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Histone deacetylases 1 and 2 are required for brain development

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ABSTRACT Epigenetic modifications of histones have been implicated in the regulation of cell specific expression of genes required for neuronal development. The best studied post-translational (epigenetic) modification of histones is the process of reversible acetylation. Two types of enzymes - histone acetyltransferases (HATs) and histone deacetylases (HDACs) establish and maintain specific patterns of histone acetylation in balance, thereby contributing to both transcriptional activation and repression of specific sets of genes. Histone deacetylases catalyze the removal of acetyl groups from selected lysine residues in the conserved tails of core histone proteins and are considered as transcriptional corepressors. A significant amount of data implicates HDACs in diverse biological processes, including tissue specific developmental program by silencing specific growth-inhibitory genes. In line with this, gene disruption studies have shown that the class I deacetylases, HDAC1 and HDAC2 play an essential role in nervous system development. In the present review, we briefly highlight current insights supporting the function of histone deacetylases in rodent brain development and discuss present knowledge referring to their role in neurogenesis, taking into consideration results obtained in culture systems and in *in vivo* studies.

KEY WORDS: *histone, deacetylase, brain, development*

Introduction

Epigenetic modifications of both DNA and histones are emerging as essential mechanisms regulating many important cellular processes including the expression of genes required for neuronal development. One type of modification is a coordinated process carried out by two classes of nuclear enzymes, histone acetylases (HATs) and deacetylases (HDACs). Histone acetylation is a particularly important modification of histone amino-termini, because increased levels of histone acetylation are associated with transcriptionally-permissive chromatin, whereas deacetylation (hypoacetylation) with gene silencing (Strahl and Allis 2000; Marks *et al.,* 2003; Saha and Pahan 2006). Thus, HATs and HDACs provide the enzymatic basis for transcriptional activation and repression, respectively, through alteration of the chromatin landscape. In addition, HDACs control gene expression by regulating acetylation of DNA sequence-specific transcription factors (Wilson *et al.,* 2006).

A substantial body of evidence has documented the necessity of HDACs function for normal developmental processes by silencing the expression of specific growth–inhibitory genes (Lagger *et al.*, 2002). The biological functions of individual HDACs have been difficult to determine due to the lack of isoform-specific pharmacological inhibitor agents. Nevertheless, the use of constitutive knockout (germline mutations) of many of the individual HDACs occurred to be lethal, either during embryonic or very early postnatal development with deleterious effects on distinct tissues or cellular processes recognized as the proximal cause of death (Lagger *et al.,* 2002; Haberland *et al.,* 2009a,b). Recent advances in this field have identified key roles for class I and class II HDACs in the proper development of specific tissues. Moreover, emerging literature now positions class I HDACS, HDAC1 and HDAC2 in particular, as important control points in brain development. The highly homologous HDAC1 and HDAC2 are detected at different stages of neuronal commitment and differentiation during central nervous system age-dependent evolution. This implicates their contribution to the regulation of the developmentally specific gene expression and to the maintenance of the CNS. These processes appear to be particularly sensitive to disruption in epigenetic gene

Abbreviations used in this paper: HDACs, histone deacetylases; HATs, histone acetyltransferases; CNS, central nervous system; ECM, extracellular matrix; VPA, valproic acid; NaB, sodium butyrate; TSA, trichostatin A.

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regulation, leading among others to syndromes associated with mental retardation (Egger *et al.*, 2004) as well as complex psychiatric disorders (Grayson *et al.*, 2005).

The primary objective of this review is to provide a brief overview of HDAC1 and HDAC2 function in neural development and summarize the current knowledge about their involvement in neurogenesis.

Overview of the HDAC family

Histone deacetylases (HDACs) are conserved enzymes that are found in organisms from *Saccharomyces cerevisiae* to humans. HDACs exist in multiprotein complexes with transcription factors, DNA-binding proteins and other chromatin modifying enzymes and their assembly into complexes is required for full deacetylase activity (Zhang *et al.*, 1999). HDACs regulate activity of their substrates by removing acetyl groups from lysine residues.

