HHS Public Access

Author manuscript

J Neurochem. Author manuscript; available in PMC 2019 April 06.

Published in final edited form as:

J Neurochem. 2018 April ; 145(2): 96–110. doi:10.1111/jnc.14309.

Complex neuroprotective and neurotoxic effects of histone deacetylases

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Abstract

By their ability to shatter quality of life for both patients and caregivers, neurodegenerative diseases are the most devastating of human disorders. Unfortunately, there are no effective or long-terms treatments capable of slowing down the relentless loss of neurons in any of these diseases. One impediment is the lack of detailed knowledge of the molecular mechanisms underlying the processes of neurodegeneration. While some neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and Amyotrophic lateral sclerosis, are mostly sporadic in nature, driven by both environment and genetic susceptibility, many others, including Huntington's disease, Spinocerebellar ataxias and Spinal-bulbar muscular atrophy, are genetically inherited disorders. Surprisingly, given their different roots and etiologies, both sporadic and genetic neurodegenerative disorders have been linked to disease mechanisms involving histone deacetylase (HDAC) proteins, which consists of 18 family members with diverse functions. While most studies have implicated certain HDAC subtypes in promoting neurodegeneration, a substantial body of literature suggests that other HDAC proteins can preserve neuronal viability. Of particular interest, however, is the recent realization that a single HDAC subtype can have both neuroprotective and neurotoxic effects. Diverse mechanisms, beyond transcriptional regulation have been linked to these effects, including deacetylation of non-histone proteins, protein-protein interactions, post-translational modifications of the HDAC proteins themselves and direct interactions with disease proteins. The roles of these HDACs in both sporadic and genetic neurodegenerative diseases will be discussed in the current review.

Graphical Abstract

In our review we describe that some members of the histone deactylase (HDAC) family, such as HDACs 2 and 3, promote neurodegeneration whereas others, such as HDACs 5, 7 and 9 protect against it. HDACs 1 and 3 have both neuroprotective and neurotoxic roles. These actions are mediated through histone acetylation, non-histone acetylation, posttranslational modifications and protein-protein interactions. The roles of these HDACs in both sporadic and genetic neurodegenerative diseases are discussed in the current review.

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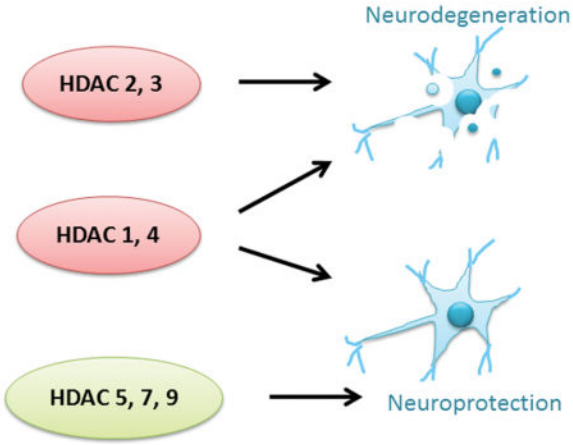
conflict of interest disclosure. The authors have no conflict of interest.



Keywords

Histone deacetylase; Neurodegenerative diseases; Neuroprotection; Huntington's disease

INTRODUCTION

Studies over the past decade have implicated HDAC proteins in a wide range of neurodegenerative diseases, including polyglutamine disorders, Alzheimer's disease, Parkinson's disease, as well as other conditions associated with neuronal loss, such as ischemic stroke(D'Mello 2009; Sleiman *et al.* 2009; Thomas 2009). Accordingly, the use of inhibitors of these enzymes as a potential therapeutic option to treat these disorders has gained much recent attention. HDAC inhibitors have been shown to be effective in numerous different mouse models of neurodegenerative diseases (D'Mello 2009; Sleiman *et al.* 2009; Thomas 2009). However, HDAC enzymes comprise a large family of proteins and it has become clear that individual HDAC enzymes play vastly different biological roles in the brain, complicating the potentially diverse effects elicited by HDAC inhibitors. The design of subtype-selective HDAC inhibitors represents a major improvement to this line of therapy, however, it is essential to elucidate the distinct and varied roles of individual HDAC proteins, for their potential clinical utility to be fully realized(Millard *et al.* 2017; Thomas 2009). This is especially important, given that many HDAC family members have been shown to exhibit both neurotoxic and neuroprotective properties, as we will review herein. This review focuses on the neurotoxic and neuroprotective roles of classical (i.e. class I and II) HDACs in neurodegenerative disorders. The role of class II HDACs (aka sirtuins) in the pathology of neurodegeneration has been covered in other excellent reviews (Ajami *et al.* 2017; Donmez 2012; Jesko *et al.* 2017) and will not be discussed in this review.

THE HDAC FAMILY OF PROTEINS

HDAC proteins comprise an ancient enzyme family, conserved in evolution from yeast to plants and animals (Gregoretti *et al.* 2004; Yang and Seto 2008). In humans, there are 18 HDAC subtypes, which have been divided into four separate classes based on sequence and structural homology (Gregoretti *et al.* 2004; Grozinger *et al.* 1999). Class I HDAC proteins

consist of HDACs 1, 2, 3 and 8, and show primarily nuclear localization (Wang *et al.* 2004). Class II HDACs can shuttle between the nucleus and cytoplasm and are further divided into two groups: class IIa, consisting of HDACs 4, 5, 7 and 9, and class IIb, consisting of HDACs 6 and 10 (Haberland *et al.* 2009; Xu *et al.* 2007; Yang and Seto 2008). Both class I and class II enzymes, typically referred to as "classical" HDACs, require zinc for catalytic activity. In contrast, the members of class III HDAC proteins, called the "sirtuins", are structurally unrelated from classes I and II and require NAD^+ for their enzymatic activity (Michan and Sinclair 2007; Sauve *et al.* 2006). HDAC11 is the sole member of class IV, and while sharing similar characteristics to HDACs in classes I and II, HDAC 11 is thought to differ in its physiological properties (Gao *et al.* 2002; Yang and Seto 2008). All of the classical HDACs, as well as HDAC11, are expressed in the brain, albeit at different levels depending on the region (Liu *et al.* 2008). Details on individual HDACs and their roles in neurodegenerative processes are discussed below.

HDAC MECHANISMS OF ACTION

The link between histone acetylation/deacetylation and transcriptional regulation was first realized more than 25 years ago by the identification of proteins with intrinsic histone acetylase and deacetylase activity (Kornberg and Lorch 1991). The initial founding members of the HDAC family were the human, HDAC1, and yeast Rpd3 proteins (Gregoretti *et al.* 2004; Yang and Seto 2008). Deletions of these genes resulted in increased acetylation levels in both core histones H3 and H4 (Rundlett *et al.* 1996). It is now well understood that regulation of histone acetylation by histone acetyltransferase (HAT) and HDAC enzymes, is a major driving force in the control of gene expression (Gregoretti *et al.* 2004; Yang and Seto 2008). Typically, increases in HAT activity promote acetylation of histone proteins leading to increased gene transcription by creating a more open conformation of chromatin, while HDAC activity involves removing the acetyl group from histones, which results in gene repression (Figure 1A). HDACs lack intrinsic DNA-binding activity and are recruited to target genes via their association with transcriptional activators and repressors, as well as their incorporation into large multiprotein complexes, often containing more than one HDAC subtype (Gregoretti *et al.* 2004; Haberland *et al.* 2009; Xu *et al.* 2007; Yang and Seto 2008).

