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Focal Nature of Neurological Disorders Necessitates Isotype-Selective Histone Deacetylase (HDAC) Inhibitors

Elizabeth A. Thomas

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Abstract Histone deacetylase (HDAC) inhibitors represent a promising new avenue of therapeutic options for a range of neurological disorders. Within any particular neurological disorder, neuronal damage or death is not widespread; rather, particular brain regions are preferentially affected. Different disorders exhibit distinct focal pathologies. Hence, understanding the region-specific effects of HDAC inhibitors is essential for targeting appropriate brain areas and reducing toxicity in unaffected areas. The outcome of HDAC inhibition depends on several factors, including the diversity in the central nervous system expression of HDAC enzymes, selectivity of a given HDAC inhibitor for different HDAC enzymes, and the presence or absence of cofactors necessary for enzyme function. This review will summarize brain regions associated with various neurological disorders and factors affecting the consequences of HDAC inhibition.

Keywords HDAC inhibitor · CNS · Therapeutic · Specificity · Epigenetic · Histone deacetylase · Clinical · Neurodegenerative

Introduction

Central nervous system (CNS) disorders comprise a diversity of pathologies. Vulnerabilities for developing neurological and psychiatric disorders are associated with complex genetic, as well as environmental, factors. Even in the cases where a single causative mutation is known, e.g., Huntington's disease (HD), other unknown factors contribute to clinical variation in disease onset, progression, and severity. Alterations in gene expression are apparent in most CNS disorders, ranging from dysregulated expression of disease genes themselves to pathology-induced activation of immediate early genes and delayed secondary effects on transcription. Studies have also suggested that a precise balance between histone acetylation and deacetylation is necessary for neuronal survival in normal conditions and that altered homeostasis is a final common endpoint in several neurodegenerative disorders [1]. At present, there are few therapies for treating any of the wide range of neurological diseases.

Despite the highly heterogeneous nature of neurological disorders, therapeutic benefits for diverse CNS disorders may be accomplished by targeting the process of gene transcription. Novel treatment strategies for these disorders have turned towards histone deacetyltransferase (HDAC) inhibitors, which act to modify gene expression. This topic has been reviewed previously [2–6]. The most commonly used HDAC inhibitors target multiple subtypes and classes of HDAC enzymes, hence likely have widespread effects throughout the brain. However, not all neurons are affected equally in any particular neurological disorder. Rather, particular brain regions or neuronal groups are preferentially susceptible to, or others preferentially protected from, pathological insults. Therefore, targeting the appropriate brain regions in different neurological disorders and avoiding unaffected regions are essential criteria if such compounds are to represent useful therapeutics. This review will summarize the focal nature of selected neurological disorders for which HDAC inhibitors have been suggested for use and features surrounding the efficacy of currently used HDAC inhibitors.

E. A. Thomas (✉)
Department of Molecular Biology, The Scripps Research Institute,
MB-10, 10550 N. Torrey Pines Rd.,
La Jolla, CA 92037, USA
e-mail: bthomas@scripps.edu

Subdivisions of the Brain

The brain is the most complex organ in the human body providing the center for intelligence, interpretation of the senses, control of movement, the neuronal basis for behavior, and executive control over most homeostatic processes. A wealth of information has emerged regarding the different neuronal and glial cell types present in the brain, and the enormous complexity of brain circuitry and networks, which together coordinate diverse functional activities. The brain consists of anatomically distinct and well-defined regions, and each is preferentially associated with particular functions. For example, the striatum functions primarily in the regulation of movement and organization of motor behavior [7, 8]. This region, consisting of the caudate nucleus, putamen, and nucleus accumbens, is the major receptive component of the basal ganglia, a group of subcortical nuclei that include the substantia nigra, globus pallidus, and the subthalamic nucleus. It is also critically involved in the generation of directed motor activity, stereotyped behaviors, and the establishment of habits [9]. The ventral striatum, also known as nucleus accumbens, is critically involved in reward behavior. A wide variety of reward-related behaviors have now been shown to be mediated by a complex neural circuit involving the nucleus accumbens and its dopamine innervation from the ventral tegmental area [10]. Another brain region associated with movement is the cerebellum, which is foremost associated with coordination of muscle activity and fine motor control.

Other defined regions include the cortex and hippocampus. In particular, the prefrontal cortex is a primary region associated with complex cognitive behavior and executive function. These involve decision making and the expression of personality and appropriate social behavior. This region is one of the largest cortical subregions making up the anterior part of the frontal lobes of the brain sub-divided. It can be subdivided into basic areas including the dorsolateral, orbitofrontal, and ventromedial prefrontal areas. A central brain region involved in learning and memory formation and storage is the hippocampus. Memory is a complex phenomenon with specific types including the formation of new memory, declarative memory, and memory retention, all of which are associated with hippocampal function [11, 12]. Evidence also indicates that the hippocampus is used in storing and processing spatial information [13]. Additional brain regions with distinct functionalities include the thalamus, which acts as a filter to screen out unimportant neuronal signals and organize and redirect those requiring further action, and the hypothalamus, which is an important regulator of appetite, arousal, and various homeostatic functions. Different CNS disorders are associated with dysfunction or degeneration of neurons in particular regions, which give rise to, or can account for, the ensuing disease phenotypes and behavioral symptoms (Table 1).

