REVIEW ARTICLE

The Gut Brain-Axis in Neurological Diseases

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Abstract

Recent evidence suggests that dysfunction of the gut-brain axis may be an important factor contributing to many diseases of the nervous system. Increased gut permeability associated with chronic gastrointestinal dysfunction, as well as changes in the composition of the gut microbiota could contribute to exposure of the enteric and central nervous system to pathogens and its metabolites, including endotoxins and pro-inflammatory cytokines. As a consequence, dysfunction of the host's immune system could contribute to an abnormal immunological response leading to auto-immune conditions, such as multiple sclerosis. So far, gut dysbiosis has been reported in association with Parkinson's disease, Alzheimer's disease, multiple sclerosis, neurodevelopmental and neuropsychiatric conditions, and cerebrovascular disease. These findings suggest that the possibility of targeting the gut microbiota could become a future therapeutic option to treat these conditions. However, before this knowledge can be useful in the clinical setting, more data is needed to establish clear causal relationships between dysfunction of the gut-brain axis and neurological diseases.

Introduction

Hundreds of millions of years of co-evolution have resulted in a complex symbiotic relationship between multicellular life and bacteria. While it is very likely that more aggressive interactions predominated in the early days, survival in the long run demanded a more harmonic relationship.

Keywords

For modern humans, the benefits of this relationship are evident when the digestive tract is considered. Commensal bacteria, which colonize the human gut shortly after birth, acquire nutrients from their hosts. In exchange, they assist the digestive process and the production of metabolites that contribute to the host's survival. The collective of host-associated microbes is denominated microbiota, and its genomic constitution, microbiome.[1]

The enteric nervous system consists of approximately 200 million neurons that control the function of the entire digestive tract. It is composed of an intrinsic network of nervous fibers and ganglia, the myenteric and submucosal plexus. The myenteric plexus controls mainly the motility of the digestive tract (peristalsis) and is located deeply between the longitudinal and circular layers of the entire digestive tract. It is composed mainly of a network of ganglia linked by unmyelinated fibers connected to the vagus nerve and sympathetic ganglia. The submucosal plexus (Meissner plexus) is located more superficially and closer to the intestinal lumen from the stomach to the colon. It is composed mainly by nervous fibers and ganglia, and controls the mucosal secretions, vascular flow and absorption.[2]

The gut-brain axis is an information exchange platform which allows two-way communication between the gut and the host nervous system. Information can be exchanged via neural network, hormones and the immune system.[3] Disruption of the delicate balance between host and gut bacteria could be a contributing factor behind many diseases. Following publications that have reported changes in the composition of the gut microbiome, in association with many digestive and non-digestive conditions, research interest in the gut-brain axis has significantly increased making it a research hot topic. This review will explore the physiology and pathophysiology of the gut-brain axis and its role in neurological diseases.

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Pathophysiology

Normal functioning of the gut-brain axis

The intestinal epithelial barrier relies on tight junctions between cells to keep its integrity and to separate the external (the gut microbiota) from the internal environment (the gut immune and nervous systems). The composition of the gut microbiota is regulated by both extrinsic factors, such as diet, lifestyle and early microbiota exposure; and intrinsic factors, such as genetic background, metabolism, and activity of the host's hormonal and immune systems.[4]

One of the most studied extrinsic factors that is able to alter the gut microbiota composition is diet. Dietary fibers are degraded by commensal bacteria in the gut and lead to the production of short-chain fatty acids (SCFA), which are beneficial to the brain. On the other hand, epidemiological studies have reported a positive correlation between increased risk of cognitive decline and consumption of high-saturated-fat food, high intake of animal protein and refined sugars.[5] The Mediterranean diet, known for its association with longevity, is also able to influence the composition of the gut microbiome, resulting in higher levels of fecal SCFA and predominance of *Prevotella* and *Firmicutes* species, a composition that appears to be more favorable to the host.[6] SCFAs are important bacterial metabolites that can reduce inflammatory response and promote CNS plasticity. A diet high in fructose has been associated with an exacerbated inflammatory response in the hippocampus, which could be a consequence of changes in the gut bacteria.[7]

