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PROBIOTICS AS A REMEDI AGAINST STRESS

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ABSTRACT

The functional connection between the gastrointestinal tract and the central nervous system of the host organism was considered. The relationship between the intestinal microbiome and the central nervous system had been analyzed. The main mechanisms of the influence of microbiota on the functions of the central nervous system were shown. The literature data on the role of the intestinal microbiome in disorders of the central nervous system were summarized. The main factors linking the intestinal microbiota and the central nervous system were given. The prospects of using bacteriotherapeutic drugs and functional food products enriched with appropriate probiotic microorganisms for the prevention and treatment of neurological disorders, as well as for maintaining the functionality of the immune system in stress subjects were highlighted.

Key words: gut microbiota, probiotics, stress, central nervous system.

INTRODUCTION

There is a functional connection between the gastrointestinal tract (GI tract) and the central nervous system (CNS) of the host macroorganism. This relationship is bi-directional and includes anatomical relationships like the vagus nerve and humoral components, including the immune system and hypothalamic-pituitary-adrenal axis. Recently, there is more experimental evidence that another key player in this interaction is the intestinal microbiota [1].

Physical and psychological stress is known to affect not only the immune system, but also hormonal and gastrointestinal homeostasis. Immune mechanisms are regulated by the hypothalamus-pituitary-adrenal axis, as well as by neuronal influences through sympathetic, parasympathetic and peptidergic/sensory innervation of peripheral tissues.

Immune and neuroendocrine systems have been shown to exert integrated responses to environmental signals and the relationship between stress and immune function has been demonstrated in many contexts, including proliferative response to mitogens and cellular activity [2].

Stress conditions can lead to an imbalance between pro- and anti-inflammatory cytokines or to an uncontrolled production of cytokines. Disregulation of innate and adaptive intestinal immune responses directed against the bacterial flora including a breakdown of oral tolerance to environmental antigens and commensals are involved in several pathogenetic mechanisms.

Moreover, the integrity of intestinal ecosystem could be affected by several external factors, including antibiotic use, radiation, altered GIT peristalsis, dietary changes, psychological and physical stress. Studies conducted either in humans and in animal

models demonstrated that psychological stress could directly affect microflora composition and sometimes with long lasting effects, with a marked decrease in lactic acid bacterie. Stress-induced gastrointestinal changes lead to the establishment of an intestinal environment less conducive to lactic acid bacteria survival, adherence, and replication. Prolonged psychological stress also results in a significant reduction in the production of mucin and a decreased presence of acidic mucopolysaccharides on the mucosal surface, which facilitates intestinal colonization by pathogenic organisms [3].

A balanced intestinal microflora is important not only for the maintenance of intestinal homeostasis, but also for the regulation of immune system functionality and with direct effects on gut-brain axis.

In the light of the interactions between CNS and intestine, the use of bacteriotherapeutical drugs (probiotics, synbiotics, immunobitics etc.), prebiotics and functional food products enriched with appropriate probiotic microorganisms can be useful to improve the intestinal homeostasis and reach the onset of dysbiosis associated with physical and psychological stress conditions.

A number of experimental studies have conducted to assess the potential effectiveness of probiotics in preventing possible changes in the immune response associated with psychological stress. In particular, the effect of probiotics was tested in healthy adult volunteers self reporting a psychological stress condition. Specific stress markers, such as the activity of saliva α-amylase (SAA), cortisol and chromogranin A of saliva (CgA); immunological parameters such as secretory immunoglobulin A (sIgA), activity of natural killer cells (NK), interleukin 8 (IL8), interleukin 10 (IL10), tumor necrosis factor-α (TNF-α) level in faeces and intestinal microbiota were evaluated. The increase in fecal IgA and IL10 levels, decrease in abdominal pain, as well as normalization of the intestinal microbiota towards a moderate increase in lactic acid bacteria and a decrease in the number of pathogenic and conditionally pathogenic microflora have been experimentally proved, in comparison with the control group of volunteers not taking bacteriotherapeutic preparations [5, 6, 7].

