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# Parkinson's Disease: Causes, Symptoms, Research, and Interventions

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## Abstract

*This paper covers several pathogenic theories of Parkinson's disease (PD); the physiology and biological pathways involved. This includes a mitochondrial DNA (mtDNA) route, a nuclear DNA route, and other hypotheses about idiopathic PD. The subsequent discussion of PD symptoms utilizes a neurological perspective, analyzing the neuroanatomical systems involved, and how they are treated. This includes medications and surgical techniques that are employed in an effort to manage symptomatology and increase health-related quality of life.*

## Keywords

Parkinson's disease, mitochondria, alpha-synuclein, dopamine agonists, pallidotomy, DBS

## Introduction

Neurodegenerative diseases are characterized by progressive and selective loss of anatomically or physiologically related neuron systems. The clinical syndromes associated with particular neuroanatomical patterns of cell loss and dysfunction are typically categorized by whether they initially affect cognition, movement coordination, sensation, vision, or autonomic control. Typical examples of such neurodegenerative diseases include Alzheimer's disease, Huntington's and Parkinson's disease (Lezi and Swedlow, 2012). Cholinergic neurons are implicated in Alzheimer's, and a degeneration of neurons in the dopaminergic system is responsible for Parkinson's disease.

Parkinson's disease (PD) is the second most common neurodegenerative disease, afflicting 1-3% of the 65+ age group. It is characterized by accumulation of abnormal protein (Lewy bodies) in the dopaminergic neurons of the substantia nigra pars compacta (SNc) and their subsequent degeneration. These are abnormal circular structures with a dense protein core and a halo of radiating fibers. They consist of aggregations of misfolded  $\alpha$ -synuclein along with neurofilaments and other proteins. This neuron loss leads to a difficulty controlling movement. The motor symptoms include bradykinesia, postural instability, muscle rigidity, and tremors. Some of the non-motor symptoms (NMS) include depression, insomnia, anxiety, apathy, psychosis, incomplete bowel emptying, impulse control disorders, and dementia.

The disease involves progressive degeneration which, as of now, cannot be stopped or slowed. There are effective medications that can be used to compensate for dopaminergic neuron loss, such as L-dopa, and other types of dopamine (DA) agonists. These work by increasing the potency of the surviving neurons and synapses, but only temporarily. Eventually, the disease will wipe out these pathways entirely. Furthermore, the disease spreads to other regions of the brain and causes other symptoms. For example, when neurodegeneration spreads to cholinergic neuronal pathways, the patient will start to show signs of dementia. For now, treatment options are limited

to symptom management. This paper discusses some of those treatment options, but first it is important to consider the PD pathogenesis and symptom origin. Then, this paper will delve into the innovations available for those suffering from PD, and explain how they work.

## Mitochondrial Pathogenesis of PD

Mitochondria are the site of bioenergetics and biosynthesis in the cell. Hans Krebs, for whom the tricarboxylic acid (TCA) cycle is named, said of his discovery "in some micro-organisms the cycle primarily supplies intermediates rather than energy, whilst in the animal and most other organisms it supplies both energy and intermediates". The energy supplied by the TCA cycle is in the form of NADH and FADH<sub>2</sub>, whose electrons are then fed into the electron transport chain (ETC) to pump protons into the inner membrane space of the mitochondrion creating a pH gradient. This gradient is then used to power the conversion of ADP into ATP. A high ATP/ADP ratio is required to catalyze the chemical reactions that comprise many of the metabolic operations of the cell.

Additionally, many of the building blocks that a cell needs to form its assortment of macromolecules are made using the intermediates of glycolysis and the citric acid cycle. For example, about half of the 20 amino acids found in human protein can be synthesized in vivo through the modification of Krebs Cycle intermediates (Reece et al., 2011). Also fatty acids are synthesized from acetyl CoA, which is produced by the conversion of pyruvate within the mitochondria. It is important to note that when the mitochondria are employed in an anabolic capacity (the building of larger molecules and utilization of TCA intermediates) they are no longer producing ATP but consuming this molecule.

There is some evidence implicating mutations in mitochondrial DNA (mtDNA) or nuclear genes coding for mitochondrial protein in the pathogenesis of PD. Several research teams working in 1989 reported a reduction of activity of Complex I of the ETC in the substantia nigra in patients with idiopathic PD (Lezi and Swedlow, 2012). This study was based on reports of healthy individuals developing Parkinson's like symptoms after consuming the compound 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). It was determined that the active metabolite

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of MPTP is taken up by the cell via the dopamine transporters, allowing them to cluster and wreak havoc in dopaminergic neurons. This particular metabolite inhibits Complex I of the electron transport chain, which was assumed to have led to the exhibition of Parkinson's symptomatology.

The suggested hypothesis is that mutations within genes coding for mitochondrial DNA or in mtDNA itself, specifically Complex I genes, can be implicated in PD pathogenesis. Complex I contains 46 protein subunits, seven of which are encoded by mtDNA. A mutation causing a decrease in Complex I activity would lead to a drop in ATP production and increased oxidative stress and cellular deterioration from the accumulation of free radicals (Lezi and Swedlow, 2012).

