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Mitochondrial Therapies for Parkinson's Disease

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Abstract

Parkinson's disease (PD) is marked by widespread neurodegeneration in the brain in addition to a selective yet prominent and progressive loss of nigrostriatal dopaminergic neurons. Of the multiple theories suggested in the pathogenesis of PD, mitochondrial dysfunction takes a center stage in both sporadic and familial forms of illness. Deficits in mitochondrial functions due to impaired bioenergetics, aging associated increased generation of reactive oxygen species, damage to mitochondrial DNA, impaired calcium buffering, and alterations in mitochondrial morphology may contribute to improper functioning of the CNS leading to neurodegeneration. These mitochondrial alterations suggest that a potential target worth exploring for neuroprotective therapies are the ones that can preserve mitochondrial functions in PD. Here, we provide a recent update on potential drugs that are known to block mitochondrial dysfunctions in various experimental models and those that are currently under clinical trials for PD. We also review novel mitochondrial survival pathways that provide hope and promise for innovative neuroprotective therapies in the future that can be explored as possible therapeutic intervention for PD pathogenesis.

Keywords

Parkinson's disease; mitochondrial dysfunction; coenzyme Q10; creatine; PGC-1 α ; sirtuins

MITOCHONDRIAL DYSFUNCTION AND PARKINSON'S DISEASE

Numerous theories have been suggested for degeneration of the nigrostriatal dopaminergic neurons in PD amongst which the role of mitochondrial dysfunction gains strongest support because mitochondria are central to a number of processes thought to be integral to PD pathophysiology. Evidence for mitochondrial dysfunction in idiopathic PD comes from a 30 to 40% decrease in complex I activity of the mitochondrial electron transport chain and reduced immunohistochemical staining for complex I subunits in patients.^{1–5} There is also evidence for misassembly of complex I due to a differential decrease in the 8 kD subunit in postmortem PD brains, as well as increased oxidative damage to complex I subunits, and

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reduced rates of electron transfer through complex I.⁶ Impairment of complex I activity has been detected in the substantia nigra (SN), as well as other brain regions from PD patients.^{3,7,8} A systemic reduction in complex I activity has been also reported in blood platelets in multiple independent studies.⁹ Strong support for a mitochondrial DNA encoded defect comes from studies which showed that complex I defects from PD platelets are transferable into mitochondrial deficient cell lines known as “cybrids.”^{10,11} A major question that arises is whether impaired complex I activity represents a primary defect contributing to PD pathogenesis or whether it is secondary to disease or due to related issues, such as medication. The former seems to be true as complex I activity does not correlate with levodopa dosage, and is normal in other neurodegenerative diseases, such as Multiple System Atrophy (MSA), suggesting that it is not a nonspecific consequence of neurodegeneration.^{12,13} A number of studies provide genetic evidence that abnormalities in mtDNA (mitochondrial DNA) may contribute to PD pathogenesis. These involve the identification of a point mutation in mitochondrial 12SrRNA found in a pedigree with Parkinsonism, deafness and neuropathy.¹⁴ We found Parkinsonism occurred in association with the Leber’s optic atrophy due to a point mutation G11778A in mtDNA.¹⁵ Using laser capture micro dissection of SN dopamine neurons from early PD patients we identified that dopamine neurons harbor high levels of somatic mtDNA point mutations, particularly the subtypes predicted to result from oxidative stress, whereas mutation levels are low in controls and in late-stage PD (Lin MT et al., unpublished observation). Another important observation linking mitochondrial dysfunction in PD is associated with a marked age-dependent increase in mtDNA deletions in laser-captured dopaminergic neurons.¹⁶ The deletions are clonally expanded and are associated with respiratory chain deficiencies.¹⁷ The levels of the deletions fall within the range known to cause known mitochondrial disease implicating the importance of mtDNA deletions in disease development. In addition to ATP synthesis, mitochondria also are a major source of various kinds of reactive oxygen species. Additionally, unlike the nuclear DNA which is shielded by histones to protect from free radical damage and DNA repair, mitochondrial DNA lack histones that may render them vulnerable to oxidative stress induced free radical damage.¹⁸

