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# Probing the role of HDACs and mechanisms of chromatin-mediated neuroplasticity

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ABSTRACT

Advancing our understanding of neuroplasticity and the development of novel therapeutics based upon this knowledge is critical in order to improve the treatment and prevention of a myriad of nervous system disorders. Epigenetic mechanisms of neuroplasticity involve the post-translational modification of chromatin and the recruitment or loss of macromolecular complexes that control neuronal activity-dependent gene expression. While over a century after Ramón y Cajal first described nuclear subcompartments and foci that we now know correspond to sites of active transcription with acetylated histones that are under epigenetic control, the rate and extent to which epigenetic processes act in a dynamic and combinatorial fashion to shape experience-dependent phenotypic and behavioral plasticity in response to various types of neuronal stimuli over a range of time scales is only now coming into focus. With growing recognition that a subset of human diseases involving cognitive dysfunction can be classified as 'chromatinopathies', in which aberrant chromatin-mediated neuroplasticity plays a causal role in the underlying disease pathophysiology, understanding the molecular nature of epigenetic mechanisms in the nervous system may provide important new avenues for the development of novel therapeutics. In this review, we discuss the chemistry and neurobiology of the histone deacetylase (HDAC) family of chromatin-modifying enzymes, outline the role of HDACs in the epigenetic control of neuronal function, and discuss the potential relevance of these epigenetic mechanisms to the development of therapeutics aiming to enhance memory and neuroplasticity. Finally, open questions, challenges, and critical needs for the field of 'neuroepigenetics' in the years to come will be summarized.



## 1. Introduction

### 1.1. Chromatin as a substrate for epigenetic control

Recent molecular, cellular, and behavioral findings have revealed the importance of epigenetic mechanisms that alter chromatin structure in maintaining stable patterns of gene expression and altering neuroplasticity associated with memory formation (reviewed in Barrett and Wood (2008) and Levenson and Sweatt (2005)), mood (Berton & Nestler, 2006; Tsankova, Renthal, Kumar, & Nestler, 2007), drug addiction (reviewed in Renthal and Nestler (2008)), neuroprotection (Kazantsev & Thompson, 2008), and other forms of experience-dependent input into the nervous system. Collectively, these findings have provided new insight into the cellular and molecular mechanisms through which gene expression affects neurotransmission and behavioral plasticity over long time periods. This in turn has led to a growing desire to understand the nature of epigenetic regulation in the nervous system in greater detail.

At the heart of epigenetic regulatory mechanisms is the fundamental unit of chromatin in all eukaryotic cells, the nucleosome, composed of 147 base pairs of DNA wrapped around two copies of specific variants of each of the core histones H2A, H2B, H3, and H4, along with one copy of the liker histone H1. By packaging DNA and controlling the access of other factors, epigenetic mechanisms provide an important level of control of gene expression throughout development and in post-mitotic cells, such as neurons.

With its repeating nucleosomal units, chromatin as a polymer is well designed to be a 'plastic' substrate that can respond to both fast and short-term changes in neuronal signaling and cell states within the nervous system. To alter gene expression states in neurons, as in all other cell types, epigenetic regulatory processes involves the dynamic interplay of two major classes of multiprotein, macromolecular complexes: (1) ATP-dependent remodeling complexes, which alter the position of nucleosomes to either increase or decrease transcription (reviewed in Racki and Narlikar (2008)); and (2) histone-modifying complexes, which post-translationally modify the N-terminal tails of histone proteins through acetylation, methylation, phosphorylation, ubiquitinylation, sumoylation, glycosylation, and ribosylation (Borrelli, Nestler,

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Allis, & Sassone-Corsi, 2008; Grozinger & Schreiber, 2002; Ruthenburg, Li, Patel, & Allis, 2007).

### 1.2. Histone deacetylase: HDACs

Of the various histone modifications, the reversible acetylation and deacetylation of the ε-amino group of lysine side chains within the N-terminal tails of histones has emerged as a central regulator of transcriptional programming and brain plasticity (Borrelli et al., 2008; Levenson & Sweatt, 2005). The enzymes responsible for the acetylation of histones are known as histone acetyltransferases (HATs), which have been shown to have a critical role in memory formation (Alarcón et al., 2004; Guan et al., 2002; Korzus, Rosenfeld, & Mayford, 2004; Levenson et al., 2004; Vecsey et al., 2007; Wood, Attner, Oliveira, Brindle, & Abel, 2006; Wood et al., 2005) and are discussed in detail in other reviews (Anamika et al., 2010; Berndsen & Denu, 2008; Selvi, Cassel, Kundu, & Boutillier, 2010), and the complementary family of histone deacetylases (HDACs), which are the focus here.

#### 1.2.1. HDAC family

HDACs remove the acetyl group from the ε-amino group of lysine side chains with the N-terminal tails of histones (and other non-histone substrates). In doing so, HDACs favor the closed, repressive state of chromatin through 'cis' regulatory mechanisms involving interaction of positively charged histone tails with negatively charged phosphodiester backbone, and the further recruitment of other transcriptional co-repressors through 'trans' regulatory mechanisms involving changes in bromodomain-mediated recruitment of proteins (Grozinger & Schreiber, 2002; Ruthenburg et al., 2007). There are a total of 18 HDAC enzymes in the mammalian genome (reviewed in de Ruijter, van Gennip, Caron, Kemp, and van Kuilenburg (2003) and Smith, Hallows, and Denu (2008)). These enzymes generally divided into four classes including class I, II, III and IV, based on sequence homology to their yeast counterparts. Among the HDACs, classes I, II and IV HDACs are the zinc-dependent hydrolases. Class I HDACs include 1, 2, 3, and 8, which have been well documented to exert deacetylase activity on histone substrates as well as non-histone substrates. Class II HDACs can be divided into class IIa members, which include HDAC 4, 5, 7 and 9, and class IIb members, which include HDAC6 and 10.

