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The Role of Innate and Adaptive Immune System in the Pathogenesis of Schizophrenia

Marziyeh Soltani[1], Yousef Mirzaei[2], Ali Hussein Mer[3], Mina Mohammad-Rezaei[4], Zahra Shafaghat[4], Soheila Fattahi[5], Fatemeh Azadegan-Dehkordi[6], Meghdad Abdollahpour-Alitappeh[7], and Nader Bagheri[8]

[1] Student Research Committee, Shahrekord University of Medical Sciences, Shahrekord, Iran
[2] Department of Medical Biochemical Analysis, Cihan University-Erbil, Kurdistan Region, Iraq
[3] Department of Nursing, Mergasour Technical Institute, Erbil Polytechnic University, Erbil, Iraq
[4] Department of Immunology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[5] Medical Plants Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran
[6] Cellular and Molecular Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran
[7] Cellular and Molecular Biology Research Center, Larestan University of Medical Sciences, Larestan, Iran
[8] Clinical Biochemistry Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran

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ABSTRACT

Schizophrenia is one of the most severely debilitating mental disorders that affects 1.1% of the world's population. The exact cause of the disease is not known, but genetics, environmental factors (such as infectious agents, season and region of birth, exposure to viruses, low birth weight, advanced paternal age, and tobacco), and immune system dysfunction can all contribute to the development of schizophrenia. Recently, the role of the immune system in schizophrenia has received much attention. Both acquired and innate immune systems are involved in the pathogenesis of schizophrenia and facilitate the disease's progression. Almost all cells of the immune system including microglia, B cells, and T cells play an important role in the blood-brain barrier damage, inflammation, and in the progression of this disease. In schizophrenia, the integrity of the blood-brain barrier is reduced and then the immune cells are recruited into the endothelium following an increase in the expression of cell adhesion molecules. The entry of immune cells and cytokines leads to inflammation and antibody production in the brain. Accordingly, the results of this study strengthen the hypothesis that the innate and acquired immune systems are involved in the pathogenesis of schizophrenia.

Keywords: Blood-brain barrier; Immune system; Inflammation; Cytokines; Psychoneuroimmunology; Schizophrenia; Therapeutics

Corresponding Authors: Fatemeh Azadegan-Dehkordi, PhD; Cellular and Molecular Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran. Tel: (+98 913) 5928 793, Fax: (+98 38) 1333 0709, E-mail: fatemehazadegan@gmail.com

Nader Bagheri, PhD;
Clinical Biochemistry Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran. Tel: (+98 918) 1731 073, Fax: (+98 38) 1333 0709, E-mail: n.bagheri1985@gmail.com

INTRODUCTION

Schizophrenia is a severe psychological disorder associated with a set of positive and negative symptoms and cognitive disorders.[1,2] Hallucinations which involve hearing, seeing, and feeling things that do not exist externally along with and delusions which are fixed misconceptions and suspicions fall under the category of positive symptoms. On the other hand, apathy and lack of pleasure are considered negative symptoms of the condition.[2] Schizophrenia patients often suffer from cognitive disorders that affect processes such as thinking, memory, and concentration.[3] Late adolescence and early adulthood are usually known as the onset age of schizophrenia.[4] Schizophrenia affects about 1.1% of the world's population.[5]

The exact cause of schizophrenia has not been determined yet, but genetic, environmental, and immune system disorders are thought to affect the progression of the disease.[7-10] In schizophrenia, there are malfunctions in the immune system including enhanced microglial density and activity as well as abnormal levels of cytokines in both serum and cerebrospinal fluid,[11] which can be due to damage to the blood-brain barrier during this disease. In schizophrenia, the integrity of the blood-brain barrier decreases and its permeability increases. Alteration in the gene expression of the molecules involved in tight junctions, such as cadherin-5 and claudin-5, can play a role in blood-brain barrier dysfunction. Increased expression of adhesive molecules on the surface of endothelial cells enhances the entry of monocytes into the brain. On the other hand, microglial cell activation by classic phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX2) is probably effective in diminishing the integrity of the blood-brain barrier.[12] As a result, the dysfunction of the blood-brain barrier causes cytokines, antibodies, and immune cells to pass from the blood to the brain.

Also, cytokines released during inflammation, such as interleukin (IL)-1β and tumor necrosis factor (TNF)-α, can increase brain endothelial permeability. The blood-brain barrier dysfunction in schizophrenia patients increases albumin and immunoglobulin (Ig) G levels. Therefore, breaking down the blood-brain barrier can enhance brain inflammation.[13] Inflammation may be the main trigger for the onset of schizophrenia. In the early stages of the disease, an increase in inflammatory cytokines such as IL-1 receptor antagonist (IL-1RA), IL-1β, IL-6, IL-8, and TNF-α is reported. There is evidence of the effectiveness of anti-inflammatory agents in the treatment of these patients.[8] Recent studies
suggest that autoimmune diseases may increase the risk of developing psychiatric disorders and immunosuppressants can be used instead of traditional drug therapies in these patients.[14]

Therefore, blood-brain barrier dysfunction and immune system disorders can play an important role in schizophrenia. The current study aims to describe the function of different cells of the innate and adaptive immune systems in the progression and suppression of schizophrenia.

The Prevalence of Schizophrenia

Schizophrenia affects approximately 24 million people, or 1 in 300 people (0.32%), worldwide. This rate is 1 in 222 people (0.45%) among adults. In the United States alone, approximately 3.5 million people are living with schizophrenia.[5] Schizophrenia is not quite prevalent, but economically, it imposes heavy costs on individuals and society.[6] The costs of schizophrenia are estimated at $2.7 million for the Italian society, more than $63 million for the United States, and $93.9 million for Europe.[5,6]

Etiology of Schizophrenia

Schizophrenia is a prevalent psychiatric disorder, but little is known about its cause and pathophysiology.[15] Schizophrenia patients are disabled in terms of memory and executive functions while performing their duties.[16] The exact cause of schizophrenia has not yet been determined, but environmental factors, genetics, and immune system disorders are thought to affect the progression of the disease.[8-10,17] Brain scanning and neuropathology studies were able to link the symptoms of schizophrenia to the structure or function of different areas of the brain.[15]

Although the dopamine and glutamate systems have different functions in neural signaling, they have been suggested to play a significant role in the pathophysiology of schizophrenia. Glutamate is the most important excitatory neurotransmitter of the

central nervous system, and glutamatergic neurons are widespread throughout the brain.[18]

Evidence suggests that glutamatergic dysfunction may be linked to the symptoms of schizophrenia and the severity of the disease.[15] Impaired regulation of the dopamine system may also play a part in the pathophysiology of schizophrenia.[19] Exposure to dangerous prenatal factors, such as radiation exposure, famine, or maternal viral infections, especially in the second trimester of pregnancy is among the important risk factors for infant schizophrenia.[16] Knowing the schizophrenia risk factors that affect early nerve growth during pregnancy can include maternal stress, nutritional deficiencies, maternal infections, intrauterine growth retardation, and complications of pregnancy and labor.[15]

Environmental factors have a significant role in the development of schizophrenia and can increase the risk of the disease.[20] Trauma is often cited as a risk factor for the disease, although there is little real evidence for it. Also, a stressful environment is often recognized as an aggravating factor in schizophrenia.[16] Among the environmental factors, the following can be mentioned in Figure 1. We explain the main factors that contribute to the etiology of schizophrenia.

