Gut microbiota and its impact on neuropsychiatric disorders

Magdalena Wójcik[1*], Justyna Dąbrowska[1], Grzegorz Boreński[1], Damian Bator[1], Joanna Milanowska[2]

[1]Student Science Club at the Department of Applied Psychology, Medical University of Lublin, Lublin, Poland
[2]Department of Applied Psychology, Medical University of Lublin, Lublin, Poland
*E-mail address: magdalena.wojcik967@gmail.com

ORCID ID:
Magdalena Wójcik https://orcid.org/0000-0002-0999-6284
Justyna Dąbrowska https://orcid.org/0000-0002-1356-6965
Damian Bator https://orcid.org/0000-0002-8464-932X
Joanna Milanowska https://orcid.org/0000-0001-9741-1583

ABSTRACT

Introduction: Over the last few decades, the interest of microbiota- gut – brain axis has increased. It is thought to have an impact on the overall health of the host. Gut microbiota and central nervous system can communicate in different ways. The connection between them is especially interesting in case of neuropsychiatric diseases

The aim of the study: The purpose of this systemic review was to collect and analyse current data of the association between gut microbiota and neuropsychiatric disorders, specifically schizophrenia and bipolar disorder

Material and method: Standard criteria were used to review the literature data. The search of articles in the PubMed and Google Scholar database was carried out using the following keywords: gut microbiota, dysbiosis, schizophrenia, bipolar disorder

Description of the state of knowledge: Dysregulation of microbiota is a potential factor in pathogenesis of brain disorders. Gut microbiome is thought to be an important part of not only normal brain development, but also modulation of host physiological systems. Studies show that the composition of microbiota in psychiatric diseases including schizophrenia and bipolar disorder differs from healthy individuals. Many environmental factors can change the composition of microbiota and therefore potentially contribute to the development of many disorders, including neuropsychiatric disorders.

Summary: Microbiota is a potential factor contributing to the onset or modulating the course of many illnesses, including brain disorders The subject of imbalanced microbiota composition give hope for finding etiology or improving treatment of many disorders. However, it still requires more studies.

Key words: gut microbiota, dysbiosis, schizophrenia, bipolar disorder

1.   Introduction

The number of bacteria in an adult's body is estimated at 100 trillion, 80% of which can be found in the gut [1]. Human body contains ten times more microbial cells than human cells. That is because of extremely high density of microbes found in the human intestinal tract (typically 10^{11}–10^{12} microbes/ml of luminal content) [2]. Alterations in bidirectional brain-gut microbiota interactions are believed to be involved in the pathogenesis of irritable bowel syndrome [3,4] and gastrointestinal disorders [5]. Dysregulation of microbiota is a potential factor in pathogenesis of brain disorders such as mood disorders [6,7] and autism spectrum disorder (ASD) [8]. Altered microbiota was also associated with eating disorders [9,10] and Parkinson's disease (PD) [11]. Intestinal microbiota is also a potential factor in balancing the HPA axis. intestinal microbes can be a reason of imbalances of the HPA axis affecting the neuroendocrine system in the brain, which can lead to anxiety-like behavioral phenotype [12]. The gut microbiome can induce beneficial effects on host health and lifespan depending on the host nutrient signaling pathways. Although gut dysbiosis disturb the interdependence leading to reduction of the beneficial effects or even reverse effects. It can also trigger the innate immune response and chronic low-grade inflammation [13]. It is now known that a healthy gut microbiota has a large impact on the overall health of the host [14]. There is a number of common features between schizophrenia and bipolar disorder, both symptomatically and biologically [15].Alterations of the gut microbiom composition were also fund within patients with bipolar disorder [16] and schizophrenia [17].

2.   The Gut – Brain Axis

A huge amount of bacteria, archaea, viruses, and unicellular eukaryotes inhabit human body. Those coexisting microorganisms are known as microbiota [18]. The presence of the microbiota differs within different parts of the gastrointestinal tract. In the stomach and small intestine few micro-organisms can be found.

However, in the colon there is a concentration of approximately 1.012 bacteria, with two main representations of *Firmicutes* and *Bacteriodetes phyla* [19]. Microbiota is known to have an important role in immune system [20, 21], the host metabolism [22, 23] and is increasingly recognized for influencing the development of host nervous system and behaviors [24].

Central nervous system (CNS) sends regulatory signals to the gut and vice versa [25]. The connection between the gut and the brain exists on many pathways including:

- the enteric nervous system (ENS)
- vagus nerve
- the immune system
- the metabolic processes of gut microorganisms [26].

