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Interactions between gut microbiota and Parkinson's disease: The role of microbiota-derived amino acid metabolism

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Non-motor symptoms (NMS) of Parkinson's disease (PD), such as constipation, sleep disorders, and olfactory deficits, may emerge up to 20 years earlier than motor symptoms. A series of evidence indicates that the pathology of PD may occur from the gastrointestinal tract to the brain. Numerous studies support that the gut microbiota communicates with the brain through the immune system, special amino acid metabolism, and the nervous system in PD. Recently, there is growing recognition that the gut microbiota plays a vital role in the modulation of multiple neurochemical pathways via the "gut microbiota-brain axis" (GMBA). Many gut microbiota metabolites, such as fatty acids, amino acids, and bile acids, convey signaling functions as they mediate the crosstalk between gut microbiota and host physiology. Amino acids' abundance and species alteration, including glutamate and tryptophan, may disturb the signaling transmission between nerve cells and disrupt the normal basal ganglia function in PD. Specific amino acids and their receptors are considered new potential targets for ameliorating PD. The present study aimed to systematically summarize all available evidence on the gut microbiota-derived amino acid metabolism alterations associated with PD.

KEYWORDS

Parkinson's disease, gut microbiota, amino acid metabolism, microbiota-host interaction, gut microbiota-brain axis

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease and affects an estimated 3 million people worldwide. The typical feature of PD is the accumulation of intracellular aggregates called Lewy bodies, composed largely of the presynaptic protein alpha-synuclein (Collier et al., 2017). In clinical practice, individuals with PD benefit from drugs developed to act on a single molecular target (Figure 1; Sarkar et al., 2016; Tambasco et al., 2018). Levodopa (L-DOPA) is still the gold standard therapy for patients with PD. However, long-term L-DOPA treatment is associated with motor fluctuations and dyskinesias. As the disease progresses, amino acid decarboxylase inhibitors (AADC inhibitors), catechol-O-methyl transferase inhibitors (COMT inhibitors), monoamine oxidase B inhibitors (MAO-B inhibitors), and dopamine receptor agonists are also used. The surgical treatment of deep brain stimulation can be used for patients with PD who have severe limitations in functioning despite optimal pharmacological treatment (Weiner, 2002; Malek, 2019). However, there is not currently a medication available to cure or halt the progression of the disease.

The intestine is a complex and dynamic ecosystem caused by various microbial communities known as the gut microbiota (Zhao and Liu, 2020). The human intestinal tract contains more than 10-100 trillion microorganisms (Duttaroy, 2021; Zhang J. et al., 2021), which contribute to food digestion, nutrient provision, and combat pathogen invasion. Numerous studies have demonstrated that the gut microbiota plays a vital role in maintaining human health and adjusting numerous physiological functions, such as the nervous system, cardiovascular system, and immune system (Izco et al., 2021). Considering the importance of host-microbiota interactions for human health, access to yet unexplored resources will lead to the discovery of new actors regulating this crosstalk and therefore new potential therapeutic targets (Alam and Neish, 2018; Chang and Kao, 2019). Although genetic, societal, environmental, and other influencing factors are closely involved in disease etiology and progression, the host-microbiota interaction is increasingly recognized for its influence in a variety of diseases (Duttaroy, 2021), such as obesity (Arnorriaga-Rodríguez et al., 2020), inflammatory bowel disease (Sankarasubramanian et al., 2020), non-alcoholic fatty liver disease (Rom et al., 2020), and Parkinson's disease (Vascellari et al., 2020). More importantly, a better understanding of the host-microbiota interaction will improve an understanding of the relationship between gut microbiota and health. Interestingly, the change in microbial composition, intestinal dysfunction, bacterial metabolites, and endocrine function in the intestine is associated with PD (Sun et al., 2017). In addition, the abundance of *Prevotellaceae* presented a declining trend in PD patients compared with healthy individuals. Simultaneously,

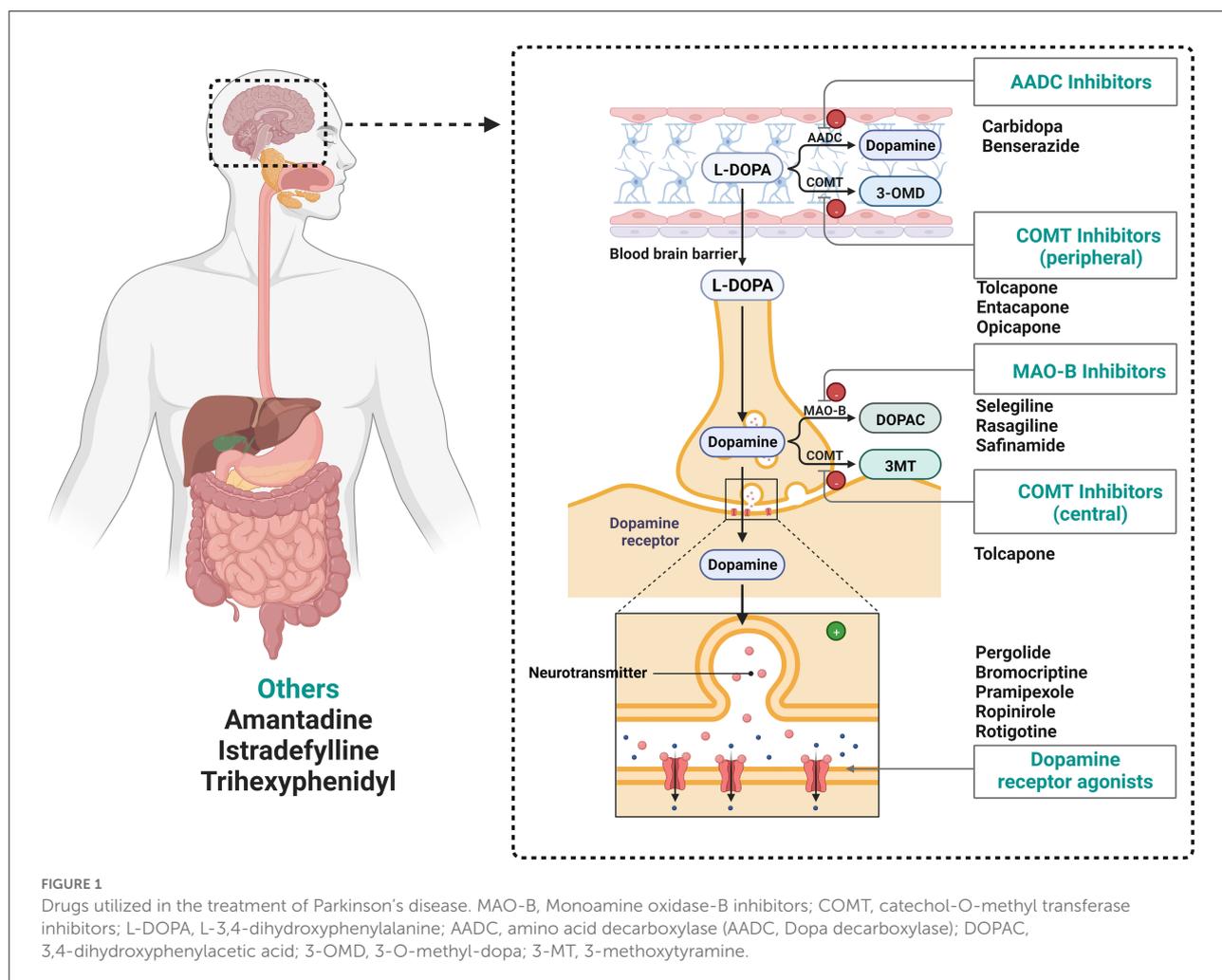
the abundance of *Enterobacteriaceae* has been found to be associated with the severity of postural instability and gait difficulty of PD patients (Scheperjans et al., 2015). Hence, the interaction between the gut microbiota and the occurrence of PD will provide a bright future for intervention, especially for the diagnosis and therapy of PD. Growing evidence suggests that the modulation of gut microbiota could be a novel therapeutic target in PD patients.

Amino acids are fundamental elements for protein and peptide synthesis. More importantly, a series of evidence indicates that amino acids are also important bioactive molecules that play key roles in signaling pathways and metabolic regulation (Sankarasubramanian et al., 2020). The gut microbiota composition related to protein metabolism in the intestinal tract is similar to that in feces and important in amino acid homeostasis and health (Bishu, 2016; Lin et al., 2017; Zhao et al., 2019). The result showed that the primary bacteria, such as *Klebsiella* spp., *Escherichia coli*, and *Anaerovibrio lipolytica*, are associated with protein metabolism. In addition, amino acids could be directly metabolized by some of these bacteria which own the ability to excrete numerous proteases and peptidases (Fan et al., 2017). Evidence shows that amino acids are exchanged between gut microbiota and the host (Metges, 2000). Thus, there is no doubt that a profound grasp of the significance of gut microbiota-derived amino acid metabolism has become imperative. Notwithstanding, the effects of amino acid metabolism on PD pathogenesis have not been comprehensively reviewed at present. In this review, detailed descriptions of the relationship between gut microbiota-derived amino acid metabolism and PD are summarized, and dysbiosis of microbial metabolite and microbiota-targeted interventions in PD disease are also discussed (Figure 2).

