Impact Of Oxidative Stress On Parkinson's Disease

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▪ Abstract

Oxidative stress has become more identified as a critical event that correlates with the deterioration of dopaminergic neurons in the pathophysiology of Parkinson's disease(PD). Even though the generation of reactive oxygen species (ROS) has been hypothesized to have a role in the development of Parkinson's disease, the cellular and molecular processes that associate oxidative stress with dopaminergic neuronal death are difficult to comprehend and poorly, understood. The primary remarks are responsible for the large generation of ROS, which counteracts to oxidative damage by attacking several macromolecules, including lipids, protein as well as nucleic acids, which ultimately results in deformities in the physiological role of those macromolecules. As a consequence, the results in these macromolecules lead to disruption in the mitochondria along with neuroinflammation, both of which, in turn, lead to an increase in the generation of ROS and then eventually, neuronal impairment. The association between these diverse pathways generates an optimistic feedback loop that promotes the gradual death of dopaminergic neurons in PD patients, and oxidative stress-mediated cell impairment seems to serve a major role in the process of neurodegeneration. Therefore, acquiring a knowledge of the cellular along with molecular processes in which oxidative stress leads to the death of dopaminergic neurons can give a viable therapeutic strategy in the treatment of Parkinson's Disease.

Keywords: Parkinson disease, Reactive Oxygen Species(ROS), mitochondria, genetic mutation, PINK1, DJ-1, LRRK.

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▪ INTRODUCTION

Dopamine levels within the corpus striatum of the nigrostriatal dopamine pathway within the brain are associated with PD, which is correlated with the deprivation of dopamine (DA) neurons within the substantia nigra pars compacta (SNpc) of the brain[7,9,10]. This DA deficiency cause deregulation of the basal ganglia circuitry resulting in both motor and non-motor manifestation such as insomnia, anxiety, as well as intellectual disabilities[5,6]. Motor symptoms include involuntary movements, resting tremors, high stiffness, and autonomic dysfunction. Non-motor symptoms include brain abnormalities and spasticity. Both the actual genesis of PD and the processes that contribute to the development of the illness continue to be mysteries[1,2,3]. At the level of the cell, PD is linked to a rise in the formation of ROS, in addition to variations in the metabolism of catecholamine [4,5]. Mitochondrial disorder, neuroinflammation, and several environmental elements are progressively viewed as crucial determinants associated with dopaminergic neuronal sensitivity in Parkinson's disease, and they are prevalent in familial as well as in the sporadic type of the disease. While the characterized familial features of Parkinson's disease engage mutations in a number of genes, mitochondrial dysfunction, neuroinflammation, as well as external factors. It is believed that the identical underlying mechanism in both instances is oxidative stress, which inevitably leads to the failure and death of cells in the affected tissues [15, 16]. On the other hand, oxidative stress arises when there is a disparity between the amount of ROS produced and the amount of cellular antioxidant activity that is present. Mitochondria are the principal locations for

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oxidative phosphorylation as they are the sites where oxidants along with superoxide radicals are created as a byproduct from the process of oxidative phosphorylation [18, 19,].

In this paper review, we fixate on the primary causes of oxidative stress developed by DA neurons. These include dopamine metabolic activity, mitochondrial dysfunction, genetic differences, and oxidative stress's impact on neuroinflammation. Despite the fact that the actual mechanism that correlate with ROS generation in connection with PD is not yet adequately elucidated, we emphasize these primary causes in this review.

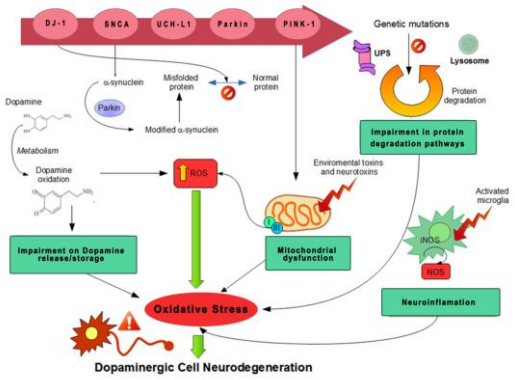


Fig: Parkinson's disease Pathogenesis

As a consequence of mutations in PD-linked genes, oxidative stress is enhanced through distinct strategic and corresponding dysfunctions. Mutations or altered transcription of these proteins lead to genomic instability, oxidative stress, and mitochondrial dysfunction[23]. As an added bonus, dopamine conversion may produce reactive dopamine quinones, which can boost the levels of reactive oxygen species (ROS). An alteration of α-synuclein expedites its aggregation[24,26].

