Gut Microbiota and Pathophysiology of Depressive Disorder

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Keywords

Gut microbiota · Pathophysiology · Probiotics · Major depressive disorder

Abstract

Background: Accumulating evidence has suggested that the bi-directional communication pathway, the microbiota-gut-brain axis, plays an important role in the pathophysiology of many neuropsychiatric diseases including major depressive disorder (MDD). This review outlines current evidence and promising findings related to the pathophysiology and treatment of MDD. **Summary:** There are at least 4 key biological molecules/systems underlying the pathophysiology of MDD: central dopamine, stress responses by the hypothalamic-pituitary-adrenal axis and autonomic nervous system, inflammation, and brain-derived neurotrophic factor. Animal experiments in several depression models have clearly indicated that gut microbiota is closely related to these molecules/systems and administration of probiotics and prebiotics may have beneficial effects on them. Although the results of microbiota profile of MDD patients varied from a study to another, multiple studies reported that bacteria which produce short-chain fatty acids such as butyrate and those protective against metabolic diseases (e.g., Bacteroidetes) were reduced. Clinical trials of probiotics have emerged, and the ma-

jority of the studies have reported beneficial effects on depression symptoms and related biological markers. **Key Messages:** The accumulating evidence suggests that research on the microbiota-gut-brain axis in major depressive disorder (MDD) is promising to elucidate the pathophysiology and to develop novel treatment of MDD, although there is still a long distance yet to reach the goals.

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Introduction

Depressive disorder is a common, debilitating psychiatric disease characterized by depressed mood, anhedonia, altered appetite, sleep disturbance, psychomotor retardation/agitation, fatigue, guilt feeling, loss of concentration, and suicidal ideation with the global point prevalence estimated at 4.4% worldwide [1]. Large-scale clinical trials have revealed that a substantial proportion of patients with major depressive disorder (MDD) fail to respond to, or achieve remission with, the current first-line antidepressants [2]. Also, many patients with MDD show poor adherence to the current antidepressants due to their adverse effects, which requires new treatment strategies with less adversity. However, the pathophysiology of MDD remains elusive, and there is no established

biochemical marker used in the daily clinical setting. This situation may result in part from the heterogeneity of MDD which might include heterogeneous subgroups with different biological mechanisms or combination of them. There are at least 4 promising biological systems/markers to potentially subtype MDD, that is, the dopamine system, stress response by the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system (ANS), chronic inflammatory markers, and dysfunction of brain-derived neurotrophic factor (BDNF) [3–5]. Growing evidence has suggested that altered gut microbiota may be involved in the pathophysiology of depressive disorder [6, 7]. In this review, related evidence is outlined in relation to the pathophysiology of MDD.

Pathophysiology of Depressive Disorder

Dopamine System

The monoamine hypothesis might be the best-known etiological hypothesis for MDD. Any classes of antidepressants exert their effects through increasing monoamine neurotransmitters (serotonin, noradrenaline, and/or dopamine) in the synaptic cleft. Given the findings from *in vitro* studies that first-line antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors inhibit the reuptake of serotonin and noradrenaline, one might suspect that these 2 neurotransmitters play more important roles than dopamine. However, the recent evidence from the cerebrospinal fluid (CSF) suggests its opposite direction. Among monoamine metabolites, homovanillic acid (HVA, a primary dopamine metabolite) but not 5-hydroxyindoleacetic acid (a primary serotonin metabolite), or 3-methoxy-4-hydroxyphenylglycol (MHPG: a primary noradrenaline metabolite), was shown to be significantly reduced in the CSF of MDD patients [8–10]. In line with this, *in vivo* animal studies using microdialysis have demonstrated that many of the SSRIs increase extracellular dopamine as well as serotonin in the prefrontal cortex, despite the fact that SSRIs do not inhibit the reuptake of dopamine *in vitro*. The increase in dopamine could be central to the antidepressant effects [11]. Indeed, at least a portion of MDD is responsive to dopamine agonists [12, 13], and such drugs increase BDNF levels in the cerebral cortex and hippocampus in animal studies [14, 15].

