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Gut Microbiome-Brain Communications Regulate Host Physiology and Behavior

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Abstract

The human gut microbiota contains more than 100 trillion bacteria that, under normal physiological conditions, have beneficial symbiotic interactions with the host. However, a growing body of evidence has shown that alternations in the composition and diversity of the gut microbiota, or dysbiosis, can influence the development and progress of metabolic and neurological disorders. Communication between the microbiota and the brain is a bidirectional system involving endocrine, metabolic (bacterial components and metabolites), immune, and neural pathways. Gut microbiota composition influences the signals transmitted from the gut to the brain. Alternatively, the brain utilizes similar mechanisms, in particular endocrine and neural signaling, to modulate the composition of the gut bacteria. In this review, we describe the recent evidence of gut microbiota interaction with the central nervous system to influence physiological and cognitive functions and the therapeutic potential of modulation of the gut microbiota composition.

Keywords: Gut microbiota; Gut-brain axis; Dysbiosis

Gut Microbiota Composition

The human microbiota contains as many as 100 trillion bacteria and there are 10 times more bacterial cells in our body than human cells [1]. Specific bacterial phyla reside in the different body habitats; *Actinobacteria, Firmicutes* and *Proteobacteria* for skin, *Bacteroidetes, Firmicutes, Fusobacteria and Proteobacteria* for the oral cavity, *Bacteroidetes, Firmicutes,* and *Proteobacteria* for the airway tract, *Firmicutes* for the urogenital tract and *Bacteroidetes* and *Firmicutes* for the gastrointestinal (GI) tract [2]. In the human GI tract, microbiota distribution is not spatially even; bacterial presence and diversity increase along the GI tract [3,4]. The gut microbiota is primarily composed of anaerobic bacteria; more than 90% of them belong to the *Bacteroidetes* and *Firmicutes* phyla with minor proportions of other phyla, including *Proteobacteria* [5].

Alteration in Microbiota Composition or Dysbiosis

Under normal physiological conditions the gut microbiota and its host have beneficial symbiotic interactions. The microbiota notably plays essential roles in the protection against epithelial cell injury [6], metabolic regulation [7], GI tract development [8], innate and adaptive immune responses, and absorption of nutrients [9,10]. Alterations in microbiota composition and dysregulation of the intestinal mucosa homeostasis have been implicated in the development and progression of pathologies. This compositional change in the microbiota and/or an abnormality in the interactions between the host and the commensal microbiota is referred to as dysbiosis. Gut microbiota dysbiosis has been linked to chronic low-grade intestinal inflammation and acute intestinal autoimmunity diseases such as Irritable Bowel Syndrome (IBS) and Inflammatory Bowel Disease (IBD) [11,12]. Abnormal microbiota composition is associated with a wide range of metabolic and behavioral disorders, such as anxiety/depression [13-15], autism spectrum disorders [16-18], hepatic encephalopathy [19], multiple sclerosis [20, 21], allergies [22], visceral pain [23,24], atherosclerosis [25] and cardiovascular risks [26]. GI microbiota dysbiosis might also be involved in the development and persistence of systemic disorders [27]. For example, obesity has been characterized by a decrease in overall diversity [28] and an increase in *Proteobacteria* abundance and in the *Firmicutes* to *Bacteroidetes* ratio [28,29] and microbiota composition is believed to influence energy balance and glucose homeostasis [30-32].

Evidence that changes in microbiota composition are correlated with metabolic and behavioral disorders has drawn attention to a potential causal role for the microbiota in pathologies and has led to the emergence of the 'microbiota-gut-brain axis' concept [33-35]. The gut–brain axis is a bidirectional communication system between the GI tract and the brain [36] via hormonal, immunological, and neural signaling. Information from the GI tract and the intestinal microbiota can reach the peripheral and Central Nervous System (CNS), concurrently the brain is able to influence GI functions such as motility and secretion but also immune responses and cytokine production [36,37].

