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Impairment of Mitochondria-Associated Processes in Parkinson's Disease

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Editorial

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INTRODUCTION TO PARKINSON'S DISEASE (PD)

Parkinson's disease (PD) is a neurodegenerative disorder, associated with a loss of dopaminergic neurons in the substantia nigra (SN) and a consequent depletion of dopamine (DA) within the striatum that cause motor abnormalities. In addition, the disorder can also affect emotions and thinking abilities [1,2]. The etiopathogenesis of PD has not yet been fully elucidated, however, research on mitochondrial dysfunction has shed light on the role of mitochondria in neuronal death. Exposure to complex I inhibitors such as: rotenone, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPP^+), and paraquat are known to develop a PD-like phenotype as a result of highly selective nigrostriatal dopaminergic degeneration in both humans and animals [3-5]. Most cases of Parkinson disease are sporadic and probably are the result of a combination of environmental exposures and genetic susceptibility. The remaining cases (15-20 %) are caused by inherited mutations (familial PD) in a number of genes which affect either protein metabolism or mitochondrial function, including Pink1, Parkin, DJ-1, and α-synuclein, thus highlighting that this dysfunction causes the disease. Moreover, it has been reported that old age is the largest risk factor for developing idiopathic PD [1,3]. It is possible due to mitochondrial failure that occurs with advancing age, accumulates within substantia nigra neurons, to reach a critical threshold in old age. Since mitochondrial functions have been reported to be affected in both sporadic and familial PD it has already become widely accepted that these alternations play a key role in the disease pathogenesis [3,4]. Here we provide an overview of mitochondrial abnormalities, which has been implicated to be important for the neurodegenerative processes of sporadic PD.

The main function of mitochondria is the production of adenosine 5'-triphosphate (ATP), the cellular energy source, thorough oxidative phosphorylation. Beyond the generation of energy, mitochondria are also involved in many other cellular activities, such as metabolism, redox signalling, calcium buffering, and apoptosis [2]. As reviewed elsewhere [2,4] aberrant mitochondrial function is known to be associated with increased generation of reactive oxygen species (ROS), inhibition of mitochondrial electron transfer chain complexes' activity, decreased ATP production, caspase 3 release, and decreased mitochondrial DNA copy number. In post-mortem PD brains, particularly in SN, a decreased activity of respiratory chain complexes, an increased level of oxidative damage and inflammation, and the presence of Lewy bodies - aggregates of abnormal protein - are found [6]. The dopaminergic neuron death in PD therefore is likely to be a consequence of mitochondrial dysfunction in combination with other disturbances, including oxidative stress, missfolding and aggregation of proteins such as α-synuclein, defects in protein degradation, and inflammation. Nevertheless, these cellular abnormalities have been demonstrated to be interconnected [1].

RESPIRATORY DEFICIENCY

A link between sporadic PD and dysfunctional respiratory chain, in particular an inhibition of complex I activity, is well established [1-4]. Research on the activity of the mitochondrial respiratory chain complexes in PD samples has revealed impaired complex I, complex II+III and complex IV in SN dopaminergic neurons as well as platelets, muscle and lymphocytes, suggesting their systemic inhibition [7].

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OXIDATIVE STRESS AND DOPAMINE METABOLISM

Oxidative stress occurs because of an overproduction of free radicals or a failure of mechanisms that limit their accumulation. It is widely accepted that the inhibition of complex I disrupts mitochondrial electron transport, leading to a decreased mitochondrial ATP production, and to an increased generation of reactive oxygen species (ROS) including the superoxide anion, hydrogen peroxide, and the hydroxyl radical [8]. The mitochondrial ROS then cause damage to DNA, proteins and lipids, thereby altering their properties. The accumulation of products of the macromolecules' oxidation such as aldehydes and isoprostanes, protein carbonyls, and base adducts from DNA has been detected in the brain tissue of animals treated with a complex I inhibitor - rotenone [9]. Oxidative damages to lipids, proteins and DNA has been revealed also in the brain from PD patients [10,11]. Moreover, oxidative damages to mtDNA, constituents of the respiratory chain and other mitochondrial factors have been shown to trigger a circle between mitochondrial impairment and oxidative stress. Indeed mitochondria are both a source and a target of ROS [8]. There is still inclusive evidence about the preferential loss of nigrostriatal DA neurons in PD, compared to other nearby catecholaminergic neurons. Considering that 80 % of the total brain DA is concentrated in striatum, their high vulnerability to oxidative damages probably is due to tremendous oxidative stress associated with redox cycling of catechols to reactive aldehydes [1,4]. A reactive dopamine metabolite 3,4-dihydroxyphenylacetaldehyde (DOPAL) has been demonstrated to preferentially cause degeneration of dopaminergic neurons leading to PD development [12] and an increased ratio [DOPAL]:[DA] was found in postmortem PD brains [13]. In addition to excessive free radical formation the depletion of reduced glutathione, the brain's primary antioxidant, has been found selectively in the SN of PD patients [14], even by 40 %, compared to age-matched controls [15].

