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Gut-Brain Axis and Two Major Neurodegenerative Diseases: A Literature Review on the Role of Microbiota

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Abstract

The gut-brain axis is a term that describes the intricate bidirectional communication network between the digestive system and the nervous system through various pathways. The most popular and undoubtedly the most decisive component of this axis is the microbiota. The microbiota is closely related to many systems and one of these systems is the nervous system. Although studies on the role of the microbiota in diseases have been conducted for many years, interest in this field has begun to increase, especially in the last decade with promising results and the widespread use of techniques such as 16S rRNA sequencing. Uncovering different factors in disease processes opens the door to a more integrated and effective approach in treatment modalities. Microbiota, one of the most mysterious examples of these factors, both brings a new perspective to the standard models of diseases and encourages new studies with valuable data. Therefore, further studies on this topic, which is a candidate to be defined as a common pathway in the background of system/organ-specific physio pathological models, is noteworthy in terms of its potential to bring a breath of fresh air to diseases that are felt desperate.

Keywords

Microbiota, Nervous System, Neurogenesis, Alzheimer Disease, Parkinson Disease

Introduction

The gut-brain axis is a term that describes the bidirectional communication between the gut and the brain [1]. This communication occurs through various metabolic, immune and signaling pathways. The brain's effects on the gut through the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis have long been recognized. The modulation of the gut on the brain, especially on behavior, has gained importance in recent years. This modulation occurs through three pathways: neural pathway, immune pathway and endocrine pathway. Recently, a third side in this communication has been identified: the microbiota. In this review we will mainly consider the mechanisms by which the gut, the microbiota and the central nervous system (CNS) interact with each other and their relationship with two major CNS diseases [2].

Many aspects of this communication are being investigated: communication pathways, interactions, mediators, influencing environmental factors and diseases. A growing number of studies are providing new insights into nutrition and therapies for a healthy brain.

The microbiota may interact with the CNS indirectly through their effects on the gastrointestinal tract or directly through their own metabolites [3]. The effects of intestinal microbiota on enteric nervous system (ENS), intestinal permeability, intestinal motility and immune system, are known [4,5]. The direct effects of intestinal microbiota on the CNS are hard to research and still very insufficient. Preclinical studies are most important source of information about the effects of the microbiota on the brain. Germ free models, specific pathogen free models, and fecal microbiota transplant models are the most commonly used study models in preclinical studies [2].

Although the number of preclinical studies has increased compared to the past, human studies are limited due to reasons such as environmental effects, high dietary diversity, genetic diversity, difficulty of structural examination, and difficulty of cognitive and emotional evaluation of people [6]. Behavioral and emotional disorders, chronic pain and neurodegenerative diseases are main focus on clinical studies. Another important component of these studies is taxonomic diversity. With the widespread use of genome-wide sequencing, the number and quality of studies in this field has increased.

Communication Mechanisms in the Gut-Brain Axis

The first step, perhaps the most important step, in understanding the gut-brain axis is to identify the communication pathways and mediators. The gut can modulate the brain through three possible pathways: neuronal, immune and endocrine pathways [9]. And these pathways have two barriers to overcome: the gut barrier and the blood-brain barrier (BBB). The microbiota can influence this communication by regulating these barriers, or by directly secreting some molecules that regulate these pathways, or by causing some to be secreted by the host [2].

1.Communication Pathways

Neuronal Pathway: Two components of neural pathways are enteric nervous system and ANS. The ENS consists of an extensive neuronal network in the intestinal submucosa and muscularis propria layer, and this network can autonomously modulate gastrointestinal functions. The ANS is a neural network consisting of sympathetic and parasympathetic nerves found in both the central and peripheral nervous systems. Main component of peripheral parasympathetic system is vagus nerve (VN) and ENS can interact with CNS via VN. The development, integrity and functions of the ENS may be regulated by the microbiota [8].

Alterations in the microbiota may cause changes in lipopolysaccharides and short-chain fatty acids (SCFAs) in the intestine, leading to changes in intestinal motility, permeability and immune response [5,9]. It may also contribute to the maturation of the ENS via 5-Hydroxytryptamine (5-HT).

