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Review

Histone deacetylases: Focus on the nervous system

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Abstract. Neurodegenerative disease strikes millions worldwide and there is mounting evidence suggesting that underlying the onset and progression of these debilitating diseases is inappropriate neuronal apoptosis. Recent reports have implicated a family of proteins known as histone deacetylases (HDACs) in various neuronal processes including the neuronal death program. Initial headway in this field has been made largely through the use of broad-spectrum HDAC inhibitors. In fact, pharmacological inhibition of HDAC activity has been shown to protect neurons in several models of neurodegeneration. The observation that HDAC inhibitors can have opposing effects in different paradigms of neurodegeneration suggests that individual members of the HDAC protein family may play distinct roles that could depend on the specific cell type under study. The purpose of this review is to detail work involving the use of HDAC inhibitors within the context of neurodegeneration and examine the roles of individual HDAC members in the nervous system with specific focus on neuronal cell death.

Keywords. Histone deacetylase, apoptosis, neuronal survival, neurodegeneration, nervous system.

Introduction

Neurodegenerative disorders have a devastating impact on patients' lives and the healthcare system as a whole. It is therefore important to attain a better understanding of neuronal function and identify potential therapeutic targets relevant to disease. Recently, a family of proteins known as histone deacetylases (HDACs) has emerged as promising targets in the treatment of these neurodegenerative diseases [1, 2]. The objective of this review is to highlight what is currently known about the role of HDACs within the nervous system and particularly the brain.

The first mammalian HDAC was isolated and characterized by Taunton and colleagues in 1996 [3]. Since that time there has been a great deal of interest placed on HDACs and their involvement in various cellular processes. HDACs have been implicated in transcriptional repression [4, 5], cell cycle progression [6], differentiation [7], and DNA replication [8] as well as response to DNA damage [9, 10]. It is perhaps not surprising that this class of proteins can elicit such a diverse set of effects given that HDACs possess the ability to alter global gene transcription through the deacetylation of chromatin [11].

Eukaryotic transcription is dependent upon DNA packaging [11]. DNA within cells is highly ordered and packaged into chromatin. The smallest organizational subunit of chromatin is the nucleosome, which is composed of 146 bp of DNA wound around a histone protein octamer [11, 12]. The ability of transcription factors to access nucleosome-bound DNA is controlled largely by DNA packaging at this level. Strong association between DNA and histones restricts

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access by transcription factors and therefore represses gene transcription [12]. Modification of histones and/or DNA can alter the strength of their association and thus can modulate transcriptional activity. Covalent addition of methyl, phosphate, or acetyl moieties has been shown to alter the nucleosome state and consequently effect transcription. Acetylation is the most characterized form of histone modification and results from the addition of an acetyl moiety to the ε-amino group of conserved N-terminal lysine residues on histones. Addition of acetyl groups to histones reduces the attractive force between positively charged histone proteins and the negatively charged DNA phosphate backbone, resulting in a more relaxed and accessible chromatin structure. It is widely accepted that there is a direct correlation between histone acetylation and observed transcriptional activity for a given segment of chromatin. Histone acetyl-transferases (HATs) facilitate histone acetylation and are thus believed to be transcriptional activators. Conversely, HDACs serve to remove acetyl groups from histones and thereby repress transcription [2, 13]. Thus, it is the interplay between HAT and HDAC activity that primarily governs local chromatin structure and gene expression. It should be noted that HDACs do not directly bind DNA sequence and require additional factors for target gene recognition [2, 14].

HDAC function is not relegated solely to the deacetylation of histones. HDACs are also known to deacetylate several non-histone proteins such as the tumor suppressor, p53, and the transcription factors, E2F and Sp1 [6, 15, 16]. Furthermore, our lab has reported that an isoform of HDAC9 that lacks a deacetylase domain, histone deacteylase-related protein (HDRP), interacts with and inhibits the neuronal apoptosis-inducing MAP kinase, c-Jun N-terminal kinase (JNK) [17, 18]. Taken together, these findings suggest a more complex role for HDACs and that deacetylase function may not be required for HDAC-mediated activity.

This report is intended to give an overview of the complex nature of HDACs in the nervous system. Current studies of class I and II HDACs are discussed in detail whereas class III HDACs (also known as nicotinamide adenine dinucleotide-dependent HDACs) are not covered in this review as they appear to be phylogenically and functionally distinct.

HDAC inhibitors and neurodegenerative diseases

The widespread use of small molecule HDAC inhibitors (HDACi) in numerous studies has led to the generation of valuable information regarding their potential as therapeutic agents for the treatment of various neurodegenerative disorders. Thus, a detailed discussion of HDACi action in the nervous system is warranted.

HDACi have been categorized in different classes based on their chemical structures [2]. The various classes of HDACi include hydroxamates, short chain fatty acids, cyclic peptides and benzamides. Trichostatin A (TSA), suberoyl anilide bishydroxamide (SAHA), scriptaid, pyroxamide and oxamflatin are well-cited examples of hydroxamates (reviewed in [2]). Among hydroxamates, TSA was the first to be characterized nearly 16 years ago [19]. Due to the high potency of this compound as an HDACi (effective in nanomolar concentrations), TSA has been used as the core chemical structure for the synthesis of new HDACi. Crystal structure studies of hydroxamates, such as TSA and SAHA have revealed that these inhibitors work by binding to the zinc ion in the HDAC active site and abolishing the deacetylase activity [20]. Whether or not other structural classes of HDACi work through direct binding to the substrate binding site remains to be identified. Amongst the short chain fatty acid class of HDACi, butyrate [21–24], phenyl butyrate [25–27] and valproic acid (VPA) [28, 29] have been widely used in laboratories. In comparison with hydroxamic acids, short chain fatty acids are much less potent as they are effective at millimolar concentrations. Apicidine, trapoxin, depsipeptide, depudesin and chlamydoccin are examples of the third class of HDACi referred to as cyclic peptides (reviewed in [2]). Depsipeptide, a bicyclic pentapeptide, has been characterized for its potency to arrest cancer cell growth [30, 31]. This compound has been used to complete two Phase I clinical trials. Favorable aspects of depsipeptide, such as its tolerability and long half-life, makes this HDACi a suitable candidate for further clinical studies (reviewed in [32]). Moreover, benzamides such as CI-994 (*N*-acetyldinaline) and MS-275 are currently in clinical trials for their ability to arrest tumor cell growth [33, 34]. Aberrant activities of HDACs and HATs have been observed in a number of central nervous system tumors [35, 36] and neurological disorders (reviewed in [37]), providing support for chemical manipulation of these enzymes as a treatment for such conditions.

HDACi have been studied in a wide range of neurodegenerative cell culture and animal models such as polyglutamine-expansion diseases, ischemia, neuronal oxidative toxicity and spinal muscular atrophy.

Polyglutmaine-expansion diseases

Neurodegenerative diseases caused by mutated proteins containing expanded polyglutamine repeats

have been studied for potential treatment by HDACi. Huntington's disease (HD) is an example in which a mutant expanded polyglutamine stretch in Huntingtin protein (Htt) is responsible for a profound deleterious neuropathology. Mutant Htt and other polyglutamine-expansion-containing proteins are known to interact with and sequester transcription factors including HATs such as CBP and P300-associated factor (P/CAF) [38–40]. This sequestration results in inhibition of HAT activity of CBP [38]. In addition, overexpression of mutant Htt protein causes reduction in histone acetylation, and this reduction in acetylation has been demonstrated to be suppressed by administrating HDACi [41]. When tested *in vivo* using *Drosophila* models of polyglutamine pathogenesis, both pharmacological and genetic inhibition of the deacetylation process were shown to reduce degeneration of photoreceptor neurons and lethality [41]. HDACi was also used in a mouse models of HD. SAHA and sodium butyrate were used to treat an R6/2 transgenic mouse model of HD and were shown to ameliorate motor impairments, extend survival, improve body weight and motor performance, and delay the neuropathological effects [42, 43].

Sodium butyrate appears to be a potential therapeutic agent for another polyglutamine-expansion disease, spinal and bulbar muscular atrophy (SBMA). SBMA is caused by expanded polyglutamine stretch in the androgen receptor and is characterized by loss of motor neurons and sensory neurons. This loss of neurons leads to clinical symptoms of muscular atrophy and weakness [44]. Administration of sodium butyrate in the drinking water of transgenic SBMA mice, increased histone acetylation in spinal cord tissue and improved the motor deficiencies caused by SBMA [45].

