MODULATION OF NEUROINFLAMMATION AND OXIDATIVE STRESS AS A THERAPEUTIC STRATEGY IN PARKINSON'S DISEASE: MOLECULAR INSIGHTS AND EXPERIMENTAL APPROACHES

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ABSTRACT

Parkinson's disease (PD) is a progressive, multifactorial neurodegenerative illness that causes both motor and non-motor symptoms in addition to the selective loss of dopaminergic neurons in the substantia nigra pars compacta. Growing data points to oxidative stress and neuroinflammation as important and related factors in the pathophysiology of Parkinson's disease. The activation of inflammasomes like NLRP3, microglial activation, and increased production of pro-inflammatory cytokines (like IL-1β and TNF-α) all contribute to a proinflammatory environment that worsens neuronal damage. A self-replicating cycle of neurotoxicity is produced when oxidative damage and lipid peroxidation are exacerbated by the buildup of reactive oxygen and nitrogen species (ROS/RNS), compromised mitochondrial function, and compromised antioxidant defense systems (e.g., SOD, GSH, catalase).The pathological interaction between neuroinflammation and oxidative stress is highlighted in this review, along with the ways in which they work together to promote α-synuclein aggregation, mitochondrial dysfunction, and disruption of the blood-brain barrier. The importance of these pathways in dopaminergic neurodegeneration has been clarified by preclinical models such as 6-OHDA, MPTP, rotenone, and LPS-induced neuroinflammation. We also assess new therapeutic approaches that target these mechanisms, such as NSAIDs, NLRP3 inhibitors, antioxidant treatments, natural polyphenolic compounds, and agents that target the mitochondria. Combining personalized medicine techniques with combination therapy may offer a more successful paradigm for altering the course of disease. A promising path toward neuroprotection and better results in Parkinson's disease is to target oxidative stress and neuroinflammation.

Keywords: Parkinson's disease; Neuroinflammation; Oxidative stress; α-Synuclein; Mitochondrial dysfunction; Antioxidants; Neuroprotection,

INTRODUCTION

Parkinson's disease (PD), dopaminergic neurons in the midbrain's substantia nigra pars compacta (SNpc) are lost, which significantly lowers striatal dopamine levels. PD is a progressive neurodegenerative disease. Motor symptoms like bradykinesia, muscular rigidity, postural instability, and resting tremor are clinical manifestations of Parkinson's disease (PD), while non-motor symptoms include mood disorders, sleep disturbances, cognitive impairment, and autonomic dysfunction[1]. The complex symptomatology is a reflection of extensive structural and neurochemical changes that extend beyond the dopaminergic system and involve glutamatergic, serotonergic, noradrenergic, and cholinergic pathways[2]. PD is characterized by the development of Lewy bodies and Lewy neurites, which are mainly made of misfolded and aggregated ?-synuclein protein. ?-synuclein buildup is linked to neuroinflammation, oxidative stress, mitochondrial impairment, autophagy-lysosomal pathway dysfunction, and neuronal dysfunction[3].

Neuronal degeneration is caused by the combined effects of these pathological cascades. According to recent data, oxidative stress and neuroinflammation are not only incidental reactions but actively contribute to the development and course of Parkinson's disease[4]. Numerous pro-inflammatory cytokines, such as TNF-?, IL-1?, and IL-6, are released by activated microglia and astrocytes, aggravating oxidative damage and neuronal death. The integrity of neurons is further compromised by the simultaneous occurrence of lipid peroxidation, DNA damage, and protein oxidation brought on by elevated levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS)[5]. PD has a complex etiology that includes aging-related processes, environmental toxins (such as pesticides like rotenone and paraquat), and genetic mutations (such as SNCA, LRRK2, PARKIN, PINK1, and DJ-1)[6].

Neurodegeneration results from the convergence of these factors on shared molecular pathways. There are symptomatic treatments like levodopa, dopamine agonists, and MAO-B inhibitors, but none of them can stop or reverse the course of the disease[7]. The development of disease-modifying treatments, especially those that target oxidative stress and neuroinflammatory pathways, and an understanding of the molecular mechanisms underlying

Parkinson's disease (PD) are therefore becoming increasingly important[8].