Molecules secreted by the microbiota can regulate the electrical activity of the ENS and may cause long-term changes in the CNS, particularly in the dorsal hippocampus [10]. In addition, some of these metabolites can be transmitted to the CNS via the VN and cause some structural changes [11].

Parkinson's disease (PD) is one of the most important clinical consequences of this transmission system. The Braak hypothesis suggests that alpha-synucleinopathy occurs in the gastrointestinal tract and is transmitted retrogradely through VN to the dorsal motor nucleus. The role of the VN on behavioral alterations have been partially demonstrated in studies in GF and SPF animals that underwent subdiaphragmatic vagotomy.

Immune Pathway: Microbiota may impact on both innate and adaptive immune system cells and functions and thus create some changes at CNS [12]. Innate immune system is body's first line defense systems against potential dangers. Intestinal barrier and BBB are two main barriers. Intestinal barrier has two 2 layers: mucus layer and basal monolayer of epithelial cell. Tight junctions such as zonula occludens proteins also contribute significantly to the integrity of this barrier. There are studies proposing that changes in the gut microbiota affect these layers and thus resulting in alterations in the permeability of the intestinal barrier [7]. Microbiota may also regulate another defensive barrier, the BBB. Studies show that GF mice have increased BBB permeability, and SCFAs and LPS are likely mediators of this effect. The microbiota may influence the adaptive immune system by regulating microglia development and function. Studies show that microglia function and maturation are impaired in GF mice compared to SPF mice and that damaged microglia functions can be normalized with SCFA supplementation [2,13]. Microbiota-immune system communication has gained particular importance in neurodegenerative diseases (NDDs) and multiple sclerosis.

Endocrine Pathway: There are two main components of microbiota-endocrine system communication: the HPA axis and enteroendocrine cells (EECs). The HPA axis modulates the body's response to stress. The HPA axis is a key component in the brain's regulatory influence on the gut. Studies in GF mice show that HPA axis activity increases in response to stress [14]. Previous studies shows development of HPA axis can affect by composition of gut microbiota. Increased stress-related changes in the gut-brain axis are related with function of NMDA receptors and neurotrophic factors [15].

EECs are one of the best-characterized pathways that influence the gut-brain axis that are sensory cells located in the gastrointestinal mucosa that secrete different types of peptide hormones. There are more than 10 different types of EECs known, and the best understood EEC types are enteroendocrine L cells and enterochromaffin cells. Gastric inhibitory peptide, ghrelin, 5-HT, somatostatin, cholecystokinin are the most well-known enteroendocrine hormones. Enteroendocrine L cells secretes mainly somatostatin and peptide YY.

FFAR 1-4 receptors are located at the apical borders of EECs. FFAR 1-4 are sensitive to long-chain fatty acids, while FFAR 2-3 are sensitive to SCFAs. Bacterial metabolites such as LPS specifically affect enteroendocrine L cells in the distal intestine. Somatostatin and peptide YY may induce behavioral changes and satiety [16].

Enterochromaffin cells synthesize most of the 5-HT produced in the body since only 5% of the 5HT produced is found in the CNS, the role of enterochromaffin cells is important in this situation. The effect of the microbiota on enterochromaffin cells is less well known than on L-type cells. One study showed a 2-fold decrease in plasma 5-HT levels in GF mice compared to normal mice. A separate study showed that plasma and hippocampal 5-HT levels were increased in GF mice, but plasma 5-HT levels were increased but hippocampal levels were unchanged in normal mice. 5-HT plays an important role in emotion, sleep, appetite, and several other important physiological functions [17].

2.Bacterial Metabolites

Bacterial metabolites originating from the intestinal microbiota can modulate the CNS directly or indirectly through their peripheral effects and can be classified as SCFAs, amino acid metabolites and others.

Short Chain Fatty Acids: Acetate, butyrate and propionate constitute 95% of the SCFAs produced by the microbiota from dietary fibers. SCFAs are probably the most studied microbiota-derived metabolites. Some microbiota species like Bacteroides, bifidobacterium, eubacterium, lachnospiraceae, lactobacillus have the ability to synthesize SCFAs [18]. Animal studies have found lower levels of SCFA in the plasma and feces of GF animals compared to healthy individuals. SCFAs have been shown to have effects on circadian rhythm, blood pressure control, gastrointestinal functions, and the immune system [2].

