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PARKINSONISM: A GENERAL MOTOR DISABILITY

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ABSTRACT: Parkinson's disease (PD) is one of the most common neurodegenerative disorders in the population above 60 years of age. The movement abnormalities in PD are credited due to an imbalance between the acetylcholine and dopamine which results in uncontrolled movements. It is characterized using resting tremor, postural impairment, bradykinesia, and rigidity. The degeneration of midbrain dopaminergic neurons and accumulation of inclusions containing α-synuclein (termed "Lewy bodies") throughout the nervous system are few of the most prominent features of PD. Still, there is no cure; we have several management options for the early treatment of PD. Several objective methods have been proposed for improving the diagnostic accuracy of PD, for enabling earlier diagnosis, to quantify the severity of disease and progress of treatment given. These methods include motor performance tests, olfaction tests, imaging techniques, and biochemical tests of blood and cerebrospinal fluid. None of the proposed methods is widely available or clinically used for PD. The validation of the objective methods takes time, and a large number of regulatory requirements need to be considered before a new instrument can be accepted as a clinical tool. It is probable that a combination of several methods will be needed for PD. The cardinal motor symptoms of PD only emerge after the degeneration of about 60-80% of the dopaminergic neurons; thus patients get diagnosed at a very late disease stage. As the disease progresses, the management of late-stage motor complications and non-motor symptoms remains particularly challenging and will benefit from further clinical research. To fully understand the etiology and mechanisms involved in the pathogenesis of PD, valid model systems are needed.

INTRODUCTION: Parkinson's disease (PD) was first described by Dr. James Parkinson in a book entitled "An Essay on the Shaking Palsy," published in 1817 [1]. It is sometimes called idiopathic Parkinsonism but usually referred to as Parkinson's disease, to honor the physician who first described it. The clinical characteristics of PD are bradykinesia, akinesias or no movement, rigidity and tremor [2].

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Many spontaneous movements like arm swinging, blinking, and swallowing is reduced or lost. Tremor will be maximal when the limb is at rest and reduced with voluntary movement. Later during the disease, there is a notorious failure in postural reflexes, impaired balance and general instability [3].

Non-motor symptoms of PD include autonomic dysfunctions, apathy, depressions, sleep disorders, fatigue, pain and dementia [4]. Epidemiological studies suggest that environmental factors may play an important role in most sporadic cases of the disease where no apparent genetic linkage was established [5]. About 1% of the population above 60 years is affected by Parkinson's disease [6]. Several reports are in accord that the occurrence of PD is more common in men than women, which

may be linked to the potential neuroprotective properties of estrogen demonstrated both *in-vitro* and *in-vivo* [7]. Parkinsonian symptoms are more predominant in premenopausal, and they are reported to require more L-DOPA during menstruation when estrogen levels are reduced [8]. Moreover, cognitive functions were found to be improved in postmenopausal women who underwent Oestrogen replacement, the latter which may delay the development of cognitive impairments and dementia in PD [9].

According to the studies conducted in America, Parkinson's disease is more prevalent in Caucasians than in African Americans, thus signifying that Caucasians are genetically more susceptible [10]. According to the studies conducted in Asia, Parkinson's disease is found to be more prevalent among the Parsi community in India, thus signifying a major genetic role in disease causation [11]. Incidences of PD are more common in the rural population. Exposure to pesticides used in agricultural practices is the main reason behind the prevalence of PD in rural areas [12].

Pathophysiology of Parkinson's disease: Parkinson's disease (PD) is characterized by an imbalance between acetylcholine and dopamine [13]. PD involves the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc), which results in the depletion of striatal dopamine [14]. This neurotransmitter regulates the excitatory and inhibitory outflow of the basal ganglia [15].

The basal ganglia are a selection of nuclei that play a key role in the control of body movements. The first coherent model of the basal ganglia circuitry was developed starting in the middle of the 80s and described how the basal ganglia integrated information from different brain regions and generated feedback signals to the cerebral cortex [16].

In existing neuro-anatomy, the striatum (putamen and caudate nucleus), the pallidus (internal and external), the subthalamic nucleus and the substantia nigra (pars compacta and reticulata) are considered the nuclei of the basal ganglia. It has been demonstrated that the nuclei as mentioned earlier play a key role in mediating motor and non-motor behavior, cognition and emotion [17].

In **Fig. 1**, the degeneration of dopaminergic neurons result in the increased inhibition of the globus pallidus external; thus the output of globus pallidus internal is inhibitory. However, this inhibitory output causes the excitation of the subthalamic nucleus. The main reason behind the occurrence of Parkinsonism is the increased inhibition of the thalamus. Finally, reduced excitation of the motor cortex results in the occurrence of rigidity, bradykinesia, and the other PD symptoms [16].

