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ORIGINAL PAPER

PGC-1α, Sirtuins and PARPs in Huntington's Disease and Other Neurodegenerative Conditions: NAD+ to Rule Them All

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Abstract
In this review, we summarize the available published information on the neuroprotective effects of increasing nicotinamide adenine dinucleotide (NAD^+) levels in Huntington's disease models. We discuss the rationale of potential therapeutic benefit of administering nicotinamide riboside (NR), a safe and effective NAD^+ precursor. We discuss the agonistic effect on the Sirtuin1-PGC-1α-PPAR pathway as well as Sirtuin 3, which converge in improving mitochondrial function, decreasing ROS production and ameliorating bioenergetics deficits. Also, we discuss the potential synergistic effect of increasing NAD+ combined with PARPs inhibitors, as a clinical therapeutic option not only in HD, but other neurodegenerative conditions.

Keywords Huntington's disease · NAD^+ · Nicotinamide Riboside · Sirtruins · PGC-1 alpha · PARPs

Introduction

Mitochondrial dysfunction and ROS production are a common pathogenic features present among many neurodegenerative conditions, such as Alzheimer's, Parkinson's and Huntington's disease (HD). HD is an autosomal-dominant neurodegenerative disorder that is considered as the flagship for studying the pathogenic pathways involved in neural death as well as for devising therapeutic intervention strategies. This is because its monogenetic cause, the relative precision to predict the age of onset, its neural specificity and availability of different pre-clinical models that re-capitulate the human phenotypes. More importantly, the number of patients suffering from this condition for which there is no current effective treatment or cure. The mutation consists of an expansion of an unstable CAG repeat located in exon 1 of the gene *IT15*. This results in a poly-glutamine expansion (> 36) in the protein product, mutant huntingtin (mHtt) [1]. HD is characterized by striatal degeneration, behavioral and cognitive impairments, and involuntary choreiform movements. The toxic effects of mHtt include transcriptional dysregulation, oxidative damage, excitotoxicity and bioenergetic defects [2–4]. One element in which all these pathways seem to converge is PGC-1α, whose activation is modulated, among others, by the NAD^+ dependent deacetylase Sirtuin 1 (SIRT1). NAD^+ cellular levels also regulate two other targets of interest in neurodegeneration: Sirtuin 3 (SIRT3), and Poly (ADP-ribose) polymerase 1 (PARP1). SIRT3 is a mitochondrial deacetylase that regulates mitochondrial transcription in response to ROS stress. PARP1 is a member of a family of enzymes that polymerize ADP ribose units using NAD^+ as a substrate and transfers them to acceptor proteins in response to DNA damage, and events such as chromatin remodeling, nuclear transcription, and cellular death [5]. Based on the role that NAD^+ plays in all these pathways that are altered in HD, we discuss the rationale for its potential therapeutic value.

PGC-1α and HD

PGC-1α is a transcriptional co-factor involved in energy production and mitochondrial biogenesis, cellular respiration and ROS detoxification. Its activity is regulated in different tissues through many stimuli such as: exercise, in the muscle; cold, in brown fat [6]; and fasting, in the

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liver [7]. It induces glucose uptake and fatty acid oxidation (muscle), adaptive thermogenesis (brown fat) and gluconeogenesis and beta-oxidation of fatty acids (liver) [8–10].

At a cellular level, there are different signaling pathways that control PGC-1α expression and activity. PGC-1α increases its own expression by an auto-regulatory loop [11]. Post-translational modifications such as phosphorylation by AMPK and p38 MAPK; methylation by PRMT1 and de-acetylation by SIRT1 promote its activity [12]. Phosphorylation by AKT and CLK2; SUMOylation by SUMO1 and acetylation by GCN5 represses it [13–16]. It is also modulated by cAMP, Ca^{2+} and CREB [17–20].