Cell viability is further jeopardized by increased oxidative stress, which results in lesser of UPS in degrading misfolded or damaged proteins. Toxic substances in the environment have been attributed to mitochondrial dysfunction, an elevation in free radical formation, and protein aggregates, including α-synuclein [27]. Disruption of complex I in mitochondria causes mitochondrial inefficiency, which in turn increases oxidative stress and diminishes ATP output, all of which contribute to the disintegration of intracellular components and inevitable cell death. In summation, the preferential death of dopaminergic neurons is correlated among many biological pathways that have been ascribed to oxidative stress [23,24].

▪ METABOLISM OF DOPAMINE

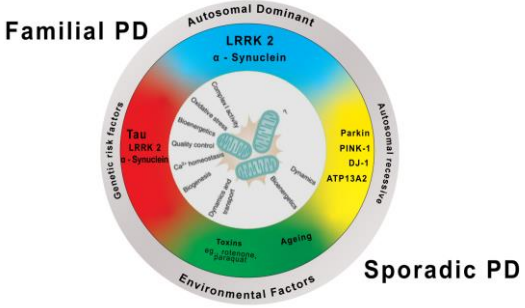
Degeneration of dopaminergic neurons in the SNpc implies DA may cause oxidative stress. Dopamine is integrated from tyrosine by hydroxylase plus decarboxylase. Synaptic vesicles store dopamine post VMAT absorption. In injured neurons, such as after L-DOPA therapy, cytosolic DA outside of the synaptic vesicle is readily converted to lethal ROS through monoamine oxidase (MAO) and also auto-oxidation [5,7,9]. In mice with less VMAT2 expression, mismanaged dopamine caused DA-mediated toxicity and dopamine neuron death [8]. This oxidative information influences mitochondrial pores and respiretion. DA auto-oxidation results in lower electron density quinones or semiquinones. Quinone production in DA neurons governs the L-DOPA-treated Parkinson's disease model triggered by neurotoxins as well as methamphetamine. α-synuclein(-syn), parkin, DJ-1, Superoxide dismutase-2, and UCHL1 can be altered by DA quinones, which have been linked to downregulation of DA transporter along with the TH enzyme, and mitochondrial dysfunction, brain mitochondrial alterations, and Complex I activity dysfunction. DA quinones can also be converted into amino chrome, where redox cycling emits superoxide radicals & depletes NADPH, generating neuromelanin, which aggregates in the human brain's SNpc. PD patients' substantia-nigra revealed boosts in L-DOPA, DA, and DOPAC cysteinyl adducts, reflecting DA oxidation's cytotoxicity. DA terminals deteriorated upon a single striatal DA injection in proportion to DA oxidation [12, 13, 15]. Mice with increased DA absorption via the DAT have oxidative damage, neuronal death, and motor dysfunction.

▪ OXIDATIVE STRESS ON DOPAMINERGIC NEURONS

As a result of the CNS's high levels of energy use, it has a significant number of mitochondria. Because many mitochondrial enzymes need iron to operate, the iron concentration of CNS cells is very high, which causes a higher

