BRAIN
REVIEW ARTICLE

The role of gut dysbiosis in Parkinson's disease: mechanistic insights and therapeutic options

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Parkinson's disease is a common neurodegenerative disorder in which gastrointestinal symptoms may appear prior to motor symptoms. The gut microbiota of patients with Parkinson's disease shows unique changes, which may be used as early biomarkers of disease. Alterations in the gut microbiota composition may be related to the cause or effect of motor or non-motor symptoms, but the specific pathogenic mechanisms are unclear.

The gut microbiota and its metabolites have been suggested to be involved in the pathogenesis of Parkinson's disease by regulating neuroinflammation, barrier function and neurotransmitter activity. There is bidirectional communication between the enteric nervous system and the CNS, and the microbiota-gut-brain axis may provide a pathway for the transmission of α-synuclein.

We highlight recent discoveries about alterations to the gut microbiota in Parkinson's disease and focus on current mechanistic insights into the microbiota-gut-brain axis in disease pathophysiology. Moreover, we discuss the interactions between the production and transmission of α-synuclein and gut inflammation and neuroinflammation. In addition, we draw attention to diet modification, the use of probiotics and prebiotics and faecal microbiota transplantation as potential therapeutic approaches that may lead to a new treatment paradigm for Parkinson's disease.

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Introduction

Parkinson's disease is a common neurodegenerative disease largely characterized by the loss of dopaminergic neurons with abnormal accumulation of α-synuclein in the substantia nigra and striatum. The main motor symptoms of Parkinson's disease are tremor, stiffness, bradykinesia and postural instability.[1,2] In addition, non-motor symptoms ranging from sensory abnormalities, behavioural changes, sleep disorders, gastrointestinal and autonomic nervous dysfunction[3–5] may precede the classical motor symptoms.[6] Non-motor symptoms play a dominant role in the clinical manifestations of Parkinson's disease and seriously influence a patient's quality of life.[7,8] More than 80% of patients with Parkinson's disease experience a variety of severe gastrointestinal symptoms such as constipation, nausea and vomiting.[9] The pathogenesis of Parkinson's disease is complex and known to be related to neuroinflammation, oxidative stress and mitochondrial dysfunction.[10–13]

In recent years, the role of the gut microbiota in neurological diseases has attracted considerable interest. The gut microbiota sends signals to the CNS and enteric nervous system through different pathways through metabolites, hormones, the immune system and afferent nerves.[14,15] The enteric nervous system communicates with the CNS through the microbiota-gut-brain axis and a mechanism has been proposed to suggest that gut microbe function participates in the occurrence and progression of the disease. Moreover, the gut microbiota provides a prospective means of treating Parkinson's disease, and research on the Mediterranean diet, probiotics and faecal microbial transplantation shows great application potential. In this review we will: (i) summarize recent studies on the relationship between the gut microbiota and Parkinson's disease; (ii) discuss the possible mechanisms through which the microbiota-gut-brain axis affects the pathogenesis of Parkinson's disease; and (iii) highlight the potential strategies for implementing microbial therapy to treat Parkinson's disease.

Alterations to gut microbiota in Parkinson's disease

Composition and characteristics of gut microbiota in Parkinson's disease

A microbiome is a general collection of microorganisms (including bacteria, archaea and lower eukaryotes) that exists in a particular environment such as the gastrointestinal tract.[16] The human gastrointestinal tract contains a rich variety of microbial communities, gathering more than 100 trillion microorganisms. A healthy host–microbial balance is very important, as it affects metabolic and immune function, while being closely associated with the development of disease.[17–19] The gut microbiota consists of several types of microorganism, including bacteria, yeasts and viruses. The main phyla of the gut microbiota in humans are Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria and Verrucomicrobia, where Firmicutes phyla and Bacteroidetes phyla account for 90% of the microbial population.[18] In healthy individuals, the link between the host and the gut microbiota is mutually beneficial, and the association may be destroyed by pathogens, viruses, fungi and other parasites. The gut microbiota is affected by delivery type, feeding mode, antibiotics, environment, gestational age and age.[20] Comparing the differences in faecal microbiota among breast-fed, formula-fed and mixed-fed infants, the study showed that the levels of Bacteroides and Actinobacteria were significantly decreased in formula-fed infants,[21] but the abundance of Enterobacteriaceae in formula-fed infants was higher than that in the other two groups at the family level.

Gut microbial dysbiosis, the alteration in the structure and/or changes in function of the gut microbiota, is related to a variety of diseases, including metabolic, gastrointestinal, autoimmune and nervous system diseases and asthma.[22] The peripheral signals from the gastrointestinal tract, including the microbiota, can promote the pathological changes in the CNS in Parkinson's disease. In recent years, several studies have investigated the composition of gut microbiota in patients with Parkinson's disease compared with healthy subjects and discovered that there were significant differences in the α-diversity and/or β-diversity in patients with Parkinson's disease.[23–25] However, the relative abundance of microbiota is inconsistently related to disease progression, possibly due to differences in methodology.[26] Li *et al.*[27] observed that the microbiota differs with Parkinson's disease progression, indicating that the characteristic gut microbiota varies markedly in different stages of the disease.[27] Studies on the alterations of gut microbiota in patients with Parkinson's disease in recent years are summarized in Table 1.

Recent studies have disclosed a decreased abundance of Prevotellaceae and Lachnospraceae families (including the genus *Roseburia*), along with an increase in the Verrucomicrobiaceae family (including the genus *Akkermansia*) and Lactobacillaceae family.[23,24,26,28–38] Prevotellaceae is a commensal mucin-degrading intestinal bacterium that is involved in the formation of intestinal mucus and affects the normal production of short-chain fatty

Table 1 Differences in bacterial taxa of family between healthy controls and Parkinson's disease patients

Research	Prevotellaceae	Lactobacillaceae	Verrucomicrobiaceae	Lachnospiraceae	Bifidobacteriaceae	Enterobacteriaceae	Pasteurellaceae	Enterococcaceae	Christensenellaceae
Keshavarzian et al.[28]		↑	↑						
Scheperjans et al.[29]	↓	↑	↑	↑					
Unger et al.[30]	↓	↑	↑			↑		→	
Bedarf et al.[31]	↓		↑						
Hill-Burns et al.[32]		↑	↑	↑	↑	↑	↑	↑	↑
Hopfner et al.[33]		↑	↑			↑		↑	
Li et al.[27]									
Heintz-Buschart et al.[34]		↑	↑		↑	↑			
Lin et al.[35]				↑	↑		↑		
Aho et al.[26]	↓	↑							
Barichella et al.[23]		↑	↑	↑	↑	↑		↑	↑
Gorecki et al.[36]		→	↑	↑					
Li et al.[24]	↓		↑	↑			↑		
Li et al.[37]		↑		↑					↑
Pietrucci et al.[38]			↑	↑		↑		↑	

↑ = a significantly increased abundance of gut microbiota at family level; ↓ = a significantly decreased abundance of gut microbiota at family level.

acids (SCFAs) through fibre fermentation. Reduced levels of intestinal mucus and the production of microbe-derived SCFAs may therefore be a mechanism by which the host experiences increased intestinal permeability, resulting in an increased risk of local inflammation across the intestinal canal.[37,39] Interestingly, Prevotellaceae has been suggested to play a possible protective role in the neurodegenerative process of Parkinson's disease via mucin synthesis and ghrelin secretion.[29,40] Intriguingly, the increase in Lactobacillaceae and decrease in Prevotellaceae are related to the decrease in the gastrointestinal hormone ghrelin, which can maintain and protect the normal dopamine function of the substantia nigra and striatum by changing mitochondrial respiration and reactive oxygen species production.[41] In the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model, ghrelin has a protective effect on dopaminergic neurons by inhibiting the accumulation and phosphorylation of α-synuclein, promoting autophagy and inhibiting endoplasmic reticulum-mediated apoptosis.[42] In addition, in a clinical study, the total and active levels of plasma ghrelin decreased in patients with Parkinson's disease, indicating that the level of plasma ghrelin may be a target for the diagnosis and treatment of the disease.[43]

Akkermansia utilize mucin as a source of energy and may therefore reduce barrier function and increase exposure to more microbial substrates across the epithelial lining.[44] *Akkermansia muciniphila* may also have beneficial effects on metabolic disorders in obese mice as well as metabolic syndrome lipid metabolism.[45] Campos-Peña et al.[46] reported that metabolic syndrome, including insulin resistance and obesity, is an essential risk factor for cognitive impairment and dementia disorders.[46] Recently, Ou et al.[47] suggested that *A. muciniphila* may improve the insulin resistance of Alzheimer's disease mice, reduce the decrease in colonic mucous cells, improve intestinal barrier dysfunction and dyslipidaemia, and delay pathological changes in the brain, indicating that there is a close connection between gut microbiota and neurological disorders; therefore, microbial intervention could provide a novel strategy for the prevention and treatment of Alzheimer's disease.[47]

Most clinical studies use intestinal faecal samples and 16S rRNA-based sequencing to evaluate the structure of gut microbiota, while one study by Bedarf et al.[31] used metagenomics shotgun analyses to allow detection of changes in species levels and to reduce viral loads in patients with Parkinson's disease.[31] The study findings vary due to differences in methodology, geographical regions, age and dietary habits. There were also differences in the composition of microbiota between faecal samples and sigmoid mucosa samples in patients with Parkinson's disease.[28] Some studies suggested that there was no significant difference in the amount of microbiota in the nasal cavity of patients with Parkinson's disease, but the nasal microbiota exhibited a higher variability in different individuals.[34] There was a strong correlation between the alterations in oral-specific microbial taxa and functional indexes in patients with Parkinson's disease.[48]

The results of the studies on animal models of Parkinson's disease are similar to those in humans. A study on the composition of caecal mucosa-associated and luminal microbiota in rotenone-induced Parkinson's disease mice showed that in the caecal mucosa, the relative abundance of the phyla Bacteroidetes and Firmicutes significantly increased in the experimental group, whereas the relative abundance of Actinobacteria and beneficial symbiotic bacteria Bifidobacterium significantly decreased.[49] A decreased abundance of mucin-degrading Verrucomicrobiae was found in a human α-synuclein overexpressing mouse model.[36] Intriguingly, the abundance of some gut microbiota increased in mice that were colonized by the faeces of patients with Parkinson's disease, including *Proteus* sp., *Bilophila* sp. and *Roseburia* sp., with a decrease in the Lachnospiracae,

Rikenellae, Peptostreptococacae and *Butyricicoccus* sp.[50] In addition, Lai *et al.*[51] discovered that the gut microbiota of the MPTP-induced model was significantly altered, especially in the Lachnospiraceae, Erysipelotrichaceae, Prevotellaceae, Clostridiales, Erysipelotrichales and Proteobacteria.[51]

Several lines of evidence in recent studies have shown that the composition of gut microbiota is affected by antibiotics, leading to the imbalance of host immune homeostasis and increased susceptibility to disease. Antibiotics may also influence the growth and colonization of bacteria in the gastrointestinal tract. Most antibiotics interfere with the composition and enzyme activity of the intestinal microbiota and inhibit enzyme activity.[52] For example, Dethlefsen and Relman[53] examined the effect of ciprofloxacin on human distal intestinal microbiota and found a decrease in bacterial diversity and a significant change in microbiota composition within a 3–4-day treatment, after which it began to return incompletely to the initial state.[53] Another study analysed the alteration of gut microbiota in 12 healthy males treated with 4-day antibiotic intervention and found that the composition of gut microbiota returned to initial baseline within 1.5 months.[54] Thus, the duration and recovery time of the alterations in gut microbiota caused by antibiotics seem uncertain. Antibiotic administration in specific pathogen-free mice temporarily altered the composition of the microbiota with a significant increase in Firmicutes and Actinobacteria and a decrease in Bacteroidetes and Proteobacteria and increased exploratory behaviour.[55] In addition, by investigating the effect of early antibiotics on intestinal microbiota, a study revealed that the composition of intestinal microbiota changed significantly and the metabolism of SCFAs was altered after treatment with subtherapeutic antibiotic therapy.[56]

In summary, the abundance of gut microbiota in patients with Parkinson's disease is significantly altered and has obvious characteristics, which may be used as potential biomarkers or therapeutic targets. However, due to differences in research methods, living environments and individuals and the time points and types of altered gut microbiota, the specific mechanisms have not been clearly elucidated.

