Symptoms and Possible Causes Cures for Parkinsons Disease

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Parkinson's disease is the world's second most common neurodegenerative disorder, afflicting nearly 10 million people worldwide.1 While it is a fairly common disease, its exact causes are unknown and there is no known cure. Since the early 1800s, Parkinson's disease has befuddled scientists. But now, cutting edge research has led scientists to believe that the solution to the Parkinson's puzzle may lie within our intestines. Before delving into its interesting connection to the gut, one must first understand the basic symptoms of Parkinson's Disease (PD). Usually, Parkinson's disease most often affects individuals over the age of 60, but in some cases, symptoms can be seen in patients before they turn 50.1 The main symptoms associated with Parkinson's disease are uncontrollable shaking, slowed movements, impaired coordination, and body stiffness. These symptoms make life for those with the disease difficult, especially as they get older. The primary cause of those symptoms is the depletion of the brain's dopaminergic neurons.1 Dopaminergic neurons are responsible for releasing dopamine, a neurotransmitter that functions to facilitate communication between the substantia nigra and the basal ganglia. This interaction helps a human fine-tune his/her movement by helping the brain determine the energy cost of a particular movement.8 Without dopamine-producing neurons, this interaction becomes impossible and results in the previously listed symptoms of the disease.

Currently, the most common treatments for Parkinson's are drugs that raise dopamine levels within the patient's brain. The most common of those drugs is Levodopa, a precursor molecule to dopamine. Levodopa is converted by the CNS into dopamine, thereby making up for the lack of dopamine produced by dopaminergic neurons. Other therapies include drugs that mimic dopamine's effects, drugs that slow the enzymatic breakdown of dopamine, and deep brain stimulation. While they are somewhat effective, today's Parkinson's treatments are only able to lessen the symptoms of the disease, as they cannot attack the root causes of the disease. However, new studies have shed light on Parkinson's Disease pathology. Those studies indicate that Parkinson's pathology may begin in the enteric nervous system.

The enteric nervous system (ENS) is the largest part of the autonomic nervous system. It is made up of hundreds of millions of neurons and is responsible for regulating the function of the gastrointestinal system. Because of its immense sophistication, the ENS can regulate the complex gastrointestinal system on its own, independent from the central nervous system (CNS). However, the ENS and CNS are linked by many afferent and efferent nerves that enable communication and the exchange of information between them. However, those same connections can also provide a pathway along which neurodegenerative diseases can spread. Scientists have postulated that Parkinson's pathology may begin in the ENS before spreading to the CNS and causing the disease's symptoms.

The ENS contains a unique type of neuron known as an enteric glial cell or EGC. EGCs can be found in the walls of the intestines and are crucial for the homeostatic regulation of many GI functions, including the regulation of the intestine's neuroinflammatory response.2 Under normal conditions, EGCs in the mucosa myenteric plexus are not activated. However, if the intestinal wall of an individual is compromised in some way, it may become permeable to the bacteria that inhabit the lumen of the small intestine.7 If able to pass through the intestinal wall, those bacteria will cause the EGCs of the small intestine to respond with a neuroinflammatory response. Sustained activation of EGCs results in an increase of the production of a misfolded protein known as α-Synuclein. α-Synuclein is a mysterious protein, as its true physiological function is not well known. However, it does play a crucial role in causing the dopaminergic cell death seen in PD patients.

α-Synuclein has been shown to build up in the dopa minergic neurons of Parkinson's patients, resulting in the death of those neurons.4 α-Synuclein also can be seen forming protein deposits within neurons known as Lewy bodies. In Parkinson's patients, Lewy bodies are often found in neural tissue and have high concentrations of α-Synuclein within them. The link between the production of α-Synuclein within the enteric glial cells of the ENS and the presence of α-Synuclein within the brain suggests that α-Synuclein may

somehow migrate from the ENS to the CNS. The exact method by which this process could occur was unknown for a long time. However, a study by Ahn et al. entitled "Initiation of Parkinson's disease from gut to brain by δ-secretase" shows how it could occur in humans. Researchers in this study looked to determine how α-Synuclein could move from the ENS to the CNS, which would demonstrate how the gut could affect Parkinson's disease pathology. They utilized the pesticide Rotenone to elicit Parkinson's-like symptoms in animal models. Rotenone is known to cause symptoms like gut dysmotility and the aggregation of α-Synuclein within the brains of animals. Also, Rotenone taken orally does not enter the circulatory system; instead, it solely acts on the ENS when it crosses the membrane of the intestines.4 These factors make Rotenone-treated mice good study subjects for Parkinson's.

