

The role of gut microbiota in selected neuropsychiatric disorders

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Summary

The gut microbiota consists of multiple microorganisms including bacteria, viruses and fungi and is referred to as the largest organ of the human body. The relationship between the host and its microbiota is of a mutualistic kind. In physiological conditions, microbiota produce vitamins, enable harvesting energy from undigested carbohydrates and ensure valid functioning of host immunity. The complicated network of connections and signalling, the so called *cross-talk*, warrants the metabolic and immunological homeostasis of the host. There is emerging evidence that the microbiota is the key component of the gut-brain axis, and its composition provides undisturbed functioning of the central nervous system (CNS) through various mechanisms, including neuronal pathways, production of bacterial metabolites and immune mediators. Alteration in gut microbiota has been linked to an occurrence of various neuropsychiatric disorders, i.e. autism, schizophrenia and depression. The gut-brain axis is the subject of many preclinical and clinical studies, as it is assumed that the insight into the underlying mechanisms of these complex interactions could be beneficial in development of novel therapeutic strategies for the treatment of neuropsychiatric conditions. This review summarizes literature regarding the gut-brain axis, its functioning and its role in the pathogenesis of selected neuropsychiatric illnesses as well as describes possible therapeutic approaches.

gut microbiota, gut-brain axis, mental disorders

1. INTRODUCTION

The term *microbiota* refers to all communities of microbes, predominantly bacteria but also fungi, viruses, archaea and eukaryotes that inhabit the host, whereas the term *microbiome* refers to a microbe's collective genome. Microbiota inhab-

it many different sites in the human body, mainly occupying the gastrointestinal tract and oral cavity, genitals, upper respiratory tract and skin [1]. The human gut contains approximately 10^{14} microbes that equals 10-fold the number of human eukaryotic cells, and the large intestine is the organ with the largest amount and diversity of microorganisms [2]. About 1000 bacterial species have been identified in the human gastrointestinal tract, and each individual is estimated to carry 160 species [3]. The composition of gut microflora varies significantly between individuals and populations, but novel metagenomic techniques have led to an identification of three so-called enterotypes—the permanent layouts of

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intestinal bacteria are characteristic to the given host and differ in the terms of dominant phyla and therefore provide variability in host metabolic processes. *Bacteroides*, *Prevotella* and *Ruminococcus* have been distinguished as enterotypes in humans [4].

The composition of human microbiota changes during the lifetime. The mode of delivery, diet, hygiene, antibiotics and stress all affect the gut microbiota. The foetal environment has been considered sterile for decades, but now evidence is emerging that the first contact with microorganisms occurs in foetal life, as DNA of non-pathogenic microbes from the Tenericutes, Firmicutes, Bacteroidetes, Proteobacteria, and Fusobacteria phyla have been identified in the placenta and Proteobacteria in amniotic fluid [5]. The early stages of life, especially the neonatal and infancy periods, present a huge effect on the composition of gut microbiota. Vaginally delivered newborns tend to acquire bacteria of the *Prevotella*, *Lactobacillus* and *Bifidobacterium* phyla, whereas newborns delivered by Cesarean section are predisposed mainly to *Staphylococcus* and *Corynebacterium* colonization [5,6]. Another factor shaping the intestinal microbiota configuration is the maternal and neonatal diet [5,7]. Breast-feeding is linked to higher occurrence rates of *Bifidobacteria* and lactic acid bacteria and decreased numbers of potential pathogens, such as *Escherichia coli*, *Bacteroides fragilis* and *Clostridium difficile* compared to formula-fed infants [7]. Contrarily, formula-fed infants present higher diversity in microbial phyla in general, with the dominance of Bacteroidetes, Clostridia, Staphylococci, Enterobacteriaceae and Streptococci [5,7]. Introduction of a solid diet results in further changes of microbiota composition, predominantly in the increase in diversity of microbial species and reduction in Proteobacteria and Bifidobacteria [7,8]. The transition takes approximately 3–5 years, and by that time, the gut microbiota resembles that of an adult [5]. Dietary habits further shape the gut microbial community in adulthood. A high protein and animal fat diet predispose to colonization with the *Bacteroides* enterotype, whereas a high fibre diet predisposes to colonization with the *Prevotella* enterotype [9].

