Beneficial Effects of Probiotics, Prebiotics, Synbiotics, and Psychobiotics in Inflammatory Bowel Disease

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Abstract: Inflammatory bowel disease (IBD) is a group of diseases characterized by inflammation of the small and large intestine and primarily includes ulcerative colitis and Crohn’s disease. Although the etiology of IBD is not fully understood, it is believed to result from the interaction of genetic, immunological, and environmental factors, including gut microbiota. Recent studies have shown a correlation between changes in the composition of the intestinal microbiota and IBD. Moreover, it has been suggested that probiotics and prebiotics influence the balance of beneficial and detrimental bacterial species, and thereby determine homeostasis versus inflammatory conditions. In this review, we focus on recent advances in the understanding of the role of probiotics, prebiotics, and synbiotics in functions of the gastrointestinal tract and the induction and maintenance of IBD remission. We also discuss the role of psychobiotics, which constitute a novel class of psychotropic agents that affect the central nervous system by influencing gut microbiota.

Key Words: Crohn’s disease, intestinal microbiota, probiotics, prebiotics, ulcerative colitis

The gastrointestinal tract (GIT) is colonized by a wide variety of microorganisms, which constitute gut microbiota. Microorganisms begin to settle in the GIT at birth, but the development of the microflora and the formation of intestinal barrier is a gradual process. The relationship between the host and the gut microbiota is most commonly referred to as commensalism, where one organism benefits from the other without affecting it. This specific microsystem evolved over several million years. The bacterial flora is involved, among others, in the renewal of intestinal epithelial cells, metabolism of food ingredients, and the modulation of the immune system, yet equally important is the influence of bacterial flora on peristalsis.

GIT of adults is colonized by approximately 10^{14} different kinds of bacterial cells (i.e., 10 times more than the total number of cells constituting the human body), representing about 500 strains that belong to 40 to 50 families. Gut microbiota of adults is dominated by 4 main groups of bacteria belonging to the genera Bacteroidetes (23%), Firmicutes (64%), Proteobacteria (8%), and Actinobacteria (3%). Of note, bacteria, which are part of the microflora, have the ability of rapid growth and adhesion to the intestinal wall, and thus they can avoid leaching out of the body.

Bacteria that have the ability to produce enzymes facilitating the distribution and absorption of nutrients are the most advantageous. Also important are the species forming the so-called “useful environment,” such as Lactobacillus acidophilus, Lactobacillus rhamnosus, Streptococcus salivarius, which have the ability to defend against bacteriophages and to weaken acute immune response. These microorganisms also have a large genetic variation, allowing them to survive in everchanging environment and adapt to new conditions.

Microbiota plays a number of functions within GIT. The immunomodulatory role, among others, relies on their influence on cytokine levels and interaction with gut-associated lymphoid tissue, which is the biggest lymphatic organ in the human body that produces 70% to 80% of the immune cells. Intestinal bacteria also play protective functions, through competition with pathogenic bacteria for receptors on the surface of the intestinal epithelium and nutrients in the environment. Moreover, gut microbiota produce a number of antimicrobial agents (e.g., bacteriocins). Of note, they also inhibit the growth of bacteria synthesizing carcinogens, such as Citrobacter rodentium, Streptococcus bovis, and Bacteroides spp., and some of them are even able to metabolize dietary carcinogens. Finally, gut microbiota plays an important structural role, which strengthens the tightness of the intestinal barrier by affecting the expression of some structural proteins constituting tight junctions between enterocytes and induces the synthesis of protective immunoglobulin A. In addition, intestinal bacteria exhibit many metabolic functions, such as affecting proliferation and differentiation of intestinal epithelial cells by supplying energy source (such as butyrate and short-chain fatty acids [SCFAs]) to the epithelium. They are also...
involved in the transformation of steroids and fatty acids, as well as in fermentation of dietary fiber and ions. In addition, intestinal bacteria synthesize several B-group vitamins and vitamin K.\textsuperscript{9}

GUT MICROBIOTA VERSUS IBD: FRIENDS OR FOES?

