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REVIEW ARTICLE

Understanding the Role of Histone Deacetylase and their Inhibitors in Neurodegenerative Disorders: Current Targets and Future Perspective

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Abstract: Neurodegenerative diseases are a group of pathological conditions that cause motor incordination (jerking movements), cognitive and memory impairments result from degeneration of neurons in a specific area of the brain. Oxidative stress, mitochondrial dysfunction, excitotoxicity, neuroinflammation, neurochemical imbalance and histone deacetylase enzymes (HDAC) are known to play a crucial role in neurodegeneration. HDAC is classified into four categories (class I, II, III and class IV) depending upon their location and functions. HDAC1 and 2 are involved in neurodegeneration, while HDAC3-11 and class III HDACs are beneficial as neuroprotective. HDACs are localized in different parts of the brain- HDAC1 (hippocampus and cortex), HDAC2 (nucleus), HDAC3, 4, 5, 7 and 9 (nucleus and cytoplasm), HDAC6 & HDAC7 (cytoplasm) and HDAC11 (Nucleus, cornus ammonis 1 and spinal cord). In pathological conditions, HDAC up-regulates glutamate, phosphorylation of tau, and glial fibrillary acidic proteins while down-regulating BDNF, Heat shock protein 70 and Gelsolin. Class III HDACs are divided into seven sub-classes (SIRT1-SIRT7). Sirtuins are localized in the different parts of the brain and neuron -Sirt1 (nucleus), Sirt2 (cortex, striatum, hippocampus and spinal cord), Sirt3 (mitochondria and cytoplasm), Sirt4, Sirt5 & Sirt6 (mitochondria), Sirt7 (nucleus) and Sirt8 (nucleolus). SIRTs (1, 3, 4, and 6) are involved in neuronal survival, proliferation and modulating stress response, and SIRT2 is associated with Parkinsonism, Huntington's disease and Alzheimer's disease, whereas SIRT6 is only associated with Alzheimer's disease. In this critical review, we have discussed the mechanisms and therapeutic targets of HDACs that would be beneficial for the management of neurodegenerative disorders.

Keywords: HDACs, SIRTs, neurodegenerative disorder, neuroprotection and neurotoxic effect, future targets.

1. INTRODUCTION

Neurodegenerative diseases are a set of hereditary or sporadic conditions that result in progressive degeneration of neurons in the specific region of the brain [1]. The prevalence of age dependent neurodegeneration is rapidly increasing in the elderly population. Central nervous system (CNS) damage is prone to cell death, demyelination, neuronal and functional deficits. Oxidative stress is involved in the pathogenesis of several neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), which leads to the generation of free radicals and initiate neurodegeneration. Reactive oxygen species (ROS) toxicity associated glial cell activation, mitochondrial dysfunction; protein misfolding and cellular apoptosis are well accepted mechanisms of neurodegeneration [2]. Mitochondria are critical in maintaining cellular energy balance, cellular differentiation and cell cycle, *etc.* Impairment in mitochondrial mechanism leads to reduced oxidative phosphorylation, eventually causing neuronal cell death [3]. Glutamate and aspartate are the major excitatory neurotransmitters present in the brain, which worked through the activation of ligand gated ion channels and some *via* G-protein coupled receptors (metabotropic glutamate receptors). Increased concentration of extracellular glutamate is responsible for excitotoxicity reported in both *in-vitro* as well as *in-vivo* studies [4].

Only symptomatic treatments are available for the management of PD, AD, Huntington disease (HD) and Amyotrophic lateral sclerosis (ALS). Available *in-vitro* and *in-vivo* studies showed that histone deacetylases protect neurons and helps in neuronal survival [5]. HDACs are involved in cell division through stabilizing chromatin structure, repression of gene expression and regulation of cellular processes such as cellular differentiation, development and multiplication [6].

Histones are water-soluble proteins around which DNA is packed and contains positively charged amino acids such as lysine, arginine and histidine [7]. Nuclear DNA is highly condensed and wrapped around the histone moiety to pack them inside the nucleus and in condensed form and cause twining of the chromosome during cellular division [8, 9].

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Histones are mainly associated with DNA and interaction between histone and DNA is regulated by two enzymes *e.g.* Histone acetyl transferases (HATs) and HDACs, presents in nucleus and cytoplasm [10]. The positive charge of lysine residue gets neutralized on the addition of acetyl group in HATs and HDACs, which decrease interaction between lysine and phosphate group in DNA, thereby inhibit gene transcription [11], while deacetylation through HDACs resulted in restoration of positive charge in condensation of chromatin followed by turning off gene transcription [12].

In mammals, there are 18 different types of HDAC enzymes, which are classified into four types based on their structural and functional homologies to yeast HDACs. There are several non-histone protein targets, including transcription factors (*e.g.*, p53, STAT1, or STAT3), cellular proteins (*e.g.*, heat shock protein (HSP90), or KU70) involved in various cellular functions such as cell cycle progression, gene expression and necrobiosis pathways [13]. Several non-histone proteins have been recognized as a substrate of HDACs [14].

Classes I, II, and III of HDACs govern the acetylation of lysine of those non histone proteins that possess neuroprotective effects [14]. The HDAC inhibitors in AD prevent the amyloid beta induced hyper phosphorylation of tau protein and the expression of genes that are responsible for cognition loss [15]. Generally, HDACI increases protein transcription, activates heat-shock proteins, anti-apoptotic Bcl-2 family members and free radical scavenger enzymes that prevent degeneration of dopaminergic neurons in PD [16]. Similarly, in HD, the HDAC1and HDAC3 selective inhibitor (RGFP966) prevent corticostriatal-dependent motor learning deficit, suppressed striatal CAG repeat expansions and reduce the accumulation of mutant huntingtin [17]. HDACIs (especially HDAC6 inhibitor) prevent autoimmune demyelination of neurons in Multiple sclerosis [18]. The HDACIs in TBI maintain the cellular functions and the expression of proteins through post translational modification of histone moiety and heat shock chaperons [19].

2. THE HDAC SUPER-FAMILIES/TYPES

The brief classification of HDAC super-families is described in Fig. (**1**).

2.1. Class I HDACs

HDAC1 and HDAC2 have a sequence similarity index of 82% [20, 21]. The recombinant HDAC1 and HDAC2 are initially inactive because their activation requires cofactors. HDAC1 and HDAC2 protein complexes are necessary for the modulation of the deacetylase activity. The sequence similarity index between HDAC3 and HDAC8 is about 34%. The amino acid region (181-333) of HDAC3 has 93% similarity with HDAC1 and HDAC2. Although, there is only 68% similarity in the corresponding region of HDAC with HDAC1 and HDAC2 [22]. For deacetylation activity and transcriptional repression, the non-conserved C-terminal region of HDAC3 is essential. In addition to NLS, an NES is also present in the 181-333 amino acid regions. HDAC8 is composed of a large catalytic domain along with NLS at the central region [23, 24]. Because of the recent discovery of HDAC8, the involvement co-repressor protein complex is still unknown.

2.2. Class II HDACs: Class II HDACs are Further Subdivided into Two Categories

2.2.1 Class IIa HDACs

This class is further divided into two sub-classes, class IIa and class IIb. Class IIa includes HDAC4, HDAC5, HDAC7 and HDAC9, while class IIb contains HDAC6 and HDAC10. Class IIa HDACs have large N-terminal extensions with conserved binding sites for the transcription factor like myocyte-specific enhancer factor 2A (MEF2) and 14-3-3 protein which are required for HDAC signaling, followed by phosphorylation through kinases, such as calcium/calmodulin dependent protein kinase (CaMK) and protein kinase D shuttle from the nucleus to the cytoplasm (10). It is hypothesized that class IIa (especially HDAC4 &5) activity is regulated by the hippocampal neurons. However, the nuclear exportation of HDAC4 is done through electrical signals but not that of HDAC5 in hippocampal neurons [25]. Nuclear exportation of HDAC5 was demonstrated to be induced *via* stimulation of calcium flux through NMDA receptor or L-type calcium channels [26].

