of major histone-based chromatin modification and a summary of known roles of class I HDACs1, 2 and 3 in memory formation, consolidation, and extinction. It then summarizes results of studies on animal models of ageing and neurodegeneration that uncovered a role of HDAC2 activity in promoting deficits in hippocampus-dependent learning and memory. Furthermore, recent studies are discussed that employed animal models of early life stress with altered HDAC1 activity that is associated with prefrontal cortex-dependent executive cognitive deficits and deficits in sensory motor gating. Together, these studies illustrate that two members of class I HDACs play specific and non-overlapping roles in the disruption of cognitive functions.

2. Chromatin modifications

Chromatin condenses and organizes genomic DNA. The basic unit of chromatin, termed nucleosome, is composed of 147 base pairs of DNA wrapped around an octamer of the histone proteins H2A, H2B, H3, and H4 (two of each). These histone proteins are composed of a globular domain and an N-terminal tail containing several residues that are substrates for bi-directional post-translational modification (acetylation/deacetylation, methylation/demethylation, ubiquination/deubiquination, etc.).

Chromatin modifications have two functions: One is to enable the recruitment of non-histone proteins involved in transcriptional activation or repression, the other is to modulate the degree of relaxation of chromatin by stabilizing or disrupting contacts between nucleosome and genomic DNA (Kouzarides, 2007). Among the many histone-based chromatin modifications, histone tail acetylation is most extensively studied. While histone acetyltransferases (HATs) catalyze the transfer of acetyl groups to histone proteins, HDACs remove them. Acetylated histones support active gene transcription by relaxing the charged association of histone tails with DNA to allow for greater access of transcription factors and RNA polymerase II (Pol II) to DNA. HDACs can rapidly deacetylate histones and, thereby, slow gene transcription rates.

HDACs are divided into 4 groups: the zinc-dependent class I (HDAC1, 2, 3, and 8), class II (class IIa HDAC4, 5, 7, and 9; class IIb HDAC6), the NAD-dependent class III (sirtuins), and class IV (HDAC10, 11) (Haberland et al., 2009). Original studies showing that upregulation of histone acetylation using HDAC inhibitors (HDACis) can enhance memory formation and long-term potentiation (LTP) (Levenson et al., 2004) and that mutations in the HAT protein CBP (CREB-binding protein) disrupt memory formation and LTP (Alarcón et al., 2004) stimulated further research on the role of chromatin modifying enzymes

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and histone modifications in modulating learning and memory. These studies are summarized below.

3. The roles of class I HDACs in learning and memory

To date, the majority of studies on the role of HDACs in cognition focused on the hippocampus that subserves roles in episodic and spatial memory and learning, i.e., cognitive processes associated electrophysiologically with LTP in various hippocampal subfields as well as with an activity-dependent induction of expression of plasticity-associated genes. In a first study, Guan et al. (2009) employed transgenic mice overexpressing either class I HDACs 1 or 2 in neurons. These studies revealed that HDAC2 overexpression (but not HDAC1 overexpression) impaired hippocampus-dependent associative and spatial learning in a Pavlovian fear conditioning paradigm and the Morris Water Maze test, respectively. HDAC2 overexpression also led to reduced levels of histone H4 protein acetylated at lysine (K) 12 (acH4K12). Conversely, HDAC2 knockout mice had increased levels of acH4K5 and acH4K12 (and acH2B) in the hippocampus, and increased associative and spatial learning. Moreover, while HDAC2 overexpressing mice had fewer pre-synaptic terminals, HDAC2 knockout mice exhibited an increase in spine density and pre-synaptic terminals (Table 1).

HDAC2 overexpression was also found to suppress the expression of synaptic plasticity and remodeling genes, including brain-derived neurotrophic factor (Bdnf) I/II, early growth response gene 1 (Egr1), glutamate ionotropic receptor AMPA type 1 (Gria1), and Fos. Moreover, the promoters of some of these genes (*Bdnf* II, *Fos* and *Gria1*) had deceased levels of acetylated histone H3 protein (Table 1). These findings led the authors to propose for the first time a role for HDAC2 as a negative regulator of memory and synaptic plasticity and hence, pointed to the potential of HDAC2 inhibitors as facilitators of learning and memory (Guan et al., 2009).

Two additional studies used fear-conditioning paradigms to further investigate the roles of class I HDACs in specific hippocampus-dependent cognitive domains of learning and memory. One study showed that, in contrast to recall of recent memories, recall of remote memories does neither lead to nitrosylation of HDAC2 nor histone acetylation-mediated neuronal plasticity in the hippocampus (Gräff et al., 2014). The authors proposed that HDAC2 nitrosylation and its subsequent dissociation from chromatin is critical for memory updating during reconsolidation, and they showed that HDACi treatment leads to increased histone acetylation after remote memory recall. Moreover, the combination of extinction training with HDACi treatment resulted in increased synaptic and structural plasticity along with an up-regulation of distinct plasticity-associated genes whose promoters experienced increased association with acetylated histones. Importantly, increased histone acetylation occurred despite unaltered levels of HDAC2, suggesting that HDAC inhibition can compensate for lack of HDAC2 nitrosylation that is otherwise critical for memory updating during reconsolidation (Gräff et al., 2014).

