



Parkinson's Disease: An Insight into Mechanisms and Model Systems

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ABSTRACT

Parkinson's disease (PD) is the most common, insidious motor-neurodegenerative disorder characterized by loss of dopaminergic neurons in substantia nigra pars compacta. In ancient Indian medical system of Ayurveda, the same pathology was documented as Kampavata, where, 'Kampa' refers to the 'shaking' or 'tremors' and 'Vata' stands for disease. PD affects the global population regardless race, clan, cast or socioeconomic barrier, with a prevalence rate of (0.3-0.8) %. More than 1 million people above the age of 60 years are affected by PD in USA alone. PD is associated with various risk factors including aging, genetic involvement and environmental neurotoxin exposure. Studies have shown that, experimental models are capable to recapitulate most of the PD symptoms, which showed imbalance in striatal neurochemistry of brain and alterations in neuroinflammatory markers, oxidative stress, neurotrophic factors and mitochondrial dysfunction. In the present review, we have accumulated all the recent updates on PD and provided a brief discussion on the toxin-induced animal models of PD.

Keywords: Parkinson's disease, Oxidative stress, Neurotransmitters, Neurotrophic factors, Animal model of PD

INTRODUCTION

Parkinson's disease (PD) is the most common motor-neurodegenerative disorder which arises when dopaminergic neurons of Substantia Nigra pars compacta (SNpc) die due to various endogenous or exogenous influences. As a result, motor functional disabilities like akinesia, catalepsy, resting tremor and dyskinesia appear among the patients [1]. Cellular and molecular research has revealed that, neuronal accumulation of hollow eosinophilic proteinaceous aggregates namely 'Lewy body' is the major putative contributor towards PD pathology. Alpha-synuclein (α -synuclein) is the prime constituent in Lewy body, which directly or indirectly initiates various cytotoxic mechanisms leading to the neurodegeneration [2].

PD is characterized by the progressive death of selected heterogeneous bundles of neurons, including the neuromelanin-laden dopaminergic neurons of the SNpc [3]. Neuronal loss is found to be more in the ventrolateral tier followed by the medial ventral tier and dorsal tier within the SNpc; however, not all dopamine neurons prediction is equally receptive [4]. It results in a regional loss of striatal dopamine, most prominently in the dorsal and intermediate subdivisions of the putamen, a process that is believed to account for akinesia and rigidity. Despite the great research efforts of the last decade, the etiopathogenesis of PD is still unknown. L-dopa and DA agonists are currently used to alleviate symptoms of PD, but most treated patients still develop a progressive functional disability that severely affects their quality of life [5]. The mechanisms responsible for cell death in PD are largely unknown. Increasing evidence suggests that neuronal death in the SNpc may be apoptotic and the neurotrophins are well reported to reduce this neuronal death [6]. Dopamine is one of the main monoaminergic neurotransmitters in the central nervous system. The mesodiencephalic dopaminergic (mDA) neurons are responsible for the major source of dopamine in the brain and also related to movement impairment in PD due to progressive loss in this region along with midbrain dopaminergic (DA) neurons of the SNpc. The cause of degeneration of DA neurons in patients with PD is not completely understood, but mitochondrial dysfunction, oxidative stress, protein aggregations, and reduced neurotrophic signaling are commonly observed in PD patients.

Pathobiology of Parkinson's Disease

Progressive loss of dopaminergic neurons is the characteristic feature of PD [7-9]. It is the most common progressive motor-neurodegenerative disease, which affects quality of life among sufferers. PD symptoms come out when a minimum loss of (50-70)% DA or ~80% DAergic neurons have been evidenced [7]. The presence of intra-cytoplasmic inclusions, composed mainly of α -synuclein and ubiquitin, are called Lewy bodies, which is the characteristic feature for PD [10]. Clinical symptoms of PD comprise both motor and non-motor symptoms. There is slowness of initiation of voluntary movements (bradykinesia) with progressive reduction in speech, muscular rigidity, resting tremor, and postural instability in PD patients. Almost 90% of PD patients experience non-motor symptoms during the course of disease. The spectrum of non-motor symptoms is also very broad and comprises neuropsychiatric conditions, such as depression, dementia, and hallucinations as well as autonomic, sensory, and REM sleeps behavior disorders [11]. Presence of neuroinflammation is the other crucial feature of PD. For example, some pro-inflammatory cytokines, such as interleukin (IL)-1 β , tumor necrosis factor (TNF)- α , and others, have been found to be at higher levels in cerebrospinal fluid samples from PD patients compared to age-matched controls [12].

