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The role of gut brain axis in the pathogenesis of Parkinson's disease

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Abstract:

Parkinson's disease (PD) is a progressive neurodegenerative disorder traditionally characterized by dopaminergic neuronal loss and α-synuclein aggregation within the central nervous system. However, increasing evidence suggests that the disease may originate outside the brain, particularly within the gastrointestinal tract, through mechanisms involving the microbiota–gut–brain axis (MGBA). This article summarizes the interactions between intestinal dysfunction, barrier dysfunction, inflammation, and α- synuclein transmission along the vagus nerve in the pathogenesis of Parkinson's disease. Alterations in microbial composition are closely linked with impaired intestinal barrier integrity, leading to neuroinflammation and dopaminergic neuron degeneration. Clinical studies further support the causal role of gut-derived signals in shaping disease onset and progression. Additionally, intestinal-derived α-synuclein has been demonstrated to propagate retrogradely to the brainstem via the vagus nerve, reinforcing the "gut-origin hypothesis." By integrating microbiology, neuroscience, and immunology, the study of MGBA not only broadens our understanding of PD etiology but also highlights novel targets for prevention and personalized therapeutic strategies.

Keywords: Parkinson disease; gut-brain axis; α-synuclein; intestinal barrier; neuroinflammation

1. Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative. Recent epidemiological data indicate a prevalence of about 1-2 cases per thousand people worldwide, making it the second largest neurodegenerative disease, with case numbers growing rapidly. At the same time, the incidence of PD increases significantly with age, and about 1% -2% of people over 65 years old in the world are affected by PD [1]. Clinically, the characteristic of PD is motor symptoms, including static tremor, myotonia, bradykinesia, postural instability, and other non-motor symptoms, such as constipation, hypoesthesia, sleep behavior disorders, and depression. These symptoms may occur several years before the onset of motor symptoms. In terms of pathological features, the core of PD includes progressive loss of dopaminergic

neurons in the substantia nigra compacta of the midbrain and the abnormal aggregation of Lewy bodies rich in α - synuclein [2].

Traditionally, the pathogenesis of Parkinson's disease has mainly focused on the abnormal aggregation and transmission of α - synuclein in the central nervous system, especially in the brain. However, this traditional theory of "central origin" has some limitations: many non-motor symptoms such as gastrointestinal dysfunction, constipation, and olfactory dysfunction can occur more than ten years before the onset of motor symptoms, which indicates that the lesions may start outside the central nervous system [3]; At the same time, there is no obvious α - syn accumulation in the brain of some early PD patients, but Lewy like lesions have been detected in the intestinal tissue, which also proves this view [4].

In this context, the "gut brain axis" theory as a new perspective has been originally proposed by Braak et al. and received extensive attention. This theory believes that Parkinson's disease may originate from the gastrointestinal tract, and pathological proteins are retrogradely transmitted to the brain stem via the vagus nerve to the center and then spread to various regions of the center [2]. Now growing evidence supports this hypothesis, for instance, the obvious deposition of α - syn in the intestinal tissue of PD patients. In addition, epidemiological studies also found that the risk of PD in animals with vagotomy was significantly reduced [5]. These findings promote the theoretical shift from "central unidirectional" to "peripheral central bidirectional" pathogenesis.

Therefore, this paper aims to explore the research progress of intestinal brain axis in the pathogenesis of Parkinson's disease in recent years, including the background and theoretical basis of the hypothesis, key experimental models and clinical research evidence, mechanism of intestinal microecology and environmental factors, possible transmission path and its potential value in early diagnosis and intervention. By summarizing the research results in this emerging field, I hope to provide a new perspective for the etiological exploration, early warning systems, and therapeutic strategy of PD.

2. Composition and physiological function of gut brain axis

The microbiota–gut–brain axis (MGBA) is a multidimensional two-way communication network integrating nervous, immune, endocrine systems and intestinal microbiota. Core components include the enteric nervous system (ENS), vagus nerve and other autonomic nerve pathways, intestinal microbiota and its metabolites, and intestinal barrier with related immune system [6]. As a local neural network, ENS can independently regulate intestinal peristalsis, secretion and blood flow, and conduct two-way information exchange with the central nervous system (CNS) through vagus nerve and other pathways [7]. Vagus nerve fibers transmit mechanical, chemical and inflammatory signals from the gut to the dorsal vagal nucleus of the brainstem. At the same time, they relay central regulatory signals back to the gut and participate in the regulation of gastrointestinal motility and secretion.

