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Neuroprotective effects of histone deacetylase inhibitors in brain ischemia

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Stroke resulting from cerebral ischemia or haemorrhage is a common cause of the death of neuronal cells and neurological dysfunction in humans. Finding therapeutics to improve outcome from brain ischemic injury has proved to be challenging. The efficacy of neuroprotective compounds identified in experimental brain ischemia models thus far have failed to successfully translate in clinical human trials. Recent experimental evidence indicates that inhibition of zinc-dependent histone deacetylases can protect neuronal and oligodendroglial cells from the damaging effects of ischemic insult, which may contribute to improved functional outcome. In this review we briefly highlight the current data supporting a beneficial role of histone deacetylation in experimental brain ischemia. We also discuss the molecular mechanism of neuroprotection.

Key words: brain ischemia, histone deacetylase inhibitors, neuroprotection, neuroregeneration

INTRODUCTION

Posttranslational (epigenetic) modifications of histones have profound effects on gene expression by modifying the accessibility of genes to the transcriptional machinery. One type of modification is a coordinated process carried out by two classes of enzyme – histone acetyltransferases (HATs) and histone deacetylases (HDACs). HDACs regulate gene expression by removing the acetyl groups of select lysine residues in the conserved tails of core histone proteins, to shift them to a positive charge, and enhancing the interaction with the negatively charged DNA. This is a reversible reaction, in balance with HATs adding acetyl groups. In general, increased histone acetylation provides a more open chromatin structure correlating with gene transcriptional activity, whereas deacetylation (decreased acetylation) is associated with repression of gene transcription (Strahl and Allis 2000, Saha and Pahan 2006, Hildman et al. 2007). Therefore, the balance of these two enzymes is a key element in the regulation of the expression of specific sets of genes. Disruption of the balance between HAT and HDAC activities leads to disequilibrium in acetylation which may have critical impact on cellular functioning (Struhl 1998).

A significant amount of data highlights the cell-specific aspect of HDAC inhibition, which seems to impair DNA repair in cancerous cells (Minucci and Pelicci 2006, Duvic and Vu 2007, Lawless et al. 2009, Kristensen et al. 2009), and displays strong protective properties in a broad range of neuropathologies. In agreement with this, treatment with various HDAC inhibitors has emerged as attractive therapeutic approach in *in vitro* and *in vivo* models of neurotoxicity and neurodegeneration as well as in acute brain ischemia (Ferrante et al. 2003, Kazantsev and Thompson 2008, Chuang et al. 2009, Langley et al. 2009, Du and Jiao 2011, Gräff et al. 2012). HDACi could possibly correct aberrant acetylation patterns and ameliorate disease state. In this review we discuss some recent data supporting the role for histone deacetylase inhibitors as treatment options for brain ischemia.

HISTONE DEACETYLASES

Histone deacetylases (HDACs) are evolutionary conservative enzymes involved in the epigenetic regula-

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tions of gene expression and protein functions. To date, 11 potential HDACs have been identified in mammalian cells and all of them are expressed in adult rodent brain. They are organized into four different subclasses (I-IV) based on function and DNA sequence similarity (Thiagalingam et al. 2003). Generally speaking, class I HDACs display an extensive presence in nuclei. In addition to well-established nuclear localization, the expression of class I HDAC isoforms has also been observed in cytoplasmic domains (Baltan et al. 2011a). The class I HDACs (HDAC 1, 2, 3 and 8) are constitutively nuclear proteins, whereas class II enzymes, further divided into class IIa and IIb, comprised of HDACs 4, 5, 6, 7, 9, and 10, can shuttle between the nucleus and cytoplasm (Khochbin et al. 2001, Wang and Yang 2001, Xu et al. 2007). Class IV, currently consist of one member, HDAC11, with little known of its function. The enzymes belonging to class I, II and III are categorized as "zinc-dependent". The sirtuins, referred to as class III HDACs (Baur et al. 2012) are structurally and enzymatically distinct NAD-dependent enzymes. Sirtuins have been discussed in recent reviews (Baur et al. 2012, Houtkooper et al. 2012).