Molecular studies have shown that histone deacetylases are involved in epigenetic modifications that shift the balance toward chromatin condensation and silencing of gene expression and protein functions. In mammals, so far 18 deacetylases have been identified (Verdin *et al.*, 2003). They are grouped into four different classes, based on DNA sequence similarity and function (Thiagalingam *et al.*, 2003). Class I HDACs (HDAC 1, HDAC2, HDAC3 and HDAC8) display an extensive presence in nuclei and show ubiquitous expression in various mammalian cell lines and tissues. Class I HDACs have been most widely studied in their classical role as histone modifiers and transcriptional repressors. Class II HDACs further organized into class IIa (HDAC4, 5, 7 and 9) and IIb

TABLE 1

CLASSIFICATION AND PHENOTYPES OF WHOLE BODY AND BRAIN-SPECIFIC KNOCKOUTS (KO) OF HISTONE DEACETYLASE (HDAC) ISOFORMS

	Co-factor	Subcellular localization	Constitutive KO defects	Conditional brain KO changes	References
Class I	Zn^{2+}				
HDAC 1		Nucleus	Lethal (E10.5); Severe proliferation defects and general growth retardation	NR	Lagger *et al.* 2002; Kim *et al.* 2008; Bardai *et al.* 2012; Kim and Bae 2011
HDAC 2		Nucleus	Die within 24h after birth; Severe cardiac defects	Enhanced memory, LTP	Montgomery *et al.* 2007; Guan *et al.* 2009; Kim and Bae 2011; Morris *et al.* 2013
HDAC 3		Nucleus/ Cytoplasm	Lethal (before E9.5) owing to defects in gastrulation	Enhanced episodic memory	Montgomery *et al.* 2008; Bardai and D'Mello 2011; Bardai *et al.* 2012; McQuown *et al.* 2011; Kim and Bae 2011
HDAC 8		Nucleus	Deficiency of cranial neural crest cells, perinatal death due to skull instability	NR	Haberland *et al.* 2009a,b
Class IIa	Zn^{2+}				
HDAC 4		Nucleus/ Cytoplasm	Lethal within 7 days owing to ectopic ossification of endochondral cartilage, which prevents expansion of the rib cage and leads to an inability to breathe	Impaired learning, LTP	Vega *et al.* 2004; Kim *et al.* 2012; Sando *et al.* 2012; Majdzadeh *et al.* 2008; Chen and Cepko 2009; Kim and Bae 2011
HDAC 5		Nucleus/ Cytoplasm	Viable; Cardiac defects	Enhanced cocaine sensitivity; anhedonia; learning and memory impairment	Haberland *et al.* 2009a,b; Renthal *et al.* 2007; Linseman *et al.* 2003; Agis-Balboa *et al.* 2013; Kim and Bae 2011
HDAC 7		Nucleus/ Cytoplasm	Embryonic lethality owing to a loss of integrity of endothelial-cell interactions and consequent rupture of blood vessels and haemorrhaging	NR	Chang *et al.* 2006; Ma and D'Mello 2011; Kim and Bae 2011
HDAC 9		Nucleus/ Cytoplasm	Viable; Cardiac defects	NR	Haberland *et al.* 2009a,b; Morrison *et al.* 2006; Kim and Bae 2011
Class IIb	Zn^{2+}				
HDAC 6		Cytoplasm	Viable; increased tubulin acetylation	Hyperactive, anxiolytic	Hubbert *et al.* 2002; Fukada *et al.* 2012; Pandey *et al.* 2007a,b; Dompierre *et al.* 2007; Rivieccio *et al.* 2009
HDAC 10		Cytoplasm	NR	NR	Kao *et al.* 2002
Class III sirtuins	NAD^{+}				
Sir 1		Nucleus	Most mice die perinatally; retinal, bone and cardiac defects	Memory deficit, no adaptive feeding response to Calorie restriction, less serum IGF1	Nakagawa and Guarente 2011; Finkel *et al.* 2009
Sir 2		Nucleus/ Cytoplasm	Viable	NR	Nakagawa and Guarente 2011
Sir 3		Mitochondria	Defects in fatty acid oxidation, cancer prone, oocytes exhibit developmental arrest after IVF, accumulation of hyperacetylated mitochondrial proteins, reduced respiration and ATP levels	NR	Nakagawa and Guarente 2011
Sir 4		Mitochondria	Appear healthy, increased mitochondrial GDH activity	NR	Finkel *et al.* 2009
Sir 5		Mitochondria	Defect in urea cycle, hyperammonemia after fasting	NR	Nakagawa and Guarente 2011
Sir 6		Nucleus	Die around 4 weeks showing premature aging phenotype (lymphopenia, loss of subcutaneous fat), hyperglycemia, increased glucose uptake, genomic instability	Exhibit growth retardation, with lower levels of pituitary growth hormone and IGF-1	Nakagawa and Guarente 2011; Sebastián *et al.* 2012
Sir 7		Nucleus	Die around 1 year showing premature aging phenotypes (kyphosis, loss of subcutaneous fat, degenerative cardiac hypertrophy), increased apoptosis	NR	Nakagawa and Guarente 2011
Class IV	Zn^{2+}				
HDAC 11		Nucleus	NR	NR	Gao *et al.* 2002