Key findings reported in the literature point towards PGC-1α as a key player in the pathogenesis of HD. Sequence variation in the PGC-1α gene modifies age of onset of HD [21–24]. Reported phenotype of PGC-1α knockout mice show a spongiform pattern of neurodegeneration in the striatum, as well as a marked behavioral hyperactivity phenotype reminiscent of HD [25, 26]. Also, defects in myelination are present in PGC-1α KO mice as well as in R6/2 and BACHD HD transgenic mouse models [27]. Striata from HD patients, knock-in HD mice, and striatal $STHdh^{Q111}$ cells (a homozygous cell-based HD model, [28]), show marked reductions in PGC-1α mRNA levels, and huntingtin interferes with the CREB/TAF4 complex [29]. Expression of PGC-1α is reduced in medium spiny neurons and its down-regulation worsens behavioral and neuropathological abnormalities in a PGC-1α knock-out-/HD knock-in mice (PGC-1α KO/KI) [29]. Microarray expression data from human brains from HD patients showed significant reductions in 24 out of 26 PGC-1α target genes [30]. PGC-1α mRNA is reduced in N171-82Q HD mice. Significant hypothermia was found in both N171-82Q and R6/2 HD mice, due to impaired PGC-1α induction of uncoupling protein 1 (UCP-1) [30]. Stimulation of extra-synaptic NMDA receptors impairs the PGC-1α cascade in HD mice [31]. There is impaired PGC-1α and PGC-1β function in HD transgenic mice, and in HD human muscle biopsies, and human myoblasts [32, 33]. PGC-1β is a homologue of PGC-1α, which is abundantly expressed in heart, skeletal muscle, brown adipose tissue and brain and is involved in mitochondrial biogenesis [34].

There is a markedly impaired ability to upregulate PGC-1α in response to an energetic stress in HD transgenic mice [32, 33]. Reductions in numbers of mitochondria in striatal spiny neurons that are HD pathologic grade-dependent correlate with reductions in PGC-1α and TFAM [35]. Mitogen- and stress-activated protein kinase 1 (MSK-1), which upregulates PGC-1α, is deficient in the striatum of HD patients and mice [36]. PGC-1α reduces oxidative stress, by increasing expression of copper/zinc superoxide dismutase (SOD1), manganese SOD (SOD2), catalase and glutathione peroxidase (GPx1) [37]. CREB regulates PGC-1α activity in response to H_2O_2, and stimuli such as exercise [8, 37, 38].

Overexpression of PGC-1α in the N171-82Q HD transgenic mice ameliorated motor deficits and it attenuated neurodegeneration, partly by alleviating oxidative stress [39]. It also virtually eliminated huntingtin aggregates by activating the transcription factor TFEB, a master regulator of the autophagy-lysosome pathway. PGC-1α and PGC-1β overexpression in rat cortical neurons co-transfected with a human huntingtin exon containing a 120 CAG expansion restores cell survival and increases mitochondrial density [40]. Indirect activation of PGC-1α by means of mitogen- and stress-activated kinase (MSK-1) [36], and by adipose-derived stem cells (ASCs) exosomes [41] restores mitochondrial function. Next, we present the neuroprotective effect observed by increasing active PGC-1α in HD through its modulation by sirtuins 1 and 3.

Sirtuin 1 and Sirtuin 3 in HD

Sirtuins are a family of class III histone deacetylases whose activity depends on NAD^+. In humans, there are 7 known sirtuins (SIRT1-7) classified mainly by their cellular localization (reviewed [42, 43]). SIRT1 and SIRT3 are of special interest in HD.

SIRT1 mRNA and protein levels are decreased in brain tissue from HD patients [44, 45]. An important role of SIRT1 in mediating neuroprotection was reported when SIRT1 overexpression showed a protective effect against motor dysfunction, and cortical and striatal atrophy, and loss of striatal neurons in both N171-82Q and BACHD transgenic mouse models of HD [46, 47]. Brain-specific knockdown of SIRT1 exacerbated brain pathology while overexpression protected in the R6/2 transgenic mouse model of HD [46]. The protective effect required the presence of TORC1. The expression of BDNF, which is lowered in HD [48], was identified as a key target of SIRT1 and TORC1 transcriptional activity. Mutant Htt interfered with TORC1/CREB to repress BDNF transcription, and SIRT1 rescued the defect both in vitro and in vivo. Interestingly, another report shows that BDNF stimulates PGC-1α dependent mitochondrial biogenesis and dendritic spine formation and synapses in the hippocampus [49]. In cell culture studies beta-catenin enhanced mutant huntingtin toxicity, whereas SIRT1 overexpression protects and reduces FOXO and beta-catenin signaling, and increases mitochondrial uncoupling protein expression [50]. Treatment of R6/2 HD mouse model with Beta-Lapachone (3,4-dihydro-2,2-dimethyl-2H-naphthol[1,2-b]pyran-5,6-dione), a small molecule obtained from the bark of the Lapacho tree, increases the levels of expression of SIRT1 and PGC-1α and ameliorates motor and mitochondrial

