

Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology

ISSN: 1017-7833 (Print) 1302-9657 (Online) Journal homepage: https://www.tandfonline.com/loi/tbcp20

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**To cite this article:** Feyza Aricioglu, Ceren Sahin Ozkartal, Gokhan Unal, Serdar Dursun, Mesut Cetin (Professor of Psychiatry) (Editor in Chief) & Norbert Müller (2016) Neuroinflammation in Schizophrenia: A Critical Review and The Future, Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology, 26:4, 429-437, DOI: 10.5455/bcp.20161123044657

**To link to this article:** https://doi.org/10.5455/bcp.20161123044657

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Published online: 25 Jan 2017.

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Review

DOI: 10.5455/bcp.20161123044657

# Neuroinflammation in Schizophrenia: A Critical Review and The Future

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**ABSTRACT:**

Neuroinflammation in schizophrenia: a critical review and the future

Schizophrenia is a serious mental illness that affects approximately 1% of the population worldwide, with positive, negative and cognitive dysfunctions and a significant deterioration in psychosocial functioning. Interactions between genetic predisposition and environmental stressors at the early stages of life, and subsequently a molecular level neurodegeneration process are important in the development of schizophrenia. Current approaches suggest that cytokines-induced neuroinflammation might have a role in the development of several psychiatric disorders, including schizophrenia. Uncontrolled microglial activation, increase in pro-inflammatory cytokines, and subsequent neurotransmitter dysfunctions can induce schizophrenia. Microglial activation induced by pro-inflammatory cytokines in central nervous system is responsible for the initiation and proceeding of the inflammatory process and consequently developing neurodegeneration. Here in this review, we aimed to provide an overview to the latest findings related to the cytokines-mediated peripheral and central immune responses in the development of schizophrenia.

**Keywords:** schizophrenia, cytokines, neuroinflammation

**Klinik Psikofarmakoloji Bulteni - Bulletin of Clinical Psychopharmacology 2016;26(4):429-37**

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**Date of submission:**
November 20, 2016

**Date of acceptance:**
November 23, 2016

**Declaration of interest:**
F.A., C.S.O., G.U., S.D., M.C., N.M.: The authors reported no conflicts of interest related to this article.

## INTRODUCTION

Schizophrenia is an important and common psychiatric disease that shows chronic progression and cannot be treated satisfactorily yet. The onset of schizophrenia usually appears in late adolescence and early adulthood[1]. Schizophrenia involves significant positive symptoms such as hallucinations, delusions, disorganized speech, and negative symptoms such as social withdrawal, lack of motivation and cognitive symptoms such as attentional and learning deficits which are generally observed together[2].

Schizophrenia is thought to emerge as a result of a neurodevelopmental pathology. A combination of genetic and epigenetic factors with communication defects in the circuits between dorsolateral prefrontal cortex and subcortical structures play a role. Although the etiology and pathophysiology of schizophrenia are not known completely, there are findings regarding that the changes in various neurotransmitter systems such as dopamine, serotonin, gamma amino butyric acid (GABA), and glutamate play role in appearance of schizophrenia symptoms.

Although the dopamine hypothesis is the driving theory behind the majority of translational research in schizophrenia, emerging evidence suggests that aberrant immune mechanisms in the peripheral and central nervous system (CNS) influence the etiology of schizophrenia and the pathophysiology of symptoms that define the illness. The initial interest in inflammatory processes comes from epidemiological data and historical observations, dating back several decades. It is known that changes occur in the mesocortical and mesolimbic dopaminergic transmission in patients with schizophrenia. In other words, while hypoactivation of the mesocortical dopaminergic transmission reaching to the prefrontal cortex is observed in schizophrenia, hyperactivation exists in the mesolimbic dopaminergic neurotransmission. While insufficient dopaminergic stimulation in the cortical D1 receptors explains the cognitive function deficiency and negative symptoms, the increase in D2 receptor stimulation in the subcortical structures are thought to be responsible of the positive symptoms of schizophrenia. The fact of psychogenic effects of psychostimulants and being able to have positive response to the treatments with antipsychotics which act by blocking the D2 receptors is consistent with the above mentioned classical dopaminergic theory[3].

