JULS REVIEWS

The Role of Gut Microbiota in Neurodegenerative Diseases

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Abstract

Background:

The human gut microbiota comprises trillions of microorganisms that live in the gastrointestinal system and interact extensively with the host. The diversity and stability of the gut microbiota have been linked to not only intestinal health but also brain function. Recent studies suggest that the gut microbiota communicates with the brain through a variety of mechanisms, in what is termed the "gut-brain axis." The neural, endocrine, immune and humoral means of signaling from the gut microbiota to the brain provide a link between gut microbiota and neurodegenerative diseases.

Purpose:

This review summarizes the current evidence that gut microbiota affects brain function through the vagus nerve, hormone signaling, the immune system and microbial metabolites. The relevance of these interactions is discussed in the context of neurodegenerative diseases, focusing particularly on Alzheimer's disease and Parkinson's disease. Furthermore, the implications to therapeutic interventions for the onset and progression of neurodegenerative diseases are highlighted.

Findings:

Preclinical studies have established the significance of the gut-brain axis and identified various mechanisms in which the gut microbiota could affect brain development and function. Several animal studies link neurodegenerative diseases to altered microbial compositions, suggesting the potential of identifying novel microbes as biomarkers. Moreover, a few animal studies use novel strategies to alter microbial compositions and thereby rescue disease phenotypes, which reveal the therapeutic potential. Research in humans largely relies on an analysis of the patient populations, with an emphasis on the association of altered microbial compositions with the onset and progression of brain pathologies. Hence, high-quality clinical studies are needed to elucidate the relative impact and causal contribution of the human microbiota to neurodegenerative diseases. Indeed, such clinical investigations may pave the way for more feasible and readily accessible means of interventions, in the forms of diet, prebiotics, probiotics and fecal transplantation.

1. Human Gut Microbiota

1.1 Gut Microbial Composition

The human gut microbiota consists of 100 trillion microorganisms that reside in the gastrointestinal (GI) system [1]. These microorganisms include bacteria, viruses, fungi, protozoa and archaea, whose collective genome is termed the gut microbiome. There is increasing evidence that the gut microbiota resembles a densely populated and diverse microbial community [2]. In particular, recent advances in DNA sequencing technology and bioinformatics tools have enabled profiling of the microorganisms inhabiting in the healthy human GI tract [3]. The gut microbiome has been found to contain four million distinct bacterial genes4, reaching 22 different phyla, 1000 different species, and 1000 viable bacteria per gram of luminal content [5, 6]. The density of microbiome is highest in the large intestine, where Firmicutes, Bacteroidetes, Proteobacteria and Actinobacteria are the most abundant organisms and constitute the core microbiome in healthy adults [5, 7].

1.2 Gut Microbial Colonization and Alterations

The human microbiome changes with age, following a certain pattern of microbial colonization of the GI tract [8]. Although bacteria have recently been found in the placenta and amniotic fluid8, the fetal GI tract is considered sterile prior to birth, with the first major microbial colonization occurring at delivery [9]. The earliest gut microbiota primarily consists of bacteria that can metabolize the lactose absorbed from milk; its composition is influenced by factors such as the mode of delivery (vaginal birth vs. cesarean section), source of nutrients (breast milk vs, formula), geography and exposure to antibiotics [10-16]. The infant microbiota continues to evolve and begins to resemble that of the adult at 2-3 years of age [17]. With the introduction of solid food, the gut becomes dominated by bacterial species associated with carbohydrate, protein and fat utilization and vitamin synthesis [18]. As such, the early development of the gut microbiota is vulnerable and perturbations

may have far-reaching impacts on health, including brain development and disease [19-22].

Although healthy adults share a core microbiome [5, 7], the gut microbiota exhibits inter-individual differences and may undergo changes throughout life [23]. The taxonomic variability within the GI tract depends on many factors, including host genetics, living environment, drug and antibiotic use, stress, infection and diet, some of which can dramatically influence the microbial composition over a relatively short period of time [23-28]. Since the relative abundances of gut microbes depend on the energy source available, diet is particularly influential to the gut microbiome [29]. In fact, short-term consumption of diets composed entirely of animal or plant products rapidly changes the microbial community and decreases inter-individual differences in microbial gene expression [30].

1.3 Gut microbiota in health and brain function

The gut microbiota interacts with the host environment and plays a critical role in maintaining human health [31]. For instance, the gut microbiota provides antimicrobial protection against pathogenic bacteria, aids in digestion and the production of essential metabolites, and regulates immune and nervous system development [32-35]. The gut microbiota also synthesizes molecules able to modify host epigenome, maintain the integrity of the gut barrier, and regulate host metabolism [36-45].