Clinical correlations between gut microbiota and Parkinson's disease

In recent years, clinical evidence has demonstrated the relationship between gut microbiota, clinical symptoms (including motor and non-motor symptoms) and disease stage in Parkinson's disease. The correlation between microbiota and the diagnosis of Parkinson's disease has been extended to the association with motor symptoms.[29] Recent studies on the clinical correlations between gut microbiota and Parkinson's disease are summarized in Table 2. Investigators have shown that the gut microbiota is significantly related to the duration,[28,35] onset time,[35] and motor and non-motor symptoms[23,25,29,34,40] of Parkinson's disease. There were also differences found in gut microbiota among different clinical motor phenotypes.[35] Minato *et al.*[57] investigated the relationship between intestinal disorders and disease progression through a 2-year follow-up of patients with Parkinson's disease and found that the decreased abundance of Bifidobacterium and *Bacteroides fragilis* was related to the deterioration of the Unified Parkinson's Disease Rating Scale (UPDRS)-I score, suggesting that the gut microbiota may be seriously influenced by disease progression.[57] Most studies only recorded the eating habits of participants and did not provide details on dietary habits. Because of the different dietary structures in different countries and regions, the composition of gut microbiota is also different. Non-motor symptoms such as gastrointestinal dysfunction, depression and anxiety may interact with gut microbiota to play a crucial role in the microbiota-gut-brain axis in Parkinson's disease. Patients with Parkinson's disease and irritable bowel syndrome-like symptoms (abdominal pain) had more non-motor symptoms, along with lower levels of Prevotella (genus and family), indicating that the gut microbiota of these patients has the potential to become a reference for exploring the gut microbiota associated with premotor symptoms in Parkinson's disease as biomarkers or therapeutic targets.[58]

Gastrointestinal dysfunction may be closely interrelated to small intestinal bacterial overgrowth and gastrointestinal *Helicobacter pylori* colonization.[59] Small intestinal bacterial overgrowth is characterized by an increased number and/or irregular type of bacteria in the small intestine and is related to symptoms including diarrhoea, flatulence, abdominal pain and abdominal distension.[60] Recently, the positive rate of small intestinal bacterial overgrowth in patients with Parkinson's disease was found to be significantly increased, and it was associated with the deterioration of gastrointestinal symptoms and motor function.[61] Another clinical study observed that small intestinal bacterial overgrowth was significantly associated with severe defecatory fluctuations, which can be attributed to peripheral factors, including changes in levodopa pharmacokinetics.[62] Since levodopa is mainly absorbed in the jejunum, small intestinal bacterial overgrowth may reduce drug absorption through intestinal mucosal inflammation or cause alterations in the metabolism of levodopa by bacteria in the lumen. In addition, antibiotics (rifaximin) can alleviate the gastrointestinal symptoms and motor fluctuations

Table 2 Research studies on the clinical correlations between gut microbiota and Parkinson's disease

Research	Gut microbiota	Clinical correlations
Keshavarzian *et al.*[28]	Lachnospiraceae ↓	Disease duration
Scheperjans *et al.*[29]	Prevotellaceae ↓	UPDRS Part III total score
Heintz-Buschart *et al.*[34]	*Anaerotruncus* sp., *Clostridium* XIVa, Lachnospiracae ↑	Motor symptoms
Lin *et al.*[35]	Pasteurellaceae ↑	Early onset
Qian *et al.*[25]	Bifidobacterium ↓	HAMD(Hamilton Depression Scale)scores
	Genera *Butyricicoccus*, *Clostridium* XlVb ↑	Cognitive impairment
	Genera *Escherichia/Shigella*↑	Disease duration
Barichella *et al.*[23]	Lactobacillaceae ↑	Motor symptoms (UPDRS Part III total score)
	Christensenellaceae ↑	NMS Quest total score
	Lachnospiraceae ↓	Gait disturbances
Pietrucci *et al.*[38]	Enterobacteriaceae ↑	Disease severity and motor impairment
	Lachnospiraceae ↓	

↑ = a positive correlation between the microbiota and symptoms; ↓ = a positive correlation between the microbiota and symptoms. HAMD = Hamilton Depression Scale; NMS Quest = Non-motor Symptoms Questionnaire; UPDRS = Unified Parkinson's Disease Rating Scale

caused by small intestinal bacterial overgrowth, illustrating the importance of correcting it.[62]

In summary, changes in gut microbiota composition are associated with the occurrence and development of Parkinson's disease. However, most studies have been cross-sectional, involving different selected populations and research methods, with no data on the relationship between the composition of specific gut microbiota and disease progression. Longitudinal cohort studies to investigate the alteration of gut microbiota in different stages of the disease will provide additional insights.

The microbiota-gut-brain axis mediates Parkinson's disease pathology

Composition of the microbiota-gut-brain axis

Although studies suggest that the microbiota is associated with the pathogenesis of Parkinson's disease, the specific mechanisms have not fully been elucidated. Changes in bidirectional microbiota-gut-brain interactions are associated with many diseases such as irritable bowel syndrome, autism spectrum disorder and Alzheimer's disease.[63–65] The bidirectional communication between the CNS and enteric nervous system, known as the gut-brain axis, provides a way for microbiota to mediate brain lesions. The microbiota-gut-brain axis consists of several components of the nervous system, including the CNS, the autonomic nervous system, the enteric nervous system and the hypothalamic-pituitary-adrenal axis. The autonomic nervous system receives afferent signals from the gastrointestinal tract and then passes them along to the CNS through the spinal cord and vagus nerve pathway and also transmits signals from the CNS to the enteric nervous system.[66,67] Physiologically, gastrointestinal motility, glandular secretion, epithelial barriers and other digestive system functions are controlled by the autonomic nervous system.[68] Additionally, the CNS regulates the gastrointestinal tract and enteric nervous system through the sympathetic and parasympathetic branches of the autonomic nervous system and the hypothalamic-pituitary-adrenal axis, which can indirectly affect the gut microbiota by changing the gut environment and releasing signal molecules. A schematic overview of the microbiota-gut-brain axis in Parkinson's disease is shown in Fig. 1.

The enteric nervous system is a relay station between the gut microbiota and brain and is one of the three branches of the autonomic nervous system (sympathetic, parasympathetic and enteric).[69] Unlike the CNS, the enteric nervous system is made up of different neural networks in the intestinal wall, where individual small ganglia are connected by dense bundles of fibres.[70] The human enteric nervous system is composed of the myenteric plexus (Auerbach's plexus), submucosal plexus and enteric glial cells (EGCs). The submucosal plexus is subdivided into three independent plexuses: the inner submucosal plexus (Meissner's plexus) below the mucosal muscle layer; the outer submucosal plexus (Schabadasch's or Henle's plexus) adjacent to the annular muscle layer; and the intermediate plexus between them.[71] The myenteric plexus regulates muscle activity, while the submucosal plexus participates in mucosal function. Nevertheless, this is not followed strictly, because some neurons in the outer submucosal plexus innervate the circular muscle, while the neurons in the myenteric plexus of the human ileum project to the mucosa.[71] EGCs are smaller than neurons and have numerous glial filaments and processes of different shapes and sizes. The markers of mature EGCs consist of glial fibrillary acidic protein (GFAP), S100 calcium binding protein β (S100B), glutamine synthetase and brain fatty acid binding protein.[72] In the enteric nervous system, EGCs are essential to the development, normal survival
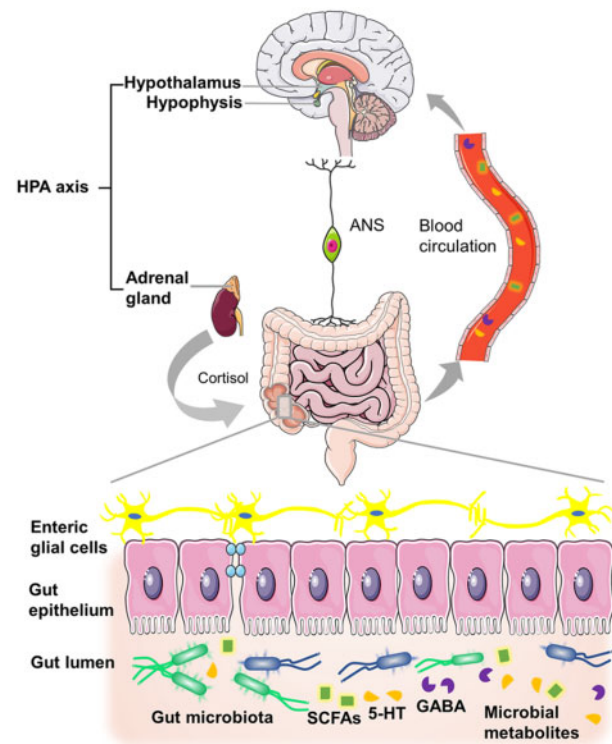

Figure 1 A schematic overview of microbiota-gut-brain axis in Parkinson's disease. In the enteric nervous system, the gut microbiota modulates brain function by releasing various signal molecules, which may enter the systemic circulation and reach target sites. The CNS physiologically dominates the gastrointestinal tract via the autonomic nervous system (ANS) hypothalamic-pituitary-adrenal (HPA) axis; in turn, the gut gives feedback to the brain to build bidirectional communication. Drawings were modified from Servier Medical Art, licensed under a Creative Commons Attribution 3.0 Unported License.

and differentiation of neurons, and glial-derived neurotrophic factor (GDNF) plays a fundamental role in maintaining the intestinal epithelial barrier.[73]

Importantly, the enteric nervous system is affected by microbiota regulation of intestinal movement and function. The average number and density of mucosal EGCs in germ-free mice is significantly decreased, but the EGC network was restored by intragastric administration of conventional intestinal microbiota, indicating that the normal development of the intestinal mucosal EGC network depends on gut microbiota.[74] In fact, gut microbiota can send a variety of signals to the host to affect the function of the enteric nervous system through intestinal Toll-like receptors (TLRs) and microbial metabolites, including SCFAs, metabolites of bile acids and neuroactive substances like GABA, tryptophan precursors and metabolites, and 5-hydroxytryptamine (5-HT).[30,75–79] Microbial metabolism and the associated metabolites regulate the homeostasis of the gut and affect the development of the CNS and Parkinson's disease by regulating the intestinal barrier, drug interactions, neurotrophic factors and the immune response. For instance, some bacterial strains can change the level of neurotransmitter precursors in the intestinal cavity and can even synthesize or regulate neurotransmitters.[80] Concentrations of norepinephrine, dopamine and 5-HT in the striatum of germ-free mice were significantly increased compared to those of specific pathogen-free mice with normal gut microbiota.[81] As a result, the regulation of intestinal transmitters such as 5-HT, melatonin, GABA, histamine and acetylcholine is a possible mechanism mediating the role of gut microbiota.