2.2.2. Class IIb HDACs

HDAC6 and HDAC10 belong to the class IIb HDAC family. HDAC6 is the main cytoplasmic deacetylase rather than HDAC10 towards histone substrates in mammalian cells [10]. HDAC6 is different from all other HDACs, as it refuses deacetylase domains and a C-terminal zinc finger protein [27]. HDAC6 possesses two non-identical catalytic domains in tandem and also has a lack of N-terminal extension [28]. Iwata *et al*. disclosed that HDAC6 is required for the autophagic degradation of aggregated huntingtin (affected protein in HD) [29]. It has the ability to associate with spinocerebellar ataxia type 3 protein (Ataxin 3), which is a neurodegenerative protein involved in the regulation of aggresomal formation [26].

2.3. Class III HDACs

Class III HDACs are the adenine dinucleotide dependence HDACs, which are further sub-classified as SIRT1, SIRT2, SIRT3, SIRT4, SIRT5, SIRT6, and SIRT7. All sirtuins have their own specific functions (neuroprotection and metabolic processes). Sirtuins are involved in various age related neurodegenerative diseases (Alzheimer's disease, Parkinson's disease dementia, cerebrovascular disease). Sirtuins may regulate various pathophysiological pathways (mitochondrial dysfunction, stress response, oxidative stress and inflammatory processes) which are associated with neurodegenerative diseases [30].

2.4. Class IV HDACs

HDAC11 belongs to the class IV HDAC super family, expressed in the brain, heart, muscles, kidneys and testes [27]. It consists of a deacetylase domain that looks like class I and II HDAC domains, and has small N- and C- terminal extensions [31, 32].

3. PHYSIOLOGICAL ROLE AND CLASS I HDACS

3.1. HDAC1

Lower expression of HDAC1 has been seen in the brain as compared to HDAC3 & HDAC11. HDAC1 is primarily

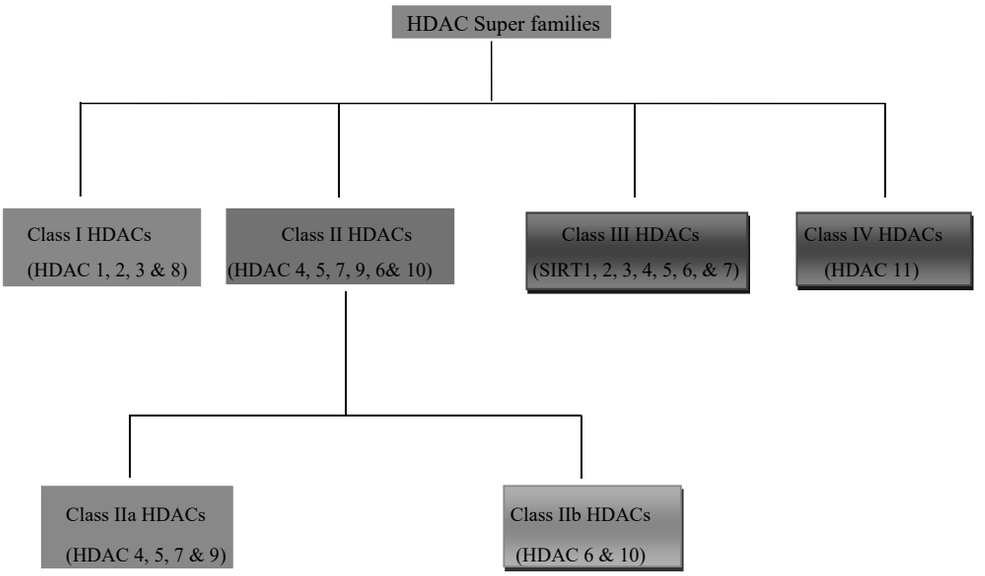

Fig. (1). Classification of HDAC super families.

present in neuronal cells like glial cells, including astrocytes and oligodendrocytes [33, 34]. Montgomery *et al.* described that HDAC1 lacking mice died before embryonic day and showed severe proliferation defects and general growth retardation [35]. HDAC lacks embryonic stem cells (ES) are associated with increased expression of cyclin-dependent kinase inhibitors (p21, p27) and the proliferation defects can also be observed in the particular type of cells (HDACs lack embryonic stem cells) [36]. Several studies revealed that 5% of genes (the peg3, H19 and Plag11 gene) are upregulated and 3% genes (Igf2 and p57genes) are down regulated in HDAC1 null embryonic stem cells, and they suggested that global repressor of transcription is not simply functioned by HDAC1, but they also functioned by the repressing or activating certain promoters in specific gene programs [37]. HDAC1 lacking zebrafish found defects within neuronal and skeletal muscle but yet these genes have not been identified [38]. The morpholino mediated HDAC3 knockdown zebrafish shows disruption in liver development [35, 39].

3.1.1. Role of HDAC1 in Neurotoxicity

HDAC1 plays a crucial role in neurotoxicity by affecting axon transport and reducing mitochondrial activity. HDAC1 binds to motor protein, such as kinesin and α-tubulin in cytosol, and decreases their ability to form complex with cargo protein followed by neurotoxicity. The cytosolic HDAC1 is expressed in the patient's brain suffering from autoimmune disease associated with demyelination of axons, such as multiple sclerosis [35]. The acetylation of p53 gene is regulated by HDAC1 and HDAC2 resulting in neurotoxic effects. HDAC1 is also involved in the pathogenesis of an autosomal dominant and progressive neurodegenerative disease [40, 41].

3.1.2. HDAC1 as Neuroprotective in Various Neurological Disorders

HDAC1 formed a neurotoxic complex in association with HDAC3, whereas HDAC1 interacts with HDRP protein (histone deacetylase related protein) showing neuroprotective effects in cultured neurons [42]. SIRT1 binds with HDAC1 and is thought to produce neuroprotective effects by preserving genomic stability [43].

3.2. HDAC2

HDAC2 has various roles in the human body. The activity of HDAC2 is essential in the regulation of pre- and postnatal brain tissue maturation [35]. HDAC2 has a greater number of genes that are responsible for learning, memory and synaptic plasticity. Inhibition of HDAC2 leads to cell death in many cells [44]. For the maturation of T-cell, the role of HDAC2 is essential [45]. Some studies revealed that HDAC2 knockout leads to microglia maturation defects [46]. The study revealed that HDAC2 knockdown mice have birth defect with severe cardiac malformation, including obliteration of the lumen of the right ventricle due to excessive proliferation of cardiomyocytes as well as bradycardia who died within first 24 hours of birth [35, 47].

3.2.1. Role of HDAC2 in Neurotoxicity

HDAC2 has been involved in the origin of various neurological disorders as well as cognitive impairment found in AD. Mutation in the SMN1 gene (survival motor neuron-1) causes fatal motor neuron and autosomal recessive disease by the duplication of SMN locus and SMN2 gene (SMN2), however, SMN1 is also coded by the SMN protein [48]. SMN1 derived protein lacking patients may experience spinal muscular atrophy (characterized by the degeneration of motor neurons in the spinal cord), the expression of that particular gene is decreased by the HDAC inhibitors [49]. Hence, it may be the possible therapeutic target for the development of drugs against spinal muscular atrophy. However, it has been found that the over expression of HDAC2 in hippocampus decrease the transcription of BDNF and c-fos which causes neuronal loss and memory impairment [50].

3.3. HDAC3

HDAC3 has a structural resemblance with HDAC8. HDAC3 is also functionally related to other class I HDACs,

but HDAC3 possesses multisubunit complexes which are different from other available complexes. For the activation of HDAC3, SMRT ((silencing mediator for retinoic acid and thyroid hormone receptors) and N-CoR (nuclear receptor co-repressor) are the essential required factors. Both these factors are structurally and functionally similar and act as co-repressors (Class II histone deacetylases: structure, function, and regulation. Isolation of a novel histone deacetylase reveal that class I and class II deacetylases promote SMRT-mediated repression). The conserved deacetylase-activating domain is present in SMRT and N-CoR for HDAC3 activation [51]. HDAC3 has the ability to form oligomers with the rest of HDACs both *in vivo* and *in vitro* [22]. Some studies have shown that HDAC3 can co-precipitate with HDACs 4, 5, and 7 *via* SMRT and N-CoR complex formation [22, 52]. HDAC3 is also found to have complex formation with HDAC related protein (HDRP) [53, 54]. In addition, HDAC3 also shares the ability of HDAC1 to form Rb–RbAp48 interaction, which showed the essential role in the cell cycle process [55, 56].

