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Understanding Parkinson's Disease from the Inside Out

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Abstract

Parkinson's disease (PD) is a relatively common neurodegenerative disorder caused by dopamine deficiency and characterized by tremor and motile difficulties. Activities of the neurotransmitter dopamine contribute to the high energy demands of neurons in the substantia nigra (which are lost in the disease), which the mitochondria of these cells work to meet. Mutations in the genes *SNCA, PINK1,* and *LRRK2* can disrupt mitochondrial function in susceptible neurons through over- or underactivity. Like the gene mutants, pesticides and MPTP also impair mitochondrial activity, unlike smoking, which protects vulnerable neurons. L-DOPA, often in combination with other drugs, is the most frequent medical prescription for PD, but surgical procedures may be used for younger patients. Drugs protecting mitochondrial components of neural cells may especially help with PD. In this review, we aim to study the biological mechanisms through which these genetic and environmental risks lead to PD and how various treatments may combat pathogenesis.

Keywords: Neurodegeneration, SNCA, LRRK2, PINK1, External Factors, L-DOPA, Brain Stimulation

1. Introduction

The common neurodegenerative disorder Parkinson's disease (PD) affects over 7 million people worldwide (Cresto, et al., 2019). Patients with Parkinson's disease experience a loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) region of the brain (Ge, et al., 2020). This degeneration of substantia nigra cells results in a deficiency in the neurotransmitter dopamine, which is synthesized in the substantia nigra and necessary for proper motion control. As a result, symptoms such as tremors; difficulty with walking, moving, coordination, and speech; rigidity; stooped posture; insomnia; and constipation indicate the pathological phenotype (*Parkinson Disease,* 2008). Also, brain cells of PD patients often contain protein aggregates known as Lewy bodies (LBs), usually made up of ∝-synuclein protein. While their role is controversial, these aggregates may interfere with crucial cell functions by impairing other proteins (Cresto, et al., 2019). Disease onset typically occurs in elderly patients (older than 60), but in around 5-10% of cases, characterized as early-onset PD, symptoms appear before 40 (Brouwer, et al., 2015). Numerous risk factors have been associated with both types, with genetic mutations often linked to early-onset, and environmental exposures more often linked to late-onset PD (Brouwer, et al., 2015).

Nevertheless, mitochondrial dysfunction in nigral cells appears to be involved in both of the neurodegenerative pathways. The objective of this literature review is to analyze the results of multiple studies regarding the role of three of the most prominent PD related genes that especially affect mitochondrial function- *SNCA*, *LRRK2*, and *PINK1* - and three environmental exposures in neurodegeneration. Furthermore, we aim to

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understand how these possible causes may enhance pharmaceutical measures for symptom improvement. This is the first of two papers in a series, the second of which describes our own statistical analysis of how the genotype of a Parkinson's patient can be used to predict their response to medications.

The rest of the paper is organized as follows: in Section 2, we provide an overview of the role of mitochondria in dopamine-producing cells as well as dopamine itself in Parkinson's disease. Section 3 discusses the three genes and how mutations in them can increase the risk of Parkinson's. In Section 4, environmental factors are studied with respect to Parkinson's risk. Section 5 reviews how various treatments may be more effective for different patients. Finally, Section 6 concludes the paper.

2. Dopamine and Mitochondria

PD patients lack dopamine, a neurotransmitter (a molecule released at the axon of a nerve cell that carries information to nearby cells) (Finley, 2014). In healthy patients, dopamine represses signals coming from the motor cortex of the brain and passing through the basal ganglia to prevent sudden jerks (*Parkinson Disease*, 2008). Dopamine released by substantia nigra cells also activates the brain's corpus striatum, a region of the basal ganglia, so insufficient dopamine levels mean that subsequent targets of the corpus striatum also suffer, and the entire motile pathway becomes impaired (*Parkinson's Disease,* 2001).