The interaction between the microbiota and the host is bidirectional, involving feedback from the host environment that affects the gut microbiota, which in turns influence host development [29]. In fact, the host stress response may induce widespread changes in the gut microbial composition. Mice experiencing social stress were found to have significantly altered bacterial community structure in the cecum and elevated levels of inflammatory cytokines [46]. Moreover, human subjects undergoing a stressful event were found to have a decrease in the relative fecal concentration of lactic acid bacteria [47], which have immunomodulating effects and may influence the gut microbial composition [48-50].

Given the roles of gut microbes in human health, dysbiosis, or the imbalance of the gut microbiota, has been implicated in numerous diseases, such as intestinal and metabolic disorders [32]. Importantly, recent research has also linked dysbiosis to neurological disorders, including Alzheimer's disease (AD), Parkinson's diseases (PD), multiple sclerosis and autism [51]. Due to the emerging significance of the relationship between the gut microbiota and brain function, the gut microbiota is perceived as a critical player in the "gut-brain axis," which describes the bidirectional communication between the gut and the central nervous system (CNS) [52]. The gut microbiota interacts with the gut-brain axis through neural, endocrine, immune and humoral means of communication [53].

2. Mechanisms of Interactions in the Gut-Brain Axis

2.1 Vagus Nerve

The CNS connects with the enteric nervous system (ENS) through sympathetic and parasympathetic nerves, linking cognitive and emotional centres in the brain with peripheral intestinal functions. Gut bacteria and their secretions influence neuronal excitation in the ENS, regulating both gut motility and sensory afferent signaling to the brain [54]. Intrinsic primary afferent neurons are the cellular targets of neuroactive bacteria and transmit microbial messages to the brain via the vagus nerve, which serves as a critical route of communication between gut microbes and the CNS [55, 56].

2.2 Neuroendocrine Signaling

Bacterial products are known to stimulate enteroendocrine cells to produce neuropeptides such as peptide YY, neuropeptide Y (NPY), cholecystokinin, glucagon-like peptide-1 and -2, and substance P57. These neuropeptides may enter the bloodstream or directly influence the ENS. Bacteria may also interfere with tryptophan metabolism in gut mucosal enterochromaffin cells58. Tryptophan is the precursor of serotonin, which functions to regulate GI secretion and motility, and mood and cognition in the brain.

In addition, gut microbes can synthesize and respond to hormones and neurotransmitters identical to those produced by humans [59]. For instance, Lactobacillus species produce acetylcholine and gamma-amino butyrate (GABA); Bifidobacterium produce GABA; Escherichia produce norepinephrine, serotonin and dopamine; Streptococcus and Enterococcus produce serotonin; and Bacillus produce norepinephrine and dopamine [59]. While bacterial use these compounds for inter-bacterial communication and microbial gene regulation, these molecules also serve as the main excitatory and inhibitory neurotransmitters of the brain, influencing its metabolism and function [60].

The bidirectionality of host-microbiota signaling is evident in this route of communication, as the growth and virulence of Escherichia coli were found to be greatly enhanced by physiologic concentrations of norepinephrine, indicating a direct impact of host stress responses on infection [61].

2.3 The immune system

The gut microbiota is involved in the regulation of the gut associated lymphoid tissue, which comprises a significant portion of the body's immune system. Structural components of gut microbes stimulate a tonic low-grade activation of the innate immune system that affects beyond the intestinal mucosal surface to the entire body [62]. For instance, bacterial cell wall lipopolysaccharides (LPS) induce synthesis of IL-18 [63]; bacterial peptides induce intestinal macrophages and T cells to produce interleukin-1beta (IL-1b) and tumor necrosis factor alpha (TNFa) [64]. Excessive stimulation due to dysbiosis, small intestinal bacterial overgrowth or increased intestinal permeability may induce systemic and/or CNS inflammation, and has been associated with several CNS disorders [29, 59].

2.4 Microbial metabolites

Short-chain fatty acids (SCFAs) such as butyric acid, propionic acid and acetic acid are the main products of bacterial metabolism. Through inhibition of histone deacetylases (HDAC) and activation of G-protein coupled receptors (GPCR), these metabolites have widespread regulatory effects throughout the body [65]. These bacterial metabolites can stimulate the sympathetic nervous system, cause mucosal serotonin release, and influence memory and learning process [68-71]. As such, the deregulation of HDAC and GPCR has been implicated in the pathophysiology of several neurodegenerative diseases [59, 66, 67]. Manipulation of the micro-

biota through diet has been found to influence behavior in mice. Mice fed with a diet promoting gut microbiota diversity exhibited an increase in physical activity, memory and a decrease in anxiety-like behavior [72].