Although deacetylation of histones and compaction of chromatin is a common mechanism of Class I and II HDACs, some individual isoforms can also target many other non-histone protein, including transcription factors, nuclear hormone receptors, molecular chaperons, inflammation mediators, signal transduction mediators and cytoskeletal elements (Glozak et al. 2005, Spange et al. 2009, Ocker 2010).

Biological functions of individual HDACs have been difficult to define due to the lack of isoform-specific inhibitors. This obstacle is related to the high sequence homology within the catalytically active sites of HDACs (Bieliauskas and Pflum 2008). Nevertheless, the use of non-specific pharmacological inhibitors indicate the implication of histone deacetylases in the whole array of biological processes including, among others, regulation of developmental program, neurogenesis, apoptosis, synaptogenesis, neurite outgrowth (Bolger and Yao 2005, Minucci and Pelicci 2006, Akhtar et al. 2009, Brunmeir et al. 2009, Chuang et al. 2009, Liu et al. 2012a).

HISTONE DEACETYLASE INHIBITORS

Histone deacetylase inhibitors (HDACi) are a heterogeneous group of agents that inhibit HDACs and promote posttranslational acetylation of lysine residues within nuclear and cytoplasmic proteins, which may alter their activity and function. In particular, HDACs inhibition can have a profound effect on the acetylation status of histone proteins within chromatin, resulting in the augmented expression of genes relevant to protection from an ischemic insult. However, inhibiting deacetylation not only affects chromatin structure. HDACis equally promote the acetylation of non-histone proteins which can determine the interactions, localization and stability of these proteins (Glozak et al. 2005).

All HDAC inhibitors function by chelating the zinc ion at the deacetylase active site. Structurally, HDAC inhibitors can be grouped into diverse classes: hydroxamic acid dervatives, aliphatic acids, benzamides, electrophilic ketanes, cyclic peptides, and a few substances not assignable to these groups (Miller et al. 2003, Langley et al. 2005, Marks and Breslow 2007, Xu et al. 2007, Murphy et al. 2014). These inhibitors exhibit some HDAC isoform selectivity. For example, selective inhibitors have been developed for HDAC6, however, in many cases these compounds exhibit a high degree of lipophilicity and are difficult to synthesize, rendering them more useful as tools for research (Dallavalle et al. 2012).

Classical, non-selective HDACis, such as the hydroxamic acid-based suberoylanilide hydroxamic acid (SAHA, vorinostat) and trichostatin A (TSA), a fungal antibiotic, inhibit most of class I, II and IV HDACs (Yoshida and Horinouchi 1999). The benzamide MS-275 and also a small chain fatty acid – valproic acid (VPA), have a narrower range of target. VPA inhibits selectively class I HDACs (Göttlicher et al. 2001, Phiel et al. 2001) and to a lesser extent class II, but not HDAC6 or 10 (Gurvich et al. 2004), while MS-275 are selective towards only a subset of class I HDACs (Khan et al. 2008, Murphy et al. 2014).

Other fatty acid derivatives, sodium butyrate (SB) and 4-phenyl butyrate (4PB) inhibit class I and II histone deacetalases. However, isoform-specific inhibition of HDACs still remains a challenging task (Khan et al. 2008, Thomas 2009).

It is very likely that the non-specificity of deacetylase inhibitors is responsible for the opposing effect noted in distinct type of cells. As is becoming apparent, HDACs inhibition appears to be mainly protective for neurons, and yet, deadly to cancerous cells. Similarly, the different effect of HDACi is also observed

in cells that contribute to inflammatory pathways, where treatment results in pro- or anti-inflammatory stimulation (Halili et al. 2009). One of the explanations of such discrepancy involves the particular function of individual HDAC isoforms in activation of different transcription factors and then expression of different sets of genes. For instance, NFκB which is a target of HDACs, can trigger transcription survival as well as apoptotic gene products (Graham and Gibson 2005). It these circumstances only the synthesis of isoform specific inhibitors will make possible to decipher the effects of HDAC inhibition on gene transcription not only *via* increased histone acetylation but also on acetylation of non-histone proteins (Bieliauskas and Pflum 2008, Thomas 2009).

