🔓 OPEN ACCESS

Review Article

Unraveling the Complexity: A Comprehensive Review of Parkinson's Disease Pathophysiology

Rojamani, N[1], Kesha M. Desai[2*], Sindhu Abraham[3]

[1]Department of Pharmacology, Faculty of Pharmacy, M S Ramaiah University of Applied Sciences, Bengaluru, Karnataka, India
[2]Assistant Professor, Department of Pharmacology, Faculty of Pharmacy, M S Ramaiah University of Applied Sciences, Bengaluru, Karnataka, India - 560054
[3]Department of Pharmaceutics, Faculty of Pharmacy, M S Ramaiah University of Applied Sciences, Bengaluru, Karnataka, India

Abstract: Parkinson's disease (PD) is a common neurological disorder that affects 1-2.5% of people over the age of 50 and is typified by Tremors and bradykinesia as motor symptoms. Non-motor symptoms also have a major effect, including autonomic dysfunction and neuropsychiatric problems. Although the major reason is yet unknown, environmental and genetic variables have a role. Since there is no conclusive diagnostic test, the diagnosis is made based on clinical symptoms. The most consistent risk factor is age, with prodromal symptoms occurring before motor signs. The pathogenesis of Parkinson's disease is influenced by mitochondrial dysfunction, oxidative stress, and defective protein processing. Levodopa serves as the cornerstone of treatment, which mostly consists of dopamine replacement. Developing neuroprotective PD treatments requires an understanding of the complex interactions between genetic, environmental, and mitochondrial variables.
Keywords: Alpha-synuclein, Lewy bodies, Neurodegeneration, Oxidative stress, Parkinson's disease, Protein misfolding.

INTRODUCTION

Primary parkinsonism's most prevalent form is Parkinson's disease (PD) and the second most prevalent progressive neurodegenerative illness is Parkinson's disease (PD). The affected population is around 1% of those over age 50 and 2.5% of those over age 70 (De Lau, L. M *et al.*, 2006). 2.0% of men and 1.3% of women will get Parkinson's disease over their lives (Oguh O *et al.*, 2012).

Idiopathic PD, sometimes referred to as sporadic PD, mostly affects older persons. Because of a Dopamine (DA) shortage in the basal ganglia, Parkinson's disease (PD) is generally linked to motor symptoms such as bradykinesia/akinesia, stiffness, and resting tremor (Obeso JA *et al.*, 2000).

Nonmotor symptoms and consequences, such as autonomic dysfunction, neuropsychiatric or neurobehavioral issues, and sensory issues, are also thought to be a significant aspect of Parkinson's disease (PD), in addition to motor symptoms (De Lau, L. M *et al.*, 2006).

Depression, anxiety, rapid eye movement sleep behaviour disorder, dementia, and other neuropsychiatric or neurobehavioral problems are all highly frequent in Parkinson's disease (PD) and are most likely caused by neurodegenerative processes in distinct neurotransmitter systems in different brain areas (Marsh L, 2000).

The pathogenic features of Parkinson's disease (PD) include misfolded a-synuclein buildup in intra-cytoplasmic inclusions known as Lewy bodies (LBs) and loss of dopaminergic neurons in the substantia nigra (SN) pars compacta (SNpc). When patients are initially identified, the SNpc has already lost a significant percentage of its dopaminergic neurons, and neurodegeneration has progressed to other parts of the central nervous system.

For most individuals, the source of the condition is unclear, however in 5%–10% of instances, several hereditary reasons have been found.

Levodopa, a prodrug that is transformed into dopamine in the brain via aromatic amino acid decarboxylase (AADC), has been the mainstay of

*Corresponding Author: Kesha M. Desai
Assistant Professor, Department of Pharmacology, Faculty of Pharmacy, M S Ramaiah University of Applied Sciences, Bengaluru, Karnataka, India - 560054

treatment for Parkinson's disease (PD) (Cotzias GC *et al.*, 1967). Usually, benserazide or carbidopa, two peripheral AADC inhibitors, are used in conjunction with levodopa. Because these combinations activate dopamine receptors in the region postrema of the medulla, which are not shielded by the blood-brain barrier, they avoid side effects like nausea and vomiting caused by levodopa. They also lessen the peripheral metabolism of the drug. For practically all Parkinson's disease patients, levodopa continues to be the most commonly used and effective antiparkinsonian medication, offering significant clinical advantages (Olanow CW *et al.*, 2001), (Lang *et al.*, 1998) Although other methods, including deep brain stimulation (DBS), are appropriate for later stages of the disease, the current treatment for Parkinson's disease (PD) is centered on dopamine replacement (Lee, A *et al.*, 2016).

Diagnosis of Parkinson's disease in epidemiological research

There is currently no easily accessible and trustworthy diagnostic test or marker for Parkinson's disease. In some situations, sophisticated imaging using single-photon-emission CT or PET may be effective in diagnosing Parkinson's disease (PD); nevertheless, even though these methods are now more easily accessible and user-friendly, their use for population-based epidemiological research is still restricted. Thus, clinical symptoms are the primary basis for diagnosing Parkinson's disease (PD) in epidemiological investigations (Litvan, I *et al.*, 2003).

Prevalence and Incidence

While age-related increases affect approximately 2% of people 65 and older, the crude prevalence rates of Parkinson's disease vary among Asian countries, ranging from 15 to 328 per 100,000. These disparities may be due to variations in research methodology, including case-finding protocols, diagnostic criteria, and age distribution in study populations (De Rijk, M.D *et al.*, 1997).

Demographic factor

Growing older is the most dependable risk factor for the onset of Parkinson's disease. This has been found by several prospective cohort studies and global descriptive epidemiological investigations. Approximately 5% of people with Parkinson's disease have symptoms before turning fifty (Van Den Eeden *et al.*, 2003; Schrag, A *et al.*, 2006).