PATHOLOGICAL HALLMARKS

The substantia nigra pars compacta (SNpc)'s progressive degeneration of dopaminergic neurons is the primary pathological hallmark of Parkinson's disease (PD), which results in a marked decrease in dopamine levels in the striatum and motor dysfunction. Lewy bodies and Lewy neurites, intracytoplasmic inclusions primarily made of misfolded and aggregated ?-synuclein protein, are a hallmark of Parkinson's disease[9]. This protein aggregates and accumulates toxically due to aberrant post-translational modifications like phosphorylation, nitration, and ubiquitination.In addition to ?-synuclein pathology, PD is associated with mitochondrial dysfunction,particularly involving complex I of the electron transport chain, which leads to reduced ATP production and excessive generation of reactive oxygen species (ROS). Neuronal death is exacerbated by oxidative stress, which damages proteins, lipids, and DNA. The release of pro-inflammatory mediators like TNF-?, IL-1?, and nitric oxide is another way that chronic neuroinflammation, which is defined by persistent activation of microglia and astrocytes, advances the course of the disease. Cellular proteostasis is upset and toxic protein aggregates can form when there are malfunctions in protein degradation systems, such as the autophagy-lysosomal pathway (ALP) and the ubiquitin-proteasome system (UPS)[5]. Neuronal survival is also jeopardized by calcium dyshomeostasis and endoplasmic reticulum (ER) stress. Autophagy, inflammatory signaling, and mitochondrial quality control are also impacted by genetic mutations in PD-associated genes like SNCA, LRRK2, PARKIN, PINK1, and DJ-1. Misfolded ?-synuclein may spread pathology by propagating between neurons in a prion-like manner, according to recent evidence[10]. According to Braak's staging hypothesis, Lewy pathology typically progresses from the brainstem and olfactory bulb to cortical regions, which correlates with the sequential emergence of motor and non-motor symptoms[11]. The neuropathological landscape of Parkinson's disease is defined by these interrelated molecular events taken together, which also offer possible targets for treatments that alter the disease[12].

RATIONALE FOR TARGETING NEURO INFLAMMATION AND OXIDATIVE STRESS

An increasing body of research points to oxidative stress and neuroinflammation as key, interconnected processes in the etiology and development of Parkinson's disease (PD)[11]. Although the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) has long been thought to be the main pathological characteristic, it is now widely acknowledged that persistent redox imbalance and long-term activation of astrocytes and microglia play a major role in neurodegeneration[13]. Tumor necrosis factor-alpha (TNF-?), interleukin-1 beta (IL-1?), interleukin-6 (IL-6), and inducible nitric oxide synthase (iNOS) are among the pro-inflammatory mediators released by activated microglia. These mediators worsen dopaminergic neuronal injury by recruiting peripheral immune cells, producing too much nitric oxide, and causing cytokine toxicity[14]. Lipids, proteins, and nucleic acids undergo oxidative modifications as a result of the overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which are mostly caused by malfunctioning mitochondria and compromised antioxidant defense systems (such as reduced glutathione and superoxide dismutase). The cycle of neurotoxicity is maintained by this oxidative burden, which also encourages ?-synuclein misfolding and aggregation in addition to contributing to neuronal apoptosis. Targeting these pathways is justified by the finding that oxidative stress and neuroinflammation are early and driving factors in Parkinson's disease pathology rather than just secondary reactions[15]. Even in the early stages of the disease, post-mortem examinations have revealed widespread gliosis and increased oxidative damage in the affected brain regions.Furthermore, inflammatory and oxidative processes are reliably used to replicate neurodegeneration in experimental models like MPTP, 6-OHDA, rotenone, and LPS-induced PD, confirming that these are pharmacologically modifiable targets. Anti-inflammatory and antioxidant interventions, from natural compounds like curcumin, resveratrol, and quercetin to synthetic drugs like NSAIDs, N-acetylcysteine, and edaravone, have shown neuroprotective effects in preclinical studies by reducing cytokine release, boosting antioxidant enzyme activity, restoring mitochondrial function, and attenuating microglial

activation. The development of disease-modifying therapies that can stop or slow the progression of the disease is critically needed, as current symptomatic therapies have limited efficacy and long-term complications (such as levodopa-induced dyskinesia). A promising treatment option is to target oxidative stress and neuroinflammation, particularly in the early or prodromal stages of Parkinson's disease.

Modification of these two interrelated pathways together may be able to break the vicious cycle of oxidative stress-driven inflammation and inflammation-induced oxidative damage, protecting neuronal integrity and enhancing clinical results.

