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Sirtuin Acetylation and Deacetylation: a Complex Paradigm in Neurodegenerative Disease

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Abstract

Sirtuins are the class III of histone deacetylases that depend on nicotinamide adenine dinucleotide for their activity. Sirtuins can influence the progression of neurodegenerative disorders by switching between deacetylation and acetylation processes. Histone acetylation occurs when acetyl groups are added to lysine residues on the N-terminal part of histone proteins. Deacetylation, on the other hand, results in the removal of acetyl groups. Pharmacological modulation of sirtuin activity has been shown to influence various neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, Huntington's disease, stroke, and amyotrophic lateral sclerosis. In this review, mechanistic perspective of sirtuins has been discussed in anti-inflammatory, antiapoptotic, and neuroprotective effects in various disorders. We have discussed the structure, neurobiology, and physiology of sirtuins in neurodegenerative disease. Recent preclinical and clinical studies and their outcome have also been elucidated. The aim of this review is to fill in the gaps in our understanding of sirtuins' role in histone acetylation and deacetylation in all neurodegenerative diseases. Here, we emphasized on reviewing all the studies carried out in various labs depicting the role of sirtuin modulators in neuroprotection and highlighted the ideas that can be considered for future perspectives. Taken together, sirtuins may serve as a promising therapeutic target for the treatment of neurodegenerative disorders.

Keywords Sirtuins · Histone deacetylases · Acetylation · Deacetylation · Neurodegenerative disease

Introduction

Sirtuins consist of a highly conserved family of deacetylases which depend on the oxidized form of NAD+ [1, 2]. The seven mammalian sirtuins have diverse subcellular localizations, targets, and enzymatic activity, a significant consideration at the time of evaluating the vivo substrates. "SIRT1, SIRT6, and SIRT7" are nuclear proteins, "SIRT3, SIRT4, and SIRT5" are mitochondrial sirtuins while "SIRT2" is a cytoplasmic protein but it can translocate into the nucleus as well [1, 3]. SIRT1 has been known to associate with apoptosis, differentiation, and oncogenic alteration and SIRT2 has been shown to deacetylate tubulin, but might also transport to the nucleus where it works as a "mitotic barrier protein." SIRT3, SIRT4, and SIRT5 are localized to the mitochondria having different enzymatic activities; SIRT6 is a chromatin-associated nuclear protein, and SIRT7 is confined to nucleoli [3]. Sirtuins are involved in the regulation of cellular homeostasis, i.e., metabolism, inflammation, senescence, and oxidative stress. Sirtuins activation is advantageous in both metabolic diseases and neurodegenerative diseases. This is because the sirtuins stimulate the mitochondrial activity, the energy centers, and mitochondrial proteins, prevent physiological changes caused by numerous pathological conditions. Sirtuins have been explored extensively during the past few years in neurodegenerative diseases such as AD, PD, HD, and ALS by several techniques including in vitro assays, cell culture, and animal models of NDD and studies of human tissue [4]. Histone acetylation occurs when acetyl groups are added to lysine residues on the N-terminal part of histone proteins. Deacetylation, on the other hand, results in the removal of acetyl groups. If the balance of acetylation and deacetylation becomes dysregulated, it is likely to cause neurodegenerative disorders. In this review, we have summarized "acetylation and deacetylation of sirtuins, the mechanism of action for sirtuins" in neurodegenerative disorders, and discuss the modulators of sirtuin activity [5, 6]. The "co-substrate NAD+," which places sirtuins at the center of the metabolic regulation of cellular energy, is the absolute requirement of the sirtuin reaction (Fig. 1). This helps to bridge the gap between nuclear

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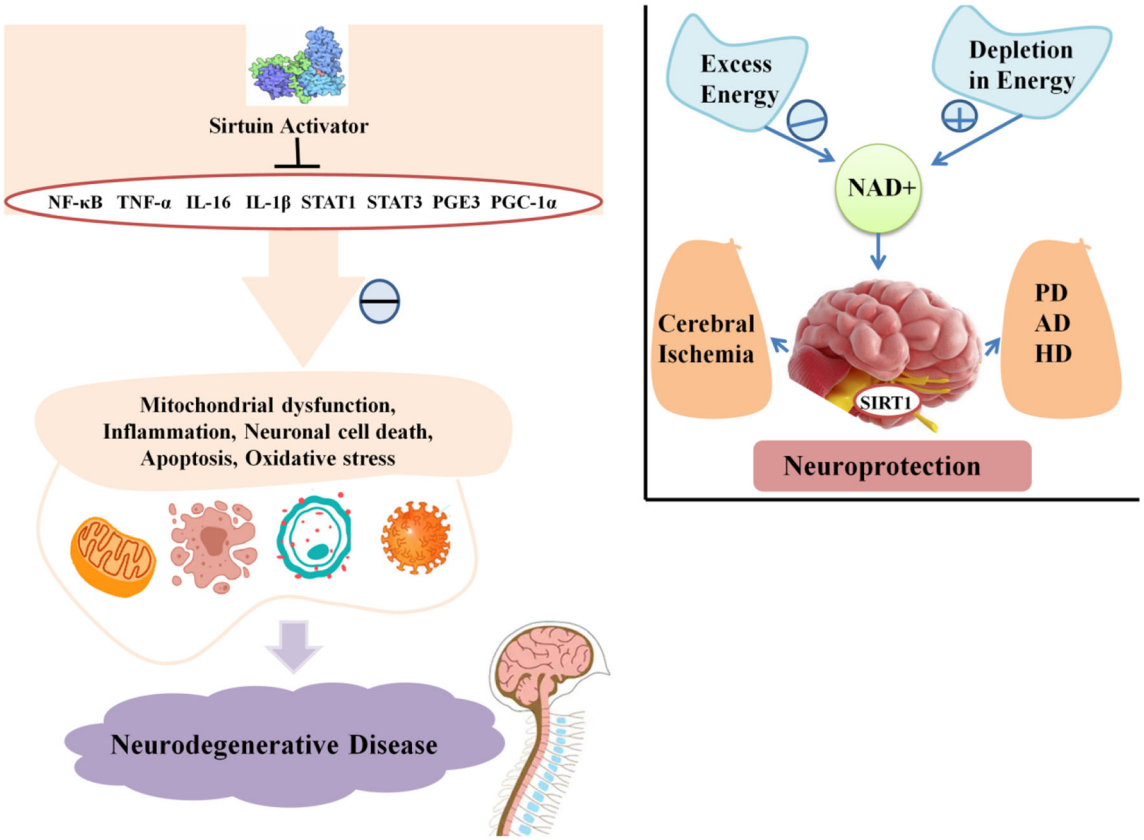

