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Special article

The intriguing role of the Gut Microbiome in the etiology and pathogenesis of Neuropsychiatric Disorders

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Abstract

Humans live in a symbiotic, evolutionarily endorsed, relationship with the plethora of microbes residing within them, but not until very recently we came to understand that our microbes are more than simply bystanders co-existing with us. They have established a communication, an inter-kingdom connection, with the host's cells, which is responsible for many physiological aspects concerning human health. The gut microbiome, by its very definition, represents the collective genome material of all microbes inhabiting our intestines, and holds tremendous capacities, for it is able to affect the host in terms of health and disease. It's intriguing the fact that the gut microbes are engaged not only in local events, but may influence remote tissues and organs as well. Via the gut-brain axis, a multichannel system of pathways connecting the two organs, microbes can affect mood, behavior and cognition and become implicated in the pathogenesis of many neuropsychological disorders. They are able to impact brain function in a variety of ways, however, their true potential lies in their ability to regulate the neural development, a delicate process whose defects can lead to long-term mental health outcomes later in life. In this article, we will review the contribution of the gut microbes in the process of neurodevelopment and attempt to shed light on the etiology of many neuropsychological disorders from the perspective of gut dysbiotic states. Unraveling the mystery behind the true meaning of symbiosis with microbes may provide novel therapeutic strategies against neuro-psychological disorders.

Key words: gut-brain axis, gut microbiome, Gut microbiota, mental health, neuro-psychological disorders.

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Introduction

For millions of years the human body was inhabited by a group of little creatures, which afterwards were named microbes. Once we learned of their existence we started to observe and study them. We found them living and thriving in every possible environment, even within us. We related them with diseases and started fighting them to extinction. In time, we discovered a connection, a prosperous symbiotic relationship between some of them and us. We came to understand that the human being isn't a solely organism, but a living ecosystem with a ratio of indigenous cells to microbes 1:1 to 1:10 [1,2]. We have yet to unravel the precise nature of this symbiotic relationship, for this is a topic of research that is still in its infancy.

The Gut Microbiome (Gut microbiota, formerly called *gut flora*), a vast ecosystem of bacteria, archaea, protozoa, parasites, fungi and viruses thrives within our intestines[1]. It carries an important role on the homeostatic regulation of the human body, on immune maturation and metabolic function [1,3]. The vast variety of its activities, the interaction and communication between the microbes and the human body cells, and the apparent importance of the microbiome on human health and development have led to its description as "a forgotten organ" [1,4].

The last years, its role has been implicated in the pathogenesis of various diseases, gastrointestinal and systemic [1,2,5,6,7]. In this article, we will study its peculiar part on development and function of the CNS, focusing on the data which correlates the microbiome with the pathogenesis of neuropsychological disorders. It's unfamiliar the fact that many forms of neuro-immune and neuro-psychiatric diseases are now being related with gut dysbiotic states (disruption of a balanced composition of the gut microbiome), the microbes' detrimental activities and gut-derived metabolites.

How microbes talk to the brain: The Gut-Brain Axis

The Gut-Brain axis is a concept of connection between the two major systems, the gut and the brain. It consists of a range of multichannel pathways that integrate and transmit the brain signals to the intestines and vice versa [8]. The brain, as the prime neural organ, controls the gastrointestinal functions (e.g. motility, muscular tension, visceral sensitivity, local immune cell activity, hormonal production, nutrient absortion) and therefore shapes the luminal microenvironment affecting bacterial establishment and growth. Although it was believed for many years that the communication between the gut and the brain was one way (top-down, from brain to intestines), nowadays this axis is found to be bidirectional [1], mediating the fundamental functions of these two peculiar systems [9,10]. There have been described several paths that convey the intestinal signals centrally. Each and every of these paths comprise what we described before as "the Gut-Brain axis".