Prodromal symptoms

Several nonmotor symptoms of PD are commonly reported by patients before the onset of classic motor symptoms (Tolosa, E *et al.*, 2021). Such prodromal symptoms can precede motor manifestations by years or even decades. Rapid eye movement (REM) sleep behaviour disorder (RBD), Constipation, Hyposmia/olfactory dysfunction.

Numerous more non-motor symptoms include urgency in the urine, impotence, anxiety, sadness, impaired colour vision, and neurocognitive dysfunction.

Cardinal features

Tremor, bradykinesia, and stiffness are the three primary motor characteristics of Parkinson's disease (PD). PD diagnostic criteria do not include postural instability as a core motor characteristic since it usually manifests much later in the disease, even though it is frequently stated as a fourth feature (R.B. Postuma *et al.*, 2015).

ETIOLOGY

Genetic and environmental variables are involved in Parkinson's disease (PD), which is a complex illness. The largest risk factor for Parkinson's disease (PD) is age; the median age of onset is 60 years old.

Genetic causes of Parkinson's disease

It is believed that a variety of variables contribute to the degeneration of dopaminergic neurons, which in turn causes Parkinson's disease. 5 to 10 % of individuals are thought to have a hereditary basis for the illness. Among others, PARK-SNCA, PARK-LRRK2, and PARK-VPS35 are examples of monogenic variants of Parkinson's disease. A further genetic risk factor for both Parkinson's disease and Ashkenazi Jews specifically is the Gaucher disease gene glucocerebrosidase or GBA1. The glucocerebrosidase protein, which is involved in lysosomal function, is produced under the direction of GBA1. Parkinson's disease risk is increased due to a decrease in glucocerebrosidase activity, an increase in glucosylceramide, and stimulation of α-synuclein aggregation caused by a genetic mutation in GBA1 (Gan-Or Z *et al.,* 2018; Mazzulli JR *et al.,* 2011).

Environmental causes of Parkinson's disease

The 1980s relationship between 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a prodrug to the neurotoxin MPP+, and parkinsonism raised questions about whether environmental or hazardous exposures may have a role in the development of Parkinson's disease (Mazzulli JR *et al.,* 2011). Woodworking, head injuries, polychlorinated biphenyls, trichloroethylene, perchloroethylene, carbon tetrachloride, pesticides (paraquat and rotenone), heavy metals (lead, manganese), well water are a few environmental factors, and toxic exposures that may be linked to Parkinson disease. Environmental risk factors also include exposure to poisons such as cyanide, organic solvents, trace metals, and carbon monoxide. On the other hand, it is believed that smoking and consuming coffee lower the risk of illness, however, research on this is still underway (Taylor, K.S.M, *et al.,* 2007; Obeso, J.A.*et al.,* 2017).

PATHOGENESIS OF PARKINSON'S DISEASE

Many processes have been linked to the pathophysiology of Parkinson's disease (PD), with α-

synuclein aggregation playing a key role in the illness's progression. Numerous additional mechanisms are also believed to be involved; research has revealed a role for aberrant protein clearance, mitochondrial dysfunction, and neuroinflammation in the development and course of Parkinson's disease (PD). The connection between these routes is yet unknown, though. Neuronal atrophy within the pars compacta area of the substantia nigra is a characteristic of the PD brain. Before 60–80% of the substantia nigral neurons die, the majority of PD patients do not exhibit any symptoms. Melanin is a chemical that gives these neurons their black colour. Little pigmentation in the substantia nigra is seen upon autopsy, indicating degeneration (White, M, 2007).

Large intraneuronal clumps called Lewy Bodies are present in substantia nigral neurons at the cellular level. These aggregates are mostly made of the protein α-synuclein (Spillantini, M.G *et al.,* 1998).

Remarkably, despite α-synuclein's widespread expression in the human brain, aggregation is exclusively seen in these neurons. An analogy between Parkinson's disease (PD), Alzheimer's disease (AD), and amyotrophic lateral sclerosis reveals a shared pathophysiology (Newell, M.E *et al.,* 2022).

Physiology of the basal nuclei
According to the basal nuclei's functional organization hypothesis, the thalamus, cerebral cortex, and basal nuclei (BN) are connected to create distinct and parallel circuits. The striatum receives glutamatergic excitatory projections from the cerebral cortex's sensory-motor and association areas. The striatum then projects through two striatal pathways to the exit of BN, which includes the substantia nigra pars reticulata (SNR) and the globus pallidus internus (GPi)/globus pallidus externa (GPe). The thalamus disinhibition is triggered by the suppression of the inhibitory striatal neurons through substance P (SP) and gamma-aminobutyric acid (GABA), which forms the basis of the direct pathway that enables the commencement and execution of voluntary movement.

In the indirect pathway, the subthalamic nucleus (STN) is inhibited by suppressing the activity of GPe neurons through the activation of inhibitory striatopallidal projections by GABA and enkephalins. Through glutamatergic projection, the STN connects to the thalamus. As a result, it causes an excitatory activity when triggered. Its control over the thalamus is then increased by its inhibition via the GPe in the indirect route. Furthermore, the majority of pallidal neurons' high discharge frequency inhibits the STN tonically.

Movement-related neurons in the GPi/GPe and SNR exhibit a phasic rise or decrease in their spontaneous discharge frequency during the performance of a particular motor act. Through inhibition of the ventral lateral (VL) nucleus of the thalamus, the phasic drop plays a critical role in motor control, promoting cortical-initiated movements, whereas the phasic rise appears to have the opposite effect. A complete description of the inputs on the GPi/GPe and the SNR neurons via direct and indirect pathways is lacking. On the other hand, it is feasible that the same set of neurons may receive both the selectively and cooperatively activated direct and indirect inputs in response to a movement that is cortically triggered.

