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Review

Factors Maintaining Chronic Inflammation in Mental Illness

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This literature review addresses the factors influencing chronic inflammation throughout life, exacerbating the severity of mental illness and contributing to its progression, along with their mechanisms. These factors include infections, disruption of the gut microbiome, insufficient physical activity and being overweight, chronic stress, and metabolic imbalance. Manipulations of these factors, including treatments supplementing standard drug therapy, can contribute to a milder course of illness, improved quality and duration of remissions, and, in some cases, overcoming resistance to ongoing therapy.

Keywords: maintenance of chronic inflammation, schizophrenia, depression, autism, infections, microbiome, physical inactivity, stress.

Current research indicates that inflammation plays a key role in the pathophysiology of chronic mental illnesses, such as schizophrenia and autistic spectrum disorders, as well as affective, personality, and neurotic disorders, leading to a huge medical burden and economic losses [1]. Studies [2, 3] have identified mechanisms for the influences of molecular inflammatory factors (cytokines, chemokines, etc.) on neurotransmission, neuroplasticity, and the vascular network of the brain, whose disruption results in psychopathological symptoms and behavioral disorders. A close relationship has also been established between systemic inflammation (bloodstream) and inflammation in the brain (neuroinflammation), which is reflected in significant correlations between inflammatory and autoimmune markers in blood serum and the severity and characteristics of psychopathological symptoms in patients with mental disorders [4–6].

Inflammation in mental illnesses includes a variety of stages and processes, including autoimmune processes. Levels of inflammation decrease during the remission phase of disorders or at the onset of remission, though generally not reaching the control level, which points to a continuing course of the pathological process in the brain despite clinical improvements in the patient's condition [7]. Inflammation in the CNS is mediated by microglial cells (resident macrophages in the brain) and astrocytes, as well as immune cells (monocytes, macrophages, T- and B-lymphocytes, etc.) which penetrate the brain parenchyma from the bloodstream or are located in the meningeal membranes [8, 9].

Etiological factors for inflammation in mental disorders include genetic predisposition [10, 11], exposure to infectious agents (bacteria, viruses) at early stages of ontogenesis, including agents determining maternal immune activation during pregnancy [12], and traumatic or toxic brain damage [13]. Also of considerable interest are factors contributing to the maintenance of chronic inflammation throughout life, exacerbating the severity of mental disorders and potentiating their progression. Manipulation of these factors, including treatments supplementing standard drug therapy, may contribute to a milder course of illness, improved quality and duration of remissions, and, in some cases, overcoming resistance to ongoing therapy [14]. These factors include infections, disruption of the gut microbiome, insufficient physical activity and excess weight, chronic stress, and metabolic imbalance.

The aim of the present work was to examine factors and mechanisms contributing to the maintenance of chronic inflammation/neuroinflammation in mental disorders.

Infections. Infectious agents, which include viruses, bacteria, fungi, and parasites (protozoa and helminths) are important factors in the maintenance of chronic inflammation in mental disorders.

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Some, such as α-herpesviruses, COVID-19, cytomegaloviruses, and Epstein–Barr virus, possess neurotropic activity and can directly affect brain tissue, resulting in microglial activation and neuroinflammation [15]. Others, circulating in the bloodstream, induce proinflammatory cytokine synthesis and activation of systemic inflammatory responses. Prolonged persistence of infectious agents in the blood is associated with increased permeability of the blood–brain barrier and the penetration of proinflammatory cytokines and immunocompetent cells into the brain, followed by activation of neuroinflammation. The long-lasting presence of pathogens in the body also leads to intoxication, decreased functional activity of macrophages, incomplete phagocytosis, weakening of defense mechanisms, and the involvement of various body systems in the pathological process [16].

Immunoinflammatory reactions are also activated by helminths present in the intestines [17]. Antigenic determinants of some pathogens (*Klebsiella*, SARS-CoV-2, *Toxoplasma*, streptococci, herpes simplex virus) have similarities with antigens of human body tissues (antigenic mimicry), which leads to the formation of autoimmune antibodies, including antibodies to nervous tissue, which contribute to secondary brain damage [18–20].

