Neuroinflammation, Gut-Brain Axis and Depression

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INTRODUCTION

Depression is one of the diseases with the highest mortality and morbidity rates in the world.1 Twenty out of every 100 people develop depression at some point in their lifetime.2 The rate of “years lived with disability” (10.3%) is longer in depression than in all other diseases.3 Therefore, depression can be defined as a serious public health problem.

Given the etiopathogenesis of depression, it is seen that it is not only a brain disorder, but also has a close relationship with all body functions, especially the immune system and the endocrine system.4 In the etiology of depression, the heritability rate is between 48% and 37%.5 However, the effect of environmental factors, especially diet and lifestyle changes, is indisputable in this etiology.6

It is thought that modern lifestyle provides a basis for immune system dysfunction due to several causes, and that the leading cause is disruption of gut microbiota composition (dysbiosis), leading to neuroinflammation and depression.7

ETIOPATHOGENESIS OF MAJOR DEPRESSION

In the 1950s, known as the golden age of psychopharmacology, the first psychopharmacological drugs were discovered and the synaptic functions have been started to be elucidated by means of spectrophotofluorometric analyses.8 During the next 2–3 decades, depression was considered as a brain dysfunction. Problems with the hypothalamic-pituitary-adrenal (HPA) axis and the role of stress have been clarified over time. The neuroinflammation hypothesis has been advocated since 2000s. Evidence obtained in the last 10 years reveals a strong and bidirectional relationship between the gut and the brain. Gut microbiota has an essential role in the formation of both health problems and neuropsychiatric disorders.7 These four dimensions (neuronal/synaptic dysfunction, HPA axis, neuroinflammation and dysbiosis) should be analyzed in detail.
Monoamine neurotransmitters (serotonin, dopamine and noradrenaline) play an important role in normal mood and anxiety/depression development. Although serotonin remains in the forefront, recent studies have also provided evidence regarding the function of other neurotransmitters in depression. The gamma-aminobutyric acid system has a hypoactive function, while the acetylcholine and glutamate system has a hyperactive function. The fact that antidepressants reduce the depressive symptoms by increasing the monoamine levels is an observation in favor of this hypothesis. However, the fact that the success rate of antidepressants is not 100% and they have a late onset of action suggests that other factors also play a role in the etiology of depression.

One of the factors causing depression is the hyperactivity of the HPA axis. The HPA axis is activated as the response of the organism to stress. In patients with depression, there is an impairment in the negative feedback mechanism that allows both hypercortisolemia and cortisol release to be halted. In addition to that, the glucocorticoid receptor sensitivity decreases in depression, and antidepressant treatments increase the amount of glucocorticoid receptors.

According to the microbiota hypothesis, the gut-brain axis may be the missing link in the etiopathogenesis of neuropsychiatric diseases. The most important component of the gut-brain axis is the intestinal bacterial content, called microbiota. The microbiota begins to form from the first day of birth. In fact, according to some studies, the seeds of the gut microbiota are spread in the intrauterine period. Gut microbiota plays an essential role in functions such as maturation of the immune system, healthy functioning of the HPA axis and endocrine system, formation and maintenance of the blood-brain barrier, neurogenesis, and myelination. In brief, the gut microbiota directly affects the development and healthy functioning of the mammalian brain.

The leading evidence consolidating this view is that the gut microbiota composition of patients with depression is different from that of healthy individuals. The microbiota of patients with depression exhibits low-diversity dysbiosis. For example, the levels of Lactobacillus, Bifidobacterium, Firmicutes, Faecalibacterium and Ruminococcus decrease, while the levels of Proteobacteria and Bacteroides increase. Results similar to human studies have been obtained in animal studies. However, consistent results cannot be obtained due to the methodological differences between the studies, and the validity of the findings continues to be discussed.

If depression patients have a specific gut microbiota composition and if this bacterial content causes depression, it should lead to the formation of depression symptoms in healthy individuals when transplanted. In order to test this hypothesis, two studies with similar design that were conducted in two centers independent of each other were published in 2016. The feces of depression patients (depression microbiota) was transplanted to microbiota-deficient rats in the study by Kelly et al., and to germ-free (born by caesarean section and grown under sterile conditions) mice in the study by Zheng et al. In both experiments, depressive symptoms and metabolic changes were determined in the experimental animals following fecal microbiota transplantation (FMT). According to the results of these studies, it can be speculated that dysbiosis may play a causal role for depression-like behaviors.

