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HDAC inhibitors and neurodegeneration: at the edge between protection and damage

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Abstract

The use of histone deacetylase inhibitors (HDACIs) as a therapeutic tool for neurodegenerative disorders has been examined with great interest in the last decade. The functional response to treatment with broad-spectrum inhibitors however, has been heterogeneous: protective in some cases and detrimental in others. In this review we discuss potential underlying causes for these apparently contradictory results. Because HDACs are part of repressive complexes, the functional outcome has been characteristically attributed to enhanced gene expression due to increased acetylation of lysine residues on nucleosomal histones. However, it is important to take into consideration that the up-regulation of diverse sets of genes (i.e. pro-apoptotic and anti-apoptotic) may orchestrate different responses in diverse cell types. An alternative possibility is that broad-spectrum pharmacological inhibition may target nuclear or cytosolic HDAC isoforms, with distinct non-histone substrates (i.e. transcription factors; cytoskeletal proteins). Thus, for any given neurological disorder, it is important to take into account the effect of HDACIs on neuronal, glial and inflammatory cells and define the relative contribution of distinct HDAC isoforms to the pathological process. This review article addresses how opposing effects on distinct cell types may profoundly influence the overall therapeutic potential of HDAC inhibitors when investigating treatments for neurodegenerative disorders.

Keywords

chromatin; epigenetics; brain; neurological disorders; myelin

1. Introduction

When evaluating potential therapeutic options for various neurodegenerative diseases, it is important to take into consideration the multiple causes and contributors to the condition. Ideally, an effective treatment would target not only the protection of neurons but also the reduction of overactive inflammatory responses. For many neurodegenerative diseases, the process is a progressive one, since an initial insult or toxic event is amplified and prolonged by the cellular responses of microglia and lymphocytes. Therefore, the ideal treatment would encompass methods to preserve neuronal integrity, diminish inflammatory responses, and

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inhibit detrimental over-activation of microglia while maintaining an environment conducive to repair and re-growth. One methodological approach that can encompass these multiple targets of treatment is the alteration of gene expression patterns that regulate a broad range of cellular processes. A similar approach has been suggested for recovery from stroke [1], where by targeting gene expression patterns in multiple cell types, it may be possible to promote conditions of growth and renewal that are critical for recovery of function.

Gene expression is regulated by many factors and enzymes that regulate the accessibility of targeted gene sequences to the transcriptional machinery. Within the nucleus, the DNA is wrapped around histone proteins and assembled into structures called nucleosomes. The acetylation of lysine residues on nucleosomal histones contributes to transcriptional activation [2]. The addition of acetyl groups is mediated by histone acetyltransferases (HATs) and their removal by histone deacetylases (HDACs). Therefore, the balance of these two enzymes modulates the expression of specific sets of genes. An imbalance between acetylation and deacetylation by HAT and HDAC enzymes may result in pathological functioning. For example, a decrease in histone acetylation is thought to contribute to several disease states, as inhibitors of HDACs have shown therapeutic effects in treating several disorders including epilepsy, mood disorders, sickle-cell anemia, T-cell lymphoma, as well as many cancers and immune diseases [for review, see 3]. Recently, the use of HDAC inhibitors (HDACIs) as therapeutic treatment options for neurological diseases has been highlighted [4-6]. Here we will review some of the recent data on the role of histone deacetylases and the use of HDACIs as treatment options for neurodegenerative disorders. Specifically, there will be a focus on the molecular mechanisms of HDAC inhibition as it relates to cell-type specific function. In addition, the roles of specific HDAC isoforms in various cell types will be addressed as they pertain to distinct diseases of the nervous system.

