

Gut-Brain Axis Association to the Brain Function

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Abstract

Nowadays, a growing amount of evidence has indicated the correlation between a variety of neurological illnesses and the gut microbiome. The gut microbiome plays an important role in the gut-brain axis (GBA), the bidirectional crosstalk between the gastrointestinal tract (GI) and the central nervous system. The objective of this review is to summarize the factors related to the GBA and the CNS functions as well as the processes behind the relationship. The interaction between the CNS, the enteric nervous system (ENS), and many other systems, links the emotional and cognitive functions of the CNS to the GI functions. The hypothalamic pituitary adrenal axis (HPA) contributes most to the stress by modulating the adaptive responses. Although most evidence supporting the roles of gut microbiome are from experiments conducted in animals, there is clinical evidence showing the improvement in the condition of some neurological disorder patients when prescribed antibiotics. Psychological stressors of varying durations can influence the components and total biomass of the gut microbiota via host-gut microbiota signaling. Chemical signalling is one of the mechanisms behind GBA. One of which being the short chain fatty acids (SCFAs), made by the fermentation process of the gut bacteria, can affect the host's illness and behaviour. Moreover, Neuronal pathways connect the gut and the brain physically through the vagus nerve. The gut microbiota also plays a critical role in the formation and expression of the peripheral immune system and the growth of the brain's intrinsic immune system. Immune cells and their inflammatory molecules have been linked to both migraine attack and the stomach's visceral pain. Thereby, the impact of CNS on microbiota composition and function is controlled by the disruption of the normal luminal/mucosal environment.

Keywords: Hypothalamic pituitary adrenal axis (HPA); gut-brain axis (GBA); short chain fatty acids (SCFAs).

1. Introduction

The term representing the interaction between the gastrointestinal system (GI) and the central nervous system (CNS) is gut-brain axis (GBA) [1]. While the brain modulates the GI tract, including both sensory and secretion, through factors of hormone, the GI system may as well directly and indirectly affect the CNS [2, 3]. The hypothalamic pituitary adrenal axis (HPA) influences the gut functions through the mediation of the stress responses by hormonal factors [4, 5].

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The gut system affects the brain functions in many directions such as cognition and behavior [6]. Thereby, the dysfunction of GBA has been connected to several neurological disorders, namely mood and anxiety disorders, multiple sclerosis, Alzheimer disease, Parkinson disease, and migraine [1, 5]. Furthermore, neurotransmitters consisting of serotonin, calcitonin gene-related peptide (CGRP), dopamine, and gamma-aminobutyric acid have been said to be involved in the GBA [7]. Inflammatory molecules, neuropeptides, gut microbiota composition, stress hormones, and dietary elements are among the components that influence the correlations between migraine and GBA [2, 3, 8]. This review aims to present the GBA-related factors which cause migraine and the mechanism behind the relationship. Thereby, based on this knowledge, new solutions resolving the migraine symptoms may be found in the future.

2. Gut-brain axis

The bidirectional crosstalk of the CNS and the enteric nervous system (ENS), connects the cognitive and emotional roles of the CNS to the gastrointestinal functions [9, 10]. The complex communication within the GBA has been revealed not to only regulate the gastrointestinal homeostasis, but also impact higher cognitive functions [9]. The main responsibilities of the gut-brain crosstalk are to regulate gut functions and connect peripheral intestinal roles and processes such as intestinal permeability, immune activation, enteric reflex, and entero-endocrine signaling with the centers of the brain, controlling cognitive function and feelings. The mechanism behind the communication of the gut-brain crosstalk involves neuro-immuno-endocrine molecules [11, 12]. The CNS, both brain and spinal cord, the autonomic nervous system (ANS), the ENS and the HPA axis are the systems involved [13, 14]. The autonomic nervous system (ANS), consisting of the parasympathetic and sympathetic limbs operate both efferent and afferent signals [15]. The afferent signals include those starting at the lumen and transmitted to the CNS through spinal, enteric, and vagal routes while the efferent signals are channeled to the intestinal wall, from the CNS [10, 16]. The HPA, a part of the limbic system, the part of the brain which is responsible for emotion responses and memory, contributes the most to the stress efferent axis by coordinating the adaptive responses to stress-related triggers [17, 18]. The system can be activated from the environmental stress and the rise in the level of systemic pro-inflammatory cytokines [3, 19, 20]. The triggers activate the hypothalamus to produce corticotropin-releasing factor (CRF) which then stimulates the pituitary gland to secrete adrenocorticotrophic hormone (ACTH) [13, 21]. ACTH triggers the zona fasciculata of the adrenal cortex to release cortisol, one of the main stress hormones which influences multiple human organs, such as the brain [9, 22]. Thereby, both hormonal and neural pathways of interaction connect the brain to the intestinal functional effector cells, such as immune cells, enterochromaffin cells, enteric brain cells, interstitial cells of Cajal smooth muscle cells, and epithelial cells [23-25]. The gut flora influence these same cells as well which then give birth to the concept of microbiome GBA [26-28].