dysfunction [51]. Resveratrol, a phenolic compound found in red grapes and red wine, activates SIRT1 and has been tested in HD models. Resveratrol treatment of a *C. elegans* model of HD was neuroprotective through activation of SIRT1 and PGC-1α [52, 53]. Resveratrol administration by oral gavage treatment (25 mg/mouse/day) of the N171-82Q transgenic mouse model of HD showed protection against mutant Htt damage on peripheral tissues [54]. Resveratrol treatment of HD cell models and sub-cutaneous treatment in a YAC128 mouse model at a dose of 1 mg/kg/day ameliorates rotarod performance, even when the model has developed striatal atrophy [55]. There is currently an ongoing clinical trial (Clinicaltrials.gov ID: NCT02336633) testing the effect of resveratrol on the rate of caudate volume loss in HD patients.

However, the use of Nicotinamide (NAM) as a NAD + precursor has sparked some controversy around the neuroprotective role of activating or inhibiting SIRT1 in HD. NAM treatment of HD R6/1 mice, delivered orally or by osmotic pumps at a 250 mg/kg/day was reported to ameliorate behavioral phenotypes (rotarod, open field and balance beam) as well as increased BDNF and PGC-1α mRNA in mouse brain [56]. NAM treatment in conjunction with co-enzyme Q10 showed a neuroprotective effect in striatal lesions of mice treated with the mitochondrial toxin malonate [57].

On the other hand, NAM has been reported as an inhibitor of SIRT1 [58]. Acetylation of mutant Htt at residue K444 in HD cell, mouse and human samples has been shown as a modification that signals its degradation by autophagy. Treatment with HDAC inhibitors trichostatin A along with NAM of N2A and rat primary cortico-striatal neurons transfected with N-terminal fragments of mutant huntingtin show neuroprotective effects. This treatment increased the K444 mutant Htt acetylated form, which in turn was targeted for autophagy [59]. In in a fly model of HD, NAM showed a reduction of degenerated photoreceptors [60]. NAM treatment of primary cortical and striatal neurons derived from YAC128 HD mice and HD human lymphoblastoid cell lines cells resulted in improvement of mitochondrial function. In vivo studies report that when NAM was subcutaneously administered in YAC128 HD mice in a chronic regimen, mitochondrial genes related to the electron transport chain were downregulated and motor dysfunction in HD mice was worsened [55]. In contrast, treatment of a 3-NP rat model showed motor improvement and neuroprotective effects [61].

These contradictory results with the use of NAM as an agonist or antagonist of SIRT1 may be due to the dosages and the route of administration of NAM. NAM can inhibit SIRT1 at certain doses, but it also can be used as a precursor of NAD^+ (reviewed in [62]). Selisistat, a very potent SIRT1 inhibitor, has shown to be neuroprotective in fly, cell (PC-12 and rat primary cortico-striatal overexpressing an 82Q N-terminal Htt fragment), and the R6/2 HD mouse model [63]. Clinical trials in healthy controls [64] and HD patients showed that Selisistat is relatively well tolerated. However, there was no evidence of its efficacy since there was no change in soluble mutant huntingtin in both groups [65, 66]. These apparent contradictory results derived from the activation or inhibition of SIRT1 might be caused by different pathways that are controlled by SIRT1 and/or the possible role played by another sirtuin: SIRT3.