Mitochondrial dysfunction due to exposures from environmental toxins has also been suggested in PD pathogenesis. The accidental discovery of the meperidine analogue MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) once used as a designer drug,¹⁹ has provided several insights on the potential role of mitochondrial complex I dysfunction in PD pathogenesis.²⁰ Similar to MPTP, other selective and more potent complex I inhibitors such as rotenone, pyridaben, and fenpyroximate when administered at low doses can reproduce many pathological features of PD, and lead to neurodegeneration in rodents, flies and in cell culture models.^{21–24} Additionally ingestion of a naturally-occurring complex I inhibitor annonacin, isolated from the plant species *Annona*, by humans has been suggested to lead to atypical parkinsonism in Guadeloupe²⁵ and experimental parkinsonism in rats.²⁶ Other pesticide toxins like paraquat which causes nonselective inhibition of all respiratory chain complexes, are also known to cause PD in both humans and experimental animal models.^{27–29}

On the familial front identification of pathogenic mutations in genes causing PD such as α -synuclein, parkin, DJ-1, PINK1, LRRK2, and HtrA2 either directly or indirectly link their

pathogenic roles with mitochondrial dysfunction, thus playing a predominant role in disease processes.³⁰ Gene duplications and pathogenic mutations in α -synuclein are associated with rare forms of PD.³⁰ Biochemical (Michael K Lee, personal communication) and electron microscopic studies in mice overexpressing human A53T α -synuclein show increased mitochondrial accumulation of human α -synuclein.³¹ These mice also develop significant mtDNA damage, impaired cytochrome oxidase (complex IV) activity leading to mitochondrial dysfunction and show increased susceptibility to neurodegeneration induced by mitochondrial toxins.³⁰ Both gene knockouts of parkin mouse and flies and overexpression of mutant parkin in flies and cells show mitochondrial abnormalities.^{30,32} Multiple independent studies have shown a direct link between parkin and its role in mitochondrial function,³⁰ especially its ability to interact with mitochondrial transcription factor A (Tfam) to enhance mitochondrial biogenesis.³³ This is significant because a conditional knockout of Tfam cause progressive loss of nigrostriatal dopaminergic neurons in mice.³⁴ Mitochondrial localization of PD associated gene DJ-1 and its ability to impact mitochondrial functions by modulating oxidative damage induced by mitochondrial toxins further enforces the significance of mitochondria in PD.^{35–37} Furthermore, PINK1, a mitochondrial kinase either due to loss of function or pathogenic mutations results in mitochondrial dysfunction and neurodegeneration due to abnormalities in mitochondrial morphology, bioenergetics, and by modulating cytochrome c release to block apoptosis in numerous *in vivo* and cell culture models including patient cell lines.^{30,38,39} Recent identification of PD cases due to loss of function mutations observed in the mitochondrial serine protease HtrA2 and its functional role in the regulation of apoptotic pathways by interacting with inhibitory apoptotic proteins and PINK1 further strengthens the importance of mitochondria in disease development.^{40,41} Although a direct role of LRRK2 mutations causing PD and its role in mitochondrial dysfunction are yet to be established, association of a small fraction of LRRK2 with mitochondria is suggestive of its role in mediating mitochondrial functions⁴² that may be key in disease development. Thus, multiple lines of studies suggest a pathogenic role of familial PD linked mutations in compromising normal mitochondrial functions in PD pathogenesis.

