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REVIEW

Anxiety, Depression, and the Microbiome: A Role for Gut Peptides

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Abstract The complex bidirectional communication between the gut and the brain is finely orchestrated by different systems, including the endocrine, immune, autonomic, and enteric nervous systems. Moreover, increasing evidence supports the role of the microbiome and microbiota-derived molecules in regulating such interactions; however, the mechanisms underpinning such effects are only beginning to be resolved. Microbiota–gut peptide interactions are poised to be of great significance in the regulation of gut–brain signaling. Given the emerging role of the gut–brain axis in a variety of brain disorders, such as anxiety and depression, it is important to understand the contribution of bidirectional interactions between peptide hormones released from the gut and intestinal bacteria in the context of this axis. Indeed, the gastrointestinal tract is the largest endocrine organ in mammals, secreting dozens of different signaling molecules, including peptides. Gut peptides in the systemic circulation can bind cognate receptors on immune cells and vagus nerve terminals thereby enabling indirect gut–brain communication. Gut peptide concentrations are not only modulated by enteric microbiota signals, but also vary according to the composition of the intestinal microbiota. In this review, we will discuss the gut microbiota as a regulator of anxiety and depression, and explore the role of gut-derived peptides as signaling molecules in microbiome–gut–brain communication. Here, we summarize the potential interactions of the microbiota with gut hormones and endocrine peptides, including neuropeptide Y, peptide YY, pancreatic polypeptide, cholecystokinin, glucagon-like peptide, corticotropin-releasing factor, oxytocin, and ghrelin in microbiome-to-brain signaling. Together, gut peptides are important regulators of microbiota–gut–brain signaling in health and stress-related psychiatric illnesses.

Key Words Gut–brain axis · Gut peptides · Gut microbiota · Anxiety · Depression

Introduction

In the last decade, the physiological significance of gut peptides has been expanded beyond gastrointestinal (GI) digestion and absorption of nutrients. The more than 20 signaling molecules released from specialized enteroendocrine cells (EECs) in the GI tract have significant endocrine and metabolic functions and are able to communicate with the brain [1]. It is now also becoming clear that the activity of EECs, which represent no more than 1% of the total gut epithelium cell population, is modulated by the gut microbiota [2–4]. Enteric bacterial diversity and composition uniquely influence the release of gut peptides, including glucagon-like peptide (GLP-1), peptide YY (PYY), cholecystokinin (CCK), corticotropin-releasing factor (CRF), oxytocin, and ghrelin [1, 5–7]. However, the mechanisms underlying EEC–microbiota interactions have yet to be fully resolved.

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Relatedly, increased emphasis has been given to the role of the microbiota and its metabolites in health and disease. Alterations in the gut microbiota may influence conditions such as obesity, allergies, autoimmune disorders, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and psychiatric disorders [8–13]. Although, several animal studies have demonstrated that the gut microbiota modulates behaviors relevant to psychiatric disorders such as anxiety-like [14–19] and depressive-like behaviors [20–22], the mechanisms underpinning such microbe–host communication has not yet been figured out. Of note, several of the same peptides and their receptors that are released into the gut are also widely expressed in the brain or signal to the brain, where these peptides play well-established roles in the neurobiology of anxiety and depression (for review, see [23, 24]).

Since the expression of these gut-derived peptides is likely to be modulated by changes in the gut microbiota, it has been proposed that these peptide hormones may have an important role in gut–brain communication [21, 25–27].

The majority of the gut-derived peptides also play a role in the central regulation of appetite and food intake, in particular via hypothalamus nuclei [28–32]. Interestingly, obesity and psychiatric disorders are commonly associated [33–37], and a Westernized diet appears to exceed beyond nutrition, modulating behavioral reward and the development of psychopathologies [38–43].

Thus, an understanding of gut peptide signaling may provide new insights into gut–brain communication to help explain how the gut microbiota may modulate pathophysiological processes relevant to brain disorders such as anxiety and depression. The latter disorders are major causes of disability and contribute considerably to the global health burden [44, 45]. Although antidepressants and anxiolytics are usually effective, these drugs are frequently associated with serious side effects [46–48]. Conversely, some patients are resistant to the therapeutic effects of conventional pharmacological therapies. Recent data from human cohorts support preclinical findings suggesting that the modulation of the gut microbiota can influence brain function [49–53]. It is therefore clear that new therapeutic strategies should be developed to prevent and/or alleviate the symptoms of depression and anxiety. Psychobiotics, which target the gut microbiota to affect mental health for the better, may be one such innovative strategy (for review, see [54–56]). In this review we will discuss the role of the microbiota–gut–brain axis in anxiety and depression, and how gut-derived signaling peptides are likely important mediators in this process.

The Gut Microbiota

We live in a microbial world where each daily action can shape our microbiome. Mammalian microbial colonization likely begins at birth [57, 58] although a diverse range of microbes have been detected in umbilical cord blood, amniotic fluid, the placenta, and the fetal membranes [59–62]. Following parturition, the gut microbiota is refined and modified until adult-like communities reach homeostasis in its diversity [63]. A variety of factors can influence the infant microbiota, including birth delivery mode, breast feeding, weaning age, and maternal lifestyle [64–66]. In addition, the use of antibiotics, diet, exercise, and disease shape the microbial landscape creating interindividual differences within the gut microbiota [25, 67–69]. Typically, within healthy adults, the composition of the intestinal microbiota remains stable over time, and the bacterial phyla Firmicutes (including *Lactobacillus*, *Clostridium*, and *Enterococcus* genus) and Bacteroidetes (e.g., *Bacteroides* genus) represent > 90% of the intestinal community [70]. These phyla are frequently correlated with the health outcomes in human and animal studies (for review, see [71, 72]).

The diversity and stability of the microbiota are important indices for the overall health of an individual. The gut microbiota may impact host health via the conversion of nondigestible carbohydrates to short-chain fatty acids (SCFAs) [15], transformation of bile acids [73, 74], action against pathogenic bacteria [75], and the modulation of host innate and adaptive immune systems [76]. For example, a reduction in microbial diversity or the complete absence of the gut microbiota alters normal immune system function [77, 78] and decreases the capacity for harvesting energy from the diet [79, 80]. Consumption of complex carbohydrates rich in dietary fibers changes the composition of the gut microbiota often increasing the abundance of Firmicutes and Bacteroides [43, 81, 82]. Prebiotic supplements, here defined as nondigestible fibers selectively metabolized by the enteric microbiome, increase the production of SCFA [15, 83]. SCFA act on G-protein-coupled receptors [free fatty acid (FFA) receptors] located along the GI tract to regulate energy homeostasis via the stimulation of leptin production in adipocytes, and the secretion of gut peptides from colonic EECs [84–87].

The Microbiota–Gut–Brain Pathways: Focus on Gut Peptides

The brain and the gut are engaged in continuous bidirectional communication. Such communication may be important in mediating physiological effects ranging from GI function to the brain and behavior, bringing about the perception of visceral events such as nausea, satiety, and pain. In turn, stressful experiences lead to altered GI secretions and motility. The clinical relevance of such bidirectional communication, along with the modification of the gut microbiota composition, is now being investigated. Bidirectional gut–brain

communication may begin as sensory information from the GI tract [88], and is consequently transformed into neural, hormonal, and immunological signals. These signals can independently or cooperatively relay information to the central nervous system (CNS). The neural and immune pathway, when relevant, are discussed throughout the paper. For an in-depth review of the literature regarding the neural and immune pathway, please see [2, 89, 90] and [11, 76, 91], respectively. Figure 1 also provide a schematic view of the gut microbiota–brain axis, including both neural and immune pathways.

The gut endocrine system is comprised of gut peptides and other signaling molecules (i.e., serotonin), which are released by different types of EECs along the GI tract in response to food intake, particularly after ingestion of carbohydrates and fats. EECs represent approximately 1% of epithelial cells in the gut lumen and are divided into subtypes according to location in the gut and class of molecules released, including peptides (Fig. 2). Recently, in an elegant study, Bellono et al. [88] demonstrated that EECs, in particular enterochromaffins, control serotonin release onto 5-HT_3 receptor-expressing primary afferent nerve fibers that extend into intestinal villi, enabling them to detect and transduce information from the gut to the nervous system.