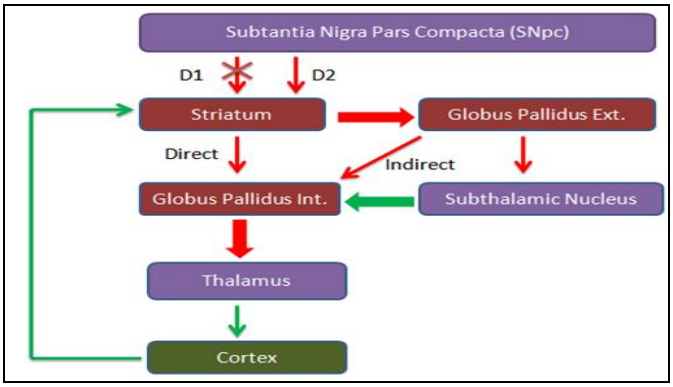

FIG. 1: THE EXCITATORY (GREEN) AND INHIBITORY (RED) OUTFLOW OF THE BASAL GANGLIA MEDIATED BY DOPAMINE

LBs are a pathological hallmark of sporadic and some familial forms of PD and indicate the involvement of protein mishandling in disease pathogenesis. The presence of Lewy bodies are reported to contribute to the manifestation of dementia in PD, but the pathology related to mild cognitive impairments in PD is less known, mainly because patients usually survive until these symptoms develop into dementia [18]. The Lewy body density was found to be five times greater in postmortem brain samples from PD patients with dementia as compared with non-demented patients with PD [19, 20].

In PD patients, Lewy bodies are more predominant in the limbic structures, cholinergic forebrain neurons, the cerebral cortex, and in the brainstem nuclei, like the noradrenergic locus coeruleus and the serotonergic raphe nuclei [21]. Presence of α-Synuclein is one of a prominent feature of Lewy bodies in idiopathic PD. α-Synuclein is normally a soluble unfolded protein, but it can aggregate into insoluble amyloid fibrils which then may form Lewy bodies, followed by subsequent ubiquity-nation and accumulation of neurofilaments [22].

At high concentrations, α-Synuclein protein self-aggregate in the cytoplasm to form Lewy-body-like fibrils and discrete spherical assemblies, and this process is accelerated in the mutant forms of α-synuclein [23]. α-Synuclein species may be associated with UPS dysfunction through binding and inhibiting the 20/26S proteasome, and mutated or aggregated forms of α-synuclein may also overwhelm the degradative capacity of the proteasome, leading to further impairment [24, 25, 26].

Etiology of Parkinson's Disease:

Genetic Mutations: Several gene mutations have been described in patients with a familial form of the disease *e.g.,* SNPCA gene mutation, Leucine-rich repeat kinase 2 gene (LRRK2) mutation, UCLH gene mutation, DJ 1 gene mutation, PINK1 gene mutation resulting in PD [27].

SNPCA Gene Mutation: SNPCA gene mutation causes an overabundance of α-synuclein, which may cause mitochondrial dysfunction and neuronal death. Damaged mitochondria promote α-synuclein production. α- Synuclein is a highly charged 140-amino acid heat-stable protein that is soluble and natively "unfolded" [28, 29]. α-Synuclein species may be associated with UPS dysfunction through binding and inhibiting the 20/26S proteasome, and mutated or aggregated forms of α-synuclein may also overwhelm the degradative capacity of the proteasome, leading to further impairment [24, 25, 26]. The consistent presence of fibrillar α-synuclein as a major component of LBs in PD [30], and the formation of LB-like inclusions containing α-synuclein following proteasome inhibition *in-vivo* [31], support this notion. LBs are a pathological hallmark of sporadic and some familial forms of PD and indicate the involvement of protein mishandling in disease pathogenesis, although we do not know whether LB formation is a primary or secondary event. The role of LB formation in PD is the subject of some controversy with both pathogenic and protective mechanisms being proposed [25].

PARKIN Gene Mutation: PARKIN normally tags protein with ubiquitin and plays a role in mitochondrial homeostasis. PARKIN gene mutation may cause impairment of the UPS and protein mishandling may also cause the molecular pathogenesis of familial and sporadic forms of PD [32]. PARKIN is involved in maintaining normal UPS function; disease-linked mutations in these genes would lead to a similar set of events precipitating in the demise of DA neurons. Structural and functional deficits in the 20/26S proteasome in the SNpc of sporadic PD patients are observed. Failure of UPS results into the accumulation of toxic misfolded proteins, which further degrade the degradative capacity of the proteasome and may lead to further impairment [26].