At the cellular level, dopamine processing generates free radicals which places increased strain on mitochondria, the double-membraned organelles responsible for producing usable energy in cells of dopaminergic neurons in the substantia nigra (Franco, et al., 2021). The large and spread-out axonal networks, the many synaptic connections, and the presence of unmyelinated axons in dopaminergic neurons all further increase the energy requirements of these cells (Ge, et al., 2020). Thus, dopaminergic mitochondria likely work to meet these energy needs until they are unable to, at which point neuronal cell death occurs (Franco, et al., 2021). Furthermore, damage in the mitochondria has been observed to lead to increased levels of mitochondrial DNA in the bloodstream, which draws immune cells to the site to initiate a potentially harmful inflammatory response (Kwon, 2021). Both of these processes contribute to the mitochondrial deterioration and subsequent neurodegeneration of substantia nigra cells that results in the dopamine deficiency seen in PD patients.

3. Genetic Factors

Growing evidence increasingly suggests that genetic factors play a role in Parkinson's disease through specific mutations which affect the function of dopamine-producing neurons. In this section, we will explore how abnormal gene products from three genes - *SNCA, LRRK2,* and *PINK1* - may interact with each other and contribute to pathogenesis. While other gene mutations have also been listed as Parkinson's risk factors, the first two of these three genes are commonly cited as two of the most prevalent risk factors, and the last, *PINK1*, though not as common a risk factor, plays a crucial role in the mitochondria of cells affected by PD.

3.1 The SNCA Gene and ∝-synuclein

Found on chromosome 4 in the human genome, the *SNCA* gene codes for ∝-synuclein, a protein that helps control the release of neurotransmitters, proper functioning at synapses, and the ability of dopaminergic neurons to alter their connections (Campêlo and Silva, 2017). It further plays a role in vesicle movement and membrane activity and comprises most of the Lewy bodies observed in brains of PD patients (Cresto, et al., 2019). Through these mechanisms, the importance of *SNCA* to PD pathology emerges. Products of *SNCA* mutations can change the processes required for normal vesicular transportation and protein processing in neuronal cells. ∝-synuclein also affects disease pathology by interacting with other PD-related genes, which will be discussed more thoroughly in the following sections (Franco, et al., 2021). Mutations in these genes may in turn contribute to ∝-synuclein neurotoxicity if these genes affect the handling of ∝-synuclein through vesicular transportation

mechanisms. This may increase the aggregation of the protein and dopaminergic neurodegeneration (Franco, et al., 2021).

Like many PD-related proteins, ∝-synuclein impacts mitochondrial fission and fusion dynamics (Cresto, et al., 2019). Fission - division of mitochondria - naturally leads to the production of smaller mitochondria and promotes the elimination of damaged portions by creating smaller loads for autophagy. In contrast, fusion produces longer mitochondria that allow for more efficient oxidative phosphorylation to meet greater energy requirements (Ge, et al., 2020). Aggregation of ∝-synuclein likely stimulates processes that remove proteins needed for mitochondrial fusion, abnormally shifting the balance towards fission (Cresto, et al., 2019). Consequently, oxidative phosphorylation and energy production may decrease.

Despite the proposed cellular impacts, few studies associate variants of *SNCA* to specific PD phenotypes, and some studies yield contradictory findings. Nevertheless, three polymorphisms in *SNCA* - REP1, rs2736990, and rs356219 and rs356165, located in the promoter, an intron, and 3' region, respectively - have often been linked to early-onset/familial PD (Campêlo and Silva, 2017). Similar polymorphisms are expected to affect sporadic PD but this context has been studied less extensively.

Finally, thus far, ∝-synuclein's aggregation into Lewy bodies has been considered from a negative perspective. This view gains support when considering that postmortem PD diagnosis consists of scanning for these protein aggregates (Espay and Stecher, 2020). However, while this Lewy body pathology occurs in almost all variations of Parkinson's, recent research suggests that its role may not be harmful. Rather, the protein aggregates may have a protective function consequent to the onset of previous, unknown cellular occurrences (Gearing & Srinivasa). Cellular particles that may have directly neurotoxic effects, though, are ∝-synuclein oligomers and protofibrils (Espay and Stecher, 2020). In line with this idea, a study showed that cells expressing a pathological mutation - G2019S in *LRRK2*, which will be discussed later - had a higher proportion of fibrillar oligomeric ∝-synuclein compared to those without the mutation (Nam, et al., 2021). Thus, it appears that PD-prevalent genotypes associate more frequently with these toxic forms. Given the presence of such aggregation and oligomerization on the more cognitive end of the neurological disease spectrum, near disorders such as Alzheimer's, it also makes sense that certain *SNCA* variants have been found to be associated with increased cognitive decline in PD patients (Espay and Stecher, 2020; Ramezani, et al., 2021). Despite these new revelations and the ubiquity of protein aggregation in many neurological diseases, more research still needs to be done to determine the precise function and possible defensive role of ∝-synuclein in PD.