generation of ROS that contributes to oxidative stress and then ultimately, neuronal death[11]. Particularly for nigral dopaminergic neurons, which seem to have a greater susceptibility to iron-induced oxidative stress, iron stimulates the formation of highly reactive oxygen species, leading to additional oxidative damage [11,14]. Studies on the brains of PD patients revealed increased amounts of iron in SN in comparison with those of controls. PD animal models, where high amounts of iron and hydroxyl radicals could possibly see in SN. also suggest the association of oxidative iron abnormal regulation with the neurodegenerative process[19]. Deferoxamine greatly lowers the amount of iron present inside the brain and protects against neuro-degeneration brought on by iron & MPTP in Parkinson's Disease mice models, further demonstrating the role of iron in the neuronal death process of PD[16]. Additionally, as the brain is rich in lipids that mediate inflammatory processes, apoptotic signals, and membrane fluidity and permeability [1]. Lipids were seen to be vulnerable to ROS-mediated impairment, especially polyunsaturated fatty acids, more prone to lipid peroxidation. As a result, membrane structure is harmed, which in turn causes neuronal damage and, eventually, death. The etiology of Parkinson's disease has been linked to oxidative stress-mediated mortality [17]. Furthermore, a higher in malondialdehyde amount, a byproduct of the polyunsaturated fatty acid peroxidation under oxidative circumstances, was observed in the SN in patients of Parkinson's disease (PD) compared to other brain areas. Cholesterol lipid hydroperoxide, alipid peroxidation marker, is also shown to be considerably higher in PD brains than in normal participants. Higher HNE amount shown in the SN and CSF fluid of Parkinson's Disease patients further supports the idea that fatty acids(polyunsaturated) contribute to the oxidative destruction of dopaminergic neuronal cells. HNE is a lipid peroxidation byproduct that induces DNA breakage and activates the caspase cascade, causing apoptotic cell death. Since glutathione was a significant non-enzymatic antioxidant in the central nervous system, HNE can also lower its levels, making neurons more susceptible to oxidative damage. Other known causes that contribute to dopaminergic neuronal susceptibility with regard to oxidative stress have been well-documented. The collective findings show that dopaminergic neurons are prone and susceptible to oxidative damage. A number of factors, including mitochondrial failure, the opening of mitochondrial permeability transition pore (mPTP), neuroinflammation, including oxidative DNA disruption due to oxidative stress, may play an important part in the neurodegenerative series of events that led to Parkinson's disease (PD). Due to the accumulation of positive feedback loops from so many different systems, pathogenic conditions go unchecked, and eventually, Parkinson's disease develops (PD).

▪ MITOCHONDRIAL DYSFUNCTION



Mitochondrial dysfunction may be a major factor in the loss of dopaminergic neurons. The etiology of PD is influenced by both hereditary and environmental variables that are linked to the disease. Direct evidence connecting mitochondrial malfunction to PD is provided by the induction of Parkinson's Disease with neurotoxins which affect mitochondrial complex I. In cellular and animal models of PD brought on by neurotoxins or hereditary factors, there is a decrease in mitochondrial complex I activity.

The discovery of (MPTP), a neurotoxin that induces symptoms of PD in drug-addicted patients, established a direct link between mitochondrial impairment and Parkinson's disease. MPTP neurotoxicity was soon confirmed in primate and rodent models. MPTP inhibitory effects on mitochondria were later discovered. It is well understood that the toxicity of MPTP in the neuron is caused by the toxic metabolite 1-methyl-4-phenylpyridinium (MPP+) of MPTP [18,19]. Astrocytes contain an enzyme termed monoamine oxidase, which

quickly degrades MPTP to 1-methyl-4-phenyl-2, 3-dihydropyridinium, which in turn, transformed to MPP+. Astrocytes emit MPP+ via the organic cation transporter 3, whereas dopaminergic neurons uptake it using the dopamine transporter. Upon accumulation, MPP+ disrupts the complex I electron transport chain, which then in turn drains ATP and generates reactive oxygen species within mitochondria. Rotenone and paraquat, two pesticides with structures related to MPTP that disrupt complex I, have also been utilized in research demonstrating that complex I disruption induces PD. Due to DA autoxidation upon catabolism, DA neurons are highly vulnerable to oxidative stress, thus ROS generation through complex I inhibition is a key mechanism for DA neurodegeneration. Damage to complex I and III, along with protein oxidation on mitochondria and in the cytoplasm, is triggered by the generation of ROS which in turn, causes the mitochondrial disorder [20, 21]. Damaged and denatured proteins accumulate when the ubiquitin-proteasomal system (UPS) is overburdened by heightened oxidative stress. Commonly utilized to generate laboratory PD model modeled sporadic PD for investigating the mechanism & researching therapies, complex I antagonists elicit the loss of DA neurons and enable animals to acquire the clinical features of PD.

