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The Microbiome-Brain Axis: Exploring the Gut-Brain Connection in Neurological Disorders

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Abstract: *The association and interaction between the central nervous system (CNS) and enteric nervous system (ENS) is well established. Essentially ENS is the second brain, as we call it. We tried to understand the structure and function, to throw light on the functional aspect of neurons, and address various disease manifestations. We summarized how various neurological disorders influence the gut via the enteric nervous system and/or bring anatomical or physiological changes in the enteric nervous system or the gut and vice versa. It is known that stress has an effect on Gastrointestinal (GI) motility and causes mucosal erosions. In our literature review, we found that stress can also affect sensory perception in the central nervous system. Interestingly, we found that mutations in the neurohormone, serotonin (5-HT), would result in dysfunctional organ development and further affect mood and behavior. We focused on the developmental aspects of neurons and cognition and their relation to nutritional absorption via the gastrointestinal tract, the development of neurodegenerative disorders in relation to the alteration in gut microbiota, and contrariwise associations between CNS disorders and ENS.*
Keywords: Nervous system; central nervous system; gastrointestinal diseases etc.

Introduction

Insights into the gut–brain system have revealed a multifaceted communication axis that ensures the adequate maintenance of gastrointestinal homeostasis. The mechanisms underlying GBA communications involve neuro–immuno–endocrine mediators. New discoveries in the field have highlighted the significance of gut bacteria in affecting these interactions. Microbial products and microbially produced metabolites act as signaling molecules that have direct or indirect effects on the CNS and the ENS (Figure 1).

The gut-brain axis, which is defined as the two-way connection between the gastrointestinal tract and brain, which controls the central nervous system as well as intestinal homeostasis This Axis connects the brain's emotional and cognitive regions with the functioning of intestines at the periphery. The central nervous system, which comprises the brain and spinal cord, enteric nervous system, the autonomic nervous system, and the hypothalamus pituitary adrenal axis, are all parts of this two-way communication network. New discoveries in the field have highlighted the significance of the gut bacteria in affecting these interactions. These bacteria

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have direct interactions with the CNS via neuroendocrine and metabolic pathways, in addition to local interactions with intestinal cells and the ENS. Microbiota interact with the gut-brain axis through a variety of methods, but the main one likely involves altering the intestinal barrier. Others being sensory afferents modulation, producing the local neurotransmitters, immune activation in mucosa, and by release of peptides. The brain also influences the gut microbiome via its efferents, by a mechanism that is dependent on the presence of neurotransmitters on the bacteria. It regulates the gut motility, secretions, mucus layer, permeability and immune function.

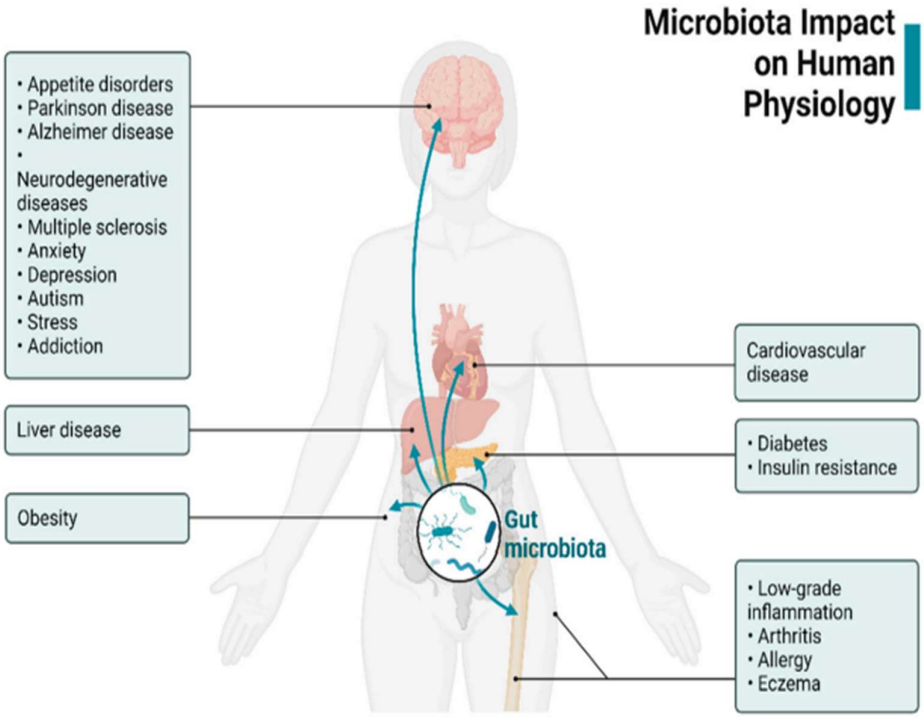

Figure 1. An illustration depicting the gut microbiome–brain axis. Created with BioRender.com

