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Mitochondrial approaches for neuroprotection

Rajnish K. Chaturvedi and **M. Flint Beal**
Department of Neurology and Neuroscience, Weill Medical College of Cornell University, 525 East 68th Street, F-610, New York, NY 10065, USA

Abstract

A large body of evidence from post-mortem brain tissue and genetic analysis in man and biochemical and pathological studies in animal models (transgenic and toxin) of neurodegeneration suggest that mitochondrial dysfunction is a common pathological mechanism. Mitochondrial dysfunction due to oxidative stress, mitochondrial DNA deletions, pathological mutations, altered mitochondrial morphology and interaction of pathogenic proteins with mitochondria leads to neuronal demise. Therefore, therapeutic approaches targeting mitochondrial dysfunction and oxidative damage hold great promise in neurodegenerative diseases. This review discusses the potential therapeutic efficacy of creatine, coenzyme Q10, idebenone, synthetic triterpenoids, and mitochondrial targeted antioxidants (MitoQ) and peptides (SS-31) in *in vitro* studies and in animal models of Parkinson's disease (PD), Huntington's disease (HD), Amyotrophic Lateral Sclerosis (ALS) and Alzheimer's disease (AD). We have also reviewed the current status of clinical trials of creatine, coenzyme Q10, idebenone and MitoQ in neurodegenerative disorders. Further, we discuss newly identified therapeutic targets including PGC-1α and Sirtuins, which provide promise for future therapeutic developments in neurodegenerative disorders.

Keywords

Coenzyme Q10; Creatine; Triterpenoids; PGC-1α; Parkinson's disease; Huntington's disease; Alzheimer's disease

Mitochondrial dysfunction in Parkinson's disease (PD)

Much evidence suggests a role for mitochondrial dysfunction in the pathophysiology of PD, a common age-associated neurodegenerative disease characterized by progressive degeneration of the nigrostriatal dopamine (DA) pathway and presence of the intraneuronal protein inclusions (Lewy bodies)[1–3]. The most compelling evidence of mitochondrial dysfunction in PD comes from the accidental discovery of the synthetic meperidine analogue 1-methyl-4-phenyl-1,2,3,6-tetrahydrodropyridine (MPTP), which causes parkinsonism by selective inhibition of mitochondrial complex-I of the electron transport chain[4, 5]. Similar to MPTP, infusion of other selective complex-I inhibitors such as rotenone, pyridaben, fenazaquin, tebunfenpyrad, trichloroethylene and fenpyroximate results in loss of the nigral dopaminergic neurons and parkinsonian phenotypes in *in vivo* models, implicating mitochondrial dysfunction in PD pathogenesis[6–8]. An impairment of mitochondrial complex-I activity has been observed in the substantia nigra (SN), platelets,

To whom correspondence should be addressed. **M. Flint Beal** (fbeal@med.cornell.edu) or Rajnish Chaturvedi (rkc2001@med.cornell.edu) Department of Neurology and Neuroscience, Weill Medical College of Cornell University, 525 East 68th Street, A-610, New York, NY 10065, USA Tel: +1 2127466575 Fax: +1 2127468532.

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and skeletal muscle of PD patients 1, 9-13, in some but not in all studies14, 15. Similarly, reduced complex-I activity and an increased susceptibility to MPP^+ were also observed in cybrids containing mitochondrial DNA from PD patients, suggesting mitochondrial DNA encoded defects in PD 16, 17, although in one study no significant reduction in complex-I activity was found18. Besides the mitochondrial complex-I defect, there is genetic evidence that suggests that mutations in mitochondrial DNA (mtDNA) also play a role in the pathogenesis of PD. We observed G11778A mtDNA point mutation in a subunit of mitochondrial complex-I in a family with parkinsonism and multisystem degeneration19. We also identified high levels of somatic mtDNA point mutations in elderly PD patients20. A mutation in mitochondrial DNA polymerase gamma (POLG1) has been observed in five Finnish families with idiopathic sporadic PD21. To date several mtDNA mutations including large scale rearrangements, point mutations, and micro deletions have been identified in the SN and other brain regions of PD patients20, 22-25. Recently, another compelling piece of evidence of mitochondrial dysfunction in PD has come from conditional knockout “MitoPark” mice, who have a disrupted mitochondrial transcription factor A (Tfam) gene in DA neurons. These mice show reduced mtDNA expression, reduced respiratory chain function in DA neurons, and a progressive PD phenotype, consistent with involvement of respiratory chain dysfunction in PD pathogenesis26. Further, there is evidence of reduced mitochondrial mass and size in the mouse SN DA neurons as compared to non-DA neurons, suggesting selective vulnerability of DA neurons may be due to mitochondrial dysfunction in PD27. In addition to mtDNA mutations, pathogenic mutations in several genes including α–synuclein, parkin, UCHL-1, DJ-1, PINK-1, LRRK-2, NURR-1, tau, and HtrA2 also directly or indirectly implicate a role of mitochondrial dysfunction in familial PD pathogenesis3, 28, 29. α–Synuclein is a major component of Lewy bodies, and gene mutations are associated with autosomal dominant familial PD28, 29. Over expression of α–synuclein in cell culture and in transgenic mice impairs mitochondrial function and increases vulnerability to MPTP30, 31. In contrast, α–synuclein-null mice are resistant to respiratory chain inhibitors such as MPTP, 3-nitropropionic acid (3-NP) and malonate, thus implicating mitochondria in α–synuclein mediated toxicity32, 33.