3.4. HDAC8

Less information is available on the HDAC8 role in brain development and function. Investigation of HDAC8 expression in mice and chicks during embryonic development demonstrated that in mice HDAC8 is solely expressed in midbrain and forebrain regions, while in chicks, it displays a broader pattern of expression [57]. HDAC8 has a similarity index of 34% with HDAC3 [58]. HDAC8 enzyme is involved in the organization of chromosomes and regulation of cell structure during cell division [59]. Cells copy their chromosomes during the S phase of cell division and arranged the DNA into two identical structures referred to as sister chromatids obtained from each chromosome [60]. Sister chromatids are attached with each other with the group of a protein called cohesion complex during the early stage of cell division; cohesion complex is removed in a later phase of cell division by a chemical reaction carried by HDAC8 that is involved in the removal of cohesion complex, so the sister chromatids are separated and moved to newly forming cell and further recycled for future cell divisions [60]. Due to its current discovery, only two different transcripts of 2.0 kb and 2.4 kb have been observed.

4. PHYSIOLOGICAL ROLE AND CLASS IIA HDACS

4.1. HDAC4

HDAC4 has a similarity index of 70% with HDAC5 and 58% with HDAC7. HDAC4 also has the ability to interact with SMRT/N-CoR, and co-repressor BCoR and CtBP [58]. HDAC4 is highly expressed in the rodent's brain during early postnatal life [61]. Accumulation of HDAC4 is seen in the cytoplasm of neurons through histochemical analysis of brain along with CRH, oxytocin, vasopressin, orexin, histamine, serotonin and noradrenalin [62]. HDACs are involved in the various signaling pathways of neurons in the brain. Nuclear translocation of HDAC4 is suppressed during the treatment with BDNF (Brain derived neurotropic factor), while the nuclear accumulation of HDAC4 is stimulated by the CaMK inhibitors. It is hypothesized that the nuclear localization of HDAC4 leads to neuronal apoptosis in various neurological disorders, whereas its inhibitors and SiRNA (small interfering RNA) decrease its expression and increases cell survival [63]. HDAC4 is required for the learning & memory and synaptic plasticity in mice as well as essential for normal cognition in mice, drosophila and humans [64, 65]. Earlier it was reported that HDAC inhibition is a negative regulator of learning, memory and synaptic plasticity [66, 67]. However, due to the majority of central neurons having the tendency to retain HADC4 in the cytoplasm; a study demonstrated that there is no detectable abnormalities seen in mRNA levels in the brain in HDAC4 deficient mice [68]. Arnold *et al*. reported that impairments in motor coordination, hyperactivity and decreased anxiety- like behaviors were seen in Hdac4bko mice [69]. Nevertheless, a recent report revealed that HDAC4 irreversibly enters neuronal nuclei under pathological conditions [70], but physiological significance of the nuclear import of HDAC4 remains to be unexplored.

4.2. HDAC5

HDAC5 is expressed in the whole part of the brain as well as peripheral tissues [71]. It is partially involved in neurodegeneration, but it has a more protective role compared with its harmful (neurodegeneration) effect. The study revealed that phosphorylation of the HDAC5 by the protein kinase C leads to the injury of the sensory neurons [72]. A study demonstrated that HDAC5 lacking mice are hypersensitive to stress results from the neurohumoral signaling. Neurohumoral signaling often activate the CaMK-PKD and calcineurin pathways which further regulate the phosphorylation of class IIa HDACs and promote their nuclear exportation [73]. Agis *et al.* reported that HDAC5 is important for the consolidation of context and tone-dependent fear memory. Hence, the author suggested that HDAC5 is crucial for the formation of fear memory but not involved in spatial memory [74].

4.3. HDAC7

HDAC7 appears in the nucleus and cytoplasm of the striatum neurons and is also found in the cortex and cerebellum. HDAC7 is expressed especially in the endothelial cells, which are responsible for the formation of the inner lining of CVS system; if the HDAC7 is deleted by the gene silencing techniques, the offspring having embryonic lethality as well as loss of integrity of endothelial cells [75, 76]. HDAC7 has a high degree of sequence similarities with HDAC5. It is transported from the nucleus to cytoplasm during muscle cell differentiation [77]. The location of HDAC7 is less clear and remains to be explored except for muscle cells [58, 78]. The overexpression of HDAC7 protects the cell from death *via* the inhibition of the expression of c-Jun in cultured neurons [79].

4.4. HDAC9

The catalytic domain of HDAC9 is present on the N-terminus. Mainly, three types of splice variants are available, including HDAC9a, HDAC9b and HDRP/HDAC9c, but HDAC9c/HDRP does not have any catalytic domain [80]. Additionally, HDAC9 also has a role in interacting with myocyte enhancer factor 2 (MFE2), which confirms the function in muscle differentiation [78]. HDAC9 plays an im-

portant role in the differentiation and development of many types of cells, including regulatory T-cells. Disorganization of HDAC9 gene involved in the congenital defect of eye in the part of anterior chamber. Genetically, HDAC9 along with HDAC11, SIRT4 and SIRT5 had shown an effect on the brain in multiple sclerosis patients [81, 82].

5. PHYSIOLOGICAL ROLE AND CLASS IIB HDACS

5.1. HDAC6

HDAC6 plays an important role in the brain in various neurological disorders. It has a role in various cellular function and deacetylase the target proteins like tubulin, cortactin, Hsp90 (DmHsp83) and Bruchpilot [83-85]. *In-vivo* study explored that the inhibition of HDAC6 increased neuronal survival and regeneration through reduction of oxidative stress. Further, some studies have also shown that axonal degeneration from kainic acid is related to a decrease in alpha tubulin acetylation [86]. In the *Drosophila* larva model, researchers examined that N-terminal deacetylase domain of HDAC6 is imperative for memory continuation and any mutation in HDAC troubled homeostatic synaptic plasticity [86, 87]. Human HDAC6 consists of 1215 amino acid residues arranged in space to form catalytic domain with a zinc finger ubiquitin-binding domain located at the C-terminus [88]. HDAC6 acts as a putative therapeutic agent in amyotrophic lateral sclerosis. Several ALS associated proteins have been found to have a relationship with HDAC6 [89].

5.2. HDAC 10

Of all class II HDACs, HDAC10 is discovered recently. HDAC10 has two splice variants [76]. A protein sequence study showed that HDAC10 has 37% overall similarity with HDAC6 [90]. The catalytic domain of HDAC10 is present on its N-terminus, and a putative second catalytic domain on the C-terminus region. HDAC10 has a regulatory role on the cell cycle as two putative Rb binding domains are present on it. The role of HDAC10 is reported in inflammatory condition like in arthritis, through elevation of cytokine (IL-1β, IL-6) [91]. These markers are well reported in neurological disorders like PD, AD, HD, and MS. However, these lines of evidence indicate that an inhibitor of HDAC10 could be beneficial in inflammation and hyper-immune associated neurodegeneration. So far, the exact role of HDAC10 in neurological disorder is not established, but it could be a useful future perspective against neurodegeneration [91, 92].

6. PHYSIOLOGICAL ROLE AND CLASS III HDACS

The silent information regulator (SIRT) belongs under the category of HDAC. There are seven classes of sirtuin proteins, denoted as SIRT1 to SIRT7, present with different enzymatic activities and localization within the mammalian cells. Sirtuins act as NAD^+- dependent deacetylases for a target protein, which is required for different biological functions [93].