Focal Pathologies in Neurological Disorders

One of the major challenges in the study of neurodegenerative disorders is explaining why mutations in ubiquitously expressed proteins have selective effects on certain neuronal populations or brain regions. This phenomenon is commonly observed in polyglutamine disorders. In other diseases, the basis of dysfunction can be predicted based on mapping of neurotransmitters systems, as in disorders involving the dopaminergic system, such as Parkinson's disease and addiction. Such disorders represent candidate neurological diseases for HDAC inhibitor therapeutics.

Polyglutamine Disorders

The polyglutamine disorders are a group of inherited neurodegenerative disorders that are caused by expansion above a particular threshold of a CAG repeat region within a protein-encoding exon (reviewed in [14]). It is widely accepted that the resulting glutamine expansion confers a toxic gain-of-function on the particular disease protein. A major enigma in the field is that, although the disease-causing proteins are ubiquitously expressed, only particular neuronal populations are affected by the mutant disease protein, resulting in distinct focal patterns of pathology and associated clinical symptoms. This is especially true for HD, spinal bulbar muscular atrophy (SBMA) and dentatorubral–pallidoluysian atrophy (DRPLA), which are discussed briefly below in the context of their central pathologies.

In HD, the CAG repeat region is located in exon 1 of the *HTT* gene, resulting in an expanded polyglutamine tract near the N terminus of the encoded huntingtin protein [15]. Disease onset is correlated with CAG repeat length (threshold ~39 repeats; longer expansions result in earlier onsets) [16], although other disease modifiers are thought to affect age of onset, which is typically in 40s [17]. Mutant huntingtin protein causes selective dysfunction and neurodegeneration of medium spiny neurons in the striatum, despite widespread expression of the huntingtin protein throughout the brain. Because the striatum is responsible for the control of movement and motor function, dysfunction in this region accounts for the severe motor abnormalities that are the primary manifestation in this disease. In fact, it has been shown that the severity of striatal pathology is correlated with the degree of motor impairments [18, 19], suggesting that striatal degeneration plays a central role in HD. Other symptoms include mood changes and cognitive

Table 1 Brain regions associated with various neurological disorders and HDAC inhibitors tested in rodent models of these disorders

Disease	Brain regions affected	HDAC inhibitor Tested	Reference
Huntington's disease	Striatum, cortex	SAHA	Hockly et al. [93]
		Phenylbutyrate	Gardian et al. [95]
		Sodium butyrate	Ferrante et al. [94]
		4b	Thomas et al. [91]
Huntington's disease (3-NP)	Striatum	Sodium butyrate	Ryu et al. [39], Ferrante et al. [94]
Spinal bulbar muscular atropy	Spinal cord	Sodium butyrate	Minamiyama et al. [98]
DRPLA	Cerebellum, cortex, GP	Sodium butyrate	Ying et al. [99]
Friedreich's Ataxia	Cerebellum, spinal cord	106	Rai et al. [100]
Spinal muscular atrophy	Brain stem, spinal cord	TSA	Avila et al. [97]
		SAHA/M344	Hahnen et al. [96]
Amyotrophic Lateral Sclerosis	Brain stem, spinal cord	Phenylbutyrate	Petri et al. [101]
		Sodium butyrate	Ryu et al. [102]
Ischemia	Hippocampus, cortex	VPA	Ren et al. [112], Kim et al. [110]
		TSA	Kim et al. [110]
		Sodium butyrate	Kim et al. [110]
		DMA-PB	Zhang et al. [113]
		SAHA	Ren et al. [112], Faraco et al. [111]
Parkinson's disease (MPTP)	Striatum, substantia nigra	Phenylbutyrate	Gardian et al. [103]
Learning memory	Hippocampus	TSA	Fontan-lozano et al. [106]
		Sodium butyrate	Fontan-lozano et al. [106]
Addiction (alcohol)	Ventral striatum	TSA	Romieu et al. [105], Pandey et al. [104]
Addiction (cocaine)	Ventral striatum	Sodium butyrate	Kumar et al. [54]
		Phenylbutyrate	Romieu et al. [105]
Schizophrenia	Prefrontal cortex	VPA	Tremolizzo et al. [109]
Cognitive function	Frontal cortex	Sodium butyrate	Fontan-lozano et al. [106]
		TSA	

DRPLA, dentatorubral pallidoluysian atrophy; 3-NP, 3-nitropropionic acid; GP, globus pallidus; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

deficits. Although clinical symptoms of HD have generally been attributed to the striatum, which undergoes the most significant pathological changes, neuronal degeneration in the cerebral cortex has also been well documented and occurs within the temporal and frontal lobes [20]. Mutant huntingtin also affects other structures, such as cerebellum, which is particularly affected in juvenile-onset HD [20–25].

SBMA (Kennedy's disease) is an X-linked disorder affecting males, with adult onset. Unlike the huntingtin protein, the disease protein in SBMA is well-characterized; pathology is triggered by a polyglutamine expansion in the N-terminal activation domain of the androgen receptor [26]. The androgen receptor is a broadly expressed member of a family of nuclear receptors, which act as transcription factors that alternate between active and inactive states by binding to specific ligands. In this disease, the cells most susceptible to degeneration are motor neurons located in the anterior horns and bulbar regions of the spinal cord. Pathology in these neurons results in muscle atrophy, weakness, and muscle fasciculations.

