\*Forum Review Article

**Title:** Mitochondrial and redox-based therapeutic strategies in Huntington's disease

**Abbreviated title:** HD mitochondrial and redox therapies

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Abstract word count: **250**; Word count (Introduction to Conclusion): **8667**; Reference number: **215**; Number of greyscale illustrations: **0**; Number of color illustrations: **6**

**Keywords:** Huntington’s Disease, mitochondrial dysfunction, oxidative stress, mutant huntingtin, therapies

**ABSTRACT**

**SIGNIFICANCE:** The molecular processes that determine Huntington’s disease (HD) pathogenesis are not yet fully understood, and until now, no effective neuroprotective therapeutic strategies have been developed. Mitochondria are one of most important organelles required for neuronal homeostasis, either by providing metabolic pathways relevant for energy production, regulating calcium homeostasis or controlling free radical generation and cell death. Because augmented reactive oxygen species (ROS) accompanied by mitochondrial dysfunction are relevant early HD mechanisms, targeting these cellular mechanisms may constitute relevant therapeutic approaches.

**RECENT ADVANCES:** Previous findings point towards a close relationship between mitochondrial dysfunction and redox changes in HD. Mutant huntingtin (mHTT) can directly interact with mitochondrial proteins, as TIM23, disrupting mitochondrial proteostasis and favoring ROS production and HD progression. Furthermore, abnormal brain and muscle redox signaling contribute to altered proteostasis and motor impairment in HD, which can be improved with the mitochondria-targeted antioxidant MitoQ or resveratrol, a SIRT1 activator that ameliorates mitochondrial biogenesis and function.

**CRITICAL ISSUES:** Various antioxidants and metabolic enhancers have been studied in HD, however the real outcome of these molecules is still debatable. New compounds have proven to ameliorate mitochondrial and redox-based signaling pathways in early stages of HD, potentially precluding selective neurodegeneration.

**FUTURE DIRECTIONS:** Unravelling the molecular etiology of deregulated mitochondrial function and dynamics, and oxidative stress opens new prospects for HD therapeutics. In this review we explore the role of redox unbalance and mitochondrial dysfunction in HD progression, and further describe advances on clinical trials in HD based on mitochondrial and redox-based therapeutic strategies.

**1 –MAIN FEATURES OF HUNTINGTON’S DISEASE PATHOGENESIS**

Huntington’s Disease (HD) is an autosomal dominant progressive neurodegenerative disorder, affecting 5 to 10 per 100,000 individuals in North America and Europe (14). The disease is caused by cytosine-adenine-guanine (CAG) repeat extension in the *HTT* gene, encoding for a polyglutamine (polyQ) tract at the N-terminus of mutant huntingtin (mHTT in humans; mHtt in non-human animals) (11). This polyQ expansion leads to conformational changes and abnormal cytoplasmic and nuclear accumulation of mHTT. CAG repeat expansion correlates with disease severity and inversely with the age-of-onset (11). Healthy individuals have approximately 25 CAG repeats in the *HTT* gene, whereas 40–50 CAG repeats or more than 60 CAG repeats cause adult- or juvenile-onset HD, respectively (78). HD particularly affects neurons in the striatum (caudate nucleus, mainly, and putamen), leading to striatal neuronal damage and striatum atrophy (140). Neuronal degeneration has been described to spread to cortical areas (140) and to other extrastriatal regions, such as the hippocampus (119), thalamus (145) and neocerebellum (173). The main symptoms associated to HD are motor impairment, such as chorea-like involuntary movements, dystonia and bradykinesia found in juvenile cases or advanced adult-onset cases, as well as cognitive and psychiatric alterations, the later occurring at pre-motor stages (111). The genetic cause of HD is well studied and described, however the cellular and molecular mechanisms involved in mHTT-mediated early neuronal dysfunction and late neurodegeneration are not fully understood. However, oxidative stress (130), mitochondrial dysfunction (146), excitotoxicity (86), and transcriptional deregulation are considered important pathological alterations observed in HD patients (**Figure 1**).

In this review we focus on redox and mitochondrial-related dysfunctional mechanisms that have been described in human and animal brain or cell HD models. Moreover, we discuss the therapeutic potential of modifying HD-related redox and mitochondrial pathways using genetic or pharmacological strategies, aiming to prevent or slow down HD progression. Herewith we dissect relevant information on dysfunctional pathways related with mitochondria and redox changes in HD and address possible HD therapeutic targets and application in clinical trials.

**2. - OXIDATIVE STRESS IN HUNTINGTON’S DISEASE PATHOLOGY AND POTENTIAL NEUROPROTECTIVE STRATEGIES**

In HD, augmented oxidative stress, defined as an imbalance between oxidants (e.g. free radicals and non-radical species) and antioxidant molecules responsible for their elimination and/or reduction, is a well-recognized pathological feature, closely linked to neurodegeneration.

Under physiological conditions, reactive oxygen species (ROS) and reactive nitrogen species (RNS) are byproducts of normal metabolism, with essential roles in cell division, cell signaling, homeostasis and autophagy, being promptly produced and eliminated, through a process denominated as “redox homeostasis” (50). However, when these cellular mechanisms fail to maintain cellular homeostasis, increased cellular stress and cytotoxicity emerges.

Endogenously, two important sources of ROS are mitochondria during electron transfer (157) and NADPH oxidase (NOX), an enzymatic complex located at plasma membrane that produces ROS to the cytoplasm (192). Accumulation of ROS in neurons, which have low levels of antioxidants, cause altered protein structure and increased oxidation, impaired DNA structure and lipid peroxidation (165), contributing to the pathogenesis of many diseases, including HD.

Redox signaling is essential for normal brain function, being involved in memory consolidation, neuronal differentiation and plasticity. The brain is one of the most metabolically active organs in the body, consuming about 20% of all oxygen (58). In particular, neurons quickly undergo oxidation not only because they retain low levels of antioxidants [25, for review], but also because they have localized high levels of iron, auto-oxidizable catecholamines and high levels of membrane polyunsaturated fatty acids and high metabolic rates and thus constant oxygen consumption (41). Additionally, neurons are post-mitotic cells that accumulate non-degradable oxidized molecules (22). In this section, we describe the evidences for ROS production in the presence of mHTT, its toxic effects related with impaired antioxidant defenses and augmented accumulation of free metal ions. Moreover, we complement the information of potential therapeutic targets aiming at ameliorating early redox changes and oxidative stress in HD.

**2.1- mHTT-INDUCED OXIDATIVE STRESS**

Numerous reports have associated HD with an imbalance in ROS and RNS production and their degradation (61). Mitochondrial complexes II, III and IV deficiency was reported in *postmortem* HD striatum (23, 64), which were related with enhanced ROS and oxidative stress in human HD samples (26).

Analysis of proteins oxidative modifications is one way of measuring ROS-mediated cytotoxicity *in vivo*. Sorolla and colleagues identified 13 oxidatively modified proteins in striatal human HD brain samples, when compared to controls, including mitochondrial enzymes (176). In HD patients, levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG), a DNA oxidation biomarker, were also increased in caudate tissue (27), as well as in serum and leukocytes (99), indicating that both nuclear and mitochondrial DNA are more oxidized in HD patients samples. 8-OHdG levels were also increased in ST*Hdh*Q111/Q111 striatal cells, derived from HD knock-in mice, and in human HD skin fibroblasts (170). Increased lipid peroxidation markers, such as malondialdehyde and 4-hydroxynonenal, were also observed in blood samples of HD patients (180). Concordantly, urine, plasma and striatal microdialysates from the R6/2 mouse model, which express exon 1 of the human *HTT* gene with ~150 CAG repeats, evidenced increased concentrations of 8-OHdG (21) and striatal lipid peroxidation (134).

NOX is one of the main sources of ROS, which activity has been used as an indicator for ROS generation *in vivo*. Cortical and striatal samples from HD *postmortem* patients showed augmented levels of brain NOX activity, more specifically, NOX2, shown to colocalize at plasma membrane lipid rafts and to be directly responsible for increased ROS levels (192). Moreover, the HD rat model induced by striatal administration of quinolinic acid (QA, *N*-methyl-D-aspartate receptor agonist) showed increased NOX-linked striatal superoxide production that increased with the addition of NADPH, a NOX substrate (104). Furthermore, studies using the HD140Q/140Q mice revealed augmented NOX activity in cortical and striatal synaptosomes and in primary neurons derived from this mouse model (192). Importantly, treatment with NOX inhibitors reduced ROS levels and neuronal cell death in HD140Q/140Q mice (192). STHdhQ111/Q111 striatal cells also showed increased oxidative damage attributable to NOX, since the NOX inhibitor apocynin attenuated ROS production and neurotoxicity, in cells exposure to chlorpyrifos (CPF), an organophosphate insecticide (48).

Evidence for increased oxidative stress is observed in different HD models. The R6/2 mouse model showed increased ROS in brain fractions (96) and striatal neurons (51). Additionally, protein carbonyls were detected in cortex (101). The R6/1 HD mouse model, which express exon 1 of the human *HTT* gene with ~116 CAG repeats and an ameliorated phenotype when compared to R6/2 mice, also showed striatal oxidative damage (133) and augmented ROS formation (135). The transgenic yeast artificial chromosome (YAC) mice expressing full-length human mHTT with 128 glutamines (YAC128) further showed increased protein carbonyls in pre-frontal cortex at 6 months of age (24), when compared with WT mice. In YAC128-derived embryonic fibroblasts, superoxide anion (O2•-) formation was increased (194). Neurons derived by human HD neural progenitor cells (NPCs) and induced pluripotent stem cells (iPSCs) were more susceptible to death than WT neurons, formed HTT aggregates under oxidative stress conditions (97) and exhibited augmented DNA damage (38). ST*Hdh*Q111/Q111 striatal cells also showed increased ROS production, lesion in mtDNA and a lower spare respiratory capacity (169). Moreover, using the same cellular model, we showed augmented intracellular (122, 151) and mitochondrial (150) ROS levels due to mHtt expression (**Figure 2**). Concordantly, Hands and colleagues previously reported that polyQ oligomerization in HeLa and PC12 cells leads to early hydrogen peroxide (H2O2) generation (66).

Exposure to 3-nitropropionic acid (3-NP, an irreversible inhibitor of mitochondrial complex II or succinate dehydrogenase), damages striatal medium spiny neurons through mitochondrial impairment and mimics many characteristics of HD (59). The 3-NP mice model of HD showed augmented oxidative stress, with increased levels of malondialdehyde and nitrites, lipid peroxidation markers, in cortical, striatal and hippocampal neurons (109, 171) and striatal astrocytes (60). 3-NP further induced increased ROS levels in HD cybrids, a cell model in which the contribution of mitochondrial defects from patients is isolated, relatively to control cells (53) and in primary rat striatal neurons (153). 3-NP-induced *C. elegans* HD model further exhibited increased oxidative stress (87). Importantly, permeability transition pore (PTP) inhibitors and vitamin E (or α-tocopherol) attenuated ROS generation, PTP opening and behavioral changes in the rat HD model induced by 3-NP (154). Moreover, other less affected brain areas in HD, such as cerebellum and hippocampus, showed increased oxidative stress. 3-NP-induced HD mice exhibited augmented ROS production, malondialdehyde, protein carbonyls and nitric oxide levels in striatum and cerebellum (46), as well as impaired oxidative defenses in the hippocampus (89). These results suggest that mHTT can exert its toxic effect by promoting ROS generation.

Antioxidants have been demonstrated to be beneficial in distinct HD models. α-Lipoic acid treatment in R6/2 and N171-82Q mice (with treatments starting at 4 weeks of age) improved survival in both HD transgenic mouse models (9), while vitamin E/α-tocopherol was tested in a clinical trial revealing selective therapeutic effect on neurologic symptoms in early HD patients (137), suggesting that antioxidant therapy may slow the rate of motor decline early in the course of the disease.

**2.2 - ALTERED ANTIOXIDANT MOLECULES AND ENZYMES IN HUNTINGTON’S DISEASE**

A relevant neuroprotective mechanism, to combat oxidative damage, is the activation of nuclear factor erythroid 2-related factor 2 (Nrf2), a pervasive transcription factor that combats oxidative stress in response to a mild oxidant stimulus. Nrf2 is known to upregulate the expression of cytoprotective and antioxidant enzymes/proteins by binding to the Antioxidant Response Element (ARE), enhancer sequences present in the regulatory regions of Nrf2 target genes (205). Under physiological conditions, Nrf2 interacts with Keap1 protein, being mostly located in the cytosol. Following stress conditions, oxidation of cysteine residues at Keap1 leads to Nrf2 disconnection; Nrf2 migrates into the nucleus, where it binds to ARE (72) and recruits transcriptional co-activators, such as CREB-binding protein (CBP) (212) to promote transcription by intrinsic histone acetyltransferase activity. Thus, when Nrf2 binds to ARE, it regulates the transcriptional activation of important antioxidant proteins and enzymes, namely glutamate-cysteine ligase (GCL), involved in the synthesis of reduced glutathione (GSH), enzymes of the glutathione cycle, glutathione peroxidase (GSH-Px) and glutathione reductase (GSH-R), glutathione-S-transferase (GST), NAD(P)H:quinone dehydrogenase 1 (NQO1), superoxide dismutase 1 (SOD1 or Cu/Zn-SOD, located in cytosol, mitochondrial intermembrane space and nuclear compartments), heme oxygenase-1 (HO-1), peroxiredoxin (Prx1), among others (81, 98). Of relevance, some of these antioxidant defenses are altered in HD.

Malonate (reversible complex II inhibitor) and 3-NP induced higher toxicity in Nrf2 knockout mice and Nrf2-deficient cells (29), suggesting the involvement of Nrf2 activity in neuronal degeneration in HD. In addition, intrastriatal transplantation of astrocytes overexpressing Nrf2 in wildtype mice was shown to have an important neuroprotective effect after exposure to malonate (29). Moreover, ST*Hdh*Q111/Q111 striatal cells presented decreased Nrf2 levels (123) and activity (76).

Overall, these studies suggest that Nrf2 positive modulation should have neuroprotective effects in HD pathogenesis. Indeed, cystamine, an inhibitor of transglutaminase activity with additional potentially beneficial effects, protected against neurodegeneration, and extended lifespan in genetic R6/2 (55) and YAC128 (144) HD models (3 weeks of age). Systemic cystamine administration led to Nrf2-dependent ARE activation in the striatum and alleviated striatal lesion volume in 3-NP-treated mice. To verify that induction of neuroprotection via cystamine occurred through Nrf2 activation, Nrf2 deficient (Nrf2-/-) animals were treated with cystamine following 3-NP-induced neurotoxicity (30), confirming that Nrf2 is essential for cystamine protection. Additionally, hesperidin, a flavanone group member, restored antioxidant protein levels and reduced the levels of malondialdehyde in striatum, cortex and hippocampus, improving locomotor activity in the 3-NP-induced HD rat model (109). We previously showed that creatine and cystamine increased viability of HD mutant cells and prevented ROS formation in HD cells subjected to H2O2 (151).

Moreover, treatment of R6/2 and YAC128 HD transgenic mice with fumaric acid ester dimethylfumarate (DMF), an orally bioavailable fumaric acid ester (FAE), which is metabolized to methyl hydrogen fumarate, induced Nrf2 nuclear migration and activation, which resulted in preserved striatal and motor cortical neurons in these HD mouse models (51). Furthermore, Gao and colleagues showed that protopanaxtriol (Ppt), a perennial herb from Chinese medicine, prevented ROS production in the striatum through increased Nrf2 activity and HO-1 expression in 3-NP mouse model, improving body weight and behavior (60).

Furthermore, sulforaphane (SFN) stimulated the Keap1-Nrf2-ARE pathway and inhibited mitogen activated protein kinases (MAPKs) and factor nuclear kappa B (NF-κB) pathways to mitigate 3-NP-induced neurotoxicity, including suppression of the lesion area, apoptosis, microglial activation, and mRNA or protein expression of inflammatory mediators, suggesting that SFN is an appellative therapeutic approach (73).

GSH is the main endogenous antioxidant involved in maintenance of cellular redox homeostasis. Different studies showed altered GSH metabolism in HD, which can contribute to redox imbalance during disease progression. Indeed, cortical samples from *postmortem* HD patients showed reduced levels of GSH (54). Decreased levels of both GSH and GSH-R in plasma were associated with caudate atrophy in HD patients (132), and studies in peripheral tissues of HD patients reported decreased GSH levels in plasma (84) and reduced GSH-Px activities in HD leukocytes (35). In addition, polyQ oligomerization in HeLa and PC12 cells induced early disturbance in GSH levels (66). Conversely, other studies showed that, in some cellular (ST*Hdh*Q111/Q111 striatal cells) and animal (R6/2) HD models, GSH levels are increased, although these augmented levels were not enough to ameliorate HD-associated oxidative imbalance (149, 208).