Inflammatory bowel diseases (IBD) refer principally to 2 chronic diseases that manifest with intestinal inflammation: ulcerative colitis (UC) and Crohn’s disease (CD). The incidence of IBD is increasing, in particular, in developed countries. Although the etiology of these inflammatory disorders is not fully understood, there is a growing body of evidence that IBD morbidity is associated largely with genetic predisposition.\textsuperscript{10} However, additional factors may be involved, such as diet, tissue damage associated with disturbance in the immune system, and abnormal intestinal microflora (quantitatively and qualitatively), what has been confirmed in murine models of IBD.\textsuperscript{10} Noteworthy, genetic and microbiota-related backgrounds of IBD may be linked. Studies have shown that people with CARD15/NOD gene mutations, which rely on decreased activation of NF-kB, reduction of proinflammatory cytokine production, and defensin secretion are predisposed to CD development.\textsuperscript{11} It has been shown that these mutations promote an increase in the number of bacteria in the distal ileum and the development of inflammation.\textsuperscript{12}

However, gut microflora may trigger changes leading to IBD. One hypothesis suggests that there is an excessive activation of gut-associated lymphoid tissue, in response to subject’s own intestinal microflora; this has been supported by experiments performed on laboratory animals.\textsuperscript{13} More specifically, transgenic mice lacking IL-2 and IL-10 housed in sterile conditions did not show the development of such inflammatory disorders. In contrast, after the introduction of physiological and nonpathogenic microflora to the environment, the inflammatory process occurred.\textsuperscript{14} Other studies found that the intervention in the intestinal microbiota by means of antibiotics significantly reduces inflammation in CD.\textsuperscript{15} Furthermore, it has been shown in patients with CD that the transfer of the contents of the ileostomy to a healthy segment of the intestine of the same patient leads to the development of inflammation, what suggests a considerable share of microbiota in the etiology of IBD.\textsuperscript{16}

The microorganism widely suspected to be involved in the initiation and development of IBD is Mycobacterium paratuberculosis. It regularly occurs in the intestinal biopsies of patients with IBD and the milk of nursing mothers diagnosed with CD; the antibodies against Mycobacterium avium paratuberculosis spp. have been detected in more than 83% subjects with CD.\textsuperscript{17} Moreover, Mycobacterium is involved in the initiation of John’s disease occurring in ruminants and symptomatically similar to CD.\textsuperscript{17,18} Of note, Mycobacterium often exists within GIT in humans without any IBD symptoms. However, there have been no studies so far that would use Mycobacterium as a diagnostic tool for early detection of IBD or clearly link these bacteria with changes within the immune system and the development of the disease.

Other potential etiologic factors for IBD may include Clostridium Mycobacterium species, Mycobacterium fortuitum and Mycobacterium kansasi\textsuperscript{19} and pathogenic strains of Escherichia coli, primarily O157 and H7.\textsuperscript{20} The latter produce enzymes that break down mucus, which forms a protective gel layer within GIT and constitutes a semipermeable barrier between the lumen and the epithelium. The changes in the mucus barrier increase permeability for bacteria and their metabolites that cause damage of epithelial cells and lead to an inflammatory process in patients with UC.\textsuperscript{21} Whereas hyperproduction of mucins and abnormal glycosylation is observed in patients with CD.\textsuperscript{22,23} Moreover, hydrogen sulfide produced by these bacteria has a negative influence on the metabolism of SCFAs. It has been shown in patients with UC that the fatty acid metabolism disorder leads to impaired secretion of intestinal epithelial protective mucus and thus exacerbates inflammation.\textsuperscript{24}

PROBIOTICS

Probiotics, from the Greek “pro bios,” meaning “for life,” according to the definition of the World Health Organization and the Food and Agriculture Organization of the United Nations are living microorganisms which, when administered in adequate amounts, confer a health benefit to the host. The first observation of the therapeutic effect of bacteria was made by the “grandfather” of modern probiotics, Ilya Mechnikov, a Nobel laureate in Medicine in 1908. Mechnikov was the first to draw attention to the relationship between a very good general state of health and longevity of Bulgarian rural population and systematically ingested sour milk containing lactic acid bacteria (Lactobacillus), which he called “the Bulgarian bacillus.”\textsuperscript{25}

