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Interactions between the gut microbiome and the central nervous system and their role in schizophrenia, bipolar disorder and depression

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Summary

The microbiome co-evolved with its human host over a long time and became essential for many processes. Bacteria play a role in maintaining human health as they digest food, produce vitamins and participate in the regulation of metabolism. By influencing the cytokine balance along with the composition and activity of leukocytes, they constantly interact with the immune system, affecting innate and adaptive immune homeostasis. A growing number of studies indicate that the microbiome in the human intestine may have an impact on the functions of the central nervous system (CNS), through identified pathways called the gut–brain axis. Recent data show that the human microbiome ecosystem interferes with the brain's development, central signaling systems and behavior. It has been proposed that disruption in the human microbiome may affect the course of psychiatric disorders. The aim of this review is to summarize the recognized pathways of the gut–brain axis that have been thoroughly studied in animal models and to evaluate the role of the dialogue between the microbiota and the central nervous system in schizophrenia, bipolar disorder and depression.

microbiome/gut–brain axis/vagus nerve/neurotransmission/hypothalamic–pituitary–adrenal (HPA) axis

INTRODUCTION

The commensal bacteria microsystem in humans consists of 3.9×10^{13} bacteria, indicating that the number of bacteria in our bodies represents the same order as the number of our eukaryotic cells [1]. A view that bacterial species exceed the number of human cell types up to five times has been accepted for a long time, however, recent work has debunked this notion. A new study suggests that the ratio of bacterial to hu-

man cells is approximately 1.3:1 [2]. Bacteria are transferred from the mother to the baby during labor. The method of delivery, diet, drugs and medications (especially antibiotics) contribute to the process of microbiome development in the infant [3]. A 1-year-old child has eventually formed individual community of microorganisms [4] so too is a new microbial ecosystem, one that resides in that person's gastrointestinal tract. Although it is a universal and integral part of human biology, the temporal progression of this process, the sources of the microbes that make up the ecosystem, how and why it varies from one infant to another, and how the composition of this ecosystem influences human physiology, development, and disease are still poorly understood. As a step toward systematically

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investigating these questions, we designed a microarray to detect and quantitate the small subunit ribosomal RNA (SSU rRNA). *Bacteroidetes* and *Firmicutes* are two bacterial phyla that account for the majority of intestinal microflora. Others, less prevalent, include *Actinobacteria*, *Archaea*, *Fusobacteria*, *Proteobacteria*, *Verrucomicrobia*. Apart from bacteria, the microbiota comprises fungi, protists and viruses, but in this paper we use this term referring only to bacteria. Although a person's microbiota constitutes a distinct, personal assembly, studies reveal that people share commonalities in the composition of bacterial populations. Depending on the proportion of bacterial genera, the human population can be divided into three enterotypes. Enterotype I is dominated by *Bacteroidetes*, enterotype II is characterized by smaller amounts of *Bacteroidetes* but higher amounts of *Prevotella*, and enterotype III is characterized by the presence of *Ruminococcus* [5] but it is still based on very few cohorts and little is known about variation across the world. By combining 22 newly sequenced faecal metagenomes of individuals from four countries with previously published data sets, here we identify three robust clusters (referred to as enterotypes hereafter).

The microbiome co-evolved with its human host over a long time and became essential for many processes. Bacteria play a role in maintaining human health as they digest food, produce vitamins and participate in metabolic regulation. By influencing the cytokine balance along with the composition and activity of leukocytes, bacteria constantly interact with the immune system, affecting the innate and adaptive immune homeostasis [6].

A growing number of studies indicate that the microbiome of the human intestine may have an impact on the functions of the central nervous system (CNS), through identified pathways called the gut-brain axis. Recent data show that the human microbiome ecosystem interferes with the brain's development, central signaling systems and behavior. It has been proposed that the disruption of the human microbiome may contribute to the aetiology and course of some psychiatric disorders [7].

The aim of this review is to summarize the recognized gut-brain axis pathways and to evaluate their role in schizophrenia, bipolar disorder and depression.