Patients with refractory epilepsy can benefit from a ketogenic diet. Olson et al[8] have studied how this type of diet can influence the gut microbiota. Higher levels of hippocampal GABA have been reported alongside an increase in *Akkermansia* and *Parabacteroides* species. This change appears to confer seizure protection, as it does not occur if germ-free mice were fed with a ketogenic diet.[8]

The vagus nerve is an important gut-brain axis pathway that allows for direct connection between these two organs. By controlling gut motility and secretion, the vagus nerve is able to change the gut environment and to control the enteric immune system response with a direct consequence to the gut microbiota. Conversely, gut bacteria produce metabolites that are able to influence both the enteric and the central nervous system and to affect the production of neurotransmitters, such as gamma-aminobutyric acid (GABA), acetylcholine and the serotonin precursor tryptophan.[1] Commensal gut bacteria are also capable of producing important nutrients, such as choline and SCFA, as well as the hormones ghrelin and leptin. They are also able to alter brain function through changes in the expression of CNS receptors.[9] Animal research using murine models have highlighted the importance of the gut bacteria, not only for preserving the health of the brain, but also for contributing to its normal development. Collins et al.,[10] have reported a decrease in nerve density, a decrease in neuronal density in ganglia, and an increase in the prevalence of nitrergic neurons in the myenteric plexus of the jejunum and ileum of germ-free mice, highlighting the importance of the gut microbiota in the normal development of the enteric nervous system.[10] Worse cognition and increased stress response have been reported in germ-free mice, a different behavioral phenotype compared to control animals.[11] The gut microbiota can also affect brain circuits responsible for motor and behavioral control.[12] Increased microbiota diversity has been associated with improved structural organization of the hippocampus, hypothalamus and caudate nucleus.[13]

Dysfunction of the gut-brain axis

A complex immune interplay is in place allowing the gut microbiota to co-exist peacefully with the host's cells. The gut immune system needs to be finely tuned to maintain its vital defensive function in the presence of commensal bacteria. Diverse pathological forces could break this delicate and complex relationship resulting in diseases.

The composition of the gut microbiota appears to be an important factor contributing to diseases. An unbalanced composition of the gut microbiota, known as dysbiosis, has been implicated not only in diseases of the gut, but also in pathologies of distant organs/systems. The immune system can be affected by dysbiosis in many ways. Activation of T-cells by changes in gut microbiota has been associated with auto-immune uveitis[14] and could have a role in other auto-immune conditions. Furthermore, systemic levels of pro-inflammatory cytokines can be affected by commensal gut bacteria and could be implicated in different conditions. Lastly, allergies have also been associated with changes in the composition of the gut microbiota.[15]

Another possible factor connecting dysbiosis to diseases is an increase in gut permeability ('leaky gut'), caused by local pathological processes. This could allow gut bacteria and/or its metabolites to reach the host's circulatory system and the brain (provided they are capable of crossing the blood-brain barrier), interfering with the normal functioning of distant structures. Furthermore, absence of normal gut microbiota in mice has been associated with increased permeability of the blood-brain-barrier, which can be reduced by exposure to pathogen-free microbiota.[16]

It is likely that, in many conditions, both gut dysbiosis and a leaky gut are required to cause diseases, as seen in patients with hepatic encephalopathy. As a consequence of increased permeability of the gut wall in the context of hepatic dysfunction, plasma levels of cytokines and bacterial endotoxins increase, leading to cognitive dysfunction. Gut dysbiosis appears to be an important pathophysiological phenomenon as well. Not only a predominance of *Alcaligenaceae* and *Porphyromonadaceae* has been reported in these patients, but it has also been correlated with cognitive dysfunction.[3]

Neurological conditions

This section focuses on the latest advances on the influence of the gut-brain axis in neurological disease. A summary is presented in Table 1.