NR – not reported.

(HDAC6 and 10) can shuttle between the nucleus and cytoplasm (Khochbin *et al.,* 2001; Wang and Yang 2001; Xu *et al.,* 2007). Of note, only HDAC6 is predominantly cytoplasmic (Guardiola *et al.*, 2002). In some cases class IIa HDACs can also act as transcriptional activators, but in either situation these enzymes primarily control gene expression by recruiting other proteins (corepressors or coactivators) (Martin *et al.*, 2007). The sirtuins, which have an uncommon property in that they require NAD^+ as a cofactor for their enzymatic activity, are referred to as class III HDACs (Imai *et al.,* 2000; Baur *et al.,* 2012). Class IV HDACs have a unique catalytic domain and are overall structurally distinct from class I and II HDACs (Gregoretti *et al.*, 2004). Class IV currently consists of one member, HDAC 11, with little known of its function. The enzymes belonging to class I, II, III and IV are categorized either "zinc-dependent" or "NAD^+-dependent" (sirtuins).

Although histones represent the most intensively studied substrates for these enzymes, at least 50 non-histone proteins of known biological function have been identified, which may be deacetylated by HDACs. These include transcription factors, transcription regulators, signal transduction mediators, DNA repair enzymes, nuclear import regulators, chaperone proteins, structural proteins, inflammation mediators (Xu *et al.*, 2007). Thus, specific modifications of a great number of HDAC substrates indicate the implication of deacetylation in the whole array of biological processes, including among others regulation of development, neurogenesis, apoptosis, synaptogenesis, and neurite outgrowth. Biological functions of individual HDACs have been difficult to define due to the lack of isoform-specific inhibitors. Nevertheless, constitutive deletion of some isoforms of class I HDACs, e.g. HDAC1 or 3 causes severe developmental defects and lethality. Based on these data we can conclude that deacetylases exert prominent influence on physiological processes. It is well known that post-translational modification of histone acetylation states occurs at various developmental stages and any disruption of HDACs function can cause severe defects (Grayson *et al.,* 2005; Veldic *et al.,* 2005) (see Table 1).