The effect of intestinal commensal bacteria on the behavior and function of the brain were shown in many scientific papers. Gastrointestinal bacteria affect the reactivity of the hypothalamus-pituitary-adrenal axis, as well as induction and maintenance of synchronized sleep (dreamless sleep). They can affect mood, sensitivity to pain and normal brain development [8].

Clinical studies have demonstrated the various pathological effects of intestinal bacteria on the central nervous system with cirrhosis and the syndrome of the small intestine, and led researchers to speculate about possible side effects on the intestinal microbiota for alcohol dependence, chronic fatigue syndrome, fibromyalgia, restless leg syndrome, autistic spectrum disorders, schizophrenia, mood disorders, degenerative or autoimmune neurological disease. Side effects are attributed to changes in the structure of the bacterial community (dysbiosis), excessive bacterial growth in the small intestine, and increased intestinal permeability [9, 10, 11, 12].

Microorganisms of the gastrointestinal tract can influence the function or dysfunction in the central nervous system due to several mechanisms that are not mutually exclusive:

1) stimulation of the host immune response leading to various patterns of systemic cytokine activation;

2) synthesis of absorbed neuroactive metabolites, including neurotransmitters;

3) changes in the neural circuit by direct microbial effects on the intestinal nervous system, with the CNS transmission through wandering and other routes [5].

CNS and neuroendocrine activity, stress reactions in particular, can affect the composition of the intestinal microbiome by differential changes in the growth of bacterial species and the production of bacterial virulence factors. Enterobacteriaceae is

a family that includes most of the aerobic Gram-negative pathogens, including the widely known *Escherichia coli*, bacteria genus *Salmonella* (salmonellosis), *Yersinia pestis*, *Klebsiella pneumonia* (pneumonia), bacteria genus *Shigella* (dysentery) and others. Representatives of this family are particularly well-versed in using stressful host reactions to enhance their bacterial growth and virulence [13].

Different types of diets also modify the composition and functions of the microbiome in complex ways, which differ in individuals and national cultures, and are the subject of current research [14, 15].

Relationship between gut microbiome and the central nervous system

The intestine receives regulatory signals from the central nervous system, and vice versa. Thus, the gut-brain relationship describes an integrative concept of physiology, which includes everything, including afferent and efferent nerve, endocrine, nutritional and immunological signals between the central nervous system and the digestive tract [16].

Mechanisms of microbiome influencing on the CNS

Classical transmission of CNS-intestine-microbial signals works through central regulation of satiety. Changes in the nature of the diet as a result of CNS control of food intake can affect the availability of nutrients for the intestinal microbiota and, consequently, their composition. Signal saturation proteins are key molecular mediators that provide this control. These peptides are transported through the blood to the brain after eating, in order to influence satiety [16]. Signal saturation proteins arise mainly in the gastrointestinal tract, but most of them also are synthesized within the brain [17]. In addition, the CNS can affect intestinal microbiome through the nerve and endocrine pathways both in direct and indirect ways. The autonomic nervous system and the hypothalamus-pituitary-adrenal axis that maintain the connection between the central nervous system and internal organs can modulate intestinal physiology, for example, motility, secretion and permeability of the epithelium, as well as systemic hormones, which in turn affect the environment in the biotopes of microbiota residence , and also the host-microbial interaction on the mucosa [18]. Stress causes defects in the epithelial barrier and subsequent activation of cells on the mucosa has been experimentally shown [19].

Mechanisms of microbiome influencing on the CNS functions. The influence of microbiome on the CNS function manifests in both normal and pathological conditions. There is a key link between the intestinal microbiome and the maturation of the central nervous system. External signals obtained from local microbiota affect prenatal and postnatal programming of brain development [20, 21]. On the other hand, the concomitant morbidity with mood disorders, such as depression and anxiety, is common in such intestinal pathological conditions as irritable bowel syndrome. Chronic inflammation or immune activation, underlying the etiology of irritable bowel syndrome, is also the driving force of the risk factor in mood disorders [22]. In the more severe case of inflammatory bowel disease, comorbidity with stress is caused by simultaneous inflammation of the intestine and changes in the microbiome. Changes in psychological actions are realized by patients before and after diagnosis of inflammatory bowel disease [23].