Past and Present Scenario of Parkinson's disease

Ancient Indian medical system of Ayurveda referred the Parkinsonian equivalent disease as 'Kampavata'. Around 175 AD, western medicine, physician Galen in his monograph described the pathobiology of PD as 'shaking palsy' [13]. In the year 1817, James Parkinson published a medical essay titled 'An Essay on the Shaking Palsy' and re-discovered the PD pathology through a case report on 3 of his patients. The description given by James Parkinson included the cardinal features of PD, which are tremors, rigidity and postural instability. According to his report, the disease developed because of abnormality in the medulla of the brain. James Parkinson inspired the medical community to investigate further and his timely article received ample of attention. After 60 years from the publication of the essay, Jean Martin Charcot, a French neurologist, named the disease as 'Parkinson's disease' after James Parkinson. Jean-Martin Charcot and his colleagues are responsible for much of the advancement and understanding PD and further added more symptoms to James Parkinson's clinical description (James 1924), which on other hand confirmed the acceptability of James Parkinson's opinion in the medical history. In 1940s and 1950s, neurosurgeons started to perform brain surgeries and found improvements in signs and symptoms of PD. In 1960s, researcher's identified differences between normal brain and PD affected brain that were associated with low levels of dopamine [14].

In 1960, the chemical differences in the brains were performed to identify PD patients. The neurodegeneration of nerve cells in part of the brain called SNpc were caused by the low levels of neurotransmitter dopamine [15-17]. The first effective medicinal treatment of the disease discovered was lead. Levodopa was the best drug to treat PD in 1960s and is still being used and in the 1960s the drug levodopa was firstly administered to treat the PD and has since become the 'gold standard' therapy for PD [18]. Since the 1960s research has continued to progress at a rapid rate. The symptoms of PD can now be effectively controlled and reduced in severity; however, there is still no cure [18].

Global Prevalence of Parkinson's Disease

After Alzheimer's disease (AD), PD is a second most common age related neurodegenerative disease. In United States, 1 million people (approx.) are affected by PD (1 of every 100 individuals) beyond the age of 50 years. The prevalence of PD also increases with age, affecting about (1 to 2)% adults above the age of 60 years and 4% of above the age of 80 years [19]. Among rest of the world US is the country having maximum patients of PD. It is estimated that approximately 630,000 people in the US have been diagnosed in 2010, with diagnosed prevalence likely to be double by 2040. The national economic burden of PD in US exceeds \$14.4 billion in 2010 (approximately \$22,800 per patient) [19].

In 1875, Henri Huchard (1844-1911) discovered the first case of Juvenile Parkinson's disease [20]. A 3 year old child was described by him, who had all the clinical features of PD. Since then, a 10 year old girl from Green Country (Oklahoma) is the youngest reported case of PD, who showed her first symptoms of PD when she was 2 years old. Population of elderly Indians has increased from 5.6% (51 million) in 1961 to 7.1% (71 million) in 2001. This

increasing life expectation of Indians results in an increased age-related diseases like PD and AD [21]. Nearly, 33 million Indians have neurological disorders and they occur twice as often in rural areas. The ‘Parsi community’ in Mumbai has the world’s highest incidences of PD where it affects about 328 out of every 100,000 people despite living in a country, India, with one of the world’s lowest incidence of PD (70 out of 100,000) [20-22].

The risk of PD increases according to hair color. People with black hair were found to be least prone to PD, while people with brown hair were 40% more likely to develop PD. Moreover, people with blonde hair were 60% more likely to develop PD [22]. The risk of PD is nearly doubled for people with red hair. In the beginning this association was seemed odd, but hair color and PD share a common biochemistry. The dopamine needed to relieve PD is initially made from L-tyrosine turning in to L-Dopa. Coincidentally, the pigment that colors hair (Melanin) is also initially made by turning L-tyrosine in to L-Dopa [23].

Epidemiology

It is estimated that 6.3 million people suffer from PD worldwide. The incidence has been approximately to 4.5-21 cases per 100,000 populations per year. The estimates of PD prevalence range from 18 to 328 per 100,000 populations, with most studies yielding a prevalence of approximately 120 per 100,000. The incidence and prevalence of PD increased with age. PD is about 1.5 times more common in men than in women. The average onset age of PD is 61, but it may begin as early as age 40 years or even before (Figure 1) [24].

