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# Histone deacetylases (HDACs) and brain function

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ABSTRACT

Modulation of gene expression is a constant and necessary event for mammalian brain function. An important way of regulating gene expression is through the remodeling of chromatin, the complex of DNA, and histone proteins around which DNA wraps. The "histone code hypothesis" places histone post-translational modifications as a significant part of chromatin remodeling to regulate transcriptional activity. Acetylation of histones by histone acetyl transferases and deacetylation by histone deacetylases (HDACs) at lysine residues are the most studied histone post-translational modifications in cognition and neuropsychiatric diseases. Here, we review the literature regarding the role of HDACs in brain function. Among the roles of HDACs in the brain, studies show that they participate in glial lineage development, learning and memory, neuropsychiatric diseases, and even rare neurologic diseases. Most HDACs can be targeted with small molecules. However, additional brain-penetrant specific inhibitors with high central nervous system exposure are needed to determine the cause-and-effect relationship between individual HDACs and brain-associated diseases.



## Introduction

The mammalian brain exercises numerous functions including the maintenance of homeostasis within the body, sensorimotor ability, learning, memory, and behavior. All these functions require precise regulation of gene expression. For instance, the brain is able to store memories for as little as a few minutes to as many as several decades. Such flexibility suggests that multiple mechanisms are involved in altering neuronal function to generate short- to long-term changes in the brain Dulac, 2010. One of the most important ways of regulating gene expression is through the remodeling of chromatin, the complex of DNA, and histone proteins around which DNA wraps. Gene expression changes when the wrapping density of DNA around the histones changes. Two main mechanisms account for this chromatin remodeling: histone post-translational modifications or DNA methylation. Most studies in the literature dealing with these epigenetic changes are found in the cancer, developmental, and stem cell biology fields. A search for "chromatin remodeling" on PubMed in June of 2014 reveals that out of more than 5400 peer-reviewed papers, only about 300 are linked to brain-related studies. Out of these, approximately half deal with histones. The range of possible histone modifications includes the following: acetylation, methylation, ubiquitylation, phosphorylation, sumoylation, ribosylation, and citrullination. Within these, the most studied modification is the acetylation of histones by histone acetyl transferases (HATs) and the removal of acetyl groups from histones by histone deacetylases (HDACs), the latter being the main focus of this review.

The post-translational modifications mentioned above occur all along the histone sequence but are more prevalent at the N-termini commonly referred to as histone tails. Other important components in histone modifications include bromodomain-containing proteins (termed reader proteins), which recognize specific acetylated histone residues, in the presence of chemical moieties and chromatin-modifying effectors, in order to affect gene expression (Campos and Reinberg, 2009). It follows that HDAC activity is an important process in regulating gene expression by physically affecting chromatin density and by regulating access to acetylated histone residues by reader proteins. The observation that a combination of several histone modifications are needed to regulate transcriptional activity has led to the formulation of the "histone code hypothesis" (Campos and Reinberg, 2009; Strahl and Allis, 2000; Turner, 2000). More specifically, this hypothesis stems from observations such as both low levels of histone acetylation and high levels of trimethylated H4K20 and H3K27 typically resulting in silenced chromatin. Additionally, hyperacetylation, and trimethylation at residues H3K4 and H3K36 have been demonstrated to be marks of active transcription (Dulac, 2010). Furthermore, acetylation at H3K9 and H3K14 has been linked to

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transcriptional activation. Thus, acetylation of histones via HATs and deacetylation via HDACs are critical parts of the histone code hypothesis.

Two categories of HDACs have been identified thus far: the "zinc-dependent" ones and the "nicotinamide-adenine-dinucleotide (NAD)–dependent" sirtuins. Depending on sequence similarity, the zinc-dependent HDAC family members are composed of class I (HDACs 1, 2, 3, and 8), classes IIa and IIb (HDACs 4, 5, 6, 7, 9, and 10), or class IV (HDAC 11). All of the zinc-dependent HDACs are expressed in the brain. It is important to note that class I HDACs are found mostly within the nucleus, whereas class II members shuttle between the nucleus and cytoplasm (Gibson and Murphy, 2010). An exception is found with HDAC6, which is located only in the cytoplasm. Isoforms of HDACs class I, II, and IV are expressed primarily in neurons, in the brain (Broide et al., 2007). Although the expression of all HDACs is relatively low in astrocytes, HDACs 2, 3, 4, 5, and 11 are expressed in oligodendrocytes (Gräff and Tsai, 2013). Of the aforementioned classes of HDACs, classes I and IIa are the most highly expressed in brain regions that are associated with learning and memory. The reader is directed to the review by Gräff and Tsai (2013) for more in-depth coverage of this information (Gräff and Tsai, 2013). The class III NAD-dependent sirtuins form a class of deacetylases highly conserved from prokaryotes to eukaryotes, with 7 isoforms in humans, forming the SIRT gene family (Grozinger et al., 2001). SIRTs 1 to 7 each have distinct cellular localization. SIRTs 1, 2, 6, and 7 are found in the nucleus, whereas SIRTs 3, 4, and 5 are located in the mitochondria (Han, 2009; Michishita et al., 2005). Histone deacetylase activity has only been confirmed with SIRTs 1, 2, 3, and 5 (Haigis and Sinclair, 2010; Han, 2009). All the SIRTs, with the exception of SIRTs 2 and 5, present higher gene expression in fetal brain compared to adult brain (Michishita et al., 2005). These data support the hypothesis that SIRTs may play crucial roles in early brain development.