Mitochondrial dysfunction in Huntington's disease (HD)

HD is an autosomal-dominant disorder characterized by lesions in the striatum of the brain that cause progressive behavioral and cognitive impairments and involuntary choreiform movements. HD is caused by the abnormal expansion of a CAG repeat in exon 1 of the *HD* gene, resulting in elongated polyglutamine stretches in the protein product known as mutant huntingtin34. Various lines of evidence suggest involvement of mitochondrial dysfunction in HD. Evidence for bioenergetic defects in HD pathogenesis comes from the finding of pronounced weight loss in HD patients, despite sustained caloric intake. Glucose metabolism is reduced in the basal ganglia and cerebral cortex of symptomatic HD patients and even of presymptomatic gene carriers, as assessed by PET imaging35-37. Further, NMR spectroscopy revealed a decrease in N-acetylaspartate (NAA) and an increase in lactate in the basal ganglia of HD patients, and was found to directly correlate with the subject's CAG repeat number38, 39. Biochemical studies revealed reduced activity of several key components of oxidative phosphorylation and the TCA cycle, including complexes II-III and aconitase, in advanced stage HD patients, while complex-I activity was unaltered40-43. Similarly, a recent study showed increased glucose utilization relative to oxygen utilization in the striatum of early HD patients44.

Mitochondrial dysfunction in HD is not restricted only to the brain, but is also evident in the peripheral tissues including muscle and platelets39, 45-47, and in cultured cells48. In muscle of symptomatic and presymptomatic HD patients, there is a reduced ATP / phosphocreatine ratio, a decreased ratio of phosphocreatine to inorganic phosphate, and impaired complex-I

activity, suggesting abnormal skeletal muscle mitochondrial energy metabolism39, 45, 46. We observed significantly reduced cellular respiration and COX activity in myoblasts from HD patients, and these defects were exacerbated in chronic energy deprivation conditions (Chaturvedi et. al., unpublished findings). In addition, lymphoblasts from HD patients and brain mitochondria from YAC transgenic mice expressing Htt with 72 repeats show mitochondrial dysfunction including a decreased membrane potential, impaired calcium ion homeostasis49, and marked morphological abnormalities50. Similarly, mouse immortalized striatal cells expressing endogenous mutant huntingtin (STHdhQ111) and the human lymphoblastoid cell lines bearing HD-causing alleles showed decreased ATP levels and ADP uptake51. Further, in striatal cells from mutant Htt knock-in mouse embryos, mitochondrial respiration and ATP production are significantly impaired48. Over expression of complex-II subunits in striatal neurons expressing Htt171-82Q restored complex-II activity and blocked mitochondrial dysfunction and cell death52.

In addition, a number of studies provide genetic evidence that mtDNA mutations may also be involved in HD pathogenesis. Recently, it was shown that HD patients have higher frequencies of mtDNA deletions in lymphocytes and leucocytes in comparison to the controls, and the number of mutations is directly related to the size of the CAG repeats expansion53, 54, This may be a consequence of oxidative damage to mtDNA. Moreover, the fact that mitochondrial toxins such as 3-NP and malonate, which selectively inhibit complex-II and induce a pathological phenotype resembling HD in human, rodents, and primates, further enforce the significance of mitochondrial dysfunction in HD pathogenesis 34, 40, 55, 56.

Mutant Htt plays an important role in mitochondrial dysfunction in HD. Several mechanisms may be involved. First, it may directly bind to the mitochondria. There is evidence from an HD mouse model, and from cultured HD striatal cells (STHdhQ111), that mutant Htt associates directly with the outer mitochondrial membrane49, 57. In addition, by electron microscopy, N-terminal mutant Htt was found to localize on neuronal mitochondrial membranes49. Second, mutant Htt protein directly increases susceptibility of mitochondria to the calcium-induced permeability transition and cytochrome c release49, 58. Similarly, mutant Htt expressing STHdhQ111 cells show a reduced mitochondrial Ca^{2+} uptake capacity, Ca^{2+}-induced decrease in mitochondrial respiration and increased mitochondrial membrane permeability in comparison with wild type cells59. Mitochondrial defects seen in these studies are a direct effect of the mutant Htt, as incubation of mitochondria from normal lymphoblasts with mutant Htt (fusion protein composed of a peptide containing a pathogenic polyglutamine tract) reproduced mitochondrial abnormalities seen in the HD patients and knock-in HD mice49. Third, besides a direct effect on the mitochondria, mutant Htt also impairs *in vitro* and *in vivo* trafficking of mitochondria in neurons, leading to loss of mitochondrial motility and eventually mitochondrial dysfunction60, 61. These findings clearly indicate that mutant Htt induces mitochondrial Ca^{2+} handling defects, respiratory deficits, and impaired mitochondrial movement which could be contributing mechanisms to mitochondrial dysfunction in HD.