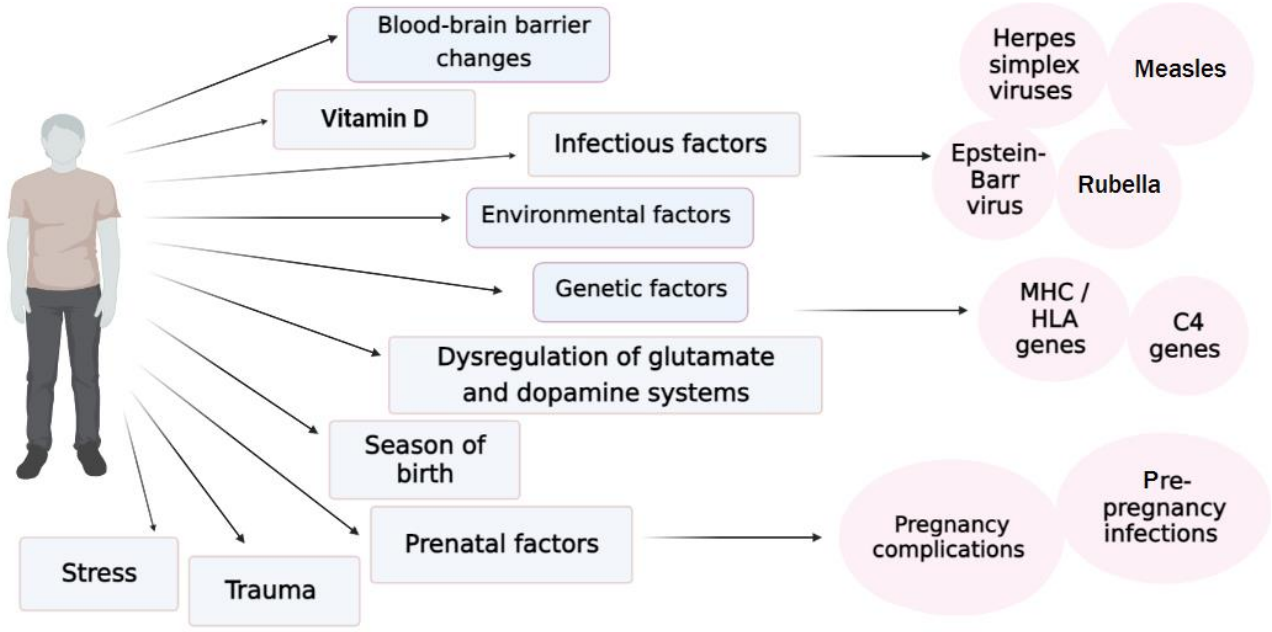

Figure 1. Etiology of schizophrenia. The exact cause of schizophrenia has not yet been determined, but it is believed that factors such as glutamate and dopamine system disorders, infectious factors, environmental factors, prenatal factors, season of birth, vitamin D levels, trauma, stress, genetic factors, and blood-brain barrier changes can have a dramatic effect on the progress of the disease.

Infectious factors

Various studies and research have demonstrated that microbial components are significantly involved in the pathogenesis, etiology, and pathophysiology of schizophrenia.[21] Herpes simplex virus (HSV), cytomegalovirus (CMV), Epstein-Barr virus, measles, and rubella are neurotropic viruses that may cause brain disorders such as schizophrenia.[21] Infectious factors such as influenza, rubella, toxoplasma, herpes simplex, and cytomegalovirus can impair neurological and behavioral development. Investigations have shown that the risk of schizophrenia is higher among children whose mothers had HSV virus antibodies.[12,21]

These infections may increase the risk of contracting the disease through a common pathway, such as cytokine responses or unique mechanisms.[22] Several studies have revealed that elevated CMV, HSV-1, *Toxoplasma gondii*, and C-reactive protein (CRP) serological levels are related to attenuated neurocognitive function in schizophrenia.[23] Some infectious factors are unlikely to directly affect the fetus's brain, for example, factors such as the influenza

virus that does not cross the placenta or an increase in Toxoplasma IgG, which is also seen in the absence of active infection.[23]

The link between infectious disease factors and the pathophysiology of schizophrenia is not restricted to viral infections.[21] Maternal exposure to infectious agents, especially bacterial infections, is associated with an increased risk of schizophrenia in children.[24] Infection and inflammation are generally involved in the pathology of mental illnesses such as schizophrenia.[25]

Maternal-to-fetal infection is considered to be one of the most likely risk factors for schizophrenia, as microbial pathogens can result in congenital brain abnormalities and several behavioral and learning impairments during childhood.[26] The prenatal period is crucial for brain development because processes such as neurulation, neurogenesis, and prenatal neuronal migration and also processes like synaptogenesis, gliogenesis, and myelination, begin during pregnancy.[24]

Thus, although exposure to infection or other risk factors in the second trimester of pregnancy increases the chances of schizophrenia, exposure to infectious factors in the first trimester and pre-pregnancy infections are also associated with an increased risk of contracting the disease.[27]

In general, prenatal viral and bacterial infections play a considerable role in schizophrenia.[28] Thus, approaches aimed at preventing and treating infections can help prevent schizophrenia.[28]

Season of Birth

One hypothesis for the pathophysiology of schizophrenia is that the season of birth is associated with the disease.[29,30] Although the exact reasons for this association remain unknown, a variety of environmental causes can be raised, including changes in sun exposure (vitamin D intake) or infections during pregnancy or early stages of life.[31] Since the sun's ultraviolet rays are involved in the synthesis of vitamin D, vitamin D production is higher in summer than in winter.[32]

Schizophrenia patients are more likely to be born in winter, and the effect of the season of birth on increasing the risk of the disease is probably due to the increased risk of viral infections.[12,20] Excessive winter and spring births in schizophrenia patients support the theory that the birth of children in the winter and spring months may be related to the development of schizophrenia.[29,31,33] About 5% to 8% of excessive childbirths in winter and spring are associated with this disorder.[27]

Prenatal Factors

Many complications during pregnancy can jeopardize nerve growth, which fall into three categories: 1) pregnancy complications such as maternal exposure to severe stress, diabetes, bleeding, incompatibility of rhesus, fetal growth and development abnormality, low birth weight, and congenital disorders; 2) abnormal growth and development of the fetus; and 3) complications of labor such as asphyxia, and emergency cesarean sections. These are all related to schizophrenia.[34-36]

In general, high blood pressure, preterm birth, low birth weight, preeclampsia, RH incompatibility, and prenatal malnutrition have been reported as risk factors for schizophrenia.[12,20] Maternal infection during pregnancy with various types of bacterial and viral infections, including influenza, is an important risk factor for schizophrenia, but since not all infectious factors can cross the placenta and reach the fetus, there are other mechanisms for this transmission. Prenatal inflammation may be involved in the fetal brain development, therefore increasing the risk of schizophrenia.[37]

In inflammatory conditions, increased pro-inflammatory cytokines and inflammation in the mother is associated with an enhanced risk of schizophrenia.[36] These factors at key times during pregnancy affect the risk of developing schizophrenia in adulthood.[37] However, the mechanisms by which risk factors cause schizophrenia remain widely unknown.[35]

Vitamin D

Studies suggest that sunlight, or vitamin D, is one of the major environmental factors in the pathophysiology of neuropsychiatric disorders such as schizophrenia.[38] The first chemical reaction for vitamin D production occurs after the skin is exposed to sunlight.

