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Histone Deacetylase (HDAC) Inhibitors - Emerging Roles in Neuronal Memory, Learning, Synaptic Plasticity and Neural Regeneration

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Abstract: Epigenetic regulation of neuronal signalling through histone acetylation dictates transcription programs that govern neuronal memory, plasticity and learning paradigms. Histone Acetyl Transferases (HATs) and Histone Deacetylases (HDACs) are antagonistic enzymes that regulate gene expression through acetylation and deacetylation of histone proteins around which DNA is wrapped inside a eukaryotic cell nucleus. The epigenetic control of HDACs and the cellular imbalance between HATs and HDACs dictate disease states and have been implicated in muscular dystrophy, loss of memory, neurodegeneration and autistic disorders. Altering gene expression profiles through inhibition of HDACs is now emerging as a powerful technique in therapy. This review presents evolving applications of HDAC inhibitors as potential drugs in neurological research and therapy. Mechanisms that govern their expression profiles in neuronal signalling, plasticity and learning will be covered. Promising and exciting possibilities of HDAC inhibitors in memory formation, fear conditioning, ischemic stroke and neural regeneration have been detailed.

Keywords: Chromatin, histone deacetylases, histone deacetylase inhibitor, histones, immune response, ischemia, osteogenic differentiation, regeneration.

1. INTRODUCTION

Chromatin in eukaryotes resides inside the cell nucleus and is the substrate for transcription processes [1-3]. The hierarchical and tight folding of 146 bp of DNA around the octameric scaffold of core histones H2A, H2B, H3 and H4 forms a nucleosome [4], the repeating units of which render a 'beads-on-a string' conformation to the chromatin. The consequent higher order structure involving linker histones H1, further compact the chromatin and present an impediment for transcription factors to access the DNA. Post translational modifications of the histone tails is a powerful mechanism to circumvent this impediment and has been implicated in gene expression programs [5]. Post translational modifications of the histones include acetylation of lysine residues, methylation of lysine and arginine residues, phosphorylation of serine residues besides ubiquitination and Adenosine Diphosphate (ADP) ribosylation [6-10]. The sites of modifications are predominantly clustered in the first few amino acids of the core histones H3, H4, H2A and H2B besides a few linker histone residues. Sequential modifications in core histones create a combinatorial 'histone code', which tunes the chromatin for gene expression and transcription [11, 12]. These site specific, covalent modifications on histone N-tails are brought about by enzymes which recruit specific moieties on the relevant amino acid residues.

Histone Acetyl Transferases (HATs) are conjugate enzymes which transfer the acetyl group of their cofactor-acetyl coenzyme A to lysine residues of histone proteins. Histone Deacetylases (HDACs) function to deacetylate the lysines on histone tails causing condensation and subsequent repression of chromatin [13]. These HDACs function with Zn^{2+} ions or NAD^{+} as cofactor (Table **1**) and almost 18 kinds of HDACs are known to be functional. Class I HDACs remain confined to the cytoplasm while class IIa and IIb HDACs are present in cytoplasm and shuttle to the nucleus on induction by Nitric Oxide or Ca^{2+}/Calmodulin-dependent Protein Kinase (CAMK) or during DNA damage [14, 15]. HDAC inhibitors are small molecules that restrain HDAC activity and maintain chromatin in the decondensed state. Chemically, HDAC inhibitors may be benzamide derivatives, cyclic tetrapeptides, depsipeptides, hydroxamic acid derived compounds, short chain fatty acids, ketones or synthetic pyridyl derivatives [16, 17] (Table **2**).

The epigenetic activity of several HDAC inhibitors is now increasingly being explored for clinical applications. HDACs and their inhibitors are now looked upon as promising candidates in regulating neuro degenerative disorders, memory formation, development and neural regeneration events. Many of these inhibitors are in the final phases of clinical trials and have proven to be effective in synergistic therapy.

This article explores the emerging role of HDAC inhibitors in neurological investigations and therapy. The specific roles of these small molecule inhibitors in disease signalling and their evolving and intricate roles in neuronal memory, learning and plasticity have been elaborately dealt

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Table 1. Histone Deacetylases – classes and isoforms.

Class	HDACs	Cofactor
Class I	HDAC1	
	HDAC2	
	HDAC3	
	HDAC8	
Class IIa	HDAC4	Zn^{2+}
	HDAC5	
	HDAC7	
	HDAC9	
Class IIb	HDAC6	
	HDAC10	
Class III	SIRT1	
	SIRT2	
	SIRT3	NAD^{+}
	SIRT4	
	SIRT5	
	SIRT6	
	SIRT7	
Class IV	HDAC11	Zn^{2+}

with. The interesting and vital roles of HDAC inhibitors in newer learning paradigms are also described.

2. HDAC INHIBITORS IN ISCHEMIA, MEMORY AND IN THE TREATMENT OF NEURODEGENERATIVE DISORDERS

2.1. HDAC Inhibitors in Treating Ischemic Strokes

Alterations in acetylation levels or acetylation homeostasis have been probed as a major signalling event in neuronal diseases and in degenerative disorders. There is a growing evidence of HDAC inhibitors involved in the pathophysiology of stroke and memory disorders.

Strokes can be ischemic involving a thrombus, embolism or cerebral artery occlusion or can be haemorrhagic due to a blood vessel rupture. Multi targeted and synergistic therapies are now being explored as promising routes to deal with the heterogeneity and complexity presented by signalling in stroke. HDAC inhibitors alter the expression patterns of genes involved in protecting ischemic insult by increasing the acetylation patterns of core histone H3. The HDAC inhibitor valproic acid has been found to reduce infarct volume and neurological deficit (in both 24 and 48 hour assays) in rat Middle Cerebral Artery Occlusion (MCAO) focal ischemia models when the inhibitor was delivered immediately after the ischemic attack and every 12 hours thereafter [18]. The treatment resulted in a significant elevation of acetylation levels of H3, which were earlier found to be reduced in the cortex and striatum of the mouse brain during ischemia. Mouse models of hypoxia-ischemia have shown protection against cerebral injury when treated with sodium 4-phenylbutyrate [19]. Valproic acid has also been found to offer protection against ischemia-reperfusion (I/R) lung injury in rat models by enhancing the activity of Heme Oxygenase (HO1) in lung tissues and by reducing oxidative stress and apoptosis induced by the injury in lung tissues [20].

Mice models of ischemic reperfusion during preconditioning with HDAC inhibitor Trichostatin-A (TSA), showed a significant reduction in infarct size and improved recovery of ventricular function. It was also observed that the protection rendered by Trichostatin-A could be countered by p38 – Mitogen Activated Protein (MAP) kinase inhibitor emphasising a significant role of p38 in the protection [21]. During ischemia, an increased activity of HDACs and the resultant deacetylation of histones H3 and H4 has been observed both *in vitro* and *in vivo*. *In vitro* experiments with cardio myocytes showed that HDAC inhibitors effectively increase the cell survival and reduce the expression of hypoxia induced factor HIF1-α. *In vivo* models of CD1 mice subjected to left anterior descending artery (LAD) occlusion showed a reduction of Vascular Endothelial Growth Factor (VEGF) induced under ischemic condition and a reduction in infarct size by 50% on administration of Trichostatin-A [22].

In murine hearts subjected to ischemia/reperfusion injury, HDAC inhibition by SAHA resulted in increased acetylation of 20S proteosome sub units (acetylated at 9 residues in the N terminal and 7 residues in the internal core region) and a consequent enhancement of proteolysis in the system [23]. SAHA treatment has been shown to exhibit cardio protective effect in the ischemic reperfusion rabbit models, where a reduction in infarct size and partial rescue of the systolic function were observed. SAHA was observed to activate autophagy. The cardio protective ability of SAHA was abrogated by the down regulation of autophagic proteins ATG7 and ATG5 [24].