Neural Avenue

Vagus nerve, the widest distributing nerve in the body, consisting of afferent and efferent neurons, is a vital part of the MGB axis. It collects all the information from intestinal events and creates signals to be transmitted through four consecutive neurons cephalically [1,11]. Afferent projections are spread into higher brain centers such as brainstem nuclei, the thalamus, the basal ganglia and the cortex [1,11]. In this way, gut microbiota can induce changes on brain function across the vagus nerve. Compatible with this notion are the experiments done in vagotomized mice, in which probiotic treatment didn't manage to change behavioral traits, although it has been previously reported to be effective [12,13]. Moreover, the sickness behavior followed by pharmaceutical induced colitis in mice was substantially attenuated following vagotomy [14]. Spinal sympathetic neurons are also conducting information from the gut to the brain through the spinal cord [1,9]. A well documented route is the activation of GPR41 (a receptor found in sympathetic ganglia) by microbial products, which transmits the luminal signals centrally[15].

Neuroendocrine Route

Enteroendocrine cells (EECs), specialized cells of the gastrointestinal tract, secrete neurotransmitters and other signaling peptides (i.e. serotonin, CCK, GLP-1, PYY) in response to

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changes on luminal contents, acting as transducers for the endocrine-CNS route [16,17]. Receptors of these peptides are found locally, on the afferent endings of the vagus nerve, but also centrally, where they are involved in behavioral responses [17]. Bacteria may produce metabolites that act as paracrine signals that influence host's cells behavior and function. C1pB protein, for example, produced by commensal microbes, can stimulate the release of PYY and GLP-1 from the EECs [18].

Microbial fermentation products may act as signaling molecules with great significance on gut-brain interaction. Short Chain Fatty Acids (SCFAs), the most studied metabolic products, originate from fibers and undigested carbohydrates [16]. It has been shown to act as modulators on intestinal hormone production and as immune regulators, with many luminal and systemic interactions [19]. They can cross the BBB, regulate microglia homoeostasis [8] and have been implicated in brain development and pathogenesis of autism [8,20]. Locally, SCFAs regulate the production of gut peptides from enteroendocrine cells [8], and the synthesis of gut-derived serotonin from enterochromaffin cells, activating afferent nerve endings to signal to the CNS [8,21]. Experiments done in animal with neurodegenerative disorders have shown a profound increase in cognitive function related to the production of SCFAs[22].

Immune Pathways

The enterocytes, the immune cells and the neurons express in their surface PRRs (Pattern Recognition Receptors) which interact with bacteria molecules or products [1,23]. TLRs, a class of PRRs, are an integral part of the local innate immune system. Activation of these receptors triggers a pro-inflammatory cytokine release (Il-1, Il-6) which spreads locally and systemically via the bloodstream, reaching the brain, to activate the Hypothalamic–Pituitary–Adrenal (HPA) axis [16]. Cytokines may also signal to the brain indirectly, via the vagus nerve [24]. Local immune activation and cytokine production against microbial antigens or products leads to a stress response that stimulates the HPA axis which, in turn, induces hormonal changes in the blood [1]. An immune-endocrine activation affect cognition and behavior, mimicking the effects of bacterial infection [4,25]. LPS production, for instance, by certain types of bacteria is responsible for activation of the immune-endocrine-nervous system and the HPA axis. On the other hand, gut colonization with helpful bacteria can reduce an exaggerated HPA response [26].

Microbial Products (Neurotransmitters, Neuromodulators)