The Microbiota-Gut-Brain Axis

The gut microbiota can modulate gut-brain axis signaling via direct and indirect mechanisms. The microbiota acts via endocrine, metabolic (bacterial components and metabolites),

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immune, and neural (vagal afferents and Enteric Nervous System (ENS)) pathways to modulate brain functions. For example, in a recent study by Duca et al, it was shown that the colonization of germ-free (GF) mice with obesity-prone microbiota remarkably increased the expressions of pro-inflammatory factors interleukin (IL)-6, TNF-α, and Toll-Like Receptor 4 (TLR4) in the hypothalamus. In addition, colonization treatment affected the expressions of hypothalamic energy-regulating neuropeptides; reducing Proopiomelanocortin (POMC) and increasing Agouti-Related Peptide (AgRP) and NeuroPeptide Y (NPY) expressions. The brain uses the same mechanisms to modulate the composition of the gut bacteria. For instance, under stressful conditions, the hypothalamus–pituitary–adrenal axis regulates the secretion of cortisol, which can have both local and systemic effects on immune cells secretion, including cytokines. Cortisol release can alter gut permeability and intestinal barrier functions, eventually leading to changes in gut microbiota composition [38,39].

Communication between the gut and the brain notably involves endocrine signaling. Enteroendocrine cells release gut peptides in response to enteric stimuli [40,41]. For example, cholecystokinin and gastrin are released in response to feeding to regulate appetite [42]. Enteroendocrine cells located in the epithelial lining possess specialized microvilli that project into the lumen. Consequently, these cells come into close contact with gut microbiota, enabling functional communication. In several studies, the gut microbiota was shown to influence the number of enteroendocrine cells and the release of gut peptides [43]. Cani et al. investigated the effect of prebiotic modulation of gut microbiota on intestinal permeability in leptin deficient (ob/ob) mice by assessing changes in the microbial composition, intestinal permeability, gut peptides, and hepatic and systemic inflammation. The mice treated with the prebiotic carbohydrates (fermentable oligofructose) showed decreased endotoxemia and hepatic inflammation as well as improved intestinal barrier function and tight junction integrity. These effects were associated with increases in the endogenous Glucagon-Like Peptide-2 (GLP-2) production and are believed to be GLP-2-dependent [44]. Moreover, colonization of GF animals with either a "lean" or an "obese" microbiota leads to replication of the donor phenotype [45,46]. GF rodents colonized with an obese–type microbiota notably exhibit a decrease in GI peptide expression, such as Glucagon-Like Peptide-1 (GLP-1) and Peptide YY (PYY) [46]. Changes in gut peptide secretion could modulate gut-to-brain neural signaling. Information between the gut and the brain is conveyed via the ENS. Vagal afferent neurons are notably in charge of transmitting sensory information from the GI tract to the CNS. Vagal signaling has been extensively studied in relation to feeding behavior and control of appetite; signals originating from the GI tract are conveyed via the vagus nerve to the Nucleus of Solitary Tract (NTS) in the brainstem and hypothalamus to regulate ingestive behavior [47]. Microbiota-induced changes in gut peptide expression have notably been associated with alterations in food intake [46].

While microbiota-driven changes in gut peptide secretion can affect gut-brain neural communication, there is evidence of a potential direct effect of bacteria on sensory pathways. Recent work has found that bacteria are able to produce neurotransmitters; bacterial colonization of GF mice resulted in over 2-fold increase in 5-hydroxytryptamine (5-HT) [48]. Specifically, commensal *Lactobacilli* and *Bifidobacteria* have been shown to produce γ-aminobutyric acid (GABA) [49] while *Escherichia spp., Bacillus spp*. and *Saccharomyces spp.* produce noradrenaline; *Candida spp., Streptococcus spp., Escherichia spp., and Enterococcus spp*. can produce 5-HT. Additionally, *Bacillus spp*. and *Lactobacillus spp*. can produce dopamine and acetylcholine, respectively [49,50]. There is growing evidence that vagal signaling is involved in microbiota-to-brain communication. Chronic treatment with *L. rhamnosus* in mice induced region-dependent changes of GABA expression in the brain and attenuated stress-related disorders, including anxiety and depression. However, these effects were blunted in vagotomized mice [13]. Similarly, Bercik et al. demonstrated that the anti-anxiety effect of *B. longum* involves vagal afferent signaling. Using a chemically induced colitis mouse model, they found that *B. longum* stabilized the anxiety-like behavior but the effect was absent in mice that were vagotomized. They proposed that anxiolytic effect of *B. longum* was attributed to its signaling to the CNS by activation of the vagal system at the level of the ENS [51].

