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REVIEW ON POTENTIAL MECHANISMS INVOLVED IN OXIDATIVE STRESS IN THE PATHOGENESIS OF PARKINSON'S DISEASE AND THE ROLE OF BIOMARKERS

Dr. Manjunatha P. Mudagal*, Gayathry P., Akhila N. R., Akanksh Das, Kmenlang Sutong and Vibhu Bhardwaj

Acharya and BM Reddy College of Pharmacy, Department of Pharmacology, Soldevanahalli, Bangalore, Karnataka, India.

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***Corresponding Author**
Dr. Manjunatha P. Mudagal
Acharya and BM Reddy College of Pharmacy, Department of Pharmacology, Soldevanahalli, Bangalore, Karnataka, India.

ABSTRACT

Parkinson's disease is a common, multifactorial neurological disorder caused by the degeneration of dopaminergic neurons in SNpc leads to dopamine deficiency. It is the second common neurodegenerative disease. Risk factors such as genetic and environmental provide an impact on the diseased condition. It was primarily characterized by the overexpression of the clumps of proteinaceous inclusions called Lewy bodies composed of alpha-synuclein & having a marked motor and non-motor features. Oxidative stress exerts a negative effect in Parkinson's disease, is a significant contributory factor in the progression of disease condition through various mechanisms including reactive oxygen species generation that promotes the oxidation of macromolecules such as lipids, proteins & nucleic acid, mitochondrial dysfunction, neuroinflammation including microgliosis, astrogliosis, lymphocytic infiltration, excitotoxicity. To provide better clinical intervention and treatment, it is essential to find reliable, robust, specific & sensitive biomarkers for Parkinson's disease. It can clearly distinguish the disease from other conditions, monitor its progression, or indicate a positive response to therapeutic intervention. This review covers the mechanisms involved in oxidative stress in the genesis of disease and current potential biomarkers, highlighting their role in Parkinson's disease.

KEYWORDS: Parkinson's disease, Pathogenesis, Neuropathology, Proteins, Oxidative stress, Biomarkers.

INTRODUCTION

Parkinson's disease is a chronic, progressive neurodegenerative disorder characterized by dopaminergic neuron death that develops in Substantia nigra pars compacta (SNpc) and accumulation of abundant intracellular proteinaceous aggregates called Lewy bodies primarily comprised of fibrillar alpha-synuclein and ubiquitinated protein in some remaining nigral neurons.[1] It is the 2nd top-most prevalent primary neurodegenerative disorder of CNS[2] & was categorized by tremor, gait disorder, bradykinesia, stiffness, postural instability, weak and clumsy limb.[3] Rather than motor symptoms, several non-motor symptoms that accompany Parkinson's disease, are sensory, psychiatric symptoms namely anxiety, depression, sleep disorder, and apathy and cognitive abnormalities include learning, memory, perception, problem-solving.[4] Neuroinflammation has also been assumed to result in oxidative stress, overproduction of cytokines, excessive activation of microglia and other inflammatory mediators, as well as ROS, which accelerate disease progression.[5] Apart from dopamine, well-known other neurotransmitters such as Glutamate, GABA, Acetylcholine also having a role in Parkinson's disease symptoms.[6] The most pervasive neurodegenerative triggers of parkinsonism are alpha-synucleinopathies (Lewy Body Disease), Multiple System Atrophy (MSA), Progressive Supranuclear Palsy (PSP), and Corticobasal Degeneration (CBD). Such ailments are described mainly based on the accumulation of the predominant proteins within degenerated neurons and glial cells. Therefore reliable biomarkers are required for early and accurate disease diagnosis to predict disease incidence and progression, as they can be used as objective and characteristic evaluation indicators of normal biological processes and pathogenic processes of the disease. The appropriate biomarkers- alone or in combination, are used to diagnose and record the progression of Parkinson's disease.[7] The featured gold standard for interpretation of Parkinson's disease is the emergence of SNpc degeneration and the "Lewy pathology". Taken into account, it usually comprises abnormal alpha-synuclein aggregates called Lewy body & Lewy neurites (altogether Lewy Pathology).[8] The Predominant location of Lewy bodies is chiefly in the brain stem and diencephalon (usually SNpc, dorsal vagal nucleus).[9] Patients associated with dementia shows the involvement of Lewy bodies and also the aggregation of alpha-synuclein intraneuronal native to the peripheral region such as olfactory and gastrointestinal tract central region include medulla, pons, cortex of nervous system which track the motor symptoms and non-motor symptoms; assisted by the participation of midbrain and ultimately to cortical region of the brain.[10-11] Impairment of subnuclei presents in SNpc along with intense wiping out neuromelanin-laden projections often taken into consideration as the most

important trademark of Parkinson'sdisease.[12] The disease is slightly more common in men than in women and the prevalence of this disease is increasing with age and it affects 1% of the total population above 60 years.[13] Worldwide estimations of Parkinson's disease by WHO showed as 35.6 million.[14] This number would be expected to double between 2005 & 2030, more than triple by 2050.[15-16] In high-income nations, the estimated age-standardized annual incidence rate is 14 per 100000 people aged 65 years or older.[17] The average prevalence of Parkinson's disease in developed countries is 0.3% in the general population, 1% in people older than 60 years, and 3% in people older than 80 years; the occurrence rate of disease is estimated to range from 8 to 18 per 100000 person-years.[18] The disease frequency ranges vary from country to country and the rate of occurrence is considerably greater in Europe and North America than in West Africa and Asia.[19] Oxidative stress having an impact on the modulation of activity in the disease progression. In this review, the association between Parkinson's disease & oxidative stress will be conferred with possible mechanisms underlying oxidative stress & highlighting the role of biomarkers.