In addition to the dopamine approach, a persistent defect is thought to exist in glutamatergic transmission, also comprising the N-methyl-D-aspartate (NMDA) receptors. It is thought that a functional disorder occurring in the dopaminergic system through the modulating effect of dopamine on glutamatergic neurons may affect glutamatergic neurotransmission over NMDA receptors[4]. Thus, in addition to dysregulation in dopaminergic neurotransmission, hypofunction of NMDA receptors is considered to be one of the core mechanisms of schizophrenia[1,4].

Axons exiting the neuron bodies in the raphe nuclei, which are highly rich in serotonin, reach to whole cortex and many subcortical structures. The serotonergic system shows a widespread distribution in the brain and yet, due to its broad functions, has been a research subject for the schizophrenia pathophysiology for a long time. It is thought that in schizophrenia, excessive serotonergic charging in the anterior cingulate cortex and dorsolateral frontal lobe induced by chronic stress may also contribute to the pathogenesis[5]. The blockade of 5-HT2A receptor by atypical antipsychotics, which is supportive for this approach, is also thought to contribute slowing down the progression of the illness. In brief, the imbalance in the cortical-subcortical dopaminergic transmission, functional changes in the serotonergic and glutamatergic transmission, as well as changes in the central GABA-ergic system - the effect on cognitive functions by its modulator role in the synapses is well-known - are neurotransmitter systems playing a role in the pathophysiology of schizophrenia[6].

Another current approach on the pathophysiology of schizophrenia is related to the increase of the glycogen synthase kinase-3 (GSK-3) activity in many psychiatric diseases including schizophrenia and affective disorders[7]. It is known that genetic susceptibility and being exposed to environmental stress in the early periods of life play an important role in the development of schizophrenia. Although genetic factors play an important role in the pathogenesis of schizophrenia, the concordance of 40–55% in monozygotic twins demonstrates that non-genetic factors also play an important role[8]. In this context, the exposure to pathological environmental factors in the developmental process increases the risk of suffering from schizophrenia in combination with

genetic susceptibility, leading to neurodevelopmental processes following an abnormal immune response.

Beside the changes in the above-mentioned neurotransmitter systems, other molecular mechanisms interacting with the effects of environmental factors contribute to the pathogenesis of schizophrenia. Data showing that an abnormal immune response might play a role in the development of schizophrenia are gradually increasing[9,10]. When the interaction of the immune response and further pathological factors playing a role in schizophrenia including the genetic susceptibility are taken into consideration, elucidating the role of inflammatory mechanisms in schizophrenia has become an important subject.

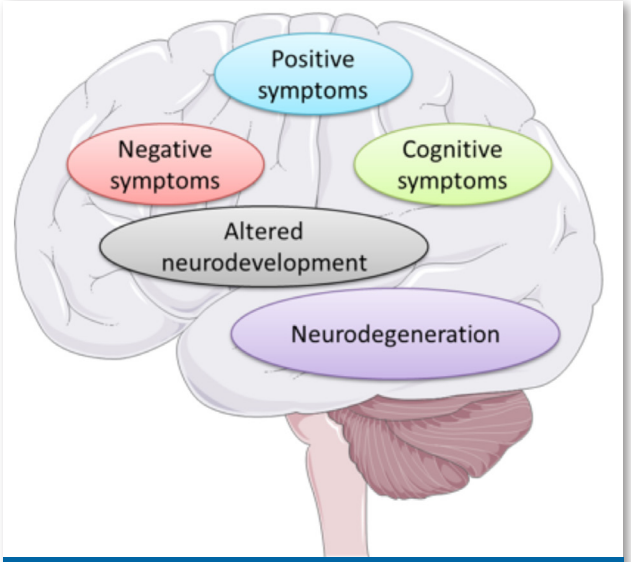



**Figure 1: An Overview to Symptoms and Etiology of Schizophrenia.** Schizophrenia is a complex and deteriorated disorder that consists of positive, negative, and cognitive symptoms. Positive symptoms include hallucinations and delusions; the negative symptoms include lack of certain abilities seen in normal people such as lack of motivation, cognitive abilities and motivation. For etiology, it is thought that the effect of altered neurodevelopment is dominant in early life while neurodegeneration is responsible in the later ages for schizophrenia.