Microorganisms' metabolism can also result in neurophysiological changes with the production of chemical substances that act locally or systemically [9]. Microbiota-derived metabolites are critical intermediaries for microbiota-gut-CNS signaling. Neuropeptides are multilateral molecules and serve as messengers in many systems (endocrine, nervous, immune) [27]. The gut microbiota can produce and emit an array of neurotransmitters, such as GABA, catecholamines, histamine, norepinephrine, 5-HT, butyric acid and dopamine [28]. These molecules are engaged in paracrine communication with the nerves, immune cells and enteroendocrine cells (influencing the hormone production of the former) and also endocrine signaling, reaching distant tissues such as the brain, and further impacting on central centers[29].The physiology of the MGB axis allows a bidirectional communication between the brain and the gut so that both gastrointestinal and psychopathological entities could be both origin and consequence of one another. Both of the systems are mutually affected and depending on the other. This hypothesis is verified indirectly from the observation of the high co-morbidity between psychiatric and gastrointestinal diseases. Many patients suffering from gastrointestinal disorders experience mood and behavioral changes, whilst a lot of patients with psychiatric diseases suffer from gastrointestinal symptoms [30,31]. Due to this entangled relationship, the gut-brain axis forms a mean for the gut microbiota to speak indirectly to the brain. In dysbiotic states, where the composition or metabolic function of the indigenous bacteria is shifted against the benefit of the host, psychiatric and neurodevelopmental illnesses may occur [8,32,33].

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How the Microbes Influence the Brain Development

Neural development commences early in embryonic life and extends from the prenatal period to post adolescence [34], with the brain remodeling continuing into the third decade of life [35]. It involves the contribution of genetic and a long list of environmental factors [35]. The process of neurodevelopment is dynamic and spans for years which makes it vulnerable to external perturbations and thus susceptible for alteration[8]. This crucial period of neurodevelopment progresses concurrently with the establishment and growth of the gut microbiome, a vital process which guides the maturation and training of the immune system [36], the development of the neuroendocrine system [8] and the regulation of many physiological functions, regional or distal. Studies suggest that there is a crucial link between gut microbiome and CNS maturation under physiological state [8,10]. Disturbance of the gut microbiome early in life has the potential to disrupt the delicate process of neurodevelopment and can contribute to long-term mental health outcomes later in life [8,34,36,37].

Neuronal development may be modulated by the participation of the neuro-endocrino-immunological system [34] with main representative the circulating levels of hormones and cytokines. In a review of GB Rogers et al.[8], it is mentioned that a pro-inflammatory maternal state may contribute to aberrant fetal development. During pregnancy, increased levels of circulating cytokines are known to negatively impact fetal neural development affecting the gene expression of fetal brain cells [38]. This kind of disturbance may come from the disruption of the immuno-regulatory role of the maternal gut microbiome [8]. Maternal gut dysbiosis can generate an inflammatory environment that also influences blood brain barrier (BBB) formation and function which in turn exposes the microenvironment of microglia and neurons to the blood stream components[8]. Embryos of GF mice develop a deregulated BBB with reduced expression of tight junction proteins, which is shown to be significantly compromised [8,39].

The activation of the maternal hypothalamic–pituitary–adrenal axis may change the normal neurodevelopmetal trajectories and it is linked with fetal neurological defects. As GB Rogers et al.[8] reviewed, any stress factor can activate the HPA axis and contribute to a broad spectrum of neurodevelopmental abnormalities [8,40]. How the maternal HPA hyperactivation impacts the fetal development remains poorly understood, but it is believed that the maternal blood cortisol can traverse the placenta and influence the gene expression of the brain cells [8,41]. The effects of prenatal stress on offspring can be mimicked to a limited degree by giving pregnant animals a synthetic glucocorticoid hormone [8,41].

Bacteria composition is associated with neuronal connectivity development and thus the quality of neuronal circuitries during pre- and postnatal life. In the review of Rogers et al.[8] is cited that the process of neurodevelopment in utero depends on serotonin which controls the neuronal cell mitosis, differentiation and synaptogenesis. Proper neuronal morphogenesis requires quantities of 5-HT an embryo can't afford, and thus depends more on maternal plasma serotonin than its own[42]. The maternal microbiome can regulate the 5-HT biosynthesis by enterochromaffin cells in the gut and therefore affect fetal neurodevelopment by influencing the level of circulating serotonin[43].