SIRT3 is a NAD + dependent deacetylase mainly located in the mitochondria. Knockdown of SIRT3 increases levels of oxidative stress in cultured myoblasts [67]. SIRT3 activity prevents formation of the mitochondrial permeability transition pore by deacetylation of cyclophilin D [68]. SIRT3 activation by NAD^+ prevents cell death [69] and protects against excitotoxicity [70]. SIRT3 regulates succinate dehydrogenase and has other effects to maintain mitochondrial integrity [71, 72]. SIRT3 effects in mitigating ROS may be in part due to increased activity of ROS detoxifying enzymes such as mitochondrial SOD2 (SOD2), which is activated by SIRT3 deacetylase activity [73, 74]. The ability of SIRT3 activation to enhance fatty acid oxidation may also be beneficial in many conditions [75–78].

Human genetic studies show that a single nucleotide polymorphism or a variable number of tandem repeats in SIRT3 are associated with longevity in man [79]. SIRT3 deficient mice do not respond to caloric restriction with a reduction in oxidative stress, and they do not increase their SOD2 activity, which is dependent on deacetylation of two critical lysine residues [76]. The SIRT3 deficient mice also show an enhanced susceptibility to cardiac hypertrophy. SIRT3 prevents age-dependent hearing loss, which is ameliorated by caloric restriction in normal mice, but not in SIRT3 deficient mice [80]. This is related to its activation by isocitrate dehydrogenase, which leads to an increase in NADPH and mitochondrial reduced glutathione. SIRT3 also deacetylates components of the electron transport chain, including complex I and III, which are believed to be major sites of reactive oxygen species (ROS) generation. Primary cortical neurons derived from SIRT3 knockout mice present hyperacetylation of mitochondrial SOD2 and cyclophylin D. These cells, and SIRT3 knockout mice are extremely vulnerable to treatment with 3 nitropropionic acid (3-NP) [81]. 3-NP is a mitochondrial toxin used to model the phenotypic and neuropathologic features of HD in rodents and primates [82, 83].

Deficiencies of SIRT3 were identified in a cell model of HD [84]. In $STHdh^{Q111}$ cells, SIRT3 levels were reduced and the cells exhibited higher levels of ROS and cell death, which was protected by trans-viniferin, a derivative compound from Resveratrol, which increased SIRT3 levels [84]. Viniferin reduced the levels of ROS and it prevented loss of mitochondrial membrane potential. The expression of mutant huntingtin reduced the deacetylase activity of SIRT3.

This in turn prevents SIRT3 deacetylation of the upstream kinase LKB1, an upstream activator of AMP-activated kinase (AMPK) and leads to a reduction in cellular NAD^+ levels and reduced mitochondrial biogenesis. Viniferin activates AMPK and enhances mitochondrial biogenesis. A knockdown of SIRT3 blocked these effects, indicating that SIRT3 mediates the neuroprotection produced by viniferin. The acetylated SOD2 and LKB1 levels were also reduced by viniferin, These findings show that a reduction in SIRT3 is a critical feature of mutant huntingtin toxicity in striatal neurons in vitro, and that increasing SIRT3 reduces the toxicity of mutant huntingtin by improving mitochondrial biogenesis and function, and reducing generation of ROS, thereby improving cell survival.

PARP1 in HD

Poly-(ADP-ribose) polymerases consist of a family of 16 enzymes reported to date [85]. As aforementioned, they polymerize ADP ribose units using NAD + as a substrate and transfer them to acceptor proteins. This is a key event in DNA repair mechanisms, response to DNA damage, and events such as chromatin remodeling, nuclear transcription, and cellular death response mediated by mitochondrial apoptosis-induced factor 1 (AIF1). This last mechanism is termed parthanatos and involves the translocation of AIF1 from the mitochondria to the nucleus mediated by over-activation of PARP1 activity due several stimuli (reviewed in [86, 87]).

