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The Gut–Brain Axis

Emeran A. Mayer, Karina Nance, and Shelley Chen

G. Oppenheimer Center for Neurobiology of Stress and Resilience and Vatche and Tamar Manoukian Division of Digestive Diseases, David Geffen School of Medicine, University of California, Los Angeles, California 90095, USA; email: emayer@.ucla.edu

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Abstract

Preclinical evidence has firmly established bidirectional interactions among the brain, the gut, and the gut microbiome. Candidate signaling molecules and at least three communication channels have been identified. Communication within this system is nonlinear, is bidirectional with multiple feedback loops, and likely involves interactions between different channels. Alterations in gut–brain–microbiome interactions have been identified in rodent models of several digestive, psychiatric, and neurological disorders. While alterations in gut–brain interactions have clearly been established in irritable bowel syndrome, a causative role of the microbiome in irritable bowel syndrome remains to be determined. In the absence of specific microbial targets for more effective therapies, current approaches are limited to dietary interventions and centrally targeted pharmacological and behavioral approaches. A more comprehensive understanding of causative influences within the gut–brain–microbiome system and well-designed randomized controlled trials are needed to translate these exciting preclinical findings into effective therapies.

INTRODUCTION

GI: gastrointestinal

IBS: irritable bowel syndrome

ENS: enteric nervous system

CNS: central nervous system

Bidirectional gut–brain (GB) interactions regulate key physiological and homeostatic functions, including food intake, immune regulation, and sleep (1). Even though alterations of GB interactions have long been postulated to play a central role in chronic abdominal pain symptoms and gastrointestinal (GI) dysfunction (2, 3), the terminology change from functional GI disorders to disorders of altered GB interactions has only recently been accepted by major professional societies (4). Even though research during the past decade has shown significant progress in understanding the pathophysiology of GB disorders like irritable bowel syndrome (IBS) and functional dyspepsia, disagreement remains about the relative contribution of peripheral (e.g., gut) and central (brain, spinal cord) mechanisms to symptom generation in these diseases, as well as other, often comorbid syndromes such as functional chest pain and functional abdominal pain. However, there is growing consensus that the pathology of chronic abdominal pain can be viewed as a dysregulation of the interplay among signaling events in the gut, enteric microbiota, enteric nervous system (ENS), and central nervous system (CNS). This dysregulation is associated with changes in gut motility and regional transit, visceral sensitivity, immune function, and mood (2).

The rapid development of microbiome science during the last 15 years has been accompanied by a shift in the understanding of the traditional GB axis to a systems biological view of gut–brain–microbiome (GBM) interactions involving bidirectional interplay between the brain and the gut including the gut-associated immune system, the enteric neuroendocrine system, the ENS, and the gut microbiome (**Figure 1**). This new view of GB interactions has also been applied to the pathophysiology of several brain disorders that had previously been attributed exclusively to pathophysiological processes limited to the brain. Results from preclinical and clinical studies have opened

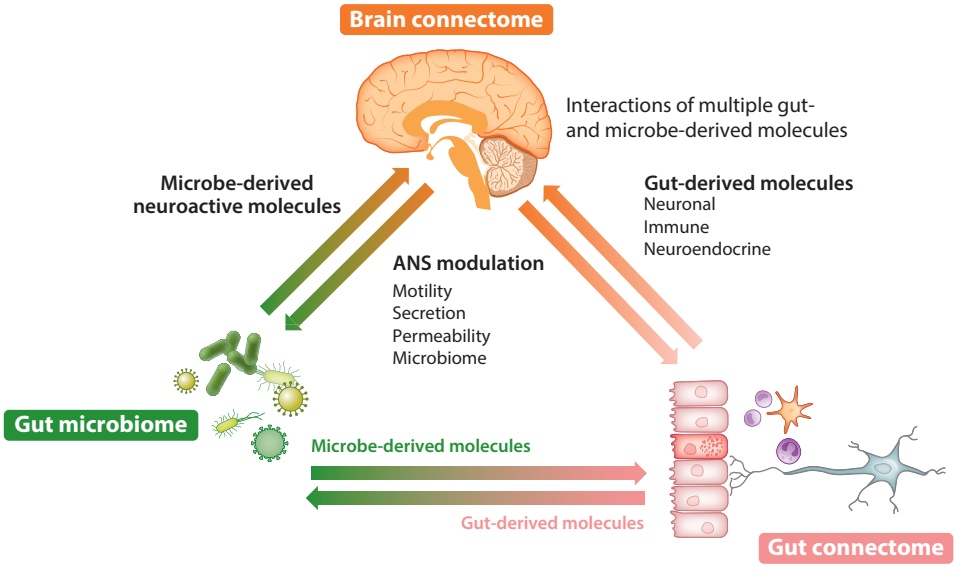

Figure 1

Systems view of gut–brain–microbiome (GBM) interactions. The brain connectome, gut connectome, and gut microbiome make up the three nodes in the GBM network. All nodes are connected by bidirectional edges with multiple feedback loops generating a nonlinear system. The gut microbiota can communicate with the brain either directly via different signaling molecules (**Figure 2**) or indirectly via the gut–brain axis. Similarly, the brain can modulate the microbiome either directly or via alterations of the gut microbial environment. Abbreviation: ANS, autonomic nervous system. Figure adapted with permission from Reference 7.

up the possibility of targeting the gut microbiota as treatment for disorders of altered GB interactions (formerly called functional GI disorders) as well as for psychiatric and neurological disorders such as depression, anxiety, Alzheimer's disease, Parkinson's disease, and autism spectrum disorder.