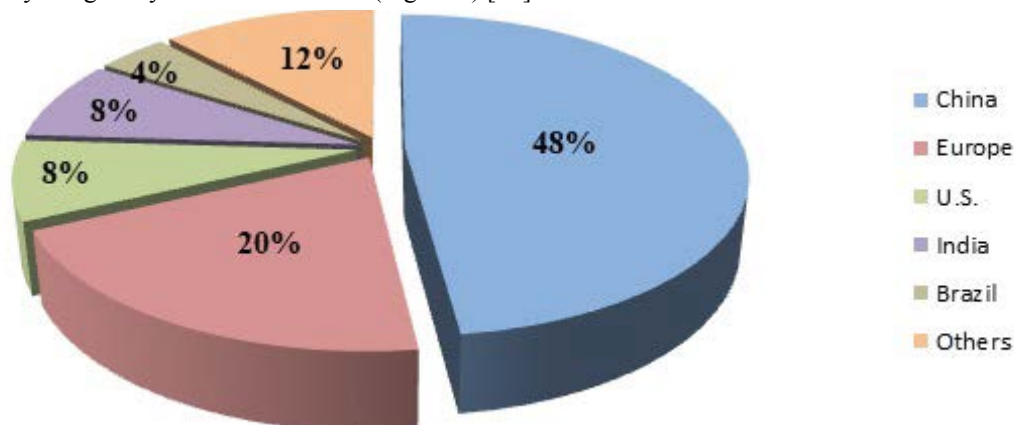


Figure 1 Distribution of individuals with Parkinson’s disease by country

Parkinson’s Disease: Diagnostic Methods and Pathological Stages

Stage I: The mildest stage of Parkinson’s disease is Stage I in which there may be unknown and unusual symptoms but they will not affect the daily routine and quality of life. Furthermore in stage I the signs and symptoms are very less and sometimes they are often missed. In this stage, tremors and other abnormalities in movement are generally onto one side of the body and they can be recovered by prescribed medications [25].

Stage II: The moderate stage of PD is Stage II, in which the symptoms are more noticeable and experienced then stage I. In this stage tremors, rigidity and abnormalities in movements may be more as compared to stage I and there is also change in the facial expressions of patient. While muscle stiffness prolongs task completion, stage II does not impair balance. In this stage signs and symptoms are on both sides of body and patient also experience speech problems. It can take months or even years for progression from stage I to stage II. There is no way to predict individual progression [25].

Stage III: The mid-stage of PD is Stage III, it is the major turning point to the progression of PD. Signs and symptoms are same as patient experienced in Stage II, except loss of balance and decreased in reflexes can also occur. In this stage, daily routine task of patient can be affected but will be completed by taking some time. If prescribed medication is combined with occupational therapy it may help to reduce the symptoms. Even care-giving through artificial intelligence-enabled instrumentation could solve the purpose of quality care for the PD sufferers [26].

Stage IV: In this stage of PD, patients were unable to survive alone because of lowering in movement and other cognitive abnormalities and for movement they require any assistance or walker to do their work. Living alone at stage IV or later may make many daily tasks impossible, and can be extremely dangerous [27].

Stage V: This stage is advanced stage and weakens the strength of PD patients. In this stage if patient stands for a while there will be severe stiffness in legs and immediately requires wheel chair and assistance and also unable to stand without falling. PD patient at this stage may experience hallucinations and fall victim to occasional delusions. Side effects from medications at stage V can outweigh the benefits [27].

Symptoms of Parkinson's disease

Motor manifestations: It is not always necessary to present all the phenotypic characters of PD present in patient. Sometimes, tremor could be absent and such dilemma brings complexities in PD diagnosis. In such silent PD events, patient's illness should lead to the careful consideration of other neurologic conditions that can present with signs of Parkinsonism, including the multiple system atrophies, progressive supranuclear palsy, corticobasal ganglionic degeneration, and others [28]. Rigidity is a motor sign more often appreciated by the examining physician than the patient; it is detected as a resistance to passive movement of the limbs [29]. Bradykinesia is another sign of PD as there is slowness in movements and decrease in strength of patient as, changes in expression of face and associated movements are also affected like swinging of arm while walking [30].

The freezing phenomenon, an additional motor feature of PD is, also referred to as "motor block". In its most typical form, freezing occurs as a sudden inability to step forward while walking. It may occur at a turn, at the beginning (start hesitation), or just before reaching the destination. It is transient, lasting seconds or minutes, and suddenly abates. Combined with postural instability, it can be devastating. Freezing does not always improve with levodopa, and, in fact, can be made worse [31].

Cognitive and psychiatric manifestations: It is increasingly clear that there are many parallel circuits within the basal ganglia, each serving a different function and each modulated by DA [32]. Thus, it is reasonable to predict that patients will have a wide variety of dysfunctions extending well beyond the classic motor disabilities associated with the disease. Indeed, patients with Parkinson's disease appear to be at increased risk for a variety of cognitive and psychiatric dysfunctions. Most common is dementia and depression. However, apathy, irritability, hallucinations, delusions and anxiety also have been reported [33].

Now days, dementia is recognized as one of the cardinal non-motor manifestations of PD. There currently is no effective symptomatic treatment of dementia, which is a major cause of disability. Aarsland, et al., identified dementia in 28% of PD patients. The prevalence depends on age; in a study of PD 65% demented patients were above the age of 85 years. PD patients with dementia show a more rapidly progressive course, and are more likely to be institutionalized, than non-demented individuals. Years ago, there was debate about whether depression is a primary manifestation of PD or a reaction to having a chronic neurologic illness. There is now little question that it is a primary manifestation [34]. Mayeux, et al., have found that 47% of PD patients show evidence of depression, and some have found an even higher incidence. Moreover, Aarsland, et al., reported that major depression is much more common among PD patients who also have signs of dementia (22%) than those who did not (2%). The depression, however, is not related to the severity of motor signs; indeed, many patients are depressed prior to the onset of frank neurologic dysfunction. Moreover, the depression is often greater than that seen in individuals with comparably debilitating motor dysfunction due to other disorders [35].