2. Histone Deacetylases

The histone deacetylases are enzymes that were originally characterized on the basis of their homology to yeast proteins and their ability to remove acetyl groups from histones. To date, 18 HDACs have been identified in mammalian cells and categorized into classes based on their domain structure and sequence homology [7]. Class I HDACs (HDACs 1, 2, 3 and 8) are grouped together based on their homology to the yeast transcriptional regulator Rpd3 and are primarily localized to the nucleus. Class II enzymes, comprised of HDACs 4, 5, 6, 7, 9 and 10, which share homology with the yeast HDA1 protein contain both nuclear import and export sequences, and can shuttle between the nucleus and cytosol [8,9]. The third class of histone deacetylases, the sirtuins (SIRT1-7), are structurally and enzymatically distinct NAD-dependent enzymes similar to yeast SIR2 (silent information regulator 2) and can be further divided into several groups based on function [10-12]. Lastly, HDAC11 has been categorized into its own group, a class IV deacetylase. Although these classes of proteins have been named histone deacetylases, their activities are not restricted only to the core histones as they can also target transcription factors, nuclear hormone receptors and even cytoskeletal elements [13, 14].

3. Histone Deacetylase Inhibitors

While the various HDACs have been classified and categorized, their individual functions continue to be defined. The role of HDAC function in cellular processes has largely been inferred by effects observed after inhibition of their enzymatic activity. Several studies have focused on effects of broad-spectrum small molecule inhibitors. Some of the most commonly used inhibitors include: the hydroxamate compounds trichostatin A (TSA) and suberoylanilide hydroxamic acid (SAHA), and the aliphatic acids, valproic acid (VPA) and sodium butyrate (NaB). It is likely that the non-specificity of these inhibitors is responsible for the contradictory

effects detected in distinct cell types. For example, HDAC inhibition appears to be mainly protective for neurons, and yet deadly to cancerous cells. Since most of the early work on HDACIs focused on the apoptotic and anti-proliferative effects in tumor and cancer cell lines, it was thought that the increased histone acetylation resulted in the transcription of pro-apoptotic genes, such as Bax and p21. However, increased acetylation also promoted the expression of pro-survival genes such as Bcl-2 and growth factors, thereby serving a protective effect in other cell types [15]. In animal models of ischemic stroke for instance, treatment with various HDACIs reduced the volume of damage, which may have occurred through reducing the toxic induction of p53, iNOS and COX2 [16], while increasing expression of protective genes such as Hsp70 and Bcl-2 [17]. One explanation for this discrepancy may be the targeted effect of HDACIs on transcription factors, resulting in transcriptional activation of diverse sets of genes. An example of a transcriptional factor target of HDACs is NF κ B, which can trigger transcription of both survival and apoptotic gene products [18]. The dichotomy in the effects of HDACIs is also observed in cells that contribute to inflammatory pathways, where treatment results in pro- or anti-inflammatory stimulation [19].

Another explanation for the diverse effects of HDACIs involves the differential role of individual HDAC isoforms. In the past few years, there has been increasing identification and synthesis of isoform specific inhibitors [for reviews, see 20,21]. This has allowed investigators to begin to decipher the effects of HDAC inhibition on gene transcription, via increased histone acetylation, and nonhistone function, as a result of altered acetylation of other targets. Broad-acting HDACIs, such as TSA, or more specific inhibitors, such as MS-275, can offset expression of genes down-regulated in models of schizophrenia and bipolar disorder. Interestingly, the inhibitor MS-275 was shown to increase histone acetylation only in the brain areas associated with the behavioral and cognitive deficits of the disease model [22]. These data suggest that targeting specific HDAC isoforms may be beneficial and potentially reduce unwanted side-effects, and that region specific isoform activity may be important for cell and tissue function in certain pathological conditions. Therefore, disease specific inhibitors can be regarded as an achievable goal for therapeutic treatment.