ANS: autonomic nervous system

ECCs: enterochromaffin cells

HPA axis: hypothalamic–pituitary–adrenal axis

SCFAs: short-chain fatty acids

INTEROCEPTION

Interoception refers to the ability of the brain to sense and process information about the internal physiological state of the body (5). While bodily signals transmitted via fine, unmyelinated vagal and sympathetic afferent fibers to the brain had long been considered the sole source of interoceptive information, microbiome science has identified gut microbes and their metabolites as another major source of signaling. A body of largely preclinical evidence supports the concept that the microbiome can influence the structure, function, and development of the brain in a bottom-up fashion thorough neuroimmune and neuroendocrine mechanisms (1, 6, 7). Interoception underlies motivational states, emotional reactions, and homeostatic reflexes (8). These reflex loops aim to maintain homeostasis in the GB axis during steady state and during perturbations, and they occur at the level of the ENS, spinal cord, brainstem, and central autonomic regions (9). Reflexes within the ENS regulate GI motility, blood flow, and secretion in the physiological state but are modulated by autonomic nervous system (ANS) inputs from the brain during threat to homeostasis of the organism (10). This modulation, which is initiated in response to salient cognitive/emotional influences, has the ability to override reflex function in the case of strong emotions or environmental stress (11). The majority of the gut microbial signals produced by the microbiota can either (*a*) modulate these homeostatic reflexes by acting locally on enteric neurons or on vagal and sympathetic afferent nerve terminals generating interoceptive signals to the CNS or (*b*) be transmitted to the brain via the systemic circulation. Most of these signaling molecules can be classified into food-related metabolites, metabolites of endogenously produced molecules, and signals made up of microbial cell wall components (**Figure 2**) (12).

Microbe-derived signals can travel to the CNS directly via the systemic circulation or indirectly by interacting with receptors on gut-based enteroendocrine cells, enterochromaffin cells (ECCs), mucosal immune system, and possibly tuft cells (13). When stimulated, these cells can release molecules that act on receptors on synaptically connected vagal and spinal afferents. The CNS responds to this input by modulating activity through the sympathetic and parasympathetic branches of the ANS as well as through the hypothalamic–pituitary–adrenal (HPA) axis (7, 14). Changes in the control of, sensitivity to, or integration of interoceptive signals at any level of the neuraxis can lead to perturbations throughout the entire system. The insular cortex of the brain is the primary cortical substrate in interoceptive processing; the posterior insula is the primary interoceptive cortex, and the anterior insula integrates sensory information with other affective and motivational inputs. Interactions between the anterior cingulate cortex and the frontotemporal networks allow interoceptive signals to integrate with complex emotional and social processes (8). Abnormalities in interoceptive signaling have been associated with symptom generation in disorders of GB interactions (2) such as IBS, functional dyspepsia and chronic abdominal pain, and psychiatric disorders, as well as with the expression of neurodegenerative and developmental disorders.

FOOD-RELATED METABOLITES

Short-chain fatty acids (SCFAs) are signaling molecules that are generated exclusively by gut microbes through the fermentation of dietary fiber, as humans lack the enzymes required to digest fiber (15). SCFAs act on a wide range of targets via activation of free fatty acid 2 (FFA2), FFA3,

