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Review article

Oxidative damage to macromolecules in human Parkinson disease and the rotenone model

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ABSTRACT

Parkinson disease (PD), the most common neurodegenerative movement disorder, is associated with selective degeneration of nigrostriatal dopamine neurons. Although the underlying mechanisms contributing to neurodegeneration in PD seem to be multifactorial, mitochondrial impairment and oxidative stress are widely considered to be central to many forms of the disease. Whether oxidative stress is a cause or a consequence of dopaminergic death, there is substantial evidence for oxidative stress both in human PD patients and in animal models of PD, especially that using rotenone, a complex I inhibitor. There are many indices of oxidative stress, but this review covers the recent evidence for oxidative damage to nucleic acids, lipids, and proteins in both the brain and the peripheral tissues in human PD and in the rotenone model. Limitations of the existing literature and future perspectives are discussed. Understanding how each particular macromolecule is damaged by oxidative stress and the interplay of secondary damage to other biomolecules may help us design better targets for the treatment of PD.

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Abbreviations: O_2^-, superoxide; $OH^\bullet$, hydroxyl radical; ATP, adenosine-5′-triphosphate; ROS, reactive oxygen species; ETC, electron transport chain; PD, Parkinson disease; SN, substantia nigra pars compacta; DA, dopamine; LB, Lewy body; L-DOPA, levodopa, l-3,4-dihydroxyphenylalanine; VTA, ventral tegmental area; PUFA, polyunsaturated fatty acid; CSF, cerebrospinal fluid; MDA, malondialdehyde; HNE, 4-hydroxy-2-nonenal; mtDNA, mitochondrial DNA

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Oxidative damage: An overview

Free radicals are chemical species that contain one or more unpaired electrons in their outer orbit. Although free radicals may be very reactive, their reactivity varies depending on the particular species. Collectively, reactive oxygen species (ROS)[1] include both oxygen radicals and nonradical derivatives of O_2 that are oxidizing agents and/or are easily converted into radicals. Three biologically important ROS in mammalian cells are superoxide (O_2^-), hydrogen peroxide (H_2O_2), and the hydroxyl radical ($OH^\bullet$, Fig. 1). Each plays a significant physiological role in the body; for instance, as part of the artillery of the immune system, O_2^- is involved in killing invading microorganisms [1], and H_2O_2 is an important signaling molecule.

In eukaryotic cells, mitochondria are the major source of oxygen radicals, which are formed during oxidative adenosine-5′-triphosphate (ATP) production. The mitochondria use about 80% of the O_2 we inhale [2–4] and during the course of oxidative phosphorylation, molecular O_2 is reduced to H_2O. However, there is normally also leakage of a very small proportion of electrons from the electron transport chain (ETC) directly to O_2 to produce O_2^-. Of the O_2 reduced in the mitochondria, 1–3% may form O_2^-; however, this may be an overestimation [5]. The relative role of each ETC complex in forming O_2^- differs by tissue, yet complex I is a major source of O_2^- in the brain [6].

Despite the requirement for O_2 to generate ATP in aerobes, oxidative toxicity/damage occurs even in ambient levels of O_2. In a seminal paper in 1956, Denham Harman first proposed that oxygen radicals were responsible for the damaging effects of O_2, and since then, the free radical theory of aging has expanded to include the mitochondrion's role in the production of ROS [7]. Because superoxide can be toxic, nearly all organisms living in the presence of oxygen contain isoforms of the superoxide-scavenging enzyme, superoxide dismutase, which catalyzes the dismutation of superoxide into O_2 and H_2O_2 [6,8]. Although H_2O_2 is not a free radical, it is a reactive oxygen species and it still may be dangerous because it can easily be converted, by interacting with Fe^{2+}, into $OH^\bullet$, one of the most destructive free radicals. ROS may also be produced by monoamine oxidase in the outer mitochondrial membrane, as well as by specific Krebs cycle enzymes [6]. In general, ROS can either directly cause damage or participate in unwanted side reactions, resulting in cell damage.