## Neuro-developmental Approach and Inflammation Relation in Schizophrenia

Studies demonstrate that schizophrenia is a psychiatric disorder with neurodevelopmental origin. The combination of environmental and genetic factors associated with diversions from the normal neurodevelopmental process starts long before the appearance of the clinical symptoms and causes the development of schizophrenia[9]. It is characteristic in schizophrenia that brain damage starts in the early periods of life and manifests after a long time[9].

Current approaches argue that schizophrenia increases the risk of developing further CNS disorders such as autism, Parkinson's disease, Alzheimer's disease, and multiple sclerosis. That may be the result of failures (disruption/malfunctions) in the fetal brain development by exposition of the fetus to inflammatory modulators[11,12]. Many current studies report that exposure to viral or bacterial pathogens during the maternal pregnancy increase the risk of developing schizophrenia. Studies demonstrated that maternal infections with influenza, toxoplasma gondii, borna disease virus, and rubella lead to an increased prevalence of schizophrenia in the offspring. In addition, schizophrenia-like behavioral disorders are also related to perinatal infections[1,8]. Fatemi and colleagues vaccinated pregnant mice with sub-lethal doses of the neurotrophic chain of human influenza virus and schizophrenia-like symptoms were observed during the postnatal period in the offspring as result of the maternal influenza infection. The authors pointed out that some of these symptoms are characteristic symptoms of schizophrenia[13,14]. Yet, it was shown that maternal exposure to infectious agents such as bacterial lipopolysaccharide (LPS) and polyribosinic and polyribocytidylic acid (poly I:C), which mimics a viral infection, lead to behavioral changes similar to schizophrenia. They concomitantly increase in the pro-inflammatory cytokine levels[10,12,15]. In another study, the application of a poly I:C injection to a pregnant mouse on the ninth day of the pregnancy, manifests itself by sensorimotor gating deficits according to prepulse inhibition of acoustic startle response Poly I:C injection performed on the seventeenth day of pregnancy results in the attenuation of memory functions[16].

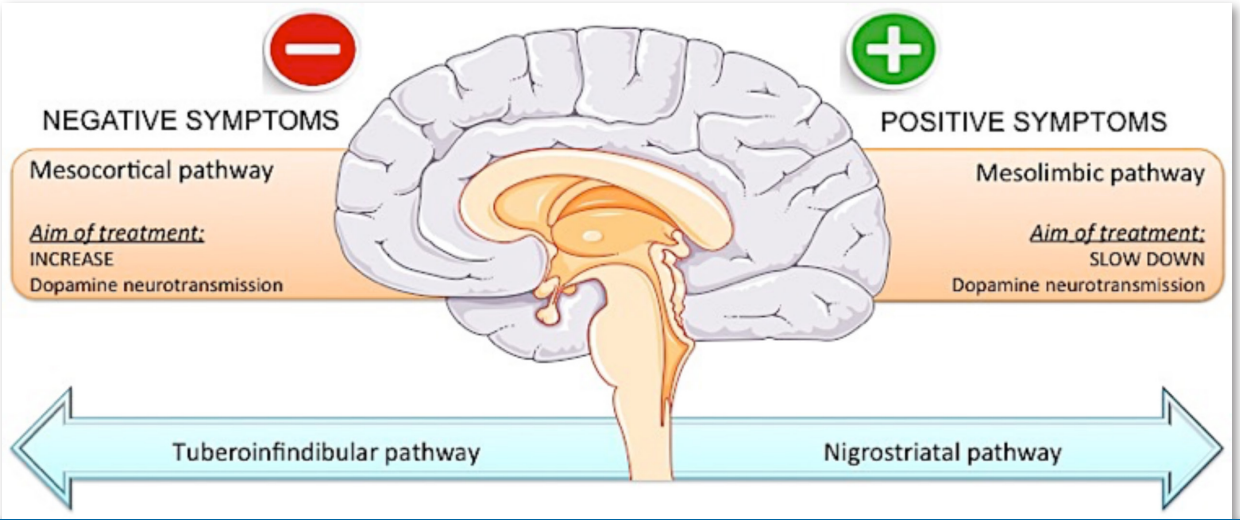



**Figure 2: Dopaminergic Hypothesis of Schizophrenia.** While hyperactivation of the dopaminergic mesolimbic pathway induces positive symptoms of schizophrenia via increased D2 receptor stimulation in the limbic areas, hypo activation of dopaminergic mesocortical pathway causes negative and cognitive symptoms with decreased D1 receptor activation in the cortical areas. Ideal treatment regimen should decrease the activation of mesolimbic pathway while it should increase the stimulation of cortical areas. Also changing in other pathways' activity (tuberoinfindibular and nigrostriatal pathways) are responsible for side effect of current antipsychotics.