This makes it possible for the movement that the direct pathway has strengthened to be downregulated at the entrances of the indirect channel. It is also possible that the inputs of the direct and indirect pathways connected to a particular movement are directed to distinct neuronal groups, each of which contributes to the cortical modulation of movement in a different way by either suppressing a conflicting motor model through the indirect pathway or reinforcing a chosen one through the direct pathway. The striatal efferent pathways are subject to competing influences from the nigrostriatal dopaminergic projection. The striatal neurons in the direct pathway appear to be stimulated, whereas the neurons in the indirect pathway appear to be inhibited. Therefore, the DA's influence on the striatum intensifies the circuit's cortical activity by promoting conduction via the direct pathway, which stimulates the thalamus, and inhibiting conduction via the indirect pathway, which inhibits the thalamus (Alexander, G.E *et al.,* 1990).

Basal nuclei and the movement control
The significant changes in movement in the disorders that impair BN, and basal nuclei are a component of the cortico-subcortical circuits involved in the programming and execution of movement (Alheid, G.F *et al.,* 1990). Numerous research on the functions and actions of the several neurotransmitters incorporated in the BN have been published. These investigations have contributed to our understanding of the function of neurotransmitters in the regulation of movement and the interplay between the various BN nuclei (Cazorla, M. *et al.,* 2014; Mograbi, K.D.M, *et al.,* 2017; Sgambato-Faure *et al.*, 2018; Sitte, H.H *et al.,* 2017).

One of the primary structures involved in rotating behaviour is the striatum, which gets a significant afferent input from neurons and connects to the GABAergic neurons of the SNR via the nigrostriatal pathway. Both SNR GABAergic and CNS dopaminergic neurons affect rotational behaviour. The CNS's nigrostriatal dopaminergic neurons and the SNR's non-dopaminergic neurons are also implicated in posture regulation. A striking asymmetry results after a unilateral 6-hydroxydopamine lesion of the nigrostriatal projection, and the animal has a propensity to rotate towards the side that was injured (homolateral rotation).

Conversely, unilateral electrolytic lesions of the SNR cause a tendency for rotation towards the unaffected side (contralateral rotation), suggesting the

presence of non-DA neurons that span or originate from the SNR. When the SNR is injected unilaterally with kainic acid, the result is spontaneous contralateral rotation that preserves the relative integrity of the central nervous system. Serotonin levels are also reduced, but there is a notable decrease in glutamic acid decarboxylase and catalase in the striatum, indicating that kainic acid is damaging the non-dopaminergic (GABAergic and cholinergic) neurons in the SNR.

Contralateral rotations resembling those caused by kainic acid are also induced by unilateral intranigral injection of ethanolamine-O-sulfate, which blocks the enzyme GABA transaminase and causes an endogenous GABA buildup within the neuron. This implies that, in contrast to nigrostriatal dopaminergic neurons, the death of GABAergic neurons in the SNR would regulate rotations. Contralateral rotations are produced by the unilateral injury of dopaminergic nigrostriatal neurons with kainic acid, which is independent of the action of nigrostriatal dopaminergic neurons, which results in a reduction in SNR neurons. As a result, in contrast to dopaminergic neurons, non-dopaminergic neurons in the SNR regulate posture and rotations (DI CHIARA, G. *et, al.,* 1977).

Unilateral pedunculopontine tegmental nucleus (PPTg) damage is related to rotational movement. The unilateral injection of GABA agonists into PPTg induces rotation and contralateral postural asymmetry. On the other hand, the opposite outcome occurs when GABAergic antagonists are injected. When kainic acid stimulates PPTg, homolateral rotations are produced. These can be prevented by bilateral atropine injections, α-methyl tyrosine (a TH blocker that lowers neuronal dopamine and norepinephrine), and haloperidol (a DA antagonist). These findings imply dopaminergic-cholinergic interactions. Systemic amphetamine causes slow rotations in unilateral kainic acid lesions in PPTg, but systemic amphetamine causes a small homolateral inclination in unilateral quinolinate lesions in PPTg. However, bilateral quinolinate lesions do not affect locomotor activity. However, when amphetamine is used in conjunction with ibotenate lesions, a slight contralateral inclination is produced. These effects may be due to a loss of a large number of cholinergic and a smaller number of non-cholinergic PPTg neurons after injury with ibotenate (Olzmann, J. A *et al.,* 2004).

Basal nuclei and Parkinson's disease
The idea that BN is involved in the automatic execution of taught movements originated from the finding that Parkinsonian patients had trouble starting motions. Hyperkinetic and hypokinetic motor disorders are the two groups of motor diseases caused by BN abnormalities. Bradykinesia, akinesia, and/or rigidity are examples of hypokinetic motor disorders. Since Parkinson's disease (PD) is characterised by bradykinesia, increased muscle tone, and slow spontaneous movements, it is considered the prototype of hypokinetic disorders (Albin R.L, *et al.,* 1989). Parkinson's disease is a variable combination of certain signs attributable to BN dysfunction, for which there is no apparent etiology.

The primary pathophysiological observations in Parkinson's disease (PD) include the degeneration of neuronal bodies (above 80%) and the anterograde loss of ascending nigrostriatal axons, along with their terminal branches that reach the putamen and caudate. This results in a decrease in dopaminergic neurotransmission and DA. Thus, a lack of DA in BN is the cause of the symptoms of Parkinson's disease. While further metabolic changes exist, it is unclear how they relate to the symptoms and indicators of Parkinson's disease (PD) (Jankovic *et al.,* 1991; Giménez, S *et al.,* 1991; Ortiz, G.G *et al.,* 2017; Melamed E, 1991).

There are four potential causes of neuronal loss:
1) Overproduction of free radicals
2) Toxins found in the environment
3) Early neuronal aging
4) Genetic factor

α-synuclein misfolding and aggregation
The majority of native α-synuclein in the brain is unfolded and lacks a definite tertiary structure (Burré, J. *et al.,* 2013). However, it can exist as stable tetramers that are resistant to aggregation in aqueous solutions (Bartels, T *et al.,* 2011). When negatively charged lipids, such as the phospholipids that constitute cell membranes, come into contact with α-synuclein, its N-terminal folds into α-helical structures (Eliezer D *et al.,* 2001).