Mutant Htt also impairs mitochondrial function by altering transcription. Htt directly binds to and down regulates the activity of several transcription factors including CREB-binding protein, TAFII130 and SP162-68. Binding of Htt on these transcription factors leads to alteration of expression of several genes involved in mitochondrial respiration and normal mitochondrial function. Htt binding on p53 causes upregulation of the downstream target genes BAX and PUMA, which leads to increased mitochondrial membrane depolarization69. Recently, Peroxisome proliferator-activated receptor-γ-coactivator (PGC-1α), which is a coactivator of several transcription factors and is a key regulator of mitochondrial biogenesis was found to be impaired in HD patients and transgenic HD

models70-72. Mutant Htt protein directly impairs the ability of PGC-1α to switch on downstream target genes such as the gene encoding UCP-1. Moreover, mutant Htt also binds with the CREB/TAF4 complex on the PGC-1α promoter and impairs the PGC-1α activity by blocking the transcription of its target genes71. Impairment of the PGC-1α function and down regulation of its mitochondrial target genes leads to abnormalities in mitochondrial function and energy metabolism, contributing to neurodegeneration in susceptible neurons70-72. Similarly, impaired PGC-1α transcription and activity impact the enzyme system that combats reactive oxygen species (ROS). This leads to down regulation of ROS defense genes encoding SOD1, SOD2, and glutathione peroxidase, resulting in increased oxidative damage and neuronal death73.

Mitochondrial dysfunction in Alzheimer's disease (AD)

AD is a late-onset, progressive, age-dependent neurodegenerative disorder, characterized by the progressive cognitive decline, and the presence of amyloid-β senile plaques and tau neurofibrillary tangles. Mitochondrial dysfunction is widely implicated in the pathogenesis of AD. Evidence for mitochondrial dysfunction in the AD pathogenesis comes from impaired activities of the three key TCA enzyme complexes, pyruvate dehydrogenase, isocitrate dehydrogenase, and α-ketoglutarate dehydrogenase, observed in postmortem AD brain and fibroblasts from AD patients74,75. Similarly, reduced respiratory chain complex I, III, and IV activity was found in platelets and lymphocytes from AD patients and postmortem brain tissue76-79. In addition to a direct mitochondrial respiratory chain defect, more recently, increased autophagic degradation of mitochondria has also been observed in AD80.

There is a growing body of evidence that mtDNA mutations also play a pivotal role in mitochondrial dysfunction in AD pathogenesis. In a recent study, 20 point mutations were detected in the mitochondrial-encoded cytochrome c oxidase subunits I, II, and III genes in AD patients81. Other studies showed two missense mutations in the mitochondrial DNA of cytochrome c oxidase and high aggregate burden of somatic mtDNA point mutations in the patients with AD82, 83, however direct sequencing of the complete mtDNA coding region has not identified disease specific mutations84. Moreover, there is also evidence that some of the proteins implicated in AD pathogenesis directly target mitochondria and cause mitochondrial dysfunction. These include, the amyloid precursor protein (APP) which binds directly to the mitochondria in cortical neuronal cells from AD transgenic mouse85. Similarly, amyloid-βfrom mutant APP transgenic mice also binds to mitochondria and causes mitochondrial dysfunction86.

Mitochondrial dysfunction in Amyotrophic lateral sclerosis (ALS)

ALS is a neurodegenerative disease, characterized by a selective loss of motor neurons in the spinal cord brainstem, and motor cortex, which leads to skeletal muscle atrophy, paralysis and death3. The etiology of ALS is unknown. Some 90% of cases are sporadic with unknown cause (SALS) and 10% are familial (FALS). Among familial cases, 20% are linked to mutations in Cu/Zn- superoxide dismutase (SOD). Several different pathogenic mechanisms have been identified in the CNS and peripheral tissues during the disease course in ALS, but mitochondrial and bioenergetic defects are implicated widely in ALS pathogenesis2. There is evidence of abnormal structure and number of mitochondria and compromised function in ALS motor neurons and skeletal muscle. That is corroborated by findings of altered respiratory chain enzyme activities and CNS energy hypometabolism in ALS spinal cord and motor cortex87-91. Morphological changes in mitochondria are the earliest detectable pathologic events followed by decreased mitochondrial respiration in the SOD1 over expressing G93A transgenic mouse 89, 92. Decreased ATP levels and impaired

respiratory chain enzyme activities were reported in motor neuron cell lines expressing mutant SOD1, suggesting involvement of mutant SOD1 in mitochondrial defects93, 94. We showed significantly decreased mitochondrial Ca^{2+} loading capacity, oxygen consumption, respiratory chain complex activities and ATP synthesis in the brain and spinal cord mitochondria from mutant SOD1 transgenic mice confirming that mutant SOD1 is associated with impaired mitochondrial dysfunction95, 96. In addition, mitochondrial dysfunction could be due to the direct interaction of mutant SOD1 with mitochondria, as mutant SOD1 localizes to the mitochondrial intermembrane space and matrix and affects mitochondrial protein import97. It also selectively associates with the outer mitochondrial membrane in spinal cord motor neurons97-99. Moreover, recently it was shown that mutant SOD1 impairs fast axonal mitochondrial transport in the anterograde direction in motor neurons derived from SOD1 G93A transgenic mice100.