Expression of HDAC1 and HDAC2 during brain development

Neuronal development relies on a number of sequential events where a pool of undifferentiated embryonic progenitor cells give rise to a variety of specialized neurons and glial cells. Several studies revealed redundant and essential roles of both, class I and II HDACs, in multiple levels of development and tissue patterning (De Rubertis *et al.,* 1996; Shi and Mello 1998; Lagger *et al.* 2002; Brunmeir *et al.,* 2009; Pillai *et al.,* 2004). To support this, some evidence indicate that constitutive deletion of most HDACs lead to severe neuronal death (Haberland *et al.*, 2009a,b). The wide expression pattern of a number of HDACs in the developing brain suggests specific roles for individual HDACs in neuronal development. Studies performed in zebrafish and, more importantly, in small mammals revealed particularly important functions of two deacetylases, HDAC1 and HDAC2, in the central nervous system development (MacDonald and Roskams 2008; Montgomery *et al.,* 2009, Hagelkruys *et al.,* 2014). Both deacetylase isoforms are ubiquitously expressed in a variety of different organisms and according to Dufourcq *et al.,* (2002) can be detected as early as the time of initiation of embryonic transcription. Nevertheless, mRNA and protein levels vary between species and early stages of development (Brunmeir *et al.*, 2009). During the later stage of embryogenesis, expression of both isoforms, HDAC1 and HDAC2, becomes mostly pronounced in the regions displaying ongoing organogenesis. Analysis of several species (e.g. *Xenopus*, *Drosophila melanogaster*, zebrafish) revealed noticeable HDAC1 expression in the developing head area, including the central nervous system and brain (Mannervik and Levine 1999; Damjanowski *et al.,* 2000; Mottus *et al.,* 2000; Pillai *et al.,* 2004).

Of note, a significant part of our knowledge about the functions of HDAC1 and HDAC2 in the embryonic nervous system development was provided by extensive studies performed on zebrafish. The study on embryonic brain development of the zebrafish has discovered the existence of a core neurogenic program regulated by histone post-translational modifications (Harrison *et al.*, 2011). Importantly, HDAC1 was identified as a factor regulating positively the transcription of key genes for neuronal specification and patterning during zebrafish development. Moreover, it was found that the mutation of *hdac1* caused several developmental defects in this species, such as failure of neuron and glia cell formation in the hindbrain, loss of segmental organization of postmitotic neurons and glia cells, and deficit in branching of motor neurons. The precise mechanism of HDAC-dependent actions are currently not well understood, however it is likely that HDAC1 is involved in the suppression of the Notch-responsive transcriptional repressor resulting in inhibition of proneural gene expression. In addition, HDAC1 has also been implicated in the regulation of developmental signalling cascade such as Hedgehog and Fgf8 during embryonic neurogenesis (Cunliffe 2004; Pillai *et al.,* 2004; Cunliffe and Casaccia-Bonefil 2006).

The *in vivo* requirement for HDAC1 and HDAC2 in normal embryonic brain development has recently been validated through analysis of mice with double deletion of both isoforms in the brain. This approach resulted in the robust abnormalities of cortical, hippocampal, and cerebellar development. The neuronal defects originated between embryonic day E14.5 and E 16.5, the time of extensive neurogenesis and neuronal migration and can be attributed to a failure of neural precursor differentiation into mature neurons and finally to excessive cell death. The mice did not survive beyond postnatal day 7. These results indicate that HDAC1 and HDAC2 act as redundant regulators of differentiation during brain structure development. In contrast, deletion of either HDAC1 or HDAC2 individually in the central nervous system does not evoke an overt developmental phenotype in mice, which live to adulthood (Montgomery *et al.*, 2009). In this publication for a selective deletion of HDAC1 or HDAC2, the authors used a Cre/loxP system in cells expressing GFAP (somatic mutation). Despite the common function of both deacetylases, recently published data revealed a major role of HDAC2 in brain development where it controls the fate of neural progenitors, thus contributing to the survival of animals (Hagelkruys *et al.*, 2014).

In addition to the neurodevelopmental abnormalities resulting from the simultaneous loss of HDAC1 and HDAC2, HDAC3 deletion also displays severe neurological deficits and premature death (Norwood *et al.,* 2014).