The protein atrophin-1 contains a polyglutamine tract, expansion of which is responsible for DRPLA [27, 28]. Atrophin-1, exhibits widespread expression in both brain and peripheral tissues and is found throughout the cytoplasm and nucleus in cells of both unaffected and affected individuals [29]. In DRPLA, neurodegeneration is detected primarily in the cerebellum, subthalamic nucleus, cerebellar cortex, and globus pallidus [30, 31]. Juvenile DRPLA cases have more widespread cerebellar neuronal loss than the more common adult onset form, including specific degeneration of Purkinje cells, in addition to the neurons of the dentate nucleus [30]. Symptoms of DRPLA include ataxia, involuntary movements, mental and emotional problems, and dementia, although these differ in adult vs. juvenile forms of the disease [30]. Degeneration of cerebellar Purkinje and dentate neurons is also a principal feature of the hereditary ataxias linked to expansion of CAG repeats, including the spinocerebellar ataxis (SCAs) 1, 2, 3, 6, 7, and 17 [32, 33]. Friedreich's ataxia, a disease caused by a GAA repeat expansion in non-coding region also exhibits

preferential loss of neurons in the cerebellum, spinal cord, and brainstem [34].

Unifying mechanisms of transcriptional dysregulation have been implicated in the pathogenesis of polyglutamine-dependent neurodegenerative diseases [35, 36]. Expanded polyglutamine tracts can disrupt transcription by multiple mechanisms, including altering the acetylation status of histones [37–40], interfering with the core transcriptional machinery [41, 42], and disrupting the binding activities of transcription factors [43], but it is unclear which mechanisms are most important to pathology. These finding have led to the suggestion that compounds that alter gene expression, such as HDAC inhibitors, might be of therapeutic value.

Dopamine System-Based CNS Disorders

The pathology in some CNS disorders is governed by the innervation patterns of neurotransmitter systems and sites of neurotransmitter receptor expression in the brain (see Table 1). This is especially true for the dopaminergic system. Dopamine serves many functions in the brain, including important roles in behavior and cognition, motor activity, motivation and reward, inhibition of prolactin production, mood, attention, and learning [44]. Its patterns of innervation explain the multiple effects of activating this system. Clinically, the three most important dopaminergic projections are the mesostriatal, mesocortical, and mesolimbic pathways [44], and each of these is associated with distinct neurological problems, as described briefly below.

The mesostriatal (also known as nigrostriatal) pathway transmits dopamine from the substantia nigra to the striatum. This is one of the most dominant pathways associated with motor control [44]. Degeneration of these dopaminergic neurons causes Parkinson's disease, a progressive neurodegenerative disorder characterized by resting tremor, difficulty in initiating movement, slowness of movement (bradykinesia), and dysarthria. Evidence also suggests that medium spiny neurons of the striatum, the targets of these projections, are also affected [45]. The mesocortical pathway transmits dopamine from the ventral tegmental area (VTA) to the frontal cortex. Dopamine transmission via this connection is essential for cognitive function [44]. Malfunctions of this pathway are associated with the devastating psychiatric disorder, schizophrenia, although neuronal degeneration is not observed in this disorder [46]. The mesolimbic dopamine system that projects from the VTA to the nucleus accumbens has been implicated in the rewarding effects of drugs of abuse [47]. Drug addiction/dependence is defined as a chronically relapsing disorder that is characterized by compulsive drug use, inability to control drug intake, and extreme drug cravings. Although drugs of abuse possess different neuropharmacological properties, activation of the dopaminergic system in the nucleus accumbens represents a common pathway by which these drugs mediate their reinforcing effects [48].

Pharmacological therapeutics targeting the dopamine neurotransmitter system have been employed, such as dopamine replacement therapy (L-DOPA) for Parkinson's disease and dopamine-blocking agents for psychiatric disorders; however, improved drug treatments are warranted. Several microarray studies have reported dramatic alterations in gene expression in Parkinson's disease ([49] and references therein), schizophrenia reviewed in [50, 51], and cocaine- or amphetamine-induced addiction reviewed in [52]. Previous studies have demonstrated that dopaminergic-mediated signaling can alter histone modifications in the striatum both on a global scale [53], as well as at specific gene promoters, such as c-fos [54] and fosB [55]. These studies have demonstrated that chromatin remodeling is an important regulatory mechanism underlying dopamine-associated effects on gene expression and ensuing behavior. Recent evidence suggests that HDAC inhibitors, by altering expression of important dopamine-associated genes, might represent useful therapeutics for these disorders (see Table 1).

Other Disorders Characterized by Selective Neuronal Loss

Amyotropic lateral sclerosis (ALS; Lou Gehrig's disease) and spinal muscular atrophy (SMA) are both characterized by neurodegeneration of motor neurons in the cerebral cortex and/or brainstem and spinal cord resulting in fatal paralysis [56]. Both upper and lower motor neurons are affected in ALS, while only lower motor neurons are affected in SMA. Upper motor neurons originating in the cerebral cortex direct the lower motor neurons in the brainstem and spinal cord to produce movements such as walking or chewing. The lower motor neurons alone control movement in the arms, legs, chest, face, throat, and tongue. Most cases of ALS occur sporadically, however, familial forms of ALS result from mutation of the superoxide dismutase 1 gene, or *SOD1* [57], which encodes a ubiquitously expressed protein. About 20–25% of all familial ALS are caused by mutations in *SOD1*; more than 125 mutations have been identified, spanning all five exons of this gene with 114 causing disease [57]. In transgenic rodents with SOD1-mediated ALS and in some human ALS cases, mutant SOD1 protein forms insoluble aggregates in the spinal cord [58]. SMA, an autosomal recessive disorder, has various forms, with different ages of onset, patterns of inheritance, and severity and progression of symptoms [59]. Despite this range of disease phenotypes, SMA is caused by mutations in a single gene, the Survival of Motor Neuron gene, which exists in two copies,

SMN1 and *SMN2* [59]. The SMN protein is ubiquitously expressed, although particularly high levels are detected in motor neurons of the spinal cord, the most affected region in SMA patients. Individuals lacking a functional *SMN1* gene express vastly reduced levels of the protein, which is correlated with the degree of disease symptom [59].