Other manifestations: The Burning Mouth Syndrome (BMS) is characterized by a painful, intraoral burning sensation, scalding or tingling. BMS may be more common in PD with one study reporting 24% prevalence. Hypomimia is a medical sign in which there is reduced degree of facial expression. It can be caused by motor impairment. Dysphagia means swallowing difficulties, and is usually caused by nerve or a muscle problem. Scoliosis is a medical condition in which a person's spine is curved from side to side. It's a complex three-dimensional deformity. Camptocormia is defined as an abnormal flexion of the trunk that appears when standing or walking and disappear in the supine position. It is also referred to as Bend Spine Syndrome (BSS). Blepharospasm is a condition in which there is sustained, forced, involuntary closing of eyelids. Dysarthria is caused due to central or peripheral nervous system

damage which is associated with disturbance in muscular control for speech. Bruxism refers to an oral activity such as clenching, grinding or bracing of teeth that can occur in sleep or in awake state. Dystonia, characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures or both, is a movement disorder. Glabellar reflex is elicited by repeatedly tapping the patients between eyebrows causing them to blink. It is seen in geriatric patients [36,37].

Pathogenesis of PD

The main pathological characteristic of PD is cell death in the substantia nigra and more specifically the ventral part of the pars compacta, affecting up to 70% of the cells by death time [38]. In PD, a cascade of neurochemical changes is initiated in the striatum and in other nuclei of basal ganglia downstream to striatum by the initial loss of dopaminergic inputs from substantia nigra pars compacta to the striatum (Figure 2) [39].

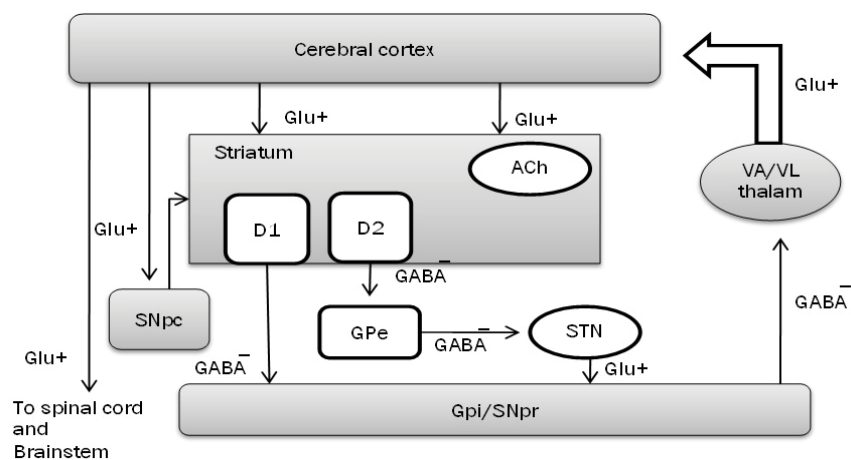


Figure 2 Normal basal ganglia: The principal input structure of the basal ganglia is striatum and receives excitatory glutamatergic input from many areas of cerebral cortex. The striatum contains projection neurons expressing predominantly D1 or D2 dopamine receptors, as well as interneurons that use acetylcholine (ACh) as a neurotransmitter. Outflow from the striatum proceeds along two routes. The striatum to the substantia nigra pars reticulata (SNpr) and globus pallidus interna (GPi), uses the inhibitory transmitter GABA as the direct pathway. The indirect pathway, from the striatum through the globus pallidus externa (GPe) and the subthalamic nucleus (STN) to the SNpr and GPi consists of two inhibitory GABAergic links and one excitatory glutamatergic projection (Glu). The substantia nigra pars compacta (SNpc) provides dopaminergic innervation to the striatal neurons, giving rise to both the direct and indirect pathways, and regulates the relative activity of these two paths. The SNpr and GPi, provide feedback to the cerebral cortex through the ventroanterior and ventrolateral nuclei of the thalamus (VA/VL), are the output structures of the basal ganglia

The changes that are thought to contribute to the excessive inhibition of motor function include:

- Enhanced inhibitory GABAergic drive from the striatum to the external region of Globus pallidus externa (GPe) and Globus pallidus interna (GPi), making GPe and GPi hypoactive
- Decreased GABAergic drive from GPe to subthalamic nucleus (STN), along with increased glutamatergic drive to STN, making this nucleus hyperactive
- Increased glutamatergic drive from hyperactive subthalamic nucleus to Globus pallidus interna (Gpi) and substantia nigra pars reticulata (SNpr), making them hyperactive

Both these nuclei (Gpi/SNr) are responsible for sending inhibitory projections to motor nuclei outside the basal ganglia. Thus, a motor thalamus and brain stem locomotor region which receives the inhibitory inputs from Gpi/SNr are overly inhibited in Parkinson's disease (Figure 3) [40-42].