Altered Stress Response

MDD is often induced by chronic stress; therefore, abnormal stress response in the HPA axis is one of the most

extensively studied biological markers for depression [16]. Initially, typical MDD subtypes such as melancholic and psychotic types were found to have enhanced HPA activity due to inadequate negative feedback of the HPA axis detected by hormonal challenge tests such as the dexamethasone (DEX) suppression test and DEX/corticotropin-releasing hormone (CRH) test. In line with this, we also reported enhanced cortisol responses in the DEX/CRH test in Japanese MDD inpatients before treatment and its recovery after treatment [17, 18]. However, subsequent studies have revealed that depressed patients as a whole showed similar [19], or even attenuated [20], cortisol responses as compared to healthy controls in the DEX/CRH test. In these studies, patients had clinical characteristics such as outpatients, chronic cases, depressive patients with psychiatric comorbidity, or long-term sick-leave patients. These inconsistent findings are related to the heterogeneity of the illness. Indeed, atypical depression and other stress-related conditions such as post-traumatic stress disorder, chronic fatigue syndrome, and fibromyalgia are associated with attenuated, rather than enhanced, cortisol responses in the HPA axis [21–23]. It is also well-known that somatic diseases such as Addison's disease and ACTH deficiency, both of which show inadequate cortisol secretion, present psychiatric symptoms similar to MDD. These observations clearly lead to the possibility that HPA axis activity can be a subtyping marker of MDD.

The ANS is another important player in stress response. Imbalance in sympathetic and parasympathetic nervous systems has been suggested in patients with MDD which could be monitored by the heart rate variability [24]. Excessive and attenuated activations of sympathetic and parasympathetic nervous systems, respectively, have been suggested to be underlying in the pathophysiology of MDD. In line, there is some evidence that vagus nerve stimulation is effective in treatment-resistant depression [25], which is closely related to the following gut microbiota described.

Inflammation

Accumulating evidence suggests that a portion of MDD has been reformulated as a chronic inflammatory disease similar to diabetes and coronary heart disease in which pro-inflammatory cytokines such as interleukin (IL)-6, IL-1 β and tumor necrosis factor- α contribute to the disease process [26]. Elevation in peripheral pro-inflammatory cytokines leads to neural inflammation; indeed, we reported increased IL-6 levels in the CSF of patients with MDD [27], which was subsequently confirmed

by a meta-analysis [28]. An important mechanism of cytokine-induced depression is the activation of the tryptophan-kynurenine pathway [29]. In line, we provided evidence supporting the elevated activation of tryptophan-kynurenine pathway by using ^{13}C -tryptophan breath test in patients with MDD [30]. Further, we showed decreased plasma tryptophan levels in patients with MDD [31, 32], which is likely to be due, at least in part, to the enhanced tryptophan-kynurenine pathway. In the brain, kynurenine is converted to quinolinic acid or 3-hydroxykynurenine in microglia, which has neurotoxic effect through the property as an N-methyl-D-aspartate receptor (NMDAR) agonist and is thought to be involved in the pathogenesis of depression.

Brain-Derived Neurotrophic Factor

Several lines of evidence from postmortem studies, animal studies, blood levels, and genetic studies have suggested that BDNF is involved in the pathogenesis of depression and in the mechanism of action of biological treatments of depression [33]. There is convincing evidence that stress reduces the expression of BDNF and that antidepressant treatments increase it [33, 34]. Moreover, glucocorticoid receptor interacts with the specific receptor of BDNF, tropomyosin receptor kinase B (TrkB), and excessive glucocorticoid interferes with BDNF signaling [3, 35, 36]. Altered BDNF function is involved in the structural changes and possibly impaired neurogenesis in the brain of depressed patients. Although BDNF levels seem to be undetectably low in the human CSF, we found reduced BDNF propeptide, which is produced in the processing of pro-BDNF to mature BDNF, in patients with MDD compared with healthy controls [37].