Pathogenesis

A key characteristic primary hallmark feature of Parkinson's disease is the neurodegeneration in SNpc and nigrostriatal (dopaminergic) tract, resulting in a decrease in striatum dopamine, needed for muscle tone and motor coordination. So an inconsistency between the cholinergic (excitatory) and dopaminergic (inhibitory) striatal mechanism occurs, the way that results in motor dysfunction. Triggering of free radicals in the presence of Fe^{2+} ions, found in basal ganglia mainly by the oxidation of aldehyde dehydrogenase and MAO-B. Glutathione and other defensive mechanism annihilated them and it potentially contributes to neuronal death, often causing lipid membrane and DNA damage. By inducing Ca^{2+} overload via the NMDA receptor, excess stimulation of excitatory transmitter glutamate may trigger 'excitatory' neuronal death. Through the administration of neuroleptics, metoclopramide (dopamine blockers), trigger drug-induced temporary or reversible symptoms of parkinsonism.[20]

Neuropathology

The key pathological characteristic of Parkinson's disease is the loss of dopaminergic neurons in the substantia nigra.[21] Usually, the most grievously infected region of substantia nigra pars compacta is the ventrolateral tier, which comprising neurons that project to the dorsal putamen of the Striatum.[22] Neuronal disruption occurs in several other regions of brain-like, locus coeruleus, Meynert nucleus basalis, pedunculopontine nucleus, raphe

nucleus, vagus dorsal motor nucleus, amygdala, and hypothalamus.[23] Many other non-dopaminergic neurotransmitter systems, like cholinergic, adenosinergic, glutamatergic, GABAergic, serotonergic, nor-adrenergic, and histaminergic, are also affected.[24] The pathological hallmark of Parkinson's is the Lewy bodies (Lewy pathology), aggregation of alpha-synuclein protein. Mainly in the neuronal phase, large alpha-synuclein aggregates from round laminated eosinophilic cytoplasmic inclusions in the neuronal body & fibrils made of insoluble alpha-syn (Lewy neurite) polymers are deposited. This accumulation impairs the functioning of the mitochondria, lysosome, endoplasmic reticulum & interacts with microtubular transport. In advanced Parkinson's disease, the depletion of pigmented neurons leads to gross depigmentation of SN,[25] directly correlated with the death of dopaminergic-neuromelanin containing neurons present in SNpc & nor-adrenergic neurons in locus coeruleus.[26] In addition to alpha-synuclein, the molecular components of Lewy bodies including proteins like Ubiquitin, Tau, Parkin, Heat shock proteins (HSPs), oxidized or nitrated proteins, cytoskeletal proteins (neurofilaments, microtubule-associated proteins, & tubulin), proteasomal & lysosomal elements.[27] The main staging system of disease by Braak & co-workers has been proposed to introduce the 6 stages of pathology in Parkinson's disease (**Table 1**) beginning from the peripheral nervous system progressively affecting the CNS rostrocaudal all-round the brain, in a chronological predictable series.[28]

Table 1: Braak six staging concept for Parkinson's disease.

Stages	Lewy body assessment
Stage 1, 2	• The lesions were primarily observed mainly in the dorsal motor nucleus, reticular formation, anterior olfactory nucleus. • Patients were considered as Asymptomatic or Pre-symptomatic, although early non-motor features may be present such as autonomic (example: constipation), olfactory, and sleep-related dysfunction.[29]
Stage 3	• The SNpc becomes active as the disease progresses with Lewy body pathology. • Neuronal loss has been observed in melanized neurons.
Stage 4	• Simultaneous entering to temporal limbic cortex • Clinical motor features.[30]
Stage 5,6	• Participation of whole neocortex, high order area such as Cortical regions (insular cortex, primary cortical areas).[31]

Following the revision of the Braak hypothesis, it indicates the association of pathology with alpha-synuclein is initiated at nasal and intestinal mucosal sites, particularly in olfactory bulb & enteric cell plexuses called the "Dual-hit hypothesis". It implies that, via the olfactory pathway, an unknown, possibly infectious, pathogen reaches the brain. Notably, PD patients also have olfactory prodromal deficits. Or the pathogen is transmitted to the intestine by

swallowing nasal secretions and it enters the vagus nerve and the CNS. The identification of Lewy Bodies in the intestinal systems, vagus nerve, derives pathological support for this hypothesis.[32]

Potential Interaction of Encoded Proteins & Their Mutation In Parkinson's Disease

Early potential targets that having a major role in the progression of Parkinson's disease. The aim of understanding the therapeutic targets to comprehend the major pathological changes noted is to effectively alleviate or bring down the progression of the disease.[33] The disease is triggered through the coordinated effects of hereditary and environmental interaction.[34] Most cases are probably to be focused due to on the complex interaction between genes and the environment. The interplay of environment and genes is a problem even in cases with known triggers is likely.[35] Majority of cases of this pathological condition cannot be explained by genetic mutation itself. However, the particular gene involved in the genetic pathogenesis of this disorder has been put emphasized by a mutation in a specific gene in hereditary Parkinson's disease.[36] 6 gene loci found in association with this diseased condition.[37] Alpha-synuclein, PARKIN, PINK-1, DJ-1, LRRK2, ATP13A2, and UCH-L1 gene mutation, which have been shown a deep involvement.[38-39]

Alpha-synuclein

The protein alpha-synuclein is abundantly found in neurons and glia within the CNS and is concentrated in the neuronal structure.[40] This is a small, soluble, acidic protein of 140 amino acid residues, and also it is a monomeric protein, primarily in cytosolic location, and a fraction has been found in mitochondria.[41] Belonging to a family of structurally homologous proteins, synuclein is mainly categorized namely as alpha-synuclein, beta-synuclein, gamma-synuclein.[42-44] The protein aggregates are the neuropathological aspect of the diseased condition which is mainly a central component of the Lewy bodies and Lewy neurites.[45] Various cellular function which may obstruct and these aggregates are present as in case of dementia with Lewy bodies (DLB) & multiple system atrophy (MSA).[46] In general, the immunohistochemistry of α-synuclein is typically a global standard in neuropathological assessment.[47] The three distinct key cognizance emerged with the repeated research findings: (1)α-synuclein pathology is prevalent in the neuritic growth process, (2) it is widespread in varying domains of the brain, (3) it is also noticeable in other synucleinopathies, including in cases of Alzheimer's disease (thus termed LB version of AD), NBIA type 1 (Neurodegeneration with brain iron accumulation, PAF (pure autonomic failure)