Mitochondrial approaches for neuroprotection

There is ample evidence showing involvement of mitochondrial dysfunction in the pathogenesis of neurodegenerative disorders, therefore, one would predict that agents that alleviate mitochondrial dysfunction could be beneficial and exert neuroprotective effects. Several bioenergetic agents that improve mitochondrial function including creatine, coenzyme Q10 (CoQ10), nicotinamide, riboflavin and lipoic acid are being tested for their neuroprotective efficacy in neurodegenerative disorders. Among them, creatine and CoQ10 are in clinical trials for PD, HD and AD.

Creatine

Creatine is a nitrogenous guanidine compound that occurs naturally in vertebrates and helps to supply energy to muscle and nerve cells. It is taken up into the brain and skeletal muscle by a sodium-dependent creatine transporter, and becomes physiologically active when it is transformed enzymatically into phosphocreatine (PCr). The creatine/phosphocreatine system, regulated by the mitochondrial creatine kinase (CK), plays an important role in maintaining energy balance in the brain. The presence of this energy buffer system keeps the ATP/ADP ratio high at sub-cellular sites where ATP is needed, which ensures that the free energy of ATP remains high. That also minimizes the loss of adenosine nucleotides, which causes cellular dysfunction.

Creatine supplementation was found to be neuroprotective in a series of *in vitro* and *in vivo* studies101. Recently, creatine was shown to enhance the survival of glutamate-treated neuronal/glial cells by modulation of Ras/NF-kappaB signaling102. Creatine treatment also promotes differentiation of cultured GABA-ir neurons and provides significant neuroprotection against glucose, serum deprivation and 3-NP induced toxicity103, 104. Chronic administration of creatine was shown to significantly increase survival, tyrosine hydroxylase immunoreactive (TH-IR) fibers density, and soma size of dopaminergic neurons in mesencephalic culture, by protecting against neurotoxic insults induced by serum and glucose deprivation, MPP^+, and 6-hydroxydopamine (6-OHDA)105, 106. In aged mice, creatine improves health and survival107. We examined the effects of creatine supplementation on MPTP-induced parkinsonism108. We found that creatine produced protection against dopamine loss, as well as an attenuation of neuron loss in the SN of mice treated with MPTP. Further, oral creatine supplementation produced dose-dependent significant protection against MPTP-induced dopamine depletion. Moreover, creatine protected against MPTP-induced loss of TH-IR neurons in the SN. We showed that prophylactic administration of oral creatine reduces the size of ischemic brain infarctions in mice109. In another study we showed that oral administration of 1% creatine in the diet significantly attenuated striatal excitotoxic lesions produced by NMDA110. Creatine and

nicotinamide in combination exerted significant additive neuroprotective effects against malonate-induced striatal lesions110. We also found additive neuroprotective effects of creatine and a cyclooxygenase-2 inhibitor in the MPTP mouse model of PD and the G93A transgenic mouse model of ALS111, 112. In rats, creatine prevented excitotoxic death of intrinsic neurons caused by intrastriatal infusion of the neurotoxin ibotenic acid113. Oral administration of creatine produces a dose-dependent improvement in motor performance and extends survival in G93A transgenic ALS mice, where it protects against loss of both motor neurons and SN neurons114. However, creatine does not exert a beneficial effect on skeletal muscle function in G93A ALS mice115. Creatine significantly attenuates elevated glutamate concentrations in cerebral cortex of G93A ALS mice116. The combination of creatine and minocycline also provides additive neuroprotective effects in the G93A mouse model of ALS117. We found that creatine significantly improves survival, improves motor performance, slows the development of brain atrophy, increases brain ATP levels, delays atrophy of striatal neurons and the formation of Htt-positive aggregates in the R6/2 and N-171-82Q transgenic mouse models of HD118-120. Creatine administration protects against glutamate and β-amyloid toxicity in rat hippocampal neurons121. Creatine is also beneficial in the animal models of traumatic brain injury, spinal cord injury and cerebral ischemia122-126. In addition, preincubation of anoxic rat hippocampal slices with creatine attenuated the decrease in PCr and ATP content127.