THERAPEUTIC APPROACHES TARGETING MITOCHONDRIAL DYSFUNCTION IN PD

Because of the significant contribution of mitochondrial dysfunction in PD pathogenesis there has been considerable interest in developing drug targets that can alleviate mitochondrial abnormalities and render neuroprotective effects. A wide range of candidate drugs that target mitochondrial dysfunction have been studied in several experimental models of PD and other neurodegenerative disorders. Of these several drugs both Coenzyme Q10 (CoQ10) and creatine have shown tremendous potential and have made it to clinical trials for PD. CoQ10 is a lipid soluble endogenous compound that serves as a cofactor for the electron transport chain by accepting electrons from complex I, II and III.⁴³ It serves as a potent free radical scavenger in the inner mitochondrial membranes and microsomal lipid membranes by reducing α -tocopheroxyl radical and by regenerating α -tocopherol.⁴³ CoQ10 is also an obligatory cofactor for mitochondrial uncoupling proteins as they function by regulating ATP production and reducing free radical generation.⁴³ Interestingly, CoQ10

levels in platelets from PD patients are reduced and it correlates with deficits in mitochondrial complex I activity.⁴⁴ CoQ10 is also known to block death due to oxidative stress,⁴⁵ apoptotic cell death by blocking Bax association with mitochondria,⁴⁶ and inhibiting mitochondrial permeability transition pore⁴⁷ known to cause cell death by increased retention of mitochondrial calcium. We have demonstrated the efficacy of various formulations of CoQ10 in blocking nigrostriatal dopaminergic neurodegeneration using various neurotoxic paradigms and various ages of mice using the MPTP model of PD.^{48,49} Additionally, oral administration of CoQ10 has shown very promising effects in phase II clinical trials for PD in a small group of de novo patients.⁵⁰ The Unified Parkinson's Disease Rating Scale (UPDRS) demonstrated dose dependent reduction in disease progression without significant side effects following CoQ10 administration which was consistent with increases in plasma concentrations of CoQ10. Although the phase III trials to further establish the efficacy of CoQ10 in a large population of PD patients are currently underway, the studies so far clearly indicate its potential as a promising therapeutic drug for PD.

Creatine is a guanidine compound and serves as a crucial energy reservoir for ATP and is a component of the creatine-phosphate system. Most of the creatine is found in the skeletal muscle and is taken up into various organs including brain by specific creatine transporters, and serves as a substrate for mitochondrial and cytosolic creatine kinase.⁵¹ It is suggested that the creatine enables mitochondrial creatine kinase to remain functionally in octameric state to inhibit the mitochondrial permeability transition pore and block apoptosis.⁵² Oxidative stress induced free radicals enable the octameric form of mitochondrial creatine kinase to convert to a dimeric state, which causes opening of the permeability transition pore to mediate cell death.⁵³ However, the neuroprotective function of creatine/phosphocreatine through creatine kinase-mitochondrial permeability transition pore system has been challenged, and instead it is suggested that creatine and phosphocreatine enhances cytosolic high energy phosphates that maintain ATP levels during oxidative stress induced neurodegeneration.^{54,55} Nevertheless, creatine has been shown in multiple independent studies to block neuronal death and increase lifespan in experimental animal models of neurodegenerative disorders.⁴³ Creatine has also been used in clinical trial for de novo PD patients and has demonstrated a marginal but statistically significant improvement based on UPDRS scale in creatine group compared to placebo treatment.⁵⁶ This study has led to a randomized multicenter clinical trial for creatine that is currently underway.⁵⁷ Although a detailed mechanistic role for the efficacy of creatine in PD models is lacking, it may help maintain dysfunctional energy metabolism possibly due to mitochondrial dysfunction. This is very important because sophisticated microarray analysis demonstrates intriguing differences in expression of genes involved in energy metabolism in SN dopamine neurons compared to other dopaminergic neurons.⁵⁸ Considering these aspects another potential strategy for neuroprotective therapy in PD is to deliver combination of two or more drugs. Studies from patients with mitochondrial disorders⁵⁹ and animal models of PD using the combinatorial approach have shown additive effects.⁶⁰ Our studies using combination of creatine and CoQ10 show significant synergistic neuroprotective effects in the MPTP-mouse model of PD than when administered singly (Yang et al., unpublished results). Our data further suggests the improved efficacy of combinatorial drug therapy and warrants future clinical trials involving combination of CoQ10 and creatine for PD.