The Role of Microbiota-Derived Metabolites

GI bacteria may modulate endocrine and neural signaling indirectly via release of metabolites and/or bacterial compounds. Short Chain Fatty Acids (SCFA) are produced by bacterial fermentation of non-digestible dietary polysaccharides; notably acetate, propionate, and butyrate [52] and have profound impacts on gut health [53-55]. Butyrate is the preferred source of energy for colonocytes over propionate, acetate, or glucose [52] and is also involved in cell proliferation and differentiation. Sodium butyrate has notably been shown *in vivo* to have preventive effects on colon cancer development [52]. Importantly, nutrient deficiency in the colon characterized by the absence of SCFA is associated with colitis, underlying the potential role of SCFA in regulating local inflammation [52]. SCFA are rapidly absorbed within the colon leading to an increase in pH in the distal colon, affecting mineral absorption, notably enhancing sodium absorption and calcium bioavailability [52]. Acetate and propionate are absorbed into portal circulation [56]. Acetate as a component of acetyl-CoA is believed to increase plasma cholesterol by contributing to cholesterol synthesis while propionate may decrease cholesterol levels by inhibiting acetate to acetyl-CoA conversion [57]. The decrease in the acetic acid-to-propionic acid ratio was suggested as a possible indicator of the hypolipidemic effect of prebiotics (inulin and fructooligosaccharides) [58]. Moreover, recent studies have demonstrated that SCFA act as endogenous ligands for two G protein-coupled receptors, free fatty acid receptor 2 (FFAR2) and 3 (FFAR3). They are expressed in the GI tract, liver, immunocytes, and adipocytes [59-61]. Acetate infusion in mice induced a decrease in circulating free fatty acids which was blunted in the FFAR2-knockout mice [62], suggesting that acetate acts via FFAR2 to control circulating free fatty acid levels and

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lipolysis. In addition, SCFA may also influence the regulation of feeding. Leptin expression is increased by SCFA infusion, leading to a decrease in food intake, but this effect was almost abolished by knockdown of FFAR3 [63]. Moreover, FFAR2 and FFAR3 activation has been shown to be involved in the production and release of gut peptides GLP-1 and PYY, resulting in decreased food intake [64, 65].

Additionally, we have recently demonstrated that Lipopolysaccharides (LPS), endotoxins from Gram-negative bacteria, affect vagal signaling to promote food intake [66]. Obesity is associated with chronic increase of circulating LPS, quoted as metabolic endotoxemia [67]. We have used mini-osmotic pumps to mimic metabolic endotoxemia and found that infusion of low dose of LPS was sufficient to alter vagal afferent neuron protein levels, impairing leptin signaling and promoting overfeeding [66]. Known probiotics, such as *Bifidobacterium spp.* have been shown to improve mucosal barrier function and reduce endotoxin levels; these changes are associated with a reduction in energy intake [68].

Bacterial metabolites, notably bacterial fermentation products such as lactic and propionic acids, not only modulate host physiology but can impact behavior. Levels of lactic acid in the cecal contents were strongly associated with occurrence of anxiety and memory loss in rats fed a high fermentable carbohydrate diet [69]. Human studies also suggest a link between fermentation products and behavior. High fecal concentrations of propionic acid correlate with anxiety in patients with IBS [70]. Additionally, increased availability of substrates for microbial fermentation, such as carbohydrate maldigestion or malabsorption, has been shown to be associated with depression in female subjects [71].

Amino acids are also degraded by gut bacteria, notably tryptophan [72], a precursor of 5-HT [73]. A growing body of evidence indicates an association between the dysregulated kynurenine arm of tryptophan metabolism and many CNS and GI disorders [74]. Kynurenine is a product of tryptophan metabolism and has neuroactive and anxiogenic characteristics [75]. Conversely, another product of the tryptophan breakdown, kynurenic acid is considered to be neuroprotective. Indeed, reduced kynurenic acid to kynurenine ratio has been found in the major psychiatric disorders such as depression and schizophrenia [76]. Compositional shift in gut microbiota and subsequent alterations in serum levels of kynurenine could result in modifications of behavior and CNS response. For instance, the administration of a probiotic, *L. johnsonii* to diabetes-prone BioBreeding rats resulted in a decrease in serum kynurenine level [77]. Conversely, GF mouse colonization increased circulating levels of kynurenine and decreased expression of genes associated with neuronal development and function [78]. Taken together, these data suggest that metabolic products of gut microbiota could be involved in the modulation of the host's brain functions and behavior.