Aside from their essential roles in gene transcription, HDAC proteins are now known to deacetylate a large and ever-growing number of non-histone proteins (Spange *et al.* 2009; Xu *et al.* 2007; Yang and Seto 2008) (Figure 1B). These include a variety of different transcription factors, structural proteins, ion channels, receptors and enzymes. Deacetylation of these proteins can have dramatic effects on their function, stability, sub-cellular localization, as well as their interactions with other proteins. For example, studies have shown that HDAC1, -2, and -3 deacetylate MAP kinase phosphatase (MKP1) and that this post-translational modification increases Mitogen-activated protein kinase (MAPK) and innate immune signaling (Jeong *et al.* 2014) (Figure 1B). Importantly, the acetylation status of transcription factors is known to alter DNA-binding properties and transcriptional activity. This means that HDAC proteins could exert their neurotoxic or neuroprotective actions through histone deacetylation and gene expression changes, or through a host of other mechanisms, some of which are described below and summarized in Figure 1. This also

might explain why unbiased gene expression studies have revealed that treatment with HDAC inhibitors do not always lead to increased gene expression changes, but rather, include both increases and decreases in gene activity (Gardian *et al.* 2005; Thomas *et al.* 2008a).

Although it was initially believed that all classical HDACs possess catalytic activity, subsequent analyses revealed that class IIa HDACs have minimal deacetylase activity at best and do not associate with histone tails (Jones *et al.* 2008; Lahm *et al.* 2007; Parra 2015). This is because a catalytic tyrosine residue, which is conserved in all HDAC proteins and necessary for catalytic activity, is replaced by a histidine residue in class II HDACs. Therefore, any effects class II HDACs have on neurodegeneration and that are blocked by HDAC inhibitors are likely mediated through association with class I HDACs that would allow acquisition of deacetylase activity. For example, Fischle and colleagues demonstrated that the HDAC domains of HDAC4 and HDAC5 do not possess intrinsic enzymatic activity as isolated polypeptides but are associated with HDAC activity only by interacting with HDAC3, via the transcriptional corepressor N-CoR/SMRT (Fischle *et al.* 2002) (Figure 1C).

Class IIa HDACs could regulate neurodegeneration by deacetylase-independent mechanism possibly through interaction with non-HDAC proteins (Ma and D'Mello 2011a; Majdzadeh *et al.* 2008a; Rawat *et al.* 2016). Several of such proteins have been identified, most of which interact with the N-terminal half of the HDACs (Martin *et al.* 2007). For example, the regulatory domains of class IIa HDACs have been shown to interact with transcriptional repressors, such as heterochromatin protein 1 (HP1) and C-terminal-binding protein (CTBP) (Figure 1C). Through such interactions, these class IIa HDACs can function as adaptors to regulate multiple types of transcriptional regulators and regulate downstream gene transcription (Bertos *et al.* 2001; Sparrow *et al.* 1999; Wang *et al.* 2000; Zhou *et al.* 2000). Consistent with this concept are recent reports describing that some HDAC inhibitors protect against neurodegeneration independently of their deacetylase activity (Olson *et al.* 2015; Sleiman *et al.* 2014).

NEUROTOXIC AND/OR NEUROPROTECTIVE PROPERTIES OF HDACS

The discovery of distinct neurotoxic or neuroprotective roles of individual HDACs has deepened our understanding of this family of proteins. However, the recent realization that a single HDAC can have both neuroprotective and neurodegenerative effects appears especially confusing. The basis of this is still unclear, but likely depends on context-specific and tissue/cell-specific effects, whereby different mechanisms are at play. For example, emerging evidence implicates several different mechanisms in the actions of HDACs, including protein-protein interactions, cellular localization (i.e. nucleus vs. cytoplasm), cell-type specificity, alternative splicing or post-translational modifications. Below, we describe the individual HDAC subtypes followed by the roles, in some cases opposing, for each HDAC in the regulation of neuronal survival in general, as well as in specific neurodegenerative diseases. We focus primarily on those HDAC subtypes showing strong expression in the CNS, as these are the ones that have been more consistently implicated in CNS diseases.

HDAC1

HDAC1 is perhaps the most widely studied members of the HDAC family. HDAC1 exhibits a high degree of homology to HDAC2 and has a high degree of functional overlap with HDAC2 for many biological processes (Gregoretti *et al.* 2004; Tsai and Seto 2002). However, it has become evident from knockout studies that HDAC1 and HDAC2 also have distinct and non-redundant biological functions (Brunmeir *et al.* 2009). HDAC1 is mostly localized to the nucleus; however, studies have also demonstrated that HDAC1 is expression in the cytoplasm (Jia *et al.* 2012). HDAC1 shows widespread expression throughout the brain, but is most abundantly expressed in the cerebellum, followed by amygdala and hippocampus (Broide *et al.* 2007a; Thomas 2009). HDAC1 is expressed primarily in neurons but it is also expressed in glial cells, including astrocytes (Broide *et al.* 2007a; Kalinin *et al.* 2013) and oligodendrocytes(Ye *et al.* 2009). Several lines of evidence have indicated that HDAC1 can have both neurotoxic and neuroprotective roles, which appear to depend, in part, by its cellular localization, non-histone acetylation and/or its interacting partners (Table 1).

Neurotoxic effects of HDAC1

Previous studies in cultured neurons have shown that neurotoxicity by HDAC1 depends on its export from the nucleus into the cytoplasm, resulting in disruption of axonal transport and mitochondrial dysfunction (Kim *et al.* 2010). The toxic effect of cytosolic HDAC1 on axonal transport was shown to be due to its ability to bind to motor proteins (i.e. kinesin heavy chains members 2A and 5) and α-tubulin, disrupting their ability to form complexes with cargo proteins (Kim *et al.* 2010)). Interestingly, cytosolic HDAC1 has been detected in the brains of patients with multiple sclerosis, an autoimmune disease linked to demyelination of axons, and in animal models of demyelination (Kim *et al.* 2010).

Other studies demonstrated that nuclear export of HDAC1 was dependent on post-translational modifications of HDAC1, whereby phosphorylation at Ser421 and Ser423 residues promoted nuclear export (Zhu *et al.* 2017). In that same study, the authors show that decreasing HDAC1 levels by genetic ablation was neuroprotective against acute neurotoxicity in hippocampal slices. The protective effect of *Hdac1* ablation was also detected in CA3 neurons in mice, which were more resistant to the excitotoxic damage induced by intraventricular injection of kainic acid (Zhu *et al.* 2017).