and in essential tremor.[48] The pathological distribution at both cellular and regional levels varies in each diseased state.[49] It possesses a capacity to adhere to negatively charged cell membrane phospholipid, which occurs through the highly conserved region, N-amphipathic domain, and β-sheet structures on protracted periods of incubation.[50-51] During a pathogenetic process, alpha-synuclein acquires neurotoxic properties so the soluble alpha-synuclein monomers at first form oligomers, then gradually merge to arrange as tiny protofibrils & ultimately big, insoluble alpha-synuclein fibrils (i.e., this aggregates that makeup Lewy pathology), due to lack of proper clearance of lysosomal or ubiquitin-proteasome system.[52-54] The other underlying cause of alpha-synuclein accumulation and aggregation is the occurrence of mutations that raise the risk of alpha-synuclein misfolding and oligomerization or deficiency in the molecular pathways that are concerned with alpha-synuclein degradation or misfolding.[55-56] There have been several independent point mutations identified.[57] Alpha-synuclein mutations are detrimental to dopaminergic neurons because of the alteration of a set of intracellular signal programs.[58] Most important 6 dominant inherited point mutations (A30P, E46K, H50Q, G51D, A53E & A53T) in the alpha-synuclein gene have been identified as rare causes for familial Parkinson's disease.[59-60] In single point mutation, a conversion of G to A at position 209, which eventually changed the code of the amino acid from Alanine to Threonine at residue 53 (A53T).[61] The first dominantly inherited mutation in Parkinson's disease to be identified was an A53T alteration of the gene encoding α-synuclein & it causes an extreme phenotypic form of PD frequently followed by dementia[62] & muscle rigidity and bradykinesia are the major clinical characteristics.[63] A53T also causes mitochondrial dysfunction- and cell death pathways mediated by endoplasmic reticulum stress.[64] These mutations can form filaments, aggregates of substantia nigra, and other brainstem neurons in dopamine neurons and make dopamine neurons more vulnerable to oxidative stress.[65] Two other point mutations (A30P, E46K) have been identified &they show the segregation with the disease.[66] The chemical process oligomerization is accelerated by A30P α-synuclein mutation, while the A53T mutation accelerates fibrilization & it accelerates alpha-syn aggregation faster than A30P alpha-syn mutation, because of its capacity to induce fibrilization.[67] The second most major cause of Parkinson's disease is autosomal dominant inherited duplication & triplication of the SNCA gene. Duplication of alpha-synuclein locus results in late-onset autosomal dominant types of PD, as shown in sporadic PD, while triplication of alpha-synuclein locus leads to a more extreme phenotype with earlier age at onset.[68]

Ubiquitin C-terminal hydrolase L1 (UCH-L1)

It is graded as a deubiquitinating enzyme (DUB). The two groups of DUB are; (1) UBPC & (2) UCH, which hydrolyses a small proportion of C-terminal ubiquitin adducts. Multiple UCH isoforms are thought to occur in humans, even so, UCHL-3 is present in all tissues, whereas UCHL-1 is specifically limited to testis or ovaries.[69] Ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1) was the extremely most abundant neuronal-specific ubiquitin recycling enzyme. It is known as neuronal-specific protein PGP 9.5, where, remarkably comprising up to 2% of the total brain protein material[70] and approximately 5% residues exist in synaptic vesicles which have mainly been shown to co-localization with alpha-synuclein.[71] It is vital for the maintenance of axonal health & stability and its loss leads to axonal degeneration & neuronal death.[72] UCHL-1 has three known enzymatic roles: (1) hydrolase activity for Lys48-linked ubiquitin chains targeted for proteasomal degradation; (2) recent newly recognized ATPase-independent dimerization-dependent ubiquitin ligase activity for Lys63 ubiquitin molecule residue; (3) A function in ubiquitin monomer homeostasis, where UCHL-1 tends to modulate free ubiquitin monomer breakdown in the cell.[73] The Ubiquitin proteasome system was a significant cellular pathway that ubiquitinates disrupted proteins & degrade them via 26S proteasome.[74] The irregularities in this pathway lead to the failure to remove & destroy misfolded proteins, which results in the accumulation of misfolded proteins in the cell contribute to the development of inclusion bodies, and cause significant loss of dopaminergic cells.[75] Oxidation of UCHL-1 & following decrease in the enzymatic activity impair neuronal function and its survival leads to the pathogenetic condition. Owing the solubility is decreased, that lead to a subsequent rise in insoluble UCHL-1.[76-77] Mutation in the gene UCHL-1 & its variation in protein activity have been found. An isoleucine 93 to methionine amino acid mutation (I93M) has been reported as a cause of autosomal dominant Parkinson's disease.[78-79]

Parkin

Parkin, an enzyme protein of 465 amino acids of approximately 52,000 M molecular mass encoded by the PARK2 gene, comprises 12 exons spanning 1.5 Mb.[80-81] It is a protein, consist of a ubiquitin homology domain at its N-terminal, by which it interacts with its protein targets[82] & comprising 2 RING fingers at its c-terminus and has been described as an E3 ubiquitin-protein ligase, needed for ubiquitination of proteins, can be activated by autophosphorylation and is necessary for the ubiquitin-proteasome deterioration of target substrates.[83] It is also an element of the ubiquitin system, is a piece of chief machinery for

the degradation of adenosine triphosphate-dependent proteins.[84] This protein appears to unfold when overexpressed in cells. A rise in the amount of unfolded proteins in the endoplasmic reticulum (ER) causes what is called endoplasmic reticulum stress,[85] resulting outcomes of which is programmed cell death.[86] Interestingly, a broad range of mutations within the parkin gene, such as exon deletions, duplications, & point mutations, eventually cause autosomal recessive early-onset Parkinsonism.[87-88] Mutations like R42P, R46P, K211N, C212Y, C253Y, C289G, and C441R, causing the defect to its mobilization to depolarized mitochondria & hinder mitophagy, contributes to the progression of a diseased state.[89]

