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Review Article

Pathophysiological Biomarkers of Parkinson's Disease

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative movement disorder, that is characterized by selective degeneration of nigrostriatal dopaminergic neurons in substantia nigra pars compacta and accumulation of misfolded α-synuclein protein. Currently, 10 million people (i.e. approximately 0.3% of the world population) suffer from PD and the incidence ranges from 5/100,000 to over 35/100,000 new cases yearly. Incidence increases 5 to 10 fold from the sixth to the ninth decades of life. PD is regarded as a movement disorder with four cardinal motor deficit signs: bradykinesia, rest tremor, rigidity and loss of posture and gait. Also, there may be some non-motor symptoms (like cognitive and sleep defect) associated with it. These symptoms of PD vary from person to person and often go unnoticed in the early stages. By the time these prominent symptoms appear, 70 - 80% neurons have already been degenerated. PD is a multifactorial neurodegenerative disease that has been linked to several pathogenic neuron-autonomous event like mitochondrial dysfunction, oxidative stress, microglial cell activation, protein aggregation and programmed cell death. In this review, we are providing brief knowledge about several probable pathophysiological biomarkers responsible for PD pathogenesis including exposure to environmental toxins/occupational hazards, dopamine auto-oxidation and metabolism,mitochondrial dysfunction and oxidative stress, Ubiquitin-proteasome system dysfunction, protein aggregation, altered calcium (Ca2+) homeostasis,neuroinflammation (cyclooxygenase-2, inducible nitric oxide, interleukin-1β, nuclear factor kappa B, tumor necrosis factor alpha), and susceptibility genes or genetic factors (PRKN, Leucine-rich repeat kinase 2 (LLRK2)).

Keywords: *Parkinson's Disease; Oxidative Stress; Neuroinflammation; Pathophysiological Biomarkers; Genetic Factor*

Abbreviations

ATP: Adenosine Triphosphate; CNS: Central Nervous System; COX-2: Cyclooxygenase-2; cNOS: Cytosolic NO Synthase; DA: Dopamine; eNOS: Endothelial NOS; GSH: Reduced Glutathione; iNOS: Inducible Nitric Oxide Synthase; IL: Interleukin; iNOS: Inducible NOS; Lbs: Lewy Bodies; MAO-B: Monoamine Oxidase-B; MPTP: 1-Methyl-4-Phenyl-1,2,5,6-Tetrahydropyridine; NADPH: Nicotinamide Adenine Dinucleotide Phosphate; NO: Nitric Oxide; NOS: Nitric Oxide Synthase; NF-Kb: Nuclear Factor Kappa B; PARP: Poly ADP-Ribose Polymerase; PD: Parkinson's Disease; RNS: Reactive Nitrogen Species; ROS: Reactive Oxygen Species; SN: Substantia Nigra; Snpc: Substantia Nigra Pars Compacta; TGF-β1: Transforming Growth Factor- B1; TNF-α: Tumor Necrosis Factor Alpha; UPS: Ubiquitin-Proteasome System; UCH-L1: Ubiquitin Carboxy-Terminal Hydrolase L1; VTA: Ventral Tegmental Area

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative movement disorder characterized by the selective deterioration of nigrostriatal dopaminergic neurons in the substantia nigra pars compacta (SNPc) and the deposition of misfolded -synuclein protein in intra-cytoplasmic inclusions known as Lewy bodies (LBs). After stroke, it is the second commonest neurological condition that causes mobility impairment [1]. Prevalence of PD increases with age- it affects 1% of the population above 50 years and 2.5% population above the age of 70. The disease occurs more frequently in men than in women in every decade of life, which is explained by the neuroprotective effects of estrogens [2,3]. Parkinson disease is clinically characterized by cardinal motor symptoms like rigidity, tremor, bradykinesia, postural insufficiency and some non-motor symptoms like neuro-psychiatric (psychosis, delirium, and compulsive/impulsive spectrum disorders), neurobehavioral (depression, anxiety, rapid eye movement) and cognitive impairment [4]. First symptoms of PD appear, when production of dopamine has been fallen below 20% of its original production or when 50% of the cells of substantia nigra (SN) have been destroyed [5].