Only three of the HDACi currently available have been tested for their potential to treat polyglutamine-expansion diseases. Sodium butyrate [46], phenyl butyrate [47] and SAHA [43] have been tested on transgenic models of HD, and they ameliorated motor deficit phenotypes in transgenic mice models tested. Amongst these three HDACi, sodium butyrate is the only HDACi that has been used in two other polyglutamine-expansion diseases, SBMA [45] and dentatorubral-pallidoluysian atrophy (DRPLA) [48]. Expanded polyglutamine repeats in the atrophin 1 protein causes DRPLA, which is accompanied by reduced acetylation of histone H3 in the brain tissue from DRPLA mice [48]. A mutated form of atrophin 1 represses transcription at least partially *via* recruitment of N-CoR/mSIN3a/HDAC complex (reviewed in [37]).

Sodium butyrate, SAHA and phenyl butyrate were effective when administered only in a short range of doses, and toxicity was readily apparent at higher doses. Given that only limited number of inhibitors has been so far tested in animal models of polyglutamine-expansion disease, more thorough studies of the effects of other HDACi are needed to find inhibitors that are effective in a broader therapeutic range and have less toxicity.

Oxidative stress induced neurodegenerative diseases

Oxidative stress has long been linked to the neuronal cell death that is associated with several neurodegenerative conditions such as Alzheimer's (AD) and Parkinson's disease (PD). Additionally, oxidative stress appears to underlie AD progression. In AD, accumulation of free radicals leads to excessive lipid peroxidation and neuronal degeneration [49, 50]. Oxidative stress also contributes to neurodegeneration in PD. Impaired electron transport chain function and activity and build up of reactive oxygen species have been observed in PD postmortem tissue as well as in animal models of the disease (reviewed in [51]). In addition, both VPA and TSA have been shown to possess an anti-inflammatory effect in PD models using primary neuronal cultures [52, 53].

HDACi have shown promising results in conferring resistance to neuronal oxidative stress. Transcription of several neuroprotective genes is regulated in response to oxidative stress. Ryu et al. [42] showed that the transcription factor Sp1 is acetylated in response to oxidative stress in neurons. HDACi have been shown to increase Sp1 acetylation and Sp1 DNA binding, which protects neurons against oxidative stress-induced death *in vitro* and *in vivo*. This study showed that Sp1 activation is necessary for the protective effects of HDAC inhibitors. Not surprisingly, Sp1 has been reported as an oxidative stress-induced transcription factor in cortical neurons and its forced expression has been shown to be neuroprotective *in vitro* against oxidative stress-induced cell death [54].

3-Nitropropionic acid (3-NP) is a mitochondrial complex II inhibitor and causes selective striatal degeneration *via* oxidative stress activated mechanisms when injected into rodents [55–57]. This treatment mimics an HD phenotype. Sodium butyrate treatments of mice injected with 3-NP have been demonstrated to reduce striatal lesions and confer protection against 3-NP toxicity [42, 46]. This further supports HDACi intervention to treat oxidative stress-induced neurodegenerative conditions.

Ischemia

Several different HDACi such as VPA, TSA, sodium phenyl butyrate and SAHA have been shown to be protective against focal cerebral ischemia. VPA reduces brain damage induced by transient focal cerebral ischemia in rats. Subcutaneous injection of VPA immediately after ischemia followed by repeated injections, was found to decrease infarct size and reduce ischemia-induced neurological deficit scores [58]. In addition, sodium 4-phenylbutyrate (4-PBA) has been demonstrated to have neuroprotective effects on cerebral ischemic injury. Treatment with 4-PBA attenuated infarction volume, hemispheric swelling, and apoptosis and enhanced neurological response in a mouse model of hypoxia-ischemia stroke [59].

SAHA is another HDACi tested for its ability to ameliorate conditions in ischemic brain disease. Histone H3 acetylation levels are drastically decreased in the ischemic brain tissue subjected to middle cerebral artery occlusion [58]. This suggests that altered acetylation status of histones might be an underlying mechanism in this neurological disorder. Treatment with SAHA was shown to increase histone H3 acetylation within the normal brain and prevent histone deacetylation in the ischemic brain. SAHA treatment also resulted in smaller infract size [60]. In this study, SAHA treatments not only caused altered histone acetylation levels but also caused higher expression of the neuroprotective proteins Hsp70 and Bcl-2 in both control and ischemic brain tissue after insult, suggesting that HDACi affect regulation of neuroprotective proteins and this altered gene expression may contribute to the resulting neuroprotection.

Spinal muscular atrophy

HDACi, SAHA, VPA and the novel benzamide, M344, have been studied for the treatment of spinal muscular atrophy (SMA). SMA is a common autosomal recessive neuromuscular disorder and is known to be caused by insufficient survival motor neuron (SMN) protein levels [61, 62]. SMN1 gene loss causes SMA, whereas SMN2 gene copy number determines the severity of the disease [63–66]. It has been reported that SAHA increases SMN2 levels in several neuroectodermal tissues including rat hippocampal brain slices and motor neuron rich-cell fractions [67]. The novel benzamide M344 also up-regulates SMN2 protein expression in fibroblast cells derived from SMA patients [68]. Hahnen et al. [67] used a panel of HDACi belonging to different classes of inhibitors for potential treatment of SMA. They showed that SAHA and M344 activate the human SMN2 gene in fibroblasts derived from patients with SMA. Amongst the various classes of HDACi tested, SAHA was reported as the most promising therapeutic agent for treatment of SMA due to its ability to substantially increase SMN protein levels at low micromolar concentrations and to completely inhibit HDAC activity at submicromolar concentrations.

Friedreich's ataxia (FRDA) is another neurodegenerative disease that has been investigated for therapeutic HDACi intervention. FRDA is an inherited neurodegenerative disease caused by hyperexpansion of GAATTC triplet repeats in the first intron of a nuclear gene that encodes the essential mitochondrial protein frataxin [69]. Frataxin insufficiency causes progressive spinocerebellar neurodegeneration resulting in symptoms such as muscle weakness, speech problems and heart disease. Hypoacetylation of histones H3 and H4 has been shown to be involved in gene silencing at expanded frataxin alleles [68]. Herman et al. [70] showed that different classes of HDACi including TSA, suberoyl bishydroxamic acid (SBHA), SAHA, the benzamide-type SAHA derivative BML-210 and VPA increase total acetylated histones in the FRDA cell line when used at their reported IC_{50}. HDACi also increased frataxin mRNA and protein level in the FRDA cell line introducing HDACi treatment as a novel method to target the cause of this disease, frataxin deficiency, rather than strategies that only treat the symptoms.

Tissue-specific HDACi

Great efforts are currently being made toward the design of more potent and less toxic candidates for the treatment of various neurodegenerative diseases. Along these lines, groups have tried to develop more selective HDACi. Recently, Simonini et al. [71] reported that N-(2-aminophenyl)-4-benzamide derivative (MS-275), a potent HDACi *in vitro*, is a brain-region selective inhibitor of HDACs. In this study the actions of MS-275 was compared with VPA for their ability to increase the acetylated status of brain nucleosomal histone tail domains. The authors reported that MS-275 is 30- to 100-fold more potent than VPA in increasing acetyl histone 3 (Ac-H3) in these brain regions and that it induces an increase in the content of Ac-H3 in the frontal cortex. However, in contrast to VPA, MS-275 failed to increase Ac-H3 content in the striatum. The development of tissue-specific HDACi like MS-275 is an important step toward targeting afflicted brain regions and reducing toxicity in unaffected regions.

Contradicting results of HDAC inhibition

Studies that have used HDACi to ascertain HDAC involvement in neuronal survival have provided conflicting results. For example, while inhibition of HDACs has been shown to block neuronal loss in *Drosophila* and a mouse model of HD [41, 43, 46], there are reports showing that treatment of cerebellar granule neurons (CGNs) with HDACi actively induces apoptosis [72–75]. One study in particular showed that three distinct pharmacological inhibitors of HDACs induce apoptosis against activity-induced survival in CGNs [72]. In contrast, other studies in CGNs have reported that VPA causes induction of α-synuclein and confers neuroprotection against glutamate excitotoxicity [76]. The opposing effects of HDACi amongst various paradigms can be explained by the tissue and stage-specific expression of different classes of HDACs. Depending on the abundance of a specific HDAC family member in different tissues and their role in regulation of various cellular functions, inhibiting HDACs could yield diverse results.