Like class I and II HDACs, the class III HDACs, the sirtuins, also have seemingly opposing effects on cell function. The activity of SIRT1, which can be enhanced with resveretrol, has been described as important for slowing the progression of age-associated changes. It can be induced by caloric restriction [12,23], and also protect neurons and slow neurodegeneration [24-26]. However, activation of SIRT1 can be harmful for energetically compromised neurons, possibly by utilizing too much of the available NAD, nicotinamide adenine dinucleotide [27, 28]. Therefore, activation of the sirtuins may serve to promote protection prior to degenerative conditions. While activation of sirtuins with resveretrol is correlated with increased cell survival and longevity, it is also associated with enhanced gliosis, which may worsen inflammatory induced damage [29]. Intriguingly, other studies have shown that inhibition of the sirtuins by nicotinamide or sirtinol, could be protective in reducing the cognitive deficits that occur during aging or with Alzheimer's [30]. More research is needed to further investigate the role of sirtuins, as well as to begin to thoroughly explore the individual contributions of all the sirtuin isoforms. Recent studies have found that while SIRT1 and cytoplasmic SIRT5 activity appear to be neuroprotective in some cases, increased SIRT2, 3 and 6 activity can promote neuronal apoptosis [31].

As is becoming apparent, deacetylase inhibition is neither always beneficial nor harmful. Identification of circumstance, isoform and disease specific function is critical for evaluating HDAC targets for therapeutic intervention. What has been lacking in the literature is a systemic incorporation of multiple factors impacted by HDAC inhibitors when investigating therapeutic treatments for multiple diseases and conditions. To this end, we have begun to approach this

issue by providing an overview of the effects of HDAC inhibition on several cell types as they pertain to neurodegenerative diseases.

4. HDAC Inhibition: Consequences by Cell Type

4.1 Neurons

When considering therapeutic targets for the treatment of neurodegenerative diseases, the obvious first choice is that of the neuron itself. The degeneration of neurons results in many devastating and debilitating diseases of the nervous system, and as such, mechanisms of increasing neuronal survival have been at the forefront of scientific research. Within the past decade, there have been many studies showing neuroprotective effects of HDACIs [for a recent review, see 32]. Some of the earliest evidence suggesting neuroprotective properties of HDACIs came from studies using animal models of Huntington's disease, which will be discussed in more detail below. It was also shown that treatment with HDAC inhibitors, such as VPA, can prevent neuronal apoptosis in excitotoxic and hypoxic conditions [33]. Similarly, low potassium-induced nuclear import of HDAC4 and subsequent apoptosis of cerebellar granule cell neurons can be prevented by HDACI treatment [34]. In models of oxidative stress and/or metabolic impairment, up-regulation of specific transcripts, targeted by the transcription factor Sp1, can help protect neurons, a protection that is enhanced with HDAC inhibition [35]. However, the increase in acetylation levels induced by HDACIs can be detrimental in some cases. There is evidence to suggest that inhibitors such as TSA and NaB can induce neuronal apoptosis [36,37], although a temporally defined treatment regimen may avoid this toxic effect [38]. Interestingly, there is also evidence suggesting that neuroprotection can result from non-enzymatic activity of HDACs, as was demonstrated by a mutated inactive form of SIRT1 [31], and the Histone Deacetylase-Related Protein, HDRP [39]. So it appears that the role of HDACs and HDAC inhibition in neuronal survival is not clearly defined.

A neurodegenerative disease that has received great attention for therapeutic HDAC inhibition is the polyglutamine disorder Huntington's disease. This movement disorder is characterized by degeneration of neurons of the basal ganglia as a result of an expanded polyglutamine stretch on the huntingtin protein. This expanded polyglutamine sequence can interact with and disrupt the normal distribution of the histone acetyltransferase CREB-binding protein (CBP) [40-45] and interfere with CBP-targeted transcription [46]. It was hypothesized that loss of the acetyltransferase activity of CBP was a major contributor to the degenerative progression seen in Huntington's disease. Indeed, studies have shown that over-expression of CBP can help to protect neurons from this polyglutamine-mediated neurotoxicity [41,43,46]. Another method available to restore this loss of acetyltransferase activity, and one that may perhaps be more clinically relevant, is HDACI treatment, which has demonstrated neuroprotective effects and a reduction in behavioral impairments in many animal models of Huntington's disease [44, 47-51]. Other neurodegenerative diseases have also shown signs of an alteration in the acetylase/deacetylase balance. In models of the motor neuron disease amyotrophic lateral sclerosis, HDAC inhibition with NaB resulted in a reduction of the clinical impairment [52, 53]. In this case, the therapeutic effect appeared to be through increased activation of NFκB signaling and reduced caspase activation. VPA has also shown promise to help recovery in peripheral nerve damage [54].

