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Research and treatment discussions regarding the potential impact of gut microbiota on Parkinson's disease

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Abstract: *Recently, the gut microbiota (GM) has been recognized as an integral part of the pathogenesis of Parkinson's disease (PD). Research found a bidirectional interaction between GM and the central nervous system (CNS), known as the "microbiome-entero-brain axis". The dysregulation of GM may contribute to the occurrence or development of PD through a variety of mechanisms. In this study, we address the potential pathways of GM disorder in PD, including peripheral α-synuclein accumulation, microglial overactivation, and disruption of dopamine (DA) metabolism. Additionally, information about fecal microbiota transplantation (FMT) and oral probiotics as therapy options for PD was provided. The identification of the role gut microflora plays in PD has sparked interest in investigating novel therapy approaches and using microbes to treat the condition.*

Keywords: *Gut microbiota, Parkinson's Disease, Microbial Therapy, Microbiome - gut - brain axis*

1. Introduction

PD is the second most common neurodegenerative disorder after Alzheimer's disease, and it is primarily associated with irreversible degeneration of dopaminergic neurons in the substantia nigra and other brain regions [1]. It is usually characterized by the widespread formation of α-synuclein in the central and peripheral nervous system (PNS). The clinical manifestations of the disease encompass tremor, rigidity, bradykinesia, and postural instability [2]. Recently, the human GM has emerged as an indispensable factor in the pathogenesis of numerous neurodegenerative disorders [3]. The available evidence suggests a bidirectional interaction between the gastrointestinal microbiota and the CNS, which is commonly referred to as the 'microbiota-gut-brain axis' [4]. It encompasses a wide range of microbial communities along the microbiota-gut-brain axis, including neuroendocrine-active molecules produced by microorganisms (such as serotonin and γ-aminobutyric acid [5]) and physiological functions that regulate the CNS, such as the impact of intestinal motility on the microbial ecosystem [6]. These connections establish a bidirectional feedback loop between human physiology and the state of the microbiome, thereby laying the groundwork for neurodegenerative diseases. Moreover, early gastrointestinal dysfunction has been regarded as a potential prodromal symptom of PD. Notably, significant distinctions in the classification of microbial communities have been observed among Parkinson's patients, even after controlling for gastrointestinal function [7].

2. Dysbiosis of the GM in PD

Gastrointestinal dysfunction is widely acknowledged in individuals diagnosed with PD and is recognized as an early prodromal symptom preceding motor manifestations [8]. A range of gastrointestinal dysfunctions associated with PD have been clinically validated, encompassing weight loss, gastroparesis, constipation, and bowel dysfunction [9, 10]. The GM in PD is characterized by reduction in the population of bacteria that produce short-chain fatty acids (SCFAs) notably Lachnospiraceae and Faecalibacterium [11, 12]. In contrast, genera such as Lactobacillus, Akkermansia, and Bifidobacterium were found to be enriched, implying that these alterations may contribute to the inflammation and gastrointestinal metabolic dysregulation observed in patients with PD [13]. PD also leads to a decrease in the capacity for synthesizing butyrate. It has been reported that administration of butyric acid can enhance motor function in animal models of PD, elevate striatal neurotransmitter levels, and attenuate degeneration of dopaminergic neurons [14, 15]. Furthermore, it effectively restored the ecological imbalance of GM, mitigated the breakdown of intestinal barrier function, and attenuated

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neuroinflammation occurrence [16]. Additionally, an increase in protein hydrolysis fermentation, and the production of detrimental amino acid metabolites such as methylphenol and phenylacetylglutamine can be found in PD. The metabolites, namely p-cresol, phenylacetylglutamine, indole, and phenylalanine, have the potential to influence various aspects of gut physiology including pH regulation in the gut environment, maintenance of mucus layer integrity, modulation of intestinal barrier function and motility. Moreover, these metabolites can also exert their effects on brain neurotransmitters, neuronal activity and neuroinflammation through systemic circulation and neural pathways.

