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Review Article

Research Progress on the Relationship between Gut Microbiota and Parkinson's Disease Symptoms and Their Prevention and Treatment

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Abstract

There is no consensus regarding the association between the composition of gut microbiota and various clinical symptoms of Parkinson's disease. This article provides a summary and discussion of the potential links between alterations in gut microbiota and its metabolites and the occurrence of motor dysfunction, mood disorders, sleep disturbances, cognitive impairments, and gastrointestinal dysfunctions in individuals with Parkinson's disease. The findings suggest that alterations in gut microbiota and its metabolites are linked to motor dysfunction, mood disorders, cognitive impairments, and gastrointestinal dysfunctions, yet do not correlate with sleep disturbances. Potential effective therapeutic strategies for Parkinson's disease are summarized based on gut microbiota, aiming to identify novel targets for disease prevention and treatment.

Keywords: Gut microbiota; Gut-brain axis; Parkinson's disease; Clinical symptoms; Review

Introduction

Parkinson's Disease (PD) is the second most prevalent neurodegenerative condition, characterized by ongoing debate regarding its etiology, frequently linked to the degeneration of dopaminergic neurons in the substantia nigra [1]. Evidence suggests a link between gut microbiota and PD, as indicated by the early onset of gastrointestinal symptoms [2]. The human gastrointestinal tract hosts over 100 trillion microbial cells, comprising bacteria, fungi, and viruses [3]. Bacteroidetes are the most abundant, while Firmicutes, Actinobacteria, and Proteobacteria are less prevalent. Greater diversity in gut microbiota can improve learning, memory, and motor function, while reduced diversity may compromise cognitive capabilities [4]. Neurotransmitters and metabolites, including Short-Chain Fatty Acids (SCFAs) derived from gut microbiota, exhibit anti-inflammatory properties and mitigate intestinal permeability, thereby limiting the influx of harmful metabolites into the bloodstream. These compounds also influence brain function through the gut-brain axis, which entails bidirectional communication among the nervous, immune, and endocrine systems [5].

The identification of alterations in gut microbiota and metabolites has the potential to forecast the risk of PD. Modulating the balance of gut microbiota can mitigate this risk, thereby serving the dual purpose of preventing and treating PD. This underscores the significance of the present article.

Methods and Materials

This study reviewed pubmed, wed of science and CNKNO.com, with the search term "Parkinson's disease" and brain-gut axis. The time was set to March 2024, and the language was set to Chinese or English.

1. The literatures were imported into Endnote 2021 for deduplication, and 798 literatures were finally included.Relationship between gut microbiota, metabolites, and PD

PD patients demonstrate alterations in gut microbiota and metabolites [6]. The reduced diversity of gut microbiota is frequently linked to PD. Specifically, there is a decrease in Prevotella, Bacteroides, Fusobacterium, Clostridium, Roseburia, Bifidobacterium, Parabacteroides, Ruminococcus, Bacteroides

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fragilis, and Butyricimonas, while Escherichia coli, Lactobacillus, Roseburia, Bacteroides vulgatus, Bacteroides fragilis, Akkermansia, Ruminococcaceae, Lactobacillus, Enterobacter, Weissella, Clostridium, and Klebsiella increase. Changes in the gut microbiota in PD are associated with increased pathogenic clusters, reduced microbiota producing SCFA, and elevated carbohydrate metabolites [7]. These alterations in gut microbiota and metabolites result in exposure to bacterial antigens and endotoxins, potentially inducing overexpression of α-Synuclein (ASYN) in the colon and brain, thereby stimulating microglia to secrete pro-inflammatory cytokines, which exacerbate or induce neuroinflammation and PD. Segmental filamentous bacteria can modulate the activation threshold of T cells, facilitate the differentiation and proliferation of naive T cells into effector T cells, and generate Th1, Th2, and Th17 cells. Notably, Th1 and Th17 cells can breach the blood-brain barrier and migrate to the brain, causing lesions. PD may induce alterations in brain-gut peptides, possibly associated with changes in gut microbiota, with some peptides closely correlated with PD severity. These brain-gut peptides encompass Neuropeptide Y (NPY), Cholecystokinin (CCK), Somatostatin (SST), Motilin (MTL), and Gastrin (GAS). Increased levels of NPY, which promotes appetite, are observed in PD rats, indicating its potential role in neuroprotection. CCK, a gastrointestinal hormone and gastric acid secretion inhibitor, exhibits increased levels in PD rats [8], potentially safeguarding the gastric mucosa. Brain-gut peptides function as mediators connecting gut microbiota with the brain, and their alterations are associated with PD changes.