Gut microbiota, in the postnatal period of life, mediate the epigenetic regulation of brain molecules involved in the neural development, such as neurotrophic factors (BDNF being the most studied of them) [44]. This is a result of microbiota - host chemical communication via the gut-brain or HPA axis where bacterial bioactive metabolites (SCFAs, neurotransmitters) and signaling molecules (peptides, endotoxins) make possible this interaction[16]. Germ free (GF) mice (sterile animals which are born and raised within germ free isolators) are a helpful tool for investigating the gut-brain correlation. Studies have shown that the absence of gut microbiota from birth has an impact on neural development and behavior [8,16,34]. GF mice are described with an excessive HPA response when exposed to mild stress, with elevated plasma ACTH and cortisol

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hormone compared to normal mice [8,26]. They also have neuroanatomical changes in brain areas such as amygdala and hippocampus [45], with reduced levels of BDNF, NMDA receptor and c-fos in the hippocampus and cortex [9,46]. The expression of BDNF, the 2A subtype of NMDA and 5-HT1a receptors in the cortex and hippocampus are microbiota regulated[26,47]. GF mice are presented with altered gene expression of myelin structural proteins in the prefrontal cortex, a brain region which has been implicated in cognitive behavior, personality expression and social behavior[48]. Specifically, it has been noticed, an increase in myelin production leading to hypermyelination of the prefrontal cortex, a process which is expected to occur later in life. These neuroanatomical changes could be correlated with the pathogenesis of emotional disorders[49].

Commensal microbes are required for programming and displaying normal social behavior, and are essential for the development of memory, repetitive behaviors and pain signaling from the body [50,51]. A dysbiotic state, with abnormal microbiota composition early in life, can result in abnormal mental development and behavior disorders which are not corrected when later microbial exposure occurs. There seems to be a maturation time window, on which exposure to microorganisms is necessary for proper CNS development, but after that, the changes in the newly formed brain remain permanent [26,52]. The association between the gut micobiota and neurodevelopment is strong. The precise nature of this relationship has yet to be unraveled mostly due to the difficulties of determining the multiple and unclear pathways that combine these systems together.

Manipulating host's brain function and behavior: An introduction to the neuropsychological disorders

Many studies experimented on GF mice or conventionally raised mice have shed light to the pathophysiological role of the gut microbiome in human brain neuropsychological diseases. GF mice receiving gut microbiome transplant from patients with depression exhibit more depression-like behaviors, in comparison with the control group of mice which were colonized with microbes from healthy donors[53]. In another experiment, the transplantation of gut microbes from a high anxiety mouse to a germ free one with low anxiety led to increased anxiety behavior in the recipient. The same experiment done in reverse showed matching results [54]. Some behavioral features seem to be transmissible via the gut microbes, and thus, the idea of brain manipulation by the gut flora appears to confirm itself. The pathways of communication remain unclear to a certain extent. The gut-brain axis plays a significant role in mediating the intestinal events and the neurochemical alteration centrally. There have been described several paths involved in this axis (for reference see chapter 2: "How microbes talk to the brain: The Gut-Brain Axis").Since the indigenous gut bacteria have a strong communication with the brain *via* the MGB axis [9,16,34], a disruption of the physiology of gut bacteria could be linked to the pathophysiology of psychopathologies. Any stress factor that influences the microenvironment of the gut microbes could also affect indirectly the cerebral development and function [8,34].

Depressive syndrome

It is right to presume that the gut microbiome is one of the many links between early environmental stress factors and the risk of developing depression later in life [55]. A disturbance of the immuno-regulatory role of the gut microbiome has been proposed to influence the developmental cues of the brain. An immune-endocrine activation could affect the process of neuronal configuration and function[5,34] via changes at the level of genetic expression of genes associated with brain development [55]. It is now known, with the assistance of animal studies, that limbic system's neurogenesis can be modified by indigenous gut microbiota[34,56]. A chronic gastrointestinal inflammation, for example, is associated with altered hippocampal neurogenesis [57], with swifts in the expression of neurotrophic factors, such a BDNF.