HDACi present and future

HDACi that are currently being used inhibit all HDAC proteins effectively. Since it has been shown that HDACs can have opposing effects it would stand to reason that the use of broad spectrum HDACi could yield confusing results. Therefore, synthesis and characterization of inhibitors that are selective against individual members of the HDAC family is essential for successful use of such inhibitors in scientific research and disease treatment. Moreover, targets of each individual HDACi need to be studied so that the side effects conferred by HDAC inhibition can be predicted and treatments of unwanted reactions can be considered. It is also essential to target the inhibitors to specific cell types that are affected in the diseases being treated to reduce systemic drug delivery. Taken together, synthesis of inhibitors against specific HDACs, identifying HDAC target genes, and targeting the drugs to the affected cell types should be the main focus of the future studies aiming to use HDACi as therapeutic agents to cure as yet non-treatable neurodegenerative diseases.

Phylogeny of HDACs

Investigation of HDAC function in neurological disease using HDACi has yielded conflicting results seemingly dependent upon the cell type or species under study [41, 43, 72, 77]. These findings along with evidence reported from a group using a *Caenorhabditis elegans* model of polyglutamine neuronal disease suggests that individual HDAC members may have distinct and sometimes opposing roles given the cellular context [78]. We have therefore placed focus upon the role of individual HDACs within the nervous system.

HDACs were originally isolated and characterized in yeast. The classification of mammalian HDACs is based upon similarity to their yeast homologs. Class I HDACs share sequence homology with the yeast Rpd3 gene, class II HDACs resemble yeast Hda1, and class III nicotinamide adenine dinucleotide-dependent HDACs are most similar to the yeast Sir2 gene (not discussed here) [79, 80]. Interestingly, HDAC11 does not clearly fall into any of these categories and currently resides in class of its own [81].

Class I HDACs (yeast RPD3-like)

HDACs 1, 2, 3, and 8 comprise the class I HDAC family. In general, these HDACs are expressed ubiquitously with the exception of HDAC8, which shows a more restricted expression pattern with highest expression in the liver [2, 82]. These HDACs consist primarily of a deacetylase domain and almost exclusively exhibit a nuclear localization [2].

HDAC1

HDAC1 contains a C-terminal nuclear localization signal (NLS) but lacks a nuclear export signal (NES) [83]. As a result, HDAC1 is found solely in the nucleus. HDAC1 is somewhat unusual in that it can interact with other HDAC family members including HDACs 2, 9, and HDRP [2]. The impact of HDAC1 activity in the nervous system is uncertain, but there is mounting evidence that this HDAC plays an important role in neuronal development and differentiation. It has been shown that expression of HDAC1 induces differentiation in retinal progenitor cells as well as motoneurons during zebrafish development and that this differentiation involves repression of Wnt and Notch signaling [84, 85]. HDAC1 involvement in neuronal differentiation is further supported by studies indicating that the cell cycle modulating protein, retinoblastoma (Rb), mediates gene repression through recruitment of HDAC1 [86]. Our lab has found that HDAC1 plays a role in cerebellar granule neuron survival by inhibiting the expression of the apoptosis-inducing transcription factor, c-Jun. We reported that HDRP facilitates recruitment of HDAC1 to the c-Jun promoter and that this recruitment results in deacetylation resulting in decreased c-Jun expression [17]. Similarly, Bates et al. [78] found

that loss of HDA-1 (homologue of mammalian HDAC1) in *C. elegans* potentiated neurodegeneration in a Huntingtin polyglutamine toxicity model.

HDAC2

HDAC2 is very similar in structure to HDAC1 (82% sequence identity) and the two are often found in complex together [2]. HDAC2, like HDAC1, is nuclear [83]. However, unlike HDAC1, HDAC2 has not been reported to associate with multiple HDACs. It appears that HDAC2 is also involved in neuronal differentiation. Evidence indicates that HDAC2 may participate in oligodendrocyte differentiation as the potent inducer of oligodendrocyte fate, myelin transcription factor 1, associates with HDAC2 [87]. Differentiation of the neuronal PC12 (pheochromocytoma) cell line requires DNA methyltransferase 3b-mediated recruitment of HDAC2 [88]. In addition, PC12 cell differentiation requires RE1-silencing transcription factor (REST) recruitment of HDAC2 [89, 90]. HDAC2 involvement in REST-mediated repression of neuronal phenotypes in non-neuronal cells provides an interesting link between HDAC2 activity and neuronal fate determination.

HDAC3

Comparison between HDAC3 and HDACs 1 and 2 reveals only a 68% sequence identity [2]. It is perhaps not surprising that HDAC3 differs considerably in localization and interacting partners. HDAC3 contains both an NLS and NES and has been observed in both the cytoplasm and nucleus [91]. It is tempting to speculate that this shuttling to and from the nucleus is meant to modulate HDAC3 deacetylase activity but one should keep in mind that HDAC3 might be performing yet to be characterized functions in the cytoplasm. HDAC3 is a rather promiscuous member of the HDAC family when it comes to associating with other HDACs. Previous studies have shown that HDAC3 can associate with complexes containing HDACs 4, 5, 7 and 9/HDRP [91–94]. HDAC3 has been linked to neuronal survival and disease. The *C. elegans* homologue of HDAC3, HDA-3, has been reported to enhance polyglutamine expansion toxicity in an HD model [78]. Conversely, HDAC3 appears to participate in the transcriptional repression of the well-characterized neuronal apoptosis-inducing factor E2F-1 [95]. Thus, more work is needed to ascertain the roles of HDAC3 within neurons.

HDAC8

HDAC8 shares the least sequence similarity to other class I HDACs (only 34% identity compared to HDAC3) [2]. While HDAC8 differs in sequence identity, this class I HDAC is true to form in that it consists primarily of a deacetylase catalytic domain [82, 96]. HDAC8 also contains an NLS that is likely responsible for its nuclear localization. Currently, there are no reports of HDAC8 expression within normal central or peripheral nervous tissue. However, HDAC8 has been detected by serial analysis of gene expression (SAGE) in brain tumor tissue, which indicates that this HDAC may still have a role in neuronal function and/or tumorigenesis [2].

Class II HDACs (yeast HDA1-like)

Class II HDACs are made up of two subgroups: class IIa HDACs 4, 5, 7, and 9 as well as class IIb HDACs 6 and 10. Class II HDACs are considerably larger than their class I counterparts. The additional non-catalytic region of class II HDACs is believed to facilitate protein interactions and therefore class II HDACs are thought to display a wider range of interacting partners. All members of class II contain both an NLS and NES and thus are observed in both the cytoplasm and nucleus.

HDAC4

HDAC4 is closely related to both HDAC5 and HDAC7 (70% and 58% sequence identity, respectively) [2]. HDAC4 is highly expressed in the heart and brain [2]. The localization of HDAC4 appears to be dependent upon calcium calmodulin (CaM) kinase and neuronal activity. Neuronal activity in cultured hippocampal neurons (HN) and CGNs stimulate cytoplasmic HDAC4 localization and this localization requires CaM kinase activity [77, 97]. Treatment of these cultures with CaM kinase inhibitor KN-62 induces nuclear translocation of HDAC4. Withdrawal of trophic factors such as HK (CGNs) or BDNF (HNs) also induces shuttling of HDAC4 to the nucleus [77, 97]. One report cites evidence that nuclear localization of HDAC4 has deleterious consequences for cultured CGNs, as enforced expression of HDAC4 results in apoptosis [77]. Previous work performed in cardiac myocytes has shown that HDACs 4, 5, 7, and 9/HDRP bind myocyte enhancement factor-2 (MEF2) and inhibit MEF2-dependent transcription [98]. There is evidence that MEF2 plays a survival-promoting role in CGNs and thus inhibition of MEF2 may be a means of HDAC4-mediated apoptosis [77, 99]. However, our lab has observed that overexpression of HDAC4 results in complete protection of CGNs from low potassium-induced apoptosis (unpublished data). Furthermore, mice lacking both copies of the HDAC4 gene develop a smaller brain and disrupted cerebellar architecture (unpublished observation). These findings appear to contradict the previous report by

Bolger and Yao [77] regarding HDAC4 induction of CGN apoptosis. Future work will be required to resolve the apparent disagreement in findings.