As a result, it is hypothesized that vitamin D levels are a mediating factor that increases the risk of schizophrenia.[39] In general, schizophrenia patients are proven to be less exposed to sunlight.[32] The pandemic also keeps people from going outside, preventing them from getting enough sunlight exposure. This results in low levels of vitamin D.[40]

Today, analytical epidemiological studies have shown that infants with vitamin D deficiency are at risk for schizophrenia later in life.[33] Vitamin D deficiency is more common in patients with neuropsychiatric disorders than in healthy individuals.[38,41] Vitamin D

deficiency during pregnancy can be a risk factor for schizophrenia during adulthood.[32]

However, there is scarce data about the association between the severity of schizophrenia and the serum level of vitamin D.[42] Vitamin D is involved in the regulation of the immune system.[33] The amount of this vitamin varies with age, ethnic origin, body mass index, and season.[32] Certain evidence suggests that this vitamin is a neurotransmitter hormone that plays a significant part in brain growth and function.[42] Vitamin D can protect neurons because it regulates nerve growth factors and neurotropic factors derived from the glial cell line. It can also protect the brain against reactive oxygen species by increasing antioxidant molecules such as glutathione in non-neuronal cells.[38] In those with vitamin D deficiency, the immune system tends to increase inflammatory markers such as TNF-α and IL-6 and create a pro-inflammatory environment, and this hyper-inflammation can lead to worse consequences in affected people.[43] Therefore, doctors usually monitor vitamin D deficiency in patients suffering from mental disorders and recommend taking supplements or doing outdoor activities to optimize bone health.[41,44]

Stress

Stressors such as mental and physical abuse, child neglect, urbanization, and poor economic and social conditions can increase the risk of schizophrenia by altering the immune system. Psychological stress is a major stimulus for increasing the severity and progression of psychiatric neurological diseases, including schizophrenia.[45,46] Stress can be related to the pathophysiology of this disease.[47]

Evidence demonstrates that patients with this disease are exposed to higher levels of psychosocial stress and often have a tense environment in the family as well as a stressful social life.[48] Schizophrenia patients use a variety of strategies to reduce their stress, and their ability to cope with stress significantly affects patients' quality of life.[49]

Changes in the immune system are followed by stress along with enhanced immune system activity, activation of the complement system, changes in microglia cells, and cortisol regulation dysfunction. When exposed to a stressor, several physiological reactions occur in the body, including an increase in circulating cortisol and the activation of the sympathetic nervous system.[45] The hypothalamic-pituitary-adrenal axis (HPA axis) usually responds to stressors and regulates the secretion of cortisol.[48] Research on patients with schizophrenia has revealed that the severity of symptoms is associated with high activity of the hypothalamic-pituitary-adrenal axis.[50] Even in relatives of schizophrenia patients, certain changes in the regulation of this axis and increased cortisol levels have been observed and reported.[51]

On the other hand, the ventral hippocampus is the main part of the brain for responding to stressors. It has been shown that changes in its structure and function can be associated with mental disorders such as schizophrenia. The hippocampus plays a crucial role in the regulation of dopamine neuron activity; therefore, it can cause or exacerbate dopamine-dependent symptoms in diseases such as schizophrenia.[45,47]

Chronic stress can alter the gene expression, density, morphology, and phagocytic activity of microglia cells by activating P2X7 receptors on the surface of microglia cells, which eventually leads to activation of the Nod-like receptor (NLR) family pyrin domain containing 3 (NLRP3) inflammation and enhanced levels of IL-1β. In patients suffering from schizophrenia, the function of cortisol in regulating inflammation is impaired as cortisol is elevated along with the levels of IL-6. Although it has anti-inflammatory effects in healthy people, cortisol may boost inflammation in these patients.

Prenatal stress also increases the expression of pro-inflammatory genes, including IL-6, IL-1β, and TNF-α. Increased production of pro-inflammatory markers, including IL-1, IL-6, IL-8, TNF-α, and CRP, results in elevated neuroinflammation.[20] Cortisol responses to stress in schizophrenia patients are highly heterogeneous, and there is a significant relationship between a person's social functioning and cortisol activity.[50] Studies have revealed that among children with a family history of schizophrenia, those who respond intensely to stress are more likely to develop the disease in the future.[47]

The Role of Genetic Factors in Schizophrenia

Genetics plays a vital role in the susceptibility to psychiatric disorders, and numerous sequencing studies have been performed to identify the risk sites.[39] Schizophrenia is a psychiatric disorder with a high degree of genetic heterogeneity, and the frequency of these risk factors, including common single nucleotide polymorphisms (SNPs), rare copy number variation (CNVs), and de novo mutations (DNMs), varies from common to rare.[52] But despite remarkable approaches in

molecular genetics, our data on schizophrenia etiopathogenesis is not yet complete.[53] Increased inflammation in schizophrenia is associated with neurobiological phenotypes.[54] This disease is a multifactorial disorder in which both genetic and environmental factors play important parts, and the rate of heritability is between 60 and 80%.[16,53,55] According to research on twins, genetic factors increase the risk of developing the disease by 1 to 80 percent. In monozygotic twins, one of the twins has a 48% chance of developing schizophrenia, while the risk is 12 to 14% in dizygotic twins.[15,28] The chance of developing the disease in the monozygotic twin of a schizophrenic patient is 40-50 percent.[16]

Genetic mechanisms, including the pathogenesis of schizophrenia, probably involve the interaction of multiple immune genes involved in the regulation of innate and adaptive immune systems related to psychosis.[54] Hundreds of genes on several chromosomes have been identified as related to schizophrenia. Genetic studies have shown a set of immunogenic genes in chromosome 6 that contain complementary major histocompatibility complex (MHC)/human leukocyte antigen (HLA) and complement component 4 (C4) genes as a sensitive locus associated with schizophrenia.[21]

Schizophrenia is closely linked to the MHC, cytokine, and complement genes.[12,56] At the genetic level, alleles of the genes encoding C4A and C4B are associated with schizophrenia.[54,57] A recent genomic study identified common genetic risks between schizophrenia and prevalent autoimmune diseases, including rheumatoid arthritis, Crohn's disease, multiple sclerosis, systemic lupus erythematosus, type 1 diabetes, and ulcerative colitis.[58] A high prevalence of some autoimmune diseases and blood cytokine abnormalities was reported in the first-degree relatives of patients with schizophrenia.[37] Patients with a family history of psychosis are at higher risk for psychiatric disorders.[17] A genome-related study identified 108 genetic loci significantly associated with the disease risk, which are highly expressed in brain and B cell tissues ($CD20^+$ and $CD19^+$).[7]

Evidence suggests that repeated deletions on chromosome q11.222 could be an important clinical cause associated with schizophrenia and is in fact one of the strongest known risk factors for this disease.[59] Genetic studies offer advanced insights into the mechanisms that increase the susceptibility to schizophrenia, particularly by identifying potential new targets for treatment.[60]

The Role of the MHC

Impaired immune responses have long been considered as a potential initiating process in schizophrenia.[61,62] MHC molecules (also called HLA in humans) are encoded by several gene loci and are located in three gene regions (MHC class I, class II, and class III) on the chromosome 6 short arm. These molecules are known to be an important set of immune molecules in humans that have recently become the subject of important research in central nervous system (CNS) disorders.[63] In humans, a very important relationship was found between different mutations in the MHC region and the size of the cerebral ventricles, especially in patients with schizophrenia.[64]