HD patients showed reduced SOD1 activity in cytosol of parietal cortex and cerebellum (27), but increased immunoreactive staining for HO-1 in cortex and striatum (28). Additionally, human HD-iPSCs further showed reduced SOD1 and Prx (32). Concordantly, decreased SOD1 activity was detected in erythrocytes derived from HD patients (35). These studies are in accordance with data from transgenic HD mice, which showed reduced SOD1 activity in older mice (at 35 weeks of age), suggesting that the antioxidant mechanism to protect cells falls with advanced disease stage and aging (163). Data showing decreased Nrf2 activity and reduced levels of GSH and SOD1/2, two relevant endogenous antioxidants, suggest a dysregulation of Nrf2-ARE pathway in different HD models, favoring cellular oxidative damage.

Importantly, Mason and co-workers, demonstrated that augmented GSH-Px activity (by genetic or pharmacological approaches) was neuroprotective in different HD models, namely in yeast, mammalian cells and Drosophila (105). Furthermore, overexpression of SOD1 in mHtt expressing cells (HD 150Q cells) decreased mHtt aggregation and proteasome malfunction induced by oxidative stress (63). The QA-induced rat HD model showed increased oxidative stress by decreasing antioxidant defense mechanisms and enhancing lipid peroxidation (LPO), protein carbonyls, and nitrate concentration (NO), as well as altering the activities of glutathione family enzymes (GSH-Px, GST, GSH-R) (183). The administration of edaravone, a potent free radical scavenger, to QA-induced rat HD model ameliorated all these QA-induced features in rat striatum (183).

Flavonoids, plant-derived compounds, were characterized as antioxidant and free radical scavengers. Recent studies have shown the positive effects of flavonoids in HD, which could be of potential clinical use. Oral administration of the flavone chrysin improved behavior and diminished oxidative stress markers (lipid peroxidation, nitrite and protein carbonyls) by significantly improving the antioxidant status (SOD1, catalase and GSH) in striatal mitochondria, enhancing the survival of striatal neurons in the 3-NP rat model of HD (189). Another flavonoid, quercetin, restored the activities of SOD1 and catalase in the same HD model (160). Similarly, rutin prevented 3-NP-induced impairment in motor function and decreased markers of oxidative stress, leading to increased activities of SOD1, GSH-Px and GSH-R (182). The flavonol kaempferol and the flavanone glycoside hesperidin had similar effects using the same HD model (91, 109). Oxytocin administration, a neurohypophysial nonapeptide with antioxidant properties, was shown to be protective in the 3-NP rat model of HD, increasing SOD1 and catalase in striatum, hippocampus and cortex (112); nicotinamide administration also augmented GSH levels in the striatum (171). Similar results, using the same HD model were assessed using curcumin, a potent antioxidant of dietary polyphenol, with free radical scavenging, iron chelating and anti-inflammatory activities (90). Furthermore, Intravenous immunoglobulin (IVIg) therapy was shown to rescue motor and cognitive deficits, prevent synaptic degeneration, increase GSH/GSSG ratio and SOD activity and inhibit ROS generation in the brains of R6/2 mice (96).

In PC12 cells overexpressing the N-terminal fragment of Htt protein with either a nonpathogenic or pathogenic polyQ repeat (Htt-103Q), showed reduced expression of the antioxidant protein Prx1. Treatment of these cells with dimercaptopropanol, a thiol-based antioxidant, combated the cytotoxicity induced by mHTT and the expression level of Prx1 (141). This study suggests the involvement of mHTT in ROS production and reveal the importance of thiol-based antioxidants as potential drugs for HD treatment.

Selenium (Se), an essential trace element present in GSH-Px structure and critical for the neuroprotective brain function, was shown to be reduced in human HD brains (42). Tolfenamic acid, a nonsteroidal anti-inflammatory drug with neuroprotective properties, was shown to exhibited antioxidant effects in both R6/1 mice and PC12 cell models, increasing GSH levels and reducing ROS accumulation, respectively, suggesting that tolfenamic acid has a good therapeutic effect in HD models (95). Moreover, fibroblast growth factor 9 (FGF9) suppressed cell death and induced upregulation and activation of Nrf2 and its downstream targets, GSH-R and SOD2 (or Mn-SOD, located in the mitochondrial matrix), in ST*Hdh*Q111/Q111 striatal cells (211). Cong and colleagues showed the positive effects of selenium nanoparticles (Nano-Se) for HD therapy by regulating HD-related neurodegeneration in transgenic HD models of *Caenorhabditis elegans* (*C. elegans*); Nano-Se significantly decreased neuronal death, relieved behavioral dysfunction, reduced oxidative stress and relieved behavioral dysfunction. This study suggests that Nano-Se has a great potential as a HD therapeutic strategy (42).

Nevertheless, antioxidants were not always effective in attenuating HD symptoms, possibly because HD-induced ROS production mainly occurs in mitochondria. A good example is the ineffectiveness of antioxidant compounds used in clinical trials, as described later in section 4. However, the use of mitochondrial-targeted antioxidants was shown to be effective in HD mouse models. The synthetic mitochondrial selective antioxidant XJB-5-13 was shown to have a very positive effect in two different HD mouse models, HdhQ (150/150) and R6/2 mice, suppressing oxidative mtDNA damage, restoring mtDNA copy number, alleviating motor decline and weight loss, and enhancing neuronal survival and mitochondrial function (142, 203). Additionally, MitoQ10 (MitoQ, or mitoquinone) administration, a lipophilic, positively-charged chain-breaking antioxidant that accumulates in mitochondria, was shown to ameliorate fine motor control through reduction of oxidative damage, which was particularly evident in the muscle of R6/2 mice, revealing a potential HD therapeutic molecule for ROS combat (139).

**2.3 - INCREASED ACCUMULATION OF METAL IONS IN HUNTINGTON’S DISEASE**

Some processes such as redox regulation, oxygen and electron transport implicate the presence of metal ions as cofactors, such as iron (Fe), copper (Cu), manganese (Mn), and zinc (Zn). These metal ions have beneficial and important roles in cell function and homeostasis. However, excessive accumulation of transition metals that are highly redox active can cause some pathological conditions. HD patients showed significantly increased levels of iron in basal ganglia, as detected by magnetic resonance imaging, which occurred in early and late stages of disease process, suggesting that augmented iron levels are related with increased neurotoxicity in HD (12, 13). Additionally, blood samples from HD patients, with genetic diagnosis of disease showed increased levels of iron, arsenic and zinc, suggesting the blood metal profile as a relevant *in vivo* tool to study and characterize HD (177).

Iron can accumulate in both neurons and glia. Neonatal iron diet supplementation in R6/2 mice promoted neurodegeneration by potentiating oxidative stress (18). Additionally, neonatal iron supplementation further caused mitochondrial iron accumulation (1). In HD, iron-containing proteins are also altered (113). The main component of mitochondrial complex II, succinate dehydrogenase, was shown to express reduced levels of Fe-S subunit Ip and subunit Fp in human *postmortem* tissue and in a HD cellular model (Htt171-82Q). Decreased subunits expression led to reduced succinate dehydrogenase catalytic activity (16). Moreover, copper can bind to the N-terminal of mHTT, favoring protein aggregation and reduced degradation (56). Concordantly, excess copper deposition in human HD striatum has been correlated with neurodegeneration (47, 57). Chen and colleagues showed that intra-cerebroventricular delivery of the iron chelator deferoxamine improved the motor phenotype of R6/2 HD mice (36). In this way, reduction in the levels of these metal ions may represent a potential protective therapy in HD.

**3 – MITOCHONDRIAL DYSFUNCTION IN HUNTINGTON’S DISEASE PATHOLOGY AND POTENTIAL THERAPEUTIC STRATEGIES**

Mitochondrial bioenergetics and dynamics are significantly linked with neuronal physiology and homeostasis. Neurons are extremely dependent on mitochondria since they are highly energy requiring cells. Indeed, mitochondria have an important role in generating adenosine triphosphate (ATP) through oxidative phosphorylation (OXPHOS). Electron leakage at complexes I and III generates O2•-; thus, altered mitochondrial function due to complexes inhibition induces oxidative stress (116). Mitochondria also have an important role in intracellular Ca2+ homeostasis, namely through the crosstalk with endoplasmic reticulum, and further regulate oxidative and nitrosative stress, neuronal survival, and cellular metabolism, including heme synthesis and iron usage (116).

Different evidences showed that mitochondrial dysfunction is closely related with HD pathogenesis. Previous studies reported ultrastructural defects in mitochondria isolated from *postmortem* HD cortical tissue and compromised oxidative function and ATP synthesis in pre-symptomatic HD carriers (158), suggesting mitochondrial dysfunction as an early relevant pathogenic mechanism. Moreover, *postmortem* HD patient’s brain specimens and human HD lymphoblasts showed abnormal mitochondrial morphology and trafficking (120). Concordantly, isolated brain mitochondria from caudate nucleus of HD patients (207) and different HD cellular (human neuroblastoma cells; ST*Hdh*Q111/Q111) and animal models (Hdh(CAG)150 knock-in mouse) showed HTT fragments in close contact with mitochondria (39, 126), suggesting a direct effect of mHTT on mitochondrial function.

Considering these observations, in this section we highlight the major findings regarding the role of mitochondrial dysfunction in HD pathogenesis, by describing mHTT-mediated altered mitochondrial membrane potential and respiration, Ca2+ buffering, mitochondrial bioenergetics and dynamics, and potential therapeutic targets for mitochondrial malfunction in HD.

**3.1 – ALTERED MITOCHONDRIAL MEMBRANE POTENTIAL AND ELECTRON TRANSFER CHAIN FUNCTION**

Normal mitochondrial activity creates an electrochemical proton gradient and thus a mitochondrial transmembrane potential (Δψm) of -150 to -180 mV, allowing ATP synthesis. Studies using *postmortem* caudate and putamen derived fromsymptomatic HD patients, mHtt-expressing striatal cells, brains of HD animal models (Htt171-82Q and 3-NP rat HD mice, with 20 weeks) and peripheral cells derived from HD patients (pre-symptomatic and symptomatic) showed a dramatic decrease in the activity of complexes II, III and mildly of complex IV (16, 25, 64, 172). Striatal mitochondria isolated from R6/1 HD transgenic mice also exhibited reduced activity of complexes II, III, IV and altered oxygen consumption rates (200). Moreover, human NPCs showed reduced oxygen consumption and ATP production (125, 202).

Different reports showed altered electron transfer chain activity, which cause impaired ΔΨm in HD. Mitochondria isolated from HD patients and HD transgenic mouse brains (with 72 or 150 polyQ repeats, respectively) showed depolarized mitochondrial membrane (129). Some studies also reported that HD lymphoblasts are highly susceptible to decreased Δψm, showing correlation with increased polyQ repeats (115). We previously showed significant changes in Δψm associated with apoptotic events in symptomatic HD cybrids (an *ex-vivo* peripheral model obtained from the fusion of HD human platelets with mtDNA-depleted rho0 cells) and in HD human B-lymphocytes (6, 53). Moreover, human neural progenitor cells (NPCs) lines carrying varying CAG repeat lengths in the first exon of *HTT* and PC12 cells treated with 3-NP showed lower ΔΨm [131,132]. Concordantly, when compared with wild-type cells, striatal ST*Hdh*Q111/Q111 cells showed significant reduction in Δψm after increasing Ca2+ concentrations (110) (**Figure 3**). Of relevance, ΔΨm defect in ST*Hdh*Q111/Q111 cells was attenuated in the presence of ADP and reduced Ca2+ uptake capacity was improved in the presence of inhibitors of the permeability transition pore (PTP) (110).

Melatonin (endogenously produced by the pineal gland and the retina) has been described to be protective in HD context, preventing toxicity induced by 3-NP. Indeed, melatonin inhibited mutant Htt-induced ΔΨm loss in ST14A cells (195); this further inhibited the release of mitochondrial proapoptotic factors, making melatonin a therapeutic strategy for counteracting cell death and improve HD-related mitochondrial features (195). Moreover, HTT phosphorylation at Ser421 restored Δψm in HD human lymphoblasts (70, 115).

Intraperitoneal administration of 3-NP induced loss of body weight, a decline in motor function, increased lipid peroxidation, nitrite and lactate dehydrogenase, and blockade of ATP synthesis by inhibiting the mitochondrial complex II activity in striatum and cortex of the treated animals. As cited above, flavonoids are important antioxidants in HD context. The administration of the flavonoid quercetin was able to reverse 3-NP induced inhibition of respiratory chain complexes, restored ATP levels, attenuated mitochondrial oxidative stress in terms of lipid peroxidation and prevented mitochondrial swelling.

Quercetin also restored the activities of SOD1 and catalase along with thiol content in 3-NP treated rats (7, 160). Concordantly, the flavonoid naringin improved mitochondrial membrane potential and mitochondrial respiratory complex enzymes activities in 3-NP-treated rats (88).

Additionally, an aqueous extract of *Centella asiatica* (CA) evoked protection against 3-NP-induced mitochondrial dysfunction, reduction in the activity of mitochondrial complex II, electron transport chain enzymes, and decreased mitochondrial viability (166). These results indicate that the protective effect of CA against neuronal damage and mitochondrial dysfunction along with its memory enhancing activity can be beneficial to reduce HD-related impairments.

Recently, Zhu and colleagues showed that nicotinamide mononucleotide adenylyltransferase (NMNAT), an evolutionarily conserved nicotinamide adenine dinucleotide (NAD+) synthase and neuroprotective factor, was also beneficial in HD; indeed, NMNAT significantly diminished mHtt-induced neurodegeneration by reducing mHtt aggregation through autophagic clearance, and improving mitochondrial function by restoring ATP levels in a Q138 expression *Drosophila* model of HD (213).

The antioxidant *N*-acetylcysteine (NAC) has been shown to be quite effective against mitochondrial complexes dysfunction in HD models. Chronic NAC administration delayed the onset and progression of motor deficits in R6/1 mice and enhanced baseline respiration, maximal ADP-stimulated respiration and respiration after consumption of ADP in HD mice (200). Similarly, 3-NP treatment reduced the activity of complexes II, IV and V in mice, which was rescued following NAC treatment (162). Similar results were obtained with lycopene administration, an antioxidant found in red and pink fruits, and SFN, in 3-NP-induced (161) and QA-induced HD models (102), respectively. Moreover, we previously demonstrated that insulin-like growth factor 1 (IGF-1) alleviated HD symptoms through improvement of mitochondrial function. We found that HD models (YAC128 and R6/2 mice, human HD lymphoblasts and ST*Hdh*Q111/Q111 cells) exhibited reduced ATP/ADP ratio, decreased O2 consumption, increased mitochondrial ROS and fragmentation, aberrant lactate/pyruvate levels and decreased mitochondrial membrane potential, and each of these parameters was shown to be rescued by IGF-1 treatment *via* upregulation of PI3K/AKT signaling in cellular and mouse models of HD (115, 117, 150).

These results suggest that NAC, lycopene SFN and IGF-1 treatment can improve mitochondrial activity, thus being a potential therapy in the treatment of HD. Furthermore, we further showed that treatment with sodium butyrate (SB), a class I and IIa histone deacetylase inhibitor (HDACis), preferentially modulating Lys acetylation sites in the nucleus, reduced pyruvate dehydrogenase (PDH) kinases PDK1, PDK2, and PDK3 mRNA levels and consequently PDH phosphorylation, culminating in increased PDH activity, mitochondrial respiration, and ATP production in YAC128 mice and ST*Hdh*Q111/Q111 cells (114). Thus, HDACis can be used in HD therapeutics to diminish HD-related deficits in mitochondrial bioenergetics and motor function.

Mitochondrial deregulation has an important role in intrinsic apoptotic pathway. Mitochondrial PTP opening leads to the collapse of the ΔΨm and release of cytochrome C, which forms a complex (the apoptosome) in the cytosol to activate caspase-9 and caspase 3 to induce apoptosis (186). Cytochrome C released from mitochondria abrogates electron flux and oxygen consumption at mitochondrial inner membrane (MIM), exacerbating mitochondrial dysfunction.

Increased cytochrome c release was detected in HD human cybrid lines, showing their increased susceptibility to intrinsic apoptosis (53). Primary rat striatal and cortical neurons treated with 3-NP and ST*Hdh*Q111/Q111 cells showed increased caspase-3 activation and increased cytochrome c levels in the cytosol and DNA fragmentation/condensation (5, 62, 153). FK506, an inhibitor of calcineurin (or protein phosphatase 3, formerly known as protein phosphatase 2B) was shown to be protective against apoptosis and necrosis in these two models (4, 153).