Axonal damage is another cause of neuronal degeneration, and histone deacetylases appear to play a role here as well. Neuronal damage due to progressive degeneration after axonal transection is inhibited in a specific mouse strain, the "Wld" mouse, demonstrating delayed Wallerian degeneration by the activity of the NAD-dependent histone deacetylase SIRT1 [55]. These mice have increased expression of an enzyme that generates NAD, and it was suggested that delayed degeneration was the result of increased SIRT1 activity. For this reason, pharmacological therapies designed to increase the supply of NAD or enhance the activity of

SIRT1 have been proposed to be effective for the treatment of neurodegenerative diseases. In contrast, another recent study examining sirtuins in the slow Wallerian degeneration mice found that the expression of another NAD-dependent HDAC, SIRT2, was reduced [56]. As SIRT2 is known to deacetylate tubulin, a correlative increase in acetylated tubulin was observed, which is thought to protect from microtubule instability and help to maintain axonal transport. For this reason, the delay in axonal degeneration has been attributed to the microtubule stability afforded by increased acetyl-tubulin. There is other evidence to suggest that inhibition of NAD consumption by use of the sirtuin inhibitor, sirtinol, can also be protective [28]. This protective effect arises from a bio-energetic standpoint, where reducing sirtuin consumption of NAD increases its availability for cellular metabolic function. Another study also suggests that an increase in available NAD can protect neurons from the axon loss and behavioral impairment induced by experimental autoimmune encephalitis, a model of the demyelinating disorder multiple sclerosis (MS) [57]. Together, these data suggest that increased NAD consumption, possibly by SIRT1, may endanger already compromised neurons.

Axonal damage can also occur from and result in impaired transport along microtubules. As another proposed toxic effect of polyglutamine aggregates in Huntington's disease was the interference with the transport of cargo along microtubules, it was suggested that increasing the acetylation of tubulin could restore this function. Deacetylation of α -tubulin by HDAC6 inhibits motor protein dependent transport of vesicles, and treatment with TSA, a broad-spectrum HDACI, restored the impaired vesicular transport and release of essential growth factors, such as brain-derived neurotrophic factor (BDNF), in a mouse model of Huntington's disease [58]. However, others have shown that the activity of HDAC6 may be essential for removal of aggregated ubiquitinated proteins and huntingtin aggregates by retrograde transport [59-61]. Targeted inhibition of SIRT2, a class III deacetylase that also deacetylates α -tubulin, may be effective, such as was found for amelioration of the toxicity of α -synuclein in a model of Parkinson's disease [62]. Additionally, recent evidence presents an HDAC6-independent perturbation of transport along microtubules. Toxic stimuli that result in axonal damage also induce a calcium-dependent export of the class I HDAC1, normally a nuclear enzyme. The presence of HDAC1 in the cytosol interrupted the interaction of cargo and motor proteins, resulting in loss of transport, neuritic swelling, and cell death [63]. This toxicity was prevented with the specific inhibitor, MS-275.