HDAC1/2-mediated acetylation of p53 has also been implicated in its neurotoxic effects (Jacob *et al.* 2011; Lebrun-Julien and Suter 2015). Studies conducted on retinal ganglion cells and Schwaan cells have shown neuroprotective effects when both the *Hdac1* and *Hdac2* genes were ablated (Jacob *et al.* 2011; Lebrun-Julien and Suter 2015). Specific *Hdac1/2* ablation inhibited this apoptotic pathway by impairing the crucial acetylation status of p53 and reducing PUMA expression, thereby contributing to the ensuing enhanced neuroprotection. In another study, a newly identified but relatively uncharacterized HDAC1/HDAC2-selective inhibitor, K560, had protective effects in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neuronal death in both *in vitro* and *in vivo* Parkinson's disease models (Choong *et al.* 2016). Treatment with K560 caused a sustained increase in

expression of XIAP (X-linked inhibitor of apoptosis) an antiapoptotic protein, leading to beneficial effects (Choong *et al.* 2016).

HDAC1 has also been linked to the pathology of Huntington's disease, an autosomal dominant, progressive neurodegenerative disease. Treatment of Huntington's disease mice with HDAC1/HDAC3-selective inhibitors was shown to elicit beneficial effects on disease phenotypes (Jia *et al.* 2012; Thomas *et al.* 2008b), although it is not entirely clear whether this was due to inhibition of HDAC1 or HDAC3, or possibly both. HDAC1 alone has been linked to Huntington's disease pathogenesis by a mechanism involving promoting autophagy and clearance of the mutant form of the huntingtin protein (Jeong *et al.* 2009; Ravikumar *et al.* 2004; Yamamoto *et al.* 2006). This was found to occur at a specifically identified lysine residue, Lys444 whereby acetylation of Lys444 facilitated trafficking of mutant huntingtin into autophagosomes, thereby promoting its clearance (Jeong *et al.* 2009). HDAC1 was implicated in this effect from knockdown studies of *Hdac1* in cultured striatal and cortical neurons and in a transgenic *C. elegans* model of Huntington's disease in which also showed increased Lys444 acetylation, improved clearance of mutant huntingtin protein and reduced neurodegeneration (Jeong *et al.* 2009). HDAC1 can also interact with HDAC3 to promote toxicity as observed in neurons primed to die both *in vitro* and in HD mice (Bardai *et al.* 2012a).

Recent studies have implicated increased levels of HDAC1/2 in synaptic dysfunction and behavioral deficits in Angelman syndrome, a neurodevelopmental disorder characterized by severe intellectual and developmental deficits caused by the loss of function of maternally inherited ubiquitin protein ligase E3A (UBE3A). Both HDAC1 and HDAC2 protein levels are robustly increased in Angelman syndrome Angelman syndrome mice along with decreased acetylation of histone H3/H4 (Jamal *et al.* 2017). Significant improvement in social, cognitive and motor impairment was described in Angelman syndrome mice after pharmacological inhibition with sodium valproate, an inhibitor selective for Class I HDACs (Jamal *et al.* 2017).

Neuroprotective effects of HDAC1

Neuroprotective roles for HDAC1 have also been reported (Morrison *et al.* 2006a),(Dobbin *et al.* 2013). While its association with HDAC3 results in a neurotoxic complex, HDAC1 interacts with histone deacetylase-related protein (HDRP) to confer neuroprotective effects in cultured neurons (Morrison *et al.* 2006a). This effect was related to a mechanism involving histone deacetylation of the c-Jun gene promoter and its repression of downstream genes (Morrison *et al.* 2006a). Another binding partner of HDAC1 is sirtuin 1 (SIRT1), a class III HDAC, which has well established neuroprotective effects (Donmez and Outeiro 2013; Outeiro *et al.* 2008). Interaction between HDAC1 and SIRT1 is thought to protect neurons by preserving genomic stability (Dobbin *et al.* 2013). Additionally, HDAC1 interacts with FUS, an RNA/DNA-binding protein mutation of which cause familial amyotrophic lateral sclerosis and frontotemporal lobar degeneration, to regulate DNA damage response and repair in neurons (Qiu *et al.* 2014; Wang *et al.* 2013). This is thought to be an important mechanism in Amyotrophic Lateral Sclerosis, whereby disease-causing mutations of FUS result in reduced association of FUS with HDAC1 (Qiu *et al.* 2014; Wang

et al. 2013). Consistent with a neuroprotective role, downregulation of HDAC1 leads to DNA damage in both cultured neurons and *in vivo* models of neurodegeneration (Kim *et al.* 2008). It is possible the reduced association with FUS facilitates the translocation of HDAC1 to the cytoplasm of degenerating neurons (Kim *et al.* 2008).

HDAC2

HDAC2, although intimately associated with HDAC1 as described above, also shows distinct roles with regards to neurotoxicity. Interestingly, HDAC2 is expressed at higher levels in the brain compared to HDAC1. It is most abundantly expressed in the hippocampus and cerebellum, followed by cortex and amygdala (Broide *et al.* 2007b; Thomas 2009). It is primarily localized in the nucleus, where it is thought to exert its effects in a more traditional manner, via regulating acetylation of histone proteins and ensuing changes in gene expression (Table 1). Past literature supports mostly a neurotoxic role for HDAC2 in the brain, as described below.

Neurotoxic effects of HDAC2

HDAC2 has been implicated in several different neurodegenerative diseases, as well as cognitive impairment, which is common to many of these disorders. Niemann-Pick type C disease is a fatal neurodegenerative disorder characterized by the accumulation of free cholesterol in lysosomes. Studies in the past five years have indicated that inhibition of HDACs is a potential treatment for this disease (Contreras *et al.* 2016), with HDAC2 being primarily implicated. HDAC2 levels and activity were shown to be increased in Niemann-Pick type C neuronal models and in *Npc1*(−/−) mice (Contreras *et al.* 2016). Neuronal gene repression in these disease models is mediated by the c-Abl/HDAC2 signaling pathway, whereby c-Abl tyrosine kinase activity increases HDAC2-induced neuronal gene repression of key synaptic genes (Contreras *et al.* 2016).

Spinal muscular atrophy is an autosomal-recessive and fatal motor neuron disease caused by mutation of the survival motor neuron (*SMN1*) gene (Lorson *et al.* 2010; Nurputra *et al.* 2013). As a result of a duplication of the SMN locus, humans express a second SMN gene, *SMN2*, which also encodes the SMN protein. Since Spinal muscular atrophy patients lack *SMN1*-derived protein, increasing expression of the *SMN2* gene has been achieved by pharmacological inhibition of HDACs, with evidence pointing to HDAC2 as being the target of these HDAC inhibitors (Kernochan *et al.* 2005; Mohseni *et al.* 2016). Importantly, the administration of HDAC inhibitors has been found to ameliorate disease phenotype in Spinal muscular atrophy mouse models (Avila *et al.* 2007; Riessland *et al.* 2010).