Expression of other genes involved in behavior has been shown to be under the influence of microbiota, notably Brain Derived Neurotropic Factor (BDNF). BDNF regulates multiple aspects of cognitive and emotional behaviors and its expression can be modulated by prebiotic supplementation. BDNF gene expression notably increased in rats when orally administrated with prebiotics, fructooligosaccharides and galacto-oligosaccharides for five weeks [79].

Immunological Mechanisms

Microbiota composition has direct effects on the host immune system at the levels of both innate and adaptive immunity [80,81]. First, the innate immune system is capable of sensing various types of bacterial components via Pattern Recognition Receptors (PRRs). PRRs recognize bacterial products like LPS, lipoproteins, and peptidoglycans and trigger the appropriate responses, such as the release of pro-inflammatory cytokines [82]. There are two types of PRRs, Toll-like receptors (TLRs) and Nod-like receptors (NLRs) [83,84]. TLRs are notably expressed on enterocytes and enteric neurons, including vagal afferent neurons [66,85-87]. TLR activation leads to activation of transcription factors, such as Nuclear Factor Kappa B (NFκB) to promote pro-inflammatory cytokine synthesis and secretion [88]. NOD activation also contributes to the onset of inflammatory responses and insulin resistance [89].

Additionally, a growing body of evidence shows that the gut microbiota coordinates T cell differentiation, enabling the full functioning of the acquired immune system. γδ intraepithelial lymphocytes play a crucial role as inhibitors of bacterial penetration during intestinal injury [90]. γδ T-helper (Th) cell differentiation can be regulated by the commensal microbiota. The microbiota is involved in generating adenosine 5' triphosphate, which then activates a subset of dendritic cells and contributes to Th17 differentiation [91]. Specifically, differentiation of Th17 cells in the lamina propria of the small intestine is correlated with the presence of bacteria from the *Cytophaga-Flavobacterium-Bacteroides* group [92]. Additionally, the stimulation of TLR5, mediated by flagellin, triggers the expression of IL-6, inducing Th17 cell programming [93]. Moreover, polysaccharide A from *B. fragilis* can protect from inflammatory diseases such as colitis by suppressing pro-inflammatory IL-17-producing $CD4^+$ T cells and inducing IL-10-producing $CD4^+$ T cells [94].

The crucial role of the microbiota in host immunity has been demonstrated with GF animal models. GF mice display defective gut-associated lymphoid tissues, the first class of intestinal defense, less cellular lamina propria, smaller and less mesenteric lymph nodes [95,96], and a reduced number of intraepithelial lymphocytes compared to the colonized animals [97,98]. They also showed decreased expressions of TLRs and class II major histocompatibility complex proteins, which act as pathogen sensors and antigen presenters, respectively [99,100]. Normal activation of TLRs appears to be critical not only for appropriate immune signaling, but also for host physiology. For example, TLR5 mainly recognizes bacterial flagellin [101] and TLR5-knockout mice exhibited profound metabolic disturbances manifested as obesity, dyslipidemia, hypertension, and insulin resistance [102].

As the proper maintenance of the gut microbiota contributes to both immunological and metabolic balances [103], dysbiosis

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may result in the dysregulation of both systems [104]. Indeed, over-activation of PRRs induced by the intestinal microbial alterations and the resulting low-grade inflammation seem to play a crucial role in the development of obesity. Recent work focusing on bacterial LPS has demonstrated that metabolic endotoxemia and the subsequent activation of TLR4 are involved in the development of type 2 diabetes and cardiovascular diseases by contributing to low-grade inflammation and disrupting energy regulation [66,105,106]. Chronic LPS injections in animal models are sufficient to induce weight gain and insulin resistance, pointing to a potential causal role for bacterial products and altered immune response in obesity and related metabolic disturbances [66,67].