3. Possible mechanisms connecting gut dysbiosis with PD

3.1 The role of microglia and the blood-brain barrier in inflammation

Microglia, as the primary immune cells in the brain, play a crucial role in sensing and clearing neuronal damage and α-synuclein protein aggregation to maintain brain homeostasis. However, in PD, microglia become hyperactivated and release excessive pro-inflammatory cytokines that exacerbate neuronal death and inflammation. Recent research indicates that the absence of a resident microbiota significantly impacts microglial morphology and maturation, leading to attenuated early responses following exposure to microbial-related molecules or pathogenic challenges such as lipopolysaccharide (LPS) or lymphocytic choriomeningitis virus. Conversely, reconstitution with a diverse microbiota can partially restore microglial characteristics [17]. Moreover, in the absence of a complex GM, microglial cells are susceptible to overall defects, including alterations in cell numbers and immature development. This can directly impair immune responses and subsequently contribute to the onset of CNS diseases. These findings suggest that the GM and microbial metabolites play a pivotal role in the maturation and function of microglial cells. Therefore, microglial cells have a multifaceted role in PD, as they can both safeguard neurons and expedite their degenerative changes. Modulating the activity and polarization state of microglial cells may serve as an efficacious strategy for treating PD [18].

The blood-brain barrier (BBB) serves as a crucial protective mechanism, preventing the infiltration of harmful substances from the bloodstream into the brain. However, in PD, studys show that compromised BBB function, resulting in increased permeability and subsequent entry of toxic substances into the brain parenchyma [19]. Furthermore, emerging research has demonstrated an intricate association between GM, microbial metabolites, and BBB permeability. In the absence of GM, BBB exhibits heightened permeability to macromolecules due to downregulated expression of zonula occludens protein within brain endothelial cells [20].

The intestinal microbiota of patients with PD often exhibits decreased levels of SCFAs and increased synthesis of LPS. SCFAs play a pivotal role in the maturation and activation of microglia, while the reduced concentration of SCFAs in the gut impairs anti-inflammatory activity, leading to local and systemic inflammation. Researchers Inject LPS into the striatum and pallidum of mice led to activation of microglia, forming pro-inflammatory and dopaminergic neuron loss models at the original injection site and substantial nigra. They found that in the CNS and PNS, LPS binds to TLR4 on microglial cells, activating them. Increased levels of inflammatory factors NLRP3 and IL-1 have been found in both the CNS and PNS [21, 22]. The activation of nuclear factor-kB or receptor-interacting protein 1-FAS-associated death domain-caspase-8 protein complex, induced by the binding of LPS to TLRs, facilitates the transcription of inflammatory mediators IL-1 and NLRP3. These findings collectively imply that intestinal inflammation is likely to exert an impact on the CNS.

3.2 Changes in DA metabolism

DA is a neurotransmitter, and an important function of DA in the brain is to regulate movement. In PD, the gradual death of dopaminergic neurons in the substantia nigra leads to the inability of DA to efficiently transfer to the striatum. As a result, people with PD experience symptoms of movement disorders, such as tremors, stiffness, slow movement, and postural instability [23].

Almost half of the DA produced in the body is synthesized by the gastrointestinal tract [24], and various GM can also contribute to DA production [25]. Although DA generated by GM cannot permeate the BBB, it can enter the bloodstream or modulate DA metabolism levels and function through receptors on intestinal epithelium or other structures. Consequently, an imbalance in GM may exert an impact on DA metabolism. However, alterations in the GM affect DA production by affecting levels of the intestinal hormone Ghrelin. Ghrelin is a gastrointestinal hormone that specifically recognizes endogenous Ghrelin receptors, also known as growth hormone secretion-stimulating receptors (GHSR). The GM synthesize

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DA's precursors, such as tyrosine. In the hypothalamus, Ghrelin binds to GHSR-expressing substantial nigra pars compacta cells and activates DA neurons in it. This enhances the transcription of tyrosine hydroxylase mRNA and increases the concentration of DA in the dorsal striatum [26], partially compensating for the lack of DA in PD.

