Microbiota–Gut–Brain Axis in Mood Disorders

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The microbiota–gut–brain axis is a bidirectional communication pathway that enables the gut microbiota to communicate with the brain through direct and indirect signaling pathways to influence brain physiology, function, and even behavior. Several taxonomic changes in the gut microbiota have been reported in neurodevelopmental disorders, mood disorders such as anxiety and depression, and neurodegenerative disorders such as Alzheimer's disease.

Microbiota–Gut–Brain | Nervous System | gut microbiota | probiotics

1. Introduction

The gut microbiota constitute a so-called virtual organ consisting of a complex ecosystem involving around one hundred trillion microorganisms, mostly consisting of bacteria, but also including viruses, fungi, and protozoa [1][2]. In humans, the caecum and distal colon are the sites of highest microbial biomass, with about 95% of gut microbes located there, while the small intestine makes a numerically lesser, although functionally considerable, contribution [3]. The host and the gut microbiota have complex interactions that are affected through different aspects of metabolism. The gut microbiota break down complex carbohydrates and proteins, while producing metabolites that have either a positive or negative impact on the host [4][5][6]. Microbial communities within the gut change in composition, diversity, and activity across the lifespan, which also has a lifelong impact on neurophysiology and behavior through the multifaceted relationship with the host [7][8].

The gut–brain axis consists of a bidirectional communication pathway between the central nervous system (CNS) and the enteric nervous system (ENS), linking the cognitive and emotional centers of the brain with peripheral intestinal functions. Thus, the microbiota of the intestinal lumen affect the CNS activities of the host, such as cognition and the stress response, and likewise the activity of the brain affects microbial composition. Recent advances in research have described the importance of the gut microbiota in influencing these interactions; thus, the microbiota–gut–brain axis is a more relevant term to describe this bi-directional communication pathway [1][9].

The balance between the human microbiome and the development of psychopathologies is interesting, since the gut microbiota can be altered through external factors such as diet, probiotics, prebiotics, and antibiotics, all of which have been demonstrated to affect brain functions and behavior. Probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" [10]. More recently, the term psychobiotic was coined to describe any exogenous influence (e.g., probiotics) whose positive effect on mental health is bacterially mediated [11][12]. Current probiotics belong mainly to the genera *Lactobacillus*

(*sensu lato*) and *Bifidobacterium*, although strains from other genera, such as *Saccharomyces* and *Bacillus*, are also commercialized. Single and multi-strain probiotic intervention studies have demonstrated beneficial effects [13] for several conditions, such as constipation [14], allergy [15], antibiotic associated diarrhea [16], and modulation of the immune system [17].

2. Pathways of Communication along the Microbiota–Gut–Brain Axis

The microbiota–gut–brain axis is a complex network of different communication pathways within the endocrine system, the hypothalamic–pituitary–adrenal (HPA) axis, the ENS, and the immune system. Regarding co-metabolism, the concept of a “leaky gut” may also play a role in the movement of metabolites. The microbiota–gut–brain axis does not solely relate to any single one of these communication pathways, but each plays an essential role.

2.1. The Autonomic Nervous System and the Enteric Nervous System

The autonomic nervous system (ANS) regulates the unconscious control of physiological homeostasis. The ENS is a network of around 500 million neurons at the interface of the gut microbiota and the host, lining the entire intestinal tract from the esophagus to the anus and which is part of the ANS. The ENS responds to receptor input from the intestine and via ganglia within the spinal cord and the brain’s medulla to coordinate various intestinal functions, such as smooth muscle activity, glandular secretion, and sphincter control [18]. Although intestinal functionality is regulated to maintain homeostasis, adaptation is possible for environmental conditions such as stress [18]. The ENS connects to the CNS (including the brain) through the vagus nerve [19], thus allowing the brain to sense the environment within the gut.

2.2. The Vagus Nerve

The vagus nerve is the most direct route of communication between the gut and the brain, thus enabling bidirectional communication. The vagus nerve has also been indicated in the etiology of Parkinson’s disease [20], Alzheimer’s disease [21], and depression [22]. What these conditions have in common is that they are influenced by the gut microbiota through their metabolites and immune-modulating activity. The vagus nerve functions both as a signaling pathway and transfers metabolites and other components to the brain [20]. The vagus nerve responds to components produced or induced by the gut microbiota, such as short chain fatty acids (SCFA), endotoxins, peptides, and cytokines [19]. Furthermore, neurotransmitters such as serotonin produced within the gut influence vagal functionality [22].