PATHOPHYSIOLOGY OF PD

Role of α-Synuclein Aggregation in PD

The SNCA gene encodes the 140-amino-acid presynaptic neuronal protein ?-synuclein, which is mainly involved in neuronal plasticity, neurotransmitter release, and synaptic vesicle trafficking. One of the main pathological features of Parkinson's disease (PD) is the abnormal aggregation of ?-synuclein, which causes Lewy bodies (LBs) and Lewy neurites (LNs) to form in the cytoplasm of neurons. Post-translationally modified ?-synuclein, especially phosphorylated (Ser129), nitrated, and ubiquitinated forms, are abundant in these intracellular inclusions and are susceptible to misfolding and ?-sheet-rich fibrillar aggregation. Numerous cellular functions, such as mitochondrial dynamics, autophagy-lysosomal function, axonal transport, and endoplasmic reticulum (ER) homeostasis, are disrupted by the toxic gain-of-function linked to aggregated ?-synuclein.The most neurotoxic forms of ?-synuclein are thought to be oligomeric and protofibrillar intermediates rather than mature fibrils. Dopaminergic neuronal apoptosis can be caused by these soluble oligomers' ability to insert into lipid membranes, create pore-like structures, and cause calcium dysregulation, oxidative stress, and mitochondrial dysfunction. Furthermore, ?-synuclein aggregates have the ability to activate microglial Toll-like receptors (TLR2/TLR4), which starts a pro-inflammatory reaction and prolongs neuroinflammation by releasing cytokines like TNF-? and IL-1?. Proteotoxic stress and inflammation are thus produced in a self-sustaining cycle.

The prion-like propagation hypothesis, which explains the topographical progression of Parkinson's disease pathology as described by Braak staging, is supported by new evidence. It postulates that misfolded ?-synuclein spreads from cell to cell via exosomes or direct transmission, seeding aggregation in healthy neurons[16].Additionally, the accumulation of ?-synuclein hinders lysosomal and proteasomal degradation pathways, which impedes cellular clearance mechanisms and exacerbates toxic accumulation. ?-synuclein is a promising therapeutic target because of its central role in the pathophysiology of Parkinson's disease. Aggregation inhibitors, immunotherapies, small-molecule chaperones, and gene-silencing methods are among the strategies being studied to lower ?-synuclein expression or increase its clearance, potentially leading to disease-modifying treatments[17].

INTERPLAY BETWEEN OXIDATIVE STRESS AND NEUROINFLAMMATION

Crosstalk between Microglial Activation and ROS

The progressive neurodegeneration seen in Parkinson's disease (PD) is largely caused by the interaction between reactive oxygen species (ROS) production and microglial activation. The central nervous system's (CNS) resident immune cells, known as microglia, have two functions: they mediate neuroinflammatory reactions and preserve homeostasis[18]. Microglia become activated and change toward a pro-inflammatory phenotype (M1-like state) in response to pathological stimuli, such as aggregated ?-synuclein, environmental toxins (e.g., rotenone), or mitochondrial debris. The NADPH oxidase (NOX2) complex, which catalyzes the reduction of oxygen to superoxide anions, is the main mechanism by which activated microglia produce significant amounts of ROS[19].

Concurrently, pro-inflammatory cytokines like IL-1?, TNF-?, and IL-6 are released by microglia, generating a feedback loop that intensifies inflammation and oxidative stress. Through lipid peroxidation, protein oxidation, and DNA damage, these ROS not only directly harm neurons but also act as signaling molecules that sustain microglial activation and increase the expression of inflammatory cytokines via the NF-?B and MAPK pathways. In addition, ROS-induced mitochondrial dysfunction in neurons releases damage-associated molecular patterns (DAMPs), such as mitochondrial DNA (mtDNA) and cytochrome c, which activate microglia's Toll-like receptors (TLRs) and worsen their inflammatory state. Persistent microglial activation

then increases the production of ROS, which causes chronic oxidative damage to dopaminergic neurons in the substantia nigra pars compacta (SNpc)[20].