Fig. 1 Sirtuin activator inhibits the different pathways which can have distressing results in terms of mitochondrial dysfunction, inflammation, neuronal cell death, and apoptosis leading to neurodegenerative diseases. In addition, brain SIRT1 exerts neuroprotection against neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD), stroke. Also, appropriate function of brain SIRT1 activity is dependent on NAD+ levels, which increases under energy crisis, and decline with high energy load

signaling and cytosolic energy status. The catabolic reactions such as protein degradation, β-oxidation, glycolysis, and citric acid cycling reduce NAD+ to NADH. When the energy is high, levels of intracellular NADH tend to increase while NAD+ tends to fall, although the ratio always favors NAD+ over NADH. NADH nourishes the mitochondria through "malate-aspartate shuttle or reducing pyruvate to lactate" to join NADH formed via "the citric acid cycle." Irrespective of its origin, NADH gets oxidized in the mitochondria by the ETC as NADH feeds into the ETC via its oxidation to NAD+ [7]. Energy is used to impel protons across the mitochondrial matrix to generate the proton gradient that initiates ATP synthesis through oxidative phosphorylation, produced by subsequent ETC reactions. NAMPT can directly influence the "NAD+/NADH" ratio in the cell. NAMPT overexpression directly increases SIRT1 activity, involving NAD+ concentration in the regulation of SIRT activity. Studies in yeast encouraged the hypothesis that the "NAD+/NADH and the NAD+/nicotinamide ratios" control sirtuin activity as the ratio of NAD+/nicotinamide is the main mechanism of sirtuin regulation [8, 9].

Methodology

A systematic literature review of Bentham, Scopus, PubMed, Medline, and EMBASE (Elsevier) databases was carried out with the help of the keywords like Sirtuins; Histone deacetylases; Acetylation; Deacetylation; Neurodegenerative disease. The review was conducted using the above keywords to understand the molecular nature of sirtuins deacetylation and acetylation in neurodegenerative disease.

Classification of Sirtuins (Fig. 1)

The Sirtuin Family The family of sirtuins is richly conserved, both structurally as well as functionally. The members of this family incorporate in various life forms such as archaea and eubacteria as well as eukaryotes, thus, existing in both the formation of chromatin and histone [1]. Sirtuins, first, revealed their consequences in Saccharomyces cerevisiae. To date, seven members of the sirtuin family have been recognized which are categorized into four classes comprising

"Class I (SIRT1, SIRT2, and SIRT3), Class II (SIRT4), and Class III (SIRT5) as well as Class IV (SIRT6 and SIRT7)" [10].

SIRT1 SIRT1 is the most studied member with different functions, such as cell cycle regulation and energy homeostasis [11]. Various experiments reveal the role of SIRT1 in the pathophysiology of neurodegenerative disorders, metabolic disease, aging, and cancer [12]. Mammalian SIRT1 is composed of both C- and N-terminal extensions serving as a spot for interaction with substrate and regulatory proteins [2]. Sir2, "the mammalian homolog of yeast silent information regulator 2", an NAD+ (nicotinamide adenine dinucleotide)–dependent deacetylase affects a varied range of cell processes via interacting with targets including PGC-1α, p53, FOXOs, NF-κB, and histones (H3 and H4) [13]. In animal models of neurodegenerative disorders, various investigations have revealed that SIRT1 activation can diminish degeneration of neurons in addition to death exerting neuroprotection [14].

SIRT2 SIRT2, a chief protein in the cytoplasm, is known to be co-localized with microtubules and α-tubulin has proved to be its major substrate [15]. Conversely, SIRT2 has known to relocate into the nucleus during the G2/M transitions as well as deacetylase histone H4 at the lysine-16 and modulates condensation of chromatin during the metaphase [16]. Numerous research findings have shown the potential for increased neuroprotection via SIRT2 inhibition concerning PD and HD. Moreover, experiments suggested that SIRT2 inhibition provides protection against neuronal loss in vivo induced via MPTP. Additionally, a recent study proved behavioral as well as neuropathological phenotypic improvement in mouse models of HD via SIRT2 inhibitor which permeates in the brain [17].

SIRT3 Out of all, only the increased expression of SIRT3 has proven to be related to longevity in humans [18]. The localization of SIRT3 has been reported in mitochondria and this placement might have prominent implications in SIRT3 function in the life span [19]. SIRT3 protects against oxidative stress via de-acetylation as well as superoxide dismutase 2 (SOD2) formations [10]. The SIRT3 and UCP4 interaction as well as SIRT3 deacetylation activity may impart essential function to mitochondria. This, in turn, might impair ROS level or augment the consumption of O2, eventually resulting in neuronal protection together with a healthy life-span (Fig. 1) [20].

SIRT4 SIRT4, an ADP-ribosyl transferase, is localized inside mitochondria and is extensively dispersed in tissues of adults as well as fetus, adult thymus, and WBCs. Its sub-cellular location was estimated via confocal microscopy as well as fractionation study, utilizing an epitope-tagged SIRT4 and examination of the endogenous protein. To date, the paramount role of SIRT4 was associated with the regulation of metabolism [21, 22]. The enzyme was discovered in the islets of Langerhans of the β-cells which express insulin and has shown to act on the mitochondrial pancreatic β-cells, also, it might be a chief factor under CR treatment conditions [23].

SIRT5 SIRT5 is a potent desuccinylase and a mitochondrial sirtuin that has a weak deacetylase activity [24]. Human SIRT5 (hSIRT5) is localized at Chr 6p23 and the product of the gene serves as a mitochondrial NAD+ dependent deacetylase having distinct substrates [1]. Studies have revealed that in mitochondrial membrane, SIRT5 interacts with cytochrome C; however, the functional consequence of cytochrome c deacetylation dependent on SIRT5 and particularly, in case, such alteration impacts apoptosis have not yet interpreted [25].

SIRT6 SIRT6, a chromatin-associated protein, combines with sites of DNA double-strand breaks. Its distribution in untreated cells has revealed diverse aggregates in the nucleus that has been shown to co-localize with the heterochromatin protein (HP1β) [26]. SIRT6 exhibits compact binding of NAD+, unlike other sirtuins, in the acetylated substrate deficiency and acts as an H3K9 deacetylase [27]. Observations revealed that SIRT6 affects DNA double-strand break repair via stabilization of DNA-dependent protein kinase on chromatin and favors its union. Finally, under oxidative stress, SIRT6 has been shown to enhance double strands break (DSB) repair and activate the poly-ADP-ribosylase activity of PARP by mono-ADP-ribosylation of PARP1 [16].

SIRT7 The human SIRT7 (hSIRT7) is localized at Chr 17q25 and its genomic sequence comprises a region of 6.2 kb and the gene consists of 10 exons [1]. SIRT7-/- mice, aging prematurely, are characterized via a progeroid phenotype as well as lethal cardiac hypertrophy. SIRT7 translocates from nucleoli to the chromatin and cytoplasm during replicative senescence and can lead to decreased rDNA transcription [28] (Table 1).

