Damage to dopaminergic neurons by oxidative stress in Parkinson's disease (Review)

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Abstract. Oxidative stress is increasingly recognized as a central event contributing to the degeneration of dopaminergic neurons in the pathogenesis of Parkinson's disease (PD). Although reactive oxygen species (ROS) production is implicated as a causative factor in PD, the cellular and molecular mechanisms linking oxidative stress with dopaminergic neuron death are complex and not well characterized. The primary insults cause the greatest production of ROS, which contributes to oxidative damage by attacking all macromolecules, including lipids, proteins and nucleic acids, leading to defects in their physiological function. Consequently, the defects in these macromolecules result in mitochondrial dysfunction and neuroinflammation, which subsequently enhance the production of ROS and ultimately neuronal damage. The interaction between these various mechanisms forms a positive feedback loop that drives the progressive loss of dopaminergic neurons in PD, and oxidative stress-mediated neuron damage appears to serve a central role in the neurodegenerative process. Thus, understanding the cellular and molecular mechanisms by which oxidative stress contributes to the loss of dopaminergic neurons may provide a promising therapeutic approach in PD treatment.

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1. Introduction
Parkinson's disease (PD) is the most common movement disorder and is clinically characterized by motor symptoms, including bradykinesia, resting tremors, rigidity and postural instability, caused by the progressive degeneration of dopaminergic neurons in the substantia nigra (SN) (1). While the underlying mechanisms contributing to the damage of dopaminergic neuron remains poorly understood, oxidative stress has been considered to be strongly linked to the loss of neurons in PD (2,3). Studies in postmortem brains have shown the increased levels of 4-hydroxyl-2-nonenal (HNE), a by-product of lipid peroxidation, carbonyl modifications of soluble proteins, and the DNA and RNA oxidation products 8-hydroxy-deoxyguanosine and 8-hydroxy-guanosine in the SN of PD patients (4-8). The link between oxidative stress and the pathogenesis of PD is further supported by animal models induced by neurotoxins, including 1-methyl-4-phenylpyridinium (MPP+), rotenone and 6-hydroxydopamine (6-OHDA), which cause the production of ROS and the progressive loss of dopaminergic neurons (9-11). Oxidative stress is an imbalance in the rate of reactive oxygen species (ROS) production and the rate of ROS scavenging, resulting in excessive accumulation of...
ROS (12). These ROS attack all macromolecules, including lipids, proteins and nucleic acids, and trigger an inflammatory response, resulting in cellular damage, mitochondrial dysfunction, oxidative DNA injury and neuroinflammation, all of which have been considered as key contributors in the neurodegenerative process of PD (13-16). Oxidative stress appears to be a central event associated with the development of PD by activating the cascade of events leading to the degeneration of these dopaminergic neurons. The present review stresses the fundamental pathological pathway of oxidative stress in the development of PD, in order to gain a better understanding of the underlying mechanisms, and to provide available evidence and future directions for potential effective therapeutic targets with enhanced efficacy in the prevention and treatment of PD.

2. Mitochondrial complex inhibition and ROS production

Mitochondria are important organelles for the maintenance of cellular homeostasis by generating and supplying energy for the cells through oxidative phosphorylation. The process of oxidative phosphorylation involves the interaction of unpaired electrons with molecular O2, resulting in the generation of a superoxide radical, an amphibolic radical that cannot easily pass through biological membranes (17,18). Subsequently, the radical O2− is converted by the mitochondrial superoxide dismutase or manganese superoxide dismutase to form hydrogen peroxide (H2O2) in the mitochondria (19). H2O2 is a relatively inactive compound that is released from the mitochondria into the cellular cytosol and nucleus where it contributes to oxidative stress. In the presence of reduced ferrous iron, H2O2 can be converted into the highly reactive hydroxyl radical, leading to further oxidative damage (20). It is widely accepted that complex I inhibition and a subsequent increase in the production of ROS is a leading cause responsible for the loss of dopaminergic neurons in PD (3,14,21). The first evidence for the link between complex I inhibition with subsequent oxidative stress and the pathogenesis of PD was the recognition that complex I inhibitor MPTP can cause acute and irreversible parkinsonian symptoms in humans (22). Subsequently, the molecular mechanism underlying the neurotoxicity of MPTP was also intensively studied. MPTP is a lipophilic molecule that can rapidly cross the blood-brain barrier. In the brain it is oxidized to form 1-methyl-4-phenylpyridinium (MPP+) by the blood-brain barrier. In the brain it is oxidized to form the radical O2−, which can be converted into the highly reactive hydroxyl radical, leading to further oxidative damage (20). It is widely accepted that complex I inhibition and a subsequent increase in the production of ROS is a leading cause responsible for the loss of dopaminergic neurons in PD (3,14,21).