Global ischemia can result from cerebrovascular trauma, cardiac arrest, near-drowning, or carbon monoxide poisoning. Brief ischemic insults cause selective, delayed death of hippocampal CA1 neurons [60]. This delay between trauma and cell death is consistent with a role for transcriptional changes in ischemic pathology, and accordingly, studies have demonstrated alterations in gene expression occurs after ischemic insult in rodents [61]. Manipulation of transcription is thought to be of therapeutic relevance to stroke therapy [62]. In particular, an increase in the expression of genes related to processes of brain injury, repair, and recovery may prove useful to reduce neurodegeneration in the hippocampus resulting from ischemic insult.

Gene Expression Regulation: Chromatin, HATs, and HDACs

Studies of chromatin remodeling have expanded our knowledge regarding the manner in which genes are regulated. Gene expression is ultimately dependent on factors that alter chromatin structure. The basic unit of chromatin is the nucleosome, which consists of 147 base pairs of DNA wrapped 1.6 times around an octamer of core histone proteins H2A, H2B, H3, and H4 [63]. The amino-terminal tails of these core histones contain amino acid residues that are sites for acetylation, methylation, phosphorylation, and ubiquitination; these posttranslational modifications alter histone interactions with DNA and nuclear proteins, resulting in changes in gene transcription [64]. Particular patterns of histone modifications correspond to various states of remodeled chromatin and to the activation or repression of distinct sets of genes. This is referred to as the "histone code" [65]. In particular, histone acetylation and deacetylation of histones are modulated by the interplay between histone acetyltransferases (HATs) and HDACs [64, 65]. Typically, increases in HAT activity lead to increased gene transcription by creating a more open conformation of chromatin, whereas HDAC activity leads to repression of gene expression through condensation of chromatin structure (Fig. 1). However, the precise mechanisms of transcriptional regulation are likely to be more complex.

HATs makes up a diverse family of proteins, including Gcn5-related *N*-acetyltransferase superfamily members, MYST proteins, global coactivators p300 and CREB-binding protein, nuclear receptor coactivators, TATA-binding protein-associated factor TAF(II)250 and its homologs, and subunits of RNA polymerase III general factor TFIIIC [66]. A review of this family of enzymes has been summarized elsewhere [67]. In contrast, HDAC enzymes comprise a more related family of proteins with structural similarities. Each exhibits a distinct brain expression pattern, which will be reviewed below.

HDAC Enzymes

The HDAC enzymes comprise a large family of proteins: 18 HDAC enzymes have currently been identified in humans [68]. These enzymes have been divided into distinct groups. Class I HDACs consists of HDACs 1, 2, 3, and 8. Class II HDACs are further distinguished into two groups: class IIa, consisting of HDACs 4, 5, 7, and 9, and class IIb, consisting of HDACs 6 and 10 [68]. Class II enzymes share significant sequence and structural homology and, like class I HDACs, require Zn for catalytic activity. Members of a third class of HDACs, called the "sirtuins," are distinct from classes I and II and require NAD^+ for their enzymatic activity [69]. Class IV is represented by a single member, HDAC11 [70], and while sharing similar characteristics to HDACs in classes I and II, this HDAC is thought to have distinct physiological roles [70, 71]. HDACs exist in large multiprotein complexes, and there is evidence that most, if not all, HDAC isoforms require interaction with other HDACs or proteins for

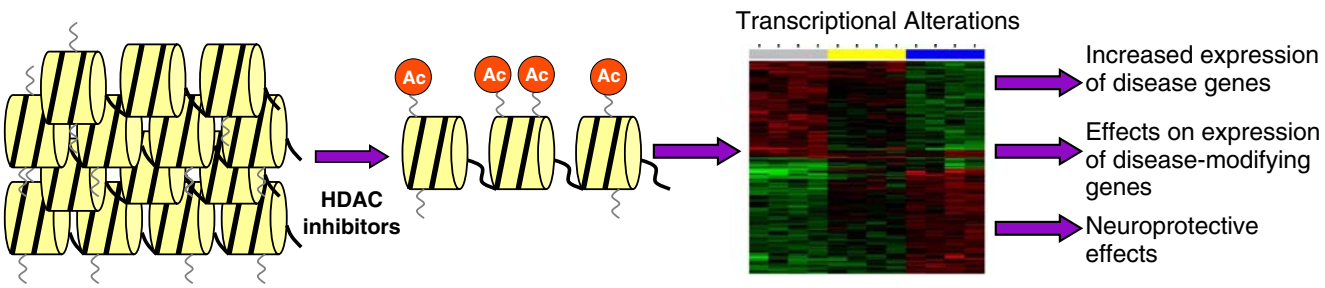

Fig. 1 Schematic depiction of the possible effects of HDAC inhibitors on histone acetylation and gene transcription

optimal enzymatic activity [72, 73]. The diversity of these multiprotein complexes and the fact that many cofactors have yet to be identified makes it difficult to interpret the potential contributions of these cofactors to brain region-specific effects.