HDACi-INDUCED NEUROPROTECTION

Treatment with various HDAC inhibitors (HDACi) has emerged as an attractive therapeutic approach for acute injury and neurodegeneration in the last decade (Langley et al. 2008, 2009, Haberland et al. 2009, Uo et al. 2009, Selvi et al. 2010). The attractiveness of these agents increased by the finding that HDAC inhibitors can also enhance neuronal plasticity and memory and thereby may contribute to improved functional recovery (Hockly et al. 2003, Fischer et al. 2007, Vecsey et al. 2007). These properties bring about increased interest to use them as emerging tools for therapeutic interventions in the context of post-acute stroke. Since then, many HDACi have been tested in experimental stroke models. One of the first tested molecule was valproic acid (VPA) (Ren et al. 2004). It is worthy to note that VPA for the last 40 years has been commonly employed as both an antiepileptic and mood stabilizer (Emrich et al. 1980, Gurvich and Klein 2002). The efficacy of VPA in diverse form of epilepsy and bipolar disorders, as well as neuropathic pain (Covington 1998) suggests that VPA acts through multiple central nervous system targets. It occurred that in addition to the mention above functions, VPA administered after induction of focal ischemia resulted in a significant reduction of infarct volume and neurological deficit scores caused by middle cerebral artery occlusion (MCAO). The mechanism of neuroprotection implicated thus far include the elevation of histone 3 (H3) acetylation, increased expression of the pro-survival heat-shock protein HSP-70 and diminished activation of pro-death caspase 3 in injured brain hemisphere. Of note, earlier study *in vitro* also clearly demonstrated that VPA can promote neuronal survival in culture subjected to glutamate-induced neurotoxicity (Hashimoto et al. 2002) or to oxygen-glucose deprivation injury (Reckling 2003).

During the last 10 years the considerable research activity has been focused on potential roles for a number of zinc-dependent HDAC inhibitors (such as VPA, TSA, SAHA, SB) used in different models of brain ischemia. The majority of studies employing focal ischemia, including transient (Ren et al. 2004, Yildrim et al. 2008, Wang et al. 2012) or permanent (Faraco et al. 2006, Kim et al. 2007, 2009, Langley et al. 2008, Liu et al. 2012b, Wang et al. 2012, Liesz et al. 2013) middle cerebral artery occlusion (MCAO).

Although permanent MCAO produces a more severe and rapid brain infarction, the basic effects of HDACi treatment presented by reduced brain infarction, suppression neuroinflammation in the ischemic region, and amelioration of neurological deficits do not depends on the severity of brain pathology. HDACi also attenuate MCAO-induced disruption of brain-blood barrier and decrease edema, at least partly by inhibiting NfκB activation as well MMP9 expression and activity (Wang et al. 2011). In addition, administration of HDAC inhibitors occurred to be effective whether given pre- or post-injury. Nevertheless, the highest beneficial effects were most evident when VPA or SB was administered at least 3 h after the ischemic onset. This time window, together with the long-lasting neurological improvement suggest that HDAC inhibition might have utility in treating acute stroke.

We have found only one published report describing the effect of HDAC inhibitor (VPA) in the experimental intracerebral haemorrhage (Sinn et al. 2007). The obtained results show suppression of hematoma expansion during the acute phase, probably by decreased levels of endogenous proteolytic enzymes – tPA and MMP9. The notable reduction of the hematoma which is an important factor of neurological deterioration (Brott et al. 1997) leads probably to the observed behavioral improvement.

All these findings show that targeting global HDAC activity is sufficient to protect neurons from ischemia-induced death (Drummond et al. 2005, Wang et al. 2012). In addition, relevant studies show that HDACi may induce sprouting of dendrites, an increase number of synapses and reinstate access to long term memories (Fischer et al. 2007).