There are studies on the interaction of SCFAs with the gut-brain axis through almost all pathways and with many neurological diseases. SCFAs can also exert cellular and extracellular effects by entering the intestine or systemic circulation. SCFAs begin their effects in the intestines by affecting both mucus production and intestinal motility. Furthermore, SCFAs have been shown to affect both intestinal permeability and the BBB by regulating tight junction proteins. It has been shown that the impaired BBB in GF mice is restored by butyrate and propionate treatment [19]. SCFAs also have some effects on cellular levels.

Inhibition of histone deacetylase (HDAC) by epigenetic modulation is a common effect of all SCFAs, and it has been shown that this inhibition can affect learning and memory [20]. SCFAs show their effects via G-protein coupled receptors FFAR2 and FFAR3, and through these receptors, SFAs can regulate the release of peptide YY and somatostatin from EECs [18]. SCFAs have anti-inflammatory effects on the immune system which them decreasing neutrophil chemotaxis and cytokine secretion, and the regulation of peripheral regulatory T cells. Our knowledge of the direct effects of SCFAs on the CNS is still insufficient. Studies have shown that only acetate passes into the CSF among SCFAs [2]. It has also been shown that SCFAs affect the CNS, especially in behavioral and mood disorders, by affecting BDNF and other neurotrophic factors [21].

Amino Acid Metabolites: The aromatic amino acids tyrosine, phenylalanine and tryptophan cannot be synthesized by animals. These amino acids can be synthesized de novo by the intestinal microbiota. The supply of aromatic amino acids is important because they are the source of catecholamines in the human body. The sources of L-dopa, dopamine, norepinephrine and adrenaline are tyrosine and phenylalanine; tryptophan is the precursor of serotonin. In addition, lactobacilli and bifidobacteria in particular can produce GABA from glutamate. Gut microbiota may have an effect on both the ENS and CNS by affecting neurotransmitter (NT) synthesis via aromatic amino acid synthesis [7].

In addition to their indirect contribution to NT synthesis, microbiota can directly synthesize some neuroactive metabolites. Recent studies show that gut microbes can convert tyrosine into a subtype called 4-ethyl phenyl sulphate (4EPS). This molecule has been shown to cross the BBB and disrupt oligodendrocyte myelination, which is associated with anxiety [18]. Microbiota plays a direct and indirect role in the synthesis of Kynurenine, another active neurometabolite derived from tryptophan. Kynurenic acid (KynA) and quinolinic acid, secondary metabolites of kynurenine, are important in gut-brain pathophysiology. KynA and quinolinic acid may only cross the BBB when this barrier is damaged, or they may be produced in the CNS via kynurenine, which crosses the BBB. Quinolinic acid is an NMDA receptor agonist and has been shown to have neurotoxic proinflammatory effects. There are studies indicating that KyA also protects neurons against glutamate-induced toxicity. Microbiota may affect kynurenine synthesis by stimulating IDO-1 enzymes in the intestine and TDO enzymes in the liver [16].

Bile Acids: Bile acids are the major lipid components of bile, and primary bile acids are synthesized from cholesterol in the liver and conjugated to secondary fatty acids and metabolites by the intestinal microbiota. Bile acids play an important role in the absorption of fat-soluble vitamins and dietary lipids. Recent studies have shown that bile acids have neuroprotective effects and low bile acid levels are associated with neurotoxicity [2]. Bile acids can act on the CNS by stimulating the release of FGF and GLP1 through the farnesoid x receptor (FXR) and the G protein-coupled bile acid receptor (TGR5). Taurodeoxycholic acid reduces neuronal cell death by stimulating the TGR5/SIRT3 signaling pathway, while the FXR/FGF signaling pathway shows anti-inflammatory effects in the CNS through the neuroimmune system [7].