Presently, the mode of action of probiotics is not fully understood. Nevertheless, some of the most common uses for probiotics include the treatment of inflammatory disorders, such as arthritis,\textsuperscript{26} radiation,\textsuperscript{27} and NSAID-induced enteropathy,\textsuperscript{28} antibiotic-induced diarrhea,\textsuperscript{29} chemotherapy-induced mucositis,\textsuperscript{30} poultice,\textsuperscript{31} and UC\textsuperscript{2,23} and CD.\textsuperscript{34,35} Noteworthy, studies on the composition of intestinal microflora showed that patients with UC and CD had an increased number of aerobic bacteria, e.g., E. coli, and anaerobic bacteria of the genus Bacteroides, and a decreased number of microorganisms of the genus Lactobacillus and Bifidobacterium,\textsuperscript{36} which suggests potential benefits of probiotics use in IBD therapy. However, application of a nonpathogenic E. coli Nisle 1917 strain in patients with CD did not cause any significant differences in the duration of remission compared with the control group. In contrast, E. coli Nisle 1917 application in patients with UC worked as effectively as mesalazine therapy alone\textsuperscript{37} (Table 1). Moreover, administration of Saccharomyces boulardii strain with mesalazine in patients with CD significantly reduced the incidence of remission compared with mesalazine-treated group.\textsuperscript{38}

In 2013, Shadnoush et al\textsuperscript{47} reported that Bifidobacterium and Lactobacillus, administered in the form of probiotic yogurt exert anti-inflammatory effects. Two hundred ten adult patients in IBD remission and 95 controls received either probiotic or plain yogurt for life.
TABLE 1. Effects of Probiotics in Patients with CD and UC

<table>
<thead>
<tr>
<th>Disease</th>
<th>Probiotic(s) Strain</th>
<th>Participants and Duration of Study</th>
<th>Dose of Probiotics</th>
<th>Main Findings</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>Saccharomyces boulardii</td>
<td>32 adults; 6 mo</td>
<td>1 g daily</td>
<td>Maintenance of remission</td>
<td>38</td>
</tr>
<tr>
<td>L. rhamnosus GG</td>
<td>45 adults; 12 mo</td>
<td>No data</td>
<td>No effect on recurrence</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>L. rhamnosus GG</td>
<td>11 adults; 6 mo</td>
<td>2 x 10^9 CFU daily</td>
<td>No effect on moderate to active disease activity</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>L. rhamnosus GG</td>
<td>75 children; 2 yr</td>
<td>1 x 10^10 CFU twice daily</td>
<td>No effect on recurrence in pediatric patients</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Lactobacillus acidophilus (johnsonii) La1</td>
<td>98 adults; 6 mo</td>
<td>2 x 10^9 CFU daily</td>
<td>No effect on postoperative recurrence</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Lactobacillus acidophilus (johnsonii) La1</td>
<td>70 adults; 12 wk</td>
<td>1 x 10^10 CFU daily</td>
<td>No effect on postoperative recurrence</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>UC</td>
<td>Escherichia coli Nissle 1917</td>
<td>116 adults; 12 mo</td>
<td>5 x 10^10 CFU twice daily (4 capsules)</td>
<td>Maintenance of remission</td>
<td>32</td>
</tr>
<tr>
<td>Escherichia coli Nissle 1917</td>
<td>327 adults; 12 mo</td>
<td>200 mg once daily</td>
<td>Maintenance of remission</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Enterococci, Bifidus, Lactobacillus</td>
<td>30 adults; 8 wk</td>
<td>1.26 g daily</td>
<td>Maintenance of remission</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Bifidobacterium brevis, Bifidobacterium bifidum, Lactobacillus acidophilus</td>
<td>21 adults; 12 mo</td>
<td>100 mL daily</td>
<td>Maintenance of remission</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>L. rhamnosus GG</td>
<td>187 adults; 12 mo</td>
<td>18 x 10^9 CFU daily</td>
<td>Maintenance of remission</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Bifidobacterium longum</td>
<td>18 adults; 4 wk</td>
<td>2 x 10^11 CFU daily</td>
<td>Decrease in inflammation</td>
<td>46</td>
<td></td>
</tr>
</tbody>
</table>

