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Huntington Disease: Current Advances in Pathogenesis and Recent Therapeutic Strategies

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ABSTRACT
Huntington's disease (HD) is an inherited autosomal, progressive neurodegenerative disorder associated with involuntary abnormal movements (chorea), cognitive impairments and psychiatric disturbances. HD is caused by an abnormal expansion of a CAG region located in exon 1 of the gene encoding the huntingtin protein (Htt) and is the causative factor in the pathogenesis of HD. However, recent evidences show that impaired mitochondrial function plays a key role in the pathogenic processes of the desease. The underlying mechanisms by which mutant Htt (mHtt) causes HD have not been fully elucidated, however mutant Htt can impair mitochondrial function by dysregulation of transcriptional processes, calcium dyshomeostasis, and defective mitochondrial bioenergetics. Mutant Htt induce intracellular Ca^{2+} in neurons affected by HD and increased intracellular Ca^{2+} excessively enter mitochondria and induce to open the mitochondrial permeability transition pores (mPTP), leading to decreased mitochondrial ATP, and neuronal death. Transcriptional processes regulated by peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1α (PGC-1α), which are critical for mitochondrial biogenesis, have also been shown to be impaired in HD. This review article discusses current developments, in determining the role of mitochondrial morphological and functional abnormalities contributing to the pathogenesis of HD and also discusses the current other possible therapeutic interventions.

Keywords: Huntington disease, neurodegenerative disorder, pathogenesis, mitochondria.

INTRODUCTION

Huntington's disease (HD) is an autosomal, neurodegenerative disease that is caused by the pathological expansion of the CAG repeat located in the exon 1 of the Huntingtin protein gene (Htt). HD is characterized by chorea, seizures, involuntary movements, dystonia, cognitive decline, intellectual impairment, and emotional disturbances. [1-8] HD usually occurs in midlife with some exceptional cases of early onset as early as 2 years and of late onset in the mid 80s. [9] The disease is fatal within 15-20 years after onset.

Tremendous progress has been made in HD research for the last two decades in terms of discovering HD gene, understanding the expanded polyglutamine repeat containing the mutant Htt protein, developing HD cell, animal models, which now include HD fly, worm, mouse, and non-human primate models [10-24] developments in decreasing the expression of the expanded polyglutamine repeat allele that has been found to damage medium spiny neurons in HD patients [25-29] developing therapeutics to reduce symptoms of HD in animal models and HD patients.

It has been demonstrated that mitochondria are the key factors in cell survival by controlling energy metabolism, apoptosis pathways and Ca^{2+} homeostasis. [30-33] The brain is acutely dependent on energy supplies for normal functioning and mitochondria are the intracellular founts of the brain's energy supplies. Any changes in functional alterations in these essential cellular energy dynamos can lead to insidious pathological changes in neurons. [34-42]

Hypothesis for mitochondrial role in neurodegenerative diseases arises from the observation that mitochondrial defects and oxidative stress can be detected in biological materials from patients with neurodegenerative conditions. Several cell biology experiments have clearly demonstrated that mitochondria play an active role in the complex cascade of events leading to cell demise in various models of neurodegenerative disorders. [5, 43, 150]

Striatal neurons are highly sensitive to impairment in energy metabolism and several studies have shown that acute poisoning with mitochondrial toxins (cyanide, sodium azide, and 3NP) is often associated with striatal degeneration in man and laboratory animals. Mitochondrial defects of genetic origins (e.g. mutation or deletion of mitochondrial DNA or

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nuclear DNA) can lead to striatal degeneration. [44-45] Recent studies have shown different possible mechanisms that link mitochondrial defects with the preferential vulnerability of the striatum in Huntington's disease.

In HD although several cerebral regions show signs of neurodegeneration, the most important neuropathological feature of this disorder is the atrophy of the striatum as seen using post mortem histological evaluation [46] or non-invasive brain magnetic resonance imaging (MRI). Detection of pre-symptomatic patients (i.e. carrying the mutation but asymptomatic) demonstrated significant atrophy of the caudate and putamen [47-49] suggesting that degenerative events (cell shrinkage or loss) begin years before the occurrence of clinical symptoms of HD. The disease preferentially affects the GABAergic medium size spiny neurons of the striatum that project to substantia nigra reticulata and pallidum. Intriguingly, large cholinergic interneurons and medium size spiny interneurons are preserved in the HD striatum. [50-51] Cortical atrophy and early degeneration of the hypothalamus are also important aspects of HD pathogenesis, and late stage HD patients show widespread brain degeneration. [52] The severity of striatal alterations is correlated with the degree of motor, cognitive and psychiatric perturbations, [53] suggesting that striatal degeneration is an important aspect of HD physiopathology. In this review we explore the current advances in determining the role of mitochondrial morphological and functional abnormalities contributing to the pathogenesis of HD and also discuss recent and other possible therapeutic interventions.