It is clear that in addition to the damaging effect of ischemia in grey matter, an important component of stroke pathology is white matter injury. Compared to our understanding of the mechanism of ischemia-induced neuronal death and protection in grey matter, white matter pathophysiology remains relatively elusive, as does the development of potential protective agents for oligodendrocyte damage. Injury to white matter and simultaneous loss of oligodendrocytes is a key to the impaired brain function associated with a variety of pathological conditions, including stroke. Thus, it is logical to state that the efficient therapeutic compound should preserve both, grey and white matter. Recent *in vitro* and *in vivo* studies show that administration of HDACi (such as VPA, SB, TSA, SAHA and MS-375) after ischemic insult promotes functional recovery of axons, reduces loss of oligodendrocytes and preserves white matter architecture (Baltan et al. 2011b, 2013, Liu et al. 2012b, Kim and Chuang 2014, Murphy et al. 2014). This protective effects correlate with reduced excitotoxicity, maintenance of ATP, preservation of axonal mitochondria and oligodendrocytes during OGD deprivation in a pure white matter tract of optic nerve (Baltan et al. 2011b, 2013).

POTENTIAL MECHANISM OF PROTECTION

Potential explanation for the beneficial effects of HDACs inhibition following brain ischemia are multifold and due to the published results influence diverse array of targets to maintain neuronal function and survival and preserve white matter in response to injury. One of the well-described modes of protective action of HDACi after ischemia is associated with the reduction of neuroinflammation. It is increasingly recognized that cerebral inflammation mediated by activated microglia and infiltrating leukocytes, including monocytes/macrophages, plays a key role in focal ischemia-induced neurodegeneration by releasing proinflammatory factors (Zheng and Yenari 2004). In support of the crucial role of neuroinflammation in the white matter injury is that macrophages/microglia are located in the damaged axonal bundles after ischemic injury (Moxon-Emre and Schlichter 2010). It is postulated that HDACs inhibitor-mediated suppression of astrocytic and microglial activation, cytokine production and down regulating pro-inflammatory factors, is likely to be important mechanism in decrease inflammation and secondary damage after stroke (Kim et al. 2007, Xu et al. 2007). An important mechanism of cerebroprotective effect induced by HDACi is the increase in interleukin-10 production, which restricted postischemic cerebral inflammatory gene up-regulation (Liesz et al. 2013). In addition, a promising therapeutic action of HDAC inhibitors may be also mediated by modifying the activity of other transcription factors such as erythroid 2-related factor. Nrf2 may represent one critical example of survival-promoting transcription factor (Martin-Montalvo et al. 2011). Activation of Nrf2 pathway has been shown to increase the resistance to oxidative stress and metabolic insult in culture, and to ischemic stroke *in vivo* (Son et al. 2010).

In general, acetylation of histone proteins with gene promoters and regulatory region, as well as transcription factors, can increase the expression of multiple genes which protein products contribute to neuroprotection, plasticity and memory (Fig. 1).

A significant amount of data show that the administration of HDACi after stroke was correlated with up-regulation of heat-shock protein, HSP70, a probable viable target for neuroprotection (Ren et al. 2004, Faraco et al. 2006, Kim et al. 2007), in addition to being a molecular chaperone assisting in proper protein folding (Rajdev et al. 2000, Hoehn et al. 2001). Importantly, VPA-mediated neuroprotection against glutamate-induced cell death was lost if HSP70 induction was blocked. Anti-apoptotic effect of HSP70 may involve multiple mechanism, such as inhibition of cytochrom c dependent activation of death-promoting caspase 3 and its downstream effectors, suppression the activity of apoptosis inducing factor (AIF) (Pandey et al. 2000, Ravagnan et al. 2001), enhanced expression of anti-apoptotic Bcl2 protein and suppression microglia/monocyte activation following experimental stroke (Yenari et al. 2005). Furthermore, inhibitors of HDACs may compensate MCAO-induced deficiency of pro-survival phospho-Akt and phospho-ERK in the ischemic hemisphere and raise significantly the level of brain-derived neurotrophic factor (BDNF) and glial-derived neurotrophic factor (GDNF) expression. Of note, increased expression of neurotrophins by HDACi treatment were found to be involved in the postischemic neuroprotection and neuronal restorative effects (Fukumoto et al. 2001, Chen et al. 2006, Hasan et al. 2013). Another target regulated positively by HDACi after ischemia is gelsolin, a protein involved in actin filament organization and

by this route contributed to neuroprotection from ischemic injury (Yidrim et al. 2008).