Animal Studies Linking Gut Microbiota and Depressive-Like Behavior

A number of studies on animal models of depressive disorder have thus far been conducted. Here, some of the cornerstone studies are introduced. Sudo et al. [38] provided evidence suggesting the importance of commensal microbiota in the development of healthy stress response in the HPA axis. They found that plasma ACTH and corticosterone elevation in response to restraint stress was substantially higher in germ-free (GF) mice than in specific pathogen-free (SPF) mice. Moreover, GF mice exhibited reduced BDNF expression levels in the cortex and hippocampus relative to SPF mice. The exaggerated HPA stress response by GF mice was reversed by reconstitution

with *Bifidobacterium (B.) infantis*. Further, the enhanced HPA response of GF mice was partly corrected by reconstitution with SPF feces at an early stage but not by any reconstitution exerted at a later stage, indicating that exposure to microbes at an early developmental stage is required for the healthy development of the HPA system. Crumeyrolle-Arias et al. [39] reported heightened anxiety-like behaviors and elevated CRH mRNA expression in the hypothalamus and reduced glucocorticoid receptor mRNA expression in the hippocampus in GF adult rats compared to SPF rats. They observed a significant decrease in HVA-to-dopamine turnover ratio (HVA/dopamine) in the prefrontal cortex, hippocampus, and striatum of GF adult rats compared to SPF rats, suggesting that gut microbes are important in the development of dopaminergic neurochemistry. Also, Liu et al. [40] demonstrated that administration of *Lactobacillus (L.) plantarum* PS128 to GF mice decreased anxiety-like behaviors and that these changes were accompanied by an increase in DA and HVA, as well as an increase in serotonin in the striatum.

In a rat maternal separation (MS) model of depression, altered colonic functions such as increased ion transport and macromolecular permeability, and increased adhesion/penetration of total bacteria were observed together with an elevated corticosterone level in the blood [41]. Probiotic treatment by *L. rhamnosus* R0011 and *L. helveticus* R0052 ameliorated the MS-induced gut functional abnormalities and bacterial adhesion/penetration, and reduced the corticosterone level. In another rat MS model, depression-like behavior, heightened mRNA level of CRH in the amygdala, reduced amount of noradrenaline in the brain, and increased peripheral IL-6 were observed; however, administration of *B. infantis* improved these abnormalities [42]. In another mouse model of depression (exposure to water avoidance stress), pretreatment of a probiotic formulation (*B. longum* R0175 and *L. helveticus* R0052) attenuated the HPA axis and ANS activities in response to water avoidance stress and prevented chronic stress-induced decreased hippocampal neurogenesis and expression changes in hypothalamic genes involved in synaptic plasticity. These central effects were associated with restoration of tight junction barrier integrity in stressed mice [43]. In a rat chronic unpredictable mild stress (CUMS) model, Gu et al. [44] reported that *L. casei* intervention improved the CUMS-induced depression-like behaviors and the gut microbiota structure changes. Further, *L. casei* intervention reversed the CUMS-induced expression changes of monoamines dopamine, noradrenaline, and serotonin, and BDNF and its receptor

TrkB signal molecules. In a chronic social defeat stress model, resilient mice were associated with increased *Bifidobacterium* counts in fecal samples, compared with susceptible mice, and pretreatment of *Bifidobacterium* increased the rate of resilient mice to the stress [45].

Regarding the effect of prebiotics, Savignac et al. [46] examined the effects of fructo-oligosaccharides and galacto-oligosaccharides on the expression of BDNF and NMDAR subunits in the rat brain. Prebiotics increased hippocampal BDNF and NR1 subunit expression relative to controls. Galacto-oligosaccharides, in particular, increased plasma peptide YY which increased BDNF expression in SH-SY5Y cell cultures, suggesting a possibility that symbiotics may enrich the gut microbiota, stimulate gut hormone, and increase BDNF expression in the brain. The same research group subsequently demonstrated that feeding neonatal rats by galacto-oligosaccharides increased a NMDAR (GluN2), a synaptic protein (synaptophysin) and BDNF in the hippocampus of 22-day-old rats [47]. This effect remained at day 56 (26 days after the feeding ceased), suggesting the importance of early exposure to prebiotics in the brain development.