MCAO mice models of ischemia/reperfusion treated with 0.05 mg/kg of Trichostatin-A showed reduction in infarct volume as well as neurological deficit score. Trichostatin-A also increased the expression of p-Akt and hence it could be considered that the activity of Trichostatin-A is partly achieved through the PI3K/Akt signalling pathway [25]. Trichostatin-A has also been shown to increase the migratory potential of primary human endothelial colony-forming cells (ECFCs). Transplantation of ECFCs pre treated with Trichostatin-A into the ischemic muscle region of mice led to a higher recovery of blood flow 4 days post injection. It was also observed that the mice injected with Trichostatin-A-ECFCs after 4 days showed increased arteriole density, establishing expression of VEGFA and reduced necrosis, indicating the revascularization capability of Trichostatin-A [26]. Butyrate, when administered during the onset of ischemia in hepatic Ischemic Reperfusion Injury (IRI) rat models showed protection of liver tissue, reducing the levels of hepatic enzymes AST and ALT, which mark liver damage. Histological observation of liver tissues showed that animals treated with butyrate featured marked reduction in the hepatocellular necrosis and infiltration of neutrophils which are prominent in IRI. Butyrate reduced the production of inflammatory cytokines, improved histone acetylation and induced Heat Shock Protein 70 (Hsp70) that helps in resistance to damage by ischemic reperfusion [27].

Cerebral ischemia depletes the levels of oligodendrocyte pool resulting in hypomyelination of white matter and subsequently impairing brain function. Recent findings have shown that sodium butyrate or Trichostatin-A provide strong protection against ischemia induced depletion of

Table 2. HDAC inhibitors, their diverse targets and potential clinical applications.

HDACi Group	HDAC Inhibitor	Target HDACs	Inhibitory Concentration	Status in Clinical Trials for Neurology	Diseases Targetted
Benzamide derivatives	MS-275/Entinostat	HDAC1, 2, 3, 9	nM	Preclinical	Duchenne muscular dystrophy, reduced neuro inflammation and cerebral amylodosis
	MGCD-0103	HDAC 2, 3, 11	mM	Preclinical	Neurodegeneration
	Belinostat	HDAC 1-10	µM	Preclinical	Glioma treatment
	Mocetinostat	HDAC 1,2,3,11	µM	Preclinical	Post-ischemic fibrosis
	Crebinostat	HDAC1,2,3,6	µM	Preclinical	Enhances memory formation, Enhance neurotropic factors and neurite growth
	Tubastatin or Tubastatin A	HDAC6/HDAC1	nM/ µM	Preclinical	Reduces the hyperactivity in animals, Rescues memory impairment during contextual fear conditioning in mice
Hydroxamic acids	SAHA/Vorinostat	Classes I, II &IV	µM	Preclinical	Memory loss, Spinal Muscular Atrophy (SMA), Focal Ischemia, Cognitive disorders, Glioblastoma, improved learning through hippocampal neuron, polyglutamine and triplet diseases
	Trichostatin A (TSA)	Classes I and II	nM	Preclinical	Fear, rescue from contextual freezing through hippocampal acetylation of histone H4, Neurodegeneration, delayed disease progression, polyglutamine and triplet diseases
	CBHA	HDAC1,3, Sirtuins	µM	Preclinical	Axonal degeneration
	Oxamflatin	HDAC1,2,3,4,6,7,8	µM	Preclinical	Neurodegeneration, Depression
	Scriptaid	HDAC1, 3, 8	µM	Preclinical	Neurodegeneration, Depression, Glioma
	Pyroxamide	Class I	µM	Preclinical	Neurodegeneration, Huntington's disease, Parkinson's disease
	NVP-LAQ824	Class I, II	nM	Preclinical	Dose dependent injection of the drug in the spinal cord induces short term attenuation of thermal hyperalgesia
	LBH589/ Panobinostat	Classes I, IIa	nM	Preclinical	Triggers the expression of the protein Survival Motor Neuron gene 2 (SMN2) in spinal muscular atrophy fibroblasts which are inert to valproic acid treatment
	I-2	Class I, II HDACs	µM	Preclinical	Improve learning and memory
Short Chain Fatty Acids	Sodium butyrate (NaB)	Classes I, IIa	mM	Phase II - dose tolerability study in ALS	Memory loss, Depression, Fear, improved learning and memory, reversal of contextual memory deficits, restoration of dendritic spine density in hippocampal neurons, alleviation of cognitive defects
	Phenyl butyrate	-	µM	Safety and tolerability study in Huntington's disease (NCT00212316)	Axonal degeneration, Huntington's disease
	Sodium Phenylbutyrate	-	mM	Safety study in ALS (NCT00107770)	Huntington's disease, Amyotrophic Lateral Sclerosis (ALS)
	Valproate/Valproic Acid (VPA)	Classes I & IIa	mM	Double blind randomised placebo controlled trial in SMA (NCT01671384, NCT00661453); Safety, dosage and effect on muscle activity studies in SMA (NCT00227266, NCT00374075, NCT01033331), Double blind randomised placebo controlled trial in AD (NCT00071721); Safety and proof of concept study in AD (NCT01729598)	Brain Ischemia, Stroke, reversal of contextual memory deficits, Spinal Muscular Atrophy, Alzheimer's disease (AD)

Table 2. contd….

HDACi Group	HDAC Inhibitor	Target HDACs	Inhibitory Concentration	Status in Clinical Trials for Neurology	Diseases Targetted
Short Chain Fatty Acids	Sodium Valproate	-	mM	Double blind randomized placebo controlled trial in ALS (NCT00136110)	Amyotrophic Lateral Sclerosis (ALS)
Depsipeptide	Romidepsin	HDAC1,2,4,6	ng/mL	Preclinical	Neurodegeneration, Depression, Neuroblastoma
Ketones	Trifluoromethyl ketone	-	µM	Preclinical	Neuroprotection following spinal cord injury
Cyclic Tetrapeptides	Apicidin	HDAC 1, 3	nM	Preclinical	Neurodegeneration, Depression
	Trapoxin	Class I, IIa	nM	Preclinical	Neuronal cell death
	HC–toxin	-	nM	Preclinical	Suppression of malignancy in neuroblastoma
	Depudecin	Class I	nM	Preclinical	Regulation of post mitotic neurons followed by counteracting neural sensitisation to cocaine
	LB-205	Pan HDAC inhibitor	µM	Preclinical	Acute traumatic brain injury –Enhance migration of astrocytes to site of injury; Reduce reactive astrocytosis
Mercapto acetamide	W2	Class II HDACs	µM	Preclinical	Improves learning and memory
Carbamide based inhibitor	BRD4884	HDAC2	µM	Preclinical	Rescues memory defects - neurodegeneration models in contextual fear conditioning
Urea based inhibitor	BRD6688	HDAC2	µM	Preclinical	Rescues memory defects - neurodegeneration models in contextual fear conditioning
Carboxamide	RGFP963	HDAC1, 2 and 3	nM	Preclinical	Induces Synaptogenesis and increase spine density in hippocampus Enhance cued fear extinction in mice models
	RGFP968	HDAC1, 2 and 3	nM	Preclinical	Induces Synaptogenesis and increase spine density in hippocampus
	RGFP966	HDAC3	nM	Preclinical	Extinction of cocaine seeking behaviour
	Selisistat	SIRT1/SIRT2	nM	Preclinical	Rescues neurodegeneration and photoreceptive function
Quinazolin-4-one derivatives	HDACi-4b	HDAC1,3,6	nM	Preclinical	Induces epigenetic changes in the germ line developmental stages Huntington's disease mice models
	HDACi-3f	HDAC6	nM	Preclinical	Improves learning in mice models
	MC1568	Class IIa HDACs	µM	Preclinical	Delays regeneration in ischemic mice models
	EVX001688; EVX	Class I and IIb	nM	Preclinical	Induces and retains an increase histone acetylation in hippocampus

oligodendrocytes as was quite evident from the enhanced levels of Myelin Basic Protein (MBP) in the ipsilateral Sub Ventricular Zone (SVZ), striatum, corpus callosum and frontal cortex, seven days post permanent middle cerebral artery occlusion [28].