PARP1 is induced in neurons in response to damage by reactive oxygen species (ROS). ROS production is exacerbated due mitochondrial dysfunction, which is a common feature in many neurodegenerative disorders [88–90]. PARP1 inhibition has been reported to have an overall neuroprotective effect in PD, AD and amyotrophic lateral sclerosis models [91–96]. In HD, oxidative stress caused by ROS production seems to be CAG length dependent [97–99]. Oxidative damage is consistently observed in HD brain tissue [100, 101], oxidative damage to DNA is present in skin fibroblasts [102] and peripheral blood monocytes [97, 103] from HD patients. DNA oxidative damage is increased in HD transgenic mice [104] and an increase in 8-oxo-dG is observed in the Libechov transgenic minipig HD model at 48 months [105]. Not surprisingly, PARP1 overexpression has been observed in neurons and glia of late stage HD post-mortem brains [106]. R6/2 mice treated with the PARP1 inhibitor INO-1001 show an increase in survival and motor coordination. These mice also show an amelioration of striatal volume loss, decrease of intranuclear huntingtin inclusions and activated microglia and increased levels of BDNF in medium spiny neurons [107]. As mentioned before, BDNF is reduced in HD and it is considered a hallmark of its pathogenesis [48]. INO-1001 treatment has a neuroprotective effect in striatal parvalbuminergic and calretininergic interneurons from R6/2 mice [108].

Nicotinamide Riboside in HD

NAD^+ potentiates the activity of SIRT1 and SIRT3 [109]. In turn, SIRT1 activation increases deacetylation of PGC-1α. PGC-1α activation by SIRT1 is a key regulator of glycolysis, gluconeogenesis and mitochondrial function [12, 110]. SIRT3 is essential for PGC-1α dependent induction of ROS-detoxifying enzymes and for mitochondrial biogenesis and PGC-1α is necessary for SIRT3 transcription [111]. PARP1 uses NAD^+ as a substrate to execute PARylation of target proteins [112]. PARP1 has not only a role in DNA damage repair, but also regulates cell bioenergetics [113, 114]. PARP1 KO mice exhibit a phenocopy of SIRT1 overexpression, especially on its metabolic profile, an increase of NAD^+ content and enhanced mitochondrial numbers in various tissues. This is mediated by activation of SIRT1 activity, measured as increased levels of deacetylated PGC-1α in muscle [115]. PARP2 inhibits SIRT1 transcription and it is thought that SIRT1 inhibits PARP1 activity by de-acetylation in a feedback [NAD^+] loop depending mechanism [116]. Since PGC-1α activation is dependent on SIRT1 and SIRT3 activities, and Sirtuins are not only dependent on NAD^+ levels but are also competing with PARP1. Therefore, an elevation of NAD^+ is a plausible strategy that can result in the neuroprotective effect of the SIRT1/3- PGC-1α pathway and at the same time, inhibit the neurotoxic effects of PARP1 activity in HD. For a review on the relationship between PARPs and Sitruins, see [112].

Therefore, there are several reports of therapeutic pharmacological intervention aimed to increase levels of NAD^+ in the brain for HD and other neurodegenerative diseases. Most of the reports face the same caveats. Increasing NAD^+ levels in brain using NAD^+ or NAD^+ precursors is limited by their cell impermeability, the different routes of administration and their lack or limited efficacy.

The neuroprotective effect of exogenous NAD^+ supplementation is reported for ischemic neuronal injury in vitro [117] and in vivo [118]. However, NAD + transport mechanisms are unknown and membrane permeability seems to be cell specific [119]. Moreover, in vivo administration is limited to IV or IP routes.

Therapeutic usage of nicotinamide adenine dinucleotide (NADH) for treatment in Alzheimer's disease (AD) patients showed no effect on cognitive functions [120]. In Parkinson's disease (PD), it is not clear if NADH is efficacious [121]. NADH was reported to improve disability scores measured by the Birkmaeyer-Neumayr scale [122–124] but these results are contradicted by other independent study [125]. There is a case report of a PD patient who showed

improvement in bradykinesia and rigidity but had unpleasant nightmares and a severe skin rash [126]. To date, no clear clinical data that supports NADH usage for PD is available and there are not clinical trials reported for NADH in HD.

NAM clinical trials in AD patients (Clinicaltrials.gov Id: NCT00580931) showed that it is safe, but there was no efficacy on cognition [127], which had been previously reported in an AD mouse model [128]. As for PD, two clinical trials are planned for treatment of PD patients with NAM (Clinicaltrials.gov Id: NCT03462680 and NCT03568968), and none for HD patients. For a complete review of the use of NAD^++ precursors in neurodegenerative diseases see [129, 130].