6.1. SIRT1

Sirtuin incorporates a protective role from environmental stress in mammalian cells [94]. During starvation, the extent of SIRT1 is increased in mammalian cells. SIRT1 controls the metabolic process in several tissues through the activation of the nuclear receptor peroxisome-proliferator activated receptor- gamma (PPAR-γ) and its transcriptional co-activator. The cell survival, proliferation and stress response are regulated by several non-histone substrates of SIRT1 like tumor suppressor p53, forkhead transcription factor FOXO3a and NF-kβ [95]. Deacetylation of DNA repair factor Ku70 (an inhibitor of Bax-mediated apoptosis) increases cell survival promoted by calorie restriction (CR) [96, 97]. A recent study showed that SIRT1 over-expression increases longevity and delays the aging in mice, and also improved cell survival and level of BDNF [98].

6.2. SIRT2

The NAD+ dependent SIRT2 was the first sirtuin to be discovered, and it is essential for transcriptional silencing *in vitro* [99]. SIRT2 is mainly a cytoplasmic protein localized in the outer loops of the myelin sheath of neurons. There are several cytoplasmic proteins, such as OLN-93, oligodendrocytes; alpha-tubulin is the predominant substrate of SIRT2 deacetylase [100]. The level of SIRT2 is upregulated by calorie restriction (CR) as well as by oxidative stress [101]. HDAC6 has a binding affinity towards SIRT2 but the evidence is still doubtful whether SIRT2 deacetylates soluble or polymerized alpha tubulin or it can be considered as microtubule deacetylase. SIRT2 deacetylase has forkhead transcription factors of class O, FOXO1 and FOXO2 that are involved in various cellular processes such as DNA repairing mechanism, metabolism and aging [102]. The depletion of sirt2 results in an increase in acetylation of mitochondrial proteins and changes in the nature of mitochondria, leads to oxidative stress [103]. The potent inhibitor of SIRT2 (Sirtinol, AGK2, Tenovin-1 and Salermide) reduces the α-synuclein toxicity [104].

6.3. SIRT3

Sirt3 is mostly present in mitochondria and has an emerging role in the regulation of mitochondrial function and prevention of oxidative stress [105]. It also regulates mitophagy to remove altered mitochondria [106]. The extension of the lifespan of neuronal cell is directly linked to SIRT3. Null SIRT3 mice do not show any reduction of cell survival but display alteration in the fatty acid oxidation under the condition of caloric restriction (CR) [107]. Over-expression of SIRT3 demonstrates the phosphorylation of CREB, stimulating the expression of PGC alpha and its target UCP1, which shows a decrease in ROS production through a positive feedback mechanism. Expression of SIRT3 has a protective role in dopaminergic neuronal cell death [108, 109].

6.4. SIRT4

SIRT4 has different functions (*i.e.* energy metabolism and regulation of TCA cycle) in different tissues; its role in the brain remains unexplored. The first reported SIRT4 was Glutamate dehydrogenase (GDH), which regulates amino acid flux into energy production [110]. A recent study showed that up-regulation of SIRT4 is facilitated by the treatment with a neurotoxin (kainic acid). SIRT4 has a protecting and promoting effect on ageing by the regulation of reactive oxygen species. SIRT4 acts as a neuroprotective agent by maintaining the level of glutamate in the synapse [111].

6.5. SIRT5

Sirt5 mainly localizes in the mitochondrial matrix and mostly expressed in the brain, heart, liver, muscle and kidney [112]. It modulates the function of mitochondrial targets and catalyze NAD^+ dependent deacetylation (demalonylation, deacetylation and desuccinylation) to maintain the metabolic status in mammalian cells [113]. Another study demonstrated that SIRT5 is an important regulator in kainate induced neurodegeneration as well as in oxidative stress [114].

6.6. SIRT6

SIRT6 is a predominant nuclear protein, which is highly associated with the heterochromatic regions. It is involved in deacetylation of various proteins, including H3-lysine 9 (H3K9) and H3-lysine 56 (H3K56) needed for the formation of telomers [115]. A study demonstrated that SIRT6 showed its protective role in neurodegenerations, those mammals lacking this protein may undergo premature ageing like processes (ostopenia, lymphopenia, lordokyphosis and metabolic defects) and also leads to the accumulation of telomere damage [116]. The phenotypic observations on SIRT6 knockout mice demonstrated that this protein is thought to regulate both DNA base excision repair (BER) and spontaneous genomic stability [117].

6.7. SIRT7

SIRT7 is located in the nucleus and nucleolus of the mitotically active cells. It interacts with ribosomal RNA and regulates RNA polymerase-I [118]. The role of SIRT7 is not fully explored in neurodegeneration. Basically, SIRT7 is anticipated to possess a major role in numerous neuronal pathways; it regulates rRNA synthesis and assembly of ribosome *via* the changes in NAD^+/NADH ratio [119]. Similarly, Sirt7 regulates the genomic stability of cells by promoting the repair mechanism of non-homologous DNA damage [120].

7. PHYSIOLOGICAL ROLE AND CLASS IV HDACS

7.1. HDAC11

Phylogenetic analysis showed that HDAC11 has a structural resemblance with HDAC3 and HDAC8, which confirms the relation of HDAC11 with class I HDACs rather than class II HDACs [121]. The catalytic domain of HDAC11 is present on N-terminus. This enzyme does not have interaction with any HDAC complexes (Sin3, N-CoR/SMRT) [122]. HDAC11 elevates the gene expression of IL-10 both in humans and animals, which leads to the activation and release of $CD4^+$ and T-cell expression, although hyper-immune activation is well demonstrated to promote neuronal loss in Parkinson's disease, which stays in accordance with the role of HDAC11. The blockade of HDAC11 *via* its specific inhibitors will be a novel approach for the treatment of Parkinson's disease [123].

8. ROLE OF HDAC IN VARIOUS NEUROLOGICAL DISORDERS

8.1. Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by loss of memory and impairment in cognition [124]. AD is the most common form of dementia. Neurofibrillary tangles (NFTs), insoluble *β*-amyloid (A*β) plaque and neuron loss are the reasons behind AD* [125]. *On the basis of hypothesis at present,* "*Amyloid cascade hypothesis," it is suggested that the accumulation of* *β*-amyloid leads to an intricate cascade of neuronal apoptosis and thus results in the development of AD. Acetylation of histone and deacetylation of histone is catalyzed by two different enzymes, histone acetyltransferase (HATs) and histone deacetylase (HDACs), respectively. The level of acetylation of histone has a significant role in the regulation of chromatin condensation and transcription of genes. Histone deacetylases regulate the level of histone acetylation and furthermore cause the downstream of gene expression. Pathology of AD is associated with the abnormality of histone acetylation. HDAC proteins may be the target for the prevention of AD [15, 40].

The study revealed that HDAC2 knockdown AD mouse shows improved hippocampus dependent memory performance and synaptic plasticity. It may become a possible target for designing drugs to treat Alzheimer's disease [126]. A study reported that HDAC2 knockdown mice have birth defect with severe cardiac malformation including obliteration of the lumen of the right ventricle due to excessive proliferation of cardiomyocytes as well as bradycardia died within the first 24 hours of birth [35]. McQuown *et al*. observed that HDAC3-Flox-modified mice (deletion of HDAC3 in the CA1 area of the hippocampus) or the mice treated with a selective inhibitor of HDAC3 (RGF136) increases the acetylation of histone and considerably increase the cognition and the expression of the nuclear receptor gene subfamily 4, group A, member 2(Nr4a2) and c-Fos is involved in cognition [127]. Bardai FH and D'Mello also found that the protein HDAC3 has a strong neurotoxic effect and this neurotoxicity directly affects cellular mechanism [15, 128]. Another study revealed that it has a protective role in AD, and down regulation of SIRT6 leads to hyper-phosphorylation of tau levels in the Alzheimer's disease [129] (Fig. **2**).