Gut microbiota and Parkinson's disease

The hypothesis of PD in the gut

Few researchers investigated the pathogenesis of PD prior to 1980. The mechanism remained elusive until the description of Lewy bodies first appeared. The main hypotheses involved in the pathogenesis of PD were as follows: oxidative stress (Trist et al., 2019), mitochondrial dysfunction (Navarro and Boveris, 2009), excitotoxicity (Ambrosi et al., 2014), inflammation, neurotrophic factor-deficiency (Lindahl et al., 2020), and the theory of gut origin (Postuma, 2015). Among them, oxidative stress and PD originating from the gut have attracted more attention. Accumulating evidence illustrated that oxidative stress may be the cause of many neurodegenerative diseases, including PD (Trist et al., 2019). Low levels of oxidative



stress could promote mitochondria elimination and protect their biological function, while opposite effects appear in high-level oxidative stress beyond the cellular capacity by affecting the mitochondrial membrane's potential and protein synthesis in cytoplasm (Lee and Wei, 2005; Barodia et al., 2017). Previous studies mainly focused on the abnormal deposition of α -syn in the central nervous system in PD pathogenesis. Recently, multitudes of studies have elucidated that gut microbiota homeostasis and metabolites are correlated with the pathogenesis of PD. Simultaneously, Yang et al. (2019) revealed the existence of a bidirectional network called GMBA. The GMBA could affect human behavior and brain neurochemistry by regulating neurotransmitters and their receptors in PD patients. Taken altogether, the gut origin hypothesis implicates the gut as a potential origin of PD pathogenesis, offering fresh insights into the mechanisms underlying PD.

A bidirectional link between intestinal disorders and neurodegeneration in the pathogenesis of Parkinson's disease

Relevant preclinical and epidemiological studies illustrated that the occurrence of common intestinal disorders, such as colorectal cancer (CRC), constipation, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and small intestinal bacterial overgrowth syndrome (SIBO), were associated with PD by affecting the central nervous system (Barboza et al., 2015). Interestingly, a bidirectional link between the brain and gut plays an essential role in the association between intestinal dysfunction and PD. The association between PD and intestinal disorders is described in Table 1.

PD and CRC are different diseases with diverse pathogenic mechanisms. Gut microbiota diversity (Xie et al., 2017),

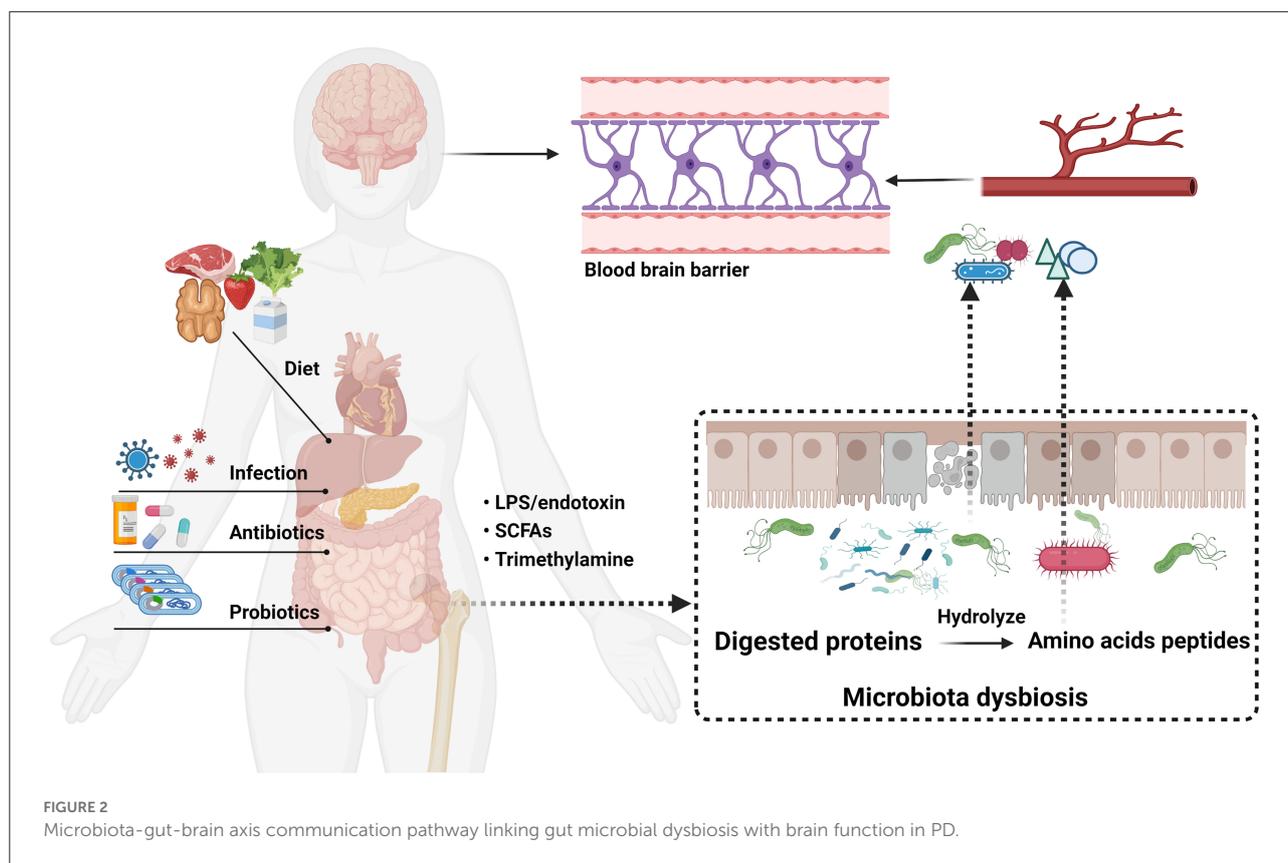
TABLE 1 The association between Parkinson's disease and intestinal disorders.

| Intestinal disorders | Connection with Parkinson's disease (PD) | Publication trends on web of science (accessed on 7 May 2022) | References |
|--------------------------------|--|---|---|
| Colorectal cancer (CRC) | 1. PD patients had a reduced risk of CRC | "Parkinson's disease" and "Colorectal cancer" (176) | Xie et al., 2017; Fang et al., 2021 |
| Constipation | 2. CRC occurrence was significantly lower in patients with PD | | |
| | 1. Constipation patients are at a 2.27-fold increased risk of developing PD compared to the control group, and this phenomenon emerges up to 20 years before diagnosis | Parkinson's disease and "Constipation" (1,016) | Kaye et al., 2006; Adams-Carr et al., 2016; Svensson et al., 2016; Gan et al., 2018; Zhou et al., 2019; Camacho et al., 2021; Kang et al., 2022; Santos García et al., 2022; Zheng et al., 2022 |
| | 2. Compared with people without constipation, regional neural activity and functional connectivity in the brain show much difference in PD patients with constipation | | |
| | 3. Constipation is associated with a sustained increased risk of a PD diagnosis and progression of neurodegenerative pathology, and there was a higher incidence for men than women | | |
| | 4. Constipation is associated with cognitive decline in PD patients | | |
| | 5. Constipation is associated with the increased severity of motor symptoms and decreased dopamine levels in PD patients in a dose-dependent manner. Simultaneously, the different constipation-loading times could lead to different clinical characteristics, especially in motor symptoms | | |
| Irritable bowel syndrome (IBS) | 1. Patients with IBS are at an increased risk of developing PD in Taiwan in both genders in an age-dependent manner | "Parkinson's disease" and "Irritable bowel syndrome" (134) | Lai et al., 2014; Mertsalmi et al., 2017; Liu B. et al., 2021; Zhang J. et al., 2021; Lu et al., 2022; Yoon et al., 2022; Zhang X. et al., 2021 |
| | 2. IBS increased PD risk only in individuals ≥ 65 years | | |
| | 3. PD patients with IBS-like symptoms had more non-motor symptoms | | |

(Continued)