All these observations in animal studies indicate that probiotics and prebiotics may have beneficial effects on behavioral and molecular abnormalities, including monoamines, markers for the HPA axis and ANS, inflammation, and BDNF, which have been postulated to play important roles in the pathophysiology of depression.

Evidence of Altered Gut Microbiota in Depression

Studies on the gut microbiota in MDD are accumulating; however, the results have been diverse from a study to another. Naseribafrouei et al. [48] seem to be the first that reported a comprehensive microbiota profile of fecal samples from MDD patients. They performed an operational taxonomic unit analysis on 16S rRNA sequence data in 37 patients with MDD and 18 controls, and reported that the order *Bacteroidales*, the genus *Alistipes*, and the genus *Oscillibacter* were increased, while the family *Lachnospiraceae* was decreased in their patients compared with the controls. Subsequently, Jiang et al. [49] investigated 46 patients with MDD and 30 healthy controls and found that *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria* were increased, while *Firmicutes* was decreased in their patients compared with the controls. At the genus level, *Enterobacteriaceae* and *Alistipes* were increased and *Faecalibacterium* was decreased. Of note, *Faecalibacterium* counts negatively correlated with de-

pression severity. In a relatively large number of subjects (58 patients and 63 controls), Zheng et al. [50] reported elevated and reduced numbers of *Actinobacteria* and *Bacteroidetes*, respectively. Lin et al. [51] reported that more phylum *Firmicutes*, less *Bacteroidetes*, and more genus *Prevotella*, *Klebsiella*, *Streptococcus*, and *Clostridium XI* were found in MDD patients. The changes of the proportion of *Prevotella* and *Klebsiella* were consistent with Hamilton Depression Rating Scale (HAM-D). However, their study was limited by the small sample size (10 patients and 10 controls). Chen et al. [52] examined the microbiota of first-episode drug-naïve MDD patients with a special attention to sex difference. They recruited 24 female MDD patients and 24 matched healthy controls and 20 male MDD patients and 20 matched controls. Compared with their healthy counterparts, increased *Actinobacteria* and decreased *Bacteroidetes* levels were found in female and male MDD patients, respectively. The most differentially abundant bacterial taxa in female and male MDD patients belonged to phyla *Actinobacteria* and *Bacteroidia*, respectively.

Concerning α -diversity of the microbiota, Jiang et al. [49] reported that treatment-resistant depressed patients showed higher diversity than healthy controls, which was an unexpected finding because higher α -diversity has been considered to be healthy. Other studies reported no significant difference in α -diversity between patients and controls [48, 50].

The operational taxonomic unit analysis based on next-generation sequencing data has a merit in analyzing comprehensive bacteria species; however, it has a disadvantage in quantification of specific bacteria, especially when the number of the bacteria is small, *Lactobacillus* species, for example. We then focused our attention to well-known beneficial bacteria, *Bifidobacterium* and *Lactobacillus* to count them by using the bacterial rRNA-targeted reverse transcription quantitative polymerase chain reaction method [53] in fecal samples of 43 patients with MDD and 57 healthy controls [54]. The patients had significantly lower *Bifidobacterium* counts and tended to have lower total *Lactobacillus* counts than the controls. Frequency of fermented milk consumption was associated with higher *Bifidobacterium* counts in the patients. In subsequent comparison between patients with bipolar disorder and controls, in contrast, we found no significant difference, although we found a significantly negative correlation between *Lactobacillus* counts and sleep disturbance score and a significantly negative correlation between *Bifidobacterium* counts and cortisol levels in the blood of the patients [55].

In a very large microbiome population cohort (Flemish Gut Flora Project, $N = 1,054$), Valles-Colomer et al. [56] studied how microbiome features correlate with quality of life and depression. They found that butyrate-producing *Faecalibacterium* and *Coprococcus* bacteria were consistently associated with higher quality-of-life indicators. *Dialister* and *Coprococcus* spp. were depleted in depression, which was replicated in an independent Dutch sample ($N = 1,064$). They obtained 56 “gut-brain modules” in fecal metagenomes. Among these, they identified the microbial synthesis potential of the dopamine metabolite 3,4-dihydroxyphenylacetic acid as correlating positively with mental quality of life and indicated a potential role of microbial γ -aminobutyric acid production in depression. 3,4-dihydroxyphenylacetic acid is known to be a predominant biologically active catabolite of quercetin glycosides and to have antioxidant potential of the colonic lumen after the ingestion of the quercetin glycoside-rich onion [57].