Feedback Loop Amplifying Neuronal Damage

In Parkinson's disease (PD), dopaminergic neuronal damage within the substantia nigra pars compacta (SNpc) is amplified by a complex feedback loop that includes neuroinflammation, oxidative stress, mitochondrial dysfunction, and protein aggregation[21]. Genetic mutations (e.g., SNCA, LRRK2, PINK1, Parkin), environmental pollutants, or age-related factors that impair mitochondrial integrity and cellular homeostasis can start this self-propagating loop. In addition to damaging mitochondrial DNA (mtDNA) and respiratory chain proteins, early mitochondrial dysfunction causes an excess of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which also hinder mitophagy and energy metabolism. Additionally, the ROS burden accelerates the formation of Lewy bodies, which are hallmark aggregates in Parkinson's disease, by promoting lipid peroxidation, protein oxidation, and ?-synuclein misfolding[22]. The buildup of misfolded ?-synuclein and damaged cell components activates microglia and astrocytes, which in turn release pro-inflammatory cytokines (e.g., IL-1?, TNF-?, IL-6) and other ROS/RNS through inducible nitric oxide synthase (iNOS) and NADPH oxidase (NOX2). This neuroinflammatory environment intensifies oxidative damage and neuronal stress, which in turn intensifies ?-synuclein aggregation and mitochondrial dysfunction. In a vicious cycle, dying neurons release DAMPs (damage-associated molecular patterns), which include heat shock proteins, ATP, and mtDNA. These DAMPs then trigger glial cells via pattern recognition receptors (like TLRs and NLRs), increasing the production of ROS and inflammatory responses. A neurodegenerative loop is maintained by persistent activation of these pathways, which eventually leads to increasing dopaminergic cell death and deteriorating motor dysfunction.Breaking this destructive feedback loop represents a key therapeutic goal. Targeting ROS generation, modulating glial activation, enhancing mitochondrial resilience, and improving protein clearance mechanisms are critical areas under investigation for neuroprotective intervention in PD[23].

THERAPEUTIC INTERVENTIONS TARGETING NEUROINFLAMMATION

Neuroinflammation plays a central role in dopaminergic neurodegeneration in Parkinson's disease (PD), making it a major therapeutic target. Nonsteroidal anti-inflammatory drugs (NSAIDs), minocycline, and immunomodulators have shown potential in reducing inflammatory cascades and delaying disease progression. NSAIDs such as aspirin and ibuprofen act by inhibiting COX-2 in activated microglia, thereby lowering pro-inflammatory prostaglandins, though long-term use is limited by gastrointestinal and cardiovascular risks. Minocycline, a tetracycline antibiotic, exhibits strong neuroprotective effects by inhibiting iNOS, MMPs, microglial activation, and pro-inflammatory cytokine release, while also reducing apoptosis and mitochondrial dysfunction [23]. Immunomodulators like glatiramer acetate, fingolimod, and monoclonal antibodies against cytokines or ?-synuclein aim to block peripheral immune infiltration and shift microglia toward an anti-inflammatory phenotype. Targeting microglial activity and the NLRP3 inflammasome has also emerged as a promising approach, with inhibitors (e.g., minocycline, P2X7 antagonists) and blockers (MCC950, OLT1177) preventing cytokine maturation and neuronal pyroptosis. Natural compounds such as curcumin, resveratrol, EGCG, and quercetin further offer anti-inflammatory, antioxidant, and mitochondrial-protective effects, though challenges with bioavailability and BBB permeability persist. Together, these pharmacological and natural agents highlight the potential of combinatorial and multi-targeted strategies to attenuate neuroinflammation and slow PD progression [21].

Therapeutic Interventions Targeting Oxidative Stress

Antioxidant Therapies in Parkinson's Disease: Focus on N-acetylcysteine and Coenzyme Q10

Dopaminergic neuronal degeneration in Parkinson's disease (PD) is largely caused by oxidative stress, which is caused by an excess of reactive oxygen species (ROS) and reactive nitrogen species (RNS), mitochondrial dysfunction, and compromised endogenous antioxidant systems. Redox-homeostasis-restoring therapeutic approaches have garnered a lot of interest, especially when combined with antioxidants like coenzyme Q10 (CoQ10) and N-acetylcysteine (NAC)[24]. Glutathione (GSH) is a vital defense molecule