Treatment of mice subjected to ischemic reperfusion injury with Class I HDAC inhibitor MS-275 reduced the infarct area, increased the expression of Super Oxide Dismutase (SOD) and catalase leading to a significant restoration of cardiac contractile function while such protection could not be rendered by the Class I/IIb HDAC inhibitor Trichostatin-A and Class IIb inhibitor Tubastatin A demonstrating the the efficiency of class specific HDAC inhibition in the treatment of ischemia [29]. Intra peritoneal administration of Sirtinol, a Class III HDAC inhibitor, confers ischemic post conditioning effect and reduction in infarct size in Bilateral Carotid Artery Occlusion (BCAO) mice models of ischemia. The motor coordination as assessed through several tests and neurologic sensitivity score (NSS) and memory formation as assessed through a Morris water maze test which showed that Sirtinol was able to reverse the memory impairment and lack of motor coordination induced by ischemia [30].

Intra peritoneal administration of Suberoyl Anilide Hydroxamic Acid (SAHA) in mouse 6- hour MCAO models showed increase in global histone acetylation levels and a dose dependent up regulation of Bcl-2 and Hsp70 [31]. Likewise, Trichostatin-A has been proven to be neuroprotective in mouse transient MCAO models of ischemia [32].

Pan HDAC inhibitors have shown success in reducing ischemia induced damage to CNS in both *in vitro* and *in vivo* models of stroke. Class I HDACs regulate the acetylation status of p53 which has a significant role in the pathology of ischemia. Optic nerves excised from mice models (wild type and p53 deficient) were subjected to Oxygen-Glucose Deprivation (OGD) and were analysed for compound action potentials with and without treatment of MS-275 (inhibits only Class I HDACs). Besides this, transient focal ischemia was imposed on both types of mice (wild and p53 deficient) which were subsequently treated with MS-275. This treatment proved to be beneficial in providing protection in the absence of p53, ruling out the involvement of p53 modulation in entinostat mediated neuroprotection [33].

A nested case control study involving 2002 stroke cases and 1153 cases with myocardial infarction analysing the treatment modes and the resultant risk for the disease indicated that patients who have been prescribed sodium valproate had a reduced risk of MI but not of stroke [34]. HDAC inhibitor Mocetinostat has been shown to reduce the scar size and the collagen levels and also improve the cardiac function *in vivo* using the coronary artery occlusion models of rats. It was also observed that the Mocetinostat treated animals showed reduced expression of collagen-1 and fibronectin in the left ventricle and in the isolated cardiac fibroblast cells, which are markers of post-ischemic fibrosis. Interleukin-6 (IL-6) levels were also found to be elevated in the cardiac cells after treatment with Mocetinostat [35].

Na^{+}/Ca^{2+} exchanger 1 (NCX1) regulates the neuro secretion and relaxation of cardiac muscles. NCX1 is repressed during stroke by RE1-silencing transcription factor (REST) and Specificity protein (Sp) transcription factors. It was observed that NCX1 is silenced by the co localization of Sp3 and REST along with HDACs 1 and 2 in the NCX1 brain promoter in transient MCAO rat model. HDAC inhibitor MS-275 was found to be neuroprotective by activating NCX1 and this effect was reversed when neurons were subjected to NCX1 silencing through siRNA and subjected to 3 hours of Oxygen and Glucose deprivation (OGD) followed by 24 hours of reoxygenation (RX) [36]. Rat primary cortical neurons subjected to oxygen - glucose deprivation to create ischemia showed an increase in neurite outgrowth and in synaptic markers GAP43 and Synaptophysin [37].

2.2. HDAC Inhibitors in Neuronal Memory

HDAC inhibitors significantly alter neuronal plasticity and memory demonstrating multiple roles of these inhibitors in salvaging tissues as well as in promoting functional recovery. The Allen Brain Atlas shows differential expression and distribution of HDAC isoforms in the mouse brain. Rat model systems studied for expression patterns have shown that most HDACs show significant expression in glial and neural progenitor cells [38-40] as against HDAC2 members whose expression profile is low in mature neurons. The loss of both HDAC1 and HDAC2 disrupts neural precursor differentiation and results in aberrant brain development [41]. These observations emphasise the roles of Class I HDACs in nerve development. It has been hypothesised for long that mutation of HATs leads to reduced levels of histone acetylation and impairs long term memory while the enhancement of acetylation levels by inhibiting HDACs serves to improve long term memory.

Recent evidences point to a strong link of epigenetic mechanisms in modulating neuronal plasticity, memory formation and memory enhancement. *De novo* gene transcription in hours following learning has been considered a prerequisite for the formation of long term memory [42]. Site directed mutants of the CREB Binding Protein (CBP) lead to impaired long term memory [43]. Long term memory enhances with HDAC inhibition. Object recognition through HDAC inhibition have been shown to bypass CREB binding interactions [44], while object location memory demands CBP mediated interactions for function [45].

Crebinostat, a new HDAC inhibitor in the clinic has been shown to upregulate several CREB target genes and to promote synapse formation, organization and stability. A hippocampus dependent contextual fear conditioning paradigm observed that mice on systemic administration of Crebinostat for 10 days exhibited enhanced memory. Crebinostat showed a marked enhancement in the acetylation profiles of H3 and H4 and derepression of early growth response 1 (Egr-1), a target gene of CREB. Crebinostat proved to be six fold more potent than SAHA in increasing the acetylation status of neuronal histones H3 and H4 and was shown to down regulate proteins like Dihydropyrimidinase-Like 4 (DPYSL4), Dihydropyrimidinase-Like 5 (DPYSL5) and Oligodendrocyte Myelin Glycoprotein (OMG) involved in neurite growth inhibition. Thus Crebinostat enhances memory through multiple routes – by increasing the acetylation status of histones, by down regulating proteins inhibiting neurite growth or by enhancing the expression of neurotropic factors [46].

Neuronal activities induced by small molecule inhibitors regulate the epigenomic landscape in the hippocampal region altering the profiles of more than 20 acetylation events. Whole genome profiling of HDAC inhibition with Trichostatin-A has been shown to induce significant alterations in the levels of H4K12 acetylation. Trichostatin-A was also found to cause histone hyper acetylation in active loci pre-marked with H3K4 trimethylation, H3K9 acetylation and H3K14 acetylation. Trichostatin-A induced alterations on the genome hence might lead to the understanding of cognitive and psychiatric disorders involving aberrant acetylation profiles. Trichostatin-A has been shown to increase the acetylation in hippocampus *in vivo*. In 3–5 month old C57/DBA F1 hybrid female mice, TSA increased the number of acetylation islands by 51, 128 and 18% for AcH3K9, Ac H314, AcH4K12 and AcH2B respectively at transcription start sites, intragenic regions and putative enhancers [47].