Microbiota modulation of the host immune response may also affect brain functions and behavior. Human [107] and animal [108,109] studies have shown that changes in microbiota composition affect circulating systemic cytokine levels via activation of TLRs [110].

Pro-inflammatory cytokines, such as IL-4, have been reported to be associated with a series of psychiatric disorders [111]. In addition, Desbonnet et al. have studied in rats the effect of probiotics on anxiety behaviors associated with maternal separation and have found that administration of probiotics *B. infantis 35624* decreased IL-6 secretion and improved depression-like behavior in pups [109].

Descending Signals from the Brain Can Modulate Microbiota Composition

The gut-brain axis is a bidirectional communication route. For example, vagal efferent neurons send motor information from the brain to the periphery [112] and central signaling can affect gut microbiota composition to modulate host physiology. The brain-gut microbiota axis is mediated via endocrine and neural pathways in both direct and indirect manners [38,113,114].

Central modulation of satiety plays a crucial role in the brain-gut microbiota pathway. The CNS is involved in controlling food intake and food preferences and resulting changes in nutrient availability for gut microbiota can lead to alteration of microbial composition. In addition, central neuropeptides such as POMC or GLP-1 are involved not only in regulating hunger and satiety, but also in GI secretion and motility [115]. This downward regulation is mediated via the vagal efferent neurons, notably for GI motility [113]. Changes in GI transit have been shown to modify microbiota composition [116]. In mice, administration of polyethylene glycol decreases gastrointestinal transit time and is associated with changes in microbiota composition, notably a decrease in the relative abundance of families *Peptococcaceae, Eubacteriaceae,* and *Anaeroplasmataceae* and an increase in families *Bacteroidaceae* and *Peptostreptococcaceae.* Similar changes can be induced via dietary manipulation of gastric motility [116]. Altered profile of gut microbiota has been linked to diseases such as IBD, which are associated with changes in GI motility [117].

The Hypothalamus–Pituitary–Adrenal (HPA) axis is known to mediate stress and anxiety responses that can influence intestinal metabolism, including gut motility and secretion, leading to environmental changes for gut microbiota [38]. A recent study demonstrated that social disruption, as a source of stress, caused dramatic changes in the gut microbiota composition in adult mice. Mice subjected to stress exhibited an increase in *Clostridium spp.* and a decrease in *Bacteroides spp.* The alteration in microbial composition was followed by increased levels of circulating inflammatory cytokines such as IL-6 and Monocyte Chemoattractant Protein 1 (MCP1) and caused increased bacterial translocation [118]. In their previous study, the authors also showed that the secondary lymphoid organs were involved in the stress-induced increase in bacterial translocation [119]. In rats, stress has also been shown to disrupt GI epithelial barrier integrity, leading to mast cell activation in the mucosa [120]. Moreover, it has been shown that early life exposure to stress, such as maternal separation, is associated with increased levels of corticosterone and immune response and altered microbiota in rat feces. These changes were associated with significant increases in the pro-inflammatory cytokines TNF-α, IL-6, and Interferon-γ (IFN-γ) [121]. This is particularly interesting as recent work has established that early perturbations in GI microbiota are persistent in adulthood [122]. While the pathways linking stress to microbiota composition remain unclear, there is evidence of direct neural communication between the host and its microbiota. The QseCsensor kinase, a bacterial adrenergic receptor, has recently been identified as a microbial receptor for epinephrine and norepinephrine directly originating from the host [114].

Microbiota Modulation as Therapeutic Strategies against Dysbiosis

Alterations in microbiota composition lead to changes in endocrine, neural, and immune signals from the GI tract and this information is then conveyed to the CNS [38]. Alternatively, central signals can modulate GI functions and microbiota composition [27]. Therefore, in a dysbiotic state, this bidirectional communication can lead to a worsening of the situation and several strategies have been developed to stop or attenuate this potential vicious circle. A growing body of evidence shows that alternations in the composition and diversity of the gut microbiota have a substantial influence on the pathophysiology of metabolic and CNS disorders, and consequently there has been a growing attention to microbiota manipulation.