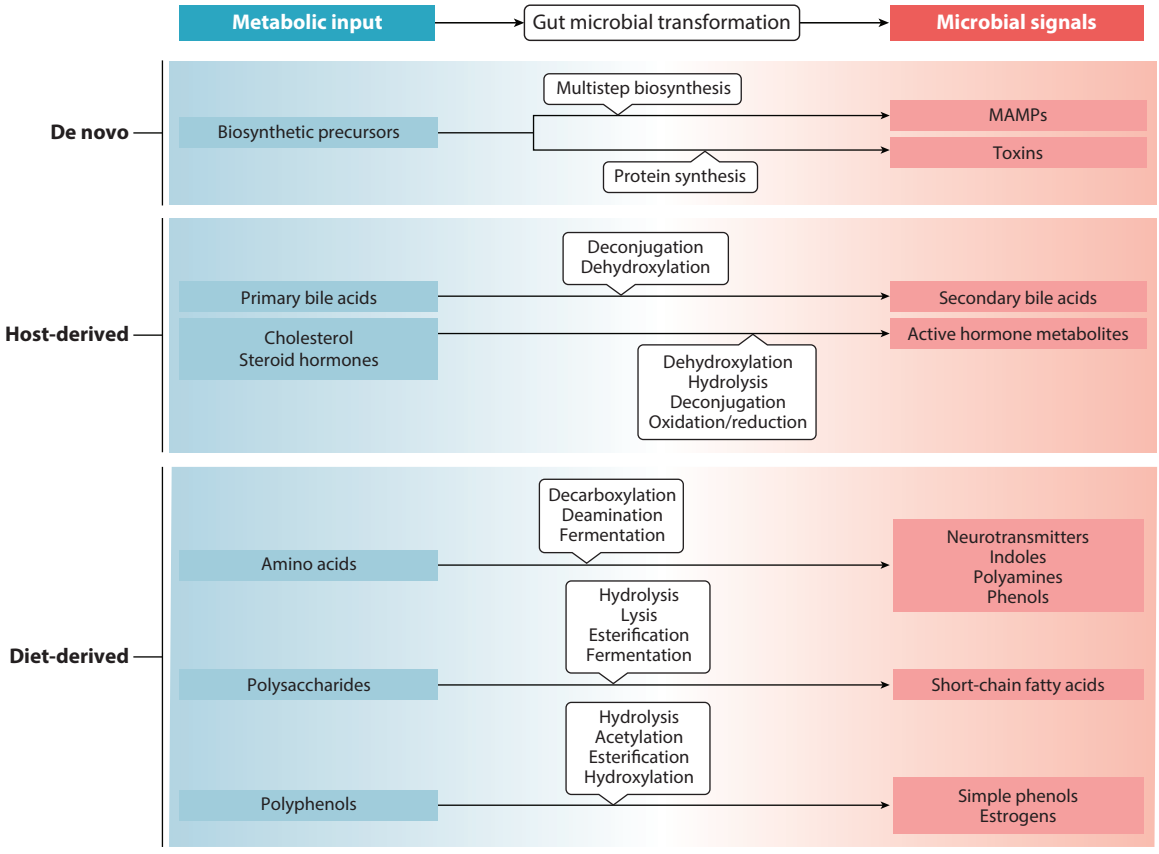

Figure 2

The gut microbiota can signal to the nervous system via three categories of signaling molecules. In immune signaling, components of the gut microbial membrane (lipopolysaccharide, MAMPs) or intact microbes can either travel through the systemic circulation to the brain, where they activate TLRs on microglia or neurons, or come into contact with TLRs on immune cells in the gut, triggering cytokine release locally and into the systemic circulation. Host-derived signaling molecules generated by the host and excreted into the small intestine are converted into absorbable neuroactive metabolites that reenter the systemic circulation. Diet-derived molecules are metabolites of amino acids, polysaccharides, and polyphenols are that metabolized by microbes into absorbable molecules with local and systemic effects. Abbreviations: MAMP, microbe-associated molecular pattern; TLR, Toll-like receptor. Figure adapted with permission from Reference 12.

GPR109a, and Olfr78 receptors and have been implicated in physiological processes ranging from neuroplasticity to gene expression, food intake, and immune system modulation (16, 17). Germ-free (GF) mice have higher levels of activation of afferent neurons projecting to brainstem nuclei in comparison to non-GF mice (18), and administration of SCFA-producing gut microbiota into GF mice suppresses such activation, suggesting that the healthy gut microbiome can suppress this neuronal signaling pathway. Preclinical and clinical studies have shown that SCFA production stimulates cells in the ileum, known as L cells, to secrete the satiety hormone glucagon-like peptide 1 (GLP-1) and cause sensations of satiety behavioral changes (19). The SCFA butyrate downregulates gene expression in the gut-associated immune system (20), suggesting that decreased levels of SCFA-producing bacteria may contribute to increased inflammation. SCFAs also modulate the synthesis of 5-hydroxytryptamine (5-HT or serotonin) in ECCs (**Figure 3**). Extensions of ECCs, so-called neuropods, are in synaptic contact with vagal and possibly sympathetic afferent nerve

GF: germ-free

5-HT: 5-hydroxytryptamine (serotonin)