that neutralizes free radicals and detoxifies peroxides. N-acetylcysteine, a precursor to GSH, restores intracellular GSH stores. NAC has been demonstrated to improve mitochondrial function, lessen oxidative damage, and slow down ?-synuclein aggregation in PD models.By modifying NF-?B signaling, it also has anti-inflammatory properties by lowering the synthesis of pro-inflammatory cytokines like TNF-? and IL-6[25]. NAC shows promise in early-phase trials for the treatment of Parkinson's disease symptoms and neuroprotection, as clinical studies show that it can cross the blood-brain barrier and increase GSH levels in the substantia nigra. An important part of the electron transport chain (ETC) and a lipid-soluble antioxidant, coenzyme Q10 is crucial for redox regulation and mitochondrial bioenergetics. In animal models of Parkinson's disease, CoQ10 supplementation has been demonstrated to reduce oxidative stress markers, mitigate mitochondrial complex I dysfunction, and maintain neuronal viability. Although early clinical trials indicated that there might be advantages in delaying functional decline, later large-scale trials produced conflicting results, perhaps as a result of variations in dosage, bioavailability, and disease stage.Because of their mechanistic significance, NAC and CoQ10 both show promise despite varying degrees of clinical efficacy. Novel delivery methods, such as liposomal formulations and nanocarriers, may improve their therapeutic results and CNS bioavailability. For efficient PD treatment, future studies should concentrate on patient stratification, the best dosage techniques, and synergistic pairings with neurotrophic and anti-inflammatory drugs[26].

EXPERIMENTAL MODELS USED TO STUDY PD-RELATED NEUROINFLAMMATION AND OXIDATIVE STRESS

6-OHDA and Rotenone Models

Two popular neurotoxin-based methods for simulating Parkinson's disease (PD) pathology in rodents are the 6-hydroxydopamine (6-OHDA) and rotenone models. These models are useful for preclinical research because they replicate important pathological characteristics like ?-synuclein aggregation, oxidative stress, mitochondrial dysfunction, and selective dopaminergic neuronal degeneration[27]. According to the 6-OHDA model, nigrostriatal dopaminergic neurons degenerate in specific regions when 6-OHDA is directly stereotaxically injected into the striatum, medial forebrain bundle, or substantia nigra pars compacta (SNpc). 6-OHDA causes oxidative stress through autooxidation and hydrogen peroxide production after entering catecholaminergic neurons specifically through the dopamine transporter (DAT). This model is widely used to assess neuroprotective treatments and investigate motor dysfunction[28].

Rotenone, an inhibitor of mitochondrial complex I, is administered systemically or intracerebrally in the rotenone model. It replicates Lewy body-like inclusions, ?-synuclein aggregation, and both motor and non-motor symptoms of Parkinson's disease. Rotenone is useful for causing chronic, progressive dopaminergic neurodegeneration because of its lipophilicity, which enables it to pass through the blood-brain barrier. Both models are useful for testing anti-inflammatory, antioxidant, and neurorestorative therapies as well as for clarifying the pathophysiology of Parkinson's disease. However, when choosing suitable models for translational research, variations in onset, reproducibility, and systemic toxicity must be taken into account[29]s.

MPTP Model

One of the most researched and proven models for simulating the pathology of Parkinson's disease (PD), especially in non-human primates and mice, is the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model. Monoamine oxidase-B (MAO-B) in astrocytes breaks down MPTP, a lipophilic neurotoxin that easily crosses the blood-brain barrier, to produce 1-methyl-4-phenylpyridinium (MPP?), the active toxic metabolite. By inhibiting complex I of the electron transport chain, MPP? is selectively absorbed by dopaminergic neurons through the dopamine transporter (DAT) and builds up in mitochondria, resulting in a marked decrease in ATP synthesis and an increase in reactive oxygen species (ROS).The hallmark of Parkinson's disease (PD) is the selective degeneration of nigrostriatal dopaminergic neurons, which is caused by a series of events that include oxidative damage, mitochondrial dysfunction, and apoptotic cell death. The MPTP model has proven useful in researching the mechanisms of mitochondrial dysfunction, oxidative stress, and neuroinflammation. It replicates many clinical features of Parkinson's disease (PD), such as bradykinesia, rigidity, and dopaminergic cell loss. Rats are typically

resistant to the toxicity caused by MPTP, but mice and primates are the most sensitive. The MPTP model is still the gold standard for assessing neuroprotective and mitochondria-targeted treatments in PD research, despite certain drawbacks like the absence of Lewy body formation[27].