The incidence of depression has significantly increased in the last few decades. One of the leading causes for this may be the global increase in the use of antibiotics. Systemic antibiotics are used even for the treatment of local infections, such as tonsillitis, and these antibiotics also kill symbiotic bacteria in the gut microbiota. It is thought that the use of antibiotics causes dysbiosis, and therefore leads to neuropsychiatric disorders. In the studies with large sample sizes conducted in this respect, a significant correlation was found between the dose and duration of antibiotic use and the probability of neuropsychiatric disorder. Similarly, it was found that infants with antibiotic exposure within the first year after birth had higher rates of behavioral problems, depression symptoms and neurocognitive impairment in the later years of life.

In conclusion, depression can be defined as a multifactorial disease in which neuronal, hormonal, nutritional, antimicrobial and microbital factors play a complex and combined role in the etiopathogenesis.

NEUROINFLAMMATION IN DEPRESSION

Neuroinflammation is a condition which involves the activation of nerve cells in the central nervous system and in which changes similar to neural degeneration are observed. The four cardinal signs, calor (heat), dolor (pain), rubor (redness) and tumor (swelling), in the classical inflammation definition by Roman Celsus are not seen in neuroinflammation. By increasing pro-inflammatory cytokines through the changes in the HPA axis and neurotransmitter synthesis, inflammation creates a kind of allostatic load, including the endocrine and nervous system.
Numerous research data indicate that immune dysregulation and chronic inflammation play a role in the onset and persistence of depression, resistance to treatment, and relapse.\textsuperscript{42-45} As a result of increased cytokines due to both peripheral chronic inflammation and central microglia stimulation, depressive symptoms may show up. Peripheral stimuli such as inflammation, chronic stress and infection may trigger the activation of microglia in the brain, resulting in release of pro-inflammatory cytokines.\textsuperscript{46} Depressive symptoms are also seen in physical diseases such as cancer, autoimmune diseases or systemic infections in which chronic inflammation has been implicated.\textsuperscript{47}

Being filtered from the leaky areas in the blood-brain barrier through active transport, the pro-inflammatory cytokines in the periphery act on the brain by the activation of endothelial cells and perivascular macrophages in the cerebral vascular walls and binding to the cytokine receptors associated with peripheral nerve fibers such as the vagus nerve.\textsuperscript{47}

Depression is frequently triggered by stress, and stress activates the immune system through the HPA axis. Psychosocial problems, sleep disorder, poor diet, insufficient physical activity and environmental stresses such as smoking activate low-grade inflammatory and oxidative stress pathways.\textsuperscript{48,49} In some cases of depression, there is an increase in the oxidation products that damage lipids, proteins and nucleic acids as a result of oxidative and nitrosative stress.\textsuperscript{50} The fact that depression frequently coexists in pro-inflammatory conditions such as obesity, myocardial infarction and autoimmune diseases is consistent with this.\textsuperscript{51,52}

Increased cytokines cause disorders in the serotonergic and noradrenergic circuitries by activating the HPA axis, or depletion of serotonin with the increased activity of the indoleamine-2,3-deoxygenase (IDO) enzyme in the tryptophan/kyurenine system.\textsuperscript{52,53} In some of depression cases, the levels of pro-inflammatory cytokine in peripheral blood, such as IL-1 beta, IL-6, IL-18, interferon-gamma (INF-γ), sIL-2R and CRP (an acute phase protein and inflammatory marker) have been shown to increase.\textsuperscript{53-58} The levels of cytokine and CRP also improve in patients whose depression improves.\textsuperscript{59}