The first thing the researchers looked at was α-Synuclein's interactions with a protein known as Tau. They found that α-Synuclein and Tau strongly bind to one another when they were cleaved by the protease Asparagine Endopeptidase (AEP). AEP cleaves the α-Synuclein protein at N103 and the Tau protein at N368. Interestingly, overexpression of the α-Syn N103 fragment in the brain has been shown to cause Lewy Body formation and motor dysfunctions.4 They also found that the complex created by the binding of Tau N368 and α-Synuclein N103 is highly cell permeable. Being able to easily cross cell membranes makes it possible for the α-Synuclein N103/Tau N368 complex to potentially leave the digestive system to enter other organs, such as the brain. That possibility was proven by a later experiment where Ahn et al. gave mice rotenone orally. After three months, immunofluorescence staining indicated that the α-Syn N103/Tau N368 complex was present in the vagus nerves of the mice treated with Rotenone. This indicated that the complex moved from the ENS through the vagus nerve to the brainstem.

The vagus nerve was identified as the main passageway by which the Lewy-body creating proteins traveled from the ENS to the substantia nigra (SN) to cause the symptoms related to Parkinson's disease. However, once at the CNS, scientists wanted to see if the α-Syn N103/Tau N368 could cause the endogenous production of α-Syn N103 in the SN. To answer this question, Ahn et al. injected mice the colons of mice with the α-Syn N103/Tau N368 complex. They found that once the complex got to the brain, it caused a local increase in the activation of AEP. Increased Ahn et al. noted that the mice showed "substantially impaired" cognitive function when compared to the control mice, demonstrating that they were experiencing dopaminergic cell death.

The findings of Ahn et al. demonstrate how the proteins responsible for Lewy body formation travel from the gut to the brain and cause dopaminergic cell death. The gut's effect on Parkinson's pathology can now be explained. First, leaky gut dysbiosis causes bacteria in the intestinal lumen to move through the intestinal wall. Those bacteria then cause a neuroinflammatory response from the intestine's enteric glial cells. Next, the EGCs start to produce abnormal amounts α-Synuclein, which builds up in the ENS. Then, the protease AEP starts to cleave α-Synuclein at N103 and Tau at N368. Those two fragments form a complex that can easily pass through cell membranes. Complexes then exit the ENS and travel to the brain via the Vagus nerve. Once in the brain, they cause endogenous production of α-Syn N103 by activating locally activating AEP. Finally, α-Synuclein builds up in the dopaminergic cells of the individual, causing Lewy body formation and cell death. Once in motion, this process would be difficult to stop due to the prion-like nature of the α-Syn N103/Tau N368 complex. However, it could be possible to create treatments targeted at preventing leaky gut itself.

It has been postulated that Parkinson's pathogenesis could be prevented by using drugs to alter the gut microbiota to prevent leaky gut and maintain the solidity of the intestinal wall.2 By using eubacteria and antibiotics, doctors could theoretically control intestinal bacteria populations to prevent them from getting through the intestinal wall and inflaming the enteric glial cells. Another possible treatment would involve the use of Fecal Microbiota Transplant (FMT). FMT involves the transplantation of fecal matter from healthy individuals into individuals with abnormal gut bacteria compositions. 9 This method is aimed at helping to reestablish a stable gut microbiota and therefore prevent conditions like leaky gut. Studies have shown that FMT has been effective in treating Ulcerative Colitis by helping to promote mucosal healing.9 Given leaky gut dysbiosis' role in Parkinson's progression, FMT could be a novel way to treat the disease.

For years, Parkinson's disease has been clouded in mystery; Its causes and pathology were a secret. However, new scientific discoveries have helped improve our understanding of the disease drastically. While we may not have all the information required to cure

Parkinson's, these new discoveries have brought us closer to finding treatments that target the disease at its source rather than mitigate its symptoms. The future of Parkinson's treatment is a little brighter, which is great news for the 10 million people who suffer from it.