Peptides are short chains of amino-acid monomers linked by amide bonds (approximately ≤ 50 amino-acid residues) that can be released from specialized neurons in the brain (where they are called neuropeptides) or in EECs as a signaling molecule through binding G protein-coupled receptors [88, 92, 93]. Peptides are able to reach receptors far from the site of their release, and are efficiently metabolized by endogenous enzymes and do not accumulate in tissues [92, 94]. There are > 100 peptides in mammals, with those relevant to gut–brain communication being mostly involved in regulating digestion and satiety. Many of the peptides found in EECs and in CNS regulating the GI tract are also found in the enteric nervous system. For example, tachykinins (i.e., substance P) and calcitonin gene-related peptide are expressed in intrinsic sensory neurons [95, 96]. Gastrin-releasing peptide stimulates the release of gastrin from G cells of the stomach and regulates gastric acid secretion and enteric motor function [97]. Vasoactive intestinal peptide communicates with adjacent postsynaptic targets to regulate circadian rhythm and inhibit gastric acid secretion and absorption from the intestinal lumen

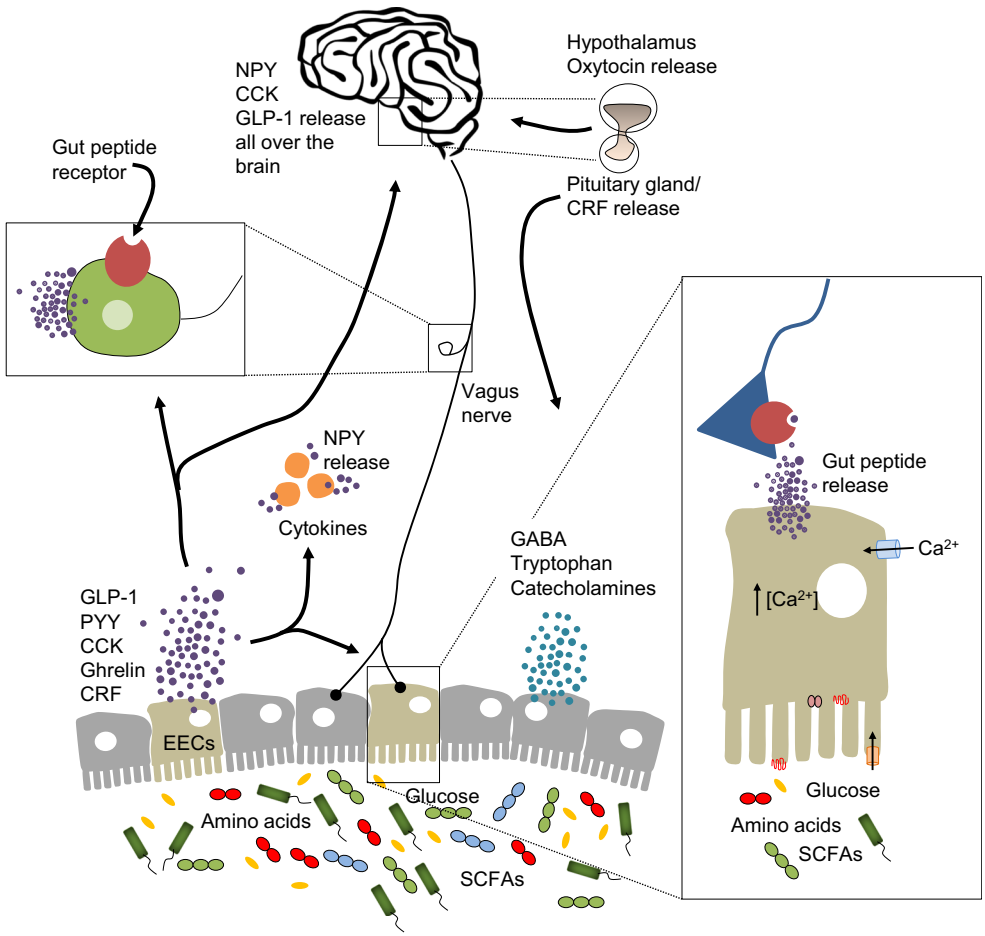

Fig. 1 Major communication pathways of the microbiota–gut–brain axis. There are numerous mechanisms through which the gut microbiota may signal the brain to control physiological processes. These include the release of gut peptides by enteroendocrine cells (EECs) where they activate cognate receptors of the immune system and on vagus terminals in the gut. Gut peptides such as neuropeptide Y (NPY) can also be released by cytokines under immune stimulation. There have been numerous reports of alterations in the gut microbiota in neuropsychiatric conditions, where gut peptides may play a key signaling role. Only a few examples of gut–brain pathway and gut peptides are represented in this figure
CCK = cholecystokinin; GLP-1 = glucagon-like peptide; CRF = corticotropin-releasing factor; PYY = peptide YY; GABA = γ-aminobutyric acid; SCFA = short-chain fatty acid

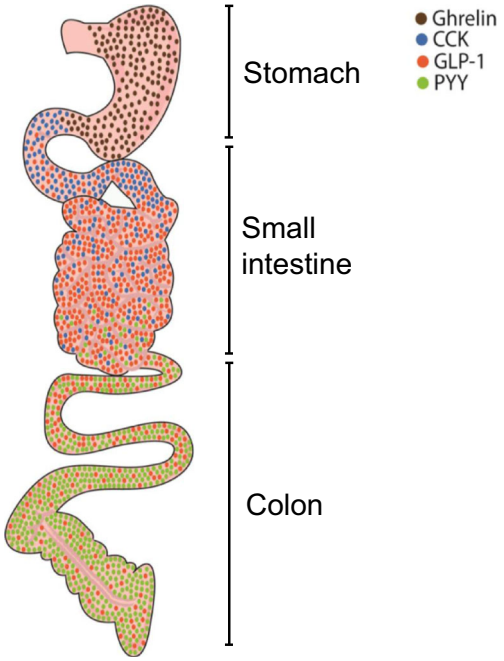

Fig. 2 Gut peptide distribution in the gastrointestinal tract. Gut peptides are released from different subgroups of enteroendocrine cells (EECs) following appropriate stimulation. The stomach is rich in ghrelin expression from A cells (brown circles), cholecystokinin (CCK) is expressed in the proximal segment of the small intestine by I cells (blue circles). The small and large intestine secretes glucagon-like peptide (GLP-1) and peptide YY (PYY) from L cells (red and green circles, respectively). Only some examples of EEC subgroups and relative hormones secreted are represented in the figure

[98, 99]. Structurally similar to vasoactive intestinal peptide, the pituitary adenylate cyclase-activating polypeptide can stimulate enterochromaffin-like cells, a type of EEC [100]. Other peptides include the opioid peptides (enkephalin, endorphins), insulin, calcitonin gene-related peptide, oxyntomodulin, glucagon, enteroglucagon, GLP-2, somatostatin, and gastrin inhibitory polypeptide, among others. Owing to their privileged location in the GI tract, it is possible that those peptides may be influenced by changes in the gut microbiota and modulate (directly or indirectly) upstream signaling to the brain. In this review we focus on peptides with known roles in anxiety and depression; for an in-depth review of others, please see [7, 101–104].

For the peptides discussed in this review, beyond the role in satiety, they can be stimulated by bacterial products that come into contact with the gut epithelium [83, 105, 106]. Distinct subtypes of EECs release different peptides in the gut. For example, the stomach contains X/A-like cells that secrete ghrelin, an orexigenic peptide. Increased ghrelin is associated with the timing of a meal. The proximal small intestine contains I cells and K cells that produce CCK and glucose-dependent insulinotropic polypeptide, respectively [5, 107]. In the distal small and large intestines are L cells, which produce GLP-1/2 and PYY. CRF, which is found in the colon and ileum, is expressed by enterochromaffin cells [108]. Moreover, an additional subset of EECs has the ability to co-express peptides, including CCK, GLP-1, and PYY [109, 110].