Stool samples from patients with depression show alterations

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in the proportion of indigenous bacteria in contrast to healthy individuals. Notably, there has been recorded increased concentration of Bacteroidetes, Actinobacteria and Proteobacteria (LPS-expressing)[58] and low numbers of Lactobacillus species[59]. It's interesting the fact that increased levels of IgA and IgM against the LPS of Gram-negative bacteria are found in depressed patients[60]; markers that indicate bacteria translocation into the bloodstream. Patients with depression have increased volatile fatty acids such as isovaleric acid found in their stool. These molecules are microbe-derived and can travel with the bloodstream up to the brain, crossing the BBB, and affecting neurotransmitter release[61]. Whether these mechanisms are involved in the pathogenesis of the depressive syndrome, or are consequences of the neuro-immunological disarrangement resulted by the depression, remains unclear.

Gut microbes are required for normal brain function. Altering the microenvironment of our gut microbes with the supplementation of probiotics (helpful bacteria) can lead to changes in the bidirectional communication between the gut and the brain and thus influencing the mood, cognition and brain function. Probiotic consumption has been linked with anti-depressant effects on animal and human models. Bacterial species such as Lactobacillus and Bifidobacterium can alleviate depressive symptoms in maternal separation models of rats[62]. Chronic treatment with Lactobacillus rhamnosus in mice can reduce stress-induced corticosterone levels, anxiety and depressive behaviors[12]. These effects where attributed to altered GABA expression in the cortex, amygdlala and hippocampus. In a recent functional magnetic resonance imaging (fMRI) study with healthy individuals, after a 4-week consumption of probiotics (Bifidobacterium and Lactobacillus) the subjects displayed reduced neural activity in brain regions that process emotion and sensation in response to emotional attention tasks [63]. Clinical data of probiotic consumption provides a novel, potentially useful, therapeutic strategy for neuropsychiatric conditions. However, more clinical trials are required to truly determine their extent of efficacy in treating neuropsychological disorders.

Anxiety and Stress

Exposure to biological stressors or environmental stimuli can trigger stress and anxiety responses, which involve the activation of the HPA axis[9]. Gut microbe's metabolism may be implicated in the pathogenesis of mood and emotional disorders. Mice inoculated with *Campylobacter jejuni* show a decrease in exploratory phenotype (anxiety's sign) and activated brain sections implicated in anxious behavior [64]. Pathogens, such as *C. jejuni* [64,65], *Citrobacter rodentium*[66] and *Trichuris muris*[67] can induce anxiety-like behavior via immunological and metabolic mechanisms (reviewed in [10]). In contrast, beneficial bacteria in the form of probiotics have shown to ameliorate anxiety and reduce stress. Lactobacillus and Bifidobacterium consumption has been associated with anxiolytic effects, normalizing anxiety phenotypes in animal models[12,62,67] GF mice behave differently in comparison with normal mice. They show increase motor activity, impaired cognition and demonstrate an exaggerated HPA stress response[9]. These behavioral traits are associated with altered expression of genes[55] leading to higher levels of neurotransmitters, decreased BDNF expression and reduced synaptic long-term potentiation[55]. Colonization by Bifidobacterium species can attenuate the exaggerated HPA stress response, with only condition the early life exposure for the inhibition to occur[26].

Schizophrenia

Schizophrenia is a complex mental disorder characterized by abnormal social behavior and failure to understand reality[68]. Schizophrenia is oftenly coexisting with gastrointestinal symptoms or disorders[69], however, whether this results from a deregulated brain-to-gut communication or is microbiota-derived remains unknown[16]. Even so, the correlation between gut dysbiosis and the pathogenesis of schizophrenia is well documented[8,36,70,71,72,73].