The success of creatine in experimental studies led to clinical trials in neurodegenerative diseases including PD, HD and ALS. We found beneficial effects using combination therapy of creatine monohydrate, CoQ10, and lipoic acid in a randomized, double-blind, placebo-controlled, crossover study in patients with mitochondrial cytopathies128. In a small pilot trial, creatine improved patient mood but had no effect on overall Unified Parkinson's Disease Rating Scale (UPDRS)129. In order to see the protective effect of creatine (10g/day) and minocycline on PD progression, a randomized, double-blind, Phase II futility clinical trial was carried out by NINDS NET-PD investigators in early PD130. Creatine was shown to reduce the UPDRS scores, and could not be rejected as futile based on the 30% DATATOP futility threshold. Moreover in this study, tolerability was 91% for creatine and 77% for minocycline. As compared to DATATOP controls, disease progression on the UPDRS was slowed by almost 50% at 1 year in the creatine treated patients. In one clinical trial creatine supplementation at 20 g/day with resistance training in PD patients resulted in increased muscle endurance and upper body strength131. Recently, the NIH announced a phase III clinical trial of creatine for PD, with a goal of recruiting 1720 participants randomized to 10g of creatine or placebo132, 133. To determine the safety and tolerability of creatine in HD we carried out a randomized, double-blind, placebo-controlled study in 64 subjects134. We found that oral administration of creatine at a dose of 8 g/day for 16 weeks is well tolerated, safe and bioavailable to the brain, and it decreased serum 8-hydroxy-2-deoxyguanosine levels, a marker for oxidative stress. Taken together, these findings clearly indicate that creatine is a promising agent for use as a neuroprotectant in a variety of neurodegenerative disorders.

CoQ10

CoQ10 is an essential biological cofactor of the electron transport chain, where it accepts electrons from complexes I and II. CoQ10, also known as ubiquinone, serves as an important antioxidant in mitochondrial and lipid membranes135. It is a particularly important antioxidant in the inner mitochondrial membrane, where it can directly scavenge free radicals through interactions with α-tocopherol135. Besides its free radical scavenging activity, it also prevents apoptotic cell death by blocking Bax binding to mitochondria, and by inhibiting activation of the mitochondrial permeability transition (MPT)136, 137. CoQ10 is a co-factor of mitochondrial uncoupling proteins (UCP), and may also exert

neuroprotective effects by activation of these proteins, leading to a reduction in mitochondrial-free radical generation101, 138. CoQ10 increases mitochondrial UCP expression in the SN of primates, and this is associated with marked neuroprotection against the MPTP toxicity101, 139. Further, increased expression of the mitochondrial UCP also protects against neuronal damage in experimental models of stroke and epilepsy101.

CoQ10 exerts neuroprotective effects in several *in vivo* and *in vitro* models of neurodegenerative disorders. It protects against paraquat and rotenone induced mitochondrial dysfunction and neuronal cell death in human neuroblastoma (SHSY-5Y) cells and primary rat mesencephalic neurons respectively140, 141. It provides neuroprotection in iron-induced apoptosis in dopaminergic neurons, and exerts anti-amyloidogenic effects by destabilizing preformed beta-amyloid fibrils *in vitro*142, 143. Further, CoQ10 protects SHSY5Y neuronal cells from β-amyloid toxicity through inhibition of the MPT pore144. Similarly, pretreatment of neuronal cells with CoQ10 maintains mitochondrial membrane potential during oxidative stress and reduces the amount of mitochondrial ROS generation145.

The protective role of CoQ10 was also studied in several toxin models. We demonstrated CoQ10 provided significant protection against MPTP induced dopamine depletion and loss of TH-IR neurons in aged mice146. More recently, we found that dietary administration of either of two formulations of CoQ10 resulted in significant protection in a chronic MPTP model induced by the administration of MPTP by Alzet pump for 1 month147. We found neuroprotective effects against DA depletion, loss of TH-IR neurons in the SN and the development of α–synuclein aggregates. The finding that CoQ10 is effective in a chronic model of MPTP toxicity is of particular interest, as this may be more relevant to PD, which is a progressive neurodegenerative disorder. Oral administration of CoQ10 exerts significant neuroprotective effects against striatal lesions in rats produced by aminoxyacetic acid, and the mitochondrial toxins malonate and 3-NP148-150. Oral administration of CoQ10 produced dose-dependent neuroprotective effects against malonate induced striatal lesions, depletion of ATP and increases in lactate concentration148. Similarly, oral administration of CoQ10 for 1 week, prior to administration of 3-NP resulted in a significant 90% neuroprotection against 3-NP induced striatal lesions150. We also demonstrated that CoQ10 produces neuroprotective effects in transgenic mouse models of ALS and HD150, 151. Recently, we found that CoQ10 treatment decreases brain oxidative stress, Aβ42 levels, β-amyloid plaque area and number, and improves cognitive performance in Tg19959 mice, a transgenic mouse model of AD (Kipiani et al., unpublished findings). A dose ranging and efficacy study of highdose coenzyme Q10 formulations in the R6/2 HD transgenic mice demonstrated that high-dose CoQ10 significantly extends survival, improves motor performance, grip strength and reduces brain atrophy in R6/2 HD mice, in a dose-dependent manner152.

As in cancer chemotherapy, combinations of two or more compounds may be a better approach for neuroprotection. The combination therapy of CoQ10 and minocycline in R6/2 transgenic mouse model of HD resulted in a significantly increased amelioration of behavioral and neuropathological deficits, extended survival, improved rotarod performance and attenuated striatal neuron atrophy, as compared to either minocycline or CoQ10 alone153. Similarly, we and others, by using CoQ10 and remacemide (NMDA antagonist) combination therapy observed significantly improved motor performance and increased survival in the R6/2 and the N-171-82Q transgenic mouse models of HD151, 154. Recently, we found that a combination of creatine and CoQ10 exerts synergistic neuroprotective effects in the MPTP model of PD (Yang et al., unpublished findings).