It is unclear why dopaminergic neurons of the substantia nigra would be uniquely susceptible. However, what is clear is that the failure of these nigral dopaminergic systems are responsible for the symptoms of PD. Based on the research done on mitochondrial involvement in dopaminergic deterioration in PD or induced PD symptoms, there is sufficient justification to investigate treatment options targeting the mitochondria, which work to encourage proper functionality and cellular respiration (Lezi and Swedlow, 2012).

### **$\alpha$ -synuclein and PD**

Researchers have discovered that a mutation on chromosome 4 will produce PD (Polymeropoulos, et al., 1996), the gene that codes for  $\alpha$ -synuclein. This protein can be found in the axon terminals and is involved in synaptic transmission in dopaminergic neurons. A mutation in this gene can result in a mistranslated and subsequently misfolded  $\alpha$ -synuclein that is toxic to the cell. These proteins group together in large aggregates called Lewy bodies which devastate normal cell function.

The majority of PD cases are sporadic. They occur without any family history or hereditary basis for the disorder. Some researchers suggest that an unknown toxin in the environment, faulty metabolism, or infection may be the culprit in these cases. There are two insecticides that are known to cause PD, and presumably there may be more. These toxins might interfere with mitochondrial signaling which, when impaired, could cause these aggregations of  $\alpha$ -synuclein to resist degradation and persist in the cytoplasm of nigral neuron systems.

### **Symptoms and Their Physiology**

The loss of the brain's most important dopamine suppliers, the neurons of the SNc, leads to a variety of symptoms. Resultant motor symptoms include tremors,

muscle rigidity, bradykinesia, and postural imbalance - the symptoms that normally come to mind when people think of Parkinson's disease. These symptoms arise directly from neuron loss in the motor regulation centers of the brain (Carlson & Birkett, 2017). Additionally, many other neural pathways are affected by damage to the substantia nigra, such as the areas where these dopaminergic neurons project, namely, the basal ganglia and the nucleus accumbens. The basal ganglia are involved in controlling movement, but they also project to the frontal lobes of the brain and play a role in thinking and executive functions. The nucleus accumbens has been linked to behavioral regulation. Thus, dopamine irregularities in this region can lead to changes in personality (Carlson & Birkett, 2017).

The causes for some of the non-motor symptoms are pretty clear, while others are more complicated and debatable. Some symptoms arise directly from a decrease in dopamine (DA) production in the substantia nigra. Other symptoms are a result of the DA agonist prescribed to the patient. This might be due to the dramatic fluctuations of DA in the brain owing to the medication schedule. Still other symptoms might be due to an increased potency in certain dopaminergic systems that have not been impacted by the disease. When the patient takes L-dopa, these functioning dopaminergic neurons release too much DA. This DA flood triggers a deficit in executive functions, according to the Dopamine Overdose Hypothesis (Dirnberger & Jahanshahi, 2013).

Other symptoms result from unrelated pathways that happen to be proximal to damaged areas of the brain. Lewy bodies are often present in the dopaminergic neurons of those with PD. Many of these misfolded proteins that cause neurodegeneration can be transferred from cell to cell (Lee, et al., 2011). This perhaps explains how the serotonergic, noradrenergic, and cholinergic systems become impacted in later stages of PD.

### **Treatments**

Since there is no cure for PD, the standard treatment is symptom management, by way of DA agonists. The most common one in use is L-dopa, a neurotransmitter (NT) precursor which dopaminergic neurons can convert to dopamine. This maximizes its potency through increasing the amount of NT present in the synaptic cleft with each firing of the surviving neurons. When other systems are involved in degeneration, such as the serotonergic, noradrenergic, and cholinergic systems, agonists for each of those NTs can be used to alleviate symptoms. Some symptoms arise from too much dopamine in the healthier dopamine pathways, or fluctuations of dopamine based

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on medication schedule (Dirnberger & Jahanshahi, 2013). These symptoms can be treated by using different DA agonists at different times and by changing doses. The reason for the variety of dopamine agonists is to reduce fluctuations and mitigate some symptoms that may arise from any one particular DA agonist.

Another possible medication is Deprenyl, which was initially discovered to be effective after the outbreak of PD among users of the drug MPTP. The idea behind it was to inhibit the activity of the monoamine oxidase-B enzyme and hopefully block the toxins from attacking and damaging the neurons. Although the drug does alleviate symptoms, it does not reverse, stop, or slow the progression of disease (Williams, 2010).

One surgical technique involved the grafting of nigral neurons taken from aborted fetuses, to replace the ones lost to PD. This was shown to work particularly well in patients who responded well to L-dopa earlier in the disease. Presumably, these patients had enough healthy neurons in the basal ganglia to process and secrete dopamine, whether intrinsic or from grafted tissue. Unfortunately, many of these patients later developed debilitating dyskinesias and the surgery is no longer recommended (Olanow, et al., 2003).

