Review

Antioxidants in Huntington's disease ☆

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ABSTRACT

Huntington's disease (HD) is a prototypical neurodegenerative disease in which there is selective neuronal degeneration, which leads to progressive disability, manifesting itself as a movement disorder, with both psychiatric and cognitive impairment. The disease is caused by a cytosine–adenine–guanine (CAG) repeat expansion in the *huntingtin* gene, which causes an expanded polyglutamine repeat in the huntingtin protein, resulting in a protein with a novel gain of function. The mutant huntingtin protein causes neuronal dysfunction and eventual cell death in which transcriptional impairment, excitotoxicity, oxidative damage, inflammation, apoptosis and mitochondrial dysfunction are all implicated. A critical transcriptional impairment may be impaired expression and function of peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), a master co-regulator of mitochondrial biogenesis and expression of antioxidant enzymes. A deficiency of PGC-1α leads to increased vulnerability to oxidative stress and to striatal degeneration. The extent and severity of the oxidative damage in HD are features well recognized but perhaps underappreciated. Oxidative damage occurs to lipids, proteins and deoxyribonucleic acid (DNA), and it has been suggested that the latter may contribute to CAG repeat expansion during DNA repair [1]. A marked elevation of oxidized DNA bases occurs in patients' plasma, which may provide a biomarker of disease progression. Antioxidants are effective in slowing disease progression in transgenic mouse models of HD, and show promise in human clinical trials. Strategies to transcriptionally increase expression of antioxidant enzymes by modulating the Nrf-2/ARE pathway, or by increasing expression of PGC-1α hold great promise for developing new treatments to slow or halt the progression of HD. This article is part of a Special Issue entitled: Antioxidants and Antioxidant Treatment in Disease.

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1. Introduction

1.1. Huntington's disease (HD)

Named after George Huntington, who provided a classic account of the condition in 1872, Huntington's disease (HD), is a fatal, dominantly inherited progressive neurodegenerative disorder, caused by a variable length CAG repeat expansion in the huntingtin (*HTT*) gene that translates into an abnormally long polyglutamine repeat in the mutant huntingtin (mhtt) protein. The disease is characterized by motor and cognitive impairment, a variable degree of personality change, and psychiatric illness [2,3]. In addition, metabolic abnormalities such as wasting and altered energy expenditure are increasingly recognized as clinical hallmarks of the disease. There is progressive disability, and death usually occurs 15 to 20 years after onset. There

are no currently available treatments to delay disease onset or retard its progression, and the focus of medical care is limited to symptom management and maximizing function. Disease manifestations can begin at any time in life; the most common age range of onset is between 30 and 50 years old, although it occurs in children and the elderly as well [4]. The number of CAG repeats in the *HTT* gene is the main predictor of the age of disease-onset, but the remaining variation is strongly heritable. Patients with HD have CAG repeat lengths above 36, with variable penetrance of repeat lengths 36–39 and complete penetrance above 39 repeats; longer repeat lengths (>60) have been associated with juvenile-onset HD [3]. Individuals at risk of inheriting the expanded CAG nucleotide can be identified before clinical onset by predictive genetic testing [5]. Although the length of CAG repeat can be used for predicting age of onset, the CAG repeat length seems to contribute less to the rate of progression and understanding the determinants of rate of progression, could help in finding means for therapeutic intervention [6].

The motor abnormality originates from dysfunction of the control of involuntary movements in a brain region known as the striatum, and is manifested as a hallmark feature of uncontrollable dance-like movements (chorea). Neuropathological analysis of HD brains reveals preferential and progressive neuronal loss of the GABAergic medium-sized spiny neurons (MSNs) in the striatum, although cortical atrophy

and damage to other brain regions including the thalamus, hippocampus, and amygdala, also occurs as the disease progresses [3,7]. The cortical atrophy progresses from the motorsensory cortex to the occipital, parietal and limbic cortices [8]. Atrophy of the basal ganglia, thinning of the cortex and atrophy of the whole brain precede the overt onset of clinical symptoms by years. The MSNs are the primary neuronal type of the caudate putamen, constituting 90% of the total population of neurons. In HD, there is clear selective vulnerability of MSNs, and yet some neurons survive, despite the expression of mhtt protein and development of aggregates [9,10]. NADPH diaphorase/NO synthetase interneurons and cholinergic interneurons are spared, and calretinin interneurons are partially spared [11,12]. In HD, the earliest cell loss appears in the GABA/enkephalin neurons projecting to the lateral globus pallidus (the indirect motor pathway) and is thought to underlie the development of chorea. Later, the GABA/substance P/dynorphin cells projecting to the substantia nigra pars reticulata and the medial globus pallidus (direct pathway) are affected, leading to motor incoordination, increased muscle tone, dystonia, and abnormal eye movements [10,13].

1.2. Preferential vulnerability of striatal neurons in the context of huntingtin

In comparison to other protein aggregation disorders, the preferential striatal degeneration appears to be intimately connected to huntingtin's protein context, but how mhtt elicits this effect remains unknown. The htt protein is a large protein (~3300 amino acids) located mostly in the cytoplasm of the cell and is ubiquitously expressed throughout the body, with the highest expression in brain and testes. The functions of htt protein have not been fully elucidated yet, although it has been shown that htt is required for neurogenesis, and the HTT gene appears to be essential for survival [14–16]. Wild-type htt is involved in developmental apoptosis and potential roles in vesicle trafficking, RNA biogenesis, endocytosis, mitosis and intracellular signaling have been inferred by its propensity for co-localization with synaptic vesicles, microtubules, spindle poles and the postsynaptic density [17–23]. Mutant htt toxicity can be attributed mainly to a toxic gain of a novel function (transcriptional modulation, protein aggregation and excitotoxicity), and partly to a loss of wild-type htt function (impaired BDNF gene expression and vesicle trafficking). Homozygous mhtt mice develop normally, whereas expression of a single allele of the mutant gene is sufficient to rescue htt-null mice from death in utero [17]. Similar to wild-type htt, mhtt is also ubiquitously expressed, with no overt selectivity for the brain regions targeted by the disease process, suggesting that another property of mhtt, or neurons within these regions, confers vulnerability to mhtt toxicity.

At any given time, ~5% of the cell's htt is found in the nucleus, suggesting that it shuttles between the nucleus and the cytoplasm [24]. The N-terminal 17-amino acid sequence of htt has been suggested to act as a nuclear export signal owing to its binding to the nuclear exporter translocated promoter region (Tpr). Expansion of the polyglutamine (polyQ) repeat interferes with this interaction causing accumulation of mhtt in the nucleus [25]. It has been shown that increasing nuclear localization of mhtt increases its cytotoxicity, indicating that a nuclear action of mhtt is required for it to induce toxicity [26]. The presence of htt aggregates, predominantly composed of N-terminal fragments of polyQ expanded htt, in the nucleus and cytoplasm of affected neurons, both in patient brains and in model systems, are a pathological hallmark of HD; suggesting that proteolytic cleavage of htt plays a key role in pathogenesis [27,28]. In vitro and animal studies show that polyQ induced toxicity is exacerbated by protein truncation. N-terminal mhtt fragments are sufficient to produce HD-like abnormal clinical syndromes in animal models [29] and truncated mhtt, in contrast to full-length mhtt, induces apoptosis [30]. Inhibition of mutant htt cleavage reduces

toxicity, indicating a causative role for htt proteolysis in HD pathogenesis [31,32].

Based on the findings that htt fragments are most abundant in cortical projection neurons, it was proposed that accumulation of mhtt fragments may contribute to the selective corticostriatal dysfunction which occurs in HD pathogenesis [33]. The fragmented htt with the expanded polyQ domain, has an increased propensity to bind to other proteins including, various transcription factors, repressors and co-factors; proapoptotic caspases, calmodulins and transglutaminases [reviewed in 34]. The events that are caused directly by mhtt or its fragments trigger cascades of both damaging and compensatory molecular processes and genetic programs. These ultimately lead to increasingly dysfunctional neurons that are susceptible to more generic stresses (Fig. 1). These stresses include oxidative injury, excitotoxic stress, disordered neurophysiology {such as increased activity of N-methyl-D-aspartate (NMDA) glutamate receptors}, expression of potentiating inflammatory signals, pro-apoptotic signals that activate caspase 8 and caspase 3, malfunctioning proteolysis, increased transglutaminase activity and energy depletion.

Many studies have provided evidence for a link between mutant huntingtin protein, and mitochondrial abnormalities—and subsequent impaired mitochondrial function and dynamics—that could ultimately lead to neuronal damage and degeneration in affected brain regions of patients with HD [35–40]. Mitochondrial dysfunction in HD may occur through aberrant transcriptional regulation, as mhtt binds to several transcriptional regulators and interferes with their function. In particular, expression of peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), a master transcriptional co-regulator of mitochondrial biogenesis and antioxidant enzymes, is reduced in HD, which may contribute to mitochondrial impairment [41–46]. We showed that there are pathologic grade-dependent reductions in numbers of striatal mitochondria that correlate with reductions in PGC-1α [36]. In addition, a direct interaction of mhtt with mitochondria or with various protein complexes may play an important role in pathogenesis, by regulating mitochondrial fission–fusion events, and mitochondrial trafficking along axons and dendrites [47]. Expression of mhtt causes abnormal mitochondrial ultrastructure, impaired calcium buffering, bioenergetic defects and mitochondrial DNA deletions, all of which may be a consequence of a failure to maintain a balance between mitochondrial fission and fusion [37,38]. Mitochondrial dynamics are abnormal in patients with HD as compared with healthy controls; there is an increased expression of mitochondrial fission proteins (Drp1 and Fis1), and of the mitochondrial matrix protein CypD; decreased levels of mitochondrial fusion proteins (Mfn1, Mfn2, Opa1 and Tomm40) occur in HD patients, and levels of CypD increase with HD progression [36,40]. Evidence of oxidative DNA damage (increased levels of the oxidative stress biomarker 8-hydroxy-2-deoxyguanosine) and loss of mitochondrial function (reduced levels of the electron transport proteins cytochrome b and cytochrome c oxidase 1) were found in individuals with HD, and these patients also exhibited markedly increased levels of mhtt oligomers in the cerebral cortex. Importantly, immunolabelling of brain samples showed the presence of mhtt oligomers in the nuclei of neurons and mitochondria of patients with HD. HD medium spiny neurons show reduced numbers of mitochondria due to reduced levels of PGC-1α [36]. Medium spiny neurons also have long projections as compared to interneurons, which may make them preferentially vulnerable to increased mitochondrial fission [36,40].