On the basis of results from animal studies, we and others initiated several clinical trials of CoQ10 in neurodegenerative disorders. We initially tested the effect of oral administration of 360mg/day CoQ10 on elevated cortical lactate concentrations in 18 patients with HD. We observed that CoQ10 treatment produced a 37% reduction in occipital cortex lactate concentrations, which was reversed following withdrawal of therapy39. Since CoQ10 and remacemide in combination was protective in a HD transgenic mouse models151, 154, the Huntington's Study Group performed the CARE-HD trial using CoQ10 and remacemide in 340 patients155. Patients were treated with CoQ10 (600mg /day) and remacemide (600mg / day), or a combination of the two for 30 months. Administration of CoQ10 resulted in a 14% decrease in disease progression. Remacemide demonstrated no efficacy. This trial was powered to be able to determine a 40% attenuation of total functional capacity decline with 80% power.

The ratio of reduced to oxidized CoQ10 is significantly reduced in the platelets and cerebrospinal fluid (CSF) of PD patients156, 157 and in plasma of ALS patients158. We found a significant reduction in CoQ10 levels in mitochondria isolated from platelets of PD patients, that directly correlated with a decrease in complex-I activity159. In this study, oral administration of CoQ10 in PD patients was well tolerated and resulted in significant, dose-dependent increases in plasma CoQ10 levels. The reduced level of CoQ10 in the platelets and CSF suggested that CoQ10 supplementation might be efficacious in the treatment of PD. Therefore, we carried out a multicenter, randomized, parallel-group, placebo-controlled, double-blind and dosage-ranging phase II clinical trial of CoQ10 in early PD patients (Parkinson Study Group)160. Patients were treated with placebo or 300, 600, or 1,200 mg/ day of CoQ10 for 16 months to see the safety, tolerability and neuroprotective efficacy of CoQ10. The primary outcome measure was the change in the UPDRS between baseline and final visits. CoQ10 was safe and well tolerated at dosages of up to 1200 mg/day and a statistically significant dose-dependent reduction in UPDRS score was evident in subjects assigned to CoQ10 compared to those assigned to placebo. Subsequently, in other open label dose-escalation clinical trials, CoQ10 dosages as high as 3,600 mg/day were safe and well tolerated in PD, HD and ALS. However, plasma CoQ10 levels reached a plateau at the 2400 mg/day dosage and did not increase further at the 3000 mg/day dosage in PD, HD or ALS patients161, 162. A recent study showed that CoQ10 does not exert symptomatic effects163. Therefore, any benefits in a phase III study of 1200 mg and 2400 mg daily (QE3 study) are likely to be neuroprotective rather than symptomatic. An NINDS sponsored clinical trial of 600 patients randomized to placebo, 1200 mg CoQ10 or 2400 mg CoQ10 has recently started. Similarly a phase III trial of 2400 mg of CoQ10 daily has recently started in HD. This dose was chosen based on the studies of plasma CoQ10 concentrations discussed above. A phase II trial of CoQ10 in presymptomatic gene positive HD patients (PREQUEL) will begin soon.

Idebenone, a synthetic analogue of CoQ10 has been studied in several neurodegenerative disorders for neuroprotection. Idebenone protects neuronal cells against β-amyloid induced toxicity164. Similarly, when used in combination with α-tocopherol, it alleviates β-amyloid induced learning and memory deficits in rats165. A multicentre, placebo controlled, double-blind trial of idebenone 45 mg twice/day orally, in patients of AD, showed statistically significant improvement of the memory, attention and behavior166. In another randomized, double-blind, placebo-controlled multicentre study 300 patients with Alzheimer type dementia were treated for 2 years, with 30 or 90 mg /day idebenone or placebo167. The outcome of study was a statistically significant improvement in the Alzheimer's Disease Assessment Scale (ADAS) score after 6 months, in a dose dependent manner. Subsequently, in two other clinical trials, idebenone was safe and tolerable up to 360 mg/day and slowed progression of cognitive deficits in patients with AD168, 169. These results are controversial since another large trial showed no benefits170. There was no significant

improvement in a small trial in HD171. Initial results of idebenone in Friedrich's Ataxia are very promising172. These findings strongly support the notion that creatine, CoQ10 and idebenone are promising neuroprotective agents in debilitating neurodegenerative disorders.

Mitochondrial targeted antioxidants/peptides

Mitochondrial-targeted antioxidants including mitochondrial CoQ10 (MitoQ) and Szeto-Schiller peptide (SS-31) play an important role in modulating ROS induced mitochondrial permeability transition and cell death, and were found to be protective in several *in vitro* and *in vivo* models of ischemia, reperfusion injury and neurodegeneration173. MitoQ is a derivative of CoQ10 conjugated to triphenylalkylphosphonium ions, which promotes uptake into mitochondria, where it can combat ROS originating in mitochondria174. MitoQ reduces ROS formation and preserves mitochondrial function after glutathione depletion, even in the cells lacking mitochondrial DNA175. Murphy and colleagues have developed MitoQ, which is currently in a phase II clinical trial for PD in New Zealand (http://www.parkinsons.org.nz/news/protectstudy.asp)174.