Upon closer inspection, it seemed as though the fetal tissue had been successful in making the proper connections with the basal ganglia. However, with time, the aggregate  $\alpha$ -synuclein deposits made their way from damaged host cells to transplanted healthy cells (Kordower, et al., 2011). Any misfolded proteins responsible for neurodegeneration can be transferred from cell to a cell close by (Lee, et al., 2011). It seems that adding healthy cells to the basal ganglia will not work unless a way is found to prevent the  $\alpha$ -synuclein from aggregating in the first place and spreading to neighboring cells.

### GPI and STN Related Therapies

The main output of the basal ganglia is from the internal division of the globus pallidus (GPi) and it is inhibitory. Researchers found that whenever there is a decrease of activity to the putamen and the caudate nucleus (which is a byproduct of SNc neuron death due to PD) there is an increase in inhibitory signaling from GPi to the motor cortex. It was suggested that destroying this area might help mitigate some of the motor symptoms. This strategy worked well and was a pretty good option but the surgery was quite risky. The optic tract is located quite proximal to the GPi and some patients were blinded by the surgery. Due to advancements in imaging and surgical techniques, this option has become safer, and can be recommended for younger patients who no longer respond

to L-dopa. Neurosurgeons can get similar results by destroying the subthalamic nucleus (STN) (Guridi, J & Obeso, 2001), which has an excitatory effect on GPi.

Another option that is growing in popularity due to refined surgical techniques is deep brain stimulation (DBS). Here, instead of destroying GPi and STN, microelectrodes are placed in these regions for the patient to stimulate as needed. This technique is as effective as brain lesions in suppressing tremors but with fewer risks (Esselink, et al., 2009). DBS might also be effective against depression and cognitive impairment in PD.

### Conclusion

There are some innovative techniques for treating PD and a lot of promising research on the horizon. Through pursuit of the various pathogenesis hypotheses, we are getting closer to understanding the mechanisms of neurodegeneration. This information is crucial to finding a strategy to reverse the disease progression. In the meantime, there are many interventions available to those suffering from PD that can dramatically improve quality of life. It is a devastating diagnosis to receive but there is plenty of hope. It is crucial that those diagnosed with PD are taught about the potential symptoms and how they can be treated. Specifically the many non-motor symptoms not directly caused by degeneration of dopaminergic neurons. Treatment of these symptoms is achieved through some of the more creative and innovative treatments discussed in this paper. These non-motor symptoms are less known by the patients but were found to be more injurious to the patient's quality of life than the classic symptoms (Duncan, et al., 2013). As the research into PD genesis, pathways and mechanisms develops, more therapies are being discovered to treat this complex and multifaceted disease.

### References

- Carlson, N.R., & Birkett, M.A.: *Physiology of Behavior*, 12th Edition, 201 (chapter 15). Boston, MA: Pearson Education Incorporated.
- Dirnberger, G. & Jahanshahi, M. Executive dysfunction in Parkinson's disease: A review. *Journal of Neuropsychology*. 2013; 7(2): 193-224.
- Duncan, G.W., Khoo, T.K., Yarnall, A.J., O'Brien, J.T., Coleman, S.Y., Brooks, D.J., et al. (2013). Health-related quality of life in early Parkinson's disease: The impact of non-motor symptoms. *Movement Disorders*, 29(2), 195-202.
- Esselink, R.A.J., de Bie, R.M.A., de Haan, R.J., Lenders, M.W.P.M., et al. Long-term superiority of subthalamic

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nucleus stimulation over pallidotomy in Parkinson disease. *Neurology*. 2009; 73(2): 151-153.

Guridi, J. & Obeso, J.A. The subthalamic nucleus, hemiballismus and Parkinson's disease: reappraisal of a neurosurgical dogma. *Brain*. 2001; 124(1): 5-19.

Kordower, J.H., Dodiya, H.B., Kordower, A.M., Terpstra, B., et al. Transfer of host-derived alpha synuclein to grafted dopaminergic neurons in rat. *Neurobiology of Disease*. 2011; 43(3): 552-557.

Lee, S.J., Lim, H.S., Masliah, E., & Lee, H.J. Protein aggregate spreading in neurodegenerative diseases: Problems and perspectives. *Neuroscience Research*. 2011; 70: 339-348.

Lezi, E., & Swerdlow, R.H. Mitochondria in neurodegeneration. *Advances in experimental medicine and biology*. 2012; 942: 269-286.

Olanow, C.W., Goetz, C.G., Kordower, J.H., Stoessl, A. J., et al. A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. *Annals of Neurology*. 2003; 54(3): 403-414.

Polymeropoulos, M.H., Higgins, J.J., Golbe, L.I., Johnson, W.G., et al. Mapping of a gene for Parkinson's disease to chromosome 4q21-q23. *Science*. 1996; 274(5290): 1197-1199.

Reece J.B., Urry L.A., Cain M.L., Wasserman S.A., Minorsky P.V., Jackson R.B.: *Campbell Biology*, 9th Edition, 2011 (pp. 180). San Francisco, CA: Pearson Education Incorporated.

Williams, R. Slowing the decline. *Nature*. 2010; 466(7310): s13-s14.