Infections, antibiotics, stress and many other factors lead to alteration in the composition

of intestinal microbiota during the lifetime, and therefore, it varies between young adults and elderly individuals [10]. Age-related gut microbiota dysbiosis may be linked to the occurrence of various neurodegenerative and neuropsychiatric disorders [7].

2. CROSS-TALK BETWEEN GUT MICROBIOTA AND THE CENTRAL NERVOUS SYSTEM

The gut-brain axis is composed of the central nervous system (CNS), enteric nervous system and digestive system and provides bidirectional communication between intestinal microbiota and the CNS [10]. The concept of connection between the gut and the brain dates back to the 1800s when the association between mood and gastric secretion was first described [11]. The gut microbial community is now considered a key factor in maintenance of the homeostasis of the CNS, and gut microbiota dysbiosis has been implicated in the onset of many neurological and neuropsychiatric conditions. The pathways behind the gut-brain cross-talk are being continuously resolved. Production of bacterial metabolites and immune mediators as well as direct neuronal signalling are mentioned as possible mechanisms [12].

2.1. Immune mediators

The immune system acts as a kind of compound between gut microbiota and the CNS. Intestinal microorganisms are usually more frequently located at sites enriched in immune cells [13]. Microbiota can stimulate immune responses and send signals to the brain via afferent nerves or by secreting molecules, such as lipopolysaccharide (LPS, a component of the cell wall of gram-negative bacteria) or peptidoglycan, into the circulatory system [7]. LPS can bind to toll-like receptors that are distributed on the monocytes, macrophages and microglia of the CNS causing the release of pro-inflammatory cytokines, i.e. interleukin-6 (IL-6) or interleukin-1 β (IL-1 β) [12]. Various pre-clinical and clinical studies have confirmed the effect of microbes on brain function and behavioural abnormalities. TLR-4 (Toll-like receptor

4) related responses have been observed in patients with irritable bowel syndrome (IBS) and depression [14], and intracerebroventricular administration of LPS has also caused depression-like behaviours [15]. In other studies, bacterial infection in mice was associated with greater neuronal activity in the afferent pathway of the vagus nerve, confirming its role in transferring the inflammation signal [16].

2.2. Microbial metabolites

Acetic, propionic and butyric acids account for microbiota-derived metabolites, namely short-chain fatty acids (SCFAs). SCFAs are products of the fermentation of non-digestible polysaccharides and act both through inhibition of histone deacetylases and activation of G-protein-coupled receptors [17]. SCFAs play an important role in maintaining health and enable communication between gut microbiota and the CNS [12]. SCFAs are known to be involved in neurotransmission modulation. Butyric and propionic acids increase the expression of tyrosine hydroxylase, an enzyme catalysing the rate-limiting step in the conversion of L-tyrosine to L-DOPA (L-3,4-dihydroxyphenylalanine) in the dopamine and noradrenaline synthesis pathways. These two acids also attenuate dopamine- β -hydroxylase, an enzyme that converts dopamine into noradrenaline [10]. Propionic acid alone is involved in modulating neurotransmission by reducing levels of serotonin (5-HT), gamma-aminobutyric acid (GABA) and dopamine *in vivo* [10]. Moreover, butyric acid has revealed antidepressant properties in pre-clinical trials, whereas high doses of propionic acid have been linked to cognitive impairment [12]. SCFAs are also capable of modulating microglial cells and astrocytes, and the specific effect is SCFA-type related. There is evidence that SCFAs show anti-inflammatory properties and could reverse microglial malformation and immaturity when administered to germ-free mice [10].

2.3. Enteroendocrine signalling

Enteroendocrine cells (EECs) are located within the intestinal wall and specialize in the synthe-

sis and secretion of various molecules and peptides, namely cholecystokinin (CCK), glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) that moderate dietary intake and absorption, satiety and insulin secretion. EECs are stimulated by gut microbiota-related molecules, i.e. SCFAs. Hormones produced by the EECs interact with receptors based within the vagal nerve afferent fibres, and therefore, EECs are involved in the functioning of the gut-brain axis [7,12].