Trimethylamine N Oxide: Trimethylamine N Oxide (TMAO) is a metabolite formed by bacterial fermentation of L-carnitine and phosphatidylcholine in the intestine and oxidation in the liver and is associated with an increased risk of cardiovascular, metabolic and cerebrovascular diseases. Although the presence of TMAO in CSF has been shown in recent studies, its exact mechanism is not known. This may be due to increased permeability of the BBB to TMAO or de novo synthesis in the brain [22]. In studies evaluating TMAO plasma levels, it was observed that TMAO levels were higher in patients with Alzheimer's disease (AD) and mild cognitive impairment (MCI) than in healthy controls, but there was no difference between patients with AD and MCI [23]. The association of TMAO with AD is mostly associated with an increased risk of vascular disease. On the other hand, there are studies showing that its association with the CNS and dementia may have an effect on cognitive functions by disrupting the BBB, causing mitochondrial dysfunction, and inhibiting the mammary target of rapamycin (mTOR) [18]. Studies have shown that TMAO given to mice caused a decrease in memory and learning, which is associated with neuroinflammation. All of these studies suggest that TMAO is associated with cognitive impairment.

Bacterial Amyloid Proteins: There are amyloid proteins that are metabolites of intestinal bacteria such as Curli and are particularly associated with the pathophysiology of NDDs. This topic is also discussed in the relevant diseases section.

3.Gut-Brain Axis Influence on Synaptic Plasticity and Neurogenesis

The reorganization of the nervous system is defined as plasticity, and synaptic plasticity and neurogenesis are examples of this process. This organization may lead to functional or structural changes.

In infants and children, plasticity plays an important role in neurodevelopment also recent research suggests that plasticity has positive effects on post-traumatic recovery, learning, and memory. Synaptic plasticity and neurogenesis are increasingly being investigated for their relationship to learning and memory and these studies revealed microbiota affect plasticity directly and indirectly. Synaptic plasticity is the long-term changes in neuronal networks. Synaptic plasticity can particularly affect cognitive and emotional changes through cellular and physiological changes [24]. Synaptic plasticity is most clearly observed in the hippocampus. Histological observations of synaptic plasticity can be seen as long-term potentiation (LTP) and long-term depression (LTD) in the hippocampus, which is associated with memory and learning. LTP is a marker of a healthy brain and is impaired in neurodegenerative patients [25]. The microbiota is associated with many processes in synaptic plasticity such as synaptic remodeling, synaptogenesis, neurogenesis. Neurogenesis is probably the most studied process in relation to the microbiota.

Neurogenesis is development and formation of new neurons from neural stem cells and is highest in early development and declines with age. So far, neurogenesis has been observed in two areas of the adult brain: subgranular zone in the dentate gyrus of hippocampus and subventricular zone of lateral ventricles for olfactory bulb [26]. Extrinsic and intrinsic factors such as stress, physical activity, learning, stem cell profile, hormones and neurotrophins are associated with the modulation of adult neurogenesis. The importance of neurotrophins has begun to be understood in recent years as the relationship between neurogenesis and depression, anxiety and AD has begun to be revealed [27]. The most studied neurotrophic factor is brain-derived neurotrophic factor (BDNF) and is the only neurotrophic factor found to be associated with the gut microbiota so far. BDNF stands out as an important regulator for the production and maintenance of LTP in the cornu ammonis 1 (CA1) region of the hippocampus. The association of BDNF with microbiota has been demonstrated even at the level of specific microbiota species, showing that BDNF expression is reduced in the CA1 region of the hippocampus in germ-free mice, and also studies show a positive correlation between BDNF levels and Lactobacillaceae and Bifidobacterium. Firmicutes and Bacteroidetes phyla are species that have been shown to have a negative relationship with BDNF levels and neurogenesis [27]. Probiotic supplementation in germ-free mice has been shown to increase LTP in correlation with BDNF expression and has been associated with improved learning and memory [28].

The microbiota may influence the regulation of synaptic plasticity through other factors besides neurotrophins. The most notable of these factors is the altered expression of genes in the amygdala and hippocampus in GF mice. Approximately 50 genes were shown to have increased or decreased expression in the hippocampus, related to all factors affecting plasticity, from the regulation of intracellular tubules to NT synthesis [21]. Studies show that gut microbiota may also regulate plasticity via NMDA receptors; NMDA receptor levels were found to be reduced in GF mice. It is known that in addition to its direct effects, microbiota can cause some changes in synaptic plasticity through some indirect pathways such as SCFA production, HPA axis and inflammation [28].