Inhibition of HDACs enhances resistance to death of neurons not only by positive regulation of pro-survival agents but also by blocking the action of transcription factors that regulate apoptosis. The tumor suppressor, p53, has been implicated as a key regulator of apoptosis in acute and chronic neurologic insults (Morrison et al. 2003). In line with this, several studies reported down-regulation of p53 in injured ischemic hemisphere. In addition, inhibitors of class I/II HDACs protected cultured cortical neurons from p53-dependent cell death by suppression of p53-dependent expression of PUMA, a critical signaling intermediate linking p53 to Bax activation. Thereby, HDAC inhibitors block Bax-dependent cell death (Uo et al. 2009, Brochier et al. 2013). However, MS 275, in contrast to other HDAC inhibitors, does not directly affect p53 acetylation, or its stability and activity. If the target for MS-275 is not p53, the drug could modulate neuronal survival by modifying the activity of other transcription factors (Murphy et al. 2014).

In addition to transcription events, non-transcriptional events may also play a role in protective action of HDACi. For example, the selective inhibition of HDAC6 increases alfa-tubulin acetylation which may underlie neurite outgrowth without altering H4 acetylation and increase the vesicular transport. It is suggested that this effect might be independent on transcription (Riveccio et al. 2009).

Taken altogether the above findings allow us to state that irrespective of the precise mechanisms involved, HDACi have potential in preventing the consequences of acute ischemic injury.

HDACI-INDUCED REGENERATION

It is clear that successful stroke treatment also need to promote plasticity and repair mechanism(s) in the post-acute phase. The reduced infarct volume and