Increase in CNS regulation by microbiome can be achieved through neural, endocrine, metabolic and immunological mechanisms.

1. The neural pathway functions through the enteric nervous system and the vagal afferent nerves, which transmit sensory information from the internal organs to the

CNS. Modulation of the intestinal microbiota with probiotics affects neuromotor functions of the intestine [24]. Activation of the vagus is necessary for a number of effects of the intestinal microbiome or probiotics on brain function [18]. Direct interaction between the microbiome and intestinal neurons is shown. It is proved that *Lactobacillus reuteri* increases the excitability of neurons of the large intestine in intact mice [25].

2. In the endocrine pathway, the intestinal microbiome plays an important role in the development and regulation of the hypothalamus-pituitary-adrenal axis, which is crucial for stress reactions. Studies in gnotobiotic mice have shown that postnatal exposure to intestinal microbiome affects the functions of the hypothalamus-pituitary-adrenal axis [26]. Enteroendocrine cells interspersed among gut epithelium, particularly enterochromaffin cells, can secrete neurotransmitters and other signaling peptides in response to luminal stimuli, and thus act as transducers for the gut-endocrine-CNS route. In addition, the vasoactive intestinal peptide - peptide hormone, synthesized in the intestine and brain, can mediate immune modulation during inflammation of the central nervous system. Although the direct effect of the microbiome on the expression of the vasoactive intestinal peptide was not detected, diet intervention can increase the level of the vasoactive intestinal peptide, which may indicate the role of the microbiome [27].

Since the main function of microbiome is to facilitate the metabolism of the host, the metabolic pathway is naturally implied in the microbiome-gut-CNS signaling. Dysregulation of serotonergic and kynurenine pathways of tryptophan metabolism affects the pathological conditions of the central nervous system: dementia, Huntington's disease and Alzheimer's disease. Probiotic treatment can alter the levels of kynurenin and improve the pathology of the central nervous system. In addition, the metabolic pathway is an important relationship between kingdoms, since host signaling molecules can be fully synthesized or mimicked by metabolites derived from a microbiota. Commensal organisms can produce a number of neuroactive molecules, such as serotonin, melatonin, gamma-aminobutyric acid (GABA), catecholamines, histamine and acetylcholine [28, 29, 30].

3. The immunological pathway, apparently, is an independent mechanism for the transmission of microbiome-gut-CNS signaling. CNS, although regarded as a site with privileged immunity, is not devoid of immune cells. There is a regular presence of macrophages and dendritic cells in the vascular plexus and meninges, microglial cells of the parenchyma of the brain and in leukocytes of the cerebrospinal fluid. Such a deviation of the CNS as autoimmunity occurs as a result of direct immune damage to nerve tissues. The commensal microbiome, which is known to form the host's immune system, affects the autoreactivity of peripheral immune cells in the CNS [12, 31]. Secondly, the association of the immune system with the central nervous system is also mediated by systemic circulation of immune factors, which is associated with neuropsychiatric disorders, such as depression. Indeed, factors that increase the markers of peripheral inflammation, such as C-reactive protein, interleukin-1, interleukin-6 and tumor necrosis factor-α (TNF-α), are also risk factors for depression [31]. In both directions of the pathway, there are anti-inflammatory mechanisms that can counteract the immune-mediated symptoms of CNS disease.

The role of microbiome in CNS disorders

Since multiple mechanisms determine the influence of microbiome on the central nervous system, a particular interest in the study is the role of microbiome in the regulation of CNS disorders. Despite the absence of epidemiological data linking the microbiome with CNS pathologies, the accumulated studies have emphasized the

importance of microbiome influence in a number of CNS disorders [32]. CNS disorders can be classified as immune-mediated (for example, autoimmune diseases of the central nervous system such as multiple sclerosis) and non-immune-mediated (eg, neuropsychiatric disorders such as autism, depression, anxiety and stress) according to the underlying etiologies. However, this dichotomy is not arbitrary, since there is often a cross-linkage of etiology. The present description summarizes the effect of the microbiome on both categories of CNS disorders.