Sirtuins as Therapeutic Targets

In the human body, various natural substrates including histones as well as non-histone are present, which upon interaction with sirtuins are concerned in numerous pathways that cause regulation of diverse physiological processes. Consequently, sirtuin regulation might be of therapeutic importance for particular diseases [3]. Small molecule SIRT activators have significant potential as a therapeutic approach for age-associated conditions and specifically neurodegenerative disorders [4]. Developing novel drugs for neurodegenerative disorder prevention needs to be much explored due to very

Table 1 Intracellular and chromosomal location, classes, molecular weight, amino acids, enzymatic activity, function, and target interactions for mammalian sirtuins that have been identified to date

Gene name	Classes	Intracellular localization	Chromosomal location	Activity	Molecular weight	Amino acids	Interactions
SIRT1	Ia	Nucleus, cytoplasmic	10q21.3	Deactylase	81.7	747	PGC-1α, FOXOs, p53, NF-κB, Ku-70, PPAR-γ, p300, pRB, LXR, NBS-1, BCL-6, USP-22, UCP-2, TORC2
SIRT2	Ib	Cytoplasmic	19q13.3	Deactylase	43.2	389	α tubulin, FOXO, histone H4, Phosphoenolpyruvate carboxykinase1 (PEPCK1), H3K18, Keratin-8, RIP1, p300, CDC20
SIRT3	Ib	Mitochondrial Nucleus	11p15.5	Deactylase	43.6	399	GDH complex I, AcCS2, , PGC-1α, OPA1, Ornithine transcarbamylase, IDH2, HMGCS2, LCA, Mitochondrial proteins, JNK2, OGG-1, CypD, Hsp10, KGDHC, LCAD, ATP synthase, NMNAT2, MPC-1, LKB-1, MnSOD
SIRT4	II	Mitochondrial matrix	12q	ADP-ribosyl-transferase	35.2	314	GDH, IDE, ANT
SIRT5	III	Mitochondrial	6p23	Deactylase	33.9	310	Carbamoyl phosphate synthetase 1 (CPSI), SOD1
SIRT6	IV	Nucleus	19p13.1	ADP-ribosyl-transferase	39.1	355	DNA polymerase β, PARP-1, Hif1α, Histones, TNFα, General control non-repressed protein 5, TRF2
SIRT7	IV	Nucleolus	17q25	Deactylase	44.8	400	RNA polymerase type 1, Hif1α, Hif2α, Histones, p53

little progression. A substantial improvement in such therapeutic areas might be possible by the detection of druggable pathways having wide applications across various neurodegenerative disorders [29]. In addition to this, a huge amount of evidence concerning their involvement in diseases such as cancer, cardiovascular disorders, and diabetes has heightened the probability of new therapeutic targets development [30]. The seven human sirtuins signify a novel enzyme targets family that can assist in the regulation of nutrient-sensing as well as utilization, metabolic rate, and metabolic diseases. There has been promising pre-clinical information available for the activation of SIRT3 and SIRT4, yet the prime focus is SIRT1 [31]. The implication of sirtuins in neurodegenerative disorders is attributed to their status as aging, stress response genes, and their high expression in CNS [32]. One of the vital roles of SIRT1 is its function in the promotion of feeding behavior during dietary restricted situations such as calorie restriction (CR) and fasting [33]. Both CR as well as small-molecule SIRT activators have revealed protection in rodent models of neurodegeneration. Resveratrol, the first identified SIRT activator, was shown to inhibit inflammation, excitotoxicity, and microglia-stimulated I/R-induced neurotoxicity [34]. Some polyphenols have been reported to be acting as SIRT1 activators whereas others might exert inhibitory effects on SIRT1. Rutin, a naturally occurring flavonol existent in fruits and vegetables, has been shown to hinder hydrogen peroxide-induced inflammation via suppression of p-NF-κB, p-ERK, p-JNK, and p-38 MAPK expression by SIRT1 activation which extraordinarily blocks the liberation of pro-inflammatory cytokines. On the other hand, in addition to promoting neurite outgrowth and neural plasticity, resveratrol inhibited both SIRT1 expression and its activity and induced FOXO3A hyper-acetylation as well as apoptosis in Hodgkin lymphoma cells and activated MAPK/SIRT1 [35]. SIRT2 is known to be evenly distributed within neurites and cytoplasm as well as their growth cones. SIRT2 can regulate the motility of neurons that strongly depends on the dynamic cytoskeletal properties, especially those of microtubules and actin filaments, and the reason being the SIRT2 capability to cause deacetylation of α-tubulin and β-tubulin. SIRT2 inhibited outgrowth of neurite as well as growth cone collapse in the post-mitotic hippocampus neurons [36]. In rat hippocampus, PGC-1α is induced via SIRT1, whereas SIRT3 is reported to be a chief mediator for PGC-1α-dependent SOD2 and glutathione peroxidase-1 induction. Various experiments established the function of SIRT3 in the positive regulation of MnSOD level as well as activity in several tissues [37]. Conversely, only one study is concerned with the role of SIRT3 in the brain where SIRT3 caused protection against excitotoxic damage in cultured mice cortical neurons suggesting the protective action of SIRT3. Yet, more such observations are required to reveal SIRT3 as well as other sirtuins role in CNS and to resolve the pattern of expression in various brain portions. However, from all the studies carried out on sirtuins, it is evident that these agents revealed exciting role in neurobiology. There is a scope for more evidence to discover

the function of sirtuin homologs in various neurodegenerative disorders. Additionally, it is noteworthy to assess whether sirtuins impact neurodevelopmental disorders assuming their high expression in development as compared to cerebral adulthood [38]. SIRT6 maintains genomic stability in the CNS and the deficiency of this sirtuin results in toxic tau stability as well as phosphorylation demonstrating the therapeutic potential in AD [39]. Studies demonstrate that SIRT3 and SIRT4 are prerequisites for cellular protection via increases in NAMPT as well as mitochondrial NAD+. Whether this protection could also be seen for neurons will be an interesting approach [40]. Activation of a proposed sirtuin family member might represent opposing consequences, reliant on pathophysiological conditions. However, particular SIRT modulators can be of great therapeutic potential against numerous neurodegenerative disorders [41] (Table 2).