Genetic knockdown studies showed that heterozygous $Hdac2^{+/-}$ mice displayed less retinal degeneration than wild-type mice in a mouse model of ischemic retinal injury (Fan *et al.* 2013). In this study, HDAC2 protein was primarily localized to the nucleus, where it likely acts to alter gene expression (Fan *et al.* 2013). HDAC2 activity accounted for approximately 35% of the total HDAC activities in the retina, suggesting that treatment with class I HDAC inhibitors could reduce ischemic retinal injury due to inhibition, in part, of this subtype (Fan *et al.* 2013).

Several studies have demonstrated detrimental effects associated with HDAC2 in the context of cognitive impairment. In one study, overexpression of HDAC2 in the hippocampus was associated with hypo-acetylation of specific lysine residues, Lys12 and Lys5, on histone H4 (Guan *et al.* 2009). This effect was accompanied by decreased synapse number and synaptic plasticity, resulting in impaired memory formation. The mechanism implicated in this effect was the binding of HDAC2 to the promoters of synaptic-plasticity-related genes, thereby negatively regulating their transcription (Guan *et al.* 2009). Another study showed that HDAC2 associates with, and reduces the histone acetylation of, genes important for learning and memory (Graff *et al.* 2012). In one study, knocking down *Hdac2* by shRNA restored the structural synaptic plasticity and memory impairments in the CK-p25 mouse model of Alzheimer's disease (Graff *et al.* 2012). Alzheimer's disease is the most prevalent neurodegenerative disease associated with cognitive impairment. These findings underline the important roles of HDAC2-regulated chromatin modification in regulating synaptic plasticity and memory formation contributing to cognitive impairment, which is relevant for a wide range of neurodegenerative disorders.

HDAC3

HDAC3 is the third HDAC identified in mammals by sequence homology with HDAC1 and HDAC2 (Gregoretti *et al.* 2004; Yang and Seto 2008). Unlike the other Class I HDACs, which are normally nuclear proteins, HDAC3 localizes to both the nucleus and cytoplasm (Takami and Nakayama 2000). Germ-line deletion of *Hdac3* is lethal, indicating a requirement for proper embryonic development (Bhaskara *et al.* 2008; Montgomery *et al.* 2008). HDAC3 is found in many tissues throughout the body, especially the brain (Mahlknecht *et al.* 1999). It is the most highly expressed class I HDAC in the brain with greatest expression in the hippocampus, cortex, and cerebellum, but also shows moderate levels of expression in other important brain regions, including the striatum, amygdala and hypothalamus (Broide *et al.* 2007a; Thomas 2009). HDAC3 is predominantly expressed in neurons, but studies have also shown expression in glial cells, including astrocytes and oligodendrocytes (Broide *et al.* 2007a; Debacker *et al.* 2012; Shen *et al.* 2005). A large body of evidence from cell culture and *in vivo* models indicates that HDAC3 promotes neurodegeneration, as described below. Further, it has been implicated as a major target for the neuroprotective effects resulting from pharmacological HDAC inhibitors. The toxic effects of HDAC3 are associated with several different mechanisms, including histone acetylation, nuclear translocation, post-translational modifications and direct interactions with disease proteins (Table 1).

Neurotoxic effects of HDAC3

The first reports of neurotoxic effects of HDAC3 were from the D'Mello lab, who showed that overexpression of HDAC3 induced cell death in cortical and cerebellar granule neurons (Bardai and D'Mello 2011). Toxicity was also seen in the HT22 neuroblastoma cell line, but not in primary kidney fibroblasts or HEK293 cells, indicating neuronal specificity for the toxic effects of HDAC3 (Bardai and D'Mello 2011). Confirming its requirement for neuronal death, shRNA-mediated suppression of HDAC3 expression protected against oxidative stress and potassium deprivation-induced cell death (Bardai and D'Mello 2011). In

this study, HDAC3-induced neurotoxicity requires phosphorylation by Glycogen synthase kinase-3 beta (GSK3β), a kinase inhibited by Protein kinase B/Akt, which is widely implicated in the promotion of neurodegeneration (Bardai and D'Mello 2011; Bardai *et al.* 2013a). Interestingly, HDAC1 participation was also required for neurotoxicity by HDAC3, as knockdown of HDAC1 was shown to reduce the neurotoxic effects of HDAC3 (Bardai *et al.* 2012b). Both HDAC1 and HDAC3 are believed to be transcriptional repressors. One target of HDAC3-mediated repression could be the cell cycle inhibitory protein, Cdkn1a ($p21^{Cip1/Waf1}$)(Knutson *et al.* 2008; Trivedi *et al.* 2008; Wilson *et al.* 2006), which is known to have has strong neuroprotective activity (Harms *et al.* 2007; Langley *et al.* 2008; Louis Sam Titus *et al.* 2017; Mallick and D'Mello 2014). Consistent with the above studies, HDAC3 does inhibit $p21^{Cip1/Waf1}$ in non-neuronal systems (Knutson *et al.* 2008; Trivedi *et al.* 2008; Wilson *et al.* 2006).

HDAC3 is also important in the context of several different neurodegenerative diseases. In Huntington's disease, knockdown of HDAC3 in mutant huntingtin-overexpressing cortical neurons protects them against cell death (Bardai *et al.* 2013b). In R6/2 transgenic mice, HDAC3 has been shown to interact with HDAC1 in the striatum and the cortex (Bardai *et al.* 2012c), two brain regions that suffer neuronal loss in Huntington's disease. This interaction was found to coincide with the onset of motor deficits (Bardai *et al.* 2013b). Consistent with these results are those showing that administration of chemical inhibitors selective for HDAC1/HDAC3, or HDAC3 alone, reduced neuropathology and improved behavioral performance in R6/2 and N171-82Q transgenic mouse models of Huntington's disease (Jia *et al.* 2012; Jia *et al.* 2015; Jia *et al.* 2016; Suelves *et al.* 2017; Thomas *et al.* 2008c; Thomas 2014). Alterations in histone acetylation and ensuing gene expression were implicated in these effects (Jia *et al.* 2012; Jia *et al.* 2015; Jia *et al.* 2016; Thomas *et al.* 2008c; Thomas 2014). Protective effects of an HDAC3-selective inhibitor, RGFP966, in yet another Huntington's disease mouse model, Hdh^{Q111} knock-in mice, was also demonstrated by a different laboratory (Suelves *et al.* 2017). Genetic reduction of HDAC3 using *Hdac3 (+/−)* heterozygous mice has been reported, and was not found to ameliorate disease phenotypes when crossed with R6/2 transgenic mice (Moumne *et al.* 2012). However, the overall protein levels of HDAC3 were only reduced 20%, hence it is likely that the reduction of HDAC3 in the *Hdac3+/−* mice was not sufficient to affect the HD phenotype (Moumne *et al.* 2012).