Diverse CNS Expression Patterns of HDACs

Previous studies have used global analyses, i.e. Northern blotting, polymerase chain reaction, to demonstrate expression of certain HDAC subtypes in the brain and other peripheral tissues [70, 74, 75]. An analysis of the developmental expression of HDAC11 has also been reported using similar techniques [76]. Recently, CNS-wide expression patterns for 11 different HDACs (classes I, II, and IV) were mapped using high-resolution in situ hybridization and imaging technology [77]. Ten 40-mer oligonucleotide probes for each isoform were designed, and in situ hybridization signals from each HDAC were compared to radiolabeled standards in order to demonstrate relative levels of expression in >50 regions of rat brain. This study revealed overlapping yet distinct expression patterns for various HDACs throughout the rat brain as outlined below; a simplified summary of these results is also shown in Table 2. Overall, HDACs 3, 5, and 11 exhibited the most abundant hybridization signals, exhibiting high levels of expression in several regions, including the cortex, striatum, thalamus, hippocampus, and cerebellum, whereas HDACs 7, 9, and 10 showed the lowest overall expression levels in the brain [77]. Additionally, distinct differences were observed in key regions important to several neurological disorders, including cerebellum, striatum, spinal cord, and hippocampus. It is possible that targeting the primary isotypes in each brain region may provide the most specific and relevant effects on gene transcription.

Cerebellum

The genes encoding class I enzymes, HDACs 1, 2, and 3, and class IIa members HDAC4 and HDAC5, exhibited high levels of messenger RNA (mRNA) expression in cerebellar granule neurons. In particular, HDAC1 showed almost a twofold higher level of expression in cerebellum compared to any other region ([77] and Table 2). The class IV HDAC, HDAC11, also exhibited high levels of mRNA expression in granule neurons as well as in Purkinje cells. A separate study detected abundant expression of HDAC6 protein in Purkinje cells, as determined by immunohistochemistry [78], although the mRNA for this isotype was found at low levels [77]. The HDACs expressed in the cerebellum, especially in Purkinje neurons, might be especially relevant to diseases associated with this region, such as DRPLA, Friedreich's ataxia, and the SCAs; hence, targeting these isoforms with novel compounds might be most appropriate for these disorders.

Striatum

Of the class I HDACs, HDAC3 showed the highest expression levels of mRNA in striatum, followed by HDAC2 ([77] and Table 2). HDAC1 showed low levels of expression in striatum, with HDAC8 not being detected at all [77]. HDAC5 of the class IIa group also exhibited high levels of expression in striatum, similar to HDAC3, whereas other members of this class showed very low mRNA levels. As a comparison, class IIb HDACs were almost undetectable in this region [77]. The mRNA levels for all HDACs were equal throughout the striatum, with no differences being detected between dorsal and ventral

Table 2 CNS expression patterns of HDAC enzymes

Brain region	HDAC1	HDAC2	HDAC3	HDAC4	HDAC5	HDAC6	HDAC7	HDAC8	HDAC9	HDAC10	HDAC11
Olf. bulb	2	2	4	4	4	1	0.5	0.5	0	0	0
Cortex	2	3	3.5	3.5	3.5	1	0.5	0	0.5	0.5	4
Striatum	0.5	2	3	1	3	0.5	0.5	0	0	0	4
Amygdala	2.5	3	3.5	3	3	1	1	1	0.5	0.5	4.5
Hippocampus	2.5	4.5	5	4.5	5	2	1	2	1	1	5
Hypothalamus	1.5	2	3.5	2.5	3.5	1	0.5	1	0	0	5
Cerebellum	4	4	5	5	5	1.5	1.5	2	0.5	0	4
Spinal cord	1	2	2.5	2	2.5	0.5	0.5	0.5	0	0	3.5
Choroid plexus	2	0	3	0	2	0	0	0	0	0	0

Data summarized from Broide et al. [77]

Expresson numbers reflect relative abundance of each isoform: 0, not detected; 1–2, low expression; 3, moderate expression; 4, high expression; 5, very high expression

striatum (nucleus accumbens). Consistent with the mRNA findings in mouse, immunohistochemistry studies have demonstrated abundant HDAC5 protein levels in human striatum, with much lower levels of HDAC1 [79]. Dysfunction of the striatum is associated with several movement disorders, especially Huntington's and Parkinson's disease, while the nucleus accumbens is ultimately associated with reward and addiction, as discussed above. Based on the expression patterns, inhibition of HDACs 3 and 5 might demonstrate the strongest effects for these disorders.

Hippocampus

All HDACs showed appreciable mRNA expression in the hippocampus but with interesting differential expression among subregions (Table 2). HDACs 1 and 8 showed greater mRNA expression in the dentate gyrus, compared to CA1-3, whereas HDAC11 exhibited abundant mRNA expression in CA1, with lower amounts in CA3 and dentate gyrus [77]. Another study demonstrated abundant HDAC11 protein levels in hippocampus by immunohistochemistry [76]. High levels of mRNA expression were also detected for HDACs 2, 4, and 5. For HDAC2, this region showed the highest level of expression compared to any other [77]. This suggests differential roles for HDAC subtypes, particularly HDAC2, in learning and memory.

Spinal cord

Divergent patterns of HDAC mRNA expression are also observed in the spinal cord but at much lower levels than those observed in other brain regions (Table 2). mRNAs for HDACs 3, 5, and 11 were expressed at the highest levels in this region, followed by HDACs 2 and 4 [77]. HDAC11 protein expression was detected in a separate study in the brainstem [76], which lies just rostral from the spinal cord. HDACs 9 and 10 mRNAs were not detected at all with the other members showing only low levels [77]. This is particularly interesting in light of the several disorders caused by motor neuron dysfunction/degeneration in this region.