Neuropsychiatric symptoms and neurodevelopmental conditions

Inducing gut dysbiosis by antibiotic use in animal models, researchers have reported that anxiety and other cognitive abilities, such as motor control, memory and learning can be influenced by gut bacteria. The ability of commensal bacteria to influence the stress response by modulating the activity of the hypothalamic-pituitary axis, and to produce neurotransmitters and neuromodulating substances is a possible explanation for the reported association between gut microbiota dysbiosis and stress and depression. Dysbiosis could also explain the higher prevalence of psychiatric comorbidities in individuals with inflammatory bowel diseases and irritable bowel syndrome.[17]

Research interest in the connection between gut bacteria and neurodevelopmental disorders, such as autism, followed the initial reports on the importance of the gut microbiome for the normal development of the central nervous system. A different composition of the gut microbiota has been reported in animal models of autism spectrum disorders. Children with autism appear to have a distinct composition of the gut microbiota, with lower levels of *Bifidobacterium*, *Firmicutes*, *Bacteroidetes*, *Akkermansia* and higher levels of *Lactobacillus*, *Clostridium*, *Suterella* and *Bacteroidetes*.[4]

A specific bacterial metabolite, propionic acid, appears to be important to the development of autism

Table 1 – Dysfunction of the gut-brain axis in neurological diseases					
Condition	Dysbiosis	Bacterial metabolites/ endotoxins	Leaky gut	Inflammation	Immune dysfunction
Autism spectrum disorders	X	X			
Amyotrophic lateral sclerosis	X	X	X		
Parkinson's disease	X	X	X	X	X
Alzheimer's disease	X	X		X	
Multiple system atrophy	X	X	X	X	
Multiple sclerosis	X	X	X		X
Cerebrovascular disease	X	X			

Different mechanisms leading to dysfunction of the gut-brain axis, which have been reported in association with neurological conditions.

spectrum disorders in animal models. Intraventricular injection of this substance has been reported to induce autism-like behaviour. Furthermore, treatment with *Bacteroidis fragilis*, can reduce the levels of propionic acid and improve behavioral symptoms.[18]

Neurodegenerative diseases

The pathophysiological processes driving many neurodegenerative conditions and leading to neuronal death remain elusive. Such processes are varied and complex and beyond the scope of this review. However, shared pathophysiological features of neurodegeneration, such as aggregation of misfolded proteins and inflammation have recently been studied from the perspective of the gut-brain axis.

Parkinson's disease

Parkinson's disease (PD) appears to be the consequence of a complex interplay between environmental and genetic factors associated with age-related neuronal loss. These factors, either isolated or in combination, lead to dysfunction of diverse neuronal structures/systems and, consequently, to neuronal death.[19] In PD, insoluble forms of alpha-synuclein (a synaptic protein found in healthy neurons) aggregate and accumulate in neurons, resulting in damage to critical cell processes such as mitochondrial activity and axonal flux. Alpha-synuclein is one of the main components of Lewy bodies, inclusions routinely found in patients with idiopathic PD.

Clinical data, showing that digestive symptoms are ubiquitous in PD, and anatomopathological studies confirming deposition of alpha-synuclein in the enteric nervous system suggest that the gut may play an important role in the pathophysiology of PD. PD can affect all levels of the digestive tract, and gastrointestinal symptoms are well known nonmotor symptoms of the disease. Constipation, specifically, is the most frequent nonmotor symptom, affecting 50 to 80% of patients. Not only it can manifest early in the disease course, but it can also precede motor symptoms by many years, which is why it is considered one of the prodromal symptoms of PD.[20]