The cross-sectional nature of these observational studies precludes inference on the cause-effect relationship. However, 2 studies [50, 58] reported that when rats or mice were transplanted with fecal matter from patients with depression, they exhibit depressive and anxiety-like behaviors together with elevated inflammatory status, indicating that altered microbiota in depressed patients has a causal effect.

As described, the findings of microbiota profiles in MDD patients are quite different across the studies. However, there are some consistent points. Multiple studies yielded decreased counts of butyrate-producing bacteria such as *Lachnospiraceae* and *Faecalibacterium* [48, 49, 56], and we found decreased counts of *Bifidobacterium* and *Lactobacillus*, which also produce short-chain fatty acids (SCFAs) [54]. Further, some studies reported decreased *Bacteroidetes* [50–52] which is associated with obesity and diabetes [59, 60]. This may be related to the well-replicated finding of bidirectional association of depression with obesity and diabetes [61].

Clinical Trials of Probiotics

At least 19 double-blind, randomized, placebo-controlled trials (RCTs) examining the effect of probiotics on depressive symptoms in a variety of disease populations or healthy people have been published [62, 63]. Goh et al. [62] concluded that the depression-reducing effect of probiotics was significant in those with clinical diagnosis of MDD whereas such an effect was not significant in the

general population. However, the evidence is still limited. To my knowledge, there are only 6 RCTs using probiotics in patients with MDD. Notably, 3 of the 6 studies were from Iranian research groups.

The first Iranian study of Akkasheh et al. [64] compared 20 patients with MDD (age 20–55 years) receiving an 8-week intervention with *L. acidophilus*, *L. casei*, and *B. bifidum* and 20 patients who received placebo. The probiotic supplement group improved in Beck Depression Inventory (BDI) score better than the placebo group (-5.7 ± 6.4 vs. -1.5 ± 4.8 , $p = 0.001$). Moreover, the insulin resistance marker, hs-CRP concentrations, and glutathione concentrations in the blood were improved in the probiotics group better than the placebo group. The second Iranian study [65] examined the add-on effect of 6-week symbiotic supplementation in 40 MDD patients (mean age of 35 years) with moderately ill (17 item HAM-D scores of 17–23) who had been treated with fluoxetine (20 mg/day) for 4 weeks. Symbiotic supplementation included *L. acidophilus*, *L. casei*, *L. bulgaricus*, *L. rhamnosus*, *B. breve*, *B. longum*, and *Streptococcus* (*S.*) *thermophilus*, and 100 mg fructo-oligosaccharide as prebiotic. There was a slightly but significantly greater reduction in the HAM-D score in the symbiotic (+fluoxetine) treated patients (Mean $\pm$ SD = -19.25 ± 1.71) than the placebo (+fluoxetine) group (Mean $\pm$ SD = -17.75 ± 2.05 ; $p = 0.024$). The third Iranian study [66] compared the effects of probiotic supplementation (*L. helveticus* R0052 and *B. longum* R0175; $N = 28$), prebiotics (galacto-oligosaccharide; $N = 27$), and placebo ($N = 26$) for 8 weeks in patients with MDD who were already treated with antidepressants. Probiotic supplementation resulted in a significant decrease in BDI score ($17.4 \rightarrow 9.1$) compared to the placebo ($18.2 \rightarrow 15.6$) and prebiotic ($19.7 \rightarrow 14.1$) supplementation. There was no significant difference between the prebiotics and placebo groups. Notably, the kynurenine/tryptophan ratio decreased significantly in the probiotic group compared to the placebo group after adjusting for serum isoleucine. In addition, the tryptophan/isoleucine ratio increased significantly in the probiotic group when compared to the placebo group.

