A REVIEW OF THE PSYCHONEUROIMMUNOLOGIC CONCEPTS ON THE ETIOLOGY OF DEPRESSIVE DISORDERS

Branka Vidrih, Dalibor Karlović, Marija Bošnjak Pašić, Melita Uremović, Ana Kovak Mufić and Ana Matošić

University Department of Psychiatry, Sestre milosrdnice University Hospital Center, Zagreb, Croatia

SUMMARY – The brain is no longer considered an immunoprivileged organ which is completely separated from the circulating immune cells by the blood-brain barrier and which shows a lowered or changed immunoreactivity. It has become clear that there are numerous interactions between the neurological, immune and neuroendocrinologic systems. The psychiatric disorder which is supposed to be connected to changes in the functioning of the immune system is depression. One of the hypotheses suggesting the pathophysiology of depression is the cytokine hypothesis of depression. According to it, the behavior changes in depressed patients are a consequence of changes in cytokines. Physiological and psychological effects of the immune activation during an infection, primarily mediated by central activity of peripherally excreted proinflammatory cytokines, are called "sickness behavior". Depression is connected with the activation of the inflammatory response system. When it comes to the immune characteristics of depressive disorders, it should be stressed that depression is a heterogeneous disorder, so different types of depression can differ not only psychopathologically but also at the immune level. Depression is characterized by disorders in noradrenergic and serotonergic neurotransmission. Proinflammatory cytokines are included in the noradrenergic and serotonergic neurotransmission in the brain areas that are thought to be involved in the pathogenesis of depression. According to this model, depression can be considered a psychoneuroimmune disease in which the peripheral immune activation is responsible (by excreting the inflammatory mediator) for various behavioral, neuroendocrinologic and neurochemical changes connected to the psychiatric condition.

Key words: *Cytokines; Major depressive disorder; Psychoneuroimmunology*

Introduction

From the perspective of psychoneuroimmunology, the brain is no longer considered an immunoprivileged organ which is completely separated from the circulating immune cells by the blood-brain barrier and which shows a lowered or changed immunoreactivity. In the last decades, it has become clear that there are numerous interactions among the neurological, immune and neuroendocrinologic systems. The concept of a two-way communication between the immune system and the central nervous system (CNS) has led to the question whether the immune system, besides its usual role, i.e. immune reaction, is included in neuropathological processes. A psychiatric disorder that is supposed to be connected to changes in the functioning of the immune system is depression. The disturbed regulation of the immune system's functional activity in depression is a phenomenon described on several occasions. Depression is connected with the activation of the inflammatory response system. Ac-

Correspondence to: *Assist. Prof. Dalibor Karlović, MD, PhD*, University Department of Psychiatry, Sestre milosrdnice University Hospital Center, Vinogradska c. 29, HR-10000 Zagreb, Croatia
E-mail: dalibor.karlovic@gmail.com

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cording to this model, depression can be considered a psychoneuroimmune disease in which the peripheral immune activation is responsible (by excreting the inflammatory mediator) for various behavioral, neuroendocrinologic and neurochemical changes connected to the psychiatric condition[1,2].

The Cytokine Etiology of Depressive Disorders

One of the hypotheses suggesting the pathophysiology of depression is the cytokine hypothesis of depression. According to it, the behavior changes in depressed patients are a consequence of changes in cytokines[3]. The word cytokine comes from two words of Greek origin: "cytos" meaning cell, and "kine" from the word "kinein" meaning to move. This term was introduced so that a group of immunomodulatory molecules could be distinguished from the hematopoietic cell growth factors. Cytokines are polypeptides or glycopeptides with a low molecular mass of 6-70 kDa excreted by macrophages due to their own function changing (autocrine effect) or the adjacent cell's function (paracrine effect). Their creation is encouraged by the antigen-specific lymphocyte T4 activation. They behave as strong molecules which are released from the cells, transport themselves to other parts of the body, and influence other cells' functions, which can lead to numerous biological effects. Their activity is closely connected to specific receptors that can be found in the cell and cell membrane[4].