α-synuclein takes on an amyloid-like, β-sheet-rich structure that is prone to aggregation in Parkinson's disease. Indeed, LBs include 5–10 nm long filaments of misfolded α-synuclein. Numerous processes, including serine 129 phosphorylation, ubiquitination, and C-terminal truncation, have been proposed to explain the conformational alterations that cause aberrant α-synuclein aggregation (Fujiwara H *et al.,* 2002; Barrett P.J *et al.,* 2015).

As a result, several α-synuclein species, such as unfolded monomers, soluble oligomers, protofibrils, and high molecular weight insoluble fibrils, are discovered in the PD brain (Baba, M. *et al.,* 1998). Current research on rats has revealed that the early oligomeric form of α-synuclein is more neurotoxic than the mature insoluble fibrils (Winner, B. *et al.,* 2011; Karpinar, D.P *et al.,* 2009). Cell-based tests confirmed these oligomers' higher toxicity compared to fibrillary α-synuclein (Winner, B. *et al.,* 2011). The oligomeric forms of α-synuclein can "seed" and hasten aberrant protein aggregation (Danzer, K.M *et al.,* 2011).

NORMAL FUNCTION AND PATHOLOGY OF MITOCHONDRIA

The intracellular powerhouse known as mitochondria is responsible for several critical biological processes, such as the generation of ROS, the control of cell death, the regulation of energy production via the mitochondrial respiratory chain (RC), and calcium metabolism (Spinazzi, M. *et al.,* 2012). Although mitochondria are a key source of free radicals in the cell that cause OS, they are also essential for the OS response (Thyagarajan, D *et al.,* 2000).

In PD pathophysiology, mitochondrial malfunction, and dopaminergic cell death are implicated. The etiology of Parkinson's disease (PD) has been linked to several variables, including aging, genetics, and environmental toxins, alone or in combination. In at least some kinds of Parkinson's disease, aberrant morphology, aberrant metabolic activity, and poor fission-fusion balance have all been reported in the mitochondria. Elevated OS may result in compromised UPS performance, thereby impacting cell viability even more. All of these might have an impact on the mitochondrial operation of protein degradation systems, such as UPS and ALP, and ultimately lead to the degeneration of dopamine neurons (Moon, H.E *et al.,* 2015).

Mitochondrial dysfunction and oxidative stress (OS) in Parkinson's disease pathogenesis

Reduced mitochondrial activity raises OS and disrupts several cellular processes, resulting in intracellular component damage and eventual cell death. OS is one of the pathogenic processes of Parkinson's disease (PD) nigral dopamine cell loss. Numerous elements of mitochondrial life cycle, bioenergetic capability, quality control, dynamic changes in shape and connectivity (fusion, fission), subcellular distribution (transport), and regulation of cell death pathways are influenced by both genetic and environmental factors (Mayeux, R *et al.,* 1992).

THE PATHOPHYSIOLOGY OF MITOCHONDRIAL DYSFUNCTION
Mitochondrial ubiquitin-proteasome system (UPS) dysfunction

Under basal metabolic settings, the UPS is in charge of the highly selective destruction of damaged or misfolded proteins in the cytosol, nucleus, and endoplasmic reticulum, as well as short-lived intracellular and plasma membrane proteins. Ubiquitin targets vulnerable proteins in the system; only unfolded ubiquitinated proteins may flow through the proteasome barrel's small opening. The pathophysiology of Parkinson's disease (PD) has been closely linked to dysfunction of the UPS and the buildup of misfolded proteins that ensue. This, together with oxidative stress, will ultimately cause the death of dopaminergic neurons. Elevated OS may result in compromised UPS performance, which might impact the survival of cells. α-synuclein, Parkin, and UCHL1 are important in

maintaining the UPS, whereas PINK1, Parkin, and DJ-1 would govern the correct operation of mitochondria (Heo, J. M *et al.,* 2011).

Parkin mutations caused ubiquitin-ligase enzymatic activity in the substantia nigra to diminish in autosomal recessive juvenile parkinsonism (Ebrahimi-Fakhari, D *et al.,* 2012). This finding lends credence to the theory that the neurodegeneration accompanying PD is caused by UPS failure. Consequently, causes cellular damage in the end. The dynamics and activity of mitochondria may also be influenced by monomeric α-synuclein. There was a definite decrease in α-synuclein aggregation due to complex-I inhibition, along with an increase in OS and ATP synthesis deficit (Lees *et al.,* 2009). These factors might potentially disrupt the regular operation of the UPS. Due to the strong link between mitochondria and UPS that results from this fact, disease-related mutations in these genes will cause the degeneration of DA neurons (Ni, H.M *et al.,* 2015).

Dysfunction of autophagy in Parkinson's disease

The autophagy lysosomal pathway (ALP) can be divided into macroautophagy (generally referred to as autophagy), microautophagy, and chaperone-mediated autophagy (CMA). A crucial part of the cell's protein quality control mechanism, autophagy-mediated protein degradation is activated when an excess of misfolded, broken, or superfluous proteins builds up. Stress or nutritional restriction do not trigger microautophagy, although they can trigger autophagy during brief intervals of time and CMA after extended durations of nutrient shortage. Unlike the UPS, the ALP is crucial for preserving cellular homeostasis because it breaks down large cytoplasmic materials including broken organelles and clumped-up, misfolded proteins.

This degradation process seems to be essential for the removal of aggregated proteins, which are a pathogenic feature of several neurodegenerative diseases, including Parkinson's disease. Apart from the UPS, autophagy is also responsible for clearing α-synuclein, which lends credence to the theory that PD neurodegeneration is primarily caused by decreased autophagic degradation of α-synuclein (Xilouri, M *et al.,* 2013). Furthermore, changes in ALP have been mechanistically connected to other PD-related genes, including LRRK2, Parkin, and PINK1. Moreover, PD-related mutations or deficiencies in ATP13A2 cause a general lysosomal impairment that includes decreased processing of lysosomal enzymes, decreased degradation of lysosomal substrates, decreased clearance of autophagosomes, lysosomal membrane instability, impaired lysosomal acidification, and diminished autophagosome clearance. These factors all work together to cause α-synuclein accumulation and cell death.