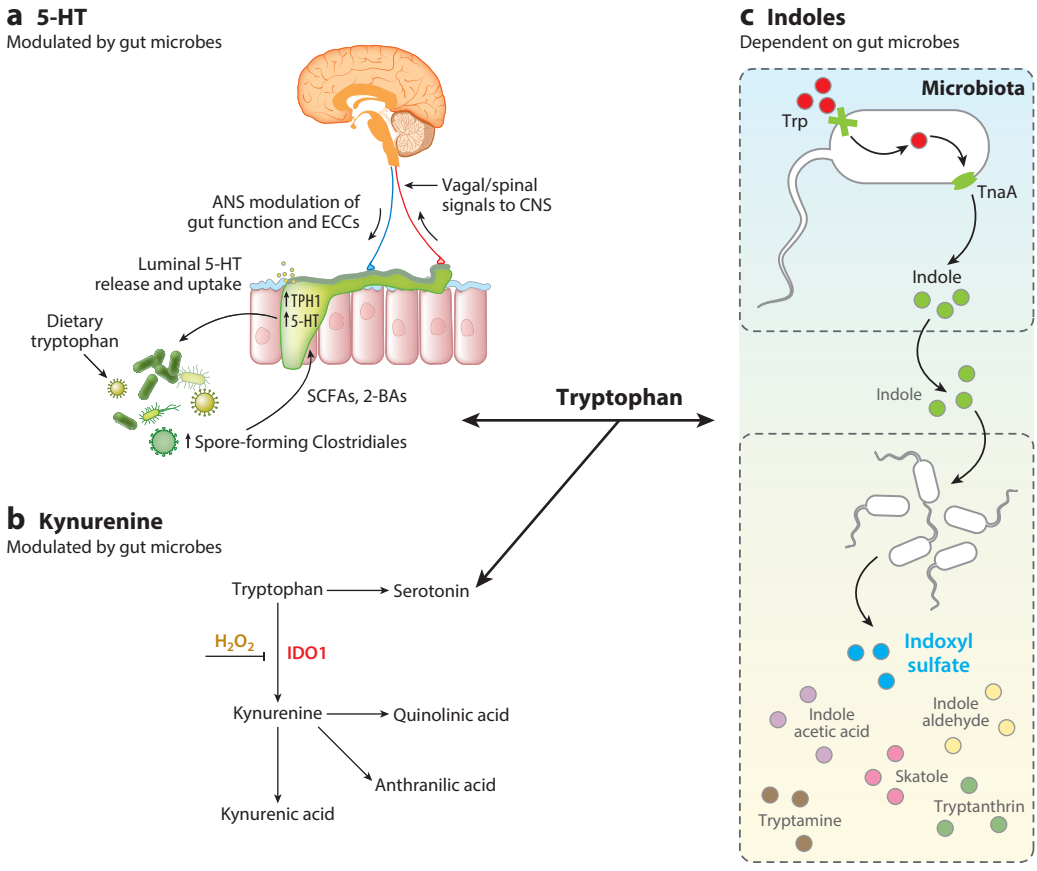

Figure 3

Gut microbes generate neuroactive metabolites from tryptophan. Gut microbes are crucially involved in the metabolism of tryptophan into 5-HT (*a*), kynurenine (*b*), and indoles (*c*). Whereas microbes play a modulatory role in the first two metabolites, indole synthesis depends entirely on gut microbial metabolism. The relative abundance of the three metabolites is dependent on tryptophan intake, on the relative abundance of involved microbial taxa, and on stress-induced input from the ANS. Abbreviations: 2-BA, secondary bile acid; 5-HT, 5-hydroxytryptamine (serotonin); ANS, autonomic nervous system; CNS, central nervous system; ECC, enterochromaffin cell; SCFA, short-chain fatty acid; TPH1, tryptophan hydroxylase type 1. Panel *a* adapted with permission from Reference 7; panel *b* adapted from Reference 22; panel *c* adapted with permission from Reference 23.

terminals (14). GF mice show decreased levels of 5-HT synthesis, which can be reversed if spore-forming bacteria are transferred into them. This reversal results from the increased metabolism of tryptophan into serotonin by stimulating the rate-limiting enzyme tryptophan hydroxylase type 1 in ECCs. The gut is responsible for most of the production of 5-HT, which acts primarily locally, as the free concentration of 5-HT released into the systemic circulation is very low and the molecule cannot cross the blood–brain barrier (BBB) (14). These findings strongly suggest that 5-HT in ECCs does not directly affect the brain. However, GF mice show not only a reduction in systemic tryptophan levels but also decreased levels of hippocampal 5-HT (21), consistent with the production of 5-HT by pontine neurons from tryptophan in the systemic circulation. A shift in tryptophan metabolism from serotonin to kynurenine has also been observed in mouse models, including GF mice and chronically stressed mice (22). Analogous results have been obtained in studies of human patients with Alzheimer's disease and IBS (22).

BBB: blood–brain barrier

METABOLITES OF ENDOGENOUSLY PRODUCED MOLECULES

Bile Acids

FGF19: fibroblast growth factor 19

LPS: lipopolysaccharide

TLR: Toll-like receptor

Bile acids are synthesized from cholesterol in the liver, and their amount and composition are strongly influenced by dietary fat intake (24). Primary bile acids are conjugated in the liver and excreted with bile into the small intestine. Certain gut microbes can metabolize these excreted primary bile acids into secondary bile acids, which are reabsorbed and have widespread effects throughout the body, including the brain. Secondary bile acids activate the expression of farnesoid X receptor in the ileum, leading to the production of fibroblast growth factor 19 (FGF19). FGF19 can enter the systemic circulation, cross the BBB, and activate the arcuate nucleus of the hypothalamus (**Figure 3**) (25). This hypothalamic activation improves regulation of glucose metabolism and suppression of HPA activity (26). L cells in the ileum express Takeda G protein–coupled receptor 5 (TGR5), which is activated by secondary bile acids that are produced solely by the intestinal bacteria and are influenced by the relative abundance of gut microbiota species (7). Signaling through TGR5 plays a role in controlling glucose homeostasis by increasing GLP-1 release by L cells, thereby regulating ingestive behavior and food intake (27).

