also lacks truly disease-improving therapies and reliable early diagnostic biomarkers, highlighting the urgency of exploring novel treatment strategies to target the potential pathophysiology of PD.

This study will explore the crucial role of the gut-brain axis in the pathogenesis of PD. An increasing number of preclinical, clinical and postmordial studies suggest that gastrointestinal dysfunction and intestinal microbiome imbalance may precede and promote the occurrence and progression of the disease. Mechanically, intestinal ecological imbalance, increased permeability and immune activation can induce systemic and neuroinflammation, promoting the misfolding of α -synuclein in the intestinal nervous system and its transmission along the vagus nerve to the central nervous system. This study aims to provide new clues for the early detection and pathophysiology of PD, and also opens up prospects for disease improvement and individualized treatment strategies targeting the gut microbiota and gut-brain communication. It is expected to reshape the management model of PD and improve the prognosis of patients.

2 The Structure and Function of The Gut-Brain Axis

2.1 Central nervous system, enteric nervous system and autonomic nervous system

The gut-brain axis is basically constructed around a complex bidirectional communication network integrating the central nervous system (CNS), the enteric nervous system (ENS), and the autonomic nervous system (ANS) (Hattori and Yamashiro, 2021; Zheng et al., 2023). The CNS, composed of the brain and spinal cord, is the main processing center for neural information, while the ENS, known as the "second brain", is embedded in the gastrointestinal tract and is composed of a large number of neurons, responsible for autonomously regulating intestinal motility, secretion, absorption and local immune response (Suganya and Koo, 2020; Zheng et al., 2023). The ENS communicates extensively with the CNS simultaneously through pathways such as vagus nerve and spinal afferent fibers, enabling rapid transmission of sensory and motor signals between the gut and the brain, thereby achieving the regulation of the digestive process by the brain and the feedback effect of gut-derived signals on brain function and behavior (Hattori and Yamashiro, 2021; Zheng et al., 2023).

The autonomic nervous system (abbreviated as ANS) is composed of two parts: the sympathetic nerve and the parasympathetic nerve. It is a key intermediate transmitter between the central nervous system and the enteric nervous system (ENS), responsible for coordinating physiological activities that are not subjectively controlled, such as heart rate, digestion, and respiratory rate (Suganya and Koo, 2020). Among them, the nerve fibers of the sympathetic nerve usually inhibit intestinal peristalsis and secretion production, while the parasympathetic nerve fibers mainly promote the progress of the digestive process through the vagus nerve and play an anti-inflammatory role (Longo et al., 2023; Zheng et al., 2023). Through these neural conduction pathways, the metabolic products of the intestinal flora or the changes in the intestinal environment caused by inflammation can be rapidly transmitted to the brain. The stress response generated by the brain, in turn, affects the physiological state and microbiota composition of the intestines. This bidirectional interaction constitutes an important structural and functional basis of the gut-brain axis in both healthy and diseased states (Hattori and Yamashiro, 2021).

2.2 Regulatory networks: HPA axis, immune system and humoral factors

In addition to neural pathways, the gut-brain axis is also jointly regulated by the hypothalamic-pituitary-adrenal axis (HPA axis for short), the immune system, and various humoral factors (Hattori and Yamashiro, 2021). The hypothalamic axis is an important part of the central neuroendocrine system. It regulates the overall stress response of the body by controlling the secretion of glucocorticoids (such as cortisol) (Rusch et al., 2023). When the HPA axis is activated, it will change intestinal permeability, regulate immune responses, affect the composition and function of intestinal flora, thereby altering the physiological state of the intestine (Bertollo et al., 2025). Conversely, signals such as microbial metabolic products or inflammatory cytokines produced in the intestinal tract can also activate the HPA axis, thereby influencing the overall stress state of the body and brain function. When a person is ill, neuroendocrine signals play a crucial role in maintaining gut-brain balance and dealing with the problem of balance disruption (Rusch et al., 2023).

The immune system is not only an important channel for signal transmission between the intestine and the brain, but also a key target of this axial regulation. In the relevant lymphoid tissue (GALT for short) in the intestine,