3.2 *PINK1* in Neurogenesis and Mitochondrial Function (with *Parkin*)

The *PINK1* gene codes for PINK1, a serine/threonine kinase consisting of 581 amino acids (Meamar, et al., 2021). Early-onset Mendelian inherited PD (autosomal recessive) is thought to be related to biallelic *PINK1* mutations. Furthermore, PINK1 serves as an important protein in mitophagy (autophagic destruction of mitochondria), mitochondrial function, and oxidative stress (Brown, et al., 2021).

Studies by Brown et al. (2021) suggested that throughout life PINK1 contributes to neurogenesis (the generation of neurons from neural stem cells). In fact, a lack of PINK1 in zebrafish led to fewer dopaminergic neurons in larvae and adults, as well as malfunctioning mitochondria and affected morphology (Brown, et al., 2021). During the study, they observed that zebrafish without properly functioning PINK1 experienced similar rates of neurogenesis compared to the controls in the TPp (an ascending dopaminergic neuron population) and the PVO (locally-projecting dopaminergic neurons of the paraventricular organ) regions in early life, but growth stopped in later life (Brown, et al., 2021). The metabolic shift from the cytoplasmic process glycolysis to the mitochondrial process oxidative phosphorylation that is associated with neural stem cell differentiation may contribute to this issue. The PINK1 variant in neural stem cells is observed to decrease oxidative phosphorylation and force an

increased reliance on glycolysis. This decreases the mitochondria's ability to produce additional ATP in the case of sudden demand (Brown, et al., 2021). Given that differentiation presents high metabolic demands, where this ability and the extra energy of oxidative phosphorylation would be very important, the PINK1 mutation can clearly hinder dopaminergic neurogenesis. However, a lack of PINK1 did not appear to affect global neurogenesis, implying a preference for dopaminergic neurons and indicating its role in PD (Brown, et al., 2021).

Regarding mitochondrial function, PINK1 has an important function of removing and/or replacing all or parts of damaged mitochondria. Localized to the mitochondria, PINK1 is normally inactive. In the event of mitochondrial damage, activation occurs on the damaged mitochondria. Subsequently, in its activated state, PINK1 phosphorylates ubiquitin on the mitochondrial surface and engages Parkin protein from the cytosol (Sekine, 2020). The binding of Parkin to this phospho-ubiquitin activates Parkin so that it can tag multiple mitochondrial proteins for destruction. At the same time, PINK1 phosphorylates additional mitochondrial proteins, increasing the number of ubiquitin chains on the mitochondria, thus creating a positive feedback loop with Parkin (Sekine, 2020). In healthy mitochondria, the PARL protein assists in PINK1 destruction through cleavage at the inner mitochondrial membrane in order to block ubiquitin phosphorylation, Parkin recruitment, and mitochondrial destruction. If mitochondrial damage is present, PINK1 builds up in the outer mitochondrial membrane, but a mutant product of *PINK1* undergoes destruction by the mitochondrial protease OMA1, preventing this buildup of PINK1 (Sekine 2020). While this mechanism would suggest that cells lacking PINK1 or Parkin would accumulate damaged mitochondria, this has not consistently been observed, suggesting additional roles for these two proteins in mitochondrial quality control in the central nervous system (Ge, et al., 2020).