Immunity and inflammation

Peripheral inflammation, infection and Parkinson's disease pathology

Research findings have suggested that both innate immunity and adaptive immunity are dysregulated in neurodegenerative diseases, especially in Parkinson's disease.[82,83] Peripheral monocytes have been shown to enhance phagocytosis in autologous serum of patients with Parkinson's disease, supporting the involvement of innate immunity.[84] Overexpression of α-synuclein promoted pro-inflammatory C-C chemokine receptor type 2 (CCR2)-positive peripheral monocyte entry into the CNS in a mouse model of Parkinson's disease, and deletion of CCR2 could prevent monocyte infiltration, α-synuclein mediated inflammation and subsequent dopaminergic neuronal death.[85] These findings support the hypothesis that peripheral derived cells may play an essential role in neuroinflammation and neurodegeneration in Parkinson's disease.

A recent study reported an increased number of T cells in post-mortem midbrains of Parkinson's disease, and T cells induced neuronal death via interleukin (IL)-17 and NF-κB activation in human induced pluripotent stem cell-derived midbrain neurons from patients with Parkinson's disease.[86] Other authors have demonstrated that cytotoxic CD8⁺ T cell infiltration occurred earlier than α-synuclein aggregation and neuronal death, suggesting adaptive immune system involvement.[87] In an α-synuclein transgenic mouse model, infiltration of CD3⁺/CD4⁺ helper T (Th) cells was increased in the brain (in close proximity to astrocytes and microglia) and this was accompanied by glial activation and enhanced expression of tumour necrosis factor (TNF) genes.[88] This suggests that infiltrating peripheral adaptive immune cells are involved in activating resident immune cells in the brain, thus enhancing neuroinflammation.[88] In addition, Th17 cells, a subset of CD4⁺ T lymphocytes, have been shown to infiltrate into the substantia nigra in an MPTP-induced mouse model. In a cell model of Parkinson's disease, Th17 cells exacerbated dopaminergic neuron death and glial activation, which was dependent on interaction with LFA-1/ICAM1.[89] Intriguingly, T cell deficiency can decrease the loss of dopamine neurons and microglial major histocompatibility complex II expression.[90] Astrocytes have been found to express co-stimulatory molecules that are necessary to activate CD4⁺ T cells.[91,92] Although disruption of the blood–brain barrier (BBB) may provide a pathway for peripheral immune cell infiltration, leading to CNS inflammation and neuron death,[93] it remains unclear whether the peripheral immune response is the cause or a result of CNS pathology.

T cells can recognize certain α-synuclein antigenic epitopes, and this is largely mediated by CD4⁺ T cells and CD8⁺ T cells in patients with Parkinson's disease.[94] A strong CD4⁺ T cell response to α-synuclein epitopes can be detected before the onset and diagnosis of Parkinson's disease.[95] The level of autoantibodies to α-synuclein has been found to be significantly increased in CSF and associated with impaired cognition in patients with Parkinson's disease.[96] These findings suggest that autoimmunity may play a role in the pathogenesis of Parkinson's disease, although it is unclear yet whether α-synuclein antibodies are pathogenic. Genome-wide association studies have alluded to a significant genetic overlap between Parkinson's disease and autoimmune diseases.[97] Studies have shown that patients with inflammatory bowel diseases have a higher risk of Parkinson's disease. In addition, inflammatory bowel diseases and Parkinson's disease share some common genetic factors.[98] In autoimmune conditions, peripheral inflammation caused by gut inflammation may trigger α-synuclein aggregation, increasing the permeability of intestinal tract and BBB and leading to neuroinflammation.[98] In a rotenone-induced Parkinson's disease mouse model, stress aggravated intestinal hyperpermeability and caused alterations to gut microbiota and inflammation in the colon as well as increased neuroinflammation in the brain.[99] *Porphyromonas gingivalis*-induced peripheral inflammation altered the gut microbiota, increased gut permeability and microglial activation and reduced dopaminergic neurons in the substantia nigra in a genetic mouse model of Parkinson's disease.[100] In another mouse model, the peripheral injection of lipopolysaccharide (LPS) increased the expression of proinflammatory cytokines in the brain and microglia activation in the substantia nigra via the NLRP3-IL-1β signalling pathway, resulting in neurodegeneration.[101] The NLRP3 inflammasome has been found to play a critical role in microbiota-mediated intestinal/peripheral inflammation and neuroinflammation in CNS diseases.[102] Previous evidence has indicated that systemic inflammation can increase the reactive oxygen species, activation of microglia and degeneration of dopaminergic neurons in the brain through peripheral inflammatory factors.[103,104] Another study revealed that the numbers of circulating lymphocytes and neutrophils were decreased with the increased plasma levels of proinflammatory cytokines after LPS injection in a 6-hydroxydopamine (6-OHDA) rat model compared with controls, suggesting that peripheral immune disorder was involved in neurodegeneration associated with Parkinson's disease.[105] In addition, lipoteichoic acid from *Bacillus subtilis* increased plasma levels of proinflammatory cytokines and caused BBB dysfunction, contributing to peripheral inflammation and neuroinflammation.[106] In a mouse model, it was found that gastric infection by *Helicobacter suis* resulted in gastric inflammation and increased gastrointestinal permeability, accompanied by an increased level of proinflammatory cytokines in serum, which was associated with systemic inflammation.[107] Additionally, this study showed inflammation at the choroid plexus, increased blood–CSF barrier permeability with subsequent neuroinflammation and activation of microglia in the brain, indicating that peripheral infection can lead to neuroinflammation in the brain via disruption of the blood–CSF barrier and systemic immune response.[107] In summary, these findings suggest that peripheral inflammation, including gut microbiota-induced intestinal inflammation, can induce systemic and CNS inflammation.

Microbiota, enteric nervous system inflammation and α-synuclein

Microbiota can mediate enteric nervous system inflammation. The gastrointestinal tract provides a place for microbiota to grow and function. The intestinal mucosa, composed of monolayer intestinal epithelial cells, provides physical and chemical barriers to protect the intestine and peripheral organs from symbiotic or pathogenic microbiota. Intestinal epithelial cells regulate the diversity and function of the gut microbiota; in turn, gut microbiota are crucial to the growth and function of these cells.[108] The gut microbiota plays a vital part in the occurrence and development of colitis induced by dextran sulphate sodium, and the lack of gut microbiota significantly reduces colitis.[109] As shown in recent studies, there are inflammatory responses in the colonic tissues of patients with Parkinson's disease and animal models, including the elevation of proinflammatory cytokines and chemokines such as TNF, IL-1β, IL-17, interferon-gamma (IFN-γ) and IL-6, as well as ECG-reactive proliferation and inflammatory cell activation.[51,77,110–113] Similarly, Schwiertz *et al.*[114] showed that calprotectin, a marker of intestinal inflammation and alpha-1-antitrypsin and zonulin, markers of intestinal barrier dysfunction, were significantly increased in patients with Parkinson's disease, which proved the hypothesis that intestinal inflammation is a contributing factor in the pathogenesis of Parkinson's disease.[114]

Additionally, Keshavarzian et al.[28] observed that the putative proinflammatory bacteria *Ralstonia* in the intestinal mucosa of patients with Parkinson's disease were significantly abundant, and the putative proinflammatory bacteria *Akkermansia*, *Oscillospira* and *Bacteroides* were significantly increased in faecal samples.[28] Another study in Asian population observed that *Bacteroides* was associated with plasma TNF levels, while Verrucomicrobiaceae abundance was correlated with plasma IFN-γ levels, suggesting that alterations in the microbiota may be closely related to the systemic inflammatory response.[40] The decrease in *Roseburia* is a characteristic of patients with Parkinson's disease. *Roseburia* can upregulate innate immune genes, including antimicrobial peptide genes, intestinal barrier function genes, and TLR-related genes such as TLR5 to enhance intestinal barrier function and reduce intestinal inflammation. In addition, *Roseburia* has a negative regulatory effect on the NF-κB pathway, promoting immune homeostasis by downregulating this inflammatory cascade.[115] Therefore, gut microbiota and its metabolites may be involved in the pathophysiology of Parkinson's disease through

intestinal inflammation, and the proinflammatory intestinal environment may trigger the pathogenesis of Parkinson's disease.[116] Figure 2 highlights a potential inflammatory mechanism of the microbiota-gut-brain in Parkinson's disease.