Acetylation and Deacetylation of Sirtuins in Neurodegenerative Disease (Fig. 2)

The most studied sirtuins in the context of neurodegenerative diseases are SIRT1 and SIRT2. These inhibit various crucial processes and restore homeostasis of proteins via reduction of toxic protein aggregates, enhance neuronal plasticity through elevation of important gene transcription which is responsible for memory and learning, decrease oxidative stress and thereby increase mitochondrial function together with the suppression of persistent chronic inflammation by inhibition of NF-κB connected with epigenetic mechanisms [41]. In this section, we have reviewed some of the studies based on sirtuins in context to neurodegeneration. It has been observed that modulating the activity of sirtuins affects the progression of various neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and spinal as well as bulbar muscular atrophy [4]. Sirtuins are directly affected by this progression through modulation of transcription factor activity and de-acetylation of proteotoxic species [5, 6]. Acetyltransferases, which transfer an acetyl residue to the ε-amino moiety of particular lysine residues from acetyl coenzyme A in histones and other proteins, catalyze the acetylation and perform chromatin activation in addition to the metabolic pathway regulation. Moreover, lysine deacetylases (KDACs) enzymes remove the acetyl moiety from the lysine of the acetylated proteins. These deacetylases are categorized into four classes including classes I, II, III, and IV [42]. Various observations have suggested that inhibition of SIRT2 has restorative effects in numerous cancers and neurodegenerative disorders.

Alzheimer's Disease

AD has been associated with gene mutations encoding amyloid precursor protein (APP), presenilins (PS1 and PS2), and

Table 2 Enlisting of various SIRT modulators used in clinical trials in neurodegenerative disorders

S. No.	Drug	Category	Mechanism	Status	Reference
1.	Resveratrol	SIRT1 activator	Resveratrol directly activates sirtuins, mimic the effects of caloric restriction and might affect regulatory pathways of diseases of aging, including AD.	Phase 2	NCT01504854
2.	Nicotinamide/Pterostilbene	SIRT1 activator	Nicotinamide riboside (NR) can increase cells' access to NAD and Pterostilben will stimulate sirtuins	Not yet recruiting	NCT04562831
3.	Resveratrol	SIRT1 activator	Resveratrol will improve the function of mitochondria (energy producing components) within the leg muscles	Phase 2	NCT02123121
4.	SEN0014196	Sirtuin inhibitor	To establish the acute phenotypical and biological effects of repeated dose application of SEN0014196q in patients with HD.	Completed	NCT01485952

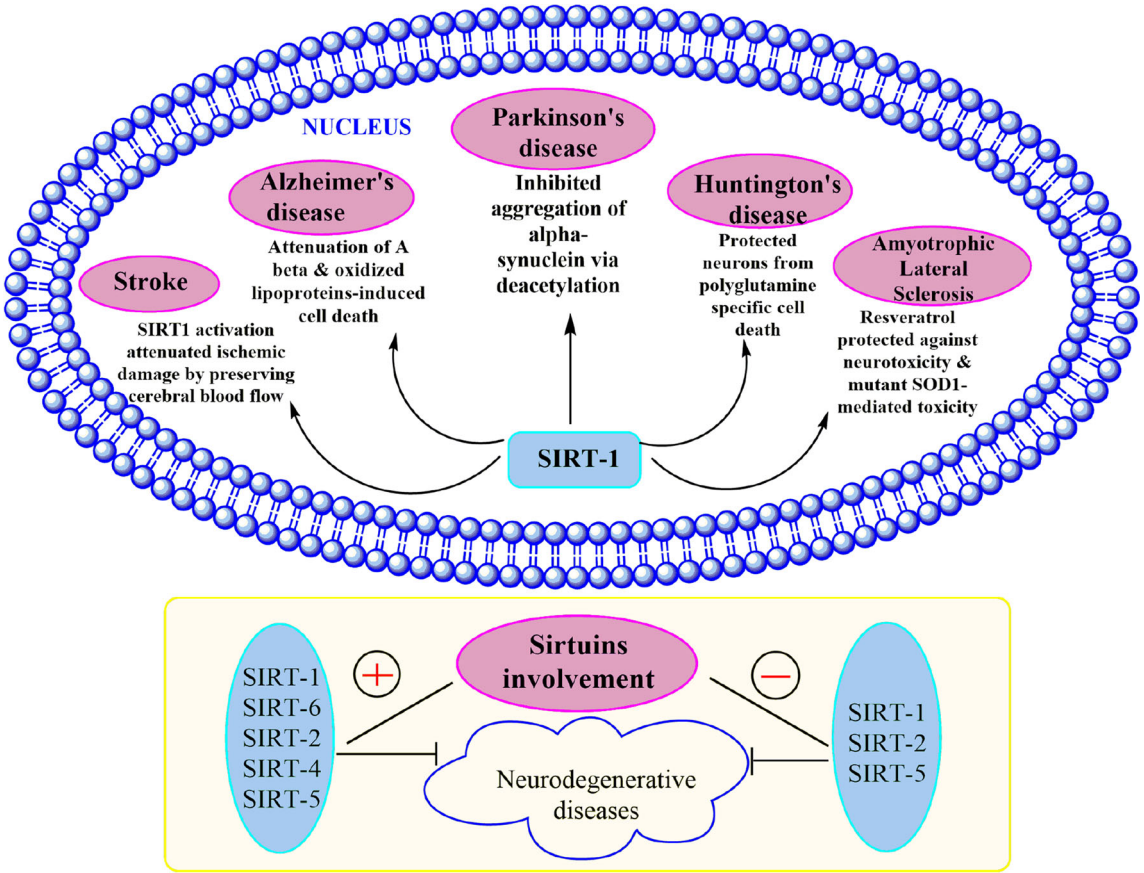

Fig. 2 An overview of SIRT1 role in neurodegenerative diseases and a proper depiction of sirtuin involvement, i.e., activators (+) and inhibitors (-) in order to manage the NDD