1. Influence of microbiome on immune-mediated CNS disorders.

Multiple sclerosis. Multiple sclerosis (MS) is a chronic demyelination of the CNS, mediated by an auto-reactive immune attack against central neuronal tissues. Historically, viral infections, such as the Epstein-Barr virus or human herpesvirus 6, have been suggested as triggers for the development of multiple sclerosis [33]. However, recent studies have discovered the contribution of microbiome and its relevant factors to the pathogenesis of multiple sclerosis. In MOG_{92-106}TCR transgenic mice, it was shown that a commensal microbiota is necessary for the development of spontaneous experimental autoimmune encephalomyelitis (EAE) [34]. The commensal microbiota is also necessary for the induced EAE model. Segmented colonization with filamentous bacteria restored the sensitivity of EAE in GF mice [35]. Antibiotic modulation of the intestinal microbiota controls the progression of EAE through a variety of cellular mechanisms. Although it is not yet known whether the intestinal microbiota affects the development of multiple sclerosis, a higher percentage of patients with MS has responded to antibodies against gastrointestinal antigens in contrast to the control group, which could indicate an altered intestinal microbiota and immune status [36].

Oral treatment with a single bacterium or a mixture of bacteria can modulate the EAE. A probiotic based on *Bifidobacterium animalis* reduces the duration of symptoms in the EAE model in rats [37]. In contrast, the probiotic strain *Lactobacillus casei* Shirota (LcS) aggravates the symptoms of EAE in rats [38].

However, more recent studies have shown that probiotics based on lactic acid bacteria, including LcS, do not enhance, but rather inhibit, EAE in rats [39]. This was confirmed by other studies using probiotic mixtures of bacterial strains of the genus *Lactobacillus*. In fact, lactobacilli (including LcS), administered alone or in combination with other strains of the genus *Bifidobacterium*, alleviate the symptoms of murine EAE, through the mutual regulation of the responses of pro-and anti-inflammatory cytokines [40-42]. Treatment with probiotics based on *Bifidobacterium fragilis* and *Pediococcus acidilactici* R037 also significantly reduced the susceptibility of mice to EAE [43]. In addition, *Salmonella*-CFA / I and Hsp65-producing *Lactococcus lactis* strains can prevent EAE in mice via Tregs-associated signals [44].

Isolated microbial products of commensal can often repeat the biological effects of parent organisms on the host organism. Some of these products proved to be a potent therapy against EAE [45].

Finally, it is reported that diets affect the development of the EAE. For example, a high-fat diet increases the severity of EAE in mice. On the contrary, a caloric restriction diet weakened the symptoms of EAE, which were associated with hormonal, metabolic and cytokine changes, rather than with suppression of the immune system. Mice fed with a high-salt diet developed a more severe form of EAE, in line with the ability of sodium chloride to activate Th17 cells [46].

Neuromyelitis optica—Neuromyelitis optica (NMO), also known as Davis disease, is an autoimmune CNS disease. It manifests as an immunomodulated demyelination of the optic nerve and spinal cord. As with multiple sclerosis, studies have not yet established a direct link between the intestinal microbiome and Davis disease. Autoreactive humoral and T-cell immunity against aquaporin 4 (AQP4), the main

protein of the CNS water channel, leads to the pathogenesis of Davis disease. It was found that patients with AQP4-seropositive Davis disease had a much higher content of antibodies to gastrointestinal tract antigens (most often dietary proteins) than in healthy people, which led to a change in microbiota composition and subsequent immune status in patients with Davis disease [36]. AQP4-specific T-cells in NMO patients showed crossreactivity to a protein of the indigenous gut commensal species, *Clostridium perfringens*, supporting a microbiota-related molecular mimicry process in NMO pathogenesis [47].