**3.2 – IMPAIRED MITOCHONDRIAL BIOGENESIS IN HUNTINGTON’S DISEASE**

Mitochondrial biogenesis is a complex multi-step process where transcription and translation of mtDNA and nuclear-encoded mitochondrial-related transcripts associate to control mitochondrial protein import and general assembly of a mitochondrial network. mtDNA is a ∼16-kb genome that encodes for 13 protein subunits of the mitochondrial electron transport chain and ATP synthase (8). Most of the mitochondrial proteins are nuclear encoded, then synthesized in the cytosol, and imported into the mitochondria. Thus, an imbalance in nuclear- and/or mitochondrial-encoded proteins synthesis, import and folding, or mutations in mtDNA, can disturb mitochondrial integrity and functionality.

Different studies provided evidences that mtDNA damage is implicated in the pathogenesis of HD (190) since mtDNA is a major target of the oxidative stress associated with mHTT. In line with that, some authors showed that the abundance of mtDNA decreases dramatically in striatal cells expressing mHtt (ST*Hdh*Q111/Q111)(169). Additionally, HD patients showed mtDNA depletion in leukocytes, which was related with increased number of mHTT polyQ repeats (94). Moreover, human peripheral HD leukocytes and striatum from transgenic HD R6/2 mice showed significantly reduced mtDNA copy number (68, 136).

Mitochondrial proteins encoded in nucleus are synthesized as precursors and maintained in the cytosol with an unfolded conformation, existing in complexes with cytosolic chaperones, such as HSP70 and HSP90, to avoid their degradation and aggregation (210). Most of these precursors contain N-terminal mitochondrial targeting sequences (MTS), which are 10–80 amino acid residues with no sequence identity, enriched with positively charged residues, in order to direct them to the mitochondria and into the correct mitochondrial compartment. Different mitochondrial proteins are located to the matrix. Once in the mitochondrial matrix, MTS are cleaved generating mature polypeptides. Moreover, cooperation between the two main mitochondrial translocases, the translocase of the outer membrane (TOM) complex at mitochondrial outer membrane (MOM) and the translocase of the inner membrane (TIM23) complex, is needed for these proteins to be imported (15). In addition, an intact mitochondrial membrane potential and the hydrolysis of ATP are essential for protein translocation through the TIM23 complex.

Highly purified synaptosomal mitochondria from presymptomatic R6/2 mice showed mitochondrial import defects. Indeed, mHTT can interact with TIM23 complex, disrupting mitochondrial proteostasis through reduced levels of nuclear-encoded proteins imported by TIM23 (204), while wild-type HTT does not associate with this translocase complex, suggesting a role of polyQ domains in these interactions (207). Interestingly, the delivery of Tim23, Tim50, and Tim17a (subunits of TIM23 complex) by lentiviral to rescue mitochondrial protein import, improved mitochondrial function and reduced cell death in mHTT-expressing neurons (207), suggesting a possible therapeutic approach against impaired mitochondrial import in HD.

Mitochondrial network is constantly renewed through nuclear- and mtDNA-encoded proteins. However, mHTT can interact and affect the function of some transcription factors involved in maintenance of mitochondrial function and biogenesis. Peroxisome proliferator-activated receptor (PPAR)γ coactivator 1α (PGC-1α) is a regulator of different metabolic processes including mitochondrial respiration and biogenesis (44), expression of nuclear-encoded subunits of each of the electron transport-chain complexes, and antioxidant defense proteins, suppressing cellular ROS formation (179). PGC-1α also regulates the expression of the mitochondrial transcription factor A (TFAM), the major transcriptional regulator of mtDNA (128) and nuclear respiratory factor (NRF)1 and 2 and PPAR α, δ and γ by forming heteromeric complexes, regulating the expression of cytochrome c and complexes I-V (128).

Striatum of early-stage HD patients showed diminished TFAM and PGC-1α levels and decreased expression of 24 out of 26 PGC-1α target genes, increasing disease severity and loss of mitochondrial function (44, 197) (**Figure 4**). Additionally, a PGC-1α coding variant was described to be associated with the age of onset of motor symptoms in HD patients (198). Moreover, spongiform lesions predominantly in the striatum were seen in PGC-1α null mice, which developed a neurological phenotype consistent with neurodegeneration, suggesting an increased susceptibility of striatal neurons to altered PGC-1α expression (93). The NLS-N171-82Q transgenic HD mouse model and ST*Hdh*Q111/Q111 cells showed reduced PGC1α, PGC1β, NRF1, NRF2 and TFAM protein and mRNA levels (34, 209).

mHTT can further interact with the PGC-1α promoter, interfering with the transcriptional activation functions of promoter-bound transcription factors, cAMP response element (CRE)- binding protein (CREB) and Transcription initiation factor TFIID subunit 4 (TAF4), which results in decreased PGC-1α expression and augmented mitochondrial abnormalities. R6/2 transgenic mice showed reduced CREB activation (127). Moreover, R6/2 transgenic and full-length mHTT mouse models of HD, subjected to treatment with bezafibrate, a pharmacologic activator of PGC-1α expression, showed improved phenotype, enhanced cell survival and reduced brain, muscle, and brown adipose tissue pathology (77). Vildagliptin also restored mitochondrial integrity along with striatal p-CREB levels in 3-NP treated rats (164) (**Figure 4**).

SIRT1 is a deacetylase of the sirtuin family that deacetylates PGC-1α, a co-transcription factor involved in mitochondrial biogenesis. In our group, we showed that resveratrol, a SIRT1 activator with antioxidant properties, increased mtDNA copies and mitochondrial-related transcription factors (TFAM and nuclear PGC1α) in HD human lymphoblasts, as well as increased expression of mitochondrial electron transport chain proteins and improved motor function in YAC128 mice (118). Moreover, β-Lapachone (βL) is a natural compound obtained from the bark of the Lapacho tree with beneficial effects on various diseases. R6/2 HD mice treated with βL showed improved rotarod performance and clasping scores as well as increased brain SIRT1 and p-CREB levels, augmented PGC-1α deacetylation, and reduced mitochondrial ROS formation (92), highlighting its role in diminishing mitochondrial dysfunction seen in HD models. As cited above, MitoQ can be an appealing HD therapeutic strategy for combating mitochondrial ROS levels. In addition, MitoQ was shown to reduce defective mitochondrial biogenesis and improve healthy mitochondrial biogenesis in ST*Hdh*Q111/Q111 cells through increased mRNA levels of biogenesis-related genes, such as PGC1α and TFAM (209). Similar results were obtained with the PPARγ agonist, thiazolidinedione (TDZ), in mHtt expressing N2A cells (37) and fasudil, simvastatin, and inhibitors of rho kinase (ROCK), known to attenuate mitochondrial dysfunction, in 3-NP-induced HD rats (2). R6/2 transgenic HD mice treated with pan-PPAR agonist, bezafibrate, showed increased PGC-1α expression and mitochondrial biogenesis, with increased functional mitochondria in striatum, and thereby improved behavior, augmented survival and reduced brain, muscle and brown adipose tissue pathology (77). Similar results were obtained with bezafibrate in BACHD mice, an HD transgenic mice which express a full-length mHTT exon 1 sequence, containing 97 mixed CAG repeats (33). As suggested by these reports, PGC-1α pathway plays an important role in mitochondrial dysfunction in HD, and thus can be seen as a possible HD therapeutic target.

**3.3 – mHTT-INDUCED MODIFIED MITOCHONDRIAL DYNAMICS**

Mitochondria are dynamic organelles and thus their structure varies constantly from a tubular network to individual mitochondria. Mitochondrial dynamics (including mitochondrial fusion and fission), mitochondrial biogenesis and elimination of unwanted mitochondria, by mitophagy, and movement are processes that must coexist in balance for normal mitochondrial network and function. Indeed, mitochondria can divide (fission) and unite (fusion) in response to different stimuli. Both dynamic processes make possible the exchange of membranes and intra-mitochondrial content or mobility of the organelle to specific subcellular locations.

Altered mitochondrial morphology and consequently neuronal dysfunction have been described in HD models, complemented with altered expression of genes involved in fission/fusion balance (147). Mitochondrial fission is regulated by dynamin-related protein 1 (Drp1), which have an effector guanosine triphosphate (GTP)ase domain and can translocate from cytosol to MOM, after a fission stimulus (85). Additionally, mitochondrial fission 1 (Fis1) and mitochondrial fission factor (Mff), located at MOM, serve as adaptors for Drp1, which allows the recruitment of Drp1. The GTPases mitofusins (Mfn) 1 and 2, present at MOM, mediate the fusion of MOMs of juxtaposing mitochondria. Moreover, mitochondrial fusion is regulated by optic atrophy 1 (OPA1), which associates with the MIM. Striatum and cortex of some HD animal models further showed reduced levels of Mfn1, Mfn2 and OPA1 and augmented levels of Drp1 and Fis1, revealing excessive mitochondrial fragmentation (43, 167). Moreover, mHTT can interact with Drp1, resulting in increased GTPase activity and consequently less efficient mitochondria and reduced energy production for neuronal function (175) (**Figure 6**). Interestingly, although mitochondrial fission has been largely associated with HD, R6/2 HD mice lacking Mff, which greatly reduced mitochondrial fission, exhibited more severe neurological phenotypes and had shortened lifespans (31), suggesting a possible protective role for mitochondrial fission in HD. However, and as shown by different authors, too much fission can be harmful, therefore manipulation of mitochondrial dynamics as a HD therapy might be applied only if an equilibrium between fusion and fission can be achieved.

Recently, Aladdin and co-workers demonstrated that skin fibroblasts from juvenile HD patients had significantly lower levels of mitochondrial fusion and fission proteins and reduced branching in the mitochondrial network. Moreover, juvenile HD fibroblasts exhibited higher proteasome activity, which was associated with elevated gene and protein expression of parkin, as well as augmented proteasomal degradation of the mitochondrial fusion protein Mfn1 in diseased cells (3). These data suggest that expansion of mHtt is linked to increased proteasome activity and faster turnover of specific substrates of ubiquitin-proteasome system in order to protect cells, which could contribute to altered mitochondrial dynamics in early phases of the disease. However, mitochondrial fusion also seems to be positive in HD models. Metformin, an antidiabetic drug, mimics caloric restriction by acting on cell metabolism at multiple levels. In HD context, metformin restored ATP levels in ST*Hdh*Q111/Q111 cells, and prevented mitochondrial membrane depolarization, excess fission and modulated the disturbed mitochondrial dynamics in HD cells (75). Moreover, the mitochondria-targeting neuroprotective compound, olesoxime, showed positive effects in the BACHD rat model of HD. Olesoxime is a small cholesterol-like molecule that accumulates at mitochondria. Its mechanism of action is not completely understood, however it has been shown to be important in mitochondrial PTP inhibition (40). Olesoxime reduced the amount of mHtt in mitochondria, restored the respiration deficits, and enhanced the expression of fusion and outer-membrane transport proteins, improving cognitive and psychiatric phenotypes, and ameliorated cortical thinning in the BACHD rat (40). 3-NP-mediated HD model mitochondria showed increased cholesterol to phospholipid ratio, suggesting decreased mitochondrial membrane fluidity, as well as ultrastructural mitochondrial changes, accompanied by organelle swelling. The administration of the antioxidants alpha-lipoic acid (ALA) and acetyl-L-carnitine (ALCAR) normalized mitochondrial lipid composition, improved striatal mitochondrial structure and ameliorated memory impairments in 3-NP-treated animals, proposing these two antioxidants as important therapeutic modulators in HD progression (108). Furthermore, HDAC6 inhibition with tubastatin A (TBA) increased acetylated alpha-tubulin levels, and induced mitochondrial motility and fusion in striatal neurons to levels observed in cortical neurons (65). Thus, pharmacological inhibition of HDAC6 deacetylase activity is a potential strategy to reduce the vulnerability of HD striatal neurons.

Mitochondria are present in different subcellular locations where high energy is required through mitochondrial trafficking, which has been shown to be deregulated in neurodegenerative diseases as HD. In neurons expressing mHTT, mitochondria are mainly localized in the cell body and less transported to dendrites, axons or synapses (anterograde movement), resulting in reduced ATP levels at these sites, followed by synaptic degeneration (168). Both N-terminal fragments and full-length mHTT can directly disturb mitochondrial trafficking in either anterograde or retrograde movement (126, 168, 191). Neurons differentiated from iPSCs from HD patients showed impaired mitochondrial trafficking and distribution, and nuclear roundness (121). In striatal and cortical neurons overexpressing mHTT protein aggregates can sequester and block mitochondrial transport machinery, hindering mitochondrial movement through neuronal projections (191), suggesting that improvement of mitochondrial movement could be a possible therapeutic strategy in HD.

**3.4 – MODIFIED MITOCHONDRIAL QUALITY CONTROL**

Loss of mitochondrial transmembrane potential (Δѱm), oxidative stress, impaired OXPHOS, altered mitochondrial dynamics, an important physiological process warranting the proper movement of mitochondria to intracellular sites of high-energy demand as well as suitable mitochondrial morphology changes, or decreased biogenesis favors the accumulation of damaged mitochondria that occurs in HD cells. Mitophagy is a highly specialized type of autophagy, responsible for elimination of dysfunctional mitochondria, playing a fundamental role in neuronal survival and energy supply. Mitophagy consist of three main steps: recognition of the mitochondrion that needs to be cleared and flag them to degradation, which occurs through tensin homolog (PTEN)-induced putative kinase 1 (PINK1) and Parkin, the latter an E3 ubiquitin ligase (138); development of the autophagic membrane to surround the organelle; and fusion of the mito-autophagosome with the lysosome. Still considering the PINK1/Parkin-dependent mitophagy pathway, in damaged mitochondria exhibiting decreased Δѱm, PINK1, which is normally imported into MIM, stabilizes at the MOM, favoring Parkin, an E3 ubiquitin ligase, translocation to mitochondria. Then, Parkin binds ubiquitin chains to MOM proteins that are recognized by autophagy adaptors such as p62. Juvenile HD fibroblasts showed increased Parkin levels (3). Indeed, PINK1 overexpression in HD flies and ST*Hdh*Q111/Q111 cells proved to be protective in these models (82). Although little is known about alterations in PINK1/Parkin-dependent mitophagy in HD, its activation may constitute an interesting therapeutic approach in this neurodegenerative disorder. This PINK1/Parkin-dependent mitophagy pathway is the most well characterized mitophagy pathway, however PINK1/Parkin-independent mitophagy may also occur (181). Moreover, under normal conditions, Htt is an important protein in the control of autophagosome dynamics, along with huntingtin-associated protein 1 (HAP1), through the regulation of dynein and kinesin. Interestingly, impaired axonal transport and maturation of autophagosomes in the presence of mHtt was related with inefficient mitochondrial degradation (199). These results suggest that inducing degradation of damaged mitochondria and favoring mitochondrial biogenesis are important therapeutic targets for HD treatment.

**3.5 – ABNORMAL CALCIUM HOMEOSTASIS AND MITOCHONDRIA-ASSOCIATED MEMBRANE (MAM) COMMUNICATION**

Mitochondria is an important organelle in the regulation of intracellular Ca2+ homeostasis, due to mitochondrial calcium uniporter (MCU) channel, which is located at MIM and allow mitochondrial Ca2+ buffering. Altered mitochondrial Ca2+ handling may participate in HD neurodegeneration. Indeed, mHTT can interact with MOM, which may induce the opening of the mitochondrial PTP. PTP opening can be stimulated by increased Ca2+, ROS or decreased adenine nucleotide levels, which can induce mitochondrial swelling, depolarization, diminished ATP levels within the organelle and cell death (110). ST*Hdh*Q7/Q7 andST*Hdh*Q111/Q111 cells treated with 3-NP showed increased apoptosis and altered Δψm, which were rescued after inhibition of mitochondrial PTP with cyclosporin A and after inhibition of MCU with ruthenium red (155). Isolated mitochondria from liver of homozygous knock-in HdhQ150/Q150 mice also demonstrated increased predisposition to PTP induction by Ca2+ (39). Lower Ca2+ retention were shown in isolated mitochondria from brains of transgenic YAC mice expressing full-length mHTT with 72 glutamines (YAC72) and HD patient’s lymphoblasts (129). Moreover, R6/1 transgenic mice further showed decreased mitochondrial Ca2+ uptake with diminished Ca2+ handling, which contributes to neuronal dysfunction and degeneration, in striatum and cortex (152).