Lewy pathology (alpha-synuclein aggregates, Lewy neurites and Lewy bodies) is found in the myenteric, submucosal plexus and mucosal fibers of patients with PD in territories innervated by the vagus nerve. The finding that Lewy bodies are also present in the dorsal nucleus of the vagus[21] led to the theory that molecular changes in alpha-synuclein initially occur in the gut and spread to vulnerable areas of the CNS, via retrograde axonal and transneural transport.[20] This theory is compatible with Braak's model of PD progression, according to which the disease enters the CNS via the olfactory or the vagus nerve.[22] The finding by Svensson et al. that patients submitted to truncal vagotomy earlier in life are less likely to develop PD supports this theory.[23]

In PD, there is increased permeability of the intestinal barrier, which could be the consequence of chronic gastrointestinal dysfunction. A leaky gut results in exposure of enteric neurons to bacterial endotoxins and local inflammation. Local aggregation of alpha-synuclein could occur as a consequence of exposure to yet unknown environmental factors associated with alpha-synuclein pathology.[24]

There is evidence to support an immune role for alpha-synuclein, such as expression of this protein in the human gut after viral infections, the ability to attract macrophages and stimulate dendritic cells, and the increased propensity of alpha-synuclein knockout mice to develop infections. Considering this putative role in immunity, alpha-synuclein could also accumulate in the enteric nervous system due to production rates far greater than the clearance rate in the presence of chronic gastrointestinal infection and inflammation.[25] However, the presence of gut microbiota may be required for the aggregation and spread of alpha-synuclein. In an alpha-synuclein overexpression mice model, germ-free animals show reduced alpha-synuclein pathology. Reduced pathology has also been achieved by treatment with antibiotics.[26]

Further exploring the relationship between the gut microbiome and PD, Scheperjans et al.,[27] reported a reduction in *Prevotellaceae* species compared with the controls, and a correlation between an excess of *Enterobacteriaceae* species and the severity of postural instability and gait dysfunction.[27] Other researchers have reported a higher prevalence of bacterial species associated with bacterial lipopolysaccharides and inflammation in PD patients and a decrease in species associated with a reduced inflammatory response.[4] Intestinal inflammation in PD can also be influenced by bacterial metabolites, such as SCFA. Lower fecal SCFA levels have been reported in PD patients, who also exhibited increased levels of intestinal inflammation.[28]

Considering the heterogeneous findings reported in the literature on the composition of the gut microbiota in PD, consistent data were reported for abundance of *Verrucomicrobiaceae* and *Akkermansia* and for decreased *Prevotellaceae*, whereas inconsistent findings were reported for *Lactobacillaceae* and *Bacteroidetes.*[29]

Specific compositions of the gut microbiota have also been studied in atypical parkinsonism. Barichella et al.,[30] compared 193 PD patients with 113 healthy controls, 22 progressive supranuclear palsy and 22 multiple system atrophy (MSA) patients. The only consistent finding between PD and healthy controls was abundance of *Lachnospiraceae*. A clinical profile of worse cognitive impairment, gait dysfunction and postural instability was associated with decreased *Lachnospiraceae* and increased *Lactobacillaceae* and *Christensenellaceae*. MSA patients had similar PD profiles, with the exception of a reduction in *Prevotellaceae* and no decrease in *Lachnospiraceae*, whereas PSP *Lactobacillaceae* were similar, and *Streptococcaceae* were reduced.[30]

Similarly to what has been reported in PD, a small study of six MSA patients showed dysfunction of the intestinal barrier and signs of intestinal inflammation associated to bacterial endotoxins. Furthermore, there was abundance of Bacteroidetes and Proteobacteria (pro-inflammatory bacteria) and a reduction in butyrate-producing bacteria (anti-inflammatory).[31]

Alzheimer's disease

Alzheimer's disease (AD) is the most common neurodegenerative condition and one of the main public health issues worldwide due to ageing of the population and the lack of a curative treatment. Its pathological signature is the deposition of neurofibrillary tau tangles and amyloid-β plaques in specific areas of the central nervous system.