There is proof for mitochondrial disruption tied with oxidative stress along with dopamine cell damage, and alterations in the genes of proteins including α-syn, PINK1, parkin, and DJ-1, were connected to familial variants of Parkinson's disease [22, 23]. The convergence of proteins within mitochondrial dynamics demonstrates a shared role in the mitochondrial activity to stress, indicating a possible physiological foundation for Parkinson's disease pathogenesis. These results demonstrate that mutations within these genes have an impact on mitochondrial activity and integrity and are linked to increased oxidative stress. It's the influence of reactive oxygen species on mitochondrial, lysosomal, as well as proteasomal activity that dictates how cells respond to oxidative injury. Brain homeostasis must be carefully managed during periods of heightened ROS levels, and this involves the exact elimination of impaired proteins by efficacious proteolysis, as well as the production of newly defensive proteins[24,25]. Because of this, protein misfolding (i.e. α-syn) may actually occur, which hinders certain proteins from being unfolded and eliminated by protein clearance mechanisms such as the ubiquitin-proteasome system (UPS) or autophagy. Protein misfolding, in concert with the abnormal function of protein degradation pathways, may play a positive role in the onset of unfavorable events associated with the neurodegenerative process of Parkinson's disease.

▪ OXIDATIVE STRESS AND GENETIC VARIATIONS

❖ SNCA

ASN, that is encoded with the SNCA gene, is involved in the transportation of synaptic vesicles, regulation of dopamine biosynthesis, neuronal growth, chaperone activity, antioxidative activities, and the inhibition of apoptosis [27,33]. In Parkinson's disease, the accumulation of ASN triggers cell death within the substantia nigra, pons, & medulla. It's also possible that ASN interferes with the function of other proteins via interactions with them, such as Parkin. Reduced capacity to scavenge ROS may enhance ASN aggregation, which is caused by SNCA mutations as well as oxidative stress. Point mutations and SNCA duplications or triplications both promote ASN aggregation. Nevertheless, the latter is responsible for the more severe phenotype, which includes early-onset PD and dementia. Transfected human cells are more vulnerable to oxidative damage when mutant SNCA is overexpressed. Furthermore, oxidation reduces ASN capacity to form the α- or β-type secondary structures essential for fibril formation.

❖ PRKN & PINK1

PRKN encoding Parkin, an E3 ubiquitin ligase that aids in the proteasome-dependent degradation of redundant as well as disorganized proteins like glycosylated ASN. For DA neurons to make it, it must protect them from ASN toxic effects plus oxidative stress. Protein carbonyls, lipid peroxides, and nitrated proteins are all markers of oxidative stress, and PRKN mutations reduce a protein's ability to bind ASN, leading to aggregation [27,28]. Failures mutations in PRKN cause recessively

inherited PD and are responsible for around 20% of sporadic EOPD and about 50% of familial EOPD.

Clinically, individuals with PRKN mutations show improvements in L-dopa responsiveness, delayed disease development, and also more symmetric occurrence, all characteristics that are shared with idiopathic PD[29,31]. Patients with PRKN mutations also have elevated rates of depression independent of its impact on executive functionality, in contrast to individuals with EOPD caused by other causes. Mutations in PRKN may potentially cause PD with a late start[33].

The protein encoded by PINK1 is PTEN-induced kinase 1, a mitochondria kinase highly expressed in the central nervous system, the heart, and skeletal muscle. PINK1 loss of function mutations, which cause recessive EOPD, account for 1-8(%) among all EOPD cases. The phosphorylation of the mitochondrial chaperone TRAP1 by PINK1 is essential for the neuroprotective effects of PINK1 over expression [30]. This protects cells from dying as a result of oxidative stress.
In this context, PINK1 is often characterized as a guard of mitochondrial quality management because of its role in preventing abnormalities in mitochondrial morphology caused by a decrease in the activity of mitochondrial enzymes, especially complex I.Knocking down PINK1 leads to mitochondrial breakage, autophagy, and increased oxidative stress, all of which contribute to decreased mtDNA synthesis and ATP production. When damaged mitochondria are detected, Parkin and PIN K 1 act together to facilitate their autophagic removal. Parkin begins destroying damaged mi tochondria when PINK1 accumulates on its outer membrane [30, 32, 33]. When PINK 1 as well as Parkin is absent, damage mitocho-ndria cannot under go autophagy, leading to an increase in ROS and eventually the death of nigral cells. Decreased DA release and synaptic plasticity accompanied impaired mitochondrial respiration and ATP generation in Pink1 deleti on mice.