In addition, HD human lymphoblasts exposed to H2O2 displayed decreased mitochondrial Ca2+ retention (115). In contrast, we showed increased Ca2+ uptake in isolated mitochondria from pre-symptomatic R6/2 and YAC128 brain mice (124). Additionally, in a study using synaptic and non-synaptic mitochondria from YAC128 mice brain, augmented Ca2+ uptake could be directly correlated with mHTT levels associated with the mitochondrial membrane (131).

Mitochondrial-associated membrane (MAM) is the connection between mitochondria and a specialized domain of the endoplasmic reticulum (ER), the best-characterized inter-organelle connection. ER-mitochondria contact sites are important regulators of lipid metabolism and Ca2+ homeostasis, and consequently modulate fundamental cellular processes such as mitochondrial morphology, cell stress induced by ROS, autophagy and apoptosis. MAMs regulate Ca2+ transfer from the ER to mitochondria in order to maintain cellular bioenergetics and mitochondrial dynamics or to induce cell death (20). Ca2+ transfer in MAMs can occur through the Ca2+ channel inositol-1,4,5-trisphosphate (IP3) receptor (IP3R), which contacts with MOM protein voltage-dependent anion channel isoform 1 (VDAC1) through the molecular chaperone glucose-regulated protein 75 (GRP75) (184) (**Figure 2**). Thus, IP3R is highly concentrated in ER-mitochondrial contact sites. Importantly, Tang and colleagues showed that mHTT can interact with type 1 IP3R (IP3R1), suggesting an important role of this ER Ca2+ channel in HD Ca2+ deregulation and neurodegeneration (188) (**Figure 5**).

The ER protein sigma-1 receptor (Sig-1R) is further localized at the ER-mitochondria junction and is usually used as a MAM marker (67). Sig-1R forms a Ca2+-sensitive chaperone complex with immunoglobulin protein/glucose-regulated protein 78 (BiP/GRP78); upon ER Ca2+ depletion or ligand stimulation, Sig-1R dissociates from BiP, prolonging Ca2+ signaling from the ER to the mitochondria by stabilizing IP3R at MAMs (67). Hyrskyluoto and coworkers showed that mHTT expression (N-terminal HTT fragment with 120 polyQ repeats or full-length HTT with 75 repeats) diminished Sig-1R expression in neuronal PC6-3 cells. Importantly, selective Sig-1R agonist PRE-084 improved Sig-1R, SOD1, SOD2 and thioredoxin 2 expression in these cells (71). PRE-084 administration also diminished caspase-3 cleavage and oxidative stress and increased calpastatin (endogenous calpain inhibitor), activating the NF-κB pathway, suggesting a protective effect of Sig-1R augmented function in HD (71). In accordance, Sig-1R downregulation with antisense RNA amplified the amount of mHTT aggregates in both the cytoplasm and nucleus. Pridopidine, which was first described as a dopamine stabilizer (143, 196), was recently shown to interact with Sig-1R (159). Different clinical trials using pridopidine showed some efficacy in HD motor symptoms (79, 103, 148), later suggesting that Sig-1R might be involved in pridopidine therapeutic effects. Squitieri and colleagues showed that pridopidine administration in a pre-symptomatic phase reduced motor symptoms of R6/2 mice, improving horizontal ladder task and open-field locomotor performances and reducing the amount of mHTT aggregation (178). Moreover, pridopidine seems to be also synaptoprotective in HD. Indeed, HD MSNs showed decreased ER Ca2+ levels due to mHTT-induced IP3R1 hyperactivity, which resulted in abnormal Ca2+ signaling in post-synaptic spines and their destabilization (187, 201). Interestingly, treatment of YAC128 mouse corticostriatal co-cultures with pridopidine prevented MSN spine loss, restored ER Ca2+ levels and decreased excessive Ca2+ release (156). Thus, in addition to the beneficial effect of pridopidine in alleviating motor symptoms in HD, it may also be important for synaptic and neuronal viability, due to Sig-1R activation.

**4 - ANTIOXIDANTS AND MITOCHONDRIAL-RELATED CLINICAL TRIALS IN HUNTINGTON’S DISEASE**

Antioxidant supplementation has been shown to be beneficial in HD mouse models, however human clinical trials using compounds with antioxidant properties have not been as efficient. A phase 2 clinical trial with sativex (early stage, n= 26; NCT01502046), a botanical extract with an equimolecular combination of delta-9-tetrahydrocannabinol and cannabidiol, was performed in HD patients. This cannabinoid mixture was previously shown to reduce inflammation and oxidative stress; however, despite being safe and well tolerated, sativex did not show improvement in HD clinical features or biomarker analysis (100). Future studies should consider higher doses, longer treatment periods and/or alternative cannabinoid combinations. Similarly, cystamine, which crosses the blood-brain barrier, was shown to improve motor impairment and behavioral abnormalities and to increase life expectancy in YAC128 and R6/2 HD mice (45, 80, 144). A phase 2 clinical trial with cystamine (early stage, n= 96; NCT02101957) was shown to be safe and well tolerated; however delayed cystamine treatment was not beneficial (193). Additionally, vitamin E/α-tocopherol was tested showing significant therapeutic effect on neurologic symptoms for patients (n=73) in the early stage of the disease (137), suggesting that antioxidant therapy may slow the rate of motor decline early in the course of HD. Indeed, a single antioxidant cannot target all oxidant species, which may explain the low efficacy of these compounds. On the other hand, slight changes in redox homeostasis and the elaborate interplay between the different pathways involved in protection against oxidative events is not completely understood. Still, it is not clear whether early ROS formation plays a protective role by promoting antioxidant expression and thus preclude the neurodegenerative process.

Mitochondrial coenzyme Q10 was previously shown to have neuroprotective effects, being an important mitochondrial cofactor of electron transport chain by accepting electrons from complexes I and II (19). Coenzyme Q10 oral administration significantly enhanced brain mitochondrial levels in mature and older animals (106). Administration of coenzyme Q10 in R6/2 mice improved survival, delayed motor deficits, weight loss, cerebral atrophy and neuronal intranuclear inclusions (52, 174). Combination of coenzyme Q10 and creatine induced additional neuroprotective effects by improving motor performance and extending survival in the R6/2 mice (206). However, a phase 3 clinical trial with coenzyme Q10 (early stage, n= 609; NCT00608881) in HD patients showed no significant rescue of Total Functional Capacity score, Functional Checklist and Independence Scale scores (107), suggesting that coenzyme Q10 does not slow the progression of functional decline in HD. Similar results and conclusions were made for creatine. Creatine enhanced neural progenitor cell survival in HD (10) and slowed down brain atrophy in premanifest HD carriers (17). Conversely, the CREST-E study of treatment with creatine failed in delaying functional decline in early manifest HD carriers (69). Possible explanations for these results include the complexity and heterogeneity of neurodegeneration, inherent limitations of preclinical models in representing the human disease, requiring a more efficient delivery of coenzyme Q10 and creatine to the brain, with coenzyme Q10 given prior to the onset of symptoms. So far, these studies indicate that coenzyme Q10 and creatine are likely ineffective in HD. A phase 3 clinical trial with ethyl-eicosapentaenoic acid (Ethyl-EPA) (manifest, n=316, NCT00146211), an omega-3 fatty acid previously shown to promote mitochondrial biogenesis (74) and modulate the expression of proteins associated with energy metabolism and ATP production in rat brain (83), was not beneficial in patients with HD during 6 months of placebo-controlled evaluation (49).

Different clinical trials with pridopidine, formerly known as ACR16, were developed (phase 3, stages I–III, n= 437, NCT00665223; phase 2 and 3, stage III, n=227, NCT00724048; phase 2, stage III, n=235, NCT01306929; phase 2, stages I-II , n=248, NCT02494778). These clinical trials showed that pridopidine was well tolerated and safe for low doses, some indicating improved motor function, suggesting that it may slow clinical progression (79, 103, 148). Meanwhile, pridopidine was shown to selectively target Sig-1R when used at low doses [195] and thus an additional clinical trial in HD patients can be envisaged.

An ongoing clinical trial for HD (phase 3, early affected, n=102, NCT02336633) is being developed using resveratrol, known to have mitochondrial protective effects, as shown by us in different HD models (118). The main goal of the study is to measure the rate of caudate atrophy before and after 1-year of treatment with resveratrol in early affected HD patients using volumetric magnetic resonance imaging.

Considering these studies, numerous compounds were shown to reduce ROS production and its toxicity and to ameliorate mitochondrial function and dynamics in HD cells and animal models, however clinical trials were not beneficial in HD symptomatic (stage III) patients. The disease complexity, along with the heterogeneity of neurodegeneration in different patients, the limitations of drug testing in preclinical models that do not represent all the characteristics of the human disease, and challenging delivery of compounds into the brain may explain the difficulty of advancing most of the innovative neuroprotective compounds into the market.

**5 - CONCLUSIONS**

HD treatments are currently based on the attenuation of disease symptoms, including motor and behavioral alterations. There are no effective neuroprotective pharmacological therapies counteracting the onset of the pathology or slowing down the neurodegenerative process and thus disease progression.

Deregulated mitochondrial function, dynamics and degradation and elevated oxidative status have been closely related with HD progression, comprising possible therapeutic targets. Based on the studies cited in this review, there are numerous compounds that ameliorate mitochondrial function and dynamics and reduce the burden of ROS production and its consequences in HD cell and animal models. Human clinical trials with antioxidant supplementation have not been as efficient as the results shown in pre-clinical studies in animal models of HD. The same applies to compounds that positively influence mitochondrial function in HD symptomatic patients, with the possible exception of resveratrol.

The use of a cocktail of drugs aimed to target ROS/oxidative damage and multiple mitochondrial defects could have a potential benefit in HD treatment. Therefore, inhibiting oxidative damage together with targeting cytoprotective pathways and mitochondrial deficiencies as a whole may afford greater protection against neuronal dysfunction and late degeneration, being beneficial in a pre-symptomatic phase, at a disease stage when the dysfunctional pathways caused by mHtt expression have been initiated. Thus, these ‘cocktail’ pharmacological strategies could be tested to promote synergistic effects in early stages of HD. On the other hand, it will be relevant to analyse whether novel gene silencing approaches applied to HD carriers, such as those using antisense oligonucleotides (185), not only reduce the levels of mHTT, but also improve mitochondrial function and redox activity, preventing neuronal dysfunction and death, along with major HD-related symptoms.

**Acknowledgments**

This work was financed by the European Regional Development Fund (ERDF), through Centro 2020 Regional Operational Programme: project CENTRO-01-0145-FEDER-000012-HealthyAging2020, the COMPETE 2020-Operational Programme for Competitiveness and Internationalisation and Portuguese national funds via FCT – Fundação para a Ciência e a Tecnologia, I.P.: projects reference POCI-01-0145-FEDER-007440 and POCI-01-0145-FEDER-029621.

**Conflict of Interest:** The authors declare no competing financial interests or any conflict of interest.

**Abbreviations:**

**Δѱm:** mitochondrial membrane potential; **3-NP:** 3-nitropropionic acid; **8-OHdG**: 8-hydroxy-2'-deoxyguanosine; **βL:** β-Lapachone; **ALA**: alpha-lipoic acid; **ALCAR:** acetyl-L-carnitine; **Apaf-1:** apoptotic protease-activating factor 1; **ARE:** Antioxidant Response Element; **ATP:** adenosine triphosphate; **Bcl-2:** B-cell lymphoma 2; **BDNF:** brain derived neurotrophic factor; **BH3:** Bcl-2 homology 3; **Bid:** BH3 interacting-domain death agonist; **Bim:** Bcl-2 interacting mediator of cell death; **BiP:** immunoglobulin protein; **CAG:** cytosine-adenine-guanine; **CBP**: CREB-binding protein; **CK:** creatine kinase; **CoQ** coenzyme Q; **CREB:** cAMP response element-binding protein; **Cu:** copper; **DMF:** fumaric acid ester dimethylfumarate; **Drp1:** dynamin-related protein 1; **ETC:** electron transport chain; **ER:** endoplasmic reticulum; **FAE:** fumaric acid ester; **Fe:** iron; **Fis1:** mitochondrial fission 1; **FGF9:** fibroblast growth factor 9; **FMN:** flavin mononucleotide; **GAPDH:** glyceraldehyde-3-phosphate dehydrogenase; **Gln:** glutamine; **GRP75:** chaperone glucose-regulated protein 75; **GRP78**: glucose-regulated protein 78; **GSH-Px:** glutathione peroxidases; **GSH-R**: glutathione reductase; **GSH-Px:** glutathione peroxidase; **GSH-R:** glutathione reductase; **GST:** glutathione-S-transferase; **GTP**: guanosine triphosphate; **H2O2:** hydrogen peroxide; **HD:** Huntington’s disease; **HDACs:** histone deacetylase inhibitor; **hESC:** human embryonic stem cells; **HO2:** perhydroxyl radical; **HO-1:** heme oxygenase-1; **Htt/HTT**: huntingtin protein/gene; **IAP1:** Inhibitor of Apoptosis Protein-1; **IGF-1**: insulin-like growth factor 1; **IP3R:** Inositol trisphosphate receptor; **iPSCs:** induced pluripotent stem cells; **IVIg:** Intravenous immunoglobulin; **K:** lysine; **LC3:** light chain 3; **LPO:** lipid peroxidation; **MAM:** Mitochondrial-associated membrane; **MCU:** mitochondrial calcium uniporter; **Mff:** mitochondrial fission factor; **Mfn:** mitofusin; **mHtt/mHTT:** mutant huntingtin protein/gene; **MIM:** mitochondrial inner membrane; **Mn:** manganese; **MOM:** mitochondrial outer membrane; **mtDNA:** mitochondrial DNA; **MTS:** mitochondrial targeting sequences; **NAC:** antioxidant N-acetylcysteine; **NADPH:** Nicotinamide adenine dinucleotide phosphate; **NAD:** β-nicotinamide adenine dinucleotide; **ND5:** NADH dehydrogenase subunit 5; **NF-κB:** factor nuclear kappa B; **NMNAT**: nicotinamide mononucleotide adenylyltransferase; **NOX:** NADPH oxidase; **Nano-Se**: selenium nanoparticles; **NRF:** nuclear respiratory factor; **Nrf2:** nuclear factor-erythroid 2-related factor-2; **O2•-:** superoxide anion; **OPA1:** optic atrophy 1; **OXPHOS:** oxidative phosphorylation; **PCr:** phosphocreatine; **PDH:** pyruvate dehydrogenase; **PGC-1α:** PPARγ – coactivator-1α; **Ppt:** protopanaxtriol; **Phe:** phenylalanine; **PINK1:** PTEN-induced putative kinase 1; **PolyQ:** polyglutamine; **PPAR:** peroxisome proliferator-activated receptor; **Prx:** peroxiredoxins; **PTEN:** phosphatase and tensin homolog; **PTP:** permeability transition pore; **QA:** quinolinic acid; **ROS:** reactive oxygen species; **RyR:** ryanodine receptor; **Sig-1R:** sigma-1 receptor; **SB**: sodium butyrate; **SDH:** succinate dehydrogenase; **Ser:** serine; **SOD:** superoxide dismutase; **SFN**: sulforaphane; **TAF4**: Transcription initiation factor TFIID subunit 4; **TBP:** TATA-binding protein; **TBA:** tubastatin A; **TDZ:** thiazolidinedione; **TFAM:** mitochondrial transcription factor A; **TIM:** translocase of the inner membrane; **TOM:** translocase of the outer membrane; **TRAK:** trafficking kinesin protein; **VDAC:** Voltage-dependent anion channel; **YAC:** yeast artificial chromosome; **Zn**: zinc.

**References**

1. Agrawal S, Fox J, Thyagarajan B, and Fox JH. Brain mitochondrial iron accumulates in Huntington’s disease, mediates mitochondrial dysfunction, and can be removed pharmacologically. *Free Radic Biol Med 120:317-329*, 2018.

2. Ahmed LA, Darwish HA, Abdelsalam RM, and Amin HAA. Role of Rho Kinase Inhibition in the Protective Effect of Fasudil and Simvastatin Against 3-Nitropropionic Acid-Induced Striatal Neurodegeneration and Mitochondrial Dysfunction in Rats. *Mol Neurobiol 53(6):3927-3938*, 2016.

3. Aladdin A, Király R, Boto P, Regdon Z, and Tar K. Juvenile Huntington’s Disease Skin Fibroblasts Respond with Elevated Parkin Level and Increased Proteasome Activity as a Potential Mechanism to Counterbalance the Pathological Consequences of Mutant Huntingtin Protein. *Int J Mol Sci* 20: 5338, 2019.