Schizophrenia is a multifactorial disorder that can involve thousands of genetic risk factors.[62] In this disease, ectopic expression is seen on chromosome 6, which is highly loaded with immune genes.[61] This gene locus is most strongly linked to schizophrenia when compared to other regions. It contains genes that play a role in the innate immunity. One specific gene, *C4A*, which is found at the major histocompatibility complex (MHC) site, is closely connected to the development of the disease.[12,65] The Notch Receptor 4 (*NOTCH4*) gene is located in the MHC region, and carries a variety of genetic risk factors for schizophrenia among populations.[52]

In schizophrenia, a persistent inflammatory process has been reported, characterized by an increase in inflammatory markers such as cytokines, chemokines, and C-reactive protein (CRP) in the peripheral blood. These biomarkers are involved in several cellular functions that may be directly or indirectly linked to MHC function.[66,67] Cytokines, following signaling to the brain, lead to neuro-immune, neuro-chemical, and behavioral changes that can lead to mood swings that result in psychiatric disorders such as schizophrenia.[60]

Due to the involvement of these molecules in cellular immune functions, including antigen processing, antigen-presenting and tolerance, the pathophysiology of schizophrenia is believed to be related, at least in part, to impaired immune processes, which can greatly affect the immune system's responses and interactions with the central nervous system.[66] Recent studies have demonstrated the expression of MHC I proteins in mammalian brains. This molecule plays a role in the basic functions of the CNS, including neurogenesis, neuronal differentiation and migration, and the formation of interneuron synapses. All of these major processes have been studied in the etiopathogenesis of schizophrenia.[64]

In general, the mechanism by which MHC genes increase the risk of schizophrenia remains largely unclear.[68] In this context, the "glutamate hypothesis of schizophrenia" has been proposed, according to which the reduction of glutamatergic signaling function through N-methyl-D-aspartate receptor (NMDAR) is the main mechanism of pathology of schizophrenia.[52,64] In that regard, in order to find the role of MHC molecules in schizophrenia, it has been found that neurons express MHC molecules, and their expression is dynamically regulated during neuronal life.[63] These molecules can regulate many aspects of brain development, including synapse formation and function, neurite outgrowth, activity-dependent synaptic refinement, and long-term hemostatic flexibility.[61]

NMDAR can facilitate synaptic plasticity through various calcium-dependent proteins. The clinical association of this receptor with schizophrenia has been investigated.[69] MHC-I can affect synaptic plasticity through the modulation of glutamate receptors, including NMDAR.[64] Interestingly, one study found that genetic diversity in the MHC region was associated with psychotropic response in schizophrenia, suggesting that the MHC region may have pharmacogenetic markers.[68]

The Role of Complement

The complement system is one of the most important innate and adaptive immune defense mechanisms and includes a set of immune system-related plasma proteins that play a role in the first line of defense against pathogens.[57,58,67] The complement system is involved in neurogenesis, brain development, and the nervous system. The components of the complement system can not only facilitate brain formation during neural development but can also lead to brain dysfunction in adults.[70]

In pathology, impaired complement cascade regulation leads to neurological dysfunction, chronic inflammation, and persistent pain.[71] This system is the main factor in triggering the inflammatory cascade and its regulation causes pathology in many diseases.[70,72] The expression of complement components is different in different inflammatory states of the brain.[73] The expression of complement proteins in the brains of healthy individuals is rather low and varies at different ages.[70]

Previous studies have shown an association between complement system disorders and psychiatric disorders such as Alzheimer's, schizophrenia, and multiple sclerosis. Recent evidence has proven that the complement system plays a significant part in the central nervous system- related diseases, including schizophrenia.[67]

In schizophrenia, the synaptic density of the cerebral cortex usually decreases, and one of the key pathways reported to diminish synapses during postpartum growth is the complement system.[74] The classic complement pathway is important for synaptic pruning during the evolution of the central nervous system.[58]

Findings from clinical studies show a malfunction in the regulation of the classic pathway in the early stages of schizophrenia.[72] In patients with schizophrenia, the complement proteins C3 and C4 are increased. The C4A and C4B protein alleles are closely related to schizophrenia. In schizophrenia, an increase in C4 and also an increase in C4 mRNA were found in the brains of patients with schizophrenia after their death. Increased C4 activity is also associated with increased synaptic pruning and decreased synapse density.[57] Research has revealed that complement proteins C1q and C3 are expressed in rodent brain synapses, and these proteins, along with microglia, can cause postpartum synaptic elimination.[57 57]

Abnormalities in the expression of C4A and other complement molecules lead to disruption of the synaptic pruning process during nerve growth.[75] As a result, structural changes in C4 can lead to altered neural C4A expression and loss of important cerebral synaptic connections.[67] Precise examination of the location of the MHC on chromosome 6, has found haplotypes in C4 (which is a key activator encoding the classic pathway of the complement system), associated with schizophrenia.

As a result, it can be said that the complement pathway has a potential role in the etiopathogenesis of this disease.[67,72,76,77] Based on the stage of the disease, complement proteins in the serum of schizophrenia patients show higher hemolytic activity than in healthy individuals.[57] In general, the activity of the complement pathway increases in schizophrenia.[67]

Although, the results from the studies evaluating the role of complementarity are contradictory. For instance, one study reported an increase in C1, C2, C3, C4, and C5 proteins and an increase in complement hemolytic activity in schizophrenic patients, while in another study, an increase in all of the above proteins except C2 was shown, and complement hemolytic activity was similar in patients with the control group.[12,57,67]

The Blood-brain Barrier Changes in Schizophrenia

For the first time, an association between schizophrenia and blood-brain barrier disorders was identified in epidemiological studies, which showed that about two-thirds of schizophrenic patients were associated with underlying diseases related to endothelial cell defects, including cardiovascular disease and metabolic syndrome.[78] The blood-brain barrier consists of tight junctions of capillary wall endothelial cells. The blood-brain barrier restricts the entry of immune cells and molecules into the central nervous system (CNS) while allowing vital molecules such as glucose to pass through, which protects sensitive nerve tissue against pathogens and immune molecules.[79]

However, in pathological conditions such as schizophrenia, the blood-brain barrier protects against CNS-directed inflammation by restricting immune cell access to the brain, it can also regulate the local inflammatory response by expressing pro-inflammatory molecules that promote the recruitment of peripheral immune cells into the CNS.[80] In schizophrenia, abnormalities in the blood-brain barrier reduce the integrity of the blood-brain barrier and increase its permeability.[81] As a result, it causes cytokines, antibodies, and immune cells to pass from the blood to the brain. Alterations in the expression of genes of molecules involved in tight junctions such as cadherin 5 (CHD5) and claudin-5 are among the causes that can play a significant role in the disruption of the blood-brain barrier.[80] Deletion of the cadherin gene in mice causes memory and learning impairments. claudin-5 is expressed on the surface of brain endothelial cells and is a major component of tight junctions in the blood-brain barrier. Mutations in the claudin-5 gene have been observed in 30% of schizophrenic patients.[82] Increased expression of adhesive molecules on the surface of endothelial cells increases the entry of monocytes into the brain.