TABLE 1 (Continued)

| Intestinal disorders | Connection with Parkinson's disease (PD) | Publication trends on web of science (accessed on 7 May 2022) | References |
|---|--|--|---|
| Inflammatory bowel disease (IBD) | <ol style="list-style-type: none"> 1. The overall risk of PD in IBD, both Crohn's disease and ulcerative colitis is significantly higher than in controls 2. IBD is associated with increased PD risk regardless of sex, especially in patients over 65 years of age. Furthermore, the therapies for IBD using corticosteroids, anti-TNF and early anti-inflammatory methods may decrease the risk of PD 3. The risk of neurodegenerative diseases is higher in IBD patients than in the non-IBD population 4. Abnormal changes in the intestinal environment trigger the onset of PD <i>via</i> the brain-gut axis 5. Gut inflammation and higher LRRK2 levels in Crohn's disease (IBD) may be a biomarker of increased risk for sporadic PD | Parkinson's disease and "Inflammatory bowel disease" (302) | <p>Lin et al., 2016; Killinger et al., 2018; Peter et al., 2018; Park et al., 2019; Villumsen et al., 2019; Zhu et al., 2019, 2022; Fu et al., 2020; Noh et al., 2020; Herrick and Tansey, 2021; Kim et al., 2022</p> |
| Small intestinal bacterial overgrowth syndrome (SIBO) | <ol style="list-style-type: none"> 1. The risk of SIBO is higher in PD patients than in non-PD patients, and SIBO could influence the progression of PD using negative and positive manners 2. SIBO may lead to fluctuation in the absorption of medications utilized to therapy PD, which could further influence the treatment of PD 3. SIBO is associated with increased motor fluctuations present in PD patients compared with individuals without SIBO | "Parkinson's disease" and "Small intestinal bacterial overgrowth syndrome" (128) | <p>Marrinan et al., 2014; Tan et al., 2014; Niu et al., 2016; Dănău et al., 2021</p> |



melatonin (Schernhammer et al., 2006), dopamine (Sarkar et al., 2015), and smoking (Hernán et al., 2002) may account for the bidirectional link between PD and CRC. The disorders of the ubiquitin-proteasome system may lead to the formation and accumulation of Lewy bodies including α -syn (Sherman and Goldberg, 2001). More importantly, the level of ubiquitin proteasome system is usually up-regulated in CRC patients (Manasanch and Orlowski, 2017). Notwithstanding, there is a clear need for more prospective studies to validate these hypotheses. Interestingly, phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) are over-expressed in CRCs (Bahrami et al., 2018), while the PI3K/Akt/mTOR activation could prevent PD via reducing the dopaminergic neuron apoptosis (Leikas et al., 2017).

Constipation, the second most common non-motor symptom of PD after anosmia, is characterized by infrequent stools, difficult stool passage, or both. Previous studies indicated that the main cause of constipation was slowed colonic transit. Furthermore, constipation is one of the indicators and occurs more than 20 years earlier than the diagnosis of PD (Frazzitta et al., 2019). Simultaneously, gastrointestinal dysfunction is a common feature of PD and could lead to the impaired absorption of L-DOPA, which also causes the motor fluctuations of PD (Svensson et al., 2016). Despite copious

research, the exact mechanism of IBS remains unclear. Genetic variation, altered gut microbiota, increased gut permeability, and low-grade inflammation are risk factors for IBS (Ohman and Simrén, 2010). Compared with those without IBS, an individual with IBS is at a 48% increased risk of PD based on the meta-analysis and systematic review methods (Zhang J. et al., 2021). The risk factors of IBS can make the gastrointestinal tract more vulnerable to bacterial endotoxin and pathogens which may cause an increase in α -syn expression and aggregation (Mertsalmi et al., 2021). Furthermore, the previous research about the correlation between the gut microbiota and the occurrence and development of IBS has been observed and the gut-brain axis plays a vital role, which was consistent with the hypothesis of “PD originates in the gut” (Braak et al., 2006; Raskov et al., 2016; Canakis et al., 2020). The altered gut microbiota and increased gut permeability can activate systemic inflammation and enteric neuroglial cells, thereby initiating the development of α -syn pathology (Klingelhoefer and Reichmann, 2015). An increasing number of clinical studies revealed that IBD could cause neuroinflammation through the gut-brain axis which was consistent with the elevated stool calprotectin levels in PD patients (Schwiertz et al., 2018). Intestinal inflammation could accelerate the aggregation of α -syn in the gut and then spread to the brain, finally leading to PD (Stokholm et al., 2016).

SIBO is characterized by the excessive levels of bacteria colonized in the small intestine causing inflammation and malabsorption. The pathogenesis, clinical manifestation, and progression of sporadic PD might be affected by SIBO (Dobbs et al., 2012; DiBaise et al., 2018; Manole et al., 2021). Several studies found that H₂-predominant vs. methane-predominant SIBO shows various effects on PD progression. In addition, because of different drug bioavailability and absorption, SIBO has conflicting effects on intestinal symptoms of PD with different pharmacological interventions (Gibson and Barrett, 2010; Maini Rekdal et al., 2019; van Kessel et al., 2019). Among the pathogenesis of PD, SIBO may cause local and systemic reactions that would further destroy the integrity of the intestinal barrier by influencing tight junctions and intestinal permeability. Many studies illustrated that the intestinal disorder may serve as a warning sign for PD.

The association pathogenesis of PD and gastrointestinal disorders was mainly focused on genetic factors, diet, environmental toxins, and gut microbiota, etc. Interestingly, PD is characterized by severe motor and NMS that can result in debilitating gastrointestinal (GI) symptoms. Specifically, the association between intestinal disorders and PD pathogenesis attracting many researchers' attention may be due to the existence of the gut-brain axis. Overall, the PD risk was higher in IBS patients than others, indicating that the intestinal disorder may serve as a warning sign for PD. Further research is warranted to explore the underlying mechanisms of this correlation.

Roles of gut microbial dysbiosis and microbial products in PD

The key pathological characteristics of PD are the accumulation of α -syn and cell death in the brain's basal ganglia, affecting an estimated three million people (more than 60 years of age) (Wolters and Braak, 2006; Sulzer, 2007). This damage to dopaminergic neurons is responsible for the distinctive movement disorder and vagal nerve dysfunction associated with PD. Until recently, the NMS including constipation, dysphagia, disrupted sleep architecture, impaired olfaction, and depression were presented in PD patients (Raval et al., 2020). A great quantity of studies has shown that constipation is an early manifestation of the neurodegenerative process underlying PD. More importantly, the NMS of GI dysfunction (i.e., constipation) often appears much earlier in PD patients, predating the onset of motor symptoms by as many as 20 years (Abbott et al., 2001; Savica et al., 2009). Many studies found that gut microbiota composition alters in various PD-related NMS, possibly pre-dating motor symptoms (Heintz-Buschart et al., 2018). Interestingly, current research studies have illustrated that gut microbial disturbance can damage the intestinal barrier

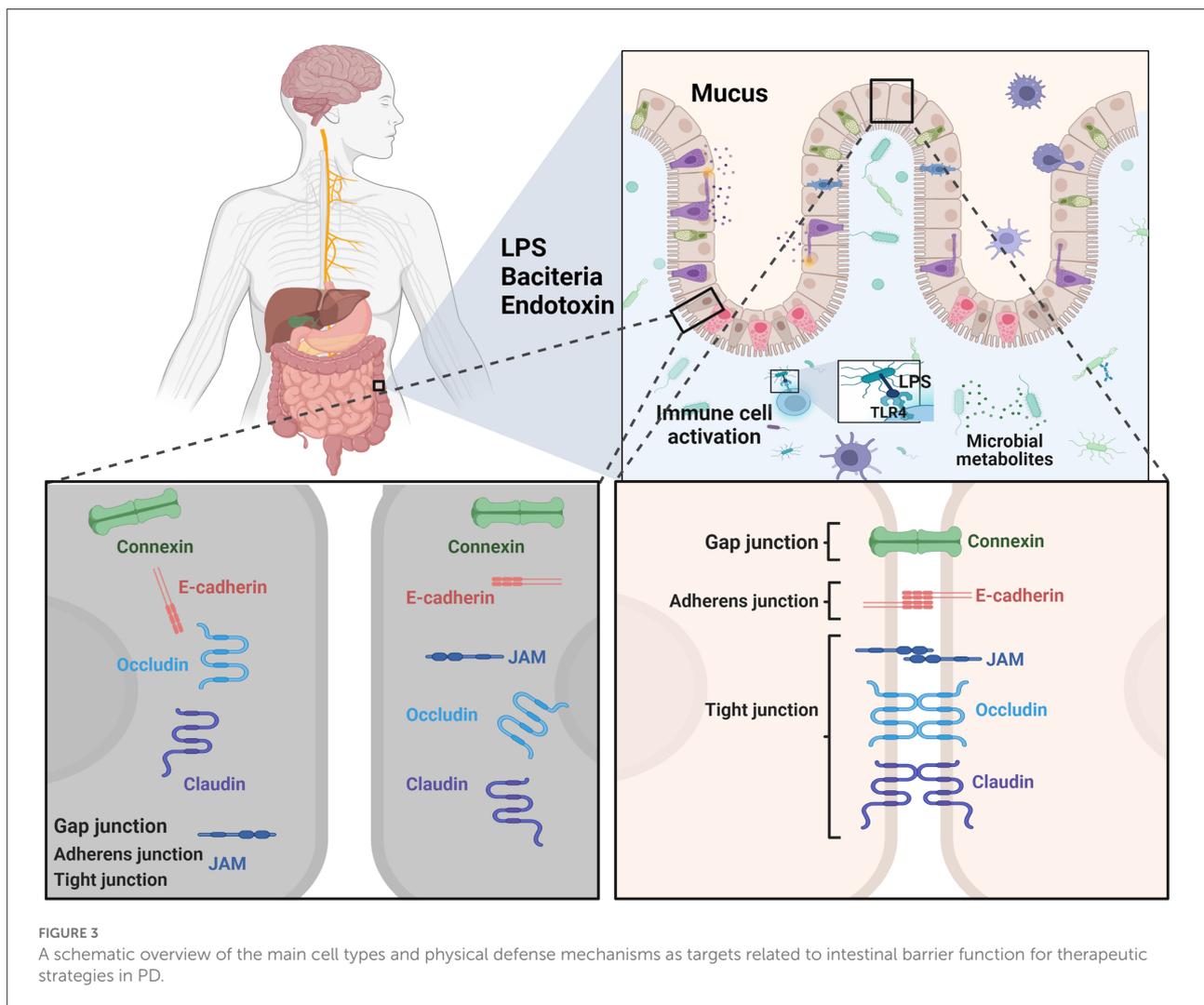
and raise chronic inflammation both in the gut (de La Serre et al., 2010; de Theije et al., 2014) and brain (Sampson and Mazmanian, 2015; Sampson et al., 2016).