DEFECTS IN PROTEIN DEGRADATION

In addition to the loss of dopaminergic neurons in the SN, another hallmark of Parkinson's disease is Lewy bodies, predominantly composed of abnormal misfolded α-synuclein. In the cytopathology of PD α-synuclein has been demonstrated to mediate disruption of cellular homeostasis, for example by increasing mitochondrial-calcium uptake, and to induce neuronal death by apoptosis and caspase-independent cell death [2,16]. There are two main pathways within neurons for degradation and removal aberrant proteins: ubiquitin–proteasome system (UPS) and autophagy. However, both systems are linked to mitochondrial function since they are highly energy dependent processes. Both the proteasome and autophagy processes have been implicated to be dysregulated in Parkinson's disease. Consequently, impairment of protein degradation occurs downstream of mitochondrial-dependent ATP depletion, which leads to an inefficient clearance of α-synuclein [2,3].

Proteasomal dysfunction is a key feature of PD pathogenesis. In postmortem tissue, a reduction in proteasome activity in the SN of PD patients has been demonstrated [17]. In addition to the reduction of energy provision the direct inhibition of the proteasome through ROS, excessively produced due to mitochondrial impairment, and an increase in mutant α-synuclein also occurs [18].

Oligomeric toxic species of α-synuclein and damaged mitochondria should be degraded through the autophagy pathway. However, due to an impaired microtubular network the autophagic clearance of α-synuclein oligomers is also inhibited and the toxic feed-back loop potentiates the neurodegeneration [18]. In a PD context, there is controversy surrounding the role of mitochondria-specific autophagy (mitophagy) in the demise of dopaminergic neurons. When damaged mitochondria, which would activate caspases and consequently apoptosis, are cleared, then the mitophagy is beneficial, since it prevents cell death. However, excessive and dysregulated autophagy, which cause a leakage of lysosomal enzymes, can initiate mitochondrial permeabilization, caspase activation and thereby cause apoptosis [2].

APOPTOSIS

In addition to an autophagic process the neuronal cell death apoptosis has been shown to occur through an intrinsic mitochondrial pathway, and more recently, some evidence suggests the contribution of endoplasmic reticulum (ER) stress [2].

Pro-apoptotic Bax protein, activated following DNA damage, induces the release of cytochrome c into the cytosol, with ensuing caspase activation and cell death [19]. Detection of several alterations of this molecular cascade in postmortem brain from PD patients, including complex I deficiency, ROS production, oxidative damage to lipids, proteins and DNA, Bax activation and activation of caspase-3 and -9, supports the scenario to the SN dopaminergic neurodegeneration [20].

Recent reports have shed light on an interesting correlation between ER and mitochondria stress emphasizing the role of crosstalk between ER -mitochondria Ca^{2+} crosstalk in Parkinson's disease. Since α-synuclein has been demonstrated to be present not only in cytosol but also in mitochondria-associated ER membranes, its overexpression is likely to trigger stress responses leading to Ca^{2+} influx into mitochondria from the ER [16,21]. Because of this a mitochondrial permeability transition pore is opened, cytochrome c is released and apoptosis occurs [22]. Interestingly, inhibition of ER Ca^{2+} release by dantrolene has been demonstrated to prevent MPP+ induced mitochondrial-dependent caspase activation, suggesting that the mitochondrial calcium uptake from ER, occurring under ER and mitochondrial stress conditions, could be responsible for apoptotic cell death during neurodegeneration [23].

NEUROINFLAMMATION

Based on data from both animal and human studies it has been established that inflammatory processes are involved in

the progressive degeneration of the dopaminergic nigrostriatal pathway and therefore contribute to the pathophysiology of Parkinson's disease [24]. Microglial activation has been demonstrated both in PD animal models [25] and in the striatum and substantia nigra of patients with Parkinson's disease [26]. Additionally pro-inflammatory cytokines such as interleukin-1 beta, interleukin-6 and tumor necrosis factor alpha have been found in the cerebrospinal fluid and ganglia of PD patients [27]. However, it is not clear whether neuroinflammation plays a primary role or is entirely secondary in PD pathogenesis [24].

In this short review we summarized the current knowledge concerning the interconnectedness of mitochondrial dysfunction and neurodegenerative processes in sporadic PD. While the mechanisms remain incompletely elucidated, the activity aimed at understanding them has been growing, which raises the prospects of novel mitochondria targeted therapies for the treatment of Parkinson's disease.

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