HDAC6, a member of Class IIb family of HDACs, regulates trafficking of neurotrophic factor [48], functions as

an alpha tubulin deacetylase [49] and modulates mitochondrial transport in hippocampal neurons during seretonergic neurotransmission influenced by the activity of Glycogen Synthase Kinase-3 beta (GSK3β) [50]. During associative learning process, representational plasticity occurs where the encoded dimensions of stimulus in the primary auditory cortex A1 region of brain are altered to augment the behaviourally important sounds. Such changes in the area of representation of the signal tones and their sensitivity and selectivity can be understood from the tonotopic map of A1 region. The extent of the area gained by a specific signal indicates the strength of the memory formed. RGFP966, a specific inhibitor against class I HDACs was found to enhance the auditory memory formation in mice subjected to sound to reward learning process. Also, RGFP966 treated mice showed enhanced plasticity in the auditory cortex A1 of the brain by increasing the sound representation linked to reward. RGFP966 also induced cortical remodelling as assessed through the signal-specific representational expansion models of auditory memory. Increased acetylation of H4K8 was observed in the A1 cortical region but not in hippocampus after treatment with the inhibitor [51].

Pharmacological intervention with HDAC inhibitors have shown reduced deficit in contextual fear memory in mice lacking a copy of the CREB binding protein. Administration of sodium butyrate into the insular cortex of the rat results in enhanced object recognition memory leaving the object location memory unaffected. The blocking of NR4a genes substantially impairs long term memory in mice. Trichostatin-A has been shown to enhance the expression of NR4a genes and hence long term memory events through transcriptional programs [52]. Class I selective HDAC inhibitors like MS-275 have proven to be more efficient in memory enhancement and in altering depression mediated behavior [53].

Recent work on mouse models of Alzheimer's disease has shown that a novel mercapto acetamide based Class II HDAC inhibitor coded W2 and a Class I and Class II based inhibitor coded as I-2 improve learning and memory by facilitating degradation of the amyloid beta peptide. The HDAC inhibitor I-2 decreased expression of β- and γ- secretase components and increased mRNA levels of Aβ degradation enzymes while W2 decreased Tau phosphorylation at Thr181, an unknown function among HDAC inhibitors [54]. Treatment of sodium valproate, sodium butyrate and vorinostat were found to completely restore contextual memory in the Alzheimer's disease mice model APPswe/PS1dE9 created with pronounced memory impairment. The three inhibitors had common inhibitory effect on Class I HDACs necessitating the need for selective inhibition of Class I HDAC isoforms for the treatment of Alzheimer's disease [55].

2.3. HDAC Inhibitors in Neuronal Plasticity

Epigenetic events play a crucial role in the modulation of plasticity related gene expression. It is an accepted fact that systemic or intra-hippocampal administration of HDACi increase memory consolidation processes in young rodents but it is not known whether these inhibitors are capable of ameliorating aging associated memory impairments. A one-day spatial learning task to investigate the effects of Trichostatin-A (injected into the dorsal hippocampus immediately after training) on long term memory consolidation in mice models of different age groups (3-4 and 18-20 months old) yielded 24 hour memory retention for the hidden platform location in young-adults but failed to prevent memory impairments in older mice. Drastic increase in the levels of H4 acetylation was seen in the dorsal hippocampal CA1 region (dCA1) and the dorso-medial part of the striatum (DMS) of young - Trichostatin-A treated mice sacrificed one hour post training. In aged mice, TSA circumvented altered H4 acetylation in the dCA1 but failed to reduce the age-associated decline in H4 acetylation in DMS. This establishes the need for a critical balance between histone acetylation and deacetylation events in regulating network plasticity during memory processes [56].

Memory reconsolidation is a process in which previously consolidated memory is recalled and updated before subsequent restoration. Behavioural and pharmacological intervention for attenuating recalled traumatic memories have been tested only on memories related to recent (day old) traumatic events. Recent fear memories were found to attenuate quickly on fear extinction training and no sign of fear response recurred after 30 days. Though remote (month old) memories also reduce after fear extinction training, the cue or context-triggered fear responses have been found to re-emerge after 30 days. Hence behavioural training is not alone sufficient to reduce remote fear memories. Histone acetylation modulated gene transcription has been found to play a role in reinstating previously stored memories during reconsolidation.

It is well established that neuronal plasticity is associated with Fos gene up regulation. Recent studies using hippocampal slices have shown hypoacetylation at the promoter of the Fos gene in mice with remote fear memories as compared to mice with recent fear memories. Inactivation of hippocampal HDAC2 by S-nitrosylation correlated with the recall of recent memories contrary to remote memory recall. This suggests that the recall of recent memories unlike remote traumatic memories is associated with an environment favourable for gene transcription that may facilitate neuronal plasticity. This demonstrates a vital role of HDACs in promoting neuronal plasticity in hippocampus during consolidation (which facilitates remote fear memory attenuation) and supports the administration of HDAC inhibitors along with behavioural therapies to eradicate remote fear memories [57].

Trichostatin-A administration prior to 'weak' - passive avoidance training in new born chicks enhanced the memory formation when tested 24 hours post training. TSA treatment also increased the expression of transcription factor c-Fos in intermediate arcopallium and dorsocaudal nidopallium regions of the brain, transcription factor ZENK in the hippocampus and intermediate medial mesopallium regions in relation with the memory enhancement [58].

A combination of HDAC inhibitor treatment and water maze training on young adult rats was found to significantly

alter the expression profile on the hippocampal region. The combinatorial approach showed an elevation in the levels of more number of genes than those altered individually by inhibitor administration or water maze training. This elevation was not limited to genes involved in regulating neuronal plasticity. Similarly the combination of HDACi with the single cognitive experience or training increased the synaptic protein expression in young rat hippocampus. But this experience dependent plasticity associated with histone acetylation is disrupted in the aged rat hippocampus [59].

Inhibitory avoidance tasks on rats subjected to cecal ligation and perforation (CLP) followed by sodium butyrate administration showed significant reversal of aversive memory impairment. The inhibition was also found to alter deacetylase activity in the hippocampal and pre frontal cortex regions of brain [60]. Intra gastric administration of HDAC inhibitor (−)-epigallocatechin-3-gallate (EGCG) has been shown to reduce β-amyloid levels and increase the expression of β-amyloid degradation enzyme Neprilysin in the brain cortex of Senescence-Accelerated Mice P8 (SAMP8) mice. EGCG treatment also rescued the cognitive behaviour in SAMP8 mice as assessed by the Morris water maze test [61].

Recently, two kinetically selective inhibitors (BRD4884 and BRD6688) of HDAC2 have been found to rescue memory deficits in a murine model of neurodegeneration (CK-p25) possessing profound deficits in spatial and associative memory. These inhibitors when used on primary mouse forebrain neuronal cultures at 10μM concentration for 24 hour duration resulted in significant increase in the levels of H3K9 and H4K12 acetylation compared to their vehicle treated controls. These inhibitors were found to rescue the memory defects associated with p25 induced neurodegeneration in contextual fear conditioning. Simulation target engagement assays, IC_{50} values and Quantitative Structure Activity Relationship (QSAR) studies on these compounds showed enhanced selectivity to HDAC2 over HDAC1 and HDAC3. These HDAC2 selective inhibitors enhance site specific acetylation leading to enhanced learning behaviour in cognitively challenged mice models [62].