Another factor that increases the pro-inflammatory cytokine concentrations is leaky gut, which develops as a result of interaction with gut microbes.\textsuperscript{60} According to the leaky gut theory, it has been suggested that microglia contributes to the production of peripheral and central pro-inflammatory cytokines in some of depressive cases. Intestinal microorganisms may cause changes in neurotransmitter levels by affecting the tryptophan metabolism.\textsuperscript{61} It was reported that the levels of IgM and IgA produced against lipopolysaccharides (LPS) of enterobacteria were higher in depressive cases than in controls. Increased levels of IgM and IgA indicate that intestinal permeability is increased, and thus, invasive enterobacteria cause systemic and central inflammation.\textsuperscript{39,62} In an animal study, the blockage of the peripheral IL-6 receptor by the anti-mouse IL-6 antibody has been shown to lead to a rapid and permanent antidepressant effect by normalizing the altered composition of gut microbiology.\textsuperscript{63}

In a 1991 paper by Smith, one of the first papers on the association between inflammation and depression, it was argued that the “food-gut-allergy axis” may play a role in macrophage activation. In this study, it was observed that especially dairy products could cause behavioral dysfunction, and fish oil was recommended for the prophylaxis of depression.\textsuperscript{64}

In summary, neuroinflammation plays a role in the pathophysiology of depression by increasing proinflammatory cytokines, activating the HPA axis, increasing the glucocorticoid resistance, affecting the synthesis and metabolism of serotonin-norepinephrine-dopamine, increasing neuronal apoptosis and negatively affecting neurogenesis and neuroplasticity.

**EFFICACY OF MICROBIOTA RESTORATION IN DEPRESSION**

Mental and physiological diseases associated with dysbiosis in gut microbiota can be reversed by restoration of dysbiosis.\textsuperscript{65,66} Microbiota can be restored by prebiotics, probiotics and FMT.\textsuperscript{66} Besides that, the importance of healthy diet is undeniable.\textsuperscript{67} Because our foods are also the nutrients of bacteria in the gut microbiota.\textsuperscript{68} These healthy foods, which are also the nutrients of beneficial bacteria in the gut, are called “prebiotics.”\textsuperscript{68} Omega-3 fatty acids, fructose-oligosaccharide, and galacto-oligosaccharide are the prebiotics that have been shown to have positive efficacy in the gut-brain axis.\textsuperscript{68} Moreover, some microbiota bacteria (Bacteroides fragilis and Faecalibacterium prausnitzii) provide the production of short-chain fatty acids (acetate, butyrate and propionate) from fiber. These fatty acids get mixed into the systemic circulation and show anti-inflammatory activity.\textsuperscript{69}

The term "probiotics" is defined as living microorganisms that produce positive effects on host’s health.\textsuperscript{66} Probiotic bacteria were termed as “psychobiotics” by Dinan et al.\textsuperscript{70} due to the improvements in neuronal functions further to their benefits on overall body health, and presented as “novel class of psychobiotics”. The positive effects of probiotics in the treatment of depression were first reported in the literature by Phillip’s paper in 1910.\textsuperscript{71} Probiotic microorganisms have been studied in a number of clinical and preclinical randomized controlled trials by being comparing with antidepressants.\textsuperscript{72,73} In the light of these studies, bacteria such as Bifidobacterium bifidum, Lactobacillus helveticus and Lactobacillus casei have been classified as psychobiotics since they exhibit anxiolytic and antidepressant characteristics.\textsuperscript{74-76}
Perhaps the most dramatic and drastic way to restore dysbiosis is FMT. FMT is the transplantation of feces taken from a healthy donor to the intestines of the patient in order to restore dysbiosis. The primary area of usage of FMT is inflammatory bowel diseases such as ulcerative colitis and Crohn’s disease. In our previous review, the potential use of FMT in neuropsychiatric indications was discussed. This preliminary paper in the literature is an important reference for FMT studies in the field of neuropsychiatry, which are still at the crawling stage. In a recent study we conducted in this field, the severities of anxiety, depression and obsession were found to decline after the FMT procedure in inflammatory bowel patients. FMT may be an alternative treatment option, especially in patients resistant to traditional treatment methods.