In the case of HDAC5, a role in the brain has been identified in response to both antidepressant action (Tsankova, Berton, Renthal, Neve, & Nestler, 2006), to chronic emotional stimuli (Renthal et al., 2007), as well as regulation of long-term potentiation (Guan et al., 2002). HDAC4 and HDAC5 have also been shown to undergo nucleocytoplasmic trafficking in response to neural activity (Chawla, Vanhoutte, Arnold, Huang, & Bading, 2003). Similarly, an additional class IIa family member, HDAC9, has recently been shown to regulate activity-dependent gene expression and dendritic growth in developing cortical neurons (Sugo et al., 2010).

Class IIb family members, HDAC6 and 10 are mainly localized in the cytoplasm. HDAC6 is unique in the family in its possession of two deacetylase domains. HDAC6 has been shown to function as both an α-tubulin (K40) deacetylase (Haggarty, Koeller, Wong, Grozinger, & Schreiber, 2003; Haggarty, Wong, Koeller, Butcher, & Schreiber, 2003), and to regulate neurotrophic factor trafficking (Dompierre et al., 2007). Through its actives as a tubulin deacetylases, HDAC6 has been identified as having an important role in the modulation of mitochondrial transport in hippocampal neurons in response to serotonergic neurotransmission in a manner that is dependent upon GSK3β activity (Chen, Owens, Makarenkova, & Edelman, 2010).

HDAC11 is classified as a class IV HDAC, and despite its high levels of expression in the mouse brain very little is know about its biological role and inhibitor sensitivity.

In contrast to the class I/II/IV HDACs, class III HDACs (sirtuins; SIRT1-7) are NAD(+)-dependent enzymes, which exhibit a non-overlapping sensitivity to most structural classes of inhibitors (reviewed in Smith et al., 2008). For reasons of limited space, and the fact that most HDAC inhibitors that have been shown to enhance memory formation do not target this class of HDACs (see below), we will not consider these family members in more detail here.

#### 1.2.2. Brain expression of HDACs

Analysis of the expression levels and distribution of HDAC1-11 in the mouse brain using the Allen Brain Atlas indicates that all isoforms are expressed at varying levels throughout the brain. Expression studies in rat have shown that most HDACs are expressed in the adult brain predominantly in neurons (Broide et al., 2007). Recent studies by MacDonald and Roskams (2008) and Guan et al. (2009) have shown that HDAC1 is predominantly expressed in glia and neural progenitor cells. In contrast, HDAC2 is more highly expressed in mature neurons and to a lesser extent in differentiated glial cells. These findings suggest important roles for class I HDACs in the development of the nervous system. Indeed, loss of both HDAC1 and HDAC2 leads to severely aberrant brain development through disruption of neural precursor differentiation (Montgomery, Hsieh, Barbosa, Richardson, & Olson, 2009).

#### 1.2.3. HDAC complexes

Numerous studies have shown that HDACs function as part of large multiprotein complexes that are targeted to chromatin by DNA binding proteins. A number of biochemically purified HDAC-containing complexes have been characterized, including Sin3 complexes, CoREST complexes, and NuRD complexes (Bantscheff et al., 2011; Grozinger & Schreiber, 2002; Ruthenburg et al., 2007). However, the exact composition and mechanisms of regulation of these chromatin-modifying complexes in the brain and in different cell types remains poorly understood but a fascinating area for future investigation. Given the differences and cofactors and complex components, there are likely a number of allosteric regulatory mechanisms that govern the function of HDACs.

### 1.3. Targeting HDACs with small-molecule probes

Efforts are underway in the field of neuroepigenetics to develop selective, brain-penetrant, small-molecule probes of chromatin-modifying and chromatin-remodeling complexes that affect neural activity-regulated gene transcription and other epigenetic mechanisms of regulation. Most advanced in this area are efforts to selectively target the enzymatic activity of members of the HDAC family. As discussed below in more detail, it has been demonstrated that it is possible with HDAC inhibitors to manipulate the acetylation state of histones in the promoters of certain genes thereby affecting neural activity-regulated gene transcription and neuroplasticity leading under certain conditions to enhanced memory formation. These findings have important implications to the fundamental mechanisms of memory and may potentially provide new avenues for therapeutic development for a range of disorders involving altered neuroplasticity.

#### 1.3.1. Classes of HDAC inhibitors

Four major classes of small-molecule probes of HDAC function presently exist, including inhibitors presently in clinical trials or already approved by the F.D.A.: (1) carboxylic acids (e.g., butyrate, valproate), (2) hydroxamic acids (e.g., trichostatin A and SAHA (suberoylanilide hydroxamic acid), (3) ortho-aminoanilines (e.g., MS-275), and 4) natural products (e.g., trapoxin, FK228) (Fig. 1A). Only the first three of these classes have to date been explored in the context of animal models of learning and memory (Table 1).