The causes of the disease include environmental and genetic factors. The genetic risk of schizophrenia relies upon genes that are involved in immune function[70,71]. This condition corre-

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lates with the clinical observation of upregulated inflammatory state in schizophrenia patients[69]. Bacteria translocation markers have been found in the blood of schizophrenic patients in significant higher levels than normal people[72], while high cytokine levels are related with the exaggeration of symptoms[73]. A breach in the intestinal epithelial barrier is thought to allow bacteria and their products to enter the bloodstream and cause an immune response[36]. Through molecular imitation, this response may trigger an attack upon host tissues, a fundamental process of autoimmune pathogenesis[9,36]. Schizophrenia patients bear a higher probability of autoimmune disorders, and have autoimmune antibodies against brain regions such as as the hippocampus, amygdala, and frontal cortex[9,74]. They are also found with a higher proportion of Th17 cells, a condition resembling an immune response emerging from gut dysbiosis[75].

Commensal microbiota is required for programming and displaying normal social behavior, and is essential for the development of memory and behavior[50,51]. The expression of BDNF, the 2A subtype of NMDA and 5-HT1a receptors in the cortex and hippocampus are microbiota regulated[26,47]. These factors have a significant role in brain development and function. Impaired BDNF expression leads to cognitive dysfunction, while NMDA antagonists mimic schizophrenia symptoms[9]. A dysbiotic state early in life, could affect the normal neurodevelopmental trajectory and lead to the genesis of psychiatric disorders, therefore the importance of a healthy gut microbiome becomes apparent.

Autism Spectrum Disorder (ASD)

Autism spectrum disorder (ASD) is the name for a group of developmental disorders characterized by impaired social interaction and communication. ASD includes a wide range, "a spectrum," of symptoms, skills, and levels of disability[76]. It is believed that the gut microbiota contributes, at least in part, in the pathogenesis of ASD. Children with ASD usually have a different gut microbiota profile when compared to same age healthy control group[29]. As mentioned in the chapter of brain development, a dysbiotic state may result in activation of the HPA axis and contributes as a risk factor for a broad range of neurodevelopmental abnormalities[8,40]. Children with ADHD, for instance, display an abnormal HPA response[77]. Colonization by strains of neurotoxin-producing bacteria, such as *Clostridia*, has been for long hypothesized as an etiology agent, at least in a subgroup of patients[78,79] (reviewed by Wang et al.[10]). A great number of *Clostridium* species, such as *Clostridium tetani*, have been found in fecal samples of autistic children.[10,80,81] Microbes' metabolic products may are also engaged in the pathogenesis of ASD[10]. Oral use of vancomycin can attenuate the symptoms of the disorder, while the interruption of the treatment leads to relapse of the autistic behavior[29,82]. In the same concept, oral treatment with probiotics (*Bacteroides fragillis*) ameliorates the defects of the disorder[83]. Microbiota composition and the pathogenesis of ASD are connected through the gut brain axis. Microbes are able to influence the synaptogenesis process, the production of neurotransmitters and the gene expression in many brain structures[8,55]. The main pathways employed by the gut microbiota are neural, endocrine and immune, as were seen in the Gut-Brain Axis section.

Eating Disorders

Eating disorders for long have been accepted as mental illnesses since the primary etiology of them seems to outset from psychopathological misrepresentation of body image and self acceptance [84]. They are defined by abnormal eating habits that negatively affect a person's physical or mental health [84]. The cause of these disorders is not clear yet. Both biological and environmental factors appear to play a role. In the last decade, there has been a growing body of literature that suggests a biological background in the etiology and progression of these conditions [4,85,86,87].

Millions of years ago, we permitted bacteria to live inside us and in turn they helped with digestion, protection from pathogens and production of useful molecules. They grow in accordance with the food we eat; nevertheless different bacteria have distinct nutritional demands. From an evolutionary point of view, bacteria that evolved ways of communicating

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with the host and enforce a feeding behavior which cultivates this kind of bacteria would impose a significant selective pressure, and thus thrive on this microbial-controlled environment [85,87]. A positive feedback loop emerges, as the host selects a specific dietary habit which nourish this kind of bacteria [4,87]. This idea of bacteria controlling their host's appetite is revolutionary. It's distrusting the fact that bacteria acquired such a capacity. However, they have had both the time and the formidable adaptive mechanism needed to fulfill this task.

