A number of alleles of polymorphic genes, dysfunctions of the hypothalamic-pituitary-adrenal axis, neurotransmitter disorders, and manifestations of immune dysregulation are associated with vulnerability to stress. Post-stress states of humans and animals are accompanied by signs of neuroinflammation, the causes and mechanisms of which remain to be elucidated.

The article discusses epigenetic mechanisms by which the intestinal microbiota might participate in the initiation and maintenance of post-stress inflammation.

**Keywords:** microbiota; stress; post-stress pathology; neuroinflammation; epigenetic modifications.
It is known that chronic neuroinflammation underlies many neurological and mental disorders (Parkinson’s disease, depression, schizophrenia, and post-traumatic stress disorder [PTSD]) [9].

However, the involvement of the microbiota of the host organism in microglia activation and in the maintenance of neuroinflammation remains unclear. One possible theory is that bacterial metabolites have the ability to influence the epigenetic modifications of genes associated with immunoregulation [12].

Epigenetic modifications are inherited molecular mechanisms in the regulation of gene expression; they do not affect the nucleotide sequence of DNA but lead to specific conformational changes in chromatin structure [13].

This article analyzes recent studies on the role of intestinal microbiota in the epigenetic control of the development of post-stress neuroinflammation.

**MICROBIOTA OF HUMAN INTESTINES**

GIT microbiota refers to the totality of all microorganisms that inhabit the human intestines (bacteria, eukaryotes, archaea, and viruses), while microbiome is defined as a complete genetic set of these microorganisms [14]. The total number of bacteria that comprise human microbiota is higher than the number of cells in the human body ($3.9 \times 10^{13}$ and $3.0 \times 10^{13}$, respectively) [15]. The human genome contains 12 times fewer genes than microbiomes. According to recent estimates, the total number of genes that make up the microbiome is 400,000 [16]. Of the total number of bacteria in an adult’s body, 80% are intestinal bacteria [6].

The composition of GIT microbiota changes throughout a person’s life [17]. Intestinal colonization by microorganisms occurs during embryo-fetal development via amniotic fluid and/or umbilical cord blood [18–20]. Bacteria have been found in the meconium of healthy newborns [21]. However, the main stage in the formation of human intestinal microbiota occurs during post-embryonic development. During and immediately after birth, the newborn comes into contact with both the mother’s microbiota and the environment; consequently, a number of commensal bacteria are acquired, which inhabit the GIT [22]. Studies show that the first years of life are a critical period for the formation of a healthy intestinal ecosystem [23].

According to the “old friends” hypothesis, such a symbiosis between the human body and the plurality of microorganisms that inhabit its intestines is the result of a lengthy joint evolution [24]. There is ample evidence that intestinal microbiota perform a number of essential functions in the host organism. They participate in the creation and maintenance of the integrity of the intestinal barrier, stimulate the regeneration of intestinal epithelial cells, produce mucus, and nourish the GIT mucosa by secreting some metabolites [25, 26].

Intestinal microbiota is involved in the maturation of the host immune system due to its capacity to stimulate innate immunity during the early stages of ontogenesis. It affects the development of the lymphoid tissue related to the intestines; activates adaptive immunity through stimulation of local and systemic immune responses [27]; participates in the synthesis of certain nutrients, hormones, and vitamins; and plays an important role in the removal of toxins.

Under normal conditions, the microbiota is able to stimulate the immune system, leading to a state of low-intensity physiological inflammation (parainflammation). It is hypothesized that such stimulation of immunity increases the tolerance of the host organism to the damaging effects of pathogenic microbes [28].

However, the intestinal ecosystem is extremely vulnerable to the effects of adverse factors. The existing balance of microorganisms can be disturbed both by psychoemotional factors (i.e., stress, including during the prenatal period) and by diet and drug intake [29]. The composition of the GIT microbiota is also determined by viruses [30] and parasitic infections of the intestine [31].

**INFLUENTIAL MECHANISMS OF GIT MICROBIOTA ON BRAIN DEVELOPMENT AND FUNCTION**

To date, adequate data has been accumulated on the relationship between the qualitative and quantitative indicators of intestinal microbiota and the severity of symptoms of anxiety and depression in both humans and rodents [32, 33].