Following secretion, gut peptides diffuse throughout the lamina propria, which is occupied by a variety of immune cells, ultimately to reach the bloodstream, to stimulate sensory neurons and potentially to act on the vagus nerve, thereby creating an intersection for gut peptidergic signaling to the brain [111]. In a complementary manner, the blood–brain barrier (BBB) selectively facilitates the transport of some peptides in the blood-to-brain direction, suggesting a direct pathway for some gut peptides that are not quickly degraded after their release [112–115].

Owing to the wide expression of peptides and their receptors in both brain and gut, in addition to their facilitated transit into the bloodstream, it seems reasonable to assume that these peptides can act beyond their primary signaling function, suggesting a possible role (most likely indirect) of the gut peptides in neuropsychiatric disorders [5]. The dynamic profile of gut peptides, including their direct link with mood disorders, and their broad role in the gut suggests that the microbiota–gut peptide–brain communication axis can be a target for psychobiotics to prevent and treat such disorders (Table 1).

The Gut Microbiota in Anxiety and Depression

The link between gut function and mental health is well appreciated (for review, see [134–136]. Depression and anxiety are often accompanied by changes in colonic motility, which, in turn, alters the composition and stability of the gut microbiota, as well as the colonic physiology and morphology [137–140]. Stress-related disorders can also alter the intestinal barrier, triggering a “leaky gut”, which could allow a microbiota-driven proinflammatory response through the translocation of certain bacterial products from the gut [141–143]. For example, Maes et al. [142, 143] found in 2 different studies that lipopolysaccharide (LPS) produced by gut bacteria could increase immune responses in depressed patients. Likewise, in IBS, a disease linked to alterations in the immune system [144], a correlation was found between gut microbiota composition and brain volumes in patients with IBS with early life trauma, suggesting a shift in the Firmicutes/Bacteroidetes ratio, with Firmicutes increased and Bacteriodetes decreased [53]. Interestingly, this study failed to identify correlations between anxiety or depression symptoms scores. However, in depressive patients without IBS symptoms, the Firmicutes/Bacteroidetes ratio was inversely correlated with the microbiota composition profiled in patients with IBS [145–147].

Similar observations have been made in animal studies. Yu et al. [148] found that depressive-like rats had the relative

Table 1 Summary of the impact of altered microbiota on peptides

Microbial manipulation	Effects	Reference
Germ-free, and mice treated with antibiotics, probiotics and prebiotics	Increases NPY and PYY	[25, 116, 117]
Mice treated with antibiotics	Decreases Y_1 and Y_2 receptors	[25]
Rodents treated with antibiotics, probiotics, and prebiotics	Increases GLP-1	[116–122]
GLP-1 knockout mice	Increases Bacteroidetes and reduced Firmicutes	[123]
Glucose-tolerant volunteers treated with *Lactobacillus reuteri* for 8 weeks	Increases GLP-1	[124]
Germ-free mice	Decreases CCK	[125, 126]
Germ-free mice and rats treated with prebiotics	Decreases ghrelin	[127–130]
Fasted germ-free mice	Increases ghrelin	[121]
Germ-free mice	Decreases CCK	[125, 126]
Intracerebral administration of CRF	Changes in the gut microbiota	[111]
Stress-inducing CRF expression	Decreases in Bacteroidetes and increases in Firmicutes	[131]
Mice treated with antibiotics from adolescence onwards	No change in CRF and decrease oxytocin	[21]
Mice treated with *Lactobacillus reuteri*	Increases oxytocin	[132, 133]
Offspring mice from high fat diet-treated dam/*Lactobacillus reuteri* treatment	Decreases oxytocin/restored after treatment	[26]

NPY = neuropeptide Y; PYY = peptide YY; GLP-1 = glucagon-like peptide; CCK = cholecystokinin; CRF = corticotropin-releasing factor

abundances of Bacteroidetes significantly increased, whereas that of Firmicutes was markedly decreased. In mice that underwent chronic stress, reductions in the genus *Bacteroides* were identified [149]. Stressed mice also have been shown to have greater populations of the genus *Clostridium*, which agrees with the gut microbiota profile in maternally separated rodents [149–151]. The genus *Clostridium* is commonly altered as a result of changes modulated by gut metabolites, such as phenylalanine, tryptophan, and tyrosine [152, 153]. Such metabolites are part of the metabolism of key neurotransmitters in mammals, including serotonin, with implications for ENS and CNS function and thus gut–brain axis signaling [154–158].

Antidepressants are well known to have antimicrobial effects, modulating the pathophysiology of the anxiety and depression by reshaping not only brain biochemistry, but also the gut microbiota [159, 160]. Conversely, certain antibiotics, such as β-lactams and tetracyclines have potential antidepressant properties in rodents and humans [161, 162]. Epidemiologic studies have suggested that some classes of antibiotics such as fluoroquinolones are associated with the development of depression and anxiety [163–166].

Although the altered gut microbiota and its effects on host metabolic phenotype during psychiatric illness remains unknown, these observations highlight the potential association of the gut microbiota with host depression and anxiety. Thus, the manipulation of the gut microbiota may be a useful tool to decode the physiological role of the gut–brain axis in psychiatric disorders [167]. The use of germ-free rodents, animals with pathogenic bacterial infections, animals exposed to probiotic agents or to antibiotics, prebiotics, and fecal microbiota transfer from another animal or human may lead to important new findings for the development of new therapeutic strategies to treat or prevent anxiety and depression.

The Neuropeptide Y Family

The members of the neuropeptide Y (NPY) family comprise NPY itself, PYY, and pancreatic polypeptide (PP). The functional role of the NPY family in gut–brain signaling is supported by the wide distribution of the 4 main NPY receptors in mammals (Y_1,Y_2, Y_4, and Y_5 receptor) (for a review, see [168]). NPY has higher affinity than PYY for the Y_1 and Y_5 receptors, whereas PYY is the stronger agonist at Y_2 receptors [168, 169]. The Y_2 receptors might also act as an autoreceptor, regulating the release of NPY, as well as other neurotransmitters, such as γ-amino butyric acid (GABA) [170–172]. The Y_4 receptors are preferentially bound by PP [169]. The Y_1,Y_2, and Y_4 receptors are found in the colon and small intestine [173]. In addition, the Y_1 and Y_2 receptors are also widely distributed within the brain, but both Y_4 and Y_5 receptors are restricted to particular areas in the brain, including the nucleus of the solitary tract (NTS), hypothalamus, and amygdala [174, 175].

The NPY family is expressed at all levels of the gut–brain axis. NPY is the most abundant peptide in the brain and is expressed from the medullary brainstem to the cerebral cortex (for review, see [175]). The presence of NPY in the NTS and the ventral hypothalamus deserves special mention since these areas are the main relays for peripheral signaling, which are particularly important for the gut–brain signaling [24]. Moreover, NPY is also found in enteric nerve plexuses and postganglionic sympathetic neurons [24, 176]. The gut peptides PYY and PP are released mainly by EECs, where PYY is expressed from L cells of the ileum and colon and released in response to feeding (Fig. 2) [5], whereas PP is synthesized from F cells of pancreatic islets and under vagal control [176, 177]. Both PYY and PP are able to cross the BBB by transmembrane diffusion and bind cognate receptors located in the area postrema [115, 178]. Moreover, these gut peptides can activate their cognate receptors located in vagal afferents to signal to the brainstem [179, 180]. In addition, PYY-positive neurons are also found in the NTS, and nerve terminals containing PYY are located in the pons, hypothalamus, and spinal cord [177].