ε4-allele of the APOE gene. Cleavage of APP via β- and γ-secretase complexes results in the production of amyloid-β (Aβ) peptides which combine and result in amyloid plaques. These amyloid plaques and neurofibrillary tangles (NFT) consisting of hyper-phosphorylated tau proteins serve to be the pathological hallmarks of AD [38]. Earlier studies highlighting the sirtuin activity modulation might impact pathology of AD revealed that resveratrol (a sirtuin agonist) causes attenuation of Aβ and oxidized lipoproteins-induced cell death in cell culture systems [43]. The APP/PS1 models of AD clearly stated that SIRT1 might enhance Aβ pathology and revealed that SIRT1 overexpression reduced plaque burden, enhanced behavioral phenotypes, and increased α-secretases mediated processing via deacetylation of retinoic acid receptor β (transcriptional activator of ADAM10). ADAM10, being α-secretases constituent, processes APP alongside an anti-amyloidogenic mechanism that can reduce the production of toxic species of Aβ42 [5, 44]. Extensive findings show that tau acetylation improves the tendency of aggregation, affects other post-translational modifications, and decreases phosphorylated tau degradation. Co-localization of tau acetylated proteins on the K280 (lysine residue 280) with the phosphorylated tau in neurofibrillary tangles has been observed in experiments of the human AD brain. The enhanced numbers of acetylated K280-positive NFT were linked with the much-advanced AD phase. Collectively, it has been interpreted that the promotion of deacetylation of tau may prove to be a convincing approach for the inhibition of tau accumulation as well as tauopathies propagation. Though, accretion has been inhibited via acetylation on four lysine residues (Lysine 259, 290, 321, and 353) in the tau microtubule-binding domain via prevention of phosphorylation at those sites. In AD cases, resveratrol might lead to inactivation of SIRT1 expression indirectly and result in neuroprotection. One of the earlier studies demonstrated that mitochondrial ROS augmentation causes an increase in expression of SIRT3 in primary hippocampal cultures [45] (Table 3). Additionally, SIRT3 mRNA is known to be upregulated in a specific spatio-temporal model in the mouse PDAPP model of Alzheimer's disease, which causes an over-expression in human APP that carries the V717F mutation and produces Aβ-plaques in mouse brains [38]. Hereby, the expression of SIRT3 mRNA is increased considerably in AD temporal cortex samples in comparison to matched controls [38]. The dysfunction of SIRT3 results in p53-mediated mitochondrial as well as neuronal damage in AD [47]. In 2017, Kaluski et al. showed that reduced levels of SIRT6 may stimulate neurodegeneration of Alzheimer's patients by

Table 3 Preclinical studies of various sirtuin modulators used in Alzheimer's disease

S. No.	Experimental model	Sirtuin activator (a)/inhibitor (i)	Effect produced	Reference
1	p25 transgenic mice	Resveratrol (a)	SIRT1 activators and molecules targeting the NAD biosynthetic pathway offer AD treatment.	[43]
2	hCMEC/D3	SRT2104 (a)	SIRT-1 activator may dose-dependently relieve the cerebrovascular endothelial damage memory by Aβ	[46]
3.	APP/PS1 models	Resveratrol (a)	SIRT1 might enhance Aβ pathology and revealed that SIRT1 overexpression reduced plaque burden.	[44]
4.	PC12 cells	Resveratrol	Attenuation of amyloid-induced cytotoxicity, apoptotic features, and intracellular ROI accumulation	[45]
5.	PDAPP model	SIRT3 modulator	Attenuation of p53-mediated mitochondrial as well as neuronal damage in AD	[47]

stimulating DNA damage, cell death, and hyperphosphorylation of tau proteins, which are ample in the central nervous system and neurons [48]. Studies demonstrated that expression of SIRT3 has increased in both mouse and human AD pathology. SIRT3 is downregulated in the frontal cortical of human brain APOE4 carriers in comparison to the non-carriers and APOE4 being the chief genetic factor in late-onset AD [49]. Therefore, SIRT3 analysis might assist in AD diagnosis [50]. A clinical study completed in 2016 has shown that daily intake of resveratrol can be helpful in altering the memory loss and daily functioning. Improvement of Ca^{2+} levels, reduction of oxidative stress and inflammation, can be of great help in future treatments to have better results.

Parkinson's Disease

PD, a motor disorder, is a neurodegenerative disorder associated with age, involves loss of dopaminergic neurons from substantia nigra in the brain. PD is also recognized for the aggregation of Lewy bodies (protein inclusions), chiefly including misfolded α-synuclein [51]. A recent study demonstrated that SIRT1 overexpression in the animal, as well as cell systems of PD, suppressed the production of α-synuclein masses via activation of molecular chaperones [52]. Pharmacological or genetic inhibition of SIRT2 has proved to be useful in rescuing α-synuclein toxicity in both in vivo and in vitro animal models of Parkinson's disease [53]. A potent SIRT2 inhibitor inhibited toxicity of α-synuclein as well as reformed inclusion morphology in the PD model. Similarly, α-synuclein toxicity was restricted by genetic inhibition of SIRT2 through smaller restricting RNA [54]. Additionally, SIRT inhibition provided protection contrary to dopaminergic cell death in both in vitro as well as in a Drosophila PD model. Additionally, oligomeric α-synuclein as well as acetylated microtubule interactions was explored as a neurodegeneration source. An augmentation of p53 acetylation by inhibition of SIRT2 lessens cytoplasmic p53 levels, and therefore, blocks the inhibition of cytoplasmic p53 on autophagy [46]. As observed in models of PD, p53 expression is increased and SIRT2 inhibition relieves autophagy function revealing the vital role it performs. Deacetylation of Foxo3a and elevated RNA, as well as Bim protein levels and consequently increased apoptosis in MPTP models of PD, are all mediated via SIRT2. In mice, genetic deletion of SIRT2 prevents chronic MPTP-induced neurodegeneration [55]. SIRT2 deletion leads to decreased apoptosis due to increased acetylation of Foxo3a and decreased levels of Bim [53]. In experimental models of PD, SIRT1 demonstrates neuroprotective activities. SIRT signaling also affects the dopaminergic system as dopaminergic SH-SY5Y cells were protected against the parkinsonian mimetic 6-hydroxydopamine by oxyresveratrol via counteraction of the SIRT-1 downregulation. Resveratrol has also proved to protect the same model and mouse induced by MPTP [37, 56]. Alpha-tubulin is also deacetylated via SIRT2 at Lys40, resulting in reduced stability of microtubules, thereby contributing to neuronal apoptosis [57]. Additionally, SIRT1 also impacts molecular chaperone pathways and prevented aggregation of α-synuclein, as discussed earlier, via deacetylation as well as activation of heat shock factor, HSF-1. The pharmacological potential of SIRT1 has been well explained via various experimental observations for neurodegenerative diseases including Parkinson's disease. Echinacoside (ECH) can enhance symptoms similar to PD in MPTP-introduced mice. The compound has been shown to hasten α-synuclein autophagy via direct conjugation with SIRT1 as well as impacting FOXO expression [58]. The SIRT2 activity in PD is controversial, yet a wide number of studies relate SIRT2 expression with neuronal cell damage and that SIRT2 inhibition might reduce neuronal cell death. AK-1, a sulfobenzoic acid derivative, is a small molecule SIRT2 inhibitor and displayed constant protection. Additionally, AK-1 cerebral delivery via an osmotic mini-

pump has proven to be safe as well as neuroprotective in a mouse FTD model (frontotemporal dementia) based on mutant tau protein expression [59] (Table 4). Furthermore, SIRT3 is likely to have a role in PD, and agents causing an increased level of dulators offer protection against MPP1-induced neuronal damage as well as SIRT-3 manipulation in SHSY5Y cells demonstrated reciprocal effects on cell death induced via rotenone [61]. There are still no clinical data available for the Parkinson's disease. Many pre-clinical studies are in progress to provide a therapeutic approach. Scientists should focus on the molecules that destabilize the factors which mediates cellular responses to low oxygen concentration and induces cell cycle arrest, rescue differentiation.