2.4. Neuronal pathways and neurotransmission

As mentioned above, the vagus nerve plays a major role in bidirectional communication between the intestine and the brain. Gut microbiota not only may activate the vagal afferent fibres directly when intestinal permeability is increased but also indirectly by producing metabolites (i.e. SCFA) or peptides by EECs. For example, in pre-clinical studies, the anxiolytic effects of probiotics have not been observed in vagotomised mice and rats, confirming that the vagus nerve represents an important pathway in transition of neuromodulating signals [18]. Microorganisms have also been associated with local production of neurotransmitters, including GABA, 5-HT, catecholamines and histamine. These neuroactive molecules are later signalled to the brain via enterochromaffin cells or vagal afferents [10]. Discussion is currently ongoing whether peripherally synthesized neurotransmitters can affect the CNS directly by crossing the blood-brain barrier (BBB) [12]. Gut microbiota has been further considered to be able to control the synthesis of brain-derived neurotrophic factor (BDNF) and other neurotrophic factors, such as glial-derived neurotrophic factor and nerve growth factor [12]. Interestingly, microbiota can also influence neuroinflammatory responses by modulating the brain's immune cells—the microglia. Neuroinflammatory processes tend to be amplified in neuropsychiatric and neurodegenerative disorders. In various clinical trials, beneficial effects of probiotics in reducing the levels of pro-inflammatory cytokines have been observed in, for example, multiple sclerosis [12].

2.5. Tryptophan metabolism

Tryptophan is a precursor of 5-HT and kynurenine. First-line antidepressants target the 5-HT system, increasing its concentrations in the brain. Gut microbiota appears to have the ability to affect mood, appetite, aggression and sleep by altering tryptophan metabolism. Germ-free mice have been reported to present higher levels of tryptophan and decreased levels of 5-HT in comparison to normally colonized mice [19]. In other studies, administration of various probiotics has been found to influence tryptophan and 5-HT levels.

3. THE GUT-BRAIN AXIS IN SELECTED NEUROPSYCHIATRIC DISORDERS

3.1. Depression

Depression is a mood disorder associated with persistent feelings of sadness and loss of interest. Pathophysiological mechanisms of depression include immunological dysregulation and alteration in functioning of the hypothalamic-pituitary-adrenal (HPA) axis. Emerging evidence links imbalanced intestinal microbiota to an increased depression occurrence rate. Patients with clinical depression generally show increased diversity in the composition of gut microorganisms with a greater number of Firmicutes, Actinobacteria and Bacteroidetes and lower number of *Bifidobacterium* and *Lactobacillus* compared with controls [7,12]. Interestingly, transplantation of gut microflora from depressed patients to GF rats results in alteration of kynurenine/tryptophan metabolism and occurrence of depression-like behaviour in transplant recipients [7,20].

There is evidence that depression coexists with cell-dependent inflammation processes and can occur along with other inflammatory diseases, including inflammatory bowel disease and multiple rheumatic conditions. Increased bowel permeability results in transition of bacteria to the circulatory system, and increased levels of circulating immunoglobulin A and M antibodies against LPS of gram-negative bacteria were reported in chronically depressed patients [21]. Moreover, higher levels of IL-6 and TNF α seen in patients with depression were successful-

ly lowered after effective antidepressant treatment [22]. In a population of Polish women, correlation has been found between SCFA concentration and depressive syndromes, implying the role of these immune modulating gut-derived molecules in the pathogenesis of depression. In this study, the levels of acetic and propionic acid were lowered in depressed patients, whereas the concentration of isocaproic acid was significantly increased compared to healthy controls [23].

3.2. Schizophrenia

Schizophrenia is a chronic mental disorder characterized by a breakdown in the relation between thought, emotion and behaviour and occurrence of symptoms including psychoses, delusions, apathy and amotivation. The aetiology of schizophrenia includes both genetic and environmental factors. Some authors suggest a role of gut microbiota in the onset and progression of schizophrenia. It often occurs with other gastrointestinal disorders, such as gastritis, colitis and coeliac disease, with the latter being a proven risk factor for development of schizophrenia [24].