Guillain-Barre syndrome. Guillain-Barre syndrome is an autoimmune disease of the peripheral nervous system. Like multiple sclerosis, the autoreactive immune attack of myelin acts as the cause of neurogenesis in Guillain-Barre syndrome. Prior infection by bacteria or viruses, such as *Haemophilus pneumoniae, Mycoplasma pneumoniae*, influenza and Epstein-Barr virus, are suggested as environmental triggers for the development of Guillain-Barre syndrome. Indeed, the cross-reaction of pathogen-stimulated antibodies against neuronal surface antigens in the process of molecular mimicry is an important mechanism of neuronal damage in Guillain-Barre syndrome, which leads to acute flaccid paralysis [32]. *Campylobacter jejuni*, a mutant species of commensals found in poultry, is the main cause of human enteritis caused by food contamination. A high risk of Guillain-Barre syndrome among patients with enteritis caused by *Campylobacter* has been shown. In addition, *Campylobacter* is associated with several pathological forms of Guillain-Barre syndrome. Thus, *C. jejuni* represents an intestinal pathogen that mediates neural autoimmunity.

Other immuno-mediated conditions. Microbiota is involved in the development of other diseases associated with the central nervous system. Meningitis - inflammation of the protective envelopes of the central nervous system. Viral or bacterial infection can lead to meningitis. Reported that the adult gut commensal *Escherichia coli* K1 were able to cause meningitis via maternal transfer to newborn infants. The polysialic acid capsule, synthesized by *E. coli* K1, controlled a critical process of transfer from the blood to the brain of this neuropathogenic strain. So far, the etiology of chronic fatigue syndrome, also called myalgic encephalomyelitis, is unknown. Immune factors, such as chronic over-activation of lymphocytes and cytokine anomalies, contribute to its pathogenesis. Increased translocation of commensal bacteria may be the cause of chronic fatigue syndrome was suggested [15, 48].

2. Influence of microbiome on non-immune-mediated CNS disorders.

Autism and depression. Autism spectrum disorder is a range of neuro-behavioral disorders characterized by disturbed social interaction and communication. Autism is the primary type of autism spectrum disorder. There is both a direct and indirect, atypical diet and diet, a link between the intestinal microbiome and the autism spectrum disorders. Disruption of the intestinal microbiota can contribute to excessive colonization by bacteria that produce a neurotoxin, and thus contributes to autistic symptoms. General changes in the intestinal microbiota or the presence of specific strains of mutants in the intestine have been implicated in autism spectrum disorders. *Clostridium tetani* can induce autism has been shown. Autistic children have a pronounced imbalance between Bacteroidetes and Firmicutes, in the direction of diminishing the latter. In addition, the altered levels of other intestinal commensals, including the genera B*ifidobacterium, Lactobacillus, Sutterella, Prevotella* and *Ruminococcus*, and the Alcaligenaceae family, correlate with the development of autism. Nevertheless, there are studies that disprove the relationship of microbiota and the development of autism. This is explained by the difference in the strategies and sampling methods applied to the analysis of the microbiota. In addition, the products of the metabolism of intestinal microorganisms also affect autism. The profile of

metabolites in autistic patients and healthy control is different, indicating changes in the microbiota [14, 15].

Depression is the main form of mood disorder that occurs as a result of neuropsychiatric disorders or immunological deregulation. Treatment with probiotics has shown efficacy in suppressing models of animal depression. Representatives of the genus *Lactobacillus* exhibit the properties of antidepressants. A probiotic mixture containing *L. rhamnosus* and strains of *L. helveticus* facilitates depression caused by excommunication from the mother, normalizing the level of corticosterone. Similarly, the strain *L. rhamnosus* JB-1 reduces depressive behavior through the regulation of corticosterone and GABA receptor in a vagally dependent manner. Representatives of the genus *Bifidobacterium* are also potent antidepressants. *Bifidobacterium infantis* alleviates depression in rats in the model of weaning from the mother. Among the mechanisms involved are the weakening of pro-inflammatory cytokines, the regulation of tryptophan metabolism and CNS neurotransmitters. Combination of probiotics on the basis of lactis acid bacteria of the genera *Lactobacillus* and *Bifidobacterium* showed a positive result in tests on models of postinfarction depression. The combined use of *L. helveticus* and *Bifidobacterium longum* improved depression by reducing proinflammatory cytokines and restoring the integrity of the gastrointestinal barrier [49].