Autophagy has been proposed as an alternate mechanism of cell death in neurotoxin models (Peng, J

et al., 2004), in the familial PD gene mutant model (Stefanis, L *et al.,* 2001), and in human PD brains (Anglade, P *et al.,* 1997). Apoptosis contributes to DA neuronal loss in the SNc of PD patients as well as in neurotoxin models. Reduced autophagy-regulating gene expression can lead to neurodegenerative illnesses, where poor quality control causes inflammation and neuronal cell population mortality. Autophagy is a characteristic of the suppression of the mammalian target of rapamycin (mTOR) kinase. Accordingly, PD development may be influenced by a combination of mitochondrial malfunction and inadequate autophagy (Choi, K.C *et al.,* 2010).

One essential quality control mechanism needed to get rid of damaged or extra mitochondria is called mitophagy, or the selective autophagy process of mitochondria (Narendra, D *et al.,* 2008). One of the main pathogenic processes underpinning mitochondrial dysfunction in autosomal recessive types of Parkinson's disease (PD), including those brought on by PINK1 and Parkin mutations, has been proposed to be defective mitophagy (Schapira, A.H.V, 2012). By functioning as a sensor and effector pair, the PINK1-Parkin signaling model has emerged as a new paradigm for preparing injured mitochondria for further degradation (Schapira A.H.V, 2012; Narendra, D. P. *et al.,* 2010).

Parkin targets damaged mitochondria and triggers mitophagy to degrade them. After one hour of treatment, HeLa cells treated with CCCP (carbonyl cyanide 3-chlorophenylhydrazone), an uncoupling agent that dissipates the mitochondrial membrane potential, showed strong recruitment of overexpressed parkin to uncoupled mitochondria. Remarkably, after extended exposure to CCCP, parkin-expressing cells mitochondria were eliminated in less than 24 hours. The function of PINK1 in parkin-mediated mitochondrial degradation was examined in the next stage. It has been discovered by many groups that parkin recruitment to defective mitochondria depends on PINK1 expression. After CCCP treatment, there was a reduction in parkin recruitment to mitochondria due to RNA interference-induced downregulation of PINK1(Pilsl, A *et al.,* 2012).

Furthermore, it was demonstrated that parkin's recruitment to mitochondria could be achieved just by PINK1 overexpression or by directing PINK1 to mitochondria using a heterologous mitochondrial membrane anchor generated from Tom20 or OPA3(Narendra, D.P *et al.,* 2010).

It is also believed that the stabilization of PINK1 at mitochondria causes parkin to translocate to uncoupled mitochondria, therefore figuring out which protease(s) is mediating PINK1 cleavage has been of significant interest. The fly homolog of the presenilin-associated rhomboid-like protease (PARL), Rhomboid-7, and PINK1, parkin have been linked genetically in

Drosophila studies, indicating that PARL facilitates PINK1 cleavage (Pilsl, A *et al.,* 2012).

Reintroducing wild-type PARL may restore the aberrant PINK1 cleavage pattern seen by fibroblasts generated from PARL-deficient animals, but a catalytically inactive PARL mutant cannot. Nevertheless, fibroblasts from PARL KO animals contain processed PINK1 isoforms, suggesting that PARL is not the exclusive PINK1-cleaving enzyme. Since PINK1 appears to be attached to the outer mitochondrial membrane and PARL is a transmembrane protein in the inner membrane of the mitochondria that catalyzes intramembrane proteolysis, the precise molecular process underlying PARL-induced PINK1 cleavage is yet unknown (Shi, G *et al.,* 2011).

Oxidative stress: There is strong evidence that oxidative stress is elevated in Parkinson's disease (PD) brain tissue as a result of mitochondrial malfunction (Dias, V. *et al.,* 2013), yet it is unclear if this stress is generated early or late in the neuron's death. Increased cellular oxidative stress is linked to mutations in DJ-1, a putative antioxidant that causes early-onset autosomal recessive Parkinson's disease (PD) (Bonifati, V *et al.,* 2003; Di Nottia *et al.,* 2017; Guzman, J.N *et al.,* 2010). Increased protein oxidation is seen in stressed nigral dopamine neurons upon DJ-1 knockout. For several reasons, it has been proposed that nigral dopamine neurons are more susceptible to oxidative and metabolic stress.

They have a tremendous deal of energy required to support their long (up to 4.5 meters) and unmyelinated axons, which have a huge number of synapses (estimated at 1-2.4 million per nigral dopamine neuron) (Bolam, J.P *et al.,* 2012; Pissadaki E.K *et al.,* 2013). Second, they demonstrate autonomous pacemaking activity involving cytosolic calcium oscillations and calcium extrusion at the expense of energy (Surmeier, D.J *et al.,* 2011); this is in contrast to the dopamine neurons in the nearby ventral tegmental area, which are relatively resilient in PD (Surmeier, D.J. *et al.,* 2017). Third, harmful oxidative stress may result from high cytosolic dopamine and its metabolites (Mosharov, E.V. *et al.,* 2009; Lotharus, J. *et al.,* 2002). Finally, it should be noted that a number of potential pathogenic pathways in Parkinson's disease (PD) are closely related to one another. Lysosome depletion can result from mitochondrial malfunction and increased oxidative stress (Dehay, B *et al.,* 2010).

CONCLUSION
The review emphasizes the complexity of the disorder, with interrelated events, demonstrating that the mitochondrial theory is the most likely explanation for the pathophysiology of Parkinson's disease (PD). With inconsistent data about other variables including nutrition, body weight, and occupational exposures, aging is the main risk factor. Finding neuroprotective medications to increase dopamine and prevent

degeneration is essential. Dopamine deficiency causes the motor symptoms of Parkinson's disease (PD), which is accompanied by brain abnormalities such as gliosis and neuronal death. The precise processes behind neurodegeneration include mitochondrial malfunction, oxidative stress, protein processing, and genetic-environmental interactions.

