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Review

The impact of reactive oxygen species and genetic mitochondrial mutations in Parkinson's disease

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ABSTRACT

The exact pathogenesis of Parkinson's disease (PD) is still unknown and proper mechanisms that correspond to the disease remain unidentified. It is understood that PD is age-related; as age increases, the chance of onset responds accordingly. Although there are no current means of curing PD, the understanding of reactive oxygen species (ROS) provides significant insight to possible treatments. Complex I deficiencies of the respiratory chain account for the majority of unfavorable neural apoptosis generation in PD. Dopaminergic neurons are severely damaged as a result of the deficiency. Symptoms such as inhibited cognitive ability and loss of smooth motor function are the results of such impairment. The genetic mutations of Parkinson's related proteins such as PINK1 and LRRK2 contribute to mitochondrial dysfunction which precedes ROS formation. Various pathways are inhibited by these mutations, and inevitably causing neural cell damage. Antioxidants are known to negate the damaging effects of free radical overexpression. This paper expands on the specific impact of mitochondrial genetic change and production of free radicals as well as its correlation to the neurodegeneration in Parkinson's disease.

Contents

Abbreviations: αS, α-synuclein; CNS, central nervous system; DA, dopamine; DAergic, dopaminergic; DAT, dopamine transporters; DDC, dopadecarboxylase; DMT_1, divalent metal transporter 1; ELLDOPA, The Earlier versus Later Levodopa Therapy; *ELO1*, *ELO2*, *ELO3*, elongase genes; EOP, early onset Parkinsonism; EP, ethyl pyruvate; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; ETC, electron transport chain; GFAP, glial fibrillary acidic protein; GSH, glutathione; iPSC, induced pluripotent stem cell; LA, lipoic acid; LD, levodopa; $LRRK_2$, leucine-rich repeat kinase 2; L-DOPA, L-3,4-dihydroxyphenylalanine; MAO-B, monoamine oxidase B; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NO, nitric oxide; Nrf2, erythroid 2-related factor 2; OS, oxidative stress; PD, Parkinson's disease; *PARK7*, parkinson protein 7; PARP, poly (ADP-ribose) polymerase; PBMCs, peripheral blood mononuclear cells; $PINK_1$, putative kinase 1; PI_3K, phosphoinositol-3 kinase; PKG, cGMP-dependent protein kinase; PUFAs, polyunsaturated free fatty acids; ROS, reactive oxygen species; SNc, substantia nigra pars compacta; TH, tyrosine hydroxylase; UPC4, uncoupling protein 4; UPC5, uncoupling protein 5.

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1. Introduction

Free radicals are highly reactive molecules with unpaired electrons that can be detrimental to the body. Cells produce these molecular species which must be balanced with antioxidants in order to maintain homeostasis (Jezek and Hlavata, 2005). The human body produces small amounts of reactive oxygen species (ROS) in order to undergo normal physiological processes including critical roles in the immune system, stimulation of growth factors, and the development of an inflammatory response (Brieger et al., 2012; Krause and Bedard, 2008). ROS are also responsible for programmed cell death, known as apoptosis, in order to regulate cell production (Brieger et al., 2012). An issue arises when free radical concentration greatly out numbers antioxidant concentration. The inhibition of ROS must be established in order to prevent subsequent oxidative stress (OS) and thus protect against cell damage. OS is also the failure to restore the injury produced by ROS, which results in DNA damage (Henle and Linn, 1997), protein collapse, enzyme failure, and lipid destruction (Lee et al., 2012). Research suggests that nearly 50% of proteins have undergone oxidation in a human at the age of 80 years (Starke-Reed and Oliver, 1989). In addition, Harmon's mitochondrial free radical theory of aging, suggests that the mitochondria are a main source of ROS production (Harman, 1972). As any human progresses with age, the amount of OS increases due to the inability of defense mechanisms to work sufficiently (Kumar et al., 2012). Furthermore, it is also hypothesized that OS also provides the framework for neurological deterioration (Kumar et al., 2012).

All neurodegenerative diseases possess axonal degeneration, prior to the death of the cell body, which may result in the chronicity of the disease (Bjartmar and Trapp, 2001; Mcsharry, 2010). The susceptibility of axons, due to their structure and metabolic needs, increases the probability of oxidative damage (Lopez-Erauskin et al., 2011; Sherer et al., 2003; Testa et al., 2005). Parkinson's disease (PD) is a complex neurodegenerative disease that mainly inhibits smooth motor ability while also having a damaging effect on cognitive function (Foltynie et al., 2004). Disabled executive operations, the inability to be attentive, visuospatial performance, and working memory are areas that undergo drastic complications (Cooper et al., 1991). The prevalence of this ailment increases staggeringly with age. With a median age of onset at 60 years, roughly 1.4% of the population will develop PD, based on evaluations conducted in the Netherlands (de Rijk et al., 1995). The severe progression of PD is related to the substantial decrease of dopaminergic neurons located in the substantia nigra pars compacta (SNc) (Mori et al., 2006). Additionally, a 5–10% loss of dopamine (DA) neurons befalls each decade of aging (Fearnley and Lees, 1991). However, the process by which it occurs has not been established.