8.2. Parkinson's Disease

Parkinson's disease (PD) is the most prevalent CNS disorder and also a second most common neurodegenerative disease mainly associated with reduced motor performance and memory impairment and affecting more than 4 million peoples worldwide. PD is characterized by the progressive hypokinesia followed by the slowness of movement, loss of postural reflex, rigidity and development of resting tremor. The prevalence of PD is 0.3-1% with age>50 years and even in greater age [130]. Histone proteins are known to provide neuroprotection *via* histone remodeling and cause acetylation, deacetylation of deoxyribonucleic acid (DNA) [32, 131]. Studies demonstrated that histone deacetylase inhibitors (HDACIs) are efficacious in PD, but how the histone acetylation prevents the neurodegeneration is still not well enlightened [132]. HDAC reduces the deacetylation of histone by using HDAC inhibitors (*i.e.* valproic acid, sodium butyrate and phenyl butyrate), which leads to chromatin relaxation and activation of multiple genes [133]. For example, brain derived neurotrophic factor, glial derived neurotrophic factor (GDNF) αsyn, Bcl-2, Bcl-XL, heat shock protein (HSP70), p21 and gelsolin have been shown to be induced upon HDAC inhibitors treatment [32, 134].

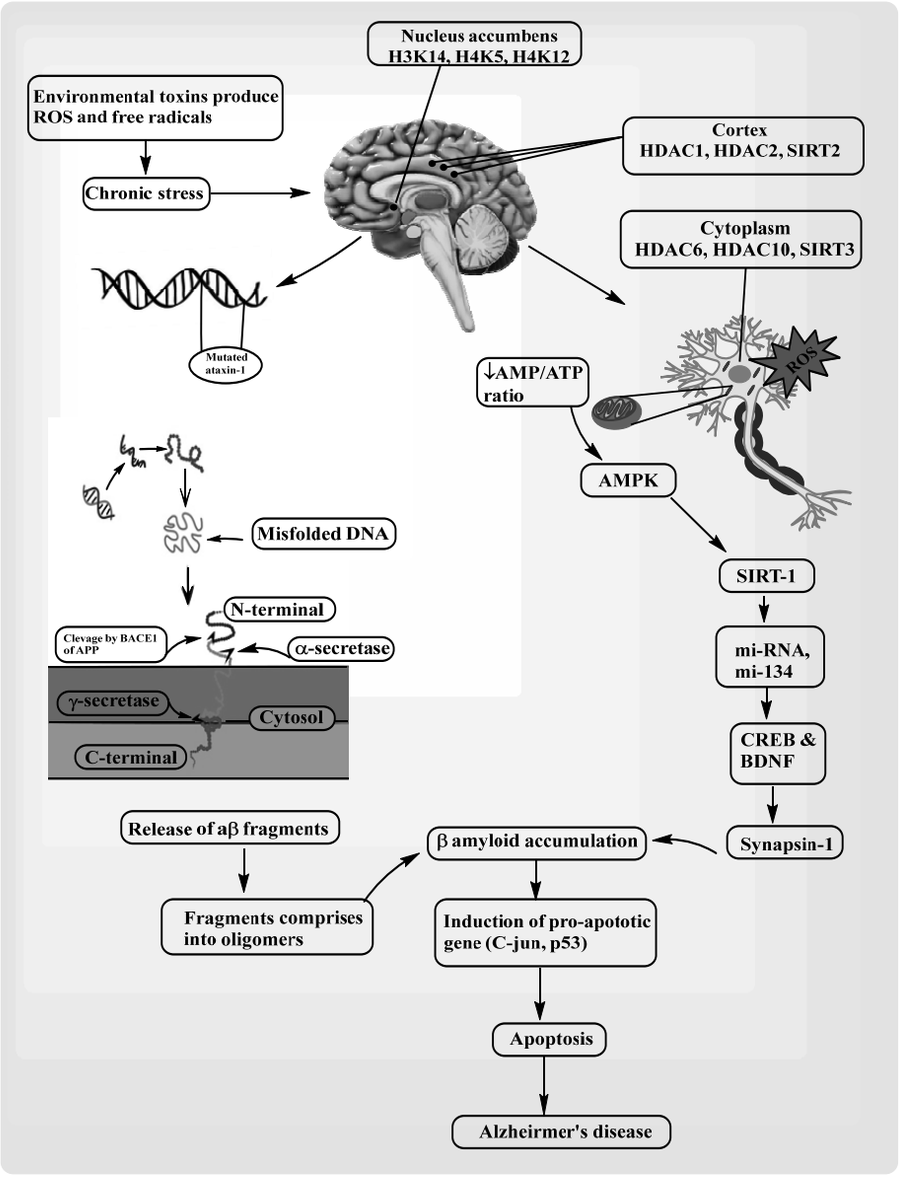

Fig. (2). HDACs and SIRTs mediated pathological mechanism of Alzheimer's disease. Histone proteins present in nucleus accumbens and cortex causes mutation on ataxin 1 through chronic stress. Mutation on ataxin 1 causes misfolded DNA which further releases aβ fragments, result beta amyloid accumulation. On the other side, in the brain neuron, presence of HDAC causes ROS production which activates AMPK followed by SIRT1 activation. SIRT1 further increases the level of CREB and BDNF. Activation of Synapsin1 leads to beta amyloid accumulation and further causes Alzheimer's disease. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

However, non-transcriptional effect of HDACs like non-histone targets of HDAC catalyzed deacetylation are also involved in neuroprotection [135]. Acetylation of α- tubulin is increased by the inhibition of HDACs, while non-histone target increases microtubule stabilization and axonal transportation with the release of BDNF [136, 137]. HDAC inhibition is also associated with the reduction of astrocyte and T-cell mediated inflammation [32, 138]. The study revealed that the depletion of SIRT5 showed motor deficits, dopaminergic degradation in substantia nigra and antioxidant activities of mitochondria in MPTP-induced PD mouse model [139]. HDACIs are beneficial therapeutic targets in neuroscience to treat various neurological disorders (Fig. **3**).

8.3. Huntington's Disease

Huntington's disease is an autosomal inherited neurodegenerative disorder caused by trinucleotide Cytosine-Adenine-Guanosine (CAG) repeats (>36) in an HD gene. Normal people have CAG repeats of 7-34. The CAG repeats length fluctuates with ageing and the repeats of CAG >100, causes juvenile onset [140]. HD is characterized by problems in movements; cognition impairment and function of the behavior [141]. Recent studies showed that transcriptional dysregulation is a mechanism of the pathogenesis of Huntington's disease. The eukaryotic gene expression depends on the alteration of histone protein. Acetylation and deacetylation of