Activating the immune system in various stages of the development may lead to different phenotypic results[10].

Increased cytokine production as the consequence of maternal infections may cause abnormal cell development and subsequently brain damage by changes of the immune function in the brain[17]. Current clinical research has reported that abnormal neuro-anatomical structures might develop in a fetus exposed to high levels of maternal IL-8[1]. Exposure to a prenatal immune attack may deteriorate the development and maturation processes of the neuronal system by changing the central and peripheral immune response system of the offspring in the pre- and postnatal period[2].

A wide body of evidence has also been accumulated regarding an aberrant reactive oxygen species and inflammation in schizophrenia. Here we highlight the roles of oxidative stress as a common mechanism by which various genetic and epidemiologic risk factors impact upon neurodevelopmental processes that underlie the schizophrenia syndrome. While there is longstanding evidence that not a single causative factor may play a role in schizophrenia, a common pathway involving oxidative stress opens the possibility for intervention at susceptible phases[18]. The vulnerability-stress-inflammation model of schizophrenia includes the contribution of stress on the basis of increased genetic vulnerability for the pathogenesis of schizophrenia, because stress may increase pro-inflammatory cytokines and even contribute to a lasting pro-inflammatory state. Immune alterations influence the dopaminergic, serotonergic, noradrenergic, and glutamatergic neurotransmission. The activated immune system activates the enzyme indoleamine 2,3-dioxygenase of the tryptophan/ kynurenine metabolism, which influences the serotonergic and glutamatergic neurotransmission via neuroactive metabolites such as kynurenic acid[19]. Neuroinflammation has been proposed as a potential mechanism underlying these brain changes; there is evidence of an increased density and activation of microglia, immune cells resident in the brain, at various stages of the illness[20].

Contrary to the traditional view that the brain is an immunologically privileged site shielded by the blood-brain barrier, studies in the past 20 years have noted complex interactions between the immune system, systemic inflammation, and the brain, which can lead to changes in mood, cognition, and behavior[21].

Understanding the neuroinflammatory mechanisms involved in schizophrenia may be essential for identifying potential therapeutic targets in order to minimize the morbidity and mortality of schizophrenia by interrupting the disease process or development[22].

**Schizophrenia and the Peripheral Immune Response**

In many clinical studies, elevated peripheral cytokine levels in the plasma of schizophrenia patients were reported. Increased serum/plasma values of prostaglandin E2, C-reactive protein, interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor (TNF)-α are an indication for an increased peripheral immune response[6,23,24].

In studies performed in first episode schizophrenia under minimal treatment or without medication, peripheral IL-6, IL-1β and TNF-α, soluble IL-1 antagonist, soluble IL-2 receptor and IL-8 up-regulation have been reported[6,24,25]. A meta-analytic study reported that cytokines such as IL-6, IL-12 TNF-α, IL-1β and interferon (IFN)-γ are increased in the blood and in the cerebrospinal fluid of the patients with acute relapse and first episode of schizophrenia[24]. Moreover, it was reported that also the monocytic immune response, which is one of the main sources of the production and secretion of pro-inflammatory cytokines, is disturbed in schizophrenia[6,26]. In many studies, it has been observed that there is significant increase in the relative and/ or absolute number of total white blood cells and monocytes in schizophrenia[6,27].

In reply to increased peripheral pro-inflammatory activity in schizophrenia, the anti-inflammatory response also increases[28]. The increase in the sIL-1RA and sIL-2R levels in the periphery seems to support this argument[6,29]. It is thought that the mentioned increase occurs in return to the pro-inflammatory stimulation to inactivate and limit the pro-inflammatory process in order to protect the organism from the progressive and harmful effects of the pro-inflammatory process[6].

Chronic low degree inflammation[19] associated with immune sensitization partly caused by the abnormal expression of inflammatory genes in the monocyte/ macrophages in response to specific environmental factors such as physical, physiological or pathogen contact may result in a more severe disease process[2].