Microbiota and Its Influence on ENS and CNS

The microbiota comprises a wide array of bacteria, viruses, fungi, and supplementary microorganisms co-existing within a single natural environment, such as the human digestive territory. The microbiome involves the whole locale of the body, which includes its microorganisms, genomes, and the adjoining ecological situations. The microbiota of the gut is a huge and complicated group of microorganisms that greatly impacts human health. Earlier, it was referred to as the microflora of the gut. The total number of studies is constantly escalating, which shows that the microbiota of the whole digestive tract can be of a key role in the growth and maintenance of the CNS and the ENS. Before their own microbiota is obtained, eutherian fetuses are exposed to products and metabolites from the maternal microbiota.

Colonization by microorganisms occurs at birth in infants. In the early stages of life, the microbial arrangement is much inspired by the way of delivery, the feeding method, the use of antibiotics, and the maternal microbial arrangement. Microbial products and microbially produced metabolites act as signaling molecules that have direct or indirect effects on the CNS and the ENS. In recent years, the development of rapid and credible sequencing technology has facilitated researchers and scientists to execute metagenomic investigations and studies, which have impacted a lot to our increased understanding of the host-microbe interface in health and disease. Now the microbiota is established as an environmental component that affects the physiology of the host by playing vital roles in, for example, host immunity, metabolism, and behavior.

Microbiota and CNS

Significant research has shown that the microbiota can stimulate the gut tissue of the host and communicate with the brain in ways that affect the host's behavior and the pathogenesis of neurological diseases. Over the past ten years, research has discovered a strong link between dysbiosis and a number of host diseases, including central nervous system disorders. Dysbiosis leads to the deregulation of the gut–brain axis pathways, which are connected to altered blood–brain barrier (BBB) permeability and inflammation of the nervous system. A variety of immunological mechanisms, including the inflammasome pathway, control both homeostasis and neuroinflammation. When a cell is activated by bacteria, danger signals, or stress, the inflammasome complex assembles, which causes the release of proinflammatory cytokines (interleukin-1 and interleukin-18), as well as programmed cell death (pyroptosis). Further investigation has revealed that the interaction between the microbiota and NFB signaling is also responsible for CNS inflammation. The microbiome has an effect on the characteristics and operation of microglia, according to recent studies. Microglia have been shown to protect the brain against a range of illness states by triggering immunological responses that may rely on the interaction between GPR43 and inflammasome signaling. Like microglia, astrocytes play a variety of critical roles in the maintenance of CNS integrity. The generation of brain cytotoxic or immunological inflammatory chemicals, which cause CNS dysfunction and neurological diseases, is now known to be significantly mediated by excessive activation of astrocytes through IFN-1 signaling. A number of internal or external variables, including compounds produced by the gut flora that act on aryl hydrocarbon receptors (AHR) in animal models, might influence astrocyte activation.

Microbiota and ENS

The microbiota of the gut controls the metabolism of amino acids, lipids, and carbohydrates; all the substances are crucial for maintaining human health and preventing metabolic disorders. The microbiota of the gut influences the metabolic nature and health by secreting short-chain fatty acids (SCFAs) by the fermentation of carbohydrates. The important SCFAs are formate, propionate, butyrate, and acetate, which are involved in maintaining the integrity of intestinal epithelium and its permeability [19]. According to reports, intestine metabolic regulation

involves the enteric nervous system (ENS), and ENS regulation is significantly affected by intestinal neurotransmitters and enteric neurons [20]. The CNS and ENS interact via the vagal nerve route, which has a strong influence on modulating gastrointestinal functions and feeding behavior. Therefore, through the gut–brain axis, the vagal nerve system also influences metabolic regulation in the intestine. Gut peptides, such as leptin, cholecystokinin (CCK), peptide tyrosine tyrosine (PYY), ghrelin, glucagon-like peptide-1 (GLP-1), leptin, 5-hydroxytryptamine (5-HT), and others that are produced by enteroendocrine cells, have receptors that are located on vagal afferent neurons (EECs). These kinds of peptides are detected by vagal afferent neurons, which transfer their respective gut information to the central nervous system and cause diverse reactions. At the same time, gut bacteria can influence the levels of gut peptides, such as leptin, CCK, PYY, ghrelin, GLP-1, and 5-HT, to regulate the vagal afferent output. Then, the microbiota can regulate intestinal metabolic metabolism.