Mitochondrial dysfunction: Role in HD

Brain examination using non-invasive methods indicated for energy metabolism problems in HD patients were reported. In particular, early striatal hypometabolism was detected *in-vivo* using positron emission tomography and fluorodeoxyglucose [44, 54] increased lactate concentrations were found in the cortex of symptomatic HD patients using proton NMR spectroscopy. [55-56] Lactate/pyruvate ratio was elevated in the CSF of HD patients. [57] In one NMR study, half of the pre-symptomatic HD patients examined showed increased lactate concentration in the striatum. [56] In muscle, phosphorus NMR spectroscopy showed reduced ATP production. [58] Despite sustained caloric intake, HD patients exhibited profound weight loss suggesting that there was energetic impairment in HD. [59-60] Studies have shown that onset of the clinical symptoms of HD are preceded by energy dysfunction, suggesting that an energy failure may play a primary role in the pathogenesis of HD. [61-67]

Mitochondria are essential organelles that are involved in many vital processes such as energy production through oxidative phosphorylation (Oxphos) via the tricarboxylic acid (TCA) cycle, fatty acid oxidation and the electron transport chain (ETC), thermogenesis, cell death mechanisms, defense against reactive oxygen species (ROS), and Ca^{2+} buffering. Early ultrastructural studies of cortical biopsies obtained from patients with either juvenile or adult onset HD showed abnormal mitochondria morphology. [68-69] Mitochondrial functional abnormalities were also observed in early studies. In a recent study examination of mitochondria from preferentially vulnerable striatal calbindin-positive neurons in moderate-to-severe grade HD patients, using antisera against mitochondrial markers of COX2, SOD2 and cytochrome c. Combined calbindin and mitochondrial marker immunofluorescence showed a significant and progressive grade-dependent reduction in the number of mitochondria in spiny striatal neurons, with marked alteration in size. Consistent with mitochondrial loss, there was a reduction in COX2 protein levels using western analysis that corresponded with disease severity. In addition, both mitochondrial transcription factor A, a regulator of mitochondrial DNA (mtDNA), and peroxisome proliferator activated receptor-co-activator gamma-1 alpha, a key transcriptional regulator of energy metabolism and mitochondrial biogenesis, were also significantly reduced with increasing disease severity. Abnormalities in mitochondrial dynamics were observed, showing a significant increase in the fission protein Drp1and a reduction in the expression of the fusion protein mitofusin. Mitochondrial PCR array profiling in HD caudate nucleus specimens showed increased mRNA expression of proteins involved in mitochondrial localization, membrane translocation and polarization and transport that paralleled mitochondrial derangement. These findings reveal that there are both mitochondrial loss and altered mitochondrial morphogenesis with increased mitochondrial fission and reduced fusion in HD. These findings provide further evidence that mitochondrial dysfunction plays a critical role in the pathogenesis of HD. [70]

Mitochondrial enzymes

In 1974 a defect in succinate dehydrogenase, a component of both the Krebs cycle and the complex II of the electron transport chain, in the caudate and to a lesser extent in the cortex of postmortem HD brains was reported. [71] Reduced expression of complex II subunits has been observed in striatum of HD patients. [72] Subsequent studies confirmed that there was a significant decrease in complex II activity in the caudate nucleus of HD brains relative to the levels in matched control brains. In addition to decreases in complex II activity, decreases in complex III activity in the caudate and putamen, and of complex IV in the putamen have been observed. [73-75] Majority of these cases showed advanced neuropathology including dramatic striatal atrophy (pathological grades 3 and 4 of HD), and therefore alterations in the source (i.e., glial, neuronal, etc.) of the mitochondria is likely to have been affected. However, in presymptomatic and grade 1 HD cases no impairment of mitochondrial complex activities was observed. [76]

Animal and cell models

Compelling evidence has been provided by the animal and cell models of HD suggesting mitochondrial function is impaired in HD and that this occurs early in the disease process and is likely fundamental to the pathogenesis of HD.