Research on the relationship between gut microbiota and PD clinical symptoms primarily focuses on motor symptoms, mood disorders, cognitive abilities, sleep disturbances, and constipation.

Motor Dysfunction

PD mice induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine exhibit a reduction in Clostridium and an increase in Escherichia coli, Bacteroides, and Proteus in fecal matter [9]. Conversely, rotenone-induced PD mice demonstrate an elevated Bacteroidetes ratio and reduced bacterial diversity [10]. This highlights the association between alterations in gut microbiota and impaired motor function, characterized by diminished motor endurance and coordination. Furthermore, PD patients exhibit an augmentation in "pro-inflammatory" bacterial families such as Lactobacillaceae, Pasteurellaceae, and Enterococcaceae, alongside a decrease in "anti-inflammatory" butyrate-producing bacteria like Bacteroidaceae, Lachnospiraceae, and Roseburia, as well as subgroups of Bacillaceae, indicating a correlation between changes in gut microbiota composition and motor symptoms in PD patients. Moreover, PD patients with motor dysfunction demonstrate diminished expression of metabolic genes and hydrogen-producing bacteria in feces, along with reduced serum lipopolysaccharide-binding protein levels, while genes associated with lipopolysaccharide biosynthesis and type III bacterial secretion systems are upregulated [11]. Patients with postural instability and gait difficulty exhibit higher levels of Enterobacteriaceae compared to those with tremors. Non-tremor PD subtypes demonstrate increased levels of Bacteroidetes, including Propionibacterium, Corynebacterium, Actinomyces, Sutterella, Pseudomonas, and Desulfovibrio, while tremor subtypes exhibit higher abundance of Bacillus, Weissella, and Akkermansia [7]. Moreover, levels of Bilophila and Pararotlania positively correlate with Hoehn-Yahr stages, whereas Salmonella shows a negative correlation. Corynebacterium and Enterococcus levels correlate positively with motor symptoms, while Veillonella levels correlate negatively. Thus, alterations in gut microbiota in PD patients are linked to motor function, with at least one microbiota change associated with PD.

Mood Disorders

Dysbiosis of the gut microbiota contributes to mood disorders in neurological diseases [12]. It influences behavioral patterns by regulating the production of key emotional substances, such as brain-gut peptides, leptin, adrenocorticotropic hormone, and cortisol, by intestinal endocrine cells [13]. Additionally, it can modulate serotonin signaling and tryptophan metabolism, leading to vagus nerve overexcitation and dysregulation of enterochromaffin cells, ultimately resulting in depression. Patients with Parkinson's Disease (PD) demonstrate increased metabolites from three Clostridium clusters and one species, along with Clostridium difficile infection and elevated indole levels, potentially exacerbating brain dysfunction and triggering emotional disturbances [14]. Furthermore, the strain Lactobacillus rhamnosus tb-1 and reduction in Lactobacillus levels induce anxiety-like behavior and stress responses. Alterations in gut microbiota can reduce Brain-Derived Neurotrophic Factor (BDNF) expression in the hippocampus and lead to changes in the composition and function of cortical and hippocampal neurons, subsequently contributing to depression [15].

Sleep Disorders

There is no substantial correlation between gut microbiota and sleep disorders [9]. Alterations in the levels of Akkermansia, Lactobacillus, Clostridium, and Prevotella may trigger sleep disturbances [16], but their association with sleep disorders in Parkinson's Disease (PD) has not been investigated.

Cognitive Impairment

Cognition is governed by the central nervous system and closely linked to gut microbiota [17]. Reduced levels of Escherichia coli and Bacillus subtilis, along with elevated levels of Shigella, can lead to the accumulation of amyloid proteins and related bacteria, resulting in cognitive impairment. However, it remains uncertain whether this impairment is primary or secondary in Parkinson's Disease (PD). Overly releasing bacterial peptides may disrupt FOXG1 gene expression and impact cognitive abilities. Regulation of the interaction between T cells and TH17 in the intestinal mucosa helps maintain gut microbiota equilibrium. Consequently, dysbiosis of gut bacteria can activate T and B cells, influencing IgA secretion and class switching in B cells, TH17 cell differentiation, and the recruitment of dendritic cells, group 3 innate lymphoid cells, and granulocytes, thereby impacting cognitive function [18].