Estrogen

Evidence supports a bidirectional relationship between plasma estrogen levels and the gut microbiome (28). Systemic estrogen is conjugated in the liver before being secreted into the small intestine in bile. The gut microbiome significantly affects estrogen levels through microbially produced β-glucuronidase. Deconjugation of estrogen by β-glucuronidase in the small intestine enables excreted estrogens to be reabsorbed by the gut, enter the systemic circulation, and be transported to sites throughout the body (29). In postmenopausal women, the reduction in gut microbiota diversity reduces the estrabolome (i.e., intestinal microbiota genes that are capable of producing enzymes that metabolize estrogens) (30), resulting in a reduced ability of the microbiome to deconjugate fecal estrogens, which in turn can lead to lower levels of systemic estrogen (28). This menopause-related and gut microbiome–dependent decrease in systemic estrogen levels might contribute to the postmenopausal increase in IBS symptoms (31).

SIGNALS OF MICROBIAL CELL WALL COMPONENTS

Evidence suggests that neurologic function and behavior may be influenced by the gut-associated immune system, which is modulated by gut microbes. Inappropriate engagement of the gut-associated immune system has been implicated in the pathophysiology and progression of several neurological disorders, neurodegenerative diseases, and psychological illnesses. Microbe-associated molecular patterns, such as lipopolysaccharide (LPS), bacterial lipoprotein, flagellin, and CpG DNA, among others, activate different cells of the immune system, particularly innate immune cells such as macrophages, neutrophils, and dendritic cells, via activation of Toll-like receptors (TLRs). TLRs play a major role in molecular communication between alterations in the gut microbiome and the homeostasis of the immune system (32). Once activated, gut-associated immune cells produce proinflammatory cytokines [interleukin (IL)-1α, IL-1β, IL-6, tumor necrosis factor α], which can reach the brain by crossing the BBB either via diffusion or via cytokine transporters. Once they reach the brain, these cytokines can act on receptors on microglia and stimulate further cytokine release and modulation of neuronal functions (17, 33). Cytokines released in the gut can also act locally on cytokine receptors on vagal afferents, causing alterations in GB signaling. The introduction of various cytokines into the periphery mediates sickness

behavior, and treatment with anti-inflammatory cytokines (e.g., insulin-like growth factor 1, IL-10) can prevent these effects (34). The pathological role of proinflammatory cytokines acting on the brain is illustrated by the observation that one-third of patients treated with IL-2 and interferon-α later develop major depressive disorder (35). Additionally, alterations of the microbiota in early life can increase the risk of developing immune disorders later in life (36). This finding suggests that small changes in the processes of gut microbiota maintenance and acquisition early may predispose individuals to stress-related disorders in adulthood (37).

BARRIERS TO GUT–BRAIN–MICROBIOME SIGNALING

The two main barriers to GBM signaling are the intestinal barrier and the BBB. Both barriers are dynamic, and factors including the gut microbiota, inflammatory signals, and stress all have the capability to modulate their permeability. In the healthy state, both barriers are tight and prevent microbiome-related immune signaling to the brain.

Intestinal Barrier

The intestinal barrier strictly separates the gut microbial ecosystem from the gut-associated immune system, despite their close proximity. The barrier consists of two principal layers. The first consists of epithelial cells that are connected by tight junctions (38). The second is a mucus layer, consisting of complex sugar molecules (glycans), with variable thickness and composition. The mucus layer is organized into a loose outer (lumen-facing) layer and an inner layer that is attached to the epithelial tissues. The outer layer is inhabited predominantly by commensal microbes, both because it is their preferred habitat for biofilm formation and because it provides nutrients (glycans) to microbes in the absence of dietary fiber (39). Dietary fiber deprivation, which is characteristic of the standard American diet, leads to thinning of the outer layer, resulting in increased permeability of microbes through the outer layer (40). The inner layer is typically bacteria-free and plays a role in protecting the epithelial cells from the microbiota via innate immune mechanisms (antimicrobial peptides), adaptive immune mechanisms (secretory immunoglobulin A), and physical separation (41). However, the diet- or chronic stress–induced thinning of the outer layer increases the likelihood that cell wall components of commensal bacteria come into contact with TLRs on extensions of dendritic cells, which triggers cytokine release from these cells as well as activation of other cells in the gut-associated immune system. Cytokine release can also lead to loosening of the tight junctions between epithelial cells, allowing microorganisms to translocate across the intestinal barrier through microfold cells, which in turn enables further local immune cell activation and dissemination throughout the systemic circulation, a condition referred to as metabolic endotoxemia (42). Several factors protect against this translocation of microbes. For example, MyD88-dependent TLR activation of Paneth cells triggers antimicrobial factors that limit the penetration of host tissue by bacteria (43). Similarly, SCFAs produced by certain gut microbes are crucial in maintaining the integrity of the intestinal structure by maintaining the tight junctions between cells and by reducing the activation of gut-associated immune cells.