Probiotics

One approach is the use of probiotics. "Probiotics are live microorganisms which when administered in adequate amounts confer health benefits on the host" [123]. Among several mechanisms for actions of probiotics, probiotics exhibit beneficial effects on the host through the modulation of the intestinal microbial composition by suppressing pathogenic bacteria such as *clostridia* and increasing or protecting beneficial populations such as *bifidobacteria* [124]. Probiotics inhibit growth of enteric pathogens by direct antimicrobial actions via production of inhibitory substances, immunomodulation via

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immune cell stimulation, competitive exclusion via blocking of epithelial binding receptors, and improvement of epithelial barrier integrity via mucin and defensins [125,126].

Probiotics can exert a direct antimicrobial ability by producing inhibitory substances such as organic acids and bacteriocins, peptides with a potent antibacterial property [127,128]. *Lactobacillus* and *Bifidobacterium spp.* exhibited anti-infective effects against enterohemorrhagic *E. coli* O157:H7 in human intestinal cells by producing lactic acid and subsequently decreasing luminal pH [129,130]. Additionally, Corr et al. demonstrated that *L. Salivarius* UCC118 protected mice from the invasive foodborne pathogen *L. monocytogenes* via stimulation of bacteriocins [130].

Probiotic bacteria can also act as immunomodulatory agents to alleviate the inflammatory response to infection in the host GI tract [131,132]. They can substantially reduce pro-inflammatory cytokine secretions such as TNF-α and IFN-γ, while stimulating anti-inflammatory cytokines such as IL-10 and TGF-β [131,133,134]. *B. breve* and *S. thermophilus* have been shown to produce metabolites which inhibit TNF-α secretion from peripheral blood mononuclear cells [131,133-135]. Some probiotic strains induce secretory Immunoglobulin A (IgA) production, leading to activation of regulatory T (Treg) and dendritic cells [136]. For example, the oral administration of *L. casei* to BALB/c mice induced activation of the gut mucosal immune system by increasing the level of IgA^+ cells [137].

Some probiotic bacteria can compete with pathogens for binding sites to the mucous layer or epithelial cells, inhibiting the effect of pathogenic bacteria on epithelial cells [138,139]. Surface-layer proteins are located outside the bacterial cell wall and are involved in tissue adherence. In a study using human epithelial (HEp-2 and T84) cells, surface-layer protein extracts from *L. helveticus* blocked the adherence of *E. coli* O157:H7 to epithelial cells [140].

In addition, probiotics are capable of improving epithelial barrier integrity by inducing the expression of mucin from the host [141]. Mucin, as the primary component of the mucosal layer in the GI tract, protects the intestinal epithelium from pathogenic invasion by forming a defensive physicochemical barrier [142]. In an *in vitro* study using the Caco-2 cell line, *L. casei* GG was shown to induce MUC2 expression, inhibiting bacterial translocation to the intestinal epithelium [141]. Some probiotics can also stimulate the release of defensins, which play a role in stabilization of epithelial barrier function as antimicrobial peptides [143]. Several probiotic strains were found to strengthen intestinal barrier function in the Caco-2 cell line by up-regulating the expression of human β-defensin 2 through induction of mitogen-activated protein kinases. They include *B. longum, B. infantis, B. breve, L. acidophilus, L. casei, L. delbrueckii ssp. bulgaricus, L. plantarum,* and *Streptococcus salivarius ssp. thermophilus* [144].