The intestinal barrier

The role of the intestinal barrier as an interface between the external and internal environments of the host is an obvious focus. The intestinal barrier facilitates the absorption of nutrients and prevents the entry of harmful intraluminal components into the blood circulation, such as endotoxins, and deleterious rhizobacteria (Furness et al., 1999; Sun and Shen, 2018). The tight junction complexes in epithelial cells, the mucosal surface, and the immune system are vital for the intact intestinal barrier and function, of which the first line of defense is the intestinal lumen itself (Figure 3; Schoultz and Keita, 2020; Gharib-Naseri et al., 2021).

Commensal luminal bacteria inhibit the colonization of pathogens by, for example, the production of bacteriocins, pH modification of the luminal content, and competition for nutrients required for the growth of pathogens (Bharadia et al., 2020). Otherwise, the commensal microbiota resides in the intestinal epithelium enhanced physiological paracellular permeability, and the mucus layer (Schoultz and Keita, 2019).

The single cell layer of epithelium consists of plentiful cell types and could divide the body and the outside luminal milieu. The tight barrier of the intestinal luminal milieu is established by a large quantity of cells and their functions (Schoultz and Keita, 2019). It is shown that antimicrobial peptides could be produced by Paneth cells by eliminating pathogenic bacteria (Wang et al., 2018). Simultaneously, innate and adaptive immune cells, such as neutrophils, T cells, monocytes, and natural killer cells, respond to the intrusion of xenobiotics and suppress the inflammation. Neutrophils, a kind of immunological cells, are among the first cells to reach inflamed areas and eliminate microorganisms through phagocytosis (Rosales et al., 2016). T-regulatory cells, a specific subpopulation of lymphocytes, are critical in the maintenance of immune homeostasis in suppressing the activation of various immune cells related to inflammation (Corthay, 2009). The crosstalk established between the gut microbiota and the intestinal epithelium is key to maintaining homeostasis in the gut. More importantly, the bi-directional communications between the innate immune system and pattern recognition receptors, such as Toll-like receptors (TLRs), scavenger receptors, and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), are crucial to the intestinal barrier homeostasis in some conditions. The intestinal epithelial and immune cells are constantly in contact with foreign material and then respond appropriately to their intrusions, protecting the host (Wells et al., 2011). This interactivity ability makes the identification of external ingredients possible based on the antigen presenting cells. Even more interesting is that these cells can migrate to the



peripheral site and transmit antigens to T-cells, leading to increased secretion of pro-inflammatory cytokines, IFN- γ for example, to improve the intestinal barrier (Wallace et al., 2014). Simultaneously, the enzyme of indoleamine 2,3-dioxygenase (Bessede et al., 2014), owning the effect of regulating the inflammatory reaction and the ability of protective effect against IBD, is responsible for the transformation of tryptophan to kynurenine (Arsenescu et al., 2011). TLRs are pro-inflammatory and conserved transmembrane receptors that can identify conserved molecular structures to detect microorganisms (Kubinak and Round, 2012). Pathogen triggered TLRs are generally understood to cause an inflammatory immune response, supporting the subsequent clearance of pathogenic microorganisms (Mayne et al., 2020). da Silva et al. (2016) found that these receptors were regulated by peripheral leukocyte responses in PD patients.

Intestinal permeability (between intestinal epithelial cells) is mainly characterized by medium-sized hydrophilic molecules

transporting along their concentration gradient in a system without the assistance of a carrier system (Schoutz and Keita, 2020). A vital function of the intestinal epithelium is the maintenance of normal intestinal barrier function, which allows the selective permeability of essential nutrients, water, and ions without the entry of bacterial toxins and pathogens (Tabler et al., 2020). The increase in intestinal permeability represents intestinal barrier function disorders. A number of studies have found that increased permeability is correlated with the development of several diseases. Higher intestinal permeability induces the translocation of gut bacteria and microbial components that initiate inflammation and oxidative stress in the enteric nervous system, resulting in enteric α -synucleinopathy in PD (Bjarnason et al., 2004). Simultaneously, these findings also have important clinical applications. Barrier integrity in IBD patients, whose endoscopy findings are normal, may be detected using confocal laser endomicroscopy, which may predict the relapses (Galipeau and Verdu, 2016).

The development of reliable and sensitive methods to measure intestinal permeability could contribute to identifying patients who are at high risk of suffering from PD and assist in the development of preventative therapies (Galipeau and Verdu, 2016). PD is characterized by an altered gut microbiota composition, the intestinal barrier, and the enteric neuroimmune system, therefore it is possible that intestinal barrier dysfunction may play a key role in PD development and/or progression. Meanwhile, the significant role of intestinal permeability has been highlighted in PD, which lays the groundwork for novel PD therapy targeting the restoration of the intestinal barrier.

Inflammation of the gut and neuroinflammation of the brain

The maturation and function of microglia are affected by the altered cell proportions, while immature phenotypes are based on the circulating levels of pro-inflammatory and anti-inflammatory cytokines contributing to host homeostasis (Erny et al., 2015). The astrocytes and microglia can produce pro-inflammatory cytokines *via* TLRs activation (Lucas and Maes, 2013). TLRs can recognize microbial-associated molecular patterns (MAMPs), such as lipopolysaccharides (LPS), and are activated by changes in the composition of gut microbiota and gut permeability (Bowman et al., 2003). LPS can activate immune cells (such as macrophages, neutrophils, and dendritic) and promote the inflammation and permeability of the gut (Rhee, 2014). In particular, the activated immune cells can release various pro-inflammatory cytokines, binding with receptors expressed in neurons and glial cells, and then spread to the brain *via* the blood-brain-barrier and can result in the neuroinflammation and death of neurons in the brain (Dantzer et al., 2000). The new research illustrated that gut leakiness and endotoxemia owing to the alteration of microbiota led to the co-occurrence of intestinal inflammation and neuroinflammation *via* the activation of the TLR4 (Alhasson et al., 2017).

Amino acids and gut microbiota-brain axis in PD

Source and composition of amino acid in dietary proteins

In the gastrointestinal tract, enterocyte peptidases further hydrolyze resultant peptide products into amino acids, dipeptides, and tripeptides for enterocyte transport into the portal venous system. At the same time, amino acids serve as substrates for protein synthesis that are utilized for energy production under extreme conditions, such as disease for example. Amino acids are classified as essential amino acids, non-essential amino acids, and conditionally essential

amino acids based on the species, age, disease, and condition dependence (Thalacker-Mercer et al., 2020). Essential amino acids, including tryptophan, valine, lysine, leucine, isoleucine, phenylalanine, threonine, and methionine, must be provided by dietary protein (Church et al., 2020; Verzola et al., 2020) and non-essential amino acids can be synthesized through other pathways.

Recently, amino acids, including total amino acid and free amino acid, have been found to exist in mushrooms, corn grain, peanut, soybean, and white rice, etc. Research has found that the average total free amino acid content of the mushroom was 4.35% (Sun et al., 2017). The relative amount of total amino acid is 8.76% in coffee silverskin (Machado et al., 2020), 10.67% in corn grain, 29.29% in peanut, 9.08% potato, and 8.49% in white rice (Hou et al., 2019). It should be noted that amino acids are substrates in polyamine synthesis by numerous enzymes in humans and microbes (Krzystek-Korpacka et al., 2020).

The absorption and metabolization of amino acids in the intestine

Amino acids perform several crucial functions in the human body, either directly or indirectly. They are the main constituents of protein in bioactive substances and adjust the balance of energy and immunity in organisms. In addition, amino acids can be catalyzed through oxidized, reduced, fissioned, or coupled pathways (Davila et al., 2013). Several reactions including transamination, deamination, and decarboxylation are required steps in this process. Lots of work demonstrated that glycine, proline, and arginine usually act as the acceptors of hydrogen, and alanine, leucine, isoleucine, and histidine are hydrogen donors in the metabolic pathways (Rist et al., 2013). The metabolisms of relevant amino acids are summarized in Figure 4. The microorganisms are mixed with endogenous proteins, such as mucous proteins, chemicals secreted by the pancreas and gastric gland in the alimentary canal (Hayashi et al., 2005). The nitrogen-containing compounds are broken down into amino acids and peptides and related enzymes are excreted *via* the exocrine pancreas. The amino acids and peptides are absorbed by bacteria or spread from the intestinal lumen to the portal vein.