In all stages of development, HDAC1 is predominantly expressed in proliferating neuro-glial progenitors, but is down-regulated as they differentiate into neurons. On the other hand, this isoform becomes maintained as progenitors differentiate into glia in the postnatal brain. In contrast, expression of HDAC2 is first induced in

a subset of progenitor cells and is up-regulated as the progenitors commit to a neuronal lineage (Fig.1). Throughout the adult brain HDAC1 expression is primarily glial while HDAC2 is expressed in neurons (McDonald and Roskams 2008; Baltan 2012).

The involvement of HDAC1 and HDAC2 in neurogenesis

Expression of both deacetylases, HDAC1 and HDAC2, in neural progenitors and stem cells embryonically as well as in adults supports their involvement in the regulation of proliferation and in subsequent phenotypic differentiation - the key steps of neurogenesis (McDonald and Roskams 2008, Humphrey *et al.,* 2008; Montgomery *et al.,* 2009). In addition, deletion of HDAC1 in mouse embryo displays significant reduction in the number of proliferating cells (Lagger *et al.*, 2002). The mechanism of action probably relates, at least in part, to up regulation of the cyclin kinase inhibitor $p21^{WAF1/CIP1}$ in HDAC1 null cells (Lagger *et al.*, 2002). A *Hdac1* mutation in the zebrafish retina, on the other hand, leads to an increase in the number of proliferating cells (Yamaguchi *et al.*, 2005). These obvious discrepancies in the results could be explained by differences in the model employed.

To further evaluate the role of HDACs–mediated effect on cell proliferation several laboratories examined the consequences of deacetylase inhibition. To date, a variety of pharmacological agents (e.g. VPA, NaB, and TSA) were tested in several cell culture systems (including progenitors isolated from neurogenic subgranular and subventricular zones of adult rats, and fetal slice cultures), displaying either a promoting (Hao *et al.,* 2004; Sintoni *et al.,* 2013) or inhibiting (Hsieh *et al.,* 2004; Liu *et al.,* 2012) effect on cell proliferation. Taken together, the obtained results are inconclusive. The obtained diverse effect may depend on the origin of precursor cells, as well as the procedures used for neural progenitor isolation.

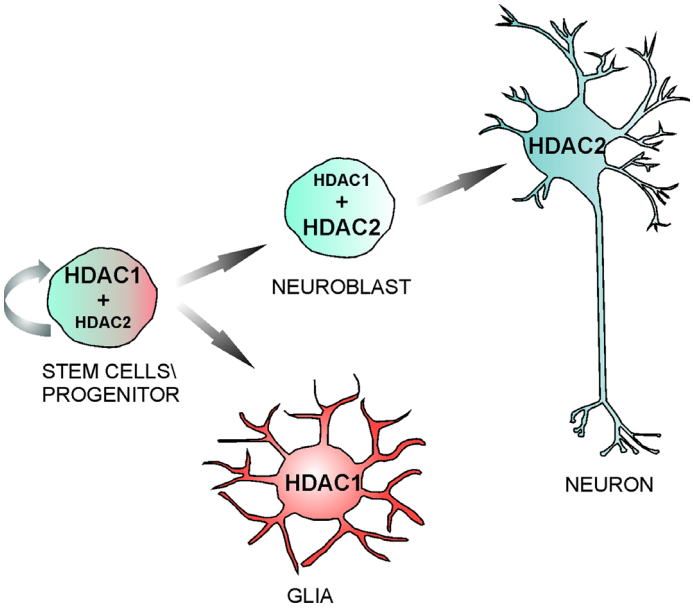

Fig. 1. Expression of HDAC1 and HDAC2 during neural development. *HDCA1 is predominantly expressed in proliferating neuro-glial progenitors, but is down-regulated as they differentiate into neurons. Expression of HDAC2 is only weakly detected in some stem/progenitors cells and is up-regulated as the progenitors commit to a neuronal lineage. Throughout the adult brain HDAC1 expression is primarily glial while HDAC2 is expressed in neurons. (According to MacDonald and Roskams, 2008, modified).*

Importantly, the decreased cell proliferation in the presence of HDAC inhibitors was accompanied by promotion of neuronal phenotypic differentiation (Hsieh *et al.,* 2004; Jessberger *et al.,* 2007; Umka *et al.,* 2010; Yao *et al.,* 2010; Zhou *et al.,* 2011a,b; Huang *et al.,* 2012; Liu *et al.,* 2012) and by simultaneous up-regulation of genes such as NeuroD, SCG19, synapsin, governing differentiation towards neurons (Hao *et al.*, 2004). By contrast, differentiation towards the oligodendrocytes and astrocytes was inhibited.