DJ-1

It is well known as PARK 7, in which the mutation was attributed to the early incidence of recessive Parkinson's disorder causes abolishing antioxidant activity, display increased vulnerability to oxidative stress, reducing protein stability. A homozygous exon 1 to 5 deletion was the first mutation found in this family, that causes the entire protein deletion.[90] The mutation involved in this gene is extremely rare occurring about 1-2% early stage of cases. It suggested being co-localized with mitochondria & up-regulation caused under high-stress conditions. The cellular processes related to DJ-1 include attenuating oxidation, RNA binding, cell transformation, & androgen receptor signaling.[91] The analysis of the diseased brain shown the oxidative damage of DJ-1 & increase the total protein content. The mutation which was found in a homozygous or heterozygous state ultimately causes the loss of the function of a protein, involving intracellular oxidation-reduction.[92] Mutant DJ-1(L166P and M26I) enhance the susceptibility of SHSY5Y cells to oxidative stress by suppressing H2O2 neuroprotection and induction of thioredoxin-1 by inhibition of factor 2 signal pathway associated with nuclear factor erythroid2.[93] The deficiency of DJ-1 in neurons results in the decrease in glutamine reflux, serine biosynthesis strengthened cellular antioxidant response cause the dopaminergic neuronal degeneration.[94]

Possible Mechanisms Underlying The Oxidative Stress In Parkinson's Disease

Oxidative stress has been a proposed key part of Parkinson's disease. It describes an imbalance between the levels of reactive oxygen species (ROS) such as free radicals and the biological system's ability to detoxify the reactive intermediates through antioxidants creating a dangerous state that contributes to cellular death. H_2O_2, hydroxyl radical, nitric oxide (NO), and superoxide radicals are free radicals that are mainly harmful to cells, while SOD,

catalase, glutathione, and uric acid are important antioxidants in the human body.[95] SOD catalyzes the transformation of radicals from superoxide to hydrogen peroxide, by catalase and glutathione peroxidase the hydrogen peroxide converts into water and oxygen. Glutathione peroxidase, which transforms nitrate into nitrite. During the rate-limiting stage of purine catabolism, uric acid is transformed by xanthine oxidase. All components of the cell, including DNA, lipids, and proteins, are destroyed by decreased activity of the antioxidant protection mechanism to defend against free-radical generation, eventually leading to cell death.[96] The relationship between oxidative stress & dopaminergic neuronal degenerations has been further confirmed with toxic substances that can trigger oxidative stress namely 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, Rotenone, OHDA.[97] Besides several other neurodegenerative disorders are analogous to oxidative stress, which indicates oxidative stress was the major contributing mechanism in neuronal degenaration.[98]

ROS In Neurotoxicity

It is a kind of free radical, unstable molecule containing oxygen and which freely interacts with other molecules present in the cell. The generation of reactive oxygen species inside the cells can induce disruption to DNA, RNA, and proteins and cause cell death.[99] Through several pathways, ROS can be generated through inter-relationship through redox-active metals & oxygen species, like through Fenton and Haber-Weiss reactions or indirect cycles which involve stimulation of enzymes such as nitric oxide synthase or NADPH oxidase.[100] The major free radicals dominant in ROS such as superoxide anion radical (O_2-), hydroxyl radical ($^{\bullet}OH$), and hydrogen peroxide(H_2O_2).[101] Superoxide anion primarily generated by the electron transport chain mitochondrial complex I and III, is immensely active & can pass effortlessly through the inner mitochondrial membrane, there it will reduce to hydrogen peroxide. It can also be generated by peroxisomes in addition to mitochondria.[102] As catalase present in the peroxisome, H_2O_2 is reduced into the water for preventing its unnecessary aggregation. Once peroxisomes are injured and the enzymes are getting down-regulated, H_2O_2 is released free into the cytosol, provide a way toward oxidative stress.[103] Around 20 percent of the body's oxygen supply is utilized by the brain, &a large fraction of that oxygen is transformed to ROS.[104] This can be produced from many sources in the brain, together in neurons and glial cells by electron transport chain (ETC), a key donor at the mitochondrial level.[105-106] Significant experimental evidence suggests that ROS, which results from abnormal dopamine metabolism, reduction in glutathione level, and elevated levels of iron & calcium depositions in SNpc, is a key contributor to dopaminergic neuronal

loss in the diseased brain.[107] In addition, the brain contains a large amount of PUFA, under oxidative stress, eventually leads to lipid peroxidation & will give rise to the production of toxic substances.[108]

Mitochondrial Dysfunction

Many authentications suggested that mitochondrial dysfunction act as a central factor in the pathogenesis of Parkinson's disease.[109] Since mitochondria play multiple roles as the source and target of ROS. It is a complex organelle with several functions. In addition to their role in energy generation, they are actively involved in calcium homeostasis, stress response, and cell death pathways. So that the dysfunction of mitochondria thus contributes to cellular damage and is associated with neurodegeneration.[110] The fundamental source for ROS is the electron transport chain because a small percentage of the superoxide anion is formed during the depletion of O_2 to H_2O.[111-112] The gradient of protons generated by the process of electron transport transversely the inner mitochondrial membrane that undertakes ATP biosynthesis via ATP synthase.[113] some dehydrogenase of Tricarboxylic acid (TCA) & complexes I, II, III also can produce superoxide anion.[114-115] The first stage in the mitochondrial electron transport chain is catalyzed by complex I (NADH: ubiquinone oxidoreductase). It draws power from NADH oxidation, transfers, and converts ubiquinol to ubiquinone. Ubiquinol is a membrane-soluble carrier that discharges a couple of Complex III electrons.[116-117] Complex II (succinate-coenzyme Q reductase) creates a connection among the tricarboxylic acid cycle & electron transport chain resulting in odd electrons being released to Complex III via ubiquinol.[118] By minimizing cytochrome c through ubisemiquinone oxidation & by the passage of protons via mitochondrial matrix into the intermembrane space, Complex III (ubiquinone-cytochrome c oxidase) hand-out greatly to proton gradient.[119] Whenever a decline in the electron transport chain, molecular oxygen will absorb electrons via Complex III take place in the formation of a superoxide anion.[120] Complex I respiratory chain deficiencies account for the majority of the generation of unfavorable neural apoptosis and are considered one of the primary causes of ROS, which will in turn the inhibit complex1. It is well observed in platelets, skeletal muscles, fibroblasts, lymphocytes, etc.[121-122] The major complex 1 inhibitors that have a preferential role include MPTP, rotenone.[123] The mechanism underlying the MPTP is, it crosses the BBB & is taken up by the astrocytes, and is metabolized to 1-methyl-4-phenylpyridinium by MAO-B oxidase further let out to extracellular space. 1-methyl-4-phenylpyridinium (MPP+) is the amine substrate for dopamine transporter & it is selectively taken into dopaminergic