Dopamine (DA) is one of the major catecholamine neurotransmitter that control the various function in human body like; movement, reward phenomena and lactation [6]. There are four major dopaminergic pathway in the brain: (i) Mesolimbic pathway- neurons are extended form ventral tegmental area (VTA) to nucleus accumbens and amygdaloid nucleus. (ii) Mesocortical pathway-neurons are projected from VTA to frontal cortex. (iii) Tuberohypophysial pathway- extends from ventral hypothalamus to the median eminence and pituitary gland (iv) Nigrostriatal pathway- This pathway account for 75% of dopamine in the brain and neurons of it extended from substantia nigra to corpus striatum. Nigrostriatal pathway is one the major dopaminergic pathway that governs the movement of body and majorly affected in PD [7].

Pathogenesis of Parkinson's disease

Parkinson's disease is a devastating neurological condition that affects at least four million people over the globe. A pathologic hallmark of this disorder, that is essential for its pathologic diagnosis, is preferential loss of DA neurons in the SNpc of midbrain [8]. Despite extensive research on brain of PD patients or experimental animal models, etiology of PD and mechanism for selective neuronal loss has not yet been fully understood [9]. Hence there are several hypotheses have been postulated and investigated the idiopathic forms of disease, however, no single factor seems to be accountable for idiopathic PD. Rather it seems to be a result of multiple factors and/or intricate cascade of events, to produce the PD pathology. There are several probable factors responsible for PD pathogenesis including exposure to environmental toxins/occupational hazards [10], dopamine auto-oxidation and metabolism [11,12], oxidative stress [13,14], mitochondrial dysfunction [15-17], iron de-regulations, proteasome dysfunction [18] and susceptibility genes [19] have been suggested to contribute in idiopathic PD pathogenesis. Some of the intricate mechanisms involved behind the PD progression are enlisted herein.

Mitochondrial dysfunction and oxidative stress in PD pathogenesis

The mitochondrion is a double membrane bound organelle found in cytosol of eukaryotic cells that generates most of cell's energy in the form of adenosine triphosphate (ATP), which essential for normal cell is functioning and homeostasis. The role of mitochondria in the pathogenesis of PD was discovered during 1970-80 in juvenile drug addicts who is consuming an opioid drug, producing MPTP (1-methyl-4-phenyl-1, 2, 5, 6-tetrahydropyridine) as their by-product. In the year 1984, MPTP-induced neurotoxicity discovery and other cumulative research findings indicated the direct involvement of mitochondrial complexI impairment in the PD pathogenesis. It is evident that, mitochondrial complexI directly involve in disease progression instigates from cytotoxic insult caused due to various potent neurotoxins as rotenone parquet and MPTP in the dopaminergic neuronal cells of substantia nigra. Mechanism involved behind MPTP cytotoxicity is that MPTP readily crosses the blood brain barrier and gets converted to MPP^+ by the enzyme monoamine oxidase B (MAO-B, present in glial cells) [20]. Following activation in the glia, MPP^+, a substrate for the DA transporter, is selectively taken up into DA nerve terminals where

it inhibits complexI of the mitochondrial electron transport chain, culminating to uncoupling of oxidative phosphorylation and production of reactive oxygen species (ROS) [21,22], which further triggers selective DA neurodegeneration, either through direct production of ROS from increasedevels of free electrons and/or indirectly through dysregulation of iron [23,24]. Moreover, there are substantial reports suggesting that there has been selective loss of reduced glutathione (GSH) levels in SN of PD patients. It is evident that GSH depletion potentiates oxidant-induced loss of mitochondrial functions, oxidative stress which triggers, damage to DNA, lipids, and protein [25]. Taken together, these observations suggest that mitochondrial dysfunction can compromise DA neuronal viability and responsible for the PD pathogenesis.