An extended study following an outbreak of bacterial gastroenteritis in Canada revealed that severe anxiety and depression are risk factors for persistent intestinal symptoms after eight years from the initial infection [34]. In 2013, the National Institute of Mental Health in the United States of America launched a program to study the mechanisms of interaction between the microbiota and the brain with the purpose of creating new drugs and developing non-invasive treatments for mental disorders.

The interaction between the brain and intestinal microbiota is often described in literature as the microbiota—intestine—brain axis [1, 6, 29, 32, 33]. Such communication takes place through neuroanatomical pathways and the endocrine and immune systems as well as via the release of certain metabolites by bacteria that can affect the nervous system [6, 35, 36].
The autonomic nervous system of the intestine and the vagus nerve provide one route by which the intestinal microbiota affects the brain. It is generally recognized that bacterial metabolites stimulate afferent neurons in the enteric nervous system [37].

It has been known since the 1930s that enteroendocrine cells are located in the intestinal epithelium. They are electrically excitable, but until recently it was believed that these cells were unable to form synapses with cranial nerves. A recent study [37] identified a type of sensory intestinal epithelial cell that contains synapses with sensitive neurons of the vagus nerve (nodose ganglia). The authors referred to these cells as neuropod cells, since, despite being a type of endocrine cells, they have the ability to form neuroepithelial networks. Using glutamatergic synapses with the vagus nerve, the neuropod cells connect the intestinal lumen directly to the brain stem. Due to the existence of such nerve networks, the brain can obtain information from the intestinal lumen within a few milliseconds.

The functional disturbances of the hypothalamus, pituitary, and adrenal glands that constitute the HPA axis contribute to the pathogenesis of post-stress pathologies [38]. The latest data indicate a significant role of intestinal microbiota in the functional disorder of these structures and, consequently, in neuroendocrine dysregulation [7].

In GF mice, stress caused by prolonged immobilization leads to a significantly greater release of corticosterone and adrenocorticotropic hormones compared with control animals with normal microbiota. Such an excessive response to stress can be partially normalized by preliminary stool transplantation from control mice and is completely restored by colonizing an individual bacterium of the Bifidobacterium infantis species in the intestine [39].

One of the possible mechanisms of such an effect of bacteria on the function of the HPA axis is the effect their metabolites have on the functioning of the glutamatergic and serotonergic synapses. GF mice showed a significant decrease in the expression of glutamate receptors (NMDA receptors) and serotonin (5HT1A receptors) in the hippocampus and cortex compared with SPF mice. Deficiencies in glutamatergic and serotonergic transmission can lead to disruptions in the function of the HPA axis, which acts on the secretion of corticotrophin-releasing hormone (CRH) in the hypothalamus. Long-term exposure to elevated levels of CRH creates a state of distress, severe depressive symptoms, insomnia, chronic anxiety, exhaustion, and a decrease in libido [6].

It has been revealed that the stress factor affecting the operation of the HPA axis can induce a change in the microbiota composition. For example, in newborn rats, early weaning from the mother not only leads to long-term changes in the functioning of the HPA axis but also has a lasting effect on the microbiota composition of the offspring [40].

Similar interactions are exhibited during exposure of adult animals to stress. In mice, the microbiota composition in a mouse model of chronic psychoemotional stress and in unstressed mice is significantly different [41]. Stress has been confirmed to decrease the amount of Bacteroides in the cecum and increase the amount of Clostridium [42].

Immune interactions represent another mechanism through which microbiota can affect the condition and functions of the nervous system. An important role in the communication between bacteria and the host is played by Toll-like receptors (TLRs), which are expressed on epithelial cells, monocytes, macrophages, dendritic cells, neutrophils, and natural killers and are also widely represented in neurons and glial cells [43]. They recognize the conservative structures of microorganisms and represent an important link in the innate immune system. After activation, TLRs bind to adapter proteins and are able to induce cytokine synthesis.

Intestinal microbiota produces neurotransmitters and other regulatory molecules that can affect both the brain and behavior. These substances include gamma-aminobutyric acid, serotonin (5-H\textsubscript{T}), dopamine, and short-chain fatty acids (SCFA) [25, 26, 44–46].