1.3. Reactive oxygen species (ROS)

Free radicals are molecules or molecular fragments containing one or more unpaired electrons in their atomic or molecular orbitals [48]. The unpaired electron(s) usually provide a large amount of reactivity to the free radical. Radicals derived from oxygen represent the most important class of radical species generated in living systems [49].
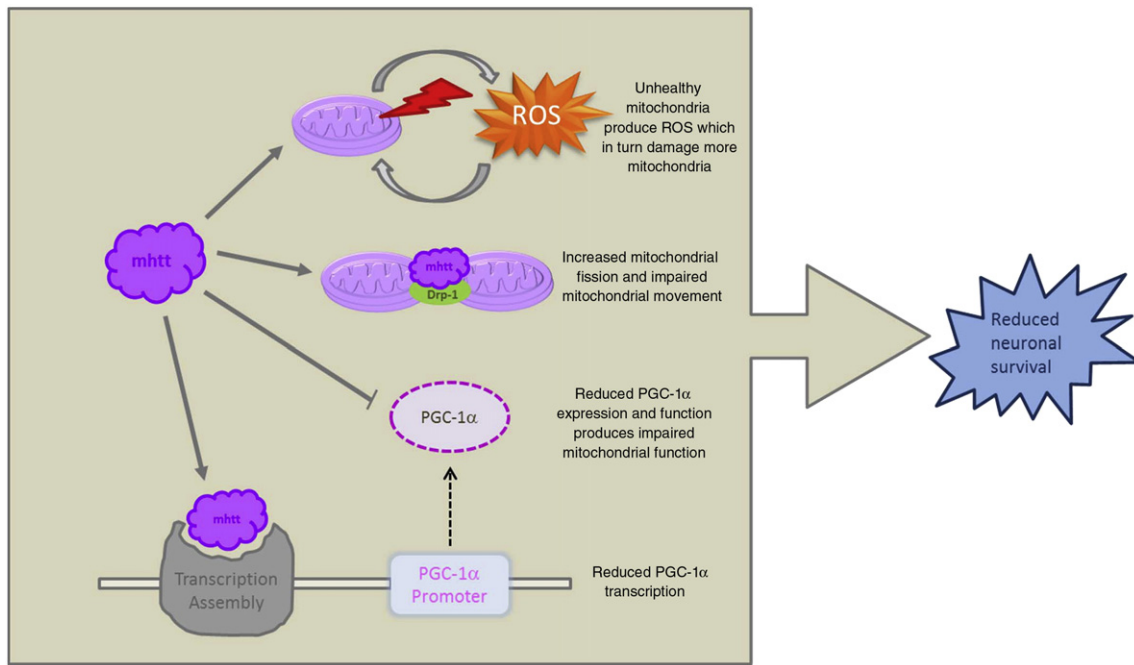
Fig. 1. (Top) Vicious cycle induced by mutant htt (mhtt): mhtt causes damage to mitochondria, which then produce harmful reactive oxygen species (ROS), which in turn damage more mitochondria. Mitochondria in mutant cells are thus particularly vulnerable to stresses such as respiratory chain complex inhibitors, Ca^{+2} and ROS. (Center) mhtt binds more tightly to the mitochondrial fission protein Drp-1, causing mitochondrial fragmentation. mhtt also impairs mitochondrial movement thus reducing ATP at nerve terminals. (Bottom) mhtt interferes with the function and/or transcription of PGC-1α, thus resulting in downregulation of PGC-1α target genes such as those involved in mitochondrial biogenesis and antioxidant defense.

Molecular oxygen (dioxygen) has a unique electronic configuration and is itself a radical. Oxygen free radicals, frequently referred to as reactive oxygen species (ROS), are normally generated during reactions of cellular metabolism.

ROS include superoxide, hydroxyl and peroxyl free radicals, as well as nitrogen intermediates (NO and peroxynitrile). The addition of one electron to dioxygen forms the superoxide anion radical ($O^{\bullet-}_2$) [49]. The production of superoxide occurs mostly within the mitochondria of a cell [50]. The mitochondrial electron transport chain is the main source of ATP in the mammalian cell and thus is essential for life. During energy transduction, a small number of electrons "leak" to oxygen prematurely, to generate superoxide, instead of contributing to the reduction of oxygen to water [51]. Superoxide is produced from both Complexes I and III of the electron transport chain, and once in its anionic form it is too strongly charged to readily cross the inner mitochondrial membrane. Recently, it has been demonstrated that Complex I-dependent superoxide is exclusively released into the matrix and that no detectable levels escape from intact mitochondria [52]. Under stress conditions, an excess of superoxide releases free iron from iron-containing molecules, which can participate in the Fenton reaction, generating the highly reactive hydroxyl radical, $^{\bullet}OH$. Additional reactive radicals derived from oxygen that can be formed in living systems are peroxyl radicals (ROO$^{\bullet}$). The simplest peroxyl radical is HOO$^{\bullet}$, which is the protonated form of superoxide ($O_2^{\bullet-}$) and is usually termed either hydroperoxyl radical or perhydroxyl radical. It is known that hydroperoxyl radical initiates fatty acid peroxidation [53]. Superoxide can also rapidly react with NO in the extracellular space to form peroxynitrite ($ONOO^{-}$), which can readily cross cell membranes and damage intracellular components [54].

ROS are produced constantly by aerobic cells through diverse metabolic pathways. They serve as specific signaling molecules in both, normal and pathological conditions, and their transient generation, within boundaries is essential to maintain homeostasis. ROS can inflict oxidative molecular damage to lipids, proteins and DNA when their production overwhelms the capacity of antioxidant systems [55–57]. The imbalance is induced by ROS mainly of mitochondrial origin. Biological

effects initiated by ROS can elicit a wide range of phenotypic responses that vary from activation of gene expression, proliferation to growth arrest, and to senescence or cell death [58–60].

1.4. Oxidative stress in neurodegeneration: why it is important

The harmful effects of ROS cause damage to macromolecules such as proteins, lipids, polysaccharides or nucleic acids, are termed oxidative stress. The intrinsic properties of neurons make them highly vulnerable to the detrimental effects of ROS: high metabolic rates; a rich composition of fatty acids prone to peroxidation; high intracellular concentrations of transition metals, capable of catalyzing the formation of reactive hydroxyl radicals; low levels of antioxidants; and reduced capability to regenerate. Neurons have intense energy demands which are met by mitochondria. Mitochondria are both targets and important sources of ROS. It has been shown that oxidative stress stimulates mitochondrial fission; the addition of hydrogen peroxide to cultured cerebellar granule neurons induced mitochondrial fragmentation within 1 h of treatment [61]. It was also shown that nitric oxide causes increased mitochondrial fission in neurons, prior to the onset of neuronal loss in a mouse model of stroke [62]. On the other hand, expression of *Mfn* or a dominant negative *Drp1* in cultured neurons, was protective against oxidative insults [61,62]. The generation of ROS appears to be increased in damaged mitochondria, and in cells with compromised mitochondrial function. Acute exposure to relatively high levels of ROS, especially in the presence of calcium, can induce the mitochondrial permeability transition, uncouple oxidative phosphorylation with catastrophic effects on mitochondrial energetics, and contribute to cytotoxicity *via* necrosis and/or apoptosis. Oxidative stress within mitochondria can lead to a vicious cycle in which ROS production progressively increases leading, in turn, to progressive augmentation of damage (Fig. 1).

Nucleic acid oxidation occurs in neurons during disease and is detected as elevated levels of 8-hydroxy-2-deoxyguanosine (8-OHDG) in DNA and 8-hydroxyguanosine in RNA. Hydroxyl radical-mediated DNA damage often results in strand breaks, DNA–protein crosslinking, and base-modifications. All of these events can lead to

neuronal injury. It is known that generation of ROS results in an attack not only on DNA, but also on other cellular components involving polyunsaturated fatty acid residues of phospholipids, which are extremely sensitive to oxidation [63]. Once formed, peroxyl radicals (ROO•) can be rearranged via a cyclization reaction to endoperoxides (precursors of malondialdehyde) with the final product of the peroxidation process being malondialdehyde (MDA). The major aldehyde product of lipid peroxidation other than MDA is 4-hydroxy-2-nonenal (HNE). Increased production of ROS also results in protein oxidation. The side chains of all amino acid residues of proteins, in particular cysteine and methionine residues of proteins are susceptible to oxidation by the action of ROS/reactive nitrogen species (RNS) [64]. Oxidation of cysteine residues may lead to the reversible formation of mixed disulfides between protein thiol groups (−SH) and low molecular weight thiols, in particular glutathione (GSH, S-glutathiolation). The concentration of carbonyl groups, generated by many different mechanisms is a good measure of ROS-mediated protein oxidation. The generation of isoprostanes has been shown to be a sensitive measure of lipid peroxidation, which are increased in cerebrospinal fluid (CSF) of HD patients [65].

Oxidative stress increases with age in the brain and the ability of cells to respond to oxidative protein damage also declines, contributing to the build-up of oxidatively damaged proteins. ROS are often present in brain regions affected by neurodegenerative diseases. Increased oxidative alterations to proteins such as α-synuclein in Parkinson's disease, β-amyloid in Alzheimer's disease and copper/zinc superoxide dismutase (SOD1) in Amylotrophic Lateral Sclerosis may result in increased protein misfolding and impaired degradation, leading to toxic accumulation of insoluble aggregates in the diseased brains and an exacerbation of neurodegeneration.

2. Evidence for oxidative damage in HD

Studies in both HD patients and experimental models of HD support a role for oxidative stress and ensuing mitochondrial dysfunction in mediating the neuronal degeneration observed in HD. Oxidative damage in HD has been previously reviewed in detail [34,66–68]. Some of the important and more recent findings are summarized below.

2.1. Evidence from HD patients and postmortem studies

Oxidative damage is well documented in plasma of HD patients, HD postmortem brain tissue, lymphoblasts and cerebrospinal fluid [34,66,68–71]. Markers of oxidative damage, including heme oxygenase (HO-1, an inducible isoform that occurs in response to oxidative stress), 3-nitrotyrosine (a marker for peroxynitrite-mediated protein nitration), and MDA, are elevated in human HD striatum and cortex as compared with age-matched control brain specimens [66]. The extent and intensity of these markers mirror the dorso-ventral pattern of progressive neuronal loss in the neostriatum, with increased immunoreactivity in the dorsal striatum as compared with the less severely affected ventral striatum. Consistent with the immunohistochemical data, biochemical assays in HD patients show significant increases in MDA and HNE brain levels, which are almost 8-fold greater than in control subjects [72].

Chen et al. [73] detected a correlation between lipid peroxidation products in plasma and degree of severity in patients with HD, and proposed using them as a potential biomarker for evaluating treatment efficacy. In a recent study, Tunez et al. [74] showed increased global oxidative stress (GOS), a reduction in antioxidant systems, and a correlation with disease stage in patients with HD. There is increased cytoplasmic lipofuscin (a product of unsaturated fatty acid peroxidation) and increased DNA fragmentation in HD patients; the latter correlated with CAG repeat length [66,75–78]. Aldolase C, GFAP, tubulin, γ-enolase, and creatine kinase B were found to be the targets of oxidative modification in both striatum and cortex

from HD patients [70]. More recently, it was shown that the oxidation of mitochondrial enzymes resulted in decreased catalytic activity in the striatum samples of HD patients, providing a link to the bioenergetic deficits observed in HD [79]. These authors also provided evidence that pyridoxal kinase and antiquitin 1 oxidation could result in decreased pyridoxal 5-phosphate availability, which in turn is necessary as a cofactor in transaminations, synthesis of glutathione, and synthesis of GABA and dopamine, two neurotransmitters that play a key role in HD pathology. These findings suggest that oxidative stress plays an important role in the pathogenesis of HD.

Additional indirect evidence comes from the studies of Lim et al. [80] and Tabrizi et al. [81]. Lim et al. [80] investigated dysfunction of Ca2+ homeostasis in mitochondria from striatal neurons of postmortem brains of HD patients. They found that mitochondria in mutant striatal neurons are unable to handle large Ca2+ loads, possibly due to the increased sensitivity of Ca2+ to the permeability transition pore opening, which dissipates the membrane potential, prompting the release of accumulated Ca2+. Harmful ROS, produced by defective mitochondria, increase in mutant cells, particularly if the damage to mitochondria is artificially exacerbated with, for example, complex II inhibitors. Mitochondria in mutant cells are thus particularly vulnerable to stresses induced by Ca2+ and ROS. The observed decrease of cell Ca2+ could be a compensatory attempt to prevent Ca2+ stress that would irreversibly damage mitochondria, and eventually lead to cell death. Furthermore, the severe impairment in the mitochondrial tricarboxylic acid (TCA)-cycle enzyme aconitase in HD brain, has been attributed to Fe–S clusters within the protein, which make it a particularly vulnerable target for free radical-mediated oxidative damage [81]. Aconitase inactivation directly correlates with the generation of superoxide produced by excitotoxicity [82]. There is evidence for a direct link between glutamate/NMDA excitotoxicity and aconitase inhibition via NO• and mitochondrial free radical generation.