Amino acids are absorbed and digested in the intestinal epithelium (Bos et al., 2005; Hu and Guo, 2021). During the process, a tremendous amount of nitrogen-containing compounds passes by the ileocecal junction and gets into the posterior part of the intestine (Blachier et al., 2007). However, some proteins are still difficult to absorb and digest completely in the small intestine. The remaining nitrogen-containing compounds without digestion are transported to the large intestine. Microorganisms play a vital role in protein hydrolysis to provide free amino acids for both host and

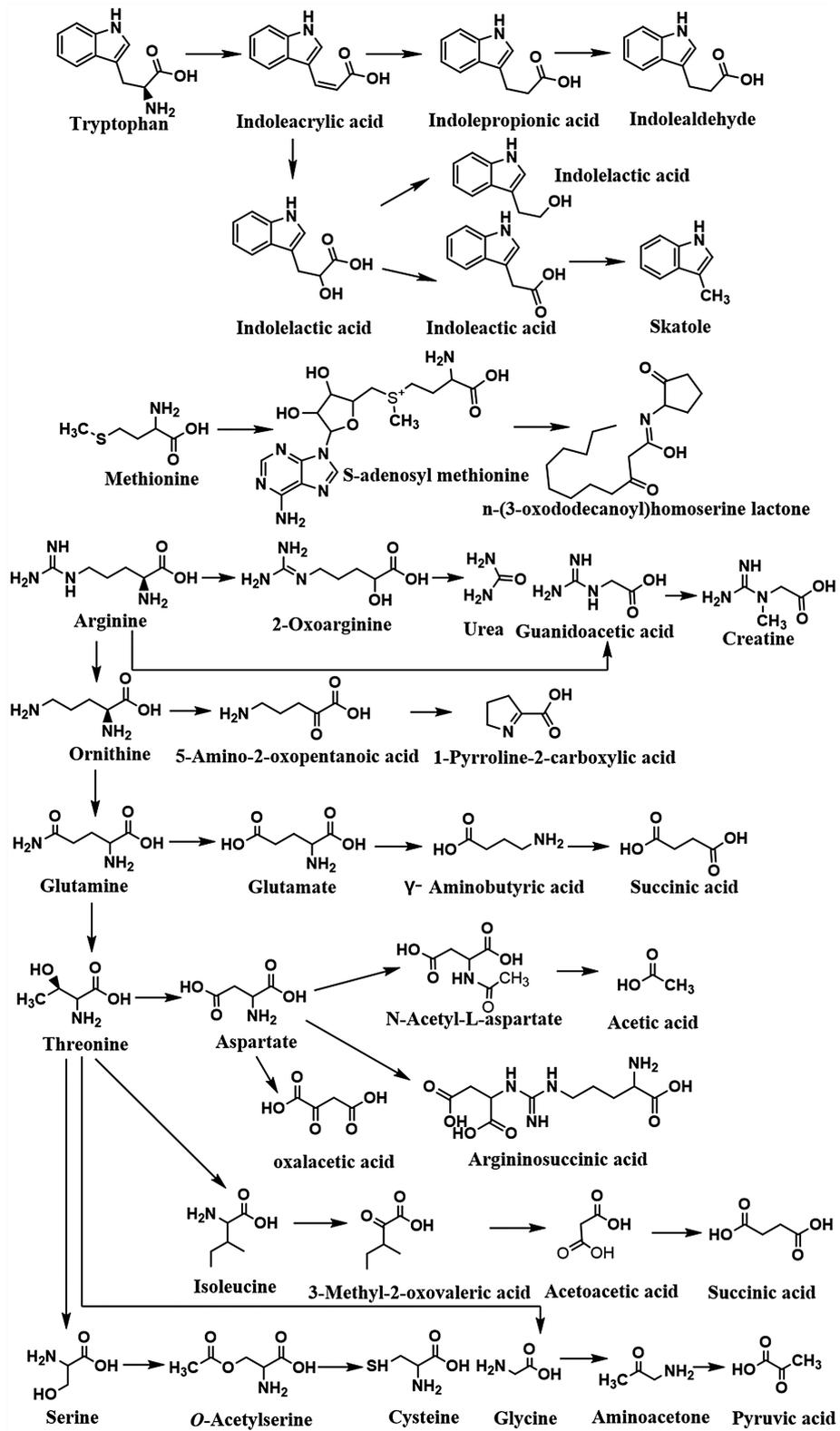


FIGURE 4
The summary of microbiota-derived amino acid metabolism profile.

microbial metabolism functions. Furthermore, most amino acids, synthesized by microorganisms, can be absorbed by the intestinal epithelial cells of the small and large intestines to implement a sequence of functions, like synthesis and catabolism (Laparra and Sanzm, 2010; Ma and Ma, 2019). The proteolysis and recycling of nitrogen-containing compounds are performed by proteolytic bacteria residing in the gastrointestinal tract (Macfarlane and Macfarlane, 2007). A large amount of amino acid maintains the immense and widespread metabolism via the function of microbiota. This diversity of amino acid metabolism in microorganisms may impart either active or passive effects on the host. Hence, adjusting protein or amino acid absorption and metabolization in the intestine may provide a strategy for shaping the amino acid fermenting bacteria and their metabolic pathways, thereby potentially affecting host metabolism.

Amino acids metabolism and gut microbiota

The roles of gut microbiota on amino acid metabolism have been well investigated (Zhao et al., 2019). The great majority of digestive products, such as small peptides, amino acids, and tripeptides, are utilized by certain microbes or transported into systemic circulation by the small intestine. The functions of amino acids between the gut microbiota and host are bi-directional (Zhao et al., 2019). The gut microbiota plays an essential role in dietary protein and nitrogen recycling. In addition, the microbial activity induced by indigestible amino acids promotes the production of metabolic end products including short-chain fatty acids (SCFA; acetate, butyrate, propionate), branched-chain fatty acids, amines, indoles, and ammonia, etc. (Macfarlane et al., 1988). Previous work revealed that bacterial metabolites appear to have beneficial or opposite effects on the host depending on their concentrations. As the major nutrients in the diet, amino acids are the basic components of proteins and peptides, and are essential for the emergence of organism-active molecules involved in the signaling pathways and metabolism modulation (Dai et al., 2015). Additionally, the gut microbiota is crucial for the metabolism and recycling of amino acids. The amino acids, deriving from the diet or the host, are utilized as the fundamental element by gut microbiota for the synthesis of proteins or produce a large number of metabolites by the nutritional metabolism, such as polyamines, phenolic, nitric oxide (NO), and hydrogen sulfide (H₂S) (Dai et al., 2015). In addition, the “essential” amino acids, as a regulator for amino acid homeostasis in humans, can be synthesized by intestinal bacteria. For instance, research has illustrated that a large number of bacteria, like *Selenomonas ruminantium*, perform de novo synthesis of amino acids in the existence of

peptides using experiments *in vitro* (Atasoglu et al., 1998; Neis et al., 2015). These results suggest that amino acid metabolism provides nutrition for gut microbiota and supports physiological action for the host (Dai et al., 2011; Collins et al., 2012). The intestinal bacterial communities are influenced by constituents of dietary protein, especially protein sources and concentrations. Proteins derived from plants are generally utilized in humans and animals. Nevertheless, crude proteins are characterized by low digestibility because of the anti-nutritional elements (He et al., 2015). By contrast, proteins originating from animals are characterized by high digestibility by aerobes in the large intestine. The homeostasis of gut microbiota (mainly in the large intestine) can be disorganized, leading to intestinal disorders (Fan et al., 2015). Consequently, it is essential to explore the connection between gut microbiota and amino acids (which are necessary for protein metabolism). In addition, comprehending the functions of different constituents of dietary protein on gut microbiota is crucial.

Regulation of gut microbiota on amino acid metabolism and synthesis

An enormous number of metabolic pathways, such as glucose, lipid, and amino acid metabolism, are regulated by gut microbiota. The composition of gut microbiota-derived metabolites in the intestinal tract is very complex. The nutrition can be provided by amino acids acquired in the diet or synthesized by the host for the gut microbiota for protein production. Amino acids can be integrated into bacterial cells as amino acid residues in proteins, and further incorporated into the metabolic pathway. Amino acids and peptides are obtained by the hydrolysis of proteins through proteases and peptidases secreted by gut microbiota. Ultimately, amino acids and peptides could be absorbed by microbiota through specific transporters. However, the small bioactive molecules will encounter various consequences under different physiological conditions of humans (Davila et al., 2013). Transamination or deamination is the first stage of amino acid catabolism, followed by oxidation or reduction. Biogenic amines are alkaline organic compounds mainly produced by decarboxylation reactions of free amino acids present by the enzyme decarboxylase (Wu et al., 2021).

Recent studies demonstrated convincingly that a large number of amino acid-fermenting bacteria are inhabited the intestinal tract (up to 1,011 per gram of dry feces) (Atasoglu et al., 1998). The “essential” amino acid of lysine, produced by bacteria, is absorbed and integrated as a whole host protein *in vivo* studies (Metges et al., 1996, 1999). The research illustrated that the ¹⁵N-lysine originated from microbial lysine with the comparison of the integration of ¹⁵N from ¹⁵NH₄Cl into the inside body system (Torrallardona et al., 1996; Gill et al., 2006).