Additionally, recent studies from our group also provide the therapeutic potential of a novel, cell permeable, mitochondrially targeted peptide antioxidant SS-31, in mouse models of Amyotrophic Lateral Sclerosis (ALS)⁶¹ and PD (Yang et al., unpublished results). SS-31 protects against oxidant-induced mitochondrial dysfunction and apoptosis in neuronal cell lines.⁶² Murphy and colleagues developed the mitochondrially targeted antioxidant MitoQ (a derivative of mitochondrial quinoline) that accumulates in the mitochondria and converts hydrogen peroxide to H₂O and O₂, to reduce toxic insults from free radicals in the mitochondria and has been shown to be effective in numerous *in vivo* models of mitochondrial dysfunction.⁶³ Currently clinical trials for MitoQ in PD patients are underway in New Zealand and the results are awaited with much anticipation. Similar neuroprotective strategies involving drugs directly targeted to mitochondria holds promise for PD and other neurodegenerative disorders where mitochondrial dysfunction plays a major role in disease pathogenesis.

The recent identification of novel cellular targets that modulate mitochondrial survival pathways also suggests the potential of these signal transduction pathways to be explored as future drug targets. PPAR-gamma coactivator 1alpha (PGC-1α) has been implicated in mitochondrial biogenesis and respiration through its ability to control number of genes such as NRF-1,-2 (Nuclear Respiratory Factor-1,-2), and Tfam.⁶⁴ PGC-1α null mice show enhanced susceptibility to MPTP-induced dopaminergic neurotoxicity whereas PGC-1α is required for induction of many ROS-detoxifying enzymes to serve as a master regulator of ROS metabolism.⁶⁵ The regulation of mitochondrial functions through the PGC-1α pathway enables it to be an attractive target for therapeutic intervention. Additionally identification of the drugable class of NAD (nicotinamide adenine dinucleotide)-dependent histone deacetylases and mono-ADP ribosyltransferases known as Sirtuins has yielded great interest due to their role in aging, mitochondrial functions, metabolism and stress tolerance.⁶⁶ There are seven Sirtuin family members (SIRT1-7) identified so far and the functions of these are still being identified. Of these SIRT1 is the most studied enzyme, and its activation has been demonstrated to deacetylate PGC-1α to induce mitochondrial biogenesis.⁶⁷ SIRT1 activation has also shown to be protective against neurodegeneration in models of Alzheimer's disease and ALS.⁶⁸ Recently using potent pharmacological inhibitors and genetic inhibition of SIRT2 via small interfering RNA rescued against α-synuclein induced PD in both flies and cell culture models.⁶⁹ Although this study emphasize the potential of SIRT2 inhibitors in ameliorating PD the molecular mechanisms are unclear and is thought due to the ability of promoting inclusion body formation by SIRT2 inhibition that lead to cell survival. There are also two mitochondrial sirtuins SIRT3 and 4, which have been shown to regulate acetylCo-A synthetase-2 and glutamate dehydrogenase activities.⁶⁶ A recent study has shown that the mammalian NAD biosynthetic enzyme Nampt (NAM phosphoribosyltransferase) can rescue cell death against genotoxic stress through the mitochondrial SIRT3 and 4 providing a link between cellular metabolism and apoptosis.⁷⁰ Although a direct correlation of mitochondrial sirtuins (SIRT3 and 4) with PD pathogenesis is yet to be established. Nonetheless, due to the crucial role of SIRT3 and 4 in regulation of key mitochondrial functions involved in cell death makes them an attractive therapeutic target in treating mitochondrial dysfunction-induced neurodegeneration in PD.

CONCLUSION

Although the etiopathogenic mechanisms for PD are not fully understood a substantial evidence for mitochondrial dysfunction in disease development are accumulating. This suggests that therapies which target to block mitochondrial dysfunction hold great promise as a treatment measure. Preliminary clinical trial data on CoQ10 and creatine for PD show exciting results, however, experimental studies emphasizes the need of combinatorial therapies in the future that may provide improved efficacy. Exploitation of novel targets such as PGC-1 α and the sirtuin family of enzymes that are known to modulate aging, mitochondrial biogenesis, metabolic homeostasis and cell death may serve as an effective measure of therapy for PD and other mitochondrial dysfunction disorders.

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