2.2. Evidence from experimental models of HD

Many of the oxidative alterations observed in human HD are recapitulated in transgenic and neurotoxin mouse models of HD [34,68]. In mice expressing a N-terminal fragment of HTT exon 1, the R6/2 mice, there are increased concentrations of 8-OHDG in the urine, plasma, striatal microdialysates, and isolated brain nuclear DNA. There is increased immunostaining for 8-OHDG and lipid peroxidation markers (MDA, HNE and 8-iso-prostaglandin) in the striatum, and a progressive increase in the level of mitochondrial DNA damage in the striatum and cerebral cortex of 7- to 12-week-old R6/2 mice, by quantitative PCR analysis, and significantly increased oxidation of a number of key cellular proteins, including the metabolic enzymes creatine kinase, aconitase, neuron-specific enolase, heat shock protein 90, and the voltage-dependent anion channel 1, suggesting that oxidative modification of cellular components may contribute to cellular dysfunction, and ultimately to progressive disease [34,83,84]. In another N-truncated mhtt transgenic model of HD, the N171-82Q mice, we found evidence of increased oxidative and nitrosative stress [85]. In full-length knock-in mice, CAG140, 8-OHDG levels are elevated in brain and urine of the animals [68]. We have also seen enhanced immunostaining for MDA, 8-OHDG and HNE in the striatum of another full length human HD transgenic mouse model, the BACHD mice (Johri and Beal, unpublished observations, [86]).

It is well known that the administration of the mitochondrial toxins, 3-nitropropionic acid (3-NP) and malonate, both of which are selective inhibitors of succinate dehydrogenase, to nonhuman primates and rodents results in CNS lesions that selectively target medium-sized spiny neurons within the striatum, recapitulating the regional and neuronal specificity of pathologic events in HD. In these toxins and in the excitotoxin models of HD, increased oxidative damage has been consistently observed [34].

3. Antioxidant therapies in HD

The accumulation of ROS in neurons, and subsequent oxidative stress are attenuated by free radical scavengers, which can be categorized as enzymatic or non-enzymatic antioxidants. Enzymatic antioxidants constitute one of the defense mechanisms against free radicals. These include superoxide dismutase (SOD), glutathione peroxidase (Gpx) and catalase (CAT). Non-enzymatic antioxidants are represented by ascorbic acid (Vitamin C), α-tocopherol (Vitamin E), glutathione (GSH), retinoic acid, carotenoids, flavonoids, and other antioxidants. The therapeutic approaches tested *in vitro*, or in toxin or transgenic models of HD and trials in HD patients are summarized below and in Table 1.

3.1. In vitro studies

3.1.1. Metalloporphyrins

Metalloporphyrins, metal-containing catalytic antioxidants, have emerged as a novel class of potential therapeutic agents that scavenge a wide range of reactive oxygen species. A manganese porphyrin has been reported to significantly reduce cell death in an *in vitro* chemical model of HD [87].

3.1.2. Ascorbic acid (Vitamin C)

Ascorbic acid (Vitamin C) is a potent antioxidant obtained exogenously, which oxidizes readily to dehydroxyascorbic acid in the presence of reactive oxygen species. Treating cultured rodent cortical neurons with glutamate resulted in significant neurodegeneration, which was completely rescued with ascorbic acid co-treatment [88].

3.1.3. α-Tocopherol (Vitamin E)

α-Tocopherol (Vitamin E) is also a potent antioxidant. Using a neuronal cell-based assay, glutamate-induced neuronal death was significantly attenuated in a dose-dependent manner by α-tocopherol [89]. Also, treatment with idebenone in this *in vitro* model resulted in complete neuroprotection in a dose-dependent manner [89].

3.1.4. Grape seed phenolic extract (GSPE)

More recently, Wang et al. [90] demonstrated that Grape seed phenolic extract (GSPE) inhibited mhtt aggregation in PC-12 cells expressing 103 glutamines fused with enhanced GFP (Htt103Q-EGFP), and reduced the carbonyl levels induced by the expression of mhtt protein. GSPE is a strong antioxidant and powerful metal chelator that can effectively reduce ROS *in vivo* and has been shown to attenuate spatial memory impairment in a mouse model of AD [91].

3.2. In chemically induced rodent and murine models of HD

3.2.1. Melatonin

Melatonin, which is an excellent scavenger of hydroxyl, carbonate, reactive nitrogen species, and other organic radicals, has demonstrated significant neuroprotection in the kainic acid rodent model of neurodegeneration [92]. Melatonin significantly reduced DNA damage and improved neuronal survival. In another study using the 3-NP model of HD, melatonin treatment significantly ameliorated the increase in lipid peroxidation, protein carbonyls and SOD activity within the striatum [93].

3.2.2. Selenium

Selenium, is an essential element required by glutathione peroxidase to form the active enzyme. Selenium dose-dependently reduced lipid peroxidation and significantly improved neuronal morphology within the striatum of rats treated with quinolinic acid, an N-methyl-D-aspartate antagonist that results in striatal neurodegeneration [94]. There was a significant improvement in striatal GABA concentrations and significant improvements in behavior, including a reduction in ipsilateral turning, in these animals as compared with untreated controls.

3.2.3. Pyruvate

Using a quinolinic acid striatal lesion model of HD, treatment with pyruvate dose-dependently protected against striatal neurodegeneration [95]. Although lower doses provided no protection, relatively higher doses provided significant neuroprotection, reducing the striatal lesion area relative to controls.

3.2.4. Idebenone

Idebenone, a benzoquinone derivative, possesses a potent antioxidant capacity and readily penetrates the brain. Intrastriatal injection of kainic acid into the rat striatum resulted in a marked reduction in the presynaptic striatal marker glutamic acid decarboxylase (GAD). Treatment with idebenone resulted in a significant, nearly complete restoration of GAD immunoreactivity [96]. However, idebenone had no effect on decreases of GAD immunoreactivity induced by quinolinic acid striatal lesions in these studies.

3.2.5. Tauroursodeoxycholic acid (TUDCA)

Tauroursodeoxycholic acid (TUDCA) is a hydrophilic bile acid with antioxidant properties. TUDCA prevented striatal degeneration and ameliorated locomotor and cognitive deficits in a 3-NP rat model of HD [97].

3.2.6. N-acetylcysteine (NAC)

Treatment of rats with N-acetylcysteine (NAC), a known glutathione precursor, before 3-NP treatment, protected against oxidative damage induced by 3-NP as measured by electron paramagnetic resonance (EPR) and western blot analysis for protein carbonyls [98]. Furthermore, NAC treatment before 3-NP administration significantly reduced striatal lesion volumes. The authors suggested that oxidative damage is a prerequisite for striatal lesion formation and that antioxidant treatment may be a useful therapeutic strategy against 3-NP neurotoxicity and perhaps against HD as well [98].

3.2.7. Creatine

Creatine is a naturally occurring compound that has been shown to act as an antioxidant [99]. Creatine also buffers intracellular energy reserves through its intermediate, phosphocreatine (PCr); stabilizes intracellular calcium; and inhibits activation of the mitochondrial transition pore [100]. Creatine supplementation significantly reduces striatal lesion volumes produced by the neurotoxins 3-NP and malonate [101,102].

3.2.8. CoQ10

The antioxidant compound CoQ10 also demonstrated efficacy in murine models of HD. CoQ10, ubiquinone, is a lipid-soluble benzoquinone which, when reduced to ubiquinol, possesses a significant antioxidant potential. In addition, CoQ10 can induce increases in Vitamin E, enhancing its antioxidant capacity. Using the mitochondrial toxins malonate and 3-NP, treatment with CoQ10 resulted in dose-dependent neuroprotection, with significant CoQ10-mediated reductions in striatal lesion volume [103,104].

3.2.9. CoQ10 and creatine

CoQ10 and creatine have additive effects on bioenergetics. We examined the effects of combined treatment of CoQ10 with creatine in the 3-NP model of HD [105]. The combination diet exerted significant additive neuroprotective effects in blocking the 3-NP-incuded striatal lesions, preserving striatal GSH levels and the ratio of GSH/GSSG, and in reducing the striatal MDA levels and 8-OHDG levels in the cerebral cortex of 3-NP treated rats [105].

Table 1
Summary of antioxidants studies in HD.

Antioxidants	Site/mechanism of antioxidant action	In HD patients	In transgenic HD mice	In chemically induced animal models of HD	References
α-tocopherol (Vitamin E)	A lipid soluble antioxidant; protects cell membranes from oxidation; acts *via* glutathione peroxidase pathway	+,+	nd	+,+ +,− (in combination with CoQ10)	[123,133,134]
Creatine	Major role in intracellular energy buffering in conjunction with phosphocreatine; effective against superoxide, peroxynitrite and hydroxyl radicals	+,+, fsp	+,+	+,+	[125,126,116,117,101,102]
CoQ10	Present on inner mitochondrial membrane, functions as electron carrier in ETC and effectively reduces singlet oxygen; prevents oxidation of bases in mitochondria and formation of lipid peroxyl radicals and protein oxidation in lipid membranes	+,+, fsp	+,+	+,+	[68,127,118,103,104]
CoQ10 + Creatine	A combination of CoQ10 and creatine is expected to have additive effects on bioenergetics and act as powerful antioxidants	nd	+,+	+,+	[105]
Idebenone	A synthetic analog of CoQ10, has antioxidant properties similar to CoQ10; recently shown to be a substrate of NAD(P)H:quinone oxidoreductase (NQO)-1 and 2	+,−, nsp	nd	+,+	[124,96]
L-carnitine	Biologically active enantiomer of carnitine, involved in transport of fatty acids into mitochondria for production of energy; protects against lipid peroxidation of membranes	+,nsp (L-acetyl carnitine)	+,+	nd	[135,119]
Lipoic acid	An essential cofactor of mitochondrial enzyme complexes; catalyzes oxidative decarboxylation of pyruvate; has the ability to scavenge reactive oxygen and reactive nitrogen species (ROS/RNS), chelate metals, also called 'antioxidant of antioxidants'	nd	+,+	nd	[111]
Apocynin	An inhibitor of NADPH oxidase activity which reduces molecular oxygen to a superoxide radical	nd	nd	+,+	[136]
BN82451	A hybrid multi-targeting molecule designed as a neuroprotective disease modifying agent; reduces excitotoxicity, oxidative stress, and inflammation, and is also a mitochondrial protective agent	nd	+,+	nd	[113]
FK-506	An immunosuppressive drug, a potent calcineurin (protein phosphatase 2B) inhibitor, has anti-inflammatory and anti-oxidant {modulation of nitric oxide synthase (NOS) and HO activities} properties	nd	nd	+,+	[106]
Grape seed phenolic extract (GSPE)	GSPE has high concentrations of Vitamin E, flavonoids, linoleic acid, polyphenols, such as resveratrol; limits lipid peroxidation and reduces inflammation	nd	+,+	nd	[90]
Kynurenine-3-monooxygenase (KMO) inhibitors	Inhibition of KMO in blood increases kynurenic acid in brain and reduces extracellular glutamate and free radical production	nd	+,+	nd	[122]
Lycopene	A phytochemical, found in red fruits and vegetables, exerts antioxidant effects by quenching singlet oxygen	nd	nd	+,+	[107]
Melatonin	Produced in the body by pineal gland, acts as a synchronizer of biological clock and also possesses a strong antioxidant activity by scavenging ROS/RNS and inhibiting NOS. Protects lipids in membranes, proteins in cytosol, DNA in nucleus and mitochondria from free radical damage	nd	nd	+,+	[92,93]
N-acetylcysteine (NAC)	A pharmaceutical drug and nutritional supplement, reduces oxidative stress by reducing ROS and lipid peroxidation and restoration of antioxidant enzymes.	nd	nd	+,+	[98]
Nordihydroguaiaretic acid (NDGA)	NDGA is a lignan found in leaves and twigs of the shrub *Larrea tridentate*, prevents lipid peroxidation and 4-hydroxynonenal adduct formation	nd	+,+	nd	[137]
Olive oil	Obtained from *Olea europea*, contains high levels of polyphenol antioxidants, CoQ10 and melatonin; displays antimicrobial, antioxidant and anti-inflammatory properties	nd	nd	+,+	[138]
Pyruvate	The carboxylate anion of pyruvic acid, is an important mediator in several metabolic pathways; acts by restoration of the glutathione antioxidant ratio, also shown to prevent lipid peroxidation and oxidative DNA damage	nd	+,+	+,+	[112,95,139]
Selenium	An essential biological trace element; biological effects are mainly due to the antioxidant function of selenoproteins, which help maintain the intracellular redox status and prevent cellular damage from free radicals	nd	nd	+,+	[94]
Synthetic triterpenoids	Triterpenoids (TPs), particularly those which are analogs of 2-Cyano-3,12-Dioxooleana-1,9-Dien-28-oic acid (CDDO), have antioxidant and anti-inflammatory properties; act *via* Nrf2/ARE pathway	nd	+,+	+,+	[85,108]
Tauroursodeoxycholic acid (TUDCA)	A hydrophilic bile acid, has anti-inflammatory and cytoprotective effects; also has antioxidant effects, mechanism of action not fully defined yet; known to act through protein kinase C/A	nd	+,+	+,+	[114,97]
Withania somnifera root extract	Contains alkaloids and steroidal lactones; shown to induce the expression of antioxidant enzymes and reduce oxidative stress markers	nd	nd	+,+	[140]