Other molecular pathophysiological mechanisms linking infection, inflammation, and psychopathological symptoms include endocrine changes, including hypocorticism, dysfunction of the hypothalamic-pituitary-adrenal system, and damage to tissues and organs with resulting functional impairment [21, 22].

Researchers using a variety of methods have confirmed links between schizophrenia, depression, and autistic disorders with a number of viruses [12, 23–25], bacteria, protozoal infections [23, 26], extracellular parasitic helminths [27, 28], and fungal and yeast infections (aspergillosis, cryptococcosis, and candidiasis), as well as combined infectious loads [22, 29–31]. Some infections can be latent, without production of specific clinical symptoms, and are detected only by laboratory diagnostics. Data have been published indicating that anti-infective or anti-helminthic therapy helps reduce the severity of psychopathological symptoms [31].

Disruption of the Gut Microbiota. The term gut microbiota refers to the microorganisms inhabiting the human gastrointestinal tract. This dynamic community primarily includes various types of prokaryotes (bacteria and other single-celled microbes lacking specialized organelles) and, to a lesser extent, fungi, parasites, and archaea. Viruses are also an integral part of this environment. The genetic and functional profile of microbial species is called the "gut microbiome (microbiota)" [32]. The composition of the gut microbiota depends on age, diet, physical activity, environmental factors, stress, other diseases, and antibiotic treatment.

The gut microbiota and its metabolites can influence mental health through the microbiota–gut–brain axis. This axis represents a bidirectional communication pathway between the immune system and the brain. Over the past decade, it has become a new epicenter in mental health research as a potentially important link in the field of immunoregulation, both in brain development and in the etiology and pathogenesis of mental disorders.

Research results indicate that patients with mental disorders exhibit significant changes in the composition of gut bacteria, with reduced diversity, and these changes are partially associated with certain forms of mental disorder, symptom severity, and responses to treatment [33–35].

Some specific types of gut bacteria, such as *Lactobacillus fermentum*, *Enterococcus faecium*, and *Alkaliphilus oremlandii*, have been found in patients with schizophrenia, though they are essentially absent from the microbiota of healthy individuals [36, 37].

A study based on a large cohort of patients with depression revealed decreases in the numbers of *Dialister* and *Coprococcus* spp. in the gut microbiome [38]. In addition, high levels of *Prevotella*, *Klebsiella*, *Streptococcus*, and *Clostridium* XI, but lower levels of *Bacteroidetes*, were found in patients with depressive disorder [39–41].

Children with autism spectrum disorders (ASD) were found to have higher levels of *Clostridium paraputri*, *Clostridium bolteae*, and *Clostridium perfringens*. Furthermore, *Clostridium difficile* and *Clostridium clostridiioforme* were found only in children with ASD, while *Clostridium tertium* was found only in healthy children [42]. Another cross-sectional case-control study showed that children with ASD had higher levels of Actinobacteria, Proteobacteria, and Bacilli [43].

However, it should be noted that some studies have yielded conflicting data on the prevalence of some types of microorganisms in patients with similar diagnoses. These discrepancies may be due to the heterogeneity of clinical forms within a single nosology, analysis of the microbiota at different stages of the disease, different ages of patients, etc. In addition, the significant differences in the composition of the gut microbiota in different people make it extremely important to obtain accurate identification of the changes characterizing individual patients, which is important for personalized treatment based on influencing the gut microbiota. It has been suggested that addition of beneficial gut microbiota absent from patients may be effective for treatment. Alternatively, reducing the harmful gut microbiota found predominantly in patients with mental disorders may also provide a therapeutic approach involving medication or functional foods [44].