CFU, colony-forming unit.

yogurt. The levels of IL-1β, TNF-α, and C-reactive protein in serum were significantly decreased in the group receiving probiotic yogurt after 8 weeks of administration, whereas IL-6 and IL-10 concentrations were significantly increased after the treatment when compared with the placebo group. These results suggest that probiotics may contribute to the maintenance of the homeostasis in GIT and regulate pro- and anti-inflammatory responses of the intestinal immunocytes. Another study that involved 21 patients with UC showed that Bifidobacteriа-fermented milk administered once per day in a volume of 100 mL for 1 year has a possible preventive effect on recurrence of UC and helps maintaining its remission.44 Furthermore, Zocco et al investigated the effect of L. rhamnosus GG, a strain of L. rhamnosus isolated in 1983, on IBD symptoms. In this study, executed on a group of 187 patients with UC, the effect of the administration of Lactobacillus GG and Lactobacillus GG in combination with mesalamine versus mesalamine alone have been compared. It has been shown that the combined treatment is more effective in prolonging the relapse-free time than the treatment with Lactobacillus GG and mesalazine alone.

Most of the presently published trials on probiotics were carried out using a preparation named VSL#3, containing 8 strains, namely Lactobacillus casei, Lactobacillus plantarum, L. acidophilus, Lactobacillus bulgaricus, Bifidobacterium longum, Bifidobacterium brevis, Bifidobacterium infantis, and Streptococcus thermophilus. It has been found that the administration of VSL#3 greatly increased the secretion of IL-10, IL-1β, and inhibited the production of IL-12.48 In the in vitro studies, stimulation of human lymphoid and myeloid dendritic cells led to the induction of IL-10 and inhibition of IFN-γ release, and the Th1-type cellular response. It was also found that the use of VSL#3 strengthens the integrity of the intestinal epithelial barrier by increasing the expression of proteins responsible for the formation of tight junctions and a reduction of the number of apoptotic epithelial cells.49 In children with UC, administration of VSL#3 resulted in the induction and maintenance of remission (92.8%), compared with the placebo group.50 Moreover, according to a recent study conducted by Shen et al.,51 VSL#3 has beneficial effect on the induction and the maintenance of UC remission in adults. To date, the role of VSL#3 in the treatment of CD has not been investigated.52,53 However, VSL#3 was found to increase the variety of bacteria species in GIT of patients with IBD.54

PREBIOTICS

Prebiotics are defined as nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in GIT, and thus improve the host’s condition.55 These functional food components include oligosaccharides, which further divide into fructo-oligosaccharides (FOS) (oligofructose and inulin), galacto-oligosaccharides (lactulose), and gluco- and xylo-oligosaccharides. The main features of prebiotics are their resistance to digestive enzymes produced by the human body, while remaining susceptible to colonic microflora fermentation.
Long-chain oligosaccharides (e.g., inulin) and short-chain oligosaccharides (e.g., oligofructose) are neither digested nor absorbed by the upper GIT. However, they undergo fermentation in the colon by anaerobic bacteria, which metabolize these oligosaccharides to SCFAs, such as acetate, propionate, and butyrate, and selectively stimulate the growth of bifidobacteria. This leads to bifidogenic effects and a decrease in intraluminal pH.\textsuperscript{56,57} The latter is particularly important for the prevention from diarrhea and inhibition of some strains of potentially pathogenic bacteria, e.g., \textit{Clostridium sp}\textsuperscript{56} (Tables 2 and 3).

Gibson et al\textsuperscript{66} demonstrated that the administration of FOS in volunteers at a dose of 15 g per day for 15 days significantly increased the number of bifidobacteria in the feces, whereas the population of \textit{Bacteroides}, \textit{Fusobacteria}, and \textit{Clostridium} decreased. The numbers of bacteria of the genus \textit{Lactobacillus} and \textit{E. coli} remained unchanged. In contrast, in a recent, randomized, double-blinded study in 103 patients with CD, the administration of FOS had no statistically significant effect compared with the control group.\textsuperscript{66}