In fact, another aspect of this quality control occurs through the regulation of mitochondrial fission and fusion. Based on some studies, PINK1 and Parkin may normally stimulate fission and restrict fusion. This can preserve mitochondrial health by isolating damaged areas (Ge, et al., 2020). Thus, greater expression of fission proteins may improve harmful effects of too much fusion, which is associated with faulty PINK1 and Parkin proteins, and minimize some PD symptoms (Ge, et al., 2020). For less severe mitochondrial damage, PINK1 and Parkin may help form mitochondrial-derived vesicles. These vesicles assist in the removal of specific dysfunctional proteins, rather than entire mitochondria. Often, MDVs formed by PINK1 and Parkin have been shown to get rid of defective elements of the electron transport chain involved in oxidative phosphorylation (Ge, et al., 2020). In yet another way, PINK1 and Parkin help regulate mitochondrial health by promoting the production of mitochondrial proteins near the surface of these organelles. In neurons, whose long structures increase the expense of transport and likelihood of misfolding errors in transit from the nucleus to the mitochondria, this localized synthesis can be especially useful. A lack of PINK1 negatively affected targeting of nuclear-encoded mitochondrial RNAs to the mitochondria in multiple cell lines (Ge, et al., 2020).

Finally, in sporadic cases of the disease, ∝-synuclein aggregates may trap Parkin proteins and impede the PINK1/Parkin pathway that aids in mitochondrial quality control, further contributing to neurodegeneration (Ge, et al., 2020). In addition, animals lacking PINK1 experienced increased sensitivity to the loss of dopaminergic neurons by the external neurotoxin MPTP (Franco, et al., 2021). Evidently, PINK1 plays crucial roles in the survival of dopaminergic neurons, both by assisting in the differentiation of new ones and regulating the energy producing mechanisms in existing ones alongside Parkin. These processes provide many possible ways that PINK1 mutations may result in PD pathology and the loss of dopaminergic neurons.

3.3 *LRRK2*: Its Independent Role and Possible Effect on ∝-synuclein and PINK1

Mutations in *LRRK2*, which codes for leucine-rich repeat kinase 2 (LRRK2), account for 3-4% of all PD cases, and the missense mutation G2019S most often correlates with PD by stimulating harmful activity of the kinase (Gonzalez-Hunt, et al., 2020). Increased LRRK2 kinase activity results in a mitochondrial loss

of function and greater mitochondrial DNA (mtDNA) damage. In line with these observations, LRRK2 inhibitors have been shown to act as neuroprotection in PD-applicable cell and rodent models. After inhibition, mtDNA damage returned to control levels - and relatively quickly (Gonzalez-Hunt, et al., 2020). Because pathogenic mutations in *LRRK2* do not severely increase kinase activity, Gonzalez-Hunt et al. (2020) suggested that medium levels of LRRK2 kinase inhibition should be enough to fix the PD phenotype. Too much inhibition resembled a loss of all LRRK2 protein, which was associated with effects on the kidneys and lungs, but too little inhibition led to a lack of neuroprotection in clinical studies (Gonzalez-Hunt, et al., 2020). While these mutations typically associate with familial cases of PD, results of such studies could have important implications for sporadic PD because LRRK2-related PD patients show similar clinical and neuropathological characteristics to sporadic PD patients (Gonzalez-Hunt, et al., 2020). Rodent models of sporadic PD and postmortem observations of brains of sporadic PD patients support this idea, as these models showed abnormally high levels of mtDNA damage in substantia nigra dopaminergic neurons (Gonzalez-Hunt, et al., 2020). Also, studies indicated that animals completely missing *LRRK2* or excessively expressing human variants of the gene (in other words, animals producing either no LRRK2 protein or too much of it) struggled with intracellular vesicle movement and function as well as protein handling. In these studies, the G2019S mutation specifically seemed to affect neuronal homeostasis and morphology (Franco, et al., 2021).