HDAC4 may also play a role in PD. Early onset PD involves the mutation of Parkin, which is an E3 ubiquitin ligase [100]. One substrate of Parkin is RanBP2, an E3 SUMO ligase [101]. RanBP2 has been shown to sumoylate HDAC4, increasing HDAC4-mediated gene repression and deacteylase activity [102]. It has been proposed that mutation of Parkin leads to a buildup of RanBP2 and in turn increased HDAC4 activity, which may contribute to the advancement of neurodegeneration in PD [101]. Additionally, HDAC4 has been identified as a major component of ubiquitinated intranuclear inclusions produced in neuronal intranuclear inclusion disease (NIID), supporting the idea of HDAC4 involvement in neurodegenerative disorders [103].

HDAC5

HDAC5 is most similar to HDAC4 (70%) and shows analogous localization except within HNs where neuronal activity alone was not sufficient to cause cytoplasmic export [2, 97]. However, the export of HDAC5 to the cytoplasm did occur after activation of calcium flux through L-type calcium channels or synaptic *N*-methyl-D-aspartate receptors [97, 104]. Like HDAC4, HDAC5 cytoplasmic localization requires CaM kinase activity and HDAC5 nuclear localization is often observed following neuronal apoptosis-inducing treatments [104]. HDAC5 shuttles to the CGN nucleus following removal of depolarizing (protective) medium [104]. Furthermore, overexpression of HDAC5 induces CGN apoptosis [104]. During our analysis of HDAC5 null mice we found that these mice have no readily observable neurological impairment. Interestingly, evidence indicates that HDAC5 is involved in repressing long-term memory integration in *Aplysia* [105]. HDAC5 has also been linked to HD, as nuclear accumulation of HDAC5 is substantially greater in the brains of HD patients [106]. Thus, HDAC5 appears to promote apoptosis of cultured neurons and may play a role in HD.

HDAC6

The relationship between HDAC6 and other class II members is an unusual one. HDAC6 shares most similarity with HDAC10; however, HDAC6 is unique because, unlike any other HDAC, it possesses two deacetylase domains. HDAC6 has been reported to associate with HDAC11, although the functional consequence of this association is unclear [81]. It has been shown that HDAC6 is expressed in most neuronal types examined thus far and is particularly high in cerebellar Purkinje cells [107]. HDAC6 resides primarily in the cytoplasm but has been observed in the nucleus [2]. Cytoplasmic localization allows HDAC6 to function in tubulin deacetylation [108]. Deacetylated tubulin is abundant in dynamic regions including neuronal growth cones [108]. HDAC6 has also been shown to assist in the removal of aggregated Htt protein and may therefore also have relevance in disease [109]. In addition, HDAC6 interacts with spinocerebellar ataxia type 3 protein, Ataxin3, and is thought to be involved in pre-aggresome and aggresome formation [110]. In fact, Kawaguchi and colleagues [111] have provided strong evidence suggesting that HDAC6 can assist in the transport of misfolded proteins to aggresomes through the ability of HDAC6 to bind both polyubiquitinated misfolded proteins as well as dynein motors. Indeed, cells lacking HDAC6 are more sensitive to misfolded protein stress thereby implicating HDAC6 function in an entire class of neuronal diseases related to protein aggregation such as AD and HD [111].

HDAC7

HDACs 4, 5, and 9 share the greatest homology to HDAC7 [2]. HDAC7 localization has thus far proved to be the same as HDAC4 [2]. HDAC7 also binds and inhibits MEF2 [112]. There are currently no reports citing the effect of HDAC7 on neuronal survival or function, although study of T cell selection has demonstrated that HDAC7 protects T cells from TCR-mediated apoptosis [113]. An interesting link between HDAC7, the mitochondria, and prostate apoptosis were revealed by Bakin and Jung [114]. They showed that HDAC7 localizes to the mitochondrial inner membrane space of prostate epithelial cells (HDAC7 contains a mitochondrial targeting presequence) and during apoptosis HDAC7 relocalizes to the cytoplasm. Given the well-documented role of mitochondria in apoptosis, it is alluring to hypothesize that HDAC7 may be performing a survival-promoting function in the mitochondria [115]. Investigation of HDAC7 function in non-neuronal systems has yielded insight into HDAC7 function within mitochondria that warrant more intense examination of HDAC7 function in neuronal processes.

HDAC9

HDAC9 is closely related to HDACs 4, 5, and 7 [2]. HDAC9 appears to be different from other HDACs in the number of splice variants that have been reported [116]. There are two major isoforms of HDAC9, a full-length isoform (HDAC9) and a smaller RNA splice variant called histone deacetylase-related protein (HDRP) [116]. Expression levels of HDAC9 and HDRP are highest in the brain and heart [116]. Both isoforms of HDAC9 exhibit the same localization

pattern as HDAC4 and can be found in the cytoplasm of CGNs in protective depolarizing medium [72]. HDAC9 and HDRP have been shown to associate with HDAC1 and HDAC3 [117]. These interactions would presumably allow HDRP to mediate deacetylation even though it lacks a deacetylase catalytic domain of its own. HDAC9 and HDRP have also been shown to bind and inhibit MEF2 but, in contrast to HDACs 4 and 5, HDRP does not induce neuronal apoptosis [72]. In fact, enforced expression of HDRP protects CGNs from apoptosis. HDRP mediates this neuroprotection by binding and inhibiting the apoptosis-inducing MAP kinase, JNK [72]. Additionally, HDRP inhibits the apoptotic marker c-Jun expression by recruiting HDAC1 to the c-Jun promoter and facilitating deacetylation and repression [72]. Antisense knockdown of HDAC9 does not affect CGN apoptosis, indicating that HDRP may be the more relevant of the two with regard to neuroprotection [72]. HDRP is the only member of the HDAC family to have reported neuroprotective properties in a mammalian system of neurodegeneration. HDAC9 has been shown to be an important repressor of acetylcholine receptor expression in muscle cells upon innervation [118]. HDAC9 has, therefore, been proposed to be important in synapse formation. Together, isoforms of HDAC9 have demonstrated the ability to protect neurons from apoptosis and stabilize synapse formation.

HDAC10

Sequence data reveal that HDAC10 is most comparable to HDAC6 with 37% sequence identity [2]. Similar to HDAC6, HDAC10 contains two catalytic domains; however, the second C-terminal catalytic domain is non-functional [119]. HDAC10 contains an NES but no NLS and can be found primarily in the cytoplasm but, interestingly, can also be detected in the nucleus [120]. HDAC10 associates with HDACs 1–5, and 7 suggesting that this HDAC10 may serve a recruiter function [2]. This is supported by the finding that HDAC10 can repress transcription without the use of its deacetylase domain [119]. There are two Rb binding domains in HDAC10, suggesting that HDAC10 may play a role in the cell cycle [121]. HDAC10 is the most recently documented member of the class II HDAC family and regrettably there is a lack of reported research involving this HDAC.

HDAC11 – Non-classical HDAC

Least is known about this unusual member of the HDAC family. Sequence analysis suggests that this HDAC is not appreciably homologous to any other HDAC [81]. It has been proposed that HDAC11 belongs in an HDAC subclass of its own [122]. HDAC11 protein localizes mainly in the nucleus where it is known to associate with HDAC6 [81]. Unfortunately, little else is known about this unique HDAC.

Conclusions

In this review, research efforts have been presented that reflect what is currently known about the individual contributions of HDAC family members as well as HDACi activity on neuronal function, differentiation, and survival. Evidence cited in this review reveals that members of this family can have opposing actions as is the case for HDAC5 and 9/HDRP in mammalian neuronal survival and HDAC1 and 3 in *C. elegans* neuronal survival. These findings may require reevaluation of the therapeutic use of broad-spectrum HDACi in disease. Such inhibition could conceivably result in undesirable side effects. Therefore, investigation into inhibitors of specific HDACs would most likely be of added research and ultimately therapeutic benefit. We have also seen that HDACs are more than histone deacetylases and that these dynamic proteins can elicit distinct functions through novel interactions and deacetylation of non-histone proteins. Interestingly, recruitment of HDACs by other HDACs also appears to be a major theme that at this time is not well understood. Hopefully, the rapid growth of interest in HDAC function will result in advancement of our knowledge with regard to this neurologically important protein family and characterization of its members will shed light on their function. We believe that future research of HDACs will impart knowledge that can be used to combat neurodegenerative disease.