3. Vulnerability of dopaminergic neurons to oxidative stress

The CNS contains a large number of mitochondria in order to meet the demands of high levels of energy consumption. Therefore, the iron content in CNS cells is particularly high, since numerous mitochondrial enzymes require iron to function, leading to the greater generation of ROS that contribute to oxidative stress and subsequently the degeneration of neurons (40). Iron promotes the generation of highly reactive oxygen species, resulting in further oxidative damage, particularly for nigral dopaminergic neurons that appear to exhibit increased sensitivity to iron-induced oxidative stress. Studies in postmortem brains of PD patients have shown higher levels of iron in the SN compared with that in controls (41,42). The link of oxidative iron dysregulation with the neurodegenerative process is also supported by PD animal models, where increased levels of iron and hydroxyl radicals could be detected in the SN (43). Administration of desferrioxamine, an iron chelator, significantly decreases the levels of iron in the brain and protects against neurodegeneration induced by iron and MPTP in PD mouse models (44), further supporting the contribution of iron in the neurodegenerative process of PD. Furthermore, the brain is enriched in lipids that participate in membrane fluidity and permeability, and mediate the inflammatory processes and apoptotic signals (45). The lipids are susceptible to ROS-mediated damage, particularly polyunsaturated fatty acids, which are the most prone to lipid peroxidation, resulting in the structural damage of membranes, consequent neuronal damage and ultimately, mortality (14). Oxidative stress-mediated death mechanism has been underlined in the pathogenesis of PD (39). Higher levels of malondialdehyde, a production of polyunsaturated fatty acid peroxidation in oxidative conditions, have also been reported in SN compared with that in other brain regions in PD (46). The lipid peroxidation marker, cholesterol lipid hydroperoxide, is also detected as significantly increased
in PD brains compared with that in control subjects (47). The reinforcement of peroxidation of polyunsaturated fatty acids to oxidative damage of dopaminergic neurons is also supported by the elevated levels of HNE detected in the SN and the cerebrospinal fluid of PD patients (5,48). HNE is a lipid peroxidation product contributing to apoptotic cell death via the activation of the caspase cascade and the subsequent induction of DNA fragmentation (49). HNE can also reduce the levels of glutathione (GSH) resulting in the vulnerability of the neurons to oxidative attack, since GSH is a major non-enzymatic antioxidant in the CNS (50). Additionally, other causal factors that are associated with the vulnerabilities of dopaminergic neurons to oxidative stress have been well documented (39). Taken together, these results indicate that the dopaminergic neurons are more vulnerable to oxidative attack. Although the mechanisms of oxidative damage in response to oxidative stress causing the progressive degeneration of dopaminergic neurons in PD is unclear, events such as mitochondrial dysfunction, the opening of the mitochondrial permeability transition pore (mPTP), neuroinflammation and oxidative DNA damage induced by oxidative stress may serve crucial roles in the process of neurodegeneration. The interaction between these various mechanisms forms a positive feedback loop that drives uncontrolled pathogenesis conditions, resulting in the development of PD (Fig. 1).