Experimental and clinical studies have found that probiotics have therapeutic effects on metabolic diseases. For example, the administration of dual probiotic strains (*L. curvatus* HY7601 and *L. plantarum* KY1032*)* to diet-induced obese mice led to not only reduced body weight gain and fat accumulation in adipose tissue, but also decreased levels of plasma insulin, leptin, and total cholesterol [145]. Pro-inflammatory genes (including TNF-α, IL-6, IL1β and MCP1) were down-regulated in adipose tissue and fatty acid oxidation-related genes were up-regulated in the liver [145]. The reduction of cytokine expressions in probiotic-treated mice may be explained by a decreased release of pro-inflammatory LPS [146]. As mentioned before [141-144], probiotic bacteria improve intestinal barrier integrity, thereby decreasing LPS translocation to the periphery and leading to reduced production of pro-inflammatory cytokines in adipose tissue. Similarly, it has been recently established that *L. rhamnosus* GG (LGG) displays anti-obesity and anti-diabetic effects when administered to high-fat diet-fed mice [147,148]. Oral administration with LGG for 13 weeks notably led to increased expression of fatty acid oxidation genes in the liver and decreased expression of gluconeogenic genes. LGG treatment also increased glucose transporter-4 gene expression in skeletal muscle and adiponectin production in adipose tissue [147,148]. In a clinical setting, *B. infantis* 35624 was orally administrated for 6 to 8 weeks to patients with gastrointestinal (ulcerative colitis) or non-gastrointestinal (chronic fatigue syndrome, psoriasis) disorders [149]. The results showed that levels of plasma C - Reactive Protein (CRP) and pro-inflammatory cytokines (TNF-α and IL-6) were significantly reduced in three inflammatory disorders compared with placebo. Furthermore, *B. infantis* 35624 significantly decreased LPS-stimulated secretion of TNF-α and IL-6 in *B. infantis* 35624-treated healthy subjects compared with the placebo group. Thus, it was concluded that the beneficial effects of *B. infantis* 35624 are applicable both locally (gastrointestinal) and systemically [149].

In addition to physiological effects, there is evidence suggesting that the use of probiotics can be applied to the treatment of psychiatric conditions [150]. The beneficial effects of probiotics on psychopathological disturbances may be explained by reduction in pro-inflammatory cytokines, competitive exclusion of pathogenic bacteria, and interaction with the CNS, resulting in changes in levels or functions of neurotransmitters [151-154]. The findings of the possible association of anxiety or depression with elevated levels of pro-inflammatory factors (TNF-α, IL-6, and CRP) indicate the involvement of inflammatory factors in psychological conditions [155]. Cytokine receptors located on peripheral nerves, including the vagal nerve, may convey inflammatory signaling to the brain, which possibly evokes psychologically unstable states such as anxiety and depression [156]. Several studies have demonstrated that *Lactobacillus* and *Bifidobacterium* strains alleviate inflammatory responses in rodents [108,157,158]. Desbonnet et al. found that the administration of probiotics *B. infantis* for 14 days improved depression-like behavior in rats with a significant attenuation in pro-inflammatory cytokines IFN-γ, TNF-α, and IL-6 [108]. Additionally, in rats subjected chronically to the forced swim test, *B. infantis* administration triggered a significant increase in plasma tryptophan concentration, known as a serotonergic precursor [108]. Another probiotic, *L. paracasei*, has been shown to produce neurotransmitter GABA [159]. In addition, probiotics

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can also exert anti-stress effects by decreasing the level of cortisol, a well-characterized stress hormone [160]. For example, a study investigating potential synergic effects of *L. helveticus* and *B. longum* administration showed that probiotic treatment attenuated anxiety- and depression-related behaviors as well as levels of serum cortisol in both rats and human subjects [161].

Taken together, these data show that certain probiotic strains can modulate various aspects of metabolic and behavioral functions. However, further experimental and clinical trials are required to identify the exact mechanisms and pathways mobilized by probiotics.

Prebiotics

In addition to probiotics, modulation of gut microbiota composition can be mediated with prebiotics. Prebiotics are "non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth or activity of one of a limited number of bacterial species, thus improving host health" [162]. Chronic administration of prebiotics such as oligofructose to genetic (ob/ob) or diet-induced obese and diabetic mice increases the expression of intestinal proglucagon and circulating GLP-1, improves glucose homeostasis and leptin sensitivity, and decreases oxidative stress, low-grade inflammation, and fat-mass accumulation [163]. These metabolic improvements are associated with compositional shift of specific gut microbiota phyla, specifically, decreased *Firmicutes* and increased *Bacteroidetes* [119]. Additionally, administration of oligofructose restores *A. muciniphila* abundance, which is associated with improved metabolic states [164]. Similarly, oligofructose administered to diet-induced obese rats reduces fat mass and weight gain with a noticeable increase in *bifidobacteria* and *lactobacilli* [165]. Importantly, oligofructose supplementation has been shown to promote weight loss in overweight and obese humans as well [166]. Another prebiotic, honey, a natural oligosaccharide-rich product, is shown to improve glycemic control in streptozotocin-induced diabetic rats [167]. It is believed that pancreatic β-cells are vulnerable to oxidative stress due to the relatively low levels of antioxidant enzymes in the pancreas, which may play a crucial role in the β-cell deterioration frequently characterized in diabetes [168,169]. In rat models with diabetes, honey supplementation was shown to decrease oxidative stress in the pancreas [170]. In addition to affecting metabolic outcomes, the daily use of prebiotics for three weeks in humans has been shown to reduce the cortisol stress response and improve emotional processing [171].