3-NP is an irreversible inhibitor of succinate dehydrogenase that inhibits both the TCA cycle and complex II activity, and in animal models, administration of 3-NP results in selective lesioning of the striatum. [77] Low doses of 3-NP administered chronically to both rodents and non-human primates resulted in pathology and symptomatology resembling HD. [78-80] It is intresting to note that striatal mitochondria contain more cyclophilin D than cortical mitochondria and are more sensitive to calcium-induced mitochondrial permeability transition pore (mPTP) opening. [81] Studies in rats exposed to intrastriatal injection of malonate (malonate being a reversible inhibitor of succinate dehydrogenase) [78] hence, support the hypothesis that impairment of mitochondrial function plays an important role

in the pathogenesis of HD. These observations have lead to the hypothesis that the expression of mutant huntingtin results in impaired mitochondrial energy metabolism and calcium handling and therefore decreases in energy levels of the cells, increases in oxidative damage, and potentially secondary excitotoxic death. [59-60]

Mitochondrial dysfunction is apparent in two well-established HD mice models; the 150/150Q mutant huntingtin knock-in mice, [82] and the R6/2 mice. [10] Mitochondria isolated from 150/150Q mutant huntingtin knock-in mice show an increased sensitivity to calcium-induced mPTP opening [83] and striatal neurons from heterozygous 150/150Q mutant huntingtin knock-in mice were more prone to undergo "deregulation" in response to NMDA compared to neurons from wild-type mice. [53] The R6/2 HD mouse model express exon 1 of the huntingtin gene with 155 CAG expansions. [84] In these mice a significant reduction in aconitase, an enzyme involved in the Krebs cycle has been reported. The activities of complex IV in the striatum and cerebral cortex were also reported to be significantly decreased in the R6/2 mice [75] Moreover, these results suggest that the deficiency in complex IV precedes neuronal death in the R6/2 mice and thus contribute to the pathogenesis. [85] A decreased stability of mitochondria from theHDR6/2 mouse muscle against calcium-induced mPTP opening has been detected. Complex-I dependent respiration of R6/2 mitochondria was more sensitive to calcium induced inhibition than wild-type mitochondria. [86] Further, significant alterations in mitochondrial ultrastructure were seen, consistent with metabolic stress in the heart of R6/2 mice [87] Overall these mouse models exhibit mitochondrial and metabolic defects that are consistent with the defects that occur in HD pathology.

Clonal striatal precursor cells established from striatal primordia of E16 embryos of wild-type ($STHdh^{Q7/Q7}$) and mutant Htt ($STHdh^{Q111/Q111}$) knock-in mice [88] have been used in studies of mitochondrial function. Mitochondria from $STHdh^{Q111/Q111}$ striatal cells, show significantly reduced respiration and ATP production as compared with mitochondria from $STHdh^{Q7/Q7}$ striatal cells, when either glutamate/malate or succinate was used as the substrate, despite equivalent levels of ETC complex activities in the two cell lines. However, when the artificial electron donor TMPD/ascorbate for complex IV was used as the substrate, there was no difference in mitochondrial respiration between two cell lines. [89] Taken together, these mouse and cell models exhibit mitochondrial impairment and metabolic deficits similar to the pathological characteristics that have been observed in HD. [90-91] Interestingly, yeast expressing mutant Htt showed a significant reduction in mitochondrial Oxphos due to an alteration in complex II and III. [92]

Lymphoblasts derived from HD patients manifest a much greater increase in mitochondrial depolarization than control samples when treated with toxins that target complexes II and IV. [93] When ATP/ADP ratios were evaluated in 40 human lymphoblastic cell lines an inverse between CAG repeat length in the HD gene and the ATP/ADP ratio was observed. [94] Mitochondrial respiration and ATP production are significantly impaired in striatal cells expressing mutant huntingtin, [89] which is considered a genetically accurate model of HD. [90] Further the mutant huntingtin-expressing cells exhibit a significant increase in sensitivity to 3-NP. [95-96]

Mitochondrial calcium handling defects

It is becoming increasingly apparent that mitochondrial calcium handling defects are associated with the pathogenesis of HD. Increased cytoplasmic Ca^{2+} levels are toxic to neurons. [97] Impaired Ca^{2+} homeostasis in HD might have different causes; mechanisms related to mitochondrial dysfunction have received the closeslo6t attention. The Ca^{2+} buffering capacity of cells expressing mutant Htt (mutant Htt) can be reduced. This was first shown by Panov et al. in lymphoblasts derived from lymphocytes of HD patients. [98] Similarly, reduced Ca^{2+} loading capacity was found in the brains of YAC72Q mice. [98] Compared to mitochondria from control cells (STHdhQ7/Q7), the mitochondria from clonal striatal cells with mutant Htt (STHdhQ111/Q111) undergo permeability transition at a lower Ca^{2+} concentration when treated with increasing Ca^{2+} loads and have a reduced capacity to take up Ca^{2+}. [99] Isolated mitochondria from transgenic rats expressing mutant Htt, show reduced rates of Ca^{2+} accumulation compared to control rats. [100]

