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GUT-MICROBIOME-BRAIN AXIS AND ITS INFLUENCE ON PARKINSON'S DISEASE

(Review Article)

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Abstract

The relationship between the nervous system and microbiota opened up research opportunities that can significantly change the management of several neurological disorders. The discovery of the microbiota-gut-brain axis helped us understand how the information is relayed between the brain and the enteric nervous system. This connection demonstrated how, in Parkinson's disease, the alpha- synuclein accumulates in different organs, resulting in a wide array of symptoms. Moreover, pathways such as the hypothalamic-pituitary axis, the neuroinflammatory pathway, and neuroactive molecules are associated with the pathophysiology of PD. The manifestation of gastrointestinal symptoms and altered gut microbiota have been noted in patients several years before other significant clinical symptoms appeared. The role of alpha-synuclein accumulation and environmental factors that disrupt the natural flora of the gut in the overall progression of PD has been observed through well documented clinical studies on mice. With the current knowledge that has been established, the alteration of gut microbiota using recently explored treatment options such as probiotics, fecal microbiota transplantation, dietary changes, and certain antibiotics can prevent the progressive symptoms of Parkinson's disease.

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that is a consequence of the loss of dopaminergic neurons in substantia nigra pars compacta. More than 10 million people suffer from PD worldwide, and about 4 percent of them are diagnosed before the age of 50. Men are1.5 times more likely to develop the condition, with the likelihood increasing with age [18].

The genetic predilection plays an important role in the development of PD in conjunction with environmental factors. Mutations in LRRK2 Gene can be found in as much as 2% of the PD population in certain ethnic groups such as North African Arab Berber, Ashkenazi Jews, and Basque groups with a prevalence that is far higher than the general population (Common Genetic Mutations, 2021). There are more than 20 different mutations that can occur within this gene, the most common one being G2019S. Mutations in the GBA gene account for about 5-10%, with more than 380 different mutations already discovered. The specific GBA1 mutation has been linked to a large accumulation of alpha-synuclein clumps. Mutations in the SNCA gene can lead to increased production of alpha-synuclein which can be toxic and accumulate in the brain [17].

Several environmental factors have been linked to the development of PD, including head trauma, exposure to metals, industrial solvents such as Trichloroethylene (TCE), and Polychlorinated Biphenyls (PCBs). The herbicide Paraquat has been largely linked to PD and banned in many countries [19]. Moreover, the area of livelihood and occupation has factors that link to PD. Several vascular events have also been linked to PD.

People living with PD experience a variety of symptoms, including movement disorders such as bradykinesia, tremor, rigidity, dyskinesia, sialorrhea (drooling), hypophonia (soft speech), and micrographia (small handwriting). They can also develop neuropsychiatric nonmovement disorders such as decreased attention span, difficulty with planning, language, and memory which can progress to dementia. They can also suffer from psychiatric disorders such as depression, anxiety, apathy, sleep disorders, hallucinations, and delusions. Gastrointestinal symptoms include constipation and early satiety. Additional symptoms include lightheadedness, sexual dysfunction, loss of taste and smell, vision problems, urinary incontinence, and weight loss. These manifestations happen due to the loss of neurotransmitter dopamine which is largely responsible for motor movement, pleasure, and emotional response.

Histopathologically, PD is characterized by the deposition of Lewy bodies, an intracellular eosinophilic structure, composed of a misfolded protein called α-synuclein which accumulates in the basal ganglia, particularly in the caudate nucleus and the putamen. Lewy bodies become cytotoxic and damage

brain cells, especially substantia nigra pars compacta in the midbrain which results in a defect in the thalamic relay to the cerebral cortex. This loss of dopaminergic neurons leads to the symptoms of PD.