Reduced fission and increased mitochondrial a ggregation have also been linked to high levels of oxidative stress.Furthermore, PINK1 can int erface with DJ-1. Mutations in PINK1 or DJ-of oxidative stress.Furthermore, PINK1 can interf ace with DJ-1. Mutations in PINK1 or DJ-1 negate the protective effect of overexpression of these proteins against MPTP-induced apoptosis. DJ-1 operates either in tandem with or as a downstream component of the PINK1/ Parkin cascade. Nevertheless, the precise mech anism through which PINK1 and DJ-1 interact remains elusive. [33]

❖ DJ-1

DJ-1 is also an additional neuroprotective protein with several roles in regulating oxidative stress, apoptosis, and inflammation. Even among those with EOPD, mutations in the DJ-1 gene account for fewer than 1% of cases. DJ-1 prevents oxidative damage to DA neurons in the substantia nigra. Higher amounts of DJ-1 were found in the cerebrospinal fluid of sporadic PD individuals, particularly during the early stages of the illness (III HY scale), leading the researchers to hypothesize that the protein protects against oxidative stress in the progression of PD [25,27]. It has been shown that in conditions of oxidative stress, DJ-1relocalizes to the mitochondria, where it may play a role in suppressing autophagy. Fibroblasts including lymphoblasts isolated from individuals with DJ-1 gene mutations for Parkinson's disease showed cytological evidence of mitochondrial fragmentation, poor bioenergetics, and heightened sensitivity to ROS including toxins. DJ-1 deletion mice were shown to be more vulnerable to MPTP poisoning than wild-type mice. Interestingly, motor function was unaffected in DJ-1 knockout mice [27].

❖ LRRK

The kinase LRRK2, also known as dardarin, plays an important role in many cellular processes. Mitochondrial network dynamics and mitophagy are controlled by LRRK2, which does so via interacting with mitochondrial fusion proteins & mitochondrial outer membrane proteins. Located within the cytoplasm, LRRK2 is essential for the kinase activity that phosphorylates proteins including ASN and tau. In addition, LRRK2 transcription or synergistic effect with ASN may amplify pathological processes in PD[35].

Mutations within the LRRK2 gene are by far the most possible cause of familial autosomal dominant PD and sporadic PD. They are now known to exist among the Basque ethnicity.

The bulk of LRRK2 mutations are located in the protein's catalytic core domains, namely the RocGTPase and Kinase domains, and have an effect on the enzyme's activity. Abnormalities in mitophagy, mitophagy lysis, and mitochondrial DNA (mtDNA) damage result from LRRK2 mutations. They promote reactive oxygen species production, inhibit peroxidase function, and hence exacerbate oxidative stress. The most common variant of the LRRK2 gene is called G2019S, and it occurs in 1018% of Ashkenazi Jews and 313% of Europeans. The G2019S mutation's penetrance varies with age, from 28% in those aged 59-69 to 51% in those aged 69–79 and 74% in those aged 79 and above[32,33]