Isotype Selective Effects of HDACs in the Nervous System

A growing body of evidence suggests that HDAC selectivity is an important issue in neurodegeneration, as it has become clear that distinct HDACs have very different cellular functions. This further highlights the need for, and relevance of, isotype-selective compounds. Studies in cell culture, *Drosophila* and *Caenorhabditis elegans* models have shed light on isotype-specific effects of HDAC enzymes in the nervous system.

Pandey and colleagues have found that inhibition of the class IIb enzyme HDAC6 may be detrimental to neurodegeneration in flies [80]. In that study, HDAC6 RNAi knockdown in a fly model of SBMA showed that depletion of HDAC6 protein levels enhanced degeneration [80]. Conversely, overexpression of HDAC6 in transgenic flies was found to be protective against neurodegeneration [80]. It has been suggested that a possible mechanism for this effect is a role for HDAC6 in the management of misfolded protein-induced stress [81]. A protective mechanism for HDAC6 has also been demonstrated in cell culture models of HD, whereby HDAC6 activity was required for autophagic degradation of huntingtin protein in HeLa cells [82]. Results from another study in flies have suggested beneficial effects of HDACs 1 and 2. Genetic knockdown of rpd3 (the fly orthologue of HDAC1/2), as well as Sirt1 and Sirt 2 orthologues, showed neuroprotective properties in a *Drosophila* model of HD that expresses mutant human Htt exon 1 protein in all neurons [83].

Studies on *C. elegans* have also provided evidence for HDAC isotype-specific effects related to the CNS. A report by Bates et al. [84] has shown that HDA-3 and HDA-1 (two different worm HDACs both representing orthologues of HDAC1/2) modulate polyglutamine toxicity in *C. elegans* neurons expressing a human huntingtin fragment with an expanded polyglutamine sequence [84]. Furthermore, these authors found that HDA-3 and HDA-1 had different targets with opposing effects on toxicity [84].

HDAC Inhibitors: The Development of Isotype-Selective Compounds

A large number of structurally diverse HDAC inhibitors have been purified from natural sources or synthetically developed, and at least 14 have progressed to clinical development [68, 85]. These inhibitors prevent deacetylation of histones, resulting in a more open chromatin conformation, which favors active gene transcription (see Fig. 1). Chemically, the HDAC inhibitors can be classified into four general chemical structure groups, including the following: (1) the small carboxylates, such as sodium butyrate, valproic acid, and sodium phenylbutyrate; (2) the hydroxamic acids, such as trichostatin A (TSA), suberoylanilide hydroxamic acid (SAHA), and their derivatives; (3) the benzamides, such as MS-275; and (4) the cyclic peptides, including apicidin and depsipeptide [86]. Examples of these are shown in Table 3. Most of these compounds, such as TSA, are broad-spectrum inhibitors, targeting both class I and II HDAC enzymes. In vitro studies using recombinant human HDAC enzymes in deacetylation assays have further elucidated the specificity of previously identified HDAC inhibitors [87]. Pan-specific

Table 3 Different specificities of HDAC inhibitor classes

HDAC inhibitor class	Compound	HDAC target	Reference
Hydroxamate	Suberoylanilide hydroxamic acid (SAHA; vorinostat)	Classes I, II, IV	Khan et al. [87], Xu et al. [68]
Hydroxamate	Trichostatin a (TSA)	Classes I, II	Bolden et al. [85], Khan et al. [87]
Small carboxylate	Sodium butyrate	Classes I, IIa	Bolden et al. [85]
Small carboxylate	Phenylbutyrate	Classes I, IIa	Bolden et al. [85]
Small carboxylate	Valproic acid (VPA)	Class I	Khan et al. [87]
Cyclic peptide	Depsipeptide	Class I	Bolden et al. [85]
Cyclic peptide	Apicidin	HDAC2/3 ≫ HDAC1/8	Khan et al. [87]
Benzamide	MS-275	HDACs1>9>2, 3	Bolden et al. [85]; Khan et al. [87]
Benzamide (pimelic diphenylamide)	4b	HDAC3 ≫ HDAC1,2	Chou et al. [89]
Benzamide (pimelic diphenylamide)	106	HDAC3 ≫ HDAC1,2	Chou et al. [89]

inhibitors include the widely used inhibitors, SAHA and TSA; however, their potencies at inhibiting class II HDACs are much lower compared to their effects on class I enzymes. TSA is the most potent inhibitor with effective concentrations in the single-digit nanamolar range [87]. VPA, although much lower in potency, exhibits specificity for class I enzymes. Other compounds show some isotype-selectivity with MS-275 preferentially inhibiting HDAC1 and HDAC9, and demonstrating no activity at class II HDACs, and apicidin showing selectivity toward HDACs 2 and 3 ([87] and Table 3). The reported potencies of common HDAC inhibitors against different HDAC substrates vary considerably in vitro. This apparent discrepancy is largely due to differences in the sources of the enzymes (natural vs. recombinant), substrates used in the assays, and assay conditions. A further caveat is that not all HDAC isoforms have been tested with the reported inhibitors.

Recent progress has been made towards the identification of novel isoform-selective HDAC inhibitors [88, 89]. Attempts to improve selectivity have focused on modifying the capping group, linker region, and metal binding moieties of pan-specific inhibitors, such as TSA and SAHA. These efforts have resulted in the development of HDAC1- and HDAC8-selective compounds of the class I group and HDAC4 and HDAC6 of the class II group (reviewed in [88]). Additionally, a family of pimelic diphenylamide HDAC inhibitors of the benzamide type has been generated by Gottesfeld and colleagues [90]. These compounds show class I specificity, demonstrating no activity against class II HDACs [89]. Furthermore, these authors demonstrated that members of this class of compounds exhibit a 15-fold selectivity for the HDAC3 isoform over HDAC1, with lower activity at HDACs 2 and 8 ([89] and Table 3). Several challenges in this area remain, including the design of new compounds based on structural information, improved screening technologies and simultaneous testing of all 11 HDACs.

