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EXPLORING THE EFFECTS OF GUT MICROBIOTA WITH THE ASSOCIATION OF PARKINSON'S DISEASE

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Abstract

Parkinson's disease is a common neurodegenerative disorder. It is associated with the central nervous system that affects movement, it often includes tremors, stiffness, and inability to plan and think. Nerve cell damage in the brain causes lower production of dopamine leading to those symptoms. There is no cure for Parkinson's disease, but there are medications that can help control the symptoms. Researchers are suggesting that dysbiosis in gut microbiota could lead to the development of a protein called alpha synuclein in the intestines, and through intestinal leakage, this protein could possibly spread pathologically to the brain by the central nervous system. This protein then folds and forms a clump blocking dopamine production and then causing symptoms of Parkinson's disease. What causes this protein to fold is still unknown. This review focuses specifically on what factors may be contributing to Parkinson's disease, the effects gut microbiota has on Parkinson's disease, and how the alpha synuclein protein plays an important role in Parkinson's disease. With all information found, dysbiosis of the intestines cannot be concluded to be the cause of Parkinson's disease.

Keywords

Parkinson's disease, Microbiota, Dysbiosis, Dopamine, Intestinal Permeability, Alpha-synuclein

Introduction

Parkinson's disease is a neurodegenerative disorder that affects dopamine producing neurons in a specific area of the brain that is called substantia nigra. The substantia nigra is located in the midbrain and plays an important role in movement, reward, and addiction. Its function is to control dopamine production and it consist of two parts, the pars compacta and pars reticulata. The pars compacta contain neurons colored in black by pigment neuromelanin, and the pars reticulata is where the dendrites function. In Parkinson's patients, the substantia nigra will cause balance problems, tremors, limb rigidity, and thinking/solving problems. Although this disease is not fatal, it is serious and has serious effects on the quality of life. About 7 to 10 million people worldwide live with Parkinson's diseases and about 4 percent of people with Parkinson's disease are diagnosed before the age of 50. Men are 1.5 times more likely to get Parkinson's disease than women. In the U.S alone, the overall cost of Parkinson's disease including treatments, loss of income, and social security are estimated to be \$25 billion per year (parkinsons.org). However, despite the research that has been done on Parkinson's, the cause is still unknown. Microbes in the gut microbiota have impacts on how disease will affect the body. In this study, there will be a focus on the effects of unbalanced gut microbiota on Parkinson's disease. This is significant because knowing exactly what links gut microbiota and Parkinson's diseases share could possibly predict how likely one is susceptible to the disease. This review will focus on exploring the microbiota in patients with Parkinson's vs patients without Parkinson's, the proteins that are associated with Parkinson's, and how dysbiosis of the gut along with the proteins effect brain stimulation.

Understanding What Parkinson's Disease is and the Associations of Parkinson's Disease

Parkinson's disease is a neurological disorder that affects the motor system. Dopamine is a chemical transmitter that allows nerve cells to send signals within the brain that allows us to control our movements. In a normal human brain, cells produce dopamine that pass signals within the brain to produce a movement of a muscle in a smooth form. In Parkinson's patients, 80 percent, and sometimes even more of the cells that produce dopamine are either dead, damaged or somehow degenerated. This will cause the cells to fire uncontrollably within the brain not allowing patients to control their movements. Symptoms of this would-be things such as tremors in the legs, arms, and hands. Also, stiffness, impaired coordination, balance problems, and slowness of movements.

Research done in Parkinson's disease has found that genetics plays a big role in this disease. There are five genes that are thought to play a role in this disease, Parkin, SCA2, Alpha synuclein, Ubiquitin carboxyl-terminal hydrolase, and DJ-1. Within these genes, it is their mutations which have been found to be the underlying cause (Gerhard, 2018). Researchers believe that environmental factors act on these specific genes which then lead to Parkinson's disease. If this mechanism can be figured out, we could possibly then disrupt it and stop it from leading to Parkinson's disease. One of the environmental factors and/or mechanisms researchers think it may be is the link of gut microbiota and the brain of Parkinson's disease patients.

The Dysbiosis of Gut Microbiota

Dysbiosis of the gut is a term used to describe the microbial imbalance of the human intestines. The human gut contains trillions of microorganisms of which include more than 1000 different species of bacteria. While we all have our own unique structure of microbiota, it physiologically impacts our health in the same ways. The gut microbiota is a composed community of microorganism inhabiting the gastrointestinal track. The composition of the microbes is host specific. Mammals gut microbiota can undergo alterations, all mammals are born with a sterile gastrointestinal tract and then are developed within the first years of life. In the first year of life especially, the gut microbiota will change through interactions with the developing immune system. Different environmental factors will also determine the composition of the gut microbiota and will have a potential to be a main determiner in life long health. The balance of gut microbiota can be affected as we age and the imbalance of microbiota is something we call dysbiosis. Dysbiosis can be linked to many health problems such as bowel disease, obesity, and now even Parkinson's disease. Differences in the gut microbiota can result in changes of substances within the gut and intestinal permeability which can influence the central nervous system.