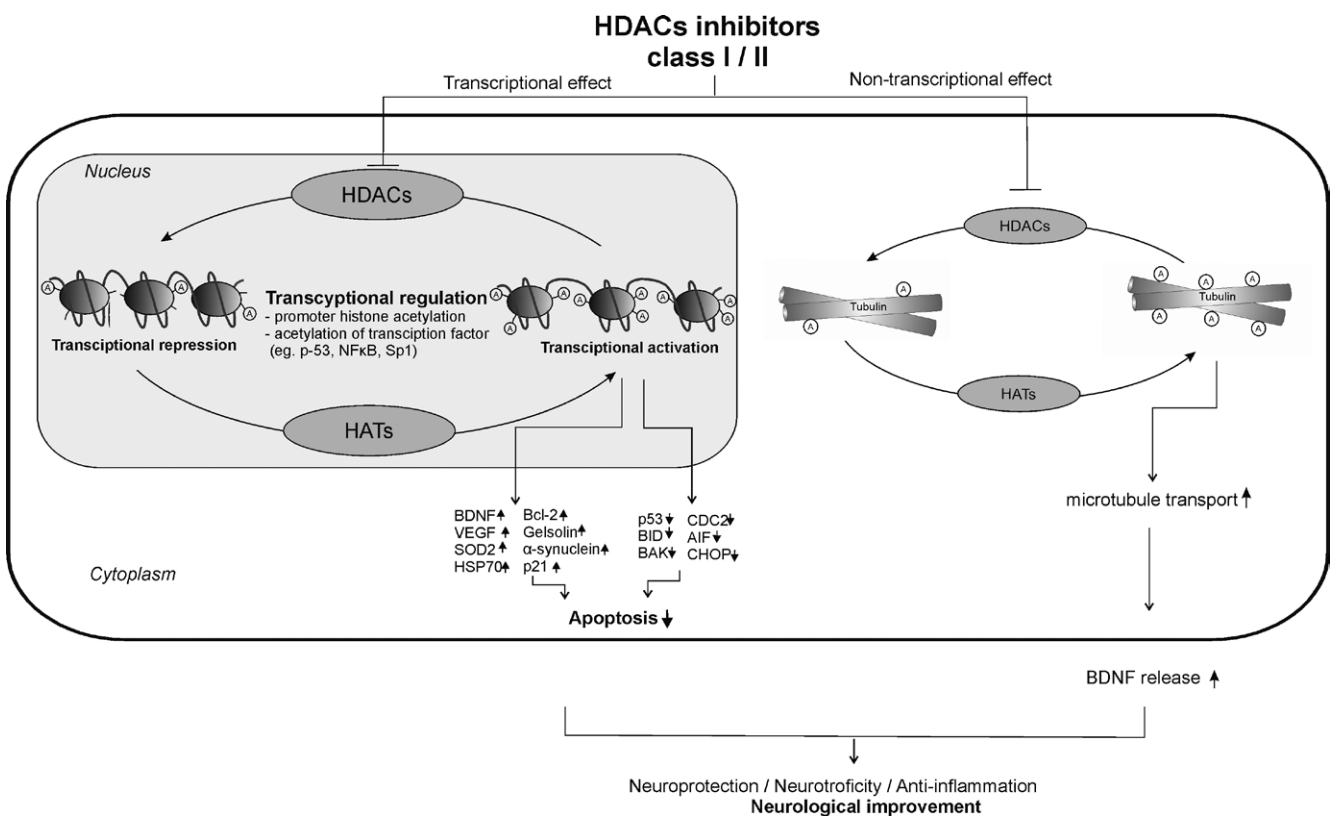

Fig.1. The cellular effects of HDACs inhibitors after stroke. Inhibition of HDAC activity has transcriptional and non-transcriptional effects. Acetylation of histone proteins within gene promoters as well as transcriptional factors can increase the expression of multiple genes which contribute to neuroprotection, plasticity and learning /memory. Acetylation of transcription factors may also decrease DNA binding and gene expression of some pro-death genes (e.g. p-53) and reduce apoptotic processes. Non-transcriptional effects of HDAC inhibitors also play critical role in neuroprotection and repair after stroke; hyperacetylation and stabilization of microtubule proteins increases vesicular transport and release of BDNF.

improved neurological performance may suggest the replacement of new neurons which contributes to the self-repair system of cerebral ischemic injury. A notable previous finding is that experimental stroke increased cell proliferation and neurogenesis in neurogenic areas – subventricular zone (SVZ) and dentate gyrus (DG) as well as in non-neurogenic regions (striatum and cerebral cortex) (Jin et al. 2001, Arvidsson et al. 2002, Parent et al. 2002, Zhang et al. 2004, Yamashita et al. 2006, Ziemka-Nałęcz and Zalewska 2012). Subsequently, a number of study reported that VPA and TSA induced neurite outgrowth and neurogenesis in vitro without an ischemic insult (Hao et al. 2004, Di Daniel et al. 2005, Yamauchi et al. 2007). Additionally, it was found that neural progenitor cells cultured in the presence of histone deacetylase inhibitors – VPA, TSA or SB, differentiated into neurons (Liu et al. 2012a), presumably by inducing the neurogenic transcription factor Neuro D (Hsieh et al. 2004). Interesting recent data indicate that VPA promotes neural differentiation *via* the increased expression of pro-neural genes Ngn1, Math1, and P15 associated with the increased acetylation of H4 (Yu et al. 2009).

Although there have been many *in vivo* and *in vitro* studies on the role of HDAC inhibitors as neuroprotective agents, very little work has been done to define their involvement in postischemic neuronal regeneration. First evidence showing stimulation of neurogenesis in the ischemic brain after administration of histone deacetylase inhibitors has been provided by Kim and coworkers (2009). Consistently, Liu and others (2012b) found that treatment with VPA enhances the number of neuroblasts in the SVZ as well as in ischemic boundary zone. It was also discovered that administration of SB or TSA, expanded the population of proliferating cells in the injured brain areas and restored the loss of neurons. The authors indicate that generation of new cells depends on the activation of BDNF-TrkB signaling and then activation of cAMP-response element binding protein (CREB). CREB was identified by Chiaramello and colleagues (2007) as a part of molecular mechanism underlying BDNF-TrkB induced migration, differentiation and survival of SVZ neuroblasts. Moreover, its phosphorylated form appeared to be a prominent transcription factor involved in the expression of numerous neuroprotective, neurotrophic, and anti-inflammatory protein molecules (Chiu et al. 2013). The presented data are consistent with findings demonstrating that HDACs inhibition by VPA and TSA leads to neuronal regeneration in cultures subjected to oxygen and glucose deprivation (OGD) and reoxygenation.