3.3 α-synuclein

Neurodegeneration associated with α-synuclein in the enteric nervous system may precede the onset of motor symptoms in PD [27, 28]. The relationship lies in the association with constipation and pathological physiological alterations within the intestinal wall [29-31]. The GM exerts an influence on enteric neuron activity, potentially impacting α-synuclein aggregation within the CNS [32-35]. Early α-synuclein pathology is frequently observed in the enteric parasympathetic nervous system [36, 37], indicating that the vagus nerve may serve as a conduit for α-synuclein propagation from the PNS to the CNS [38]. The vagus nerve plays a pivotal role in mediating the bidirectional communication between the GM and the brain, as it serves as a conduit for transmitting microbial influences [39, 40].

4. The utilization of microbiota therapy in PD

4.1 Oral probiotics

The mechanism of action of probiotics in PD may involve modulating the intestinal environment, suppressing the proliferation of detrimental GM, thereby ameliorating gastrointestinal symptoms [41]. The abundance of precursor components in stool samples of patients with PD has been found to be significantly reduced [42], a phenomenon that can be effectively rectified through probiotic intervention. Another illustrative example pertains to individuals afflicted with PD who are also infected by Helicobacter pylori. Research studies have demonstrated that these patients exhibit diminished absorption rates of levodopa [43]. Another example pertains to PD patients who are infected with Helicobacter pylori. Research has indicated that these patients exhibit a diminished absorption rate of levodopa. The eradication of Helicobacter pylori through the utilization of specific probiotics may prove advantageous for these individuals. Researchers have discovered that the probiotic strain Lactobacillus casei CECT 7366 inhibits the growth of Helicobacter pylori [44], thus offering a promising avenue for future research in PD. Moreover, supplementation with lactic acid bacteria also demonstrates anti-Helicobacter pylori effects and may provide valuable insights for forthcoming studies on PD [45].

4.2 FMT

FMT is a therapeutic approach involving the transfer of a healthy individual's fecal microbial community into the recipient's gut, with the aim of establishing a normalized GM. This intervention aims to ameliorate dysbiosis in the gastrointestinal tract, modulate immune and metabolic functions, mitigate intestinal inflammation, and ultimately reduce the incidence of neuroinflammation and neuronal damage. Following FMT, a reduction in neuroinflammation was observed in a mouse model of PD, characterized by decreased activation of glial cells, including microglia and astrocytes, as well as inhibition of the TLR4/TANK-binding kinase 1 (TBK1)/TNF signaling pathway [46, 47], elevated levels of dopaminergic neurons and tyrosine hydroxylase in the striatum, accompanied by augmented concentrations of DA, serotonin, and their respective metabolites. In summary, FMT shows promise in the treatment of PD, as it can influence DA metabolism through various pathways to enhance both motor and non-motor symptoms. FMT has demonstrated significant effectiveness and allows for the customization of fecal samples based on individual microbiota composition or even the creation of ideal microbiota using synthetic biology techniques. However, it is important to acknowledge that FMT procedures are intricate, expensive, and may entail risks such as infection, immune responses, and metabolic disruptions. Moreover, there are challenges associated with determining the optimal transplantation route, frequency of dosage administration, monitoring methodologies, among other factors.

5. Conclusions

Recent research suggests that the GM may play a role in the development of PD, as maintaining a healthy balance of GM could potentially decrease the risk of various neurological disorders, including PD. The initial accumulation of α-synuclein in PD might originate in the intestines and then spread to the CNS through intercellular transmission. Disruptions in gut bacteria can create an inflammatory

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environment, which can also communicate with the brain through systemic pathways and disrupt the function of the BBB. Additionally, an imbalanced GM that leads to reduced DA production is considered a significant contributing factor to DA deficiency observed in PD. Therefore, an imbalance within microbial communities residing in the host's gut may contribute to both motor and non-motor symptoms observed in PD.

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