Similarly, a novel peptide antioxidant (SS-31) targeted to the inner mitochondrial membrane prevents apoptosis, necrosis, oxidative stress and inhibition of the mitochondrial electron transport chain176. SS-31 protects neuronal cells against tert-butyl-hydroperoxide (tBHP) induced mitochondrial depolarization and apoptotic cell death by reducing intracellular ROS, decreasing markers of apoptotic cell death and caspase activity177. It decreases mitochondrial ROS production and inhibits the MPT and mitochondrial swelling. SS-31 also prevents Ca^{2+} induced cytochrome c release and inhibits 3-NP-induced activation of the MPT pore and mitochondrial depolarization in isolated mitochondria178. It is also effective against myocardial ischemia-reperfusion injury in both *ex vivo* and *in vivo* models176, 179. Recently, we investigated the therapeutic effects of SS-31 in neuronal cells, stably transfected with either wildtype or mutant Cu/Zn superoxide dismutase (SOD1), and in the G93A mouse model of ALS180. We found SS-31 mediated significant neuroprotection against cell death induced by hydrogen peroxide in SOD1 neuronal cells. Further, daily intraperitoneal injections of SS-31 (5 mg/kg), starting at 30 days of age, led to a significant improvement in survival and motor performance in the G93A transgenic mouse model of ALS. SS-31 treated G93A ALS mice showed decreased cell loss and a decrease in immunostaining for markers of oxidative stress in the lumbar spinal cord, as compared with the vehicle-treated mice. Both SS-31 and SS-20 also produce complete protection against MPTP neurotoxicity (Yang et al., unpublished findings). These studies suggest that mitochondrial drug-targeting strategies are effective in several *in vitro* and *in vivo* models of neurodegenerative disorders. In the future selective manipulation of mitochondrial function may allow effective treatment of debilitating neurodegenerative disorders.

Triterpenoids

Synthetic triterpenoids (TP), analogues of oleanolic acid, are powerful inhibitors of oxidative stress and cellular inflammatory processes, and thus may be neuroprotective in neurodegeneration. Synthetic TP compounds are potent inducers of the antioxidant response element (ARE)–Nrf2–Keap1 signaling pathway and are useful in a variety of the cancers including leukemia, multiple myeloma, osteosarcoma, breast and lung cancer181. Following activation by TP, Nrf2 dissociates from Keap1, translocates to the nucleus, and binds to the ARE promoter sequences, leading to coordinated induction of a battery of cytoprotective genes including antioxidant and anti-inflammatory genes182.

Nrf-2 over expression is protective in a rat model of cerebral ischemia183. Neuronal cultures derived from the Nrf2 knockout mice show increased susceptibility to oxidative stress, as well as damage produced by mitochondrial electron transport chain complex

inhibitors such as MPP^+ and rotenone184. In the Nrf2 knockout ($Nrf2^{-/-}$) mice, injection of the mitochondrial complex-II inhibitor 3-NP causes increased motor deficits and striatal lesions as compared to the $Nrf2^{+/+}$ mice, and these toxic effects of 3-NP were protected by adenoviral mediated over expression of Nrf2185. Additionally, the Nrf2 activator tertbutylhydroquinone, has attenuated 3-NP toxicity in $Nrf2^{+/+}$ mice, but not in $Nrf2^{-/-}$ mice185. Further, $Nrf2^{-/-}$ mice also show profound susceptibility to striatal lesions produced by the mitochondrial complex-II inhibitor malonate186. Conversely, the implantation of intrastriatal grafts of astrocytes over expressing Nrf2 produces neuroprotection against the neurotoxic effects of malonate. Recently, we tested neuroprotective effects of the synthetic triterpenoid CDDO-methyl amide (2-cyano-*N*-methyl-3,12-dioxooleana-1,9(11)-dien-28 amide; CDDO-MA), a potent activator of the Nrf2/ARE signaling, in the 3-NP rat model and MPTP mouse model (Yang et al., unpublished findings). We found that CDDO-MA exerts significant neuroprotective effects against MPTP and 3-NP induced toxicity. It reduces t-butylhydroperoxide induced ROS generation, attenuates MPTP-induced nigrostriatal dopaminergic neurodegeneration and reduces 3-NP induced striatal lesions. In another study we found that CDDO-MA also increases the expression of genes involved in mitochondrial biogenesis including PGC1-α, in the spinal cord of G93A ALS transgenic mice, (Kiaei et al., unpublished findings). These studies suggest a potential neuroprotective effect of triterpenoids in cell and animal models of neurodegenerative disorders, and these compounds hold great promise as therapeutic agents for these disorders.