4. Almeida S, Domingues A, Rodrigues L, Oliveira CR, and Rego AC. FK506 prevents mitochondrial-dependent apoptotic cell death induced by 3-nitropropionic acid in rat primary cortical cultures. *Neurobiol Dis 17(3):435-44*, 2004.

5. Almeida S, Laço M, Cunha-Oliveira T, Oliveira CR, and Rego AC. BDNF regulates BIM expression levels in 3-nitropropionic acid-treated cortical neurons. *Neurobiol Dis 35(3):448-56*, 2009.

6. Almeida S, Sarmento-Ribeiro AB, Januário C, Rego AC, and Oliveira CR. Evidence of apoptosis and mitochondrial abnormalities in peripheral blood cells of Huntington’s disease patients. *Biochem Biophys Res Commun 374(4):599-603*, 2008.

7. Amanzadeh E, Esmaeili A, Rahgozar S, and Nourbakhshnia M. Application of quercetin in neurological disorders: from nutrition to nanomedicine. *Rev Neurosci* 30: 555–572, 2019.

8. Anderson S, Bankier AT, Barrell BG, De Bruijn MHL, Coulson AR, Drouin J, Eperon IC, Nierlich DP, Roe BA, Sanger F, Schreier PH, Smith AJH, Staden R, and Young IG. Sequence and organization of the human mitochondrial genome. *Nature 290(5806):457-65*, 1981.

9. Andreassen OA, Ferrante RJ, Dedeoglu A, and Beal MF. Lipoic acid improves survival in transgenic mouse models of Huntington’s disease. *Neuroreport 12(15):3371-3*, 2001.

10. Andres R, Wallimann T, and Widmer H. Creatine supplementation improves neural progenitor cell survival in Huntington’s disease. *Brain Circ 2(3):133-137*, 2016.

11. Ayala-Peña S. Role of oxidative DNA damage in mitochondrial dysfunction and Huntington’s disease pathogenesis. *Free Radic Biol Med* 62: 102–110, 2013.

12. Bartzokis G, Cummings J, Perlman S, Hance DB, and Mintz J. Increased basal ganglia iron levels in Huntington disease. *Arch Neurol 56(5):569-74*, 1999.

13. Bartzokis G and Tishler TA. MRI evaluation of basal ganglia ferritin iron and neurotoxicity in Alzheimer’s and Huntingon’s disease. *Cell Mol Biol (Noisy-le-grand) 46(4):821-33*, 2000.

14. Bates GP, Dorsey R, Gusella JF, Hayden MR, Kay C, Leavitt BR, Nance M, Ross C a., Scahill RI, Wetzel R, Wild EJ, and Tabrizi SJ. Huntington disease. *Nat Rev Dis Prim*: 1:15005, 2015.

15. Bausewein T, Mills DJ, Langer JD, Nitschke B, Nussberger S, and Kühlbrandt W. Cryo-EM Structure of the TOM Core Complex from Neurospora crassa. *Cell 170(4):693-700.e7.*, 2017.

16. Benchoua A, Trioulier Y, Zala D, Gaillard MC, Lefort N, Dufour N, Saudou F, Elalouf JM, Hirsch E, Hantraye P, Déglon N, and Brouillet E. Involvement of mitochondrial complex II defects in neuronal death produced by N-terminus fragment of mutated huntingtin. *Mol Biol Cell 17(4):1652-63*, 2006.

17. Bender A and Klopstock T. Creatine for neuroprotection in neurodegenerative disease: end of story? *Amino Acids 48(8):1929-40*, 2016.

18. Berggren KL, Chen J, Fox J, Miller J, Dodds L, Dugas B, Vargas L, Lothian A, McAllum E, Volitakis I, Roberts B, Bush AI, and Fox JH. Neonatal iron supplementation potentiates oxidative stress, energetic dysfunction and neurodegeneration in the R6/2 mouse model of Huntington’s disease. *Redox Biol 4:363-74*, 2015.

19. Beyer RE. An analysis of the role of coenzyme Q in free radical generation and as an antioxidant. *Biochem Cell Biol 70(6):390-403*, 1992.

20. Boehning D, Patterson RL, Sedaghat L, Glebova NO, Kurosaki T, and Snyder SH. Cytochrome c binds to inositol (1,4,5) trisphosphate receptors, amplifying calcium-dependent apoptosis. *Nat Cell Biol 5(12):1051-61*, 2003.

21. Bogdanov MB, Andreassen OA, Dedeoglu A, Ferrante RJ, and Beal MF. Increased oxidative damage to DNA in a transgenic mouse model of Huntington’s disease. *J Neurochem* 79: 1246–9, 2001.

22. Bórquez DA, Urrutia PJ, Wilson C, Van Zundert B, Núñez MT, and González-Billault C. Dissecting the role of redox signaling in neuronal development. *J Neurochem* 137: 506–517, 2016.

23. Brennan W a, Bird ED, and Aprille JR. Regional mitochondrial respiratory activity in Huntington’s disease brain. *J Neurochem* 44: 1948–1950, 1985.

24. Brocardo PS, Mcginnis E, Christie BR, and Gil-Mohapel J. Time-course analysis of protein and lipid oxidation in the brains of Yac128 huntington’s disease transgenic mice. *Rejuvenation Res 19(2):140-8*, 2016.

25. Browne SE. Mitochondria and Huntington’s disease pathogenesis: Insight from genetic and chemical models. In: *Annals of the New York Academy of Science 1147:358-82,* 2008.

26. Browne SE and Beal MF. Oxidative damage in Huntington’s disease pathogenesis. *Antioxid Redox Signal* 8: 2061–73, 2006.

27. Browne SE, Bowling AC, MacGarvey U, Baik MJ, Berger SC, Muqit MM, Bird ED, and Beal MF. Oxidative damage and metabolic dysfunction in Huntington’s disease: Selective vulnerability of the basal ganglia. *Ann Neurol* 41: 646–53, 1997.

28. Browne SE, Ferrante RJ, and Beal MF. Oxidative stress in Huntington’s disease. *Brain Pathol* 9: 147–63, 1999.

29. Calkins MJ, Jakel RJ, Johnson DA, Chan K, Kan YW, and Johnson JA. Protection from mitochondrial complex II inhibition in vitro and in vivo by Nrf2-mediated transcription. *Proc Natl Acad Sci U S A* 102: 244–9, 2005.

30. Calkins MJ, Townsend JA, Johnson DA, and Johnson JA. Cystamine protects from 3-nitropropionic acid lesioning via induction of nf-e2 related factor 2 mediated transcription. *Exp Neurol 224(1):307-17*, 2010.

31. Cha MY, Chen H, and Chan D. Removal of the Mitochondrial Fission Factor Mff Exacerbates Neuronal Loss and Neurological Phenotypes in a Huntington’s Disease Mouse Model. *PLoS Curr 10:*, 2018.

32. Chae J Il, Kim DW, Lee N, Jeon YJ, Jeon I, Kwon J, Kim J, Soh Y, Lee DS, Seo KS, Choi NJ, Park BC, Kang SH, Ryu J, Oh SH, Shin DA, Lee DR, Do JT, Park IH, Daley GQ, and Song J. Quantitative proteomic analysis of induced pluripotent stem cells derived from a human Huntington’s disease patient. *Biochem J 446(3):359-71*, 2012.

33. Chandra A, Sharma A, Calingasan NY, White JM, Shurubor Y, William Yang X, Flint Beal M, and Johri A. Enhanced mitochondrial biogenesis ameliorates disease phenotype in a full-length mouse model of Huntington’s disease. *Hum Mol Genet 25(11):2269-2282*, 2016.

34. Chaturvedi RK, Calingasan NY, Yang L, Hennessey T, Johri A, and Beal MF. 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(16):3190-205*, 2010.

35. Chen C-M, Wu Y-R, Cheng M-L, Liu J-L, Lee Y-M, Lee P-W, Soong B-W, and Chiu DT-Y. Increased oxidative damage and mitochondrial abnormalities in the peripheral blood of Huntington’s disease patients. *Biochem Biophys Res Commun* 359: 335–40, 2007.

36. Chen J, Marks E, Lai B, Zhang Z, Duce JA, Lam LQ, Volitakis I, Bush AI, Hersch S, and Fox JH. Iron Accumulates in Huntington’s Disease Neurons: Protection by Deferoxamine. *PLoS One 8(10):e77023*, 2013.

37. Chiang M-C, Cheng Y-C, Nicol CJ, Lin K-H, Yen C-H, Chen S-J, and Huang R-N. Rosiglitazone activation of PPARγ-dependent signaling is neuroprotective in mutant huntingtin expressing cells. *Exp Cell Res* 338: 183–193, 2015.

38. Chiu FL, Lin JT, Chuang CY, Chien T, Chen CM, Chen KH, Hsiao HY, Lin YS, Chern Y, and Kuo HC. Elucidating the role of the A 2A adenosine receptor in neurodegeneration using neurons derived from Huntington’s disease iPSCs. *Hum Mol Genet 24(21):6066-79*, 2015.

39. Choo YS, Johnson GVW, MacDonald M, Detloff PJ, and Lesort M. Mutant huntingtin directly increases susceptibility of mitochondria to the calcium-induced permeability transition and cytochrome c release. *Hum Mol Genet 13(14):1407-20*, 2004.

40. Clemens LE, Weber JJ, Wlodkowski TT, Yu-Taeger L, Michaud M, Calaminus C, Eckert SH, Gaca J, Weiss A, Magg JCD, Jansson EKH, Eckert GP, Pichler BJ, Bordet T, Pruss RM, Riess O, and Nguyen HP. Olesoxime suppresses calpain activation and mutant huntingtin fragmentation in the BACHD rat. *Brain 138(Pt 12):3632-53*, 2015.

41. Cobley JN, Fiorello ML, and Bailey DM. 13 reasons why the brain is susceptible to oxidative stress. *Redox Biol 15:490-503*, 2018.

42. Cong W, Bai R, Li Y-F, Wang L, and Chen C. Selenium Nanoparticles as an Efficient Nanomedicine for the Therapy of Huntington’s Disease. *ACS Appl Mater Interfaces* 11: 34725–34735, 2019.

43. Costa V, Giacomello M, Hudec R, Lopreiato R, Ermak G, Lim D, Malorni W, Davies KJA, Carafoli E, and Scorrano L. Mitochondrial fission and cristae disruption increase the response of cell models of Huntington’s disease to apoptotic stimuli. *EMBO Mol Med 2(12):490-503*, 2010.

44. Cui L, Jeong H, Borovecki F, Parkhurst CN, Tanese N, and Krainc D. Transcriptional Repression of PGC-1α by Mutant Huntingtin Leads to Mitochondrial Dysfunction and Neurodegeneration. *Cell 127(1):59-69*, 2006.

45. Dedeoglu A, Kubilus JK, Jeitner TM, Matson SA, Bogdanov M, Kowall NW, Matson WR, Cooper AJL, Ratan RR, Beal MF, Hersch SM, and Ferrante RJ. Therapeutic effects of cystamine in a murine model of Huntington’s disease. *J Neurosci 22(20):8942-50*, 2002.

46. Denny Joseph KM and Muralidhara. Enhanced neuroprotective effect of fish oil in combination with quercetin against 3-nitropropionic acid induced oxidative stress in rat brain. *Prog Neuro-Psychopharmacology Biol Psychiatry 40:83-92*, 2013.

47. Dexter DT, Jenner P, Schapira AHV, and Marsden CD. Alterations in levels of iron, ferritin, and other trace metals in neurodegenerative diseases affecting the basal ganglia. *Ann Neurol 32 Suppl:S94-100*, 1992.

48. Dominah GA, McMinimy RA, Kallon S, and Kwakye GF. Acute exposure to chlorpyrifos caused NADPH oxidase mediated oxidative stress and neurotoxicity in a striatal cell model of Huntington’s disease. *Neurotoxicology 60:54-69*, 2017.

49. Dorsey ER, Shoulson I, Leavitt B, Ross C, Beck CA, de Blieck EA, Greenamyre JT, Hersch SM, Kieburtz K, Marder K, McCallum C, Moskowitz C, Oakes D, Rosenblatt A, Shinaman A, Frucht S, Marder K, Moskowitz C, Margolis R, Corey-Bloom J, Hersch SM, Mook L, Shannon K, Jaglin J, Sanchez-Ramos J, Dure LS, Guttman M, Feigin A, Shannon B, Anderson KE, Racette BA, Higgins D, Agarwal P, Seeberger L, Montellano S, Kostyk S, Seward A, Nance M, Raymond LA, Decolongon J, Suchowersky O, Beglinger L, Paulson H, Como P, Barbano R, Zimmerman C, Wojcieszek J, Jog M, Horn C, Colcher A, Geschwind MD, Dubinsky RM, Martin W, Wieler M, LeDoux MS, Harrison MB, Morgan JC, Dill B, Singer C, Quesada M, Kartha N, Wernette K, Frank S, Fernandez H, Jennings D, Kelsey T, Hunter C, Beck C, Bourgeois K, de Blieck EA, Deuel L, McCallum C, McMullen N, Ross V, Rumfola L, Watts A, Weaver C, Winebrenner T, Tariot PN, Watts A, Clarke A, Mallard N, Stewart R, Strausser B, Scott D, Adams W, Agarwal A, Ammel M, Bond L, Bordelon Y, Burkholder J, Burton L, Caviness JN, Diamond A, Diggin M, Fite-Weatherford M, Forsyth J, Fussell B, Goldstein J, Gray C, Greene JG, Guzijan M, Hill J, Hutchinson E, Jankovic J, King P, Klimek ML, Langbehn D, Lucarelli N, MacDonald M, Malikowski M, Manku M, McCall M, Miyasaki J, Molho E, Moore RY, Mysore J, Oliger C, Oppert D, Patterson S, Pendley D, Peterson S, Phillipson C, Podskalny G, Rini C, Shahed J, Tempkin T, Tucker L, Vareha R, and Wheelock V. Randomized controlled trial of ethyl-eicosapentaenoic acid in huntington disease. *Arch Neurol 65(12):1582-9*, 2008.

50. Droge W. Free Radicals in the Physiological Control of Cell Function. *Physiol Rev* 82: 47–95, 2002.

51. Ellrichmann G, Petrasch-Parwez E, Lee DH, Reick C, Arning L, Saft C, Gold R, and Linker RA. Efficacy of fumaric acid esters in the R6/2 and YAC128 models of huntington’s disease. *PLoS One* 6(1):e16172, 2011.

52. Ferrante RJ, Andreassen OA, Dedeoglu A, Ferrante KL, Jenkins BG, Hersch SM, and Beal MF. Therapeutic effects of coenzyme Q10 and remacemide in transgenic mouse models of Huntington’s disease. *J Neurosci 22(5):1592-9*, 2002.

53. Ferreira IL, Nascimento M V., Ribeiro M, Almeida S, Cardoso SM, Grazina M, Pratas J, Santos MJ, Januário C, Oliveira CR, and Rego AC. Mitochondrial-dependent apoptosis in Huntington’s disease human cybrids. *Exp Neurol* 222: 243–255, 2010.

54. Flint Beal M, Matson WR, Storey E, Milbury P, Ryan EA, Ogawa T, and Bird ED. Kynurenic acid concentrations are reduced in Huntington’s disease cerebral cortex. *J Neurol Sci 108(1):80-7*, 1992.

55. Fox JH, Barber DS, Singh B, Zucker B, Swindell MK, Norflus F, Buzescu R, Chopra R, Ferrante RJ, Kazantsev A, and Hersch SM. Cystamine increases L-cysteine levels in Huntington’s disease transgenic mouse brain and in a PC12 model of polyglutamine aggregation. *J Neurochem 91(2):413-22*, 2004.

56. Fox JH, Connor T, Stiles M, Kama J, Lu Z, Dorsey K, Liebermann G, Sapp E, Cherny RA, Banks M, Volitakis I, DiFiglia M, Berezovska O, Bush AI, and Hersch SM. Cysteine oxidation within N-terminal mutant huntingtin promotes oligomerization and delays clearance of soluble protein. *J Biol Chem 286(20):18320-30*, 2011.

57. Fox JH, Kama JA, Lieberman G, Chopra R, Dorsey K, Chopra V, Volitakis I, Cherny RA, Bush AI, and Hersch S. Mechanisms of copper ion mediated Huntington’s disease progression. *PLoS One 2(3):e334*, 2007.

58. Gadoth, N., and Goebel HH. *Oxidative Stress and Free Radical Damage in Neurology*. (edited by Gadoth N and Göbel HH)., Totowa, NJ, Humana Press, 2011.

59. Gao Y, Chu S-F, Li J-P, Zuo W, Wen Z-L, He W-B, Yan J-Q, and Chen N-H. Do glial cells play an anti-oxidative role in Huntington’s disease? *Free Radic Res 48(10):1135-44*, 2015.

