Gut microbiota and parkinson's disease

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Abstract
It is possible for the non-motor symptoms (NMS) of Parkinson's disease (PD), which include constipation, sleep difficulties, and olfactory impairments, to appear up to 20 years before the motor symptoms of the disease. There is a growing body of research that suggests the pathology of Parkinson's disease may begin in the gastrointestinal tract and progress to the brain. Numerous studies provide credence to the idea that the microbiota in one's gut communicates with one's brain in Parkinson's disease (PD) via way of the immune system, a certain amino acid metabolism, and the neurological system. Through what has become known as the "gut microbiota-brain axis" (GMBA), the gut microbiota is thought to play an important part in the modulation of several neurochemical pathways. In the process of mediating the crosstalk between the gut microbiota and the physiology of the host, many of the metabolites produced by the gut microbiota, such as fatty acids, amino acids, and bile acids, carry signaling activities. In Parkinson's disease (PD), the quantity of amino acids and species-specific alterations of amino acids, such as glutamate and tryptophan, may interfere with the signaling transmission between nerve cells and disrupt the normal operation of the basal ganglia. Certain amino acids and the receptors that bind to them are being looked at as new possible targets for the treatment of PD. The purpose of the current investigation was to compile and analyze all of the evidence that is currently available on the gut microbiota-derived amino acid metabolic changes that are related to PD.

1. Introduction
Researchers have discovered that amino acids offer a significant contribution to the maintenance of human health. In recent years, the microbiota of the gut has garnered a significant amount of attention, propelling it to the forefront of the focus of biomedical research. The equilibrium of the bacteria that live in the digestive tract and the host both play an important part in a number of illnesses, one of which is the impairment of the neurological system. Notably, the microbiota in the gut, which is a major determinant of bidirectional communication between the gut and the brain, could be regulated by a number of different mechanisms. Furthermore, it is illustrated that the microbiota and its produced biochemical messengers are major aspects of maintaining a balanced intestinal microenvironment [1-5].

Amino acid molecules that originate from the microbiota can modulate immunological function, gastrointestinal physiology function,
and the makeup of the microbiota, all of which are beneficial to the host's health. In Parkinson's disease, a lack of dopamine in the striatum contributes to hyperactivity in the output pathways of the subthalamic nucleus. This leads to an abnormal increase in certain microbiota-derived amino acid molecules, such as glutamate, which are involved in the degeneration of the nigrostriatal system based on excitotoxicity mechanisms [6-8].

The second most prevalent form of neurodegenerative disease is known as Parkinson's disease (PD). The non-motor symptoms include constipation, postural hypotension, REM sleep disturbance, apathy, and dementia. The motor symptoms include tremors, stiffness, bradykinesia, and postural instability. PD presents itself in a unique way in each patient, but researchers have identified three major subtypes of the condition: those with the symmetrical motor disease, poor cognition, REM sleep disturbance, postural hypotension, and relatively rapid progression; those with intermediate symptoms; and those with tremor-dominant, unilateral, and slowly progressive disease [9-12].

There is a lengthy prodromal phase associated with Parkinson's disease, and this phase is frequently linked to non-motor symptoms such as REM sleep disturbance dysfunction. Aggregation of alpha-synuclein along critical neural networks in the autonomic nervous system, brainstem, and cortex has offered a unifying molecular basis for therapeutic intervention in Parkinson's disease [13]. This is the case despite the diversity of the symptoms and the heterogeneity of the clinical presentation of the disease. The neuropathological hallmark of multiple system atrophy, often known as MSA, is the accumulation of alpha-synuclein in oligodendrocytes [14]. Multiple System Atrophy is a related but more aggressive form of Parkinson's disease. Moreover, the neuropathological characteristic of Lewy body dementia is the diffuse deposition of alpha-synuclein inclusions in both the cortex and the brainstem [15].

2. Anatomy: Gastrointestinal Tract and Associated Brain Areas: Central Control of Gastrointestinal Motility

The gastrointestinal tract (GIT) represents a significant conduit through which the human body is subjected to external stimuli. It is innervated autonomously by the enteric nervous system (ENS), the largest component of the peripheral nervous system, consisting of numerous hundreds of neurons and glial cells that outnumber them. This network of neurons and glial cells within the GIT provides a complex and dynamic system for regulating and controlling the digestive processes [16]. The level of genetic variation found among neuronal and glial cell clusters is akin to that of cerebral cells. Neurons can be classified into three distinct categories, namely motoneurons, secretomotor neurons, and interneurons, and they have the capacity to produce acetylcholine, nitric oxide synthase, catecholamines, GABA, and a diverse range of neuropeptides. These findings suggest that the genetic variation in neuronal and glial cell groups is not only extensive but also highly complex, with a multitude of signaling pathways and biochemical processes involved in their regulation [17].