HDAC3 has been shown to interact with wild-type huntingtin protein, but not with the mutant form (Bardai *et al.* 2013b). Although not interacting directly with HDAC3, mutant huntingtin promotes the disassociation of HDAC3 from the normal version of the protein permitting it to interact with HDAC1, leading to neurodegeneration (Bardai *et al.* 2013b). The significance of the interaction between HDAC3 and normal huntingtin remains to be investigated but is likely to be necessary for its contributions to proper brain development and functioning of the nervous system. Indeed, genetic ablation of either the *HTT* gene or HDAC3 has severe effects on brain development and function (Norwood *et al.* 2014; Saudou and Humbert 2016).

In other neurodegenerative diseases, pharmacological inhibition of HDAC3, also with RGFP966, protected CA1 hippocampal neurons against oligomeric beta-amyloid-induced impairment of synaptic plasticity (Krishna *et al.* 2016), having implications to Alzheimer's

disease. HDAC3 has also been linked to Parkinson's disease, a progressive neurodegenerative disease characterized by the loss of dopaminergic neurons in the substantia nigra (Olanow and Tatton 1999). Leucine-rich repeat kinase-2 (LRRK2), mutations of which are the most common genetic cause of both familial and sporadic Parkinson's disease (Mata *et al.* 2006), binds to HDAC3 and phosphorylates it at Ser424, which resulted in a stimulation of HDAC3 activity (Han *et al.* 2017). Additionally, LRRK2-mediated toxicity following 6-hydroxydopamine treatment increased HDAC3 phosphorylation and its nuclear localization (Han *et al.* 2017).

Death of injury-induced retinal ganglion neurons in mice was also associated with the translocation of HDAC3 to the nucleus (Schmitt *et al.* 2014). Consistent with a role for nuclear HDAC3 has been implicated in neuronal loss in rats subjected to ischemic stroke and in cultured cortical neurons subjected to oxygen-glucose deprivation (OGD) (Yang *et al.* 2016). Administration of the HDAC3-selective inhibitor, RGFP966, depleted HDAC3 from the nucleus and protected against neuronal loss both *in vivo* and in cultured neurons (Yang *et al.* 2016). A separate study described a substantial increase in HDAC3 expression soon after the induction of ischemic stroke in mice (Chen *et al.* 2012). In this study, it was found that knockdown of HDAC3 using shRNA methods protected cortical neurons from OGD-induced death (Chen *et al.* 2012). Thus, reduction of HDAC3 activity either pharmacologically or using shRNA-mediated knockdown was shown to be protective against ischemic stroke [102,103].

Recent studies provide evidence that HDAC3 might contribute to the pathogenesis of other inherited polyglutamine diseases, such as the spinocerebellar ataxias (SCAs) (Underwood and Rubinsztein 2008). Like Huntington's disease, six of the SCAs (1, 2, 3, 7, 6 and 17) are caused by an expanded CAG repeat mutation in the coding regions of the relevant disease genes (Underwood and Rubinsztein 2008). HDAC3 has been shown to interact with disease proteins for three of these, SCA1, 3 and 7, which are caused by mutations in the *ATXN1, ATXN3* and *ATXN7* genes, respectively (Underwood and Rubinsztein 2008). These autosomal-dominantly inherited disorders are characterized by aggregation of the mutant polyQ-expanded protein, nuclear inclusions and repeat-dependent neurotoxicity (Paulson *et al.* 1997; Underwood and Rubinsztein 2008).

Ataxin-1, the disease protein for SCA1, has been found to interact selectively with HDAC3 in transfected cells (Venkatraman *et al.* 2014). Interestingly and in contrast to mutant Htt, the HDAC3-ataxin 1 interaction was not polyglutamine-dependent (Venkatraman *et al.* 2014), which could suggest that inhibition of HDAC3 in this context may interfere with normal ataxin-1 regulatory properties. Indeed, ablating the HDAC3 gene selectively in Purkinje cells of SCA1 (154Q/2Q), knock-in mice resulted not in beneficial effects, but in early onset ataxia, and progressive degeneration (Venkatraman *et al.* 2014).

HDAC3 has also been shown to interact with ataxin-3, which is mutated in SCA3, also known as Machado-Joseph disease (Kawaguchi *et al.* 1994; Riess *et al.* 2008). While interacting with both normal and polyQ-expanded ataxin-3 in cultured cells and in the human pons, normal ataxin-3-containing protein complexes showed increased HDAC activity, whereas polyQ-expanded ataxin-3-containing complexes had reduced HDAC

activity in specified chromatin regions (Evert *et al.* 2006). Although the broadly-acting HDAC inhibitor, sodium butyrate, was found to reverse transcriptional downregulation and ameliorate ataxic symptoms in a transgenic mouse model of SCA3 (Chou *et al.* 2011), the consequences of selective HDAC3 inhibition, however, are less clear; it is possible that disruption of the HDAC3 repressor complex by polyQ-expanded ataxin-3 may liberate HDAC3 to elicit toxic effects in neurons, as observed in Huntington's disease models (Bardai *et al.* 2013a). Finally, HDAC3 was found to interact and stabilize both normal and polyQ-expanded ataxin-7(Chou *et al.* 2011). HDAC3 expression and interaction with ataxin-7 was elevated in neurons and glia of the cerebellum in SCA7 transgenic mice in a polyQ-dependent manner (Duncan *et al.* 2013).

HDAC4

HDAC4 is expressed widely in the brain with highest expression in the cerebellum, hippocampus and olfactory bulb (Broide *et al.* 2007b; Thomas 2009). It is a protein essential for development, as evident in *Hdac4* knock-out mice, which die in early postnatal life (Vega *et al.* 2004). HDAC4 is normally expressed in the cytoplasm, but is also known to exhibit signal-dependent shuttling between the cytoplasm and nucleus, which is regulated in part by calcium/calmodulin-dependent kinase-mediated phosphorylation (McKinsey *et al.* 2000). Confusingly, the cellular localization of HDAC4 differentially contributes to its protective versus toxic effects; with some studies showing, that nuclear HDAC4 is protective in one disease model, and toxic in another. Interestingly, recent studies demonstrated that, in fact, HDAC4 has no deacetylase activity in the brain (Mielcarek *et al.* 2013b). This finding suggests that HDAC4 exerts its effects via interactions with other HDAC proteins or other regulatory proteins. HDAC4 was first shown to be a neuroprotective protein; however, further studies have demonstrated neurotoxic properties as well, as discussed below.

Neuroprotective effects of HDAC4

Neuroprotective effects of HDAC4 were reported over a decade ago (Majdzadeh *et al.* 2008b). In early studies, overexpression of HDAC4 protected both cultured cortical neurons and cerebellar granule neurons against low potassium-induced apoptosis (Majdzadeh *et al.* 2008b). This HDAC4-mediated neuroprotection did not require its HDAC catalytic domain and was not inhibited by chemical inhibitors of HDACs. Also in that study, the authors showed that the cerebellum of HDAC4 knockout mice displayed extensive degeneration of Purkinje neurons (Majdzadeh *et al.* 2008b). Neuroprotective roles for HDAC4 have also been demonstrated in other studies that described that HDAC4 promoted the survival of retinal neurons during development and protected photoreceptors in a mouse model of retinal degeneration (Chen and Cepko 2009). The protective action of HDAC4 was suggested by these authors to be dependent on the activity of hypoxia-inducible factor 1 alpha (Chen and Cepko 2009). A more recent study described that HDAC4 protects neurons from death induced by a blockade of neuronal activity or by reduction of NMDA activity (Chen *et al.* 2014). Nuclear translocation of HDAC4 is observed after ischemic stroke and this has been suggested to have a protective effect in promoting neuronal recovery and remodeling (Kassis *et al.* 2015; Kassis *et al.* 2016).