neurons, so the Complex I of mitochondrial electron transport chain will get disrupted, results in a decline in ATP production and rise in the generation of ROS.[124-125] Rotenone is the other complex 1 inhibitor, was it active in the oxidative damage to proteins and Lewy body-like inclusions.[126] Other evidence of dysfunction of mitochondria-associated with oxidative stress and damage to dopaminergic cells derives from the observation that mutation in genes encoded in proteins such as alpha-syn, parkin, DJ-1, or PINK is associated with hereditary forms of the disease, provides a physiological basis for the pathology of Parkinson's disease.[127] These observations conveyed that the mutation in the protein encoded by genes affect the mitochondrial function and an increase in oxidative stress provide a deleterious condition in the neurodegeneration.[128-129]

Neuroinflammation

Neuroinflammatory mechanisms are also likely the essential contributor to the cascade of neuronal degeneration events.[130-131] These mechanisms largely comprised of Microglial activation, astrogliosis, and lymphocytic infiltration.[132]

Microglial Activation

The concept of neuroinflammation primarily begins with a concept of microglial activation.[133] Microglia are a specialized population of macrophages & components of the innate immunity system found in CNS. They remove damaged neurons & infections are important for maintaining the health of the CNS, which is activated upon brain injury and immune challenge.[134] An major inception of superoxide & nitric oxide is activated microglia, which in turn leads to oxidative & nitrative stress throughout the microenvironment of the brain. By generating other potentially toxic factors, such as glutamate and pro-inflammatory cytokines like TNF-alpha, IL-1β, IL-6, and IFN-γ & an accompanying relation with alpha-synuclein results of pro-inflammatory mediators in CSF and basal ganglia induce activation of microglia.[135-136] Not only alpha-synuclein but also LRRK2, DJ-1, parkin are also involved, which provide a way for the microglial activation and lead to neurodegeneration.[137] Microglial activation is described as a double-edged sword, such as by eliminating endogenous or exogenous compounds and they act as neuroprotective cells and having a high level of glutathione and glutathione peroxidase, perform to shield them against harmful hydrogen peroxide level, on the other hand, the death of dopaminergic neuron release oxidized proteins, lipids, and DNA that are identified by microglia as damaged molecules, triggering their activation. In turn, microglial activation

leads to an over-production of cytokines, chemokines, ROS, reactive nitrogen species, causing the neurotoxic vicious cycle[138-139] (**Figure 1**). Plasma and serum analysis have also been showing the upregulation of proinflammatory cytokines and also serum level of MIF(macrophage inhibitory factor) is increased.[140] The receptors for these cytokines are expressed by dopaminergic neurons, implying that they are responsive to these cytokines. For example; TNF alpha receptor-1 is expressed in dopaminergic neurons and increases the expression of this receptor. While cytokines can actively exert toxic effects by binding to their receptors and activating second messenger pathways, they can also indirectly generate cytotoxic effects.[141] The enzymes such as iNOS (inducible nitric oxide synthase) or COX 2, that can also produce toxic reactive species.[142]

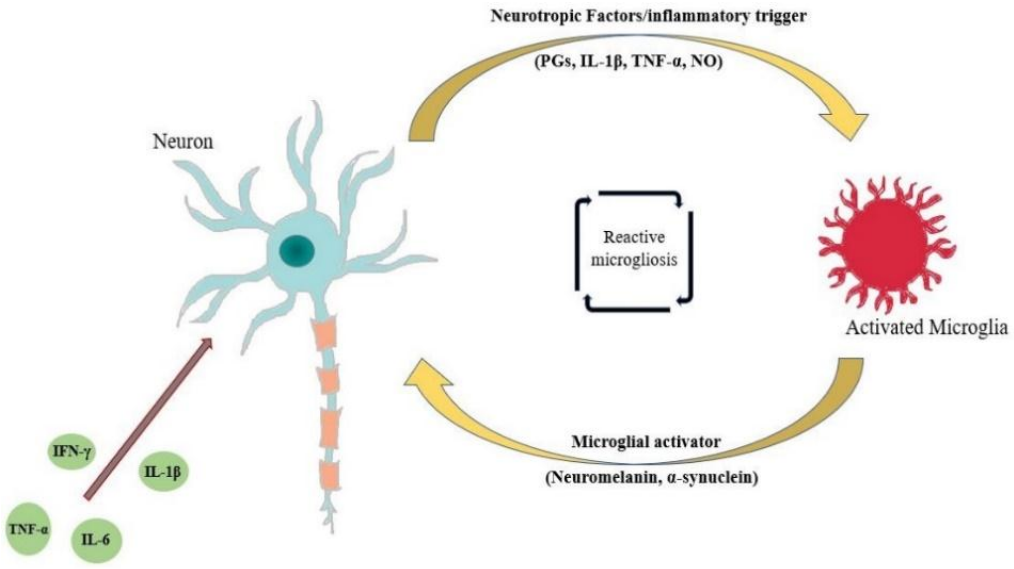

Figure 1: Neurotoxic microglial activation.