The results of rat models with neuropsychiatric or inflammatory diseases show that blood-brain barrier dysfunction has been associated with affecting microglial function.[83] In pathological conditions, the blood-brain barrier integrity can worsen due to microglial reactivity. However, the function of the blood-brain barrier can be improved by administering the anti-inflammatory drug minocycline. Changes in blood-brain barrier permeability are connected with producing autoantibodies against NMDARs in the brain.[83] On the other hand, activation of microglia cells by nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) is probably effective in eliminating the integrity of the blood-brain barrier.[12]

Furthermore, cytokines released during inflammation can increase the permeability of the brain endothelium. For example, during inflammation, the secretion of IL-1β and TNF-α can alter the permeability of brain endothelium. The blood-brain barrier malfunction in patients with schizophrenia increases albumin and IgG levels. Therefore breaking the blood-brain barrier can boost the inflammation in the brain.[13] Blood-brain barrier function is often compromised in many brain pathologies, as well as in other vascular, inflammatory, and infectious diseases.[13] Evidence shows increased blood-brain barrier permeability in a subgroup of patients with schizophrenia.[84] A study found that 14 of 39 patients with schizophrenia spectrum disorders had symptoms of blood-brain barrier permeability, including 9 patients with elevated serum/cerebrospinal fluid (CSF) albumin ratio.[85] A meta-analysis by Orlovska-Waast et al., on 32 studies concluded that patients with bipolar disorder and schizophrenia may show blood-brain barrier abnormalities, but the authors also noted that the quality of the available studies is relatively low.[86]

Several research reported elevated vascular endothelial adhesion molecules and integrin receptor levels during schizophrenia.[87] A study focusing on P-glycoprotein, an efflux pump in the blood-brain barrier, showed that it can be more active in schizophrenia, but the results of this study need to be repeated for full confirmation.[88] Increased blood-brain barrier permeability can have detrimental effects on the brain as a result of the pro-inflammatory cells and molecules entry into the brain.[84] Although there is no consensus on the best way to monitor the increase in blood-brain barrier permeability in patients with schizophrenia, several new candidates including matrix metalloproteinase-9, ubiquitin carboxyterminal hydrolase-L1, neurofilaments, brain-derived neurotrophic factor, miRNA in addition to S100B and glial fibrillary acidic protein are available for future studies.[89]

Beyond the blood-brain barrier, peripheral inflammatory responses can reach the CNS through the meninges (the multilayered protective tissue that surrounds the brain and spinal cord). Cytokines can accumulate in the dural cerebrospinal fluid (CSF) and pass through the brain and endothelial cells without tight junctions. Moreover, cytokine signaling, particularly in the meninges, directly binds to neurons' surface

receptors in the frontal cortical regions and changes the function of neurons resulting in social behaviors and cognitive alterations in mouse models.[90]

The Role of Innate Immune System Responses in Schizophrenia

The innate immune system is the body's first line of defense against pathogens, which identifies pathogens in a nonspecific manner and does not provide long-term immunity. Innate immune cells include monocytes, macrophages, dendritic cells and granulocytes, natural killer (NK) cells, and mast cells. Cytokines, interferons, and complement system proteins are also part of the innate immune response.[89,91,92] Studies on the role of innate immunity in schizophrenia revealed an increase in monocytes and NK cells ($CD4^+$, $CD56^+$) and a decrease in dendritic cells.[93-96]

Microglial Cells

Microglial cells are one of the most important members of the innate immune system in the central nervous system. Microglia cells are macrophages that reside in the CNS and include 10% to 20% of the CNS cells. These cells are involved in maintaining homeostasis in the CNS, removing apoptotic cells through phagocytic activity, and helping oligodendrocyte cells with myelination; they also play a part in the development of the nervous system and synaptic pruning.[97,98]

Microglia cells are derived from myeloid precursors in the fetal yolk sac and early embryogenesis, they migrate to developing areas of the CNS. From the 5th week of pregnancy in humans, microglial progenitors are present around the neural tubes.[99] Eventually, fetal microglia are transformed into mature microglia by regulatory factors such as PU-1, IL-34, and CSF-1 and distributed throughout the central nervous system.[100]

Microglia cells can also be generated from peripheral blood monocytes that enter the CNS due to the destruction of the blood-brain barrier. Normally the blood-brain barrier does not allow the immune cells and molecules to enter the brain.[100]

In a healthy brain, the microglial cells are in the form of quiescent, ramified microglia, or resting microglia. The danger signals that compromise the CNS homeostasis, are identified by ramified microglia via pattern recognition receptor, and their phenotype changes to reactive microglia.[101] Reactive microglia can have phagocytic activity or act as antigen-presenting cells to lymphocytes. Various factors including injury, infection, stress, disease, and lack of light activate the resting microglia and also increase the interaction of microglia with neurons.[102] Microglia activated by increased expression of Toll-like receptors (TLRs), phagocytic receptors (CR3, CR4), scavenger receptors (CD36, CD91), release of cytokines and complement proteins, and production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and phagocytic NADPH oxidase, causes neuronal destruction, increased synaptic pruning and white matter abnormalities and eventually leads to schizophrenia.[97,99,103-107]

Microglial activation can be categorized into two different groups: the classical M1 and the alternative M2.[108] M1 microglia induce inflammation and neurotoxicity by the release of a range of pro-inflammatory compounds including NO, IL-1β, TNF-α, IL-6, and glutamate, while M2 microglia induce neuroprotection by releasing anti-inflammatory cytokines, and growth factors, neurotrophic growth factors, both of which are involved in the pathogenesis of neurodegenerative diseases, therefore microglia act as a double-edged sword in neurodegenerative diseases.[109]

The Role of Acquired Immune Responses in Schizophrenia

Type 1 and Type 2 Helper T Cells

During the acquired immune response based on cytokine production, transcription factor expression, and executive functions, different groups of T cells appear. These cells can boost mucus protection and distinguish pathogens from normal flora. Immature Th cells express CD4 and are divided into two groups with different functions: 1) Th1 cells that secrete IL-2 and INF-γ and 2) Th2 cells that produce IL-4, IL-5, and IL-10. In addition, Th1 often induces an immune response in response to intracellular bacterial infections, and Th2 cells stimulate B cells to respond to extracellular bacterial infections.[110] In schizophrenic patients, the balance between Th1 and Th2 cells is disturbed, such that Th2 responses increase in these patients, which is accompanied by an increase in IgE, IL-4, and IL-10. A reduction in IL-2 and INF-γ indicates a decrease in Th1 responses in these patients.[93,111]

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Helper T 17 Cell

Th17 is a subtype of $CD4^+$ T cells. These cells are distinct from Th1 and Th2 cells in terms of differentiation and function. IL-6 and IL-23 along with IL-1β can induce human TH17 cells, while in mice IL-6 in combination with transforming growth factor (TGF)-β) is essential for the development of Th17.[112,113] Th17 cells express cytokines such as IL-6, IL-17A, IL-17F, IL-21, IL-22, IL23, IFN-γ, GM-CSF, and transcription factor RORC2 and STAT3. It also expresses CCR6, IL-23R, IL-1R and CCR4.[110] The role of TH17 cells in the pathophysiology of inflammatory disorders, especially autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, as well as in neurological inflammations such as Parkinson's disease, Alzheimer's disease, and schizophrenia has been elucidated.[114,115]

Blood-brain barrier malfunction can cause immune cells, including Th17, to enter the brain. The interaction of Th17 cells with microglia via TCR-MHC activates microglia and produces cytokines like IL-1β, TNF-α, and IL-6, followed by the release of oxygen and nitrogen free radicals and oxidative stress. Th17 cells can also cause inflammation and nerve damage in schizophrenia by producing cytokines such as IL-17 and IL-22. Th17 cells, on the other hand, may enter the brain via interaction between CCR6 and related CCL20 ligands, which are primarily produced by choroid plexus epithelial cells. IL-23 may disrupt the blood-brain barrier and facilitate the penetration of Th17 cells into the brain.[110]