The motor, sensory, and secretory modalities of gastrointestinal tract may be influenced by the signals coming from the brain, but also visceral signals from gastrointestinal tract are able to influence brain function [27]. The autonomic system leads afferent signals emerging from the lumen, transmitted through enteric, spinal and vagal pathways to CNS, but also the efferent signals form CNS to the intestinal wall [28]. The vagus nerve (VN) is the tenth cranial nerve.VN contains approximately 80% afferent and 20% efferent fibers [29]. It is thought to be an important component in the communication pathway between the bacteria exposed to the gut and the brain [30].The afferent fibers of vagus nerve are crucial for conveying visceral information to the brain [31]. Immune-related and neural signals coming from bacteria, including 'probiotic' organisms, are transmitted from the gut through blood circulation or directly via the vagus nerve to the CNS [32]. Vagus nerve is thought to be able to dampen peripheral inflammation and to decrease intestinal permeability due to the cholinergic anti-inflammatory pathway that was represented through its fibers [33].The gut microbiota is linked with the immune system due to its ability of the commensal microbiome to regulate the maturation of the mucosal immune system. However, the pathogenic microbiome causes immunity dysfunction [34]. Another function of microbiota in immune system is its ability to influence the activation of peripheral immune cells that regulate responses to neuroinflammation, brain injury, autoimmunity and neurogenesis [35]. It has been suggested that composition of gastrointestinal microbiota has a role in resilience to stress- and immune-related disorders and dysfunction of stress- and immune-systems [36]. Gram-negative bacteria can bind of the lipopolysaccharide (LPS) component of their cell walls to toll-like receptors present at monocytes, macrophages and microglia and through this stimulate production of pro-inflammatory cytokines [37].The immune system of host is thought to be able to sense gut bacterial metabolites in addition to pathogen-associated molecular patterns (PAMP). Moreover, recognition of those can influence the host immune response concerning disease and inflammation in the gut and beyond [38]. Short-chain fatty acids (SCFA) are the major end products of bacterial degradation of soluble fiber in the large intestine. The main short-chain fatty acids produced during this process are acetale, propionate and butyrate. SCFA are a group of bacterial metabolites with pleiotropic effects on host immune and energy state [39]. It is well known that SCFA, especially butyrate, play an import ant role in maintaining the colonic epithelium [40]. SCFA may reduce migration and proliferation of immune cells, decrease many types of cytokines and cause apoptosis, thus suppress inflammation.

Nevertheless, clear alterations of SCFA concentrations in blood or various tissues may be the reason for disorders related to immunological and metabolic imbalances [41].

3.   Gut microbiota and neuropsychiatry

Gut microbiome is thought to be an important part of not only normal brain development, but also modulation of host physiological systems which are significant in stress-related disorders [42]. Emotional and physiological stress influence the composition of gut microbiota [43]. Moreover, it has been suggested that gut microbiota affects brain function via the inflammasome signalling platform which influence inflammatory pathways altering brain function and due to this affecting depressive- and anxiety-like behaviours [44].

"Developmental programming" is a process in which environmental factor occurs in a sensitive or vulnerable developmental period , especially In early life, influencing structure and function of organs which may last throughout life. One of these factors is gut microbiota [45]. Factors like caesarean section, formula feeding and early-life antibiotic exposures can influence microbiome establishing and potentially affect health of the host [46].

In case of many neuropsychiatric diseases it is still not fully understood what causes them. Without knowing the accurate biological target of those diseases , it makes it difficult to treat them successfully [47].

Gut microbiota has influence on many aspects of host's functioning. The study by Manderino et.al (2017) performed on neurologically-healthy older adults suggests association between composition of the gut microbiome cognitive test performance. In this study participated 43 older adults. Tests of their stool samples showed different distributions of *Bacteroidetes*, *Firmicutes*, *Proteobacteria* and *Verrucomicrobia* compering Intact and Impaired groups [48]. Another aspect of gut microbiota is the association with mood disorders. Stressors and pathogens can cause inflammatory responses either exaggerated or prolonged which is an important factor in depression's pathogenesis for a subset of depressed individuals [49]. Other factor that increase inflammatory responses is intestinal permeability caused by depression, childhood adversity, stressors, and diet [49]. Bacteria in the genus *Lactobacillus* which increase the health of the host, during stress is consistently reduced [50]. It has been suggested that gut microbiota plays a role in balancing the hypothalamic-pituitary-adrenal (HPA) axis and if imbalance occurs it can lead to an anxiety-like behavioral phenotype [51]. Studies in animals showed that gut bacteria influence behavior, Brain-Derived Neurotrophic Factor (BDNF) levels and serotonin metabolism [52]. In the study by Sharon (2019) gut microbiota from human donors with autism spectrum disorder (ASD) or typically-developing (TD) controls was transplanted into germ-free mice. The study showed that ASD and TD microbiota produce differential metabolome profiles in mice. colonization with ASD microbiota is enough to induce characteristic autistic behaviors. Moreover, the administration of specific metabolites is able to correct those behaviors in mice [53]. Gut microbiota is also linked to dietary habits. Changes in dietary fibers can change composition of gutmicrobiota. Diet is a main factor determining composition of the colonic microbiome. However, the host genetic background and the colonic milieu can also influence this composition [54]. It is possible that gut microbiota influence the gut–brain axis in eating disorder altering appetite control and brain function as part of their the genesis [55].