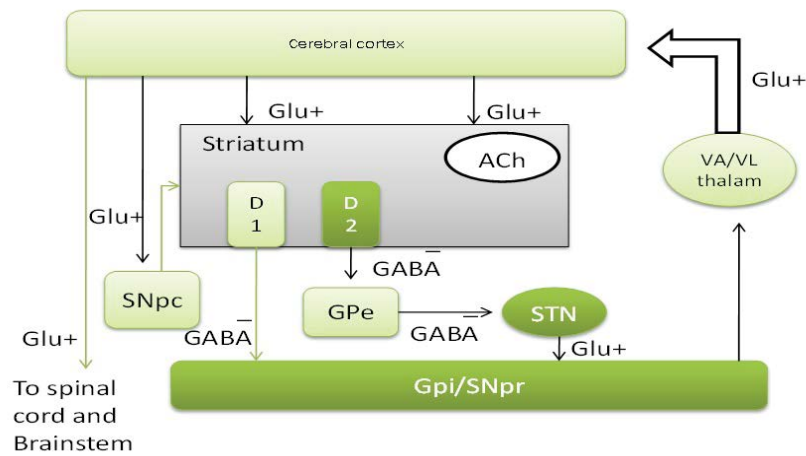


Figure 3 Basal ganglia in Parkinson's disease: The primary defect is destruction of the dopaminergic neurons of the SNpc. The striatal neurons that form the direct pathway from the striatum to the SNpr and GPi express primarily the excitatory D1 dopamine receptor, whereas the striatal neurons that project to the GPe and form the indirect pathway express the inhibitory D2 dopamine receptor. Thus, loss of the dopaminergic input to the striatum has a differential effect on the two outflow pathways; the direct pathway to the SNpr and GPi is less active (structures in light green), whereas the activity in the indirect pathway is increased (structures in dark green). The net effect is that neurons in the SNpr and GPi become more active. This leads to increased inhibition of the VA/VL thalamus and excitatory input to the cortex is reduced

Neurotransmitter and Parkinson's Disease

Dopamine

Dopamine is the most abundant catecholamine neurotransmitter in the brain and it plays an important role in a variety of functions including locomotor activity, cognition, emotion, positive reinforcement, food intake and endocrine regulation. Dopamine system is believed to be involved in both physiological as well as pathophysiology of basal ganglia disorders like PD. In spite of excitatory glutamate and inhibitory GABA, dopamine has proved to be a regulatory neurotransmitter in basal ganglia [43]. Despite the high concentrations of dopamine that exist in the striatum, there is increasing evidence that dopamine or one of its metabolites might be neurotoxic. Dopaminergic and glutamatergic systems interact closely at the level of medium spiny neurons. Dopaminergic nigrostriatal neurons synapse mainly on to the necks of dendritic spines of medium spiny projection neurons whereas glutamatergic cortical afferents synapse specifically on the head of the same dendritic spines. There is compelling data that dopamine or its metabolites or both can generate ROS. Number of investigators found major loss of D2 receptors as compared to D1 receptors in substantia nigra as well as the GPe in early stages of PD. As the disease progresses vulnerability to both D1 and D2 receptors is increased in PD patients [44]. SNpc-DA neurons are the most vulnerable population of neurons in PD. It has been suggested that their loss is multifactorial and related to the characteristic features of these cells: complex morphology, high energy demand, high calcium flux and DA metabolism. Consequently, these neurons are particularly susceptible to various stressors, which contribute to their preferential loss. It has been reported that optimal DA level are required for efficient behavior and cognitive performance. Also, alteration in DA level in dorsal striatum leads to altered motor behavior in PD [45].

Glutamate

Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system. Its presence in normal concentration is required for the normal brain functioning; however, its presence in excess can lead to excitotoxic cell death. The excessive release of glutamate into the substantia nigra from both the cerebral cortex and the STN, can be an important pathophysiological factor in PD. The activation of ionotropic glutamate receptors (NMDA, kainate and AMPA) allows an influx of Ca^{2+} ions, which can activate a variety of potentially destructive processes, such as an activation of nitric oxide synthase with the resulting generation of cytotoxic nitric oxide and peroxynitrite. So, the agents that acts to restore normal glutamatergic function may provide therapeutic interventions that bypass the severe motor side effects associated with current dopamine replacement therapy [46].

GABA

GABA is the main inhibitory neurotransmitter in the CNS. The principal neurons in the striatum i.e. about 77-97% of medium spiny projection neurons are GABAergic neurons. It has been reported that GABAergic neurotransmission within basal ganglia gets altered in PD. GABA mediates its function via ionotropic (GABA_A and GABA_C) and metabotropic GABA_B receptor [47]. GABAergic ionotropic receptors are ligand gated ion channels involved in fast synaptic transmission whereas metabotropic GABA_B receptors belong to family of GPCR and are responsible for the neuromodulator effect of GABA. Neurons are excited by glutamate, inhibited by GABA, over and under activation of these two systems has been well implicated in the pathophysiology of neurological disorders like PD and has been reported that GABAergic neurotransmission within basal ganglia gets altered in PD [48].