1 Monneret, C. (2005) Histone deacetylase inhibitors. Eur. J. Med. Chem. 40, 1 – 13.
2 de Ruijter, A. J., van Gennip, A. H., Caron, H. N., Kemp, S. and van Kuilenburg, A. B. (2003) Histone deacetylases (HDACs): Characterization of the classical HDAC family. Biochem. J. 370, 737 – 749.
3 Taunton, J., Hassig, C. A. and Schreiber, S. L. (1996) A mammalian histone deacetylase related to the yeast transcriptional regulator Rpd3p. Science 272, 408 – 411.
4 Wolffe, A. P. and Guschin, D. (2000) Review: chromatin structural features and targets that regulate transcription. J. Struct. Biol. 129, 102 – 122.
5 Knoepfler, P. S. and Eisenman, R. N. (1999) Sin meets NuRD and other tails of repression. Cell 99, 447 – 450.
6 Marzio, G., Wagener, C., Gutierrez, M. I., Cartwright, P., Helin, K. and Giacca, M. (2000) E2F family members are differentially regulated by reversible acetylation. J. Biol. Chem. 275, 10887 – 10892.
7 Marks, P. A., Richon, V. M. and Rifkind, R. A. (2000) Histone deacetylase inhibitors: inducers of differentiation or apoptosis of transformed cells. J. Natl. Cancer Inst. 92, 1210 – 1216.

8 Iizuka, M. and Stillman, B. (1999) Histone acetyltransferase HBO1 interacts with the ORC1 subunit of the human initiator protein. J. Biol. Chem. 274, 23027 – 23034.
9 Sakaguchi, K., Herrera, J. E., Saito, S., Miki, T., Bustin, M., Vassilev, A., Anderson, C. W. and Appella, E. (1998) DNA damage activates p53 through a phosphorylation-acetylation cascade. Genes Dev. 12, 2831 – 2841.
10 Chen, Y., Lee, W. H. and Chew, H. K. (1999) Emerging roles of BRCA1 in transcriptional regulation and DNA repair. J. Cell Physiol. 181, 385 – 392.
11 Wade, P. A. (2001) Transcriptional control at regulatory checkpoints by histone deacetylases: molecular connections between cancer and chromatin. Hum. Mol. Genet. 10, 693 – 698.
12 Strahl, B. D. and Allis, C. D. (2000) The language of covalent histone modifications. Nature 403, 41 – 45.
13 Annunziato, A. T. and Hansen, J. C. (2000) Role of histone acetylation in the assembly and modulation of chromatin structures. Gene Expr. 9, 37 – 61.
14 Pazin, M. J. and Kadonaga, J. T. (1997) What's up and down with histone deacetylation and transcription? Cell 89, 325 – 328.
15 Gu, W. and Roeder, R. G. (1997) Activation of p53 sequence-specific DNA binding by acetylation of the p53 C-terminal domain. Cell 90, 595 – 606.
16 Bouwman, P. and Philipsen, S. (2002) Regulation of the activity of Sp1-related transcription factors. Mol. Cell. Endocrinol. 195, 27 – 38.
17 Morrison, B. E., Majdzadeh, N., Zhang, X., Lyles, A., Bassel-Duby, R., Olson, E. N. and D'Mello, S. R. (2006) Neuroprotection by histone deacetylase-related protein. Mol. Cell. Biol. 26, 3550 – 3564.
18 Hibi, M., Lin, A., Smeal, T., Minden, A. and Karin, M. (1993) Identification of an oncoprotein- and UV-responsive protein kinase that binds and potentiates the c-Jun activation domain. Genes Dev. 7, 2135 – 2148.
19 Yoshida, M., Kijima, M., Akita, M. and Beppu, T. (1990) Potent and specific inhibition of mammalian histone deacetylase both *in vivo* and *in vitro* by trichostatin A. J. Biol. Chem. 265, 17174 – 17179.
20 Finnin, M. S., Donigian, J. R., Cohen, A., Richon, V. M., Rifkind, R. A., Marks, P. A., Breslow, R. and Pavletich, N. P. (1999) Structures of a histone deacetylase homologue bound to the TSA and SAHA inhibitors. Nature 401, 188 – 193.
21 Della Ragione, F., Criniti, V., Della Pietra, V., Borriello, A., Oliva, A., Indaco, S., Yamamoto, T. and Zappia, V. (2001) Genes modulated by histone acetylation as new effectors of butyrate activity. FEBS Lett. 499, 199 – 204.
22 Kim, M. S., Son, M. W., Kim, W. B., In Park, Y. and Moon, A. (2000) Apicidin, an inhibitor of histone deacetylase, prevents H-ras-induced invasive phenotype. Cancer Lett. 157, 23 – 30.
23 Dangond, F. and Gullans, S. R. (1998) Differential expression of human histone deacetylase mRNAs in response to immune cell apoptosis induction by trichostatin A and butyrate. Biochem. Biophys. Res. Commun. 247, 833 – 837.
24 Yang, J., Kawai, Y., Hanson, R. W. and Arinze, I. J. (2001) Sodium butyrate induces transcription from the G alpha(i2) gene promoter through multiple Sp1 sites in the promoter and by activating the MEK-ERK signal transduction pathway. J. Biol. Chem. 276, 25742 – 25752.
25 He, L. Z., Tolentino, T., Grayson, P., Zhong, S., Warrell, R. P., Jr., Rifkind, R. A., Marks, P. A., Richon, V. M. and Pandolfi, P. P. (2001) Histone deacetylase inhibitors induce remission in transgenic models of therapy-resistant acute promyelocytic leukemia. J. Clin. Invest. 108, 1321 – 1330.
26 Zhou, D. C., Kim, S. H., Ding, W., Schultz, C., Warrell, R. P., Jr. and Gallagher, R. E. (2002) Frequent mutations in the ligand-binding domain of PML-RARalpha after multiple relapses of acute promyelocytic leukemia: analysis for functional relationship to response to all-trans retinoic acid and histone deacetylase inhibitors *in vitro* and *in vivo.* Blood 99, 1356 – 1363.
27 Pili, R., Kruszewski, M. P., Hager, B. W., Lantz, J. and Carducci, M. A. (2001) Combination of phenylbutyrate and 13-cis retinoic acid inhibits prostate tumor growth and angiogenesis. Cancer Res. 61, 1477 – 1485.
28 Gottlicher, M., Minucci, S., Zhu, P., Kramer, O. H., Schimpf, A., Giavara, S., Sleeman, J. P., Lo Coco, F., Nervi, C., Pelicci, P. G. and Heinzel, T. (2001) Valproic acid defines a novel class of HDAC inhibitors inducing differentiation of transformed cells. EMBO J. 20, 6969 – 6978.
29 Marks, P., Rifkind, R. A., Richon, V. M., Breslow, R., Miller, T. and Kelly, W. K. (2001) Histone deacetylases and cancer: causes and therapies. Nat. Rev. Cancer. 1, 194 – 202.
30 Kitazono, M., Bates, S., Fok, P., Fojo, T. and Blagosklonny, M. V. (2002) The histone deacetylase inhibitor FR901228 (desipeptide) restores expression and function of pseudo-null p53. Cancer Biol. Ther. 1, 665 – 668.
31 Shih, C. and Teicher, B. A. (2001) Cryptophycins: a novel class of potent antimitotic antitumor depsipeptides. Curr. Pharm. Des. 7, 1259 – 1276.
32 Piekarz, R. and Bates, S. (2004) A review of depsipeptide and other histone deacetylase inhibitors in clinical trials. Curr. Pharm. Des. 10, 2289 – 2298.
33 Pauer, L. R., Olivares, J., Cunningham, C., Williams, A., Grove, W., Kraker, A., Olson, S. and Nemunaitis, J. (2004) Phase I study of oral CI-994 in combination with carboplatin and paclitaxel in the treatment of patients with advanced solid tumors. Cancer Invest. 22, 886 – 896.
34 Acharya, M. R., Karp, J. E., Sausville, E. A., Hwang, K., Ryan, Q., Gojo, I., Venitz, J., Figg, W. D. and Sparreboom, A. (2006) Factors affecting the pharmacokinetic profile of MS-275, a novel histone deacetylase inhibitor, in patients with cancer. Invest. New Drugs. 24, 367 – 375.
35 van den Boom, J., Wolter, M., Blaschke, B., Knobbe, C. B. and Reifenberger, G. (2006) Identification of novel genes associated with astrocytoma progression using suppression subtractive hybridization and real-time reverse transcription-polymerase chain reaction. Int. J. Cancer. 119, 2330 – 2338.
36 Kamitani, H., Taniura, S., Watanabe, K., Sakamoto, M., Watanabe, T. and Eling, T. (2002) Histone acetylation may suppress human glioma cell proliferation when p21 WAF/Cip1 and gelsolin are induced. Neurooncology 4, 95 – 101.
37 Butler, R. and Bates, G. P. (2006) Histone deacetylase inhibitors as therapeutics for polyglutamine disorders. Nat. Rev. Neurosci. 7, 784 – 796.
38 Steffan, J. S., Kazantsev, A., Spasic-Boskovic, O., Greenwald, M., Zhu, Y. Z., Gohler, H., Wanker, E. E., Bates, G. P., Housman, D. E. and Thompson, L. M. (2000) The Huntington's disease protein interacts with p53 and CREB-binding protein and represses transcription. Proc. Natl. Acad. Sci. USA 97, 6763 – 6768.
39 Nucifora, F. C. Jr., Sasaki, M., Peters, M. F., Huang, H., Cooper, J. K., Yamada, M., Takahashi, H., Tsuji, S., Troncoso, J., Dawson, V. L., Dawson, T. M. and Ross, C. A. (2001) Interference by huntingtin and atrophin-1 with cbp-mediated transcription leading to cellular toxicity. Science 291, 2423 – 2428.
40 McCampbell, A., Taylor, J. P., Taye, A. A., Robitschek, J., Li, M., Walcott, J., Merry, D., Chai, Y., Paulson, H., Sobue, G. and Fischbeck, K. H. (2000) CREB-binding protein sequestration by expanded polyglutamine. Hum. Mol. Genet. 9, 2197 – 2202.
41 Steffan, J. S., Bodai, L., Pallos, J., Poelman, M., McCampbell, A., Apostol, B. L., Kazantsev, A., Schmidt, E., Zhu, Y. Z., Greenwald, M., Kurokawa, R., Housman, D. E. et al. (2001) Histone deacetylase inhibitors arrest polyglutamine-dependent neurodegeneration in *Drosophila.* Nature 413, 739 – 743.
42 Ryu, H., Lee, J., Olofsson, B. A., Mwidau, A., Dedeoglu, A., Escudero, M., Flemington, E., Azizkhan-Clifford, J., Ferrante, R. J. and Ratan, R. R. (2003) Histone deacetylase inhibitors prevent oxidative neuronal death independent of expanded polyglutamine repeats via an Sp1-dependent pathway. Proc. Natl. Acad. Sci. USA 100, 4281 – 4286.