TLRs, a type of pattern recognition receptor, can recognize molecules of microbial origin, which are called microbiota-associated molecular patterns. Currently, 13 types of TLRs have been reported in mammals, among which TLR2 and TLR4 are expressed at low levels in the human colon, with high expression of TLR3 in the small intestine and colon while TLR5 is mainly expressed in the colon.[117] In particular, TLR2 is expressed in enteric neurons, glial cells and smooth muscle cells of the intestinal wall.[118] Researchers observed that *TLR2* gene-deficient (*Tlr2⁻/⁻*) mice had significantly reduced enteric neurons and glial cells and showed stronger colonic inflammation in response to external stimulation.[118] The increased expression of TLRs can increase the permeability of the intestinal epithelial barrier and increase the susceptibility of host colonic inflammation, indicating that they play a crucial role in maintaining intestinal immune homeostasis.[119,120] In the study of
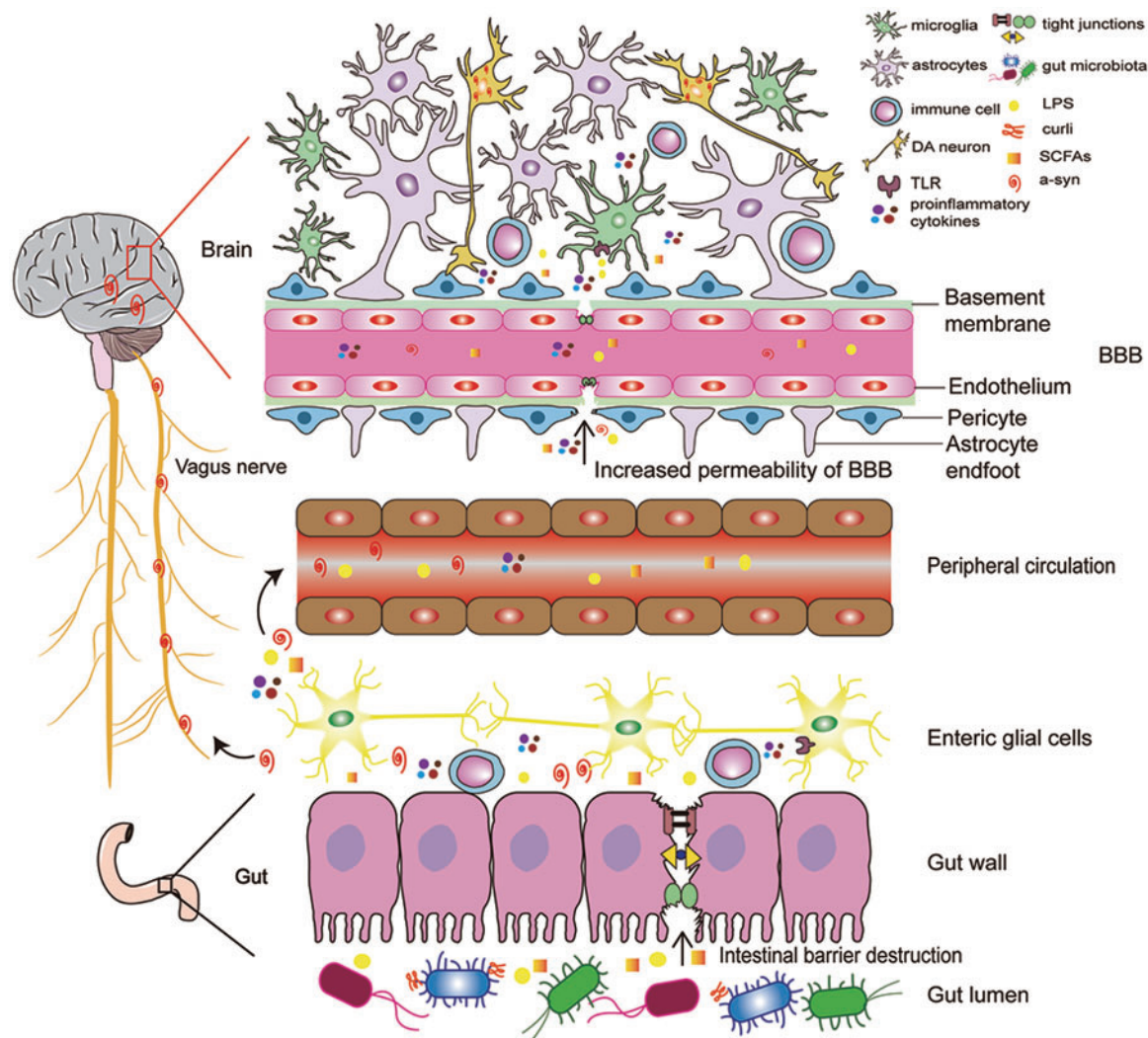
Figure 2 A potential inflammatory mechanism of microbiota-gut-brain in Parkinson's disease. Gut microbiota and their metabolites are involved in the occurrence of intestinal inflammation by regulating the integrity of the intestinal mucosal barrier by activating inflammatory cells, releasing proinflammatory factors and accumulating α-synuclein in the gut. Microbial metabolites such as LPS can also participate in intestinal inflammation and neuroinflammation through the expression of TLRs. Blood circulation and the vagus nerve provide a pathway for intestinal inflammation and the transmission of α-synuclein by which the neurotoxins produced in the gut enter the brain. The lack of BBB integrity, activation of microglia, proliferation of astrocytes and production of pro-inflammatory factors are specific manifestations of microbiota-mediated neuroinflammation. DA = dopaminergic.

intestinal biopsies from patients with Parkinson's disease, it was reported that the immune response of TLR4, cytokines and chemokines, as well as the number of CD3 + T cells, increased in the lamina propria of colonic tissue.[120] Microarray analysis of sigmoid mucosa samples illustrated that the expression of *TLR4* mRNA was significantly higher compared with that in controls. Intriguingly, *TLR4* gene knockout significantly alleviated the effects of rotenone on intestinal barrier destruction, reduced the expression of GFAP in the myenteric plexus and colonic α-synuclein aggregation, decreased microglial activation in the substantia nigra and the loss of dopaminergic cells and alleviated the impairment of motor function.[120] These findings suggest that gut microbiota may trigger immune activation of the colonic mucosa through the TLR4 signalling pathway, leading to neuroinflammation and subsequent neurodegeneration in Parkinson's disease. Faecal microbiota transplantation (FMT) can improve the metabolic disorder of gut microbiota in MPTP mice by inhibiting the TLR4/TBK1/NF-kB/TNF signalling pathway, thus reducing intestinal inflammation and neuroinflammation, verifying the mechanism of communication between the gut and the brain.[121] In addition, the increase in *Bacteroides* spp., Enterobacteriaceae and *Clostridium* in rats with acute colitis mediates the occurrence of intestinal inflammation by upregulating TLR2 and TLR4.[120] The increase in TLR4, TLR5 and the proinflammatory factor IL-6 and the decrease in the anti-inflammatory factor IL-10 in the mucosa of patients with irritable bowel syndrome were related to alterations in the gut microbiota.[122] Cytokines and chemokines related to gut microbiota or pathogen-derived products may be involved in the pathogenesis of intestinal inflammation via TLRs.[122] The gut microbiota also activated intestinal cells that produce IL-10 in MyD88/TLR2/PI3K-dependent pathways to maintain mucosal homeostasis.[123] In addition, TLR4 plays an important role in regulating enteric neuron survival and intestinal motility; moreover, by activating TLR4, the gut microbiota can regulate gastrointestinal motility.

Furthermore, similar to *Tlr2*^{−/−} mice, the wild-type mice lacking gut microbiota also have enteric nervous system and GDNF deficiencies, which can be partially repaired by administration of TLR2 agonists.[118] This research suggests that TLR2 signalling can regulate intestinal inflammation by modulating enteric nervous system structure, neurochemical coding and intestinal neuromuscular function. A recent study found that a TLR2 activator can restore the inhibition of enteric nervous system neurogenesis caused by decreased gut microbiota and modulate the structure and function of the system.[124] Additionally, the activation of TLR2 can restore intestinal neurogenesis and increase the number of nitrergic neurons in germ-free mice.[124] Intestinal longitudinal smooth muscle cells activate TLR2 and TLR5 to produce specific neurotrophic factors such as GDNF under the stimulation of bacterial pathogen-associated molecular patterns, which recognize conservative microbial products, to correct the abnormal phenotype of enteric neurons in *Tlr2*^{−/−} mice.[125] These results suggest that the gut microbiota can regulate the structure and function of the enteric nervous system through the TLR signalling pathway.

Gut microbiota mediates the aggregation of α-synuclein in the enteric nervous system. EGCs play a key role in maintaining intestinal permeability and regulating intestinal inflammation.[126] Changes in the expression and phosphorylation of intestinal GFAP were found in colon biopsies of patients with Parkinson's disease, indicating that there is reactive proliferation of EGCs in Parkinson's disease, which leads to local inflammation and may spread to the CNS.[110] EGCs may act as an entrance for enterotoxin into the CNS, especially in neurodegenerative diseases. Intestinal barrier dysfunction and increased intestinal permeability caused by inflammation in patients with Parkinson's disease provide conditions for the circulation of inflammatory factors and the exposure of the enteric nervous system to the microbiota and their harmful products.[77] Increased intestinal permeability is associated with increased bacteria and exposure to the bacterial endotoxin in Parkinson's disease, while increased intestinal α-synuclein and 3-nitrotyrosine staining (associated with oxidative stress) leads to high intestinal permeability.[127] LPS produced by gut microbiota treatment can increase the accumulation of α-synuclein in the enteric nervous system and increase intestinal permeability.[128] An increase in Gammaproteobacteria, an LPS-producing Gram-negative bacterium, was found in the faeces of patients with Parkinson's disease.[36] Moreover, LPS intervention resulted in a significant decrease in the tight junction proteins zona occludens 1 (ZO-1) and e-cadherin in intestinal epithelial cells of Thy1-α-synuclein mice, indicating that there is a relationship between gut microbiota and the pathogenesis of Parkinson's disease, thus supporting the hypothesis that α-synuclein spreads from the intestine to the CNS in the pathogenesis of Parkinson's disease.[36] In addition to LPS, gut microbiota may affect the aggregation of α-synuclein through other products or metabolites. Functional amyloid proteins are widely found in the microbiota, including *Escherichia coli*, which produce curly amyloid fibres to regulate gut and host function.[129] Microbial functional amyloids can also induce the accumulation of neuronal proteins such as A-β, α-synuclein and tau, mediating the transmission of the disease through the gut-brain axis.[130] Exposure to curli-producing bacteria increases the deposition and accumulation of α-synuclein in intestinal ganglion cells (myenteric plexus and submucosa) and the brain, respectively, as well as increasing the inflammatory response in the brain.[131] In particular, the components of the bacterial amyloid protein CsgA can accelerate the production of α-synuclein aggregation. Colonization of curli-producing *E. coli* in α-synuclein-overexpressing mice aggravated motility injury and gastrointestinal dysfunction, while promoting the accumulation and inflammatory response of α-synuclein in the intestine and brain, resulting in increased expression of the proinflammatory cytokines IL-6 and TNF in brain-derived CD11b + microglia.[132] Moreover, the increased production of cytokines in the midbrain and colon indicates that microbiota play an important role in α-synuclein production and neuroinflammation.[132]

Recently, pathological changes in α-synuclein in the enteric nervous system of Parkinson's disease patients were observed, which provided a new direction for hypotheses on the pathogenesis and pathological origin of Parkinson's disease.[133] According to Braak's hypothesis, environmental factors may start a pathological process via the olfactory bulb or the intestinal nerve plexus. Inflammation and oxidative stress are caused by swallowing nasal secretions, which leads to the accumulation of α-synuclein in the CNS.[134] The double-hit hypothesis proposed by Hawkes *et al.*[135] supports their theory, pointing out that α-synuclein pathology is transmitted to the midbrain through two different routes, namely, from the nasal cavity to the temporal lobe or from the stomach, followed by nasal secretions in swallowed saliva.[135] After penetrating the epithelium, the pathogen can enter the axon of Meissner's plexus and transmit through the synapse to the preganglionic parasympathetic motor neurons of the vagus nerve. At present, many animal experiments have observed the spread of α-synuclein pathology from the intestine to the brain along the gut-brain axis, and pathological changes in the CNS can be observed by injecting α-synuclein into the intestinal wall of the gastrointestinal tract.[136–139] Recently, using non-human primate models, investigators have observed that α-synuclein aggregated from patients with Parkinson's disease can induce nigra-striatal injury and enteric nervous system pathology after intestinal or striatal injection, indicating that α-synuclein may spread not only rostrally but also caudally, that is, from the gut to the brain and from the brain to

the gut.[140] It is suggested that the pathological process of Parkinson's disease is not limited to the brain-gut or gut-brain, but it is also possible that the pathological processes in the enteric nervous system and CNS develop separately during disease progression. In Parkinson's disease, the vagus nerve seems to play a fundamental role in the gut-brain transmission of pathological α-synuclein.[141] Vagotomy can prevent the transmission of pathological α-synuclein to the CNS in animal models.[137,138] Further study reported that vagotomy could prevent the development of Parkinson's disease symptoms in rats and inhibit the misfolding of α-synuclein in intermuscular neurons.[142] A cohort study in Denmark showed that total vagotomy can significantly reduce the risk of secondary Parkinson's disease.[143] In contrast, another study with a follow-up of patients after vagotomy argued that vagotomy was not associated with the risk of Parkinson's disease in Sweden.[144] However, the results of a 5-year follow-up indicated that the risk of Parkinson's disease was lower 5 years after vagotomy, and similar results were also observed in the 10-year follow-up after vagotomy. The possible reason is that during selective or highly selective vagotomy, α-synuclein pathology caused in other parts of the gastrointestinal tract may still find a way to the vagus nerve and then to the brainstem. Remarkably, a recent study did not find pathological damage to α-synuclein in the vagus nerve in an animal model of Parkinson's disease, which does not support the hypothesis that α-synuclein pathology is transmitted through the vagus nerve and the dorsal motor nucleus of the vagus nerve.[140] They observed that the concentration of α-synuclein in whole blood of monkeys, who received the injection of pathological α-synuclein into the enteric nervous system, was significantly higher compared to the control group and positively correlated with the immunoreactivity of α-synuclein in enteric neurons. Therefore, they proposed a possible mechanism by which the general circulation acts as a pathway for the long-distance bidirectional transmission of endogenous α-synuclein between the intestinal tract and CNS.

