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Review Article

Brain and Gut Brain: Integrating Interactions in Health and Disease

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Abstract

This a review study that purposed to explore the extent of integration between the microbiome in intestine and brain. This is achieved by the gut brain access (GBA). Interactions between gut brain (GB) and brain have been reported. Brain can impact the microbiome of intestine through GBA. This can affect the structure and functional properties of gut microbiome. On the other hand, gut microbiome can release neurotransmitters that impact the function of brain. Now, we are looking for the diseases from a complicated point of view, and better understanding of such interactions have become crucial to control diseases in future. Taken together, the present study showed that gut brain and the brain exchanges information that are processed and facilitated by microbiome in both intestine and brain. Controlling of microbiome is thought to be featured in the future as a therapeutic strategy that acts to improve pathogenicity of diseases.

Keywords: Gut Brain; Gut Brain Access; Microbiome; Integration; Disease

Introduction

Gut-Brain

The gut-brain axis (GBA) is a bidirectional communication system that connects the central and enteric nervous systems. It connects the brain's emotional and cognitive centers with peripheral digestive processes. The relevance of gut bacteria in affecting these interactions has been highlighted in recent study. This relationship between microbiota and GBA appears to be bidirectional, with neurological, endocrine, immunological, and humoral interactions allowing communication from gut microbiota to brain and from brain to gut microbiota [1]. Insights into the gut-brain crosstalk have shown a complex communication mechanism that is expected to have many effects on motivation, and higher cognitive functions in addition to ensuring normal gastrointestinal homeostasis. The term "gut-brain axis" (GBA) encapsulates the complexity of these interactions [2]. Its job is to keep track of and integrate gut activities, as well as to connect the brain's affective and cognitive centers to peripheral intestine functions and mechanisms include immune activation, intestinal permeability, enteric reflex, and entero-endocrine communication. Neuro-immuno-endocrine mediators are involved in GBA communication processes. The central nervous system (CNS), including the brain and spinal cord, the autonomic nervous system (ANS), the enteric nervous system (ENS), and the hypothalamus pituitary adrenal (HPA) axis are all part of this bidirectional communication network. The sympathetic and parasympathetic limbs of the autonomic system control both afferent signals originating in the lumen and relayed to the CNS via enteric, spinal, and vagal pathways, as well as efferent signals from the CNS to the intestinal wall. The HPA axis is a key stress efferent axis that regulates the organism's adaptive responses to a variety of stressors [3].

It is a part of the limbic system, which is a vital region of the brain that's mostly responsible for memory and emotional reactions. Environmental stress, as well as elevated systemic pro-inflammatory cytokines, activate this system, which stimulates adrenocorticotropic hormone (ACTH) secretion from the pituitary gland, which leads to cortisol release from the adrenal glands, by secreting the corticotropin-releasing factor (CRF) from the hypothalamus. Cortisol is a stress hormone that has an impact on a variety of human organs, including the brain. Thus, the brain can impact the actions of intestine functional effector cells such as immune cells, epithelial cells, enteric neurons, smooth muscle cells, Cajal interstitial cells, and enterochromaffin cells by

combining neurological and hormonal lines of communication. These same cells, on the other hand, are influenced by the gut microbiota [4], which has lately been studied for its role in brain-gut reciprocal connections. The concept of a microbiome GBA is starting to gain traction. The enteric microbiota is found in the human gastrointestinal system, and while each person's microbiota profile is unique, the relative abundance and distribution of these bacterial phylotypes along the intestine are similar in healthy people. Firmicutes and Bacteroides are the two most prominent phyla, accounting for at least 34% of the microbiome [5]. This microbial population plays a crucial role in the host's metabolic and physiological activities, as well as maintaining its homeostasis during life.

The Microbiota's Role in GBA

The enteric microbiota appears to have a significant impact on GBA, interacting not only locally with intestinal cells and the ENS, but also directly with the CNS via neuroendocrine and metabolic pathways. The most persuasive evidence of a gut microbe-brain relationship in humans came more than 25 years ago, when doctors saw that patients with hepatic encephalopathy improved dramatically after taking antibiotics [6]. Meanwhile, new evidence suggests that the microbiota has a role in anxiety and depressive-like behaviors [7,8], as well as dysbiosis in autism. Autistic people, in fact, have different microbiotas depending on the severity of the disorder [8,9]. Dysbiosis is also seen in functional gastrointestinal disorders (FGID), which are linked to a disturbance of GBA and are highly associated with mood disorders [10-12]. Both brain-gut and gut-brain dysfunctions have been documented, with the former being more prevalent in irritable bowel syndrome (IBS) [13]. The disruption of the GBA produces abnormalities in intestinal motility and secretion, as well as visceral hypersensitivity and entero-endocrine and immune system cellular modifications. The presence in IBS patients of alterations in microbiota composition with defects both in its stability and diversity, the development of post-infectious IBS, the possible coexistence with small intestinal bacterial overgrowth, and the efficacy of tr have all been linked to the microbiota [14]. Furthermore, the IBS-specific phenotype of visceral hypersensitivity can be transmitted to previously germ-free rats via the microbiome of IBS patients [15]. The simultaneous dysregulation of both GBA and the gut microbiota in the etiology of IBS has led to the suggestion that this FGID be classified as a microbioma-GBA illness [16].