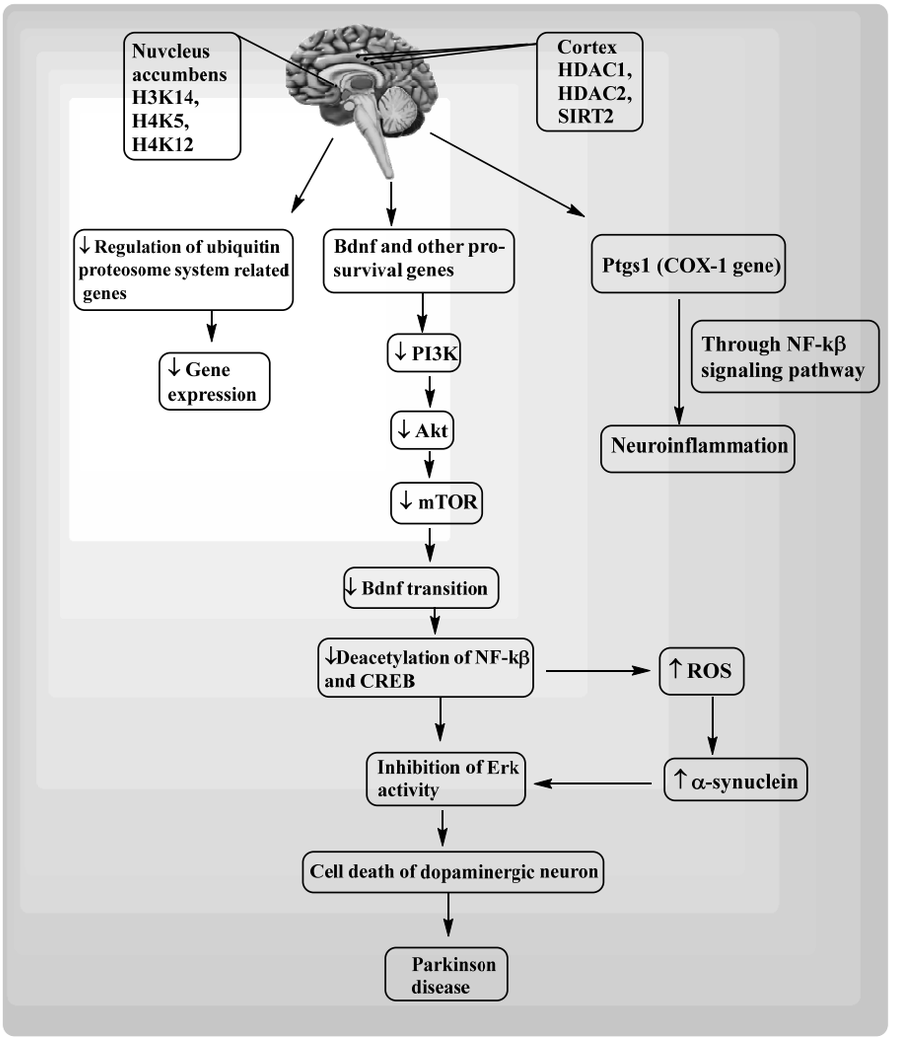

Fig. (3). HDACs and SIRTs mediated pathological mechanism of Parkinson disease. Histone proteins present in nucleus accumbens and cortex causes activation of COX-1. Gene (ptgs1, Prostaglandin-Endoperoxide Synthase 1) causes neuroinflammation through NF-kβ signalling pathway. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

histone moiety play a crucial role in gene expression. The mutation in the IT15 gene (mHTT), that is located on the short arm of the chromosome 4(4p 16.3), which leads to an alteration in histone acetyl transferase (HATs) activity and believe that the change in HAT activity may be the mechanism of transcriptional dysregulation in Huntington's disease [142, 143].

Gardian and Colleagues observed the neuroprotective activity of HDAC inhibitor (phenylbutyrate). The administration of phenylbutyrate at 75 days of age in transgenic HD mice (HD-N171-82Q) increased survival rate and decreased the degradation of the striatum and ventricular enlargement, but there was no effect seen on motor coordination. With the following phenylbutyrate treatment, there was an increased acetylation of histone H3 & H4 in the striatum and concurrently there was a decrease in methylation of histone H3 [144]. Jia *et al*. described that class I inhibitors have shown neuroprotective effects in different HD models *via* targeting HDAC1 and HDAC3 [145]. *In-vivo* evidence suggested that down regulation of HDAC1 prevents cognitive decline and motor dysfunction in HD mouse model [76] (Fig. **4**).

8.4. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a serious neurodegenerative disorder caused by the loss of neurons in the motor cortex, brainstem. ALS is associated with the paralysis of voluntary muscles. Symptoms of motor neurons come in middle age, and death occurs within 2-5 years after symptoms expression. ALS can be either genetic or non-genetic. Superoxide dismutase 1(SOD1), TAR-DNA binding protein 43 (TDP-43) encodes the mutant gene, which is responsible for ALS [146, 147].

The nerve-skeletal muscle interaction through HDAC4 may be the potential target in ALS. In a mouse model, the silencing of HDAC4 in skeletal muscle caused early onset of ALS, suggesting a potential risk in the use of inhibitor of HDAC for the treatment of ALS [148]. There are several combinations of drugs available to treat ALS, like combination treatment with SAHA (a pan HDACI), RGFP109 (HDAC1/3 inhibitor), and arimoclomol decreases the loss of nuclear hallmark of ALS (FUS). ALS associated FUS mutation rescued by HDACI through DNA repair mechanism [149] (Table **1**).

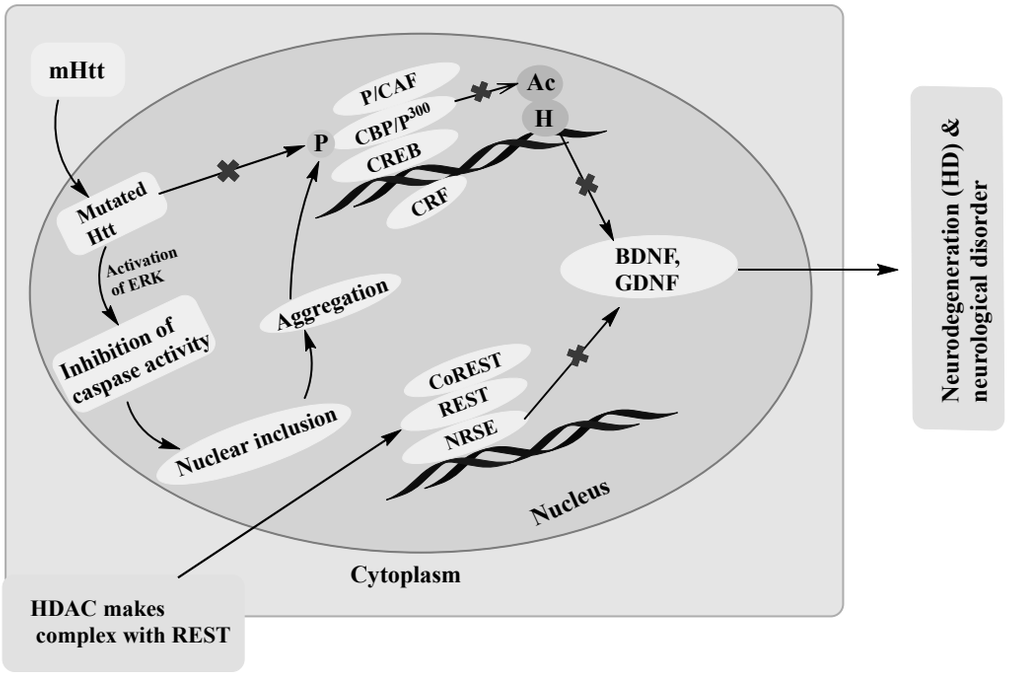

Fig. (4). Mutated huntingtin (mHtt) mediated Huntington pathology through making complex with HDACs. The complex formed between CREB, REST and mutant huntingtin (mHtt). Normally, Htt bonded with REST, a transcriptional repressor in the cytoplasm. Htt does not intrude with CREB phosphorylation and acetyltransferase activity of CBP which results transcriptional activation followed by neuroprotective activity. In HD, CREB phosphorylation and CBP acetyltransferase activity is inhibited by mutant huntingtin. In the nucleus, REST interacts with NRSE and BDNF transcription is repressed which results neuronal death. Whereas HDACIs are responsible for increase the CREB phosphorylation and histone acetyltransferase activity with addition of restoring BDNF expression and shows neuroprotection. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

Table 1. Mechanistic role of HDAC family, in various neurological disorders and their localization in brain.

Class	Sub Class	Modulat-or	Sub Cellular Localization	Pathophysiological Role/Disease		Drug Target		References
				Gene/ Protein Upregulated	Gene/ Protein Downregu-lated	Specific Drugs	Examples	
Class I	HDAC1 (Neurotoxic/ protective)	HDAC3 (-ve modu-lator) AD	Hippocampus, cortex	**Parkinsonism**		Sodium butyrate, Phenyl butyrate	Butyric acid, Valproic acid	[27, 150-154]
				NF-kB, $p21^{ras}$ $P21^{rac}$ Glutamate	BDNF GDNF HSP70 Alpha- synu-clein Bcl2 Gelsolin			
				Alzheimer's Disease				
				HSP90 Alpha-synuclein Beta-catenin Tau protein H4k8 acetylation Acetylation (H3k9, H3k14, H4k5,&H4k12)	gluR1, PSD95 Neprilysin Tubulin acetylation		Tubastatin A Lacosamide	

(Table 1) contd….

