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Case Review

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The Most Common Neurotransmitter to Elucidate the Relation between the Microbiota and Depression

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Depression is a major public health problem, which is a serious and recurrent disease associated with mortality and decline in the quality and function of a healthy life. It is estimated that 9% to 27% of the Turk population is at risk of having a depressive episode during life. It is present at all ages. Today, it is estimated that 4% of children are affected by this disease. This prevalence increases from 14 to 20% among adolescents and it is also important for the elderly. Although it is known that depression usually starts during adolescence, the age of onset decreases to 3 years old. Mental health, an essential component of health, is a state of well-being, an aptitude of the mind to work normally and respond appropriately to environmental stimuli. One speaks of mental disorders when this state of well-being is disturbed by specific conditions (depression, schizophrenia, bipolar disorders). Today, many effective treatments exist to treat this pathology. Chemical treatments (antidepressants) helping to relieve depressive symptoms, often associated with medical and psychotherapeutic support, and physical treatments such as diet and gut microbiota. Intestinal microbiota is considered to be associated with the neuro-endocrine-immune pathways, generating the concept of the gut-brain axis. The first evidence of the gut-brain axis came from a work of an army surgeon through monitoring gastric juices secreted by intragastric fistula he found that intestinal function was related with mood [1]. About 60% of anxiety and depression patients are described to have intestinal function disturbance, such as in irritable bowel syndrome (IBS). As the concentration of γ-aminobutyric acid (GABA) in the central nervous system of patients with depression is reduced, and decreased inhibitor GABA neurotransmission may play a role in the etiology of MDD. Serotonergic heteroreceptors have a direct effect on GABAergic cells. Serotonin signaling usually exerts an excitatory effect on GABAergic neurotransmission via 5-HT2A, 5-HT3, and possibly 5-HT7 receptors; however, it should be noted that 5-HT1A receptors appear as a 5-HT-mediated mechanism in GABA inhibition.

The effect of gut microbiota and microbiom on disorders are also discussed, with the aim to propose some new therapeutic strategies for depression from neurological disorders. Among the bacteria found in the reviewed studies to be lower in MDD [2], *Bifidobacterium* is an efficient producer of GABA [3]. Several bacterial strains are known to produce serotonin directly [4]. Modulation of neurotransmitter production is one possible means by which the gut microbiome may affect the brain, with direct relevance to depression.

Antidepressant medication is one of the most common treatment modalities in depression. However, despite the the high number of current antidepressant, only one third of depressive patients have showed significant improvement in response to first-line treatment. In addition, some patients have resistance to antidepressants. Additionally, the presence of a period of several weeks to months in which no therapeutic effect is observed after treatment with antidepressant makes this disease more important. Considering all of these, the identification and determination of new therapeutic approaches to depression have been needed. Therefore in recent studies, it is aimed to determine the relationship between various molecules, cells and signaling pathways and pathogenesis of depression and focus on the development of new molecular targets.

There are many theories about the aetiology of depression and some of them involve neurotransmitters. Depression seems to be

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linked to disturbances in brain circuits or neural pathways that convey signals with the monoamine neurotransmitters serotonin or noradrenaline. Low levels of these monoamines in certain neurones are correlated in some way with depression.

The earliest theories of the biologic basis of depression suggested dysfunction of central nervous system (CNS) pathways served by the major monoamine neurotransmitters norepinephrine, serotonin (5-hydroxytryptamine or 5-HT), and dopamine. These neurotransmitter system pathways are normally involved in the regulation of vital bodily functions (eg, energy, sleep, appetite, libido, and psychomotor behavior), which often are disturbed in depressed patients. Dysregulation of norepinephrine, serotonin, and dopamine systems, individually or in combination, therefore was believed to be associated with the pathophysiology of depression. Gut microbiota has significant effects on the structure and function of the enteric and central nervous system including human behaviour and brain regulation.

Figure 1: Brain-gut-microbiome interactions related to serotonin signaling.

There are also communication signals carried by the blood between the brain and the digestive system. Furthermore, there is an astonishing similarity between the brain and the digestive system neural network in terms of cell biology. There are 30 different neurotransmitters in the gastrointestinal tract. These substances include psycho-active substances such as serotonin, dopamine, opiate, which affect our brain, our thinking organ, and our psychological state. 90 percent of the serotonin, known as the happiness hormone, is found in the digestive system. Serotonin is a monoamine neurotransmitter (5-HT) substance in the brain, popularly known as the happiness hormone. The hormone serotonin plays an important role in the digestive system, blood cells and central nervous system. Although it owes its popularity to the tasks of happiness and well-being in the brain, 90% of serotonin in the body, it is found in enterochromaffin cells in the digestive system and is used to regulate bowel movements. Serotonin is an important hormone that has the ability to regulate neuron networks in our brain as well as taking part in the main digestive system. also this hormone has very important tasks including important functions such as circadian rhythms, detection of neuron networks. Regulation of the secretion mechanism of this molecule is one of the treatment methods used in many disorders. As a neurotransmitter it has tasks in a wide range of areas including growth, reproduction, behavior and aging.