CNS inflammation

Microbiota may trigger CNS neuroinflammation. Neuroinflammation, including microglial proliferation, T cell infiltration, increased expression of inflammatory factors and glial cell activation, has been proven to be an important pathology of Parkinson's disease.[145,146] In recent years, studies have implied that gut microbiota may be involved in this process. Erny et al.[147] illustrated that germ-free animals display global deficiency in microglia and the genes needed to express type I interferon receptors such as Janus kinase 3 (Jak3) and signal transducer and activator of transcription 1 (Stat1), were reduced.[147] Additionally, major histocompatibility complex class I-related β2 microglobulin (B2m), used as a marker of early immune function of microglia, was also found to be decreased. In addition, most of the cytokines and chemokine pathways in the microglia of germ-free mice are affected, which leads to a decrease in the innate immune response, resulting in a decline in the ability to resist bacterial and viral infections.[147] The function of microglia can be restored by the reconstruction of gut microbiota or their metabolites, indicating that microbiota may also be involved in the activity of the innate immune system in the brain via microbial metabolites and intestinal secretions.[147] The decreased activation of CNS microglia and proinflammatory factors, including TNF and IL-6, was found to reduce α-synuclein aggregation and improve motor function in germ-free-α-synuclein overexpressing mice compared with specific pathogen-free-α-synuclein overexpressing mice, which suggests that the microbiota is involved in the process of neuroinflammation in Parkinson's disease mice.[50] FMT can reduce the increased

number of astrocytes, decrease the activation of microglia in the MPTP mouse model and participate in suppressing neuroinflammation by inhibiting the TLR4/TBK1/NF-KB/TNF-α signalling pathway.[121]

A clinical study revealed that the level of serum LPS-binding protein in patients with Parkinson's disease was lower than that in controls, indicating that increased intestinal permeability and increased invasion of Gram-negative bacteria leads to an increase in LPS in the circulatory system.[148] Additionally, predictive meta-genomics showed a significant increase in genes involved in endotoxin biosynthesis and the type III bacterial secretion system (associated with pathogens) in the faecal microbiome of patients with Parkinson's disease.[28] Recently, a predictive analysis of the function of gut microbiota by functional prediction analysis showed that pathways involved in the biosynthesis of LPS and LPS proteins increased in Parkinson's disease.[38] Microbial LPS has a potential effect on CNS inflammation. The peripheral inflammation induced by systemic LPS administration increased the activation of microglia and proinflammatory cytokines, destroyed the BBB, and aggravated the polarization of the A1 phenotype of astrocytes and the loss of dopamine neurons in the substantia nigra and striatum of MPTP mice.[149] The overactivation of microglia may also lead to the loss of dopaminergic neurons. Therefore, peripheral inflammation also plays a vital role in the pathogenesis of Parkinson's disease. In animal experiments, intranasal injection of LPS could activate microglia in the olfactory bulb and substantia nigra through IL-1β/IL-1R1 signalling, increase pS129 α-synuclein-positive cells in the olfactory bulb and substantia nigra and reduce the number of tyrosine hydroxylase (TH)-immunoreactive cells, suggesting the loss of dopaminergic cells.[150] Microglia are the most abundant immune cells in the brain, and they are also the first responders to bacterial or viral infection in the brain, mediating downstream immune responses activated by pathogens.[147,151] Microglia in the CNS express pattern recognition receptors such as TLRs, which respond to pathogen-associated molecular pattens and recognize invasive pathogens as immune mechanisms for host defense.[152] Excessive activation of microglia can lead to the production of inflammatory cytokines such as TNF, IL-1β, IL-6 and INF-γ, which may have harmful effects on dopaminergic neurons.[153] It has been reported that paraquat activates innate immunity via the TLR4-MyD88-dependent pathway, inducing microglial activation and inflammation. Inhibition of TLR4 can downregulate this process, indicating that this receptor plays an important role in paraquat-mediated microglial inflammation.[154,155] TLR4 gene-deficient mice partially resist MPTP toxicity by suppressing the activation of microglia in the substantia nigra.[156] A recent in vitro cell experiment revealed that TLR4 gene knockout could polarize BV-2 microglia treated with paraquat to the M1 phenotype, inhibit the expression of proinflammatory factors and reduce the migration and phagocytic activity of microglia, suggesting that TLR4 mediates the neuroinflammation of microglia.[157] TLRs are expressed not only in microglia but also in neurons.[158] The activation of neuronal TLR2 in the brains of patients with Parkinson's disease results in increased proinflammatory cytokine (TNF) levels and recruitment of microglia to amplify neuroinflammation as well as increased expression of α-synuclein.[158] Most Lewy bodies with positive immunoreactivity toward α-synuclein have strong TLR2 immunoreactivity, which confirms that there is a strong correlation between TLR2 and α-synuclein pathology in the Parkinson's disease brain.[158] Pathological α-synuclein aggravates the progression of Parkinson's disease by activating microglia, while the absence or overstimulation of microglia can affect the spread of α-synuclein in the brain.[153,159] Increased activation of TNF/TNFR1 signalling following chronic activation of microglia can give rise to TNF-mediated

necroptotic neuronal cell death,[160] which represents a possible therapeutic target in Parkinson's disease.[161]

The BBB consists of the endothelial cell layer and its basement membrane, the connected tight junction proteins and the surrounding pericytes and astroglial end feet.[162] Its function is to separate circulating blood and regulate the transport of solutes in the blood to the brain and from the brain to the blood. Dysfunction of the BBB is associated with neurodegenerative diseases.[163] The BBB was shown to be damaged in MPTP-treated mice.[89,164] Similarly, BBB damage induced by 6-OHDA is related to the loss of dopamine neurons and activated microglia.[165] Microglia have dual effects on the integrity of the BBB. In the process of systemic inflammation, microglia can migrate to cerebral vessels to regulate the integrity of the BBB due to the release of the chemokine CCL5 from endothelial cells.[166] In the early stage of inflammation, microglia form tight junctions by expressing the *CLDN5* gene (claudin-5) to maintain the integrity of the BBB, which can also help a series of toxic circulatory molecules (such as inflammatory cytokines, ions and immune cells) activate microglia and astrocytes and aggravate neuroinflammatory damage and BBB dysfunction.[166] With the development of inflammation, microglia form a phagocytic phenotype to destroy the integrity of the BBB by phagocytosis of the terminal feet of astrocytes.[166] maintain

Braniste *et al.*[167] demonstrated that BBB permeability was increased due to the destruction of tight junction structure and the low expression of transmembrane tight junction proteins (including occludin and claudin-5) in the brains of germ-free mice compared with pathogen-free mice.[167] The integrity of the BBB in germ-free mice was enhanced by transplanting faecal microbiota from the pathogen-free mice or by using microbial SCFAs, suggesting that the microbiota can regulate the function of the BBB.[167] There is an interaction between intestinal microbial metabolites and the BBB. Sodium butyrate (NaB) can improve BBB damage in Parkinson's disease mice by upregulating occludin and ZO-1 after its intragastric administration in an MPTP mouse model.[168] Propionic acid inhibits the pathways associated with non-specific microbiota infection through CD14-dependent mechanisms, inhibits the expression of LRP-1 and protects the BBB from oxidative stress through nuclear factor erythroid 2-related factor 2 (NRF2) signals.[169] In contrast, another study reported that NaB significantly increased the BBB permeability of a traumatic brain injury mouse model by increasing the expression of tight junction-related proteins (occludin and ZO-1).[170] Peripheral injection of LPS aggravated BBB damage in the substantia nigra and striatum of MPTP mice.[149] LPS may increase the blood-to-brain uptake of α-synuclein by destroying the BBB.[171] In addition, LPS affects the transport of neurotoxins by changing the expression of plasma membrane monoamine transporters on the BBB, leading to disease.[172]

Microbial metabolites
Short chain fatty acids

Intestinal SCFAs, including formic acid, acetic acid, propionic acid and butyric acid, are molecules produced in food fermented by gut microbiota.[173] Studies have found that SCFAs are associated with a variety of diseases such as rectal cancer,[174] pancreatitis,[175] abnormal energy metabolism,[176] constipation,[177] blood lipid metabolism,[178] sleep disorders[179] and Alzheimer's disease.[180] Microbial SCFAs play a key role in microbiota-gut-brain axis signal communication and are involved in immune, neural and endocrine gut-brain axis communication to mediate the occurrence of disease.[181] However, in the gut-brain axis of Parkinson's disease, the specific mechanism of SCFAs remains unknown. The faecal microbiota of patients with Parkinson's disease shows a decrease in the production of SCFAs or their producing microbiota in most clinical studies.[28,30,37,77,182] A similar study confirmed the overabundance of opportunistic pathogens in the gut microbiota of patients with Parkinson's disease with reduced levels of SCFA-producing bacteria and/or increased levels of carbohydrate metabolites.[183] The decrease in SCFAs may promote intestinal inflammation and greatly increase the risk of α-synuclein deposition in the gastrointestinal tract.[27] However, several studies have revealed that butyric acid in faecal samples significantly increased compared to the control group in an MPTP-induced mouse model.[121,184] Microbial SCFAs modulate Parkinson's disease via the microbiota-gut-brain axis, as shown in Fig. 3.