In other studies, HDAC4 was found to be necessary for the ability of DNJB6 proteins, a subclass of heat shock proteins, to reduce polyglutamine aggregation and toxicity (Hageman *et al.* 2010). This finding clearly has relevance for the entire class of polyglutamine disorders. Again, HDAC4 did not regulate the acetylation status of the DNAJB6 proteins suggesting that this cooperative neuroprotection was HDAC-independent or via an interaction with another HDAC subtype (Hageman *et al.* 2010).

Neurotoxic effects of HDAC4

In contrast to the findings mentioned above, several other studies have reported that HDAC4 participates in promoting neurodegeneration. Although the nuclear translocation of HDAC4 was shown to be protective in ischemic stroke (Kassis *et al.* 2015; Kassis *et al.* 2016), nuclear accumulation of HDAC4 was found to be associated with neuronal cell death in a mouse model of Ataxia Telangectasia (Herrup *et al.* 2013; Li *et al.* 2012). This effect-required de-phosphorylation of HDAC4 by the protein phosphatase 2A, whose activity is enhanced in this disease (Li *et al.* 2012). In another study, genetic reduction of HDAC4 resulted in elevated expression of brain-derived neurotrophic factor (BDNF), which led to reduced disease symptoms and increase life span in the R6/2 transgenic mouse model of Huntington's disease (Mielcarek *et al.* 2013a). Again, in contrast to that finding, cytoplasmic HDAC4 was shown to be particularly neurotoxic, whereby HDAC4 was found to associate with huntingtin protein in the cytoplasm, and co-localized with cytoplasmic inclusions (Mielcarek *et al.* 2013a). Huntington's disease-related global transcriptional alteration and nuclear aggregation of huntingtin were not affected by HDAC4 reduction (Mielcarek *et al.* 2013a). In another study, a reduction in the level of HDAC4 in the cortex of R6/2 transgenic mice was observed after administration of SAHA, a broadly-acting HDAC inhibitor that has protective effects in disease mice (Mielcarek *et al.* 2011).

Translocation of HDAC4 to the nucleus was also associated with detrimental effects in cultured cerebellar granule neurons in response to low-potassium or excitotoxic glutamate conditions (Bolger and Yao 2005). Also in that study, treatment with the neuronal survival factor BDNF suppresses HDAC4 nuclear translocation, whereas a proapoptotic Calcium/calmodulin-dependent protein kinase inhibitor stimulated HDAC4 nuclear accumulation (Bolger and Yao 2005).

HDAC5

HDAC5 is abundantly expressed throughout the brain and peripheral tissues (Broide *et al.* 2007a). HDAC5 is known to undergo nuclear-cytoplasmic shuttling and to be a critical transcriptional regulator (McKinsey *et al.* 2000). Although compelling evidence for the involvement HDAC5 in regulating neurodegeneration is lacking, there are studies implicating HDAC5 in neuroprotective effects. For example, HDAC5 has been shown to play a pivotal role in stimulating axonal regrowth after injury (Cho and Cavalli 2012; Cho *et al.* 2013; Whalley 2014). This required the export of HDAC5 from the nucleus and interaction with filamin A in the axons (Cho *et al.* 2013; Cho *et al.* 2015). Other studies showed that injury to sensory axons resulted in HDAC5 phosphorylation by protein kinase C, which promoted axon regeneration (Cho and Cavalli 2012; Cho *et al.* 2013).

HDAC5 was also investigated in the role of memory function and Alzheimer's disease pathogenesis in a mouse model (Agis-Balboa *et al.* 2013). Loss of HDAC5 was found to impair memory function, but did not affect pathogenesis, in a mouse model for amyloid pathology (Agis-Balboa *et al.* 2013). These findings suggest a novel role for HDAC5 in memory consolidation and suggests that selective HDAC inhibitors for the treatment of Alzheimer's disease should avoid targeting HDAC5.

HDAC6

HDAC6 has two features that distinguishes it from all the other HDACs: it is exclusively cytoplasmic and it has two catalytic domains (Gregoretti *et al.* 2004). Initially described to be a specific alpha-tubulin deacetylase, HDAC6 was later found to deacetylate other substrates, including tau, heat shock protein 90, the actin binding protein cortactin, the tumor suppressor macrophage stimulating 1 and the beta-catenin transcription factor (Cook *et al.* 2014; Kekatpure *et al.* 2009; Li *et al.* 2016; Li *et al.* 2008; Zhang *et al.* 2007). Both the neuroprotective and neurotoxic effects of HDAC6 have been associated with altered acetylation of target proteins, not a result of histone acetylation and ensuing effects on chromatin (Table 1).

Neuroprotective effects of HDAC6

Earlier studies examining the role of HDAC6 in the regulation of degeneration concluded that it played a protective role, acting by enhancing the clearance of potentially harmful misfolded proteins and protein aggregates(Guthrie and Kraemer 2011; Pandey *et al.* 2007). This action of HDAC6 was accomplished through a variety of different mechanisms. Through a C-terminal zinc finger domain (ZnF-UBP) HDAC6 binds mono- and polyubiquinated misfolded proteins and, through association with dynein motor proteins, transports these potentially toxic proteins via microtubules to form aggresomes sequestering them (Kawaguchi *et al.* 2003; Pandey *et al.* 2007). One such potentially toxic protein that HDAC6 has been found to transport to aggresomes is misfolded and polyubiquitinated DJ-1 (mutations of DJ-1 cause a genetic form of Parkinson's disease) (Olzmann *et al.* 2007). The eventual clearance of autophagosomes through lysosomal fusion also was shown to involve HDAC6 (Lee *et al.* 2010a). In addition to ubiquitinated proteins, HDAC6 can promote the clearance of ubiquitinated mitochondria through mitophagy (Lee *et al.* 2010b). Other studies have shown that HDAC6 can promote clearance of misfolded proteins by stimulating the synthesis of heat shock proteins through the activation of heat shock transcription factor 1 (HSF1) (Boyault *et al.* 2007). Through activation of HSF1 and the expression of heat-shock proteins, HDAC6 was found to prevent alpha-synuclein aggregates in cultured cells (Du *et al.* 2014). Inhibition of HDAC6 enhanced alpha-synuclein aggregation and toxicity (Du *et al.* 2014). Not surprisingly, HDAC6 inhibition in mice was reported to upregulate α-synuclein oligomers levels and exacerbate nigrostriatal dopamine neurodegeneration (Du *et al.* 2014). In addition to stimulating chaperone activity through HSF1 activation, HDAC6 can stimulate the chaperone activity of HSP90 by directly deacetylating it (Bali *et al.* 2005; Kovacs *et al.* 2005).

