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The role of intestinal microbiota in the pathogenesis of depression

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Abstract

Depression, due to its prevalence and serious impact on life, is a significant medical and social issue. It affects an increasing number of people, irrespective of age and living environment. It is estimated that over 300 million people worldwide suffer from it. Searching for the cause of these disorders, researchers became interested in the composition of the intestinal microbiota, looking for a possible genesis of the disease. The increased interest in this topic in recent years has resulted in an increased number of studies and scientific publications addressing this issue and suggesting that the composition of the intestinal microbiota may have a significant contribution to the pathogenesis of depression. However, our understanding of this area is still incomplete and therefore should be the subject of further research in the future.

Keywords: *depression, microbiota, bacteria, pathogenesis*

Introduction and Purpose

Depression is a recurrent and increasingly common disease that significantly reduces the quality of life. The number of patients is constantly growing, and this tendency is especially visible among young people. This disease is characterized by a wide range of pathological changes, which does not allow us to fully understand its etiology. Searching for the cause of depression, scientific research has been carried out which shows that the intestinal microbiota influences not only the physiology of the digestive tract but also the functioning of the central nervous system through the microbiota-gut-brain axis. This article aims to present how disorders in the intestinal microflora might contribute to the onset of depression.

Description of the state of knowledge

Over the last ten years, there has been a significant increase in knowledge about the impact of intestinal bacterial flora on brain function, behavior, and therefore mental health. The term 'microbiota' refers to the populations of organisms present in various body ecosystems, such as the intestinal microbiota. The human intestinal microbiota consists of over a thousand different species and approximately seven thousand subspecies of microorganisms. For example, different families of bacteria reside in the human intestine, such as Actinobacteria, Firmicutes, Proteobacteria, and Bacteroidetes [1]. Rook et al. significantly contributed to the development of knowledge about the interactions of the human body with the microorganisms inside it, claiming that the interactions between the intestinal microbiota and its host depend on metabolites and nucleic acids produced by microorganisms, which are then transported to the systemic circulation. and can induce the activation of inactive genes through epigenetic mechanisms [2]. The shared endocrine signaling pathways between bacteria and their host are considered crucial in the interaction between the host endocrine system and the microbiota [1]. Research has shown that intestinal microorganisms have the ability to bidirectionally communicate with the central nervous system through the vagus nerve, stimulate the immune system, tryptophan metabolism, and synthesize neuroactive molecules such as histamine, melatonin, and acetylcholine. This communication is also influenced by the permeability of the intestinal barrier and metabolites resulting from food fermentation, e.g. short-chain fatty acids. In addition, the intestinal microbiome secretes neurotrophins and proteins, including brain-derived neurotrophic factor (lower levels of it may cause mood disorders) [5]. These complex interactions suggest that the development of the intestinal bacterial flora is closely related to the development of the human nervous system. Therefore, disturbances in the microflora at an early stage of human development may contribute to brain development disorders and the development of mental disorders. Improper homeostasis of the intestinal microbiome leads to the secretion of the pro-inflammatory cytokines and

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the formation of inflammation in the central nervous system, which contributes to the pathogenesis of mental diseases containing an inflammatory component, including depression (in the course of depression, increased concentrations of pro-inflammatory cytokines are observed: interleukin (IL)- 1β, IL-5, IL-6, and tumor necrosis factor α and increased concentrations of plasma positive acute phase proteins) [4]. This is the so-called "inflammatory theory of depression", which may also be explained by the kynurenine pathway, in which tryptophan supplied with food is metabolized. It is the main source of neurotransmitters such as serotonin and melatonin [3].

The release of pro-inflammatory cytokines occurs due to disruption of the intestinal barrier, resulting in the activation of the inflammatory immune response. Cytokines (Interferon α, IFN-β, TNF-α and IFN-γ) reduce the availability of serotonin with an increase in the concentration of neurotoxic tryptophan metabolites by activating indoleamine 2,3-dioxygenase, an enzyme involved in the conversion of tryptophan into kynurenine, thus shifting tryptophan from the serotonin production pathway, reducing its concentration and increasing the concentration of tryptophan metabolites that have an adverse effect on the CNS. Kynurenine is transformed by two metabolic pathways that lead to the formation of 3-hydroxy-kynurenine and quinolinic acid or kynureninic acid. 3-hydroxy-kynurenine increases oxidative stress affecting the CNS, increases ROS production, contributing to neuronal apoptosis, and impairing the function of serotonergic and noradrenergic receptors. Kynureninic acid, on the other hand, is an antagonist of NMDA receptors and therefore has a neuroprotective effect. In turn, quinolinic acid is a strong agonist of NMDA receptors, which has a neuroexcitatory and neurotoxic effect, causing an increase in the concentration of glutamate in the synapse and a decrease in the level of γ-aminobutyryl acid in the brain. The influence of cytokines on depressed mood, depressive symptoms, as well as disruption of circadian rhythms and binding therefore, fatigue and nervousness were observed already in the 1990s when using cytokine therapy. The "hygienic hypothesis of depression" assumes that the increase in the incidence of depression may be related to impaired immunoregulation, which may result from limited exposure to certain microorganisms and parasites that properly stimulate the maturation of the human immune system, e.g. dendritic cells involved in, among others, in the suppression of the inflammatory response.