Thus, a major unmet clinical need is the development of compounds that increase NAD^+ levels in brain when orally administered at sub-mM concentrations and that show high efficacy. Nicotinamide riboside (NR) is a precursor of NAD^+ that presents a very interesting pharmacological profile along many neurodegenerative conditions.

NR promotes Sir2 (yeast homologue of Sirt1)-dependent repression of recombination, improves gene silencing and extends life span in yeast and mice [131, 132]. NR is metabolized through a novel biosynthetic pathway, namely by action of nicotinamide riboside kinase enzymes [133, 134] (reviewed in [135]).

NR enhances NAD^+ effects in mammalian cell lines [136], and therefore provides a potential means of increasing SIRT1 activity with subsequent increased PGC-1α activity and mitochondrial biogenesis. NR supplementation to mammalian cells and mice increased NAD^+ levels in tissue and mitochondria, and activated SIRT1, SIRT3, and PGC-1α, enhancing oxidative metabolism and protecting against a high fat diet [137].

One of the first clues of the potential neurotherapeutic effect of NR was treatment of a mouse with impaired hearing in which neurite degeneration is caused by noise damage. In this case, NR showed a neuroprotective effect through activation of SIRT3 [138].

NR treatment of PD models is reported to have neuroprotective effects. In a very elegant report [139], the authors treated 2 different PD models with NR. The first is an iPSC-derived neuronal cell model from PD patients bearing 3 different mutations (N370S, L444P, and RecNci) at the lysosomal enzyme b-Glucocerebrosidase (GBA) gene. After treatment with NR, these cells showed an increase of NAD^+ and NAM. Chronic NR treatment increased mitochondrial numbers, showed elevation of TFAM and restored mitochondrial function. The other is a fly model that expresses the N370S human GBA gene. After treatment with NR, age dependent dopaminergic neuronal loss and climbing activity deficits were reversed.

NR reduced cognitive deficits and upregulated PGC-1α which enhanced degradation of BACE1, and reduced Aβ1-42 in a transgenic mouse model of AD [140]. On a seminal paper [141], NR treatment of an AD mouse model carrying a null allele of DNA polymerase beta, showed multiple beneficial effects. The 3xTG-AD mice, which simultaneously express 3 AD mutations: TauP301L, Presenilin 1, and the Swedish APP, were crossed with a polymerase beta heterozygous strain. Polymerase beta (Polβ) is a key component of the base excision repair mechanism (BER) in both nuclear and mitochondrial DNA [142, 143] (reviewed in [144]). 3xTG-$ADPol^{+/-}$ mice have a more robust AD human phenotype in terms of olfactory dysfunction, DNA damage accumulation in brain and selective AD associated neurodegeneration [145–147]. NR treated 3xTG-$ADPol^{+/-}$ mice showed increased NAD^+ levels in the brain, improvement in cognition, memory and motor functions, recovery of hippocampal synaptic plasticity, and decreased neuroinflammation as well as Tau phosphorylation.

Furthermore, the authors showed that DNA oxidative damage due ROS production and mitochondrial dysfunction is recovered not only in these mice, but also in fibroblasts derived from AD patients treated with NR. In the 3xTG-$ADPol^{+/-}$ mice, the NR neuroprotective effect was mediated by activation SIRT3, and higher levels of de-acetylated SOD2 were found. The authors also report a dramatic reduction in Poly ADP ribose (PAR) levels due diminished activity of PARP1 [141].

If NR is capable of ablating oxidative damage in an AD mouse model defective in a key player of BER, it is reasonable to think that a similar neuroprotective effect could be seen in HD. ROS has been reported to modulate mutant huntingtin translocation from the cytoplasm to the nucleus by sulfoxidation of a methionine residue (M8) located at the N-terminal part of normal huntingtin which in turn allows phosphorylation of two serine residues (S13 and S16) [148] critical for huntingtin nuclear localization [149]. Through a series of elegant experiments in human fibroblasts [150], normal huntingtin shown to translocate in a soluble form to the nucleus and localize at DNA which had been damaged by micro-irradiation or oxidative stress. This mechanism is dependent upon phosphorylation by the DNA damage response protein ataxia-telangiectasia mutated (ATM), in which recessive mutations cause cerebellar atrophy [151]. Of note, NR treatment of ataxia telangiectasia models shows neuroprotective effects [152]. In the nucleus, it was shown to be co-localized with members of the BER pathway. The ensuing DNA repair mechanism through the proposed scaffolding function of Huntingtin [153, 154] is altered in the context of the mutant allele.