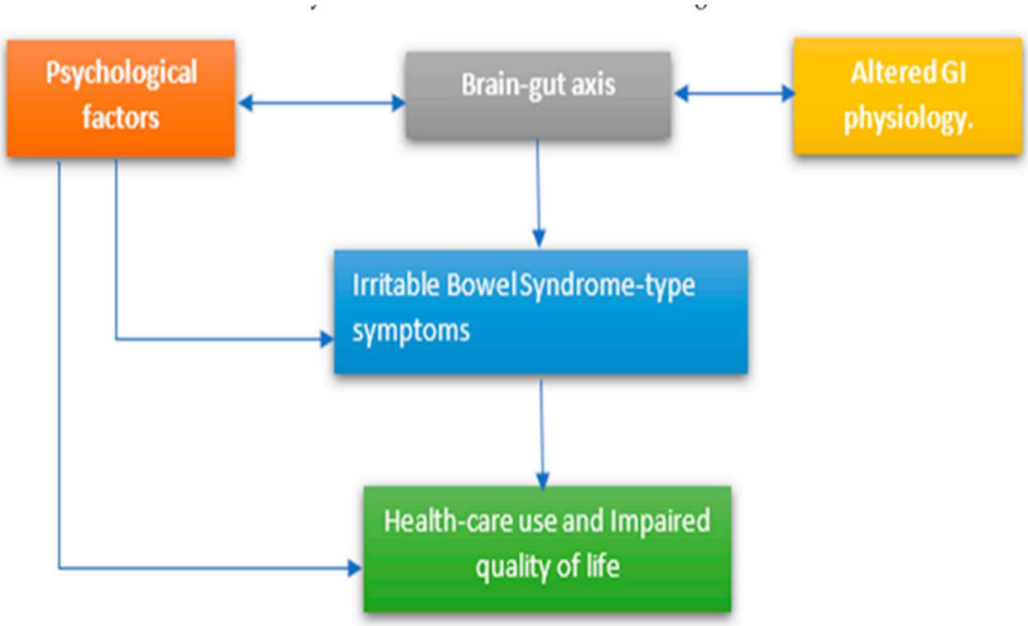

Figure 2. Biopsychosocial model for IBD

Neurodegenerative Disorders and Involvement of ENS

Inflammatory and neurodegenerative disorders can also have an effect on ENS, significantly affecting the quality of living for people. The gastrointestinal tract is greatly affected by Parkinson's disease, with oropharyngeal dysphagia and esophageal dysphagia, anorectal dysfunction, gastroparesis, small intestine and colonic dysmotility, hypersalivation, in addition to the neurologic manifestations caused by the loss of dopaminergic neuronal cells of the central nervous system, with severe deterioration of motor activity. Numerous investigations over the last 40 years have revealed a neurodegenerative pathophysiology in the gastrointestinal tract that is comparable to that in the central nervous system. To be specific, enteric dopaminergic neuronal loss and the presence of Lewy bodies and synuclein deposits in

enteric cells—markers for neuronal degeneration in Parkinson's disease—were discovered. In bioptic and postmortem studies on patients with constipation-related Parkinson's disease, fewer dopaminergic neurons were found in the colon. In certain cases, less amount of dopamine was detected using HPLC, i.e., High-Performance Liquid Chromatography in muscularis externa. Phosphorylated synuclein immune-positive neuritis was discovered in patients' submucosal ganglia during routine colonic biopsies. More recently, conventional staining with H&E, i.e., haematoxylin/eosin, was carried out on the jejunum and colon of certain patients who passed away from Parkinson's disease, revealing the existence of atrophic or pyknotic neuronal cells in both submucosal and myenteric plexuses. Additionally, deposits of synuclein were seen with degenerative changes and in some intact neurons, indicating that the buildup of synuclein occurs before neurodegeneration.

Conclusion

The microbiota–gut–brain axis has been closely studied over the past few decades, leading to more understanding of its effects. This review aimed to present the ENS and CNS interlinkage, describing the gut microbiome playing a key role in the growth and maintenance of ENS and CNS and how it is referred to as the second brain influencing gut– microbiota–brain axis under both physiological and pathological circumstances. Moving forward, it will provide more insight into the field of preventive gastroenterology. Then, it centralized the attention to CNS disorders with ENS implications, with special emphasis on neurodegenerative diseases like Parkinson's disease, Alzheimer's disease, multiple sclerosis, and other neurological disorders. Nutrition and cognition are also discussed with details of neurologic involvement in IBD, IBS, GI functional disorders, as well as stress-induced GI disorders. Future studies should aim to dissect and identify gut–brain access at the molecular level with much more detail. Clinical studies and trials are needed to precisely dissect the molecular pathways. Of key significance would be what specific microbiome metabolites reach the CNS, what they exactly do at that level, and through which mechanism. Establishing this association will open up new possibilities for various therapeutic strategies to combat the most debilitating disorders faced by society today

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