At minimum, four unique morphologies and chemical codings are discernible among glial cells. Such cells have the capacity to exhibit S100B, the reactive gliosis marker GFAP, PDGFR, or proteolipid-protein. With this diversity in play, the functional roles of glial cells can vary significantly depending on the specific molecular expression pattern and structural configuration [18, 19]. Glial cells, which are non-neuronal cells, are also present in the brain. In addition to neurons, both glial cells and neurons are distributed throughout the entire gut wall, spanning from the esophagus to the anus, as well as from the serosa to the mucosal layer. These cells are responsible for the formation of intricate networks observed in both ganglionic and aganglionic plexus. This suggests that glial cells play a crucial role in the development and function of enteric nervous system [20-23].

The EN displays a considerable range across the gut axis, which mirrors the multifaceted functional dissimilarities present...
among the different segments of the gut [24]. The regulation of gastrointestinal motility is carried out by neural circuits composed of various neuronal subtypes and glial cells. Despite the autonomous nature of the digestive tract, it can be influenced to differing degrees by the central nervous system (CNS) through various extrinsic inputs, with the vagus nerve being the most significant among them. The brain-gut axis serves as a crucial connection between the CNS and the digestive tract, in which the vagus nerve plays a prominent role. The brain-gut axis consists of two main pathways that link the brain and gut. This interdependent relationship between the brain and gut highlights the importance of the vagus nerve in the regulation of gastrointestinal motility. Ultimately, the complex and intricate nature of the neural circuits that govern gastrointestinal motility underscores the need for further study and understanding in this area [25-28].

The connection between the gut and the brain involves two distinct links. One of these links depends on humoral variables like cytokines, hormones, or bacterial metabolites from the gut microbiome. The other connection relies on a hardwired connection known as the vagus nerve. The vagus nerve contains up to 50,000 fibers that go in both directions. However, the vast majority of these fibers are afferent fibers, accounting for about 90% of all fibers. The efferent fibers provide parasympathetic motor impulses that originate in two brainstem nuclei - the dorsal motor nucleus of the vagus and the ambiguus nucleus [29-32]. These nuclei contribute to gastrointestinal motility. The afferent fibers are responsible for delivering information from the gut, while the efferent fibers provide these stimuli. Besides the direct input from the brainstem, there are several other pathways of impact represented, such as sympathetic fibers from prevertebral ganglia that connect the gut with thoracic segments of the spinal cord. These fibers connect the gut with the thoracic segments of the spinal cord, thereby playing a vital role in the gut-brain axis. The gut microbiome, cytokines, and hormones may also influence the gut-brain axis, highlighting the complexity of the interaction between the gut and the brain [24, 33-35].

3. The role of inflammation in the pathogenesis and progression of Parkinson's disease

The role of immune system aging in the context of neurodegeneration is a highly neglected and insufficiently researched factor. This is especially true when one considers that age is the major risk factor for many neurodegenerative illnesses. Immunosenescence is distinguished by its fundamental characteristics, which are an age-related immunodeficiency and an inflammatory aging process known as inflammaging. Inflammaging is defined by excessive low-level production of circulating inflammatory mediators, or cytokines, most notably C-reactive protein (CRP), interleukin-6, and tumor necrosis factor (TNF), from chronically stimulated innate and adaptive immune cells [36, 37]. The phenomenon of inflammaging is known to be linked with an augmented propensity for chronic maladies, including but not limited to cancer and cardiovascular disease. As individuals grow older, both the innate and adaptive immune systems gradually lose their efficacy, and this decline is further exacerbated in patients diagnosed with Parkinson's disease. Therefore, it is crucial to investigate the underlying mechanisms of inflammaging and its impact on immune system function to develop effective therapeutic strategies [38] (Figure 1).

The aging of the immune system is the most unappreciated and understudied contributing element in the study of neurodegeneration. This is especially true when one considers that age is the major risk factor for many neurodegenerative illnesses. Immunosenescence is distinguished by its fundamental characteristics, which are an age-related immunodeficiency and an inflammatory aging process known as inflammation. Inflammaging is defined by excessive low-level production of circulating inflammatory mediators, or cytokines, most notably C-reactive protein (CRP), interleukin-6, and tumor necrosis factor (TNF), from chronically stimulated innate and adaptive immune cells [36, 37]. Inflammaging is
associated with an increased risk of developing chronic diseases such as cancer and cardiovascular disease. Both the innate immune system and the adaptive immune system become less effective with age and are also significantly affected in people with Parkinson’s disease [38].