Currently, it is known that peripheral immune changes modulate the brain functions and behaviors in various neuropsychiatric diseases. As the result of recurrent injections of purified and recombinant cytokines, which are used in the treatment of viral diseases and uncontrolled cancer, acute psychotic episodes characterized by depression or excitation have been reported in at least 20% - 30% of the patients[15].

It is suggested that peripheral immune stimulation can stimulate the local synthesis of pro-inflammatory cytokines in the brain and affect the brain functions. It has been observed that intraperitonal LPS injections in mice induced an increase in the mRNA expression of some pro-inflammatory cytokines (IL-8, IL-1β and TNF-α) in the hypothalamus and are associated with symptoms such as decrease in food intake[30].

There are factors such as weight changes, sleep, smoking, and age which influence the results of immunological studies and prevent to achieve consistent results in investigating the peripheral cytokine changes[6]. In addition, further factors such as glucose intolerance, obesity, or the use of antipsychotics affect the peripheral cytokine levels and may cause not to achieve consistent results in this subject[1].

**Schizophrenia and Neuroinflammation**

Currently, neuroinflammation can be determined by means of positron emmision tomography (PET) scan in diseases such as Alzheimer, Parkinson, and multiple sclerosis. Doorduin and colleagues have demonstrated findings indicating the presence of neuro-inflammation in the focal region after the onset of psychosis in the hippocampi of patients with schizophrenia compared to the healthy control group[8].

In view of this, the importance of microglia attracts attention because of its modulatory and mediatory role in the inflammatory process in the CNS[31]. Microglia cells are the first and main constituent of the active immune defense in CNS, considered to be the permanent macrophages of CNS as they have functions such as cleaning the brain from damaged/ lesion neurons and infectious agents[31].

Accumulated findings on the interactions between inflammation and CNS, the damaging consequences of inflammation for brain cells in schizophrenia, the possible origins of inflammation and increased oxidative/ nitrosative stressin the disorder, and current pharmacological strategies to deal with these processes (mainly treatments with anti-inflammatory or antioxidant drugs as add-ons to antipsychotics)[32] are pinpoints in the pathology and in innovative therapeutic approaches in schizophrenia. It is possible that the inflammatory response from microglial activation can contribute to the brain pathology, as well as influence the treatment response. This review highlights the role of inflammation in the pathophysiology of psychiatric disorders, such as major depressive disorder, bipolar disorder, schizophrenia, and autism. More specifically, the role of microglial activation and associated molecular cascades are discussed[33].

Neuronal activities of pro-inflammatory cytokines occur by the mediatory effect of the microglia cells. Results, which refer to the concordance between the progress of schizophrenia and increase of microglial activation and pro-inflammatory cytokines, have been revealed by various studies[34,35]. Microglia cells build around 20% of the glial cell population in CNS; they preferably exist in the basal ganglion, substantia nigra, and hippocampus. The primary duty of the microglia is the stimulation of the innate immunity; they also play a role in the inflammatory process. Under normal conditions inhibitory and activating signals are in balance and microglia cells are down-regulated or in resting state. When signals such as the presence of cytokines announce danger for the brain, microglia cells are activated. While active microglia cells increase the synthesis of many receptors, they also increase the production of pro-inflammatory cytokines significantly[1,6]. Despite the observation of an increase in microglia density in the brain of schizophrenia patients in some studies, no significant increase has been observed in some other studies[36,37]. Therefore, it can be suggested that the increase in microglial activity may not be correlated with the microglial density. On the other hand, possible methodological factors influencing the results have to be taken into account.

The up-regulation of cyclooxygenase (COX) expression and the increase of pro-inflammatory cytokines such as IL-1β, IL-6 in the cerebrospinal fluid (CSF) seem to support the active central inflammation hypothesis in schizophrenia[6,38].