Blood–Brain Barrier

The BBB functions as a regulator of molecular traffic between the cerebrospinal fluid and the circulatory system (44). The gut microbiota can modulate the permeability of the BBB by similar mechanisms, as it regulates the intestinal barrier. Upregulation of the expression of tight junction proteins, like Claudin-5 and occludin, by the gut microbiota decreases BBB permeability

(45). GF mice have a more permeable BBB than control mice, and introduction of a healthy microbiome into GF mice partially restores barrier function (44). Colonization of the gut with SCFA-producing bacteria also decreases the permeability of the BBB, suggesting that SCFAs play an important role in the development and maintenance of the BBB (46). Disruption of the BBB can be caused by systemic immune activation, often modeled by injecting animals with LPS, which results in a 60% increase in BBB permeability. However, due to the interspecies variability of BBB response, the generalizability of preclinical data to interactions of the human microbiome is limited.

MODULATION OF THE GUT CONNECTOME AND MICROBIOME VIA THE AUTONOMIC NERVOUS SYSTEM

GBM interactions represent a system with bidirectional communication channels and multiple feedback loops. The ANS has the ability to modulate intestinal barrier integrity, GI motility, secretory processes, and the mucosal immune response. These ANS-induced changes in the microbial habitat can affect the relative abundance and diversity of microbial taxa (2). In addition, many commensal and pathogenic microbes in the gut are sensitive to norepinephrine and dopamine, which, when released from sympathetic postganglionic neurons into the gut lumen, can cause the expression of virulence genes, increased growth, and increased interactions with the gut (47). Intestinal transit in certain regions of the gut is highly variable at certain times, including diurnal variations, and has the ability to modulate the microenvironment of the lumen through changes in gut water content and nutrients. Changes in regional transit and GI motility are also highly influenced by dietary fiber content, emotional states, stress levels, and sleep. Deleterious consequences for the GI tract barrier function can result from acute and chronic stress (48, 49). Preclinical stress models have shown that permeability of the intestine increases after stress and causes gut microbiota and metabolite translocation through a weakened epithelial barrier. Catecholamine signaling also weakens the mucus barrier in cases of psychological stress (50). However, these effects are partly compensated for by increased tight junction protein expression following stress (51).

IMPLICATIONS OF NEW INSIGHTS INTO GUT–BRAIN–MICROBIOME DISORDERS

GBM science, based largely on preclinical studies, has suggested that the gut microbiome plays a role in the pathophysiology of functional GI disorders as well certain psychiatric and neurological disorders (1). In the following subsections, we focus on recent insights into the role of the GBM system in IBS, one of the most common disorders of altered GB interactions, and briefly review therapeutic approaches aimed at the GBM system in this disorder, including diet, behavioral, and pharmacological interventions. Recent preclinical and clinical findings have associated the GBM system with possible disease mechanisms in other disorders, including autism spectrum disorder, attention-deficit/hyperactivity disorder, Parkinson's disease, Alzheimer's disease, multiple sclerosis, and epilepsy. The putative role of the gut microbiome in these disorders is reviewed elsewhere (1).

IRRITABLE BOWEL SYNDROME

Altered Gut–Brain Interactions

IBS affects 9–11% of the world population and is characterized by chronically recurrent abdominal pain associated with alterations in bowel habits (52). The majority of patients exhibit increased

stress responsiveness, increased anxiety, and comorbidities with other chronic pain syndromes. An extensive body of research has led to the new definition of IBS as a disorder of altered GB interactions (4), acknowledging the role of such interactions in emotional processing, attention, perception of visceral sensations, and pain processing (53). These maladaptive interactions manifest clinically as the characteristic IBS symptoms of altered bowel habits and recurrent abdominal pain. Changes in the processing of interoceptive signals from the gut (visceral hypersensitivity) and other body regions (esophagus, stomach, urinary bladder, muscle) and associated changes in homeostatic reflexes provide plausible explanations for many IBS symptoms and comorbidities. While the mechanisms underlying the characteristic hypersensitivity remain only partly understood, findings are most consistent with alterations in endogenous pain modulation systems at all levels of the GB axis, in particular the spinal cord, brainstem, and insular cortex.