The CAG repeat in the Htt gene is affected in a length-dependent manner, by oxidative stress. DNA damage to this region is increased due a failure of the BER mechanism. Formation of abnormal secondary structures at the CAG repeat, inability of the BER components to access damaged

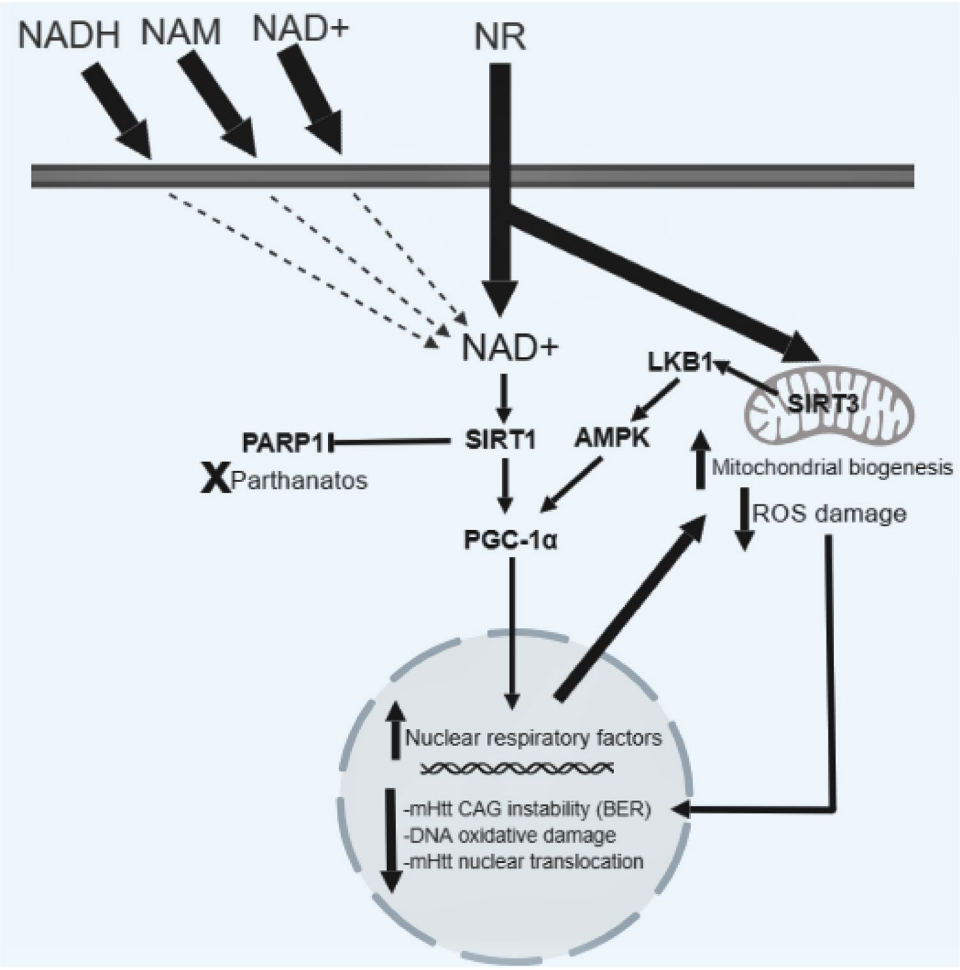

Fig. 1 Proposed neuroprotective effect of elevating cellular levels of NAD^+ in HD. NAD^+ and NAD^+ precursors are used as a pharmacological strategy to replenish cellular NAD^+ (thick arrows). Each one of them differ in their capacity to cross the cellular membrane. When NAD^+ levels are elevated, SIRT1 deacetylase activity is promoted, which in turn, can inhibit PARP1 role in cellular death by the parthanatos mechanism. In this same scenario, SIRT1 activates PGC-1α, which in turn increases the transcription of elements involved in reduction of ROS damage and mutant huntingtin (mHtt) aggregation in the nucleus. When NR is used as an NAD+ precursor, it increases NAD^+ levels in the mitochondrial This activates deacetylase activity of SIRT3 and as a result, mitochondrial proteins that maintains its functional integrity as well ROS mitochondrial de-toxifying enzymes activity is triggered. Also, SIRT3 activates LKB1, an upstream regulator of AMPK, that results in another activation pathway of PGC-1α. ROS ablation prevents DNA oxidative damage and therefore, CAG instability of the N-terminal coding region of mutant huntingtin caused by overactivation of BER pathway and the nuclear localization of mutant huntingtin regulated by ATM. Figure created with www.biorender.com

sites as well as the disruption of the ratios needed to execute it, is in part responsible for the tissue specificity of the CAG tract instability, which is one of the best characterized early HD phenotypes [155–158]. Lack of 8-Oxoguanine DNA Glycosylase (OGG1), an enzyme of the BER pathway in charge of removing 8-oxoguanine lesions, diminishes somatic instability of the CAG huntingtin tract [159]. Uncoordinated activity of OGG1 with Ligase 1 (LIG1) is reported to be responsible for modulation of the CTG/CAG repeat in human Htt [160]. LIG1; Apurinic endonuclease (APE1); and Flap structure-specific endonuclease 1 (FEN1) were found to be downregulated in the striatum of HD mice [161]. FEN1 and Polβ have been implicated in the instability of the CAG expansion present in HD [162]. FEN1 and scaffold protein X-Ray Repair Cross Complementing 