Class	Sub Class	Modulat-or	Sub Cellular Localization	Pathophysiological Role/Disease		Drug Target		References
				Gene/ Protein Upregulated	Gene/ Protein Downregu-lated	Specific Drugs	Examples	
-	-	-	-	**Huntington's Disease**		-	-	-
				Glial fibrillary acidic protein				
	HDAC2 (Neuro-toxic/protective – NR)	-	Nucleus	**Parkinsonism-**		Butyric acid Valproic acid	-	[151, 154]
				NF-kB, $p21^{ras}$ $P21^{rac}$ Glutamate P53 E2F1 GATA4	BDNF GDNF HSP70			
	HDAC3 (Neuro-toxic)	-	Nucleus/ cytoplasm	**Alzheimer's-**		Valproic acid RGFP963 EGCG		[152, 154-158]
				Aβ peptide GSK3β Tau phosphorylation Tau acetylation β secretase cleavage of APP amyloid β(1-42) accumulation	BDNF PSD95 GluR1 HSP acetylation			
				Huntington's –		Vori-nostatTSA RGFP966		
				Implicate aberrant transcriptional patterns Helps fuel CAG repeats expression Negative regulation of gene expression Histone methylation caspases Site- specific acetylation of mutant huntigtin Histone acetylation				
	HDAC 8(Neuro-toxic/protective-(NR)		Nucleus	**Huntington's –** Negative regulation of gene expression Histone methylation caspases Site- specific acetylation of mutant huntigtin Histone acetylation		Phenyl butyrate		[17, 154, 159-161]
				Amyotrophic lateral sclerosis				
				Mir206/FGFBP 1-mediated muscle reinnervation	α- tubulin acetylation histone skeletal muscle electrical potentials myogenic genes expression	ACY-738 or tubastatin, Sodium phenyl-butyrate, MC1568		

(Table 1) contd….

Class	Sub Class	Modulat-or	Sub Cellular Localization	Pathophysiological Role/Disease		Drug Target		References
				Gene/ Protein Upregulated	Gene/ Protein Downregu-lated	Specific Drugs	Examples	
Class II (a)	HDAC 4 (Neuro-protective) S	-	Nucle-us/cytoplasm	**Amyotrophic lateral sclerosis-**		ACY-738 or tubas-tatin, Sodium phenyl-butyrate, MC1568	Valproic acid Trichostatin A BML-210	[154, 161, 162]
				Mir206/FGFBP 1-mediated muscle reinner-vation	Histone acety-lation α- tubulin acetylation myogeneic genes expres-sion			
	HDAC5 (Neuro-toxic/protective)	-	Nu-cleus/cytoplas m	**Alzheimer's-**		Valproic acid EGCG	Trichostatin A BML-210	[14, 27, 152, 154]
				plays a role in the consolida-tion of contex-tual and tone dependent fear memories Alpha-synuclein Beta-catenin Tau protein	PSD95 Neprilysin Tubulin acety-lation			
-	-	-	-	**Parkinsonism-**		Phenyl butyrate	Valproic acid	
				Essential for spatiotemporal con-trol of ERG (early response gene) programme during memory encod-ing Histone H3 lysine 9 Acetylation				
	HDAC7 (neuro-protective)	-	Nu-cleus/cytoplas m	**Parkinsonism**		Valproate, RGFP109	TSA, Vorinostat, sodi-um phenyl butyr-ate	[163]
				Decrease beta catenin activity in chondrocytes interact with Bcl6 Decrease BDNF and GDNF expression				
	HDAC9 (Neuro-toxic/protective-NR)	-	Nu-cleus/cytoplas m	**Amyotrophic lateral sclerosis**		MC1568 ACY-738	Valproic acid Trichostatin A BML-210	[154, 159-161]
				FGFBP1-mediated muscle reinnervation	Skeletal mus-cle electrical potentials, myogenic genes			
Class II(b)	HDAC6 (Neuro-protective /toxic)	-	Cytoplasm	**Huntington's Disease**		Vorinostat	TSA Phenylbutyrate RGFP966	[154, 157]
				Accumulation of misfolded pro-tein Glial fibrillary	Decrease tubulin acety-lation Histone acety-lation			
	-	-	-	**Alzheimer's Disease**		Tubastatin A MPT0G21 1	4-Phenylbutyrate Tubacin EGCG	[152, 154]
				HDAC6-HSP90 binding Tau hyperphos-phorylation	Tubulin acety-lation			

(Table 1) contd….

Class	Sub Class	Modulat-or	Sub Cellular Localization	Pathophysiological Role/Disease		Drug Target		References
				Gene/ Protein Upregulated	Gene/ Protein Downregu-lated	Specific Drugs	Examples	
-	-	-	-	**Parkinsonism**				
				Deacetylation of Prxl and Prxl2 (peroxiredoxin) Oxidative cell injury	BDNF& GDNF ex-pression	Valproate	TSA, Vorinostat, sodi-um phenyl butyr-ate	[27, 154]
	HDAC10 (Neuro-Toxic/protective-NR)	-	Cytoplasm	**Alzheimer's Disease**				
				plays a role in the consolida-tion of contex-tual and tone dependant fear memories	Tubulin acety-lation	Valproic acid EGCG	Trichostatin A BML-210	[154]
Class III (sirtuins)	Sirt 1	-	Nucleus	**Alzheimer's Disease**				
				Fear learning& memory in wild type mice on treatment, Granulin ex-pression Synepsin1 ex-pression	mi-RNA mi-134 ex-pression CREB& BDNF expres-sion	Crebinostat Salisistate	Valproate RGFP963 EGCG	[154]
	Sirt 2	-	Cortex, stria-tum, hippo-campus, spinal cord	**Parkinsonism**				
				Regulate microtu-bule function, cell cycle, oxidative stress, Autophagy, overexp- ession increases α synu-clein aggregation	Glutamate transporter 1 and gluta-mate/ aspartate transporter	AGK-2	Trichostatin A BML-210	[154, 164, 165]
-	-	-	-	**Huntington's Disease**				
				Increase accu-mulation of polyglutamine in the N termi-nus of neuron	Histone acety-lation	Vorinostat	Trichostatin A BML-210	[154, 157]
	-	-	-	**Alzheimer's Disease**		-	Vorinostat, sodi-um phenyl butyr-ate Trichostatin A	[166]
				Abnormally overexpressed and deacetylates tubulin which results microtu-bule stabilization				
	Sirt 3	-	Mitochon-dria/Cytoplas m	**Alzheimer's Disease**		-		[167]
				Dysregulation of sirt 3 linked to mitochondrial dysfunction, Over expression restored the ex-pression of ND2 and ND4 and increase mitochondrial oxygen consumption by repressing mito p53 activity, Shows strong deacetylaseactivity				

(Table 1) contd….

Class	Sub Class	Modulat-or	Sub Cellular Localization	Pathophysiological Role/Disease		Drug Target		References
				Gene/ Protein Upregulated	Gene/ Protein Downregu-lated	Specific Drugs	Examples	
-	-	-	-	**Parkinsonism-**		-	-	[168, 169]
				Sirt 3 acts indirectly on PINK1 and the sirt3-FOXO3 pathway activates mitophagy *via* PINK1 parkin pathway Decrease level of superoxide (SOD-2) and glutathione peroxi-dase expression in MPTP induce SIRT KO mice in vivo, Clinically not reported				
	Sirt 4	-	Mitochondria	**Alzheimer's Disease**		-	Vorinostat Quicinostat s	[111, 169]
				Specific role of Sirt 4 is not well reported but shows various phys-iological role in various tissues. Recent study shows Sirt 4 is up-regulated in brain on treatment with kainic acid decrease the level of glutamate leads to neuro-degeneration.				
	Sirt 5	-	Mitochondria	**Parkinsonism**		-	Valproic acid	[169]
				Expression of sirt5 seen in MPTP induced nigrostriatal degeneration in SIRT5 KO mice.				
	Sirt 6	-	Mitochondria	**Alzheimer's Disease**		-	Vorinostat Quicinostat s	[169, 170]
				Recent study shows that sirt 6 increase the stability of tau protein while decrease level of sirt6 in-crease the hyperphosrylated tau levels				
	Sirt7	-	Nu-cleus/Nucleol us	Specific role of sirt7 in neuro-degenerative diseases and brain not well reported		-		[30, 118]
-	Sirt8	-	Nucleolus	Expression of Sirt8 is not well reported in neurodegenerative disorders.		-	-	[170]
Class IV	HDAC11 (Neuroto-xic/protective-NR)	-	Nucleus (cornu Am-monis1)/spinal cord	**Schizophrenia**		-	-	[171]
				EGF FGF Interleukin-10	BDNF GDNF Nerotrophin-3(NT-3)			