2.3. Immune Signaling

The gut microbiota are essential for the healthy development and function of the peripheral immune system and for the development and maturation of the innate immune cells of the brain (reviewed in [23]). Within the intestine, the

mucosa provides the barrier between the inside 'self' and outside 'non-self', consisting of digesta and resident and in-coming microbes. Inflammatory responses and impairment of intestinal barrier function often go hand in hand. The induction of proinflammatory cytokines, such as interleukin (IL)-1β, IL-6, IL-18, and tumor necrosis factor (TNF)-α, have all been associated with depression [19][24] and increased peripheral inflammation has been observed in many psychiatric diseases such as depression, anxiety, and even autism spectrum disorder (reviewed in [25]). Circulating cytokines can access the brain through direct transportation across the blood–brain barrier (BBB). Interestingly, increased BBB permeability is a feature of many neuropathological conditions (reviewed in [25]). Modulating the microbiota may therefore reduce an inflammatory response, improve intestinal barrier function, and prevent proinflammatory cytokines directly accessing the brain. Known pathogens such as *Helicobacter pylori*, *Clostridium perfringens*, *Shigella flexneri*, enterohemorrhagic *Escherichia coli*, and enteropathogenic *E. coli* degrade intestinal barrier function, while organisms like *Faecalibacterium prausnitzii* and *Akkermansia muciniphila* may improve it [26]. Further, selected probiotic strains from the genera *Lactobacillus* (*sensu lato*) and *Bifidobacterium* have been observed to improve barrier function and exert anti-inflammatory effects [27][28].

2.4. Enteroendocrine Regulation

The complex interaction between digesta and the small and large intestine induces the release of an array of gastrointestinal hormones from specialized enteroendocrine cells (EECs) distributed in the gut epithelium. These hormones, among others, regulate gastric emptying, intestinal motility, appetite, and postprandial glucose metabolism [29]. Gut microbes can influence appetite and feeding behaviors by modulating the production of such hormones from EECs.

L-cells, which are embedded mainly in the ileal and colonic epithelium, secrete glucagon-like peptide-1 (GLP-1) in response to nutrients in the small intestine. However, more distally in the intestine they are activated by luminal factors including SCFAs, bile acids, and microbial metabolic products. GLP-1 can interact with the HPA axis and the immune system [30]. In humans, GLP-1 and its receptors have been suggested to reduce anxiety [31]. Glucose-dependent insulinotropic polypeptide (GIP) is released in response to macronutrients from the enteroendocrine K-cells, distributed predominantly in the upper small intestine. GIP has been shown in animal models to reduce anxiety-like behavior [32]. Cholecystokinin (CCK) is secreted in response to the ingestion of macronutrients by enteroendocrine I-cells, located in the duodenum and upper jejunum, and stimulates the release of digestive enzymes and bile. CCK further contributes to reduced appetite [29], and has been observed to increase anxiety-like behavior [31]. Peptide YY (PYY) is co-released with GLP-1 from L-cells. PYY participates in the regulation of appetite and energy intake and has been reported to reduce stress and anxiety responses, and to improve mood [33]. Ghrelin is mainly produced in the gastric mucosa and is involved in the regulation of intestinal motility and appetite [34]. Ghrelin is found in plasma in two major forms: acyl-ghrelin increases appetite and decreases insulin secretion and sensitivity, while des-acyl-ghrelin suppresses appetite and increases insulin secretion and sensitivity [35]. Ghrelin secretion is increased in response to stress; however, chronic stress over time leads to ghrelin resistance and increased secretion of ghrelin, and this has been associated with cravings [36].

2.5. Neurotransmitters

Neurotransmission, i.e., the process driving the transfer of information between neurons and their targets, can be influenced by the gut microbiota, which have been shown to produce a range of major neurotransmitters such as dopamine, norepinephrine, serotonin, γ-aminobutyric acid (GABA), nitric oxide (NO), melatonin, histamine and acetylcholine (Ach). These neurotransmitters provide a possible mechanism of action for how the effects of the gut microbiota on mental and brain health are mediated.