REFERENCES

- De Lau, L. M., & Breteler, M. M. (2006). Epidemiology of Parkinson's disease. *The Lancet Neurology*, *5*(6), 525-535.
- Oguh, O., & Videnovic, A. (2012). Inpatient management of Parkinson disease: current challenges and future directions. *The Neurohospitalist*, *2*(1), 28-35.
- Obeso, J. A., Stamelou, M., Goetz, C. G., Poewe, W., Lang, A. E., Weintraub, D., ... & Stoessl, A. J. (2017). Past, present, and future of Parkinson's disease: A special essay on the 200th Anniversary of the Shaking Palsy. *Movement disorders*, *32*(9), 1264-1310.
- Marsh, L. (2000). Neuropsychiatric aspects of Parkinson's disease. *Psychosomatics*, *41*(1), 15-23.
- Cotzias, G. C., Van Woert, M. H., & Schiffer, L. M. (1967). Aromatic amino acids and modification of parkinsonism. *New England Journal of Medicine*, *276*(7), 374-379.
- Olanow, C. W., Watts, R. L., & Koller, W. C. (2001). An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. *Neurology*, *56*(suppl_5), S1-S88.
- Lang, A. E., & Lozano, A. M. (1998). Parkinson's disease. New England Journal of Medicine, 339(15), 1044-1053.
- Lee, A., & Gilbert, R. M. (2016). Epidemiology of Parkinson disease. *Neurologic clinics*, *34*(4), 955-965.
- Litvan, I., Bhatia, K. P., Burn, D. J., Goetz, C. G., Lang, A. E., McKeith, I., ... & Wenning, G. K. (2003). SIC Task Force appraisal of clinical diagnostic criteria for parkinsonian disorders. *Movement disorders*, *18*(5), 467-486.
- De Rijk, M. D., Tzourio, C., Breteler, M. M., Dartigues, J. F., Amaducci, L., López-Pousa, S., ... & Rocca, W. D. (1997). Prevalence of parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON Collaborative Study. European Community Concerted Action on the Epidemiology of Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *62*(1), 10-15.
- Van Den Eeden, S. K., Tanner, C. M., Bernstein, A. L., Fross, R. D., Leimpeter, A., Bloch, D. A., & Nelson, L. M. (2003). Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. *American journal of epidemiology*, *157*(11), 1015-1022.
- Schrag, A. and Schott, J.M., 2006. Epidemiological, clinical, and genetic characteristics of early-onset parkinsonism. *The Lancet Neurology*, *5*(4), pp.355-363.
- Tolosa, E., Garrido, A., Scholz, S. W., & Poewe, W. (2021). Challenges in the diagnosis of Parkinson's disease. *The Lancet Neurology*, *20*(5), 385-397.
- Postuma, R. B., Berg, D., Stern, M., Poewe, W., Olanow, C. W., Oertel, W., ... & Deuschl, G. (2015). MDS clinical diagnostic criteria for Parkinson's disease. *Movement disorders*, *30*(12), 1591-1601.
- Gan-Or, Z., Liong, C., & Alcalay, R. N. (2018). GBA-associated Parkinson's disease and other synucleinopathies. *Current neurology and neuroscience reports*, *18*, 1-10.
- Mazzulli, J. R., Xu, Y. H., Sun, Y., Knight, A. L., McLean, P. J., Caldwell, G. A., ... & Krainc, D. (2011). Gaucher disease glucocerebrosidase and α-synuclein form a bidirectional pathogenic loop in synucleinopathies. *Cell*, *146*(1), 37-52.
- Taylor, K. S. M., Cook, J. A., & Counsell, C. E. (2007). Heterogeneity in male to female risk for Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *78*(8), 905-906.
- White, M. (2007). Alpha-Synuclein Misfolding and Aggregation in Parkinson's Disease. *Eukaryon*, *3*(1), 27.
- Spillantini, M. G., Crowther, R. A., Jakes, R., Hasegawa, M., & Goedert, M. (1998). α-Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with Lewy bodies. *Proceedings of the National Academy of Sciences*, *95*(11), 6469-6473.
- Newell, M. E., Adhikari, S., & Halden, R. U. (2022). Systematic and state-of the science review of the role of environmental factors in Amyotrophic Lateral Sclerosis (ALS) or Lou Gehrig's Disease. *Science of The Total Environment*, *817*, 152504.
- Alexander, G. E., & Crutcher, M. D. (1990). Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends in neurosciences*, *13*(7), 266-271.
- Alheid, G. F., Heimer, L., Switzer, R. C., & Paxinos, G. (1990). The human nervous system.
- Cazorla, M., de Carvalho, F. D., Chohan, M. O., Shegda, M., Chuhma, N., Rayport, S., ... & Kellendonk, C. (2014). Dopamine D2 receptors regulate the anatomical and functional balance of basal ganglia circuitry. *Neuron*, *81*(1), 153-164.
- Mograbi, K. D. M., de Castro, A. C. F., de Oliveira, J. A. R., Sales, P. J. B., Covolan, L., Del Bel, E. A., & de Souza, A. S. (2017). Effects of GABA a receptor antagonists on motor behavior in pharmacological Parkinson's disease model in mice. *Physiological Reports*, *5*(6), e13081.
- Sgambato-Faure, V., & Tremblay, L. (2018). Dopamine and serotonin modulation of motor and non-motor functions of the non-human primate striato-pallidal circuits in normal and pathological states. *Journal of Neural Transmission*, *125*(3), 485-500.
- Sitte, H. H., Pifl, C., Rajput, A. H., Hörtnagl, H., Tong, J., Lloyd, G. K., ... & Hornykiewicz, O. (2017). Dopamine and noradrenaline, but not serotonin, in the human claustrum are greatly reduced in patients with Parkinson's disease: possible functional implications. *European Journal of Neuroscience*, *45*(1), 192-197.
- Di Chiara, G., Olianas, M., Del Fiacco, M., Spano, P. F., & Tagliamonte, A. (1977). Intranigral kainic acid is

evidence that nigral non-dopaminergic neurones control posture. *Nature*, 268(5622), 743-745.