4. Reactive oxygen species and mitochondrial dysfunction

Mitochondria are the primary intracellular source of ROS, and for this reason the organelles are frequently exposed to oxidative stress (51,52). The complex of the ETC is one of the main cellular targets of ROS-induced oxidative stress, and oxidative damage of the ETC leads to the inhibition of ATP production and further generation of ROS (53). Consequently, the vicious cycle between the defects in the ETC and the subsequent production of ROS drive the uncontrolled oxidative stress that may play a central role in the progressive degeneration of dopaminergic neurons and have been underlied in PD pathogenesis (3). The proteins of the ETC complex are encoded by mitochondrial and nuclear genomes.Mitochondrial DNA (mtDNA) encodes 13 proteins that are all ETC complex subunits involved in oxidative phosphorylation and ATP production (54). Due to the proximity to the ETC complexes and the lack of histone protein protection, mtDNA is vulnerable to ROS attack (55). The damage to mtDNA and subsequent defects in the production of these proteins could induce mitochondrial dysfunctions that are implicated in a multitude of diseases or pathological conditions (53). The accumulation of defects in mtDNA has been detected in nigral dopaminergic neurons of elderly individuals and sporadic PD subjects (56-58). Inhibition of mtDNA expression leads to dysfunction in the respiratory chain in dopaminergic neurons accompanied by progressive parkinsonism in mouse models (59). High levels of mtDNA deletions could be also detected in the midbrain brains of PD models induced by rotenone, which inhibits ETC, resulting in the production of ROS (60). These studies suggest that oxidative ETC and mtDNA damage may be involved in the degeneration of dopaminergic neurons in oxidative conditions.

Figure 1. ROS trigger a cascade of events leading to the degeneration of neurons. Oxidative stress serves a central role in the neurodegenerative process by triggering the cascade events, including mitochondrial dysfunction, impairment of nuclear and mitochondrial DNA, and neuroinflammation, which in turn cause more ROS production, thus forming a vicious cycle. These vicious cycles generate an uncontrolled pathogenesis condition that drives the progressive degeneration of dopaminergic neurons in Parkinson's disease. ROS, reactive oxygen species; ETC, electron transport chain; mPTP, mitochondrial permeability transition pore.
Mitochondria are crucial organelles for Ca\(^{2+}\) storage, and mitochondrial Ca\(^{2+}\) is important in the regulation of diverse cellular functions (61). The synthesis of ATP, for example, is dependent on Ca\(^{2+}\) signals to promote the flow of electrons down the respiratory chain by increasing the mitochondrial NADH-to-NAD ratio through the activation of the dehydrogenases in the mitochondria (62,63). The maintenance of a Ca\(^{2+}\) gradient between the cytosol and the mitochondrial matrix is important for mitochondrial functions. The driving force of mitochondrial Ca\(^{2+}\) uptake is mainly dependent on the mitochondrial transmembrane potential across the inner mitochondrial membrane (IMM), which translocates H\(^{+}\) ions to the intermembrane space (IMS) and generates a membrane potential difference (64). Mitochondrial Ca\(^{2+}\)-mediated nitric oxide synthase activation may result in increased production of NO\(^{·}\). The interaction of NO\(^{·}\) with O\(_{2}\)\(^{−}\) produces a highly reactive radical ONOO\(^{−}\) that causes further damage to ETC and more ROS production (53,65,66). In fact, an increase in mitochondrial Ca\(^{2+}\) has been reported to increase production of ROS in neurons, resulting in oxidative ETC damage (67). This has particularly importance in dopaminergic neurons with exposure to frequent influxes of calcium (68). The interaction between Ca\(^{2+}\) overload and ROS production causes further damage to the ETC and uncontrolled oxidative stress, resulting in mitochondrial lipid, protein and DNA oxidation, and subsequently, cytotoxicity (69). The vicious circle between Ca\(^{2+}\) overload and oxidative stress favors the sustained opening of the PTP, which causes the mitochondrial membrane potential to collapse and the mitochondria to swell, resulting in pro-apoptotic mediator release into the cytosol from the mitochondria (70-72). The opening of the mPTP has been reported to serve a crucial role in the pathogenesis of neurodegenerative disorders, including PD (73,74).