Anxiety and stress. Anxiety and stress are common forms of mood disorders with a nervous, endocrine and immunological basis. The impact of stressors, such as chemical, biological or environmental inducements, can cause stress and anxiety reactions that activate the hypothalamus-pituitary-adrenal axis [20, 22].

Sterile mice show increased motor activity and reduced anxiety in comparison with specific SPF mice (normal-pathogen-free) with normal intestine microbiota. This behavioral phenotype is associated with higher levels of neurotransmitters and a decrease in synaptic long-term potentiation in the central nervous system of sterile mice. Reduction of anxiety-like behavior in sterile mice is confirmed by later studies, and is explained by other neurochemical changes, such as a decrease in receptors of neurotransmitters and an increased metabolism of tryptophan. Therefore, it is postulated that the intestinal microbiome regulates a given value for the hypothalamus-pituitary-adrenal axis. Gut related pathogens can aggravate anxiety. Infection with *C. jejuni* increases anxious behavior by inducing the protein c-Fos, a marker of neuronal activation. Induction of C-Fos protein was also noted in worsening anxiety when *Citrobacter rodentium* was infected, while *Trichuris muris* increased anxiety with immunological and metabolic mechanisms. The use of probiotics can alleviate anxiety. Specific genera of genus *Lactobacillus* and *Bifidobacterium* have anxiolytic effects. Probiotic treatment with certain strains of *B. longum, B. infantis, L. helveticus* or *L. rhamnosus*, either individually or in combination, normalizes behavioral phenotypes in animal anxiety models. *Lactobacillus farciminis* also suppresses stress-induced processes in the intestine and weakens the stress response of the hypothalamus-pituitary-adrenal axis. Using of a probiotic consisting of *L. helveticus* and *B. longum* showed an anxiolytic activity in rats and positive psychological effects in healthy people [14, 15, 20].

Pain. Nociceptive pain caused by peripheral nervous reaction to inducements and signaling in the central nervous system can be facilitated by probiotic modulation of the microbiome. Antinociceptive effects are observed in species of the genus *Lactobacillus*. *L. farciminis* improved the stress-induced hypersensitivity to colorectal stretching in rats. *L. reuteri* also relieved visceral pain caused by colorectal stretching in normal rats. *L. paracasei* normalizes visceral hypersensitivity to colorectal stretching of mice suffering from the use of antibiotics. *Lactobacillus acidophilus* has analgesic effect for pain in the intestines by induction of opioid and cannabinoid receptors. *B. infantis*

reduced pain induced by colorectal stretching, both in visceral normal and visceral hypersensitive rats, as well as in the rat model of post-inflammatory hypersensitivity of the colon [50].

Other neuropsychiatric symptoms. The microbiota is associated with other neuropsychiatric disorders, where a mixture of immunological and non-immunological etiology is involved. Sterile animals show defective memory and cognitive abilities. Memory dysfunction occurs in sterile mice regardless of the effects of stress was found. Probiotics improve infectious memory dysfunction and diabetes-induced cognitive defects. Propionic acid reduces the social and cognitive abilities of the mouse. Changes in intestinal microbiota caused by diet also also modulate mouse cognitive and learning behaviors. Changes in the microbiota were found with hepatic encephalopathy. With Down's syndrome, there was a change in serum antibodies with a change in oral microbiota. Changes in the oral microbiota were also observed in comatose patients. A positive correlation between schizophrenia and serological surrogate markers of bacterial translocation was found [8, 9, 13, 14, 16].

Factors binding microbiome and central nervous system

Since microbiome belong to the collective genomes of general microbiota, microbiota studies are broad in scope and include: the overall composition of the microbiota or specific bacteria, products of the microbiota metabolism, external microbiota change, and integrity status of the barrier affecting the host-microbiota contact. Thus, it is worth summarizing the factors mediating influence of the microbiome on CNS disorders.

1. *Hygiene*.