Additionally, gut microbiota-derived lysine and threonine were shown to be crucial for free lysine and threonine in a study on nitrogen adequate diets in humans (Metges et al., 1999). Furthermore, this research found that the abundance of gut microbiota was associated with the precursors generated by humans related to “essential” amino acids (Metges et al., 1999).

A genome-wide analysis illustrates that a number of *clostridium* species, *Clostridium acetobutylicum* for example, have comprehensive genes for the biosynthesis of amino acids, whereas *Clostridium perfringens* lack the genes for amino acid biosynthesis such as lysine, serine, glutamic acid, and aromatic amino acids (Kevin et al., 2016). Hence, in order to elucidate the functions of amino acids from the perspective of bacterial species, it is necessary to understand the biosynthesis of amino acids in microorganisms. However, nitrogen and amino acids, required for the growth and fermentation of glycolytic bacteria, could be provided by the residual dietary proteins in the large intestine (Mafra et al., 2013). Various *Lactobacillus* and *Bifidobacterium* strains can produce γ -aminobutyric acid which is a neural active substance (Barrett et al., 2012). It is acknowledged that imidazole propionate can be transformed into histidine-derived metabolite by gut microbiota (Koh et al., 2018). Moreover, gut microbiota can produce tryptophan owing to the existing of tryptophan decarboxylase in the intestinal tract (van de Wouw et al., 2017). Given the above, amino acids can be utilized for the synthesis of bacterial cell components and catabolized. Major amino acid-fermenting bacteria in the intestinal tract are concluded in Table 2.

Amino acids as precursors for microbially derived short-chain fatty acids

The literature reports that short-chain fatty acids (SCFAs) constitute a major class of fermentation products. The microbiota-derived carbohydrates of SCFAs are cardinal examples of beneficial metabolites (Sonnenburg and Sonnenburg, 2014). Acetate (accounts for ~50–70%), propionate (produced by the species of *Phylum Firmicutes*), and butyrate (produced by a small quantity of *Phylum Firmicutes*, such as *Faecalibacterium prausnitzii* and *Roseburia hominis*) (Sokol et al., 2008; Machiels et al., 2014) are SCFAs. These SCFAs supply key metabolic signaling that underlies homeostasis and the function of colonic Tregs by different molecular mechanisms (Mu et al., 2017; Yang, 2022). In faith, a wide variety of amino acids generated from microbial protein fermentation in the large intestine can be presented as precursors for short-chain fatty acid synthesis (Ciarlo et al., 2016). The great majority of amino acids such as glutamate, ornithine, and glycine can be metabolized by anaerobic bacteria and utilized for the synthesis of butyrate (Neis et al., 2015). Zou et al. (2021) reported that phenylalanine, tyrosine, and tryptophan could

be metabolized to indolic and phenolic compounds *via* the gut microbiota. However, indolic and phenolic compounds can be utilized to mitigate inflammatory responses. Concurrently, it plays a significant role to promote the comprehension of the pathophysiology of diseases.

SCFAs have many ameliorative effects on gut health. First, SCFAs can maintain the integrity of the intestinal barrier and exert therapeutic potential for intestinal inflammation (Lewis et al., 2010). For instance, butyrate can activate adenosine monophosphate kinase (AMPK) or down-regulate the expression of claudin 2 to regulate the expression of tight junction proteins, eventually enhancing intestinal barrier function (Daly and Shirazi-Beechey, 2006; Peng et al., 2009). Second, SCFAs contribute to the mucous production in the gastrointestinal tract (Dalile et al., 2019). The research (Gaudier et al., 2009) illustrated that butyrate regulated MUC2 gene expression to regulate the production of mucin. Additionally, SCFAs can affect gastrointestinal motility by inhibiting histone deacetylases (Cherbut et al., 1998). Ultimately, SCFAs can interact with vagal afferents by influencing inflammation and hormonal regulation (Dalile et al., 2019).

To summarize, amino acids can alter the gut microbiota composition by forming an intestinal microenvironment favorable to the survival and proliferation of certain microbes (Libao-Mercado et al., 2009). Conversely, gut microbiota delivers energy and reduces co-factors *via* providing amino acids to meet the needs of the host (Metges, 2000). Gut microbiota owns the substitutable role (both the host nutrition and physiology) in amino acid metabolism, and the phenomenon shows the bidirectional process between amino acids and gut microbiota (Macfarlane and Macfarlane, 2012). Briefly, SCFAs play numerous biological roles: (1) constitute an energy source for muscles; (2) implicate in the transportation and metabolism of epithelial cells; and (3) influence epithelial cell growth and differentiation.

Amino acid transporters in the large intestine

It is widely known that several amino acids are likely absorbed in the large intestine. The significance of the balance between whole-body proteins and amino acids is still unclear, especially in humans. The amino acids and peptide transporters in the intestinal tract contribute to amino acid absorption and metabolism in the large intestine (Hendriks et al., 2012).

A tremendous amount of solute carrier (SLC) transporters, which contain a large number of families of distinct transporters, are adopted to transport amino acids and peptides (including di- and tripeptides). Many above-mentioned transporters are expressed in the large intestine. There is evidence for transporter

TABLE 2 Major amino acid-fermenting bacteria in the digestive tract.

| Amino acids | Intestinal bacteria | Metabolite | Related mechanisms in PD | Trends in PD | Niches | References |
|---------------|---------------------------------|--|--|--------------|-----------------|--|
| Phenylalanine | <i>Subdoligranulum</i> | Phenylpropionate | Phenylalanine is the precursor of dopamine and could participate in protein sequences in all tissues | Ascend | Rumen | Hirayama et al., 2016 ; Dodd et al., 2017 |
| | <i>Lactobacillus</i> | Phenyl lactate | | | Small intestine | |
| | <i>Clostridium</i> | Phenylacetate | | | Cecum | |
| | <i>Pepto streptococcus</i> spp. | Phenyl pyruvic acid 4-OH-phenylpyruvic acid Ammonia CO ₂ | | | Colon | |
| Asparagine | <i>Fusobacterium nucleatum</i> | Aspartic acid | Related to oxidative stress and dopamine cell degeneration in PD | Descend | Small intestine | Nagaraja et al., 2021 |
| | <i>Escherichia coli</i> | Ammonia | | | Large intestine | |
| | <i>Klebsiella pneumoniae</i> | CO ₂ | | | Colon | |
| | <i>Campylobacter jejuni</i> | | | | Feces | |
| | <i>Bacteroides fragilis</i> | | | | | |
| Tryptophan | <i>Lactobacillus</i> spp. | Indole | Associated with psychiatric problems in advanced PD | Descend | Stomach | Hatano et al., 2016 ; Dehghani et al., 2019 ; Liu B. et al., 2021 ; Liu J. R. et al., 2021 |
| | <i>Bifidobacterium</i> spp. | Indole ethanol | | | Small intestine | |
| | <i>Clostridium</i> spp. | Indolepropionic acid | | | Colon | |
| | <i>Pepto streptococcus</i> spp. | Indolelactic acid | | | | |
| | <i>Bacteroides</i> spp. | Indoleacetic acid | | | Feces | |
| | <i>Clostridium sporogenes</i> | Skatole | | | | |
| | <i>Ruminococcus gnavus</i> | Tryptamine | | | | |
| | | Indolealdehyde | | | | |
| | | Indoleacrylic acid | | | | |
| Lysine | <i>Clostridium sticklandii</i> | Lysine-5,6-aminomutase | Acylation of lysine neutralizes may change the conformation of proteins | Ascend | Stomach | Potrykus et al., 2008 ; Wan et al., 2019 |
| | <i>Porphyromonas gingivalis</i> | Lysine | | | Small intestine | |
| | | | | | Colon | |
| | | | | | Feces | |
| | | 2,3-aminomutase | | | | |
| | | 2,5-diaminohexanoate | | | | |
| | | Dehydrogenase | | | | |
| | | 3,5-diaminohexanoate | | | | |
| | | Dehydrogenase | | | | |
| | | 3,6-diaminohexanoic acid | | | | |

(Continued)