## HDACs and brain development

It has been reported that maternal care of offspring has positive effects on brain development and on the ability of offspring to cope with stress in adult life. This has been experimentally linked to histone acetylation and DNA methylation in rats. Indeed, pups of high-grooming females show increased expression of the glucocorticoid receptor compared to offspring of low-grooming females (Weaver et al., 2004). The increased expression correlates with low levels of DNA methylation and high levels of histone acetylation at exon 17 promoter of the glucocorticoid receptor gene, resulting in high binding of the transcription factor EGR1, known to regulate this gene (Weaver et al., 2004). Conversely, offspring of low-grooming mothers present high levels of DNA methylation and low levels of histone acetylation at this region, resulting in low EGR1 binding. Interestingly, injection of the HDAC inhibitor trichostatin A (TSA) in the brain of adult offspring from low-grooming mothers ablates the negative effects on glucocorticoid receptor expression (Weaver et al., 2004). These data suggest that acetylation is a crucial step in the establishment of brain glucocorticoid receptors early in life and HDACs are probably activated in offspring by maternal behavior. These data do not, however, preclude a possible role of HATs in this type of epigenetic programming. Further support for the role of acetylation in brain development comes from studies showing that the class III HDAC SIRT1 is critical for driving the differentiation of cells toward an astroglial lineage, away from a neuronal fate Prozorovski et al., 2008. However, nonacetylation roles of HDACs may also be critical in brain development because the class III HDAC SIRT4 that shows no deacetylase activity also appears to play a significant role in the development of astroglia from radial glia, in association with glutamate dehydrogenase-1 (Komlos et al., 2013). Indeed, SIRT4 is highly expressed in astrocytes in the postnatal brain and in radial glia in embryonic tissues, whereas expression decreases during development.

## HDACs and memory

Learning and memory are subject to rigorous epigenetic control involving multiple mechanisms of neuronal chromatin modifications. Since the report by Swank and Sweatt (2001) showed that exposing mice to novel tastes increased histone lysine acetylation due in part to increased HAT activity in the insular cortex, there have been numerous reports suggesting that histone acetylation is involved in memory formation. For instance, it is well established that the cAMP response element binding protein (CREB) binding protein (CBP) is important for memory formation and that CBP works as a transcription factor and as an HAT. Korzus et al. (2004) have shown that only long-term memory is impaired in a transgenic mouse model where the HAT activity of CBP is removed. The authors do not observe any negative effect on short-term memory in the absence of HAT. This long-term memory impairment, however, is rescued when the animals are treated with the pan HDAC inhibitor TSA (Korzus et al., 2004), demonstrating that acetylation is critical for the stabilization of short-term memory into long-term memory. In a seminal paper where both HDAC1 and HDAC2 were overexpressed and deleted in 4 novel mouse lines, HDAC2, but not HDAC1, was identified as a regulator of associative and spatial memory (Guan et al., 2009). HDAC2-overexpressing mice showed impaired memory performance, whereas HDAC2-knockout mice had enhanced memory performance.

Reviews of the literature from 2001 to 2014 indicate that most studies linking acetylation to memory have utilized HDAC inhibitors to demonstrate that increased lysine acetylation resulting from the inhibition of HDACs enhances cognition in rodents (Korzus et al., 2004; Levenson and Sweatt, 2005; Swank and Sweatt, 2001). Different HDACs appear to have specific roles in different types of learning and memory regulation. By pharmacologically inhibiting the class I HDAC, HDAC1 with the small molecule MS-275, Bahari-Javan et al. (2012) demonstrated that fear memory extinction is impaired. This conclusion is further supported by the observation that overexpressing HDAC1 in the mouse hippocampus results in enhanced extinction of contextual fear memories (Bahari-Javan et al., 2012). Bahari-Javan et al. (2012) also show that memory extinction training resulted in deacetylation of the HDAC1 target, H3K9 (Bahari-Javan et al., 2012). Further support for the role of class I HDACs in fear memory extinction comes from the recent findings of Hait et al. (2014) who have reported that the phosphorylated form of FTY720 (fingolimod), an Food and Drug Administration–approved drug for treatment of multiple sclerosis, inhibits class I HDAC activity and facilitates fear extinction memory (Hait et al., 2014). Inhibition of HDAC3, the most highly expressed class I HDAC in the brain, has been shown to increase acetylation of H4K8 and enhance long-term object recognition memory in mice, implying that HDAC3 is a negative regulator of long-term memory formation (McQuown et al., 2011; Malvaez et al., 2013).

The class IIa HDAC, HDAC4, has been shown to play an important role in synaptic plasticity and memory formation (Kim et al., 2012; Sando et al., 2012). Studies conducted by Kim et al. (2012) as well as those by Sando et al. (2012) show that silencing or truncation of HDAC4 results in impairment of spatial learning and memory, as assessed by the Morris water maze or the Barnes Maze. Interestingly, Kim et al. (2012) do not observe any memory impairment in the absence of HDAC5, suggesting that within class IIa HDACs, the effect on learning and memory is specific to HDAC4. Interestingly, Agis-Balboa et al. (2013) have shown that HDAC5 is important for the consolidation