THE INTERPLAY BETWEEN THE MICROBIOME AND THE HPA AXIS

Gut bacteria influence the brain by modulating the hypothalamic-pituitary-adrenal (HPA) axis, thus becoming a potent player participating in the body's stress response. It has been shown that the development of the HPA axis is determined by postnatal microbial colonization [8]. Disturbances in HPA axis functioning have been discovered in germ-free mice, alongside enhanced stress reactivity and impaired cognition [9]. However, this exaggerated acute stress response in germ-free mice can be reverted with bacterial transplant from healthy mice [10]. This effect occurs in normally colonized organisms as well – increased gut permeability leads to bacterial translocation that in turn results in HPA axis response and immune activation [11]. HPA axis reaction against acute stress may be ameliorated by probiotic treatment [12]. In rats early life stress (maternal separation) increases blood corticosterone levels and leads to immune activation as well as changes in gut microbiota [13]. However, this effect can also be reverted, as corticosterone release is normalized with probiotic pre-treatment [14] – *Lactobacillus* is a probiotic species found to be capable of reducing corticosterone levels [9]. In addition, early maternal separation is responsible for persisting changes in rats' behavior, the HPA axis balance and gut microbiota, and *Bifidobacterium infantis* is another probiotic species that has the ability to normalize stress-related behavior [15]. One study has shown that *Lactobacillus helveticus* and *Bifidobacterium longum* also have beneficial psychological effects that are paired with plasma cortisol reduction [16]. Not only can stress-associated behavior be modified with the help of probiotic bacteria, but there is a possibility to induce whole phenotypes by means of a microbiota transplant. Anxious or non-anxious phenotype in mice may be obtained after transplantation of intestinal microorganisms from an animal with the same phenotype [17]. What is more, a double-blind, randomized parallel group study revealed that after 30 days of oral treatment with a probiotic formulation comprising *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 24-hour urinary free cortisol was lower than in the control group. Reduction of anxi-

ety-like behavior in rats and alleviation of social distress in human volunteers have also been observed [18] a probiotic formulation (PF). Those findings indicate that gut bacteria are potent modulators of HPA axis in the long run. Schmidt et al. provide support for this hypothesis. They found that treatment with prebiotics, substances promoting the growth of beneficial bacteria, alters the cortisol-awakening response and emotional reaction in healthy human subjects [19]. Intestinal bacteria can modulate the HPA axis indirectly by acting on the vagus nerve, whose stimulation leads to HPA axis activation [20].

Bacteria have a huge impact on the HPA axis but the association between neuroendocrine reactions and the microbiome is bidirectional. Olfactory bulbectomy-induced depression in mice leads to disturbances in the microbial profile. It was found that this model of depression and anxiety displays elevated corticotropin-releasing factor (CRF) expression as well as increased c-Fos activity, serotonin levels and colon motility. Those changes are associated with an altered intestinal microbiome and with HPA activation [21]. Numerous signaling molecules influence the composition of gut microbiome, including chemicals released from enteric neurons, enterochromaffin cells and vagal afferents. CRF, an initial neurohormone of HPA response, may shape bacterial population, taking into account that it may affect gut functions in multiple ways by acting on the CRFR2 (corticotropin-releasing factor receptor 2), thus modulating stress-induced gut permeability, motility, immune and inflammatory response [22,23].

THE IMMUNE-SYSTEM MEDIATED INTERACTIONS BETWEEN THE MICROBIOME AND THE BRAIN

Although the brain is a distant organ for intestinal bacteria, microorganisms that reside in the gut can exert their influence on the CNS via the immune system, not to mention the fact that even the immune-privileged CNS appears to be persistently inhabited by innocuous alpha-proteobacteria [24]. Commensal microbiota modulates the autoreactivity of immune cells against the central nervous system [25]. The microbiome plays a role in the pathogenesis of numerous immune-mediated disorders such as spon-

dyloarthritis, rheumatoid arthritis and even experimental autoimmune encephalitis. Germ-free mice are resistant to those diseases [26] and their immune cells do not normally express toll-like receptors (TLR) – their lack makes an adequate immune and neuroendocrine response impossible [27]. Studies using TLR4 knockout mice support the notion that the immune system is one of the key moderators participating in the dialogue between the brain and gut bacteria as TLR4 knockout mice do not respond with HPA axis activation after administration of gram-negative bacteria [28].