Bacterial enzymes may also produce neurotoxic metabolites such as D-lactate and ammonia. D-lactate is a product of microbial fermentation of carbohydrates. High plasma levels of D-lactate resulted from intestinal hyperpermeability or abdominal surgeries were associated with symptoms of chronic fatigue syndrome [73-76], which could be improved by administration of specific dietary supplements [77-79]. Ammonia, produced in the intestinal tract by bacterial ureases, is normally taken up by the liver and consumed in the urea cycle; however, cirrhosis may allow absorbed ammonia to escape hepatic metabolism and lead to direct neurotoxic injury [80]. In addition, ammonia may alter the function of the blood-brain barrier, impairing intracerebral synthesis of neurotransmitters serotonin and dopamine [81].

3. Relevance in neurodegenerative diseases

Given the various interactions between the gut microbiota and the brain, a hypothesis has emerged to link gut microbes to multiple neurodegenerative disorders, ranging from AD and PD to multiple sclerosis, and amyotrophic lateral sclerosis [52]. A common mechanism is thought to be an impaired gut barrier associated with aging, bacterial overgrowth or abdominal surgeries [51]. Increased intestinal permeability allows gut microbiota-induced immune activation to lead to a systemic inflammatory response, which impairs the blood-brain barrier and promotes neuroinflammation, ultimately leading to neural injury and degeneration [21, 82-88]. This aberrant microbiota-to-CNS pathway results in the characteristic neuropathological features of AD and PD, namely the deposition of beta-amyloid in AD [82, 87, 88] and misfolding and aggregation of alpha-synuclein in PD [89].

3.1 Alzheimer's disease

IAD is characterized by an extracellular aggregation of amyloid plaques and intracellular deposition of tau in neurofibrillary tangles. Such aberrant protein accumulation is involved in neurodegeneration and cognitive impairment. Increasing lines of evidence in the form of animal models and correlational studies support the involvement of gut microbes in the pathogenesis of AD [52, 82, 85-88].

Recent preclinical studies suggest a correlation between amyloid plaque deposition and changes in the gut microbial composition. In a mouse model carrying mutated human genes associated with AD, the gut microbiota diversity was shown to regulate host innate immunity and affect beta-amyloid deposition [90]. In addition, preparation of germ-free AD mice reduced amyloid plaque deposition in the brain [91]. The recolonization with gut microbes from conventional AD mice, but not wild-type mice, restored amyloid plaques [91], suggesting the necessity of the gut microbiota in the development of AD pathology. Other AD mouse models have also been shown to possess an altered gut microbiota, which became more pronounced with advancing age [92, 93]. Furthermore, AD mice treated with probiotics from early ages showed changes in gut microbial composition, which led to a reduction in AD progression as demonstrated by brain structural markers and cognitive performance [94].

Although few studies in human patients have been published, these correlational studies also indicate a link between AD and alterations in the gut microbiota. In particular, a lower abundance of anti-inflammatory taxa Eubacterium and high abundances of pro-inflammatory taxa Escherichia and Shigella in the stool were associated with pro-inflammatory cytokines and amyloid deposition in the brain [95].

The link between AD and gut microbes is related to increased gut permeability, which allows microbes and microbial products to enter the circulation and reach the brain, contributing to the development of AD pathology. In particular, infections with microbes such as Herpes simplex virus type 1, Chlamydia pneumonia and spirochaete are thought to be involved in the pathogenesis AD or increase the disease risk [96-100]. Notably, LPS was found in amyloid plaques in the AD brain [101] and present in elevated levels in the plasma of AD patients [102]. Rats injected with LPS in the ventricles also showed inflammatory and pathological features seen in AD patients [103]. In addition, bacteria and fungi secrete a large amount of amyloid proteins that may accumulate in the CNS, leading to increased AD risk [104]. Amyloid proteins derived from gut microbes may prime the innate immune system to enhance the inflammatory response to cerebral amyloid proteins [105].

3.2 Parkinson's disease

PD is characterized by an accumulation of alpha-synuclein in the brain, which affects nerve cells that produce dopamine, leading to motor and non-motor symptoms. Gastrointestinal disturbances commonly precede motor symptoms by several years [106]. Similar to AD, the importance of gut microbes in the pathophysiology of PD has been demonstrated by mouse models and correlational studies in human patients.

In a PD mouse model overexpressing alpha-synuclein, antibiotic treatments improved its motor functions whereas oral administration of specific microbial metabolites promoted motor deficits and alpha synuclein aggregation [107]. In addition, colonization of these mice with feces from PD patients, but not healthy donors, aggravated existing neuroinflammation and motor deficits [108].

A number of published human cross-sectional studies also show an altered gut microbial composition in PD patients compared to appropriate controls, as shown in fecal or mucosal samples [52]. Collectively, these studies show lower abundances of anti-inflammatory Blautia, Coprococcus, Roseburia and Fecalibacterium [109], and higher abundances of pro-inflammatory Proteobacteria [109] and Enterococcaceae [110]. The pattern of changes is consistent with the features of peripheral and central inflammation seen in PD patients.