LRRK2 may also play important roles with other gene products, especially ∝-synuclein. For example, the *LRRK2* protein product may phosphorylate ∝-synuclein, which could affect PD development, though more data is needed to verify this idea (Franco, et al., 2021). G2019S may increase accumulation of ∝-synuclein, contributing to Lewy body formation and quickening the aggregation of ∝-synuclein in vesicles or lysosomes (Nam, et al., 2021). However, phosphorylation of ∝-synuclein on Ser129 serves as an effective marker for its aggregation because phosphorylated-synuclein levels are low when not aggregated, and results from certain studies indicate that this phosphorylation is not directly done by LRRK2, a potential opposition to the G2019S aggregation hypothesis (Cresto, et al., 2019). Nevertheless, interactions with 14-3-3 proteins propose a possible mechanism for the pathological association of the two proteins. A region of LRRK2 binds to 14-3-3 proteins, which perform many cellular functions, including blocking pro-apoptotic factors to stimulate cell survival. This binding promotes consistent cytoplasmic distribution of LRRK2 and may block LRRK2 kinase activity. Less binding leads to LRRK2 gathering in cytoplasmic pools and increases harmful kinase activity (Cresto, et al., 2019). This event can occur if the 14-3-3 proteins get trapped in Lewy bodies, which involve ∝-synuclein. LRRK2 and ∝-synuclein also act together to affect mitochondrial function. Mutant forms of the proteins have been shown to reduce the production of ATP and the mitochondrial membrane potential while increasing oxidative stress, contributing to mitochondrial deterioration in dopaminergic neurons (Cresto, et al., 2019). Likely, LRRK2 and ∝-synuclein also increase the toxicity of inhibitors of mitochondrial complex I, which acts in the electron transport chain used in oxidative phosphorylation (Cresto, et al., 2019).

LRRK2 also works with the protein products of other PD-related genes, such as *PARK2*, *PARK7, PINK1,* and *VPS35* to aid in lysosomal and organelle activity. Most of the proteins encoded by these genes contribute to the handling of proteins and their destruction (Franco, et al., 2021). Malfunctioning mechanisms could lead to cell damage. While the role of LRRK2 in Parkinson's still requires further study, excessive kinase activity clearly contributes to the toxicity of mutant forms of the protein, and LRRK2 also appears to have a profound effect on other proteins involved in disease progression (Franco, et al., 2021).

Many other genes have been linked to PD, and this review covers three. Franco et al. provide descriptions of the roles of many more genes possibly involved in the disease (Franco, et al., 2021). However, the three featured in this review appear to have some of the most significant effects on mitochondrial malfunction in dopaminergic neurodegeneration.

4. External Factors

The dysfunctional protein products of mutated genes have not been extensively studied in the context of sporadic PD, which usually emerges later in life. However, significant associations have been drawn between various environmental exposures and the risk of developing PD later in life. Pesticides and MPTP (a chemical found in some illegal drugs which produces free radicals) increase the risk for PD (Campêlo and Silva, 2017; *Parkinson's Disease*, 2001). Conversely, many studies have shown an inverse relationship between cigarette smoking and PD pathogenesis (*Parkinson's Disease*, 2001).

Pesticides have been shown to increase susceptibility to PD by promoting damage to the substantia nigra (*Parkinson Disease,* 2008). One pesticide, rotenone, acts as a mitochondrial complex I inhibitor, which would impair oxidative phosphorylation (Ge, et al., 2020). Support for these claims comes from studies such as that conducted by Brouwer et al. (2015) in the Netherlands. The team used mortality data from the large Netherlands Cohort Study and gathered information on occupational exposures to find associations between the exposures and PD-related death (Brouwer, et al., 2015). Of the environmental factors studied, only pesticides and extremely low frequency magnetic fields (ELF-MF) appeared to have an important correlation with PD, and the findings regarding pesticide use, though non-significant, were consistent with other studies. The study did not find a significant association with the duration of exposure or cumulative exposure to pesticides and PD mortality, though. While none of these results achieved statistical significance, pathology resulting from pesticide use still has important implications for the onset of PD, given its reproducible results across studies and the proposed mechanisms for mitochondrial dysfunction (Brouwer, et al., 2015).