Astrogliosis

Besides astrogliosis is the other key aspect of neuroinflammation.[143] Astrocytes are glial cells & the most common abundant type of cell in the human brain, that are vital for maintaining neuronal health and provide structural and metabolic assistance, regulation of synaptic transmission, H_2O support, blood flow inside the brain. They provide neurotropic molecules namely GDNF which is particularly essential for the betterment and survival of dopaminergic neurons.[144] Additionally, when microglia initiates an immune response, astrocytes surround that region gradually builds a shield to obstruct the spreading of the toxic signal to surrounding healthy tissue.[145] Emerging evidence implicating that brain damages such as brain injury, oxidative stress, the function of astrocytes become transiently or

permanently disrupted in Parkinson's disease.[146-147] Astrocytes release inflammatory cytokines that may affect surrounding neurons during the process of reactive astrogliosis, also involve both molecular & morphological changes such as induced generation of ROS and lipid peroxidation due to the production of NO by iNOS which may diffuse towards neurons, excessive formation of gap junction between astrocytes, formation of scars, activation of apoptotic mechanisms that cause neuronal dopaminergic death.[148-149] Furthermore, in SN of post-mortem PD patients, the upregulation of S100b (Calcium-binding proteins) which act as a cytokine, primarily expressed by astrocytes has been shown. This increase in the iNOS production may lead to the activation of COX-2 (proinflammatory enzyme) in microglia, as well as increased NO and superoxide radical formation (**Figure 2**). The function of astrocytes in disease pathology was not well known also there has been a theory stating that such glial cell which may prevent and or worsen nigrostriatal injury due to disturbed balance.[150]

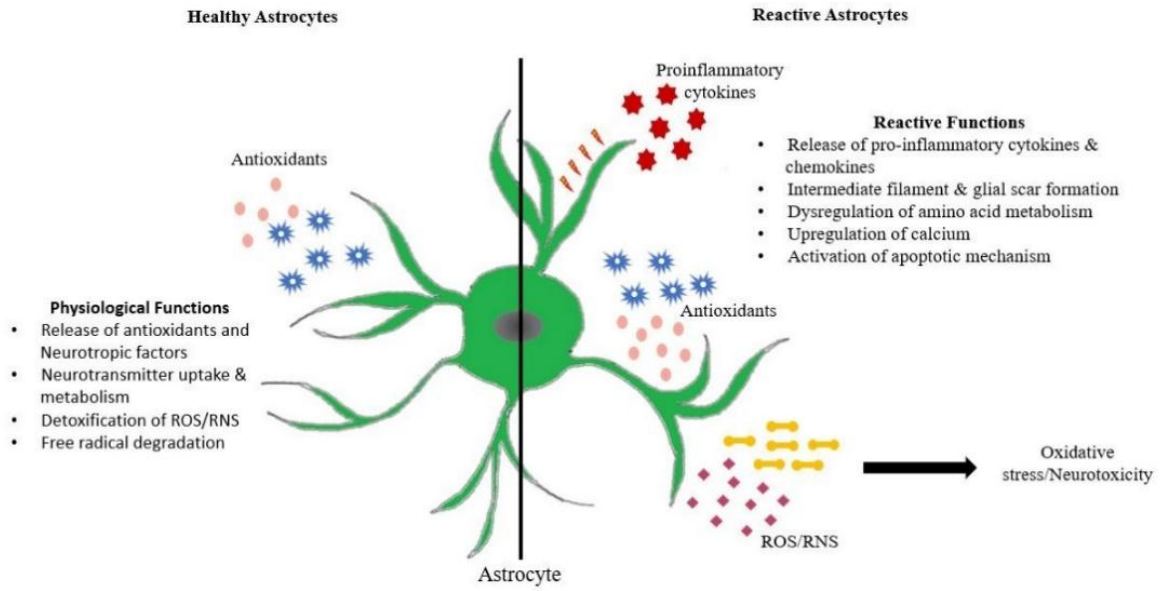

Figure 2: Role of astrocytes in Parkinson's disease pathogenesis.

Lymphocytic Infiltration

Lymphocyte infiltration is the other major key aspect in neuroinflammation mainly via the presence of T lymphocytes, a major endogenous mediator of neuroinflammation. B cells and natural killer cells have not been recognized. Helper T- cells (CD4+, Th) and killer T- cells (CD8+) stand active & will involve in the immune response. Th1, Th17, Granulocyte macrophage-colony stimulating factor-producer T-cells have also been documented to cause the acquisition of neurotoxic microglia to be resulting in increased release of neuroinflammatory cytokines and chemokines[151] (**Figure 3**). In PD patients, reduced serum

levels of naïve lymphocytes were noticed while the number of activated T cells was increased, reflecting that there is a peripheral activation in PD pathology. These data indicate that immunogenic factors produced by impaired dopaminergic neurons have the potential ability to amplify the pathological process by inducing a detrimental immune response.[152] Although activation of microglia and inflammatory changes are commonly seen as a cause of neuronal destruction. In Genome-Wide Association Studies (GWAS), the identification of Human Leukocyte Antigen (HLA) as a causative reason of Parkinson's disease, raises the possibility of increase the widespread in a pro-inflammatory situation in disease, the predominant principle source of neuronal failure in certain conditions, or as a minimum an increasing threat of Parkinson's disease as a genotype modifier.[153] The most apparent immune-related disease risk variants, positioned in the HLA region (HLA-DRB1 & HLA-DRB5).[154] The major histocompatibility complex (MHC) protein encoded by the HLA gene, which is actively engaged in the presentation of antigen & its immunity. The above complex remains on the surface of antigen-presenting cells such as microglia & facilitate the activation of T cell.[155] Such preliminary findings lift the assumptions that depletion of dopaminergic neurons caused by genetic defect or exposure to environmental toxic substances will lead the way for mild to moderate peripheral inflammation.[156]