+,+ = tested, beneficial effects.
+,− = tested, no beneficial effects.
nd = not determined.
nsp = not sufficient power.
fsp = further studies in progress.

3.2.10. FK-506 (also known as Tacrolimus or Fujimycin)

FK-506 is an immunosuppressive drug mainly used to lower allograft rejection and also in topical preparations. Recently, the neuroprotective effects of FK-506 were reported in the 3-NP model of HD [106]. FK-506 treatment significantly reduced behavioral deficits, MDA levels, nitrite concentration, and restored antioxidant enzyme levels of SOD and catalase, and levels of dopamine and norepinephrine in the striatum, cortex, and hippocampus.

3.2.11. Lycopene

Lycopene, a carotenoid pigment and phytochemical naturally found in fruits and vegetables, reduced oxidative stress markers and improved behavior in a 3-NP induced rodent model of HD [107].

3.2.12. The synthetic triterpenoid, CDDO-methyl amide

The synthetic triterpenoid, CDDO-methyl amide (2-cyano-N-methyl-3,12-dioxooleana-1,9(11)-dien-28 amide; CDDO-MA), activates the Nrf-2/ARE pathway resulting in induction of NAD(P)H dehydrogenase (quinone) 1 (NQO-1), and suppression of inducible nitric oxide synthase (iNOS). This compound is several times more potent than its naturally occurring distant parent, oleanolic acid. CDDO-MA treatment significantly attenuated 3-NP induced loss of striatal NeuN stained neurons, blocked the depletion of striatal GSH, preserved the ratio of GSH/GSSG and reduced MDA levels in the striatum and cerebral cortex of 3-NP treated rats, providing evidence that blocking oxidative stress by inducing the Nrf-2/ARE pathway may be an effective therapeutic approach for treatment of HD [108].

3.3. In transgenic mouse models of HD

3.3.1. Lipoic acid

Lipoic acid is an essential cofactor for many enzyme complexes and is present in mitochondria as the cofactor for pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase. It is an effective antioxidant and has been used to treat disease associated with impaired energy metabolism [109]. It also induces the Nrf-2/ARE pathway [110]. In both the R6/2 and N171-82Q transgenic mouse models of HD, dietary supplementation with lipoic acid resulted in significant extension of survival, and delayed weight loss in N171-82Q transgenic mice [111].

3.3.2. Pyruvate

Pyruvate plays a major role in glycolysis, and also possesses significant antioxidant capacity. Treatment with dichloroacetate, which stimulates pyruvate dehydrogenase, improved the HD phenotype of both R6/2 and N171-82Q mice, suggesting that, in addition to its antioxidant capacity, pyruvate may promote neuroprotection by improving energetic potential [112].

3.3.3. BN82451

BN82451 is a brain-permeable compound that exerts neuroprotective effects, including the inhibition of lipid peroxidation. Administration of BN82451 in R6/2 mice resulted in a significant extension of survival, significant improvements in motor function, with improvements in gross morphology, striatal volume, and striatal neuronal areas, and a significant decrease in the number of ubiquitin positive aggregates in R6/2 mice as compared with untreated control mice [113].

3.3.4. TUDCA

TUDCA prevents the production of reactive oxygen species, mitigates mitochondrial insufficiency and apoptosis, in part, by inhibiting Bax translocation from cytosol to the mitochondria. Keene et al. [114] showed that systemically administered TUDCA significantly reduced striatal neuropathology, decreased striatal apoptosis, reduced the size of ubiquitinated neuronal intranuclear htt inclusions and improved locomotor and sensorimotor deficits in the R6/2 transgenic HD mouse.

3.3.5. Creatine

Creatine exists in the cell both as free creatine and phosphocreatine (PCr) which together comprise the total creatine pool. In tissues with high energy requirements such as skeletal muscle and brain, PCr serves as a short term energy buffer in which adenosine diphosphate is phosphorylated to adenosine triphosphate. This phosphorogroup transfer is catalyzed by the important creatine kinase (CK) enzyme [115]. Creatine supplementation in the R6/2 and the N171-82Q transgenic mouse models produced an improvement in motor performance, extended survival, attenuated the loss of body weight and brain weight and reduced neuronal atrophy [116,117].

3.3.6. CoQ10

Located in the inner mitochondrial membrane, CoQ10 is essential for complex I and II electron transfer activities during oxidative phosphorylation, and plays a vital role in ATP production. Treatment with CoQ10 significantly increases levels of mitochondrial CoQ10 in the brain [104]. We showed that CoQ10 administration significantly attenuates brain weight loss, gross brain atrophy, ventricular enlargement, striatal neuron atrophy, extends survival, and improves motor performance in R6/2 mice [118].

We showed the additive neuroprotective effects of CoQ10 and creatine in improving motor performance, survival and striatal atrophy in the R6/2 transgenic mouse model of HD, providing evidence that the combination has improved efficacy as compared with either compound alone [105].

3.3.7. L-carnitine

L-carnitine (4-N-trimethylammonium-3-hydroxy-butyric acid) plays a role in the control of the mitochondrial acyl-coenzyme A/coenzyme A ratio, peroxisomal oxidation of fatty acids, and also acts as a free-radical scavenger. It is effective in preventing cell membrane damage caused by reactive oxygen species. Recently, administration of a relatively high dose of L-carnitine to N171-82Q transgenic mice was shown to extend the survival, ameliorate motor performance, and decrease the number of intranuclear mhtt aggregates [119].

3.3.8. Grape seed phenolic extract (GSPE)

Grape seed phenolic extract (GSPE) treatment in both fly and R6/2 mouse models of HD effectively extended lifespan in both models, and reduced motor deficits in the R6/2 mice, demonstrating preclinical efficacy of GSPE in HD treatment [90].

3.3.9. Synthetic triterpenoids

Synthetic triterpenoids, which are analogs of 2-Cyano-3,12-Dioxooleana-1,9-Dien-28-Oic acid (CDDO), are of great interest because of their antioxidant and anti-inflammatory properties. We recently showed that administration of triterpenoids, which activate the Nrf-2/ARE transcriptional pathways, are neuroprotective in the N171-82Q transgenic mouse model of HD [85]. Triterpenoids significantly preserved the striatal volumes of the N171-82Q mice, by preventing the atrophy of the medium spiny neurons, and they rescued behavioral deficits, extended survival, attenuated peripheral pathology, and reduced 8-OHDG, MDA and 3-nitrotyrosine immunoreactivity in the striatum [85]. We used two derivatives in this study, CDDO-EA and CDDO-TFEA, which have better brain penetration than the previously used derivative (CDDO-MA), and therefore have great promise from a therapeutic standpoint for disorders of the central nervous system.

3.3.10. Kynurenine-3-monooxygenase inhibitors

Metabolites of the kynurenine pathway of tryptophan metabolism include kynurenic acid, which is a broad spectrum inhibitor of excitatory amino acid receptors. Both we and others showed that there are marked decreases of kynurenic acid levels in HD postmortem brain tissue [120]. Both glutamate-mediated excitotoxicity and free

radical formation occur with decreased kynurenic acid concentrations. Recently, the administration of kynurenic acid was shown to block neurodegeneration in a *Drosophila* model of HD [121]. Furthermore, the oral administration of JM6, an inhibitor of kynurenine-3-monooxygenase, which does not cross into the brain, was shown to increase kynurenic acid levels and reduce extracellular glutamate in the brain [122]. Chronic administration of JM6 extended life span, prevented synaptic loss and decreased microglial activation in the R6/2 transgenic mouse model of HD [122].

3.4. Clinical trials in HD patients

Successful preliminary demonstration of α-tocopherol to limit oxidative damage and neurodegeneration led to a clinical assessment of its potential in human HD [123]. A year-long placebo-controlled, double-blind study was carried out in patients with mild to moderate HD symptoms. Although α-tocopherol had no effect on neurologic or neuropsychiatric symptoms in the treatment group overall, post hoc analysis showed a significant effect on neurologic symptoms in HD patients early in the course of the disease. Peyser and colleagues [123] concluded that α-tocopherol therapy may slow the rate of motor decline early in the course of HD.

As a result of the positive *in vitro* and *in vivo* studies (Sections 3.1 and 3.2 above), a double-blind, placebo-controlled trial of idebenone in 92 HD patients was performed [124]. A clinical trial with idebenone had no effect on primary outcome measures when compared with placebo controls. This trial, however, was not sufficiently powered to detect a significant drug effect, other than a complete cessation of disease progression, more subtle beneficial effects of idebenone may have been present and have been undetected, and therefore require further multicenter trials.