5. Oxidative stress and the opening of the mPTP

The mPTP is a poly-protein transmembrane channel that is formed at contact sites between the outer mitochondrial membrane (OMM) and the IMM. Despite controversy over the structural constituents of the mPTP, the voltage-dependent anion channel (VDAC) in the OMM, the adenine nucleotide translocator (ANT) in the IMM, the B-cell lymphoma-2 (Bcl-2) family proteins in the cytosol and cyclophilin D (CyPD) in the matrix appear to be essential components (53). Normally, mPTP is impermeable, and the VDAC and the ANT are separated by the IMS. The opening of the mPTP occurs during the interaction of the ANT with the VDAC, and CyPD serves a crucial role in this process (75). Generally, CyPD is a mitochondrial matrix protein. When activated under the condition of oxidative stress, this protein can be translocated to the IMM where it interacts with the ANT and changes its conformation, leading to the binding of the ANT to the VDAC and the subsequent activation of the mPTP (75). The permeation of the OMM depends on the Bcl-2 family of proteins, including Bcl-2-associated X protein (Bax) and Bcl-2 homologous killer (Bak) (76). These proteins are located in the cytosol, but translocate and oligomerize into the OMM in response to oxidative stress. ROS promote the translocation of CyPD to the IMM, and Bax and Bak to the OMM, thus serving a crucial role in the opening of the mPTP (53). The opening causes the collapse of the mitochondrial transmembrane potential and the disturbance of the H\(^{+}\) gradient across the IMM, which inhibits the production of ATP and causes further generation of ROS, ultimately leading to cell death (77,78).

The release of mitochondrial apoptogenic proteins from the opening pore into the cytosol serves a crucial role in mPTP-mediated cell death, of which cytochrome c is the most potent apoptotic inducer (79,80). The released cytochrome c triggers the activation of caspase-9 via the interaction with apoptotic protease-activating factor 1 (Apaf1) (80). Apaf1 is a cytoplasmic protein that contains several domains associated with its functional and regulatory role (81). The binding of cytochrome c with the special domain of Apaf1 results in the protein forming an oligomeric apoptosome that is required for the activation of pro-caspase-9. Caspase-9 cleaves pro-caspase-3 resulting in its activation and the subsequent cleavage of DNA, the irreversible step toward apoptotic cell death (79,80). Apoptosis-inducing factor (AIF) is another apoptotic factor released from the mitochondria into the cytosol triggering caspase-independent apoptosis (53). AIF is a mitochondrial protein expressed in the IMS between the IMM and the OMM, and can be released in response to apoptotic signaling (82). The cytosolic AIF then translocates to the nucleus where it binds to DNA to instigate chromatin condensation (83) (Fig. 2). The contribution of other apoptotic mediators released from the opening of the mPTP to apoptosis has been well documented (53,84). Several mechanisms have been revealed to antagonize the opening of the mPTP. The translocation and oligomerization of Bax and Bak into the OMM, for example, can be antagonized by the antiapoptotic proteins Bcl-2 and Bcl-xL via sequestration and inhibition of the activator proteins that are required for the activation of these pro-apoptosis proteins (84). Glycogen synthase kinase-3β (GSK-3β) can be also implicated in the modulation of the opening of mPTP (85,86). GSK-3β is a Ser/Thr protein kinase expressed in the cytosol, nucleus and mitochondria of all eukaryotic cells, and is involved in modulating a wide range of biological functions (87,88). GSK-3β activation promotes the upregulation of the levels of Bax (89,90), and facilitates its mitochondrial localization by directly phosphorylating Ser163 of this protein (91). Mitochondrial GSK-3β modulates the process of oxidative phosphorylation that is implicated in the production of ROS, the key inducer of the opening of the mPTP (92). Studies in cell and animal models of PD have shown that GSK-3β inhibition can protect dopaminergic neurons from the toxicity of MPP\(^{+}\)/MPTP (93-96), and the blockage of the opening of the mPTP may be involved (97).

Overall, the oxidative stress-mediated opening of the mPTP is one of the pathways responsible for the apoptosis of dopaminergic neurons in PD, and understanding the mechanisms involved is essential to the development of effective therapies for neurodegenerative diseases.