There are number of sources and mechanisms for the generation of ROS are recognized including the metabolism of DA itself, mitochondrial dysfunction, iron, neuroinflammatory cells, calcium, and aging. Oxidative stress received more attention in PD because of the oxidative metabolism of dopamine yield hydrogen peroxide (H_2O_2) and other ROS [26-28]. However, inhibition of complex I function can cause increased production of ROS such as superoxide anions that can generate highly reactive hydroxyl radicals and peroxynitrites ($ONOO^-$) [29,30]. It has been also reported that the excessive peroxynitrite triggers the activation of poly ADP-ribose polymerase (PARP) that is a highly energy dependent process and leads to the cleavage of NAD^+ into ADP-ribose and nicotinamide. PARP activation rapidly depletes NAD^+ stores, thereby impairing mitochondrial function, glycolysis, and ATP synthesis [31].

Auto-oxidation/metabolism of dopamine

Dopamine is an unstable molecule that undergoes auto-oxidation to generate the dopamine quinones and free radicals. This reaction is catalyzed by metals, oxygen or enzymes (such as tyrosinase) [32]. Dopamine quinones can cyclize to form aminochrome, which is highly reactive and leads to the generation of superoxide and depletion of cellular NADPH. Aminochrome can form adducts with proteins (like alpha-synuclein) which is a precursor of neuromelanin, a brain pigment that may contribute to neurodegeneration by triggering neuroinflammation [33]. Under normal conditions, dopamine levels are regulated through oxidative metabolism by MAO-A (present in catecholaminergic neurons). However, with neuronal degeneration in PD and aging, MAO-B located in glial cells increases and becomes the predominant enzyme to metabolize dopamine [34]. The MAO-B mediated metabolites of dopamine (3,4-dihydroxyphenyl-acetaldehyde, ammonium molecule and H_2O_2) further causes an insurgence in ROS levels [35].

Ubiquitin-proteasome system dysfunction

The Ubiquitin-proteasome system (UPS) is the main pathway responsible for cells degradation and removal of damaged and unwanted proteins. During oxidative stress, the efficient clearance of these unwanted materials by the proteasome is considered as a defence mechanism, since degradation lessens the threat of oxidized proteins forming toxic aggregates. Thus, dysfunction of UPS could lead to the accumulation of cytotoxic damaged proteins that eventually results into neuronal death. UPS dysfunction can be occurs due to (i) Mutations in the genes for parkin and Ubiquitin carboxy-terminal hydrolase L1 (UCH-L1), (ii) Inhibition of mitochondrial Complex I and (iii) alpha-synuclein also impairs proteasomal function.

Protein aggregation

One of the pathological features of PD is aggregation of α-synuclein and subsequent formation of intra cytoplasmic large protein aggregates called LBs. Post mortem reports of PD patients have revealed the presence of LBs in all dead and dying dopaminergic neurons of SN. The main protein in LB is α-synuclein, a 140 amino-acid-long neuronal protein which is found in the highly ubiquitinated form [36,37]. Lee and co-workers (2006) have reported that α-synuclein fibrillization could be enhanced by post-translational modifications, oxidative and nitrative stress, and interaction with metals, such as aluminum, copper, and iron. It is apparent that the accumulation of unfolded or misfolded proteins by insufficient clearance represents a major stress to the cells which further activates the cellular chaperones to assist

in refolding of proteins. Moreover, it is also evident that cells use an efficient degradation process to eliminate proteins with unwanted conformations; primarily through the ubiquitin/proteasome pathway [38,39]. Further, the ubiquitin/proteasome pathway involves tagging of misfolded proteins with a small peptide ubiquitin. The defect in the capacity of ubiquitin proteasome system to clear damaged ubiquitinated proteins causes an accumulation of misfolded proteins which aggregate and form LBs. Pertaining to it, cumulative evidences suggest that defect in ubiquitin proteasome system is a major factor behind the etiopathogenesis of PD [40,41].