Fig. 1. Inflammatory manifestations in PD [39]. (This figure is distributed under the terms of the Creative Commons Attribution License (CC BY)). The diagram illustrates the various forms of inflammation observed in individuals with Parkinson’s disease (PD). The initial step entails intestinal dysbiosis and inflammation. This leads to an increase in the levels of circulating pro-inflammatory cytokines, which is the second step. The third step involves the activation of innate and adaptive immune cells and changes in frequency. The last two steps include blood-brain barrier permeability and peripheral immune cell infiltration of the central nervous system, as well as neuroinflammation, which are all indicative of a pro-inflammatory immune phenotype in PD. Furthermore, ROS, or reactive oxygen species, may also be involved in the process.

Inflammatory bowel illness as well as dysbiosis of the gut. Braak et al. proposed a theory in 2003 that the etiology of Parkinson’s disease (PD) begins in the gastrointestinal tract [40], and that related gastrointestinal dysfunction, such as a history of constipation, preceded motor symptoms and a diagnosis of PD in the clinic by decades 3,205. This theory was published in 2003. Since that time, the concept has undergone additional development to include contributions from the gut microbiota and intestinal inflammation as a mechanism driving pathology [41, 42]. It has been extensively reported that there are differences in the microbial composition of the gut between individuals with Parkinson’s disease (PD) and controls, which suggests that the gastrointestinal environment and its microbial residents are influenced in PD [43]. In patients with Parkinson’s disease (PD), several studies have found changes in the
relative abundance of certain bacteria. These bacteria include Prevotellaceae, Bifidobacterium, Akkermansia, and Lactobacillus. However, the results of these studies often differ due to differences in study design and methodology, patient populations, and choice of controls [44-47].

It is still unknown how specific taxa of gut bacteria could contribute to or trigger PD; however, a number of studies have shown associations between motor symptoms or disease progression as well as conditions associated with early, pre-motor stages of PD and the relative abundance of certain bacterial families within fecal samples from patients [48, 49]. This is despite the fact that it is still unknown how specific taxa of gut bacteria could contribute to or trigger PD. In addition, alterations in the bacterial composition of the gut have been linked to intestinal inflammation in people with PD [50, 51]. Patients with Parkinson's disease have been found to have higher levels of numerous inflammatory mediators in their stool compared to controls. These include IL-1, IL-1, CXCL8, CRP, and calprotectin. Furthermore, the levels of some of these molecules are inversely associated with the age of PD symptom onset, which suggests that they could contribute to the development of the disorder [52]. There is apparently a correlation between the levels of Bacteroides and Verrucomicrobia and the plasma levels of TNF and IFN-217, respectively. These data provide support for the idea that gut dysbiosis is associated with an inflammatory milieu, which may play a role in the beginning stages of the disease associated with PD. Research is still being done to figure out how to successfully target the microbiome of the gut in order to prevent or delay the onset of Parkinson's disease [53, 54].

4. Intestinal Bacteria

The gut dysbiosis that is reported in people with PD varies greatly from one report to the next due to the fact that the compositions of the intestinal microbiota vary from country to country, even in healthy persons. In addition, the taxonomic identities of the organisms found in each report are distinct from one another due to the fact that they vary depending on which database was used in the metagenome study. At the moment, SILVA is the taxonomic database that is utilized the majority of the time; however, Greengenes, the Ribosome Database Project (RDP), and NCBI are also occasionally utilized [55-57].

Akkermansia and Catabacter were the only enterobacteria genera that showed an increase in PD at the genus level. Lactobacillaceae and Akkermansia were shown to have a higher prevalence of PD at the family level. Additionally, in our own dataset, the presence of Akkermansia increased together with the progression of PD, but Faecalibacterium and Roseburia declined along with the progression of PD. Recent studies [58, 59] that included at least 100 patients with Parkinson's disease demonstrate that the prevalence of Akkermansia has increased whereas the prevalence of Lachnospiraceae, Roseburia, and Faecalibacterium has decreased. Short-chain fatty acids (SCFAs) are produced by Lachnospiraceae, Roseburia, and Faecalibacterium. Butyric acid is the most prevalent of these acids. In addition, Lactobacillaceae levels are frequently found to be elevated in patients with PD. However, the increase in Lactobacillaceae was primarily caused by a confounding impact of a catechol-O-methyltransferase (COMT) inhibitor, and it was also partially caused by a confounding effect of constipation. There was no significant difference in lactobacillaceae between people with Parkinson's disease who did not take a COMT inhibitor and healthy participants [60]. The absolute number of bacteria cannot be determined by the metagenome analysis of 16S rRNA sequencing data; only the relative abundance of each bacterium can be determined. Using quantitative reverse transcription PCR of 16S rRNA, it has been conducted an earlier study in which it has been examined absolute counts of 19 typical intestinal taxa that encompassed 71.3% of total intestinal bacteria. Based on our findings, it has been reported that the overall intestine bacterial count was lower in PD patients in comparison to healthy individuals [61]. Additionally, the overall number of intestinal bacteria was shown to have decreased in PD after two years [60]. The absolute counts of all of the bacteria that live in the digestive tract have only infrequently been reported, and the
clinical implications of decreased bacterial counts are still unclear.