Majeed et al. [67] from India recruited 40 MDD patients with comorbid irritable bowel syndrome. Significant improvement in depression severity and irritable bowel syndrome symptoms was observed in the intervention group ($N = 20$) with *Bacillus coagulans* MTCC after 90 days in comparison with the placebo group ($N = 20$). Serum myeloperoxidase, an inflammatory biomarker, was significantly reduced in the probiotic group in comparison with the placebo group. Rudzki et al. [68] from

Poland examined the effect of augmentation of SSRI treatment with probiotic bacteria *L. Plantarum* 299v (LP299v) for 8 weeks on cognitive performance and inflammation-related molecules in MDD patients (mean age 39 years; analyzed for 30 participants in the LP299v group and 30 participants in the placebo group). There was no significant effect of probiotics on the improvement of depressive symptoms assessed with HAM-D. However, the probiotics group showed better improvement in attention task and in episodic verbal learning and memory task, compared to the placebo group. Biochemical monitoring revealed that there was a significant decrease in kynurenine concentration in the LP299v group compared to the placebo group. Reininghaus et al. [69] from Austria reported RCTs on 61 inpatients (mean age of around 30 years) with MDD by probiotics ($N = 28$) or placebo ($N = 33$). The probiotics composed of 9 bacteria species: *B. bifidum* W23, *B. lactis* W51, *B. lactis* W52, *L. acidophilus* W22, *L. casei* W56, *Lactobacillus paracasei* W20, *L. plantarum* W62, *L. salivarius* W24, and *L. lactis* W19. Biotin (vitamin B7) was added on for both groups. The microbiota profile became differed after 4 weeks of treatment, that is, *Ruminococcus gauvreauii* and *Coprococcus* 3 were more abundant, and β -diversity was higher in the probiotics group than the placebo group after 28 days. However, improvement of the psychiatric symptoms was not significantly different. Notably, this study group examined the zonulin level in the blood as a marker of intestinal barrier function; however, they did not find any significant effect of time (before v. after treatment) or treatment (probiotics v. placebo) on the zonulin level.

There are notable other studies that report the beneficial effects of probiotics (*L. casei* Shirota) on perceived stress, stress-induced abdominal dysfunction, and sleep disturbances in healthy populations [70, 71]. The effect of this probiotic on MDD patients has recently emerged, reporting that better response was associated with abundance of *Actinobacteria* including *Bifidobacterium* in the gut microbiota of the patients [72].

Mechanisms

There are many possible pathways linking the gut microbiota and the pathophysiology of MDD. Those related to the dopamine system, stress response, inflammation, and BDNF are described before. Here, I raise only a few additional factors. Animal studies have revealed that chronic stress induces excessive gut permeability (“Leaky

gut”) which allows toxic substances such as lipopolysaccharide to act on the intestine or penetrate the body and then leads to inflammation in the gut and eventually to neural inflammation through the toll-like receptor-4 pathway [73]. In line, increased intestinal inflammation induced by lipopolysaccharide or bacterial infection correlates with elevated microglial activation and release of pro-inflammatory cytokines in the brain [74]. Also, such altered gut permeability could be reversed by prebiotic treatment [75, 76]. It has been demonstrated in humans as well that psychological stress and elevated CRH increase intestinal permeability [77, 78]. However, evidence for increased permeability in patients with MDD is still scarce. The study of Calarge et al. [79] might be the only one that examined the relationship between gut permeability and depressive symptoms. They recruited unmedicated adolescent female patients with major depressive episode and healthy subjects to evaluate gut permeability by using the lactulose to mannitol test, the gold standard to evaluate intestinal permeability [80]. They found that lactulose to mannitol ratio was significantly positively associated with depression severity, particularly neurovegetative symptom severity. However, in a clinical trial of the probiotics [69], zonulin level was unrelated to the probiotic treatment. Our recent study also failed to provide supporting evidence for the effect of a probiotic on intestinal permeability assessed with the lactulose to mannitol test [72]. More studies are clearly required to conclude whether gut permeability is elevated in patients with MDD and thus “leaky gut” is substantially involved in the pathogenesis of MDD.

