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Current perspective of mitochondrial biology in Parkinson's disease

Navneet Ammal Kaidery [a], Bobby Thomas [a, b, *]

[a] Departments of Pharmacology and Toxicology, Augusta, GA 30912, United States
[b] Neurology Medical College of Georgia, Augusta University, Augusta, GA 30912, United States

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ABSTRACT

Parkinson's disease (PD) is one of the most common neurodegenerative movement disorder characterized by preferential loss of dopaminergic neurons of the substantia nigra pars compacta and the presence of Lewy bodies containing α-synuclein. Although the cause of PD remains elusive, remarkable advances have been made in understanding the possible causative mechanisms of PD pathogenesis. An explosion of discoveries during the past two decades has led to the identification of several autosomal dominant and recessive genes that cause familial forms of PD. The investigations of these familial PD gene products have shed considerable insights into the molecular pathogenesis of the more common sporadic PD. A growing body of evidence suggests that the etiology of PD is multifactorial and involves a complex interplay between genetic and environmental factors. Substantial evidence from human tissues, genetic and toxin-induced animal and cellular models indicates that mitochondrial dysfunction plays a central role in the pathophysiology of PD. Deficits in mitochondrial functions due to bioenergetics defects, alterations in the mitochondrial DNA, generation of reactive oxygen species, aberrant calcium homeostasis, and anomalies in mitochondrial dynamics and quality control are implicated in the underlying mechanisms of neuronal cell death in PD. In this review, we discuss how familial PD-linked genes and environmental factors interface the pathways regulating mitochondrial functions and thereby potentially converge both familial and sporadic PD at the level of mitochondrial integrity. We also provide an overview of the status of therapeutic strategies targeting mitochondrial dysfunction in PD. Unraveling potential pathways that influence mitochondrial homeostasis in PD may hold the key to therapeutic intervention for this debilitating neurodegenerative movement disorder.

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* Corresponding author. Departments of Pharmacology & Toxicology and Neurology, Medical College of Georgia, Augusta University, Augusta, GA 30912, United States.
E-mail address: bthomas1@augusta.edu (B. Thomas).

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1. Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease after Alzheimer's disease affecting more than 4 million people worldwide (Dorsey et al., 2007). Clinically, PD is diagnosed by the presence of motor symptoms that includes rest tremor, rigidity, bradykinesia, and postural instability. The pathological hallmark of PD includes the progressive loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc), and the presence of cytoplasmic and neuritic inclusions named as Lewy bodies (LBs) and Lewy neurites (LNs) that are composed of α-synuclein (Lang and Lozano, 1998a, 1998b). Though the clinical hallmarks and pathological features of PD have been extensively studied, the exact molecular basis underlying DA neuron degeneration remains incompletely understood. Clinically PD cases are mostly sporadic and not classified traditionally as a genetic disease. However, rare familial forms have been identified that account for about 15% of all the PD cases. Despite these differences, both sporadic and familial forms of PD share common clinical, pathological and biochemical features and thus, potential insights into the function and dysfunction of PD-associated gene products have helped elucidate common pathways in PD pathogenesis. Accumulating evidence indicates that both sporadic and familial PD directly or indirectly coalesce on mitochondrial homeostasis thereby providing a link between mitochondrial dysfunction and PD pathogenesis (Banerjee et al., 2009). In the following sections, we discuss current perspectives of mitochondria in sporadic and familial PD and review therapeutic strategies targeting mitochondrial dysfunction in PD and the status of their clinical development.