60. Gao Y, Chu S, Li J, Zhang Z, Yan J, Wen Z, Xia C, Mou Z, Wang Z, He W, Guo X, Wei G, and Chen N. Protopanaxtriol protects against 3-nitropropionic acid-induced oxidative stress in a rat model of Huntington’s disease. *Acta Pharmacol Sin* 36: 311–22, 2015.

61. Gil JM and Rego a C. Mechanisms of neurodegeneration in Huntington’s disease. *EurJNeurosci* 27: 2803–2820, 2008.

62. Goffredo D, Rigamonti D, Zuccato C, Tartari M, Valenza M, and Cattaneo E. Prevention of cytosolic IAPs degradation: A potential pharmacological target in Huntington’s Disease. *Pharmacol Res 52(2):140-50*, 2005.

63. Goswami A, Dikshit P, Mishra A, Mulherkar S, Nukina N, and Jana NR. Oxidative stress promotes mutant huntingtin aggregation and mutant huntingtin-dependent cell death by mimicking proteasomal malfunction. *Biochem Biophys Res Commun* 342: 184–190, 2006.

64. Gu M, Gash MT, Mann VM, Javoy-Agid F, Cooper JM, and Schapira AH V. Mitochondrial defect in Huntington’s disease caudate nucleus. *Ann Neurol* 39: 385–389, 1996.

65. Guedes-Dias P, de Proença J, Soares TR, Leitão-Rocha A, Pinho BR, Duchen MR, and Oliveira JMA. HDAC6 inhibition induces mitochondrial fusion, autophagic flux and reduces diffuse mutant huntingtin in striatal neurons. *Biochim Biophys Acta - Mol Basis Dis 1852(11):2484-93*, 2015.

66. Hands S, Sajjad MU, Newton MJ, and Wyttenbach A. In vitro and in vivo aggregation of a fragment of huntingtin protein directly causes free radical production. *J Biol Chem* 286: 44512–44520, 2011.

67. Hayashi T and Su TP. Sigma-1 Receptor Chaperones at the ER- Mitochondrion Interface Regulate Ca2+ Signaling and Cell Survival. *Cell 131(3):596-610*, 2007.

68. Hering T, Birth N, Taanman JW, and Orth M. Selective striatal mtDNA depletion in end-stage Huntington’s disease R6/2 mice. *Exp Neurol 266:22-9*, 2015.

69. Hersch SM, Schifitto G, Oakes D, Bredlau A-L, Meyers CM, Nahin R, and Rosas HD. The CREST-E study of creatine for Huntington disease. *Neurology* 89: 594–601, 2017.

70. Humbert S, Bryson EA, Cordelières FP, Connors NC, Datta SR, Finkbeiner S, Greenberg ME, and Saudou F. The IGF-1/Akt pathway is neuroprotective in Huntington’s disease and involves huntingtin phosphorylation by Akt. *Dev Cell 2(6):831-7*, 2002.

71. Hyrskyluoto A, Pulli I, Törnqvist K, Huu Ho T, Korhonen L, and Lindholm D. Sigma-1 receptor agonist PRE084 is protective against mutant huntingtin-induced cell degeneration: Involvement of calpastatin and the NF-κB pathway. *Cell Death Dis 4(5):e646*, 2013.

72. Itoh K, Chiba T, Takahashi S, Ishii T, Igarashi K, Katoh Y, Oyake T, Hayashi N, Satoh K, Hatayama I, Yamamoto M, and Nabeshima Y. An Nrf2/Small Maf Heterodimer Mediates the Induction of Phase II Detoxifying Enzyme Genes through Antioxidant Response Elements. *Biochem Biophys Res Commun* 236: 313–322, 1997.

73. Jang M and Cho IH. Sulforaphane Ameliorates 3-Nitropropionic Acid-Induced Striatal Toxicity by Activating the Keap1-Nrf2-ARE Pathway and Inhibiting the MAPKs and NF-κB Pathways. *Mol Neurobiol* 53: 2619–2635, 2016.

74. Jeng JY, Yeh TS, Chiu YH, Lee YC, Cheng HH, and Hsieh RH. Linoleic acid promotes mitochondrial biogenesis and maintains mitochondrial structure for prevention of streptozotocin damage in RIN-m5F cells. *Biosci Biotechnol Biochem 73(6):1262-7*, 2009.

75. Jin J, Gu H, Anders NM, Ren T, Jiang M, Tao M, Peng Q, Rudek MA, and Duan W. Metformin Protects Cells from Mutant Huntingtin Toxicity Through Activation of AMPK and Modulation of Mitochondrial Dynamics. *NeuroMolecular Med 18(4):581-592*, 2016.

76. Jin YN, Yu Y V., Gundemir S, Jo C, Cui M, Tieu K, and Johnson GVW. Impaired Mitochondrial Dynamics and Nrf2 Signaling Contribute to Compromised Responses to Oxidative Stress in Striatal Cells Expressing Full-Length Mutant Huntingtin. *PLoS One* 8(3):e57932, 2013.

77. Johri A, Calingasan NY, Hennessey TM, Sharma A, Yang L, Wille E, Chandra A, and Beal MF. Pharmacologic activation of mitochondrial biogenesis exerts widespread beneficial effects in a transgenic mouse model of Huntington’s disease. *Hum Mol Genet 21(5):1124-37*, 2012.

78. Julayanont P, Heilman KM, and McFarland NR. Early-motor phenotype relates to neuropsychiatric and cognitive disorders in huntington’s disease. *Mov Disord*: 1–8, 2020.

79. Karl K, McGarry A, McDermott MP, Kayson E, Walker F, Goldstein J, Hyson C, Agarwal P, Deppen P, Fiedorowicz J, Kostyk S, Wright A, Leavitt B, Nance M, LeDoux MS, Shannon KM, Siderowf A, Cudkowicz M, Rabinowitz K, Ross V, Watts A, and Tedroff J. A randomized, double-blind, placebo-controlled trial of pridopidine in Huntington’s disease. *Mov Disord 28(10):1407-15*, 2013.

80. Karpuj M V., Becher MW, Springer JE, Chabas D, Youssef S, Pedotti R, Mitchell D, and Steinman L. Prolonged survival and decreased abnormal movements in transgenic model of Huntington disease, with administration of the transglutaminase inhibitor cystamine. *Nat Med 8(2):143-9*, 2002.

81. Keum YS and Choi BY. Molecular and chemical regulation of the keap1-Nrf2 signaling pathway. *Molecules* 19: 10074–10089, 2014.

82. Khalil B, El Fissi N, Aouane A, Cabirol-Pol MJ, Rival T, and Liévens JC. PINK1-induced mitophagy promotes neuroprotection in Huntington’s disease. *Cell Death Dis 6(1):e1617*, 2015.

83. Kitajka K, Puskás LG, Zvara Á, Hackler L, Barceló-Coblijn G, Yeo YK, and Farkas T. The role of n-3 polyunsaturated fatty acids in brain: Modulation of rat brain gene expression by dietary n-3 fatty acids. *Proc Natl Acad Sci U S A 99(5):2619-24*, 2002.

84. Klepac N, Relja M, Klepac R, Hećimović S, Babić T, and Trkulja V. 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: 1676–1683, 2007.

85. Knott AB, Perkins G, Schwarzenbacher R, and Bossy-Wetzel E. Mitochondrial fragmentation in neurodegeneration. *Nat Rev Neurosci 9(7):505-18*, 2008.

86. Kolodziejczyk K and Raymond LA. Differential changes in thalamic and cortical excitatory synapses onto striatal spiny projection neurons in a Huntington disease mouse model. *Neurobiol Dis* 86: 62–74, 2016.

87. Kotlar I, Colonnello A, Aguilera-González MF, Avila DS, de Lima ME, García-Contreras R, Ortíz-Plata A, Soares FAA, Aschner M, and Santamaría A. Comparison of the Toxic Effects of Quinolinic Acid and 3-Nitropropionic Acid in C. elegans: Involvement of the SKN-1 Pathway. *Neurotox Res 33(2):259-267*, 2018.

88. Kulasekaran G and Ganapasam S. Neuroprotective efficacy of naringin on 3-nitropropionic acid-induced mitochondrial dysfunction through the modulation of Nrf2 signaling pathway in PC12 cells. *Mol Cell Biochem 409(1-2):199-211*, 2015.

89. Kumar P, Kalonia H, and Kumar A. Nitric oxide mechanism in the protective effect of antidepressants against 3-nitropropionic acid-induced cognitive deficit, glutathione and mitochondrial alterations in animal model of Huntington’s disease. *Behav Pharmacol 21(3):217-30*, 2010.

90. Kumar P, Padi SSV, Naidu PS, and Kumar A. Possible neuroprotective mechanisms of curcumin in attenuating 3-nitropropionic acid-induced neurotoxicity. *Methods Find Exp Clin Pharmacol 29(1):19-25*, 2007.

91. Lagoa R, Lopez-Sanchez C, Samhan-Arias AK, Gañan CM, Garcia-Martinez V, and Gutierrez-Merino C. Kaempferol protects against rat striatal degeneration induced by 3-nitropropionic acid. *J Neurochem 111(2):473-87*, 2009.

92. Lee M, Ban JJ, Chung JY, Im W, and Kim M. Amelioration of huntington’s disease phenotypes by beta-lapachone is associated with increases in sirt1 expression, creb phosphorylation and pgc-1α deacetylation. *PLoS One 13(5):e0195968*, 2018.

93. Lin J, Wu PH, Tarr PT, Lindenberg KS, St-Pierre J, Zhang CY, Mootha VK, Jäger S, Vianna CR, Reznick RM, Cui L, Manieri M, Donovan MX, Wu Z, Cooper MP, Fan MC, Rohas LM, Zavacki AM, Cinti S, Shulman GI, Lowell BB, Krainc D, and Spiegelman BM. Defects in adaptive energy metabolism with CNS-linked hyperactivity in PGC-1α null mice. *Cell 119(1):121-35*, 2004.

94. Liu CS, Cheng WL, Kuo SJ, Li JY, Soong BW, and Wei YH. Depletion of mitochondrial DNA in leukocytes of patients with poly-Q diseases. *J Neurol Sci 264(1-2):18-21*, 2008.

95. Liu P, Li Y, Yang W, Liu D, Ji X, Chi T, Guo Z, Li L, and Zou L. Prevention of Huntington’s Disease-Like Behavioral Deficits in R6/1 Mouse by Tolfenamic Acid Is Associated with Decreases in Mutant Huntingtin and Oxidative Stress. *Oxid Med Cell Longev* 2019: 1–13, 2019.

96. Liu S, Yu X, Zhu J, Liu X, Zhang Y, Dong Q, Ma S, and Liu R. Intravenous immunoglobulin ameliorates motor and cognitive deficits and neuropathology in R6/2 mouse model of Huntington’s disease by decreasing mutant huntingtin protein level and normalizing NF-κB signaling pathway. *Brain Res* 1697: 21–33, 2018.

97. Liu Y, Qiao F, Leiferman PC, Ross A, Schlenker EH, and Wang H. FOXOs modulate proteasome activity in human-induced pluripotent stem cells of Huntington’s disease and their derived neural cells. *Hum Mol Genet 26(22):4416-4428*, 2017.

98. Loboda A, Damulewicz M, Pyza E, Jozkowicz A, and Dulak J. Role of Nrf2/HO-1 system in development, oxidative stress response and diseases: an evolutionarily conserved mechanism. *Cell Mol Life Sci* 73: 1–27, 2016.

99. Long JD, Matson WR, Juhl AR, Leavitt BR, and Paulsen JS. 8OHdG as a marker for Huntington disease progression. *Neurobiol Dis* 46: 625–634, 2012.

100. López-Sendón Moreno JL, García Caldentey J, Trigo Cubillo P, Ruiz Romero C, García Ribas G, Alonso Arias MAA, García de Yébenes MJ, Tolón RM, Galve-Roperh I, Sagredo O, Valdeolivas S, Resel E, Ortega-Gutierrez S, García-Bermejo ML, Fernández Ruiz J, Guzmán M, and García de Yébenes Prous J. A double-blind, randomized, cross-over, placebo-controlled, pilot trial with Sativex in Huntington’s disease. *J Neurol 263(7):1390-400*, 2016.

101. Lou S, Lepak VC, Eberly LE, Roth B, Cui W, Zhu XH, Öz G, and Dubinsky JM. Oxygen consumption deficit in Huntington disease mouse brain under metabolic stress. *Hum Mol Genet 25(13):2813-2826*, 2016.

102. Luis-García ER, Limón-Pacheco JH, Serrano-García N, Hernández-Pérez AD, Pedraza-Chaverri J, and Orozco-Ibarra M. Sulforaphane prevents quinolinic acid-induced mitochondrial dysfunction in rat striatum. *J Biochem Mol Toxicol 31(2)*, 2017.

103. Lundin A, Dietrichs E, Haghighi S, Göller ML, Heiberg A, Loutfi G, Widner H, Wiktorin K, Wiklund L, Svenningsson A, Sonesson C, Waters N, Waters S, and Tedroff J. Efficacy and safety of the dopaminergic stabilizer pridopidine (ACR16) in patients with Huntington’s disease. *Clin Neuropharmacol 33(5):260-4*, 2010.

104. Ma MW, Wang J, Zhang Q, Wang R, Dhandapani KM, Vadlamudi RK, and Brann DW. NADPH oxidase in brain injury and neurodegenerative disorders. *Mol Neurodegener 12(1):7*, 2017.

105. Mason RP, Casu M, Butler N, Breda C, Campesan S, Clapp J, Green EW, Dhulkhed D, Kyriacou CP, and Giorgini F. Glutathione peroxidase activity is neuroprotective in models of Huntington’s disease. *Nat Genet* 45: 1249–1254, 2013.

106. Matthews RT, Yang L, Browne S, Baik M, and Beal MF. Coenzyme Q10 administration increases brain mitochondrial concentrations and exerts neuroprotective effects. *Proc Natl Acad Sci U S A 95(15):8892-7*, 1998.

107. McGarry A, McDermott M, Kieburtz K, DeBlieck EA, Beal F, Marder K, Ross C, Shoulson I, Gilbert P, Mallonee WM, Guttman M, Wojcieszek J, Kumar R, LeDoux MS, Jenkins M, Rosas HD, Nance M, Biglan K, Como P, Dubinsky RM, Shannon KM, O’Suilleabhain P, Chou K, Walker F, Martin W, Wheelock VL, McCusker E, Jankovic J, Singer C, Sanchez-Ramos J, Scott B, Suchowersky O, Factor SA, Higgins DS, Molho E, Revilla F, Caviness JN, Friedman JH, Perlmutter JS, Feigin A, Anderson K, Rodriguez R, McFarland NR, Margolis RL, Farbman ES, Raymond LA, Suski V, Kostyk S, Colcher A, Seeberger L, Epping E, Esmail S, Diaz N, Alan Fung WL, Diamond A, Frank S, Hanna P, Hermanowicz N, Dure LS, and Cudkowicz M. A randomized, double-blind, placebo-controlled trial of coenzyme Q10 in Huntington disease. *Neurology 88(2):152-159*, 2017.

108. Mehrotra A, Sood A, and Sandhir R. Mitochondrial modulators improve lipid composition and attenuate memory deficits in experimental model of Huntington’s disease. *Mol Cell Biochem 410(1-2):281-92*, 2015.

109. Menze ET, Tadros MG, Abdel-Tawab AM, and Khalifa AE. Potential neuroprotective effects of hesperidin on 3-nitropropionic acid-induced neurotoxicity in rats. *Neurotoxicology 33(5):1265-75*, 2012.

110. Milakovic T, Quintanilla RA, and Johnson GVW. Mutant Huntingtin expression induces mitochondrial calcium handling defects in clonal striatal cells: Functional consequences. *J Biol Chem 281(46):34785-95*, 2006.

111. Morreale MK. Huntington’s disease: Looking beyond the movement disorder. *Adv Psychosom Med* 34: 135–142, 2015.

112. Moslemi M, Motamedi F, Asadi S, and Khodagholi F. Peroxisomal Malfunction Caused by Mitochondrial Toxin 3-NP: Protective Role of Oxytocin. *Iran J Pharm Res IJPR* 18: 296–307, 2019.

113. Muller M and Leavitt BR. Iron dysregulation in Huntington’s disease. *J Neurochem 130(3):328-50*, 2014.

114. Naia L, Cunha-Oliveira T, Rodrigues J, Rosenstock TR, Oliveira A, Ribeiro M, Carmo C, Oliveira-Sousa SI, Duarte AI, Hayden MR, and Rego AC. Histone deacetylase inhibitors protect against pyruvate dehydrogenase dysfunction in huntington’s disease. *J Neurosci 37(10):2776-2794*, 2017.