TABLE 2 (Continued)

| Amino acids | Intestinal bacteria | Metabolite | Related mechanisms in PD | Trends in PD | Niches | References |
|----------------------------|-----------------------------------|-----------------|---|--------------|-----------------|--|
| Serine | <i>Fusobacterium</i> | Acetate | Signaling molecule to regulate the growth, repair, and maintenance of brain functions | Ascend | Stomach | Campbell et al., 1967 ; Schierack et al., 2007 ; Donatti et al., 2020 |
| | <i>Varium</i> | Lactate | | | Small intestine | |
| | <i>Campylobacter jejuni</i> | Pyruvate | | | Colon | |
| | <i>Bacteroides fragilis</i> | Ammonia | | | | |
| | <i>Acidaminococcus fermentans</i> | Malate | | | Feces | |
| | | CO ₂ | | | Rumen | |
| | <i>Clostridium aminophilum</i> | | | | Cecum | |
| | <i>Clostridium perfringens</i> | | | | Stomach | |
| | <i>Clostridium sticklandii</i> | | | | Large intestine | |
| | <i>Pepto streptococcus</i> spp. | | | | | |
| Aspartic acid | <i>Fusobacterium nucleatum</i> | Asparagine | Related to oxidative stress, and dopamine cell degeneration in PD | Descend | Small intestine | Sugihara et al., 1974 ; Guccione et al., 2008 |
| | <i>Escherichia coli</i> | Fumarate | | | Colon | |
| | | Oxaloacetate | | | | |
| | <i>Campylobacter jejuni</i> | | | | Feces | |
| | <i>Acidaminococcus fermentans</i> | | | | | |
| Glutamine | <i>Clostridium aminophilum</i> | Pyroglutamate | Involved in the glutamate-glutamine cycle | Ascend | Mouth | Donatti et al., 2020 ; Kumari et al., 2020 |
| | <i>Selenomonas ruminantium</i> | Acetate | | | Small intestine | |
| | <i>Acidaminococcus fermentans</i> | Butyrate | | | Large intestine | |
| | | Ammonia | | | Stomach | |
| | <i>Clostridium perfringens</i> | CO ₂ | | | | |
| | | | | | Colon | |
| | <i>Pepto streptococcus</i> spp. | | | | Feces | |
| <i>Streptococcus bovis</i> | | Rumen | | | | |

(Continued)

TABLE 2 (Continued)

| Amino acids | Intestinal bacteria | Metabolite | Related mechanisms in PD | Trends in PD | Niches | References |
|-----------------------------------|-----------------------------------|-----------------|--|--------------|-----------------|--|
| Glutamate | <i>Campylobacter jejuni</i> | | | | Cecum | |
| | <i>Klebsiella pneumoniae</i> | | | | | |
| | <i>Escherichia coli</i> | | | | | |
| | <i>Fusobacterium nucleatum</i> | | | | | |
| | <i>Clostridium aminophilum</i> | 2-Oxaloacetate | Participating in the disruption of the normal basal ganglia function, thus leading to neuronal death | Descend | Mouth | Donatti et al., 2020 ; Jiménez-Jiménez et al., 2020 ; Kumari et al., 2020 |
| | <i>Selenomonas ruminantium</i> | Ammonia | | | Small intestine | |
| | <i>Acidaminococcus fermentans</i> | GABA | | | Large intestine | |
| | | CO ₂ | | | | |
| | <i>Clostridium perfringens</i> | | | | Stomach | |
| | <i>Campylobacter jejuni</i> | | | | Colon | |
| Glutamic acid | | | | | Feces | |
| | | | | | Cecum | |
| | <i>Klebsiella pneumoniae</i> | | | | | |
| | <i>Escherichia coli</i> | | | | | |
| | <i>Fusobacterium varium</i> | | | | | |
| | <i>Fusobacterium nucleatum</i> | | | | | |
| | <i>Fusobacterium nucleatum</i> | Glutamate | Glutamic acid is a precursor of glutathione and may reflect an increase in oxidative stress in the disease progression | Descend | Small intestine | Rychlik and Russell, 2002 ; Whitehead and Cotta, 2004 ; Anderson et al., 2009 ; Vascellari et al., 2020 |
| | <i>Fusobacterium varium</i> | Ammonia | | | Large intestine | |
| | | Acetate | | | | |
| | <i>Escherichia coli</i> | Butyrate | | | Stomach | |
| <i>Selenomonas ruminantium</i> | GABA | | | | | |
| <i>Acidaminococcus fermentans</i> | CO ₂ | | | | | |
| | 2-Oxaloacetate | | | | | |
| <i>Clostridium aminophilum</i> | 2-ketoglutarate | | | | | |

(Continued)

TABLE 2 (Continued)

| Amino acids | Intestinal bacteria | Metabolite | Related mechanisms in PD | Trends in PD | Niches | References |
|-------------|-----------------------------------|---|---|--------------|--|--|
| Histidine | <i>Fusobacterium nucleatum</i> | Urocanate | Suppressive neurotransmitter effects and hormone secretion | Ascend | Mouth | Attwood et al., 1998 ; Kumari et al., 2020 ; Sylte et al., 2020 |
| | <i>Fusobacterium varium</i> | Ammonia | | | Small intestine | |
| | <i>Klebsiella pneumoniae</i> | Glutamic acid Histamine CO ₂ | | | Large intestine Colon Feces Rumen | |
| Glycine | <i>Fusobacterium nucleatum</i> | Acetate | Glycine could stimulate the release of dopamine and acetylcholine | Ascend | Mouth | Luan et al., 2015 ; Kumari et al., 2020 ; Sánchez-Andrea et al., 2020 |
| | <i>Clostridium perfringens</i> | Pyruvate | | | Small intestine | |
| | <i>Bacteroides fragilis</i> | Serine | | | Large intestine Stomach Colon Feces | |
| Threonine | <i>Fusobacterium nucleatum</i> | Acetate | Signaling molecule to regulate the growth, repair, and maintenance of brain functions | Ascend | Mouth | Donatti et al., 2020 ; Wu and Deng, 2020 ; Karkache et al., 2021 |
| | <i>Escherichia coli</i> | Ammonia | | | Small intestine | |
| | <i>Pepto streptococcus</i> spp. | Propionate | | | Large intestine | |
| | <i>Clostridium sporogenes</i> | n-butyrate | | | | |
| | <i>Clostridium sticklandii</i> | Ketobutyrate | | | Stomach | |
| | <i>Clostridium difficile</i> | Lactate | | | Colon | |
| | <i>Clostridium perfringens</i> | CO ₂ | | | Feces | |
| | <i>Megasphaera elsdenii</i> | | | | | |
| | <i>Acidaminococcus fermentans</i> | | | | | |
| Arginine | <i>Bacteroides fragilis</i> | | | | | |
| | <i>Fusobacterium nucleatum</i> | 2-Oxoarginine | Serve as a helpful clinical diagnostic biomarker for PD | Ascend | Mouth | Amano et al., 2020 ; Donatti et al., 2020 ; Martí I Líndez and Reith, 2021 |

(Continued)

TABLE 2 (Continued)

| Amino acids | Intestinal bacteria | Metabolite | Related mechanisms in PD | Trends in PD | Niches | References |
|-------------|---------------------------------|--|--|--------------|--------------------------|---|
| | <i>Escherichia coli</i> | Guanidinoacetic acid | | | Small intestine | |
| | <i>Klebsiella pneumoniae</i> | Creatine | | | Large intestine | |
| | <i>Clostridium sticklandii</i> | Urea | | | Stomach | |
| | <i>Clostridium perfringens</i> | Putrescine | | | Colon | |
| | <i>Selenomonas ruminantium</i> | Spermine | | | Feces | |
| | | Agmatine | | | Cecum | |
| | | Ammonia | | | Rumen | |
| | | CO ₂ | | | | |
| Alanine | <i>Staphylococcus aureus</i> | Isovalerate | Alanine may point to mitochondrial dysfunction, oxidative stress, and inflammation markers in PD | Ascend | Small intestine | Nielsen et al., 2020 |
| | <i>Streptococcus</i> spp. | Isocaproate | | | Large intestine | |
| | | Ammonia | | | Feces | |
| | Gram negative bacteria | | | | | |
| | <i>Escherichia coli</i> | | | | | |
| | <i>Selenomonas ruminantium</i> | | | | | |
| | <i>Prevotella</i> spp. | | | | | |
| | <i>Bacteroides</i> spp. | | | | | |
| | <i>Clostridium</i> spp. | | | | | |
| | Ruminal bacteria | | | | | |
| Valine | <i>Staphylococcus aureus</i> | Ammonia | Related to myelination dysfunction of the neurons. | Descend | Large intestine | Toczyłowska et al., 2020 |
| | <i>Streptococcus</i> spp. | CO ₂ | | | | |
| | | Acetate | | | | |
| | <i>Escherichia coli</i> | Isobutyrate | | | | |
| | <i>Klebsiella</i> spp. | | | | | |
| | <i>Selenomonas ruminantium</i> | | | | | |
| | <i>Megasphaera elsdenii</i> | | | | | |
| Methionine | <i>Klebsiella pneumoniae</i> | S-adenosyl-L-methionine n-(3-oxododecanoyl) homoserine lactone | Associated with hyperhomocysteinemia | Ascend | Small intestine Colon | Toczyłowska et al., 2020 |
| | | | | | Feces | |
| Leucine | <i>Pepto streptococcus</i> spp. | Isovalerate | Contribute to muscle wasting, twitching, and tremors. | Descend | Rumen | Luan et al., 2015; Ma et al., 2020; Vascellari et al., 2020 |
| | | Isocaproate | | | Small intestine | |

(Continued)