Fecal Microbiota Transplant (FMT)

FMT refers to "the process of instilling a liquid suspension of stool from a healthy donor into the patient's upper gastrointestinal tract through a nasogastric/nasoduodenal catheter or gastroscopy, or into the colon through a colonoscopy or a rectal catheter" [172]. It has been used for more than 50 years primarily for the treatment of *C. difficile* infection, but recently, there has been a growing interest in utilizing this bacteriotherapy for metabolic syndrome [173]. In related trials, FMT recipients showed more diversity and more similarity to the donor in composition of the fecal microbiota after transplantation with an increased proportion of *Bacteroidetes* and decreased proportion of *Proteobacteria* [5]. Moreover, Vrieze et al. have reported that insulin sensitivity of recipients with metabolic syndrome increased 6 weeks after infusion of intestinal microbiota from lean donors [173]. The therapeutic effects of FMT also can be applicable to other disorders, such as Parkinson's disease [174], chronic fatigue syndrome [175], and childhood regressive autism [176].

Bariatric Surgery

Bariatric surgery (weight loss surgery) is the most effective treatment for morbid obesity and is considered when other attempts have failed. The procedure facilitates a marked weight loss and improves metabolic parameters, including insulin sensitivity, pancreatic β-cell function, and inflammatory status as well as cardiovascular risk factors [177,178]. Reduced food reservoir and malabsorption have been suggested as possible mechanisms underlying the health-promoting influences of bariatric surgery, but a growing body of evidence suggests a beneficial role of altered gut microbiota profile following the surgery [179]. Indeed, certain procedures such as the Roux-en-Y Gastric Bypass [RYGB] have been reported in humans and animals to cause a marked increase in *Gammaproteobacteria*, decrease in *Firmicutes*, and loss of methanogen bacteria [179], which are associated with metabolic improvements after treatment [180,181]. The RYGB surgery in rats with normal weight caused a decrease in *Firmicutes* with significantly higher proportion of *Proteobacteria* compared to the control rats treated with sham operation [182]. Additionally, abundance of the butyrate-producing *F. Prausnitzii* species, considered to reduce low-grade inflammation, was increased following RYGB in the study.

Conclusion

A growing body of experimental and clinical evidence shows the potential involvement of the gut microbiota with metabolic and neuropsychiatric disorders and has drawn attention to the concept of 'microbiota-gut-brain axis'. The gut microbiota can modulate gut-brain axis signaling via endocrine, metabolic, immune and neural mechanisms.

Similarly, the same pathways are used by the brain to modulate the composition of the intestinal microbiota. However, in a dysbiotic state, this bidirectional communication can lead to the pathophysiological progress of metabolic and CNS disorders, and consequently there has been a growing attention to microbiome-based therapeutics, ranging from probiotics, prebiotics, fecal microbiota transplant to bariatric surgery. Still, there are unknowns regarding the role of the gut microbiota in metabolic and CNS disorders to be addressed prior to further development of new therapeutics. First, we need specific identification of potential mechanisms or pathways by which microbiota manipulation can affect the host physiology and psychology. Second, it is crucial to clarify the influence of maternal gut microbiota and infant nutrition on the microbial development in early childhood and throughout adulthood. Third, the impact of variation in the gut microbiota needs to be elucidated on drug

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metabolism, bioavailability, and toxicity as well as on microbiota-gut-brain communication. This could be approached with the use of GF animals and ones colonized with existing microbial strains to determine the effect of specific bacteria on host physiology and related therapeutic strategies. Overall, further understanding of the interaction of the microbiota-gut-brain axis with the host's metabolism will guarantee more successful and promising improvements in the treatment of metabolic and CNS diseases.

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