IBS-D: IBS with diarrhea

IBS-C: IBS with constipation

IBS-M: IBS with mixed bowel habit

Alterations in the Gut Microbiome

In contrast to the well-established alterations in GB interactions, a causal role for an altered gut microbiome in IBS symptoms remains to be determined, even though several cross-sectional studies have reported changes in fecal microbial community composition in IBS subjects on the basis of disease subtype (IBS-D, IBS-C, IBS-M), symptom severity, patient age (pediatric versus adult), and/or compartment (mucosa versus stool) (54). Recent evidence suggests that even though IBS patients can be subgrouped on the basis of gut microbial community structure, the microbial composition does not differ between patients and healthy controls (55, 56). In one study, a dysbiotic IBS subgroup differed in regional brain volume from a group with normal gut microbiota (56), suggesting a relationship between microbial community composition and brain structure. However, because both microbiota-defined subgroups met the IBS diagnostic criteria and did not differ in any clinical parameters, these findings call into question a causative role for dysbiosis in IBS symptoms. The absence of group differences in the microbial composition between healthy control subjects and individuals with IBS has been reproduced elsewhere, though IBS symptom severity was found to be correlated with dysbiosis (57). A more recent cross-sectional study revealed significant differences among IBS subtypes in the distribution of Clostridiales. Relative abundance of Clostridiales was correlated with significant differences in levels of fecal SCFAs, which together were associated with altered fecal cytokine levels (58). Even though this study aimed to identify mechanistic pathways in gut–microbe–host interactions, the findings need to be confirmed in a study with a control population and a larger sample size.

The diverse findings from these IBS microbiota studies have been attributed to the extensive range of techniques employed; differences in sample source, IBS subtype, and patient sex; differential effects of the ANS on other aspects of physiology (e.g., mucus secretion, intestinal permeability and mucosal immunity) (1); and many other influences that affect microbial composition and function (e.g., age, diet, antibiotic exposure, geography, probiotic intake, medication exposure) (54, 59). Further complicating this dynamic is the need to factor in the CNS-mediated aspects of motility and gut physiology, including sleep quality and stress. The examination of much larger cohorts in longitudinal studies that also integrate clinical phenotypes and diet is needed in order to gain a more comprehensive understanding of these populations.

If disturbances of the gut microbiome play a causal role in IBS symptoms, then microbiome manipulations should be able to influence visceral sensitivity and IBS symptoms. One study showed that transferring the microbiota of IBS patients to GF rats resulted in visceral hypersensitivity in the recipients (60). Other studies have shown that visceral hypersensitivity in rodents can be induced with microbiome manipulation by using antibiotics, infection, or endotoxins (61). Additionally, early-life stress in the maternal separation model causes alterations in microbial

composition and visceral hypersensitivity in adult animals (62), and the administration of probiotic strains including *Lactobacillus acidophilus* and *Bifidobacterium infantis* may reduce visceral hypersensitivity (63).

RCT: randomized controlled trial

Psychiatric comorbidities such as anxiety and, to a lesser extent, depression are commonly associated with IBS (64, 65). Additionally, prior diagnosis of depression and anxiety is a risk factor for subsequent IBS development (66, 67). Probiotic treatment in both preclinical and clinical studies exerts small antidepressant-like effects (68), leading to the concept of psychobiotics (69). These findings suggest an association between the gut microbiome in IBS and CNS disturbances. However, it remains to be determined whether these alterations reflect changes in CNS function as a result of changes in microbiota composition, or whether the associated microbiome changes are the consequence of altered influence of the brain on the gut.

Therapies Targeting the Gut–Brain–Microbiome System

IBS therapeutic approaches including diet and several brain-directed therapies are targeted at different levels of the GBM system.

Diet. The effects of enteric microbial manipulations in controlled clinical trials in patients with depression and/or IBS have been evaluated with probiotics, antibiotics, and the low-FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet (70). Several studies have demonstrated the effectiveness of a low-FODMAP diet in the short-term treatment of IBS symptoms (71, 72), and diet-induced changes in the gut microbiome (73) have been implicated as an underlying mechanism. The low-FODMAP diet results in decreased production of gas and osmotically active microbial metabolites as a result of decreased microbial fermentation. This reduction in microbial gas production in a hypersensitive gut is thought to lead to improvements in the perception of bloating, flatulence, and pain (74). In line with this theory, several randomized controlled trials (RCTs) in adults have demonstrated that intake of a low-FODMAP diet improves IBS symptoms, regardless of subtype, as well as health-related quality of life, anxiety, and activity impairment in adults with IBS (74). However, even though these results seem to support a role for the gut microbiome in some IBS symptoms, and despite the finding that the low-FODMAP diet appears to be useful for short-term treatment of some IBS symptoms, such a diet is not recommended as long-term treatment for IBS patients. Long-term compliance is low, and the long-term reduction of complex carbohydrates in the diet is associated with a decrease of gut microbial diversity and richness, particularly of butyrate-producing strains, an effect with well-known negative consequences on gut health. To avoid these long-term problems, patients are recommended to selectively reintroduce eliminated food items following a course of treatment with the low-FODMAP diet. There is limited evidence for the effectiveness of a ketogenic diet in treating IBS, but the evidence is weak, and similar to the low-FODMAP diet, in a ketogenic diet the elimination of complex carbohydrates is inconsistent with current beliefs about the benefits of a largely plant-based diet on gut health and gut immune function. An alternative approach is to have IBS patients start with a Mediterranean-type diet with its general health benefits, encourage them to keep a food diary, and ask them to identify food items that reproducibly and consistently worsen their symptoms. Food items thus implicated may differ between patients, but once such items have been identified by a patient, a reduction in intake or elimination of the item is recommended. The result is a personalized diet with well-documented health benefits that does not compromise gut microbial health. Encouraging the patient to tailor their own personal diet provides them with an increased sense of control (self-efficacy) and reduced symptom-related anxiety.