Studies on the deficiency of this hormone have shown that serotonin deficiency will be fatal. Recent studies have shown that various environmental factors that are effective in early life contribute to the development of psychiatric disorders such as depression. Especially chronic stress exposure is an important risk factor for depression [5,6]. Another mechanism associated with depression is the occurrence of irregularity in the hypothalamo-pituitary-adrenal (HPA) axis that is activated in response to stress and is involved in the regulation of glucocorticoid production [7]. The HPA axis releases a large amount of glucocorticoids when exposed to stress, and when stress is eliminated, HPA activity is restored to normal by feedback regulation [8].

However, it has been reported that high levels of glucocorticoid in the blood are maintained in patients with depression due to a dysfunction in the feedback mechanism, and when it is eliminated, HPA activity is restored to normal by feedback regulation [9]. Recent research reveals that friendly, harmful and probiotic microorganisms living in the gastrointestinal tract stimulate the immune system, neural pathways and subsequent central nervous system. These microorganisms produce neuroactive substances such as γ-aminobutyric acid (GABA) and serotonin, which play a role in the intestinal brain axis. Preclinical animal experiments show that some probiotic bacteria have anxiolytic and antidepressant effects. In this article, the effect of serotonin and GABA, one of the neurotransmitters that have the closest relationship between depression and intestinal microbiota, controls the bowel axis of the brain is reviewed. Because the effects of intestinal microbiota and bacteria on human health seem to be the focus of attention in neuroscience for the next decade. For example; *Bifidobacterium infantis* is predominant in neonatal intestine and probiotic drugs. Due to its antidepressant effect, this bacterium has been identified as “psychobiotic” [10]. In cell culture studies, gut microbiota have been found to make precursers to neurotransmitters, such as tryptamine and neurotransmitters including GABA, serotonin, norepinephrine, and dopamine. Among the bacteria found in the reviewed studies to be lower in MDD, Bifidobacterium is an efficient producer of GABA. Several bacterial strains are known to produce serotonin directly [11].

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Figure 2: Alteration in neurotransmitters, hormones and inflammatory factors by gut dysbiosis can modify brain and gut functions.

In another experiment, a decrease in both anxiety and depression scores was observed in mice given *Lactobacillus rhamnosus* for 28 days [12]. The most striking results were determined by the following experiment; anxiety-like behavior obtained by high-fat diet, *Lactobacillus farciminis* administration has been shown to reduce HPA axis response plasma Adreno-Crotico-Tropin Hormone (ACTH), Corticosteroid level, Corticotropin Releasing Hormone (CRH) levels in mice [13]. Bacterioides family was found to be associated with depression in clinical studies [14]. At the same time, it was observed that serum IgM and anti-IgA lipopolysaccharide levels were increased [15]. In healthy individuals, milk fermented with probiotic bacteria positively affects emotional centers. In the researchers of Tillisch's fellowship are the only study to investigate the relationship between probiotics and healthy brain functions using fMRI (functional Magnetic Resonance Imaging) in 2013 years. Berk and fellowship reported that depression has a chronic, low-level inflammatory condition, which may be associated with intestinal permeability disorder in 2015. As other researchers have pointed out, microbiota is now considered to be the key role between unhealthy nutrition and depression.

I am in a very early stage regarding the research, evidence suggests that intestinal microbiota plays an important role in the bidirectional interactions occurring between the intestine and the nervous system. This communication, happens by means of several pathways, and recent findings point to the vagal nerve, neuroendocrine systems, neurotransmitters of the CNS and inflammatory factors as responsible for this connection. It is expected that therapies targeting gut microbiota and the microbiota-gut-brain axis will play an important role in the treatment and prevention of depression in the near future.

Given the evidence of microbial function that transcends taxonomic classification, and the ecological nature of the microbial community, approaches such as bacterial growth rate and genome-scale metabolic modeling may prove useful in better understanding the contribution of the gut microbiome to depression etiology.

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Conflicts of Interest

No conflicts of interest.

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