Studies of the potential mechanisms of the influence of the microbiota on the brain are mainly conducted in experiments using animal models. The gut microbiota has been shown to be able to influence the brain: via the vagus nerve; by altering the expression of enzymes affecting tryptophan metabolism, this being an essential amino acid which is a precursor neurotransmitter synthesis; and also via metabolites able to alter neuroimmune signaling [45].

In the context of analyzing the role of the microbiome in maintaining inflammation in mental disorders, the most

important aspect appears to be the influence of enzymes and other metabolites synthesized by the gut microbiota on the maintenance of the epithelium and, consequently, the integrity of the intestinal wall, as well as their interaction with several key signaling molecules and cells of the immune system [34]. It is through contact with the immune system that microorganisms inhabiting the gut can cause or prevent inflammation, both locally in the intestine and at the systemic level.

Activation of inflammation may be associated with increased intestinal permeability ("leaky gut"), which is facilitated by certain types of bacteria. In this case, metabolites and components of the microbial cell wall (lipopolysaccharide) enter the bloodstream, and the body responds by producing cytokines and other mediators that trigger or maintain the inflammatory response [46]. The persistence of this situation can lead to subacute or chronic inflammation and the development of inflammation-associated diseases, including diseases of the brain.

The gut microbiota produces short-chain fatty acids (SCFA), including acetic, propionic, and butyric acids. In addition to participating in neural networks by influencing the expression of genes involved in the neurotransmitter synthesis, SCFA also affect microglia and astrocytes; the specific effect (pro- or anti-inflammatory) depends on the type of SCFA [34, 47].

Epidemiological, experimental, and clinical studies have shown that many types of probiotics (especially *Lactobacillus* and *Bifidobacterium*), prebiotics (e.g., dietary fiber, alpha-lactalbumin), synbiotics, postbiotics (e.g., SCFA), dairy products, spices (e.g., *Zanthoxylum bungeanum*, curcumin, and capsaicin), fruits, vegetables, and medicinal herbs can prevent and control mental disorders by modulating the gut microbiota, by mechanisms including increases in beneficial and decreases in harmful gut microbiota. Thus, supplementation with these dietary components may be a potential strategy for the prevention and treatment of mental disorders, complementing pharmacotherapy and psychotherapy. However, further research is needed to substantiate the clinical use of probiotics, prebiotics, etc.

Insufficient Physical Activity. It is well known that physical exercise has beneficial effects on physical health, especially in the prevention and treatment of metabolic disorders, including diabetes, obesity, and cardiovascular diseases. The role of physical exercise as an adjunct to the treatment and prevention of mental disorders has received minimal attention until recently. In the last decade, a significant amount of research has addressed this issue, which is linked with the accumulation of experimental and clinical data on the protective effect of physical exercise against the development and maintenance of chronic inflammation.

The anti-inflammatory effect of regular physical activity has been shown to be mediated by stimulation of an anti-inflammatory environment, as well as a decrease in visceral fat mass. It has been established that contracting skeletal muscles have hormone-producing activity and release a variety of signaling molecules – myokines, including interleukins (IL)-6, -15, and -8, which go on to stimulate the production and release of anti-inflammatory molecules such as lysozyme and lactoferrin.

The first discovered and most studied myokine is IL-6. There is presumably a direct link between glycogen depletion and the production of muscle-derived IL-6, which, despite its proinflammatory activity, also displays anti-inflammatory properties when expressed as a muscle myokine [48]. The systemic effect of circulating IL-6 is primarily realized at the level of adipose tissue and the liver, and is also aimed at mobilizing the body's energy resources. Thus, studies on human adipocyte cultures have shown that IL-6 has a lipolytic effect mediated by increasing the activity of lipoprotein lipase [49].