There are conflicting results about the role of Th17 cells in schizophrenia. An increase and decrease in Th17 cells in schizophrenia has been reported in several studies. In a study, the number of Th17 cells and the levels of IFN-γ and IL-6 in schizophrenia patients were shown to be higher than in healthy individuals.[116]

In patients with schizophrenia, an increase in Th17 cells and a decrease in the ratio of Th2 to Th17 cells suggest an alteration in cell balance towards an increase in Th17. The ratio of $CD4^+$ to $CD8^+$ cells was not significantly different in these patients.[117]

Activation of TLRs as well as prenatal infection plays a vital part in Th17 cell homeostasis. Prenatal infections can lead to the differentiation of T cells towards Th17 subtype. Th17 activation via a second hit and failure to regulate the Th17 signaling may cause Th17 to penetrate the brain by disrupting the blood-brain barrier. It also activates the microglia cells and subsequently oxidative stress pathways, which may increase the risk of schizophrenia.[118]

Regulatory T Cells

Regulatory T cells (Tregs) are a distinct subtype of $CD4^+$ T cells identified by markers such as CD25 and transcription factors like Foxp3. Treg cells are able to inhibit T cell proliferation through contact-dependent mechanisms and secretion of IL-10 and TGF-β. Treg cells also inhibit immune responses to self-antigens and prevent inflammatory processes.[66,119,120]

In schizophrenia patients without pharmacotherapy, we see a decrease in Tregs because an increase in inflammatory cytokines such as IL-6 along with IL-1 and IL-23 induces the transcription factor RORγt and a decrease in Foxp3, resulting in the secretion of IL-17A. The decreased number of Treg cells and loss of Foxp3 expression can increase the rate of autoimmune diseases so patients with schizophrenia have a 29% increased risk of developing autoimmune diseases. Therefore, an increase in Tregs can be effective as a regulatory response to the inflammatory immune response in patients with schizophrenia.[119,120] Another study showed a significant increase in the proportion of Treg cells in schizophrenia patients under pharmacotherapy.[66]

The Role of B Cells

B cells are part of the specific immune system that is responsible for various functions in the specific immune system. One of the most well-known roles of B cells is antibody production. B cells are able to present antigens to T cells through their MHC-II complex. In addition, they can secrete cytokines and chemokines that are involved in regulating immune responses and tissue repair. Dysfunction of B cells can lead to autoimmune diseases and hyper-inflammation.[9,121]

Furthermore, it has recently been elucidated that there are certain types of B cells involved in the development of the nervous system. B-1a cells which proliferate in the developing brain and mediate the growth of oligodendrocytes, release natural antibodies and are involved in innate immunity. During pathological disorders like spinal cord injury, autoimmune encephalomyelitis, and stroke, B-2 cells release pathogenic antibodies and therefore aggravate the disease.

Besides, regulatory B cells suppress inflammation via IL-10 secretion and play a beneficial role in pathological conditions. Hence, B cells can be involved

in the pathogenesis of schizophrenia. After brain damage, immune cells such as T cells, B cells, neutrophils, and macrophages enter the damaged CNS site. B-cell deficiency improves function after a spinal cord injury. B cells and plasma cells can be found in abundance in the CSF and damaged spinal cord and secrete pathogenic antibodies. Injection of purified antibodies from serum after spinal cord injury leads to movement disorders. Anti-CD20 therapy leads to function improvement after spinal cord injury by suppressing the inflammation.[122] Antigenic mimicry and infection contribute to auto-tolerance breakdown and produce autoantibodies in schizophrenia.[123]

An increase in B cells has been shown in patients with schizophrenia.[124] Self-reactive B cells that have escaped the tolerance mechanisms are able to produce antibodies. The production of such antibodies is known to be a risk factor for schizophrenia. Evidence suggests that neuronal antibodies are involved in only a small percentage of patients with psychosis and schizophrenia.[9]

Currently, there is conflicting data about the involvement of anti-nervous system antibodies in the pathophysiology of schizophrenia. This discrepancy between studies may be partly due to methodological differences, the antibody tests, the diagnosis, and the chronicity of the disease.[125] These autoantibodies can be produced against CNS antigens. The role, function, and position of these antigens are mentioned below.

Central Nervous System Antigens

N-methyl-D-aspartate Receptor

NMDAR is an ion channel with four different subunits located at the surface of neurons. NMDAR consists of a heterotetramer complex that contains two mandatory GluN1 subunits and two GluN2 subunits or a combination of GluN2 and GluN3 subunits. Two duplicate subunits of GLUN1 are produced by the *GRIN1* gene and have 8 isoforms. The GLUN2 gene has 4 isoforms (A-D) and the GLUN3 gene has 2 isoforms (A-B). NMDAR plays a major role in the development and function of the nervous system, synaptic plasticity, and memory formation.[2,126]

Dipeptidyl-peptidase-like Protein 6

Dipeptidyl-peptidase-like Protein 6 (DPPX) is a membrane glycoprotein and an auxiliary subunit of the Kv4.2 potassium channel that is involved in increasing the surface expression of Kv4.2 channels. It is mainly expressed in the hippocampus, cerebellum, and corpus striatum.[127] Kv4.2 and DPPX channels are distributed throughout the nervous and intestinal systems.[128]

The results of a study demonstrated that the presence of antibodies against DPPX leads to a reduction in DPPX clusters and Kv4.2 protein. As a result, patients develop psychological disorders, CNS hypertension, and gastrointestinal symptoms.[129] DPPX antibodies are mainly from the IgG4 subclass. The over-excitability of neurons can be the result of losing the DPPX modulation of potassium current. Most patients with DPPX encephalitis suffered from brainstem malfunction, severe diarrhea, and weight loss. Many patients with DPPX encephalitis have specific gastrointestinal symptoms even before the onset of neuropsychiatric symptoms, which refers to the expression of DPPX in the myenteric network (a network of nerves between the layers of muscular proprioceptors in the gastrointestinal tract).[127]

Voltage-gated Potassium Channels

Voltage-gated potassium channels (VGKCs) are transmembrane channels that return a stimulated cell to rest after each nerve impulse. These channels complex with several other proteins, including leucine-rich glioma-inactivated protein 1 (LGI1) and contactin-associated protein-like 2 (CASPR2). Therefore, these potassium channels along with LGI1 and CASPR2 are involved in the modulation of excitability of neurons in the CNS and peripheral nervous system (PNS).[130]

Leucine-rich Glioma-inactivated Protein 1

LGI1 is a nerve protein secreted by neurons.[128,130] This protein is mainly expressed in the hippocampus and neocortex.[128] It is thought to be involved in fine-tuning synaptic growth and function.[130]

LGI1 binds to membrane proteins containing the metalloproteinase 22 domain (ADAM22) in postsynaptic neurons and to the proteins containing the metalloproteinase 23 domain (ADAM23) in presynaptic neurons, and through the interaction with these two proteins, it forms a bridge between pre- and post-synaptic neurons and plays an important role in synaptic maturation.[128,131]