Inhibitors of HDAC1, 2 and 3 - RGFP963 and RGFP968 were shown to induce synaptogenesis and increase spine density in hippocampus as compared to the HDAC3 selective inhibitor RGFP966. It was also observed that distinct transcriptional profiles were regulated by RGFP963 and RGFP966 in the hippocampal region of mature mice brain. In the mouse model of Alzheimer's disease, only RGFP963 was able to rescue the memory formation [63]. Class I specific HDAC inhibitor RGFP963 but not HDAC3 specific inhibitor RGFP966 was able to enhance the consolidation of cued fear extinction in animal models [64]. These studies indicate that HDAC1 and/or HDAC2 may be involved in the regulation of fear extinction and memory but not HDAC3.

Meningitis, the pneumococcal infection in the nervous system can lead to impaired memory, learning and attention deficit if not treated early in humans. Sodium butyrate administered as an adjuvant therapy along with antibiotics in mice models of meningitis created by intracisternal (i.c.) injection of *Streptococcus pneumoniae* suspension for 10 days showed marked improvement in memory formation as assessed through the inhibitory avoidance tasks. Sodium butyrate was also found to increased the expression of BDNF and Glial cell line-Derived Neurotrophic Factor (GDNF) in the hippocampal region [65].

Intra peritoneal administration of Class III HDAC-Sirtuin 2 (SIRT2) as a fusion protein with PEP1 in 7 week old mice for 3 weeks was seen to reduce new object recognition. But parallel administration of sodium butyrate sub cutaneously along with SIRT2 increased the time taken for new object recognition. Administration of SIRT2 alone reduced the expression of Ki-67, a marker of cell proliferation in the dentate gyrus region while sodium butyrate ameliorated this effect [66].

Recently, a novel HDAC inhibitor EVX001688 (EVX) with high penetrance in brain has been showed to induce and retain an increased histone acetylation in hippocampus. Acute systemic administration of EVX or sodium butyrate in young rats before contextual fear conditioning training did not alter memory retention, though they are known to elevate acetylation of histones. Pre training treatment with EVX also did not influence age associated spatial memory formation demonstrating that increase of histone acetylation in hippocampus alone is not suffiecient for the pro-cognitive effect of the inhibitor [67].

Treatment of animal models of Taupathy (rTg4510) with the HDAC6 specific inhibitor Tubastatin has been shown to increase the acetylation of alpha tubulin in brain. rTg4510 mice treated with Tubastatin showed reduced hyperactivity as assessed from an open field test that accounts for anxiety and general activity of the animals. Tubastatin also increased the freezing during contextual fear conditioning and rescued the memory impairment during water maze test [68].

2.4. HDAC Inhibitors Regulate Synaptic Function, Learning and Fear Conditioning

In gain of function and loss of function mouse models, over expression of HDAC2 in specific neurons have been shown to decrease dendritic spine density, synapse number, synaptic plasticity and memory formation. Chronic treatment with SAHA was shown to improve impaired learning and decrease synapse number caused by HDAC2 over expression while these could not be altered in mice deficient of HDAC2 [39]. HDAC2 knockout mice have been shown to enhance the extinction of conditioned fear response and associative learning, without influencing non associative learning or episodic memory while HDAC1 knockout mice did not elicit such neuronal responses [69]. Hence treatment to cognitive disorders might involve targetting HDAC2 mediated neuroplasticity, exploiting the function of HDAC2 as memory suppressor.

Molecular and behavioural mechanisms during conditioned behaviour have been well documented [70, 71]. While the presence of a reliable signal for shock facilitates learning during fear conditioning, the absence of shock weakens the fear response mediated by fear extinction mechanisms. Systemic administration of HDAC inhibitor

sodium butyrate and intra hippocampal administration of Trichostatin-A have been shown to enhance extinction. Administration of these drugs prior to a 3 minute contextual extinction session decreases context evoked fear to levels equivalent of those observed with a 24 minute extinction session [72].

Cue-associated memory formation is regulated in the basolateral amygdala (BLA) region of brain and is vital to understand the behavioural responses due to drug addiction such as morphine. Conditional Place Preference (CPP) is a preclinical behavioural model used for assessing the effect of drugs. It has been observed that intra-BLA treatment of Trichostatin-A is able to enhance the acquisition, expression, extinction of morphine-induced CPP and reduced reinstatement. Trichostatin-A treatment also improved the levels of histone H3 acetylation and BDNF in the basolateral amygdala [73]. Intra hippocampal administration of Trichostatin-A enhanced Inhibitory Avoidance (IA) memory retention after a 11- day training regime. This enhancement is prevented during functional inactivation of BLA by Muscimol [74]. Mice conditioned with cocaine showed increased acetylation levels of histone H3K14 and H4K8 in the hippocampal region on administration of a single intraperitoneal injection of sodium butyrate before conditioning [75]. Chronic treatment of butyrate for 28 days attenuated the reduction in freezing time of isoflurane exposed mice during contextual fear conditioning [76].

Selective inhibition of HDAC3 during extinction consolidation have been shown to invoke distinct patterns of histone acetylation related to gene expression within the infra limbic cortex, hippocampus and nucleus accumbens. This leads to the understanding that drug seeking behaviour requires HDAC3, the inhibition of which accelerates memory processes involved in extinction of such behaviour [77]. Pavlovian fear conditioning paradigm and Morris water maze paradigm experiments on HDAC1/2 over expressing mice showed that HDAC2 over expressing mice showed impaired hippocampal mediated memory formation and learning. Down regulation of HDAC2 has been shown to enhance associate learning in mice. Over expression of HDAC2 in neurons was also shown to decrease spine density, synaptic plasticity and memory [39].

Enhancing the levels of fear extinction has been increasingly looked upon as a viable therapeutic strategy in post traumatic disorders. Valproic acid treatment prior to extinction training was found to be capable of rescuing extinction learning as well as retrieval in mice which have impaired contextual fear extinction [78]. Treatment of rats with Vorinostat immediately after fear conditioning led to longer freezing response time indicating enhancement of original fear memory. Vorinostat treatment followed by two extinction trainings after fear conditioning showed a reduction in the freezing time. This indicates that Vorinostat also enhanced the extinction of conditioned fear [79]. A HDAC6 selective inhibitor 4b, derived from Quinazolin-4-one structure showed increased neurite outgrowth in the neuronal cells (PC12 and SH-SY5Y) and increased α-tubulin acetylation. Another such inhibitor 3f was shown to improve learning in the mice models with hippocampal lesions due to β-amyloid accumulation [80].

2.5. HDAC Inhibitors in Motor Neuron Diseases

Motor neuron diseases present pathological conditions similar to that of neurodegenerative diseases and include Huntington's disease, Amylotrophic lateral sclerosis, muscle/ spinal atrophy and bulbar palsy, which hamper voluntary muscle movements of the body. Current treatment strategies for these diseases are devised at targetting the associated psychological and symptomatic conditions. HDAC inhibitors are now being examined for effective treatments in Huntington's disease [81-83], spinal muscular atrophy [84] and amyotrophic lateral sclerosis [85-87]. Their success in clinical trials have also been well documented [88-91].

Huntington's Disease (HD) is a severe cognitive, psychiatric and motor functional disorder characterised by the loss of neurons in vital regions of the brain like cortex, striatum and hypothalamus. Genetically, the expansion of the poly glutamine regions in the Huntingtin (Htt) protein has been known to cause this condition. HDAC inhibitors sodium butyrate, Trichostatin-A and SAHA were shown to arrest the neuronal degeneration caused by the poly glutamine expansion in Drosophila HD models and to also improve the survival [92]. Myoclonus is a rare phenomena associated with the Huntington's disease, where there is involuntary twitching of muscles. Patients with myclonus do not benefit from the antidopaminergic therapy. Seven out of eight patients with Myoclonic hyperkinesia associated HD, when treated with valproic acid showed significant improvements in motor functions, suggesting the possible application of valproic acid as an alternative treatment for HD [93].