TABLE 2 (Continued)

| Amino acids | Intestinal bacteria | Metabolite | Related mechanisms in PD | Trends in PD | Niches | References |
|---------------|----------------------------------|-------------------------------|--|--------------|-----------------|---|
| | <i>Clostridium bifermentans</i> | Ammonia | | | Cecum | |
| | | CO ₂ | | | | |
| | <i>Clostridium sporogenes</i> | Acetate | | | Colon | |
| | | Isobutyrate | | | Large intestine | |
| | <i>Clostridium sticklandii</i> | | | | | |
| | <i>Clostridium difficile</i> | | | | | |
| | <i>Prostheco bacter</i> | | | | | |
| Isoleucine | <i>Pepto streptococcus</i> spp. | Isovalerate | Contribute to muscle wasting, twitching, and tremors | Descend | Rumen | Kumari et al., 2020 ; Vascellari et al., 2020 |
| | <i>Clostridium bifermentans</i> | Isocaproate | | | Small intestine | |
| | <i>Clostridium sporogenes</i> | Ammonia | | | Cecum | |
| | <i>Clostridium sticklandii</i> | CO ₂ | | | | |
| | | Acetate | | | Colon | |
| | <i>Clostridium difficile</i> | Isobutyrate | | | Large intestine | |
| Linoleic acid | Bacteroidaceae | 9-,13-oxoODEs | Associated with protective effects and may reflect an excess of oxidative stress | Descend | Small intestine | Vascellari et al., 2020 |
| | <i>Streptomyces griseorubens</i> | Ammonia | | | Colon | |
| | | CO ₂ | | | | |
| | | Acetate | | | Feces | |
| Tyrosine | <i>Clostridium</i> | Ferulic acid | Tyrosine is then further hydroxylated to produce Dopa by tyrosine hydroxylase | Ascend | Stomach | Kumari et al., 2020 |
| | <i>Bacteroides</i> | 4-Hydroxycinnamic acid | | | Small intestine | |
| | <i>Bifidobacterium</i> | 4-Hydroxyphenylacetic acid | | | Colon | |
| | | 4-Hydroxyphenylpropionic acid | | | Feces | |
| | <i>Faecalibacterium</i> | 3-Hydroxybenzoic acid | | | | |
| Pyruvate | <i>Faecalibacterium</i> | Acetate | Reduced pyruvate may be related to impairment in energetic and repair functions | Descend | Rumen | Toczyłowska et al., 2020 ; Shen et al., 2021 |
| | <i>Clostridium bifermentans</i> | Formate | | | Small intestine | |
| | <i>Clostridium sporogenes</i> | Lactate | | | Large intestine | |
| | | Lactoyl-CoA | | | | |
| | | Acryloyl-CoA | | | Cecum | |
| | | Propionyl-CoA | | | Colon | |
| | | Propionate | | | | |

expression at different levels, such as the protein level and the gene expression level. Peptide transporter 1 (PEPT1), encoded by SLC family 15 member 1 (SLC15A1), is involved in the intestinal uptake of oligopeptides and peptide-mimetic drugs (Liu et al., 2019). As we have seen previously, SLC15A1 is the unique transporter that has been verified at the protein level in the human large intestine. The host relies on the system L transporters to obtain essential amino acids, such as SLC7A5, also known as L-type amino acid transporter (LAT)1, SLC7A8, also known as LAT2, SLC43A1, also known as LAT3, and SLC43A2, also known as LAT4. Both SLC7A5 and SLC7A82 are amino acid exchangers, while SLC43A1 and SLC43A2 facilitate amino acid proliferation (Wang and Holst, 2015). Some of the amino acids, such as tryptophan, tyrosine, isoleucine, leucine, valine, and phenylalanine, can be transported into cells via LAT1 and LAT2. Meanwhile, the other amino acids, such as Leucine, isoleucine, valine, phenylalanine, and methionine can be transported into cells by LAT3 and LAT4 (Wang and Holst, 2015). Furthermore, SLC6A14, coupled with a Na^+ gradient, a Cl^- gradient, and membrane potential, shows higher expression in the colon than in the ileum and presents special characteristics with much a better sense of amino acids than the other three transporters (Anderson et al., 2009). Simultaneously, SLC36A1, also called proton-assisted amino acid transporter 1 (PAT1), shows a similar ability to SLC6A14. In addition, other transporter genes expressed in the large intestine discussed in current research also attract our attention. Furthermore, the SLC transporter functions of amino acids and peptides in the large intestine require further study.

Amino acids regulate the intestinal epithelial barrier functions

The elementary mechanism of intestinal homeostasis relies on complex molecular crosstalk between host and gut microbiota. It is demonstrated that the catabolites of tryptophan by bacteria are various, such as tryptamine, skatole, indoleacrylic acid, indoleacetic acid, indolelactic acid, indolepropionic acid, and indolealdehyde, which are the ligands of the aryl hydrocarbon receptor. A recent study indicated that the catabolite of indole could improve intestinal epithelial barrier functions by regulating certain gene expressions (Roager and Licht, 2018). Simultaneously, the catabolite of indolepropionic acid acted as a ligand of the pregnane X receptor and showed the effect of adjusting the intestinal barrier function at the existence of indoles (Venkatesh et al., 2014). In addition, catabolite indoleacrylic acid was found to promote goblet cell differentiation and mucus production to regulate intestinal barrier function. In summary, the catabolites of tryptophan have the effect on improving intestinal barrier

function by regulating the pregnane X receptor and aryl hydrocarbon receptor. The study demonstrated that glutamine improved IL-13-induced barrier dysfunction by up-regulating the expression of the tight junction protein claudin-1, through preventing the PI3K-Akt signaling pathway (Li et al., 2021), and consequently damaged the intestinal barrier function and increased intestinal permeability. At the same time, glutamate can up-regulate the expression of tight junction proteins and protect the diquat-induced oxidative stress to promote intestinal epithelial cell growth and health based on the new biochemical.

The role of amino acids in Parkinson's disease

There is increasing evidence that dopamine dysfunction plays an important role in the pathogenesis of PD. There is also increasing evidence to suggest that the other amino acids, such as glutamate, γ -aminobutyric acid, homocysteine, and large neutral amino acids in the brain were involved in the pathogenesis of PD (Yuan et al., 2013; Figura et al., 2018). According to the research, dopamine treatment is associated with elevated homocysteine in Parkinson's disease (Kuhn et al., 1998). The three amino acids of glutamate, cysteine, and glycine are involved in the synthesis of glutathione. The ratio of the two forms of glutathione (reduced and oxidized forms) can affect the cellular redox status. Mitochondrial complex I has been considered central to the pathogenesis of PD. However, low glutathione concentrations may inhibit mitochondrial complex I (Müller et al., 2016). Meanwhile, the finding suggests that branched-chain amino acids (leucine, isoleucine, and valine) can serve as nitrogen donors to maintain the balance of glutamate-glutamine in astrocytes and neurons (Zhang et al., 2022). Branched-chain amino acids could promote the catabolism of glutamate which may exert beneficial effects on PD. Interestingly, tyrosine and phenylalanine are the key substrates for the production of dopamine in PD. The elevation of phenylacetyl-L-glutamine was positively correlated with firmer stool and constipation severity among PD patients. Simultaneously, gut microbiota-derived tryptophan catabolites could adjust the inflammatory response *via* affecting pro-inflammatory cytokines and lipogenesis in macrophages and hepatocytes (Shao et al., 2021). To compound the issue, glutamic acid and γ -aminobutyric acid are related to the clinical heterogeneity of PD, the symptoms of Parkinson's disease, and especially to the parkinsonian tremor (Yuan et al., 2013). Promisingly, the detection of amino acid neurotransmitter levels may offer new insight into the pathogenesis and early diagnosis of Parkinson's disease. Therefore, more stringent studies with a larger sample size are needed to explore the changes

in amino acid neurotransmitter levels during Parkinson's disease progression.

Conclusions

Researchers have found that amino acids provide powerful support for human health. In recent years, the gut microbiota has received great attention, putting it in the spotlight of biomedical research. The balance of intestinal microbes and the host play a vital role in several disorders, including the impairment of the nervous system. Notably, gut microbiota, a major determinant of bidirectional communication between the gut and brain, could be regulated by a number of mechanisms, and it is illustrated that the microbiota and its produced biochemical messengers are major facets of maintaining a balanced intestinal microenvironment. Microbiota-derived amino acid molecules contribute to host health through modulating immune function, gastrointestinal physiology function, and microbiota composition. Striatal dopamine depletion in PD contributes to the hyperactivity of subthalamic nucleus output pathways, resulting in an abnormal increase in specific microbiota-derived amino acid molecules (glutamate for example), which are involved in the degeneration of the nigrostriatal system based on the excitotoxicity mechanisms. All the studies have shown that GMBA may be significantly correlated with PD pathogenesis.

Although microbiota-host interaction has drawn much attention both from clinicians and researchers in recent years, it still calls for a deeper understanding of the complex GMBA communication. Furthermore, microbiota-derived amino acid metabolism is a crucial factor suggesting major perturbations of the microbiome. These studies illustrated that amino acids metabolized by gut microbiota might affect the degeneration of the nigrostriatal system in PD patients. Gut microbiota and amino acids may be potential therapeutic targets for PD.

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Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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