115. Naia L, Ferreira IL, Cunha-Oliveira T, Duarte AI, Ribeiro M, Rosenstock TR, Laço MN, Ribeiro MJ, Oliveira CR, Saudou F, Humbert S, and Rego AC. Activation of IGF-1 and Insulin Signaling Pathways Ameliorate Mitochondrial Function and Energy Metabolism in Huntington’s Disease Human Lymphoblasts. *Mol Neurobiol 51(1):331-48*, 2014.

116. Naia L, Ferreira IL, Ferreiro E, and Rego AC. Mitochondrial Ca2+ handling in Huntington’s and Alzheimer’s diseases – Role of ER-mitochondria crosstalk. *Biochem Biophys Res Commun* 483: 1069–1077, 2017.

117. Naia L, Ribeiro M, Rodrigues J, Duarte AI, Lopes C, Rosenstock TR, Hayden MR, and Rego AC. Insulin and IGF-1 regularize energy metabolites in neural cells expressing full-length mutant huntingtin. *Neuropeptides 58:73-81*, 2016.

118. Naia L, Rosenstock TR, Oliveira AM, Oliveira-Sousa SI, Caldeira GL, Carmo C, Laço MN, Hayden MR, Oliveira CR, and Rego AC. Comparative Mitochondrial-Based Protective Effects of Resveratrol and Nicotinamide in Huntington’s Disease Models. *Mol Neurobiol* 54: 5385–5399, 2017.

119. Nanetti L, Contarino VE, Castaldo A, Sarro L, Bachoud-Levi AC, Giavazzi M, Frittoli S, Ciammola A, Rizzo E, Gellera C, Bruzzone MG, Taroni F, Grisoli M, and Mariotti C. Cortical thickness, stance control, and arithmetic skill: An exploratory study in premanifest Huntington disease. *Park Relat Disord 51:17-23*, 2018.

120. Napoli E, Wong S, Hung C, Ross-Inta C, Bomdica P, and Giulivi C. Defective mitochondrial disulfide relay system, altered mitochondrial morphology and function in Huntington’s disease. *Hum Mol Genet* 22: 989–1004, 2013.

121. Nekrasov ED and Kiselev SL. Mitochondrial distribution violation and nuclear indentations in neurons differentiated from iPSCs of Huntington’s disease patients. *J Stem Cells Regen Med 14(2):80-85*, 2018.

122. Oliveira AM, Cardoso SM, Ribeiro M, Seixas RSGR, Silva AMS, and Rego AC. Protective effects of 3-alkyl luteolin derivatives are mediated by Nrf2 transcriptional activity and decreased oxidative stress in Huntington’s disease mouse striatal cells. *Neurochem Int* 91: 1–12, 2015.

123. Oliveira AM, Cardoso SM, Ribeiro M, Seixas RSGR, Silva AMS, and Rego AC. Protective effects of 3-alkyl luteolin derivatives are mediated by Nrf2 transcriptional activity and decreased oxidative stress in Huntington’s disease mouse striatal cells. *Neurochem Int* 91: 1–12, 2015.

124. Oliveira JMA, Jekabsons MB, Chen S, Lin A, Rego AC, Gonçalves J, Ellerby LM, and Nicholls DG. Mitochondrial dysfunction in Huntington’s disease: The bioenergetics of isolated and in situ mitochondria from transgenic mice. *J Neurochem 101(1):241-9*, 2007.

125. Ooi J, Langley SR, Xu X, Utami KH, Sim B, Huang Y, Harmston NP, Tay YL, Ziaei A, Zeng R, Low D, Aminkeng F, Sobota RM, Ginhoux F, Petretto E, and Pouladi MA. Unbiased Profiling of Isogenic Huntington Disease hPSC-Derived CNS and Peripheral Cells Reveals Strong Cell-Type Specificity of CAG Length Effects. *Cell Rep* 26: 2494–2508.e7, 2019.

126. Orr AL, Li S, Wang CE, Li H, Wang J, Rong J, Xu X, Mastroberardino PG, Greenamyre JT, and Li XJ. N-terminal mutant huntingtin associates with mitochondria and impairs mitochondrial trafficking. *J Neurosci 28(11):2783-92*, 2008.

127. Paldino E, Balducci C, La Vitola P, Artioli L, D’Angelo V, Giampà C, Artuso V, Forloni G, and Fusco FR. Neuroprotective Effects of Doxycycline in the R6/2 Mouse Model of Huntington’s Disease. *Mol Neurobiol 57(4):1889-1903*, 2019.

128. Palikaras K and Tavernarakis N. Mitochondrial homeostasis: The interplay between mitophagy and mitochondrial biogenesis. *Exp Gerontol 56:182-8*, 2014.

129. Panov A V., Gutekunst CA, Leavitt BR, Hayden MR, Burke JR, Strittmatter WJ, and Greenamyre JT. Early mitochondrial calcium defects in Huntington’s disease are a direct effect of polyglutamines. *Nat Neurosci 5(8):731-6*, 2002.

130. Paul BD, Sbodio JI, Xu R, Vandiver MS, Cha JY, Snowman AM, and Snyder SH. Cystathionine γ-lyase deficiency mediates neurodegeneration in Huntington’s disease. *Nature* 509: 96–100, 2014.

131. Pellman JJ, Hamilton J, Brustovetsky T, and Brustovetsky N. Ca2+ handling in isolated brain mitochondria and cultured neurons derived from the YAC128 mouse model of Huntington’s disease. *J Neurochem 134(4):652-67*, 2015.

132. Peña-Sánchez M, Riverón-Forment G, Zaldívar-Vaillant T, Soto-Lavastida A, Borrero-Sánchez J, Lara-Fernández G, Esteban-Hernández EM, Hernández-Díaz Z, González-Quevedo A, Fernández-Almirall I, Pérez-López C, Castillo-Casañas Y, Martínez-Bonne O, Cabrera-Rivero A, Valdés-Ramos L, Guerra-Badía R, Fernández-Carriera R, Menéndez-Sainz MC, and González-García S. Association of status redox with demographic, clinical and imaging parameters in patients with Huntington’s disease. *Clin Biochem 48(18):1258-63*, 2015.

133. Pérez-Severiano F, Escalante B, Vergara P, Ríos C, and Segovia J. Age-dependent changes in nitric oxide synthase activity and protein expression in striata of mice transgenic for the Huntington’s disease mutation. *Brain Res 951(1):36-42*, 2002.

134. Pérez-Severiano F, Ríos C, and Segovia J. Striatal oxidative damage parallels the expression of a neurological phenotype in mice transgenic for the mutation of Huntington’s disease. *Brain Res* 862: 234–237, 2000.

135. Pérez-Severiano F, Santamaría A, Pedraza-Chaverri J, Medina-Campos ON, Ríos C, and Segovia J. Increased Formation of Reactive Oxygen Species, but No Changes in Glutathione Peroxidase Activity, in Striata of Mice Transgenic for the Huntington’s Disease Mutation. *Neurochem Res 29(4):729-33*, 2004.

136. Petersen MH, Budtz-Jørgensen E, Sørensen SA, Nielsen JE, Hjermind LE, Vinther-Jensen T, Nielsen SMB, and Nørremølle A. Reduction in mitochondrial DNA copy number in peripheral leukocytes after onset of Huntington’s disease. *Mitochondrion 17:14-21*, 2014.

137. Peyser CE, Folstein M, Chase GA, Starkstein S, Brandt J, Cockrell JR, Bylsma F, Coyle JT, McHugh PR, and Folstein SE. Trial of d-α-tocopherol in Huntington’s disease. *Am J Psychiatry 152(12):1771-5*, 1995.

138. Pickrell AM and Youle RJ. The roles of PINK1, Parkin, and mitochondrial fidelity in parkinson’s disease. *Neuron 85(2):257-73*, 2015.

139. Pinho BR, Duarte AI, Canas PM, Moreira PI, Murphy MP, and Oliveira JMA. The interplay between redox signalling and proteostasis in neurodegeneration: In vivo effects of a mitochondria-targeted antioxidant in Huntington’s disease mice. *Free Radic Biol Med 146:372-382*, 2019.

140. Pini L, Jacquemot C, Cagnin A, Meneghello F, Semenza C, Mantini D, and Vallesi A. Aberrant brain network connectivity in presymptomatic and manifest Huntington’s disease: A systematic review. *Hum Brain Mapp* 41: 256–269, 2020.

141. Pitts A, Dailey K, Newington JT, Chien A, Arseneault R, Cann T, Thompson LM, and Cumming RC. Dithiol-based compounds maintain expression of antioxidant protein peroxiredoxin 1 that counteracts toxicity of mutant huntingtin. *J Biol Chem 287(27):22717-29*, 2012.

142. Polyzos AA, Wood NI, Williams P, Wipf P, Jennifer Morton A, and McMurray CT. XJB-5-131-mediated improvement in physiology and behaviour of the R6/2 mouse model of Huntington’s disease is age- and sex- dependent. *PLoS One 13(4):e0194580*, 2018.

143. Ponten H, Kullingsjö J, Lagerkvist S, Martin P, Pettersson F, Sonesson C, Waters S, and Waters N. In vivo pharmacology of the dopaminergic stabilizer pridopidine. *Eur J Pharmacol 644(1-3):88-95*, 2010.

144. Van Raamsdonk JM, Pearson J, Bailey CDC, Rogers DA, Johnson GVW, Hayden MR, and Leavitt BR. Cystamine treatment is neuroprotective in the YAC128 mouse model of Huntington disease. *J Neurochem 95(1):210-20*, 2005.

145. Ramirez‐Garcia G, Galvez V, Diaz R, Bayliss L, Fernandez‐Ruiz J, and Campos‐Romo A. Longitudinal atrophy characterization of cortical and subcortical gray matter in Huntington’s disease patients. *Eur J Neurosci* 51(8):1827-1843, 2019.

146. Reddy PH, Mao P, and Manczak M. Mitochondrial structural and functional dynamics in Huntington’s disease. *Brain Res Rev* 61: 33–48, 2009.

147. Reddy PH and Shirendeb UP. Mutant huntingtin, abnormal mitochondrial dynamics, defective axonal transport of mitochondria, and selective synaptic degeneration in Huntington’s disease. *Biochim Biophys Acta - Mol Basis Dis* 1822: 101–110, 2012.

148. Reilmann R, McGarry A, Grachev ID, Savola J-M, Borowsky B, Eyal E, Gross N, Langbehn D, Schubert R, Wickenberg AT, Papapetropoulos S, Hayden M, Squitieri F, Kieburtz K, Landwehrmeyer GB, Agarwal P, Anderson KE, Aziz NA, Azulay J-P, Bachoud-Levi AC, Barker R, Bebak A, Beuth M, Biglan K, Blin S, Bohlen S, Bonelli R, Caldwell S, Calvas F, Carlos J, Castagliuolo S, Chong T, Chua P, Coleman A, Corey-Bloom J, Cousins R, Craufurd D, Davison J, Decorte E, De Michele G, Dornhege L, Feigin A, Gallehawk S, Gauteul P, Gonzales C, Griffith J, Gustov A, Guttman M, Heim B, Heller H, Hjermind L, Illarioshkin S, Ivanko L, Jaynes J, Jenckes M, Kaminski B, Kampstra A, Konkel A, Kopishinskaya S, Krystkowiak P, Komati SK, Kwako A, Lakoning S, Latipova G, Leavitt B, Loy C, MacFarlane C, Madsen L, Marder K, Mason S, Mendis N, Mendis T, Nemeth A, Nevitt L, Norris V, O’Neill C, Olivier A, Orth M, Owens A, Panegyres P, Perlman S, Preston J, Priller J, Puch A, Quarrell O, Ragosta D, Rialland A, Rickards H, Romoli AM, Ross C, Rosser A, Rudzinska M, Russo C V., Saft C, Segro V, Seppi K, Shannon B, Shprecher D, Simonin C, Skitt Z, Slawek J, Soliveri P, Sorbi S, Squitieri F, Suski V, Stepniak I, Sungmee P, Temirbaeva S, Testa C, Torvin-Moller A, Uhl S, Vangsted-Hansen C, Verny C, Wall P, Walker F, Wasserman P, Witkowski G, Wright J, Zalyalova Z, and Zielonka D. Safety and efficacy of pridopidine in patients with Huntington’s disease (PRIDE-HD): a phase 2, randomised, placebo-controlled, multicentre, dose-ranging study. *Lancet Neurol* 18: 165–176, 2019.

149. Ribeiro M, Rosenstock TR, Cunha-Oliveira T, Ferreira IL, Oliveira CR, and Rego AC. Glutathione redox cycle dysregulation in Huntington’s disease knock-in striatal cells. *Free Radic Biol Med* 53: 1857–1867, 2012.

150. Ribeiro M, Rosenstock TR, Oliveira AM, Oliveira CR, and Rego AC. Insulin and IGF-1 improve mitochondrial function in a PI-3K/Akt-dependent manner and reduce mitochondrial generation of reactive oxygen species in Huntington’s disease knock-in striatal cells. *Free Radic Biol Med* 74: 129–44, 2014.

151. Ribeiro M, Silva AC, Rodrigues J, Naia L, and Rego AC. Oxidizing Effects of Exogenous Stressors in Huntington’s Disease Knock-in Striatal Cells—Protective Effect of Cystamine and Creatine. *Toxicol Sci* 136: 487–499, 2013.

152. Rosenstock TR, Bertoncini CRA, Teles A V., Hirata H, Fernandes MJS, and Smaili SS. Glutamate-induced alterations in Ca2+ signaling are modulated by mitochondrial Ca2+ handling capacity in brain slices of R6/1 transgenic mice. *Eur J Neurosci 32(1):60-70*, 2010.

153. Rosenstock TR, De Brito OM, Lombardi V, Louros S, Ribeiro M, Almeida S, Ferreira IL, Oliveira CR, and Rego AC. FK506 ameliorates cell death features in Huntington’s disease striatal cell models. *Neurochem Int 59(5):600-9*, 2011.

154. Rosenstock TR, Carvalho ACP, Jurkiewicz A, Frussa-Filho R, and Smaili SS. Mitochondrial calcium, oxidative stress and apoptosis in a neurodegenerative disease model induced by 3-nitropropionic acid. *J Neurochem 88(5):1220-8*, 2004.

155. Ruan Q, Lesort M, MacDonald ME, and Johnson GVW. Striatal cells from mutant huntingtin knock-in mice are selectively vulnerable to mitochondrial complex II inhibitor-induced cell death through a non-apoptotic pathway. *Hum Mol Genet 13(7):669-81*, 2004.

156. Ryskamp D, Wu J, Geva M, Kusko R, Grossman I, Hayden M, and Bezprozvanny I. The sigma-1 receptor mediates the beneficial effects of pridopidine in a mouse model of Huntington disease. *Neurobiol Dis 97(Pt A):46-59*, 2017.

157. Sabharwal SS and Schumacker PT. Mitochondrial ROS in cancer: Initiators, amplifiers or an Achilles’ heel? *Nat Rev Cancer 14(11):709-21*, 2014.

158. Saft C, Zange J, Andrich J, Müller K, Lindenberg K, Landwehrmeyer B, Vorgerd M, Kraus PH, Przuntek H, and Schöls L. Mitochondrial impairment in patients and asymptomatic mutation carriers of Huntington’s disease. *Mov Disord* 20: 674–679, 2005.

159. Sahlholm K, Sijbesma JWA, Maas B, Kwizera C, Marcellino D, Ramakrishnan NK, Dierckx RAJO, Elsinga PH, and Van Waarde A. Pridopidine selectively occupies sigma-1 rather than dopamine D2 receptors at behaviorally active doses. *Psychopharmacology (Berl) 232(18):3443-53*, 2015.

160. Sandhir R and Mehrotra A. Quercetin supplementation is effective in improving mitochondrial dysfunctions induced by 3-nitropropionic acid: Implications in Huntington’s disease. *Biochim Biophys Acta - Mol Basis Dis 1832(3):421-30*, 2013.

161. Sandhir R, Mehrotra A, and Kamboj SS. Lycopene prevents 3-nitropropionic acid-induced mitochondrial oxidative stress and dysfunctions in nervous system. *Neurochem Int*, 2010.

162. Sandhir R, Sood A, Mehrotra A, and Kamboj SS. N-acetylcysteine reverses mitochondrial dysfunctions and behavioral abnormalities in 3-nitropropionic acid-induced Huntington’s disease. *Neurodegener Dis 9(3):145-57*, 2012.