In addition, PD patients also showed increased abundances of Akkermansia, Lactobacillus and Bifidobacterium and a decreased abundance of Lachnospiracaea [111]. Functional analysis related these changes to pathways involved in the metabolism of plant-derived compounds and xenobiotic degradation, suggesting that diet may influence the progression of PD [111]. Interestingly, a decrease in Prevotellaceaeand an increase in Enterobacteriacaea were shown in German and Finland cohorts [112, 113], but not in U.S. cohorts [109, 110, 114, 115]. Such differences may be related to, among other factors, different dietary habits in European and North American populations.

The link between PD pathology and alterations in the gut mi-

crobiota may be related to a pro-inflammatory intestinal state triggered by gut microbial products, leading to alpha synuclein deposition in the ENS that reaches the brain via the vagus nerve. This has been supported by the fact that the earliest PD brain lesions appear in the motor nucleus of the vagus nerve [116]. Local inflammation likely induces microbial products, such as LPS, to leak out from the gut causing systemic pro-inflammatory status, or reach the brain via the bloodstream or the vagus nerve to worsen neuroinflammation and alpha-synuclein deposition [51]. Indeed, increased levels of serum LPS have been found in PD patients [117].

4. Limitations and clinical implications

4.1 Challenges and limitations

It is important to emphasize that the majority of evidence supporting the role of the gut microbiota in the pathophysiology of neurodegenerative diseases has come from observations in animal models [52]. While directly demonstrating the causation of altered gut microbial compositions in the progression of neurodegenerative diseases, these animal models may harbor differences in neurophysiology, immune responses, enteric microbiology, and therefore do not fully recapitulate the complete human phenotype.

Although several human studies demonstrate a link between gut microbes and AD or PD, these studies also have certain limitations. In particular, most were small in size and rely on fecal sampling to determine the gut microbiota population. Therefore, the study population may or may not have represented the general disease population, and could have been confounded by several factors, such as diet, medication and comorbidity that could influence the composition of gut microbiota [118-120]. Despite efforts to correct confounders in a few studies [121-122], it may prove difficult to assign the relative contributions of different factors to the microbial pattern in AD or PD patients. Given the bidirectionality of the gut-brain axis, the direction of causation between alterations in gut microbiota and neurodegenerative diseases could not be determined in these correlation studies [118, 123-125].

Nonetheless, establishing a direct link between the gut microbiota and key features of neurodegenerative diseases will open up new diagnostic and therapeutic opportunities. The last sections will briefly discuss clinical implications for the involvement of gut microbiota in neurodegenerative diseases.

4.2 Biomarkers

Gut microbes produce various metabolites, many of which are involved in host metabolism or maintenance of a healthy gut environment. These metabolites are detectable in the blood, urine, feces, or breath of the host. Disease-related microbes and metabolites, if identified, could serve as novel biomarkers, allowing for a useful and non-invasive method of identifying persons at risk for or in early stages of neurodegenerative diseases. In particular, high-throughput sequencing, metagenomics, metabolomics and other techniques allow for the study and profiling of microbes and metabolites in individuals [29].

4.3 Potential Therapeutic Interventions

Several animal studies use novel strategies to modify microbial compositions and rescue disease phenotypes [91, 94, 107, 108], revealing the therapeutic potential of altering the gut microbiota by the means of diet, probiotics, prebiotics and fecal transplantation. Probiotics are microbes administered to the host to confer health benefits [126], while probiotics are molecules metabolized by gut bacteria to favor specific changes in the activity and composition of the gut microbiota that benefit host health [127]. Diet, prebiotics and probiotics have been shown in clinical trials to lead to improvement of a variety of diseases and changes in emotional reactivity and brain activity [128-136]. As such, management of the gut microbiota via diet, prebiotics, probiotics and fecal transplantation may hold potential in the realm of preventive medicine and treatment of neurodegenerative diseases [29].

Conclusion

The gut microbiota changes throughout life in response to various factors and plays a critical role in human health, including brain function. Preclinical studies have established the significance of the gut-brain axis in the progression of neurodegenerative diseases. While animal studies have linked neurodegenerative diseases to altered microbial compositions, research in humans relies largely on correlative analysis of patient populations and has several limitations. Hence, high-quality human clinical studies are needed to elucidate the actual impact of the human microbiota on neurodegenerative diseases. In particular, the directionality of causation and relative contributions of gut microbes to disease pathology remain to be determined. Such clinical investigations may pave the way for novel diagnostic tools as well as more feasible and readily accessible means of interventions, in the forms of diet, prebiotics, probiotics and fecal transplantation.

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