Another study implicated HDAC1 in fear extinction. Here, a virus-mediated gene transduction resulted in an acute overexpression of HDAC1 in the dorsal hippocampus (Bahari-Javan et al., 2012). While the emotional phenotype, short- and long-term memory, and executive cognitive phenotypes were unaltered in these mice, their contextual fear extinction was significantly facilitated, and the opposite effect was observed when mice were treated either with the HDAC1-prefering inhibitor MS-275 or injected with HDAC1 small interfering RNA (siRNA). The authors showed that, during extinction training, HDAC1 is recruited to promoters of plasticity-associated genes, including *FOS* and *Egr2*. This results in lower levels of acH3K9 (a mark of active gene transcription) and increased the levels of H3K9me3 (a mark of gene silencing) at these promoters (Table 1). Conversely, MS-275 treatment and HDAC1 siRNA increased the levels of acH3K9 and decreased the levels of H3K9me3 (Bahari-Javan et al., 2012).

Finally, an earlier study showed that a broad acting HDAC inhibitor produces long-term novel object recognition memory that persists beyond normal memory retention, suggesting that HDACs may function as memory suppressor genes (Stefanko et al., 2009). A subsequent study (McQuown et al., 2011) specifically implicated HDAC3 in long-term memory formation. This study used floxed HDAC3 mice that were infused with virus expressing Cre recombinase bilaterally into the hippocampus. This HDAC3 deletion led to long-term memory formation for object recognition beyond the time of normal memory retention. Regions of HDAC3 deletion also had decreased HDAC4 expression, elevated levels of acH4K8, and elevated training-induced expression of nuclear receptor 42a (Nr4a2; Table 1). The authors proposed that the effect of HDAC3 deletion is due to a disruption of the HDAC3/nuclear receptor co-repressor 1 (NCoR1) that is normally required for memory repression (McQuown et al., 2011).

Altogether, these studies showed that class I HDACs 1, 2 and 3 are causally involved in memory formation, consolidation and extinction, with HDAC2 acting as a major mnemonic constraint (Gräff and Tsai, 2013). The following section summarizes results of studies that investigated how altered activity of these class 1 HDACs contributes to the cognitive decline associated with neurodegenerative diseases and the ageing brain.

4. The roles of class I HDAC activity in animal models of ageing and neurodegeneration

A major risk factor for neurodegeneration and cognitive decline is the ageing brain. With increasing life expectancy, the prevalence of cognitive decline and dementia increased, largely in form of Alzheimer's Disease (AD), and is projected to increase even further within the next decades (Hebert et al., 2003). Age-related cognitive decline, mostly evident for learning and memory-related functioning, is accompanied (among others) by reduced expression of genes that affect synaptic function, axonal integrity and myelination, as well as vesicular transport and mitochondrial function (Lu et al., 2004). The promoters of these genes show marked DNA damage, are selectively damaged by oxidative stress, and show reduced base-excision repair (Lu et al., 2004).

With advanced age, various hippocampal subfields exhibit impaired LTP, the electrophysiological correlate of these cognitive functions (Burke and Barnes, 2006), as well as reduced activity-dependent induction of plasticity-associated genes (Blalock et al., 2003). However, studies on human brain and on model systems suggest that the rate of ageing is not fixed. Rather, it is plastic and open to modification. Human brain ageing is accompanied by memory loss and reduced synaptic connectivity (but not by significant neuronal loss), suggesting that loss of the ability to access stored memories underlies age-dependent memory deficits (Bishop et al., 2010). Similarly, studies on animal models of neurodegeneration suggest that neural plasticity is not lost but rather constraint (Gräff and Tsai, 2013).

The first study on the role of chromatin remodeling in the recovery of neurodegeneration-induced impairment of learning and memory relied on a bi-transgenic mouse model in which the expression of p25, a proteolytic cleavage product of the protein serine/threonine kinase Cdk5 activator p35, is under the control of the calcium/calmodulin-dependent protein kinase II (*Cam*KII) promoter that can be switched on or off in a doxycycline-dependent manner (CK—p25 Tg mice). p25 hyperactivates Cdk5. While a transient, 2-week long postnatal induction of p25 expression in the hippocampus led to enhanced LTP and facilitated hippocampus-dependent associative and spatial learning and memory via a mechanism involving increased dendritic spine and synapse formation, prolonged p25 induction (6 weeks) caused brain atrophy and loss of hippocampal neurons, impaired LTP, and loss of the ability to form new memories (Fischer et al., 2005) (Table 2). However, Fischer et al. (2007) also showed that, although a 6-week induction of p25 expression in adult mice results in substantial brain atrophy, a 4-