Intestinal microbiota affects ENS, immune cells and endocrine glands by producing active metabolites (e.g., short chain fatty acid SCFAs, tryptophan metabolites, and neurotransmitter precursors), thus indirectly or directly regulating central function [8]. In parallel, the intestinal mucosal barrier and gut associated lymphoid tissue (GALT) act as the immune defense line, which not only prevents pathogens and toxins from entering the circulation but also transmits the peripheral immune state to the central nervous system by secreting immune factors and cytokines. Under physiological conditions, MGBA maintains normal operation of gastrointestinal function, metabolic homeostasis, immune tolerance and emotional cognition [9]; However, in pathological states (e.g., Parkinson's disease, depression, irritable bowel syndrome), microbial imbalance, barrier dysfunction, immune overactivation and neural regulation disorder can interact, resulting in intestinal brain bidirectional regulation imbalance [10].

3. Imbalance of intestinal microbiota and Parkinson's disease

In recent years, many studies have shown that the intestinal flora of patients with Parkinson's disease (PD) shows a significant imbalance trend, and the most typical changes include the significant decrease of Prevotella and the relative increase of akkermansia. This change is accompanied by the weakening of intestinal barrier function, such as the decreased expression of tight junction proteins (such as ZO-1 and occludin), which may lead to endotoxin (such as lipopolysaccharide, LPS) and microbial metabolites more likely to penetrate the system circulation, thus inducing neuroinflammation and abnormal accumulation of α-synuclein [11].

In these imbalances, microbial metabolites such as LPS and short chain fatty acids (SCFAs) play a two-way role. On the one hand, LPS, as a powerful inflammatory activator, induces inflammation in the central nervous system (CNS) through toll-like receptor 4 (TLR4) signaling pathway and promotes neurodegenerative lesions; On the other hand, SCFAs has anti-inflammatory and neuroprotective

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effects at physiological concentrations, but its imbalance may also cause adverse effects [12]. These metabolites may regulate central inflammation through the neuroendocrine immune interaction pathway.

There are growing evidence about the mechanism of how intestinal flora affects central nervous system inflammation. Intestinal imbalance can mobilize the immune network of the body, including the activation of T cells and inflammatory factors. Common peripheral inflammatory markers in PD patients, such as TNF-α and CCL2, are increased, which are related to the severity of the disease [13]. At the same time, the enhanced intestinal permeability allows LPS and other microbial derived molecules to enter the system circulation, further inducing the immune response in the brain, promoting the activation of glial cells and intensifying the aggregation and diffusion of α-synuclein.

Animal models and fecal bacteria transplantation experiments provide important experimental evidence of causal correlation. In the classic experiment, the feces of PD patients were transplanted into model mice, and the motor function of recipient mice was significantly deteriorated, which clearly supported the view that intestinal flora directly mediated PD phenotype. In specific models, such as the PD mouse model induced by rotenone, fecal bacteria transplantation can inhibit the central inflammatory response and protect the function of dopaminergic neurons; The mechanism involves LPS-TLR4 Signal Suppression. Other studies have pointed out that in the MPTP induced model, fecal bacteria transplantation also plays a regulatory role in activating TLR4/PI3K/AKT/NF-κB signaling pathway [12].

In general, there is a close relationship between intestinal flora imbalance, metabolic product disorder and central inflammation in PD patients, and animal experiments and fecal bacteria transplantation model further verify these causal relationships. The imbalance of intestinal flora leads to the release of LPS and other pro-inflammatory molecules, the activation of central inflammation and abnormal behavior. These mechanisms together constitute the key role of the gut brain axis in the pathogenesis of PD and provide theoretical support for the intervention of PD by adjusting the balance of flora in the future. Future studies still need to further clarify the role of specific flora or metabolic pathways, and explore precise intervention strategies to delay or reverse the course of PD.

4. Intestinal origin and vagal transmission of α - synuclein

Studies on the possibility that α- synuclein (α-SYN) may start in the gut and spread along the vagus nerve to the central nervous system in Parkinson's disease (PD) have increased rapidly. Much evidence point out that Lewy bodies and α-syn aggregation exist in the intestinal nerve plexus, indicating that they are formed in the early stage of PD or in the periphery, which supports the hypothesis of "intestinal origin" onset. Pathological studies have found that Lewy bodies can be detected in the gastrointestinal tract of PD patients, especially in the Meister plexus or Auerbach plexus of the stomach and small intestine, indicating that α- syn accumulation has occurred in the intestine before the occurrence of central lesions [4].