CONCLUSION

This review established the current knowledge about HDAC and its inhibitors. The role of several HDAC inhibitors is represented in various neuronal insult and neuroprotection in different cell lines, *in vivo* preclinical animal models and information on clinical evolution. This review also focused on the application of HDAC inhibitors in cognition, neuroplasticity and memory. The role of HDAC inhibitors is toxic rather than being neuroprotective in certain cases. Different classes of HDACs have different functions, while class 1 HDACI has been shown to reduce atrophy and fibrosis proliferation, class 2 HDACI shows interference with delayed maturation. *In vitro* studies on primary cell culture shows the regulation of neuroprotection as well as neuronal cell death by HDACs. The functions of different HDACs are correlated with each other- HDAC1 has been known to be protective when it interacts with HDAC9, whereas neurological insult during interaction with HDAC3. In some specific tissues, HDAC shows acute toxicity. Expression of HDAC3 in healthy mice induces death of cerebral neurons and rat cortical neurons. Inhibition of GSK3β pathway has been shown to be effective against neuro toxicity caused by HDAC3, which is phosphorylated by GSK3β.

Class III HDACs (SIRTs) achieved both neuro-protection and neuro-toxic effects in neuronal cells. Overexpression of SIRT1 and SIRT3 render protection to neurons. There are several problems associated with HDAC inhibitors because of their lack of specificity and isoform selectivity. The lack of knowledge of off-target specificity of HDAC inhibitors raised a concern to find out the exact drug action. In the upcoming years, the novel drug design with HDAC inhibitors may increase its specificity and effectiveness by overcoming problems associated with HDAC inhibitors currently. Future research on HDACIs is expected to have a potential neuroprotection activity against neurodegenerative disorders.

FUTURE PERSPECTIVE

Available reports demonstrated that hypoacetylation of histones and transcriptional changes are involved in various neurodegenerative disorders. In the present scenario, treatment with class I and class II HDACIs overcome these deficiencies and prevent neuronal degeneration [132]. HDAC inhibition-induced neurotrophins in neuronal tissue as well as in microglial cells, is believed to be a significant target as therapeutics. Class I and class II inhibitors reduce microglia activation *in-vivo* and *in-vitro* conditions that would be protective strategy to combat neurological disorders by overcoming neuroinflammation [172].

Non-transcriptional cascades, like microtubule stabilization through acetylation, have been implicated as neuroprotective in various neurodegenerative diseases [173]. In PD, transcription of free radical scavenger, heat shock proteins and apoptotic proteins (Bcl-xL, caspases) are up regulated by the expression of HDACs (HDAC1, 2, 5, 7 & 11) in dopaminergic neurons, result dopaminergic neuronal loss in SNPc of brain and showed PD like symptoms and shows PD like symptoms [174]. In Huntington's disease, HDAC (especially HDAC 3) causes corticostriatal dependent motor learning deficit and also increases the CAG repeat expansion in striatum. The mHTT undergoes proteolysis and fragmented into oligomeric form which is accumulated into the nucleus and cytoplasm. In cytoplasm, it interacts with mitochondria and altered respiratory chain and ATP production [175]. Thus, the inhibition of HDACs, especially HDAC 3 by the specific inhibitor, takes a critical role in the treatment of HD.

This review focuses on the important functions of sirtuins and HDAC in modulating neurodegeneration in central nervous system [176]. This review focuses on important functions of sirtuins and HDAC in modulating neurodegeneration in the central nervous system [176]. The exact functions of sirtuins are still unexplored, but some evidence suggest that sirtuins are important player in several brain disorders (AD, PD and HD) [177, 178]. However, further study is needed to explore the molecular role of sirtuins which may help to develop novel strategies against neurodegenerative diseases. The sirtuin information regulator provides a significant role in alleviating neurodegenerative disorders [176].

The neuronal morphology is mainly affected by SIRT1. In the future, in the treatment of diabetes and obesity, SIRT1 may be a novel approach [179, 180]. In the case of AD, SIRT1 modulation may be a valuable strategy to facilitate aggregate clearance [181]. Reduction of SIRT1/3 miRNA/protein levels observed in pathological condition of AD. The expression of SIRT1 to SIRT7 undergoes changes in ageing brain [182]. Especially SIRT1, 2, and 3 have a role in AD and other categories are still unknown [183]. In the case of PD, SIRT1 in response to resveratrol may render MPTP induced neurodegerative mouse model in addition, also SIRT5 have a protective role against PD mouse model [184].

In case of HD, modulation of SIRT1 with treatment may alleviate the expression of glutamine repeat toxicity. In the future, inhibition of SIRT2 will be much more consistent with the current scenario [185]. In the future, targeting SIRT3 in HD might improve mitochondrial insult and oxidative stress [186]. In ALS, dietary treatment with resveratrol may not be sufficient to show effect, whereas intraperitoneal injection may show symptomatic relief and neuro survival. SIRT3 protect ALS patient through prevention from mitochondrial stress and cell death [187]. So, from this review, we hypothesized that in the coming years, drug targets to HDACs and SIRTs would be grateful to alleviate neurodegenerative disorders.

LIST OF ABBREVIATIONS

HDAC	=	Histone deacetylase
HDACI	=	Histone deacetylase inhibitor
DNA	=	Deoxyribonucleic Acid
HAT	=	Histone acetyl transferase
STAT	=	Signal transducers and activators of transcription
HSP	=	heat shock protein
PD	=	Parkinson's disease
Bcl	=	B-cell lymphoma
HD	=	Huntington's disease
CAG	=	cytosine-adenine-guanine
MS	=	Multiple Sclerosis
TBI	=	Traumatic Brain Injury
NAD	=	Nicotinamide adenine dinucleotide
RPD	=	RNA polymerase domain
Sin	=	serine recombinase
CoREST	=	conserved neuronal co-repressor
PRC	=	Polycomb repressive complex
NuRD	=	Nucleosome remodeling and histones deacetylation
MEF	=	Myocyte-specific enhancer factor
CaMK	=	Calcium/calmodulin dependant protein kinase
SIRT	=	Sirtuins
ES	=	Embryonic stem cell
HDRP	=	Histone deacetylase related protein
HOP	=	Homeodomain protein
SMN	=	Survival of motor neuron
CRH	=	Corticotropin releasing hormone

BDNF	=	Brain derived neurotrophic factor
SiRNA	=	Small interfering RNA
ALS	=	Amyotrophic lateral sclerosis
IL	=	Interleukin
PPARγ	=	Peroxisome proliferator activated receptor gamma
FOXO	=	class O of forkhead box transcription factors
NF-kB	=	Nuclear Factor kappa-light-chain-enhancer of activated B cells
CR	=	Calorie restriction
CREB	=	cAMP response element-binding protein
ROS	=	Reactive Oxygen Species
MPTP-1	=	methyl-4-phenyl-1,2,3,6-tetrahydropyridine
H3K9	=	lysine 9 of histone 3
BER	=	Base excision repair
rRNA	=	Ribosomal RNA
NADH	=	nicotinamide adenine dinucleotide hydrogen
$CD4^+$	=	cluster of differentiation 4
NFTs	=	Neurofibrillary tangles
Aβ	=	Amyloid Beta
αsyn	=	Alpha synuclein
Bcl-xL	=	B-cell lymphoma-extralarge
mHTT	=	Mutant huntingtin
SOD	=	Superoxide dismutase
TAR-DNA	=	trans-activation response element DNA
TDP	=	Ribothymidine 5′-diphosphate
SAHA	=	Suberoylanilide hydroxamic acid
FGFBP	=	Fibroblast growth factor binding protein
EGF	=	Epidermal growth factor
FGF	=	Fibroblast growth factor
REST	=	Repressor element-1 (RE1) silencing transcription factor
NRSE	=	Neuron restrictive silencer element
mTOR	=	mammalian target of rapamycin
Erk	=	Extracellular signal regulated kinase
P/CAF	=	p300/CBP associated factor

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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