Astrocytes have regulatory roles in neuronal transformation, axon guiding, synaptogenesis, and brain plasticity. Furthermore, they regulate microglial functions by their stimulating and inhibiting effects in accordance with the immune environment[15]. Astrocytes can produce cytokines. Furthermore, activated astrocytes produce further substances and reactive oxygen species responsible of the inflammatory reaction. Many remarkable studies report that damaged astrocyte functions play important roles in the neuro-inflammatory pathology in schizophrenia[39]. The S100B protein in the CNS is a calcium binding protein, the biggest amount of S100B is produced by activated astrocyte cells. The increase in this protein levels is related to brain damage and thought to be related with apoptosis and neuronal death[40]. Elevated serum/CSF levels of S100B have been observed in schizophrenic patients. This indicates a hyperactivation of astrocytes in schizophrenia patients. Furthermore, S100B has the property of generating direct functional effect on microglia cells. For this reason, S100B protein can be a reagent, which provides information about microglia and astrocyte functions in schizophrenia[27]. The increase of S100B expression is related to the activity increase of astrocytes rather than their density increase[6].

**Evidence from Clinical Therapeutic Trials**

Studies investigating the role of inflammation in schizophrenia are not limited to preclinical studies. Various clinical therapeutic studies based on the anti-inflammatory approach show promising results. The COX-2 inhibitor celecoxib showed favorable results in several studies[41]. Laan et al. showed that 3 month adjuvant aspirin treatment reduced the total and positive scores on the Positive and Negative Syndrome Scale (PANSS) compared to the placebo group even if it could not improve the cognitive function in schizophrenic patients[42]. In a similar study, it was demonstrated that the PANSS scores and plasma IL-1β levels decreased with 11 week risperidone treatment, while TNF-α and brain derived neurotrophic factor (BDNF) significantly increased. Moreover, dextromethorphan add-on-therapy to risperidone had greater and earlier improvement in which symptoms and also decreased plasma IL-1β, TNF-α and BDNF[43]. In a recent meta-analysis, it was revealed that non-steroidal anti-inflammatory drug adjunctive therapy has beneficial effect on symptoms of schizophrenic patients, especially in early stages of the disorder[44]. Sommer et al. showed that anti-inflammatory agents such as aspirin, estrogen, and N-acetylcysteine have favorable effects on symptoms of schizophrenia[45]. In addition, celecoxib also showed positive effects on cognition.

In a double blind, placebo controlled trial, it has been shown that pioglitazon, an antidiabetic drug showing as well anti-inflammatory properties, potentiated the antipsychotic effect of risperidone. A decrease of negative subscale of PANSS in 40 chronic schizophrenia patients could be demonstrated[46]. In another randomized placebo controlled study, the effects of an adjuvant therapy of pravastatin, which has also anti-inflammatory properties, were evaluated. It was proven that the PANSS positive symptom score was decreased in the sixth week of the add-on-therapy in patients[47]. In the same direction, studies designed with minocycline which has antibiotic, neuroprotective, and anti-inflammatory effect showed that minocycline could improve schizophrenia symptoms and shows beneficial effect on early stage schizophrenia patient[48,49].

## CONCLUSIONS

Schizophrenia is a complex mental illness in which genetic predisposition plays an important role along with progression of the defects in the neurotransmitter systems. Furthermore, neurodegenerative processes and neurodevelopmental deviations are observed. At present, current antipsychotic medications acting effective on the dopaminergic transmission are insufficient in restoring the negative and cognitive functions, which play an important role in the progression of the disease and are sometimes encountered as the limiting factors for the treatment. In this context, new approaches possibly elucidating the complex pathogenesis of the disease are gradually increasing. Among these approaches, studies performed in recent years showed that abnormal inflammatory responses might have play a role in the pathophysiology of schizophrenia. Obtaining promising results by adding anti-inflammatory agents such as minocycline, which is an antibiotic belonging to tetracycline group, and acetyl salicylic acid which is a non-selective COX inhibitor, celecoxib which is a selective COX-2 inhibitor as adjuvant to the standard therapy with antipsychotics is supportive to this approach.

In this regard, elevated pro-inflammatory cytokine levels in plasma and CSF of schizophrenic patients have been reported in the studies. Immune activation, which occurs by various mechanisms in the fetus brain during the development period, could lead to schizophrenia in the future periods of life.

Today, peripheral immune changes in various neuropsychiatric diseases are known to modulate brain function and behavior. Truly elucidating the role of inflammatory mechanisms, which are increasingly reported in schizophrenia, is promising in understanding the pathophysiology of the disease and for establishing effective therapeutic approaches.

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