SCFA are metabolic products of intestinal microbiota; they are used by the host cells as an energy source for ATP synthesis. Simultaneously, some of the salts of such acids (propionate, butyrate) are involved in the epigenetic modifications in mammalian cells. Thus, bacteria of the genera Clostridium, Eubacterium, and Butyribrio are able to synthesize and supply butyrate from indigestible fibers into the gastrointestinal tract lumen. Butyrate has an inhibitory effect on histone deacetylase (HDAC) and thus is involved in the epigenetic modification of histones [44].

Several receptors for SCFA in various tissues are known. Free fatty-acid receptor 2 (FFAR2), free fatty-acid receptor 3 (FFAR3), and hydroxyacyl-CoA dehydrogenase receptor 2 (HCDAR2) (also known as G protein-coupled receptor 109) have been extensively studied. In dendritic cells, these G-protein-associated transmembrane proteins affect cell metabolism, inflammation, and oxidative stress [25]. In lymphocytes, the activation of these receptors by agonists such as SCFA regulates the expansion, differentiation, and functionality of T cells [26], which is one of the mechanisms of SCFA action on the immune system.
There is evidence of the presence of SCFA receptors (e.g., FFAR3) in the CNS of rats and in the peripheral nervous system of mice [47]. To date, there is no evidence of the presence of FFAR2 and FFAR3 receptors on microglial cells [48]; however, it has been revealed that SCFA affects the maturation and activity of microglial cells in laboratory animals [8, 49]. Changes in both the structure and density of microglial cells in sterile mice were recorded. The same phenotype can be reproduced by inhibiting the expression of FFAR2 and FFAR3 – SCFA receptors [6].

In rats, the HCAR2 receptor (more specifically, its mRNA and the corresponding protein) was found in the microglial cells of the substantia nigra. Previous work shows that β-hydroxybutyric acid reduces the manifestation of motor dysfunction in rats in a model of Parkinson’s disease. This positive effect is associated with the suppression of microglial activation and a decrease in the production of proinflammatory cytokines, which prevents the loss of dopaminergic neurons in the substantia nigra. The authors demonstrated that β-hydroxybutyric acid acts on microglial cells via HCAR2 receptors and reduces the activation of the NF-κB signaling pathway (a key inflammatory mediator). HCAR2 knockdown cancels the anti-inflammatory effect and decreases NF-κB activity [50].

Other key metabolites of the intestinal microbiota, including S-adenosylmethionine, acetyl-CoA, nicotinamide adenine dinucleotide, and ATP, are necessary cofactors for enzymes that regulate DNA methylation and histone modifications [51]. Thus, folate (a metabolite of *Bifidobacterium* spp. and other bacteria) is a methyl-group donor and is crucial for the production of S-adenosylmethionine, which is also a methyl-group donor and a substrate for DNA methyltransferases [52].

**POST-STRESS PATHOLOGIES AND IMMUNE RESPONSE**

In recent years, neuroimmune regulation disorders have been actively investigated in various mental disorders, including in post-stress conditions. There is convincing evidence of the signs of neuroinflammation in neurotic and stress-related disorders in humans and in animal models (mice and rats) of similar psychopathologies. Most studies evaluate the levels of proinflammatory cytokines in the blood of patients with PTSD, and postmortem studies on sections of the human brain are rare.

It was revealed that the levels of proinflammatory cytokines, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor (TNF), are significantly increased in the blood of patients with PTSD compared with both the control and patients with a history of injury without the development of symptoms of the disease [9].

These data indicate the presence of peripheral inflammation in PTSD, but they do not indicate its role in the pathogenesis of the disease. The connection between peripheral inflammation and PTSD pathogenesis is indicated by the fact that the higher levels of cytokines detected in the blood plasma of military personnel before their participation in hostilities are associated with an increased risk of PTSD development after their return from flashpoint areas [53]. In addition, a higher level of glucocorticoid-dependent production of cytokines and T-cell proliferation before the hostilities is associated with the increased severity of PTSD symptoms in soldiers after returning from combat areas [54].