- Olzmann, J. A., Brown, K., Wilkinson, K. D., Rees, H. D., Huai, Q., Ke, H., ... & Chin, L. S. (2004). Familial Parkinson's disease-associated L166P mutation disrupts DJ-1 protein folding and function. *Journal of Biological Chemistry*, 279(9), 8506-8515.

- Albin, R. L., Young, A. B., & Penney, J. B. (1989). The functional anatomy of basal ganglia disorders. *Trends in neurosciences*, 12(10), 366-375.

- Jankovic, J. (1991). Horizontes del tratamiento de la enfermedad de Parkinson. *En: Optimización del tratamiento del Parkinson. Madrid: Egraf*, 61-75.

- Giménez, S. (1991). Trasplantes cerebrales en la enfermadad de Parkinson. *En: Optimización del tratamiento del Parkinson. Madrid: Egraf*, 23-40.

- Ortiz, G. G., González-Usigli, H., Pacheco-Moisés, F. P., Mireles-Ramírez, M. A., Sánchez-López, A. L., Torres-Sánchez, E. D., ... & González, V. S. (2017). Physiology and pathology of neuroimmunology: Role of inflammation in parkinson's disease. In *Physiology and Pathology of Immunology*. IntechOpen.

- Melamed, E. (1991). Problemas asociados a la terapia crónica con levodopa. *En: Optimización de tratamiento del Parkinson. Madrid: Egraf*, 77-92.

- Burré, J., Vivona, S., Diao, J., Sharma, M., Brunger, A. T., & Südhof, T. C. (2013). Properties of native brain α-synuclein. *Nature*, 498(7453), E4-E6.

- Bartels, T., Choi, J. G., & Selkoe, D. J. (2011). α-Synuclein occurs physiologically as a helically folded tetramer that resists aggregation. *Nature*, 477(7362), 107-110.

- Eliezer, D., Kutluay, E., Bussell Jr, R., & Browne, G. (2001). Conformational properties of α-synuclein in its free and lipid-associated states. *Journal of molecular biology*, 307(4), 1061-1073.

- Fujiwara, H., Hasegawa, M., Dohmae, N., Kawashima, A., Masliah, E., Goldberg, M. S., ... & Iwatsubo, T. (2002). α-Synuclein is phosphorylated in synucleinopathy lesions. *Nature cell biology*, 4(2), 160-164.

- Barrett, P. J., & Greenamyre, J. T. (2015). Post-translational modification of α-synuclein in Parkinson′s disease. *Brain research*, 1628, 247-253.

- Baba, M., Nakajo, S., Tu, P. H., Tomita, T., Nakaya, K., Lee, V. M., ... & Iwatsubo, T. (1998). Aggregation of alpha-synuclein in Lewy bodies of sporadic Parkinson's disease and dementia with Lewy bodies. *The American journal of pathology*, 152(4), 879.

- Winner, B., Jappelli, R., Maji, S. K., Desplats, P. A., Boyer, L., Aigner, S., ... & Riek, R. (2011). In vivo demonstration that α-synuclein oligomers are toxic. *Proceedings of the National Academy of Sciences*, 108(10), 4194-4199.

- Karpinar, D. P., Balija, M. B. G., Kügler, S., Opazo, F., Rezaei-Ghaleh, N., Wender, N., ... & Zweckstetter, M. (2009). Pre-fibrillar α-synuclein variants with impaired β-structure increase neurotoxicity in Parkinson's disease models. *The EMBO journal*, 28(20), 3256-3268.

- Danzer, K. M., Ruf, W. P., Putcha, P., Joyner, D., Hashimoto, T., Glabe, C., ... & McLean, P. J. (2011). Heat-shock protein 70 modulates toxic extracellular α-synuclein oligomers and rescues trans-synaptic toxicity. *The FASEB journal*, 25(1), 326.

- Spinazzi, M., Casarin, A., Pertegato, V., Salviati, L., & Angelini, C. (2012). Assessment of mitochondrial respiratory chain enzymatic activities on tissues and cultured cells. *Nature protocols*, 7(6), 1235-1246.

- Thyagarajan, D., Bressman, S., Bruno, C., Przedborski, S., Shanske, S., Lynch, T., ... & DiMauro, S. (2000). A novel mitochondrial 12SrRNA point mutation in parkinsonism, deafness, and neuropathy. *Annals of neurology*, 48(5), 730-736.

- Moon, H. E., & Paek, S. H. (2015). Mitochondrial dysfunction in Parkinson's disease. *Experimental neurobiology*, 24(2), 103.

- Mayeux, R., Denaro, J., Hemenegildo, N., Marder, K., Tang, M. X., Cote, L. J., & Stern, Y. (1992). A population-based investigation of Parkinson's disease with and without dementia: relationship to age and gender. *Archives of neurology*, 49(5), 492-497.

- Heo, J. M., & Rutter, J. (2011). Ubiquitin-dependent mitochondrial protein degradation. *The international journal of biochemistry & cell biology*, 43(10), 1422-1426.

- Ebrahimi-Fakhari, D., Wahlster, L., & McLean, P. J. (2012). Protein degradation pathways in Parkinson's disease: curse or blessing. *Acta neuropathologica*, 124, 153-172.

- Lees, A. J., Hardy, J., & Revesz, T. (2009). Parkinson's disease. *The Lancet*, 373(9680), 2055-2066.

- Ni, H. M., Williams, J. A., & Ding, W. X. (2015). Mitochondrial dynamics and mitochondrial quality control. *Redox biology*, 4, 6-13.

- Xilouri, M., Brekk, O. R., & Stefanis, L. (2013). Alpha-synuclein and protein degradation systems: a reciprocal relationship. *Molecular neurobiology*, 47, 537-551.

- Peng, J., Mao, X. O., Stevenson, F. F., Hsu, M., & Andersen, J. K. (2004). The herbicide paraquat induces dopaminergic nigral apoptosis through sustained activation of the JNK pathway. *Journal of Biological Chemistry*, 279(31), 32626-32632.