Researches show growing evidences that the intestinal microbiota plays a substantial role in nutrient extraction and host metabolism [56].

4.   Schizophrenia and bipolar disorder

Schizophrenia (SCZ) is a severe psychotic disorder which core features are cognitive impairment, negative and positive symptoms. It affects approximately 1% of the adult population worldwide over the average lifetime [57,58]. Genetic factors combined with environmental insults such as prenatal infection, perinatal complication, and cannabis use are considered to be the cause of schizophrenia [59]. Bipolar disorder (BD) is a chronic disorder of a recurring character with symptoms of mood state and energy fluctuations. Functional decline, cognitive impairment, and a reduction in quality of life are observed in patients suffering from bipolar disorder [60]. Mood fluctuates between episodes of mood elevation (mania) and depression with interlaced periods of euthymia [61]. BP affects around 2.4% of the global population [60]. Bipolar disorder and schizophrenia have many features in common such as some of the characteristic symptoms and the lifelong course. Etiology of both diseases is not fully understood and they are classified by their phenotypic features [62].Common genetic etiologies have been found between schizophrenia and bipolar disorder [63]. Severe mental illnesses (SMI), mainly schizophrenia and bipolar disorder (BD), are a leading global cause of disability and they are considered one of the most notable causes of death worldwide [64]. In the study by Zheng et al. (2019) the gut microbial communities of patients with SCZ and healthy controls (HCs) was compared. The study revealed that the microbial composition of patients with SCZ was less diverse than that of HC individuals. There was also an association between microbiota composition of SCZ patients and lower α-diversity stores comparing to HC group. It was explained that a high α-diversity is thought to represent a marker of "good" health status. Moreover, results of the study showed unique bacterial taxa linked to SCZ severity. In the same study microbiomes of SCZ group and HC group were transferred to mice. Compared to mice with HC group microbiota, those with human SCZ microbiomes presented changes in gut microbial composition and behavioral phenotypes proper to SCZ. However, those behavioral phenotypes may be nonspecific [65]. The study by Liang et al. (2019) compared the metabolic signatures of the cortex, cerebellum and striatum in schizophrenia microbiota and healthy microbiota recipient mice. Results showed relevant differences of the metabolite signatures between those two groups. Moreover, according to the study disruptions of glycerophospholipid and fatty acyl metabolism were linked to the onset of schizophrenia-related behaviors [66]. In the study by Hu et al. (2019) the gut microbiota in depressed patients with bipolar disorder before and after quetiapine treatment was characterized and compared with healthy controls. Result showed major differences between BD and HC groups. *Bacteroidetes* and *Firmicutes* dominated respectively in the gut microbiota composition in untreated BD patients and HCs.Moreover, lower levels of butyrate-producing bacteria was observed in untreated patients. Comparing BD and HC group, greater diversity of gut micro biota was observed in HCs. Quetiapine treatment caused significant changes in gut microbial composition. Large genera of *Klebsiella* and *Veillonella* were observed in treated patients [67]. In the study by Aizawa et al. (2019) fecal samples from patients with bipolar disorder and healthy controls were examined and bacterial counts were compared.

As the results, there were no significant differences in bacterial counts between those two groups. Although, *Lactobacillus* counts and sleep showed negative correlation. A negative correlation between *Bifidobacterium* counts and cortisol levels in patients were found. The results suggests that these bacteria may play a role in sleep and stress response in the patients [68].

5.   Conclusion

Over the last few decades, gut microbiota has become a subject of interest in many fields of science. The microbiota – gut – brain axis is thought to be involved in immune system, the host metabolism, central nervous system and behaviors. Microbiota is a potential factor contributing to the onset or modulating the course of many illnesses, including brain disorders. Different ways of connection between gut microbiota and central nervous system were described. The connection between them is especially interesting in case of neuropsychiatric diseases. There are many studies on both animals and humans, pointing the potential role of microbiota dysbiosis in psychiatric illnesses. Revealing the etiology of schizophrenia or bipolar disorder would make the treatment of them much more effective. However, the subject of microbiota is still in its infancy and require more studies.

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