3. The Microbiota–Gut–Brain Axis in Stress and Related Disorders, and Opportunities by Probiotics to Relieve or Prevent Symptoms

Nutritional psychiatry has developed as a recent field of research given the implication of the microbiota-gut–brain axis in influencing stress-related behaviors, including those relevant to anxiety and depression. A key question is whether targeting the microbiota–gut–brain axis may offer a therapeutic strategy for preventing and/or treating the symptoms of stress-related disorders. To date, several probiotic interventions conducted in healthy participants and psychiatric patients have reported beneficial physiological and psychological effects on several endpoints related to stress and mood.

3.1. Stress, Anxiety and Probiotics

Stress occurs when the normal homeostasis of an organism is disrupted because of an actual or perceived threat and can be categorized as either acute or chronic. Acute stress activates the HPA axis, causing an immediate release in cortisol to respond appropriately to the stressor, which can induce anti-inflammatory responses, thereby preparing the individual for defense against the presented threat. Over time, chronic stress leads to dysregulation of the HPA axis, increasing the risk of consequent side effects, such as mood and stress-related disorders, cancer [37], cardiorespiratory, metabolic, and immune system problems (reviewed in [38]). Today, chronic stress is a rapidly growing global societal challenge [39].

Stress can alter the gut–brain axis and has been shown to have a direct impact on the gut microbiota across numerous different animal models, including rodents [40][41][42] and non-human primates [43][44] (also reviewed in [45] [46]). Cortisol, the primary stress hormone, has a direct influence on the ENS and vagus nerve, resulting in alterations in the gut microbiota composition [23]. A pioneering preclinical study conducted in germ-free (GF) mice found an exaggerated HPA axis response to stress, which could be normalized by subsequent colonization with *B. infantis* [47]. Acute stress has been shown to influence the microbiota community profile in mice by causing alterations in the relative proportions of the main microbiota phyla [48]. Chronic stress is linked to decreased fecal lactobacilli in rhesus macaques experiencing maternal separation early in life, concomitant with an increase in offspring stress-related behaviors [43]. Furthermore, the transfer of maternal vaginal microbiota from stressed dams to non-stressed pups resulted in an alternation in their response to stress later in life [49]. In humans, infants of mothers with high cumulative stress levels during pregnancy had an altered gut microbiota composition with lower levels of lactobacilli and bifidobacteria, higher levels of potentially pathogenic bacterial taxa, and an increase in maternally reported adverse health symptoms [50].

There is growing evidence to suggest that manipulating the gut microbiota through probiotics could modulate stress-related behavior and HPA axis activity [45]. To date, the focus has been on bifidobacteria and lactobacilli, with both preclinical and clinical studies demonstrating promising effects on stress and psychiatric disorders such as anxiety and depression [23][46][51]. In this regard, preclinical models have shown beneficial effects of bifidobacteria and lactobacilli to ameliorate stress-induced behavioral alterations across the lifespan, indicative of a link between the gut microbiota and the stress response. For example, *Companilactobacillus farciminis* prevented the hyperactivation of the HPA axis elicited by acute stress, which the authors hypothesized was a result of the prevention of excessive gut permeability associated with acute stress [52]. Sprague Dawley rats exposed to chronic restraint stress also showed improved anxiety- and depression-like behavior and improved cognitive function following administration of *Lactobacillus helveticus* MCC1848 [53]. *Lactiplantibacillus plantarum* supplementation alleviated heightened stress responses as a result of both chronic unpredictable stress and sleep deprivation stress [54]. Supplementation with *Bifidobacterium* spp. has also been reported to alleviate stress-induced behavioral alterations in preclinical models [55][56]. Likewise, *L. paracasei* Lpc-37 attenuated anxiety- and depression-related behavior in mice following chronic stress and reduced corticosterone[2].