Hygienic hypothesis states that the absence of infection with infectious agents in childhood, parasites and commensals increase susceptibility to type 2 T-helper (Th2) - responsible for allergic diseases. However, there is a correlation between improved sanitation and an increase in Type 1 T helper (Th1), responsible for autoimmune diseases, such as type 1 diabetes and multiple sclerosis. Th1-response is aimed at intracellular microbes mediated by interferon-γ (IFN-γ); while the Th2 response targets helminths and allergens characterized by interleukin-4 (IL-4) and IL-13. Thus, abnormal immune development is a potential mechanism linking hygiene and immune-mediated CNS disorders [2-4]. Hygiene has a specific, depending on the situation, rather than a universal effect on neuro-chemistry and neuro-behavioral manifestations.

2. *Using of antibiotics*.

Antibiotics cause a selective change in the intestinal microbiota. The fact that antibiotics balance the Th1 / Th2 balance in the Th2 direction is consistent with the hygiene hypothesis. An earlier study also showed a decrease in pro-inflammatory cytokines, including IFN-γ and IL-17, when antibiotics are treated with autoimmune encephalomyelitis. While, intact natural killer cells, necessary for protection from autoimmune encephalomyelitis, were not induced by antibiotics. Studies confirm the useful role of antibiotic therapy in neuro-behavioral disorders. Antibiotic therapy reduces stress reactions and brings short-term benefit to children with autism with a regressive onset. The main mechanisms may include a decrease in the concentration of lipopolysaccharides in the lumen (and, therefore, potentially reduced chronic inflammation) and changes in CNS signals, such as hippocampal neurotrophic brain factor expression. In general, antibiotics can restore the original immune and neuro-hormonal status, formed with the help of a commensal microbiome, and, consequently, change the predisposition to CNS disorders [2-4, 15].

3. *Microbiota composition*.

The effect of microbiota composition of a CNS disorder can be demonstrated by various methods, including infection-induced microbiota, studies using SPF and gnotobiotic mice, monocolonization of sterile mice, and metagenomic approaches, such as microbial microchips and the profiling of 16S rRNA. In addition, compositional changes in microbiota can be indirectly reflected by profiling the titers of metabolites and cometabolites of microbiota and serum antibodies against microbiota and diet components. Since the study of microbiota enterotypes is still in its infancy, efforts to locate enterotypes specific for the disease are limited. Two mouse enterotypes, ET1 and ET2, which were strikingly similar to the enterotypes Ruminococcus and Bacteroides in humans, were determined, respectively. Mice ET2 showed higher levels of fecal calprotectin, a biochemical marker of inflammatory bowel disease. For CNS disorders, a specific relationship with enterotypes has not yet been established. In addition, the need to clarify the cause and effect should be taken into account, since CNS disorders can affect the diet or be concomitant with bowel epithelial dysfunction, both scenarios affect the composition of the microbiota [2-4, 14, 15].

4. *Probiotics*.

The intake of useful living bacteria, also known as probiotics, is a therapeutic way of using microbiota components for treatment. Probiotics can regulate immune manifestations, especially in the case of autoimmunity of the CNS. *B. fragilis* is a known probiotic strain that promotes increasing in the amount and functional maturation of Foxp3 + Treg in both autoimmune encephalomyelitis and inflammatory bowel diseases. Lactic acid bacteria are key components of anti-inflammatory probiotic mixtures that can also function by stimulating IL-10 + Foxp3 + Tregs. Moreover, the genetic modification of natural strains is another powerful probiotic approach. Probiotics can alleviate neuropsychiatric disorders with the help of hormonal and neurochemical mechanisms. For example, *B. longum* NCC3001 can normalize the expression of the mouse brain neurotrophic factor by the hippocampus, and *L. rhamnosus* (JB-1) can exert differential regulation of GABA transcription in various areas of the CNS. Probiotics can transmit anxiolytic effects in various types of neuro-behavioral disorders, indicating a common neuronal and endocrine etiology of these disorders. For example, *L. helveticus* R0052 and *B. longum* R0175 can improve both anxiety and depression in rats. Neuronal mechanisms that are associated with direct bacterial activation or inhibition of neurons, can explain the antinociceptive effects of probiotics [14, 15].