6. Oxidative stress and neuroinflammation

Neuroinflammation is a protective mechanism of the CNS against infectious insults and injury by activation of the innate immune system in the brain to destroy and remove the detrimental agents and injured tissues (98). However, uncontrolled inflammation can cause excessive cell and tissue
damage, ultimately leading to chronic inflammation and progressive destruction of normal tissue. The elevated levels of ROS production serve an important role in the activation of a strong proinflammatory response, and the link between oxidative stress and inflammation and tissue injury has been well documented (15). The inflammatory damage has been underlined in the pathogenesis of neurodegenerative diseases, including Alzheimer’s disease, Huntington’s disease, multiple sclerosis and PD (99-102). The inflammatory response is a complex process involved in a series of cellular and molecular processes, including the activation of immune cells, the induction of certain intracellular signaling pathways and the release of inflammatory mediators in the brain (103). The activation of microglia is an initiator in inflammation-mediated neuronal injury. Microglia are the resident immune cells of the brain that become activated in response to brain injury or immune challenge (104). Activated microglia are an important source of superoxide and nitric oxide, triggers of oxidative and nitrative stress in neurotoxicity; they can also produce proinflammatory cytokines such as glutamate and tumor necrosis factor-α (TNF-α), which are potentially toxic agents in the brain microenvironment (105-106). Inflammation-derived oxidative stress and cytokine-dependent toxicity have been suggested to be involved in the loss of dopaminergic neurons in PD (107-109). Postmortem studies revealed the presence of inducible NO synthase (iNOS) and proinflammatory cytokines, including TNF-α, interleukin-1β (IL-1β), IL-2 and IL-6, in the SN of PD patients (110-112). A series of proinflammatory cytokines, including TNF-α, IL-1α, IL-1β and IL-6, and activated microglia have also been identified in PD animal models (113-118). As one important cytokine, TNF serves a crucial role in inflammation-mediated neurodegeneration, since elevated levels of this cytokine can be persistently detected in the affected areas of the SN in PD (119). In addition to the induction of proinflammatory signaling pathways resulting in cell damage (16), TNF can promote the secretion of NO by increasing the expression of iNOS in microglia (120). Furthermore, TNF can activate NADPH oxidases, leading to the production of ROS, which contribute to oxidative stress and in turn result in an uncontrolled inflammatory response (16). The dopaminergic neurons are particularly susceptible to microglia-mediated toxicity due to the highest density of microglial cells being distributed in the SN of the brain (121,122). Microglia activation promotes the production of proinflammatory cytokines, which cause dopaminergic nigrostriatal neuron degeneration in MPTP models of PD (123). Animal models of PD have shown that suppression of the inflammatory response, results in the protection of neurons from the damage induced by neurotoxin (124,125). These data indicate a close association between microglial activation and the degeneration of dopaminergic neurons in PD pathogenesis.

Figure 2. ROS facilitate the opening of the mPTP, resulting in neuronal apoptosis. The mPTP is a poly-protein transmembrane channel structurally consisted of a number of constituents, including the VDAC in the OMM, the ANT in the IMM, the Bcl-2 family of proteins in the cytosol and CyPD in the matrix. ROS are a crucial inducer in the opening of the mPTP. Under oxidative conditions, the cytosol proteins Bax and Bak translocate and oligomerize into the OMM resulting in the permeation of the OMM. ROS can also activate the mitochondrial matrix protein CyPD, thus facilitating its translocation to the IMM. The translocated CyPD interacts with ANT and changes its conformation, leading to the binding of ANT to VDAC and subsequently, mPTP activation. The opening of the mPTP releases pro-apoptotic mediators, including cytochrome c, from the mitochondria into the cytosol. The released cytochrome c triggers the activation of pro-caspase-9 via the interaction with Apaf1. Caspase-9 cleaves pro-caspase-3 resulting in its activation and subsequent DNA cleavage. AIF is another apoptotic factor released from the IMS between the IMM and the OMM through the mPTP into the cytosol. The cytosolic AIF is then translocated to the nucleus where it binds to DNA to instigate chromatin condensation. ROS, reactive oxygen species; mPTP, mitochondrial permeability transition pore; VDAC, voltage-dependent anion channel; OMM, outer mitochondrial membrane; ANT, adenine nucleotide translocator; IMM, inner mitochondrial membrane; Bcl-2, B-cell lymphoma-2; CyPD, cyclophilin D; Bax, Bcl-2-associated X protein; Bak, Bcl-2 homologous killer; Apaf1, apoptotic protease-activating factor 1; AIF, apoptosis inducing factor; IMS, intermembrane space.
Dopaminergic neuronal death releases noxious endogenous mediators, including oxidized proteins, lipids and DNA, in the extracellular space, which can also activate the microglia, resulting in the release of multiple proinflammatory cytokines. Proinflammatory factor production subsequently exacerbates damage to the neurons via oxidative stress and cytokine toxicity (19), causing the injured neurons to release further noxious endogenous mediators and resulting in a continuous inflammatory response (104). This positive feedback loop between activated microglia and damaged neurons forms a neurotoxic vicious cycle and an uncontrolled, prolonged inflammatory process, and is hypothesized to be partially responsible for the gradual loss of dopaminergic neurons in PD (126,127). Thereby, inhibiting the inflammatory response generated by microglia activation may be show benefits in neurodegenerative conditions.