LGI1 also interacts with postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, postsynaptic density protein 95 (PSD95), and presynaptic potassium channels. By binding to ADAM22, LGI1 regulates synaptic currents mediated by the AMPA receptor in the hippocampus, although the exact details of this process are not known. Anti-LGI1

antibodies disrupt its interaction with ADAM22, reducing the expression of AMPA receptors in postsynaptic neurons, and possibly reducing potassium channel function in presynaptic neurons, leading to neuronal excitability.[128,131]

Contactin-associated Protein-2

The CASPR2 protein is an axonal transmembrane protein. This protein is essential for the clustering of potassium Kv1 channels in myelinated neurons. The anti-CASPR2 antibody can reduce the expression of this channel via internalizing the potassium Kv channel, which leads to excessive release of acetylcholine and increased neuronal excitability.[130,131]

Aquaporin-4

Aquaporin 4 (AQP4) is the most common water channel in the mammalian brain and spinal cord and is expressed in astrocytes throughout the CNS, allowing them to control the homeostasis of water throughout the nervous system by interfering with the diffusion of water across the blood-brain barrier. AQP4 also has remarkable functions in neurotransmission potassium channel activity and potassium homeostasis.[132-134]

AQP4 controls two-way fluid exchange due to its overexpression in the blood-brain barrier and the CSF barrier. Thus, the loss of polarization of AQP4 at the end feet of astrocytes may lead to the failure of the blood-brain barrier.[135] It has also been observed in Parkinson's patients that a deficiency in aquaporin 4 reduces TGF-β, which may be the cause of increased microglia cell activity.[136]

α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid Receptor

The α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) is known to be a gated ion channel composed of GluA 1-4 tetrameric subunits and is a member of the glutamate receptor family. These channels mediate rapid excitatory synaptic transmission, which is essential for learning, memory, and synaptic plasticity. Antibodies target the extracellular domains of GluA1 and GluA2 subunits in AMPAR and reduce AMPAR-mediated current by increasing the channel internalization.[128]

Myelin

The myelin sheath is spirally wrapped all around the nerve cell axon and originates from Schwann cells in the PNS and oligodendrocytes in the CNS and is part of them. When the myelin sheath is intact, nervous signals can be rapidly sent and received. But if for any reason the immune system reacts to myelin as a threat, it produces an immune response to the myelin and the cells that produce it, disrupting the transmission of nervous signals.[137]

Myelin-associated Glycoprotein

Myelin-associated glycoprotein (MAG) is a transmembrane protein expressed on the surface of myelinating oligodendrocytes in the CNS and Schwann cells in the PNS. The interaction of MAG with neuronal gangliosides maintains the myelin-axon distance. The axon myelination increases the conduction speed in the CNS and PNS in vertebrates. Thus, MAG plays an important role in the development and function of the nervous system, and its abnormal function is associated with demyelination and degenerative disorders of the nervous system.[138]

Myelin Oligodendrocyte Glycoprotein

Myelin oligodendrocyte glycoprotein (MOG) belongs to the superfamily of immunoglobulins, which has a variable domain of extracellular immunoglobulin, a transmembrane domain, and a cytoplasmic ring.[139]

MOG is present particularly on the myelin sheath surface in the CNS and is expressed by oligodendrocytes (cells that produce myelin in the central nervous system).[139,140] The expression of MOG begins with myelination, so it is a significant marker for differentiating the maturation of oligodendrocytes and also has a key part in the formation and maintenance of myelin sheaths.[139,140]

Gamma-aminobutyric Acid Receptor

Gamma-aminobutyric acid receptors (GABARs) are inhibitory receptors in the CNS that act through γ-aminobutyric acid mediators (inhibitory neurotransmitters). GABARs are in two forms, type A and type B. GABAR type B is found in the CNS and PNS. G protein-coupled receptors cause long-term reductions in neuronal excitability by inhibiting adenylate cyclase.[128,141]

These receptors modulate the release of neurotransmitters including dopamine, serotonin, and γ-aminobutyric acid, and generate slow inhibitory signals.[142]

Glycine Receptor

Glycine receptors are anion ligand-gated channels in the cerebellum, brainstem, spinal cord, hippocampus, and hypothalamus. These receptors exist in two forms: homopentamer (5 α subunits) or heteropentamer (3 α and 2 β subunits). These subunits are symmetrically located around a chloride-permeable central pore. Glycine can activate glycine receptor inhibitory channels and NMDAR stimulatory channels. Glycine may be released from nervous cells by the alanine-serine-cysteine-1 transporter and astrocyte cells by the Gly Transporter.

Because GlyT1, similar to NMDAR, is at the postsynaptic level, GlyT1 is believed to modulate NMDAR activation by lowering glycine levels in the synaptic cleft. The glycine affinity for NMDARs is significantly higher than that of GlyRs. Therefore, under physiological conditions where both GlyRs and NMDARs are expressed, glycine mainly exerts a stimulating effect. Besides excessive glycine produced during pathological conditions including epilepsy and ischemia can enter the extra-synaptic sites for inhibitory GlyR activation and counteract the damage. Under such circumstances, GlyR-mediated inhibitory function may be more powerful than NMDAR-mediated stimulatory function.[143]

Immunoglobulin-like Cell Adhesion Molecule 5

IgLON5 is a member of the superfamily of cell adhesive molecules (IgLONs) consisting of 3 Ig domains and is attached to the membrane by a glycosyl phosphatidyl inositol.[144,145] IgLONs can be found on the surface of oligodendrocytes and neurons.[145]

IgLONs construct heterophilic and homophilic complexes on the cell surface and regulate the arborization of dendritic, and neurite growth, and the formation of synapses in both the developing and adult brains.[144]

Alpha-7 Nicotinic Acetylcholine Receptor

The alpha-7 nicotinic acetylcholine receptor (α7nAChR) belongs to the nicotinic acetylcholine receptor, which is mostly distributed in the CNS and has five α7 subunits. These receptors are highly permeable to Ca^{2+} ions and bind to acetylcholine to alter the cell membrane permeability, causing rapid signal transduction. These receptors are also involved in learning and memory. α7nAChR has an important role in the auditory gating and dysfunctioned signaling of this channel may result in auditory hallucinations, which is a major symptom of psychotic disorders including bipolar disorder and schizophrenia. *CHRNA7* which is the gene encoding α7AChR is a potential candidate gene in schizophrenia. Some studies have shown that the α7AChR protein is one of the most remarkable medicines in the treatment of Alzheimer's disease and schizophrenia.[146,147]

The Cytokine Profile in Schizophrenia

Schizophrenia is a multifactorial disorder of unknown cause, with impaired immune function, including atypical circulating cytokines levels.[11] The immune response is mainly mediated by cytokines, which are primarily produced by an important member of adaptive immunity, T lymphocytes. These mediators can be divided into 5 groups: 1) pro-inflammatory cytokines which include IL-6, TNF-α, IL-1, and IL-8 families involved in the onset and exacerbation of inflammatory responses; 2) Th1 cytokine, IFN-γ, IL-2, and IL-12, which elicit a pro-inflammatory response and function in autoimmune diseases and defense against intracellular parasites; 3) Th2 cytokines including IL-4, IL-5, and IL-13, which counterbalance the effects of Th1 cytokines 4) Th17 cytokines such as IL-17 and IL-23, which are mainly involved in inflammatory processes and defense against extracellular pathogens; 5) regulatory cytokines including IL-10 and TGF-β, which primarily suppresses immune responses.[148,149]

The involvement of cytokines in schizophrenia was suggested about 30 years ago. Since then, extensive studies have examined the changes in cytokine levels during schizophrenia, the changes after antipsychotic treatment, and their association with clinical signs and symptoms. The data from such research are quite debatable. It is still not clear whether these alterations in the cytokine levels play any part in psychotic symptoms. In addition, the therapeutic and diagnostic consequences of these changes are not determined.[11,150-152]

In this regard, we discuss the most important inflammatory and anti-inflammatory cytokines investigated in schizophrenia patients.