The formation of amyloid plaques could be influenced by gut bacteria. Amyloid metabolites can be produced by the intestinal microbiota, which could contribute to inflammation and increase vascular permeability, resulting in amyloidogenesis.[32] Furthermore, bacterial endotoxins are also able to increase the formation of amyloid plaques by influencing amyloid-β peptide fibrillogenesis.[33]

An additional piece of the puzzle comes from studies showing that individuals with AD infected by *H.pylori* have a more severe AD phenotype compared to non-infected controls.[34] Furthermore, eradication of *H.pylori* appears to improve cognitive function.[35] A possible explanation has been given by Wang and colleagues who have demonstrated that *H.pylori* can contribute to neurodegeneration by inducing tau hyperphosphorylation.[36]

A peripheral inflammatory state has been described in individuals with cognitive impairment in the context of amyloidosis. Gut microbiota could play an important role in this phenomenon, since it has been associated with an increase in pro-inflammatory bacterial species, such as *Escherichia* and *Shigella*, and a decrease in anti-inflammatory species of bacteria, such as *E.rectale.*[37] The role of the gut microbiome in AD is strengthened by studies showing cognitive function improvement through the use of probiotics, both in animal models and in patients with the disease.[4]

Multiple sclerosis

The availability of an animal model of multiple sclerosis (MS) and a surge in research interest in this condition, associated with the development of novel immunomodulatory treatments, have led many authors to study the influence of the gut-brain axis in the development of MS.

As stated previously, auto-immune diseases could be triggered by activation of T-cells by gut commensal bacteria, a phenomenon that has been shown to occur in an animal model of relapsing-remitting MS. The importance of gut bacteria in activating T-cells is highlighted by the finding that germ-free mice do not develop encephalomyelitis, unless they receive fecal transplant.[38]

This abnormal immune response appears to be modulated by bacterial metabolites. In the same animal model, long-chain fatty acids are associated with exacerbation of the disease, whereas SCFA improves symptoms.[39] Tryptophan is a precursor of serotonin and its levels can be regulated by the gut microbiota. This substance appears to be beneficial to a mouse model of MS,[4] probably as a consequence of its ability to control microglial activation and reduce inflammation in the CNS .[40]

The role of the gut microbiota in the development of multiple sclerosis is also supported by studies with human subjects. Similar to other conditions, increased gut permeability has been reported in individuals with MS. While there is still no specific gut microbiota composition associated with MS, similarities with

non-neurological auto-immune pathologies and inflammatory bowel disease have been reported, such as an increase in *Archea* and reduction in *Clostridium* and *Bacteroidete.*[1]

Cerebrovascular disease

Cerebrovascular disease is an important cause of morbidity and mortality worldwide. Commensal gut bacteria could be connected to the development of stroke by diverse factors. Diet contributes to atherosclerosis and other risk factors of cerebrovascular disease, such as arterial hypertension, dyslipidemia and diabetes. It can also have a direct effect on the composition of the gut microbiota, making any correlations between dysbiosis and atherosclerosis susceptible to many confounding factors. However, recent research suggests that the gut microbiota may have a more direct role to play in atherosclerosis and cerebrovascular disease.

Trimethylamine n-oxide (TMAO) is a metabolite produced by gut bacteria from dietary choline and is extensively found in body tissues and fluids. It has been implicated in both cardiovascular and cerebrovascular diseases. In a large prospective study involving more than 4,000 people, plasma levels of TMAO were correlated with cardiovascular events. The importance of gut bacteria in producing TMAO was highlighted by the fact that treatment with antibiotics reduced its levels.[41] Furthermore, individuals with stroke and transient ischemic attack have lower levels of TMAO compared to individuals with asymptomatic atherosclerosis.[42]

Animal models show that supplementation of phosphatidylcholine metabolites (including TMAO and choline) can increase the expression of macrophage receptors associated with atherosclerosis. This effect appears to require the presence of gut bacteria. In germ-free mice, choline supplementation is not associated with an increase in atherosclerosis and leads to a reduction in aortic plaque size.[43,44] These findings need to be interpreted with caution since both choline and TMAO can be influenced by diet, and gut microbiota has so far been associated with both protective and harmful effects in the origin and course of atherosclerosis.[11]