3. Role of microbiota in GBA

The gut microbiota has been proved by evidence from experimental and clinical studies that it plays a vital role in the GBA [29, 30]. While the enteric microbiota interact with the intestinal cells and ENS, the neuroendocrine and metabolic pathways also allow it to directly interact with CNS [22, 31]. In humans, evidence proving the gastrointestinal microbe-brain interaction arose from the observation of patients with hepatic encephalopathy, a

nervous system disorder due to severe liver disease [32, 33]. Prescribing oral antibiotics to the patients allows them to recover fast [8, 34]. Furthermore, specific microbiota alterations are observed in autistic patients depending on the severity of the disease [35, 36]. Thus, the evidence indicates the responsibilities of microbiota in affecting depressive-like behaviors and anxiety [21, 37, 38].

Functional gastrointestinal disorders (FGID), which are greatly involved with affective disorders, cause dysbiosis [39-41]. There has been evidence suggesting that both brain-gut and gut-brain functions are interrupted [42]. On the other hand, Irritable bowel syndrome (IBS), the gut-brain dysfunctions are more dominant [43, 44]. The disruption of GBA leads to changes in intestinal movement and secretion, causing the cells of the immune system and entero-endocrine to be altered and visceral hypersensitivity [39]. Microbiota interact with a variety of the different pathophysiological IBS targets which are supported by multiple evidence; IBS patients show unstable and indiverse gut microbiome, the growth of post-infectious IBS, the possibility of association with bacterial proliferation in the small intestine and the efficacy of certain probiotics and non-systemic antibiotics [45]. Moreover, by transferring the gut microbiome of IBS patients to germ-free (GF) mice, visceral hypersensitivity phenotype becomes visible in the previously GF mice [15, 46]. The dysfunction of both GBA and the gut microbiota in the pathophysiology of IBS has led to the suggestion that FGID can be classified as a microbiome-GBA disorder [47, 48].

4. Gut microbiota to the brain

GBA refers to a system of interconnection consisting of numerous biological systems which enables bidirectional crosstalk between gut microbes and the brain [4, 49]. This communication is critical for animals' microbial, central nervous, and gastrointestinal systems to maintain homeostasis [2, 50]. Direct and indirect signaling pathways are present in these biological networks, and they are carried out by neurotransmitters, neuronal networks, and the immune system, among other mechanisms. Knowing the diversity of biological systems included, it is likely that many pathways and processes synchronize to modulate multiple aspects of disease pathogenesis, and additional study is in demand in order to decipher the process [51].

5. From brain to gut microbiota

Psychological stressors of varying durations influence the components and total biomass of the gut microbiota [52]. Indeed, short-term stressors also affect the microbiota, being exposed to a social stressor for only two hours can dramatically alter the gut microbiota composition and decrease the proportional amount of the significant microbiota phyla [53]. These impacts are believed to be regulated via the ANS and HPA, directly and indirectly via host-gut microbiota signaling [54]. In conjunction with the endogenous pain-modulator pathways, these efferent neural pathways comprise what is known as the "emotional motor system" [55].

The direct effect is influenced by the release of signaling molecules by neurons, immune cells, and enterochromaffin cells under the control of the brain, which may affect the microbiota [42]. Neurotransmitter receptors on bacteria enable the interaction between CNS effectors and microbes [27, 54]. It has been reported in several studies that bacteria contain binding sites for enteric neurotransmitters, which are produced by the

host, and that these binding sites can impact the function of microbiota components, thereby increasing the body's susceptibility to inflammatory and infection stimuli [56]. *Pseudomonas fluorescens* has been found to have a high affinity for the GABA system, with binding characteristics familiar to those of a neural receptor [56]. A receptor for epinephrine/norepinephrine produced by the host, in which adrenergic antagonists specifically inhibit, can be found on *Escherichia coli* O157:H7 [57-59]. Additionally, the brain take part in modulating gut functions such as intestinal fluid handling, acid, bicarbonate, and mucus secretion, motility, and mucosal immune response, which are all necessary for the preservation of the mucus layer and biofilm, which are composed of diverse metabolic niches and microhabitats involved with the mucosa [60, 61]. The disruption of the normal mucosal environment caused by a dysfunction of GBA can then impact the gut microbiota [62].