▪ NEUROINFLAMMATION BY OXIDATIVE STRESS

Neuroinflammation is also a protective response of the central nervous system (CNS) to viral attacks and injury that includes the engagement of innate immune responses within the brain to clear toxic chemicals and damaged tissues. However, chronic inflammation and the progressive loss of normal tissue may result from unchecked inflammation if it damages several cells and tissues [39]. The link shared between oxidative stress, inflammation, as well as tissue damage is documented, and increased levels of ROS generation play a vital part in activating a robust proinflammatory response. There is mounting evidence that links inflammation to the onset of neurodegenerative diseases including multiple sclerosis, Alzheimer's, Huntington's, and PD[36]. The complex inflammatory response involves many different cellulars as well as molecular activities, such as the stimulation of immune cells, encouraging the particular intracellular signaling pathways, and the liberation of inflammation-related mediators within the brain. Microglial activation is seen as an early stage of Inflammation-induced neuronal impairment [38,40]. Microglia, the brain's innate immune cells, get activated in response to immunological stress or brain injury. Superoxide and nitric oxide, known to induce oxidative and nitrative stress in neurotoxicity, are produced by activated microglia; proinflammatory cytokines, including glutamate and tumor necrosis factor- (TNF), are also produced, and they may be hazardous in the brain microenvironment. Dopaminergic cell loss in Parkinson's disease has been linked to oxidative stress all as well as cytokine-dependent toxicity.

Postmortem examinations of Parkinson's disease patients SNs demonstrated the presence of inducible nitric oxide synthase (iNOS) including proinflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1, IL-2, & IL-6. Multiple Proinflammatory cytokines including tumor necrosis factor, interleukin-1, and interleukin-6, and activated microglia have been detected in
PD animal models [25, 27].

Increased levels of TNF, a prominent cytokine, may be seen in the SN areas affected by Parkinson's disease, suggesting a function for this cytokine in the inflammation-mediated neurodegeneration. Increased expression of iNOS in microglia is one mechanism by which tumor necrosis factor (TNF) increases NO production and also induces proinflammatory signaling pathways that lead to cell damage. It has been shown that TNF may stimulate NADPH oxidase, and lead to the production of ROS, which in turn adds to oxidative stress with an uncontrollable inflammatory response [37,39]. Dopamine neurons are especially vulnerable to microglia-mediated toxicity because there are so many microglial cells in the SN. MPTP models of Parkinson's disease show that activation of microglia leads to increased generation of pro-inflammatory cytokines, which in turn leads to the loss of dopaminergic nigrostriatal neurons [8, 14].

Reduced inflammation in PD models protects neurons from neurotoxin-induced damage. Activation of microglia has been linked to the loss of dopaminergic neurons, which may play a key role in the development of PD[38]. Toxic endogenous mediators, such as oxidized proteins, lipids, and DNA, are released into the extracellular spot during the death of dopaminergic neurons. These mediators may activate microglia, which then creates a

number of pro-inflammatory cytokines. Neuronal damage is exacerbated by the generation of proinflammatory factors, which in turn allows injured neurons to create even more damaging endogenous mediators, leading to a chronic inflammatory response [40].

The key feedback between activated microglia and impaired neurons is associated with a neurotoxic destructive cycle with an unregulated, prolonged inflammatory response, both of which are likely to contribute to the gradual death of dopaminergic neurons seen in PD. Treating neurodegenerative disorders may benefit from blocking the inflammatory response caused by microglia stimulation36, 40]

▪ CONCLUSION

Dopaminergic neurons are destroyed and progressively lose their function due to a variety of complex processes that are involved in the etiology and progression of Parkinson's disease. These processes may occur independently or in conjunction with one another. Result of the fact that dopaminergic neurons are often subjected to oxidative stress, which in turn leads to a chain reaction of events including mitochondrial disorder, cognitive deficits of nuclear DNA as well as mtDNA, & neuroinflammation, and this, in turn, leads to an extension of ROS production, oxidative stress appeared to act a vital part in the process of neurodegeneration. The formation of this negative feedback cycle may play a critical role in the progressive loss of dopaminergic neurons in Parkinson's disease. Because of this, restricting ROS production and obstructing the interconnection in the signaling cascade may alleviate the severeness of the disease and slow its progression of the disease.

▪ CONFLICT OF INTEREST:

The authors declare no potential conflict of interest.

▪ AUTHOR CONTRIBUTIONS FOR THE CREDIT WORK:

SR and CV designed the study's overall structure. The study was carried out by SR and CV. The data and contradictions in the data were examined by SR and CV. SR first drafted the article, which was then amended by CV, after data confirmation.

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