Serotonin

Serotonin (5-hydroxytryptamine, 5-HT) was discovered in central nervous system and in peripheral tissues 60 years ago in blood [49]. It was first identified as a vasoconstrictor substance that is released from platelets during the coagulation of blood, and later as a monoamine neurotransmitter in the brain. Serotonergic system is the largest single system in the brain and serotonergic neurons are widely distributed throughout the mammalian brain. There are 9 groups of serotonergic cell bodies which are located mainly in the area of brain stem raphe nuclei. Serotonergic nerve terminals could be found in nearly all other regions of the central nervous system. It plays a critical role as a growth factor in the immature brain, directing both proliferation and maturation [50]. In the normal brain, there are dense serotonergic innervations of the basal ganglia from the raphe nuclei, particularly the Dorsal Raphe Nuclei (DRN) that also send projections to the frontal cortex, limbic system and diencephalon. In particular, the striatum and the output regions of the basal ganglia, the Substantia Nigra Pars Reticulate (SNpr), and Medial Globus Pallidus (Gpm) receive a dense serotonergic input, thus suggesting a potential role for serotonin in PD [51].

Norepinephrine

Norepinephrine (NE) is a catecholamine with wide range of autonomic, motor and cognitive functions of the brain. NE is synthesized from dopamine by dopamine β-hydroxylase. It is released from the adrenal medulla into the blood as a hormone, and is also a neurotransmitter in the central nervous system where it is released from noradrenergic neurons [52]. NE acts via binding to adrenergic receptors. Beyond its roles as a neurotransmitter, the actions of NE are involved in one or more mechanisms linked to neurodegeneration in the PD brain. In PD, NE synthesis affected due to deterioration of neurons and maximum content decreases in tissue concentration in several brain regions [53].

Mitochondrial Dysfunction and PD

Mitochondria are exposed to a highly oxidative environment, and the process of oxidative phosphorylation is associated with the production of ROS [54]. Much evidence suggests a major role for mitochondrial dysfunction in the pathogenesis of PD, and in particular, defects in mitochondrial complex-I of the respiratory chain. A complex-I defect could most obviously contribute to neuronal degeneration in PD, through decreased ATP synthesis as well as damage caused by excess production of ROS [55]. There are consistent findings of decrements in complex-I activity in the SNpc of PD patients, but the cause of this is unknown. The alterations in complex-I activity may play a role in the pathogenesis of PD, it is further supported, by the observation that a single nucleotide polymorphism in the gene encoding the NADH dehydrogenase 3 enzyme of complex-I, causing an amino acid change from threonine to alanine, leads to a significantly reduced risk of developing PD in Caucasian populations [56]. A reduced activity of the mitochondrial I and IV have been observed in patients with PD in the SNpc. Both acute and chronic depletion of glutathione levels in dopaminergic cell lines *in vitro* results in reversible inhibition of mitochondrial complex I activity via S-nitrosation of mitochondrial complex I subunits. Several epidemiological studies suggest that pesticides and other environmental toxins (especially MPTP) inhibit complex-I and replicates most features of PD in humans and in animal models [57].

Neuroinflammation and PD

One of the major cell types which are involved in the inflammatory responses in the Central Nervous System (CNS) is Microglia [58]. In 1988, the presence of reactive microglia in the SNpc of human post-mortem brain tissue, which is the evidence revealed for the first time suggesting the involvement of neuroinflammation in PD pathogenesis

[59]. There is pronounced activation of microglia in various regions of PD brain indicated by Positron Emission Tomography (PET). Moreover, activation of microglia in the SNpc and striatum is profound in various types of PD animal model. Further biochemical analysis reveals higher levels of proinflammatory mediators including Tumor Necrosis Factor- α (TNF- α), Interleukin-1 β (IL-1 β) and Interferon-gamma (IFN- γ) in the midbrain of PD patients [60]. These data strongly suggest the involvement of immune components in PD pathogenesis. Persistent activation of the abundant number of microglia in the midbrain region is likely the direct result of elevated levels of cytokines acting in an autocrine manner to potentiate inflammatory responses (e.g. auto amplification of reactive oxygen species, nitric oxide and superoxide radicals to form a highly oxidizing peroxynitrite species) [61,62].

Excitotoxicity and PD

It is evident that excitotoxicity is a mechanism of cell death in PD. Elevated levels of glutamate in the synaptic cleft also contribute to the neurodegeneration of dopaminergic neurons in PD [63]. Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system, its presence in normal concentration is required for the normal brain functioning; however, its presence in excess can lead to excitotoxic cell death. The excessive release of glutamate into the substantia nigra from both the cerebral cortex and the STN can be an important pathophysiological factor in PD [64]. An impairment of oxidative phosphorylation will enhance vulnerability to excitotoxicity. Substantia nigra neurons possess N-methyl-D-aspartate receptors and there are glutamatergic inputs into the substantia nigra from both the cerebral cortex and the subthalamic nucleus. After activation of excitatory amino acid receptors, there is influx of calcium followed by activation of neuronal Nitric Oxide (NO) synthase, which can then lead to activate a variety of potentially destructive processes, such as an activation of Nitric oxide synthase with the resulting generation of cytotoxic nitric oxide and peroxynitrite [65].