Normal microbiota appears to be important for recovery following vascular lesions. Depletion of microbiota by broad spectrum antibiotics after occlusion of the middle cerebral artery results in decreased survival in an animal model.[45] Furthermore, stroke outcomes can be improved by fecal transplant.[46]

Treatment with *C butyricum* decreases neuronal injury and improves cognitive function in brain injury induced by ischemia/reperfusion after bilateral carotid common artery occlusion.[47]

Dysbiosis has been shown to occur after stroke and influence its outcome by negatively affecting the size of the lesion and contributing to inflammation. Reduced diversity and abundance of *Bacteroidetes* have been reported after stroke (46). Stroke and transient ischemic attack patients have been reported to harbor more opportunistic pathogens, such as *Enterobacter*, *Megasphaera*, *Oscillibacter*, and *Desulfovibrio*, and fewer commensal or beneficial genera, including *Bacteroides*, *Prevotella*, and *Faecalibacterium.*[42] Furthermore, an abundance of *Peptococcaceae* and *Prevotellaceace* has been correlated with stroke severity.[48]

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis is a neurodegenerative condition which affects primarily the motor neuron. It is an aggressive condition that commonly leads to death a few years after diagnosis. Changes of the gut-brain axis have also been reported in animal models of this condition, such as dysfunction of the gut epithelium and of the gut immune system, and a reduction in the prevalence of bacterial species that produce butyrate.[49] Interestingly, butyrate supplementation can increase survival in the same animal model.[50]

Conclusions

The gut-brain axis is an exciting research topic, which has received a great deal of attention from the scientific community in recent years. However, the role of the gut-brain axis in the development of neurological diseases is far from established. Evidence that the gut microbiota and its metabolites interfere with the host's immune and endocrine systems, affecting neurological function and its vasculature, derives mainly from studies showing correlations, not causality.[4] More prospective studies are needed to demonstrate a causal relationship. When studying neurodegenerative conditions with disease progression spanning several years, one also needs to consider that changes in microbiota occur much faster, complicating even more the interpretation of causality. Another important issue is that the majority of studies published so far have used animal models, limiting extrapolation of their findings to humans.

Furthermore, it is also important to consider the many confounding factors associated with human fecal experiments that are likely to contribute to the heterogeneity of findings, such as diet, demographic, clinical and socioeconomic factors, as well as sample collection, laboratory procedures and genetic sequencing techniques. Ideally, control populations should be selected with a similar risk profile. For example, using controls from households could help minimize dietary variations.[29]

The potential benefits that could derive from research on the gut-brain axis in neurological disease are the identification of biomarkers of neurodegeneration and the development of novel treatments, such as the use of probiotics and fecal transplant. However, there is still no good quality evidence to support clinical use. Administration of the probiotics *Lactobacillus* and *Bifidobacterium* to PD patients can improve constipation, but it does not affect other symptoms of the disease.[51] More data is needed, particularly after reports of worse outcomes with the use of probiotics in immunocompromised patients and in individuals with pancreatitis.[11]

Considering the influence of the gut microbiota in several modifiable risk factors of cerebrovascular disease and its influence in post stroke complications, in theory many benefits could derive from targeting the gut microbiota. More data is needed to address the feasibility of targeting the gut microbiota by using antibiotics, probiotics or fecal transplant .[11]

Despite recent advances in our understanding of the gut-brain axis, more data is needed to address if this knowledge can be useful in the clinical setting. Future research needs to establish more clear causal relationships between the gut bacteria and different neurological conditions and whether targeting the microbiota is a safe and beneficial therapeutic option.

Author contributions

Conception and design of the research: Barbosa PM, Barbosa ER. Acquisition of data: Barbosa PM, Barbosa ER. Writing of the manuscript: Barbosa PM, Barbosa ER. Critical revision of the manuscript for intellectual content: Barbosa ER.

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