163. Santamaría A, Pérez-Severiano F, Rodríguez-Martínez E, Maldonado PD, Pedraza-Chaverri J, Ríos C, and Segovia J. Comparative analysis of superoxide dismutase activity between acute pharmacological models and a transgenic mouse model of Huntington’s disease. *Neurochem Res* 26: 419–24, 2001.

164. Sayed NH, Fathy N, Kortam MA, Rabie MA, Mohamed AF, and Kamel AS. Vildagliptin Attenuates Huntington’s Disease through Activation of GLP-1 Receptor/PI3K/Akt/BDNF Pathway in 3-Nitropropionic Acid Rat Model. *Neurotherapeutics* 17: 252–268, 2020.

165. Schieber M and Chandel NS. ROS function in redox signaling and oxidative stress. *Curr Biol* 24(10):R453-62, 2014.

166. Shinomol GK and Muralidhara. Prophylactic neuroprotective property of Centella asiatica against 3-nitropropionic acid induced oxidative stress and mitochondrial dysfunctions in brain regions of prepubertal mice. *Neurotoxicology 29(6):948-57*, 2008.

167. Shirendeb U, Reddy AP, Manczak M, Calkins MJ, Mao P, Tagle DA, and Reddy PH. Abnormal mitochondrial dynamics, mitochondrial loss and mutant huntingtin oligomers in Huntington’s disease: Implications for selective neuronal damage. *Hum Mol Genet* 20: 1438–1455, 2011.

168. Shirendeb UP, Calkins MJ, Manczak M, Anekonda V, Dufour B, McBride JL, Mao P, and Reddy PH. Mutant Huntingtin’s interaction with mitochondrial protein Drp1 impairs mitochondrial biogenesis and causes defective axonal transport and synaptic degeneration in Huntington’s disease. *Hum Mol Genet 21(2):406-20*, 2012.

169. Siddiqui A, Rivera-Sánchez S, Castro MDR, Acevedo-Torres K, Rane A, Torres-Ramos C a, Nicholls DG, Andersen JK, and Ayala-Torres S. Mitochondrial DNA damage is associated with reduced mitochondrial bioenergetics in Huntington’s disease. *Free Radic Biol Med* 53: 1478–88, 2012.

170. Siddiqui A, Rivera-Sánchez S, Castro MDR, Acevedo-Torres K, Rane A, Torres-Ramos CA, Nicholls DG, Andersen JK, and Ayala-Torres S. Mitochondrial DNA damage Is associated with reduced mitochondrial bioenergetics in Huntington’s disease. *Free Radic Biol Med 53(7):1478-88*, 2012.

171. Sidhu A, Diwan V, Kaur H, Bhateja D, Singh CK, Sharma S, and Padi SS V. Nicotinamide reverses behavioral impairments and provides neuroprotection in 3˗nitropropionic acid induced animal model ofHuntington’s disease: implication of oxidative stress˗ poly(ADP˗ ribose) polymerase pathway. *Metab Brain Dis* 33: 1911–1921, 2018.

172. Silva AC, Almeida S, Laço M, Duarte AI, Domingues J, Oliveira CR, Januário C, and Rego AC. Mitochondrial respiratory chain complex activity and bioenergetic alterations in human platelets derived from pre-symptomatic and symptomatic huntington’s disease carriers. *Mitochondrion* 13: 801–809, 2013.

173. Singh-Bains MK, Mehrabi NF, Sehji T, Austria MDR, Tan AYS, Tippett LJ, Dragunow M, Waldvogel HJ, and Faull RLM. Cerebellar degeneration correlates with motor symptoms in Huntington disease. *Ann Neurol 85(3):396-405*, 2019.

174. Smith KM, Matson S, Matson WR, Cormier K, Del Signore SJ, Hagerty SW, Stack EC, Ryu H, and Ferrante RJ. Dose ranging and efficacy study of high-dose coenzyme Q10 formulations in Huntington’s disease mice. *Biochim Biophys Acta - Mol Basis Dis 1762(6):616-26*, 2006.

175. Song W, Chen J, Petrilli A, Liot G, Klinglmayr E, Zhou Y, Poquiz P, Tjong J, Pouladi MA, Hayden MR, Masliah E, Ellisman M, Rouiller I, Schwarzenbacher R, Bossy B, Perkins G, and Bossy-Wetzel E. Mutant huntingtin binds the mitochondrial fission GTPase dynamin-related protein-1 and increases its enzymatic activity. *Nat Med 17(3):377-82*, 2011.

176. Sorolla MA, Rodríguez-Colman MJ, Tamarit J, Ortega Z, Lucas JJ, Ferrer I, Ros J, and Cabiscol E. Protein oxidation in Huntington disease affects energy production and vitamin B6 metabolism. *Free Radic Biol Med 49(4):612-21*, 2010.

177. Squadrone S, Brizio P, Abete MC, and Brusco A. Trace elements profile in the blood of Huntington’ disease patients. *J Trace Elem Med Biol* 57: 18–20, 2020.

178. Squitieri F, Di Pardo A, Favellato M, Amico E, Maglione V, and Frati L. Pridopidine, a dopamine stabilizer, improves motor performance and shows neuroprotective effects in Huntington disease R6/2 mouse model. *J Cell Mol Med 19(11):2540-8*, 2015.

179. St-Pierre J, Drori S, Uldry M, Silvaggi JM, Rhee J, Jäger S, Handschin C, Zheng K, Lin J, Yang W, Simon DK, Bachoo R, and Spiegelman BM. Suppression of Reactive Oxygen Species and Neurodegeneration by the PGC-1 Transcriptional Coactivators. *Cell 127(2):397-408*, 2006.

180. Stoy N, Mackay GM, Forrest CM, Christofides J, Egerton M, Stone TW, and Darlington LG. Tryptophan metabolism and oxidative stress in patients with Huntington’s disease. *J Neurochem* 93: 611–623, 2005.

181. Strappazzon F, Nazio F, Corrado M, Cianfanelli V, Romagnoli A, Fimia GM, Campello S, Nardacci R, Piacentini M, Campanella M, and Cecconi F. AMBRA1 is able to induce mitophagy via LC3 binding, regardless of PARKIN and p62/SQSTM1. *Cell Death Differ 22(3):419-32*, 2015.

182. Suganya SN and Sumathi T. Effect of rutin against a mitochondrial toxin, 3-nitropropionicacid induced biochemical, behavioral and histological alterations-a pilot study on Huntington’s disease model in rats. *Metab Brain Dis 32(2):471-481*, 2017.

183. Sumathi T, Vedagiri A, Ramachandran S, and Purushothaman B. Quinolinic Acid-Induced Huntington Disease-Like Symptoms Mitigated by Potent Free Radical Scavenger Edaravone—a Pilot Study on Neurobehavioral, Biochemical, and Histological Approach in Male Wistar Rats. *J Mol Neurosci* 66: 322–341, 2018.

184. Szabadkai G, Bianchi K, Várnai P, De Stefani D, Wieckowski MR, Cavagna D, Nagy AI, Balla T, and Rizzuto R. Chaperone-mediated coupling of endoplasmic reticulum and mitochondrial Ca2+ channels. *J Cell Biol 175(6):901-11*, 2006.

185. Tabrizi SJ, Leavitt BR, Landwehrmeyer GB, Wild EJ, Saft C, Barker RA, Blair NF, Craufurd D, Priller J, Rickards H, Rosser A, Kordasiewicz HB, Czech C, Swayze EE, Norris DA, Baumann T, Gerlach I, Schobel SA, Paz E, Smith A V., Bennett CF, and Lane RM. Targeting huntingtin expression in patients with Huntington’s disease. *N Engl J Med 380(24):2307-2316*, 2019.

186. Tait SWG and Green DR. Mitochondria and cell death: Outer membrane permeabilization and beyond. *Nat Rev Mol Cell Biol 11(9):621-32*, 2010.

187. Tang TS, Guo C, Wang H, Chen X, and Bezprozvanny I. Neuroprotective effects of inositol 1,4,5-trisphosphate receptor C-terminal fragment in a Huntington’s disease mouse model. *J Neurosci 29(5):1257-66*, 2009.

188. Tang TS, Tu H, Chan EYW, Maximov A, Wang Z, Wellington CL, Hayden MR, and Bezprozvanny I. Huntingtin and huntingtin-associated protein 1 influence neuronal calcium signaling mediated by inositol-(1,4,5) triphosphate receptor type 1. *Neuron 39(2):227-39*, 2003.

189. Thangarajan S, Ramachandran S, and Krishnamurthy P. Chrysin exerts neuroprotective effects against 3-Nitropropionic acid induced behavioral despair—Mitochondrial dysfunction and striatal apoptosis via upregulating Bcl-2 gene and downregulating Bax—Bad genes in male wistar rats. *Biomed Pharmacother 84:514-525*, 2016.

190. Theodore M, Kawai Y, Yang J, Kleshchenko Y, Reddy SP, Villalta F, and Arinze IJ. Multiple nuclear localization signals function in the nuclear import of the transcription factor Nrf2. *J Biol Chem* 283: 8984–8994, 2008.

191. Trushina E, Dyer RB, Badger JD, Ure D, Eide L, Tran DD, Vrieze BT, Legendre-Guillemin V, McPherson PS, Mandavilli BS, Van Houten B, Zeitlin S, McNiven M, Aebersold R, Hayden M, Parisi JE, Seeberg E, Dragatsis I, Doyle K, Bender A, Chacko C, and McMurray CT. Mutant Huntingtin Impairs Axonal Trafficking in Mammalian Neurons In Vivo and In Vitro. *Mol Cell Biol 24(18):8195-209*, 2004.

192. Valencia A, Sapp E, Kimm JS, McClory H, Reeves PB, Alexander J, Ansong KA, Masso N, Frosch MP, Kegel KB, Li X, and DiFiglia M. Elevated NADPH oxidase activity contributes to oxidative stress and cell death in Huntington’s disease. *Hum Mol Genet 22(6):1112-31*, 2013.

193. Verny C, Bachoud-Lévi A-C, Durr A, Goizet C, Azulay J-P, Simonin C, Tranchant C, Calvas F, Krystkowiak P, Charles P, Youssov K, Scherer C, Prundean A, Olivier A, Reynier P, Saudou F, Maison P, Allain P, von Studnitz E, and Bonneau D. A randomized, double-blind, placebo-controlled trial evaluating cysteamine in Huntington’s disease. *Mov Disord* 32: 932–936, 2017.

194. Wang JQ, Chen Q, Wang X, Wang QC, Wang Y, Cheng HP, Guo C, Sun Q, Chen Q, and Tang TS. Dysregulation of mitochondrial calcium signaling and superoxide flashes cause mitochondrial genomic DNA damage in Huntington disease. *J Biol Chem* 288: 3070–3084, 2013.

195. Wang X, Sirianni A, Pei Z, Cormier K, Smith K, Jiang J, Zhou S, Wang H, Zhao R, Yano H, Kim JE, Li W, Kristal BS, Ferrante RJ, and Friedlander RM. The melatonin MT1 receptor axis modulates mutant Huntingtin-Mediated Toxicity. *J Neurosci 31(41):14496-507*, 2011.

196. Waters S, Ponten H, Klamer D, and Waters N. Co-administration of the dopaminergic stabilizer pridopidine and tetrabenazine in rats. *J Huntingtons Dis 3(3):285-98*, 2014.

197. Weydt P, Pineda V V., Torrence AE, Libby RT, Satterfield TF, Lazarowski ERR, Gilbert ML, Morton GJ, Bammler TK, Strand AD, Cui L, Beyer RP, Easley CN, Smith AC, Krainc D, Luquet S, Sweet IRR, Schwartz MW, and La Spada AR. Thermoregulatory and metabolic defects in Huntington’s disease transgenic mice implicate PGC-1α in Huntington’s disease neurodegeneration. *Cell Metab 4(5):349-62*, 2006.

198. Weydt P, Soyal SM, Landwehrmeyer GB, and Patsch W. A single nucleotide polymorphism in the coding region of PGC-1α is a male-specific modifier of Huntington disease age-at-onset in a large european cohort. *BMC Neurol 14:1.*, 2014.

199. Wong YC and Holzbaur ELF. The regulation of autophagosome dynamics by huntingtin and HAP1 is disrupted by expression of mutant huntingtin, leading to defective cargo degradation. *J Neurosci 34(4):1293-305*, 2014.

200. Wright DJ, Renoir T, Smith ZM, Frazier AE, Francis PS, Thorburn DR, McGee SL, Hannan AJ, and Gray LJ. N-Acetylcysteine improves mitochondrial function and ameliorates behavioral deficits in the R6/1 mouse model of Huntington’s disease. *Transl Psychiatry 5(1):e492*, 2015.

201. Wu J, Ryskamp D, Birnbaumer L, and Bezprozvanny I. Inhibition of TRPC1-Dependent Store-Operated Calcium Entry Improves Synaptic Stability and Motor Performance in a Mouse Model of Huntington’s Disease. *J Huntingtons Dis 7(1):35-50*, 2018.

202. Xu X, Tay Y, Sim B, Yoon SI, Huang Y, Ooi J, Utami KH, Ziaei A, Ng B, Radulescu C, Low D, Ng AYJ, Loh M, Venkatesh B, Ginhoux F, Augustine GJ, and Pouladi MA. Reversal of Phenotypic Abnormalities by CRISPR/Cas9-Mediated Gene Correction in Huntington Disease Patient-Derived Induced Pluripotent Stem Cells. *Stem Cell Reports 8(3):619-633*, 2017.

203. Xun Z, Rivera-Sánchez S, Ayala-Peña S, Lim J, Budworth H, Skoda EM, Robbins PD, Niedernhofer LJ, Wipf P, and McMurray CT. Targeting of XJB-5-131 to Mitochondria Suppresses Oxidative DNA Damage and Motor Decline in a Mouse Model of Huntington’s Disease. *Cell Rep 2(5):1137-42*, 2012.

204. Yablonska S, Ganesan V, Ferrando LM, Kim JH, Pyzel A, Baranova O V., Khattar NK, Larkin TM, Baranov S V., Chen N, Strohlein CE, Stevens DA, Wang X, Chang YF, Schurdak ME, Carlisle DL, Minden JS, and Friedlander RM. Mutant huntingtin disrupts mitochondrial proteostasis by interacting with TIM23. *Proc Natl Acad Sci U S A 116(33):16593-16602*, 2019.

205. Yamazaki H, Tanji K, Wakabayashi K, Matsuura S, and Itoh K. Role of the Keap1/Nrf2 pathway in neurodegenerative diseases. *Pathol Int* 65: 210–219, 2015.

206. Yang L, Calingasan NY, Wille EJ, Cormier K, Smith K, Ferrante RJ, and Flint Beal M. Combination therapy with Coenzyme Q10 and creatine produces additive neuroprotective effects in models of Parkinson’s and Huntington’s Diseases. *J Neurochem 109(5):1427-39*, 2009.

207. Yano H, Baranov S V., Baranova O V., Kim J, Pan Y, Yablonska S, Carlisle DL, Ferrante RJ, Kim AH, and Friedlander RM. Inhibition of mitochondrial protein import by mutant huntingtin. *Nat Neurosci 17(6):822-31*, 2014.

208. Yeun SC, Mao Z, Johnson GVW, and Lesort M. Increased glutathione levels in cortical and striatal mitochondria of the R6/2 Huntington’s disease mouse model. *Neurosci Lett 386(1):63-8*, 2005.

209. Yin X, Manczak M, and Reddy PH. Mitochondria-targeted molecules MitoQ and SS31 reduce mutant huntingtin-induced mitochondrial toxicity and synaptic damage in Huntington’s disease. *Hum Mol Genet 25(9):1739-53*, 2016.

210. Young JC, Hoogenraad NJ, and Hartl FU. Molecular chaperones Hsp90 and Hsp70 deliver preproteins to the mitochondrial import receptor Tom70. *Cell 112(1):41-50*, 2003.

211. Yusuf IO, Chen H-M, Cheng P-H, Chang C-Y, Tsai S-J, Chuang J-I, Wu C-C, Huang B-M, Sun HS, and Yang S-H. Fibroblast growth factor 9 activates anti-oxidative functions of Nrf2 through ERK signalling in striatal cell models of Huntington’s disease. *Free Radic Biol Med* 130: 256–266, 2019.

212. Zhu M and Fahl WE. Functional characterization of transcription regulators that interact with the electrophile response element. *Biochem Biophys Res Commun* 289: 212–9, 2001.

213. Zhu Y, Li C, Tao X, Brazill JM, Park J, Diaz-Perez Z, and Zhai RG. Nmnat restores neuronal integrity by neutralizing mutant Huntingtin aggregate-induced progressive toxicity. *Proc Natl Acad Sci* 116: 19165–19175, 2019.