43 Hockly, E., Richon, V. M., Woodman, B., Smith, D. L., Zhou, X., Rosa, E., Sathasivam, K., Ghazi-Noori, S., Mahal, A., Lowden, P. A., Steffan, J. S., Marsh, J. L. et al (2003) Suberoylanilide hydroxamic acid, a histone deacetylase inhibitor, ameliorates motor deficits in a mouse model of Huntington's disease. Proc. Natl. Acad. Sci. USA 100, 2041 – 2046.

44 La Spada, A. R., Wilson, E. M., Lubahn, D. B., Harding, A. E. and Fischbeck, K. H. (1991) Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy. Nature 352, 77 – 79.

45 Minamiyama, M., Katsuno, M., Adachi, H., Waza, M., Sang, C., Kobayashi, Y., Tanaka, F., Doyu, M., Inukai, A. and Sobue, G. (2004) Sodium butyrate ameliorates phenotypic expression in a transgenic mouse model of spinal and bulbar muscular atrophy. Hum. Mol. Genet. 13, 1183 – 1192.

46 Ferrante, R. J., Kubilus, J. K., Lee, J., Ryu, H., Beesen, A., Zucker, B., Smith, K., Kowall, N. W., Ratan, R. R., Luthi-Carter, R. and Hersch, S. M. (2003) Histone deacetylase inhibition by sodium butyrate chemotherapy ameliorates the neurodegenerative phenotype in Huntington's disease mice. J. Neurosci. 23, 9418 – 9427.

47 Gardian, G., Browne, S. E., Choi, D. K., Klivenyi, P., Gregorio, J., Kubilus, J. K., Ryu, H., Langley, B., Ratan, R. R., Ferrante, R. J. and Beal, M. F. (2005) Neuroprotective effects of phenylbutyrate in the N171 – 82Q transgenic mouse model of Huntington's disease. J. Biol. Chem. 280, 556 – 563.

48 Ying, M., Xu, R., Wu, X., Zhu, H., Zhuang, Y., Han, M. and Xu, T. (2006) Sodium butyrate ameliorates histone hypoacetylation and neurodegenerative phenotypes in a mouse model for DRPLA. J. Biol. Chem. 281, 12580 – 12586.

49 Retz, W., Gsell, W., Munch, G., Rosler, M. and Riederer, P. (1998) Free radicals in Alzheimer's disease. J. Neural Transm. Suppl. 54, 221 – 236.

50 Butterfield, D. A., Drake, J., Pocernich, C. and Castegna, A. (2001) Evidence of oxidative damage in Alzheimer's disease brain: central role for amyloid beta-peptide. Trends Mol. Med. 7, 548 – 554.

51 Beal, M. F. (2003) Mitochondria, oxidative damage, and inflammation in Parkinson's disease. Ann. N. Y. Acad. Sci. 991, 120 – 131.

52 Peng, G. S., Li, G., Tzeng, N. S., Chen, P. S., Chuang, D. M., Hsu, Y. D., Yang, S. and Hong, J. S. (2005) Valproate pretreatment protects dopaminergic neurons from LPS-induced neurotoxicity in rat primary midbrain cultures: role of microglia. Brain Res. Mol. Brain Res. 134, 162 – 169.

53 Chen, P. S., Peng, G. S., Li, G., Yang, S., Wu, X., Wang, C. C., Wilson, B., Lu, R. B., Gean, P. W., Chuang, D. M. and Hong, J. S. (2006) Valproate protects dopaminergic neurons in midbrain neuron/glia cultures by stimulating the release of neurotrophic factors from astrocytes. Mol. Psychiatry 11, 1116 – 1125.

54 Ryu, H., Lee, J., Zaman, K., Kubilis, J., Ferrante, R. J., Ross, B. D., Neve, R. and Ratan, R. R. (2003) Sp1 and Sp3 are oxidative stress-inducible, anti-death transcription factors in cortical neurons. J. Neurosci. 23, 3597 – 3606.

55 Brouillet, E., Hantraye, P., Ferrante, R. J., Dolan, R., Leroy-Willig, A., Kowall, N. W. and Beal, M. F. (1995) Chronic mitochondrial energy impairment produces selective striatal degeneration and abnormal choreiform movements in primates. Proc. Natl. Acad. Sci. USA 92, 7105 – 7109.

56 Schulz, J. B., Henshaw, D. R., MacGarvey, U. and Beal, M. F. (1996) Involvement of oxidative stress in 3-nitropropionic acid neurotoxicity. Neurochem. Int. 29, 167 – 171.

57 Kim, G. W. and Chan, P. H. (2002) Involvement of superoxide in excitotoxicity and DNA fragmentation in striatal vulnerability in mice after treatment with the mitochondrial toxin, 3-nitropropionic acid. J. Cereb. Blood Flow Metab. 22, 798 – 809.

58 Ren, M., Leng, Y., Jeong, M., Leeds, P. R. and Chuang, D. M. (2004) Valproic acid reduces brain damage induced by transient focal cerebral ischemia in rats: potential roles of histone deacetylase inhibition and heat shock protein induction. J. Neurochem. 89, 1358 – 1367.

59 Qi, X., Hosoi, T., Okuma, Y., Kaneko, M. and Nomura, Y. (2004) Sodium 4-phenylbutyrate protects against cerebral ischemic injury. Mol. Pharmacol. 66, 899 – 908.

60 Faraco, G., Pancani, T., Formentini, L., Mascagni, P., Fossati, G., Leoni, F., Moroni, F. and Chiarugi, A. (2006) Pharmacological inhibition of histone deacetylases by suberoylanilide hHydroxamic acid specifically alters gene expression and reduces ischemic injury in the mouse brain. Mol. Pharmacol. 70, 1876 – 1884.

