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Mitochondria targeted therapeutic approaches in Parkinson's and Huntington's diseases

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ABSTRACT

Substantial evidence from both genetic and toxin induced animal and cellular models and postmortem human brain tissue indicates that mitochondrial dysfunction plays a central role in pathophysiology of the neurodegenerative disorders including Parkinson's disease (PD), and Huntington's disease (HD). This review discusses the emerging understanding of the role of mitochondrial dysfunction including bioenergetics defects, mitochondrial DNA mutations, familial nuclear DNA mutations, altered mitochondrial fusion/fission and morphology, mitochondrial transport/trafficking, altered transcription and increased interaction of pathogenic proteins with mitochondria in the pathogenesis of PD and HD. This review recapitulates some of the key therapeutic strategies applied to surmount mitochondrial dysfunction in these debilitating disorders. We discuss the therapeutic role of mitochondrial bioenergetic agents such as creatine, Coenzyme-Q10, mitochondrial targeted antioxidants and peptides, the SIRT1 activator resveratrol, and the pan-PPAR agonist bezafibrate in toxin and genetic cellular and animal models of PD and HD. We also summarize the phase II–III clinical trials conducted using some of these agents. Lastly, we discuss PGC-1α, TORC and Sirtuins as potential therapeutic targets for mitochondrial dysfunction in neurodegenerative disorders. This article is part of a Special Issue entitled 'Mitochondrial function and dysfunction in neurodegeneration'.

Introduction

Neurodegenerative disorders are characterized by the loss of specific neuronal population, impairment of cognitive and locomotion functions, motor in coordination, and impaired behavior and personality. Accumulations of mutant proteins such as α-synuclein, and mutant huntingtin (Htt) are major pathological hallmark in Parkinson's disease (PD) and Huntington's disease (HD) respectively. A large body of evidence suggests a central role of mitochondrial dysfunction in the pathophysiology of these chronic neurodegenerative disorders. Here we discuss the role of mitochondrial dysfunction, mitochondrial bioenergetics, mitophagy, mitochondrial fusion/fission and transcriptional dysregulation in the pathogenesis of these neurodegenerative diseases.

Mitochondrial dysfunction in Parkinson's disease (PD)

Several lines of evidence implicate mitochondrial dysfunction in the pathophysiology of PD, a chronic, progressive, age associated neurodegenerative disorder characterized by degeneration of dopaminergic neurons and the presence of α-synuclein containing Lewy Bodies in the nigrostriatal pathway (Beal, 2005; Lin and Beal, 2006). Several studies reviewed below implicate mitochondrial dysfunction in PD pathogenesis.

Bioenergetic defects in PD

Evidence of specific involvement of mitochondrial dysfunction in the pathogenesis of PD was brought to the forefront following accidental infusions of the toxin 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 (Burns et al., 1985; Langston et al., 1983). Other complex-I inhibitors such as pyridaben, rotenone, fenazaquin, tebunfenpyrad, trichloroethylene and fenpyroximate cause degeneration of dopaminergic neurons in flys, rodents and humans, implicating mitochondrial dysfunction in PD (Chaturvedi and Beal, 2008a). These mitochondrial toxins inhibit the mitochondrial electron transport complex activity (Panov et al., 2005a), increase the mitochondrial permeability transition, reduce mitochondrial movement (Borland et al., 2008) and increase mitochondrial nitric oxide synthase (NOS) activity (Gomez et al., 2007), suggested involvement of mitochondrial complex-I in PD pathogenesis. More direct evidence for involvement of mitochondrial dysfunction in PD pathogenesis comes from studies of complex-I activity in PD patients. There is an impairment of mitochondrial complex-I activity in the substantia nigra (SN), platelets, and skeletal muscle of PD patients (Beal, 2005; Chaturvedi and Beal, 2008a; Lin and Beal, 2006).