Huntington's Disease

Huntington's disease (HD), an autosomal-dominant neurodegenerative disease, is a rapid and gradual neuronal loss, mainly in the striatum and the cortex that leads to muscle coordination impairment, dementia addition to cognitive decline.

Table 4 Preclinical studies of various sirtuin modulators used in Parkinson's disease

S. No.	Experimental model	Sirtuin activator (a)/inhibitor (i)	Effect produced	Reference
1.	A53T mouse model	Sirt 1 activator	Activation of SIRT1 in the brain is useful in treating α-synuclein aggregation and related toxicity	[52]
2.	MPTP mouse model	Resveratrol (modulator of SIRT 1)	Resveratrol can be regarded as powerful preventive therapy of neurodegenerative diseases.	[56]
3.	Cellular Models of Parkinson's Disease	Resveratrol (a)	SIRT1 activator RES prevented "oxidative stress, b (1-42) peptide (Ab42) and and the familiar Parkinson's disease" linked a-synuclein (A30P) [a-syn(A30P)].	[60]
4.	FTD model (fronto--temporal dementia	AK1 (i)	SIRT2 inhibitors would be a good therapeutic avenue for tauopathies including FTD and Alzheimer's disease.	[59]

SIRT1 upregulations or treatments with resveratrol-recovered neurons from the Huntington (HTT) induced damage in a Caenorhabditis Elegans HD model [62]. SIRT2 loss or decrease had no impact on α-tubulin or H4K16 acetylation or biosynthesis of cholesterol in the brain of wild-type mice. Besides, as assessed through a series of behavioral as well as physiological tests, SIRT2 ablation or genetic deletion had no impact on the progression of HD. Therefore, SIRT2 inhibition is unable to control disease progression in the R6/2 mouse HD model and SIRT2 inhibition has been chosen as the therapeutic approach for HD [63]. Sirtuins represent remarkable insights as a pharmacological approach for HD, as their targets are associated with survival as well as metabolic signaling pathways, leading researchers to explore their function in HD [63]. SIRT1 is the utmost significant sirtuin for epigenetic regulation that is a central process for metabolic control and transcription which is disturbed in HD [64]. SIRT1 deficiency impairs HD phenotype while elevating SIRT1 genetically demonstrates neuroprotective action in various mouse HD models. Numerous associations exist amongst the SIRT1 deacetylation function and its neuroprotective role. Ultimately, the therapeutic approach for HD could be achieved by pharmacological interventions targeting SIRT1 [65]. Increased neuronal survival, as well as CREB-regulated TORC1 (transcription coactivator 1) and BDNF (brain-derived neurotrophic factor), is activated via SIRT1 in HD. However, SIRT2 inhibition is of therapeutic importance in HD via decreasing both neuronal cholesterol and SREBP2 trafficking [66]. Also, studies demonstrate that resveratrol treatment offered protection to neurons that overexpress a Huntington portion from cytotoxicity mediated via Huntington in a daf-16-dependent approach in C. elegans HD models. Furthermore, in a mouse HdhQ111 knock-in model, resveratrol protected neurons from polyglutamine-specific cell death [54]. Mutant Huntington also caused mitochondrial function impairment via inhibition of PGC-1α expression in mouse HD model [67]. After that, in HD subjects and HD transgenic mice striatum, decreased expression of the PFC-1 alpha target gene was reported [68]. Subsequently, regulation of PGC-1α activity can be attributed to SIRT1, and thereby, it can be concluded that upregulation of the proposed pathway triggers SIRT1 neuroprotection in HD models [69]. A new thiazole-containing deacetylase SIRT2 inhibitor has been found to have neuroprotective effects, as shown in both the ex vivo brain slice and the Drosophila HD model [70]. Selisistat, a highly specific SIRT1/SIRT2 inhibitor, is effective in suppressing HD pathology in mammalian cells, Drosophila, and mouse models, creating an excellent approach for SIRT1-lowering human regimens to make the compound, in addition to various other diseases, an effective drug for the treatment of HD [71] (Table 5). Sirtuin deacetylases have been investigated in various studies as therapeutic targets for delaying HD progression. In polyglutamine cytotoxicity

Table 5 Preclinical studies of various sirtuin modulators used in Huntington's disease

S. No.	Experimental model	Sirtuin activator (a)/inhibitor (i)	Effect produced	Reference
1.	N171-82Q transgenic mouse model	SRT501-M (a)	Resveratrol-induced activation of SIRT1 is an effective therapy in n brown adipose tissue (BAT), in HD transgenic mice.	[72]
2.	3-NP-induced neurotoxicity	Resveratrol (a)	Resveratrol may have therapeutic benefit in the treatment of HD	[73]
3.	N171-82Q and BACHD mouse models of HD	SIRT 1 activator	SIRT1 activators with high specificity and bioavailability may represent a promising approach for the treatment of HD.	[74]
4.	R6/2 mice	SIRT modulator	TORC1-CREB pathway plays a Critical role in mediating SIRT1 neuroprotection in HD model	[75]
5.	Mouse models of HD	Selisistat (i)	Suppression of HD pathology in mammalian cells and mouse models	[71]

nematode models, both resveratrol treatment and SIRT1 genetic over-expression are neuroprotective [72]. On the other hand, the Drosophila models indicate the contrary, with pharmacological reductions of SIRT1 or SIRT2 summarized neuroprotection [76]. In these animal models, the effect of sirtuins on HD pathogenesis is different and the reason has yet to be identified. A randomized interventional clinical trial was conducted to determine the safety and tolerability following repeated doses of SEN0014196 (EX-527/selisistat) over two weeks at two dose levels in patients with Huntington's disease. Gene transcription could potentially be used in the future to help with the treatment of Huntington's disease. Pathways with a unique approach should be considered given with the drug. This will help to attain a therapeutic target for the disease.