R6/2 mice models of HD express an N-terminal portion of human huntingtin with a polyQ stretch. Treatment of R6/2 mice with sodium butyrate increased motor function as well as the expression profiles of α and β globins and MAP kinase phosphatase-1. Globins are highly involved in oxygen transport and storage and hence increased expression of these globins by HDAC inhibitor treatment could offer neuroprotective effects through increase in levels of oxidative phosphorylation [94]. Double cross mice obtained as hybrid of HDAC4 KO mice and the HD transgenic mice R6/2 showed effective restoration of the synaptic function in the mice as assessed by a paired-pulse stimulation paradigm (where double crossed mice showed restoration of the higher paired-pulse ratios observed in the corticostriatal synapses of R6/2 mice) designed for the experiment [95].

Microarray analysis of expression profiles of Huntington's disease transgenic mice model N171-82Q reveal alterations in DNA methylation and transcription related genes like DNMT1, DNMT3A, GADD45B, RNF4, SIN3A. PARP1, MBD1, MECP2, *etc.*, in the mice brain when treated with HDAC1/3 selective inhibitor HDACi-4b. The inhibitor mediated DNA methylation was prominent in the Y-chromosome genes. Transgenic offsprings from the HDACi 4b treated male transgenic mice were found to have increased expression of KDM5d in the brain cortex both at mRNA and protein levels. A concomitant decrease in the H3K4methylation was observed in the mice brain, indicating that HDAC inhibitor 4b could induce epigenetic changes in the germ line developmental stages of mouse brain. HDACi-4b was administered as sub-cutaneous injection for these

experiments as the inhibitor dissolves poorly in water [96]. Using the same mice model N171-82Q, treatment with HDACi phenyl butyrate was earlier found to reduce lethality and to attenuate both gross brain atrophy and neuronal atrophy [97].

Complete loss of Sir2(-/-) in Drosophila models of Htt mutant led to compromised motor and photoreception function while the Htt challenged Sir2 (+/-) animals possessed improved function. This indicates that loss of a single copy of Sir2 amleliorates the pathology in models depicting HD. Htt challenged Drosophila treated with a selective inhibitor Selisistat, rescued the neurodegeneration and photoreceptive function besides improving the life span of the Htt challenged Drosophila model [98].

Amyotropic Lateral Sclerosis (ALS) is a motor neuron disease whose initial stages are characterised by asymmetric movement of muscles. A fraction of ALS is familial and associated with mutation in the Super Oxide Dismutase (SOD1) gene. Valproic acid treatment has been shown to improve the survival of ALS mice models with SOD mutation (SOD1/G93A) [99]. Oral administration of sodium phenyl butyrate to the same G93A transgenic mice reduced the atrophy in brain, astrogliosis and neuronal loss in the spinal cord. Rotarod analysis on G93A mice treated with sodium phenyl butyrate showed improved motor functions. Sodium phenyl butyrate showed increased expression of NFκB in the spinal cord of the mice, a molecule known to exert neuroprotective effect in mammals [100]. Intra peritoneal administration of phenyl butyrate has been shown to rescue motor functions in G93A mice [86].

Spinal Muscular Atrophy (SMA) is an inherited motor neuron disorder, which affects the voluntary muscle movement and activity. There are two copies of the gene survival motor neuron gene, SMN1 and SMN2. Most of the SMA patients show loss of survival motor neuron gene 1 (SMN1) and possess the other copy SMN2. SMN2 alone is not sufficient to produce levels of protein that prevent the motor neuron degeneration. Mutations in exon 7 of the gene have been found to produce truncated/spliced SMN2 protein which cannot exhibit functions through oligomerisation. Hence, improving the expression of full length SMN2 has been long since explored as a possible therapeutic option for SMA.

HDAC inhibitors 4-phenyl butyrate, valproic acid and M344 were found to increase the full length SMN protein levels in the primary fibroblast cells isolated from SMA patients [101-103]. Sodium butyrate was observed to increase the levels of SMN protein in lymphoid cells and also in the *in vivo* transgenic Smn2/2 mice models. The tails of SMA transgenic mice showed muscular atrophy, sub cutaneous edema and reduction in muscle fibre diameter, which were completely rescued by oral treatment of the mice with sodium butyrate [104]. SAHA, M344 and valproic acid were found to increase the SMN protein expression in organotypic hippocampal brain slice cultures (OHSCs) as well as motorneuron-enriched cell cultures, while MS-275 did not record such increase in expression [105]. Sodium 4-phenylbutyrate increased the expression of SMN protein in the leukocytes of the SMA patients [106]. Seven out of twenty SMA patients treated with valproic acid showed an increase in mRNA and protein expression of SMN2 [107]. Intra-peritoneal administration of Trichostatin-A to the Smn–/–SMN2+/+SMNΔ7+/+ SMA mice model has been found to improve the motor functions and rescue the phenotypes of SMA. Trichostatin-A improved the survival of animals and increased the number and size of myofibers [108]. Patients with type III/IV SMA treated with valproic acid for 8 months showed a increased muscle strength and function [109].

Valproic acid was found to decrease the excitation in the axon terminals of motorneurons in lymphoblastoid cells isolated from SMA patients. The inhibitor also showed inhibition of the voltage gated calcium channels essential for motor neuron excitation [110]. HDAC inhibitor Trichostatin-A and proteasome inhibitor bortezomib were found to increase the SMN protein levels in the patient derived fibroblast cells in an additive manner. Peripheral tissues of mice co treated with Trichostatin-A and bortezomib showed higher expression of SMN proteins compared to that in the Trichostatin-A or bortezomib alone treated mice [111]. SAHA treatment was found to rescue death and improve survival in two transgenic mice models of SMA : US-SMA (one SMN2 per allele covering the genomic region of SMN2 alone and homozygous) and Taiwanese -SMA (two copies of SMN2 including adjacent region of SMN2 and is heterozygous). SAHA treatment increased the SMN protein levels, reduced motor neuron degeneration in spinal cord and increased the size of muscle fibers [112].

Clinical Trials on SMA

A comparative analysis of the available clinical trials were performed to identify the efficiency of drug treatments against the type II and III SMAs. This analysis included the clinical trials on SMA patients treated with creatine, phenylbutyrate, gabapentin, thyrotropin releasing and hydroxyurea. None of these drugs showed potency in treating type II and III SMA [113].

3. HDAC INHIBITORS IN NEURAL REGENERATION

Pharmacological interventions halt progression but do not completely cure disease symptoms, hence necessitating regenerative medicine in addition to drugs. Though drugs like Prednisone slow progression of muscular dystrophy, myoblast and muscle cell derived stem cell transplantation are looked upon as effective routes. Therapies for Spinal Muscular Atrophy have been elusive and require validation in animal models. Inhibition of HDACs using SAHA, mCarboxy cinnamic acid bis-hydroxamide (CBHA), Suberoyl bishydroxamic acid (SBHA), MS 275, M344, valproic acid, Trichostatin-A and phenyl butyrate have been found to be more efficient in reversing degeneration in mouse models [114].