SCFAs play a crucial role in intestinal inflammation and intestinal barrier function. In a mouse model of intestinal inflammation, the amount of inflammation was found to be negatively correlated with the total concentration of SCFAs and butyrate.[185] The intervention of acetate could alleviate inflammation in a dextran sulphate sodium-induced colitis mouse model, reduce the proinflammatory factors TNF-α and IL-17 in colon tissue and increase the anti-inflammatory factor IL-10 but had no significant effect on $Ffar2^{-/-}$ (GPR43-deficient) mice, suggesting that SCFAs may be located in GPR43 and affect the immune response.[186] Furthermore, acetate can inhibit the production of TNF-α by LPS-stimulated mononuclear cells.[186] SCFAs could regulate the size and function of the colonic regulatory T cell (cTreg) pool in mice and protect mice from colitis in a *Ffar2* (the gene that encodes GPR43)-dependent manner, and cTregs regulate colonic homeostasis and control inflammation by limiting the proliferation of CD4 T cells, indicating that microbial metabolites modulate adaptive immunity and contribute to maintaining gut and host homeostasis.[187] Arpaia *et al.*[188] reported that propionic acid and butyric acid in the faeces of germ-free mice and microbiota-deficient mice treated with a broad-spectrum antibiotic intervention were significantly decreased compared with specific pathogen-free animals, while commensal bacteria produced butyrate and propionate could promote the differentiation of extrathymic CNS1-dependent Treg cells and participate in the regulation of inflammation.[188] Butyrate can also promote the production of IL-10 by regulating the differentiation of Th1 and Th17 cells and inducing the expression of mature protein 1 (Blimp1), ameliorating colonic inflammation and maintaining intestinal homeostasis.[189] IL-10 is an important anti-inflammatory cytokine that plays an essential role in regulating intestinal homeostasis and inhibiting intestinal inflammation. In addition, butyrate intervention can reduce the level of endotoxin in faeces and serum to suppress inflammation.[190] The destruction of the intestinal barrier provides an entrance for intestinal pathogenic microbiota, and SCFAs serve important function in the maintenance of intestinal barrier function. Butyrate can protect cells from increased paracellular permeability and destruction of the epithelial barrier by LPS, increase the expression of tight junction claudins by activating the Akt/mTOR signalling pathway and downregulate the expression of TLR4 to decrease the expression of the inflammatory cytokines.[191] In addition, the protective role of SCFAs on intestinal barrier function is also shown in colonic oxygen metabolism. Butyrate protects intestinal barrier function by maintaining hypoxia inducible factor, a transcription factor that coordinates intestinal barrier protection.[192] Nevertheless, several studies have indicated that a higher concentration of SCFAs in faeces is associated with a lower diversity of gut microbiota, higher intestinal permeability (measuring plasma LPS-binding protein), obesity and cardiac metabolic disorders.[193]

SCFAs may be able to modulate neuroinflammation in Parkinson's disease. NaB, as a histone deacetylase inhibitor
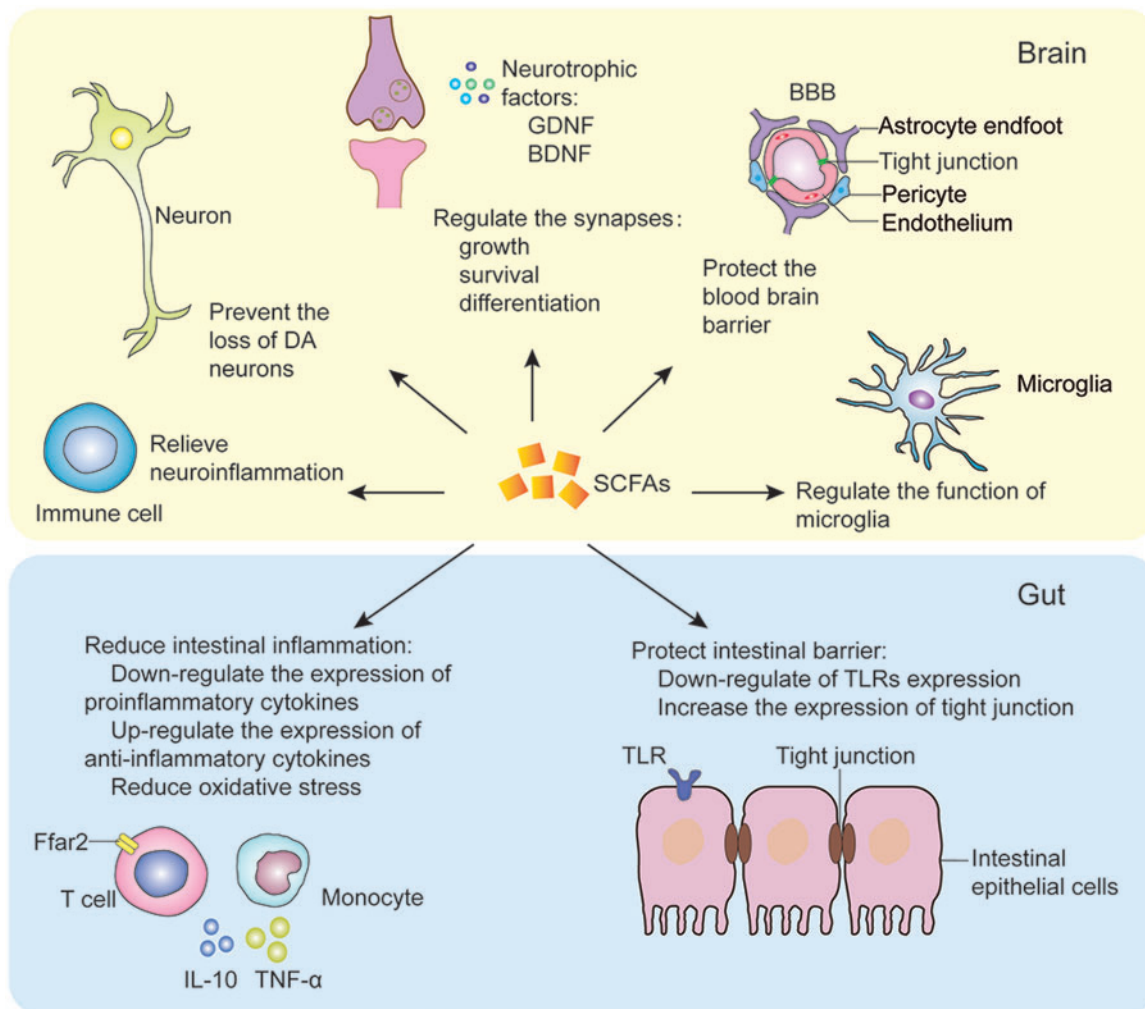
Figure 3 A potential mechanism of SCFA involvement in the gut-brain axis in Parkinson's disease. Microbial metabolite SCFAs can directly or indirectly affect intestinal and brain function in Parkinson's disease. SCFAs can reduce intestinal inflammation by regulating the release of inflammatory factors and protecting the intestine from inflammation in a Ffar2-dependent manner. In addition, SCFAs regulate the tight junction between intestinal epithelial cells to maintain the integrity of the intestinal barrier. In the brain, SCFAs play an essential role in the growth and differentiation of synapses and neurons via the release of neurotrophic factors. SCFAs also reduce neuroinflammation, inhibit the activation of microglia and protect the BBB in Parkinson's disease. DA = dopmainergic.

(HDACi), can reduce the degeneration of dopaminergic neurons and improve dyskinesia in a rotenone-induced *Drosophila* Parkinson's disease model.[194] Furthermore, HDAC-knockout *Drosophila melanogaster* is resistant to rotenone-induced motor injury and early death.[194] SCFAs play a crucial role in regulating dopamine neuron loss, the CNS inflammatory response, microglial function and neurotrophic factor production. NaB can regulate apoptosis-related proteins (Bcl-2 and Bax) in the brains of Parkinson's disease mice to reduce neuronal apoptosis.[168] In a 6-OHDA rat model, NaB reduced oxidative stress, decreased the level of the proinflammatory cytokine TNF, increased BDNF and H3 histone acetylation, rescued the decrease in dopamine levels and prevented neuronal loss and neuronal pyknosis in the striatum.[195] NaB can also reduce α-synuclein-induced DNA damage in a dopaminergic neuronal model by upregulating the genes involved in DNA repair.[196] A recent study on the effect of propionate on rotenone-treated dopaminergic neurons showed that the survival rate of TH+ dopaminergic neurons increased significantly, indicating that propionic acid increased the expression of the *TH* gene, decreased the expression of the α-synuclein gene, and increased the expression of intracellular STAT3 protein to

promote neuroprotection.[197] In addition, SCFAs from intestinal microbiota are key molecules regulating the maturation, morphology and function of microglia.[147] Microglial defects in germ-free mice are reversible and can be reconstructed by reintroducing microbial metabolites such as SCFAs.[147] Using human THP-1 monocytic cells and differentiated human HL-60 myelomonocytic cells to simulate the selective immune function of human microglia, Wenzel *et al.*[198] found that single or mixed use of SCFAs could inhibit the secretion of IL-1β, monocyte chemoattractant protein-1 and TNF by stimulated human THP-1 microglia-like cells.[198] Formate and valerate significantly decreased the phagocytosis of stimulated human THP-1 microglia-like cells and the production of reactive oxygen species.[198] These results suggested that SCFAs can regulate the homeostasis of neuroinflammation by regulating the function of damaged microglia. Neurotrophic factors including nerve growth factor, GDNF and BDNF can regulate the growth, survival and differentiation of neurons and synapses in the CNS and play an important role in learning and memory ability.[199,200] NaB attenuated MPTP-induced neuronal loss in the nigral striatal pathway and prevented activation of astrocytes and microglia by upregulating BDNF and GDNF.[201] Lai *et al.*[202] found the protective

effect of valproic acid on dopaminergic neurons in the substantia nigra after injection of 6-OHDA, and the BDNF levels in the striatum and substantia nigra of rats treated with valproic acid were also significantly increased compared with levels in the control group.[202] Moreover, a study also revealed that NaB increased the number of cells expressing BDNF in different brain regions after cerebral ischaemia.[203] Most studies found that SCFAs have beneficial effects on Parkinson's disease by reducing oxidative stress, anti-inflammation and neuroprotection. However, some studies showed that the increase in SCFA levels was related to the pathophysiology of Parkinson's disease mice and led to neuroinflammation.[50] In summary, SCFAs seem to play a protective role in Parkinson's disease, but the specific mechanism remains to be explored.

Bile acids

Bile acids are metabolites produced by cholesterol in the liver, which are further metabolized by gut microbiota to unconjugated, secondary and tertiary bile acids in the intestine. In recent years, it has been found that there is an important bidirectional relationship between intestinal microbiota and bile acids. Bacteria can regulate the composition of bile acids in the lumen, and intestinal microbiota can produce different kinds and quantities of bile acid derivatives; in turn, bile acids have an effect on the survival and growth of microbiota, which is vital to human health and disease.[204–206]

Gut microbiota and metabolite bile acids may interact in the intestinal tract and affect immunity. Cholic acid treatment can alter the balance of gut bacterial phyla in rats, by increasing Firmicutes and decreasing Bacteroidetes.[207] Bile acids can, moreover, eliminate bacterial overgrowth and reduce bacterial translocation and endotoxemia.[208] The activation of the bile acid receptor FXR (farnesoid X receptor) can protect the distal small intestine from the proliferation of bacteria and their harmful effects, while maintaining the integrity of the epithelial barrier.[209] In dextran sulphate sodium-induced colitis mice, bile acids can increase the number of RAR-related orphan receptor γ + Treg cells in the intestine and reduce the symptoms and signs of colitis in mice.[206] However, the gut microbiota also plays an important role in bile acid metabolism. Sayin *et al.*[210] analysed the bile acids of the whole gut-liver system of germ-free and routinely-fed mice and showed that in the role of gut microbiota, the bile acid levels decreased in the gall bladder and small intestine, while they increased in the caecum, colon, faeces and serum, indicating that gut microbiota influenced the composition of bile acids in various parts of the enterohepatic circulatory system.[210] The gut microbiota may inhibit the synthesis of cholesterol 7a-hydroxylase (CYP7A1) and bile acids by promoting the expression of FXR-dependent fibroblast growth factor 15.[210] In addition, the gut microbiota plays a pivotal role in deconjugation and dehydroxylation and in bile acid desulphation. Gut dysbiosis in patients with inflammatory bowel diseases leads to bile acid dysmetabolism, which is strongly associated with chronic gut inflammation.[211] The changes in bile acids in the faeces of rats treated with antibiotics indicated that alterations in the intestinal microbiota would have an impact on the bile acid pools in plasma and faeces.[212]