The presence of full length mutant huntingtin at physiological levels in clonal striatal cells has been clearly demonstrated to result in deficits in mitochondrial-dependent calcium handling. [89, 99, 101] When subjected to increasing calcium concentrations, mitochondria from mutant huntingtin-expressing cells were significantly more sensitive to calcium-induced decreases in state 3 respiration and $\Delta\Psi_m$ than mitochondria from wild-type cells. [94] Further, mutant huntingtin-expressing cells had a reduced mitochondrial calcium uptake capacity in comparison with wild-type cells. [89, 99, 102] Decreases in state 3 respiration was associated with increased mitochondrial membrane permeability. The $\Delta\Psi_m$ defect was attenuated in the presence of ADP and the decreases in calcium uptake capacity were abolished in the presence of mPTP opening inhibitors. [89] Treatment of the mutant huntingtin expressing cells with HDAC inhibitors (trichostatin A or sodium butyrate) ameliorated the mitochondrial calcium handling defects, suggesting the involvement of transcriptional dysregulation. [101] These findings clearly indicate that mutant huntingtin-expressing cells have mitochondrial calcium handling defects and that the increased sensitivity to calcium-induced mitochondrial depolarization maybe a contributing mechanism to the mitochondrial dysfunction in HD. Although mutant huntingtin induced transcriptional dysregulation likely contributes to the mitochondrial dysfunction in HD, direct effects cannot be ruled out. Choo *et al.* showed that huntingtin was present in a purified mitochondrial fraction in association with the outer mitochondrial membrane in clonal striatal cells established from wild-type and mutant huntingtin knockin mice. [83] Further, a recombinant truncated mutant huntingtin construct, but not a wild-type, directly induced mPTP opening in isolated mouse liver mitochondria, an effect that was prevented completely by cyclosporin A (CsA) and ATP. [83] In addition to increasing the sensitivity of mitochondria to Ca^{2+}-induced mPTP opening, mutant Htt could contribute to the vulnerability of medium size spiny neurons (MSNs) by causing increased Ca^{2+} loading. mutant Htt directly interacts with C-terminal region of the type 1 inositol 1,4,5-trisphosphate (InsP3) receptor (InsP3R1), resulting in increased sensitivity of InsP3R1 to activation by InsP3. [103] The implication of InsP3R1 activation for mutant Htt-induced toxicity was corroborated in MSN cultures from a HD mouse model using a pharmacological approach [104]

and in a Drosophila HD model using genetic experiments. [105] Moreover, mutant Htt enhances the activity of N-methyl D-aspartate receptors (NMDARs) harboring the NR2B subunit, resulting from increased NMDAR trafficking to the plasma membrane. [106-108] Importantly, MSNs express high levels of the NR2B subunit, implying a greater sensitivity to excitotoxicity caused by NMDAR activation. [109-110]

Mitochondrial transcriptional dysregulation

Abnormal transcriptional regulation of nuclear-encoded mitochondrial genes may be involved in HD pathogenesis. Indeed, mutant Htt has been found to bind to several transcription factors, including TATA binding proteins, [111-112] Sp1, [113] and the nuclear scaffold protein NAKAP. [114] Mutant Htt interaction may interfere with the gene expression, activity, and transcriptional regulation of HD neurons. This possibility is supported by recent studies of PGC1α (potent suppressor of reactive oxygen species [ROS]) in HD. [115-117,172] PGC1α was found decreased in HD postmortem brains, in cell lines expressing mutant Htt, and in HD mouse models, suggesting that the mutant Htt promotes the increased production of ROS; this increase in ROS may promote the interaction of Htt with the outer membrane of mitochondria, ultimately leading to decreased levels of PGC1α in mutant HD neurons. [115-117]