Secondary damages that follow initial insults of the Central Nervous System (CNS) such as ischemic, genetic or mechanical result in axonal degeneration and associated loss of function [115, 116]. Restoration of functions of damaged CNS axons is an important event in regeneration, and is challenged by the neurite growth inhibition enabled by factors such as Myelin-Associated Glycoprotein (MAG).

Treatment with Trichostatin-A and other inhibitors have shown that HDAC6 inhibition promotes neuronal regeneration and survival. Oxidative stress, a major player in neurodegeneration, results in HDAC6 over expression and a deacetylation of the cytoskeletal component tubulin. Inhibition of HDAC6 reverses the acetylation profile facilitating regeneration of neurons [117]. HDACis also reverse the symptoms of Duchenne muscular dystrophy [118].

Sodium butyrate has been shown to induce the differentiation of embryonic stem cells into neural cells followed by a selective culturing method [119]. BDNF gene expression stimulation by neuro steroids has been known to associate with regeneration and plasticity of neuronal cells. Trichostatin-A, sodium butyrate and valproic acid were found to stimulate Glial Fibrillary Acidic Protein (GFAP) in rat C6 glioma cells *in vitro* which is reversed with the inhibition of neurosteroid synthesis [120].

Remyelination enables formation of the myelin sheath back on the demyelinated axons and is a critical process in a functional central nervous system. Histone deacetylases have been identified to play important role during the process. HDACs are recruited to silence the oligodendrocyte differentiation inhibitors and stem cell markers in demyelinated young brains, and to enable synthesis of new myelin. Inhibition of HDACs with valproic acid was found to increase expression of stem cell markers and oligo dendrocyte differentiation inhibitors in oligodendrocyte progenitor cells and decrease myelin expression but not in the microglial cells or astrocytes [121].

In the mammalian central nervous system, the regeneration events are negligible in mature neurons and the genes responsible for axon growth are transcriptionally altered. In the case of spinal cord injury, in the site of injury/lesion, the connection of spinal cord with that of brain is hampered leading to loss of sensory functions below that location because of improper axon regeneration. Current therapeutic strategy to block the extracellular inhibitors of axon growth facilitates only minimal axonal regeneration. Epigenetic events have been recently found to play important roles in regulating axon regeneration. Class I/II specific HDAC inhibitor Trichostatin-A was found to induce the expression of GAP43, a marker for axonal regeneration in post natal cerebellar granule neuron cultures apart from increasing the acetylation levels on histone H3K9 and H3K14 and inducing expression of p300 and P/CAF. p53 was found to be acetylated at K320 and K373 post treatment with TSA. It was observed that neurons expressing mutant p53 (p53 K320R) showed poor neurite outgrowth and reduced number of neurites even with TSA treatment. A probable mechanism has been proposed based on these understandings where Class I and II HDACs could be maintaining the hypoacetylation of genes involved in neuronal outgrowth and addition of TSA inhibits these HDACs and allows p53 to form transcriptional complex with p300 and P/CAF to facilitate the expression of genes associated with axonal growth [122]. Treatment of dorsal root ganglion (DRG) neurons with TSA and MS-275 increased H4 acetylation levels in the promoter regions of regeneration associated genes like Sprr1a, Npy, Galanin, and Vip. DRG neurons isolated from mice treated with TSA or MS-275 showed longer axons as observed from the neurite growth assay. Mice models of spinal cord injury (where the ascending sensory fibers of fasciculus gracilis was completely severed) treated with MS-275 and TSA showed higher number of DexTR-labeled ascending sensory axon fibres in the centre of the lesion. Besides the rescue of axonal fibres, more number of injured fibers were found to traverse the epicentre of the lesion in the inhibitor treated mice indicating axonal regeneration [123]. miR-138 has been found to play important role in the axon growth during development and nerve injury. Expression of miR-138 was found to increase during development in cultured mouse embryonic cortical neurons. Introduction of mimics of miR-138 into the mice DRGs *in vivo* through electroporation significantly reduced the expression of SIRT1. Adult DRG neurons treated with the specific inhibitor for SIRT1, EX527 blocked axon regeneration. These indicate that SIRT1 and mi-138 constitute a negative feedback loop and are effectively involved in regulating axonal regeneration [124]. Valproic acid treatment 8 hours post spinal cord injury in rats significantly rescued the locomotor functions. VPA treatment induced neurite overgrowth in neurons isolated from spinal cord and hippocampus of fetal rats on embryonic day 14 and exposed to Nogo-A peptide [125].

Mechanisms of Regeneration through Histone Deacetylases

Histone deacetylases play a critical role in regulating axonal regeneration post spinal cord injury. Calcium influx from the site of injury induces phosphorylation of HDAC5, which mediates its export from nucleus and transocation to the distal end of the injured axon. HDAC6 induces the dendritic outgrowth in post mitotic neurons through ubiquitination of Cdc20. Both HDAC6 and SIRT2 function as deacetylases for tubulin. Since tubulin deacetylation is known to affect the formation of growth cone in injured axon tips by destabilising microtubules, pharmacological intervention to inhibit these deacetylases could serve as a better therapeutic route for axonal regeneration [126].

HDAC Inhibitors offer Protection Against Neurotoxicity

Neurotoxicity refers the condition where exposure to certain substances result in altered functioning of the nervous system. Excessive accumulation of amyloid-β, higher concentrations of glutamate and oxygen radicals in brain are the most common form of neurotoxins that affect brain function and cause motor function disorders, dysfunction of autonomic nervous system and cognitive deficits. Antibiotics and clinical drugs, organ transplantation, radiation therapy and drug abuse can also lead to different forms of neurotoxicity.

Cell free supernatant from the human astrocyte U-373 cells stimulated with Interferon-γ (50U/ml) were able to induce neurotoxicity in human neuroblastoma cells SH-SY5Y and pretreatment of U-373 cells with HDAC inhibitor SAHA for 1 hour was able to prevent the same. It was observed that SAHA pre treatment was able to reverse the morphological changes (shrinking of cytoplasm) in SH-SY5Y cells induced by IFN-γ. SAHA treatment was found to also increase the inflammatory chemokine ITA-C and to increase the phosphorylation of STAT3. It should also be

noted that SAHA treatment does not affect the viability of the neuronal cells and also provides protection against the IFN-γ mediated neurotoxicity [127]. The hydroxyquinoline class anti fungal drug Clioquinol is known to be neurotoxic at higher doses and to cause subacute myelo-optico neuropathy (SMON). Clioquinol has been found to reduce the histone acetylation levels and inhibit the Neurite Growth Factor (NGF) - induced Trk autophosphorylation in the PC12 cells. Treatment of HDAC inhibitor TSA reversed these effects induced by Clioquinol [128]. Increased stimulation of neurotransmitters like glutamate leads to excitotoxicity in nerve cells. Excitotoxicity in organotypic cerebral slices of 7-day-old Wistar rats induced by glutamate transporter blocker, DL-threo-β-benzyloxyaspartate (DL-TBOA) reduced cell viability and treatment with HDAC2 and HDAC3 selective inhibitors AH51, AH61 and AH62 was able to rescue this neural cell death [129].