Due to the beneficial effects of creatine supplementation in our neurotoxin HD and transgenic mouse HD models (Sections 3.2 and 3.3 above), we carried out a 16-week, randomized double-blind placebo control phase II clinical trial on the safety and tolerability of 8 g per day of creatine in HD patients [125]. This study illustrated that creatine supplementation significantly reduced elevated serum levels of 8-OHDG back to baseline levels seen in controls. An open-label add-on study of creatine showed further benefits in HD patients. In particular, there was a slowing of the ongoing cortical atrophy. It was also shown that higher doses as high as 30 g daily exerted clinical benefits in the HD patients [126]. In view of this, a double blind placebo controlled phase III clinical trial has been approved and is currently ongoing at a large number of centers, which are part of the Huntington Study Group. In this clinical trial, patients will be titrated up to the maximum tolerated dose, and then they will be assessed utilizing the United Huntington Disease Rating Scale (UHDRS) as well as on quality of life scales, cognition and a variety of other measures.

Based on favorable preclinical CoQ10 efficacy, several human safety and tolerability trials have been conducted using CoQ10 [68]. In each trial, CoQ10 was found to be safe and tolerable. A multicenter clinical trial (CARE-HD) of CoQ10 (600 mg/day) found a trend toward slowing in total functional capacity decline over 30 months, a significant slowing in decline on the independence scale, and a significant beneficial effect on measures of cognitive function. Because the single target dose did not significantly affect the specified primary outcome of the trial, a higher CoQ10 dose study is underway, to investigate whether it will provide greater efficacy in HD patients. This dosage-escalation trial of CoQ10 demonstrated that higher dosages of this compound appear to be generally safe in subjects with HD and in healthy controls [127]. The present phase III trial of the Huntington Study Group is testing CoQ at a dosage of 2400 mg/day in 608 patients over 60 months.

4. Future perspectives: mitochondrial medicine

Oxidative stress and mitochondrial dysfunction in HD are intertwined and as such, blocking one should improve the other. Many of the therapeutic compounds described in the Section 3 above, not only block the oxidative stress, but also improve mitochondrial function in HD. "Mitochondrial medicine" describes efforts to directly manage mitochondrial dysfunction as well as attempts to directly or indirectly manage its consequences, such as reducing oxidative stress or blocking the mitochondrial integration with programmed cell death. Traditional attempts to enhance mitochondrial function or block mitochondrial dysfunction have included therapies with vitamins or such co factors that generate bioenergetic pathway intermediates or feed electrons to the respiratory chain. Mitochondria-targeted antioxidants may enhance the therapeutic benefits of such therapy.

Another important therapeutic approach is to improve the function of PGC-1α in HD. PGC-1α, the master co-regulator of energy metabolism also plays a role in the suppression of oxidative stress. PGC-1α induces mitochondrial uncoupling proteins and antioxidant enzymes, including SOD1, manganese SOD (SOD2), and Gpx-1 [128]. There is substantial evidence for impairment of PGC-1α levels and activity in HD [41–46]. PGC-1α knockout mice exhibit mitochondrial dysfunction, defective bioenergetics, a hyperkinetic movement disorder and striatal degeneration, which are features also observed in HD [129,130]. Selective ablation of PGC-1α leads to increased striatal neuron degeneration, and increased susceptibility to the mitochondrial toxin 3-NP in HD transgenic mice [41]. In concert with the decreased expression and impaired function of PGC-1α, antioxidant systems are impaired. Therefore, therapeutic approaches targeting PGC-1α may be beneficial both in improving mitochondrial function and biogenesis as well as in restoring the expression of antioxidant enzymes and ameliorating oxidative damage in HD. One such compound is bezafibrate, which is a pan-PPAR agonist, which increases expression of PGC-1α, and has shown efficacy in reducing oxidative damage, and improving behavioral deficits, survival, and striatal atrophy in a transgenic mouse model of HD [Johri and Beal, unpublished observations]. A number of other agents including pioglitazone, a PPAR-γ agonist, and thiazolidinedione also show efficacy in exerting neuroprotective effects against mutant htt toxicity both *in vitro* and *in vivo* [131,132]. Agents which can transcriptionally activate the Nrf-2/ARE pathway, leading to increased expression of antioxidant enzymes, and chaperone proteins, as well as reduce the production of oxidants by iNOS and cyclooxygenase-2, are also promising agents for neuroprotection in HD [85]. An advantage of these approaches is that they modulate endogenous neuroprotective pathways, and that they involve catalytic processes which are not consumed but are regenerative, allowing ongoing antioxidant effects. Mitochondrial medicine and transcriptional modulation of antioxidant pathways therefore hold great promise for the development of neuroprotective therapies to ameliorate or halt the progression of HD.

Acknowledgements

References

[1] I.V. Kovtun, Y. Liu, M. Bjoras, A. Klungland, S.H. Wilson, C.T. McMurray, OGG1 initiates age-dependent CAG trinucleotide expansion in somatic cells, Nature 447 (2007) 447–452.
[2] M.A. Nance, Clinical aspects of CAG repeat diseases, Brain Pathol. 7 (1997) 881–900.
[3] J.P. Vonsattel, M. DiFiglia, Huntington disease, J. Neuropathol. Exp. Neurol. 57 (1998) 369–384.