PGC-1α is a transcription coactivator that interacts with a range of transcription factors involved in a wide variety of biological responses, including adaptive thermogenesis and mitochondrial biogenesis of several tissues, including brain tissues. [118] Recently, using brain tissues from HD mice, postmortem brain tissues from HD patients, several researchers independently studied the connection between PGC-1α and HD mitochondrial bioenergetics. [115-117] Cui and colleagues (2006) studied striatal neurons from postmortem brain tissues from HD patients, brain tissues from an HD knock-in mouse model that over-expresses mutant Htt, and cultured striatal neuronal cells from a knockin mice expressing 111 polyglutamines. [115] They found a decrease in mRNA expression of PGC-1α in all 3 sources of striatal neurons, suggesting that mutant Htt interferes with the formation of the CREB/TAF4 complex that regulates transcription of the gene encoding PGC-1α. Using HD mice lines, Weydt and colleagues (2006) studied the connection between PGC-1α and adaptive thermogenesis in HD [117] and found marked hypothermia at baseline temperatures, following cold exposure in two truncated HD mouse models. St. Pierre and colleagues (2006) found an increased expression of genes encoding ROS defense enzymes, including copper/zinc superoxide dismutase (SOD1), manganese SOD (SOD2), catalase, and glutathione peroxidase. [116] In a study of PGC-1α-deficient mice, they also found that the basal expression of SOD1, SOD2, and catalase was considerably lower in the heart and brain of PGC-1α-deficient mice, regions known to be sensitive to oxidative stress, suggesting that the activation of PGC-1α protects HD neurons from mitochondrial toxicity caused by mutant Htt.

In another study of PGC1α, the hypothesis that mutant Htt influences the mitochondria via the interaction of polyglutamine repeats or the decrease in PGC-1α expression was tested. [119] They compared gene expression changes due to mutant Htt expressed in STHdh(Q111/Q111) cells with changes in gene expression produced by 3-NP treatment of wild-type striatal cells. In general, the HD mutation did not mimic 3-NP features, although both changes in gene expression produced a state of energy collapse that was mildly alleviated by the PGC-1α-coregulated nuclear respiratory factor 1. Moreover, unlike 3-NP, the HD polyglutamine repeat did not significantly alter mitochondrial pathways in STHdh(Q111/Q111) cells, despite a decrease in Ppargc1α gene expression. Instead, the HD mutation enriched for processes linked to the normal functioning of huntingtin and of NFκ-B signaling. Thus, rather than directly impacting mitochondria, the HD polyglutamine repeats protein may modulate some aspect of Htt's activity in metabolizing extra-mitochondrial energy.

Findings from these studies suggest that in HD pathogenesis, PGC-1α may play a significant role in protecting neurons against mitochondrial toxicity and oxidative damage by increasing PGC-1α transcription and interaction with several transcription factors in HD neurons.

Mitochondrial DNA defects

It has been hypothesized that age-dependent mitochondrial DNA (mtDNA) damage plays a role in HD pathogenesis. Investigation of mitochondrial DNA defects in two HD mouse models: the chemically induced 3-nitropropionic acid model and the HD transgenic mouse model of the R6/2 strain containing 115–150 polyglutamine repeats in the HD gene. [120] They found that mitochondrial toxin 3-NPA inhibits complex II of the ETC and causes neurodegeneration that resembles HD in the striatum of postmortem brain specimens from HD patients and the HD mice. They measured nuclear and mtDNA damage by quantitative PCR in the striatum of 5 and 24 month old untreated and 3-NPA-treated C57BL/6 mice. They found an increase in damage in both nuclear and mitochondrial genomes in the untreated 24 month old mice. 3-NPA induced 4–6 times more damage in the mtDNA than in the nuclear DNA in the 5-month-old mice; mtDNA damage was repaired by 48 h after 3-NPA treatment. In the 24 month old mice, 3NPA caused equal amounts of nuclear and mitochondrial damage that persistent in both genomes for 48 h. QPCR analysis showed a progressive increase in the levels of mtDNA damage in the striatum and cerebral cortex of 7–12 week-old R6/2 mice. Striatum exhibited eight-fold more damage to the mtDNA than to the nuclear gene. These data suggest that mtDNA damage is an early biomarker for HD-associated neurodegeneration, and they support the hypothesis that mtDNA lesions may contribute to the pathogenesis observed in HD. [120]

It has been reported that pathological changes in HD brains may also be present in peripheral tissues. [121] They further reported that Leukocyte 8-hydroxydeoxyguanosine and plasma malondialdehyde were elevated, and activities of erythrocyte Cu/Zn-superoxide dismutase and glutathione peroxidase were reduced in 16 HD patients when compared to 36 age- and gender-matched controls. Deleted and total mtDNA copy numbers were increased, whereas the mRNA expression levels of mtDNA-encoded mitochondrial enzymes were not elevated in the HD leukocytes compared to the leukocytes from normal controls. Plasma malondialdehyde levels also significantly correlated with HD disease severity. These results indicated that means to suppress oxidative damage may be beneficial in restoring mitochondrial function in HD patients.