Stress alters the amount and quality of mucus secreted [63, 64]. Dogs' postprandial gastric and intestinal motility is affected by acoustic stress, which causes a temporary slowing of gastric emptying and delays the retrieval of the migrating motor complex pattern [7, 15, 65]. Through the central secretion of CRF, psychological stress also raised the number of times of cecocolonic spike-burst activity occur [66]. Prebiotics and dietary fibres, in particular, can be profoundly affected by regional and world-wide alterations in GI transit [67, 68]. Changing intestinal permeability, which allows bacteria to perforate the epithelium and trigger an immune reaction in the mucous membranes, may also affect microbiota composition and role, according to some theories about brain function [69]. Colonic paracellular permeability is raised by acute stress via increased interferon- γ production and a fall in ZO-2 and occluding mRNA expression [70]. The brain, via the ANS, can also influence immune function. This disproportion in histamine and tryptase secretion is caused by the sympathetic branch modulating the amount, activity and degranulation of mast cells [71]. On the other hand, some mast cell mediators as CRF can raise epithelial permeability to bacteria, allowing germs to reach immune cells in the lamina propria [72]. Additionally, increased susceptibility to colitis and depression can be observed in adult rats, which developed colonic barrier dysfunction with association to corticotropin-releasing hormone (CRH) receptors, after experiencing mild stress related to neonatal maternal separation [73]. Bilateral olfactory bulb removal caused depression-like behaviour in mice, which was linked to increased central CRF expression and levels of serotonin and changes in colonic motility and the intestinal microbial profile [14]. Furthermore, effect of stress on the microbiota habitat is an increase in the release of α -defensin, an antimicrobial peptide, by Paneth cells [28, 74].

6. Chemical signalling between the gut and the brain

When the gut flora communicates with the nervous system, it can assist in modulating the animal host behaviour and homeostasis [75]. This crosstalk can take place through both direct and indirect signalling [76]. For example, short-chain fatty acids (SCFAs) are lipids made by bacteria in your intestine when fermenting food like fibre [77]. In preclinical models, these lipids can affect CNS by affecting neuroplasticity, the immune system, and gene expression. SCFAs can affect illness and behaviour [77]. The activity of a neuronal factor correlated to depression, brain-derived neurotrophic factor, was discovered to be modified by SCFA sodium butyrate treatment (BDNF) [78]. According to the same research team, the chronic treatment of exogenous sodium butyrate to mice for 28 days causes a drastic reduction in depressive-like symptoms [78]. The enteric microbiota also has an indirect chemical signalling effect on the nervous system and behaviour, as demonstrated by microbial regulation of the neuroendocrine system [75, 78]. Enteroendocrine cells (EECs) in the gut lining,

which produce hormones such as glucagon-like peptide 1, can modulate their hosts' hunger and feeding habits [79]. This is accomplished by regulating gut microorganisms' generation of endocrine signals (GLP1) [80]. Mice without an endogenous microbiota, dubbed GF mice, consume less food than typical mice with complete microbiota [81]. The production of GLP1 is lower in GF mice, as well as antibiotic-treated mice, compared to those conventionally colonized, indicating that the gut bacteria can influence this endocrine-mediated behaviour [80]. In response to the bacterial metabolite indole, Gastrointestinal L cells, which stimulates colonic vagal afferent activity, secrete the hormone GLP1, which has been shown to affect rats' levels of food intake and hunger [80, 81]. Additionally, the gut microbiota regulates neurotransmitter concentrations in model systems, implying that microbes operate as mediators for the nervous system's traditional signaling chemicals [82]. Microorganisms in the gut can synthesise neurotransmitters and induce neurotransmitter production in their animal hosts [54, 83]. So, the neurotransmitter gamma-aminobutyric acid is produced by microorganisms like *Parabacteroides*, *Bifidobacterium*, *Bacteroides*, and *Escherichia* spp (GABA) [74].

7. Neuronal pathways for gut–brain interactions

Neuronal pathways connect the gut and the brain physically [84]. The vagus nerve, which runs from the hindbrain to the gut and ENS, is the most well-known of these neural networks [85]. The gut flora plays a role in the maturation and activity of ANS, although this area of research is still relatively unexplored at this time [86]. There are fewer nerves that connect the colonic epithelium to the brain in GF mice, but these nerves can be restored by the growth of bacteria in the colon [84]. Furthermore, the gut microbiota has an effect on the formation of gut neuroglia in mice, which are essential for gut homeostasis and neural network upkeep [84]. According to recent findings, Through chemical transmission, the gut bacteria can impact the activity of enteric neurons [84]. For example, activating aryl hydrocarbon receptors in matured mice can control gut motility by affecting the ENS [16, 87].