MPTP has a similarly harmful effect regarding PD risk. As mentioned previously, MPTP, a byproduct of illegal production of the opioid desmethylprodine, leads to the synthesis of free radicals, which can increase oxidative stress (Ge, et al., 2020; *Parkinson's Disease*, 2001). In the body, MPTP gets converted to MPP+, a mitochondrial complex I inhibitor like rotenone. This can cause acute-onset parkinsonism with selective SNpc neuronal degeneration, yet again emphasizing the importance of proper mitochondrial function in preventing the loss of dopaminergic substantia nigra neurons (Ge, et al., 2020). In addition, MPTP may interact with genetic risk factors to further increase the vulnerability of these dopaminergic neurons to degeneration. For example, animals lacking proper PINK1 protein showed increased sensitivity to MPTP-induced dopaminergic neuron deficiency (Franco, et al., 2021). Likewise, in studies with mice, MPTP more severely affected those with the *LRRK2* G2019S mutation and did not harm mice without ∝-synuclein (Cresto, et al., 2019). In all of these cases, MPTP, like many other factors affecting the onset of Parkinson's, appears to impair the mitochondria in dopaminergic neurons, either directly or through proteins.

Surprisingly, in the observations of Brouwer et al. (2015), the percent of current smokers with PD cases was fewer than that of non-smokers for both genders. In addition, smokers saw lower PD mortality than non-smokers (Brouwer, et al., 2015). This relationship has gained more support in meta-analyses than other environmental factors, such as alcohol consumption (Campêlo and Silva, 2017). Multiple mechanisms have been proposed for its neuroprotection. Cigarette smoking may decrease levels of monoamine oxidase B (MAO-B), an enzyme that assists in dopamine decomposition (Campêlo and Silva, 2017; *Parkinson's Disease*, 2001). A reduction in MAO-B allows dopamine levels to increase while hydrogen peroxide production and oxidative stress decrease. Cigarette smoking may also lead to increased cytochrome P-450 enzyme activity, which promotes the processing of antipsychotic drugs and the detoxification of harmful substances such as MPTP (Campêlo and Silva, 2017). Furthermore, changes in the genes coding for cytochrome P-450 have been shown to interact with chemicals in tobacco smoke, though the process behind these interactions remains unknown (Campêlo and Silva, 2017). Thus, smoking may indirectly restore mitochondrial function in dopaminergic neurons by blocking the dangers of other toxins.

5. Treatment Options

Regardless of the cause of onset, PD currently has no cure, so patients seek various forms of symptom management. Levodopa (L-DOPA) remains the most common pharmaceutical treatment, but surgical procedures such as pallidotomy, thalamotomy, and deep brain stimulation provide relief in certain cases. These treatments, including the pros, cons, and circumstances that accompany them, will be explained in the subsequent text.

5.1 L-DOPA and Drug Therapies

Currently the most effective drug treatment for PD, L-DOPA consists of a dopamine precursor to replace the neurotransmitter lost throughout the disease. Unlike dopamine itself, the chemical can cross the blood-brain barrier through an active transport system, where it then gets converted into dopamine by amino acid decarboxylase (AADC) (Sian, et al., 1999). This addition helps relieve some motor symptoms caused by dopamine insufficiency, such as tremor, bradykinesia, and jerkiness. Strong and consistent response to L-DOPA occurs within the first one to three years of administration (Lane, 2019). This period is also referred to as the ON-phase or honeymoon period, and patients typically experience significantly better quality of life. Nevertheless, progression of the disease leads to decreased responsiveness to L-DOPA (Lane, 2019).

The relief provided by L-DOPA may also come at a cost, as the drug often comes with significant side effects, especially with long-term use (Lane, 2019). These effects include gastrointestinal issues, hemorrhage, and depression/confusion. Later, motor variations and L-DOPA induced dyskinesias (LID) may arise and often require dose reduction. While rare in the first year of treatment, a study reported the frequency of LID as up to 90% by nine years post-treatment initiation (Lane, 2019). The dyskinesias can be choreic, consisting of unusual movement (often in the neck and limbs), or dystonic, consisting of long-lasting muscle contractions. It is typically seen as uncontrollable motion and occurs at the peak-dose of L-DOPA, when the plasma L-DOPA concentration is highest, or at the end or beginning of the L-DOPA dose, when L-DOPA levels are low (Lane, 2019). This unique side effect is thought to be linked to the severity of striatal dopaminergic denervation. Increased risk of LID has also been associated with MPTP exposure, longer Parkinson's duration and higher L-DOPA dose (both of which correlate with PD severity), earlier onset of PD, and certain genetic variations (Lane, 2019). Despite the controversies with L-DOPA, patients often prefer LID to worsening PD symptoms, maintaining L-DOPA relevance in PD therapy.