It has been considered that bacteria can enhance inflammatory response and that the imbalance of gut dysbiosis can disrupt the blood-brain barrier and increase neuro-inflammation. (Jankovic, 2018). It has been shown that many Parkinson's patients have a reduced number of *Prevotellaceae* family and an increased number of *Enterobacteriaceae*. The shift associated with these two bacterial families shows a decrease in mucin synthesis and increase in intestinal permeability, this is consistent with inflammatory pathways and protein miss-folding (Jankovic, 2018). Gut bacteria are able to control the differentiation and function of the immune cells in the

intestine and brain. Typically, patients with Parkinson's disease experience intestinal inflammation such as constipation and many years later is followed by motor defects.

What Different Factors Affect the Composition of Gut Microbiota

In a conducted case study (Keshavarzian, 2011) there were 13 taxa, 8 genera, and 7 families that were associated with Parkinson's disease. A few of those were only potentially confounded, but most were robust. Deletion of chain fatty acids in Parkinson's disease was also found. Chain fatty acids are made by bacteria in the gut, such as *Lachnospiraceae*. *Lachnospiraceae* was shown to have reduced levels in those patients with Parkinson's disease (Jankovic, 2018). This is suggesting Parkinson's patients have unbalanced dysbiosis of the gut.

This study (Keshavarzian, 2011) also suggests that there may be an increase in activity of Parkinson's in pathways that degrade xenobiotics (substances foreign to the body), atrazine (herbicide), and a few others. According to the U.S Environmental Protection Agency, atrazine is the most common herbicide contaminant in ground water found here in America. This is important because exposure to this herbicide by drinking water or by elsewhere is known to increase the risk of developing Parkinson's disease in animal models. This suggest that herbicides could also play a role in gut microbiota. If atrazine found in ground water that people drink is known to increase the risk of developing Parkinson's in animal models, then it should be a serious concern for humans as well.

A study conducted (Gerhard, 2018) used gut bacteria from Parkinson's patients and healthy controls to transplant fecal matter into genetically susceptible mice. The mice with gut bacteria from the Parkinson's patient revealed enhanced motor impairment compared to the microbiota

from the healthy controls. This suggests that certain microbes from the Parkinson's patients holds disease-like symptoms unlike the healthy controls that were used.

Possible Causes of Dysbiosis

Supporting evidence suggests that there is a link between dysbiosis of gut microbiota and Parkinson's disease. But what is the cause of dysbiosis? Epidemiological evidence shows pesticide exposure to Parkinson's disease with some specific pesticides being known to impact gut microbiota. Parkinson's patients may be missing or have a reduced number of protective microbes in their microbiota causing dysbiosis to result in differential production of microbial molecules (Keshavarzian, 2011).

Other researchers propose that physical and psychological stress, dietary factors, and antibiotics all contribute to intestinal dysbiosis. A study conducted shows that exposure to psychological stress results in lower production of mucin and acidic mucopolysaccharides on the mucosal surface of the intestines. Because mucopolysaccharides and mucin are both needed for inhibiting adherence of pathogenic microorganisms to intestines mucosa, a decrease in either will contribute to colonization by pathogenic microorganisms (Hawrelak, 2004). A well-balanced diet will benefit people by assisting with the growth of more beneficial microorganisms, while some other diets with assist gut microbiota activity that can be harmful to the host. Lastly, antibiotics are the most significant cause of dysbiosis of the intestines. Antimicrobial agents will influence dysbiosis of the intestine by its spectrum of activity, dosage and length of time taken. Depending on all of these factors will tell how much dysbiosis is happening and how dysbiosis starts affecting molecules and gut barriers (Hawrelak, 2004).

When dysbiosis has occurred, molecules start getting altered and the functions of gut barriers and intestinal permeability changes. The rearranged microbiota products inside the intestines, such as proteins may leave the intestines and travel to brain via central nervous system. Alpha synuclein, a protein that is a neuropathological hallmark of Parkinson's disease may appear in the gut before it appears in the brain because of dysbiosis. These observations may have led to the assumptions that Parkinson's disease starts in the gut and then spreads to the brain by a leaky gut membrane (Pereira, 2018).

Effects of Increased Intestinal Permeability

Intestinal permeability is a term used to describe the ability of substances such as bacteria and proteins to pass through the gut and into the body by cells that line the gut wall. Once substances are released through the gut they can travel to the brain by the central nervous system. A study conducted (Forsyth, 2011) tested to see if Parkinson's patients show increased intestinal permeability to microbes in the intestines. This was done by assessing the permeability of the gut with Parkinson's patients and healthy controls. Intestinal biopsies of both groups were taken and the bacterial translocation and the protein alpha synuclein were both observed. Intestinal hyper permeability was found to significantly correlate with *E. coli* bacteria and alpha synuclein protein in the Parkinson's patients. This suggests that the Parkinson's patients do in fact have a leaky gut barrier compared to the healthy controls who did not. Once the gut starts leaking materials, they can enter into the blood stream and cause widespread inflammation. They can also travel to the brain by the central nervous system.