Within the last decade, genes related to PD such as PARK7 (DJ-1), Parkin, leucine-rich repeat kinase 2 ($LRRK_2$), and PTEN induced putative kinase 1 (PINK1) have been linked to the impairment of cellular processes due to the genetic mutation (Bonifati et al., 2003; Kitada et al., 1998; Paisan-Ruiz et al., 2004; Valente et al., 2004). Neurons and neuroglia cells are intensely more receptive to oxidative impairment compared to other body tissue (Kumar et al., 2012). OS corrupts susceptible neurons, progressing to neural breakdown, making this process a probable underlying cause of neurodegenerative diseases such as PD (Moore et al., 2005). Furthermore, additional organelles have been associated with the generation of ROS such as the endoplasmic reticulum (ER). According to Lee et al., the significant stimulation of toxicity related to the omission of lipid elongase genes (*ELO1*, *ELO2*, and *ELO3*), located within the ER, results in ROS buildup (Lee et al., 2011). Disruption of lysosomal membrane permeability also contributes to the pathogenesis of PD. Mitochondria produced ROS, are responsible for irregular permeability and lysosomal structural deficiencies, which may eventually result in neuron cell death (Vila et al., 2011). Though the precise mechanism corresponding to ROS generation related to PD is unknown, it is theorized that neural degeneration can result in an overabundance of free radical concentration due to mitochondrial dysfunction (Adam-Vizi, 2005). This review aims to expand on the novel role of this specific organelle.

2. Mitochondrial role in ROS production in neurons

Oxidative phosphorylation within the mitochondria accounts for the majority of ATP production in cells. Mitochondrial dysfunction is closely related to the increased ROS formation in PD (Yan et al., 2012). The deterioration of dopaminergic (DAergic) neurons is triggered by the pathogenic mitochondrial mechanism enabling OS production. Coincidentally, the postmortem brain tissue of the substantia nigra in PD patients indicates stimulated levels of lipid peroxidation, high oxidation of proteins and DNA, and reduction of glutathione which strengthens the notion that this type of stress is involved (Reale et al., 2012). The rate limiting enzyme involved in catecholamine production is enzyme tyrosine hydroxylase (TH), which is responsible for the catalysis of tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA) (Molinoff and Axelrod, 1971). Additionally, this enzyme serves as a reliable indicator of dopaminergic neuron depletion (Reale et al., 2012). TH is known to stimulate the generation of hydroxyl radicals (Haavik et al., 1997), promoting the neurodegeneration of DA neurons (Fig. 1). The mitochondrion remains a site of ROS since free radicals, including superoxide, are produced via oxidative phosphorylation within the respiration chain. Consequently, neurons that do not acquire an efficient quantity of ATP undergo increased ROS formation as well as cell death of mitochondria signaling pathways which inhibit devices, like synapses, from receiving proper amounts of energy (Braun, 2012; Correia et al., 2012; Cozzolino et al., 2012).

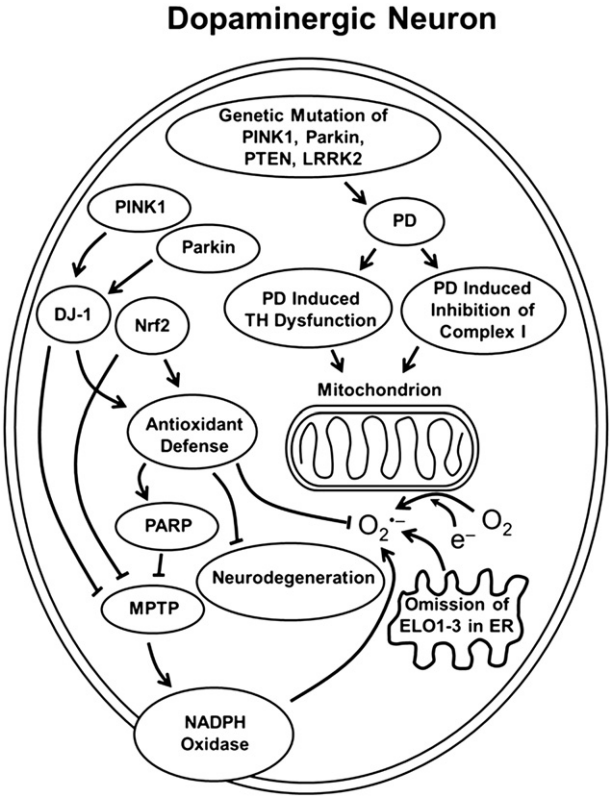

Fig. 1. The schematic demonstrates an intracellular oxidative stress (OS) pathway induced by Parkinson's disease (PD) and a corresponding antioxidant defense system in dopaminergic neurons.