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Mitochondrial DNA defects in PD

Reduced complex-I activity was also observed in cybrids containing mitochondrial DNA from PD patients, suggesting that mitochondrial DNA encoded genetic defects may be causative in some patients with PD (Gu et al., 1998). Interestingly, defects in complex-I activity are transferable from PD patients to cybrids, which showed reduced mitochondrial membrane potential, mitochondrial respiration, impaired mitochondrial biogenesis and abnormal Ca2+ handling (Gu et al., 1998; Keeney et al., 2009a; Trimmer and Bennett, 2009). Similarly, the levels and functions of the mitochondrial neuronal survival factor, which regulate the activity of complex-I are also decreased in brain tissue of PD patients (She et al., 2011). PD cybrids show reduced SIRT1 phosphorylation, reduced peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC-1α) levels, reduced cellular respiration and similar molecular and mitochondrial respiratory properties to those observed in mitochondria in PD brain (Borland et al., 2009; Esteves et al., 2010). Transfer of mtDNA from human genomic DNA to PD cybrids resulted in increased mtDNA gene copy numbers, Tfam and ETC. proteins, cellular respiration, and mitochondrial movement velocities and restored mitochondrial dysfunction (Keeney et al., 2009b). These studies in PD suggest direct involvement of mitochondrial dysfunction in PD pathogenesis.

Mitochondrial DNA mutations in PD

There is genetic evidence that suggests that, besides the mitochondrial complex-I defect, mutations in mitochondrial DNA (mtDNA) also play a role in the pathogenesis of PD. Several clonal, somatic mtDNA deletions/rearrangements mutations have been observed in the PD patients, implicating a role of mtDNA mutations in mitochondrial dysfunction and dopaminergic cell death (Gu et al., 2002; Ikebe et al., 1995; Simon et al., 2004). We observed the G11778A mtDNA point mutation which encodes a subunit of mitochondrial complex-I, in a family with parkinsonism (Simon et al., 1999). The presence of increased clonally expended mtDNA deletions is associated with respiratory chain deficiency in the substantia nigra of aged PD patients (Kraytsberg et al., 2006). Recently mutations in the mitochondrial biogenesis and mitochondrial homeostasis regulating mitochondrial chaperone mortalin were reported in PD patients (Burbulla et al., 2010). Evidence of mitochondrial dysfunction in PD has also come from conditional knockout "MitoPark" mice, which have a disrupted Tfam gene in DA neurons (Ekstrand et al., 2007). Mitopark mice have reduced mtDNA, reduced respiratory chain activity in DA neurons, a progressive loss of DA neurons and progressive PD phenotype, strongly supporting a role of respiratory chain dysfunction and mitochondrial dysfunction in PD pathogenesis (Ekstrand et al., 2007).

Gene mutations implicate mitochondrial dysfunction in PD

Besides mtDNA mutations and respiratory chain defects, pathogenic mutations in genes such as α-synuclein, parkin, UCHL-1, DJ-1, PINK-1, LRRK-2, NURR-1, tau, and HtrA2 directly or indirectly implicate a role of mitochondrial dysfunction in familial PD (Chaturvedi and Beal, 2008a; Kwong et al., 2006; Lin and Beal, 2006; Thomas and Beal, 2007). Several studies have suggested that α-synuclein is localized to mitochondria and its accumulation leads to increased ROS generation and impairment of complex-I in the substantia nigra and striatum of PD brain (Devi et al., 2008; Thomas and Beal, 2007). In a PD Drosophila model α-synuclein causes dysregulation of proteins involved in normal mitochondrial function (Xun et al., 2008). Similarly, α-synuclein over expressing transgenic mice and neuronal cells show impaired mitochondrial function, increased mtDNA damage, and impaired activity of cytochrome oxidase (Hsu et al., 2000; Song et al., 2004; Thomas and Beal, 2007). Interestingly, α-synuclein over expressing mice have increased susceptibility to MPTP, while knockout mice are resistant to mitochondrial respiratory chain inhibitors such as MPTP, 3-nitropropionic acid (3-NP) and malonate, suggesting involvement of mitochondria in α-synuclein mediated toxicity (Dauer et al., 2002; Klivenyi et al., 2006; Thomas and Beal, 2007).