While the advantages of selective inhibitors over pan-specific inhibitors remains to be determined, such compounds will help elucidate the roles of individual HDAC isoforms in basic biological processes and pathology of disease, as well as in the side effects associated with these compounds. For example, we found that one of the HDAC3-preferring compound, HDACi 4b, demonstrated beneficial effects in a mouse model of HD, including delaying weight loss, ameliorating motor deficits, and showing neuroprotective effects on brain atrophy [91]. We further found that HDACi 4b showed no cell-cidal or apoptotic effects at concentrations <50 μM, which are tenfold higher than that previously reported for SAHA [92] and 50-fold higher than its expected therapeutic effects [91]. This suggests the effects of HDAC inhibitors to induce apoptosis and cell-cycle arrest are not mediated via HDAC3.

HDAC Inhibitors as Therapeutics for Neurological Disorders

During the past 5 years, several studies have identified HDAC inhibitors as candidate drugs for the treatment of neuropsychiatric and neurodegenerative disorders. This topic has been the focus of several excellent reviews (see [2–5, 35]). The consequences of HDAC inhibition may restore transcriptional balance to disease or disease-modifying genes, activate neuroprotective mechanisms or correct pertubations in histone acetylation homeostasis (Fig. 1). The major development in this area has been made largely through the use of broad-spectrum HDAC inhibitors. Initial findings demonstrated beneficial properties of these classical compounds in cell culture models; however, in vivo studies in mice have provided the best insight regarding the potential therapeutic effects of HDAC inhibitors in neurodegenerative disorders. These studies have demonstrated therapeutic benefits in a wide diversity

of neurological disorders (Table 1). Studies have demonstrated beneficial effects of SAHA [93], sodium butyrate [94], phenylbutyrate [95], and 4b [91] in HD transgenic mouse models; TSA, SAHA, and M344 in a mouse model for SMA [96, 97]; sodium butyrate in a transgenic mouse model of SBMA [98]; sodium butyrate in DRPLA transgenic mice [99]; the 4b-related compound, 106, in a Friedreich's ataxia mouse model [100]; phenylbutyrate and sodium butyrate in ALS transgenic mice [101, 102]; and phenylbutyrate in a Parkinson's disease lesion model [103]. On the addiction forefront, TSA was found to prevent the development of alcohol withdrawal-related anxiety in rats [104] and TSA and phenylbutyrate effective at inhibiting cocaine self-administration [105]. Furthermore, sodium butyrate and TSA reversed learning and memory impairments in mouse models, suggesting their usefulness in preventing learning and memory impairments in aging and in neurodegenerative disorders [106]. HDAC inhibitors have also been proven beneficial in psychiatric disorders despite the vast heterogeneity of these disorders. Valproic acid has long been used as a therapy for bipolar disorder and in combination therapy for schizophrenia [107, 108] and has also shown clinical benefit in a mouse model of schizophrenia [109]. Several HDAC inhibitors have also been shown to exhibit neuroprotective properties in brain ischemia models, including VPA, TSA, sodium butyrate, DMA-PB, and SAHA [110–113]. Such neuroprotective mechanisms may suggest therapeutic benefit for other disorders related to oxidative stress and inflammation.

Based on the promising in vitro and in vivo findings, clinical trials have been initiated to evaluate the safety and efficacy of HDAC inhibitors, including phenylbutyrate, for the treatment of HD, ALS, and SMA. The beneficial properties of HDAC inhibitors in neurological disorders may result from correcting the aberrant expression of a disease gene (i.e., Friedreich's ataxia, ALS, and SMA), altering expression of pathology-driven or disease-modifying genes (polyglutamine disorders) or showing neuroprotective effects (Parkinson's disease and ischemia; Fig. 1). Determining the effects of these HDAC inhibitors in different brain regions is essential for specific targeting afflicted brain regions and advancing human therapies.

Brian Region-Specific Consequences of HDAC Inhibition

Given the diversity of expression patterns of HDAC enzymes in the brain and the emergence of HDAC isotype-specific effects, one would expect HDAC inhibitors to elicit different effects in different brain regions. Indeed, recent studies have supported this notion. This suggests that rational guidelines could be developed for predicting the effects of HDAC inhibitors in particular brain regions.

Histone Acetylation

Simonini et al. [114] have reported differences in histone acetylation between two widely used HDAC inhibitors, MS-275 and valproic acid in different brain regions. These authors reported that MS-275 increased levels of acetylated histone H3 in the hippocampus and frontal cortex but failed to increase acetylated H3 content in the striatum [114]. This effect could be explained by considering the preferential