Gut microbiota affects permeability of BBB as well. Braniste et al. [81] reported that GF mice, beginning with intrauterine life, displayed increased BBB permeability during adulthood compared to SPF mice with a normal gut flora. The increased BBB permeability was associated with reduced expression of the tight junction proteins occludin and claudin-5 in the frontal cortex, striatum, and hippocampus. Exposure of GF adult mice to a SPF gut microbiota decreased BBB permeability and up-regulated the expression of the tight junction proteins. Also, mono-colonization of the intestine of GF adult mice with either *C. tyrobutyricum*, a butyrate-producing bacteria, or *Bacteroides thetaiotaomicron*, which produces mainly acetate and propionate, decreased BBB permeability. SCFAs such as butyrate are known to enhance the integrity of BBB and the intestinal epithelial barrier by facilitating the assembly of tight junctions [82]. The increased BBB permeability allows pro-inflammatory cytokines and inflammation-inducing proteins such as fibrinogen to penetrate

the BBB and enter into the brain, which leads to neural inflammation. This accords with the observation of an elevated CSF-to-serum albumin ratio, an indicator of BBB permeability, in some MDD patients [83, 84]. Further, at least a portion of patients with MDD showed abnormally increased fibrinogen level in their CSF when compared with healthy controls [85].

Another possible mechanism is the reciprocal interaction between the gut microbiota and the ANSs. Dysregulation of the ANSs, that is, overactivation of the sympathetic nervous system and attenuated activity of the parasympathetic nervous system occur under chronic stress. Stress activates the HPA axis and facilitates release of catecholamines such as noradrenaline into the circulatory system which activates the sympathetic nervous system. Noradrenaline influences growth, infectivity and virulence of the enteric bacteria such as the Gram-negative bacteria *Yersinia enterocolitica* and *Escherichia coli* in a non-immune manner [86]. Such changes in the gut microbiota may contribute to emotional dysfunctions including depression via activation of immune responses or viscerosensory pathways. On the other hand, beneficial microbes, *L. johnsonii*, for example, was shown to induce activation of vagal sensory neurons (a main peripheral structure of the parasympathetic nervous system) innervating the gastrointestinal tract [87]. Butyrate is also known to activate intestinal vagus nerves by directly acting on the terminals [88]. The involvement of vagus nerves is supported by the observation that anxiolytic effects of chronic treatment with *L. rhamnosus* (JB-1) were eliminated by vagotomy [89]. In line, vagus nerve stimulation has been shown to be effective in the treatment of MDD [90].

Taken together, SCFA (butyrate, in particular)-producing bacteria could be a next-generation probiotics [91] which could also be a next-generation treatment strategy for MDD. In addition, intervention into lifestyles (healthy diet, exercise, and appropriate use of antibiotics) that influence the gut microbiota [92, 93] will be an important strategy in the treatment of MDD.

Conclusion

Clinical and animal studies have indicated that gut microbiota plays important roles in the central dopamine system, stress response, inflammation, and BDNF, all of which have been suggested to be key molecule/system in the pathophysiology of MDD. The effects on intestinal barrier and BBB permeability and interactions with ANSs

may be involved in the link between gut microbiota and clinical depression. Although the results of microbiota profile of MDD patients varied across studies, there seem to be a consensus that bacteria which produce SCFAs such as butyrate and those protective against metabolic diseases (e.g., Bacteroidetes) might be beneficial. Clinical trials of probiotics on patients with MDD have emerged, and the beneficial effects on depression symptoms and related biological markers have been reported. Therefore, SCFA-producing bacteria could be a next-generation treatment option for clinical depression and intervention into lifestyles that leads to healthier gut microbiota will also be important. Although there is still a long way to achieve adequate understanding the role of the gut-brain axis in MDD, research on this field is promising to elucidate the pathophysiology and new treatment strategies of MDD.

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Statement of Ethics

This is a review study and does not include data collection from human subjects or animal experiments.

Conflict of Interest Statement

The author received research grants from Yakult Honsha Co., Ltd, Daiichi Sankyo Co., Ltd, and Takeda pharmaceutical Co., Ltd, and Toyobo Co. Ltd, and applied for patents with Toyobo Co. Ltd.

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