Cytokines are messengers which, along with hormones and neurotransmitters, are very significant factors in the communication among human cells. They encompass a heterogeneous group of messenger molecules which synthesize immunocompetent cells such as lymphocytes and macrophages in order to regulate immune reactions. Cell activation and differentiation, chemotaxis and wide-spectrum cell proliferation are the effector functions of these proteins. The activity of cytokines depends on their concentration in the micro-environment and the expression strength of specific receptors on the surface of the target cell. In the human body, each live cell with a nucleus creates cytokines whose type and quantity of secretion depend on the type and phase of cell differentiation and activation. They can be positive and negative regulators of the immune response. They deliver information to the target cell which has the respective receptor. What occurs is gene activation with causal phenotypic or functional changes of the target cell. Inhibitors can stop the cytokine synthesis and release by modulating their biological activity or by inhibiting the ability of the target cell to respond. Although their specific biological activities can vary, two main cytokine groups can be distinguished: inflammatory and anti-inflammatory. The former group consists of cytokines directly or indirectly included into the inflammatory processes, such as interleukins IL-1, IL-6, interferon (INF-γ) and tumor necrosis factor (TNF)-α. The latter group includes cytokines known for suppressing the immune response (IL-4, IL-10, IL-13). Based on dominant biological activities, cytokines are divided into three basic groups[5,6]: I Mediators of innate immunity [Proinflammatory cytokines (TNF-α, IL-1, IL-6)], [Interferon type I (INF-α, INF-β)], [Activators of NK and T cells (IL-12, IL-18)]; II Mediators of acquired immunity (IL-2, INF-γ, IL-4, IL-5, IL-10 and TGF-β); and III Stimulators of hematopoiesis [IL-3 and factors of colony growth (GMCSF, GCSF, MCSF)].

This division corresponds to biological and structural differences as well as similarities of these mediators. The term interleukin is accepted and used for a group of mediators responsible for the communication between leukocytes. Today, 29 types of interleukins are known, i.e. IL-1 to IL-29. There are also more than 30 cytokines. Many of them are growth factors, while some have an antiviral activity and are called interferons (INF). They regulate the growth and differentiation of the immune system's cells, of T and B lymphocytes and macrophages, but also the volume and length of inflammatory response. They modify the biological response and are interconnected into a cytokine regulation network. The increased cytokine excretion is not only linked to infections, but also to autoimmune and neurodegenerative diseases[7,8].

Peripheral cytokine synthesis depends to a great extent on the activation state of the immune system. In pathological conditions, such as acute or chronic inflammation or tissue damage, the immune system is activated, while the activity of macrophages increases, which contributes to the synthesis increase and cytokine excretion, e.g., IL-1, IL-6 and TNF-α. Changes in cytokine synthesis on the periphery can

be caused by neuroendocrine influence on the immune system. Considering this, the activity of corticosteroids, which are synthesized in the adrenal cortex as the final product of the hypothalamic-pituitary-adrenal (HPA) axis, is most important. These hormones, especially cortisol, are included in the regulation of the immune response and cytokine synthesis. While low corticosteroid concentrations act on the synthesis of inflammatory mediators in a stimulating way, high concentrations are immunosuppressive[9-12]. The neurotransmitters acetylcholine, dopamine, noradrenaline and serotonin are included in the functional status of the immune system as mediators through the influence on the hypothalamic corticotropin releasing factor (CRH) secretion. For example, while acetylcholine, dopamine, and noradrenaline have a stimulating effect on hypothalamic cells, serotonin suppresses the hypothalamic CRH secretion as well as the ACTH synthesis in the pituitary gland.

Besides a somatic stress such as infection, chronic inflammation, tissue damage, exposure to mental stress affects the synthesis of inflammatory mediators as well. Changes in the level of noradrenaline/serotonin neurotransmission and the activity of the HPA axis are included in the synthesis of inflammatory mediators to a significant extent[13].