8. Gut microbiota–brain signalling through the immune system

CNS and the gut flora, directly and indirectly, affect the immune system [11]. The gut flora plays a critical role in the formation and performance of the peripheral immune system, and it is essential to understand how it works [12, 88]. Additionally, the microbiota is required for the proper growth, maturation, and stimulation of microglia, the brain's intrinsic immune cells [89]. In comparison to conventional mice, GF mice had more immature microglia in many brain locations, according to cell morphology and transcriptional signals of maturation in microglia; this conclusion is backed by study in antibiotic-treated mice [84]. Microglia-mediated immune programming appears to be dependent on indicators from bacterial metabolism, as evidenced by the restoration of microglial morphology and function in GF mice following treatment with bacterial-derived SCFAs [88]. Microglial function and development may require the presence of intricate microbiota and/or particular bacterial taxonomic groups, as the ability to restore microglial deficits in GF mice was restored when a complex microbiota was transferred to the mice [90, 91]. Another study found that giving GF mice a combination of four *Bifidobacterium* species may impact microglia growth and stimulation via transcriptional methods [91]. While microglial morphology and gene expression changes are more prominent during the embryonic and adult phases of GF mice, the influence of gut microbiota on microglia appears to be gender and

time-specific [76]. Thus, future studies examining the microbiota's impact on neurons should take sex into account as a significant biological variable [76]. Notably, altered microglia function has been associated with stress, behavioural, and neurodegenerative disorders, suggesting that microglial influences on the gut microbiome may influence human neurological illnesses [76]. Additionally, the gut microbiota and the brain communicate via circulating cytokines via the systemic immune system [12]. An increased level of peripheral inflammation is observed in several neuropsychiatric disorders, including anxiety, depression, and an autism spectrum disorder. Cytokines and chemokines can be synthesized by microglia and perivascular macrophages or directly transported across the blood-brain barrier (BBB) into the CNS [92]. The gut flora affect the permeability of the BBB, as evidenced by reports that GF mice have higher BBB permeability compared to conventional mice, which may be partly resulted from the decrease in the expression of tight-junction proteins such as claudin 5 and occludin, among other things [92]. Alterations to the BBB integrity caused by infections, autoimmune diseases, and injuries increase the brain's accessibility to circulatory system-borne microbial products and increase the brain's susceptibility to subsequent pathology [92]. Many neuropathological diseases have increased BBB permeability, underlining the potential importance of linkages between systemic immunity and brain outcomes [93].

9. The involvement of inflammation in migraine headache and role of gut microbiome

Immune cells and their inflammatory molecules such as interleukin (IL)-1, IL-6, and IL-18, tumour necrosis factor-alpha (TNF- α), and interferon-gamma (IFN- γ) have been linked to the stomach as afferent ending sensitizers and stimulators of visceral pain [54]. Moreover, proinflammatory cytokines such as IL-1, IL-6, IL-8, and TNF- α have been connected to migraine pain and have been shown to be elevated during migraine attacks [20, 94]. Most studies examining the gut microbiota's role in various disorders employ "germ-free" murine models [95]. Since these organisms are raised in a sterile environment, they lack microbiota [96]. The significance of the immune system in GBA and microscopic pathobiology is also backed by researches referring that an increased level of nociception induced by inflammatory triggers can be reduced in GF mice in comparison with conventional mice [97]. This finding emphasizes the critical role of gut microbiota in priming the host for adjustment to environmental stress factors that cause pain [97, 98].

Notably, the gut microbiota composition has a significant influence on GBA [97]. This occurs through two distinct mechanisms: indirect signalling, which includes neurotransmitters, inflammatory molecules, and hormones derived from the microbiota, and direct connection to activating vagus nerve end terminals [99]. Additionally, the mechanism is bidirectional in this case, as the CNS can influence enteric microbiota via the parasympathetic and the sympathetic nervous systems as well as the release of neuroendocrine peptides [100, 101]. Psychological and physical stressors can alter the profile of the intestinal microbiota [18]. These stressors cause the secretion of CRH in the hypothalamus, which causes cortisol to be secreted by the adrenal glands [15, 102, 103]. They may also cause changes in the intestines' permeability by altering the intestines' microbiota profile. Finally, dysbiosis may result from these events [14, 104].

10. Conclusion

Gut microbiota is of vital importance in the gut-nervous system axis of communication. It engages with the CNS through the regulation of brain chemistry and exerting influence over neuroendocrine systems participating in stress response, anxiety, and memory function. Numerous of these indicators are shown to be strain-specific, meaning that certain probiotic strains may play a function in the treatment of neurologic disorders as a new adjuvant method. On the flip side, the gut microbiota can also be altered by the psychological stressors of different durations. Thereby, the composition and total biomass of the gut flora may be changed due to stressors. Additionally, the impact of CNS on microbiota profile is almost certainly controlled by an interruption of the typical luminal/mucosal environment, which can be rebuilt through probiotics and possibly through diet. This interaction can be seen in clinical practice in functional gastrointestinal disorders (FGID), particularly IBS, which is now recognised as a microbiome-GBA disorder. GBA not only impacts the CNS but also the immune system directly and indirectly which highlights the importance of GBA to human physical and mental health.

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