Microbiota and Neurodegenerative Diseases

The microbiota is an extremely important determinant involved in many metabolic processes and disease development pathways. As mentioned above, there is a close interaction between the gut microbiota (GM) and the nervous system through different mechanisms. This interaction may result in the maintenance of neuronal homeostasis or the progression of the pathological process that also affects neurological diseases [29].
Although studies on the role of microbiota in diseases have been conducted for many years, interest in this field has started to increase, especially in the last decade, with promising results and the widespread use of techniques such as 16S rRNA sequencing. This increase has naturally manifested itself in the field of neurology, where many diseases have a chronic course. Neurological diseases are generally classified into common clusters such as cerebrovascular diseases, neurodegenerative diseases and demyelinating diseases. Although there are microbiota studies on many neurological diseases in these groups, we decided to select diseases that are relatively common, have a larger database and have a more clearly defined relationship with the microbiota. For this reason, we will only mention two prominent examples that can be considered as prototypes of neurodegenerative diseases; AD and PD.

1.Microbiota and Alzheimer's Disease

Dementia is a neurodegenerative condition characterized by a progressive deterioration in intellectual capacity as a result of impairment in at least two cognitive domains, affecting more than 55 million individuals globally [30,31].

The number of dementia cases is expected to exceed 150 million by 2050 [32]. Despite this prevalence, dementia (essentially all NDDs) does not yet have a curative or preventive treatment. Therefore, understanding a major factor in the pathophysiology, such as the microbiota, will contribute to the treatment of all neurological diseases in which the microbiota plays a role. The relationship between microbiota and cognition has been investigated for more than a decade and a clear association between dysbiosis and cognitive modulation has been found [33]. Microbiota composition has also been associated with cognitive dysfunction associated with chronic inflammation and metabolic syndrome.34 Furthermore, diet and exercise have been identified as important factors associated with impaired microbiota and cognition, emphasizing the importance of modifiable risk factors [34, 35]. Indeed, in its latest study published in 2024, the Lancet Commission updated the modifiable risk factors for dementia and stated that approximately 45% of them are potentially manageable/preventable [36]. Therefore, the microbiota, whose role is not yet well understood, has the potential to contribute to the expansion of therapeutic approaches.

AD is the most common type of dementia, accounting for 60-80% of dementia cases, and is the single most common NDD [30,37]. The main clinical features include memory impairment, visuospatial deficits, object loss, language decline, and impaired executive functioning; various psychiatric symptoms and hallucinations may occur in advanced stages [38]. Extracellular deposition of amyloid beta (Aβ) protein (amyloidosis) and intracellular deposition of neurofibrillary tangles resulting from hyperphosphorylation of tau protein (tauopathy) are the main features of AD pathophysiopathology. These mechanisms are thought to be followed by neuroinflammation, oxidative stress from reactive oxygen species (ROS), mitochondrial dysfunction and neuronal loss leading to eventual atrophy [39]. However, beyond neuroinflammation secondary to defective protein deposition, this pathogenesis is also thought to be secondary to systemic inflammation [40,41]. For example, a study published in Nature in 2017 suggested that peripheral systems are also involved in Aβ metabolism and communicate with central pathways, and that systemic abnormalities in AD are indicative of the disease process rather than secondary to cerebral degeneration [42].

In parallel, some studies have suggested that the oral microbiota plays a role in AD pathogenesis by inducing local and systemic inflammation through pathogenic bacteria and inflammatory mediators [43-45].

In addition to the oral microbiota, the lung microbiota, and GM in particular, are also associated with AD [46,47]. The role of the lung microbiota is only now being investigated, but the literature on the association of GM with AD is much more extensive. For instance, pathogenic bacteria (such as Escherichia Coli and Salmonella spp.) have been identified that produce amyloid-like "curli" protein with functional similarities to Aβ, and it has been suggested that this promotes central Aβ pathology through neuroendocrine activation [48,49]. Thus, GM plays a role in AD pathogenesis through some of the mechanisms mentioned above. These mechanisms include the nervous system pathway [direct bidirectional interaction through the vagal nerve (VN) and enteric nervous system (ENS)], the immune system pathway [proinflammatory cytokines triggered by lipopolysaccharides (LPS) and specific metabolites such as polysaccharide A (PSA)] and the small molecule metabolite delivery system pathway [neurotransmitters, bile acids, short-chain fatty acids (SCFAs) produced by microbiota bacteria]; The integrity of the intestinal barrier and blood brain barrier (BBB) is crucial for the activation of these pathways, while SCFAs play a role in maintaining synaptic plasticity and BBB integrity [50-52].