- Stefanis, L., Larsen, K. E., Rideout, H. J., Sulzer, D., & Greene, L. A. (2001). Expression of A53T mutant but not wild-type α-synuclein in PC12 cells induces alterations of the ubiquitin-dependent degradation system, loss of dopamine release, and autophagic cell death. *Journal of Neuroscience*, 21(24), 9549-9560.

- Anglade, P., Vyas, S., Javoy-Agid, F., Herrero Ezquerro, M. T., Michel, P. P., Marquez, J., ... & Agid, Y. (1997). Apoptosis and autophagy in nigral neurons of patients with Parkinson's disease. *Histology and histopathology*.

- Choi, K. C., Kim, S. H., Ha, J. Y., Kim, S. T., & Son, J. H. (2010). A novel mTOR activating protein protects dopamine neurons against oxidative stress by repressing autophagy related cell death. *Journal of neurochemistry*, 112(2), 366-376.

- Narendra, D., Tanaka, A., Suen, D. F., & Youle, R. J. (2008). Parkin is recruited selectively to impaired

mitochondria and promotes their autophagy. *The Journal of cell biology*, *183*(5), 795-803.

- Schapira, A. H. V. (2012). Targeting mitochondria for neuroprotection in Parkinson's disease. *Antioxidants & redox signaling*, *16*(9), 965-973.
- Narendra, D. P., Jin, S. M., Tanaka, A., Suen, D. F., Gautier, C. A., Shen, J., ... & Youle, R. J. (2010). PINK1 is selectively stabilized on impaired mitochondria to activate Parkin. *PLoS biology*, *8*(1), e1000298.
- Pilsl, A., & Winklhofer, K. F. (2012). Parkin, PINK1 and mitochondrial integrity: emerging concepts of mitochondrial dysfunction in Parkinson's disease. *Acta neuropathologica*, *123*, 173-188.
- Shi, G., Lee, J. R., Grimes, D. A., Racacho, L., Ye, D., Yang, H., Ross, O. A., Farrer, M., McQuibban, G. A., & Bulman, D. E. (2011). Functional alteration of PARL contributes to mitochondrial dysregulation in Parkinson's disease. Human molecular genetics, 20(10), 1966–1974. https://doi.org/10.1093/hmg/ddr077
- Dias, V., Junn, E., & Mouradian, M. M. (2013). The role of oxidative stress in Parkinson's disease. *Journal of Parkinson's disease*, *3*(4), 461-491.
- Bonifati, V., Rizzu, P., Van Baren, M. J., Schaap, O., Breedveld, G. J., Krieger, E., Dekker, M. C., Squitieri, F., Ibanez, P., Joosse, M., & van Dongen, J. W. (2003). Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. *Science, 299*(5604):256-259. doi: 10.1126/science.1077209. PMID: 12446870.
- Di Nottia, M., Masciullo, M., Verrigni, D., Petrillo, S., Modoni, A., Rizzo, V., ... & Silvestri, G. (2017). DJ-1 modulates mitochondrial response to oxidative stress: clues from a novel diagnosis of PARK7. *Clinical genetics*, *92*(1), 18-25.Guzman, J. N., Sanchez-Padilla, J., Wokosin, D., Kondapalli, J., Ilijic, E., Schumacker, P. T., & Surmeier, D. J. (2010). Oxidant stress evoked by pacemaking in dopaminergic neurons is attenuated by DJ-1. *Nature*, *468*(7324), 696-700.
- Bolam, J. P., & Pissadaki, E. K. (2012). Living on the edge with too many mouths to feed: why dopamine neurons die. *Movement disorders: official journal of the Movement Disorder Society, 27*(12), 1478–1483. https://doi.org/10.1002/mds.25135
- Guzman, J. N., Sanchez-Padilla, J., Wokosin, D., Kondapalli, J., Ilijic, E., Schumacker, P. T., & Surmeier, D. J. (2010). Oxidant stress evoked by pacemaking in dopaminergic neurons is attenuated by DJ-1. *Nature*, *468*(7324), 696-700.
- Pissadaki, E. K., & Bolam, J. P. (2013). The energy cost of action potential propagation in dopamine neurons: clues to susceptibility in Parkinson's disease. *Frontiers in computational neuroscience*, *7*, 13.
- Surmeier, D. J., Guzman, J. N., Sanchez-Padilla, J., & Schumacker, P. T. (2011). The role of calcium and mitochondrial oxidant stress in the loss of substantia nigra pars compacta dopaminergic neurons in Parkinson's disease. *Neuroscience*, 198, 221–231. https://doi.org/10.1016/j.neuroscience.2011.08.045
- Surmeier, D. J., Schumacker, P. T., Guzman, J. D., Ilijic, E., Yang, B., & Zampese, E. (2017). Calcium and Parkinson's disease. *Biochemical and biophysical research communications, 483*(4), 1013–1019. https://doi.org/10.1016/j.bbrc.2016.08.168
- Mosharov, E. V., Larsen, K. E., Kanter, E., Phillips, K. A., Wilson, K., Schmitz, Y., Krantz, D. E., Kobayashi, K., Edwards, R. H., & Sulzer, D. (2009). Interplay between cytosolic dopamine, calcium, and alpha-synuclein causes selective death of substantia nigra neurons. *Neuron, 62*(2), 218–229. https://doi.org/10.1016/j.neuron.2009.01.033
- Lotharius, J., & Brundin, P. (2002). Pathogenesis of Parkinson's disease: dopamine, vesicles and alpha-synuclein. Nature reviews. Neuroscience, 3(12), 932–942. https://doi.org/10.1038/nrn983
- Dehay, B., Martinez-Vicente, M., Caldwell, G. A., Caldwell, K. A., Yue, Z., Cookson, M. R., Klein, C., Vila, M., & Bezard, E. (2013). Lysosomal impairment in Parkinson's disease. *Movement disorders: official journal of the Movement Disorder Society, 28*(6), 725–732. https://doi.org/10.1002/mds.25462.