Actions from the Microbiota of the Stomach to that of the Brain

There has been a surge in experimental study, mostly on animals, aiming at determining the role of the microbiota in GBA modulation. The use of germ-free (GF) animals, probiotics, antibiotics, and infection studies [17] have all been employed as technical solutions. Bacterial colonization of the gut is critical for the growth and maturation of both the ENS and the CNS, according to studies in GF animals [18,19]. The absence of microbial colonization is linked to changes in neurotransmitter expression and turnover in both nervous systems [20], as well as sensory-motor changes in the gut, including delayed gastric emptying and intestinal transit [21], reduced migrating motor complex cyclic recurrence and distal propagation [22], and enlarged cecal size [23]. Reduced gene expression of enzymes involved in the production and transport of neurotransmitters, as well as that of muscle contractile proteins, was linked to neuromuscular defects [24]. After animal colonization in a bacterial species-specific manner, all these aberrations are restored. Microbiota modulates stress reactivity and anxiety-like behavior, as well as regulating the set point for HPA activity, according to studies conducted on GF animals. In general, these animals had lower anxiety [25] and a higher stress response with higher levels of ACTH and cortisol [26]. Microbial colonization of the gut normalizes the axis in an age-dependent manner, with reversibility of the exaggerated stress response observed only in very young mice after GF colonization, indicating the existence of a critical period during which neural regulation plasticity is sensitive to microbiota input [27]. Memory dysfunction has also been documented in GF mice [28] which is likely due to decreased production of brain-derived neurotrophic factor (BDNF), one of the most critical factors involved in memory. This molecule is a neurotrophic factor that affects various aspects of brain processes and cognitive functions, as well as muscle repair, regeneration, and differentiation [29]. It is mostly found in the hippocampus and cerebral cortex. Finally, since an increase in serotonin turnover and changed levels of associated metabolites have been found in the limbic system of GF mice [30], the presence of the microbiota leads in modulation of the serotoninergic system. Studies on the influence of gut microbiota alteration using probiotics and/or antibiotics have further backed up the impact of bacteria on GBA. Microbiota influences anxiety and the HPA system via affecting brain neurochemistry, according to these research [31]. GABA mRNA in the brain was altered in a region-dependent manner after chronic treatment with Lactobacillus rhamnosus JB-1. GABAB1b rose in the cortical cingulate and prelimbic areas while decreasing in the hippocampus, amygdala, and locus coeruleus in compared to mice on a regulated diet. The expression of GABAA2 mRNA was reduced in the prefrontal cortex and amygdala but increased in the hippocampus. Probiotics, on the other hand, reduced stress-induced cortisol release, as well as anxiety and depression-related behavior [32].

Similarly, in specific-pathogen-free animals, transitory changes in microbiota composition caused by oral antimicrobials (neomycin, bacitracin, and pimaricin) boosted exploratory behavior and BDNF expression in the hippocampus region [33]. Furthermore, in a rat model of IBS, changing the microbiota composition with the probiotic's association VSL#3 causes an increase in BDNF expression, mitigation of age-related changes in the hippocampus [34], and reversion of neonatal maternal separation-induced visceral hypersensitivity [35]. A change in the expression of subsets of genes implicated in pain transmission and inflammation has also been documented in this later model of stress, which was reset by the early life administration of probiotics. The vagus nerve, which

conveys information from the luminal environment to the CNS, appears to be involved in microbial communication with the brain. In fact, vagotomized mice showed no neurochemical or behavioral effects, indicating that the vagus is the key modulatory constitutive communication channel between the microbiota and the brain [32].

The anxiolytic effect produced with a therapy with Bifidobacterium longum in a model of chronic colitis associated with anxiety-like behavior was lacking in mice that were vagotomized before the development of colitis [36]. Microbiota may interact with GBA by a variety of methods, the most important of which is likely modification of the intestinal barrier, which can affect all of the underlying compartments. As recently documented in an animal model of water avoidance stress, probiotic species-specific central effects are linked to the restoration of tight-junction integrity and the protection of the intestinal barrier. Pretreatment of rats with a probiotic formulation containing Lactobacillus helveticus R0052 and Bifidobacterium longum R0175 restored tight junction barrier integrity and reduced HPA axis and autonomic nervous system activity, as measured by plasma cortisol and catecholamine levels. Probiotics also reduced alterations in hippocampus neurogenesis and expression of synaptic plasticity-related genes in the hypothalamus. Microbiota can also interact with GBA by modulating afferent sensory nerves, as demonstrated by Lactobacillus reuteri, which affects gut motility and pain perception by increasing their excitability by blocking calcium-dependent potassium channel opening [37].