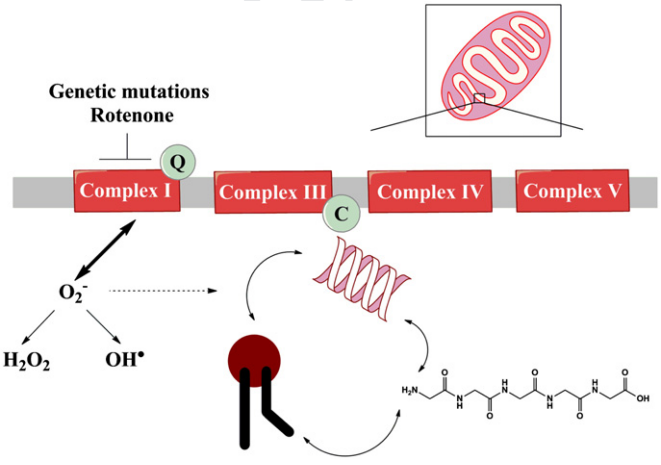

Fig. 1. Mitochondrial dysfunction may lead to oxidative damage of macromolecules. Genetic mutations or environmental factors inhibit complex I activity and/or result in mitochondrial impairment. Mitochondrial dysfunction produces ROS. The resultant ROS may damage macromolecules, including nucleic acids, lipids, and proteins. An oxidized macromolecule can then damage another macromolecule, leading to a vicious cycle of oxidized products.

An imbalance between the production of ROS and the ability to detoxify the reactive intermediates results in oxidative stress. Excessive ROS can damage all macromolecules, including nucleic acids, lipids, and proteins, leading to an overall progressive decline in physiological function. Nucleic acids, both RNA and DNA, are subject to oxidative damage, with DNA damage occurring most readily at guanine bases. Free radical damage to fatty acids (known as lipid peroxidation), results in lipid degradation and cell membrane damage. ROS attack on proteins may be reversible or irreversible, often leading to either a loss function or protein aggregation. Oxidative damage has been characterized and implicated in aging [9], as well as in a variety of diseases such as cancer [10] and neurological disorders, including Parkinson disease (PD) [11].

Direct measurement of ROS is often difficult because of their short life span and there is not a practical method for ROS measurement in the living human brain. Thus, much of the current evidence for oxidative stress in neurological disease comes from measurement of oxidative modifications of various cellular components. In PD, there is considerable evidence for ROS-mediated damage in postmortem brain samples as well as in other tissues, even outside of the central nervous system. Moreover, animal models also provide convincing evidence for oxidative stress in PD. In fact, many of the current animal models of PD utilize oxidative stress as a means to selectively damage the nigrostriatal dopamine system to replicate the clinical, pathological, and biochemical features of PD [12]. In this regard, fly, rat, and nonhuman primate models using rotenone, a mitochondrial complex I inhibitor, replicate many of the core characteristics of PD and provide evidence for oxidative stress [12]. Here we review the recent evidence for oxidative damage to nucleic acids, lipids, and proteins in both the brain and the peripheral tissues in human PD and in the rotenone model thereof.

Introduction to Parkinson disease

PD is the most common neurodegenerative movement disorder. A central pathological hallmark of PD is the selective loss of dopamine (DA) neurons in the substantia nigra pars compacta (SN). These dopaminergic neurons are required for proper motor function, and their loss is associated with tremor, rigidity, bradykinesia, and postural instability. To date, treatments address only the symptoms; they do not alter the inexorable progression of the disease—and PD patients continue to experience a higher mortality rate compared to the general population [13–15]. Even with expert treatment, PD patients typically deteriorate over time and endure considerable motor and cognitive disability in the years after diagnosis.

A second neuropathological hallmark of PD is the Lewy body (LB), which is a cytoplasmic spherical proteinaceous inclusion. LBs have been reported to contain various proteins including but not limited to α-synuclein, ubiquitin, parkin, and neurofilaments [16–18]. Whether LBs are neuroprotective or pathogenic in PD is controversial and is reviewed elsewhere [18]. The mechanisms by which α-synuclein and other proteins aggregate to form Lewy

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