Microbiota and the NPY, PYY, and PP: Relevance to Anxiety and Depression

There is abundant evidence that the central NPY system affects stress-related disorders such as anxiety and depression (for a review, see [181, 182]). Additionally, NPY signaling also has modulatory properties involving neuroprotection, neurogenesis, and neuroinflammation [183, 184]. The Y_4 receptor, which is mainly activated by peripheral PP, modulates anxiety and fear-related disorders in rodents [174, 185, 186]. PP is about 100 times more potent than NPY in Y_4 activation, suggesting that PP/Y_4 receptors can be an important route of gut–brain communication in the pathogenesis of anxiety and depression.

Following a meal, PP and PYY are released and inhibit gastric emptying via the targeting of receptors on the intestinal epithelium, as well as vagus nerve signaling [187–189]. By activating Y_4 receptors in the gut, PP reduces intestinal motor activity and facilitates nutrient absorption, an effect likewise exerted by PYY [24, 188, 190]. Interestingly, it has been suggested that hunger in rodents could promote fear extinction through Y_4 receptor signaling [185, 191]. Although the gut microbiota was not investigated in these studies, the results strongly suggest a potential role for gut–brain communication through Y_4 signaling. The expression of NPY in the hypothalamus (where NPY plays a major role in feeding behavior and stress response) is increased in adult, healthy, germ-free mice when compared with conventionally raised mice [116]. In addition, Schéle et al. [116] found that administration of leptin reduced NPY expression in germ-free mice but not in conventionally raised mice, suggesting that the gut microbiota may decrease leptin sensitivity, effects that are dependent on vagal signaling [192].

Despite its elevation by food intake, circulating PYY can also be increased by exercise and stress [193, 194], conditions that also modify the gut microbiota [195, 196]. It is important to note that more studies linking changes in PYY and the gut microbiota are needed. Correlative evidence exists between PYY and the gut microbiota, where elevation in PYY in obese individuals was associated with changes in the gut microbiota [197]. Interestingly, PYY secretion is influenced by activation of FFA receptors by SCFA [85, 198–200]. Moreover, the SCFA butyrate can increase the expression of receptors that sense microbial compounds (Toll-like receptors), which, in turn, increases the expression of PYY [201]. Given the importance of microbiota-generated SCFAs such as butyrate, the role of the SCFA in mediating PYY expression through immune cells could be an important link in microbial–host communication and PYY signaling. The use of dietary compounds to modulate the gut microbiota has been a useful approach to investigating the role of intestinal bacteria in PYY expression. For instance, PYY expression is upregulated in the ileum after treatment with prebiotic galacto-oligosaccharides (GOS) [202]. Although plasma PYY is increased after oligofructose treatment in healthy rats [202, 203], oligofructose did not alter plasma PYY levels in obese mice [204]. A separate study in rodents demonstrated that bacterial proteins produced after nutrient-induced *Escherichia coli* growth may signal the CNS via increased plasma PYY [205]. The same effect was observed after the intake of probiotics. Hong et al. [202] found an upregulation of intestinal PYY with the commensal bacteria *Bifidobacterium bifidum* in rats. However, a study in humans showed that plasma PYY was unaffected after treatment with barley kernel bread, an indigestible carbohydrate source, and a mixture of the probiotics *Bifidobacterium animalis*, *Lactobacillus reuteri*, and *Lacobacillus plantarum* [206]. Despite the interspecies variability, the contrasting results found in humans and animals could be owing to the selective spectrum of bacteria that can modulate PYY expression. For this, Rajpal et al. [207] investigated selective spectrum antibiotics and found that only an alteration of Gram-negative bacteria (which, in turn, increased the population of Firmicutes) improved metabolic aspects, including PYY, in rodents.

Evidence of direct involvement interaction between the NPY system and the gut microbiota modulating behavior is lacking. Perhaps the most convincing evidence of the gut NPY family signaling brain function is found within the context of depression and anxiety associated with colitis. For example, in a colitis disease model, it was found that an increase in the colonic synthesis of NPY was associated with decreased colonic Y_1 receptor expression [208, 209]. Moreover, circulating levels of plasma PYY and NPY are also enhanced in patients with IBD, suggesting that the

epithelial levels of NPY and PYY are exhausted by excessive release of these peptides from EECs and intestinal neurons [173]. In addition, NPY-depleted mice are resistant to developing colitis and the levels of colonic PYY are decreased in rats with chemically induced colitis or patients with IBS [24, 173, 208]. The effects of colitis on behavior are also modified by NPY or PYY. For example, depletion of NPY or PYY in mice prevents the anxiogenic and depressive-like behavior often promoted by colitis [210]. Moreover, the effect of increased expression of NPY on immune function, is mediated mainly via NPY receptors located on immune cells [173, 211], as well as through the modulatory role of TLR on PYY expression [201]. Crosstalk between the immune system and the brain neurocircuitry can drive the development of depression and raise anxiety [212]. Thus, it is likely that gut microbiota contributes indirectly to NPY release and signaling to affect its homeostatic role in balancing the brain's response to stress in the brain. Recently, it was shown that the depletion of the gut microbiota in adult mice upregulated NPY expression within the amygdala and hypothalamus, followed by cognitive deficits [25], an effect also observed in rats housed in environmental enrichment [213]. However, anxiety- or depression-like behaviors were unaffected in these animals [25]. Interestingly, hypothalamic NPY was also found increased in germ-free mice [116]. Germ-free mice usually present an anxiolytic phenotype behaviorally [214]. In fact, the anxiolytic profile of NPY is associated with its central levels to promote a change in the anxiety phenotype of the animals [215]. Moreover, Schéle et al. [116] demonstrated the role of NPY in counteracting the increased plasma levels of corticosterone in germ-free rodents. Of note, germ-free rodents have an exaggerated release of corticosterone after acute restraint stress [27, 216]. In contrast, plasma NPY levels decreased after the introduction of conventional intestinal microbiota in germ-free mice [217], a shift also observed by Sudo et al. [216] with the corticosterone levels after recolonization of germ-free mice. Interestingly, a fiber-supplemented diet did not affect plasma PYY in germ-free rats, a result that was not observed in conventional mice [218]. Finally, NPY and PYY are also antimicrobial peptides, influencing the composition and function of the gut microbiota [219].

Although a mechanism pointing to how the gut microbiota influence the NPY system and then modulate brain function and behavior, it is worth noting that NPY receptors are expressed on immune cells, brain neurons, primary afferents in the gut, and sympathetic neurons. Thus, in addition to the literature mentioned above, this indicates that NPY, PYY, and PP somehow participate in the reciprocal interaction between the brain, the gut, and the immune system, therefore warranting investigation of their pathophysiological implications within the context of the microbiota–gut–brain axis.

GLP-1

GLP-1, an incretin hormone, is a 30 amino-acid peptide derived from the post-translational processing of preproglucagon, which is involved in the neural regulation of food intake, body weight, the modulation of the hypothalamic–pituitary–adrenal (HPA) axis, and overall response to stress via activation of the GLP-1 receptor (for review, see [220–223]).

In the brain, GLP-1 is present in the NTS and the olfactory bulb [5, 224]. In the NTS, GLP-1 fibers directly innervate hypophysiotrophic CRF neurons in the paraventricular nucleus (PVN), where GLP-1 activates the HPA axis response [225]. GLP-1 receptor is abundantly found in brain regions that are critical for the regulation of both metabolic and endocrine responses [226]. In the periphery, GLP-1 is secreted by L cells, which also secrete PYY in the ileum and the colon in response to neuronal and hormonal signals (Fig. 2) [5, 110], whereas the GLP-1 receptors are distributed in the gut, pancreatic β-cells, kidney, and in the vagus nerve [222, 227].