Normal Gut Microbiome

Microbiota refers to the entire population of organisms that colonizes a particular location. The gut microbiome is a collective population of bacteria, viruses, protozoa, fungi, other microorganisms, and their genetic material present in the gastrointestinal tract. The relationship between gut flora and the human body is a mutualistic one. The main four phyla in the gut are Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. The composition of these species varies across the digestive tract, playing different roles, including nutrient and mineral absorption, production of enzymes, vitamins, and amino acids, and synthesis of short- chain fatty acids. The normal gut microbiome has a significant impact on the metabolism, immune function, neuroendocrine responses, and intestinal-barrier function [9]. The overall effectiveness of the microbiome has a significant role in the gut-brain axis, hence, playing a crucial role in the pathophysiology of several neurodegenerative disorders [5].

The Gut-Brain axis

The discovery of gastrointestinal diseases associated with different mental health conditions has led to the acknowledgment that there is not just an information pathway from the brain to the gut but also vice versa. This resulted in the establishment of this bidirectional pathway called the gut-brain axis [3].

The communication between the gut and the brain involves several systems including the central nervous system (CNS), enteric nervous system (ENS), autonomic nervous system with both parasympathetic (PNS) and sympathetic (SNS) branches, the endocrine and the inflammatory system [18]. It also includes neurotransmitters and neuroregulators by the bacteria and barriers like the blood-brain barrier and the mucosal barrier in the intestine [11]. The brain interacts with the gut through CNS to regulate its motility and its secretory and sensory functions whereas the gut interacts with the brain through the neuroimmune and neuroendocrine pathways, activating the vagus nerve which then will send signals to the brain [14].

Enteric Nervous System

The gastrointestinal tract, from the esophagus to the anus is innervated by the ENS. Any change in the population of the gut microbiome causes the nerves to change the neuronal physiology and neuronal gene expression to adapt to it. This shows that ENS is plastic, which means that it can sense and react to the changes in the microbiome which makes it an integral part of this axis [14].

HPA Axis

The HPA (Hypothalamic-Pituitary-Adrenal) axis is another form of communication in the gut-brain axis. Its main function is to respond to stress but it also controls digestion, the immune system, mental health, sexuality, and energy transfers [14]. When there is stress the paraventricular nucleus (PVN) of the hypothalamus releases corticotropin-releasing factor (CRF) which acts on the anterior pituitary to release adrenocorticotropic hormone (ACTH) which then acts on the zona fasciculata of the adrenal glands to release cortisol, this redirects the blood to major organs like the brain, heart and also the major limbs through the SNS which means that the GI tract receives less blood for its functions [11]. In germ-free mice, the HPA axis is seen to be hyperactive along with alterations in the hippocampal NMDA and 5-HT1A receptor mRNA expression which are known to regulate the CRF release. Furthermore, vagal stimulation studies done on rodents showed an increase in CRF mRNA expression and an elevation in ACTH and corticosterone levels in the plasma which shows that there is an interaction between the HPA axis and the vagus nerve [4].

Neuroinflammatory pathway

The gut microbiome also interacts with the brain through the neuroinflammatory pathway but this interaction is species-specific [14]. When there is any kind of stressor or any pathologic state, the gut permeability increases either through leak and pore pathway in the tight junctions or through unrestricted pathways through apoptotic leaks which results in the bacteria or its toxins entering the mucosa and the bloodstream, this is known as leaky gut [14]. This activates the pro-inflammatory factors like cytokines

(IL-1, IL-6, TNF-α) to activate the HPA axis through receptors [3, 4] Therefore the neuroinflammatory and the HPA axis goes hand in hand to crosstalk with the brain. The immune system's hyperresponsiveness can also lead to the inflammation of the CNS and can increase the permeability of the BBB through LPS [15,16,24].

Neuroactive molecules

The enteric bacteria produce many neuroactive molecules like serotonin, catecholamines, glutamate, γ-aminobutyric acid (GABA), and short-chain fatty acids (SCFAs). Some reports show that these bacteria can modulate the level of neurotransmitters through TLRs and heat shock proteins through these neuroactive molecules. However, it is still undetermined if these molecules have any other effects on the host or if they can be delivered to CNS via systemic circulation [24].