DJ 1 Gene Mutation: DJ 1 is a molecular chaperone with roles in antioxidant gene expression and possibly counter oxidative stress in mitochondria. DJ-1 does not appear to be localized to LBs in sporadic PD and other synucleinopathies but does co-localize with tau-positive inclusions in some neurodegenerative tauopathies and with α-synuclein-positive glial inclusions in multiple system atrophy [33, 27], which suggests that DJ-1 may play a diverse role in seemingly distinct neurodegenerative diseases. Furthermore, insoluble forms of DJ-1 are dramatically increased in the brains of sporadic PD patients perhaps also implicating DJ-1 in sporadic forms of this disease [34]. The physiological function of DJ-1 is unclear, but evidence suggests that DJ-1 may function as an anti-oxidant protein or as a sensor of oxidative stress. For example, DJ-1 demonstrates an acidic shift in isoelectric point in cultured cells following oxidative stress owing mainly to oxidation of cysteine residues, particularly Cys106, which can be converted to a cysteine sulfinic acid (Cys-SO_2H) [35, 36]. DJ-1 can also eliminate hydrogen peroxide in vitro by oxidizing itself suggesting that it may function, in part, as a direct scavenger of ROS [37].

In cultured cells, overexpression of DJ-1 protects against oxidative injury whereas knockdown of DJ-1 by short interfering RNA enhances the susceptibility to oxidative stress. DJ-1 is a component of the UPS and may confer protection by functioning as a molecular chaperone or protease to refold or promote the degradation of misfolded or aggregated proteins [37].

Oxidative Stress and Lipid-peroxidation: In Parkinson's disease it is accepted that oxidative stress is critically involved in the dopaminergic neuron death since the SN of PD patients exhibits increased levels of oxidized lipids, proteins and

DNA and a decrease in the levels of glutathione (GSH) [38]. There is evidence of oxidative stress in the brains of PD patients. Sufficient data is available which indicates the presence of increased levels of malondialdehyde (MDA), and lipid hydroperoxide, products of lipid peroxidation in the substantial Niagra pars compacta (SNpc) region in the brain of PD patient [39]. Oxidative stress has received the most attention in PD because of the potential of the oxidative metabolism of dopamine to yield hydrogen peroxide (H_2O_2) and other reactive oxygen species (ROS) [40]. Oxidant stress and consequent cell death could develop in the SNpc under circumstances in which there is (a) increased dopamine turnover, resulting in excess peroxide formation; (b) a deficiency in glutathione (GSH), thereby diminishing the brain's capacity to clear H_2O_2; or (c) an increase in reactive iron, which can promote OH^- formation.

Indeed, postmortem studies in PD brains demonstrate increased iron, decreased GSH, and oxidative damage to lipids, proteins, and DNA, suggesting that the SNpc is in a state of oxidant stress [41]. Most attention has been directed to the finding of a selective decrease in the reduced form of glutathione (GSH) in the SNpc in PD [42]. A reduction in GSH may impair H_2O_2 clearance and promote OH^- formation, particularly in the presence of increased iron. The cause of the decrease in GSH in PD is unknown. The major enzymes linked with glutathione synthesis remain unaffected. There is, however, a significant increase in the level of gamma-glutamyl transpeptidase, the enzyme responsible for the translocation of glutathione precursors and metabolism of the oxidized form of glutathione (GSSG) [44]. Increased ϒ-GTT helps to survive cells to recruit glutathione precursors into the cell to replenish diminished levels of GSH or a compensatory mechanism to remove potentially toxic GSSG formed as a consequence of oxidant stress [39].

Inflammation: Inflammation has also been proposed as a possible mechanism in the pathogenesis of PD. Activated microglia have been observed in the substantia nigra, putamen, where DA loss is prominent, and also in the hippocampus of patients with PD, which has been suggested to be responsible for neuronal dysfunction and cognitive decline in PD [43]. Activated microglia produce a variety of inflammatory cytokines, including interleukin (IL)-2. Furthermore, activated microglia can be phagocytic and release pro-inflammatory factors such as TNFα, prostaglandin E2 (PGE2), INFγ, and ROS such as NO^-, H_2O_2, and O^{2-}, which are all toxic to neurons [44]. Furuya and colleagues reported that caspase-11, which is predominantly expressed in microglia in the SN, can produce cell death by regulating the expression of cytotoxic cytokines. Caspase-11 null mice were resistant to the neurotoxic effects of an acute MPTP treatment [45]. However, inhibition of microglia activation relieved the degeneration of DAergic neurons [46, 47]. Increased levels of inflammatory cytokines have also been found in the nigrostriatal regions and cerebrospinal fluid (CSF) of patients with PD. Clinical studies have shown that IL-2 levels are increased in the caudate nucleus and the CSF of the patients with PD [48]. Since DAergic neurons are more vulnerable to inflammatory cytokines, these cytokines have been implicated in cognitive impairment in PD [43].