Neuronal differentiation at the expense of glial differentiation has been noted with a variety of HDAC inhibitors in both embryonic and glial progenitors (Hsieh *et al.,* 2004; Laeng *et al.,* 2004; Siebzehnrubl *et al.,* 2007). This data implicate the necessity of HDAC to repress neuronal genes and then to allow glial differentiation. This hypothesis is consistent with lower levels of acetylated histones in astrocytes and oligodendrocytes in comparison to neurons and neural progenitors. Accordingly, it may be supposed that during differentiation of glial lineages deacetylation is more extensive (Hsieh *et al.*, 2004). In addition, the notable expression of HDAC1 in glial cells during postnatal development may indicate a particular engagement of this isoform in deacetylation during glial development (MacDonald and Roskams, 2008).

In an attempt to delineate the specific function of HDACs "dominant-negative" stem cell lines expressing mutants of HDAC isoforms - HDAC1, HDAC2, and HDAC3, with reduced enzymatic activity but with preserving the ability to form protein complexes, were constructed (Humphrey *et al.*, 2008). It was found that the transduction of fetal stem cells with these mutants shifted cell fate choice to oligodendrocytes. These results indicate that in stem cells HDACs may normally complex with repressors of oligodendrocyte or astrocyte differentiation. Furthermore, the repressor complex may be displaced by glia promoting complexes shortly after mitotic arrest. This suggestion remains in line with the requirement of HDACs activity for maturation of post-mitotic oligodendrocytes (Marin-Husstege *et al.,* 2002). The mentioned above differences in outcomes may reflect the cellular context in which HDAC inhibition occurs.

There is general agreement that histone deacetylases play an essential function in regulating differentiation of neural precursor cells to oligodendrocytes in the developing brain in rodents (Marin-Husstege *et al.,* 2002; Shen *et al.,* 2005; Ye *et al.,* 2009; Chen *et al.,* 2011; Jacob *et al.,* 2011). It was reported that genetic ablation of HDAC1 and HDAC2 in the mouse blocks oligodendrocyte differentiation by activation of Wnt/beta catenin signaling pathway. The differentiation process is in part initiated by deacetylation of histone H3 by HDACs, which leads to down-regulation of myelin inhibitor gene expression and prevents progenitor cells from choosing neuronal or astrocytic lineage commitment (Ye *et al.*, 2009).

In contrast, astrocytic differentiation was not affected by loss of HDAC1 and 2 in progenitor cells. Cells lacking HDAC1 and 2 together were able to differentiate into astrocytes at similar levels as wild-type controls.

The described above finding that treatment with inhibitors of adult or embryonic neuronal precursors specifically induces the differentiation to neurons (Hsieh *et al.,* 2004; Shakèd *et al.,* 2008; Balasubramaniyan *et al.,* 2006) is rather astonishing in light of data showing that deletion of HDAC1and HDAC2 induces cell death

during differentiation to neurons specifically (Montgomery *et al.*, 2009). A similar phenotype has been noted in a lower organism such as zebrafish where mutants for HDAC1 show a blockade of neuronal differentiation *in vivo* through the activation of the neurogenic repressor which in consequence leads to significant apoptosis of neural progenitor cells in hindbrain (Cunliffe *et al.,* 2004; Stadler *et al.,* 2005). Moreover, neuronal precursors transduced with a mutant HDAC1 devoid catalytic activity showed a 50% reduction in neuronal specification (Humphrey *et al.*, 2008). It may be speculated that HDAC proteins remain integrated within transcriptional complexes despite the presence of HDAC inhibitors. In contrast, the complete absence of HDAC proteins may perturb protein-protein integration required for modulation of transcriptional programs that are otherwise insensitive to HDAC inhibition. Thus, taking into account that available inhibitory agents are not highly-specific, studies using conditional knock-out mice presenting complete loss of function provide more insight into the direct role of histone deacetylation in regulating specific aspects of neurogenesis and the potential molecular mechanism.