However, the lack of convincing data on the signs of neuroinflammation in the brains of patients with stress-related neurotic disorders does not conclusively explain how the level of peripheral cytokines reflects the involvement of neuroimmune processes in the development of post-stress conditions.

Therefore, the use of animal models seems to offer promising clarification of this issue. In the mouse model, on day 8 after exposure to stress, an increase in the level of monocytes circulating in the blood and increased anxiety in behavioral tests were revealed. On day 24 after the exposure to stress, anxiety behavior and increased proinflammatory cytokine mRNA levels in microglial cells (IL-1β, TNF, and IL-6) were still noted, although there were no peripheral signs of inflammation [55]. There is also evidence of increased expression of the same cytokines in the rat hippocampus in the PTSD model; this effect persisted for two weeks after exposure to stress [9].

The brain microglial cells are derived from macrophages, which are cells that are capable of actively capturing and digesting particles that are foreign or toxic to the body, such as bacteria and the remains of dead cells. Microglial cells are the first line of defense in brain injuries and infectious diseases and become activated in the case of some neurological and mental disorders [6]. Microglial cells migrate to the CNS during prenatal development. They are actively involved in brain development via participation in the formation of synapses and nerve cells and in the prevention of excessive activation of neurons [6].

**MICROBIOTA AND POST-STRESS INFLAMMATION**

Recently, the interaction between the GIT microbiota and the brain has been considered as one of the fa...
tors in the emergence of a number of psychiatric and neurological diseases, which suggests the concept of a human as a superorganism or a holobiont with all its complexity.

In the perinatal period, the functional development of the mammalian brain is subject to both internal and external signals. Epidemiological studies have revealed a relationship between microbial pathogenic infections during this time and common disorders of the nervous system development, such as autism and schizophrenia [2, 5, 35]. The rodent models revealed that the effect of microbial pathogens in the early postnatal periods of development causes a disorder of cognitive functions and contributes to the development of symptoms of anxiety [56, 57].

A comparison between the GIT microbiota in patients with PTSD and healthy subjects exposed to a single stress factor [58] revealed a decrease in the relative number of bacteria (Actinobacteria, Lentisphaerae, and Verrucomicrobia) in patients with PTSD. The data from this study are consistent with the findings of post-stress pathologies in animal models [59]. It was concluded that a deficiency of the above microorganisms may lead to an increased vulnerability to PTSD.

Most studies of the microbiota–intestine–brain axis were focused on animal models. The use of GF mice enabled an evaluation of the effect of microbiota on behavior, as well as the determination of the effect of specific bacteria or dietary changes on the interaction between the microbiota, the intestines, and the brain. It has been established that the most pronounced aspects of such mice are disorders in the functioning of the immune system. Similar disorders are observed in patients with behavioral symptoms of anxiety [60].

GF mice show signs of neuroinflammation in those brain structures that are involved in the pathogenesis of stress-related disorders [61]. An increased level of proinflammatory IL-1β in the amygdala of GF mice is detected along with a decrease in the BDNF neurotrophic factor [62].

The SCFA produced by intestinal microbiota affect neuroimmune regulation through modulation of the state and functioning of the brain microglial cells. These metabolites can inhibit HDAC, i.e., they can regulate epigenetic changes at the system level, which is combined with a change in the microglial-cell phenotype from activated to anti-inflammatory [45, 46].

Folates, butyrates, and acetates produced by bacteria are involved in DNA-methylation processes in the cells of the host organism. For example, folates (a vital product of Bifidobacterium spp.) are necessary for the synthesis of S-adenosylmethionine, which is a methyl-group A donor for DNA methyltransferases [58].

These data support the hypothesis of the effect of intestinal microbiota on physiological processes in the host organism by influencing the epigenetic modifications of the host genome.

**EPigenetic modifications and post-stress inflammation**

In the modern sense, epigenetic modifications are molecular mechanisms of gene-expression regulation that do not affect the nucleotide sequence of the DNA; however, specific conformational changes in chromatin structure occur [13, 63].

Epigenetic modifications can be inherited and reversible. They are involved in the processes of cell differentiation in multicellular organisms and changes in gene-expression profiles in response to changing environmental conditions [51, 52, 61].