LPS-Induced Neuroinflammatory Models

An established experimental paradigm for examining the role of neuroinflammation in the pathophysiology of Parkinson's disease (PD) is the lipopolysaccharide (LPS)-induced model. Gram-negative bacteria's outer membrane contains LPS, which activates microglia's toll-like receptor 4 (TLR4). This results in a strong activation of NF-?B signaling and the production of proinflammatory mediators like cyclooxygenase-2 (COX-2), interleukin-1? (IL-1?), IL-6, tumor necrosis factor-alpha (TNF-?), and inducible nitric oxide synthase (iNOS).LPS mimics the inflammatory environment seen in Parkinson's disease (PD) by gradually destroying dopaminergic neurons in the substantia nigra pars compacta (SNpc) when administered intrastriatally, intracerebroventricularly, or systemically. The oxidative/nitrosative stress, chronic microglial activation, and non-cell-autonomous mechanisms of neuronal death are all highlighted in this model. The LPS model is useful for analyzing the immunopathogenic features of Parkinson's disease because it relies on immune-mediated pathways rather than direct mitochondrial inhibition, as neurotoxin-based models do. It is especially helpful for testing NLRP3 inflammasome blockers, microglial inhibitors, and anti-inflammatory medications. The LPS model complements other toxin-based PD models in preclinical research and offers important insights into how sustained neuroinflammation contributes to dopaminergic neurodegeneration, despite lacking characteristics like ?-synuclein aggregation and Lewy body formation[30].

Genetic Models (e.g., SNCA, PARKIN mutations

Our knowledge of the etiology of Parkinson's disease (PD), particularly in familial cases, has been greatly improved by genetic models of the disease. Among the most researched genes for simulating Parkinson's disease-related neurodegeneration are mutations in SNCA (?-synuclein) and PARK2 (Parkin). Transgenic mice that overexpress human wild-type or mutant SNCA (e.g., A53T, A30P) exhibit mild dopaminergic neuron loss, synaptic dysfunction, Lewy body-like inclusions, and progressive ?-synuclein accumulation. Despite frequently lacking the strong nigrostriatal degeneration observed in humans, these models are essential for researching protein aggregation, synaptic toxicity, and intracellular trafficking abnormalities. An E3 ubiquitin ligase involved in mitophagy is called PARK2 (Parkin). Neuronal vulnerability is exacerbated in Parkin-deficient models by mitochondrial dysfunction, elevated oxidative stress, and impaired clearance of damaged mitochondria.

Environmental-genetic interactions are important, though, because these models frequently need extra stressors (such as toxins or aging) to exhibit overt neurodegeneration. In order to simulate mitochondrial dysregulation, inflammation, and vesicle trafficking abnormalities in Parkinson's disease, other genes such as LRRK2, PINK1, and DJ-1 have also been investigated. Genetic models are limited in their ability to replicate sporadic PD, even though they represent monogenic PD forms. However, in precision medicine approaches to Parkinson's disease, they are crucial for investigating molecular mechanisms, finding biomarkers, and validating targeted therapies.

Molecular and Biochemical Markers Assessed

Pro-inflammatory Cytokines

The neuroinflammatory response linked to the pathophysiology of Parkinson's disease (PD) is mediated in large part by pro-inflammatory cytokines. Important cytokines, such as interleukin-1? (IL-1?), tumor necrosis factor-alpha (TNF-?), and interleukin-6 (IL-6), are released when microglia and astrocytes in the substantia nigra pars compacta (SNpc) become activated. These mediators worsen dopaminergic neuronal damage by fostering a pro-inflammatory milieu through autocrine and paracrine signaling pathways. The production of reactive oxygen species (ROS) and nitric oxide (NO), which cause mitochondrial dysfunction and oxidative damage, is increased when IL-1? stimulates the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS).

. IL-6 regulates astrocytic reactivity and immune cell recruitment, whereas TNF-? triggers apoptotic cascades and aids in the disruption of the blood-brain barrier (BBB) through its receptors TNFR1 and TNFR2. The inflammatory

cascade is accelerated by these cytokines, which also increase NLRP3 inflammasome activity. Patients' plasma, cerebrospinal fluid, and post-mortem PD brains have all shown elevated levels of these cytokines, which may indicate that they are involved in both central and peripheral immune dysregulation.

A promising therapeutic approach to reduce neuroinflammation and slow the progression of Parkinson's disease-related neurodegeneration is to target pro-inflammatory cytokines and their signaling pathways.