Muccioli et al\textsuperscript{70} showed that the improvement of the structure and function of the intestinal barrier after the application of prebiotics is associated with a decreased activity of the endocannabinoid system (ECS) in the gut and an increased level of GLP-2, what stimulates synthesis of proteins forming tight junctions. However, the most important mechanism of prebiotic action involves SCFAs. It has been demonstrated that increasing the SCFAs concentration in the intestine (as a result of the consumption of prebiotics) enhances growth of protective bacteria (symbionts), while limiting the growth of pathobionts.\textsuperscript{71} SCFAs improve mucosal barrier function, increase intestinal mucus synthesis, stimulate the production of regulatory T cells (Treg) and immunosuppressive cytokines (e.g., IL-10) and reduce the levels of proinflammatory mediators.\textsuperscript{71,72} Noteworthy, there is also evidence that acetate, propionate, and butyrate administration alone or as a mixture results in an increased number of Treg cells and increased level of IL-10 within the colonic interstitium.\textsuperscript{72} Smith et al\textsuperscript{72} suggested that SCFAs, in particular propionate, exert their effects by inhibiting histone deacetylases 6 and 9 in a GPR43-mediated process.

**SYNBIOTICS**

A combination of prebiotics and probiotics, named synbiotics, is believed to exert synergistic effects. Namely, synbiotics influence the development of beneficial intestinal microflora through prebiotics, whereas probiotics inhibit the growth of pathogenic bacteria.

Synbiotics help reduce the concentration of undesirable metabolites, including nitrosamines, inactive carcinogens, and prevent constipation and diarrhea of various etiologies.\textsuperscript{73,74} For example, studies in rats whose diet included inulin, oligofructose, \textit{L. rhamnosus}, and \textit{Bifidobacterium lactis} showed an increased level of immunoglobulin A in the gut.\textsuperscript{75} Because synbiotics are able to reduce cholesterol levels and blood pressure,\textsuperscript{76} they are used in the treatment of patients with liver disease.\textsuperscript{77} Moreover, most of the synbiotics improve absorption of calcium, magnesium, and phosphorus.\textsuperscript{78}

Synbiotics also contribute to the reduction of harmful microflora, such as \textit{Clostridium perfringens} and other endopathogens.\textsuperscript{75} In line, administration of a combination of \textit{Lactobacillus paracasei} and FOS led to an increase in \textit{Lactobacillus} and \textit{Bifidobacterium} and a decrease in \textit{Clostridium} and \textit{Enterobacterium}.\textsuperscript{79} It has also been shown that the combination of \textit{L. paracasei} and maltodextrin resulted in a decrease in \textit{E. coli} colonization in the jejunal piglets.\textsuperscript{79}

Several studies have been undertaken in patients with IBD. In a double-blind randomized controlled trial, Furrie et al\textsuperscript{66} demonstrated that administration of \textit{L. rhamnosus} GG for 12 weeks at a dose of 10 billion CFU twice daily to patients with CD resulted in a significant improvement of clinical symptoms and a decrease in fecal calprotectin, an important marker of intestinal inflammation.

**TABLE 2. Main Benefits of Prebiotics and Potential Mechanisms of Their Action in Animal Models of IBD**

<table>
<thead>
<tr>
<th>Animal Model</th>
<th>Prebiotics</th>
<th>Dose of Prebiotics</th>
<th>Effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSS-induced colitis in rats</td>
<td>Inulin</td>
<td>1% in drinking water, or 400 mg/kg</td>
<td>Reduction of colitis severity</td>
<td>58</td>
</tr>
<tr>
<td>TNBS-induced colitis in rats</td>
<td>Galacto-oligosaccharides</td>
<td>4 g/kg</td>
<td>No reduction of colitis; modification of gut microflora</td>
<td>59</td>
</tr>
<tr>
<td>DSS-induced colitis in rats</td>
<td>FOS</td>
<td>63 g/kg</td>
<td>No reduction of colitis</td>
<td>60</td>
</tr>
<tr>
<td>HLA-B27 transgenic rats</td>
<td>Inulin and oligofructose</td>
<td>5 g/kg</td>
<td>Reduction of colitis; decrease in proinflammatory cytokines</td>
<td>61</td>
</tr>
<tr>
<td>HLA-B27 transgenic rats</td>
<td>Inulin and fructo-oligosaccharides</td>
<td>8 g/kg</td>
<td>Increase in \textit{Bifidobacterium spp}; Reduction of chronic intestinal inflammation</td>
<td>62</td>
</tr>
<tr>
<td>DSS-induced colitis in rats</td>
<td>Goat’s milk oligosaccharides</td>
<td>20 g/kg</td>
<td>Reduction of colitis; recovery of damaged colonic mucosa</td>
<td>63</td>
</tr>
<tr>
<td>DSS-induced colitis in rats</td>
<td>Lactulose</td>
<td>300–1000 mg/kg</td>
<td>Reduction of colitis in a dose-dependent manner</td>
<td>64</td>
</tr>
</tbody>
</table>