Neurotoxic roles for HDAC6

Several other studies suggest that HDAC6 can promote neurodegenerative disease pathology (Bali *et al.* 2005; Du *et al.* 2014; Kovacs *et al.* 2005). Treatment of cultured cortical neurons with HDAC6 selective inhibitors was found to protect them against oxidative stress-induced death and to promote neurite extension (Rivieccio *et al.* 2009). HDAC6-mediated deacetylation of tubulin was found to negatively affect the recruitment of kinesin and dynein motor complexes leading to the impairment of axonal transport (Dompierre *et al.* 2007). Conversely, loss of HDAC6 activity was found to enhance microtubule stability, axonal transport and microtubule-mediated mitochondrial transport, effects that all promote neuronal survival (Chen *et al.* 2010; Dompierre *et al.* 2007; Kim *et al.* 2012). In addition to tubulin, HDAC6 can deacetylate the tau protein. This action results in reduction of tau clearance which promotes aggregation and toxicity (Cook *et al.* 2014). Reduction of HDAC6 by genetic ablation or pharmacological inhibition was found to prevent cognitive impairment in Alzheimer's disease mice (Govindarajan *et al.* 2013). Because amyloid plaque burden was not affected, the beneficial actions were thought to be due to effects on tau.

Detrimental effects of HDAC6 have also been implicated in other neurodegenerative diseases. Pharmacological inhibition of HDAC6 improved mitochondrial trafficking, axonal transport and BDNF release in mutant huntingtin overexpressing neurons (Dompierre *et al.* 2007). Although not delaying disease onset, HDAC6 deletion extended the survival of SOD1(G93A) mice and maintained motor axon integrity indicating a role for HDAC6 in Amyolateral Sclerosis pathogenesis (Taes *et al.* 2013).

While most previous studies have utilized tubacin to inhibit HDAC6, other inhibitors have been recently developed with better pharmacological properties (Wang *et al.* 2017). These HDAC6-selective inhibitors have been shown to ameliorate disease phenotypes in mouse models of Alzheimer's disease (Zhang *et al.* 2014), Charcot-Marie-Tooth disease (Benoy *et al.* 2017) and in cell culture models of Huntington's disease (Guedes-Dias *et al.* 2015) and tauopathy (Cook *et al.* 2014), confirming earlier findings. Based on their well demonstrated beneficial effects, HDAC6 inhibitors may represent a promising therapeutic approach against different neurodegenerative diseases. A complicating issue though that warrants further investigation, however, is that genetic knockdown of HDAC6 has been described to have different effects in Huntington's disease mouse models. In one study using the R6/2 mouse model, HDAC6 knockdown did not modify disease progression (Bobrowska *et al.* 2011). However, another study using the related R6/1 described no effect on motor deficits but an exacerbation of some disease phenotypes was observed with HDAC6 deletion (Ragot *et al.* 2015). Surprisingly, given the worsening of symptoms, tubulin acetylation as well as BDNF expression was found to be increased in this study (Ragot *et al.* 2015).

HDACs 7, 8, 9,10 and 11

In contrast to class I and IIa HDACs, HDACs 7, 8, 9 and 10 are expressed at relatively low levels in the brain (Broide *et al.* 2007b; Thomas 2009). There is limited information on the role of these family members in relation to neurodegenerative conditions. For example, there have been no studies to date linking HDAC8 or HDAC10 to neurodegenerative diseases.

However, a few studies have demonstrated neuroprotective effects of HDACs 7, 9 and 11, which are mentioned below.

In cultured neurons, overexpression of HDAC7 can protect against death by inhibiting the expression of c-Jun (Ma and D'Mello 2011b). Interestingly, HDAC inhibitors failed to reduce neuroprotection and a catalytically-dead form of HDAC7 was fully protective indicating that neuroprotection by HDAC7 is independent of deacetylase activity (Ma and D'Mello 2011b). In other studies, researchers described that R6/2 Huntington's disease mice hemizygous for *Hdac7* deletion do not show any amelioration of disease phenotype (Benn *et al.* 2009). While this suggests that HDAC7 is not involved in Huntington's disease pathogenesis, a compensatory effect of other HDACs resulting from HDAC7 reduction cannot be ruled out. Also possible is that a more complete reduction of HDAC7 is necessary for a beneficial effect in this aggressive mouse model of disease.

While the effects of HDAC9 on neurodegeneration are unclear, HDRP, a truncated form of HDAC9 resulting from alternative splicing, protects cultured neurons from death (Morrison *et al.* 2006b). As with HDAC7, protection was found to be due to the inhibition of c-Jun gene transcription through deacetylation of the c-Jun promoter (Morrison *et al.* 2006b). Although completely lacking a catalytic domain, the inhibitory effect on the c-Jun promoter is mediated through the recruitment of HDAC1. Consistently, neuroprotection by HDRP is reduced by treatment with HDAC inhibitors (Morrison *et al.* 2006b). It has been suggested that whether HDAC1 protects or promotes neuronal death is dependent on whether it interacts with HDRP or HDAC3 (Bardai *et al.* 2012a). Besides c-Jun, HDRP can protect neurons through interaction with the amino enhancer of split, a member of the Groucho/GRG family of proteins (Zhang *et al.* 2008).

Based on proteins that interact with it, HDAC11 has been suggested to be involved in the regulation of survival of motor neuron complex-dependent splicing (Joshi *et al.* 2013). In T-cells, downregulation of HDAC11 results in mis-splicing of ataxin-10(Joshi *et al.* 2013), the disease protein for SCA10, a neurodegenerative disorder characterized by cerebellar dysfunctions and seizures, but not a polyglutamine disease like the other SCA diseases.

Conclusions

Our review covers the roles of classical HDACs (classes I, II and IV) in the regulation of neuronal death and survival, and their known associations with neurodegenerative pathologies. In some cases, HDACs have been described to both promote and protect against neurodegeneration. This could be due to several reasons, including differences in contexts or models used, as well as different mechanisms of actions. These depend on the cellular localization and post-translational modifications of the individual HDAC, the acetylation of histone and non-histone proteins or their diverse binding partners. Also becoming clear is that at least some HDACs can be expressed as different isoforms. For example, HDAC5, HDAC7 and HDAC9 can be each produced as two separate isoforms (Di Giorgio and Brancolini 2016; Yang and Seto 2008), introducing another variability that has not yet been adequately explored. While there is substantial evidence supporting the use of HDAC inhibitors as a potential therapeutic option for many of the discussed neurodegenerative

diseases, one must strongly consider the specificity of these agents for the different HDAC family members.

Acknowledgments

This work was supported by NIH grant NS040408 to Santosh D'Mello.