Following release into the bloodstream, GLP-1 is rapidly degraded, resulting in < 10% of secreted GLP-1 reaching systemic circulation as a result of enzymatic degradation [221]. Thus, it is likely that GLP-1 acts locally in a paracrine fashion in the intestine. Indeed, vagal afferent neurons express the GLP-1 receptor, activation of which induces firing of the respective vagal afferent neurons and most likely stimulation of NTS [228, 229]. As the NTS projects GLP-1 neurons directly to the paraventricular nucleus of the hypothalamus, it is plausible to affirm that GLP-1 restricts feeding behavior, which is dependent of the vagal pathway [230–232]. Although it is unlikely that nutrient-induced GLP-1 enters the circulation to act centrally to lower food intake, it has been proposed that rather than entering the systemic circulation, GLP-1 is released into the lymph [233–235]. GLP-1 levels in the lymph were found to be higher, lasting longer than in the bloodstream, supporting a plausible model where GLP-1 does reach the brain given its transport via the lymph [233]. If not, it is also known that intestinal intraepithelial lymphocytes can modulate energy availability, host microbial responses, and mucosal integrity through the activation of GLP-1 receptors in immune cells, and regulate the migration of lymphocytes and natural killer T cells [123, 236].

Gut Microbiota and GLP-1: Relevance to Anxiety and Depression

GLP-1 is widely recognized for its role in lowering postprandial blood glucose via augmentation of glucose-dependent insulin release and inhibition of glucagon secretion (for review, see [237]). Interestingly, brain abnormalities and cognitive deficits similar to those found in depressive patients are also frequently identified in individuals with metabolic

disorders [238–241]. It is particularly relevant that patients with diabetes are twice as likely to suffer from anxiety and depression than the general population [242, 243]. Growing evidence supports the role of GLP-1 in the central effects of metabolic syndrome, as GLP-1 in anxiety appears to be related to the improvement of the glucoregulation in diabetic states, with subsequent reduction in proinflammatory cytokines and an increase in neuroprotection [244, 245]. For example, reduction of the phyla Firmicutes and Bacteroidetes in the gut ameliorates insulin resistance under conditions of a high-fat diet by stimulating GLP-1 secretion in mice [246]. Moreover, anxiety-like behavior in diabetic mice was blunted by a GLP-1 receptor agonist [247, 248], whereas in nondiabetic animals, the impact of a GLP-1 receptor agonist was less clear in reducing anxiety-like behavior [249–251]. However, chronic systemic stimulation of GLP-1 receptors promoted antidepressant-like effects in rodents, coupled with increasing hippocampal neurogenesis, suggesting plasticity-related effects could underpin such effects [252–255]. Furthermore, a GLP-1 receptor agonist was able to reverse LPS-induced depressive-like behavior without directly affecting inflammatory cytokines [256]. Taken together, it is likely that attenuation of glucose fluctuations by GLP-1 is responsible for its neuroprotective effects, especially during plasma hyperglycemia.

Evidence suggests a key role for SCFA in modulating GLP-1 expression through the stimulation of FFA2 and FFA3 receptors in rodents [83, 105, 257–260]. Moreover, butyrate-induced GLP-1 secretion is attenuated in FFA3 receptor-depleted mice [105], thereby supporting a role for the gut microbiota in GLP-1 release. Indeed, germ-free or antibiotic-treated mice have elevated plasma and intestinal GLP-1 levels, as well as increased proglucagon expression in the colon [118, 205, 246, 261–263]. The expression of GLP-1 in the hypothalamus of germ-free mice is higher than in conventionally colonized animals [116]. Probiotics such as *Bifidobacterium animalis* and *Bifidobacterium bifidum* increase intestinal and plasma GLP-1 levels in rodents [119, 202, 259]. GLP-1 is also upregulated in mice after treatment with the prebiotics GOS, oligofructose, and inulin-type fructans [127, 202, 264–266]. The depletion of GLP-1 in rodents alters the composition of the enteric microbiota [123] and abolishes the antidiabetic actions of oligofructose in mice [266]. Collectively, these findings suggest the gut microbiome influences central and peripheral GLP-1 production through L cells in the gut.

The effects observed in animals can also be found in humans. In healthy volunteers, a mixture of barley kernel bread and *Bifidobacterium animalis*, *Lactobacillus reuteri*, and *Lactobacillus plantarum* increased levels of plasma of GLP-1 without affecting metabolic outcomes [206]. The result was observed in glucose-tolerant volunteers, where the daily administration of *Lactobacillus reuteri* or the commercially available VSL#3 (a formulation with 8 strains of commensal bacteria, including different strains of *Bifidobacterium* and *Lactobacillus*) increased GLP-1 release into the blood, without a change in insulin sensitivity or body fat distribution [120, 124]. In patients with mood disorders and the presence of cognitive deficits, it was found that 4-week treatment with a GLP-1 agonist reverted the cognitive deficits without affecting metabolic parameters, suggesting GLP-1 target offers beneficial effects in some symptoms that can be overrepresented in psychiatric disorders [267].

Taken together, the localization of GLP-1 and the GLP-1 receptors in the gut–brain axis underscores the importance of the microbiota in the modulatory role for GLP-1 in the central regulation of energy homeostasis, which may influence depression and anxiety associated with metabolic dysfunctions.

CCK

CCK is derived from a 115 amino-acid precursor and is converted into multiple isoforms, which range from 4 to 58 amino acids in length, with a wide range of physiological effects such as the control of gastric emptying, gallbladder contraction, pancreatic enzyme release, and suppression of appetite (for review, see [268]). Generally, CCK acts through the G protein-coupled receptors CCK_1 and CCK_2 receptors to modulate other neurotransmitters, such as GABA, glutamate, dopamine, and acetylcholine.

CCK is also found abundantly in the peripheral and central nervous systems [23]. Within limbic areas, CCK is generally co-localized with $5\text{-}HT_3$ and CB_1 receptors, which participate in regulation of mood (for review, see [269–271]). In the gut, CCK is released postprandially from I cells of the small intestine (Fig. 2), although mature EECs have the ability to co-express CCK with GLP-1 and PYY [5, 110]. Both CCK_1 and CCK_2 receptors have distinct patterns of expression. CCK_1 is found mainly within the periphery, including vagal afferent terminals along the mucosal epithelium, whereas CCK_2 is widely distributed in the brain, overlapping with CCK distribution [23, 272].

Gut Microbiota and CCK: Relevance to Anxiety and Depression

The role of CCK in emotional behaviors is seen primarily through the activation of the CCK_2 receptors in limbic regions, mainly the basolateral amygdala and, to some extent, cortical areas and the hippocampus. Both human and rodents studies indicate a positive correlation of CCK levels and increased anxiety-like behavior [273–275]. Moreover, systemic administration of CCK-8 elevated the levels of brain-derived neurotrophic factor in the rat hippocampus, suggesting a neuroplasticity-related effect mediated by CCK [276].

CCK is the first peptide released postprandially to reduce food intake in both obese and lean individuals, remaining in

the bloodstream for about 3 h [277, 278]. Then, CCK acts on its cognate receptors in the periphery located mainly on vagal afferent neurons that project to the NTS [2, 279, 280]. Indeed, vagotomy in mice attenuates the effects of CCK on gastric emptying, whereas the administration of LPS abolishes CCK-induced inhibition of food intake [281, 282]. Gut CCK has also been implicated in the pathophysiology of both IBS and IBD. The densities of CCK cells are reduced in IBD, which may lower the levels of gastric secretion, such as bicarbonate, pancreatic enzymes, and bile salts, resulting in the development of IBS [283, 284]. Interestingly, a potential role for CCK in regulating the immune system has also been suggested in mice. Mice lacking T-cell receptors, which develop inflammation on the colonic epithelium, have been associated with a decrease in the number of EEC cells specialized in secreting CCK [285]. As CCK has been reported to have anti-inflammatory effects, reduced expression of CCK in the gut may have an impact on gut inflammatory diseases, with subsequent consequences in IBD or IBS comorbidity.

CCK signaling is also modulated by the gut microbiota. Obese rodents, which have drastic changes in the composition of gut microbiota, exhibit reduced response to CCK in the nodose ganglia [286], as well as decreased CCK signaling in the brain [287, 288]. Moreover, depletion of CCK_1 in mice reduces firing in NTS neurons, indicating that the activation of the vagal afferent neurons was inhibited [289]. However, germ-free mice have reduced concentrations of gut CCK and delayed intestinal transit [125, 126], whereas infection of germ-free rodents with *Giardia* increased colonic expression of CCK [283], corroborating previous studies showing that intestinal infection could facilitate CCK stimulation of vagal afferent neurons [290, 291].

