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The gut microbiota and mental health

Sara Moqbil, Sylwiusz Niedobylski, Katarzyna Laszczak, Konrad Warchoł, Eryk Mikos

Sara Moqbil; 0000-0003-1230-1444
Sylwiusz Niedobyski; 0000-0001-7266-623X
Katarzyna Laszczak; 0000-0002-5084-0273
Konrad Warchoł; 0000-0001-9467-680X
Eryk Mikos; 0000-0003-0507-2882

Abstract

INTRODUCTION AND PURPOSE

Recent studies have shown that changes in the microbiome, probiotic and antibiotic supplementation, can significantly modulate various forms of neuropsychiatric disorders - such as depression, anxiety and stress-related disorders. There is growing body of evidence pointing to a bidirectional correlation along the brain-gut microbiota line. This axis is connected through endocrine, immune and neuronal pathways. The nerves that make up the enteric nervous system transmit modifications occurring in the gastrointestinal tract and through the vagus nerve to the central nervous system (1). The main purpose of this review is to update recent information on the correlation between the gut microbiota and mental health.

STATE OF KNOWLEDGE

Interactions between the gastrointestinal system and brain function have become an important field of psychiatric research in recent years. Probiotics are thought to be a potentially valuable player in the treatment of many neuropsychiatric disorders. However, the role of specific gut microbiota species in the development of these disorders remains unclear.

CONCLUSIONS

Increasing knowledge of the correlation between gut microbiota and mental health may improve the quality of treatment for patients with neuropsychiatric conditions. Further research on larger groups is needed to assess whether probiotics can modify altered psychological well-being and be integrated into current, conventional treatments.

Key words: gut microbiota, mental health

INTRODUCTION

Proper gut function is determined by the healthy functioning of the central nervous system. Simultaneously, by sending signals to the brain, immune factors and hormones released from the gut affect brain function. New researches indicate that gut bacteria can activate neuronal pathways and central nervous system (CNS) signaling systems. Since this correlation was discovered, many studies have focused on the use of probiotics in patients with neuropsychiatric disorders. Understanding the gut microbiota-brain axis may be crucial in uncovering the exact mechanisms of depression, stress, anxiety-related behaviors and the human body's resistance to them.

DEPRESSION

A study on rats that were separated from their mothers during the neonatal period showed that a decrease in depressive symptoms was observed after administration of the probiotic - *Bifidobacterium infantism.* The same behavioral effect was observed after administration of citalopram [2]. The results of 2019 study indicate that the gut microbiota may be contributing in the pathogenesis of major depressive disorder (MDD. Group consisted of thirty one patients with MDD, thirty patients with bipolar disorder with current major depressive episode (BPD) and thirty healthy controls. They have been tested using faecal samples analyzed by shotgun metagenomics sequencing. The genera like - *Bacteroides, Clostridium, Bifidobacterium, Oscillibacter and Streptococcus* - were significantly decreased in healthy individuals compared to MDD and BPD patients. Additionally, the MDD group showed significantly increased *Firmicutes* and *Actinobacteria* and decreased *Bacteroidetes* compared to the BPD patients. Differences in gut microbiota between MDD and BPD patients suggest that specific bacterial species could potentially serve as biomarkers for these disorders [3]. Shaohua Hu et al. conducted a study revealing that untreated depressed patients with bipolar disorder (BD) demonstrate changes in the gut microbiota [4]. 140 samples from 72 BD patients and 45 healthy controls were tested. A definite enrichment of *Firmicutes phylum, Roseburia, Faecalibacterium and Coprococcus* genera was found in healthy individuals, while *Bacteroidetes phylum, Parabacteroides, Bacteroides and Halomonas* genera were more abundant in BD patients. Additionally, it was concluded that BD treatment with quetapine also significantly affects the diversification of the gut microbiome - treated patients have higher levels of butyrate-producing bacteria. Similar findings were presented in a study on 54 patients, 27 of whom suffered from major depressive disorder (MDD). Analysis of fecal samples by 16S rRNA sequencing showed that MDD patients had a significantly lower level of microbiome diversity compared to healthy controls, with *Firmicutes* being the most reduced phylum [5]. The possible involvement of the microbiome in the pathophysiology of depression has led researchers to study the effects of taking probiotics in patients with