Chronic inflammation is another suspected cause for schizophrenia. As stated before, a damaged intestinal barrier leads to translocation of lumen microorganisms to the circulatory system and development of a chronic gut microbiota-derived inflammatory state. Evidence supporting this theory includes the presence of soluble CD14 and lipopolysaccharide binding protein in the serum of schizophrenic patients as well as elevated serum levels of antibodies against *Saccharomyces cerevisiae*—all of which count for bacterial translocation markers [25]. Furthermore, elevated levels of inflammatory markers, i.e. CRP, have been observed in patients suffering from schizophrenia, and the levels of these markers have correlated with disease severity [26].

Gastrointestinal infection with *Toxoplasma gondii* is an additional risk factor for schizophrenia. The protozoan can alter gut microbiota composition leading to a decrease in the diversity of lumen microorganisms and increased lumen translocation. *T. gondii* is suspected to cause a psychotic state by either stimulating the immune system or through production of pro-psychot-

ic metabolites by disturbed microflora [12]. Viruses affecting the bacteria, the bacteriophages, also have the ability to change the composition of microbiota, and therefore can alter gut-brain signalling [10]. Moreover, schizophrenia development has been linked to infection with *C. difficile*, as elevated levels of urine metabolites synthesized by *Clostridium* species have been found in patients with schizophrenia [27].

3.3. Autism spectrum disorder

Autism spectrum disorder (ASD) is a group of disorders characterized by impairment in social interaction and communication together with repetitive behaviours. The aetiology of ASD is poorly determined; however, evidence is emerging linking ASD to gut microbiota. Alterations in the composition of gut microbiota have been established both in animal and humans models with ASD. Increased levels of *Bacteroidetes*, *Clostridium* and *Lactobacillus* and lowered levels of *Firmicutes* have been found in faecal samples of children with ASD compared to healthy subjects [28]. Interestingly, treatment with oral vancomycin and probiotics may improve stereotyped behaviour, supporting the theory of the gut-brain connection in ASD; however, further large well-controlled studies are necessary to verify this thesis [25,28].

As in other neuropsychiatric conditions, disruption of the gut epithelial barrier, causing “leaky gut syndrome” and passage of bacteria and their metabolites into the bloodstream, have been reported in ASD patients. Increased circulating levels of pro-inflammatory cytokines (IL-1 β , IL-6, IL-8), TNF α and TGF β have also been observed in these patients [28]. Furthermore, autistic patients show increased levels of SCFAs in faecal samples. Nevertheless, SCFAs seem to play differential roles in ASD. Propionic acid, one of the SCFAs often added to dairy products, may affect autistic behaviour, as autistic symptoms have been observed shortly after administration of a dairy diet, whereas elimination of PPA from the diet has resulted in improvement in speech and communication skills, lower hyperactivity and better focusing [25]. Contrarily, administration of butyrate has improved repetitive behaviours in mice [7].

Hyperserotonemia has a role in the pathogenesis of ASD. Elevation of 5-HT levels in ASD is suspected to arise from increased intestinal synthesis of this monoamine by EECs stimulated by gut microflora dysbiosis and chronic low-key inflammation. On the other hand, decreased synthesis of 5-HT has been reported in the brains of autistic individuals, explaining the reduced cognitive function and mood impairment specific for ASD [28].

3.4. Attention deficit hyperactive disorder

Attention deficit-hyperactive disorder (ADHD) is a neurodevelopmental disorder with the core symptoms of hyperactivity, impulsivity and inattention. The pathogenesis of ADHD is unclear, but disturbances in dopamine and norepinephrine pathways are listed as one of the most prevalent among the possible pathogenic mechanisms.