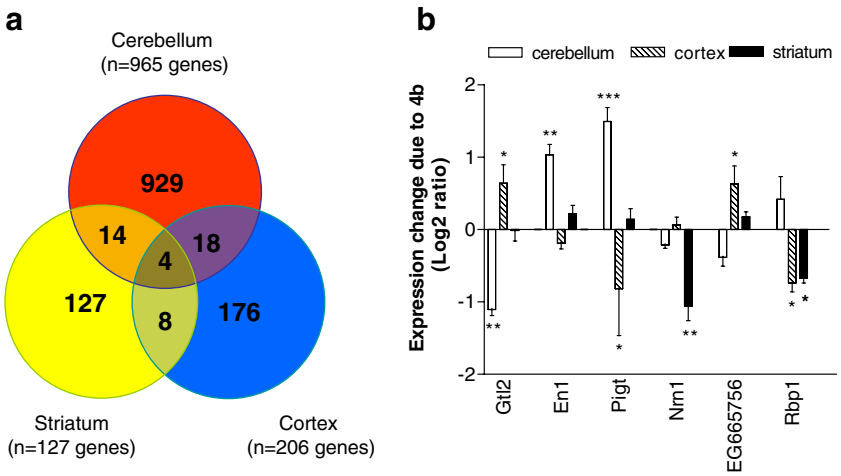

Fig. 2 **a** Venn diagram depicting overlap of HDACi 4b-induced gene expression changes in the cerebellum, cortex and striatum of normal (wt) mice. The numbers in parentheses reflect the total number of differentially expressed probesets at $p<0.01$ for each brain region. **b** Examples of differential effects of HDACi4b treatment on ubiquitously expressed genes in three different brain regions. Data are expressed as the log2 ratios of the normalized expression values from drug-treated vs. vehicle-treated wt mice. Data shown in **a** and **b** are taken from the microarray datasets published in reference [91]. The genes shown are indicated by their official UniGene gene symbols

activity of MS-275 for HDACs 1 and 2 and the low expression of these isoforms in the striatum compared to hippocampus. In contrast, valproic acid was equally effective at eliciting histone H3 hyperacetylation in striatum, hippocampus, and frontal cortex, which is consistent with its ability to target all class I HDACs, with the inclusion of HDAC3, which shows abundant expression in the striatum [77].

Gene Expression

Several studies have examined the effects of HDAC inhibitors on gene expression, and results have indicated that HDAC inhibitors tested do not show widespread effects on transcription but rather cause alterations in only subsets of genes, depending on the cellular context or tissue type. Most of the studies using classical HDAC inhibitors have been performed in cell culture. Early differential display experiments with lymphoid cell lines cultured with TSA showed that only 2% of 340 genes examined were altered in their expression [115]. More recent studies using microarray analysis have shown still that only a limited number of genes are affected by the HDAC inhibitors TSA, MS-275, valproic acid, and SAHA in cancer and hepatoma cell lines and osteoblast cell cultures [116–118].

More recent microarray studies performed in vivo not only have provided insight into the complexities of brain gene expression but also support the observations that HDAC inhibition does not elicit global effects on gene transcription. Studies have found that sodium butyrate and phenylbutyrate exhibit a limited number of expression differences in the cortex and striatum of HD transgenic mice (R6/2 and N171-82Q mice), although the effect of drug on wild-type (wt) mice was unclear [94, 95]. In the sodium butyrate report, only three genes were found to be significantly altered in their expression in both striatum and cortex of R6/2 mice [94]. Our own microarray studies using HDACi 4b found dramatically different effects of drug treatment in three separate brain regions, cortex, striatum, and cerebellum of both wt and HD transgenic mice (R6/2 mice) [91]. Nonetheless, in each brain region, HDACi 4b treatment corrected the abnormalities in gene expression of ~85% of the genes that were co-regulated by both disease and drug treatment [91]. With this compound the biggest effect was detected in the cerebellum; this may be expected based on the HDAC3-preferring properties of HDACi 4b and the abundant expression of HDAC3 in the cerebellum (Table 2).

Further scrutiny of our microarray dataset (see supplementary data from [91]) revealed striking brain region-governed differences in wt mice. A Venn diagram showing the numbers of genes whose expression was significantly altered by HDACi 4b treatment in each brain region of wt mice reveals that there is very little overlap in genes commonly regulated by HDACi 4b in different regions (Fig. 2), despite the fact that many of these genes are ubiquitously expressed. Ubiquitous patterns of expression for subsets of genes from each brain region were supported by images in the Allen Brain Atlas, a comprehensive in situ hybridization database providing basic expression patterns for thousands of genes expressed in the mouse brain (http://www.allenbrainatlas.com). Furthermore, it was found that 58.5%, 26.6%, and 32.6% of expression changes elicited by HDACi 4b treatment in the cerebellum, cortex, and striatum, respectively, exhibited brain region specificity for the expression change; that is, 32.6% of the genes, whose expression was altered in striatum, showed only significant changes in striatum and not in cortex or cerebellum. In addition, 6.2%, 25%, and 6.1% of expression changes in cerebellum, cortex, and striatum, respectively, showed an opposite direction of change in at least two different brain regions. Examples of these genes, which are all ubiquitously expressed, and their expression changes due to HDACi 4b treatment in these three brain regions are shown in Fig. 2.

Conclusions

Neurological disorders are dramatically different in their etiologies, focal pathologies, and current treatment approaches. Despite these diversities, HDAC inhibitors may represent relevant options for improved treatments for neurological disorders. Progress in this field has been accelerated by the development of isoform-selective compounds, although investigations with additional inhibitors are needed to further test the clinical efficacy and side effects associated with inhibition of individual HDAC enzymes. An important goal is to coalesce particular HDAC targets with distinct areas of pathology in order to achieve selective expression alterations in only the relevant region(s) for a given disorder. The data summarized herein provide information regarding which isoforms might best be targeted for different CNS disorders. Further examination of precise cell-type specific expression of HDAC enzymes (both mRNA and protein) is also warranted, which will allow in-depth investigations of neuronal vs. glial mechanisms related to HDAC inhibitor therapy.

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