Gastrointestinal Dysfunction

Gastrointestinal dysfunction is closely associated with Small Intestinal Bacterial Overgrowth (SIBO) and Helicobacter pylori. SIBO is characterized by diarrhea, abdominal pain, and bloating. Its prevalence is significantly higher in PD patients and correlates with gastrointestinal symptoms and motor function deterioration. Moreover, SIBO is significantly linked to severe fecal fluctuations [19], denoting variations in the frequency of watery, loose, hard, and pellet-like stools, which are associated with changes in levodopa pharmacokinetics. Antibiotics can mitigate gastrointestinal symptoms and motor fluctuations caused by SIBO, highlighting the importance of addressing SIBO.

Constipation is a prevalent gastrointestinal symptom in PD patients, often accompanied by increased intestinal permeability and inflammation, associated with elevated levels of Bacteroides, purines, D-alanine, L-lactic acid, and D-ribose. Reduced carbohydrate fermentation and butyrate synthesis capacity, along with increased protein hydrolysis, are closely tied to PD constipation. As Short-Chain Fatty Acids (SCFAs) promote bowel movements, PD constipation patients frequently lack SCFAs. The fecal microbiota composition of PD constipation patients compared to healthy controls indicates an increase in Pseudomonas and Collinsella, and a decrease in Veillonella and Fusobacterium. Conversely, compared to non-constipated PD groups, there is a decrease in Megamonas and Holdemania, and an increase in Pseudomonas, Streptococcus, and anaerobes. The quantities of Streptococcus, Selenomonas, Veillonella, anaerobes, Pseudomonas, and Bacteroides are positively correlated with the severity of constipation, while the quantities of Holdemania and Megamonas are negatively correlated with constipation severity [20]. This underscores the close relationship between changes in gut microbiota and constipation in PD patients.

PD Treatment Based on Gut Microbiota

Probiotics

A sufficient quantity of probiotics can enhance host health [21]. Probiotic therapy stands as the prevailing remedy for gut microbiota imbalance. It serves to restore microbial and immune equilibrium, fortify intestinal epithelial integrity, prevent disruption of the intestinal barrier, regulate the mucosal immune system of the gastrointestinal tract, curb pathogen proliferation, and safeguard dopaminergic neurons by impeding the aggregation of ASYN. This underscores the effectiveness of gut microbiota modulation in PD treatment. Probiotic formulations, as part of probiotic therapy, regulate gut microbiota, dampen inflammation through cytokine production, and mitigate oxidative stress by reducing reactive oxygen species levels to address PD. Prebiotics, classified as dietary fibers, bolster host well-being by selectively fostering the growth of Lactobacillus and Bifidobacterium [22]. In essence, prebiotics do not directly impact the intestine but exert an indirect influence by stimulating the growth and proliferation of probiotics.

Diet

Consumption of wheat products, dairy, and meat may lead to changes in gut microbiota. Conversely, fruits, grains, vegetables, and fish can increase the levels of Short-Chain Fatty Acids (SCFA) and Prevotella, reducing intestinal inflammation and neurodegeneration to protect neurons. Conversely, foods rich in saturated fatty acids, animal protein, and sugar can lead to a decrease in Lactobacillus, an increase in Enterobacter, and Helicobacter pylori, thereby increasing the risk of cognitive dysfunction [1,23]. Caloric restriction can alleviate neurochemical defects and motor disorders in PD. Transitioning from a low-fat, plant fiber-rich diet to a high-fat or high-sugar, high-calorie diet can induce changes in gut microbiota within a day, driven by shifts in the ratio of carbohydrates and proteins. Imbalanced dietary nutrition can affect brain function. Hence, adjusting the proportions of carbohydrates, fiber, and protein in the diet to regulate gut microbiota balance can prevent or treat central nervous system diseases such as PD. Intermittent fasting can protect neurons through the brain-gut axis system and prevent neuronal degeneration, while a vegetarian diet can increase gut microbiota diversity, enhance SCFA production, and boost anti-inflammatory effects [24].