Oxidative Stress and PD

The neuronal loss seen in SNpc of PD patients is associated with mitochondrial dysfunction and high level of oxidative damage to the macromolecules including DNA, proteins and lipids [66]. Dopaminergic neurons are particularly sensitive to oxidative stress because the metabolism of dopamine generates high levels of ROS (Reactive Oxygen Species) as dopamine can auto-oxidize at normal pH into toxic dopamine-quinone species, superoxide radicals and hydrogen peroxide. These are usually detoxified in a healthy cell; however, an imbalance between ROS production and detoxification can quickly lead to cell toxicity [67]. Post-mortem studies have shown decreased levels of glutathione (the main brain antioxidant) in the SNpc of patients [68]. Catalase catalyzes the decomposition of hydrogen peroxide to water and oxygen is found to be increased during oxidative damage. ROS degrade polysaturated lipids into malondialdehyde (MDA), the levels of which have been found to be increased in PD [69].

Experimental Models of Parkinson's disease

Several toxic animal models are currently in use in primates and rodents and, interestingly, with the exception of 6-hydroxydopamine (6-OHDA) and MPTP, these models are actually pesticide based. There are some drawbacks to the use of these models, but this fact does not negate the value of these animal models to the study of PD [70]. They have opened crucial doors to increase our knowledge base of the events that may lead to the PD neurodegenerative process [71]. Such animal models are providing useful means to observe the therapeutic efficacy of various drugs and phytochemical ingredients like silymarin, morin, resveratrol, naringenin, etc. [72,73]. Even CRISPR/Cas9 genome editing tool has showed promising outcome while dealing with such animal model system [74].

MPTP Induced Parkinsonism: MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is a neurotoxin precursor to MPP⁺, which causes Parkinson's disease by destroying dopaminergic neurons in the substantia nigra of the brain. MPTP as a model of PD was developed after an accidental event that happened in 1980s when several drug addicts from California developed Parkinsonian like syndrome after intravenous use of synthetic meperidine that was contaminated with MPTP (Figure 4) [75,76].

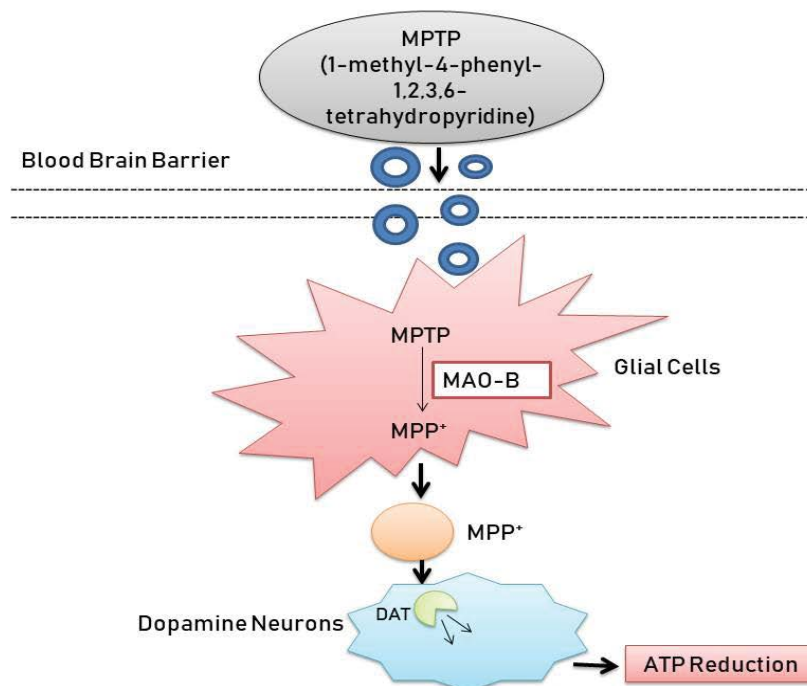


Figure 4 Representation of mechanism of MPTP induced PD (DAT: Dopamine Transporter; MPP+: 1-methyl-4-phenylpyridinium; MAO-B: Monoamine Oxidase B; ATP: Adenosine Triphosphate)

MPTP is highly lipophilic and after systemic administration crosses the blood-brain-barrier and is converted by monoamine-oxidase B (MAO-B) to MPP⁺ within astrocytes [77]. The astrocytes with the help of cation transporter 3 (OCT-3) cause release of MPP⁺ (1-methyl-4-phenylpyridinium) into extracellular spaces. From extracellular spaces MPP⁺ is taken up by the dopamine (DA) transporter [78]. Since midbrain neurons contain the highest concentration of dopamine transporters/cell once in the cell, MPP⁺ can move through several cellular compartments: it can enter into mitochondria where it interferes with complex I of the electron transport chain and inhibits it. Blockade of this complex I leads to a reduction in cellular ATP. Inhibition of mitochondrial complex I not only interferes with Adenosine Triphosphate (ATP) synthesis, but also results in enhanced production of superoxide anion radical [79].