Parkin (PARK2) is a ubiquitin E3 ligase, in which mutations result in early onset autosomal recessive juvenile PD (Thomas and Beal, 2007). Parkin knockout mice and flies exhibit decreased levels of proteins involved in mitochondrial function, reduced complex I and IV activity, reduced respiratory capacity, decreased mitochondrial integrity and increased susceptibility to the complex-I inhibitor rotenone (Casarejos et al., 2006; Palacino et al., 2004; Thomas and Beal, 2007). Mutations in PTEN induced kinase 1 (PINK1; PARK6) are associated with an autosomal recessive familial form of early-onset parkinsonism (Thomas and Beal, 2007). We observed that mutations in PINK1, or PINK1 knock-down lead to decreased mitochondrial respiration and ATP synthesis, and increased α-synuclein aggregation in cell based PD models (Liu et al., 2009). PINK1 knockout mice have decreased mitochondrial respiration activity, increased mitochondrial dysfunction, and enhanced susceptibility to oxidative stress (Gautier et al., 2008; Gispert et al., 2009). Loss-of-function mutations in the DJ-1 (PARK7) locus are associated with rare autosomal recessive early-onset PD (Thomas and Beal, 2007). DJ-1 knockout rodents and flies are more susceptible to cell death mediated by oxidative damage, while DJ-1 over expression has cytoprotective effects (Irrcher et al., 2010; Lavara-Culebras and Paricio, 2007). Similarly, DJ-1 knockout mice and human carriers of the DJ-1 mutation showed impaired mitochondrial respiration, increased mitochondrial ROS levels, reduced mitochondrial membrane potential, altered mitochondrial morphology, and accumulation of defective mitochondria (Krebiehl et al., 2010). Mutations in leucine-rich repeat kinase 2 (LRRK2; PARK8) is involved in sporadic and autosomal dominant early and late-onset PD. LRRK2 *Caenorhabditis elegans* mutants and G2019S-LRRK2 mutations harboring DA neurons, showed mitochondrial dysfunction and increased susceptibility to mitochondrial toxins (Nguyen et al., 2011; Saha et al., 2009). A recent study showed that LRRK2 mutations are associated with dynamin-like protein (DLP1) mediated mitochondrial fission (Wang et al., 2012a). Altogether, ample evidence suggests pivotal role of familial nuclear DNA mutations in mitochondrial dysfunction in PD pathogenesis (Table 1).

Mitochondrial dysfunction in Huntington's disease (HD)

Huntington's disease (HD) is an incurable and fatal autosomal-dominant neurodegenerative disease, characterized by neuronal degeneration mainly in the striatum with progressive behavioral and cognitive deficits and involuntary choreiform movements. HD is caused by an abnormal CAG repeat expansion in exon 1 of the *HD* gene, resulting in formation of an increased polyglutamine region in the mutant huntingtin (Htt) protein. How the mutant Htt protein elicits its toxic effects remains elusive, but several lines of evidence suggested involvement of transcriptional dysregulation, impaired mitochondrial energy metabolism, increased protein aggregation, and enhanced oxidative damage in HD pathogenesis (Browne and Beal, 2004).

Impaired bioenergetics and decreased mitochondrial complexes activities in HD

Several studies suggest involvement of mitochondrial dysfunction in HD (Chaturvedi and Beal, 2008a). A number of studies have shown that HD patients are in negative energy balance (Djousse et al., 2002; Goodman et al., 2008; Pratley et al., 2000). In addition, well-recognized metabolic deficits occur in the brain and muscle in HD patients. There is glucose hypometabolism on positron emission tomography imaging, even in presymptomatic gene carriers (Antonini et al., 1996; Feigin et