SCFAs play an important role in the maturation and adequate functioning of the microglia which includes myelination and neurogenesis [14,16]. The bacteria that produce them include Faecalibacteriumprausnitzii, Clostridium leptum, Eubacterium rectale, and Roseburiaspp [15]. The germ-free mice studies show a decrease in the number and its maturity whereas antibiotic- treated mice show a decrease in its maturity alone. This shows that there is more information yet to be determined on how the SCFAs affect the microglia. Since it affects the maturity of the microglia, preclinical evidence shows that it is a signaling metabolite required for the microbiome-related development and maintenance of BBB via epigenetic modification [16]. Other functions of SCFAs also includes the alteration of chemotaxis, phagocytosis and gut integrity, induction of reactive oxygen species (ROS), they also have anti-inflammatory, antitumorigenic, and antimicrobial effects [23].

Enterochromaffin cells

The communication between ECCs and the CNS is a true example of the bidirectional interaction of the gut-brain axis. The main function of ECCs is the production of 5-HT and its storage. 5-HT is produced from dietary tryptophan and it is responsible for gut motility and secretion. ECCs 5- HT production is additionally regulated by SCFAs and 2 BA (bile metabolites).

Thus, the presence of all these pathways shows a clear indication of the bidirectional gut microbiome brain axis.

The relation between alpha-synuclein and PD

The major neuropathological indication of PD 1) the accumulation of intraneuronal cytoplasmic inclusions called Lewy bodies which contain aggregates called alpha-synuclein and other proteins like E3-ubiquitin ligase parkin and 2) the reduced levels of dopamine in the striatum due to degeneration of the dopamine neurons in the substantia nigra pars compacta [8].

Synuclein is a relatively small protein (14kda) that is predominantly expressed in the presynaptic terminals and is mostly found in the cerebral cortex, hippocampus, substantia nigra, striatum, and olfactory bulb, and also outside the CNS in biological fluids like the CSF, blood, and plasma. It plays an important role in maintaining the stability of the neuronal membrane, synaptic signaling, and dopaminergic transmission which is dysregulated in PD.

Modification in the α-syn structure occurs secondary to oxidative stress, proteolysis, or fatty acid concentration and phospholipids, which results in misfolded proteins that oligomerize and form fibrils (which develop into inclusion bodies) and may sometimes have prion-like properties. A study conducted where intracerebral injections of sarkosyl-insoluble α-synuclein from brains of patients with dementia with Lewy bodies showed to induce hyperphosphorylated α-synuclein pathology in wild-type mice can help provide a novel model for the pathology progression [13].

A “dual-hit hypothesis” postulated by Braak and colleagues states that the initial alpha- synuclein aggregates occur outside the basal ganglia in the olfactory pathways, namely the gigantocellular reticular nucleus, caudal raphe nuclei, coeruleus-subcoeruleus complex, glosso- pharyngeal vagal complex, and the Enteric Nervous System (ENS) secondary to insult from toxins or microorganisms. The vagus nerve provides a medium for the ascending transportation of the alpha-synuclein from the ENS to the brainstem up to the cortical area.

The most common GI manifestation in 80% of PD patients is constipation which may be explained by the neurodegeneration of the alpha-synuclein aggregates in the ENS occurring likely due to increased

intestinal permeability or inflammation. Additionally, it is frequently observed that these changes manifest before the appearance of motor symptoms strengthening the hypothesis that PD has a primary connection to the gut [8,13].

Patients with PD have shown higher levels of intestinal alpha-synuclein when compared to healthy controls and this finding is of significance as it shows that overexpression may lead to increased alpha-synuclein aggregation in the intestines and brains of mice and humans. Several studies conducted have shown the presence of phosphorylated α-synuclein in 61.6% of PD samples and Lewy bodies/Lewy neurites in 72.4–100.0% of PD samples when compared to the presence of just 0.0–33.0% of α-synuclein in the healthy population.