Importantly, bile acids play a neuroprotective role in neurodegenerative diseases such as Alzheimer's disease, Huntington's disease and Parkinson's disease.[213] Tauroursodeoxycholic acid (TUDCA), an endogenous bile acid, has a neuroprotective effect in models of Parkinson's disease.[214–216] TUDCA plays a neuroprotective role by regulating c-Jun N-terminal kinase activity and the cellular redox threshold and activating the Akt survival pathway.[214] In the MPTP-induced model, TUDCA regulated the number of

functional mitochondria through the PINK1/Parkin-mediated pathway and upregulated mitochondrial reversal, which can prevent MPTP-induced neuronal apoptosis, cortical neuronal production of reactive oxygen species and ATP depletion to exert its neuroprotective effect.[216] In addition, TUDCA plays an antioxidant role by promoting NRF2 activation and further enhances the expression and activity of its downstream target enzyme glutathione peroxidase in the brains of MPTP mice.[217] The results demonstrated that TUDCA can not only induce the expression of antioxidant enzymes but also improve their biological activity and eliminate the toxic effect of reactive oxygen species.[217] Furthermore, TUDCA also relieves neuroinflammation in Parkinson's disease by inhibiting the activation of astrocytes and microglia, regulating the synthesis of ANXA1 in microglia and preventing the upregulation of proinflammatory factors and the decrease in anti-inflammatory factors in the brain.[215,218] A recent study found that TUDCA can alleviate the typical motor symptoms of Parkinson's disease caused by MPTP, including spontaneous activity, the ability to initiate movement and tremor.[218] In general, TUDCA can improve the loss of dopaminergic neurons and decreased ATP levels as well as mitochondrial dysfunction and neuroinflammation in Parkinson's disease models. In addition, ursodeoxycholic acid (UDCA) has a protective effect on the function of mitochondria and dopaminergic neurons in a Parkinson's disease model.[219] In a rotenone model, UDCA can reduce dyskinesia, prevent the decrease in striatal dopamine content and reduce the expression of NF-κB, TNF and IL-1β.[220] UDCA can also downregulate the expression of the striatal proapoptotic gene *Bax* and upregulate the expression of the anti-apoptotic gene *Bcl2* to inhibit apoptosis and restore the integrity of mitochondrial morphology and function induced by rotenone.[220] Generally, bile acids, affected by the metabolism of intestinal microbiota, play an essential role in antioxidant, anti-inflammatory and neuroprotective activities in the pathogenesis of Parkinson's disease.

Neurotransmitters

Gut microbiota can also mediate disease by affecting the release of neurotransmitters in the intestine. Serotonin is a monoamine neurotransmitter. The vast majority of 5-HT in the human body is synthesized by enterochromaffin cells, a type of enteroendocrine cell, via the rate-limiting enzyme tryptophan hydroxylase 1 (TPH1).[221] In the periphery, serotonin plays an important role in regulating intestinal peristalsis and epithelial secretion, while promoting the development and maintenance of enteric neurons. The gut microbiota plays a key role in promoting serotonin secretion, inducing enteric nervous system maturation by releasing 5-HT and activating the 5-HT4 receptor.[222] After antibiotic treatment, the level of 5-HT in the colon and faeces of mice or germ-free mice decreased significantly, and the expression of TPH1 in colon tissue also decreased, while the reconstruction of intestinal microbiota recovered the decrease in 5-HT in germ-free mice.[79,223] Gut microbiota and their metabolites, such as SCFAs and cholate, can increase TPH1 expression and 5-HT production in the colon by signalling to enterochromaffin cells.[79,221] *Clostridium ramosum* was found to promote the secretion of 5-HT in the intestinal tract.[224] The level of plasma 5-HT in patients with Parkinson's disease was decreased compared with that in controls, and the decrease in plasma serotonin markers was related to the severity of depression and pain.[225] Serotoninergic medication may therefore reduce the risk of cognitive decline in Parkinson's disease.[226] In addition, microbiota also participate in the regulation of neurotransmitters by affecting the production of GABA, the main inhibitory neurotransmitter in the human brain. Intestinal *Lactobacilli* and *Bifidobacteria* can produce GABA involved in the regulation of the

microbiota-gut-brain axis.[227] *Bacteroides*, *Parabacteroides* and *Escherichia* species actively express the GABA production pathway to participate in brain signal transduction.[228] The GABA-producing microbiota increased the level of GABA in the lumen of the small intestine, thus affecting the health of the host and improving depression-like behaviour.[229] In the 6-OHDA model, 5-HT, GABA and bone marrow stem cells have protective effects on neuronal injury induced by oxidative stress.[230] The researchers reported that the level of GABA decreased in the basal ganglia in patients with Parkinson's disease, and there were significant differences in GABA levels among the Parkinson's disease motor subtypes, indicating that GABA is involved in the pathogenesis of this disease.[231] GABA produced by bacteria has a protective effect on degenerative neurons.[232]

Intervention mediated by the microbiota-gut-brain axis

Diet

With alterations in diet, the microbial abundance and production of fermentation products such as SCFAs and phytochemicals will change significantly.[233] Diet can also affect the composition of the gut microbiota and the neural activity of the CNS through the microbiota-gut-brain axis. Among them, the Mediterranean diet is a well-known healthy diet model characterized by a large number of plant foods, such as fruits, vegetables, cereals, legumes, nuts and bread, low and medium amounts of dairy products, olive oil as the main source of fat, low and medium amounts of fish and meat, and low amounts of red meat, with the use of spices instead of salt.[234] In addition, it is necessary to eat in a pleasant and familiar environment, rest after meals and engage in sports and social activities at the same time. The Mediterranean diet has been associated with the health status of a variety of diseases, such as cardiovascular disease, obesity, metabolic syndrome and cancer.[235] A case-control study reported that the higher the compliance with a Mediterranean diet, the lower the risk of Parkinson's disease and the lower the score of the Mediterranean diet, the earlier the age of onset of Parkinson's disease, but it did not indicate whether low Mediterranean dietary compliance was the result or cause of Parkinson's disease.[236] Adherence to the Mediterranean diet was significantly associated with a low incidence of prodromal Parkinson's disease, which indicated that the Mediterranean diet is helpful.[237] A recent randomized clinical trial investigated the effect of the Mediterranean diet on cognitive function in patients with Parkinson's disease and found that adhering to the Mediterranean diet significantly increased executive function, language, attention, memory and improved cognitive function.[238] Therefore, the Mediterranean diet may be a promising intervention strategy to attenuate onset and development of Parkinson's disease.

High dietary fibre is one of the characteristics of the Mediterranean diet. Dietary fibre is an important energy source for caecal and colonic microbiota. Under specific intestinal conditions, anaerobes activate complex metabolic pathways to produce metabolites such as SCFAs. Dietary fibre and SCFAs stimulate the production and secretion of intestinal mucus to protect the intestinal epithelium from microbial invasion and reduce the chance of infection.[239] Subtle changes in dietary fibre structure may strongly affect the composition and function of gut microbiota.[240] De Filippo et al.[241] compared the faecal microbiota of European children and African children from a rural village in Burkina Faso, among which the latter had a high content of dietary fibre.[241] The results indicated that the children in Burkina Faso showed an increased abundance and diversity of microbiota with significantly increased levels of Bacteroidetes and reduced levels of Firmicutes.

The concentration of SCFAs in the Burkina Faso group was significantly higher than that in European children, and the abundance of Enterobacteriaceae (*Shigella* and *E. coli*) was significantly decreased compared with the European children.[241] Therefore, a high-fibre diet protects children in the Burkina Faso group from inflammation and intestinal inflammatory disease. Similarly, a comparative study analysed the bacterial species in faecal samples of people from different regions in the USA, including urban people with a protein-rich diet and rural people with mainly corn and cassava-based diets and found that there were significant differences in the phylogenetic composition of faecal microbiota among these individuals.[242] Furthermore, De Filippo et al.[243] observed that when food rich in fat and monosaccharides was introduced into the African diet, which is traditionally a diet of grains, legumes and vegetables, the gut microbiota was altered, accompanied by a progressive decrease in SCFAs.[243] Accordingly, changes in diet greatly alter the characteristics and functions of gut microbiota to mediate human health.

Olive (*Olea europaea* L.) oil, the main source of fat in the Mediterranean diet, mainly contains monounsaturated fatty acids, which have antioxidant activity and inhibit synuclein aggregation.[244] Phenolic compounds in olive oil have anti-inflammatory, antioxidant, neuroprotective and immunomodulatory activities.[245] In addition, the Mediterranean diet contains several antioxidants, including vitamin E, vitamin C, folic acid and polyphenols.[246] Yang et al.[247] prospectively evaluated the relationship between the dietary antioxidants vitamins C and E and carotene and the risk of Parkinson's disease and found that dietary vitamin E and carotene intake can reduce the risk of developing the disease.[247] These antioxidants can neutralize the role of oxygen free radicals to reduce oxidative damage. A recent study in Caenorhabditis *elegans* Parkinson's disease models showed that the main olive oil polyphenols, hydroxytyrosol and oleuropein aglycone, can reduce the accumulation of α-synuclein in muscle cells and prevent the neurodegeneration of dopaminergic neurons containing α-synuclein.[248]

In addition to the familiar Mediterranean diet, dietary treatments related to the prevention or treatment of Parkinson's disease include a ketogenic diet and fasting therapy. A ketogenic diet was found to improve motor and nonmotor symptoms in patients with Parkinson's disease.[249] Additionally, Zhou et al.[184] reported that a fasting-mimicking diet can reduce the loss of dopaminergic neurons in the substantia nigra of MPTP-induced Parkinson's disease mice.[184] Intermittent fasting can protect neurons in animal models of disease, reduce the number of dopaminergic neurons and improve motor function in Parkinson's disease.[250] Although animal experiments have shown that a ketogenic diet and fasting are effective in preventing Parkinson's disease, a large number of clinical trials and detailed consensus on standardized programmes are needed to explore whether they are beneficial to patients with Parkinson's disease. In summary, diet can regulate the alteration of gut microbiota and has an impact on the brain by anti-inflammation, reducing oxidative stress and neuroprotection. Diet-mediated therapy can be used as a new strategy for the treatment and prevention of Parkinson's disease (Fig. 4).