DSS, dextran sulfate sodium; TNBS, 2,4,6-trinitrobenzenesulfonic acid.
indicated that the prebiotic Synergy 1, in combination with *Bifidobacterium longum*, led to an improvement of sigmoidoscopy scores and a decrease in β-defensin, TNF-α, and IL-1α in biopsy samples from patients with UC. The study provides strong preliminary evidence that synbiotic administration may be beneficial in IBD treatment. In another trial,80 35 patients with CD were divided into 2 groups, those who received a combination of *Bifidobacterium longum* and a prebiotic Synergy 1 (containing FOS/Inulin mix) and a placebo group. A significant histological improvement was observed in the synbiotic group compared with controls (tissue samples for histological evaluation were collected at initiation of the study and after 3 and 6 mo). Although the synbiotic had little effect on mucosal IL-18, IFN-γ, and IL-1β, there was a significant decrease in TNF-α expression after 3 months (P = 0.041). Interestingly, the level of TNF-α did not change further after 6 months of the symbiotic treatment. These studies show the potential beneficial effect of synbiotics, but their role in anti-IBD therapy remains to be determined.

**PSYCHOBIOTICS**

Frequent coexistence of intestinal disorders, such as irritable bowel syndrome or IBD and mental disorders, especially depression and anxiety,81 suggests a specific connection between GIT and the central nervous system (CNS), often termed the gut–brain axis.82 The importance of the microflora in the regulation of GIT function reflects the need to extend this concept to a term microbiota–gut–brain axis (MGBA).83 MGBA constitutes a bidirectional communication pathway including neural, endocrine, and immune mechanisms. Neuronal mechanisms include the enteric nervous system with several neurotransmitters and neuromodulators, such as serotonin, acetylcholine, and corticotropin-releasing factor (Fig. 1). The latter is particularly noteworthy because of its participation in the increase of the permeability of the intestinal barrier under stress conditions.84,85 The autonomic nervous system, which is another component of MGBA, consists of sympathetic and parasympathetic branches. Several studies have shown that proinflammatory cytokines may have a direct effect on the CNS through the activation of afferent nerve fibers, which transmit impulses to the specified regions of the brain, e.g., the solitary tract nucleus.86 In turn, efferent innervation can mediate the inflammatory response, affecting inter alia the α-7 nicotinic receptor in immune cells, thereby reducing cytokine secretion.87 A crucial role is played here by the vagus nerve, a parasympathetic branch of autonomic nervous system, which constitutes a vital line of communication between the gut microbiota and CNS, as described below.

The endocrine factors regulating MGBA include, among others, cortisol. Its secretion is regulated by the hypothalamic–pituitary–adrenal axis under stress conditions. Cortisol may affect immune cells by modulating the secretion of cytokines, as well as the composition and functions of the microbiota. However, intestinal bacteria have the ability to produce a number of neurohormones, such as serotonin, melatonin, γ-aminobutyric acid (GABA), catecholamines, histamine, acetylcholine, and SCFAs. All of these likely participate in the communication between the gut microbiota and may also exert peripheral and systemic action and affect behavior and brain function.88