61 Strasswimmer, J., Lorson, C. L., Breiding, D. E., Chen, J. J., Le, T., Burghes, A. H. and Androphy, E. J. (1999) Identification of survival motor neuron as a transcriptional activator-binding protein. Hum. Mol. Genet. 8, 1219 – 1226.

62 Lorson, C. L., Strasswimmer, J., Yao, J. M., Baleja, J. D., Hahnen, E., Wirth, B., Le, T., Burghes, A. H. and Androphy, E. J. (1998) SMN oligomerization defect correlates with spinal muscular atrophy severity. Nat. Genet. 19, 63 – 66.

63 Lefebvre, S., Burglen, L., Reboullet, S., Clermont, O., Burlet, P., Viollet, L., Benichou, B., Cruaud, C., Millasseau, P., Zeviani, M., Le Paslier, D., Frézal, J. et al. (1995) Identification and characterization of a spinal muscular atrophy-determining gene. Cell 80, 155 – 165.

64 Wirth, B. (2000) An update of the mutation spectrum of the survival motor neuron gene (SMN1) in autosomal recessive spinal muscular atrophy (SMA). Hum. Mutat. 15, 228 – 237.

65 Burghes, A. H. (1997) When is a deletion not a deletion? When it is converted. Am. J. Hum. Genet. 61, 9 – 15.

66 Feldkotter, M., Schwarzer, V., Wirth, R., Wienker, T. F. and Wirth, B. (2002) Quantitative analyses of SMN1 and SMN2 based on real-time lightCycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. Am. J. Hum. Genet. 70, 358 – 368.

67 Hahnen, E., Eyupoglu, I. Y., Brichta, L., Haastert, K., Trankle, C., Siebzehnrubl, F. A., Riessland, M., Holker, I., Claus, P., Romstock, J., Buslei, R., Wirth, B. and Blumcke, I. (2006) *In vitro* and *ex vivo* evaluation of second-generation histone deacetylase inhibitors for the treatment of spinal muscular atrophy. J. Neurochem. 98, 193 – 202.

68 Riessland, M., Brichta, L., Hahnen, E. and Wirth, B. (2006) The benzamide M344, a novel histone deacetylase inhibitor, significantly increases SMN2 RNA/protein levels in spinal muscular atrophy cells. Hum. Genet. 120, 101 – 110.

69 Campuzano, V., Montermini, L., Molto, M. D., Pianese, L., Cossee, M., Cavalcanti, F., Monros, E., Rodius, F., Duclos, F., Monticelli, A., Zara, F., Canizares, J. et al. (1996) Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. Science 271, 1423 – 1427.

70 Herman, D., Jenssen, K., Burnett, R., Soragni, E., Perlman, S. L. and Gottesfeld, J. M. (2006) Histone deacetylase inhibitors reverse gene silencing in Friedreich's ataxia. Nat. Chem. Biol. 2, 551 – 558.

71 Simonini, M. V., Camargo, L. M., Dong, E., Maloku, E., Veldic, M., Costa, E. and Guidotti, A. (2006) The benzamide MS-275 is a potent, long-lasting brain region-selective inhibitor of histone deacetylases. Proc. Natl. Acad. Sci. USA 103, 1587 – 1592.

72 Morrison, B. E., Majdzadeh, N., Zhang, X., Lyles, A., Bassel-Duby, R., Olson, E. N. and D'Mello, S. R. (2006) Neuroprotection by histone deacetylase-related protein. Mol. Cell. Biol. 26, 3550 – 3564.

73 Salminen, A., Tapiola, T., Korhonen, P. and Suuronen, T. (1998) Neuronal apoptosis induced by histone deacetylase inhibitors. Brain Res. Mol. Brain Res. 61, 203 – 206.

74 Boutillier, A. L., Trinh, E. and Loeffler, J. P. (2002) Constitutive repression of E2F1 transcriptional activity through HDAC proteins is essential for neuronal survival. Ann. N. Y. Acad. Sci. 973, 438 – 442.

75 Boutillier, A. L., Trinh, E. and Loeffler, J. P. (2003) Selective E2F-dependent gene transcription is controlled by histone