Within these mechanisms, the GM composition of patients with AD shows some differences. A study examining gut microbiome changes in a group of patients with AD found a decrease in microbial diversity as well as compositional differences [53]. Although studies have reported different results in terms of phylum abundance [47], a decrease in Firmicutes abundance and an increase in Bacteroides abundance stands out as a relatively common finding in many studies (in addition to the mechanisms listed in the previous paragraph, Bacteroides species are important in influencing P-glycoprotein levels) [49, 51-55]. It has been noted that regional differences may play a role in reporting these inconsistent results [56]. However, the relatively consistent results of the findings regarding these two major phyla of gut flora in humans can be seen in the fact that a Firmicutes/Bacteroides ratio has been described in therapeutic research [57,58]. Current microbiota-based therapeutic approaches for AD include a broad spectrum, primarily probiotics and prebiotics (plus symbiotics and postbiotics), fecal microbiota transplantation (FMT), antibiotics, gut microbiota-derived metabolites (SCFAs, secondary bile acids, etc.), bacteriophages and diet, but no promising treatment is yet available and further studies are needed [49, 57-59]. The recently reported magnesium-L-threonate treatment highlights the importance of further study as an alternative candidate for AD treatment through modulation of the gut-brain axis [60].

2.Microbiota and Parkinson's Disease

PD is the second most common NDD and the most common neurodegenerative movement disorder with 8.5 million PD patients reported in 2019 [61]. PD is characterized by motor and non-motor symptoms (NMSs). Tremor, bradykinesia, rigidity and postural instability are the main motor symptoms. Besides that, there is a wide range of NMSs, mostly disorders of the gastrointestinal tract, autonomic, cognitive and behavioral symptoms. Most NMSs are associated with gastrointestinal syndromes. In particular, constipation, dysphagia, gastroparesis, and irritable bowel syndrome without diarrhea have been associated with an increased prevalence in PD compared to other neurological disorders [62]. Although constipation is the most common gastrointestinal symptom, the prevalence of other gastrointestinal symptoms is also high compared to other neurological disorders [63]. For example, one study showed a very high rate of esophageal dysmotility in PD patients with a prevalence of 80% [62].

One possible suspected cause of this condition is the microbiota. NMSs can often precede motor symptoms. Constipation may be present for an estimated one or two decades before PD is diagnosed [64]. All this suggests that PD may cause pathological changes in the gastrointestinal tract before affecting the CNS, so researchers have been looking for evidence of preclinical stages of PD in the gut for some time. PD is one of the most common diseases whose interaction with the gut-brain axis has been studied. Much of the research focuses on gut-brain communication pathways and potential signaling mediators. The microbiota has a key role in this research. PD is an NDD characterized by neuroinflammation and Lewy pathology [65]. Lewy bodies and Lewy neurites are accumulations of alpha-synuclein (α-syn) in the CNS [66]. α-syn is a molecule with high synthesis in the presynaptic terminals of neurons, especially in the ENS [67]. In 2002, Braak and colleagues described the correlation between Lewy pathology and disease progression [68]. The following year, Braak and colleagues hypothesized that PD is of gut origin [69]. According to the Braak model, Lewy pathology is not random. Projection neurons with long unmyelinated or poorly myelinated axons are susceptible to damage. The disease process starts in the CNS in the dorsal motor nucleus of the VN and ascends rostrally through the midbrain [70].