Despite the changes observed in CCK levels in obese animals, plasma concentrations of CCK were not different in severely obese patients *versus* normal-weight individuals [292]. Federico et al. [292] did not observe changes in the gut microbiota after obese patients underwent bariatric surgery. Taken together, the results from this study show that circulating CCK may not be modulated by changes in the gut microbiome facilitated by alterations in energy metabolism.

The importance of the microbiota in the modulatory role for CCK in the central regulation of energy homeostasis may influence depression and anxiety associated with obesity and represent a potential target in this specific aspect of emotionality.

Ghrelin

Ghrelin is a 28 amino-acid stomach-derived peptide known for its powerful physiological orexigenic and adipogenic effects, as well as for its contribution toward the stress response, anxiety, and depression [293–297]. Ghrelin is the endogenous ligand of the growth hormone secretagogue receptor type 1a and was first discovered for its stimulation of growth hormone secretion from the pituitary [293]. The ghrelin receptor (growth hormone secretagogue receptor type 1a) is expressed in the brain predominantly in the anterior pituitary gland, arcuate nucleus, amygdala, substantia nigra, ventral tegmental area, and raphe nuclei, whereas peripheral expression is found in the pancreatic islets, adrenal gland, and thyroid [298, 299].

Ghrelin is secreted by A cells of the stomach (Fig. 2) [293, 299], although other peripheral organs such as the testis, placenta, kidney, small intestine, and pancreas also express low levels of ghrelin [28]. There is also evidence for the synthesis of ghrelin in the brain, albeit at a much lower level, in specific neuronal cells of the hypothalamus [28, 300]. Of note, central ghrelin expression remains highly controversial as no significant amounts could be detected in rodent neuronal cells, and ghrelin receptor-expressing neurons did not receive synaptic inputs from ghrelin-immunoreactive nerve terminals in these species, suggesting considerable inconsistency between different studies [299, 301].

Peripherally produced ghrelin exerts its appetite-inducing effects centrally after passing through the BBB [112, 302–304]. In addition, ghrelin axon terminals were found to innervate other hypothalamic peptidergic systems, such as agouti-related peptide- and proopiomelanocortin neurons in the arcuate nucleus and CRF in the PVN, suggesting that interactions between ghrelin and NPY/AGPR, proopiomelanocortin, and CRF circuits are critical for energy homeostasis and stress responses [305–307]. Nevertheless, it appears that in addition to its effects on feeding, ghrelin enhances the release of NPY onto GABAergic nerve terminals adjacent to CRH neurons, disinhibiting these neurons and stimulating CRF release into the pituitary–hypophyseal portal circulation, driving increased ACTH secretion from the pituitary [28, 308].

Gut Microbiota and Ghrelin: Relevance to Anxiety and Depression

Ghrelin crosses the BBB via active transport and direct diffusion, making the ghrelinergic system ideally placed to play an important role in the stress response [112, 297, 302]. Physiological state, such as fasting, strongly affects the transport of ghrelin into the brain [302]. However, different stressors, such as social defeat and restraint stress in rodents, can increase long-term ghrelin levels in the stomach [309–311]. Mice lacking endogenous ghrelin have a dampened circulating glucocorticoid response following an acute stressor due a deficit in the PVN response needed to stimulate ACTH from the pituitary [295, 311]. Moreover, mice lacking growth hormone secretagogue (GHS) receptors are more susceptible to stress and exhibit anxiety- and depressive-like

behavior [309, 312]. Recently, some studies have demonstrated that hunger (which increases ghrelin levels) can instigate the search for food even under stressful and anxiogenic conditions, a sign of adaptation for survival [185, 313, 314]. In agreement with the survival theory, recent studies have shown that repeated injection of GHS receptor agonists into the amygdala increases stressor-inducing fear memory formation, whereas antagonists of GHS receptor administered during repeated stressors prevented fear memory formation, as well as anxiety and depression-like phenotypes in mice [296, 315]. Thus, ghrelin may regulate the network designed to enhance survival potential by increasing vigilance, fear, and controlling anxiety. This framework provides a model through which ghrelin could have myriad actions on mood, depending on contextual states and physiological feedback mechanisms.

Although released in the stomach, the regulatory role of ghrelin in appetite is mainly achieved centrally within the arcuate nucleus and the brainstem [316, 317]. Thus, the regulatory role of ghrelin in the CNS may be affected by the gut microbiota via vagus nerve to the NTS. Indeed, germ-free mice have lower levels of plasma ghrelin under basal conditions than conventional mice [128, 129]. However, after a period of fasting, germ-free mice have higher plasma ghrelin concentrations than conventionally colonized mice, which could reflect a direct effect of fasting and not the microbiota profile on ghrelin release [121]. Interestingly, serum ghrelin levels are negatively correlated with the abundance of certain gut bacteria, including the commensal *Bifidobacterium* and *Lactobacillus* strains [318]. In addition, chronically elevated plasma ghrelin, associated with changes in the gut microbiota, can prevent anxiety- and depression-like behavior through ghrelin receptors [309]. Ghrelin has also been shown to decrease in response to the prebiotic supplementation inulin and oligofructose uniquely in obese and lean rodents, with obese rats showing attenuated ghrelin levels [117, 122, 127]. However, oligofructose does not change plasma ghrelin levels in obese rats fed a high fat/high sucrose diet [203]. In addition, ingestion of conjugated linoleic acid induced changes in the gut microbiota, increasing *Bacteroides*/*Prevotella* species and ghrelin levels in the gastric mucosa of mice [319]. Increased ghrelin was also observed in rats after treatment with a diet containing 10% cocoa or cocoa fiber, which was negatively associated with *Bifidobacterium* and *Streptococcus* [320], whereas infection with pathogenic *Toxoplasma gondii* lowered ghrelin serum levels in rats [321]. A negative correlation between Firmicutes and ghrelin levels was observed both in humans and rodents [322, 323]. Moreover, the SCFA butyrate, as well as physical exercise, reduce serum ghrelin levels through involvement of FFA3 receptor [105, 318]. Of note, physical exercise alters the composition of the microbiota in the cecum and increases the concentration of butyrate in the cecal content of rats [324].

In humans, the relationship between the gut microbiota and ghrelin levels seems to mirror that in rodents where the relative abundance of bacterial taxa such as Bacteroides was negatively correlated with plasma ghrelin, which, in obese patients, was increased [130, 197, 292]. Interestingly, plasma ghrelin did not return to levels found in normal weight individuals after obese patients underwent bariatric surgery, despite a postoperative increase of *Lactobacillus* and *Streptococcus* [292]. The use of dietary capsaicin was shown to increase the Firmicutes/Bacteroidetes ratio, which was associated with decreased plasma ghrelin levels and an increase in butyrate [325]. Although dietary capsaicin was given to healthy subjects, this study may warrant future investigations into how the manipulation of the enteric microbiome may achieve lowered ghrelin levels in people. Reduced ghrelin levels could have implications in daily stress, minimizing incidence of psychiatric disorders. For example, injection of ghrelin in healthy humans increased plasma glucocorticoids levels [326].

Ghrelin has recently attracted attention not only as a hunger hormone, but also because of its role in modulating aspects of stress, including anxiety-like behavior and fear. In concert with other gut peptides, ghrelin signaling through the gut–brain axis may tune communication between the periphery and brain during daily life stressors. Nevertheless, a direct link between the gut microbiota and the modulation of ghrelin remains absent.