Microbiota can also alter ENS function by manufacturing chemicals that act as local neurotransmitters, such as GABA, serotonin, melatonin, histamine, and acetylcholine [38], as well as generating a physiologically active form of catecholamines in the gut lumen [39]. Lactobacilli also create nitric oxide [40] and hydrogen sulfide, which affects gut motility by interacting with the vanilloid receptor on capsaicin-sensitive nerve fibers [41]. Bacterial metabolites are also attracted to the ENS. Short-chain fatty acids (SCFAs), such as butyric acid, propionic acid, and acetic acid, are one of the main products of bacterial metabolism and can stimulate sympathetic nervous system [42], mucosal serotonin release [43], and alter memory and learning processes [44]. In this context, it's worth noting that dietary alteration of microbiota may have an impact on behavior. Mice fed a 50 percent lean ground beef diet had a higher diversity of gut flora than mice fed regular rodent chow, as well as more physical activity, reference memory, and less anxiety-like behavior [45]. Given the ability of gut microbiota to alter nutrient availability and the close relationship between nutrient sensing and peptide secretion by enteroendocrine cells, microbiota-GBA interaction could also occur through the release of biologically active peptides from enteroendocrine cells that can affect the GBA [46]. Galanin, for example, increases glucocorticoid production from the adrenal cortex via stimulating the central branch of the HPA axis (i.e., the release of CRF and ACTH). Galanin can also promote adrenocortical cell cortisol secretion and adrenal medulla norepinephrine release directly [47]. In humans, ghrelin has a strong ACTH/cortisol-releasing action, and it is thought to play a role in the modulation of the HPA response to stress and nutritional/metabolic changes [48].

Finally, mucosal immune activation is influenced by bacteria. Increased substance P expression in the ENS is caused in rats after treatment with oral antimicrobials, a result that is reversed by the administration of Lactobacillus paracasei, which also reduces antibiotic-induced visceral hypersensitivity [49]. Proteases may play a role in the effects of microbiota on immunological activation. These enzymes become the end-stage effectors of mucosal and enteric neuronal injury in intestinal-immune related diseases [50]. Increased protease concentrations have been seen in IBS patients' feces, which have been linked to certain intestinal bacterial species [51].

In IBS, the current working concept is that an aberrant microbiota triggers mucosal innate immune responses, which increase epithelial permeability, activate nociceptive sensory pathways, and dysregulate the enteric nervous system [52]. The effects of Helicobacter pylori (H. pylori), a gastric mucosa-colonizing bacterium, on the GBA may be mediated via similar processes. The effects of this microorganism could be caused by both neurogenic inflammatory processes and a lack of microelements because of functional and morphological abnormalities in the digestive tract [53]. Nonetheless, unambiguous evidence on the direct and immediate effects of H. pylori infection on the GBA are still absent, and the connection between functional dyspepsia and H. pylori infection in clinical practice is not well characterized. In fact, the number of people who need to be treated to cure one incidence of dyspepsia is 14 (95 percent CI 10-25, implying that the increase in H. pylori related upper FGID has a complex origin [54].

From Brain to Gut Microbiota

Different types of psychological stressors, regardless of length, affect the composition and total biomass of the intestinal microbiota. Also, the use of short stressors effects the microbiota, being the exposure to social stressor for only 2 h considerably able to change the community profile and to diminish the relative proportions of the key microbiota phyla [55]. These effects may be mediated both directly by host-enteric microbiota signaling and indirectly by changes in the intestinal milieu via the parallel neuroendocrine output efferent systems (i.e., autonomic nervous system and HPA). The so-called "emotional motor system" [2] is made up of several efferent neural pathways that are linked to pain-modulator endogenous pathways. The direct influence is mediated through the secretion of signaling molecules by neurons, immune cells, and enterocromaffin cells, which may change microbiota and is regulated by the brain. Communication between CNS effectors and bacteria relies on the presence of neurotransmitter receptors on bacteria. Several studies have found that bacteria have binding sites for enteric neurotransmitters produced by the host, which can impact the function of microbiota components, adding to an increased risk of inflammatory disease [56]. Pseudomonas

fluorescens has been found to have a high affinity for the GABA system, with binding characteristics like those of a brain receptor [57].