Cytokine Transport into the Central Nervous System

Since the majority of cytokines are relatively big hydrophilic molecules, they do not pass through the blood-brain barrier under physiologic conditions. However, there are spots without the blood-brain barrier (circumventricular region) or less restrictive areas like the organum vasculosum of the lamina terminalis and eminentia mediana, where a passive transport of cytokines from the blood to the brain parenchyma is possible. The integrity of the blood-brain barrier can be damaged by trauma or pathological conditions, which leads to the increased access of different inflammatory cells and molecules, including cytokines. Moreover, cytokines can contribute to the damaging of the barrier and there is also a possibility for TNF-α to lead to barrier degeneration.

The mechanism of active transport could also be included in cytokine transfer through the barrier. After entering the brain parenchyma, peripheral cytokines bind to the corresponding receptors on the surface of different cells including microglia, astrocytes and neurons. Specific IL-1, IL-2 and TNF-α receptors were discovered on glial cells and hippocampus neurons.

Besides passing through the blood-brain barrier, cytokines can bind to receptors on vascular endothelial cells activating in such a manner the second messenger; a direct mechanism of signalization in the CNS can thus be enabled.

Another possible indirect route to cytokine-mediated communication of the immune system and brain is *via* vagus signalization. Afferent vagal fibers, which go from the immune system organs in which cytokines are secreted, can enable a sensor input on the functional status of the immune system in the nucleus tractus solitarius, which is in medulla oblongata.

Besides infiltration and indirect signalization from the periphery, cytokines (including IL-6 and TNF-α) and their receptors are synthesized by the brain, mainly in astrocytes and microglia. In certain circumstances, neurons are supposed to have the ability to secrete cytokines. Cytokine synthesis was found in several brain areas, including circumventricular region, hypothalamus, hippocampus, cerebellum, basal ganglia and nucleus of medulla oblongata. The role of central cytokine synthesis has not yet been clarified, so proinflammatory cytokines, including IL-6 and TNF-α, are considered to be contributing to neurodevelopmental and neuroplastic processes, synaptogenesis and tissue recovery[14-18].

Besides positive effects, cytokines can have negative effects on the function of brain tissue, such as promoting neuronal impairment after stroke. Furthermore, cytokine synthesis in glial cells can be caused by antigenic impulses (virus infection), local or peripheral inflammatory reaction, or brain injuries. Cytokines are linked to the activity on monoaminergic transmission. Systemic administration of IL-6 was found to increase 5-HT neurotransmission in hippocampus, nucleus accumbens and frontal cortex, and it decreased the concentration of dopamine in nucleus accumbens. Neuroendocrine effects of peripheral and central proinflammatory cytokines, such as IL-6, include the activation of the HPA axis, which is reflected by increased plasma concentrations of CRH,

vasopressin, ACTH and corticosteroids. Although proinflammatory cytokines are potent activators of the HPA axis, it should be stressed that in physiological circumstances cytokines are able to stimulate the HPA axis to a certain extent because this neuroendocrine system's activity is regulated by the inhibitory feedback mechanisms. The negative feedback mechanism, which is characteristic of the HPA axis, stops its further stimulation with increased concentrations of corticosteroids. Excessive stimulation of corticosteroid receptors in the hypothalamus and pituitary gland resulting from increased corticosteroid excretion causes decrease in the synthesis of CRH and ACTH, thus limiting the extent to which the HPA axis can be stimulated[19,20].

The Phenomenon of "Sickness Behavior"

Physiological and psychological effects of immune activation during an infection, primarily mediated by central activity of peripherally excreted proinflammatory cytokines, are called "sickness behavior"[21]. Sickness behavior is accompanied by elevated temperature and various behavioral reactions, including decreased appetite, anorexia, weight loss, sleep disorders, psychomotor impairment, decreased interest in physical and social environment, libido loss, disorders of cognitive abilities, dysphoria, anhedonia and depressive mood. Most of these reactions are hypothalamus-mediated. It seems that these behavioral changes are an expression of a centrally motivated condition which reorganizes a sick person's priorities in order to fight the infectious agent[22]. However, not only has this behavior been seen during the infection, but also after systemic or central administration of cytokines. Chemotherapy, which often includes treatment with proinflammatory and antivirus cytokines (IL-2, TNF-α, INF-α), is connected to depressive symptoms and symptoms similar to influenza, as well as cognitive disorders[23]. Immunotherapy based on INF-α, which is often used in chronic hepatitis C therapy, is connected to symptoms of cognitive disorder, hopelessness, fatigue and depressive mood. The fact that symptoms of sickness behavior disappear almost instantly after the interruption of cytokine therapy supports the causal role of cytokines in the pathogenesis of this state[24,25].