HDACi (TSA and SB) not only counteract ischemia-induced loss of oligodendrocytes in the injured hemisphere but also promote differentiation of oligodendroglial progenitors into mature cells. This process was associated with elevation of myelinated axonal density in the peri-infarct region (Liu et al. 2012b, Kim and Chuang 2014). The HDAC isoforms involved in the protective effects on oligodendrocytes after ischemic stroke remain unidentified. Paradoxically, it was reported that HDAC1 and HDAC2 activity are required to regulate oligodendrocyte differentiation (Ye et al. 2009), and that HDAC1 and HDA2 functions are critical for myelination and survival of Schwann cells in peripheral nervous system (Jacob et al. 2011). These results do not necessarily negate the importance of HDAC1 and HDAC2 inhibition in mediating the effects reported above, because of the different experimental conditions employed ischemic stroke *versus* normal, non-pathological conditions of the cited study. Future investigations exploring the role of specific isoforms involved in the pathophysiology of white matter injury and the beneficial effect of HDAC inhibitors will provide crucial information for therapeutic interventions. Although it is not at all clear if the notable amplifications of neurogenesis post-stroke contributes to subsequent restoration of function, the ability of HDACi to promote migration and neuronal differentiation could be exploited therapeutically (Kahle and Bix 2013).

Concurrently, VPA treatment enhanced postischemic angiogenesis by increasing microvessel density, facilitating endothelial cell proliferation, and up-regulating rate of cerebral blood flow (rCBF) in the ipsilateral cortex. This may contribute to the long-term functional outcome. These events may be associated with up-regulation of hypoxia inducible factor 1 alfa (HIF1alfa) and its downstream proangiogenic vascular endothelial growth factor (VEGF) as well as extracellular matrix metalloproteinases MMP2/9 (Sun et al. 2003, Shimotake et al. 2010, Wang et al. 2012). In addition, newly-generated vessels provide additional neurotrophic support to concurrent neurogenesis and synaptogenesis, and this ultimately may lead to functional recovery.

EFFECT OF HDACI IN NEONATAL HYPOXIA-ISCHEMIA

Despite ever growing information highlighting the beneficial role of HDACi after stroke in adult brains only a few available reports were addressed upon their effect in injured immature brains (Kabakus et al. 2005, Fleiss et al. 2012, George et al. 2013). These experiments were performed with the use of different experimental models, thus it is not possible to make the explicit conclusion related to the effect of HDACi. The data reported by Kabakus and coauthors (2005) showed only the tendency towards regression of cerebral infarct after VPA administration to 7 day-old pups subjected to hypoxia-ischemia (H-I). Nevertheless, the preliminary study performed by our group on the same model demonstrate beneficial effects SB expressed by reduced volume of brain lesion. Furthermore, SB treatment enhanced significantly the number of neuroblasts and progenitors of oligodendrocytes (Ziemka-Nalecz et al., unpublished data presented on 9th FENS Forum of Neuroscience).

Fleiss and colleagues (2012) examined the neuropathological and functional effects of the TSA in a model of neonatal lipopolysacharide-sensitized hypoxic-ischemic brain injury (LPS/HI) in mice. One striking feature of their results is that TSA diminished grey and white matter damage only in females. The neuroprotection was associated with increased acetylation of histone H4 and correlates with improved long-term learning. Interestingly, the beneficial effect of TSA was not connected neither with caspase-3 activation nor up-regulation of heat shock protein HSP70 and gelsolin, implicated in the neuroprotection observed in adult animals. Moreover, none of the inflammatory mechanisms assessed that are known to mediate neuroprotection by HDACi in adults correlated with improved outcome in TSA-treated neonatal females. TSA did not result in decrease the total number of microglia cells or NFkB-mediated reductions in cytokine expressions. TSA either did not impair oligodendrocyte maturation, which increases the possible clinical relevance of this strategy. Therefore it appears that TSA exerts neuroprotection *via* mechanism unique to neonates, yet unknown. This is consistent with the fact that many aspects of the evolving post-ischemic brain injury differ in the immature brain and thereby the efficacy of neuroprotectants can differ between adults and neonates (Cheng et al. 1997, Zhu et al. 2005). It is also possible that LPS sensitization may antagonize TSA efficacy in this model.