Fecal Microbiota Transplantation (FMT)

FMT therapy involves the transfer of fecal suspension from a healthy individual's gastrointestinal tract to another healthy individual's gastrointestinal tract, enabling modulation of the recipient's gut microbiota. It is a direct and superior method for treating PD. By adjusting gut microbiota composition, enhancing intestinal barrier function, inhibiting pathogens, and boosting immunity, FMT increases the abundance of Clostridium difficile, reduces the quantities of Enterobacter and Escherichia coli, decreases activation of substantia nigra astrocytes and microglia, reduces Short-Chain Fatty Acid (SCFA) production, and elevates serotonin and dopamine levels in the striatum. This alleviates gut dysbiosis, reduces intestinal permeability, mitigates intestinal and neural inflammation, and achieves neuroprotection and PD treatment. Although current evidence suggests high safety and minimal adverse effects of FMT, its long-term efficacy remains incompletely understood [25].

Traditional Chinese Medicine (TCM)

Traditional Chinese Medicine (TCM) can ameliorate gut microbiota dysbiosis, promote the growth of beneficial bacteria, inhibit the proliferation of pathogenic bacteria, and maintain intestinal microenvironmental balance. The etiology and pathogenesis of PD in TCM mainly involve kidney deficiency and blood stasis. Kidney-tonifying and blood-activating herbs can regulate gut microbiota, protect intestinal barrier function, and alleviate dopaminergic neuron damage. Gansong (Rhizoma Kaempferiae) can influence the gut microbiota composition in PD rats, with its ethanol extract alleviating motor dysfunction in PD rats, reducing striatal ASYN, TNF-α, IL-1β, and NF-κB levels. It mitigates colonic and striatal ASYN aggregation and relieves intestinal and neural inflammation by modulating gut microbiota and reducing pro-inflammatory cytokine levels [26]. Gut microbiota can be understood in TCM terms as the qi of the spleen and stomach, and the balance of yin and yang. TCM itself possesses properties of cold, heat, yin, and yang. Therefore, upon entering the body, it acts to balance yin and yang. Hence, the role of TCM in balancing gut microbiota is analogous to that of FMT [27].

Acupuncture

Acupuncture can reduce the loss of substantia nigra neurons, regulate basal ganglia neurotransmitters, oxidative stress, abnormal folding of α-synuclein, immune response, anti-apoptosis, and promote neural stem cell proliferation [28]. Based on the gut microbiota and brain-gut axis theory, the efficacy of acupuncture in treating PD has been validated. The "awakening and intestinal regulation" acupuncture method can regulate the enteric nervous system and endocrine system, improve gut microbiota diversity, and increase the quantity of beneficial bacteria. Gut microbiota and the brain-gut axis theory can provide new directions for acupuncture treatment of PD.

Massage

Abdominal massage can regulate gut microbiota, but there is no research exploring the effectiveness of massage therapy for PD from the perspective of gut microbiota. Massage acts on the body in the form of mechanical force, transmitting nerve impulses to the central nervous system in the form of electrical signals. Abdominal pressure stimulation can increase intestinal epithelial permeability, promote luminal microbial translocation, and induce immune responses in the intestinal mucosa, thereby affecting brain function through the gut-brain axis.

Therefore, based on gut microbiota and the brain-gut axis, massage can serve as an adjunctive therapy for PD.

Others

Gene therapy holds great potential in PD treatment [29]. Additionally, colonic irrigation can significantly reduce the quantity of Clostridium species and other bacteria, affecting host metabolism, immunity, and dynamic equilibrium, and can serve as an adjunctive therapy for PD [30].

Discussion

The composition of gut microbiota is influenced by various factors such as age, gender, diet, geography, and ethnicity, and most PD patients have varying degrees of comorbidities, which may also affect the composition of gut microbiota. However, current research on the relationship between gut microbiota and PD often fails to adequately control for confounding factors that influence gut microbiota composition. Therefore, to more accurately study the relationship between gut microbiota and PD, it is essential to rigorously control for differences in disease and other influencing factors among individuals.

Determining the composition of human gut microbiota, understanding its trends, and assessing whether there is a predisposition to PD or understanding the progression of PD are of paramount importance. If individuals exhibit the characteristic gut microbiota composition of PD patients but do not manifest PD symptoms, intervening promptly to modulate gut microbiota could theoretically delay or even prevent the onset of PD. This could contribute significantly to PD prevention and alleviate the future burden of PD on society. For patients already exhibiting PD symptoms, intervention targeting their gut microbiota has shown to be beneficial for their recovery.

Author Statements

Conflict of Interest Statement

The authors have declared that no competing interests exist.

Author Contributions

LLZ and BH provided the concept and design, LLZ drafted the manuscript, and SFC and BH reviewed the manuscript.

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