6-OHDA: 6-OHDA is selective catecholaminergic neurotoxin used to induce PD like symptoms in rat brain by loss of DA neurons in striatum part of brain as same as MPTP neurotoxin model. Since, 6-OHDA model cant cross the blood brain barrier therefore system fails to induce Parkinsonism. Therefore to induce PD like symptoms 6-OHDA is injected (unilateral injection) into the SNpc [80]. The effect of PD like symptoms can be achieved in 12 h or (2-3) days and effects is same as we found in acute MPTP model. There is progressive retrograde neuronal degeneration in the SNc and VTA through intranigral administration of 6-OHDA. The pattern of DA loss in animals bearing a full lesion (>90%) again mirrors seen that in PD, with the SNc showing more cells loss compared to the VTA. As in PD, DA neurons are killed, and the non-DA neurons are preserved. However, like in the MPTP model, 6-OHDA does not produce LB-like inclusions in the nigrostriatal pathway [81,82]. Traditionally, behavioral assessments of motor impairments in the unilateral 6-OHDA model are done by drug-induced rotation tests. However, in both rat and mice drug-free sensorimotor behavioral tests have been developed that may be helpful for the preclinical testing of new symptomatic strategies [83].

Paraquat: Paraquat (N,N'-dimethyl-4,4'-bypiridinium) (PQ) is a herbicide widely used that exhibits a structural resemblance to MPP⁺, and, because of this structural similarity, it was reasoned that PQ should behave like MPP⁺ [84]. Epidemiological reports suggest that pesticide use increases the risk of developing PD, but, in the case of PQ, there have been only 95 cases of PD linked to its toxicity in humans. PQ exerts its deleterious effects through oxidative stress mediated by redox cycling, which generates ROS [85]. In particular, the superoxide radical, hydrogen peroxide, and hydroxyl radicals lead to the damage of lipids, proteins, DNA and RNA. Recent evidence on the effects of PQ in the nigrostriatal DA system is somewhat ambiguous as some researchers report that, following the systemic

application of this herbicide to mice [86]. Animals' exhibit reduced motor activity and a dose-dependent loss of striatal TH-positive striatal fibers and midbrain SNpc neurons. No PQ-induced changes occur in the nigrostriatal DA system claimed by other researchers. However, Rappold, et al., demonstrate that PQ, in high doses, employs the Organic Cationic Transporter-3 (OCT-3) and the Dopamine Transporter (DAT) and is toxic to the DA neurons in the SN, in a newer recent study. Furthermore, they suggest that the damage done by PQ is caused by radicalized PQ and facilitated by the glial cells. This means that PQ behaves like MPP+ in exerting its toxic effects. Although this study increases our understanding of how PQ may work, it does not end the controversy about PQ and PD [87].

Rotenone: Chronic systemic exposure to rotenone in rats causes many symptoms of PD, including nigrostriatal DA degeneration. The rotenone-administered animal model also reproduces all of the behavioral features reminiscent of human PD. Importantly; many of the degenerating neurons have intracellular inclusions that resemble LB morphologically [88]. These inclusions show immunoreactivity for α -syn and ubiquitin as did the original LB. Usually, rotenone is administered by daily intraperitoneal injection, intravenously or subcutaneously. Recently, rotenone has been tested in mice through chronic intragastric administration, or as a stereotaxic injection or infusion directly in the brain recapitulating the slow and specific loss of DA neurons. However, administration of rotenone causes high mortality in rats and, somehow, is difficult to replicate [89].

CONCLUSION

The neurobiology of PD is multifactorial and there is less success in the therapeutic paradigm applied for the disease so far. Hence, there is an urgent need to mechanistic study and analysis for conclusive cure. Till date, symptomatic rectification is the only means of applicable treatment for PD. Even in such therapeutic approach there are several demerits, which mainly due to inappropriate side-effects. Therefore, in the present study we have aimed to provide a vivid insight into the PD pathology and highlighted several mechanistic pathways those are associated with PD progress. Growing evidences suggest that the oxidative stress, neuroinflammation and excitotoxicity play major role in pathogenesis of PD. It also suggests that the imbalance of striatal neurochemistry and alterations in neurotrophic factors in brain play major role in pathophysiology of PD. Different experimental models have been reported to induce PD like symptoms and disturbed pathological conditions associated with PD. Such models are adequately providing insights about the actual scenario of PD pathology. More research and studies are the need of time to intervene all the possible pathways associated with PD pathology, which in turn could provide better therapeutic promise in future.

DECLARATIONS

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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