Recent research has shown that, when biopsies of intestines were conducted on healthy individuals who later would develop PD, increased synuclein immunoreactivity was observed which further establishes the presence of abnormal alpha-synuclein accumulation before motor symptoms due to CNS degeneration occurs [2].

Microbiome alterations in PD patients

Studies conducted have demonstrated increased intestinal permeability (leaky gut) in patients with PD and it speculated that this is sufficient to expose the enteric neurons to the pro- inflammatory bacterial products like Lipopolysaccharide (LPS) which in turn can induce an inflammatory response and oxidative stress thereby resulting in the accumulation of pathological alpha-synuclein in the ENS [22].

Fecal samples of PD patients analyzed showed gait and postural instability which was associated with increased levels of Enterobacteriaceae [2]. Prevotellaceae are organisms responsible for mucin production in the mucosal layer of the gut, production of SCFA's, and release of thiamine and folate. PD patients also revealed decreased levels of Prevotellaceae which is linked to reduced mucin synthesis, and production of alpha synucleinopathies via disruption SCFA modulated clearance mechanisms. Increased levels of Lactobacillaceae is shown to reduce the hormone ghrelin which is involved in physiological nigrostriatal dopamine activity [1].

Additional studies showed an increase in the pro-inflammatory Proteobacteria of genus Ralstoniain the mucosal and fecal composition and reduced anti-inflammatory properties due to an SCFA butyrate because of reduced levels of bacteria such as Blautia, Coprococcus, and Roseburia [10].

Finally, a study conducted in rotenone (pesticide) induced mouse-model of PD showed alteration in the cecal mucosa and luminal microbiota with a decrease in beneficial bacterial genus Bifidobacterium [20].

With the given findings and studies done to establish a correlation between alteration in gut microbiome and development of PD symptoms, it can be advocated that the enteric nervous system plays an important role in neurodegenerative diseases.

Upcoming Treatment Options for PD

The current mainstay treatment of PD is L-Dopa/Carbidopa (DOPA decarboxylase inhibitors) combination. Other drugs like Bromocriptine (Dopamine agonists), Selegiline (MAO-B inhibitor), and Entacapone (COMT inhibitor) all work primarily on increasing dopamine levels in the brain to diminish motor symptoms. To date, there are no disease-modifying therapies available. Accumulating evidence has established that alterations in the Enteric Nervous System (ENS) affect the progression of PD. Consequently, investigations on medication that alter the gut microbiome and their effects on the progression of PD are ongoing. The influence of Probiotics, dietary changes, and Fecal Microbiota Transplant are a few of the popular topics that researchers venture into [6,7,12,21,25,26]

Conclusion

Parkinson's disease is a neurodegenerative disease caused by the accumulation of inclusions called Lewy bodies in the brain. It is characterized by bradykinesia, tremor, rigidity, etc., and is a disease with a grim outcome. In the past few years, there has been a growing field of research trying to establish the connection between the Enteric Nervous System and the development of neurological diseases. This paper tries to bring more clarity and provide in-depth information about the relationship between our gut and PD, by focusing on how alteration in the gut microbiome is a root cause of the problem.

Recent studies, several of which are included in this review, have established that the gut and brain are interconnected to each other by more than one pathway. The most common hypothesis is related to the modification of the gut microbiome. This entails Prevotellaceae, Bifidobacterium, and Enterobacteriaceae causing oxidative stress which leads to the disruption of SCFAs, which results in the formation of alpha-synuclein aggregates. These aggregates then travel up to the cortical areas of the brain in an ascending fashion using the vagus nerve and result in the dysfunction seen in PD. Further Studies will better elucidate the role of gut microbiome in the development and progression of PD.

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