Abbrebiations

CTBP	C-terminal-binding protein
GSK3β	Glycogen synthase kinase-3 beta
SOD1	superoxide dismutase-1
HDAC	histone deactylase
HP1	heterochromatin protein 1
HSF1	heat shock factor-1
LRRK2	Leucine-rich repeat kinase-2
MKP-1	Mitogen-activated protein kinase phosphatase
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NRSF	Neural-restrictive silencer factor
N-Cor/SMRT	The nuclear receptor co-repressor 2/ silencing mediator for retinoid and thyroid hormone receptors complex
NF-κB	Nuclear factor-kappa B, PolyQ, polyglutamine
SCA	spinocerebellar ataxia, UBE3A, ubiquitin protein ligase E3A (UBE3A)
XIAP	X-linked inhibitor of apoptosis
ZnF-UBP	N-Cor/SMRT, The nuclear receptor co-repressor 2/ silencing mediator for retinoid and thyroid hormone receptors complex C-terminal zinc finger domain

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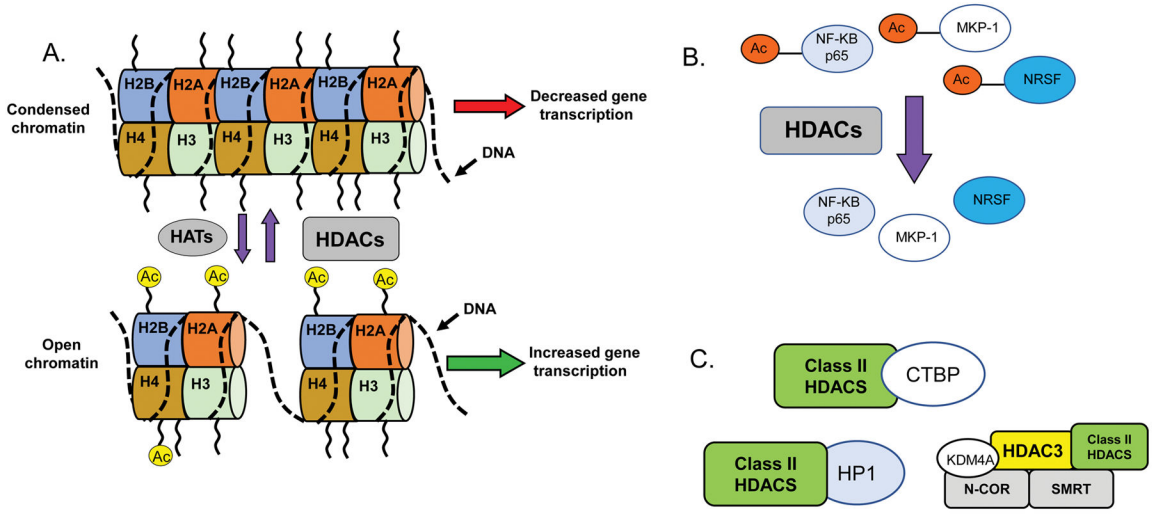

Figure 1.

Different mechanisms of actions for HDAC proteins. A. Traditional effects of HDAC to alter histone acetylation and chromatin structure leading to changes in gene transcription. B. HDACs can also deacetylate non-histone proteins including transcription factors, such as Nuclear factor-kappa beta (NF-KB), Mitogen-activated protein kinase phosphatase 1 (MKP-1) and Neural-restrictive silencer factor (NRSF), among others. C. Examples of interactions of class II HDACs with regulatory proteins, including Heterochromatin protein 1 (HP1) and C-terminal-binding protein (CTBP). Class II HDACs, such as HDAC4 and HDAC5, can also interaction with class I HDACs, such as HDAC3, as part of transcriptional regulatory complexes. The nuclear receptor co-repressor 2/ silencing mediator for retinoid and thyroid hormone receptors (N-Cor/SMRT) complex is shown as an example.

Table 1

Summary of the neuroprotective and/or neurotoxic properties of HDAC proteins. Mechanisms of action were categorized broadly into the following groups: Protein-protein interactions, Post-translational modifications, Non-histone acetylation, Histone-acetylation, Deacetylase-independent. Note: for some studies summarized in the text, specific mechanisms for the individual HDAC proteins were not known, hence are not shown here. N/A, not applicable.

Class	HDAC subtype	Neuroprotective/Neurotoxic	Mechanism	References
I	HDAC1	Neurotoxic	Protein-protein interactions	Bardai et al. (2012) Kim et al. (2010)
		Neurotoxic	Post-translational modifications	Zhu et al. (2017)
		Neurotoxic	Non-histone acetylation	Jacob et al. (2011) Jeong et al. (2009) Lebrun-Julien et al. (2015) Ravikumar et al. (2004)
		Neurotoxic	Histone-acetylation	Jamal et al. (2017)
		Neuroprotective	Non-histone acetylation	Morrison et al. (2006)
		Neuroprotective	Protein-protein interactions	Dobbin et al. (2013) Qiu et al. (2014) Wang et al. (2013)
	HDAC2	Neurotoxic	Histone-acetylation	Contreras et al. (1859) Graff et al. (2012) Guan et al. (2009) Kernochan et al. (2005) Mohseni et al. (2016)
	HDAC3	Neurotoxic	Post-translational modifications	Bardai et al. (2011) Bardai et al. (2013) Schmitt et al. (2014)
		Neurotoxic	Protein-protein interactions	Bardai et al. (2012) Bardai et al. (2013) Duncan et al. (2013) Kawaguchi et al. (1994)
		Neurotoxic	Histone-acetylation	Chou et al. (2011) Jia et al. (2012) Jia et al. (2015) Jia et al. (2016) Thomas et al. 2008 Thomas et al. (2014) Suelves et al. (2017)
	HDAC8	None reported	N/A	N/A
IIa	HDAC4	Neurotoxic	Post-translational modifications	Li et al. (2012) Herrup et al. (2013) Bolger et al. (2005)
		Neuroprotective	Protein-protein interactions	Hageman et al. (2010) Majdzadeh et al. (2008)
	HDAC5	Neuroprotective	Protein-protein interactions	Cho et al. (2013) Cho et al. (2015)
		Neuroprotective	Post-translational modifications	Cho et al. (2012) Cho et al. (2013)
	HDAC7	Neuroprotective	Deacetylase-independent	Ma et al. (2011)
	HDAC9	Neuroprotective	Non-histone acetylation	Morrison et al. (2006)
		Neuroprotective	Protein-protein interactions	Bardai et al. (2012) Zhang et al. (2008)
IIb	HDAC6	Neuroprotective	Non-histone acetylation	Bali et al. (2005)

Class	HDAC subtype	Neuroprotective/Neurotoxic	Mechanism	References
				Cook et al. (2014) Kekatpure et al. (2009) Kovacs et al. (2005) Li et al. (2008) Li et al. (2016) Zhang et al. (2007)
	HDAC6	Neuroprotective	Protein-protein interactions	Boyault et al. (2007) Kawaguchi et al. (2003) Pandey et al. (2007)
		Neurotoxic	Non-histone acetylation	Chen et al. (2010) Cook et al. (2014) Dompierre et al. (2007) Kim et al. (2012)
	HDAC10	None reported	N/A	N/A
IV	HDAC11	Neuroprotective	Protein-protein interactions	Joshi et al. (2013)