The characteristics of the immune system activation in depressive disorder include an increase in the number of circulating lymphocytes and phagocytes, serum levels of the activated immune cell indicators, reduction in the levels of negative acute-phase proteins, as well as increased secretion of proinflammatory cytokines. Besides the cytokine hypothesis of depression, the increased plasma concentrations of proinflammatory cytokines (IL-6) found in patients with depression seem to correlate with the severity of the psychiatric disorder and with activity measures of the HPA axis[26].

Furthermore, the centrally motivated state induced by the activity of cytokines on the CNS can offer a probable explanation for the occurrence of various behavioral, psychological and cognitive symptoms of depression. This thinking is supported by the observations of symptoms similar to depression in non-depressed persons who receive cytokine therapy in the treatment of carcinoma and hepatitis C[27,28].

Depression can be considered a genetic disease, so the genetics of the immune system associated with depression was investigated. Polymorphism of certain genes (e.g., the gene which codes TNF-α) is considered to have greater predisposition for the development of depressive disorder.

Heterogeneity of Immune Characteristics of Depressive Disorders

When it comes to the immune characteristics of depressive disorders, it should be stressed out that depression is a heterogeneous disorder, so different types of depression can differ not only psychopathologically but also at the immune level. Many somatic disorders are accompanied by depression: acute and chronic infections, non-infectious conditions related to inflammations, for example, rheumatoid arthritis, carcinoma, Alzheimer's disease, multiple sclerosis and other neurodegenerative diseases. Depressive symptomatology connected to other diseases does not necessarily have to be strictly a psychological reaction to pain, distress and inability associated with somatic diseases, but can be directly caused by the immune system activation and cytokine excretion. Depressive symptoms accompanying the immune reaction can be alleviated by pretreatment with cytokine synthesis inhibitors and cytokine antagonists or by manipulating cytokine genes. Most frequently, the side effects of

cytokine therapy that develop early in the treatment (usually within two weeks) include symptoms similar to influenza: fever, fatigue, headache, and myalgia. Psychiatric side effects typically occur later in the treatment, within one to three months, and include dysphoria, anhedonia, anxiety, fatigue, anorexia, psychomotor impairment and cognitive disorders. While the symptoms similar to influenza resolve with treatment continuation, neuropsychiatric side effects can disappear only after therapy cessation or by including antidepressants[29-31].

