PROBIOTICS AND STRESS FACTORS

Starovoitova Svitlana

docent, PhD

Department of Biotechnology and Microbiology

Faculty of Biotechnology and Ecological Control

National University of Food Technologies

Kyiv, Ukraine

Annotation. The functional connection between the gastrointestinal tract (GIT) and the central nervous system (CNS) of the host organism was considered. The relationship between the intestinal microbiome and CNS had been analyzed. The main mechanisms of the influence of microbiota on the functions of CNS were shown. The literature data on the role of the intestinal microbiome in disorders of CNS were summarized. The prospects of using probiotics 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.

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 [1, 2, 5, 6].

Clinical studies have demonstrated the various pathological effects of intestinal bacteria on CNS 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 [1, 6].

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. Different types of diets also modify the composition and functions of the microbiome in complex ways, which differ in individuals and national cultures [3, 4, 5].

The intestine receives regulatory signals from CNS, 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 GIT.

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. Signal saturation proteins arise mainly in GIT, but most of them also are synthesized within the brain. 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 CNS 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. Stress causes defects in the epithelial barrier and subsequent activation of cells on the mucosa has been experimentally shown [1, 2].

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 CNS. External signals obtained from local microbiota affect prenatal and postnatal programming of brain development. 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. 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 [2, 4, 6].

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. Activation of the vagus is necessary for a number of effects of the intestinal microbiome or probiotics on brain function. 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 [1].

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. 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 CNS. 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 [1, 2, 5, 6].

Dysregulation of serotonergic and kynurenine pathways of tryptophan metabolism affects the pathological conditions of CNS: dementia, Huntington's disease and Alzheimer's disease. Probiotic treatment can alter the levels of kynurenin and improve the pathology of CNS. 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 [1, 6].

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. Secondly, the association of the immune system with CNS 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 [1]. In both directions of the pathway, there are anti-inflammatory mechanisms that can counteract the immune-mediated symptoms of CNS disease.

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. 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.

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. The intake of 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. *Bifidobacterium 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. 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 *Lactobacillus 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 [1, 5, 6].

Conclusions. Microbiome controls the canonical aspects of CNS, 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 CNS 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. Probiotics and functional food products enriched with probiotic microorganisms can influence the effect of the intestinal microbiome on CNS and brain function. 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 individuals.

Literature:

1.Wang Y., Kasper L.H. The role of microbiome in central nervous system disorders // Brain. Behav. Immun. – 2014. - Vol. 38. – P. 1–12.

2. Старовойтова С.А., Карпов А.В. Иммунобиотики и их влияние на иммунную систему человека в норме и при патологии // Biotechnology. Theory and Practice. – 2015. - №4. – С. 10 - 20.

3. Starovoitova S., Karpov A. Functional food products with immunocorrective action // 8th Central European Congress on Food 2016 — Food Science for Well-being (CEFood 2016): Book of Abstracts. — 23-26 May 2016. — K.: NUFT, 2016. – P. 294.

4. Castellazzi A., Tagliacarne S.C., Soldi S., Valsecchi C. Stress and immune function: there is a role for the gut microbiota? // 9th Probiotics, prebiotics and New Foods, Nutraceuticals and Botanicals for Nutrition and Human and Microbiota Health. Università Urbaniana, Rome-September 10-12 2017. – P. 19.

5. Starovoitova S., Karpov A. Probiotic microorganisms as basis of immunobiotics and their therapeutics effects // International Students Journal of practical Conference of Students and Young Scientists «Science and Medicine: A Modern View of Youth», 20-21 April, 2017. – Almaty, 2017. – P. 552 - 553.

6. Старовойтова С.А. Пробиотики и стресс // Материалы V Международной научной конференции молодых ученых и студентов «Перспективы развития биологии, медицины и фармации» (8-9 декабря 2017 года, г. Шымкент, Республика Казахстан). – Вестник ЮКГФА. – 2017. - Том 3, №4. – С. 6-7.