2. Mitochondrial dysfunction in sporadic Parkinson's disease and the role of environmental toxins

Mitochondria are membrane-bound organelles found in every eukaryotic cell and are especially abundant in tissues with high-energy demands, such as brain and muscle. The major function of mitochondria is energy metabolism, predominantly oxidative phosphorylation (OXPHOS). The OXPHOS system comprises of 5 major multi-subunit complexes: complex I (NADH dehydrogenase-ubiquinone oxidoreductase), complex II (succinate dehydrogenase-ubiquinone oxidoreductase), complex III (ubiquinone-cytochrome c oxidoreductase), complex IV (cytochrome *c* oxidase), and complex V (ATP synthase). Although the mitochondrial OXPHOS system generates adenosine triphosphate (ATP), crucial for many essential cellular processes, mitochondria are the main cellular source of reactive oxygen species (ROS) and involved in calcium homeostasis and in the regulation and initiation of cell destructive pathways, which could underlie selective DA neurodegeneration in PD (Banerjee et al., 2009). Complex I is a major entry point of the respiratory chain and its deficiencies can be translated into a dramatic loss of bioenergetics functions leading to mitochondrial instability. Complex I also produce most of the ROS generated in intact mitochondria. There are numerous complex cellular mechanisms in place to help minimize the harmful effects of ROS, and yet intracellular ROS production is implicated in aging and many neurodegenerative pathologies (Grimm and Eckert, 2017). A link between complex I dysfunction and PD was established when several groups reported reduced complex I activity in the SN of the human brain, the major site of neuronal loss in PD (Schapira et al., 1990a, 1990b; Janetzky et al., 1994). Since then complex I defects has been reported in a variety of other tissues including frontal cortex, platelets, and skeletal muscle of patients with sporadic PD (Parker et al., 1989, 2008; Keeney et al., 2006; Krige et al., 1992; Benecke et al., 1993; Benecke et al., 1993, 1993; Bindoff et al., 1991; Blin et al., 1994; Cardellach et al., 1993). However, it is important to note that many laboratories could not confirm complex I defect in PD (Banerjee et al., 2009). Such inconsistency in the experimental data may likely be explained by significant methodological differences and individual variability of PD patients. The most compelling evidence of mitochondrial dysfunction as a causal source of PD was obtained in the 1980s following accidental exposure of drug abusers to an illicit drug contaminated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), an inhibitor of mitochondrial complex I, that resulted in irreversible parkinsonian syndromes almost indistinguishable from PD (Langston et al., 1983). The revelation of MPTP mechanisms has resulted in a gold mine of information regarding the involvement of mitochondria in PD. MPTP is metabolized to its toxic form MPP+ (1-methyl-4-phenylpyridinium ion) by mitochondrial monoamine oxidase B and undergoes selective uptake to DA neurons through the dopamine transporter (DAT) and is rapidly concentrated in the mitochondria by an energy-dependent process (Heikkila et al., 1984; Gainetdinov et al., 1997; Ramsay et al., 1987). Mitochondrial accumulation of MPP + specifically inhibits the oxidation of NAD (nicotinamide adenine dinucleotide) -linked substrates (Nicklas et al., 1985) by blocking the electron transfer through the complex I of the electron transport chain. Several studies reproduced the parkinsonian features induced by MPTP in both primate and murine models (Blesa et al., 2012). A considerable body of evidence epidemiologically links exposure to environmental toxicants like rotenone and paraquat (also known to inhibit mitochondrial respiration) to PD (Blesa et al., 2012; Tanner et al., 2011). The herbicide paraquat is a free radical generator that inhibits mitochondrial respiratory chain activity and causes DA neuron loss, accompanied by α-synuclein aggregation (Day et al., 1999; Manning-Bog et al., 2002). Similarly, chronic administration of the classic complex I inhibitor rotenone in rodents has been reported to produce multisystem degeneration including loss of nigrostriatal DA neurons and LB-like inclusions (Betarbet et al., 2000; Hoglinger et al., 2003; Lapointe et al., 2004).

The general perception is that complex I inhibition causes bioenergetics failure leading to ATP depletion and subsequent cell death. Supporting this view, MPP + treatment causes a significant depletion of ATP in whole brain and synaptosomal preparations (Scotcher et al., 1990; Cosi and Marien, 1998) (Fig. 1). It appears that complex I activity should be reduced more than 50% to cause a significant ATP depletion in non-synaptic brain mitochondria (Davey and Clark, 1996). However ATP is only mildly reduced

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