The regulation of gene expression by methylation of regulatory DNA sequences, histone modification, non-coding RNA, and post-transcriptional RNA processing is included in the most well-known epigenetic mechanisms.

DNA methylation consists of the attachment of a methyl group to carbon in the cytosine molecule at position 5 to form 5-methylcytosine. The methylation of the promoter regions of genes often leads to an inhibition of transcription. However, the hydroxymethylation of the same sequence can stimulate gene expression [64]. These changes are catalyzed by a group of enzymes, namely, DNA methyltransferases, for example, DNMT1, DNMT3A, and DNMT3B (which catalyze methylation), and TET1-3 and IDH1-3 (which catalyze hydroxymethylation).

Histone modifications are more diverse and complex than DNA methylation. Various amino acids of histone tails can be methylated, acetylated, and phosphorylated. These modifications can increase or decrease gene expression depending on the type of change and its position [63]. For example, the acetylation of histone residues leads to the increased availability of nucleosomal DNA for transcription factors, thereby increasing the expression levels of the corresponding genes. Histone acetylation consists of the transfer of the acetyl group from acetyl coenzyme A to histone lysine and is catalyzed by lysine acetyltransferase. The acetylation process is balanced by the deacetylation of histones and the removal of the acetyl group from lysine, which is catalyzed by HDAC [65].

Complex combinations of DNA methylation and histone modifications interact with more than 1000 microRNAs. In turn, each microRNA can bind to the transcripts of hundreds of genes depending on the type
of tissue, thereby increasing the complexity of the transcriptional response of the body without increasing the number of genes.

The epigenetic regulation of gene expression is considered to be a mechanism of interaction between the environment and the genome. It is likely that a traumatic event (stress factor) causes the persistent epigenetic modifications in loci associated with immune dysregulation and increases the risk of PTSD. The question of the degree of reversibility and durability of such modifications remains relevant.

To date, there is evidence of a lower level of methylation of the promoter regions of genes associated with immune response, including proinflammatory IL-18 and IL-8, in the blood of patients with PTSD compared with the control [66–68]. The main limitation of these studies consists of the measurement of the level of DNA methylation (mDNA) in serum or whole blood without considering the cellular composition. Therefore, the results discussed may not reflect PTSD-specific changes in the peripheral immune system cells. In this regard, future studies should determine the level of mDNA in homogeneous cell populations [69]. There are no postmortem studies available in which the brains of patients with PTSD are compared with the norm; therefore, no data are available on the level of methylation of cytokine genes in the brain microglial cells of patients [66].

A comparison of the methylation level of genes associated with the development of inflammation in blood and microglial cells in PTSD animal models will enable an understanding of how the previously identified differences in peripheral mDNA levels correlate with the epigenetic modifications of DNA in the brain.

Intestinal microbiota is considered as a factor that actively affects the development of the nervous system, the functional state of the brain, and behavior via epigenetic modifications of genes associated with neuroinflammation [61]. As detailed above, metabolites of the GIT microbiota (butyrate and propionate) inhibit HDAC and thus affect the activation of the host genome transcription [51].

In patients with chronic gastritis, the presence of Helicobacter pylori in the GIT is specifically associated with DNA hypermethylation in the region of the O6-methylguanine-DNA methyltransferase (MGMT) gene promoter, which reduces the expression of the MGMT protein in gastric epithelial cells [70]. MGMT is a nuclear protein that plays a key role in repairing DNA damage caused by simple alkylating agents and is considered as a tumor-growth-suppressor gene.

Animal studies have revealed that such epigenetic changes in the cells of the gastric mucosa are associated with inflammation induction as a result of an H. pylori infection – but not with the bacterium itself. Significant suppression of inflammation by the immunosuppressive drug, cyclosporin A, did not affect the colonization of H. pylori; however, it blocked DNA hypermethylation [70].

Another example is the protein (Rv3423.1) of Mycobacterium tuberculosis, which exhibits histone acetyltransferase activity in host cells and acetylates histone H3 at the K9/K14 positions [71]. In addition, Rv1988, another secreted mycobacterial protein that interacts with chromatin, has methyltransferase activity and methylates histone H3 at the H3R42 position, which suppresses the expression of affected genes [72].