7. Damage to nucleic acids by oxidative stress

DNA integrity is required for cell survival. Under physiological conditions, DNA is often subjected to damage by endogenous and environmental toxic agents, and un repaired DNA damage leads to genetic and protein instability, and subsequent cell death. Nucleic acids, RNA and DNA, are particularly susceptible to oxidative damage, with DNA damage being a key contributor to a number of different diseases (128). Dopaminergic neurons are frequently exposed to ROS attack, resulting in DNA oxidative damage due to the high levels of ROS production. In PD, increased levels of 8-hydroxyguanine, the marker of DNA oxidative damage, have been detected selectively in the SN (7,129). The number of strand breaks in nuclear DNA have also been reported to be elevated in the SN compared with that in other areas of the brain, and evidence of alterations to DNA conformation and stability in the SN has also been documented (129). mDNA is more susceptible to oxidative damage than nuclear DNA (130). Postmortem studies in the brains of patients with PD have shown increased levels of mtDNA damage marker abasic sites in the SN. Abasic sites were also shown in brain tissue from PD mouse models treated with the neuronal toxin rotenone, which causes oxidative stress by inhibiting the mitochondrial complex (131). Abasic sites are DNA segments that have lost a purine or pyrimidine base, leading to the blockage of the polymerase during the replication and transcription of DNA (132). These studies demonstrate that dopaminergic neuron injury could be ascribed to the oxidative damage of nuclear DNA and mtDNA, which alters its coding properties or interferes with normal metabolic function, and subsequently results in cell death (128). ROS attack on DNA may be reversible or irreversible, dependent on the efficiency of its repair. Effective repair of damaged DNA is required to preserve its integrity and maintain the viability of the cell, particularly in dopaminergic neurons. A number of cellular mechanisms are devoted to the repair of DNA (133). A previous study determined an association between variants in DNA repair and an increased risk of PD (134). As a critical regulatory protein for DNA repair, proliferating cell nuclear antigen (PCNA) serves a central role in the repair of damaged DNA in a variety of pathological conditions via the interaction with numerous enzymes and regulatory proteins (135,136). PCNA-dependent repair of DNA has been reported to contribute to the reserve in the DNA integrity of the dopaminergic neurons under oxidative conditions (137,138). We previously studied in vitro the mechanism of the degeneration of dopaminergic neurons in PC12 cells induced by MPP+, which causes ROS production by inhibiting complex I, leading to oxidative DNA damage and subsequent neuronal cell death. The results showed that MPP+ treatment significantly reduced PCNA expression in the neuronal PC12 cells and increased the level of cell apoptosis. The reversal of PCNA expression markedly promoted cell survival in PC12 cells with MPP+-induced neurotoxicity, supporting the hypothesis of the PCNA-dependent apoptotic pathway as a potential molecular mechanism in PD pathogenesis associated with DNA damage in oxidative conditions (139). These results may provide a potential target for the reversal of oxidative DNA damage-mediated neuronal death in PD pathogenesis.

8. Conclusion

The pathogenesis and progression of PD are complex and involved in a series of diverse mechanisms that alone or together contribute to the damage and gradual loss of dopaminergic neurons. Oxidative stress appears to serve a central role in the neurodegenerative process, since dopaminergic neurons are frequently exposed to oxidative stress, which triggers a cascade of events, including mitochondrial dysfunction, impairment of nuclear DNA and mtDDA, and neuroinflammation, which in turn cause more ROS production. The formation of this vicious cycle may serve a central role in the progressive degeneration of dopaminergic neurons in PD, therefore, the inhibition of the production of ROS and the blockage of the interactions in the signaling pathway may alleviate the severity and development of the disease. This require further elucidation.

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Competing interests

The authors declare that they have no competing interests.

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