Treatment with probiotics acts on the brain through the immune system. Cytokines are potent regulators of brain functioning. Peripherally produced pro-inflammatory cytokines like interleukins IL-1 and IL-6 can induce sickness behavior. Recent studies highlighted the role of cytokines in the pathogenesis of depression, bipolar disorder and schizophrenia. Gut bacteria affect the immune balance of its host so they may have an impact on brain functioning. *Bifidobacterium infantis* is one of the probiotic bacteria found to be capable of altering the profile of pro- and anti-inflammatory cytokines [29]. In one study, probiotic bacteria *Lactobacillus helveticus* prevented mice on a high-fat diet from developing anxious and depressive behavior, however, this effect was not observed in the group of immunocompromised mice [30]. Unsurprisingly, interactions between the immune system, gut microbiota and the brain are bidirectional. Social disruption changes the microbiome and the immune system functions as an intermediary. Bailey et al. have shown that the composition of murine intestinal bacteria changes along with alterations in cytokine levels after repeated stress exposure [31] however, is not well understood. To determine whether the microbiome contributes to stressor-induced immunoenhancement, mice were exposed to a social stressor called social disruption (SDR).

THE MICROBIOME AND NEUROTRANSMISSION

An intriguing aspect of brain-gut studies is the question of how the microbiome interferes with the neurotransmitters system. Interestingly, gut microorganisms have been shown to have an

ability to synthesize neurotransmitters and neuromodulators. Both *Lactobacillus* and *Bifidobacteria* species have been shown to produce gamma-aminobutyric acid (GABA), *Escherichia*, *Bacillus* has been shown to synthesize norepinephrine (NE), *Lactobacillus* can produce acetylcholine, *Streptococcus*, *Escherichia* and *Enterococcus* produce 5-HT (5-hydroxytryptamine – serotonin), while *Bacillus* can synthesize dopamine (DA) [32,33]. It has been proposed that those neurotransmitters released into the intestinal lumen may stimulate epithelial cells to release modulators affecting neurotransmission within the enteric nervous system (ENS) or acting directly on primary afferent axons [6,34].

Moreover, it has been shown that the microbiome can affect the CNS directly via the vagus nerve. Bravo et al. have shown that sustained treatment with probiotic bacteria, *Lactobacillus rhamnosus* (JB-1), induced alterations in the GABAergic system in mice. It induced region-dependent changes in GABAB1b mRNA in the brain, with an increase in the cingulate and pre-imbic regions and concomitant reduction of its expression in the hippocampus, amygdala and locus coeruleus. Additionally, it has decreased GABA α 2 mRNA expression in the pre-frontal cortex and amygdala and increased its expression in the hippocampus. Changes were associated with a reduction of stress-induced corticosterone as well as anxiety and depression-related behavior. Interestingly, vagotomy prevented behavioral and neurochemical effects of *Lactobacillus rhamnosus* (JB-1) [35]. Our experimental data have shown that vagus nerve stimulation influences the physiology of the dopaminergic system, so if probiotic bacteria modulate the vagus nerve, it may also have an impact on dopamine-related brain regions [36]. Heijtz et al. have shown that germ-free mice present elevated dopamine turnover in the striatum and this alteration is associated with their hyperactive phenotype [37] many of which are associated with immunity and nutrient intake. Here, we report that colonization by gut microbiota impacts mammalian brain development and subsequent adult behavior. Using measures of motor activity and anxiety-like behavior, we demonstrate that germ free (GF). Studies on germ-free mice have also shown disruption of the hippocampal serotonergic system associated with elevat-

ed levels of serotonin and its metabolites [38] including that of the CNS. However, there is a paucity of data pertaining to the influence of microbiome on the serotonergic system. Germ-free (GF). Interestingly, this murine model also presents hippocampal-dependent memory impairments [9]. The abovementioned data indicate that large intestine microbiome influences brain development, neurotransmitters systems, cognitive functioning and behavior. Thus, searching for associations between the microbiome and mental health appears to be justified.