[4] S.B. Dunnett, A.E. Rosser, Cell therapy in Huntington's disease, NeuroRx 1 (2004) 394–405.
[5] N.S. Wexler, J. Lorimer, J. Porter, F. Gomez, C. Moskowitz, E. Shackell, K. Marder, G. Penchaszadeh, S.A. Roberts, J. Gayan, D. Brocklebank, S.S. Cherny, L.R. Cardon, J. Gray, S.R. Dlouhy, S. Wiktorski, M.E. Hodes, P.M. Conneally, J.B. Penney, J. Gusella, J.H. Cha, M. Irizarry, D. Rosas, S. Hersch, Z. Hollingsworth, M. MacDonald, A.B. Young, J.M. Andresen, D.E. Housman, M.M. De Young, E. Bonilla, T. Stillings, A. Negrette, S.R. Snodgrass, M.D. Martinez-Jaurrieta, M.A. Ramos-Arroyo, J. Bickham, J.S. Ramos, F. Marshall, I. Shoulson, G.J. Rey, A. Feigin, N. Arnheim, A. Acevedo-Cruz, L. Acosta, J. Alvir, K. Fischbeck, L.M. Thompson, A. Young, L. Dure, C.J. O'Brien, J. Paulsen, A. Brickman, D. Krch, S. Peery, P. Hogarth, D.S. Higgins Jr., B. Landwehrmeyer, Venezuelan kindreds reveal that genetic and environmental factors modulate Huntington's disease age of onset, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 3498–3503.
[6] A. Rosenblatt, K.Y. Liang, H. Zhou, M.H. Abbott, L.M. Gourley, R.L. Margolis, J. Brandt, C.A. Ross, The association of CAG repeat length with clinical progression in Huntington disease, Neurology 66 (2006) 1016–1020.
[7] M.R. Hayden, B. Kremer, in: C. Scriver, A. Beaudet, W. Sly, D. Valle (Eds.), The Metabolic and Molecular Basis of Inherited Disease, 8th ed., McGraw-Hill, New York, USA, 2001, pp. 5677–5701.
[8] H.D. Rosas, D.H. Salat, S.Y. Lee, A.K. Zaleta, V. Pappu, B. Fischl, D. Greve, N. Hevelone, S.M. Hersch, Cerebral cortex and the clinical expression of Huntington's disease: complexity and heterogeneity, Brain 131 (2008) 1057–1068.
[9] A. Reiner, R.L. Albin, K.D. Anderson, C.J. D'Amato, J.B. Penney, A.B. Young, Differential loss of striatal projection neurons in Huntington disease, Proc. Natl. Acad. Sci. U. S. A. 85 (1988) 5733–5737.
[10] R.L. Albin, A. Reiner, K.D. Anderson, L.S.t. Dure, B. Handelin, R. Balfour, W.O. Whetsell Jr., J.B. Penney, A.B. Young, Preferential loss of striato-external pallidal projection neurons in presymptomatic Huntington's disease, Ann. Neurol. 31 (1992) 425–430.
[11] R.J. Ferrante, N.W. Kowall, M.F. Beal, E.P. Richardson Jr., E.D. Bird, J.B. Martin, Selective sparing of a class of striatal neurons in Huntington's disease, Science 230 (1985) 561–563.
[12] R.J. Ferrante, M.F. Beal, N.W. Kowall, E.P. Richardson Jr., J.B. Martin, Sparing of acetylcholinesterase-containing striatal neurons in Huntington's disease, Brain Res. 411 (1987) 162–166.
[13] R.L. Albin, A.B. Young, J.B. Penney, The functional anatomy of basal ganglia disorders, Trends Neurosci. 12 (1989) 366–375.
[14] J.K. White, W. Auerbach, M.P. Duyao, J.P. Vonsattel, J.F. Gusella, A.L. Joyner, M.E. MacDonald, Huntingtin is required for neurogenesis and is not impaired by the Huntington's disease CAG expansion, Nat. Genet. 17 (1997) 404–410.
[15] I. Dragatsis, M.S. Levine, S. Zeitlin, Inactivation of Hdh in the brain and testis results in progressive neurodegeneration and sterility in mice, Nat. Genet. 26 (2000) 300–306.
[16] A. Reiner, I. Dragatsis, S. Zeitlin, D. Goldowitz, Wild-type huntingtin plays a role in brain development and neuronal survival, Mol. Neurobiol. 28 (2003) 259–276.
[17] M.P. Duyao, A.B. Auerbach, A. Ryan, F. Persichetti, G.T. Barnes, S.M. McNeil, P. Ge, J.P. Vonsattel, J.F. Gusella, A.L. Joyner, M.E. MacDonald, Inactivation of the mouse Huntington's disease gene homolog Hdh, Science 269 (1995) 407–410.
[18] D. Rigamonti, S. Sipione, D. Goffredo, C. Zuccato, E. Fossale, E. Cattaneo, Huntingtin's neuroprotective activity occurs via inhibition of procaspase-9 processing, J. Biol. Chem. 276 (2001) 14545–14548.
[19] M. DiFiglia, E. Sapp, K. Chase, C. Schwarz, A. Meloni, C. Young, E. Martin, J.P. Vonsattel, R. Carraway, S.A. Reeves, F.M. Boyce, N. Aronin, Huntingtin is a cytoplasmic protein associated with vesicles in human and rat brain neurons, Neuron 14 (1995) 1075–1081.
[20] P. Harjes, E.E. Wanker, The hunt for huntingtin function: interaction partners tell many different stories, Trends Biochem. Sci. 28 (2003) 425–433.
[21] J. Velier, M. Kim, C. Schwarz, T.W. Kim, E. Sapp, K. Chase, N. Aronin, M. DiFiglia, Wild-type and mutant huntingtins function in vesicle trafficking in the secretory and endocytic pathways, Exp. Neurol. 152 (1998) 34–40.
[22] J.P. Caviston, E.L. Holzbaur, Huntingtin as an essential integrator of intracellular vesicular trafficking, Trends Cell Biol. 19 (2009) 147–155.
[23] J.D. Godin, K. Colombo, M. Molina-Calavita, G. Keryer, D. Zala, B.C. Charrin, P. Dietrich, M.L. Volvert, F. Guillemot, I. Dragatsis, Y. Bellaiche, F. Saudou, L. Nguyen, S. Humbert, Huntingtin is required for mitotic spindle orientation and mammalian neurogenesis, Neuron 67 (2010) 392–406.
[24] A. Sawa, E. Nagata, S. Sutcliffe, P. Dulloor, M.B. Cascio, Y. Ozeki, S. Roy, C.A. Ross, S.H. Snyder, Huntingtin is cleaved by caspases in the cytoplasm and translocated to the nucleus via perinuclear sites in Huntington's disease patient lymphoblasts, Neurobiol. Dis. 20 (2005) 267–274.
[25] S. Imarisio, J. Carmichael, V. Korolchuk, C.W. Chen, S. Saiki, C. Rose, G. Krishna, J.E. Davies, E. Ttofi, B.R. Underwood, D.C. Rubinsztein, Huntington's disease: from pathology and genetics to potential therapies, Biochem. J. 412 (2008) 191–209.
[26] B.I. Bae, M.R. Hara, M.B. Cascio, C.L. Wellington, M.R. Hayden, C.A. Ross, H.C. Ha, X.J. Li, S.H. Snyder, A. Sawa, Mutant huntingtin: nuclear translocation and cytotoxicity mediated by GAPDH, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 3405–3409.
[27] V.C. Wheeler, J.K. White, C.A. Gutekunst, V. Vrbanac, M. Weaver, X.J. Li, S.H. Li, H. Yi, J.P. Vonsattel, J.F. Gusella, S. Hersch, W. Auerbach, A.L. Joyner, M.E. MacDonald, Long glutamine tracts cause nuclear localization of a novel form of huntingtin in medium spiny striatal neurons in HdhQ92 and HdhQ111 knock-in mice, Hum. Mol. Genet. 9 (2000) 503–513.
[28] M. DiFiglia, E. Sapp, K.O. Chase, S.W. Davies, G.P. Bates, J.P. Vonsattel, N. Aronin, Aggregation of huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain, Science 277 (1997) 1990–1993.
[29] S. Palfi, E. Brouillet, B. Jarraya, J. Bloch, C. Jan, M. Shin, F. Conde, X.J. Li, P. Aebischer, P. Hantraye, N. Deglon, Expression of mutated huntingtin fragment in the putamen is sufficient to produce abnormal movement in non-human primates, Mol. Ther. 15 (2007) 1444–1451.
[30] D. Martindale, A. Hackam, A. Wieczorek, L. Ellerby, C. Wellington, K. McCutcheon, R. Singaraja, P. Kazemi-Esfarjani, R. Devon, S.U. Kim, D.E. Bredesen, F. Tufaro, M.R. Hayden, Length of huntingtin and its polyglutamine tract influences localization and frequency of intracellular aggregates, Nat. Genet. 18 (1998) 150–154.
[31] J.P. Miller, J. Holcomb, I. Al-Ramahi, M. de Haro, J. Gafni, N. Zhang, E. Kim, M. Sanhueza, C. Torcassi, S. Kwak, J. Botas, R.E. Hughes, L.M. Ellerby, Matrix metalloproteinases are modifiers of huntingtin proteolysis and toxicity in Huntington's disease, Neuron 67 (2010) 199–212.
[32] A. Johri, M.F. Beal, Hunting-ton for new proteases: MMPs as the new target? Neuron 67 (2010) 171–173.
[33] F.R. Fusco, Q. Chen, W.J. Lamoreaux, G. Figueredo-Cardenas, Y. Jiao, J.A. Coffman, D.J. Surmeier, M.G. Honig, L.R. Carlock, A. Reiner, Cellular localization of huntingtin in striatal and cortical neurons in rats: lack of correlation with neuronal vulnerability in Huntington's disease, J. Neurosci. 19 (1999) 1189–1202.
[34] S.E. Browne, M.F. Beal, Oxidative damage in Huntington's disease pathogenesis, Antioxid. Redox Signal. 8 (2006) 2061–2073.
[35] S.E. Browne, M.F. Beal, The energetics of Huntington's disease, Neurochem. Res. 29 (2004) 531–546.
[36] J. Kim, J.P. Moody, C.K. Edgerly, O.L. Bordiuk, K. Cormier, K. Smith, M.F. Beal, R.J. Ferrante, Mitochondrial loss, dysfunction and altered dynamics in Huntington's disease, Hum. Mol. Genet. 19 (2010) 3919–3935.
[37] V. Costa, M. Giacomello, R. Hudec, R. Lopreiato, G. Ermak, D. Lim, W. Malorni, K.J. Davies, E. Carafoli, L. Scorrano, Mitochondrial fission and cristae disruption increase the response of cell models of Huntington's disease to apoptotic stimuli, EMBO Mol. Med. 2 (2010) 490–503.
[38] W. Song, J. Chen, A. Petrilli, G. Liot, E. Klinglmayr, Y. Zhou, P. Poquiz, J. Tjong, M.A. Pouladi, M.R. Hayden, E. Masliah, M. Ellisman, I. Rouiller, R. Schwarzenbacher, B. Bossy, G. Perkins, E. Bossy-Wetzel, Mutant huntingtin binds the mitochondrial fission GTPase dynamin-related protein-1 and increases its enzymatic activity, Nat. Med. 17 (2011) 377–382.
[39] A. Johri, R.K. Chaturvedi, M.F. Beal, Hugging tight in Huntington's, Nat. Med. 17 (2011) 245–246.
[40] U. Shirendeb, A.P. Reddy, M. Manczak, M.J. Calkins, P. Mao, D.A. Tagle, P.H. Reddy, Abnormal mitochondrial dynamics, mitochondrial loss and mutant huntingtin oligomers in Huntington's disease: implications for selective neuronal damage, Hum. Mol. Genet. 20 (2011) 1438–1455.
[41] L. Cui, H. Jeong, F. Borovecki, C.N. Parkhurst, N. Tanese, D. Krainc, Transcriptional repression of PGC-1alpha by mutant huntingtin leads to mitochondrial dysfunction and neurodegeneration, Cell 127 (2006) 59–69.
[42] P. Weydt, V.V. Pineda, A.E. Torrence, R.T. Libby, T.F. Satterfield, E.R. Lazarowski, M.L. Gilbert, G.J. Morton, T.K. Bammler, A.D. Strand, L. Cui, R.P. Beyer, C.N. Easley, A.C. Smith, D. Krainc, S. Luquet, I.R. Sweet, M.W. Schwartz, A.R. La Spada, Thermoregulatory and metabolic defects in Huntington's disease transgenic mice implicate PGC-1alpha in Huntington's disease neurodegeneration, Cell Metab. 4 (2006) 349–362.
[43] J.K. McGill, M.F. Beal, PGC-1alpha, a new therapeutic target in Huntington's disease? Cell 127 (2006) 465–468.
[44] R.K. Chaturvedi, P. Adhihetty, S. Shukla, T. Hennessy, N. Calingasan, L. Yang, A. Starkov, M. Kiaei, M. Cannella, J. Sassone, A. Ciammola, F. Squitieri, M.F. Beal, Impaired PGC-1alpha function in muscle in Huntington's disease, Hum. Mol. Genet. 18 (2009) 3048–3065.
[45] R.K. Chaturvedi, N.Y. Calingasan, L. Yang, T. Hennessey, A. Johri, M.F. Beal, Impairment of PGC-1alpha expression, neuropathology and hepatic steatosis in a transgenic mouse model of Huntington's disease following chronic energy deprivation, Hum. Mol. Genet. 19 (2010) 3190–3205.
[46] A. Johri, A.A. Starkov, A. Chandra, T. Hennessey, A. Sharma, S. Orobello, F. Squitieri, L. Yang, M.F. Beal, Truncated peroxisome proliferator-activated receptor-gamma coactivator 1alpha splice variant is severely altered in Huntington's disease, Neurodegener. Dis. 8 (2011) 496–503.
[47] P.H. Reddy, P. Mao, M. Manczak, Mitochondrial structural and functional dynamics in Huntington's disease, Brain Res. Rev. 61 (2009) 33–48.
[48] B. Halliwell, J.M.C. Gutteridge, in: B. Halliwell, J.M.C. Gutteridge (Eds.), Free Radicals in Biology and Medicine, 3 rd ed., Oxford University Press, 1999.
[49] D.M. Miller, G.R. Buettner, S.D. Aust, Transition metals as catalysts of "autoxidation" reactions, Free Radic. Biol. Med. 8 (1990) 95–108.
[50] E. Cadenas, H. Sies, The lag phase, Free. Radic. Res. 28 (1998) 601–609.
[51] P. Kovacic, R.S. Pozos, R. Somanathan, N. Shangari, P.J. O'Brien, Mechanism of mitochondrial uncouplers, inhibitors, and toxins: focus on electron transfer, free radicals, and structure–activity relationships, Curr. Med. Chem. 12 (2005) 2601–2623.
[52] F.L. Muller, Y. Liu, H. Van Remmen, Complex III releases superoxide to both sides of the inner mitochondrial membrane, J. Biol. Chem. 279 (2004) 49064–49073.
[53] J. Aikens, T.A. Dix, Perhydroxyl radical (HOO•) initiated lipid peroxidation. The role of fatty acid hydroperoxides, J. Biol. Chem. 266 (1991) 15091–15098.
[54] J.S. Beckman, W.H. Koppenol, Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and ugly, Am. J. Physiol. 271 (1996) C1424–C1437.
[55] G. Barja, Free radicals and aging, Trends Neurosci. 27 (2004) 595–600.
[56] A. Boveris, Biochemistry of free radicals: from electrons to tissues, Medicina (B Aires) 58 (1998) 350–356.
[57] G. Lenaz, The mitochondrial production of reactive oxygen species: mechanisms and implications in human pathology, IUBMB Life 52 (2001) 159–164.
[58] W. Droge, Free radicals in the physiological control of cell function, Physiol. Rev. 82 (2002) 47–95.

[59] K. Hensley, K.A. Robinson, S.P. Gabbita, S. Salsman, R.A. Floyd, Reactive oxygen species, cell signaling, and cell injury, Free Radic. Biol. Med. 28 (2000) 1456–1462.

[60] T. Finkel, Reactive oxygen species and signal transduction, IUBMB Life 52 (2001) 3–6.

[61] A. Jahani-Asl, E.C. Cheung, M. Neuspiel, J.G. MacLaurin, A. Fortin, D.S. Park, H.M. McBride, R.S. Slack, Mitofusin 2 protects cerebellar granule neurons against injury-induced cell death, J. Biol. Chem. 282 (2007) 23788–23798.

[62] M.J. Barsoum, H. Yuan, A.A. Gerencser, G. Liot, Y. Kushnareva, S. Graber, I. Kovacs, W.D. Lee, J. Waggoner, J. Cui, A.D. White, B. Bossy, J.C. Martinou, R.J. Youle, S.A. Lipton, M.H. Ellisman, G.A. Perkins, E. Bossy-Wetzel, Nitric oxide-induced mitochondrial fission is regulated by dynamin-related GTPases in neurons, EMBO J. 25 (2006) 3900–3911.

[63] W.G. Siems, T. Grune, H. Esterbauer, 4-Hydroxynonenal formation during ischemia and reperfusion of rat small intestine, Life Sci. 57 (1995) 785–789.

[64] E.R. Stadtman, Role of oxidant species in aging, Curr. Med. Chem. 11 (2004) 1105–1112.

[65] T.J. Montine, M.F. Beal, D. Robertson, M.E. Cudkowicz, I. Biaggioni, H. O'Donnell, W.E. Zackert, L.J. Roberts, J.D. Morrow, Cerebrospinal fluid F2-isoprostanes are elevated in Huntington's disease, Neurology 52 (1999) 1104–1105.

[66] S.E. Browne, R.J. Ferrante, M.F. Beal, Oxidative stress in Huntington's disease, Brain Pathol. 9 (1999) 147–163.

[67] M.F. Beal, R.J. Ferrante, Experimental therapeutics in transgenic mouse models of Huntington's disease, Nat. Rev. Neurosci. 5 (2004) 373–384.