The magnitude of the increase in serum IL-6 levels during physical exertion is determined by its intensity and duration. Pedersen and Febbraio [50] found that during 2 h of cycling, the serum IL-6 concentration increases by a factor of 8–11; and during a 3-h workout it can increase 30-fold, reaching 25 pg/ml. The authors noted that during intense and prolonged running, the IL-6 level can increase 1000-fold, which is comparable to the increase in the content of this cytokine during sepsis. However, the increase in IL-6 in sepsis is associated with an increase in circulating tumor necrosis factor (TNF)-α, which is not seen during physical exertion.

Several meta-analyses have shown that physical activity has an antidepressant effect on patients with mild and moderate depression [51, 52]. The training programs described in a large number of published studies on the effects of physical exercise on the course of depression are heterogeneous and include exercises of different intensities, durations, and frequencies. A review by Chinese authors [53] noted that clinical studies use a variety of aerobic and anaerobic exercises: different types of bicycles (bicycle, exercise bike, ergometric bicycle, and recumbent bicycle), swimming, jogging or treadmill running, cross-training, jump rope, step aerobics and cardio machines, kickboxing, strength exercises using resistance bands, dumbbells, Swiss balls, etc., stretching exercises, strength training, Pilates, and yoga, as well as traditional Chinese exercises such as Tai Chi and Qigong. The most common way to determine the intensity of training is to establish the amount of time a person trains each week or each day. Other studies have also used the metabolic equivalent, heart rate or maximum heart rate, maximum oxygen uptake, maximum power output, the Borg scale, kilocalories burned per 1 kg of body weight per week, and perceived exertion ratings. Exercise program durations range from four to 24 weeks, with most experiments lasting 12 weeks.

Experimental studies in mice have also indicated a link between physical exercise and stress-induced depression-like behavior. Investigations have shown that physical

exercise (voluntary running in a wheel) alleviated depression-like behavior in mice, which was linked with decreases in central and peripheral inflammatory marker levels [54, 55]. These animals also showed improved gut function and increased central dopamine expression, leading the authors to suggest that exercise, in addition to its anti-inflammatory effect, may also exert its antidepressant effect through mechanisms involving gut permeability and dopamine metabolism [54, 55].

It should be noted that some studies not confirming the antidepressant effect of physical exercise have also been published [56]. It is likely that the existence of different viewpoints corresponds to the heterogeneous nature of depression, as well as different types and intensity of physical exercise.

A study examining the effects of different levels of physical activity on the cognitive functions of patients with depressive disorder showed that the cognitive functions of participants in the high-intensity group significantly improved as compared with the low-intensity group. Both groups showed improvements in symptoms of depression and cognitive functions in areas such as psychomotor reaction speed, visuospatial memory, and executive functions [57]. However, a systematic meta-analysis by Sun et al. [58] showed that physical exercise does not have a significant effect on the overall cognitive function or individual cognitive domains in patients with depressive disorder. However, it was noted that combining physical exercise with cognitive activity could significantly improve overall cognitive function. The effectiveness of physical exercise in reducing symptoms of depression and improving cognitive functions has been demonstrated in different age groups, including elderly patients [59–61].

The results of several meta-analyses have indicated that physical activity has significant positive effects on the ability to take part in social interactions, communication skills, and motor skills in children and adolescents with autism [62, 63]. Several studies have also demonstrated the effectiveness of aerobic exercises (brisk walking, treadmills, cycling, elliptical trainers), as well as yoga and traditional Chinese practices, in improving the condition of patients with schizophrenia and dementia [64, 65].

Thus, clinical studies generally indicate that physical exercise is effective as an adjunct to comprehensive therapy in patients with mental disorders. However, further research is needed to assess the optimal modality and intensity of exercise for different psychopathological conditions and to identify biological markers contributing to the selection of personalized approaches to evaluating the effectiveness of physical exercise. The molecular mechanisms of the influences of physical activity on the condition of patients with mental disorders have as yet received insufficient study, though it is clear that physical exercise is able to exert regulatory influences on processes associated with inflammation, neuroplasticity, oxidative stress, the endocrine system, and neurotransmission, i.e., processes making significant contributions to the pathophysiology of mental disorders [66, 67].