Oxidative Stress Markers (MDA, NO, SOD, GSH)

One of the main pathological mechanisms of Parkinson's disease (PD) is oxidative stress, which results from an imbalance between antioxidant defenses and reactive oxygen/nitrogen species (ROS/RNS). In both clinical and experimental models of Parkinson's disease, oxidative stress status is regularly assessed using a number of biomarkers. One well-known indicator of lipid peroxidation that shows oxidative damage to cell membranes is malondialdehyde (MDA). Increased lipid degradation brought on by ROS overproduction is indicated by elevated MDA levels in the plasma, brain tissue, and cerebrospinal fluid of PD patients. Although nitric oxide (NO) is a physiological signaling molecule, too much of it produced by inducible nitric oxide synthase (iNOS) can be neurotoxic. Protein nitration, DNA damage, and mitochondrial dysfunction result from its reaction with superoxide, which produces peroxynitrite.

The primary antioxidant enzyme that catalyzes the conversion of superoxide radicals into hydrogen peroxide is called superoxide dismutase (SOD). Unchecked superoxide buildup is a result of PD patients' decreased SOD activity. In the substantia nigra of Parkinson's disease (PD) brains, glutathione (GSH), a significant non-enzymatic antioxidant, is also significantly reduced, impairing cellular resistance to oxidative damage. By quantifying these markers, we can better understand the role of redox imbalance in the pathophysiology of Parkinson's disease and evaluate the effectiveness of treatment[31].

Neurotransmitter Levels (DA, DOPAC, HVA)

A significant drop in dopamine (DA) levels in the striatum is caused by the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) in Parkinson's disease (PD), which has a significant impact on motor control. The primary motor symptoms of Parkinson's disease (PD), such as bradykinesia, rigidity, and tremor, are caused by dopamine depletion. Dopamine is a crucial neurotransmitter that controls movement, reward, and motivation. Monoamine oxidase (MAO) breaks down dopamine enzymatically to produce 3,4-dihydroxyphenylacetic acid (DOPAC), which is then converted to homovanillic acid (HVA) by catechol-O-methyltransferase (COMT).

Changes in these metabolite concentrations reveal information about neuronal integrity and the rate of dopaminergic turnover. As dopaminergic terminals are lost in Parkinson's disease (PD), DOPAC and HVA levels are markedly decreased in the brain, cerebrospinal fluid (CSF), and urine. In clinical and experimental PD models, the biochemical markers of disease severity and progression are DA, DOPAC, and HVA, which can be measured using methods like high-performance liquid chromatography (HPLC). Additionally, these indicators are crucial for assessing the effectiveness of medications like L-DOPA, dopamine agonists, or neuroprotective substances that try to restore dopaminergic function.

Histopathological and Immunohistochemical Markers

When evaluating neurodegenerative changes and molecular alterations in Parkinson's disease (PD), histopathological and immunohistochemical analyses are essential tools. Lewy bodies, which are cytoplasmic inclusions mainly made of aggregated ?-synuclein, and the selective loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) are the two main histopathological characteristics of Parkinson's disease (PD). While Luxol fast blue (LFB) can measure demyelination, histological stains like hematoxylin and eosin (H&E) are used to assess general neuronal architecture and degeneration. In PD models, Nissl staining reveals chromatolysis and neuronal loss. Tyrosine hydroxylase (TH) is one immunohistochemical marker used to identify dopaminergic neurons; decreased TH immunoreactivity is indicative of dopaminergic degeneration. The accumulation of the protein in Lewy pathology is confirmed by ?-Synuclein immunostaining, which can identify both soluble and aggregated forms of the protein. In order to gain insight into neuroinflammation, Iba-1 and GFAP are frequently used to measure microglial and

astrocytic activation, respectively. The pathological landscape is further characterized by other markers like 4-HNE (oxidative stress), COX-2 (inflammation), and cleaved caspase-3 (apoptosis). When combined, these immunohistochemical and histopathological tools offer a comprehensive picture of Parkinson's disease progression and are crucial for confirming neuroprotective treatments in test models[32]

Table 1. Pathophysiological Mechanisms and Therapeutic Strategies Targeting Neuroinflammation and Oxidative Stress in Parkinson's Disease