Mitochondrial Dysfunctioning: Mutations in five genes encoding α-synuclein, parkin, UCH-L1, PINK1, and DJ-1 are associated with familial forms of PD through pathogenic pathways that may commonly lead to deficits in mitochondrial and UPS function. PINK1, parkin, and DJ-1 may play a role in normal mitochondrial function, whereas parkin, UCH-L1, and DJ-1 may be involved in normal UPS function. α-Synuclein fibrillation and aggregation are promoted by pathogenic mutations, oxidative stress, and oxidation of cytosolic dopamine (DA), leading to impaired UPS function and possibly mitochondrial damage. α-Synuclein may normally be degraded by the UPS [49]. Some environmental toxins can inhibit complex-I and lead to mitochondrial dysfunction [50, 51]. Impaired mitochondrial function leads to oxidative stress, deficits in ATP synthesis, and α-synuclein aggregation, which may contribute to UPS dysfunction [52].

Impairment of the Ubiquitin-Proteasome System: Impairment of the UPS and protein mishandling may also cause the molecular pathogenesis of familial and sporadic forms of PD [32]. PARKIN, UCH-L1, and DJ-1 may be involved in maintaining normal UPS function; disease-

linked mutations in these genes would lead to a similar set of events precipitating in the demise of DA neurons. Structural and functional deficits in the 20/26S proteasome in the SNpc of sporadic PD patients are observed. Failure of UPS results into the accumulation of misfolded proteins, which further degrade the degradative capacity of the proteasome and thus leading to further impairment in PD [26].

Exposure to Manganese and Other Catecholamine-Depleting Agents: Manganese is an essential trace mineral necessary for normal development and biological function [53]. Excessive exposure to manganese is a well-recognized occupational and environmental hazard, which can lead to an extrapyramidal syndrome, referred to as manganism [54]. Although this condition has motor symptoms that resemble PD, it also has several characteristics features different from PD, such as dystonia and the lack of response to dopamine replacement therapy [14]. Catecholamine-depleting agents like Reserpine and Alpha-methyl-para-tyrosine (AMPT) are known to induce Parkinsonism. The first animal model for PD was demonstrated by Carlsson in the 1950s using rabbits treated with reserpine. Reserpine is a catecholamine-depleting agent that blocks vesicular storage of monoamines. Alpha-methyl-para-tyrosine (AMPT), like reserpine, serves as an effective catecholamine-depleting agent. By directly inhibiting tyrosine hydroxylase (the rate-limiting enzyme in dopamine biosynthesis), the nascent synthesis of dopamine in neurons of the substantia nigra pars compacta and the ventral tegmental area is prevented [55].

Experimental Models of Parkinson's Disease: Valid animal models that mimic the progressive disease state of PD are essential tools to better understand the early pathogenesis of PD. Exposure to certain neurotoxins like 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP), 6-Hydroxy-dopamine (6-OHDA), Rotenone and Paraquat can induce Parkinson's disease. These neurotoxins are known to produce the key features of PD like certain motor defects, progressive loss of dopaminergic neurons in substantia nigra pars compacta (SNpc), and the formation of Lewy bodies [56]. Since 6-OHDA and MPTP models are known to induce an acute ablation of the dopaminergic system; they are not successful enough to study the progressive nature of PD [57]. Below is a brief overview of major experimental models of PD.

Mouse models using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) are among the most widely used. MPTP mouse models have shed light on the pathophysiology as well as some of the causes of the disease. MPTP model has provided investigators with a reliable and valid model for studying symptomatic relief and neuroprotective effect of drugs. MPTP resembles some known environmental compounds, including herbicides such as paraquat [58] and the garden insecticide/fish toxin, rotenone [59]; both have been shown to induce degeneration of dopaminergic neurons [60, 61]. The neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (MPTP) results in a clinical syndrome closely resembling Parkinson's disease (PD) in both man and primates. MPTP is a meperidine analog which is metabolized to 1-methyl-4-phenylpyridinium (MPP+) by the enzyme monoamine oxidase B (MAO-B).