The present data does not allow us to state if both deacetylase isoforms act independently on one another or cooperate. In fact, HDAC2 is expressed in proliferating progenitors in both the embryo and adult, and is up-regulated in neuroblasts where it could potentially act together with HDAC1 to regulate the cell cycle (Yamaguchi *et al.*, 2005). On the other hand, upon lineage specification into either glial cells or neuroblasts and postmitotic neurons, HDAC1 and 2 present different cellular and subcellular expression and utilize different signaling pathways to influence their substrates. Finally, HDAC2 activity is necessary to inhibit astrocyte differentiation while HDAC1 is not (Humphrey *et al.*, 2008). This may suggest that HDAC2 is involved in silencing glial gene expression, while HDAC1 silences neuronal genes (Humphrey *et al.,* 2008; MacDonald and Roskams 2008). Moreover HDAC1 is not crucial for enzymatic function of HDAC2 in embryonic stem cells, however overexpression of HDAC2 cannot compensate for the loss of HDAC1 (Lagger *et al.*, 2002).

Epigenetic regulation of neurodevelopment contributes to the structural brain tissue pattern during neurogenesis and further continues to impact on cell migration. In accordance with this, alterations in the level of human or *C. elegans* HDAC1 affected cell migration (Whetstine *et al.,* 2005; Zinovyeva *et al.,* 2006), probably by regulating genes involved in the architecture of ECM.

HDACs appear to be also decisive for early synaptogenesis and promotion of synaptic network stability. It is worth pointing out, that the roles of HDACs in control of excitatory synapse maturation and function are covered by Akhtar *et al.,* (2009) and Guan *et al.,* (2009) and will not be addressed in detail. Nevertheless, it is postulated that HDAC1 and HDAC2 form a developmental switch that controls excitatory synapse and function which is dependent on the maturational state of the neurons. During the early synapse development HDAC1 and HDAC2 restrict the progression of excitatory synapse maturation and thereby most probably suppress excitatory neurotransmission. An opposite effect (augmented excitatory neurotransmission) was noted when neuronal networks mature and synapse numbers significantly increase. Interestingly, under the same conditions, HDAC activity does not impact inhibitory neurotransmission, which showed an over 50 fold increase over development, suggesting network specificity in the epigenetic control of synaptic circuits. Together, these results indicate that HDAC1 and 2 are critical regulators of excitation-inhibition balance in developing synaptic networks through their control of excitatory drive (Akhtar *et al.,* 2009; Jawerka *et al.,* 2010).

Conclusion

Collectively, the data presented in this mini review highlight the potential significance of HDAC1- and HDAC2–mediated epigenetic regulation of different stages of brain development. It is becoming clear that an extensive number of developmental decisions and differentiation programs depend on HDAC1 and HDAC2 as cofactors. Considering the potential function of HDACs in the nervous system development it should be remembered that histones are not the sole target or substrate of HDAC1 as well as HDAC2. Several HDAC isoforms have been shown to regulate acetylation of a plethora proteins e.g. tubulin, p53, and Hsp90 (Yao *et al.,* 2001; Hubbert *et al.,* 2002; Ito *et al.,* 2002) thus, we cannot rule out the possibility that they might play a more direct role in the nervous system development. Moreover, cell type specific functions still remain to be seen, cross regulatory mechanisms and regulations of deacetylase activity. Future development of this research should be able to increase available data and, in addition, to clarify the role of individual HDACs in different steps of neurodevelopment.

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