Disturbances in the intestinal flora are associated with the so-called leaky gut syndrome, i.e. increased intestinal permeability. This disorder leads to the translocation of Gram-negative bacteria into the blood and an immune reaction against their lipopolysaccharides (LPS). This was first demonstrated by Maes et al. (2008). They showed that depressed patients have significantly increased concentrations of immunoglobulins (Ig) M and A against lipopolysaccharides of Gram-negative enterobacteria, which normally occur in the intestinal lumen. Their work allowed the conclusion that depression is accompanied by increased permeability of the intestinal walls and an immune response against these antigens. Factors that have a particularly negative impact on the functioning and selectivity of the intestinal barrier include increased concentrations of IL-1β, IL-6, TNF-α, and IFN-γ, increased production of free oxygen radicals, nitric oxide (NO), decreased concentration of antioxidants (e.g. glutamine), infections and alcohol and drug abuse (especially non-steroidal anti-inflammatory drugs). An important step for the contemporary increase in interest in the role of intestinal microbiota in pathogenesis depression was the discovery by Morikawa et al. in 1998 that IFN-γ, TNF-α, and IL-1 cause the activation of serotonin transporters, which leads to a decrease in its concentration in the extracellular space. In turn, Abe et al. found that Interferon α also modulates the functioning of 5-HT1A and 5-HT2 receptors [4].

Changes in the number of microorganisms in the course of intestinal dysbiosis are attributed to the hypothesis of neurotransmitter deficiency causing mood disorders. Strains such as Bifidobacterium dentium and Lactobacillus are capable of producing GABA. In turn, Escheridia, Bacillus, and Saccharomyces can produce norepinephrine and Lactobacillus - acetylcholine. Candida, Streptococcus, Escheridia, and Enterococcus produce serotonin, and Bacillus - dopamine. Moreover, it has been proven that bacteria included in the intestinal microbiota produce butyrate, which can cross the blood-brain barrier and has neuroprotective and antidepressant effects [5,6]. An important element of immune signaling is the NLRP3 inflammasome, which is responsible for the activation of inflammatory processes in situations of stress and is present in many types of immune cells. One of the main mechanisms of its action is the activation of pro-inflammatory pathways and the HPA axis (hypothalamic-pituitary-adrenal axis), which may exacerbate depressive symptoms and anxiety. The degree of NLRP3 activation under stress may also be associated with changes in the composition and functioning of the intestinal microbiome. The increased risk of depressive behavior occurs as a result of the overgrowth of bacterial strains that cause the body's inflammatory response with a simultaneous decrease in the number of strains that modulate and inhibit inflammation [5,7]. In 2016, Kelly et al. observed that the microbiota of people suffering from depression differs significantly from the control group. In patients, the intestinal microbiota was characterized by a higher number of bacteria of the genera Holdemania, Gelria, Anaerofilum, Eggerthella, Paraprevotella, Turicibacter and a lower number of bacteria of the Dialister and Prevotella strains. In the same year, Aizawa et al. proved that the microbiota in healthy people contains more bacteria from the Bifidobacterium group. In 2019, Valles-Colomer et al. analyzed stool samples from 1,070 people using the 16S rRNA genetic sequencing method. The researchers' goal was to check whether the presence of specific bacterial strains correlated with depression rates and quality of life. The results showed that the populations of Dialister and Coprococcus spp. bacteria were lower in people whose results indicated depression, while the presence of SCFA-producing Faecalibacterium and Coprococcus was consistently associated with higher scores on the quality of life scale [13]. However, studies conducted in 2014-2015

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allowed us to notice a lower number of intestinal bacteria of the Lachnospiraceae genus in people with depression compared to healthy people[8]. Microorganisms from the Lachnospiraceae family participate in the breakdown of carbohydrates into short-chain fatty acids. Therefore, reducing the number of such bacteria accelerates the reduction of SCFA production, resulting in intestinal barrier dysfunction [9]. Moreover, in another study by Jiang et al., a negative correlation was observed between the severity of depression symptoms and the number of bacteria of the Faecalibacterium genus [8]. The phyla Bacteroidetes and Proteobacteria also attract special attention, and their number is greater in patients with depression [9].