CRF

CRF is a 41 amino-acid residue peptide that plays a key role in orchestrating the endocrine, behavioral, and GI responses to stress (for review, see [327–329]). CRF is abundantly expressed in neurons of the PVN of the hypothalamus where it is released through effector neurons, which, in turn, mediate neural control of adrenocorticotropic hormone (ACTH) release from pituitary corticotrophs. Then, ACTH passes into systemic circulation to cause the release of cortisol (in humans) or corticosterone (in rodents) from the adrenal glands [328, 330]. Apart from hypothalamic CRF, this peptide and its receptors are also expressed throughout several other limbic regions and in the gut [331, 332]. In the gut, CRF is mainly localized in enterochromaffin cells of the colon [333, 334], and in submucosal and lamina propria cells, but not in epithelial cells in the ileum [335]. CRF can bind two G protein-coupled receptor subtypes, namely CRF_1 and CRF_2 receptors, with different affinities. Apart from receptor binding, CRF also binds to CRF-binding protein with high affinity. CRF-binding protein is thought to play an inhibitory role in which it binds CRF to prevent the activation of CRF receptors [336]. CRF is centrally expressed on GABAergic, glutamatergic, and dopaminergic neurons [337], and can modulate the

catecholaminergic response to stress by activating the noradrenergic neurons in the locus coeruleus or regulating the synthesis and release of adrenaline in the adrenals [329, 330]. Bethin et al. [338] found that immune activation induced by endotoxin produced a robust rise in plasma corticosterone in CRF or CRF_1 receptor knockout mice, comparable with wild-type mice. Since the gut microbiota strongly affects the immune system, intestinal diseases where the gut microbiota is changed, such as IBS and IBD, may induce the expression of inflammatory cells, which, in turn, can increase expression of glucocorticoids but not CRF.

Gut Microbiota and CRF: Relevance to Anxiety and Depression

Functional CRF_1 receptors are essential for the activation of the endocrine response to stress [169]. However, when acute stress reactions become more frequent, it can lead to the development of stress-related disorders, including anxiety and depression (for review, see [329, 339]). Whereas the absence of CRF_1 receptors impairs basal and stress-induced HPA axis response and induces an anxiolytic- and antidepressant-like effect [329, 340, 341], CRF_1 overexpression results in an anxiogenic- and depressive-like profile in rodents and humans [342–346]. Interestingly, antidepressant treatment normalizes expression of CRF and CRF_1 receptors in association with remission of depression [329, 344, 346].

The CRF system also induces functional changes within the gut, including slowed gastric emptying, colonic motile stimulation, and impairment of the intestinal epithelial barrier, each an effect independent of a stressful situation [347, 348]. Recently, a study has found that a single administration of CRF modified the gut microbiota in rats, with specific reductions in *Lactobacillus* [349]. Although the inhibitory effect of central CRF on gut motility and permeability does not change with peripheral injection of CRF or the removal of different HPA axis components [108, 350–352], acute stress in mice induced the release of intestinal CRF independently of the HPA axis [131]. Sun et al. [131] also observed changes in gut microbiota composition, which was reverted with a probiotic supplement. The central administration of CRF in rodents induces depressive and anxiolytic-like behavior, which was followed by changes in the intestinal microbial community [138]. Furthermore, the intestinal microbiota can interfere in host CRF signaling. Germ-free rodents have increased hypothalamic CRF gene expression, as well as circulating levels of ACTH and corticosterone to acute restraint stress in adulthood [27, 216]. These effects in the HPA axis are normalized in recolonized germ-free mice [216]. Taken together, such data indicate that CRF-mediated activation of the HPA axis depends on the gut microbiota. Interestingly, the depletion of the gut microbiota via antibiotic treatment in mice from weaning onward does not alter hypothalamic mRNA CRF expression in adulthood, even when mice underwent acute restraint stress [21], suggesting gut microbiota-mediated CRF signaling may occur during early life. Prenatal stress induced depressive-like behavior in adulthood mice, which led to a long-lasting change of the enteric microbiota composition associated with an exaggerated HPA axis response to stress [353–355]. Early-life stress such as maternal separation results in changes in the gut microbiota followed by an increase in stress reactivity, including a decrease in *Lactobacillus* in adult mice [137]. *Lactobacillus* also suppressed plasma corticosterone and hypothalamic CRF-expressing cells in rats that underwent water-avoidance stress [356]. Using a mixture of 8 bacterial strains, including *Lactobacillus* and *Bifidobacterium*, Abildgaard et al. [357] observed lowered hippocampal transcript levels of CRF receptors followed by marked reduction in depressive-like behavior in rats. Furthermore, social stress in mice also induced changes in the microbiota, which were accompanied by changes in cytokine and chemokine levels [149]. Taken together, these data support a role for the gut microbiota as a potential treatment intervention to blunt stress reactivity.

Preclinical data from prenatal stress studies have been confirmed in clinical trials. Infants of mothers with high self-reported stress and high levels of salivary cortisol during pregnancy had a significantly higher relative abundance of Proteobacteria and lower relative abundances of lactic acid bacteria (i.e., *Lactobacillus*, *Lactoccus*, *Aerococcus*) and Bifidobacteria [358]. Nonetheless, those infants with altered microbiota composition exhibited a higher level of infant GI symptoms and allergic reactions, highlighting the functional consequences of aberrant colonization patterns in early life, which can contribute to psychiatric comorbidities. Increased CRF concentration in the cerebrospinal fluid was also reported in depressive patients and victims of suicide [359, 360]. Interestingly, administration of *Clostridium butyricum* from the phylum Firmicutes can block increased CRF levels in patients before surgical procedures [361]. These patients also presented a reduced degree of anxiety before surgery, suggesting an interesting effect of probiotics in mediating CRF expression to modulate stress reactivity. However, how gut microbes initiate such a response through CRF signaling is still unknown. A better understanding of CRF–microbiota interactions may identify potential gut microbiota-targeted interventions to enhance resilience in stress situations.

Oxytocin

Although oxytocin facilitates parturition and lactation in females, decreased oxytocin levels have been linked with

depression (not only postpartum depression) and maternal neglect [362, 363]. Oxytocin is synthesized by the magnocellular neurons in the supraoptic and paraventricular nucleus of the hypothalamus and secreted to the circulation by the posterior pituitary or to nerve terminals located mainly in the anterior pituitary, amygdala, hippocampus, and the bed nucleus of the stria terminalis (for review, see [364]). Peripherally, oxytocin and OXT receptors are mainly expressed in the uterus, with low expression in many other tissues and organs, including kidney, pancreas, adrenal, and adipose tissue [365]. Interestingly, oxytocin can be found in enteric neurons; however, gut OXT receptors are not only found in enteric neurons, but they are also found in enterocytes [366]. There is little evidence that oxytocin is modulated by gut bacteria, although gut microbiota seems to influence oxytocin in the brain [21, 26]. Moreover, there is cross reactivity in binding of oxytocin and vasopressin with its respective receptor, where oxytocin binds its receptor with only 10 times greater affinity than vasopressin [367].

Gut Microbiota and Oxytocin: Relevance to Anxiety and Depression

Oxytocin-expressing neurons within the hypothalamus are stimulated by stress-mediated noradrenaline release, which elevates oxytocin levels in mammals to counteract the physiologic actions of stressors (for review, see [368–371]). Oxytocin secretion is also directly modulated by various classical immune cytokines, such as inteleukin-1β and interleukin-10 [372, 373], an effect that minimizes immunologic insults and exerts protective effects by restoring host homeostasis. Moreover, the administration of oxytocin exerts an antidepressant-like effect in rodents [374–377], whereas lowered oxytocin levels observed in nonweaned rats induces a depressive-like phenotype, which correlates positively with changes in the gut bacterial taxa [378]. Experimental stress in rodents is associated with the downregulation of OXT receptors in the amygdala [378]. Since stress can alter the gut microbiota composition, it is not surprising that there is interaction between oxytocin and the gut microbiome. Interestingly, gut microbiota depletion from early adolescence impacts oxytocin signaling, reducing both hypothalamic oxytocin and vasopressin levels in mice subjected to stress [21, 379]. Normalized oxytocin levels in stressed animals was followed by a reduction of anxiety-like behavior and correction in cognitive deficits [21]. However, mice fed with *L. reuteri* restored hypothalamic oxytocin neurons, as well as social behaviors, in a study investigating the effects of maternal high-fat diet on the offspring [26]. Interestingly, the effects observed above are dependent on vagal signaling, which blunted the effects of *Lactobacillus* on host plasma and hypothalamic oxytocin [132, 133]. Oleoylethanolamide, a product of fat absorption, which has antidepressant-like and neuroimmune properties [380, 381], excites vagal afferent neurons and stimulates both axonal and somatodendritic oxytocin secretion [382–384]. Oleoylethanolamide-inducing activation of the NTS in rodents precedes the activation of oxytocinergic neurons in the PVN, and the latter response appears to be mediated by noradrenergic projections from the NTS to the PVN [383], suggesting that gut-signaling oxytocin may be mediated by oleoylethanolamide. Nonetheless, plasticity in the oxytocin system is likely a protective coping mechanism in response to stress shaped by the gut microbiota during the early life stage, mainly through maternal exchange, which can contribute to depressive phenotypes when offspring become adults. However, additional studies are needed to demonstrate a functional role of the gut microbiota in the host oxytocin system.