Stroke

The energy metabolism impairment induced by ischemia is a vital factor responsible for brain damage as well as recovery [77, 78]. A cellular disturbance of histone and other protein acetylation has been considered a common aspect of neurodegeneration in addition to the well-defined mechanism of cell death (say calcium, acute inflammation, excitotoxicity, and apoptosis) [79]. The use of HDAC (histone deacetylase) inhibitors based on the intense effect of histone acetylation on gene expression has been estimated in stroke and TBI studies in recent years [80]. These inhibitors elevate the levels of histone acetylation, suppress transcription factors (p53), and decrease the inflammatory gene expression (IL-1β, COX), and increase the extracellular clearance of glutamate, or stabilizes the integrity of mitochondria and thereby, exerts neuroprotection [81]. Although researches have mainly focused on Class I and II family members of HDAC inhibitors, more insights are needed for the HDAC III inhibitors in regard to ischemia [80]. Sirtuins are HDAC proteins that are dependent on NAD+ and associated with a variety of cell functions that relate to cell phase regulation, aging, and cell metabolism [82]. SIRT3 is one of seven known human SIRTs. It is the primary regulator for various important proteins in the mitochondria's energy metabolism. For instance, glycolytic metabolism is increased due to SIRT3 loss which permits the metabolically challenged cells to sustain extensively. Therefore, SIRT3 loss may elevate the glycolytic metabolism and assist in maintaining the survival of the vulnerable neurons. Additionally, SIRT1, a leading sirtuin located in the nucleus, coordinates with SIRT3 to proliferate cellular energy stores maintaining cellular energy homeostasis. Several studies have reported that both SIRT1 and SIRT3 favor transcriptional repression of nuclear genes that encode proteins concerned with metabolic stress sensing or deacetylating non-histone proteins (liver kinase B1; LKB1) [83]. LKB1, a nuclear enzyme, is activated via deacetylation together with the conventional activation by 14-3-3 family proteins. LKB1 deacetylation stimulates the cytosolic translocation from the nucleus and thereby, facilitating the activation further resulting in I/R injury. Hence, it has been concluded that SIRT3 loss could be of therapeutic importance in stroke, possibly mediated via LKB1 activation inhibition. Earlier research has shown that SIRT3-mediated deacetylation may reactivate metabolic enzymes that help to survive the need for increased ATP formation through mitochondrial β-oxidation during ischemic stress [84]. A substantial elevation in acetylation of p53 as well as NF-κB (p65) post SIRT1 inhibition/deletion has been observed regarding the mechanism concerning SIRT1- induced neuroprotective action. The increased acetylation may illuminate the associated elevated ischemic damage, assuming the role of both proteins in the pathophysiology of stroke [85]. In a study published as recently as 2017 in Neuroscience, studies on SIRT6 showed that it may be responsible for protecting the brain from cerebrovascular ischemia and may be identified as a potential therapeutic target for ischemic stroke [86]. In conclusion, SIRT1 plays a vital role in endogenous neuroprotective effects as its inhibition may aggravate ischemic damage associated with elevated

p53 and p65 acetylation, leading mediators of both inflammatory and apoptotic pathways resulting in brain injury in this situation [87] (Table 6). Resveratrol has a free radical scavenging and antioxidant effects due to which it has a potential to protect the cells against oxidative stress and ischemia/reperfusion (I/R) induced neuronal death. There is a clinical trial showing the role of resveratrol in improving physical function by studying the changes in mitochondrial function and physical function. Drugs which promote neuron survival, neurological improvement, and prevent the expressions of eNOS, VEGF should be used in future studies.

Amyotrophic Lateral Sclerosis

ALS, the most common motor neuron disease, is a greatly progressive disease that impacts the strength of muscles and coordination. Over the past two decades, unintentional mutations in a functionally varied range of genes such as TDP43, SOD1, UBQLN, and FUS have been explored, in addition, various etiologies have been anticipated which emphasize diverse facets of disease progression [90]. Recent research revealed that such genes might get changed in diseased sporadic forms to perform a vital role in familial ALS [91, 92]. The role of SIRT1 in the loss of neurons with age has also been observed in ALS. The fundamental causes of neuromuscular junction attenuation, as well as subsequent motor neuronal death in ALS, have not yet been determined. The SOD1 (G93A) mutant mouse is a less commonly used animal ALS model. As already discussed, resveratrol has shown to enhance motor function as well as survival in the SOD1 mouse model by modulating p53 acetylation [93]. Alteration in SIRT1 deacetylase activity showed no impact on protein levels in the healthy aged organism. Nevertheless, treatment with resveratrol did not improve function or elevated longevity in mouse ALS models [94]. Region-specific alterations were observed in the immunoreactivity of SIRT1 expression in CNS in similar mouse models. SIRT1 elevated cerebral cortical pyramidal cells, CA-1 hippocampal pyramidal cells, and dentate gyrus cells, spinal cord, and thalamus [53]. One of the studies revealed that transgenic mice expressing a mutant SOD1 demonstrated motor neuron as well as axon degeneration in the spinal cord. Upregulation of SIRT1 in ALS mouse models and neuronal cell cultures treated with ionomycin and hydrogen peroxide was observed. Resveratrol treatment offered protection against neurotoxicity prompted via SOD1G93A, which was equivalent to the reduction in PGC-1α acetylation, signifying that resveratrol acts via the SIRT1 pathway in ALS models [95] (Table 7). In 2020, a study has been started with nicotinamide riboside/pterostilben for the treatments of amyotrophic lateral scleroses which increases the cell access to NAD+ and stimulates sirtuins. Nicotinamide riboside is a precursor of NAD^+ which will to regulate sirtuin function and protect against neurodegenerative disease. This combination can also be used in other NDD like Huntington's or Parkinson's. Combination of any other analog of resveratrol and NAD+ can also be a striking target for future studies.

Modulators of Sirtuin Activity

Modulation of sirtuins can improve pathological conditions. So, it is important to take measures to identify compounds that activate or inhibit specific sirtuins. Studies mostly include SIRT1 modulators (main nuclear sirtuin) as compared to other sirtuins but they may prove to be likewise attractive targets for the modulators. Coming on the biochemical activation of sirtuin, which is NAD+ dependent, is directly linked to the energetic and redox status of the cell as measured by the NAD+:NADH ratio, absolute levels of NADH, NAD+, and NAD+ catabolite, nicotinamide [98, 99]. There are two arbitrator steps in the generation of NAD+ which is initiated by

Table 6 Preclinical studies of various sirtuin modulators used in ischemic injury

S. No.	Experimental model	Sirtuin activator (a)/ inhibitor (i)	Effect produced	Reference
1.	Primary cortical neurons	AK1 and AGK2 (i)	Reduced apoptotic cell death via SIRT2 inhibition and downregulation of Akt/FOXO3a and MAPK pathway under in vitro ischemic conditions	[87]
2.	SIRT1 homozygous mice	• Activator 3 (a) • Sirtinol (i)	Mice treated with activator 3 showed reduced infarct sizes and, on the other hand, mice treated with sirtinol attenuated ischemic injury	[85]
3.	Adult male Balb/c mice	Resveratrol (a)	Neuroprotective effect on delayed phase after focal cerebral ischemic injury	[88]
4.	Primary cortical neurons	Icariin (a)	Increases SIRT1 expression and has neuroprotective effects	[89]

Table 7 Preclinical studies of various sirtuin modulators used in amyotrophic lateral sclerosis