GABA, which is the main inhibitory neurotransmitter in the CNS, seems to play the most important role in physiological processes within MGBA. Changes in the expression of GABA receptors are associated with the pathogenesis of anxiety and depression that often co-occur with functional GI disorders. Noteworthy, the effect of a prebiotic *L. rhamnosus* (JB-1) on the expression of GABA receptors in the CNS has been demonstrated in the animal model of depression. This modulation occurs through the vagus nerve. In addition, the administration of the probiotic resulted in the reduction of the content of corticosterone and restricted behaviors associated with depression and anxiety, hence the term psychobiotic has been applied. Importantly, neurochemical and behavioral influences of JB-1 were absent in mice after vagotomy, indicating that the vagus nerve is a key element of communication between intestinal microbiota and CNS.89

In another study, a mouse model of colitis induced by dextran sulfate sodium has been used to assess the influence of the strain *Bifidobacterium longum* NCC 3001 on animal behavior.90 Administration of the probiotic decreased anxiety behavior in dextran sulfate sodium–treated mice but did not affect intestinal inflammation or the expression of brain-derived neurotrophic factor mRNA.91 As in the previous case, the behavioral changes were
lost in mice after vagotomy. Thus, the anxiolytic effect of *Bifidobacterium longum* NCC 3001 involves vagal integrity and may involve MGBA but is independent of gut immunomodulation or brain-derived neurotrophic factor production.

Wall et al.\(^9^2\) demonstrated that the administration of *Bifidobacterium* strain to mice affects the fatty acid composition of the brain. Mice receiving *Bifidobacterium* for 8 weeks had a higher concentration of arachidonic acid and docosahexaenoic acid, compared with control group. Arachidonic acid and docosahexaenoic acid are important in brain development and play a role in neurotransmission and protection against oxidative stress.\(^9^3,^9^4\)

Microbiota and probiotics may exert an effect on MGBA through the immune system.\(^9^5,^9^6\) A number of studies have shown that intestinal bacteria can reduce the concentration of proinflammatory cytokines, such as TNF-\(\alpha\), IFN-\(\gamma\), and IL-6 and modulate the concentration of anti-inflammatory cytokines, e.g., IL-10.\(^9^7\) The proinflammatory cytokines play a key role in the activation of hypothalamic–pituitary–adrenal axis; namely IL-1\(\beta\), IL-6, and TNF-\(\alpha\) increase the permeability of the intestinal barrier and aggravate inflammation, whereas IFN-\(\alpha\), IFN-\(\gamma\), and TNF-\(\alpha\) activate an enzyme of the kynurenic pathway, indoleamine 2,3-dioxygenase, which transfers tryptophan from the serotonin

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**FIGURE 1.** Bidirectional communication in the MGBA. Microbiota communicates with the gut–brain axis through a direct interaction with mucosal cells through immune cells and neural endings. Gut microbiota dysbiosis results in the synthesis of several microbial compounds, which gain access to the brain through the bloodstream, leading to incorrect gut–brain axis signaling and associated consequences for CNS functions that result in disease states. 5-HT, 5-hydroxytryptamine.
In addition, cytokines can exert a direct effect on the CNS through a variety of mechanisms, including passing through the permeable regions for some cytokines in the blood–brain barrier or by activating the afferent nerve fibers, e.g., the vagus nerve.  

The ECS has also been implicated in the MGBA. ECS consists of the endogenous arachidonate-based lipids, enzymes that synthetize and degrade the endocannabinoids and cannabinoid receptors. At present, it is clear that ECS is involved in maintenance of the gut homeostasis through modulation of GIT motility and anti-inflammatory actions (for review, see Refs. 101–103). Interestingly, it has also been shown that the L. acidophilus strain modulates expression of cannabinoid receptors in the spinal cord. This may give a new insight into the anti-inflammatory actions in the GIT mediated by ECS and encourages more studies to fully understand the complex system linking intestinal microbiota, gut, and brain.

**SUMMARY**

Numerous studies provide valuable information on the biology and function of the intestinal microbiota and the impact of microbiota changes on IBD. Despite available information, we still do not fully understand the mechanisms by which changes in the gut microbiota affect IBD. Clinical trials in humans are small in numbers, thus it is presently difficult to determine the full value of the administration of probiotics, prebiotics, and synbiotics in patients with CD/UC. However, presently available studies have demonstrated that certain bacterial species exert valuable effects on the GIT in IBD and are helpful especially in the maintenance of remission.

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