5. Increased intestinal permeability in both IBD and PD

Patients suffering from inflammatory bowel disease have been shown to exhibit a reduction in tight junction expression, which leads to an increase in paracellular permeability. Furthermore, recent studies have highlighted that patients diagnosed with Parkinson’s disease have lower levels of occludin and ZO-1 expression in their colon biopsies. This suggests that there may be a correlation between the two diseases with regards to their effects on intestinal permeability [62]. The epithelial tight junctions, which link neighboring enterocytes and regulate paracellular permeability through the lateral intercellular space, are of utmost significance among the structures present in the IEB [63] [Figure 2].

![Diagram of tight junctions](image)

**Fig. 2.** Tight junctions (TJs) of epithelial intestinal cells play an essential role in regulating paracellular permeability, thereby forming selective barriers [63]. (This figure is distributed under the terms of the Creative Commons Attribution License (CC BY)). The composition of TJs is primarily constituted by a variety of proteins, the most notable being zonula occludens-1 (ZO-1), claudins, and occludin. These proteins serve as integral components of TJs, and their interplay ensures that only select molecules are allowed to pass through the intercellular space, while others are excluded. Therefore, the molecular architecture of TJs is crucial for maintaining the homeostasis of epithelial tissues and preserving their physiological functions.
Several studies have demonstrated that individuals with Parkinson’s disease exhibit substantially elevated levels of sucralose in their urine, yet their urine contains normal quantities of mannitol and lactulose [64], suggests that the colon of these patients has hyperpermeability. The markers of heightened intestinal permeability, specifically alpha-1-antitrypsin and zonulin, which are elevated in individuals suffering from inflammatory bowel disease, have been demonstrated to be significantly amplified in patients with Parkinson’s disease in comparison to controls of similar age [65]. This is the case even though both of these markers are up in IBD patients. The markers in question, although not tailored to a specific ailment, do provide support for the notion that enhanced intestinal permeability is indeed a contributor to Parkinson’s disease. Elevated levels of intestinal permeability result in augmented susceptibility to antigens and microorganisms present within the lumen [60], the promotion of immunological reactions and intestinal inflammation subsequently triggers the expression of excessive -synuclein in the colon or propels its misfolding [66].

6. The hypothesis of PD in the gut

Prior to 1980, only a small number of researchers explored the pathogenesis of Parkinson’s disease. The mechanism remained a mystery until the time when the description of Lewy bodies was published for the first time. Oxidative stress [67], mitochondrial dysfunction [29], excitotoxicity [68], inflammation, neurotrophic factor-deficiency [69], and the notion of gastrointestinal origin were the primary hypotheses that were considered to be involved in the etiology of Parkinson’s disease (PD). Among these, PD that originates from the gut and oxidative stress has received a greater amount of attention. Oxidative stress has been linked to a number of neurodegenerative illnesses, including Parkinson’s disease (PD), as data accumulated to support this theory [67]. While low levels of oxidative stress could promote mitochondrial elimination and safeguard their biological function, large levels of oxidative stress beyond the capability of the cell could have the opposite effect by changing the potential of the mitochondrial membrane and protein synthesis in the cytoplasm [70, 71].

The aberrant accumulation of α-syn in the central nervous system has been the primary focus of research done in the past on the pathophysiology of Parkinson’s disease. In recent years, a plethora of studies have shed light on the fact that the development of Parkinson’s disease is linked to the homeostasis of gut microbiota as well as metabolites. Concurrently, it has been disclosed [63] the presence of a bidirectional network that they referred to as GMBA. By modulating neurotransmitters and the receptors that they are attached to, the GMBA may alter human behavior as well as the neurochemistry of the brain in PD patients. When considered as a whole, the gut origin hypothesis suggests that the gut may be a possible origin of the pathogenesis of Parkinson’s disease (PD), hence providing new insights into the mechanisms that underlie PD.

7. Conclusion

All of the investigations have pointed to the possibility of a significant correlation between GMBA and the pathophysiology of PD. In spite of the fact that the interaction between microbiota and hosts has received a lot of attention in recent years from both physicians and researchers, there is still a need for a deeper comprehension of the complicated GMBA relationship. In addition, the microbiota-derived amino acid metabolism is a significant element that points to large alterations in the microbiome. Amino acids metabolized by gut microbiota might have an effect on the progression of nigrostriatal degeneration in people with Parkinson’s disease (PD). Gut It’s possible that microbiota and amino acids could be used as treatment targets for PD.

Conflict of Interests

All authors declare no conflict of interest.

Ethics approval and consent to participate

No human or animals were used in the present research.
Consent for publications

All authors read and approved the final manuscript for publication.

Informed Consent

The authors declare not used any patients in this research.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

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