5. *Microbiota metabolites*.

Microbiota metabolism products are often effective components responsible for the transmission of microbiota-intestinal-CNS signals. This is especially noticeable in the case of capsular polysaccharide A (PSA) *B. fragilis*, since PSA can repeat the functions of its parental organism. PSA exhibits anti-inflammatory effects in autoimmune encephalomyelitis and activates the intestinal neurons sensitive to it. PSA is a unique zwitterion and is mentioned as a symbiotic factor for commensalism [17]. Bacterial extracellular ATP and lipopolysaccharides (LPS) lead to chronic inflammation, which contributes to the pathogenesis of neuro-immune and neuropsychiatric disorders. Metabolites and cometabolites of microbiota are critical intermediaries for the transmission of microbiota-intestinal-CNS signals. Commensals generate a number of neuroactive substances. For example, the species *Lactobacillus* and *Bifidobacterium* can produce an inhibitory neurotransmitter-gamma-aminobutyric acid (GABA). A group of fatty acids with aliphatic tails of 2 to 6 carbon atoms are products of fermentation of dietary fiber by microbiota. This group of fatty acids is recognized as an important immune regulator [28].

6. *Diet*.

Types of diets can modulate the intestinal microbiota by changing the availability of nutrients. Dietary interference can affect the content of genes of intestinal microbiota was shown. A lower microbial content was identified as less healthy and associated with metabolic dysfunction and mild inflammation. A dietary formula with a higher fiber content can improve the microbiota quantitatively. Unhealthy diet schemes that contain a high level of fat or salt can accelerate neuronality during encephalomyelitis [46]. Western diet can adversely affect behavior and memory, similar to anxiety, depending on the immune status. A diet with a high level of polyunsaturated fatty acids facilitates depression. These experimental data may indicate saturated fat as a risk factor for both neuro-immune and neuropsychic disorders. In combination, modulation of microbiome is the integral mechanism underlying the diet-based treatment [2-4].

7. *Intestinal permeability.*

Permeability of the intestine is directly or indirectly related to the role of the microbiome in CNS disorders. Humoral and cellular immune response to the microbiota in the circulation, persistent mild inflammation and neuropsychiatric pathology associated with inflammatory bowel disease suggest a violation of the epithelial barrier of the mucosa [36]. Probiotic treatment with several species of the genus *Lactobacillus* restored the integrity of the barrier. Dysbiosis and destruction of the mucous membrane are interrelated phenomena. Microbiota and its ligands support cell-cell connections that are critical for the integrity of the barrier. During an inflammatory bowel disease, an abnormal microbial composition is established in the intestine of the host. In turn, the cascade of the inflammatory process during inflammatory diseases of the intestines can strengthen the intestinal dysbiosis. Although, it is very difficult to determine the initial cause of dysbacteriosis and hyperpermeability of the intestine in the course of development of the pathogenesis of the central nervous system.

CONCLUSION

Microbiome controls the canonical aspects of the central nervous system, immunity and behavior in norm and in pathology. Nevertheless, the details of the role of microbiome in CNS disorders are unknown. First, it is necessary to clarify the relative contribution of the immune, nervous and endocrine pathways in the communication between the microbiome and the central nervous system in pathological conditions. Secondly, it is extremely important to find out the factors that play in microbiome-based therapy, and to further clarify the effective components. Thirdly, care should be taken when transferring data from animal models to humans using existing microbiome studies.

The microbiome study has a perspective for prognosis and therapy associated with CNS disorder. Bacteriotherapeutic preparations and functional food products enriched with the corresponding probiotic microorganisms can influence the effect of the intestinal microbiome on the central nervous system and brain function, as evidenced by numerous experimental studies. Along with the diet, these functional nutritional components and medicines can not only restore intestinal homeostasis to improve cognitive or emotional function. They can also be used to prevent and treat neurological disorders, as well as to maintain the functionality of the immune system in stressful individals.

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