In 2009, physical exercise was included by the World Health Organization and the National Institute for Health and Clinical Excellence of Great Britain in the recommendations for the treatment of depression as an adjunctive method. Individual exercise programs should be compiled taking patients' age, sex, physical fitness, financial capabilities, and preferences into account. In addition, training should be supervised by physiotherapists, personal trainers, and other medical personnel [53, 68].

Chronic Stress. Chronic stress is a non-specific systemic reaction occurring when the body is exposed to various internal and external negative factors for long periods of time [69]. Unlike acute stress, which causes adaptive physiological and hormonal processes supporting the survival of the organism, chronic stress can have long-term maladaptive effects with pathological consequences for almost all body systems (immune, nervous, endocrine, cardiovascular) [70].

Activation of the hypothalamic-pituitary-adrenal (HPA) system plays a crucial role in the stress response, though the consequences of its activation in acute and chronic stress are fundamentally different. Acute stress causes a surge in catecholamine secretion in the adrenal medulla, with cortisol release, leading to a sharp influx of energy, enhanced cognitive functions, increased immunity, reduced sensitivity to pain, and increased blood pressure – all aimed at survival (the "fight or flight" or sometimes "freeze" response). After the stressors subside, the release of stress hormones diminishes, mainly as a result of negative feedback in the HPA axis, and homeostatic equilibrium is achieved. Chronic stress leads to persistently elevated or persistently diminished daily cortisol levels (with lower than usual levels in the morning and higher than usual levels in the evening). The most serious consequence of increased glucocorticoid secretion due to activation of the HPA axis is the development of resistance of glucocorticoid receptors located on immunocompetent cells, including microglia, which leads to elevated synthesis of inflammatory mediators (NF-kB, TNF-α, IL-1, IL-6) and the development/maintenance of chronic inflammation/neuroinflammation [71].

Thus, chronic stress causes inflammatory changes in both the peripheral immune system and the brain [72, 73]. Dysregulation of the HPA axis and glucocorticoid resistance of immune cells are currently regarded as the main mechanisms [74, 75]. In addition to glucocorticoids, the sympathetic nervous system and associated neurotransmitters, such as adrenaline and neuropeptide Y, can influence the immune system and inflammatory function [72, 76]. Thus, catecholamines, cytokines, glucocorticoids, and other mediators secreted in response to stressors are key players in stress-related proinflammatory changes.

Large quantities of data have accumulated over the past two decades indicating that chronic stress may be a common risk factor for more than 75% of physical and mental disorders, increasing morbidity and mortality from these conditions [77]. Among mental disorders, chronic stress is primarily associated with the development of psychoemo-

tional disorders, such as anxiety and depressive disorders, as well as post-traumatic stress disorder [72].

The role of glucocorticoids as important regulators of the body's metabolic networks also undergoes changes on the background of chronic stress, shifting metabolism towards catabolism, disrupting the use of energy-rich substrates at both the cellular and systemic levels, and contributing to processes associated with metabolic syndrome [78]. Synergistic effects are also characteristic of inflammation, which closes the vicious circle of stress-inflammation-metabolic disorders, leading to general neuroimmunoendocrine dysregulation. In this regard, it can be suggested that metabolic imbalance determined by chronic stress and leading to a systemic increase in markers of inflammation and microglial activation exacerbates the course of other mental disorders and chronic somatic diseases, where the pathogenetic link is chronic inflammation.

Research interest is focused not only on studies of the mechanisms of the influence of chronic stress on inflammation/neuroinflammation, but also on studies of the link between stress in early childhood and the level of inflammatory activity in healthy adolescents and adults. For example, a prospective longitudinal study of more than 4600 children showed that adverse life events such as physical or sexual abuse, separation from the mother or father, or placement in foster care in early childhood are associated with higher levels of IL-6 and C-reactive protein in adolescence [79].