The Influence of Cytokines on Neurotransmitters

Depression is characterized by disorders in noradrenergic and serotonergic neurotransmission. Hypothetically speaking, the activation of the immune system can be causally linked with these disorders in signalization. Proinflammatory cytokines are involved in the changes in noradrenergic and serotonergic neurotransmission in the brain regions that are thought to be involved in the pathogenesis of depression (hypothalamus, hippocampus, amygdala and prefrontal cortex), decreased activity of presynaptic 5-HT neurons (a reflection of a decrease in 5-HT synthesis), changes in the 5-HT reuptake in the synaptic cleft as well as changes in postsynaptic 5-HT receptors. 5-HT synthesis depends mainly on the availability of tryptophan precursors in the brain (and it has a competitive relation with amino acids such as valine, leucine and phenylalanine for the same cerebral transport mechanisms at the level of the blood-brain barrier). Cytokines reduce tryptophan availability by activating the enzyme which metabolizes it, indoleamine-2,3-dioxygenase. Such an excessive indoleamine-2,3-dioxygenase stimulation can lead to a tryptophan decrease in serum, which is accompanied by a significant reduction of 5-HT synthesis. Low tryptophan availability in the brain can become the main event underlying the deficit of serotonin, which accompanies depressive disorder[32,33]. The development and severity of depressive symptoms, especially depressive mood, anorexia and concentration loss in patients receiving immunotherapy, correlate positively with the decrease in plasmatic concentrations of tryptophan during the treatment[34]. Moreover, proinflammatory cytokines intensify the 5-HT transmission, which can lead to quick depletion of the reserves in the conditions when the presynaptic 5-HT availability is low due to decreased 5-HT synthesis, caused by low tryptophan availability. It has been observed that the occurrence of depressive and anxiety symptoms after the cytokine-induced stimulation of indoleamine-2,3-dioxygenase can also result in intensified metabolite synthesis of indoleamine-2,3-dioxygenase, mediated by the kynurenine pathway, e.g., 3-hydroxykynurenine (3OHKYN) and quinolinic acid (QUIN), neurotoxic substances involved in several neurodegenerative conditions, e.g., Parkinson's disease. An intensified synthesis of these kynurenine metabolites has been noted in psychiatric anxious and depressive disorders. 3OHKYN can cause increased monoamine oxidase (MAO) activity as well as the hyperproduction of free radicals that contain a reactive oxygen species (ROS) atom and are often linked to depression. The hyperproduction of free radicals can have a negative influence on the function and density of serotonergic and catecholaminergic receptors by inducing changes in membrane viscosity. What results from increased MAO activity is the lower concentration of 5-HT and catecholamine. In this way, besides direct decrease of 5-HT availability, indoleamine-2,3-dioxygenase can contribute to monoaminergic disorders seen in depression in an indirect way. Besides presynaptic serotonergic disorders, which can be linked to the increased indoleamine-2,3-dioxygenase activity, peripheral immune activation can also be involved in the modification of activities of transporters for 5-HT and/or the number and sensitivity of postsynaptic receptors (including 5-HT1A and 5-HT2A receptors). Such changes can influence the 5-HT transmission and can cause serotonergic impoverishment in depressive disorder. The activation of radicals and exogenous administration of proinflammatory cytokines can induce depressive symptomatology, partially even through the modulation of monoaminergic transmission[35,36].

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Sažetak

PREGLED PSIHONEUROIMUNOLOŠKIH SPOZNAJA O ETIOLOGIJI DEPRESIVNIH POREMEĆAJA

B. Vidrih, D. Karlović, M. Bošnjak Pašić, M. Uremović, A. Kovak Mufić i *A. Matošić*

Mozak se više ne smatra imunoprivilegiranim organom koji je potpuno odvojen od cirkulirajućih imunih stanica krvno moždanom barijerom i koji pokazuje smanjenu ili promijenjenu imunoreaktivnost. Jasno je da postoje brojne interakcije između neurološkog, imunog i neuroendokrinog sustava. Psihijatrijski poremećaj za koji se pretpostavlja da je povezan s promjenama u funkcioniranju imunog sustava je depresija. Jedna od hipoteza koja objašnjava patofiziologiju depresije je citokina hipoteza; prema tom shvaćanju promjene ponašanja u depresivnih bolesnika posljedica su promjena u citokinima. Fiziološki i psihološki učinci imune aktivacije tijekom infekcije, koji su primarno posredovani središnjim djelovanjem periferno izlučenih proupalnih citokina, jednim imenom nazivaju se "bolesnim osjećanjem". Depresija je povezana s aktiviranjem sustava upalnog odgovora. U svezi s imunološkim značajkama depresije treba napomenuti da je depresija heterogeni poremećaj, što znači da različiti tipovi depresije mogu biti ne samo psihopatološki različiti, nego se jedni od drugih mogu razlikovati i na imunološkoj razini. Depresija je obilježena poremećajima u noradrenergičnoj i serotoninergičnoj neurotransmisiji. Proupalni citokini uključeni su u promjene u noradrenergičnoj i serotoninergičnoj neurotransmisiji u moždanim regijama za koje se misli da su uključene u patogenezu depresije. Prema tom modelu ona se može smatrati psihoneuroimunom bolešću u kojoj je periferna imuna aktivacija potaknuta lučenjem medijatora upale odgovorna za brojne ponašajne, neuroendokrine i neurokemijske promjene koje su povezane s psihijatrijskim stanjem.

Ključne riječi: *Citokini; Veliki depresivni poremećaj; Psihoneuroimunologija*