Moving from preclinical to clinical evidence, probiotics have been proven to have some success in ameliorating mood in a number of clinical studies [57][58]. The combination of *L. helveticus* R0052 and *B. longum* R0175 are probably among the best investigated and although there are some conflicting results, studies indicate that the combination can reduce stress and anxiety[3]. Improvements in mood scores were observed in elderly participants following administration with a milk drink containing *Lacticaseibacillus casei*, proving most beneficial in the participants that reported the lowest mood scores at baseline [59]. A multi-species combination of *Streptococcus thermophilus*, *Lactobacillus delbrueckii* subsp. *bulgaricus*, *Lactococcus lactis*, *Lactobacillus acidophilus*, *L. plantarum*, *Bifidobacterium animalis* subsp. *lactis* and *Limosilactobacillus reuteri* administered to healthy participants elicited anxiolytic effects [60], whereas another multi-species combination (nine strains, including *Lactobacillus* (*sensu lato*), *Lactococcus*, and *Bifidobacterium*) ameliorated cognitive reactivity to sad mood in healthy participants [61]. Of note, one later study using the same combination demonstrated that the neurocognitive benefits of this multi-species probiotic became evident only when the participants were stressed, highlighting the need to carefully characterize study populations [62]. A multi-species combination (containing *L. fermentum* LF16, *Lacticaseibacillus rhamnosus* LR06, *L. plantarum* LP01, and *B. longum* BL04) induced significant improvements in mood, with a reduction in depressive mood state, anger, and fatigue, and an improvement in sleep quality in healthy volunteers [63]. *L. plantarum* DR7 administration to stressed adults alleviated stress and anxiety, as well as improving several aspects of memory and cognition, enhanced serotonergic signaling, and decreased plasma cortisol and proinflammatory cytokines [64]. Intake of *L. plantarum* HEAL9 also led to a significant decrease in the plasma levels of two inflammatory markers (soluble fractalkine and CD163) following exposure to an acute stress test [65]. A 12-week intervention with *Lactobacillus gasseri* and *B. longum* also resulted in positive changes in stress and salivary cortisol measurements and concomitant improvements in immune response in healthy participants [66]. Four-week consumption of *B. longum* 1714 attenuated cortisol output and subjective anxiety in response to the cold pressor test[4]. Similarly, *L. paracasei* Lpc-37 reduced self-reported perceived stress in healthy males compared to the placebo after five-week consumption[5]. Healthy medical students undergoing university

examinations had reduced levels of stress following the consumption of a fermented milk containing the probiotic *L. casei* Shirota [67]. Furthermore, increases in salivary cortisol reported during an exam stress period were also reduced in a healthy student population supplemented with *L. plantarum* 299v [68]. A multi-species probiotic administered to healthy college students was found to improve panic anxiety, neurophysiological anxiety, negative affect, worry, and increase negative mood regulation [69]. Further, supplementation with *L. casei* Shirota [70] and *Bifidobacterium bifidum* R0071 [71] reduced the physical symptoms of exam stress, including the onset of stress-induced gastrointestinal symptoms and colds. Finally, an open-label study conducted in highly stressed information technology specialists found that administration of *L. plantarum* PS128 improved several self-reported and objective measures of mood, anxiety, stress, and sleep [72].

Taken together, these examples highlight significant results and describe an intriguing role of probiotics in mood, anxiety, stress, and related behaviors such as sleep. A recent meta-analysis demonstrated that probiotic consumption could result in a reduction of subjective stress levels in healthy volunteers and may alleviate stress-related subthreshold anxiety and depression levels [57]. However, further clinical studies are required to provide a deeper understanding of the strain specificity and mechanisms of action of probiotics to help fully realize their role in stress management and the relief of the symptoms of anxiety.

3.2. Depression and Probiotics

Major Depressive Disorder (MDD) is a common psychiatric disorder characterized by depressed mood or significantly reduced pleasure or interest in all activities and is currently a leading cause of disability worldwide. Emerging evidence shows that the dysfunction of the gut–brain axis may be implicated in the etiology of depression. In support of this, the gut microbiota are impacted by MDD and associated with changes to gut epithelial permeability and increased systemic inflammation with elevated levels of C-reactive protein, IL-1β, IL-6, and TNFα in depressed patients compared with healthy controls [73]. Furthermore, the “leaky gut” phenomenon resulting from disrupted gut barrier function is proposed to contribute to MDD. In this context, MDD patients show elevated serum concentrations of immunoglobulin (Ig)-M and IgA against lipopolysaccharides of Gram-negative bacteria compared to healthy controls [74], suggesting an increase in bacterial translocation from the gut and subsequent inflammatory response, potentially contributing to an MDD phenotype.