There are also numerous studies demonstrating that social stressors in adolescence and adulthood are associated with increased levels of inflammatory activity. Social stressors related to conflict, threat, social isolation, and rejection, as well as negative social interactions involving friends, peers, teachers, or family members in daily life, have been shown to have a particularly strong impact [72, 80–82].

Thus, it can be concluded that data from different research areas indicate that chronic stress is associated with elevated inflammatory activity and can serve as a trigger or a factor involved in maintaining and/or exacerbating the course of mental disorders. The types of stressors most strongly associated with inflammation include an increased risk of physical or social threat (social conflict, rejection, isolation).

Metabolic Disorders. Clinical and experimental studies indicate that the immune system is involved in metabolic disorders. Different components of the immune system (cellular and humoral) undergo changes in metabolic diseases, which include atherosclerosis, type 2 diabetes mellitus, non-alcoholic fatty liver disease, and obesity/overweight [83].

The scientific literature increasingly accumulates data indicating that metabolic disorders, primarily those related to energy metabolism, are associated with severe mental disorders, including schizophrenia, major depressive disorder, bipolar disorder, anxiety disorders, anorexia nervosa, and neurodevelopmental disorders such as autism and attention deficit hyperactivity disorder [84, 85]. However, the causal relationships, as well as the precise mechanisms underlying metabolic disorders in mental disorders, remain poorly understood [86].

Systemic inflammatory cytokines, as well as cytokines synthesized by cells of metabolic tissues – adipokines, hepatokines, myokines, and osteokines – have been shown to make significant contributions to the development of abnormal glucose and lipid metabolism. The mechanisms involved are as yet not fully understood but are related to the accumulation of lipids in organs and tissues, especially adipose and hepatic tissue, to changes in energy metabolism, and to inflammatory signals received from various cell types, including immune cells.

Some proinflammatory cytokines, such as TNF-α and IL-1β, have been shown to take part in disrupting insulin and lipid signaling pathways, thereby affecting insulin sensitivity and lipid metabolism [87–90]. In addition to the fact that elevated levels of proinflammatory cytokines associated with disorders of lipid and carbohydrate metabolism can contribute to microglial activation and the development of neuroinflammation [91], increases in the permeability of the blood–brain barrier can arise as a result of adipokines, saturated fatty acids, and toxic molecules, whose entry into the bloodstream is associated with increased intestinal wall permeability; increased blood–brain barrier permeability also contributes to the development of neuroinflammation and, ultimately, a higher risk of mental disorders [92, 93]. A population-based cohort study involving more than 200,000 people associated high levels of glucose and triglycerides and low levels of high-density lipoproteins with higher future risks of depression, anxiety, and stress-related disorders [94].

Although the nature of the relationships between mental, inflammatory, and metabolic disorders currently remains unclear, this area of research is very promising, as it opens up new approaches to the treatment of mental disorders. These approaches are related to the elimination of metabolic disorders, including by non-pharmacological methods such as diet and lifestyle changes [95, 96].

Conclusions. In general, the data presented in this review on the most significant factors influencing multilevel chronic inflammation in mental disorders show that factors related to infection, lifestyle, psychosocial stress, metabolic disorders, and others should be taken into account when treating patients. Each of these factors, individually and collectively, can contribute to the development and progression of mental pathology, while potentiating each other and exacerbating the course of illness. Systemic disorders are found in patients with combinations of factors triggering and sustaining inflammation, requiring multimodal treatment. Studies have shown that identifying factors maintaining chronic inflammation and correcting them by adjuvant therapy or lifestyle changes can help reduce levels of inflammation and increase the effectiveness of traditional treatment. However, further research is needed for a better understanding of the mechanisms of the influences of these factors on chronic inflammation, as well as for supporting identification of clin-

ical, metabolic, and immunological markers contributing to the personalization of therapy. Consideration of factors contributing to the maintenance of chronic inflammation is also advisable when developing strategies for the prevention and early diagnosis of mental disorders.

The authors declare no conflict of interest.

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