Epigenetic mechanisms are key mediators in the development of chronic inflammation due to the induction of the gene expression of proinflammatory cytokines, including IL-1, IL-2, IL-6, TNF, and COX2 induction, and the NF-κB transcription factor [58]. For example, the increased expression of TNF during the development of irritable bowel symptoms in Danio rerio fish is associated with a loss of function of uhfr1, a gene that encodes the ubiquitin-like protein (an epigenetic regulator), and leads to the hypomethylation of the TNF-gene promoter. Consequently, an increase in TNF expression mediated by microbiota leads to the recruitment of immune cells, chronic inflammation, apoptosis, and the dysfunction of intestinal epithelial cells as a barrier [73].

The demethylation of a small promotor region of the IL-2 gene was detected in mouse T cells after their activation. The composition of the microbiota changed; as a result, the IL-2 gene expression, which is one of the inflammatory mediators, increased. In addition, the maturation of naive CD4 T cells to T-helper cells is characterized by the rapid acetylation of histone H3 in IL-4/IL-13 gene clusters [74].

Based on these studies, demethylating agents and histone deacetylase inhibitors are currently considered in the literature as epigenetic therapy drugs that target chromatin in rapidly dividing cells [75]. Such agents that affect the epigenetic modifications of genes associated with inflammation can be the metabolites of intestinal microorganisms. Generally, microbiota is a new target for the development of methods for the elimination of neuroinflammation and post-stress pathologies via exposure to the epigenome.

**MICROBIAL THERAPY IN MENTAL DISEASES**

The discovery of the relationship between the microbiota, immunity, inflammation, epigenetic modifications, and mental health suggested that exposure to GIT mi-
Probiotics and their role in mental health

Probiotics are living beneficial microorganisms that are used to provide health benefits when ingested or applied to the body. They are often used as dietary supplements or added to foods to enhance their nutritional value. Probiotics are known to have a wide range of beneficial effects on human health, and recent research has highlighted their potential role in mental health.

**The Role of Probiotics in Mental Health**

Several studies have investigated the potential of probiotics in mental health, particularly in conditions such as depression, anxiety, and stress. Research has shown that probiotics can improve mood, reduce anxiety, and alleviate symptoms of depression, possibly by modulating the gut-brain axis.

**Mechanisms of Action**

The mechanisms by which probiotics exert their beneficial effects on mental health are not fully understood. However, it is believed that probiotics can influence the gut microbiota, which in turn can affect the brain. The gut microbiota plays a crucial role in the gut-brain axis, and changes in gut microbiota have been linked to various mental health conditions.

**Evidence for Probiotics in Mental Health**

There is growing evidence to support the use of probiotics in mental health. Studies have shown that probiotics can improve overall psychological condition compared with the placebo [94]. A meta-analysis of randomized controlled studies of patients diagnosed with major depression showed that probiotics reduce depressive symptoms [93]. A meta-analysis of seven studies involving healthy volunteers revealed that supplements with probiotics improve the overall psychological condition compared with the placebo [94].

**Conclusion**

There is convincing evidence of the signs of neuroinflammation in patients with post-stress pathologies and in experimental animal models of acute and chronic stress.

Clarification of the causes of such disorders in immunoregulation at the molecular level is urgently required. It has become clear that the composition of intestinal microbiota affects the functioning of brain microglial cells and the behavior of experimental animals in general. The study of the microbiota–intestine–brain interaction is a promising area of research in the field of biological psychiatry.

Due to the active development of high-performance genome-sequencing technologies, the composition of the human GIT microbiota has been studied in sufficient detail. A concept has been formed about the taxonomic distribution and diversity of microbial communities of the intestine under normal conditions and in the case of various pathologies. Some metabolites of the intestinal microbiota can affect the epigenetic modifications of the host cell genome. A study of the role of microbiota in such gene modifications associated with neuroinflammation will deepen the understanding of the mechanisms of...
post-stress pathologies and will facilitate the identification of new targets for their therapy.

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