Based on this, Braak et al. Put forward the classic hypothesis that α-syn pathology diffuses from the peripheral gut along the vagus nerve "from bottom to top" to the brain stem and central nervous system, which is the so-called Braak staging path. Braak hypothesis pointed out that Lewy pathology first appeared in the enteric nervous system (ENS) and dorsal motor nucleus (DMV) and then spread to the substantia nigra and other central structures [14]. This mode of transmission has been supported by several animal models and clinical circumstantial evidence: in the PD transgenic mouse model, after the injection of preformed fibers (PFF) at the α-syn site into the gastrointestinal tract, pathological α-syn can be transmitted to the brain stem along the vagus nerve, and finally deposited in the central nervous system, inducing PD like lesions [4].

Further experimental studies revealed that α-Syn was not only derived from intestinal nerve cells. Chandra et al. Pointed out that in the special transgenic mouse model (sncabow), the expression of human α-Syn was limited to intestinal epithelial cells. The results showed that pathological α-syn could be transferred from these intestinal epithelial cells to the ganglia of the common cervical vagus nerve and further spread to the brain stem. If the inferior septal vagotomy is performed before expression induction, the dissemination of α-syn in the distal brainstem can be reduced, providing strong experimental support, indicating that intestinal epithelial cells (such as EECS) may be used as non-neuronal sources to participate in the transmission of α-syn to the central nervous system through the form of "nerve cell transmission" [15].

Vagotomy has been shown to delay the pathological transmission of PD in animal and human studies. In the animal model, intragastric injection of rotenone induced α-syn aggregation, which then propagated along the vagus nerve to DMV and substantia nigra. Once the vagus nerve is cut off, the transmission path is blocked, and pathological changes fail to spread to the central nervous system [16]. In human epidemiological studies, although the incidence of PD in patients with total vagotomy is not significantly

different from that in the control, the risk of PD in patients with at least 5 years interval is significantly reduced (HR ≈ 0.59), suggesting that vagal nerve integrity may play a key role in disease progression [16]. Although the evidence is still controversial and inconsistent, it adds empirical support for the "gut brain" transmission pathway.

Clinical observation also revealed that intestinal symptoms (such as constipation) were often used as non-motor prodromal symptoms of PD, which appeared many years earlier than typical motor symptoms, further confirming that α - syn and pathology may have accumulated in the intestine. This is consistent with the clinical data of patients with long-term constipation or other gastrointestinal dysfunction and is one of the important clinical types of evidence of the "intestinal origin" hypothesis [15].

It is worth noting that in recent years, the possibility of "retrograde transmission" or "two-way transmission" has also been proposed: α-syn may not only move from the gut to the central nervous system but also spread from the central nervous system to the gut. The specific mechanism and clinical significance are still being explored [17]. In addition, some studies have shown that α-syn transmission may also rely on blood circulation rather than relying solely on the vagus nerve, further suggesting the complexity of α-syn transmission mechanism in vivo [17].

5. Disruption of intestinal barrier and neuroinflammation

Many studies have detected non-invasive markers such as calprotectin and zonulin and found that these indicators in serum and feces of PD patients were significantly increased, suggesting that intestinal inflammation and barrier function damage are common. For example, Dumitrescu et al reported that the serum calprotectin and fecal zonulin levels in PD patients were significantly higher than those in the control group (serum 26.69 ng/ml vs. 19.43 ng/ml, fecal 100.19 ng/ml vs. 37.3 ng/ml, $P<0.005$), supporting the prevalence of impaired intestinal barrier function [18]. Klann et al. Also pointed out that in patients with PD, calprotectin, zonulin and α-1 -antitrypsin were observed to be increased in feces, and tight junction proteins such as Zo -1 and occludin were detected to be decreased or abnormally distributed in rectal sections, further highlighting the structural damage of intestinal barrier [19]

This barrier damage makes endotoxin such as lipopolysaccharide (LPS) easy to penetrate the intestinal epithelium, enter the intestinal wall and even the systemic circulation. Shannon et al. Pointed out that in patients with PD, the expression of TLR4 in intestinal wall increased, while the LPS -binding protein (LBP) in plasma decreased (reflecting the increase of LPS in the system) [20]. This kind of LPS penetration can not only activate local immunity in the intestine and destroy tight junctions but also trigger peripheral immune system responses through systemic circulation. Brown's "endotoxin hypothesis" further emphasizes that LPS is increased in the blood due to the destruction of intestinal barrier, which can activate peripheral innate immunity and then affect the neuroinflammatory state [21].