Calcium and PD pathogenesis

Calcium (Ca^{2+}) homeostasis is essential for neuronal function and survival. Intracellular Ca^{2+} signaling in neurons is extremely fine-tuned, because it controls gene transcription, membrane excitability, neurotransmitters secretion and many other cellular processes, including synaptic plasticity. A continuous Ca^{2+} influx is necessary to modulate physiological DA release by SNPc DA neurons, but, its long-lasting presence may synergize with the exposure to risk factors (i.e. aging, mitochondrial toxins, mutations) and generate metabolic stress and mitochondrial damage [42]. There is increasing evidence that dysregulation of intracellular calcium homeostasis plays an important role in the pathogenesis of Parkinson's disease. The calcium pathway intersects with mitochondrial function and oxidative stress both of which are involved in the pathogenesis of Parkinson's disease [43]. Epidemiological studies on patients under clinical trial with L-type channel antagonists for the treatment of hypertension have shown a reduced risk of developing PD [44]. Moreover, Ross and its coworker observed an increased activity of calcium-stimulated phospholipase A2 in putamen, which was inferred to be due to either decreased dopaminergic input in striatum or to a DA nerve terminal degenerative process. Furthermore, over expression of calpain-II, a calcium-dependent protease has been reported in the parkinsonian SN, suggesting a rise in intracellular calcium concentrations is involved in the mechanism leading to the dopaminergic cell death in PD.

Neuroinflammation

Inflammation of the neural tissues is a chief defensive mechanism linked with rejuvenation of normal shape and functions of the brain and reduces the effect of an injury. Several lines of evidence supported the role of neuroinflammation in the pathophysiology of PD which is mediated mainly through activated microglia cells. Further, in PD, increasing neuropathological and biochemical data suggests that neuroinflammatory pathways are activated. Preclinical and epidemiological data currently clearly imply that persistent neuroinflammation may be a slow and steady reason for neuronal failure throughout the asymptomatic period of Parkinson's disease, despite the fact that there is little evidence to support this. Microglias are phagocytic cells which constitute about 15% of all cells of the brain [45]. They provide an immune surveillance in the CNS during their resting state by eliminating endogenous or exogenous toxicants and protect neuron from toxic levels of H_2O_2 *by their high levels of GSH and glutathione peroxidase [46].* Moreover, as we know, neural inflammation works in the existence of activated microglia and reactive astrocytes in the various parts of the CNS, express contribution of the adaptive immune system raise the production of cytokines, chemokines, prostaglandins, a spill of matched proteins and reactive oxygen species and reactive nitrogen species (ROS/RNS), and decreased secretion of trophic factors responsible for the normal maintenance of neuronal viability. Thus, neuronal death aggravated by microglia further induces the activation of microglial cells, creating a neurotoxic vicious cycle [47,48]. Also, numerous activated microglia and T lymphocytes have been detected in the SN of patients with PD along with an increase of pro-inflammatory mediators in the brain and cerebrospinal fluid [49] which includestumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), IL-2, IL-4, IL-6, transforming growth factor-α (TGF- β1), cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS).

Interleukin-1β (IL-1β)

Interlukin-1β is a host cytokine which is involved in the initiation of proinflammatory pathway in the CNS and leads to the activation of microglia. It is originate in the cerebrospinal fluid and post-mortem strata of PD patients [50]. It is undeniable that the persistent appearance of IL-1β in the SN at pro-inflammatory levels causes permanent and marked dopaminergic neuronal loss in the SN [51].

Cyclooxygenase-2 (COX-2)

Cyclooxygenase (COX) is an enzyme that catalyzes the conversion of arachidonic acid to the largely bioactive prostaglandins in a controlled rate by using molecular oxygen. There are two main types of COX enzymes that are COX-1 and COX-2. The COX-1 enzyme is a housekeeping enzyme constitutionally present in all tissues, whereas COX-2 enzyme get's activated or triggered to introduce inflammation and this isoform is also essentially expressed in some tissues that are present in kidneys and brain. COX-2 expression may regulate microglial activation and may play a chief role in enhancing the inflammatory response with toxic effects. COX-2 may contribute to the progression of neurodegeneration through the production of toxic free radicals and increasing local glutamate concentration to toxic levels [52].