A receptor for host-derived epinephrine/norepinephrine exists in Escherichia coli O157:H7, which can be inhibited specifically by adrenergic antagonists [58]. Furthermore, the brain plays a key role in the regulation of gut functions such as motility, acid, bicarbonate, and mucus secretion, intestinal fluid handling, and mucosal immune response, all of which are critical for the maintenance of the mucus layer and biofilm, where individual bacteria grow in a variety of microhabitats and metabolic niches associated with the mucosa [59]. The disruption of the usual mucosal environment caused by GBA dysfunction can then impact gut flora. Stress increases fluctuation in size and quality of mucus discharge [60]. In dogs, acoustic stress alters postprandial motility, delaying the recovery of the migrating motor complex pattern and causing a transitory slowdown of stomach emptying [61].

Through the central release of CRF, mental stress also increases the frequency of cecocolonic spike-burst activity [62]. Changes in gastrointestinal transit, both regional and global, can have a significant impact on the delivery of essential nutrients to the enteric bacteria, particularly prebiotics and dietary fiber. Changes in intestinal permeability may also influence microbiota composition and function, allowing bacterial antigens to permeate the epithelium and trigger an immunological response in the mucosa. Acute stress increased colonic paracellular permeability by increasing interferon-g production and decreasing ZO-2 mRNA expression, as well as occluding [63]. The immune system may be modulated by the brain via the ANS. In stress-related muscular failure, the sympathetic branch regulates the number, degranulation, and activity of mast cells, resulting in an imbalance in tryptase and histamine release [64]. Other mast cell products, such as CRF, can increase epithelial permeability to bacteria, allowing bacteria to enter the lamina propria and attack immune cells [2]. Corticotropin-releasing hormone receptors are also involved in colonic barrier malfunction in adult rats as a result of mild stress in neonatal mother separation [65], which leads to depression and increased vulnerability to colitis [66]. In rats, bilateral olfactory bulbectomy caused depression-like behavior linked to higher brain CRF expression and serotonin levels, as well as changes in colonic motility and microbial profile [67].

Another proposed stress-induced change in the microbiota habitat is an increase in the release of a-defensin, an antimicrobial peptide, by Paneth cells [68]. Finally, it is worth noting that stress-related changes in the gut promote the expression of pathogenic bacteria. Pseudomonas aeruginosa expression is induced by norepinephrine produced during surgery, which could lead to gut sepsis [69]. Furthermore, norepinephrine can accelerate the proliferation of various intestinal pathogens and boost the virulent characteristics of Campylobacter jejuni, as well as favor the expansion of non-pathogenic and pathogenic E. coli isolates [70]. Neurodegenerative disorders (NDs) disrupt vital activities not just in the central nervous system (CNS), but also in the gut, implying that they affect both CNS and gut-innervating neurons. Although the CNS biology of NDs is still being researched, little is known about how gut-innervating neurons, such as those that connect the gut to the brain, are impacted by or involved in the etiology of these debilitating and progressive illnesses. Recent research has revealed how the CNS and gut biology, with the help of gut-brain connecting neurons, control each other's functions [71].

In the clinical management of inflammatory bowel disease, malnutrition is a key issue (IBD). Our knowledge of the relationship between eating behavior and intestinal inflammation is still in its early stages. Patients with active Crohn's disease have high hedonic food urges and emotional eating patterns, which may help to alleviate symptoms of low mood, anxiety, and sadness. IBD patients' impulsivity features may lead them to appealing food intake as an immediate reward rather than future health concerns. In ileal inflammation, the peptide response of enteroendocrine cells (EEC) to food intake is upregulated, which could lead to changes in gut–brain transmission, which could affect appetite and eating behavior. In conclusion, eating behavior in intestinal inflammation may be influenced by a complex interplay of gut peptides, psychological and cognitive factors, disease-related symptoms, and inflammatory burden [72].

Malnutrition is a significant issue in the treatment of inflammatory bowel diseases (IBD), Crohn's disease (CD), and ulcerative colitis (UC). Malnutrition can be caused by a variety of factors, including inadequate dietary intake, micronutrient deficits caused by poor nutrient use or loss, and malabsorption caused by mucosal inflammation or resection [73]. Furthermore, increased protein catabolism rates [74]. in response to increased protein requirements ascribed to intestinal and systemic inflammation are linked to the negative nitrogen balance seen in CD (e.g., acute-phase protein, pro-inflammatory cytokine, and fecal calprotectin FCP production). Malnutrition is exacerbated by a number of additional factors, including illness load, appetite loss, disordered eating, and other related symptoms including nausea and diarrhea, all of which have a detrimental influence on IBD patients' quality of life [72].

Conclusions

The present study showed that gut brain and the brain exchanges information that are processed and facilitated by microbiome in both intestine and brain. Controlling of microbiome is thought to be featured in the future as a therapeutic strategy that acts to improve pathogenicity of diseases.

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