Calpains are cysteine proteases, whose controlled activation in the central nervous system is required for proper synaptic function and memory. Hyperactivation of calpains can lead to calcium overload and resultant damage to nerve cells causing neuronal toxicity. In neurodegenerative conditions like Alzheimer's disease, higher activity of calpain and downregulation of the calpain inhibitor Calpastatin have been reported. Treatment of the cells with ionomycin, which is a calcium ionophore caused autolysis of calpain 1 and calpain 2. HDAC inhibitor TSA was found to increase the expression of calpastastin in SH-SY5Y neuroblastoma cells and was found to attenuate autolysis of calpain 1 alone. Increased levels of histone H3 and H4 acetylation were observed on the Calpastastin promoter region upon TSA treatment [130]. Aroclor 1254 is a Polychlorinated biphenyl (PCB) mixture that causes neuronal cell death. Exposure of SH-SY5Y neuroblastoma cells to A1254 led to time dependent reduction in cell viability. Treatment with class II HDAC inhibitor MC-1568 but not class I HDAC inhibitor MS-275 was able to attenuate the A1254 induced cell death. A1254 was found to reduce the Synapsin-1 levels through increasing RE-1-silencing transcription factor (REST) and to increase HDAC3 levels which interacts with REST. MS-275 treatment reduced the binding of HDAC3 in Synapsin-1 promoter thereby increasing its expression levels while inhibiting the A1254 induced neuronal cell death [131]. Cytosolic localisation of HDAC1 has been observed in the corpus callosum region of mice exposed to the copper chelator and neurotoxin cuprizone. Treatment of glutamate and TNF-α were found to cause HDAC1 export from nucleus associated with reduced neuronal cell viability and axonal damage. It was also found that shRNA mediated silencing of HDAC1 reduced the neurite beading induced by glutamate and TNF-α. This indicates the localisation of HDAC1 as a potential target to overcome neurotoxicity [132].

Specificity of HDAC Inhibitors

Though HDAC inhibitors demonstrate enhanced potential in treating neural disorders, the specificity of these small molecules on different HDAC substrates is a concern in therapy. The class specific isoforms of HDAC possess high structural identity and pose a challenge in development of inhibitors with precise targetting capabilities. The sequence similarity among the Zinc - catalytic sites of various HDACs makes inhibitor design more difficult.

One major reason for the toxicity of HDAC inhibitors could be the lack of precise targetting of enzymes by these molecules. Diverse strategies have been employed to address this issue. Altering the zinc binding groups of HDAC inhibitors and introduction of aromatic rings in the linker regions through click chemistry have been explored to design more potent HDAC inhibitors [133]. Novel pharmacophore models and minor structural alterations in the zinc binding groups, linker and cap region have evolved in the past two years to provide novel drug molecules with precise targets [134-136].

Valproic acid and sodium butyrate are often used to treat bipolar disorders and acute mania but these inhibitors are not effective in treating schizophrenia patients. MS-275 shows more potency as a brain selective HDAC inhibitor than valproate. Imipramine is more selective to inhibition of HDAC5 and correlates with BDNF mRNA transcripts 3 and 4 in the hippocampus [137].

Due to lack of specificity, many HDAC inhibitors target all classical HDAC enzymes and impinge on cellular signalling influencing key pathways targetting diseases. Genome wide studies on expression levels of genes and mRNA transcripts in different regions of the brain are necessary to elicit more information on the precise targets of these inhibitors. Several of the HDAC inhibitors do not cross the Blood Brain Barrier. Literature documents the potential of SAHA, SB and VPA to cross the blood brain barrier. Some of the benzamides have also been reported to possess greater penetration to brain regions. This warrants a more systematic study of HDAC distribution in different regions of the brain to design inhibitors specific to their HDAC substrates.

5. CONCLUSION

HDAC inhibitors have also proven to be ideal candidates in treating ischemic strokes, motor neuron diseases and Fragile X syndrome in patients. This review has focussed on novel applications of these small molecule inhibitors in learning and plasticity, neuronal memory and in ischemic strokes. Toxic effects accompanying long term administration have also been reported in certain cases. HDACi have shown detrimental effects post ischemic damage. While Class I HDAC inhibition using MS-275 has shown reduced proliferation leading to atrophy and fibrosis, Class II HDAC inhibition post ischemia is seen to interfere with differentiation leading to delayed maturation.

Valproic acid had a pro apoptotic effect on ES cell derived neural progenitor cells (NPC) of glutamatergic neurons, but not on their progeny. Valproic acid inhibits HDAC activity and induces the apoptosis of NPCs that are fated to differentiate into glutamatergic neurons [138].

HDAC inhibitors have been shown to play protective as well as toxic roles in cells. *In vitro* studies on primary neurons indicate regulation of neuronal survival as well as cell death by HDACs. It is also to be noted that the interactions of HDACs with their counterparts regulate their

functions - HDAC1 has been shown to be neuroprotective when it interacts with HDAC9 but neuro toxic during interactions with HDAC3 [139]. Histone Deacetylases confer neuro protective effects through the inhibition of Cyclin Dependent Kinases (CDK) and progression through cell cycle. HDAC3 confers acute toxicity in specific cell types. Expression of HDAC3 in healthy mice triggers death of cerebellar granular neurons, rat cortical neurons and HT22 cells derived from the hippocampus. But the administration of HDAC3 does not compromise the viability of HEK293 and HeLa cells. Inhibition of GSK3β has been shown to render protection to the neuro toxicity induced by HDAC3, which is directly phosphorylated by GSK3β [140].

Class III HDACs - Sirtuins show both protective and toxic effects on cells. It has been shown that over expression of SIRT1 and SIRT5 render protection to granule neurons from low potassium-induced apoptosis, whereas the over expression of SIRT2, SIRT3, and SIRT6 promotes neuronal death [141].

Patients with neuroendocrine tumours showed severe cardiac effects after administration of depsipeptide. The fifth dose of depsipeptide (FK228) precipitated fatal ventricular arrhythmia, asymptomatic grade 2 ventricular tachycardia and prolonged QTc (delayed repolarisation). These events were also accompanied by nausea, anorexia and constitutional fatigue in patients [142]. The cardiac toxicity reported in depsipeptide studies might be due to previous history of cardiac dysfunction in patients considered for the study. The cardio toxicity profiles after HDAC inhibition hence need to be followed in order to assess its efficacy and nontoxic behaviour in patients [143].

The non-specific effects of HDAC inhibitors on DNA is a major concern of their administration to patients and hence is a limiting factor to potential applications in clinic.

Despite toxicity concerns, HDAC inhibitors are evolving as safe drugs in therapy. Since epigenetic routes to therapy provide the advantage of reversibility, treatment regimes employing these inhibitors hold more promise and efficiency and make them more valuable targets for diverse diseases. Synergistic therapy involving administration of a HDAC inhibitor along with a conventional drug like paclitaxel, bortezomib or cisplatin has helped minimize side effects arising out of prolonged HDACi treatment and has shown success in the clinic [144-146]. Molecular signaling cascades of histone deacetylases and their inhibitors would hence continue to be explored for newer clinical applications and therapy in the next few decades.

Pharmacological intervention through HDAC inhibition in the central nervous system has demonstrated considerable success in pre clinical models of ischemia, neuro degenerative disorders and in other neurological diseases. The realisation of these models with a focus on translational therapy in clinics has not been completely achieved. Lack of understanding of HDAC function in neurons and the nervous system is a major reason for this impediment. Development of inhibitors that induce selective chromatin remodelling events to tune specific gene expression patterns, accurate dosage settings and specificity will trigger a new wave of drugs with refined strategies for treatment of neurological disorders.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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LIST OF ABBREVIATIONS

HATs	=	Histone Acetyl Transferases
HDACis	=	Histone Deacetylase inhibitors
HDACs	=	Histone Deacetylases
NaB	=	Sodium Butyrate
SAHA	=	Suberoyl Anilide Hydroxamic Acid
TSA	=	Trichostatin-A
VPA	=	Valproic acid

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