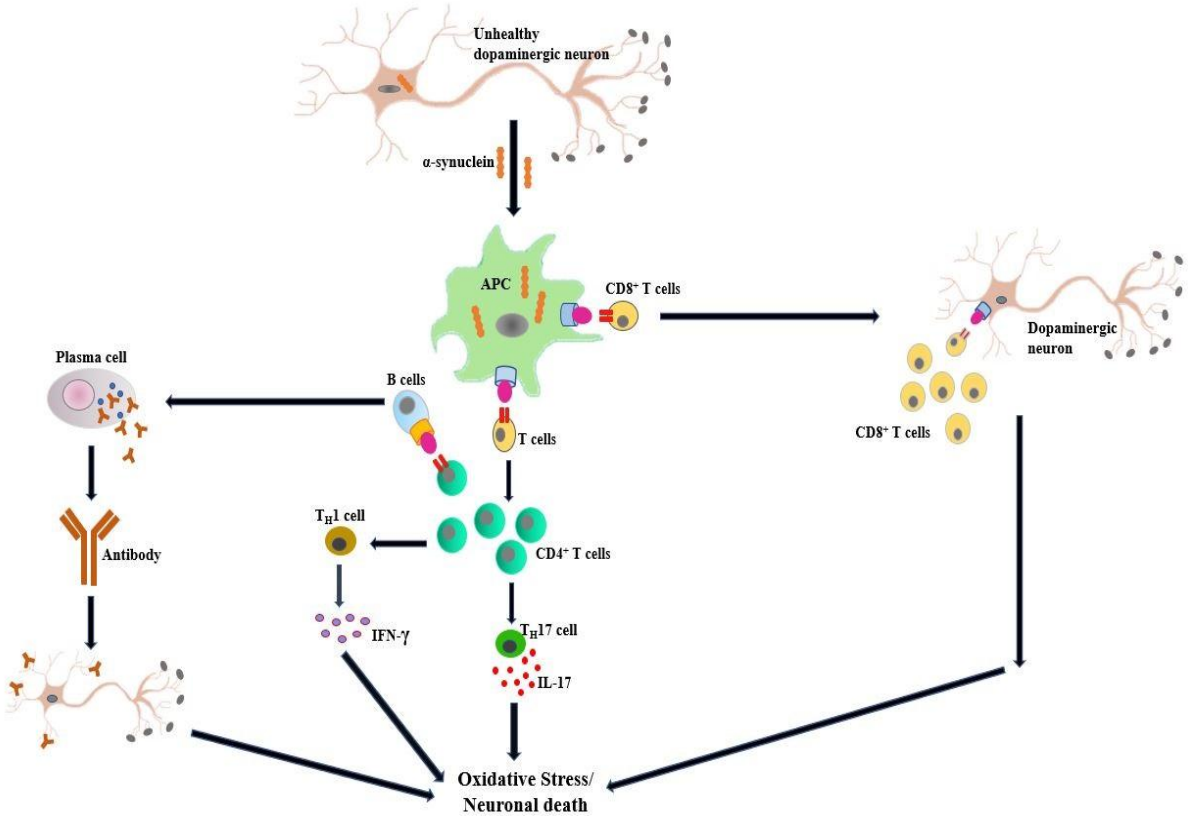

Figure 3: The mechanism involved in T cell-mediated neuroinflammation.

Biomarkers of Oxidative Stress In Parkinson's Disease

Biomarkers are naturally occurring molecule, gene or characteristic that is objectively measured & evaluated as an indicator of normal biologic processes, pathogenic processes or pharmacologic response to a therapeutic intervention.[157] It is an indicator of a particular state of a disease or an organism, normal and abnormal biologic process & could be a chemical, physical, or biological parameter. It is a parameter that can be used to assess disease progression or treatment effects, also supported early diagnosis, disease prevention, drug target identification, & drug response.[158] The characteristics of an ideal biomarker should be sensitive, reproducible, closely correlated with disease pathophysiology, easy to measure, inexpensive, non-invasive, and thoroughly validated.[159-160] The findings reflect that it provides a way to enhance our understandings of PD pathogenesis.[161]

8-hydroxydeoxyguanoisne (8-ohdG)

It is one of the DNA lesions caused by the ROS by oxidation of guanine residues and hydroxyl radicals and DNA generates 8-OHdG. The level of this biomarker is selectively increased in diseased patients. It is consistently seen high level in CSF compared to that of standard control.[162] The concentration of this marker is increased in SN, peripheral blood, Urine of Parkinson's disease.[163]

Glutathione

Glutathione, which is a most thiol-reducing agent acts as an antioxidant that excludes free radicals that might destruct dopaminergic neurons & could be lethal to dopaminergic neurons thereby acting also as a neuroprotective agent. Overall glutathione contains reduced GSH & oxidized forms, preserves redox homeostasis, eliminates metabolic waste, & provides a reservoir for amino acids in the brain. Post-mortem assessment of PD patients nigral tissue showed GSH deficiency, indicating the decreased ability of cellular waste metabolization capacity and protection against ROS, RNS and H2O2.[164] Auto-oxidation of the DA produces H_2O_2 & causes the destruction of GSH. Subsequently, H_2O_2 is transformed into hydroxyl radicals, that are extremely reactive capable of interacting with cellular macromolecules. The formation of hydroxy radicals catalyzed by iron plays a significant role in the formation of oxidative stress & loss of dopaminergic neuronal loss. The declined level of GSH seen substantia nigra and corpus striatum, suggest that accumulation of hydroxyl radical is elevated due to GSH down-regulation.[165]

Coenzyme Q10

Coenzyme Q10 is a constituent of the electron transport chain,[166] mainly present in cytosol & plasma. It is a vital cofactor in the mitochondrial respiratory chain, oxidative phosphorylation & regarded as a relevant antioxidant. Invitro and in-vivo experiments also reported flaws in mitochondrial complex 1 leading to redox equilibrium destruction, leading ultimately to neuronal toxicity. Since it is a lipophilic antioxidant, it will scavenge the radicals present inside the membrane. A reduced concentration of this coenzyme indicated a surge in free radicals, leads to neuronal degeneration. The progression of the disease is substantially retarded by coenzyme Q10 and was clinically accessible as a peripheral biomarker.[167]

Lipid peroxidation products

Oxidative degradation of lipids is termed lipid peroxidation. It is promoted by free radicals on membrane lipids, which can abstract hydrogen from the methylene group.[168] Lipid peroxidation interferes with membrane organization, protein, and DNA impairment.[169] Several studies have revealed the altered level of lipid peroxidation products such as isoprostanes, MDA in neurodegenerative brain tissues. The level of HNE(4-hydroxy-2,3-nonenal) in CSF is high and the level of MDA,[170] isoprostanes is high in the plasma of diseased patients.[171] These studies demonstrated that oxidative stress plays a major role in PD through lipid peroxidation.[172]