Folding of Alpha Synuclein Protein

Other research on gut microbiota and the association of Parkinson's disease show from conducted studies (Jankovic, 2018) of fecal samples taken within the duration of two years or less, that the count of bacteria is different with Parkinson's patients and healthy controls, but the type of bacteria specifically is almost the same. There were no different bacteria found that were typically more present in one of the study groups. This is suggesting that the type of bacteria present within the intestines is not as relevant as the balance that allows enough good bacteria to remain present.

Typically, in previous studies, the healthy controls and the Parkinson's patient's intestinal bacteria type remained pretty much the same. It was the count that was higher or lower within the two groups that was different, with Parkinson's patients having more dysbiosis than the healthy controls. What seems to be present in most case studies is the alpha synuclein protein in association with intestinal permeability. Alpha synuclein is a protein found in the human body. Within the brain, it is specifically found at the end of nerve cells (those which send signals throughout the brain allowing movement) which are responsible for releasing chemicals such as dopamine. Dopamine is the neurotransmitter that is involved with the control of voluntary and involuntary movements. These alpha synuclein proteins in a Parkinson's patients are hypothesized to form and leak out of the intestines because of dysbiosis and intestinal permeability, travel up to the brain via central nervous system, and form a sort of clump that is toxic at the end of nerve cells that release dopamine. This folded alpha synuclein protein will block the ability of dopamine to release and can even lead to cell death. Because dopamine is

unable to release, patients with Parkinson's cannot control voluntary and involuntary movements with the blockage of this protein inside the brain. What causes this protein to fold and is still unknown and is being studied.

Promoting Good Intestinal Health

Making sure there is not increase in intestinal permeability is more crucial than people may think. Leaky gut walls are usually caused by the type of diet that one is consuming. Diets that consume of a lot of grain, wheat, sugar, processed meats, and oils are those more susceptible to have increase intestinal permeability (healthline.com). Other factors play a role in increased intestinal permeability also, such as nonsteroidal anti-inflammatory drugs which include Acetaminophen, Tylenol, and Ibuprofen. Taking rounds of antibiotics and chronically being stressed has also been known to cause leaky intestines.

Symptoms of increased intestinal permeability may be constipation, diarrhea, bloating, excessive burping and gas, migraines, weight gain, autoimmune conditions, fatigue and food allergies (healthline.com). There is testing that can be done to determine if one is having increased intestinal permeability. Those tests would include bacterial dysbiosis test, blood tests checking for IgG and IgA antibodies produced by the immune system, a comprehensive stool and digestive analysis test (healthline.com). Increased intestinal permeability develops slowly over years, and healing the gut also takes time. It can take anywhere from three months to a year by eating healthier, taking probiotics, and keeping stress levels under control to repair a leaky gut.

Conclusion

While we all have our own unique structure of microbiota, it physiologically impacts our health in the same ways. The balance of our gut microbiota can be affected as we age by diet, drug consumption, environmental factors, and even our genetics. The imbalance of our microbiota can have consequences to our health. The research done on gut microbiota with the association of Parkinson's disease shows almost always that the count of bacteria is different with Parkinson's patients vs healthy controls, but the type of bacteria found between the two groups is typically the same. While it is unsure if increased intestinal permeability from microbiota causes Parkinson's disease, it is hypothesized that dysbiosis in the intestine might be the reason for neuro-inflammation that leads to the alpha synuclein protein folding in patients with Parkinson's. What causes this protein to fold and clump is still unknown. Research is suggesting it may start in the dysbiosis of the intestines and then lead to the development of intestinal alpha synuclein, and through increased intestinal permeability, it pathologically spreads to the brain and folds. Because of this protein folding, nerve cells that send signals throughout the brain by releasing chemicals like dopamine are interrupted by the folding of the toxic protein. This follows by the symptoms of Parkinson's disease, such as tremors, stiffness, imbalance, and ability to plan and think. In conclusion, this review found out that increased intestinal permeability may be the cause of the alpha synuclein protein leaking out of the gut and spreading to the brain by the central nervous system. This review also found that dysbiosis of the gut could be where the start of Parkinson's disease occurs many years before diagnosis. Lastly, this review found that alpha synuclein plays a very important role in contributing to Parkinson's disease because it blocks dopamine production by folding. With all information found, dysbiosis cannot be concluded to be the cause of Parkinson's disease. As there is no cure for Parkinson's disease,

managing the microbiota would be the most helpful thing to do, yet also very challenging. Although a good diet may decrease intestinal permeability, there is no control over genetics, environmental factors, pathogens, antibiotics, and immunity.

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