However, it should be remembered that not only the composition of the intestinal microbiota is important, but also the possibilities of its modification. This can be done using probiotic preparations and prebiotics. Bacteria that have a positive effect on mental health in appropriate amounts are called psychobiotics. Their action may be based on the secretion of neuroactive substances (e.g. GABA and serotonin), increasing the concentration of oxytocin and influencing the HPA axis. Psychobiotics include, among others, Lactobacillus plantarum strain 299V, PS128 (its long-term use has a positive effect on well-being in depression), and Bifidobacterium infantis, which has a positive effect on the regulation of the HPA axis, and what is important for further scientific research - in the future it may prove effective in the context of increasing the level of tryptophan in plasma, as this was the effect it had in studies conducted on rats [5]. Steenbergen et al. examined the impact of 8 bacterial strains (Bifidobacterium bifidum W23, Bifidobacterium lactis W52, Lactobacillus acidophilus W37, Lactobacillus brevis W63, Lactobacillus casei W56, Lactobacillus salivarius W24 and Lactobacillus lactis W19 and W58) on the well-being of patients. Patients supplemented a total of 5x109 CFU (colony-forming unit) for 4 weeks, and the patients' well-being was examined using the LEIDS scale (Leiden Index of Depression Sensitivity). The results showed a greater decrease in depression symptoms in the group in which probiotic therapy was used [5,10]. In turn, Takada et al. checked the influence of the Lactobacillus casei Shirota strain on the stressful factor of an exam. The authors of the study created a study group of medical students whom they observed for 8 weeks before and during the exam. Stress levels were measured by checking the concentration of cortisol in saliva. The results showed lower cortisol concentrations, and therefore less stress, in students subjected to probiotic therapy [5,11]. The search for a probiotic that has a beneficial effect in people with mood disorders is still the subject of research and numerous discussions, which will certainly result in an increase in the number of studies and scientific reports on this subject in the future. A recent experimental study using the Bifidobacterium longum NCC3001 strain showed, in addition to improving gastrointestinal symptoms, minimizing depressive symptoms in patients with irritable bowel syndrome [5,12]. Bambling et al. put forward a hypothesis that treatment-resistant depression would have a biological basis related to the phenomena of dysbiosis and inflammation. Therefore, a study was conducted in which a group of 12 patients suffering from confirmed treatment-resistant depression simultaneously took drugs from the group of selective serotonin reuptake inhibitors and a combination of probiotics (S. thermophiles, L. acidophilus, and B. bifidum), as well as magnesium orotate for a period of 8 weeks. In 8 out of 12 participants, a significant reduction in the severity of depressive symptoms and improvement in self-esteem were observed. Most importantly, during the 16-week observation period, when SSRIs were still used but the combination of probiotics and magnesium orotate was discontinued, depressive symptoms recurred. The authors of the study plan to conduct randomized trials on a larger scale in the future [14,15].

Despite the increasing number of scientific studies on the role of intestinal microbiota in the pathogenesis of depression and the use of probiotic therapy in the treatment of this disease, there are still many questions that researchers will seek answers to in the coming years. One such issue is the impact of probiotic supplementation on the regulation of emotions in healthy people because while in the group of people suffering from depression, the results clearly indicate the effectiveness of such supplements, the results in healthy people are still not clear. The effectiveness of the use of probiotics in people over 65 years of age also awaits confirmation, as the research results obtained so far have not yielded the expected results, while they are effective in younger people. This suggests that the composition of the probiotics used should be adapted to the patient's age [1,16]. However, probiotic therapy is not the only method of modifying the composition of intestinal bacterial flora. Faecal microbiota transplantation (FMT) is also used, which has so far been used as a treatment for Clostridium difficile infections, irritable bowel syndrome, and inflammatory bowel diseases [1,17], but may soon also be used to treat neurobehavioral disorders related to the gut-brain, as well as developmental disorders of the nervous system and mental diseases [1,18]. The effectiveness of FMT should be further investigated, especially for the treatment of mental illness [1].

Conclusions

Intestinal microbiota disorders may play a role in the pathogenesis of depression by contributing to brain development disorders in childhood and adolescence. Improper homeostasis of the intestinal microbiome results in the secretion of pro-inflammatory cytokines and, as a result, inflammation in the central nervous system, which contributes to the pathogenesis of mental diseases containing an inflammatory component. Interferon α, IFN-β, TNF-α, and IFN-γ reduce the availability of serotonin with an increase in the concentration of neurotoxic tryptophan metabolites by activating indoleamine 2,3-dioxygenase (an enzyme involved in the conversion of tryptophan into kynurenine). Disturbances in the intestinal flora may be associated with leaky gut syndrome, i.e. increased intestinal permeability. This disorder leads to the translocation of Gram-negative bacteria into the blood and an immune reaction against their lipopolysaccharides (LPS). In addition to the composition of the intestinal microbiota, the possibility of modifying it

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through probiotic supplementation or fecal microbiota transplantation (FMT) is also important. Studies indicate the effectiveness of probiotic therapy in alleviating depressive symptoms, particularly in individuals under 60 years of age. Future research should focus on assessing the effectiveness of probiotic supplements in regulating emotions in healthy individuals, given the current ambiguity in research findings, and on examining probiotics that will prove effective in people over 65 years of age. The effectiveness of FMT in the treatment of mental illnesses should also be the subject of future research.

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