Psychobiotics: Towards a New Class of Psychiatric Treatments

Psychobiotics are defined as an exogenous intervention to effect changes in mental health via modulation of the gut microbiome (for review, see [54, 56]). This may include not only prebiotics and probiotics, but also diet and exercise that affect enteric bacterial communities [54]. Few studies have shown results that may support a clinical role for psychobiotic intervention. For example, changes in diet even for a short duration (24 h) can drastically alter the composition of the gut microbiota [385]. Moreover, the quality of the diet (i.e., a typical Western diet rich in fat and protein) drastically reduces *Bifidobacteria* and butyrate-producing bacteria [386, 387], whereas a Mediterranean diet, which is thought of as a healthy diet, shows significant increases in SCFAs [43]. An overview of epidemiological studies showing the impact of diet on SCFA produced by the gut microbiota can be found in Ríos-Covián et al. [388].

Regarding direct administration of probiotic or other commercially available formulations to manipulate the gut microbiota, a study found that students who ingested *Lactobacillus* spp. had lower plasma cortisol, which can be interpreted as a measure indicative of reduced anxiety during a stressful situation [389]. In a separate investigation, participants consumed a fermented milk product containing *Lactobacillus casei* self-reported the same as the control subjects [49]. However, when only participants whose baseline mood scores were lower (indicative of an antidepressive state), probiotic supplementation resulted in significantly more of this group of participants self-scoring as happy rather than depressed compared with placebo [49]. In yet another study, healthy participants who ingested *Lactobacillus helveticus* and *Bifidobacterium longum* showed less self-reported negative mood and decreased urinary cortisol [50, 390]. A similar effect was also observed in healthy participants who consumed a mixture of *Bifidobacterium bifidum* and *Bifidobacterium lactis*, and *Lactobacillus acidophilus, Brevibacillus brevis*, *Brevibacterium casei*, *Bifidobacterium*

salivarius, and *Lactococcus lactis* [51]. Allen et al. [52] found that healthy individuals fed *Bifidobacterium longum* had attenuated levels of cortisol and reduced subjective anxiety in response to the socially evaluated cold stress pressor test. A similar effect was observed following consumption of a commercially available prebiotic Bimuno® galacto-oligosaccharides, where individuals showed a reduction in waking-cortisol response and decreased attentional vigilance to negative *versus* positive information, suggesting a role in modulating depression [391]. Schmidt et al. [391] found that Bimuno galacto-oligosaccharides intake decreased attentional vigilance to negative *versus* positive information. However, the probiotic *Lactobacillus rhamnosus* failed to alter mood, anxiety, and stress-related measures when subjects faced a socially evaluated cold pressor test [392], an effect previously observed in rodents [20]. Taken together, the above findings highlight the challenges associated with translating promising preclinical studies to healthy human subjects. Studies in populations with mental disorders are therefore required to assess the potential benefit of the manipulation of the gut microbiota as a therapeutic strategy. In recent studies investigating patients with depression and anxiety, a mixture of the probiotics *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium bifidum* found a significant decrease in depression scores [393], whereas a separate investigation of the effects of *Bifidobacterium longum* on anxiety and depression in patients with IBS demonstrated probiotic treatment reduced depression but not anxiety scores and increased the quality of life in patients with IBS [167], indicating that this probiotic may reduce limbic reactivity.

Psychobiotics: Targeting Gut Peptides

There are major challenges associated with the development of peptide therapeutics, including limited peptide stability, a short duration of action, and the ability to cross the BBB [394, 395]. Such limitations may reduce the potential of exogenous-delivered peptides to reach specific target sites, which may fail to reflect the effect of the endogenously derived peptide [396]. Although several approaches have been designed to address the efficacy of the peptide delivery, the majority are concerned with targeted modification of peptide chemistry.

Targeting the release of the gut peptides may be an approach to be considered in conjunction with future breakthroughs in psychobiotics. Advances in the field of pharmacomicrobiomics, which focuses on the interpretation of intraindividual human microbiomes stratified according to different lifestyles, may highlight how an improved understanding of the human microbiome may lead to the development of psychobiotic therapeutic agents [397, 398].

Thus, psychobiotics could be designed to target, for example, specific EECs to elicit the release of controlled endogenous peptides without upstream consequences. Personalized medicine may consider questions of the individual's own microbiome, thereby necessitating the personalization of psychobiotics. This could focus potential peptide-mediated immune responses, improve vagal signaling, or modulate neuropeptide expression in brain regions associated with mental health.

Another interesting approach is the development of targeted antimicrobials. Since the nature of bacteria that occupy overlapping niches is to compete for the same nutrients, antimicrobials such as bacteriocins may help gain terrain over neighbor competitors. Bacteriocins are ribosomally synthesized peptides that are produced by bacteria to eliminate neighboring cells through toxic and immune functions, while protecting itself and its progeny [399–402]. Moreover, a recent paper described that commensal bacteria are able to produce G-protein-coupled receptor agonists to regulate the GI tract physiology, including metabolic hormones and glucose homeostasis [4].

Therefore, the manipulation of gut peptides via psychobiotics may represent a promising opportunity to target mental disorders from the site of the GI tract. Identification of the mechanism(s) underlying the activity of gut peptides and how might the gut microbiota modulate the peptide physiology may facilitate greater understanding of gut to brain communication and its role in the neurobiology of the anxiety and depression.

Conclusion

We are at the very early stages of understanding the complexities of communication along the microbiota–gut–brain axis. However, there is already strong evidence to support the influence of the enteric microbiome on brain function in health and disease, suggesting the gut microbiome plays a crucial role in normal brain development, as well as modulation of host physiological systems important in stress-related disorders. Among the diverse pathways by which the gut can signal the brain, the endocrine system seems to play an important role, as it is capable of modulating not only other endocrine functions, but also the neural and immune systems. As suggested here, peptides released by specialized cells in the gut participate in gut-to-brain communication. Peptides may be envisaged to orchestrate the molecular, functional, behavioral, and autonomic reactions that take place in response to alterations of the gut microbial community. There is significant anatomical and functional overlap of peptides released in the gut and brain, suggesting that these peptides exert common downstream effects on neural systems involved in mental health. Nevertheless, the dynamic changes in peptides and respective receptor expression in the gut and brain of rodents and humans with altered microbiota attests to a profound role of the gut bacteria on peptides. Understanding how the gut

microbes might influence peptide physiology should be a central objective of future research in this field. The generation of specialized psychobiotics to modify gut hormone secretion from EECs may represent feasible and therapeutic microbiota-based strategies for the treatment of depression and anxiety disorders. Interestingly, microbiota-derived metabolites might be able directly to modify gut-peptide receptors, displaying gut-peptide mimicry. Rising interest in this area of research will no doubt lead to greater insights into the mechanism(s) underlying microbiome–gut–brain communication, and provide novel understanding of the potential for microbial-based therapeutic strategies that may aid in the treatment of mood disorders.

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