deacetylase activity during neuronal apoptosis. J. Neurochem. 84, 814 – 828.
76 Leng, Y. and Chuang, D. M. (2006) Endogenous alpha-synuclein is induced by valproic acid through histone deacetylase inhibition and participates in neuroprotection against glutamate-induced excitotoxicity. J. Neurosci. 26, 7502 – 7512.
77 Bolger, T. A. and Yao, T. P. (2005) Intracellular trafficking of histone deacetylase 4 regulates neuronal cell death. J. Neurosci. 25, 9544 – 9553.
78 Bates, E. A., Victor, M., Jones, A. K., Shi, Y. and Hart, A. C. (2006) Differential contributions of *Caenorhabditis elegans* histone deacetylases to huntingtin polyglutamine toxicity. J. Neurosci. 26, 2830 – 2838.
79 Gray, S. G. and Ekstrom, T. J. (2001) The human histone deacetylase family. Exp. Cell Res. 262, 75 – 83.
80 Johnson, C. A. and Turner, B. M. (1999) Histone deacetylases: complex transducers of nuclear signals. Semin. Cell Dev. Biol. 10, 179 – 188.
81 Gao, L., Cueto, M. A., Asselbergs, F. and Atadja, P. (2002) Cloning and functional characterization of HDAC11, a novel member of the human histone deacetylase family. J. Biol. Chem. 277, 25748 – 25755.
82 Buggy, J. J., Sideris, M. L., Mak, P., Lorimer, D. D., McIntosh, B. and Clark, J. M. (2000) Cloning and characterization of a novel human histone deacetylase, HDAC8. Biochem. J. 350, 199 – 205.
83 Johnstone, R. W. (2002) Histone-deacetylase inhibitors: novel drugs for the treatment of cancer. Nat. Rev. Drug Discov. 1, 287 – 299.
84 Yamaguchi, M., Tonou-Fujimori, N., Komori, A., Maeda, R., Nojima, Y., Li, H., Okamoto, H. and Masai, I. (2005) Histone deacetylase 1 regulates retinal neurogenesis in zebrafish by suppressing Wnt and Notch signaling pathways. Development 132, 3027 – 3043.
85 Cunliffe, V. T. (2004) Histone deacetylase 1 is required to repress Notch target gene expression during zebrafish neurogenesis and to maintain the production of motoneurones in response to hedgehog signalling. Development 131, 2983 – 2995.
86 Nicolas, E., Morales, V., Magnaghi-Jaulin, L., Harel-Bellan, A., Richard-Foy, H. and Trouche, D. (2000) RbAp48 belongs to the histone deacetylase complex that associates with the retinoblastoma protein. J. Biol. Chem. 275, 9797 – 9804.
87 Romm, E., Nielsen, J. A., Kim, J. G. and Hudson, L. D. (2005) Myt1 family recruits histone deacetylase to regulate neural transcription. J. Neurochem. 93, 1444 – 1453.
88 Bai, S., Ghoshal, K., Datta, J., Majumder, S., Yoon, S. O. and Jacob, S. T. (2005) DNA methyltransferase 3b regulates nerve growth factor-induced differentiation of PC12 cells by recruiting histone deacetylase 2. Mol. Cell. Biol. 25, 751 – 766.
89 Ballas, N., Battaglioli, E., Atouf, F., Andres, M. E., Chenoweth, J., Anderson, M. E., Burger, C., Moniwa, M., Davie, J. R., Bowers, W. J., Federoff, H. J., Rose, D. W. et al. (2001) Regulation of neuronal traits by a novel transcriptional complex. Neuron 31, 353 – 365.
90 Iwase, S., Januma, A., Miyamoto, K., Shono, N., Honda, A., Yanagisawa, J. and Baba, T. (2004) Characterization of BHC80 in BRAF-HDAC complex, involved in neuron-specific gene repression. Biochem. Biophys. Res. Commun. 322, 601 – 608.
91 Yang, W. M., Tsai, S. C., Wen, Y. D., Fejer, G. and Seto, E. (2002) Functional domains of histone deacetylase-3. J. Biol. Chem. 277, 9447 – 9454.
92 Fischle, W., Dequiedt, F., Fillion, M., Hendzel, M. J., Voelter, W. and Verdin, E. (2001) Human HDAC7 histone deacetylase activity is associated with HDAC3 *in vivo*. J. Biol. Chem. 276, 35826 – 35835.
93 Fischle, W., Dequiedt, F., Hendzel, M. J., Guenther, M. G., Lazar, M. A., Voelter, W. and Verdin, E. (2002) Enzymatic activity associated with class II HDACs is dependent on a multiprotein complex containing HDAC3 and SMRT/N-CoR. Mol. Cell. 9, 45 – 57.
94 Zhou, X., Richon, V. M., Rifkind, R. A. and Marks, P. A. (2000) Identification of a transcriptional repressor related to the noncatalytic domain of histone deacetylases 4 and 5. Proc. Natl. Acad. Sci. USA 97, 1056 – 1061.
95 Panteleeva, I., Rouaux, C., Larmet, Y., Boutillier, S., Loeffler, J. P. and Boutillier, A. L. (2004) HDAC-3 participates in the repression of e2f-dependent gene transcription in primary differentiated aeurons. Ann. N. Y. Acad. Sci. 1030, 656 – 660.
96 Hu, E., Chen, Z., Fredrickson, T., Zhu, Y., Kirkpatrick, R., Zhang, G. F., Johanson, K., Sung, C. M., Liu, R. and Winkler, J. (2000) Cloning and characterization of a novel human class I histone deacetylase that functions as a transcription repressor. J. Biol. Chem. 275, 15254 – 15264.
97 Chawla, S., Vanhoutte, P., Arnold, F. J., Huang, C. L. and Bading, H. (2003) Neuronal activity-dependent nucleocytoplasmic shuttling of HDAC4 and HDAC5. J. Neurochem. 85, 151 – 159.
98 McKinsey, T. A., Zhang, C. L. and Olson, E. N. (2001) Control of muscle development by dueling HATs and HDACs. Curr. Opin. Genet. Dev. 11, 497 – 504.
99 Linseman, D. A., Cornejo, B. J., Le, S. S., Meintzer, M. K., Laessig, T. A., Bouchard, R. J. and Heidenreich, K. A. (2003) A myocyte enhancer factor 2D (MEF2D) kinase activated during neuronal apoptosis is a novel target inhibited by lithium. J. Neurochem. 85, 1488 – 1499.
100 Kitada, T., Asakawa, S., Hattori, N., Matsumine, H., Yamamura, Y., Minoshima, S., Yokochi, M., Mizuno, Y. and Shimizu, N. (1998) Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature 392, 605 – 608.
101 Um, J. W., Min do, S., Rhim, H., Kim, J., Paik, S. R. and Chung, K. C. (2006) Parkin ubiquitinates and promotes the degradation of RanBP2. J. Biol. Chem. 281, 3595 – 3603.
102 Kirsh, O., Seeler, J. S., Pichler, A., Gast, A., Muller, S., Miska, E., Mathieu, M., Harel-Bellan, A., Kouzarides, T., Melchior, F. and Dejean, A. (2002) The SUMO E3 ligase RanBP2 promotes modification of the HDAC4 deacetylase. EMBO J. 21, 2682 – 2691.
103 Takahashi-Fujigasaki, J., Arai, K., Funata, N. and Fujigasaki, H. (2006) SUMOylation substrates in neuronal intranuclear inclusion disease. Neuropathol. Appl. Neurobiol. 32, 92 – 100.
104 Linseman, D. A., Bartley, C. M., Le, S. S., Laessig, T. A., Bouchard, R. J., Meintzer, M. K., Li, M. and Heidenreich, K. A. (2003) Inactivation of the myocyte enhancer factor-2 repressor histone deacetylase-5 by endogenous Ca(2+)// calmodulin-dependent kinase II promotes depolarization-mediated cerebellar granule neuron survival. J. Biol. Chem. 278, 41472 – 41481.
105 Guan, Z., Giustetto, M., Lomvardas, S., Kim, J. H., Miniaci, M. C., Schwartz, J. H., Thanos, D. and Kandel, E. R. (2002) Integration of long-term-memory-related synaptic plasticity involves bidirectional regulation of gene expression and chromatin structure. Cell 111, 483 – 493.
106 Hoshino, M., Tagawa, K., Okuda, T., Murata, M., Oyanagi, K., Arai, N., Mizutani, T., Kanazawa, I., Wanker, E. E. and Okazawa, H. (2003) Histone deacetylase activity is retained in primary neurons expressing mutant huntingtin protein. J. Neurochem. 87, 257 – 267.
107 Southwood, C. M., Peppi, M., Dryden, S., Tainsky, M. A. and Gow, A. (2007) Microtubule deacetylases, SirT2 and HDAC6, in the nervous system. Neurochem. Res. 32, 187 – 195.
108 Hubbert, C., Guardiola, A., Shao, R., Kawaguchi, Y., Ito, A., Nixon, A., Yoshida, M., Wang, X. F. and Yao, T. P. (2002) HDAC6 is a microtubule-associated deacetylase. Nature 417, 455 – 458.
109 Iwata, A., Riley, B. E., Johnston, J. A. and Kopito, R. R. (2005) HDAC6 and microtubules are required for autophagic degradation of aggregated huntingtin. J. Biol. Chem. 280, 40282 – 40292.

110 Burnett, B. G. and Pittman, R. N. (2005) The polyglutamine neurodegenerative protein ataxin 3 regulates aggresome formation. Proc. Natl. Acad. Sci. USA 102, 4330 – 4335.
111 Kawaguchi, Y., Kovacs, J. J., McLaurin, A., Vance, J. M., Ito, A. and Yao, T. P. (2003) The deacetylase HDAC6 regulates aggresome formation and cell viability in response to misfolded protein stress. Cell 115, 727 – 738.
112 Dressel, U., Bailey, P. J., Wang, S. C., Downes, M., Evans, R. M. and Muscat, G. E. (2001) A dynamic role for HDAC7 in MEF2-mediated muscle differentiation. J. Biol. Chem. 276, 17007 – 17013.
113 Dequiedt, F., Van Lint, J., Lecomte, E., Van Duppen, V., Seufferlein, T., Vandenheede, J. R., Wattiez, R. and Kettmann, R. (2005) Phosphorylation of histone deacetylase 7 by protein kinase D mediates T cell receptor-induced Nur77 expression and apoptosis. J. Exp. Med. 201, 793 – 804.
114 Bakin, R. E. and Jung, M. O. (2004) Cytoplasmic sequestration of HDAC7 from mitochondrial and nuclear compartments upon initiation of apoptosis. J. Biol. Chem. 279, 51218 – 51225.
115 Petit, P. X., Susin, S. A., Zamzami, N., Mignotte, B. and Kroemer, G. (1996) Mitochondria and programmed cell death: back to the future. FEBS Lett. 396, 7 – 13.
116 Petrie, K., Guidez, F., Howell, L., Healy, L., Waxman, S., Greaves, M. and Zelent, A. (2003) The histone deacetylase 9 gene encodes multiple protein isoforms. J. Biol. Chem. 278, 16059 – 16072.
117 Sparrow, D. B., Miska, E. A., Langley, E., Reynaud-Deonauth, S., Kotecha, S., Towers, N., Spohr, G., Kouzarides, T. and Mohun, T. J. (1999) MEF-2 function is modified by a novel co-repressor, MITR. EMBO J. 18, 5085 – 5098.
118 Mejat, A., Ramond, F., Bassel-Duby, R., Khochbin, S., Olson, E. N. and Schaeffer, L. (2005) Histone deacetylase 9 couples neuronal activity to muscle chromatin acetylation and gene expression. Nat. Neurosci. 8, 313 – 321.
119 Guardiola, A. R. and Yao, T. P. (2002) Molecular cloning and characterization of a novel histone deacetylase HDAC10. J. Biol. Chem. 277, 3350 – 3356.
120 Tong, J. J., Liu, J., Bertos, N. R. and Yang, X. J. (2002) Identification of HDAC10, a novel class II human histone deacetylase containing a leucine-rich domain. Nucleic Acids Res. 30, 1114 – 1123.
121 Fischer, D. D., Cai, R., Bhatia, U., Asselbergs, F. A., Song, C., Terry, R., Trogani, N., Widmer, R., Atadja, P. and Cohen, D. (2002) Isolation and characterization of a novel class II histone deacetylase, HDAC10. J. Biol. Chem. 277, 6656 – 6666.
122 Gregoretti, I. V., Lee, Y. M. and Goodson, H. V. (2004) Molecular evolution of the histone deacetylase family: functional implications of phylogenetic analysis. J. Mol. Biol. 338, 17 – 31.