1 (XRCC1), another BER player, are recruited by both normal and mutant huntingtin in the nucleus, but they fail to execute DNA repair due oxidative stress [151]. Mutations in XRCC1 are reported to lead to an overactivation of PARP1 in a cerebellar ataxia context [163]. As we previously mentioned, PARP1 inhibition is reported to have a neuroprotective effect in neurodegeneration models of HD and cerebellar ataxia.

NAD^+ replenishment via NR has been reported to have an overall neuroprotective effect through different neurodegenerative disease models [139, 141, 152, 164, 165]. Unpublished data from our group show that NR increases NAD^+

levels in several cell lines and NR increases NAD^+ levels in brain tissue and in brain mitochondria. The magnitude of the increases exceeds two-fold in brain mitochondria, an effect unknown for any other precursor to NAD^+. We confirmed that $STHdh^{Q111}$ cells treated with NR showed an activation of SIRT1, SIRT3, and PGC-1α, enhancing oxidative metabolism and providing an overall neuroprotective effect. We have tested NR pharmacological effects in two HD models: R6/2 and BACHD and both showed an amelioration of HD motor and molecular phenotypes. Chronic NR treatment has been reported to be safe [166, 167]. A clinical trial (clinicaltrials.gov ID: NCT02921659) in healthy patients with a dose of 1000 mg per day for 6 weeks, has been reported to be safe, effective in terms of NAD^+ elevation, and well-tolerated [168].

In sum, NR usage as a pharmacologic agent for enhancing NAD^+ content within the brain is a logical, viable and encouraging next step to take in terms of HD treatment (Fig. 1). NR is expected to have a pleiotropic neuroprotective effect by restoration and enhancement of mitochondrial function via the Sirtruin1-3/Pgc-1α pathway. It is also reasonable to expect that by eliminating ROS related stress signals, NR treatment can at least delay translocation of mutant huntingtin to the nucleus, which is an early event in HD pathogenesis. Ablation of ROS stress can have an effect on oxidative DNA damage, which is the key signaling event for BER activation. Thus, an effect on somatic on the CAG length instability via BER is expected. With this, along with an increase of NAD^+, PARP1 overactivation will be diminished. This raises the possibility of a synergistic effect of PARP1 inhibitors with NR treatment for HD.

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