S. No.	Experimental model	Sirtuin activator (a)/inhibitor (i)	Effect produced	Reference
1.	SOD1 G93A mutant mouse	Resveratrol (a)	No improvement in function or elongation of longevity in mouse ALS models	[94]
2.	SOD1 G93A transgenic mice	AK7 (i)	No significant effect on disease onset or survival	[96]
3.	SOD1 G93A transgenic mice	HDAC6 deletion	Extended the survival of animal, maintenance of motor axon integrity.	[97]
4.	Rat cortical primary neurons transfected with SOD1 G93A gene	Resveratrol (a)	Attenuation of SOD1-G93A mediated neurotoxicity	[43]

the conversion of NMN via the NAMPT enzyme and NMNAT then converts "NMN to NAD+". NAMPT has been recognized as the "rate-controlling step" in the biosynthesis of NAD+ where overexpression of NAMPT increased cellular NAD+ levels. Still, distinct subcellular pathways control NAD+ biology which is being investigated with the identification of a "mitochondrial-enriched NMNAT isoform" [100].

Sirtuin Activators

The biochemical activation of the activity of sirtuin relies on nicotinamide adenine dinucleotide (NAD+). Sirtuin activation, as measured by the NAD+: NADH ratio, the absolute levels of NAD+, NADH, and the NAD+ catabolite, nicotinamide, may affect the energetic and redox status of the cell. Polyphenols are the secondary metabolites of plants that represent a large group of compounds containing one or more hydroxyl groups with aromatic rings. Resveratrol, found in red wine and grape skins, increases the affinity of sirtuin1 for substrates of acetylated peptides. Resveratrol promoted Pparg coactivator 1 alpha (PGC-1α) deacetylation via sirtuin1, resulting in decreased insulin resistance, body weight, and increased motor survival and function in mice with high-fat diet-induced obesity. Compounds such as SRT1460, SRT1720, and SRT2183 were found to be more potent than resveratrol and activate sirtuin1 [101]. SRT1720, being the most promising sirtuin1 activator, SRT1720 also improved the glucose homeostasis, mitochondrial function, and increased sensitivity to insulin in mouse models of type 2 diabetes [102]. SRT2 proved to be neuroprotective in mouse models of Huntington's disease and has been also tested for Phase IIa trial in patients with metabolic, cardiovascular, and inflammatory diseases. Several clinical trials have been accomplished to estimate safety, tolerability, pharmacokinetics, and bioavailability of SIRT activators [103].

Sirtuin Inhibitors

Studies have shown that sirtinol, a cell-permeable inhibitor of sirtuin NAD+-dependent histone deacetylases, reduces inflammation in the skin's capillary endothelial cells as a target for skin disorders. Cambinol is a chemically stable compound that shares a β-naphthol pharmacophore with sirtinol and splitomicin, eventually inhibiting both sirtuin1 and sirtuin2 in vitro. Cambinol competes with polypeptides that are acetylated, indicating that it binds close to the site of substrate binding. Several studies have shown that cambinol is well tolerated in mice and inhibited the development of xenografts of Burkitt lymphoma by inducing apoptosis and hyperacetylation of oncoprotein BCL6 and p53 [104]. Another is Suramin, a derivative of urea that shows similar characteristics and competes with both the substrate's acetylated lysine and NAD+ for binding. However, it is known that it has a neurotoxic activity that limits its therapeutic use. Indole derivatives, selisistat (EX-527), a selective sirtuin1 inhibitor, can easily penetrate cells, and oxindole, a selective sirtuin2 inhibitor, inhibits α-tubulin deacetylation in MCF-7 mammary cells [103]. Administration of selisistat might strongly increase the p53 protein acetylation at K382 following the initiation of DNA damage in tumor cell lines and human mammary epithelial cells. Selisistat shows neuroprotective activity in both mitotic and postmitotic mammalian cellular Huntington's disease models [105]. AK7, a SIRT2 inhibitor reveals neuroprotective effects in Parkinson's disease, Huntington's disease models, and other neurodegenerative disorders. Treatment with AK7 protects dopaminergic neurons against aSyn-induced neurotoxicity, dopamine loss, and preserves functional performance. AGK2, a potent sirtuin2 inhibitor, induces cell death and decreases the ATP level intracellularly. AGK2 treatment led to an increase in acetylated tubulin, increased necrosis of pheochromocytoma (PC12) cells without affecting autophagy, and induced caspase-3-dependent apoptosis in C-6 glioma cells. In addition to AGK2, mutant α-syn neurotoxicity, dopaminergic neuron degeneration from α-syn toxicity gets ameliorated via sirtuin2 inhibition. Salermide, a reverse amide and a sirtuin1 and sirtuin2 inhibitor, was well tolerated by mice at conc. up to 100 mm and promotes apoptotic neuron death induced by mechanical injury in vitro and in vivo [106].

Conclusion Remarks

In neurodegeneration, sirtuins are known to block multiple key processes. Sirtuins restore protein homeostasis via reducing toxic protein aggregates and improve neural plasticity via elevating gene transcription. This is important for learning, memory, and enhancing mitochondria function by decreasing oxidative stress, and chronic inflammation via several mechanisms. The effects of sirtuins and their regulation are extremely complex. Extensive sirtuin activation leads to histone deacetylation and various non-histone proteins, affecting different cellular functions, e.g., both SIRT1 and SIRT2 appear to have conflicting effects on the misfolded aggregation of proteins [107]. Sirtuin activation may have deviant results, depending on pathophysiological circumstances. Still, specific modulators of sirtuin could have an extensive therapeutic prospective against various neurodegenerative disorders. More studies are needed to investigate the inconsistencies and develop new activators that can allow BBB and improve the functions of the CNS in NDD models. The overconsumption of NAD+ (the bio-energetic molecule in the cell) is one of the potential problems associated with SIRT1 activation, as energy depletion has been a major factor in NDD neuronal cell death [108]. Sirtuins thus have great potential in neurodegeneration as therapeutic targets. Despite having sufficient data, the feasibility of emerging sirtuin-based therapy for NDD has yet to be shown in animal models and human trials as the safety of human subjects are the main concern in the development of novel therapies.

Abbreviations NAD+, nicotinamide adenine dinucleotide; NDD, neurodegenerative disease; AD, Alzheimer's disease; PD, Parkinson's disease; HD, Huntington's disease; ALS, amyotrophic lateral sclerosis; NMN, nicotinamide mononucleotide; NAMPT, nicotinamide phosphoribosyltransferase; NMNAT, nicotinamide/nicotinic acid mononucleotide adenylyltransferase; ETC, electron transport chain; eNOS, endothelial nitric oxide synthase; VEGF, vascular endothelial growth factor

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Declarations

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