4 mtDNA deletions based on the size of deletion: 9 kb, 7.5 kb, 7 kb, and 5 kb in the mitochondrial DNA of HD patients have also been investigated. [122] Studying a group of 60

Iranian patients clinically diagnosed with HD and 70 healthy age-matched Controls, they found that 41 of the 60 HD patients exhibited polyglutamine expansion. [122] The 19 HD patients who did not show expansion exhibited clinical symptoms of HD. One of the four mtDNA deletions was in at least 90% of the samples from HD patients. Multiple deletions were also observed in 63% of the HD patients. None of the normal controls showed mtDNA deletions. The sizes and locations of the deletions did not correlate with expanded polyglutamine repeats or subject age. The study presented evidence that HD patients had higher frequencies of mtDNA deletions in lymphocytes compared to the controls. Overall, this study suggests that mutant Htt and instability in polyglutamine repeats may cause mtDNA damage in neurons affected by HD.

Findings from these studies suggest that mutant Htt cause mitochondrial DNA defects in HD brains and peripheral tissues from HD patients.

Current and future therapeutic strategies

Considering role of mitochondrial defects found in HD patients and HD models lead to neuronal dysfunction and eventually death, correcting these defects may provide beneficial effects. Whereas gene transfer-based experiments recently led to the discovery of potential therapeutic targets that could improve mitochondria in HD (such as PGC-1alpha or the mitochondrial complex II), preclinical studies are yet required to precisely determine whether it is possible to modulate these systems in vivo. From a practical perspective, the targeting of these complex systems will require important and long-term developments. However, a few strategies which were suggested many years ago have shown great promise in preclinical and even clinical studies. [151] In cells expressing mutant Htt, accumulation of p53 has been showed to induce neuronal death. Reducing accumulation of p53 using RNA interference and the p53 inhibitor pifithrin-α suppresses mutant Htt-induced mitochondrial depolarisation. Intraperitoneal injection of pifithrin-α in 171-82Q HD transgenic mice restores levels of complex IV activity to normal levels. [123] It can be suggested that pifithrin-like drugs could be neuroprotective in patients.

The loss of mitochondrial Ca^{2+} handling observed in cell lines derived from knock-in mouse model can be corrected by treatment with the HDAC inhibitors trichostatin A or sodium butyrate, suggesting that acting on transcription defects could correct some of mitochondrial defects produced by mutant Htt. [101] Treatment with HDAC inhibitors in mouse models of HD reduces striatal atrophy and motor deficits. [124-125] These beneficial effects in mice could at least in part involve amelioration of mitochondrial physiology.

Brain fuel supplementation may be considered as another approach. The most promising compound that could be efficacious in increasing brain energy metabolism is creatine, a compound produced endogenously and acquired exogenously through diet. [126] Diet supplementation with creatine (in the range of 600 mg/kg) in mice expressing the N-terminal part of mutant huntingtin is neuroprotective. It extends life span in transgenic mice, and reduces motor dysfunction and striatal atrophy. [126-128] Creatine is well tolerated in patients. [129] It seems that creatine produces an actual biological effect in HD patients since blood levels of 8-hydroxy-2′-deoxyguanosine (8OH2′dG), a biomarker of oxidative stress that is elevated in untreated HD patients are near control levels in patients with creatine treatment. Ongoing clinical trials may determine within few years whether creatine treatment can slow the progression of the disease.

Production of ROS is likely increased in HD patients and HD mouse models. [130, 54, 131, 21, 152, 169] Reducing ROS production using compounds with antioxidant properties has been tested in HD models. [132, 168, 170] For example, ascorbate treatment in R6/2 mice ameliorates behavioural deterioration. [133] The newly developed antioxidant BN82451 protects and extends survival in R6/2 mice. [134] The most debated but still very promising compound is coenzyme Q10, which has antioxidant properties and plays an important role in the transfer of electrons in the respiratory chain. [135] Transgenic R6/2 mice treated with coenzyme Q10 alone or in association with the NMDA receptor antagonist remacemide show increased survival, attenuated weight loss, improved motor performances, and reduced striatal atrophy when compared with untreated transgenic mice. [136-137] Clinical trials with relatively low dose showed no major protective effects, suggesting that higher doses may be necessary.

Dimebon or Dimebolin hydrochloride an antihistamine drug that has been used clinically in Russia to reduce cognitive deficits in Alzheimer's disease (AD) patients. Its molecular formula is $C_{21}H_{25}N_3$, and its molecular weight is 319.433. It has been proposed that Dimebon may inhibit mitochondrial permeability transition pore and protect neuronal mitochondria from mutant proteins such as Aβ, mutant Htt and other mitochondrial toxic insults. [138] Recent studies suggest that Dimebon may have cognition-enhancing effects in healthy individuals. [139]

In a recent study of clinical trials of AD patients from Russia, Dimebon was found to be safe, well tolerated, and significantly improved the clinical course of patients with mild-to-moderate AD. [140] Recently, Medivation, Inc., has completed phase II clinical trial of Dimebon in HD patients, and the outcome of this initial clinical trial will be useful to the families of HD patients, and also to the researchers of mitochondrial and HD fields.