Cognitive behavioral therapy. Cognitive behavioral therapy (CBT) is a promising potential therapy for the treatment of IBS symptoms. CBT provides a framework where patients are able to associate their symptoms with stressors, reduce anxiety levels, encourage health-promoting behaviors, assume greater responsibility and control regarding the treatment, and improve pain tolerance (75). Recent studies compared clinic-based CBT, home-based CBT, and IBS education in terms of their effectiveness for treatment of IBS symptoms, quality of life, change in stool consistency, psychological distress, and patient satisfaction (76). Both clinic- and home-based CBT effectively improved IBS symptoms 12 months after treatment, while IBS education did not (77, 78). Patients receiving home-based CBT likely showed greater persistence due to the emphasis of this approach on self-monitoring and learning strategies to correct faulty threat appraisals that can cause dysregulated GB interactions. Through self-monitoring, patients learn that their symptoms do not randomly appear and are part of a chain of behaviors that are both controllable and predictable. These cognitive changes, such as an increased sense of control, enable patients to learn symptom self-management skills (77), similar to what is accomplished with an individualized patient-focused diet. A recent study in IBS subjects demonstrated an association between symptomatic improvement (compared with nonimprovement) and significant brain changes, and outcome was predicted by baseline microbiome composition (78a).

CBT: cognitive behavioral therapy

Medications targeting the gut–brain–microbiome system. The primary targets of pharmacological treatments for IBS are symptoms of altered bowel habits and the presumed underlying mechanisms of altered regional motility and fluid secretion (79). While the majority of these treatments have shown some benefit in subsets of patients based on bowel habits, in most cases their effectiveness above placebo does not exceed 10%. Antibiotics represent the main category of gut microbiome–targeted medications. While observational studies have implicated antibiotic use in an increased prevalence of IBS, broad-spectrum nonabsorbable antibiotics have been used to treat increased microbial abundance in the distal small intestine (so-called small intestinal bacterial overgrowth). Several RCTs have evaluated the nonabsorbable broad-spectrum antibiotic rifaximin for IBS treatment (80). A meta-analysis of five studies demonstrated that a 2-week course of rifaximin was associated with a 10% improvement of global IBS symptoms above placebo, with an odds ratio of 1.6. The number needed to treat has been reported at 8 to 11. Species richness in fecal samples was significantly reduced from baseline after rifaximin treatment (81). Together, observational studies with broad-spectrum antibiotics suggest an increased risk of IBS development, while several RCTs with the nonabsorbable broad-spectrum antibiotic rifaximin have demonstrated small clinical benefits in IBS-D patients. The fact that the small and inconsistent symptom improvement in these patients was not associated with a change in the gut microbiome is consistent with the concept that gut microbial dysbiosis does not play a causative role in symptoms in IBS patients. Similar evidence has come from several negative trials of fecal microbial transplantation in IBS patients. Surprisingly, while the gut microbial composition in one of these studies was altered, symptom severity actually increased (82).

CONCLUSIONS AND FUTURE DIRECTIONS

Our understanding of the GB system has undergone a fundamental revision in the past 5 years. A major factor in this revision has been the rapid development of gut microbiome science, which has added a crucial component to the interactions between the gut and the brain. While GB interactions have long been implicated in the pathophysiology of functional GI disorders, in particular IBS, the new concept of a GBM system with bidirectional interactions among the brain, the gut connectome, and the gut microbiome has led to a revolutionary reevaluation of the

pathophysiology of several brain disorders in psychiatry and neurology (1, 83). The incorporation of the gut microbiome in the pathophysiology of these disorders has also led to a renewed interest in the links among nutrition, the gut microbiome, and these disorders. Even though the role of the GBM system was first explored in rodent models, a growing number of studies support a causative role of gut dysbiosis and dietary habits in several human diseases that currently are unsatisfactorily treated. Despite intense interest in the development of specific microbially targeted therapies, treatment approaches are largely limited to dietary approaches. Important barriers to the understanding and practical application of microbiome-targeted therapies include the difficulty of translating findings from artificial mouse models (like genetically identical GF mice raised under identical conditions) to heterogeneous human patient populations and the small number of RCTs evaluating the therapeutic effectiveness of specific microbially targeted interventions like diet or the use of pre- and probiotics. In terms of the effectiveness of fecal microbial transplantation for conditions other than *Clostridioides difficile* colitis, the resistance to colonization of an intact gut microbial ecosystem has slowed progress. Personalized microbiome-targeted therapies based on baseline microbiome composition and the use of genetically engineered microbes that can replace lost functionality and overcome colonization resistance are being considered as future approaches.

DISCLOSURE STATEMENT

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