[68] E.C. Stack, W.R. Matson, R.J. Ferrante, Evidence of oxidant damage in Huntington's disease: translational strategies using antioxidants, Ann. N. Y. Acad. Sci. 1147 (2008) 79–92.

[69] N. Klepac, M. Relja, R. Klepac, S. Hecimovic, T. Babic, V. Trkulja, Oxidative stress parameters in plasma of Huntington's disease patients, asymptomatic Huntington's disease gene carriers and healthy subjects: a cross-sectional study, J. Neurol. 254 (2007) 1676–1683.

[70] M.A. Sorolla, G. Reverter-Branchat, J. Tamarit, I. Ferrer, J. Ros, E. Cabiscol, Proteomic and oxidative stress analysis in human brain samples of Huntington disease, Free Radic. Biol. Med. 45 (2008) 667–678.

[71] I. Tasset, F. Sanchez, I. Tunez, The molecular bases of Huntington's disease: the role played by oxidative stress, Rev. Neurol. 49 (2009) 424–429.

[72] N. Stoy, G.M. Mackay, C.M. Forrest, J. Christofides, M. Egerton, T.W. Stone, L.G. Darlington, Tryptophan metabolism and oxidative stress in patients with Huntington's disease, J. Neurochem. 93 (2005) 611–623.

[73] C.M. Chen, Y.R. Wu, M.L. Cheng, J.L. Liu, Y.M. Lee, P.W. Lee, B.W. Soong, D.T. Chiu, Increased oxidative damage and mitochondrial abnormalities in the peripheral blood of Huntington's disease patients, Biochem. Biophys. Res. Commun. 359 (2007) 335–340.

[74] I. Tunez, F. Sanchez-Lopez, E. Aguera, R. Fernandez-Bolanos, F.M. Sanchez, I. Tasset-Cuevas, Important role of oxidative stress biomarkers in Huntington's disease, J. Med. Chem. 54 (2011) 5602–5606.

[75] H. Braak, E. Braak, Allocortical involvement in Huntington's disease, Neuropathol. Appl. Neurobiol. 18 (1992) 539–547.

[76] I. Tellez-Nagel, A.B. Johnson, R.D. Terry, Studies on brain biopsies of patients with Huntington's chorea, J. Neuropathol. Exp. Neurol. 33 (1974) 308–332.

[77] N.J. Butterworth, L. Williams, J.Y. Bullock, D.R. Love, R.L. Faull, M. Dragunow, Trinucleotide (CAG) repeat length is positively correlated with the degree of DNA fragmentation in Huntington's disease striatum, Neuroscience 87 (1998) 49–53.

[78] C. Portera-Cailliau, J.C. Hedreen, D.L. Price, V.E. Koliatsos, Evidence for apoptotic cell death in Huntington disease and excitotoxic animal models, J. Neurosci. 15 (1995) 3775–3787.

[79] M.A. Sorolla, M.J. Rodriguez-Colman, J. Tamarit, Z. Ortega, J.J. Lucas, I. Ferrer, J. Ros, E. Cabiscol, Protein oxidation in Huntington disease affects energy production and vitamin B6 metabolism, Free Radic. Biol. Med. 49 (2010) 612–621.

[80] D. Lim, L. Fedrizzi, M. Tartari, C. Zuccato, E. Cattaneo, M. Brini, E. Carafoli, Calcium homeostasis and mitochondrial dysfunction in striatal neurons of Huntington disease, J. Biol. Chem. 283 (2008) 5780–5789.

[81] S.J. Tabrizi, M.W. Cleeter, J. Xuereb, J.W. Taanman, J.M. Cooper, A.H. Schapira, Biochemical abnormalities and excitotoxicity in Huntington's disease brain, Ann. Neurol. 45 (1999) 25–32.

[82] M. Patel, B.J. Day, J.D. Crapo, I. Fridovich, J.O. McNamara, Requirement for superoxide in excitotoxic cell death, Neuron 16 (1996) 345–355.

[83] M. Perluigi, H.F. Poon, W. Maragos, W.M. Pierce, J.B. Klein, V. Calabrese, C. Cini, C. De Marco, D.A. Butterfield, Proteomic analysis of protein expression and oxidative modification in r6/2 transgenic mice: a model of Huntington disease, Mol. Cell. Proteomics 4 (2005) 1849–1861.

[84] K. Acevedo-Torres, L. Berrios, N. Rosario, V. Dufault, S. Skatchkov, M.J. Eaton, C.A. Torres-Ramos, S. Ayala-Torres, Mitochondrial DNA damage is a hallmark of chemically induced and the R6/2 transgenic model of Huntington's disease, DNA Repair (Amst) 8 (2009) 126–136.

[85] C. Stack, D. Ho, E. Wille, N.Y. Calingasan, C. Williams, K. Liby, M. Sporn, M. Dumont, M.F. Beal, Triterpenoids CDDO-ethyl amide and CDDO-trifluoroethyl amide improve the behavioral phenotype and brain pathology in a transgenic mouse model of Huntington's disease, Free Radic. Biol. Med. 49 (2010) 147–158.

[86] M. Gray, D.I. Shirasaki, C. Cepeda, V.M. Andre, B. Wilburn, X.H. Lu, J. Tao, I. Yamazaki, S.H. Li, Y.E. Sun, X.J. Li, M.S. Levine, X.W. Yang, Full-length human mutant huntingtin with a stable polyglutamine repeat can elicit progressive and selective neuropathogenesis in BACHD mice, J. Neurosci. 28 (2008) 6182–6195.

[87] A. Petersen, R.F. Castilho, O. Hansson, T. Wieloch, P. Brundin, Oxidative stress, mitochondrial permeability transition and activation of caspases in calcium ionophore A23187-induced death of cultured striatal neurons, Brain Res. 857 (2000) 20–29.

[88] M.D. Majewska, J.A. Bell, Ascorbic acid protects neurons from injury induced by glutamate and NMDA, Neuroreport 1 (1990) 194–196.

[89] M. Miyamoto, T.H. Murphy, R.L. Schnaar, J.T. Coyle, Antioxidants protect against glutamate-induced cytotoxicity in a neuronal cell line, J. Pharmacol. Exp. Ther. 250 (1989) 1132–1140.

[90] J. Wang, C.M. Pfleger, L. Friedman, R. Vittorino, W. Zhao, X. Qian, L. Conley, L. Ho, G.M. Pasinetti, Potential application of grape derived polyphenols in Huntington's disease, Transl. Neurosci. 1 (2010) 95–100.

[91] J. Wang, L. Ho, W. Zhao, K. Ono, C. Rosensweig, L. Chen, N. Humala, D.B. Teplow, G.M. Pasinetti, Grape-derived polyphenolics prevent Abeta oligomerization and attenuate cognitive deterioration in a mouse model of Alzheimer's disease, J. Neurosci. 28 (2008) 6388–6392.

[92] T. Uz, P. Giusti, D. Franceschini, A. Kharlamov, H. Manev, Protective effect of melatonin against hippocampal DNA damage induced by intraperitoneal administration of kainate to rats, Neuroscience 73 (1996) 631–636.

[93] I. Tunez, P. Montilla, M. Del Carmen Munoz, M. Feijoo, M. Salcedo, Protective effect of melatonin on 3-nitropropionic acid-induced oxidative stress in synaptosomes in an animal model of Huntington's disease, J. Pineal Res. 37 (2004) 252–256.

[94] A. Santamaria, R. Salvatierra-Sanchez, B. Vazquez-Roman, D. Santiago-Lopez, J. Villeda-Hernandez, S. Galvan-Arzate, M.E. Jimenez-Capdeville, S.F. Ali, Protective effects of the antioxidant selenium on quinolinic acid-induced neurotoxicity in rats: in vitro and in vivo studies, J. Neurochem. 86 (2003) 479–488.

[95] J.K. Ryu, S.U. Kim, J.G. McLarnon, Neuroprotective effects of pyruvate in the quinolinic acid rat model of Huntington's disease, Exp. Neurol. 183 (2003) 700–704.

[96] M. Miyamoto, J.T. Coyle, Idebenone attenuates neuronal degeneration induced by intrastriatal injection of excitotoxins, Exp. Neurol. 108 (1990) 38–45.

[97] C.D. Keene, C.M. Rodrigues, T. Eich, C. Linehan-Stieers, A. Abt, B.T. Kren, C.J. Steer, W.C. Low, A bile acid protects against motor and cognitive deficits and reduces striatal degeneration in the 3-nitropropionic acid model of Huntington's disease, Exp. Neurol. 171 (2001) 351–360.

[98] M.A. Fontaine, J.W. Geddes, A. Banks, D.A. Butterfield, Effect of exogenous and endogenous antioxidants on 3-nitropionic acid-induced in vivo oxidative stress and striatal lesions: insights into Huntington's disease, J. Neurochem. 75 (2000) 1709–1715.

[99] J.M. Lawler, W.S. Barnes, G. Wu, W. Song, S. Demaree, Direct antioxidant properties of creatine, Biochem. Biophys. Res. Commun. 290 (2002) 47–52.

[100] E. O'Gorman, G. Beutner, M. Dolder, A.P. Koretsky, D. Brdiczka, T. Wallimann, The role of creatine kinase in inhibition of mitochondrial permeability transition, FEBS Lett. 414 (1997) 253–257.

[101] R.T. Matthews, L. Yang, B.G. Jenkins, R.J. Ferrante, B.R. Rosen, R. Kaddurah-Daouk, M.F. Beal, Neuroprotective effects of creatine and cyclocreatine in animal models of Huntington's disease, J. Neurosci. 18 (1998) 156–163.

[102] D.A. Shear, K.L. Haik, G.L. Dunbar, Creatine reduces 3-nitropropionic-acid-induced cognitive and motor abnormalities in rats, Neuroreport 11 (2000) 1833–1837.

[103] M.F. Beal, D.R. Henshaw, B.G. Jenkins, B.R. Rosen, J.B. Schulz, Coenzyme Q10 and nicotinamide block striatal lesions produced by the mitochondrial toxin malonate, Ann. Neurol. 36 (1994) 882–888.

[104] R.T. Matthews, L. Yang, S. Browne, M. Baik, M.F. Beal, Coenzyme Q10 administration increases brain mitochondrial concentrations and exerts neuroprotective effects, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 8892–8897.

[105] L. Yang, N.Y. Calingasan, E.J. Wille, K. Cormier, K. Smith, R.J. Ferrante, M.F. Beal, Combination therapy with coenzyme Q10 and creatine produces additive neuroprotective effects in models of Parkinson's and Huntington's diseases, J. Neurochem. 109 (2009) 1427–1439.

[106] P. Kumar, H. Kalonia, A. Kumar, Possible nitric oxide modulation in protective effect of FK-506 against 3-nitropropionic acid-induced behavioral, oxidative, neurochemical, and mitochondrial alterations in rat brain, Drug Chem. Toxicol. 33 (2010) 377–392.

[107] P. Kumar, A. Kumar, Effect of lycopene and epigallocatechin-3-gallate against 3-nitropropionic acid induced cognitive dysfunction and glutathione depletion in rat: a novel nitric oxide mechanism, Food Chem. Toxicol. 47 (2009) 2522–2530.

[108] L. Yang, N.Y. Calingasan, B. Thomas, R.K. Chaturvedi, M. Kiaei, E.J. Wille, K.T. Liby, C. Williams, D. Royce, R. Risingsong, E.S. Musiek, J.D. Morrow, M. Sporn, M.F. Beal, Neuroprotective effects of the triterpenoid, CDDO methyl amide, a potent inducer of Nrf2-mediated transcription, PLoS One 4 (2009) e5757.