Schizophrenia, bipolar disorder and the microbiome

Studies have identified an association between schizophrenia and microbiome disruption [39]. The research of Severance et al. [40], measuring markers of intestinal inflammation and bacterial translocation, uncovered the presence of structural damage to the gastrointestinal barrier in schizophrenia patients. Patients with recent-onset as well as chronic schizophrenia present elevated levels of antibodies against commensal fungus – *Saccharomyces cerevisiae* [40]. Autopsy findings show a structural damage in the gastrointestinal system of individuals with schizophrenia. Intriguingly, among 82 patients with schizophrenia in a study by Hemmings, 92% had colitis, 88% enteritis and 50% gastritis [41]. Mice models displaying features of schizophrenic behavior, after treatment using the human commensal (*Bacteroides fragilis*), presented corrected gut permeability, altered microbial composition and ameliorated defects in communicative, stereotypic, anxiety-like and sensorimotor behaviors [42].

Colonic bacteria of patients with short bowel syndrome have been shown to form D-lactic acid from unabsorbed carbohydrates. Accumulation of this acid in the blood causes cognitive dysfunction and ataxia symptoms [43] Fukushima et al. have shown that increased levels of D-lactate were one of the major contributors to the discrimination between controls and schizophrenia patients [44]. Thus, in future studies, it may be viable to evaluate whether an increase of D-lactate in schizophrenia may be associated with microbiota disruptions.

The microbiome may have an impact on inducing weight gain in schizophrenia patients after antipsychotic treatment. Olanzapine administration evoked significant changes in the bacterial phyla of the gut in female rats, resulting in an increase of *Firmicutes* and decrease of *Bacteroides*. Those changes were associated with increased markers of systemic inflammations including interleukins IL-6, IL-8, tumor necrosis factor alpha (TNF- α) and IL-1 β .

Immunological dysregulation and disproportion of the inflammatory/anti-inflammatory cytokines balance have been noted both in schizophrenia and bipolar disorder. An altered microbiome may result in dysregulation of immunological homeostasis, and thus it may contribute to the development of both mental disorders [45]. Similarly to patients with schizophrenia, patients with bipolar disorder present with elevated antibodies against commensal *Saccharomyces cerevisiae*, indicating an increased immunological response against intestinal antigens [46]. Moreover, both groups of patients present elevated serum levels of the soluble form of CD14 protein, which is a surrogate of bacterial translocation marker [47]. The putative role of the microbiome in bipolar disorder is supported by the case of a successful treatment of a 21-year-old patient with bipolar disorder using a special nutrition formula [48]. The authors suspect that the positive effects of the treatment were associated with its effect on the intestinal microflora [48]. Recently, a case has been presented of a resolution of a manic episode followed by treatment targeted on the brain-gut axis [49].

DEPRESSION AND THE MICROBIOME

A growing body of research points to the major role of low-grade inflammation in the pathophysiology of depression. Disturbances of microbiota and its association with its host have recently become another new pathway suspected of inducing inflammatory response in depression [50]. Jiang et al. have shown that microbiome disturbances exist in patients with depression. In particular, patients are characterized by an overrepresentation of bacteria from *Enterobacteriaceae* family and *Alistipes* genus. Interestingly, a negative correlation has been found between

depressive symptoms and the amount of *Faecalibacterium* [51]. It has been shown that clinical depression is accompanied by elevated levels of immunoglobulin A and/or M against gram-negative bacteria belonging to human gut microflora [52,53], such as: *Hafnia alvei*, *Pseudomonas aeruginosa*, *Morganella morganii*, *Proteus mirabilis*, *Pseudomonas putida*, *Citrobacter koseri* or *Klebsiella pneumoniae* [50,54,55]. An inflammatory reaction of the body against lipopolysaccharide in the outer membrane of gram-negative bacteria and bacterial translocation were proposed as key factors that participate in the development of clinical depression [56].

CONCLUSIONS

The data indicate an association between large intestine microbiome and central nervous system functioning in humans. Research on patients with bipolar disorder, unipolar depression and schizophrenia as well as animal studies identified microbiome disruption in those entities. The studies presented here provide the basis for a careful analysis of mutual interactions between the microbiome and the gut-brain axis that should be performed to determine the role of those interactions in the pathogenesis of mental disorders. Awareness of the significance of those mechanisms may lead to a future search for new therapeutic interventions focused on the gut-brain axis in schizophrenia, bipolar disorder and unipolar depression.

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