4.2 Lymphocytes

As many diseases of the nervous system are exacerbated by the response of the immune system, the effect of HDAC inhibition on lymphocytes and other immune cells is an important one. HDACs help regulate the memory of T cells [64], and are therefore important for proper immune function, but may also exacerbate damage in cases where inflammation is excessive. Many HDACIs have shown anti-inflammatory effects that can be therapeutic in suppressing immune cell function and inflammatory cytokine production [65,66] and reducing the transcription of the cytokine IL-2 [67]. Inhibition of HDACs can reduce inflammatory responses both by regulating the synthesis of cytokines, and by inducing apoptosis and cell cycle arrest of inflammatory CD4⁺ T cells [68]. There is evidence that HDACIs can reduce immune initiated increases in cytokines and inflammatory products, resulting in reduced demyelination and axon loss in an animal model of multiple sclerosis, where demyelination occurs as a result of aberrant immune activity [69]. For a more detailed discussion on the role of HDACIs in immune function, see the review in this issue (XXX).

4.3 Astrocytes/Microglia

Numerous degenerative disorders of the nervous system have an associated activation of microglia, which can release many neurotoxic cytokines [70]. Inhibition of HDACs has been

shown to both reduce [71] and potentiate [72] pro-inflammatory molecule release with lipopolysaccharide (LPS) treatment. These studies suggest that differential effects can be expected depending upon which HDACI is tested, the dose used, and the brain area examined. Treatment with the HDACI SAHA blocked the ischemia induced reduction of H3 acetylation, reduced the expression of COX2 and increased anti-apoptotic expression of Bcl-2 and Hsp70 in a mouse model of cerebral occlusion [17], as well as increased the acetylation of H3 and reduced transcript levels of iNOS, COX2 and IL-1 β in cultured glial cells and LPS injected striatum [71]. Although, TSA treatment enhanced LPS induced expression of IL-6, TNF- α and iNOS in glial cultures and hippocampal slices [72]. Studies have also found that HDAC3 can deacetylate, and therefore reduce, NF κ B-regulated transcription and that inhibitors of HDACs, such as TSA, can enhance cytokine stimulated responses [73,74]. However, there is also evidence that activity of the class III HDAC SIRT1 can reduce expression of inflammatory molecules such as iNOS and cathepsin B stimulated by the Alzheimer's disease associated peptide amyloid- β by deacetylation of the RelA/p65 subunit of NF κ B [75]. Therefore the deacetylation of targets, such as the transcription factor NF κ B, is not necessarily restricted to a single class of HDACs, or to a specific pro or anti-inflammatory outcome. Additionally, several HDACIs have been shown to induce apoptosis of microglial cells [76], thereby reducing the inflammatory response and lesion size in animal models of closed-head injury [77]. The apoptotic effect on glial cells is potentially a therapeutic mechanism for treatment of glioblastomas, and treatment of glioma cell lines results in growth arrest [78] and cell death [79]. However, as indicated above, there is a potential to induce further inflammatory responses as well.

HDAC inhibition can also increase transcription of protective molecules, such as growth factors like brain-derived neurotrophic factor (BDNF) and glial-derived neurotrophic factor (GDNF). For example, VPA increases GDNF and BDNF transcription in astrocytes, protecting midbrain neurons from neurotoxic insult, such as may occur in development of Parkinson's disease [80]. Another way that HDACIs may provide a neuroprotective effect is by reducing the amount of extracellular glutamate that contributes to excitotoxic damage. TSA treatment of astrocytes can block the down-regulation of a glutamate transporter, and in turn increase the amount of glutamate the astrocytes take up when stimulated with a neurotoxic compound that mimics Parkinson's disease [81]. Along these lines, further evidence suggests that an alternative method of reducing glutamatergic signaling in astrocytes also leads to hyperacetylation of promoters for neurotrophic factors and their increased production and release, supporting the importance of targeting this cell type when studying therapeutic options for the treatment of neurodegeneration [82].