[109] L. Packer, H.J. Tritschler, K. Wessel, Neuroprotection by the metabolic antioxidant alpha-lipoic acid, Free Radic. Biol. Med. 22 (1997) 359–378.

[110] K.P. Shay, R.F. Moreau, E.J. Smith, A.R. Smith, T.M. Hagen, Alpha-lipoic acid as a dietary supplement: molecular mechanisms and therapeutic potential, Biochim. Biophys. Acta 1790 (2009) 1149–1160.

[111] O.A. Andreassen, R.J. Ferrante, A. Dedeoglu, M.F. Beal, Lipoic acid improves survival in transgenic mouse models of Huntington's disease, Neuroreport 12 (2001) 3371–3373.

[112] O.A. Andreassen, R.J. Ferrante, H.M. Huang, A. Dedeoglu, L. Park, K.L. Ferrante, J. Kwon, D.R. Borchelt, C.A. Ross, G.E. Gibson, M.F. Beal, Dichloroacetate exerts therapeutic effects in transgenic mouse models of Huntington's disease, Ann. Neurol. 50 (2001) 112–117.

[113] P. Klivenyi, R.J. Ferrante, G. Gardian, S. Browne, P.E. Chabrier, M.F. Beal, Increased survival and neuroprotective effects of BN82451 in a transgenic mouse model of Huntington's disease, J. Neurochem. 86 (2003) 267–272.

[114] C.D. Keene, C.M. Rodrigues, T. Eich, M.S. Chhabra, C.J. Steer, W.C. Low, Taurursodeoxycholic acid, a bile acid, is neuroprotective in a transgenic animal

model of Huntington's disease, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 10671–10676.

[115] M.A. Tarnopolsky, M.F. Beal, Potential for creatine and other therapies targeting cellular energy dysfunction in neurological disorders, Ann. Neurol. 49 (2001) 561–574.

[116] R.J. Ferrante, O.A. Andreassen, B.G. Jenkins, A. Dedeoglu, S. Kuemmerle, J.K. Kubilus, R. Kaddurah-Daouk, S.M. Hersch, M.F. Beal, Neuroprotective effects of creatine in a transgenic mouse model of Huntington's disease, J. Neurosci. 20 (2000) 4389–4397.

[117] O.A. Andreassen, A. Dedeoglu, R.J. Ferrante, B.G. Jenkins, K.L. Ferrante, M. Thomas, A. Friedlich, S.E. Browne, G. Schilling, D.R. Borchelt, S.M. Hersch, C.A. Ross, M.F. Beal, Creatine increases survival and delays motor symptoms in a transgenic animal model of Huntington's disease, Neurobiol. Dis. 8 (2001) 479–491.

[118] R.J. Ferrante, O.A. Andreassen, A. Dedeoglu, K.L. Ferrante, B.G. Jenkins, S.M. Hersch, M.F. Beal, Therapeutic effects of coenzyme Q10 and remacemide in transgenic mouse models of Huntington's disease, J. Neurosci. 22 (2002) 1592–1599.

[119] E. Vamos, K. Voros, L. Vecsei, P. Klivenyi, Neuroprotective effects of L-carnitine in a transgenic animal model of Huntington's disease, Biomed. Pharmacother. 64 (2010) 282–286.

[120] M.F. Beal, W.R. Matson, E. Storey, P. Milbury, E.A. Ryan, T. Ogawa, E.D. Bird, Kynurenic acid concentrations are reduced in Huntington's disease cerebral cortex, J. Neurol. Sci. 108 (1992) 80–87.

[121] S. Campesan, E.W. Green, C. Breda, K.V. Sathyasaikumar, P.J. Muchowski, R. Schwarcz, C.P. Kyriacou, F. Giorgini, The kynurenine pathway modulates neurodegeneration in a *Drosophila* model of Huntington's disease, Curr. Biol. 21 (2011) 961–966.

[122] D. Zwilling, S.Y. Huang, K.V. Sathyasaikumar, F.M. Notarangelo, P. Guidetti, H.Q. Wu, J. Lee, J. Truong, Y. Andrews-Zwilling, E.W. Hsieh, J.Y. Louie, T. Wu, K. Scearce-Levie, C. Patrick, A. Adame, F. Giorgini, S. Moussaoui, G. Laue, A. Rassoulpour, G. Flik, Y. Huang, J.M. Muchowski, E. Masliah, R. Schwarcz, P.J. Muchowski, Kynurenine 3-monooxygenase inhibition in blood ameliorates neurodegeneration, Cell 145 (2011) 863–874.

[123] C.E. Peyser, M. Folstein, G.A. Chase, S. Starkstein, J. Brandt, J.R. Cockrell, F. Bylsma, J.T. Coyle, P.R. McHugh, S.E. Folstein, Trial of D-alpha-tocopherol in Huntington's disease, Am. J. Psychiatry 152 (1995) 1771–1775.

[124] N.G. Ranen, C.E. Peyser, J.T. Coyle, F.W. Bylsma, M. Sherr, L. Day, M.F. Folstein, J. Brandt, C.A. Ross, S.E. Folstein, A controlled trial of idebenone in Huntington's disease, Mov. Disord. 11 (1996) 549–554.

[125] S.M. Hersch, S. Gevorkian, K. Marder, C. Moskowitz, A. Feigin, M. Cox, P. Como, C. Zimmerman, M. Lin, L. Zhang, A.M. Ulug, M.F. Beal, W. Matson, M. Bogdanov, E. Ebbel, A. Zaleta, Y. Kaneko, B. Jenkins, N. Hevelone, H. Zhang, H. Yu, D. Schoenfeld, R. Ferrante, H.D. Rosas, Creatine in Huntington disease is safe, tolerable, bioavailable in brain and reduces serum 8OH2'dG, Neurology 66 (2006) 250–252.

[126] M.F. Beal, Neuroprotective effects of creatine, Amino Acids 40 (2011) 1305–1313.

[127] Huntington Study Group, Pre2CARE InvestigatorsH.C. Hyson, K. Kieburtz, I. Shoulson, M. McDermott, B. Ravina, E.A. de Blieck, M.E. Cudkowicz, R.J. Ferrante, P. Como, S. Frank, C. Zimmerman, K. Ferrante, K. Newhall, D. Jennings, T. Kelsey, F. Walker, V. Hunt, S. Daigneault, M. Goldstein, J. Weber, A. Watts, M.F. Beal, S.E. Browne, L.J. Metakis, Safety and tolerability of high-dosage coenzyme Q10 in Huntington's disease and healthy subjects, Mov. Disord. 25 (2010) 1924–1928.

[128] J. St-Pierre, S. Drori, M. Uldry, J.M. Silvaggi, J. Rhee, S. Jager, C. Handschin, K. Zheng, J. Lin, W. Yang, D.K. Simon, R. Bachoo, B.M. Spiegelman, Suppression of reactive oxygen species and neurodegeneration by the PGC-1 transcriptional coactivators, Cell 127 (2006) 397–408.

[129] T.C. Leone, J.J. Lehman, B.N. Finck, P.J. Schaeffer, A.R. Wende, S. Boudina, M. Courtois, D.F. Wozniak, N. Sambandam, C. Bernal-Mizrachi, Z. Chen, J.O. Holloszy, D.M. Medeiros, R.E. Schmidt, J.E. Saffitz, E.D. Abel, C.F. Semenkovich, D.P. Kelly, PGC-1alpha deficiency causes multi-system energy metabolic derangements: muscle dysfunction, abnormal weight control and hepatic steatosis, PLoS Biol. 3 (2005) e101.

[130] J. Lin, P.H. Wu, P.T. Tarr, K.S. Lindenberg, J. St-Pierre, C.Y. Zhang, V.K. Mootha, S. Jager, C.R. Vianna, R.M. Reznick, L. Cui, M. Manieri, M.X. Donovan, Z. Wu, M.P. Cooper, M.C. Fan, L.M. Rohas, A.M. Zavacki, S. Cinti, G.I. Shulman, B.B. Lowell, D. Krainc, B.M. Spiegelman, Defects in adaptive energy metabolism with CNS-linked hyperactivity in PGC-1alpha null mice, Cell 119 (2004) 121–135.

[131] H. Kalonia, P. Kumar, A. Kumar, Pioglitazone ameliorates behavioral, biochemical and cellular alterations in quinolinic acid induced neurotoxicity: possible role of peroxisome proliferator activated receptor-Upsilon (PPARUpsilon) in Huntington's disease, Pharmacol. Biochem. Behav. 96 (2010) 115–124.

[132] M.C. Chiang, C.M. Chen, M.R. Lee, H.W. Chen, H.M. Chen, Y.S. Wu, C.H. Hung, J.J. Kang, C.P. Chang, C. Chang, Y.R. Wu, Y.S. Tsai, Y. Chern, Modulation of energy deficiency in Huntington's disease via activation of the peroxisome proliferator-activated receptor gamma, Hum. Mol. Genet. 19 (2010) 4043–4058.

[133] S. Kasparova, Z. Sumbalova, P. Bystricky, J. Kucharska, T. Liptaj, V. Mlynarik, A. Gvozdjakova, Effect of coenzyme Q10 and vitamin E on brain energy metabolism in the animal model of Huntington's disease, Neurochem. Int. 48 (2006) 93–99.

[134] H. Kalonia, P. Kumar, A. Kumar, Targeting oxidative stress attenuates malonic acid induced Huntington like behavioral and mitochondrial alterations in rats, Eur. J. Pharmacol. 634 (2010) 46–52.

[135] C.G. Goety, C.M. Tanner, J.A. Cohen, J.A. Thelen, V.S. Carroll, H.L. Klawans, R.G. Fariello, L-acetyl-carnitine in Huntington's disease: double-blind placebo controlled crossover study of drug effects on movement disorder and dementia, Mov. Disord. 5 (1990) 263–265.

[136] P.D. Maldonado, E. Molina-Jijon, J. Villeda-Hernandez, S. Galvan-Arzate, A. Santamaria, J. Pedraza-Chaverri, NAD(P)H oxidase contributes to neurotoxicity in an excitotoxic/prooxidant model of Huntington's disease in rats: protective role of apocynin, J. Neurosci. Res. 88 (2010) 620–629.

[137] J. Lee, B. Kosaras, S.J. Del Signore, K. Cormier, A. McKee, R.R. Ratan, N.W. Kowall, H. Ryu, Modulation of lipid peroxidation and mitochondrial function improves neuropathology in Huntington's disease mice, Acta Neuropathol. 121 (2011) 487–498.

[138] I. Tasset, A.J. Pontes, A.J. Hinojosa, R. de la Torre, I. Tunez, Olive oil reduces oxidative damage in a 3-nitropropionic acid-induced Huntington's disease-like rat model, Nutr. Neurosci. 14 (2011) 106–111.

[139] J.K. Ryu, H.B. Choi, J.G. McLarnon, Combined minocycline plus pyruvate treatment enhances effects of each agent to inhibit inflammation, oxidative damage, and neuronal loss in an excitotoxic animal model of Huntington's disease, Neuroscience 141 (2006) 1835–1848.

[140] P. Kumar, A. Kumar, Possible neuroprotective effect of *Withania somnifera* root extract against 3-nitropropionic acid-induced behavioral, biochemical, and mitochondrial dysfunction in an animal model of Huntington's disease, J. Med. Food 12 (2009) 591–600.