Taking into account the extent of functions of the gut-brain axis and the influence of the diet on brain function, it is logical to assume the gut bacteria as an intermediate link between eating disorders and extreme feeding patterns [4,85]. Acting on the gut–brain axis, gut bacteria could affect brain function and alter the appetite control, thus considering as part of the genesis of eating disorders [4,88]. As the illness develops, abnormal eating habits can further affect the microbiota's ecosystem which potentially feeds back to the brain function, eventually creating a positive loop which maintains the disorder [4].

Studies have not been yet conducted on humans, but animal models help investigate the influence of gut microbes on host behavior. In the review of Lam YY et al. [4], the authors cite a few plausible mechanisms. The first includes the control of gut bacteria over the production of appetite-regulating hormones. In the gut reside enteroendocrine cells which produce hormones or peptides (such as cholecystokinin) in response to various stimuli and release them into the bloodstream for systemic effect, diffuse them as local messengers, or transmit them to the enteric nervous system to activate nervous responses [89]. These cells express Toll-like Receptors which are activated by binding with bacterial products (lipopolysaccharides - LPS and flagellin) causing the modification of secretion of hormones that regulate hunger and satiety [4,90]. LPS can also enter to the bloodstream and disrupt the physiological permeability of the BBB [91], to augment the effect of circulating hormones and cytokines on central appetite systems. Other direct effect of LPS is the induction of an anorexic response by activating central pathways [91]. Lastly, in a recent experiment, prebiotic food supplementation in healthy subjects led to an increase in production of gut hormones (PYY and GLP-1) and promoted the impression of satiety, lowering hunger rates [92]. Changing the microenvironment of the gut and the microbiota composition seems to contribute to alterations in appetite sensation.

Another pivotal mechanism practiced by gut bacteria to manipulate host's food intake is by producing peptides that mimic the role of the host's appetite-regulating hormones. These peptides can regulate food intake with two major ways (mentioned in [4]). The first, and direct one, is by imitating the effect of the genuine appetite hormone on its receptor, while the second one is far more complex. The peptides produced by the gut microbiota may trigger an immune response towards themselves (since they are bacterial products) with the antibodies also cross-reacting with the host's appetite hormones since they are molecular analogues with these bacteria derived peptides [4,87]. The latter has actually been confirmed, as Fetissov et al. [93] presented a subgroup of patients with Anorexia Nervosa and Bulimia Nervosa that had autoantibodies against the α-MSH (melanocyte stimulating hormone). The circulating level of these autoantibodies was found to be related to the psychological features of these diseases [93]. Similar with the concept of interference with appetite central regulation, bacteria may also manipulate the dopaminergic rewarding system of the brain, affecting the pleasure and the desire for a specific dietary regimen [85].

Conclusion

Living in a microbe-free world is an unimaginable concept. Bacteria appeared on Earth long before the first human ever emerged. We evolved together and form a symbiotic relationship. They accompany us from our birth until the time of our departure. The microbes affect us in the most significant way, but only the last few years we became aware of such influence. The fact that they are involved in the process of neurodevelopment, on brain function and the pathogenesis of many systemic dis-

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eases gives them substantial authority upon us. We need to learn how to optimize this relationship and comprehend the mechanisms promoting health or disease. Novel therapeutic strategies (probiotics, microbiota transplantation, genetic engineer of indigenous microbes) may appear in the near future and replace partially effective existing treatments. The most difficult attempt is to unravel the mysteries behind this state of symbiosis. Exploring the secrets of the microworld of our microbes may finally give an answer to a significant argument that puzzles humanity for a long time: "are we really us?"

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