Tumor necrosis factor alpha (TNF-α)

A pleotrophic polypeptide, tumour necrosis factor alpha (TNF-α) plays an important role in brain immune and inflammatory activities such as cell survival, proliferation, differentiation, and death. Moreover, TNF-alpha is a key immune signal transducer with cytotoxic and stimulatory capabilities. TNF levels are high in the CSF fluid and post-mortem brains of Parkinson's disease patients, as well as in animals treated with dopaminergic neurotoxins such as MPTP and 6-OHDA, which are used to imitate nigral degeneration in non-human primates and rats [53]. TNF's high expression near the site of neurological damage shows that this potent pro-inflammatory cytokine is a mediator of neuronal injury, and thus a potential target for the therapy of Parkinson's disease. Several reported studies provides evidences about the involvement of TNF-α in PD such as i) An early report by Aloe., *et al.* [54] showed that TNF over expression in the CNS of transgenic mice resulted in decreased TH staining in the striatum, and ii) intranigral injection of an adenoviral vector expressing soluble mice TNF- α. TNF- α induced neurodegeneration in rats caused by persistent production of this cytokine resulted in forelimb akinesia and an unique inflammatory response in the rat brain [55].

Nuclear factor kappa B (NF-κB)

Nuclear factor kappa B - a protein complex (transcription factor) and it play an important role in the immune system, where it acts to excite antibodies. Moreover, it is also play a role in learning and memory and stress reactions. Further, NF-κB pathway involved in ameliorating neuron damage associated with excitotoxicity, ischemia/hypoxia, energy deprivation and oxidative stress [56,57] and there is also an evidence supporting a dual role of NF-κB in neurodegenerative diseases such as PD. While NF-κB promotes neuronal survival when activated, it is also responsible for the proliferation and activation of glial cells, some of whom can cause pathological inflammation. To combat inflammation, NF-κB promotes the apoptosis and the expression of mediators such as TGF-β1 and cyclopentenone prostaglandins, along with the transcription of genes like Baxand p53. It was found that 6-OHDA induced oxidative stress in the DA neurons of rat SN via an NF-κB dependent p53 signalling pathway.

Inducible nitric oxide (iNOS)

Nitric oxide (NO) is a free radical playing a key messenger role in a wide range of physiologic processes including vasodilatation, immune response and neurotransmission. NO is derived from L-Arginine by cytosolic NO synthase (cNOS) in the presence of nicotinamide adenine dinucleotide phosphate (NADPH) and molecular oxygen. Till date there are three types of NOS have been recognized: neuronal NOS (nNOS), endothelial NOS (eNOS) and inducible NOS (iNOS) [58]. iNOS is calcium-independent NOS whose expression is induced in an extensive range of cells and tissues by cytokines and other mediators and it acts as a transcriptionally synchronized enzyme that synthesizes nitric oxide from L-Arginine (act as a host in the pathophysiology of systemic inflammation). The iNOS is expressed in astrocytes and microglia when respond to inflammatory stimuli. Several reported studies provided evidences that there is an increase in the levels of nNOS and iNOS expression in the nigrostriatal region and basal ganglia in the post mortem PD brains. NO has been also proposed to have a role in the inflammatory processes occurring in PD. During the metabolism of DA in the SN region the iNOS reacts with the superoxide anions and release per-oxinitrite that is measured one of the most important damaging molecules in the dopaminergic neuronal cell [59].