depression. The 8- week prospective open-label trial of 40 patients with treatment-resistant major depressive disorder (TRD) involved treatment with *Clostridium butyricum* MIYAIRI 588 (CBM588) in combination with conventional antidepressants (flvoxamine, paroxetine, escitalopram, duroxetine, and sertraline). The results confirmed the effectiveness and tolerability of patients on this treatment, with 70% of patients responding to it. Additionally, a remission rate of 35% was achieved [6]. As one of many factors, detrimental kynurenine catabolites are responsible for contributing to the pathophysiology of depression. A double-blind, randomized, placebo controlled study examined the levels of kynurenine and its metabolites after treatment with the probiotic Lactobacillus Plantarum 299v (LP299v). The improvements in cognitive function in depressed patients and significant reductions in kynurenine levels were observed [7]. A randomized clinical trial conducted on patients with MDD compared the effects of probiotic and prebiotic supplementation. The effects of treatment were tested using the Beck Depression Inventory (BDI) score. The most significant decrease in the index (17.39-9.1) was observed in 28 patients in the probiotic group compared to the placebo group and the prebiotic group, in which no significant effect was observed (19.72-14.14) [8]. A randomized, triple-blind, placebo-controlled trial of 71 patients assigned to a probiotic and a placebo group found that - although probiotics did not significantly affect the microbiota of depressed patients - they were associated with the depression susceptibility variable. *Ruminococcus gnavus* significantly and positively correlate (0.37) with DASS depression score. The coccus was significantly more abundant in depressed patients (72%), in the healthy group its abundance was 25%. A higher relative abundance characterized the group of patients in the severe range of depression according to the BDI scale [9].

STRESS AND ANXIETY DISORDER

Accumulating evidence indicates links between disordered gut microbiome composition and stress or anxiety behaviors. Studies on rats have shown that neonatal stress affects the diversity and composition of the gut microbiota, which in turn may contribute to changes in stress-related behaviors [10]. The involvement of gastrointestinal bacteria in the activation of stress circuits has been demonstrated by studies using oral administration of *Citrobacter rodentium* and *Campylobacter jejuni*. The vagal pathways are the connecting axis [11,12]. Abnormalities in GABA receptor expression underlie the pathogenesis of anxiety and depression, much of which occurs concurrently with gut dysfunction. The correlation of gastrointestinal bacteria with GABA neurotransmitter expression was demonstrated in a study conducted on mice exposed to chronic treatment with *L. rhamnosus* (JB-1). Treatment was shown to induce region-dependent changes in GABA(B1b) mRNA expression in the brain. Compared to control-fed mice, expression increased in cortical regions (cingulate cortex and prelimbic cortex), whereas it decreased in the hippocampus, amygdale and locus coeruleus [13]. In another study, rats were subjected to a 4-week chronic mild stress (CMS) model to investigate the potential effects of Lactobacillus fermentum PS150 (PS150) on anxiety and depressive behaviors. PS150 supplementation has resulted in preventing serotonin reduction and neurodegeneration in the brain [14]. Results of the randomized, double-blind, placebo-controlled study on 60 Japanese medical students exposed to taking heat-inactivated *Lactobacillus gasseri* CP2305 once daily for 24 weeks revealed that this treatment significantly reduced anxiety and sleep disturbances. These factors were assessed by the Spielberger Anxiety Questionnaire and the Pittsburgh Sleep Quality Index. Additionally, administration of CP2305 resulted in an upregulation in the composition of the gut microbiota disrupted under stress (stress factors cause a decrease in *Bifidobacterium spp.* and an increase in *Streptococcus spp.)* [15]. Yi-huan Chen et al. examined microbiome composition in 36 patients with active generalized anxiety disorder (GAD) compared with 24 healthy controls.

Faecal samples were analyzed by sequencing the 16S gene and anxiety levels were assessed using the Hamilton Anxiety Rating Scale and the Anxiety Self-Assessment Scale. Lower abundance of *Firmicutes* and *Tenericutes* was observed in patients with active GAD. *Bacteroides* and *Escherichia-Shigella* abundance showed a positive correlation with anxiety severity, in contrast to *Eubacterium_coprostanoligenes_*group, *Ruminococcaceae_*UCG-014, and *Prevotella_*9, which correlate positively with anxiety reduction [16]. The effect of taking probiotics on stress relief was examined in a 12-week randomized, double-blind, placebo-controlled study. A group consisting of 103 middle-aged stressed adults took the probiotic *Lactobacillus plantarum* P8. Using the DASS-42 questionnaire, it was presented that P8 supplementation led to lower anxiety and stress scores. It also had a positive effect on cognitive traits and memory [17].

CONCLUSIONS

The reviewed studies provide valuable insight into the gut microbiota-brain axis. The discovery of this bidirectional relationship provides a foundation for understanding the impact of microbiota diversity and probiotics on central nervous system functioning. Thorough studies on larger groups will accurately determine the role of probiotics in the treatment of numerous neuropsychiatric disorders and may improve the quality of life of these patients.

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