Differences in the gut microbiota composition of ADHD patients have been reported. ADHD has shown greater abundance of the genus *Bifidobacterium* compared to healthy individuals [29]. In the same study, in the ADHD group, *Bifidobacterium* was responsible for elevated levels of cyclohexadienyl dehydratase (CDT), an enzyme crucial for the synthesis of phenylalanine. Phenylalanine is an essential but exogenous amino acid able to cross the BBB, which acts as a precursor to dopamine and noradrenaline in the brain. As stated before, both dopamine and noradrenaline are key monoamines in ADHD pathogenesis; therefore, increased levels of microbial-derived phenylalanine may cause disturbances in dopamine and noradrenaline synthesis and may be responsible for ADHD symptoms. In another study, elevated levels of Bacteroidaceae have been confirmed among ADHD children, and *Neisseria* and *Bacteroides* spp. have been identified as possible biomarkers of ADHD [30]. Furthermore, the authors postulated a negative correlation between hyperactivity and alpha diversity (described as the number of species in relation to the abundance of species in a sample) in the ADHD group.

Neuroinflammation triggered by alteration in intestinal microbiota composition may be another factor affecting ADHD symptoms. Stud-

ies have described increased levels of pro-inflammatory molecules, i.e. IL-16, in the serum of ADHD patients [31]. Moreover, neuronal damage and disturbed neurotransmission observed in ADHD patients are reported to be a result of increased oxidative stress partially caused by altered gut microbiota [32].

3.5. Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia in elderly individuals and is characterized by the loss of memory and behavioural changes. Pathophysiologically, AD is related to the excessive production and accumulation of amyloid beta ($A\beta$) in the brain as well as the hyperphosphorylation of tau protein and formation of neurofibrillary tangles [33]. Following the emerging studies, it has been hypothesized that gut microbiota and its by-products can facilitate the inflammatory state that contributes to the manifestation of AD.

Some of the bacteria constituting the intestinal tract, i.e. *Bacillus subtilis* and *E. coli*, have been associated with the peripheral production of amyloid that later easily diffuses into the bloodstream and the brain due to the increased lumen and BBB permeability [34]. Gut microbiota alteration with an increase in the number of pro-inflammatory bacteria of the Proteobacteria phylum and a reduction in the number of anti-inflammatory bacteria of the phyla Firmicutes and Bacteroidetes have been noted in AD patients [35]. Increased levels of amyloid and other microbial-derived molecules trigger an inflammatory state in the CNS and therefore contribute to the cognitive impairment commonly observed in AD.

Additionally, dysregulation of tryptophan metabolism caused by intestinal dysbiosis is believed to play a major part in the pathogenesis of AD [33]. Furthermore, reduced BDNF levels observed in AD may also be responsible for increased anxiety and cognitive dysfunction. The interplay between BDNF, gut microbiota and AD symptoms has been established in studies concerning germ-free mice [36].

4. TREATMENT APPROACHES

As dysregulation of the gut-brain axis is known to accompany various mental and neurodevelopment disorders, it is not surprising to expect an impact on the treatment of these chronic conditions by altering impaired or incomplete gut microbiota. Possible therapeutic approaches are mainly comprised of supplementing the patient with probiotics and prebiotics or modulating their dietary habits [10].

Microorganisms that provide one's health with distinctive benefits are called probiotics. More evidence is accumulating that shows the beneficial effects of probiotics on the symptoms of neuropsychiatric conditions. Restoration of gut permeability by an increase in mucin production, reduction of low-level systemic inflammation by a decrease in production of IL-12, TNF α and INF α and higher production of anti-inflammatory cytokines as well as the modulation of neurotrophic factors are listed among those advantages. It is crucial to understand that administering probiotics to patients during clinical trials is still not commonly practised. One of the first researchers to perform such a trial was Benton, who introduced healthy individuals to probiotic capsules or probiotic yogurt and compared his findings to a group not receiving probiotics. The result showed an improvement in the anxiety and depression levels within the group receiving probiotics [37]. In the same study, patients with chronic fatigue syndrome reported decreased anxiety and depression levels, whereas patients with schizophrenia did not benefit significantly from probiotic treatment; nonetheless, their peristalsis improved. The ASD group showed better ability to comply with commands and to concentrate after being exposed to *Lactobacillus acidophilus*. Consequently, another study concluded that probiotics may play a vital role in prevention of neuropsychiatric disorders, such as ASD [38]. Oral administration of *B. fragilis* has also ameliorated distinctive symptoms, i.e. anxiety, stereotypical behaviour and sensory-motor gating, in animal models of ASD [39]. Results showing the possible treatment methods are still preliminary, and more thorough investigation is necessary to assess reliable outcomes. As far as cognitive functions are concerned, there are so far no evident positive re-