In an effort to minimize some of these effects, L-DOPA can be administered with other drugs. For example, carbidopa inhibits L-DOPA degradation outside the blood-brain barrier, so less external L-DOPA therapy produces the same effect (Rao, 2015). MAO-B inhibitors, such as selegiline, are also used and seem to protect substantia nigra cells from free radical damage (*Parkinson's Disease*, 2001). Furthermore, Manalo and Medina (2020) used the nematode *C. elegans* to suggest that caffeine may be taken with L-DOPA as a neuroprotectant. Dopaminergic neurons were better protected and abnormal motion was decreased when caffeine was provided in an environment with high dopamine concentration. This is an especially interesting result when considering that caffeine has been shown to protect from PD, as well (Manalo and Medina, 2020).

To delay L-DOPA use, doctors may prescribe dopamine agonists such as Ropinirole and Pramipexole in the early stages of PD. These drugs function by activating dopamine receptors on cell surfaces. The side effects of such therapies include fewer motor variations and shorter duration of effects compared to L-DOPA at the cost of decreased symptom and impulse control (Rao, 2015).

5.2 Surgery

For patients with earlier onset Parkinson's who no longer respond to medical treatments, surgery may be used. Thalamotomy, careful destruction of the thalamus, and pallidotomy, careful destruction of part of the Globus Pallidus interna (GPi), are two examples (*Parkinson Disease*, 2008). A more common and safer treatment, deep brain stimulation, consists of inserting an apparatus similar to a

pacemaker to electrically stimulate parts of the brain with dopamine deficiency (*Parkinson Disease*, 2008). This procedure causes less damage to brain tissue and can be reversed (Khabarova, et al., 2018). It can also decrease the frequency of dyskinesias and tremor, while reducing pharmaceutical therapy dosage (Rao, 2015). Using information from the previous sections, these surgical procedures would likely be more valuable in genetic PD cases, as these typically appear at a younger age and leave patients more time to develop pharmaceutical resistance. Nevertheless, surgical risks should be considered, and the procedure should only be used for appropriate surgical candidates when medical options have failed.

6. Discussion and Concluding Remarks

As we have seen in the previous sections, the destruction of dopaminergic neurons in the substantia nigra of the brain significantly contributes to the development of PD. Through analyzing the current research, we have undertaken a comprehensive study of three major genetic players and three major environmental factors that alter the risk of this dopaminergic neurodegeneration. The effects of *SNCA*/∝-synuclein, PINK1, and LRRK2 on mitochondrial activity, viability, and damage all demonstrate how studying genes involved in mitochondrial processes is critical to minimizing the loss of neurons in the substantia nigra. This idea is echoed by the neurotoxic effects of pesticides and MPTP and the protective effect of smoking. Current medications aim to combat the dopamine deficiency in Parkinson's, but given the cases of early onset often associated with genetic causes, surgery is also a valid treatment consideration. In addition, due to the negative side effects that come with almost all current treatments, research continues to seek a cure. Perhaps a drug that targets mitochondrial function could be a future possibility, especially one that exerts protection on complex I of the electron transport chain. This therapy would allow mitochondria to continue producing energy in demanding dopaminergic neurons, even if genetic or environmental toxins impair the functions of their components. Nevertheless, the exact mechanisms of PD development are still quite obscure, making optimal treatment difficult.

In our future studies, we utilize this paper's information to conduct a data analysis on the effectiveness of some current therapies for variously caused PD cases. We will use Parkinson's data from FoxDen through the Michael J. Fox Foundation to compare specific genetic mutants with the severity of Parkinson's symptoms. Through this study, we hope to gain additional insights on the impact of mutant genetic products and external factors on the effectiveness of medication.

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