Pathological Mechanism	Key Features	Molecular Players	Therapeutic Strategies	References
Neuroinflammation	Microglial/astrocytic activation, cytokine overproduction	IL-1β, TNF-α, IL-6, NF-κB, NLRP3	NSAIDs, minocycline, NLRP3 inhibitors, microglial suppressants	[32]
Oxidative Stress	ROS/RNS accumulation, lipid peroxidation, antioxidant depletion	MDA, NO, SOD, GSH, Catalase, 4-HNE	N-acetylcysteine, Coenzyme Q10, EGCG, curcumin	[33]
α-Synuclein Aggregation	Lewy body formation, proteostasis impairment	SNCA, ubiquitin–proteasome system, autophagy-related genes	Polyphenols (e.g., baicalein, curcumin), autophagy inducers (rapamycin)	[34]
Mitochondrial Dysfunction	Decreased ATP, complex I inhibition, cytochrome c release	Complex I, PINK1, Parkin, Drp1	MitoQ, SS-31, mitophagy enhancers (e.g., urolithin A)	[35]
BBB Disruption	Loss of barrier integrity, immune cell infiltration	Tight junction proteins (occludin, claudin-5), MMPs	Barrier-protective agents, anti-inflammatory compounds	[36]
Apoptosis	Caspase-3 activation, DNA fragmentation	Caspase-3, BAX, Bcl-2, cytochrome c	Anti-apoptotic agents, mitochondrial stabilizers	[37]

Table 2. Common Experimental Models Used in Parkinson's Disease Research

Model	Induction Agent	Pathological Features	Advantages	Limitations	References
6-OHDA	6-Hydroxydopamine	Selective dopaminergic neuronal loss, motor deficits	Rapid onset, reproducible lesions	Requires intracerebral injection, no α-syn aggregation	[38]
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine	Nigrostriatal degeneration, mitochondrial dysfunction, motor symptoms	Mimics human PD pathology, used in primates	No Lewy bodies, not effective in rats	[39]
Rotenone	Mitochondrial complex I inhibitor	Systemic mitochondrial dysfunction, α-syn aggregation, oxidative stress	Environmental relevance, systemic delivery	High variability, peripheral toxicity	[40]
LPS	Lipopolysaccharide	Neuroinflammation, cytokine release, microglial activation	Mimics inflammatory component of PD	No dopaminergic specificity, no Lewy bodies	[41]
Genetic models	SNCA, PARKIN, LRRK2 mutations	α-Syn aggregation, impaired mitophagy, progressive neuronal loss	Models familial PD mechanisms	Slow progression, incomplete motor phenotype	[42]

CURRENT CHALLENGES AND FUTURE DIRECTIONS

Current treatments for Parkinson's disease (PD) remain largely palliative, addressing symptoms without halting neurodegeneration. Levodopa (L-DOPA) is still the gold standard for motor symptoms, yet long-term use often leads to dyskinesias and motor fluctuations. Adjuncts such as dopamine agonists, MAO-B, and COMT inhibitors provide modest benefits but carry neuropsychiatric risks. Importantly, none of these therapies target core disease mechanisms, including mitochondrial dysfunction, oxidative stress, neuroinflammation, and α-synuclein aggregation. Progress is further hindered by the blood–brain barrier, limiting delivery of neuroprotective agents. Experimental approaches like deep brain stimulation, gene therapy, and stem cell transplantation show promise but remain limited. Since motor symptoms appear only after major neuronal loss, early detection is critical. Emerging biomarkers (α-synuclein species, oxidative stress markers, cytokines, DAT-SPECT, PET) and genetic profiling (SNCA, LRRK2) may enable earlier intervention. Combination therapies and precision medicine, integrating pharmacogenomics and multi-omics, offer hope for tailored,

disease-modifying strategies.

CONCLUSION

For Parkinson's disease (PD), addressing oxidative stress and neuroinflammation has great therapeutic potential. Disease progression, α-synuclein aggregation, and dopaminergic neuronal degeneration are all influenced by these interrelated pathological processes. Anti-inflammatory drugs, antioxidants, and mitochondrial protectants have the potential to reduce neuronal damage and enhance clinical results, according to recent research. The effectiveness of these interventions in regulating oxidative damage, cytokine release, and microglial activation has been confirmed by experimental models. In addition to traditional dopaminergic treatments, a multimodal strategy combining these tactics could provide synergistic neuroprotection. To achieve significant disease modification in Parkinson's disease, future therapies should concentrate on biomarker-guided treatment, early intervention, and personalized medicine.

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