Recently, to determine the neuroprotective effects of Dimebon the effects of Dimebon in primary striatal neuronal cultures from wild type mice and YAC128 HD transgenic mice were investigated. [141] It has been found that Dimebon acts as an inhibitor of NMDA receptors and voltage-gated calcium channels in neurons from wild-type mice and YAC128 mice. It was also found that the application of 50 μM Dimebon stabilized glutamate-induced Ca^{2+} signals in YAC128 medium spiny neurons and protected cultured YAC128 medium spiny neurons from glutamate-induced apoptosis. Lower concentrations of Dimebon (5 μM and 10 μM) did not stabilize glutamate-induced Ca^{2+} signals and did not exert neuroprotective effects in experiments with YAC128 medium spiny neurons. Evaluation of Dimebon against a set of biochemical targets indicated that Dimebon inhibits alpha-Adrenergic receptors, Histamine H1 and H2 receptors, and Serotonin 5-HT2c, 5-HT5A, 5-HT6 receptors with high affinity. Dimebon also had significant effects on a number of additional receptors. Findings of this study suggest that Dimebon may have beneficial effects in HD neurons through its capacity to neurons by altering NMDA receptors and voltage-gated calcium channels.

Several laboratories across the world are actively involved to investigate the mode of neuroprotective action of Dimebon in neurodegenerative diseases by investigating cell and mouse

models of neurodegenerative diseases, including Huntington's and Alzheimer's. However, further research is still needed to test the efficacy of Dimebon and other molecules that reduce the induction of intracellular Ca^{2+} and entry of excessive $Ca^{2+}$to the mitochondria, and ultimately inhibit mitochondrial pore opening and in transgenic mouse models of neurodegenerative diseases, including HD

It has been suggested that the neuroprotective properties of cyclosporine A (CsA) are due in part to its ability to prevent mPTP opening in response to high levels of calcium or oxidative stress. [142-143] Exposure to high levels of calcium or oxidative stress results in the mPTP opening of the inner mitochondrial membrane, causing disruption of $\Delta\Psi_m$, and swelling of mitochondria. [143-145] *In-vitro* CsA attenuates apoptosis induced by the mitochondrial complex1 inhibitor rotenone, [146] and also the calcium ionophore A23187. [143] CsA also prevents $\Delta\Psi_m$ loss resulting from exposure to NMDA in cortical neurons. [142] Additionally, CsA and bongkrekic acid significantly attenuated NMDA-induced calcium peak and $\Delta\Psi_m$ loss in YAC128 medium-size spiny neurons (MSNs). [17] The YAC128 mouse model express full-length human huntingtin with 128 glutamine repeats and exhibits selective striatal neurodegeneration and large increases in apoptosis after NMDA receptor activation. [147-148] Also, CsA has been demonstrated to be neuroprotective *in-vivo*. Using procedures which facilitate molecule penetration of blood brain barrier, CsA has reduced neuronal death in ischemia reperfusionm, [149] hypoglycemia, [153] and traumatic brain injury. [154] In addition, Leventhal and colleges demonstrated that treatment with CsA protected striatal neurons toxicity induced by 3-NP in vitro and in vivo. [144] Interestingly, CsA prevented ultrastructural mitochondrial alterations and decreased apoptosis in myoblasts obtained from Ullrich congenital muscular dystrophy patients. [145] Therefore, CsA or new mPTP opening inhibitors may be of potential therapeutic benefit by protecting vulnerable neurons populations affected in HD.

3-Nitropropionic acid (3-NP) is an irreversible inhibitor of mitochondrial succinate dehydrogenase that has been used to explore the molecular mechanisms of cell death associated with mitochondrial dysfunction and neurodegeneration for Huntington's disease (HD). Brain-derived neurotrophic factor (BDNF) is a neurotrophin that may regulate neuronal survival and differentiation. Experimental evidence derived from both clinical as well as basic research suggests a close association between BDNF deficiency and HD pathogenesis. Delineation of BDNF-mediated neuroprotective actions against 3-NP toxicity may add in the development of therapeutic intervention for HD where mitochondrial dysfunction is known to play a crucial role in pathogenesis of this devastating disease. [155-156,171]