MPTP has been shown to accumulate within the mitochondria as MPP^+ [62], which, through its interaction with complex I of mitochondrial oxidative phosphorylation, causes a reduction in mouse striatal and midbrain ATP levels. This reduction in conjunction with the increased generation of reactive oxygen species most likely results in the ultrastructural abnormalities that befall mitochondria and the rest of the cell. The major advantage of this model is that the behavioral syndrome closely bears a resemblance to the clinical features of idiopathic PD [63, 64, 65].

The first toxin-induced animal model of PD to be generated was the 6-OHDA model [66]. 6-OHDA model involves the unilateral ablation of the dopaminergic neurons, which project from the SNpc to the striatum. 6-OHDA is a hydroxylated analogue of dopamine with a high affinity for DAT, which does not cross the blood-brain barrier and thus must be locally injected into the brain. After entering into the cell through DAT-mediated transportation, 6-OHDA tends to accumulates in mitochondria where it inhibits complex I. 6-OHDA can also auto-oxidate, resulting in the production of hydrogen peroxide (H_2O_2) [67].

6-OHDA is directly injected into the SNpc or into the medial forebrain bundle (MFB), which harbors the projections of the A9 dopaminergic cells that originates in the SNpc and end in the striatum. Dopaminergic neurons start to degenerate 12 h after the 6-OHDA injection, and after 2-3 days there is a marked loss of dopaminergic terminals in the striatum is observed which is accompanied by dopamine depletion and leads to 90-100% loss of dopaminergic neurons [67]. It is common to perform SNpc/MFB 6-OHDA lesions unilaterally, leaving one hemisphere intact, which increases the viability of the animals and provides a useful model system to study and quantify L-DOPA-induced dyskinesias and stereotypes [68]. Unilaterally lesioned animals display a characteristic rotational behavior when challenged with drugs that stimulate striatal dopamine receptors directly or indirectly, such as apomorphine, L-DOPA and amphetamine [69]. In another 6-OHDA-induced model the injections are made into the striatum, often bilaterally, resulting in a comparatively milder and progressive loss of dopaminergic neurons over 4-6 weeks post-injection [70].

Rotenone is a naturally occurring, a highly lipophilic cytotoxic pesticide. Rotenone exposure is known to produce certain hallmark features of PD which include nigrostriatal dopaminergic degeneration and formation of alpha-synuclein filamentous inclusions in brain samples of PD patients. Chronic exposure to pesticides is a known risk factor of PD, which has led to numerous studies on agricultural pesticides and neuro-degeneration, and to the discoveries of additional toxin-induced animal models of PD. Chronic systemic injections of the pesticide rotenone induce Parkinsonism in rats by entering dopaminergic neurons in a DAT-independent manner and inhibiting mitochondrial complex I [71]. Inhibition of complex I lead to the formation of ROS, and subsequently to selective nigrostriatal dopaminergic degeneration [72].

The herbicide paraquat, which is structurally similar to MPP^+, is also used as a systemic model of PD. In contrast to MPTP and rotenone, paraquat is incapable of crossing the blood-brain barrier. Paraquat is known to enter the brain *via* amino acid transporters [73], and dopaminergic neurons *via* DAT [74]. Within the neuron paraquat go through redox cycling to produce the free radical superoxide, thus inducing oxidative stress-mediated neurotoxicity [74]. The toxicity of this herbicide is mediated through the formation of monocationic radical by NADPH: cytochrome P-450 reductase and NADH: ubiquinone oxidoreductase reduction of paraquat. In comparison to MPP+ and rotenone, the affinity of paraquat complex is much low, therefore complex do not appear to be part of its neurotoxic mechanism [73].

CONCLUSION: Unfortunately, our understanding of the critical molecular events causing neuro-degeneration in PD is limited, and consequently there is little progress in the pharmacotherapy of PD, especially to interfere with the disease progression. The genuine complexity of PD as a syndrome with multiple aetiologies should be kept in the spotlight to ensure progress in the field. Thus, it seems logical to stress the importance of the ability to diagnose potential Parkinsonian patients accurately.

Many simulated animal models of PD have been developed to understand the pathogenesis and test potential therapeutics of this disease. Such simulated models are useful to screen drugs for symptomatic treatment of the disease, besides these models, transgenic and knockout models are useful for evaluating the role of genetics in PD. With using the model of toxins, it is possible to develop a progressive model by tempering the toxic doses.

Future scope of the study involves improvement in the screening and the evaluation of Anti-Parkinsonian drugs and developmental processes. The above-mentioned animal models can prove to be helpful in understanding mechanisms for the death of dopaminergic neurons. Hence, it is necessary to investigate these animal models to understand the involvement of mitochondrial dysfunction, energy (ATP) depletion, free-radicals production, apoptosis, and glutamate excitotoxicity in the pathogenesis of PD.

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