George and coworkers (2013) investigated long-term treatment of VPA and TSA upon stroke-injured immature mice (12 days old), using permanent ligation of the carotid artery. Presented data demonstrate that chronic, two weeks HDACi treatment did not modify the severity of brain atrophy assessed two months after the insult. In contrast to data reported by Fleiss and others (2012) the sex-related differences were not observed. Significant increase of neurogenesis in dentate gyrus with both TSA and VPA treatment were noted in the injured as well as uninjured animals but only at specific time point after administration of BrdU – marker of proliferation. It may mean that the high level of plasticity and neurogenesis cannot be up-regulated any further by manipulations with HDACi. In agreement with this statement, Foti and coauthors (2013) using neurosphere assays to determine neural stem cells (NSC) regulation by HDACi found that clinically used HDACi like VPA and TSA can perturb postnatal neurogenesis. It supports generally accepted view that HDAC activity is essential for oligodendrocyte differentiation in the developing rodent brain (Shen et al. 2005, Lyssiotis et al. 2007, Ye et al. 2009). Therefore, blockage of HDAC activity by inhibitors or ablation of HDAC1 and HDAC2 genes during the early postnatal stage, when myelination forms, prevents oligodendrocyte differentiation and leads to hypomyelination (Romm et al. 2005, Lyssiotis et al. 2007, Shen and Casacia-Bonnefil 2008, Ye et al. 2009). However, the effect of HDACi on suppression of oligodendrocytes differentiation is transient and only takes place during the first postnatal week (Shen et al. 2005). In addition, a temporary defined treatment regimen avoids this toxic effect (Langley et al. 2008).

The results obtained with HDAC inhibitors indicate that the functions of these agents in the nervous system injury are diverse and depend greatly on the developmental stage. For example, there is evidence that HDAC2 is critical for adult neurogenesis, but not required for embryonic neurogenesis (Jawerka et al. 2010). Which of HDAC among 11 members are targets for neuroprotection is unknown at present. Equally unknown is whether therapeutic efficacy can be obtained by targeting a single HDAC. *In vitro* studies showing that HDAC6-selective inhibition can protect against oxidative stress-induced neuronal death (Kozikowski et al. 2007) may provide some sugges-

tions that targeting a single HDAC isoform may indeed be neuroprotective in stroke. However, it should be also noted that SB, inhibitor of the class I HDAC, which does not inhibit HDAC6, occurred to be protective in the same *in vitro* oxidative stress model (Langley et al. 2008). Most current HDACs inhibitors are broad-spectrum inhibitors, and their use does not take into account the possible stage-and context-specific expression of different HDACs. Although considerable progress has been made in elucidating the effects of HDACi in brain ischemia, this area are still in early stage of discovery.

CONCLUSIONS

Based on the combined findings it may be hypothesized that HDACi provide a suitable option for brain in the clinical manifestations of stroke to facilitate successful translation of experimental ischemia research to clinical trials. However, considering the beneficial effects of HDACi in experimental stroke studies commonly use in rodents, it is worthy to underline that efficacy of drug in young, healthy, in majority male animals appears to be very poor predictor of clinical outcome. No studies assessed the neuroprotective effectiveness of HDAC inhibitors in "aged" animals, while the aged persons usually suffer from stroke.

In addition, not all currently available HDAC inhibitors are well tolerated when administered chronically. For instance, TSA have basal toxicity and prolonged treatment at high doses induces neuronal death *in vitro* and *in vivo*, so compromising their neuroprotective effect (Boutillier et al. 2002, Jeong et al. 2003). Also the other HDAC inhibitor, valproic acid, despite that is well tolerated in children and adolescents may have detrimental effects on postnatal neural development, which have not been fully explored. This agent is a potent teratogen in both humans and mouse models (Gurvich and Klein 2002). The teratogenic activity is associated with neural tube closure defects (Nau et al. 1991). It became clear that nontoxic analogues of these HDACi, targeting specific isoforms will help treat the injury of the nervous system.

Conclusion: The neuroprotective and regenerative actions of histone deacetylase inhibitors indicate that they may be considered as therapeutic agents after brain ischemia. However, new, nontoxic analogues targeting individual HDAC isoforms are still needed.

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