ANTIMICROBIAL EFFECT OF CONVENTIONAL ANTIDEPRESSANTS

The synaptic effect of antidepressants is well known. However, in recent years, it is thought that antidepressants not only have an effect on neurotransmitter systems, but also regulate the gut-brain axis by altering gut microbiota. The primary function of antidepressants leading to this effect is the mechanism of antimicrobial action. The first antidepressant inducing monoamine oxidase inhibition (MAO-I) is iproniazid, an antituberculosis drug. Over the years, it has been clarified that MAO-I antidepressants inhibit bacterial cell wall synthesis. In addition, selective serotonin reuptake inhibitor (SSRI) drugs inhibit the efflux pump, while tricyclic antidepressants (TCAs) exhibit an antibiotic effect by inhibiting both antiplasmid and DNA gyrase. Ketamine also exhibits an antimicrobial effect on Enterococcus, Staphylococcus and Candida albicans by inhibiting both antiplasmid and DNA gyrase.

FUTURE PROJECTIONS

With the better understanding of the role of dysbiosis in the etiopathogenesis of depression, new treatment approaches have acquired currency. For example, in a recent study, probiotics (Lactobacillus acidophilus, Bifidobacterium bifidum, Streptococcus thermophilus) and magnesium orotate (1,600 mg/day) were started to be administered to treatment-resistant depression patients (n=12) in addition to the SSRIs they were currently receiving. In the eighth week of the administration, there was a statistically significant decrease in depression scores and an increase in the quality of life. The interesting result of the study is that relapse was observed in the 16 h week, although the patients continued to use SSRIs following the discontinuation of probiotic and magnesium orotate supplement. The most significant weakness of this study is the small sample size. In a recent meta-analysis study, the results of 10 studies (n=1,349) were analyzed, and it was found that probiotic supplement had no significant therapeutic effect on mood.

There is numerous evidence that the microbiota composition in patients with depression is impaired due to various reasons (antibiotic use, unhealthy diet, stress, genetic causes, city life, etc.). Besides the publications arguing that microbiota-based or as we propose, “fecomodulation” treatments (psychobiotic, probiotic and FMT) have antidepressive effect in order to restore dysbiosis, there are also studies demonstrating that they are ineffective. In order to clarify the contradictory results, there is a need for studies investigating immunological, endocrine and metabolic parameters, as well as microbiota composition analyses to be conducted on large samples.

CONCLUSION

In the past 70 years, very important scientific developments and discoveries were achieved for the etiopathogenesis and treatment of depression. Effective and reliable antidepressant drugs have been put into use with the advancement of the monoamine hypothesis and modern psychopharmacology. However, the success rates of antidepressants are not satisfactory due to delay in treatment efficacy, inadequacy in remission rates and side effects that may prevent the continuation of the treatment (weight gain, sexual dysfunction, sedation, etc.).

The microbiota hypothesis, which is an alternative to the monoamine hypothesis, argues that the main problem in the etiopathogenesis of depression is dysbiosis. Low-grade inflammation occurs due to leaky gut and endotoxemia arising on the basis of dysbiosis. Neuroinflammation occurs as a reflection of systemic inflammation. The problems in the monoaminergic system are the result of neuroinflammation. Conventional antidepressants not only have an effect on the levels of neurotransmitters in the synaptic gap, but also fix dysbiosis. Using the fecomodulation treatments, the source of the problem is intervened in the treatment of depression. Among these treatments, FMT provides the most dramatic and drastic effect.

Although the first study on the use of probiotics in the treatment of depression was published in 1910, the interest of the current science in the issue has increased after the 2005 paper by Logan and Katzman. Both animal experiments and randomized controlled clinical trials suggest that probiotics are effective in the treatment of depression. However, obtaining
conflicting results makes it difficult to reach a definitive conclusion. There are only a few clinical studies on the use of FMT in neuropsychiatric indications.

In conclusion, there is promising evidence for the use of fecomodulation treatments in neuropsychiatric indications, especially depression. The significance of fecomodulation treatments, which aim to fix dysbiosis in the treatment and prophylaxis of depression, appears to increase in the near future.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: All authors. Data curation: Alper Evrensel, Barış Önen Ünsalver. Formal analysis: Alper Evrensel, Barış Önen Ünsalver. Investigation: Alper Evrensel, Barış Önen Ünsalver. Methodology: All authors. Project administration: Alper Evrensel. Resources: Alper Evrensel, Barış Önen Ünsalver. Software: All authors. Supervision: Mehmet Emin Ceylan. Validation: All authors. Visualization: All authors. Writing—original draft: Alper Evrensel, Barış Önen Ünsalver. Writing—review & editing: All authors.

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