Preclinical models of depression, such as the maternal separation model [75] and the Flinders-sensitive rat model [76], have demonstrated alterations in the gut microbiota composition and inflammation. In humans, many studies have examined alterations in the gut microbiota in MDD patients compared to healthy controls [77][78][79][80]. Specifically, MDD patients are reported to have an altered gut microbial compositional profile relative to healthy controls [79][80][81]. Patients with MDD have been reported to have reduced abundances of Bacteroidetes, Firmicutes, and Actinobacteria with a concomitant outgrowth of Proteobacteria [80][81], and increased abundance levels of *Alistipes* spp. [79]. The Flemish Gut Flora project provided further associations between the gut microbiota profile in a depressive cohort by highlighting the absence of *Coprococcus* and *Dialister* species in patients with depression [82]. However, several variations have been reported across these studies, which may be due to the small sample sizes or the effects of adjunct medications [46].

The use of probiotics for the reduction of symptom severity in MDD has gained attention in recent years, indicated by increasing numbers of preclinical and clinical studies that have supported the anti-depressive efficacy of probiotics. Accumulating preclinical evidence indicates that single-strain or multi-species preparations may be effective in improving the behaviors related to depression (reviewed in [46]). In a recent study, a multi-species probiotic combination of *L. plantarum* LP3, *L. rhamnosus* LR5, *B. lactis* BL3, *B. breve* BR3 and *Pediococcus pentosaceus* PP1 alleviated depressive-like behaviors and decreased corticosterone levels in mice subjected to restraint stress [83]. Similarly, *L. plantarum* WLPL04 alleviated anxiety- and depressive-like behaviors and chronic stress-induced cognitive dysfunction in mice, while also reversing abnormal alterations in the composition of the gut microbiota [84].

In humans, administration of *B. longum* NCC3001 for six weeks to adults with irritable bowel syndrome (IBS) and mild to moderate anxiety and/or depression reduced depression scores and enhanced the participants' quality of life, which was associated with alterations in brain activation patterns in the limbic system. No improvement in anxiety scores were observed in this cohort [85]. Another study investigated the effect of *B. coagulans* MTCC 5856 in patients experiencing co-morbid IBS symptoms with MDD and found that the probiotic significantly improved symptoms of both depression and IBS [86]. Slykerman and colleagues found that *L. rhamnosus* HN001 supplementation during pregnancy resulted in a significant reduction of postnatal depression and anxiety symptoms [87]. An improvement in cognition was reported in a cohort of depressed patients receiving *L. plantarum* 299v compared to the placebo group [88]. MDD patients who were administered *L. acidophilus*, *L. casei*, and *B. bifidum* for eight weeks also reported ameliorations in self-reported depression scores [89]. In patients with MDD who were taking antidepressant drugs for three months or more, consumed the combination of *L. helveticus* R0052 and *B. longum* R0175. This resulted in significantly reduced depressive symptoms as measured using the Beck Depression Inventory (BDI), compared to the placebo group[3]. Finally, an open-label study conducted in patients with treatment-resistant depression highlighted the potential of probiotics as an adjunct therapy with antidepressant drugs [90].

Further evidence to support these clinical findings are reported in several systematic reviews [91][92][93]. However, it is important to note that several intervention studies failed to demonstrate any beneficial effects on improving overall mood (reviewed in [94][95][96]). It is evident from the preclinical research that specific bacterial strains play a role in ameliorating depressive-like behaviors, and certain clinical studies have demonstrated a role for probiotics towards alleviating symptoms of depression; however, the exact bacterial species and/or strains and mechanisms underpinning their beneficial effects remain unclear. Nevertheless, current research highlights the importance of a healthy microbiome for patients suffering from depression. Future studies into the strain-dependent nature of putative probiotics in patients with clinically diagnosed MDD are warranted to evaluate their therapeutic potential.

4. Conclusions

The promise of probiotic treatments for MDD is complicated by the heterogeneous nature of both the gut microbiota composition and depressive symptoms in the clinical setting, depression subtypes, and probiotic formulations. However, despite these obstacles, selected probiotics have been shown to improve symptom severity

in mood disorders and so there is promise that early interventions with probiotics to restore the gut microbiota composition could reduce the risk of the development of mood disorders such as depression and anxiety in later life[1]. Further clinical investigations into the role of probiotics on mental and brain health and to investigate optimal probiotic composition, dosage and duration of supplementation, employing high quality randomized, double-blind, placebo controlled clinical trials in different populations, are essential and certainly warranted.

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