The activation of peripheral inflammation can aggravate the activation of microglia in the central nervous system through a variety of mechanisms, thereby accelerating the degradation of dopaminergic neurons. Milde et al. Pointed out in the study in 2021 that the plasma LPS level of some PD patients, especially the high-risk dementia group, increased significantly, and injecting a considerable concentration of LPS into the blood of healthy people can quickly induce inflammatory reactions in vivo and brain and activate microglia [22]. The activation of microglia and astrocytes observed in LPS injection model animals further supports this mechanism: systemic or local injection of LPS will induce a strong neuroinflammatory response in the substantia nigra and striatum, accompanied by neurodegenerative changes [23]. At the same time, systemic inflammation may also damage the integrity of the blood-brain barrier (BBB), allowing more peripheral inflammatory factors, immune cells and endotoxin to enter the central nervous system, aggravating neuroinflammation and promoting neuronal damage.

These mechanisms connect the causal chain between intestinal barrier destruction, peripheral inflammatory activation and central nervous system inflammation. Yang et al. Did not have a consistent significant correlation between zonulin or LBP and intestinal permeability in 2022 (may be limited by the sample size), but they still support the importance of intestinal inflammation and intestinal leakage in PD[24]. Shannon's model further emphasizes that intestinal LPS penetration can open the chain reaction, destroy the barrier and aggravate the inflammatory reaction [20]; The review of *Nature Reviews Immunology* systematically pointed out that intestinal imbalance led to the rise of peripheral inflammatory cytokines. After entering the central nervous system, these cytokines can activate microglia and T cells through innate and adaptive immune pathways, forming systemic inflammatory symptoms linked with the central nervous system [25].

PD patients are often accompanied by impaired intestinal barrier function, which is manifested by decreased tight junction proteins and increased permeability markers such as zonulin, which promote LPS and other inflammatory stimuli to enter the system circulation and activate the pe-

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ripheral immune response; Subsequently, systemic inflammation further acts on the central nervous system through the blood-brain barrier, triggering microglia activation and neurodegeneration. This inflammatory pathway from intestinal destruction to central damage not only provides a holistic understanding of the pathological mechanism of PD but also provides a possible direction for future intervention in the development of PD by restoring intestinal barrier (such as using tight junction regulator), reducing LPS invasion or regulating inflammatory response.

6. Conclusion

Parkinson's disease (PD) is a neurodegenerative disease caused by multiple factors. Its traditional research has long focused on the damage of dopaminergic neurons in the central nervous system. However, the evidence accumulated rapidly in recent years has continuously promoted the transformation of research perspective to the "peripheral central" linkage, especially the key role of the "gut brain axis" (MGBA) in the pathogenesis of PD has become increasingly prominent. From the imbalance of intestinal microbiota and the destruction of barrier function to the activation of central immune response by toxins and inflammatory factors across the blood-brain barrier, and then to the transmission path of intestinal derived α - synuclein along the vagus nerve, this series of mechanisms jointly construct the pathological pathway framework of "from intestine to brain".

The gut brain axis not only provides strong support for the interpretation of clinical phenomena such as early onset of non-motor symptoms and multiple origins of pathological starting points, but also reveals a new target for the prevention and treatment of PD. Especially in the early stage of disease, the intervention methods such as intestinal flora remodeling, barrier function protection, and inflammation regulation are reversible and operable, and have important potential as the "primary prevention" and even "delayed progression" strategies of PD. Probiotics, fecal bacteria transplantation, diet regulation and tight junction regulators have become the focus of frontier research.

Looking forward to the future, it should strengthen the following aspects: first, at the level of mechanism research, need to clarify the specific roles and mutual regulation of different flora, metabolites and immune factors in MGBA pathway; Secondly, it combines neuroscience, microbiology, immunology and systems biology, and combines multi omics technology with artificial intelligence model to analyze the evolution path of individualized pathology; Third, translational medicine needs to promote high-quality, long-term follow-up human cohort research, explore the early warning ability of intestinal biomarkers, and verify the safety and efficacy of probiotic intervention.

In conclusion, the study of gut brain axis not only expands the understanding of the pathogenesis of PD but also provides an unprecedented breakthrough for the early screening, individualized diagnosis and treatment and systematic intervention of neurodegenerative diseases. As an important bridge connecting peripheral and central nervous system, MGBA is gradually moving from pathological interpretation to clinical intervention, and its research prospect is worthy of high expectation.

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