Neuromelanin

Catecholaminergic neurons contain neuromelanin, which is a dark polymer pigment & tends to always be widespread in the human brain, but it is missing from those brains of several smaller animals. Substantia nigra containing neuromelanin are infected in a diseased state.[173] The aggregation of neuromelanin-containing neurons tends to be the defensive phenomenon that avoids different mechanisms of neurotoxicity. It acts as an iron storage system in the substantia nigra dopaminergic neurons where no ferritin has been observed. While in a disease state, the damaged neurons release neuromelanin which will lead to the triggering of the vicious cycle in neuroinflammation.[174] It also guards neurons against oxidative stress facilitated by the free radicals, metals, etc. The rate of neuromelanin can be calculated by Magnetic resonance imaging techniques and information on substantia nigra degeneration has been shown to provide and is an important biomarker for Parkinson's disease.[175]

Plasma Uric acid level

Uric acid is an essential natural antioxidant that behaves like a free radical scavenger & iron chelator that will reduce oxidative stress.[176] It has been found to prevent dopaminergic cell death.[177] The reduced level of uric acid was found in the SN of the diseased population compared to that of the normal population.[178] Moreover, this having a strong binding capacity to iron, leads to oxidative damage by the generation of reactive oxygen species.[179] Urate may be a significant determinant in disease susceptibility& it was found to be decreased in the serum, CSF.[180] The concentration of urate in CSF is approximately 7% than that of plasma. It is found in plasma as a sodium salt. At physiological concentration, it effective as ascorbate to avoid the lipid peroxidation by hydrogen peroxide scavenges nitrogen radicals. Furthermore, the administration of the urate causes the decline in oxidative stress & mitochondrial dysfunction of human dopaminergic neurons due to iron ions, rotenone, etc. In conclusion, it is a risk factor and a prognostic indicator of Parkinson's disease.[181]

Serum BDNF

Brain-Derived Neurotrophic factor belongs to a family of neurotrophins that control the survival and functioning of CNF neurons.[182] It is a potent inhibitor of cell death triggered by apoptosis & dopaminergic neurodegeneration by neurotoxins, indicating that it would likely be used in the development of disease therapies.[183] Concerning neurological disorder, the expression of BDNF is decreased, and was found in the nigrostriatal dopamine region.[184] On the other side, the glial cell in the SN of the patients expressed an elevated level of BDNF in response to the signal generated from failing neurons. In the case of 6-OHDA induction, the intra-striatal graft of fibroblast genetically engineered to develop BDNF partially obstruct the loss of bodies of the nigrostriatal dopaminergic pathway.[185] BDNF not only having a trophic action but also has a potential capacity for the regulation of cognitive processes.[186] The level of BDNF is increased by the use of antiparkinson's drugs & it represents a possible peripheral marker in cognitive functioning.[187]

Serum IGF-1

An Insulin-like growth factor is put forward as a marker for the early detection and protection from the depletion of dopaminergic neurons.[188] Moreover, the meta-analysis showed that the signalling pathway of IGF-1 is dysregulated in substantia nigra tissues.[189] Moreover, serum IGF-1 levels were reported to be a threat for Parkinson's disease in people related to altered

motor function and transcranial sonography of substantia nigra &closely associated with Unified Parkinson's Disease Rating Scale (UPDRS-III). It was proof of confirmation that it forecast the progression of motor symptoms and executive performance diminish in disease patients.[190]

p-Tau and p-Tau/aβ42 ratio

Amyloid-beta 1-42 (Aβ42) has been reported to be lower in the cerebrospinal fluid (CSF), a biomarker in PD, can be used for predicting cognitive decline in idiopathic Parkinson's disease, though to a lesser extent than that of Alzheimer's disease.[191] This decrease may be due to the monomers being deposited in the brain that restricts their diffusion to the CSF.[192] Also CSF total Tau (t-tau) & phosphorylated tau-181 (p-tau), is more complex target than that of Aβ, lower in PD patients compared to the control population. On the other hand, an elevated level of tau is reported in patients having dementia.[193]

CONCLUSION

Neurodegenerative diseases impose a significant health risk not only on the affected individual but also on their families and society. It becoming more common and rapidly increasing in the aged population worldwide. Although several mechanisms have been hypothesized for the pathogenesis of Parkinson's disease, it remains elusive. The lines of evidence reveal that the oxidative stress underlying Parkinson's disease was complex & it involves multiple mechanisms. Important key contributing factors culpable for oxidative stress are ROS neurotoxicity, dysfunction of mitochondria, dysregulation of immunity, increase in iron and calcium depositions. What this put forward that, oxidative stress can be an initiator &being a component for neurodegeneration. Nevertheless, an intense investigation has shown that the disease remains incurable. All of these factors lead to excessive production of Ros. When ROS overwhelms the antioxidant defense system, lipid peroxidation, protein oxidation, and DNA oxidation take place. The goal in the development and validation of disease-specific biomarkers is to facilitate the early diagnosis of disease, prediction of progression, and monitoring of therapeutic efficacy. The application of objective biomarkers and the evaluation of oxidative stress is an avenue for the diagnosis of Parkinson's disease.

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Author's Contributions

1. First Author: Dr Manjunatha P Mudagal

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2) Critical revision of the article

2. Corresponding Author: Gayathry P

Contributions

1) Conception or design of the work

2) Data collection

3) Data analysis and interpretation

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ABBREVIATIONS

SNpc-substantia nigra pars compacta

CNS-central nervous system

ROS-reactive oxygen species

GABA- gamma-Aminobutyric acid

MAO-B-monoamine oxidase B

NMDA- N-methyl-D-aspartate

HSP-heat shock protein

PINK-1-PTEN-induced kinase 1

DLB-dementia with Lewy bodies

MSA-multiple system atrophy

SNCA-alpha-synuclein

DUB- deubiquitinating enzyme

UCH- ubiquitin C-terminal hydrolases

SOD-superoxide dismutase

NO-nitric oxide

6-OHDA-6-hydroxydopamine

ETC-electron transport chain

PUFA-polyunsaturated fatty acid

MPTP- 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine

GDNF- Glial cell line-derived neurotrophic factor

iNOS-inducible nitric oxide synthase

COX-2- cyclooxygenase-2

MHC- major histocompatibility complex

GSH-glutathione

CSF-cerebrospinal fluid

MDA-malondialdehyde

BDNF- Brain-derived neurotrophic factor

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