Since the main pathologies in PD are inflammation and synucleinopathy, the effects of microbiota on PD have continued to be investigated in this direction [71].
The microbiota can influence gut-brain communication through direct microbial effectors or host gut cell-derived proteins induced by the microbiome. The gut and brain can communicate with each other in two possible ways: neuronal pathways and blood circulation. Much of the current research focuses on neuronal pathways as a potential communication pathway in synucleinopathies. Research shows that the VN is a promising channel for communication in synucleinopathies. Although most of the current studies show that the VN is the main pathway, there are some models and postmortem studies for alternative neural pathways [72, 73]. In addition to neural pathways, blood circulation has recently gained importance. The isolation of α-syn from blood, which contains erythrocyte-derived extracellular vesicles, shows a new avenue for research [74].

The microbiota can act through signaling molecules produced by gut microbes or host molecules stimulated by GM. The most important molecules investigated as microbiota-derived that contribute to the progression of synucleinopathy are amyloid proteins and SCFAs. Some recent studies show that curli proteins, mentioned in “Alzheimer's Disease”, can also induce α-syn aggregation [75]. Apart from curli proteins, PSM proteins are other molecules that may be associated with synucleinopathy and are synthesized by Staphylococcus aureus [76]. Prevotella and Clostridia are the leading producers of SCFAs, the effects of which are listed above [77]. Decreased levels of SCFAs and the bacteria that produce them are observed in the feces of PD patients [78,79]. Some studies have shown that there may be a reciprocal exchange between fecal and serum SCFA levels, which may be explained by increased intestinal permeability. SCFAs regulate the integrity of the BBB and are also involved in intestinal permeability [80]. There are studies showing increased intestinal permeability in PD patients compared to healthy controls [81]. In addition, altered microbiota may affect synucleinopathy by changing the levels of gut hormones and peptides. Studies show reduced levels of ghrelin and neuropeptide Y in PD patients [82]. Furthermore, GM may regulate the composition of bile acids, and bile acids may function as a signaling molecule in the brain [83]. One study has shown an association between increased bile acid levels and PD [84].

Since bacterial culture is difficult, the application of 16S rRNA gene sequencing has greatly increased the number of studies in this field. Most of our knowledge on the relationship between PD and microbiota comes directly from studies on microbiota taxonomy. These studies have provided important insights into the changing microbiota and their impact on PD patients. For example, to mention one of the most recent ones, a meta-analysis conducted in 2024 showed an increase in Bifidobacteriaceae, Ruminococcaceae, Rikenellaceae, Lactobacillaceae, Verrucomicrobiaceae and Christensenellaceae groups, and a decrease in Prevotellaceae, Lachnospiraceae, Erysipelotrichaceae and Faecalibacterium groups in PD patients compared to healthy volunteers [85]. There are also studies that found a relationship between Helicobacter pylori and PD [86]. In most of the studies, it was concluded that individuals with PD have a different profile in terms of microbiota composition than healthy controls, and proinflammatory bacteria and cytokines were found more intensely [87, 88].

Studies showing the relationship between microbiota and PD have led to new therapeutic targets. Diet, prebiotics, probiotics and FMT are the most studied therapeutic areas. FMT is a safe treatment for Clostridioides difficile infection. It is not yet approved for the treatment of any other disease. Due to the increasing number of studies showing the relationship between PD and microbiota, FMT trials have been conducted in this patient group in recent years. Two of these studies are placebo-controlled and randomized trials. These studies had small sample sizes and relatively short follow-up periods. A placebo-controlled, double-blind phase 2 study was recently published.89 In this study, the results showed a statistically significant improvement in MDS-UPDRS scoring during the off period. All these studies provide an important avenue for understanding the pathophysiology and treatment of PD and other NDDs and should be continued.

Conclusion

Although studies on the gut-brain axis and the role of the microbiota in neurodegenerative disease processes are still relatively limited, there are already identified associations with many neurological and systemic diseases. Even within the current state of knowledge, microbiota-targeting recommendations aimed at modifiable risk factors have a critical complementary role in the management of these diseases. With new studies being added to the literature every day, it is highly likely that in the future these physiopathological relationships will be more clearly defined and new therapeutic possibilities will emerge.

Author contribution statement

TM and İMM provided communication with the journal; TM, BS and İMM generated ideas; TM and BS took part in literature search and writing; TM did the editing.

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None Declared.

Ethical approval

Since no live subjects were used in the research, there are no ethical issues.

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