Probiotics

The composition of the intestinal microbiota could affect different organ systems, including the cardiovascular, nervous, immune and metabolic systems.[251] Microbial therapy, in the form of probiotics, may be a novel strategy for the treatment of Parkinson's disease. Probiotics are defined as non-viable food components that confer health benefits to the host that are associated with modulating the microbiota. Recent studies have shown that probiotics play a role in relieving the gastrointestinal symptoms of
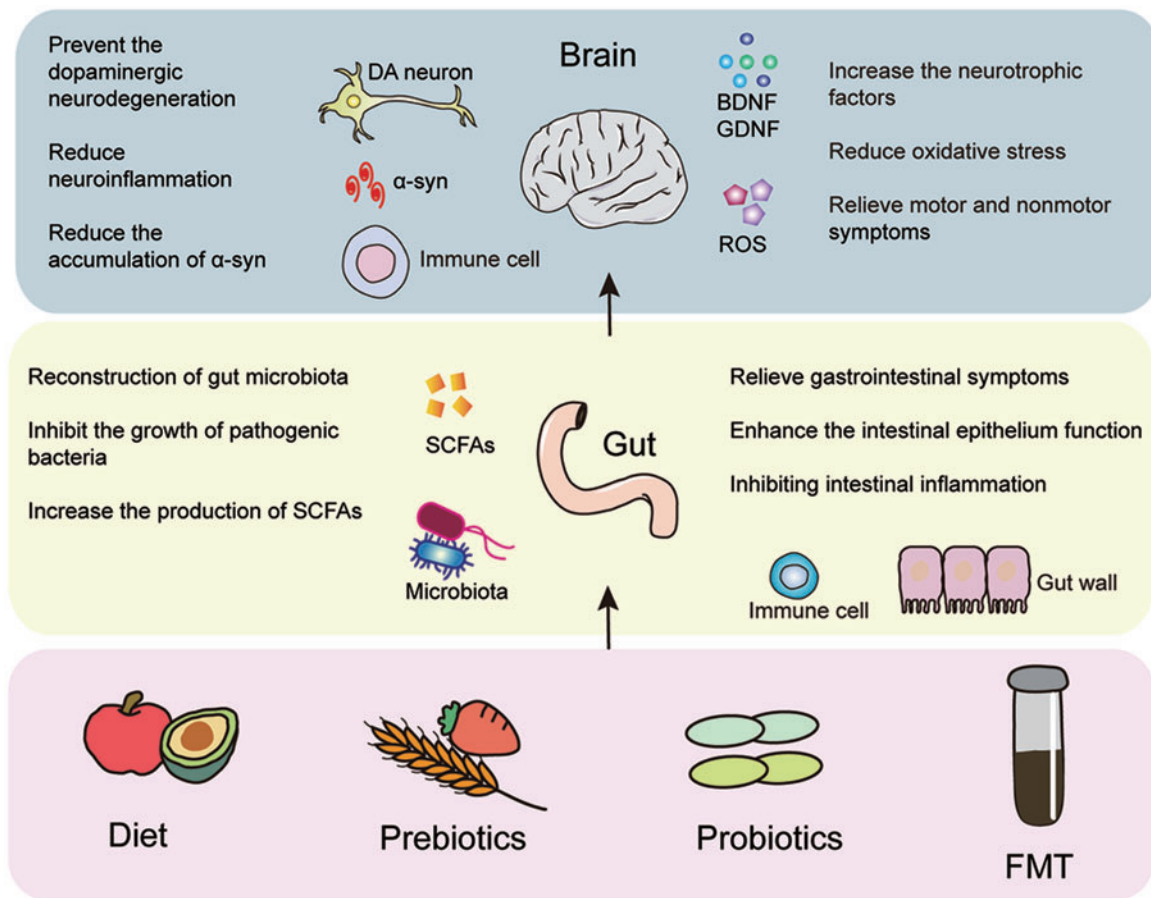
Figure 4 Potential therapies mediated by the microbiota-gut-brain axis in Parkinson's disease. In the intestine, a high-fibre, low-fat diet can change the types of intestinal microbiota and increase the content of SCFAs. In addition, microbial therapy such as probiotics, prebiotics, synbiotics and FMT increase beneficial microbiota and inhibit pathogenic bacteria. In general, they play a role in anti-inflammation, increasing epithelial barrier function and reducing gastrointestinal dysfunction. In the CNS, diet and microbial therapy can prevent dopamine neurodegeneration and loss, reduce neuro-inflammation and play a neuroprotective role. ROS = reactive oxygen species.

Parkinson's disease, especially constipation, abdominal pain and abdominal distension.[252,253] However, the exact mechanisms and safety of using probiotics in Parkinson's disease have not fully been clarified, although the mechanisms may involve relieving symptoms, inhibiting inflammation, avoiding antioxidant stress and neuronutrition.[254,255] A double-blind placebo controlled study of Symprove[TM], a large bowel active probiotic and non-motor symptoms of Parkinson's disease (the SymPD study) is currently underway in the UK.[256] A clinical study has shown that probiotic bacteria can increase the production of SCFAs and decrease pro-inflammatory cytokines in patients with Parkinson's disease, indicating that probiotics may be a potential treatment for this disease (Ghyselinck *et al.*, in press).

Prebiotics and micronutrients

Prebiotics are mainly indigestible food fibres, which benefit the host's health by selectively stimulating the growth and/or activity of some microbiota in the gut. The FAO/WHO defines prebiotics as 'a nonviable food that confers health benefit(s) on the host associated with modulation of the microbiota'. The most common sources of prebiotics include soybeans, raw oats, unrefined wheat and barley, indigestible carbohydrates and indigestible oligosaccharides. Some artificially produced prebiotics include inulin, galacto-oligosaccharide, fructo-oligosaccharide and single-chain fatty acids.[257] Prebiotics have beneficial effects on Parkinson's disease

by promoting gastrointestinal peristalsis, improving immune function and relieving constipation. Eating fermented milk containing a variety of probiotic strains and prebiotic fibre could improve the symptoms of constipation in patients with Parkinson's disease.[252] Studies have shown that prebiotics (including galacto- and fructo-oligosaccharides) can effectively normalize motor and nonmotor abnormalities and restore the level of dopamine transporters in the striatum induced by rotenone.[258] The level of BDNF in the hippocampus of rats increased after the administration of galacto- and fructo-oligosaccharides.[259] The results proved that the proliferation of intestinal microbiota mediated by prebiotics may increase the expression of BDNF in the brain through the participation of intestinal hormones. BDNF plays an important role in regulating the composition and function of the CNS. The main function of prebiotics is to stimulate the growth and activity of beneficial microbiota in the gastrointestinal tract, thereby bringing health benefits to the host. Prebiotics deliver beneficial effects in Parkinson's disease by producing microbiota metabolites such as SCFAs. At present, however, there is little clinical evidence on prebiotics in patients with Parkinson's disease, so a large number of trials are required to thoroughly investigate the mechanism. ingredient

Faecal microbiota transplantation

Faecal microbiota transplantation, known as faecal transplantation or faecal bacteriotherapy, involves injecting or transplanting

liquid filtrate from a healthy donor into the recipient's intestines to treat specific diseases.[260,261] FMT can reconstruct gut microbiota, change intestinal microbial diversity and restore abnormal intestinal microbiota comprehensively and extensively. At present, FMT has been used in patients with many diseases, such as recurrent *Clostridium difficile* infection, inflammatory bowel disease, metabolic syndrome and obesity.[262–265] FMT has been regarded as an effective and safe treatment for patients with recurrent *C. difficile* and has been approved by the Federal Drug Administration in the USA.[266] The results of a recent randomized, single-blind and controlled trial demonstrated that the endoscopic index of Crohn's disease severity decreased 6 weeks after FMT.[267] However, a single FMT may not be enough to induce significant changes in patients; this requires confirmation through large-scale studies.

FMT may be a potential therapeutic method for the regulation of gut microbiota in animal models. Intragastric administration of *Faecalibacterium prausnitzii* could significantly reduce the severity of colitis in mice with moderate or severe chronic colitis, suggesting that this species is an anti-inflammatory bacterium with the potential to treat inflammatory bowel disease.[268] Additionally, *F. prausnitzii* can produce butyrate to promote Foxp3 and block the downstream pathway of IL-6/STAT3/IL-17 by inhibiting HDAC1, maintaining the Th17/Treg balance and playing a significant anti-inflammatory role in colorectal colitis rodents.[269] *F. prausnitzii* can also reduce intestinal inflammation by affecting paracellular permeability and enhancing intestinal epithelium barrier function.[270,271] In addition, recent studies have reported that *Roseburia intestinalis* decreased the disease activity index score, intestinal mucosal epithelial injury and mucosal lymphocyte infiltration, while inhibiting intestinal inflammation, by increasing the number of Treg cells and the expression of anti-inflammatory cytokines in a mouse model of colitis.[272,273]

Moreover, FMT has also been proposed as a therapeutic approach in neurological diseases such as multiple sclerosis, Parkinson's disease, autism spectrum disorder, Alzheimer's disease and epilepsy.[274–276] The regulatory effects of FMT on intestinal microbiota may have an impact on the symptoms or progression of nervous system diseases through immune, endocrine, metabolic and neural pathways. In animal experiments, Sampson *et al.*[50] found that the high expression of α-synuclein in mice that were colonized by the gut microbiota of patients with Parkinson's disease increased motor dysfunction.[50] In addition, these mice showed changes in SCFAs, with lower concentrations of acetate and higher concentrations of propionate and butyrate, substantiating that the alteration of gut microbiota is a crucial risk factor for Parkinson's disease.[50] FMT significantly relieved the metabolic disorder of gut microbiota in Parkinson's disease mice, alleviated body injury and increased the contents of dopamine and 5-HT in the striatum to protect Parkinson's disease mice by inhibiting nerve inflammation and reducing TLR4/TNF signal transduction.[121] FMT may play a vital role in regulating the gut microbiota, but animal models have some limitations. Whether the results of animal experiments can be extrapolated to humans is unclear. At present, there is limited evidence for the application of FMT in patients with Parkinson's disease. A clinical study reported that constipation and movement symptoms were significantly relieved after a single FMT treatment in a patient with Parkinson's disease with constipation, and leg tremor almost disappeared 1 week after FMT treatment.[277] However, caution is needed in drawing conclusions from a single case study and future clinical trials are needed to clarify the role of FMT in Parkinson's disease. For the treatment of nervous system diseases, multiple FMTs may be needed to achieve a sustained effect. The exact mechanism by which gut microbiota plays a role in FMT through the gut-brain axis remains poorly understood.

FMT is associated with adverse reactions and side effects, including diarrhoea, fever and abdominal pain.[278,279] The major challenges with FMT include the high costs of sample preparation and preservation as well as the selection of faecal donors.[262] A survey ascertained that doctors have a relatively high awareness and acceptance of FMT but are most concerned about patients' acceptance of the treatment, followed by a lack of guidelines and ethical constraints.[280] Limited studies on the clinical applications of FMT have provided an opportunity to address some of the gaps in knowledge through better designed clinical trials.

Conclusion

Case control studies show changes in gut microbiota composition in patients with Parkinson's disease compared with healthy individuals, and there are suggestions of a link between microbiota alterations and disease progression. The microbiota-gut-brain axis, which connects the peripheral and central nervous systems, provides a pathway whereby microbiota may contribute to the pathogenesis of Parkinson's disease, although the exact mechanism remains to be elucidated. The gut microbiota and their metabolites can modulate the immune system and regulate local and systemic inflammation, epithelial barrier function and neurotrophic factors. More studies are needed to investigate the characteristics of microbiota composition at different stages of Parkinson's disease with the aim of discovering new biomarkers for the early diagnosis and monitoring of disease progression. Microbial therapies such as probiotics and FMT can relieve gastrointestinal symptoms and even motor symptoms of Parkinson's disease; however, the safety and effectiveness of FMT requires further evaluation in clinical trials.

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Competing interests

The authors report no competing interests.

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