sults of probiotic treatment within the group of healthy subjects, whereas the group of patients with mild symptoms of hepatic encephalopathy has gained some improvement of motor skills and attention as a result of probiotic consumption [10]. Similarly, a small improvement in cognitive function was reported after 12 weeks of treatment with probiotics among patients with AD, although those results need further examination and rechecking [40].

Other therapeutic approaches include using prebiotics and modulating dietary habits. The term prebiotics refers to food particles that are not consumed in the digestive process and stimulate the development of gut microbiota. Prebiotics include, above all, galacto-oligosaccharides, fructo-oligosaccharides, inulin and oligofructose. All of the above show a positive impact on normalizing and stabilizing gut microflora by favouring the growth of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* [10]. As a result, according to some novel publications, prebiotics regulate the microbial-gut-brain axis and improve both psychological distress symptoms and the profile of inflammatory mediators [10,41]. Systematic review of randomized controlled trials assessing the role of probiotics in the functioning of the CNS in both animals and humans has concluded that treatment with *Bifidobacterium* and *Lactobacillus* for 2 weeks in animals and 4 weeks in humans show efficacy in improving psychiatric disorder-related behaviours, such as anxiety, depression, ASD-related symptoms, obsessive-compulsive disorder-related symptoms and memory abilities [42]. Currently, the effect of beta-galacto-oligosaccharides on anxiety – and depressive-like behaviours is to be investigated in a genetic animal model of depression [43].

Rapid changes in the dietary habits of individuals can have a major impact on gut microbiota. There is an evidence that even short-term alterations in one's diet can shift the gut microbiome and change the quality and quantity of distinctive microorganism species. A diet mainly composed of meat can promote the growth of bile-tolerant classes of bacteria, such as *Bilophila* and *Bacteroides*. At the same time, it depletes the development of Firmicutes, including *Lactobacillus*. Subsequently, a plant-rich diet can reverse this process [44]. Additionally, it was proved that

“Western” type of diet, i.e. high-fat and high-sugar diet, may lead to a decrease in *Bacteroides* levels and an increase in Proteobacteria and Firmicutes levels. The impact on gut microbiome is, of course, due to the capability of bacteria to decompose protein and carbohydrates in meat – and plant-rich diets. How fast the composition of microorganisms within GI tract shift is naturally individual, but it is notable that some changes can occur rapidly and are not easily reversible.

In addition, in recent years, emphasis has been placed on finding novel treatment methods. One of them is faecal microbiota transplantation (FMT), which has already been proved effective in the treatment of recurrent *C. difficile* infection. Nowadays, many studies are being conducted to show its usefulness in the therapy of other conditions in which gut microbiota dysregulation can occur. In IBS, it is assumed to be as much as up to 90% effective in diminishing its symptoms [45]. Also, clinical trials are verifying the beneficial effects of FMT in controlling ASD-related cognitive symptoms. In a study performed in a group of children with ASD treated with microbial transfer therapy (FMT after 2 weeks of antibiotic therapy), improvements in behavioural symptoms were observed [46]. The results are promising, yet preliminary.

5. CONCLUSION

The gut-brain axis can regulate neuropsychological processes by interfering with neuronal pathways or by the production of microbial metabolites and immune mediators. Dysregulation of its components has been observed in various neuropsychiatric conditions, i.e. ASD, schizophrenia or AD. The results of preclinical studies of the gut-brain axis has increased our knowledge concerning its functioning; nonetheless, further well-controlled large clinical trials are necessary to verify these findings in humans. Moreover, despite promising results regarding the beneficial effects of psychobiotics in the management of neuropsychiatric illnesses, further investigations are required to establish its role as a first-line treatment option.

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