Genetic factors

Earlier Parkinson's disease was considered as a non-genetic disorder of sporadic origin (not linked genetically) but in the last few decades, increased research toward PD's genetic component, and clearly suggests that, PD is also a familial disorder. Genetic factor plays an important role in early onset of PD. The *α*-synuclein (α-syn) knockout mice are resistance to MPTP toxicity, suggesting a new link between genes and PD [60]. PARK2 is the parkin gene that forms the basis for autosomal recessive juvenile - PD without LBs formation due to mutation in parkin protein [61]. Studies showed that the heterozygous mutations in glucocerebrosidase (GBA) and mutations in novel genetic loci – Ubiquitin carboxyl-terminal hydrolase isozymeL1 (UCHL1), Parkinson disease protein 7 (PARK7/DJ1), Omi/HtrA2, GRB10 interacting GYF protein 2 (GIGYF2), fibroblast growth factor 20 (FGF20), pyridoxal (pyridoxine, vitamin B6) kinase (PDXK), eukaryotic translation initiation factor 4 gamma, 1 (EIF4G1) and Parkinson disease protein 16 (PARK16) increased the risk of PD [62]. In addition to this genetic variation in 3 genes (LRRK2, MAPT, and SNCA) and loss-of-function in another (GBA) are now well established risk factor for PD [63].

PRKN

The PRKN gene, one of the leading genome in humans, provides directions for creating the parkin protein [64]. In Parkinson's disease, it works in tandem with the PINK1 mitochondrial protein, which is a product of another gene [65]. The Parkin mutation is responsible for more than half of all familial cases and ten to twenty percent of all cases in children and adolescents. According to hypotheses, sporadic and hereditary Parkinson's disease may share a common pathway of improper protein aggregation regulation and Ubiquitin-proteasome system dysfunction. Parkin has a versatile neuroprotective activity (against -synuclein toxicity, proteasomal dysfunction, oxidative stress, kainite-induced and dopamine-mediated toxicity) that may have therapeutic value in the future. As a result, any reduction in parkin level or activity may cause damage to neuronal integrity [66].

The Leucine-rich repeat kinase 2 (LLRK2)

The LRRK2 gene and theα-synuclein (*α-syn*) gene (SNCA) are two essential genes in Parkinson's disease. The *α-syn* build-up and pathology may be influenced by LRRK2 malfunction, resulting in altered cellular activities and signalling pathways through the kinase activation of LRRK2.Microglial activation is activated as a result of *α-syn* aggregation. Microglial activation is considered to be the source of neuroinflammation and neuronal death in PD. Understanding the complex relationship between LRRK2, *α-syn*, and microglia could lead to the development of targeted PD clinical treatments [67,68].

Conclusion

Parkinsonism is now characterized as a disease of a dispersed brain network, with clear evidence of co - occurring disorders in the basal ganglia, thalamus, and cortex. Dopamine loss in the putamen and other basal ganglia nuclei, as well as the loss of dendritic spines on striatal output neurons, appear to severely disrupt the activity of neurons throughout the basal ganglia, thalamus, and cortex, and may even lead to aberrant activation of brain areas that are not part of the immediate basal gangliathalamic circuit. Moreover, PD is a complicated neurological disease whose genesis and pathogenic mechanisms are still unknown. Environmental variables may potentially have a role in the development of PD, though the link between the disease and factors including smoking, coffee, and pesticide exposure is still unclear. The movement problem is caused by the death of dopaminergic neurons in the SNpc, but it also affects a variety of other brain regions. LBs, which mostly include aggregated *α-syn*, are a histopathological hallmark of PD, although it's unclear how they cause neurodegeneration. While existing dopamine restoration medications provide excellent clinical relief for many patients with Parkinsonism, they are usually preceded by severe side effects, as well as wear-off events and other motor irregularities. More comprehensive characterization of Parkinsonian brain activity anomalies will aid in the development of better and more precise anti-parkinsonian treatments. By knowing of these pathogenic pathways allow us for better recognition of newer pathophysiological targets, and subsequently helps in

the improvement of disease-modifying therapeutic treatment in future. Therefore, here we tried to explain possible pathophysiological biomarkers responsible for PD pathogenesis and its disease progression.

Conflict of Interest

Authors declare no conflict of interest.

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