4.4 Oligodendrocytes

The loss of myelin in demyelinating disorders contributes to axonal damage and subsequent neurodegeneration [83]. As demyelinated axons have impaired signal transduction and are vulnerable to extracellular insult, they are a therapeutic target for recovery from diseases such as MS. The use of HDACIs has been proposed for the treatment in such diseases because of the neuroprotective and anti-inflammatory effect of TSA in models of experimental allergic encephalomyelitis [65,69]. However, the potential use of HDACIs in demyelinating diseases should be considered with caution, since HDAC activity is required for the differentiation of oligodendrocyte progenitors during development and repair of demyelination [84-88]. Treatment of neonatal pups with HDACIs during the first two weeks of postnatal development impairs the ability of progenitors to mature into myelin-forming cells and results in hypomyelination [85]. Similarly, inhibition of HDACs during the repair phase of cuprizone-induced demyelination in young adult animals, impairs remyelination [88]. Recovery from demyelination in this experimental model is a bi-phasic event. The first period is characterized by expansion of the pool of undifferentiated oligodendrocyte progenitors and high levels of

transcripts involved in the maintenance of the progenitor pool. The second period is characterized by the differentiation of these cells into oligodendrocytes and the HDAC-dependent down-regulation of genes inhibiting the expression of myelin transcripts [88]. This process is quite effective in young adults, but not in older mice, where the lower levels of HDACs [86] and their impaired recruitment to the promoter of genes that need to be down-regulated in oligodendrocyte progenitors, interfere with the differentiation of these cells [88]. It is important to mention, however, that treatment with HDACIs has negative effects on the differentiation of oligodendrocyte progenitors only during a specific temporal window (i.e. when the cell needs to reduce inhibition). Indeed, treatment of young adult mice did not affect myelin formation once the oligodendrocytes had differentiated [85]. An additional concern regarding the possible use of HDACI treatment in demyelinating disorders is the potential reactivation of the JC virus, a human polyomavirus that can remain silent in healthy individuals, but when reactivated can induce leukoencephalopathy [89]. HDACI treatment was shown to induce hyperacetylation of the JC virus promoter and activation of the viral transcripts [90], which can lead to selective destruction of oligodendrocytes.

Additional caution regarding the use of HDACIs in demyelinating disorders is the consideration that it may also affect the expression of cytoskeletal-regulating molecules. HDAC inhibition of differentiating oligodendrocyte progenitors, for instance, increases the expression of the actin-severing protein gelsolin and of the microtubule-severing protein stathmin [91] with potential detrimental consequences on myelin stability and the efficiency of remyelination.

5. Summary

As we have described, the advent of HDACI treatment for many diseases has provided some promising results. For neurodegenerative disorders in particular, the use of small molecule HDACIs has shown some promise as a possible treatment method with a goal of minimizing, slowing and possibly reversing the deleterious effects. However, the fact that HDACs act on a wide variety of substrates, including nucleosomal histones, transcription factors and cytosolic proteins within multiple cell types (Fig. 1) suggests that in some cases, the beneficial effect on the pathology may be associated with some unintended harmful effects. Since many factors contribute to the transcriptional and proteomic profile of the cell, it is an enormous task to identify every consequence of any specific treatment. In some cases, the neuroprotective properties of HDACIs are desired, but may also involve activation of inflammation or suppression of much needed immune function. For this reason the use of broad-spectrum HDACIs leaves us on the edge between protection and damage. Only by targeting specific isoforms and specific cells types, will we be able to pull back from that ledge and find the protection and therapeutic results that will help treat the degenerative diseases of the nervous system.

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Figure 1. Multicellular targets of HDACs

This diagram illustrates the pleiotropic effects of HDACs in multiple cell types. HDACs can induce apoptosis in cancer cells (a), anti or pro-inflammatory effects in microglial cells (b), survival or apoptosis in neurons (c); inhibit the differentiation of oligodendrocyte progenitors (d); reduce inflammatory responses and induce protective effects of astrocytes (e); reduce inflammatory responses and induce immunosuppression in lymphocytes (f). Additionally, HDACs may affect axonal transport (upper right inset). Deacetylation of tubulin (depicted as removal of blue dots from microtubules) inhibits both anterograde (green) and retrograde transport (red). By preventing tubulin deacetylation HDACs are able to restore transport.