PGC-1α plays a central role in regulating the expression of mitochondrial genes and recent findings have implicated this coactivator in neurodegenerative processes. Several studies have also suggested the possibility that agents that enhance PGC-1alpha function will exert therapeutic benefits in HD patients. [172-173] Another key regulator of PGC-1α function is the NAD^+ dependent deacetylase SIRT1. [157-158] SIRTs catalyze both deacetylation and ADP-ribosylation reactions which are coupled to the cleavage of NAD^+ and result in deacetylated lysine, O-acetyl-ADP-ribose and nicotinamide. [158] PGC-1α is a substrate of a SIRT1 and deacetylation of PGC-1α results in the upregulation of mitochondrial metabolic genes. [157] Treatment with resveratrol (a well-known antioxidant and sirtuin activator) specifically rescued early neuronal dysfunction phenotypes induced by mutant polyglutamines expression in *Caenorhabditis elegans.* [159] In others studies, treatment of mice with resveratrol significantly increased their aerobic capacity, as evidenced by their increased running time and consumption of oxygen in muscle fibers. These effects were explained by the fact that in addition to being an antioxidant, resveratrol activates SIRT1 resulting in subsequent deacetylation and activation of PGC-1α, and thus induction of OX/PHOS and mitochondrial biogenesis genes which improved mitochondrial function. [160, 174] These and other findings suggest that an increase in SIRT1 activity in HD could facilitate activation of the PGC-1α-PPARγ signaling pathway and thus improve mitochondrial function. PGC-1α is a potent co-activator of the type II nuclear receptor PPARγ. A variety of endogenous compounds activate PPARγ including 15-deoxy-Δ12, 14-prostaglandin J2 (15Δ-PGJ2) and nitrolinoleic acid (LNO2). [161] Further, there are numerous exogenous agents including the thiazolidinediones (TZDs) (rosiglitazone, pioglitazone, troglitazone) that are PPARγ agonists. [162-163] PPARγ agonists have been shown to be neuroprotective and improve mitochondrial function. [164-166, 102] It was also demonstrated that when rosiglitazone was administered orally to mice substantial amounts were found in the brain and after 7 days of treatment there was clear evidence of mitochondrial biogenesis in the brain. [167] In our studies pretreatment of mutant striatal cells with the PPARγ agonist rosiglitazone prevented the loss of $\Delta\Psi_m$, mitochondrial calcium deregulation, and oxidative stress overproduction in response to thapsigargin. Additionally, the PPARγ signaling pathway was significantly impaired in the mutant huntingtin striatal cells with decreases in PPARγ expression and reduced PPARγ transcriptional activity. Also, treatment with rosiglitazone increased mitochondrial mass levels, further suggesting a role for the PPARγ pathway in mitochondrial function in striatal cells. [102] These findings suggest that activation of the PPARγ signaling pathway could ameliorate the mitochondrial deficits in HD. Therefore PPARγ agonists could represent a potential tool to consider in the treatment of neurodegenerative disorders, including HD.

Mitochondria likely play a key role in HD, although the exact mechanisms by which mutant Htt causes damage selectively to medium spiny neurons and cortical neurons in patients with HD are still under debate. Of interest, the striatum might be particularly vulnerable to mitochondrial defects through multiple mechanisms involving molecular factors which are selectively present in this brain region. As discussed above, recent studies suggest that transcriptional dysregulation and calcium dyshomeostasis are keys players in HD progression and pathogenesis However, studies have also suggested that mutant Htt cause mitochondrial DNA defects in HD brains and peripheral tissues from HD patients. Mutant Htt interferes with the formation of the CREB/TAF4 complex that regulates transcription of the gene encoding PGC-1α. PGC-1α may play a significant role in protecting neurons against mitochondrial toxicity and oxidative damage by increasing PGC-1α transcription and interaction with several transcription factors in HD neurons. PGC-1α is a potent co-activator of the type II nuclear receptor PPARγ. PPARγ agonists have been shown to be neuroprotective and improve mitochondrial function. Neuroprotective properties of

cyclosporine A (CsA) are due in part to its ability to prevent mPTP opening in response to high levels of calcium or oxidative stress. Therefore, CsA or new mPTP opening inhibitors may be of potential therapeutic benefit by protecting vulnerable neurons populations affected in HD. Dimebon inhibits alpha-Adrenergic receptors, Histamine H1 and H2 receptors, and Serotonin 5-HT2c, 5-HT5A, 5-HT6 receptors with high affinity. Dimebon also had significant effects on a number of additional receptors. Findings of this study suggests that Dimebon may have beneficial effects in HD neurons through its capacity to neurons by altering NMDA receptors and voltage-gated calcium channels

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