Nicotinamide, Lipoic acid, Carnitine, β-hydroxybutyrate and estradiol

Nicotinamide is a precursor of nicotinamide adenine dinucleotide (NADH), which is a substrate for complex-I of the electron transport chain as well as other biochemical pathways. Nicotinamide prevents MPTP induced neurodegeneration in mice139. Lipoic acid is a disulfide compound that is found naturally in mitochondria as a coenzyme for pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, and also has antioxidant effects128, 187, 188. We found that α-lipoic acid exerts significant neuroprotective effects in transgenic mouse models of HD and ALS128, 187, 188. Carnitine and β-hydroxybutyrate has shown to protect against MPTP toxicity189-191. Similarly, estradiol has shown neuroprotective efficacy in animal models of stroke, Alzheimer's disease (AD), and Parkinson's disease (PD)192.

PGC-1α and Sirtuins (Sir2)

Recently, PGC-1α, a transcriptional regulator, which is involved in mitochondrial biogenesis and respiration, has emerged as a new therapeutic target for neurodegenerative disorders72. PGC-1α regulates diverse metabolic functions in different tissues by activating a cascade of thousands of genes including the nuclear respiratory factors-1 and 2 (NRF-1 and NRF-2), mitochondrial transcription factor (Tfam) and estrogen related receptor-α (ERR-α)72. Recently, a role of impaired function of PGC-1α in HD pathogenesis was suggested and decreased PGC-1α expression was observed in HD transgenic mice and HD patients70-72. Similarly, we observed a reduction of PGC-1α and expression of its target genes in the muscle of HD transgenic mice and HD patients (Chaturvedi et al., unpublished findings). Further in another study it was demonstrated that PGC-1α reduces oxidative stress by inducing the expression of ROS scavenging enzymes73. Dopaminergic neurons in PGC-1α null mice are much more susceptible to MPTP toxicity73. Conversely, PGC-1α over expression protects neural cells from oxidative stress induced by mitochondrial toxins71. These studies provide compelling evidence for a role of PGC-1α in the pathogenesis of neurodegenerative diseases, and thus it is a promising therapeutic target for neurodegenerative disorders2, 72.

Sirtuins (silent information regulators) are member of the NAD^+ dependent histone deacetylase family of proteins in yeast, and its homologs in mice and humans, that participate in a variety of cellular processes including mitochondrial functions, cellular metabolism, energy metabolism, gluconeogenesis, cell survival and aging193. Sirtuin activation improves mitochondrial function, extends lifespan, and promotes longevity in various species including yeast193. Activation of sirtuins may, therefore, potentially delay the onset of age-related neurodegenerative disorders. The mammalian Sirtuin gene family has seven homologues (SIRT 1-7). SIRT-1 activation by resveratrol increases survival of motor neurons from transgenic ALS mice and reduces learning impairment and neurodegeneration in AD mouse models by decreasing the acetylation of SIRT1 substrates PGC-1α and p53194. In addition, direct injection of SIRT1 lentivirus in the hippocampus of AD transgenic mice shows significant neuroprotection194.

Recently, resveratrol, which is very potent activator of SIRT1, was shown to improve the survival of mice placed on a high caloric diet195. There was increased insulin sensitivity, reduced insulin-like growth factor levels, increased AMP kinase activity, increased PGC-1α activity, increased mitochondrial number and improved motor function. Similarly, resveratrol in another study improved motor function in mice which was accompanied by a decrease in PGC1α acetylation leading to increased activity and mitochondrial biogenesis196. This was attributed to increased SIRT1 activity. Increased intracellular NAD^+ concentration activates SIRT1 in brain following caloric restriction and this results in a reduction in amyloid pathology in a mouse model of Alzheimer disease197. Increased SIRT1 protected against hippocampal degeneration in another mouse model of Alzheimer disease194. Resveratrol also protects against 3-NP induced motor and behavioral deficits198. In a recent study it was found that over expression of SIRT1 deacetylase and SIRT1 activation by resveratrol significantly protects against microglia-dependent amyloid-β toxicity by inhibiting NF-kB signaling199. Altogether, theses studies provide strong evidence for involvement of Sirtuins in neuroprotection and targeting of Sirtuins could be an attractive therapeutic approach in neurodegenerative disorders.

Conclusion and future perspective

Analysis of postmortem brain tissue from patients as well as experimental studies in animal models indicate that mitochondrial dysfunction and oxidative damage play a central role in the pathogenesis of a number of common neurodegenerative diseases including PD, AD, HD and ALS. Therefore, therapeutic agents having the ability to target mitochondria and reduce mitochondrial dysfunction hold great promise for therapeutic interventions. Several agents, including creatine, CoQ10, MitoQ and idebenone are presently in clinical trials and show promising neuroprotective effects in these disorders. In the future, larger clinical trials with larger numbers of patients will provide more definitive information on the therapeutic efficacy of these compounds. Phase III clinical trials for PD and HD have commenced this year. Mitochondrial targeted antioxidants (MitoQ) and peptides (SS-31) are also of great interest, as they combat against ROS at their site of origin in mitochondria. In addition, combination therapy with two or more compounds may be more efficacious than a single compound for neuroprotection. Identification of new therapeutic targets including PGC-1α and Sirtuins may provide new avenues for therapy of neurodegenerative diseases.

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