The balanced production of Th1- and Th2-related cytokines plays an important role in immune responses, and their imbalance has a significant impact on the initiation and development of immune-related disorders. In schizophrenic patients, we see an imbalance of Th1 and Th2 responses, a decrease in the level of Th1-related cytokines, and an increase in the level of Th2-related

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cytokines.[153] However, some studies report no evidence of changes in the ratio of Th1/Th2 cytokines in patients with schizophrenia.[154]

However, changes in the level of some cytokines are observed in these patients. The level of IL-1β, which is one of the main pro-inflammatory cytokines and is mainly secreted by monocytes, macrophages, microglia, and lymphocytes,[155] is increased in schizophrenic patients.[92,156,157] Some studies show that the level of IL-1β is related to the severity of symptoms in these patients.[11,158] A decrease in IL-1β levels has been reported in response to treatment with antipsychotics, such as risperidone.[92,156,157,159,160]

In a study, the serum levels of interleukin IL-1β, IL-2, IL-6, TNF-α, and IFN-γ in schizophrenia patients were investigated before and after treatment with risperidone. IL-6, IL-1β, and TNF-α serum levels were significantly higher in patients before treatment compared to after treatment, and IFN-γ and IL-2 levels of schizophrenia patients were significantly lower after treatment compared to before treatment. It appears that alterations in cytokines levels may have an important part in the psychopathology of patients.[161]

So, the improvement of cognitive deficits by minocycline is related to the improvement of patients' negative symptoms and the reduction of IL-1β and IL-6 serum levels. Therefore, the adjunctive treatment of minocycline is effective in improving the cognitive deficits of patients with schizophrenia, and this effect may be due to the inhibition of microglia and the reduction of pro-inflammatory cytokines.[162]

It has also been shown that IL-6 and IL-1β levels decrease shortly after treatment with antipsychotic drugs such as risperidone.[163] However, in the long term, their levels are elevated or remain unchanged. [160,164,165] The increase of IL-6 and Il-1β can be due to the side effects of antipsychotics such as metabolic syndrome during long-term use.[166]

Several studies have been conducted on anti-inflammatory cytokines in schizophrenia patients, among which we mention the most important ones. IL-10 is one of the anti-inflammatory cytokines mainly secreted by activated Tregs, Th2 lymphocytes, and regulatory B lymphocytes.[167] This cytokine helps to decrease the production of reactive oxygen species and oxidative stress.[168] It also reduces the secretion of IFN-γ and IL-2 by Th1 lymphocytes and pro-inflammatory cytokines by macrophages.[155]

There are also contradictions regarding IL-10, both increased levels of IL-10 [156] and unchanged levels were shown in the blood of patients compared to the control group.[169]

A positive relation was reported between IL-10 levels and the severity of negative symptoms, general psychopathology, attention deficit, and aggressive behaviors.[11]

Existing meta-analyses show no effect of antipsychotic drugs on IL-10 levels,[159,160] however, another meta-analysis review showed a reduction in peripheral IL-10 levels in response to antipsychotic treatment.[170]

IL-35 is a member of the IL-12 heterodimer cytokine family.[155] IL-35 is produced by Regulatory B cells (Bregs), Treg Foxp3$^{+,}$ and active dendritic cells.[171,172] IL-35 secreted from Breg cells through the activation of receptors such as (IL-12Rb2 and IL-27Rb) causes the expansion of Breg cells, as well as inducing Foxp3^{+} Treg cells.[171]

IL-35 inhibits Th1 and Th17 cell proliferation. Even though IL-35 can inhibit the proliferation of Th1, the IFN-γ produced by Th1 strongly inhibits the transcription of Ebi3 and p35. IL-35 also inhibits Th2 proliferation by suppressing IL-4 and GATA3 expression. It can also convert Th2 cells to Treg, although this pathway is blocked by IFN-γ. IL-10, like TGF-β and IL-35, can induce induced T regulatory cells (iTregs) proliferation.[171] Thus, it is an inhibitory cytokine and inhibits the functions of the immune system by inhibiting Th17 differentiation and promoting Treg proliferation.[171,172]

Decreased IL-35 expression has been associated with inflammatory diseases such as inflammatory bowel disease, liver fibrosis, myocarditis, encephalomyelitis, and autoimmune disease.[173-176] Administration of rIL-35, IL-35 gene therapy, or IL-35-containing cell transfer may reduce the symptoms of the disease. For example, IL-35þ Tregs transfer reduces the symptoms of colitis, and administration of rIL-35 reduces airway inflammation in allergies and the severity of osteoarthritis.[174,177,178] Similarly, the overexpression of IL-35 protects against acute Graft-versus-host disease (GVHD), myocarditis, and atherosclerosis.[179-181]

The only study that investigated the serum levels of this cytokine in schizophrenic patients indicated a decrease in the level of IL-35 in patients compared to the control group.[182]

Therefore, it is expected that according to the conditions of inflammation in schizophrenia, the

administration of IL-35 may have therapeutic effects in patients, although much research needs to be done. Cytokine-based therapies have had a major impact on our understanding and treatment of a wide range of autoimmune disorders and cancers.[183]

In this regard, identifying the profile of cytokines before a psychotic episode can determine strategies to prevent relapse.

Therapy

In spite of medical approaches, finding a proper treatment for schizophrenia is still challenging, and inadequate results are still very common.[184] Antipsychotic drugs were discovered more than 50 years ago, but dopamine was later shown to have a central role in the clinical effectiveness of these drugs.[18] The dopamine system can be used as a treatment for psychotic symptoms of schizophrenia.[19]

The dopamine D2 receptor is one of the G protein-coupled receptors that has become the most common target for antipsychotic drugs.[185] Thus, all first-line therapies for schizophrenia function primarily via dopamine D2 receptor antagonists.[18] Drugs that target glutamatergic and dopaminergic–related neuropeptides have been suggested as a therapeutic method for schizophrenia.[185] Antipsychotic drugs have also been shown to regulate the HPA axis.[51]

Antipsychotic drugs are very effective in treating the first attack of schizophrenia, and at least 70% to 80% of patients can recover completely in a short time.[186] In general, therapeutic aims for schizophrenia include targeting the symptoms, preventing recurrence, and enhancing the function of the adaptive immune system.[187]

However, only 20% of patients show favorable outcomes following treatment. In the remaining patients, the symptoms become chronic. These patients have a poor response to antipsychotic drugs.[187]

Educating patients about the importance of taking their medications can help improve them. This treatment includes cognitive behavioral therapy.[187]

First-generation antipsychotics act primarily by blocking dopamine D2 receptors while second-generation antipsychotics, with the exception of aripiprazole and brexpiprazole, with dopamine and serotonin antagonism. In addition to the effects of dopamine and serotonin, second-generation antipsychotics have many effects on other receptors, such as alpha-adrenergic, histamine, and cholinergic. They may also have indirect effects on glutamatergic receptors, particularly the NMDA receptor.[188]

Since the discovery of chlorpromazine for the treatment of schizophrenia, studies have focused on dopamine dysfunction in the disease.[185] In refractory patients, clozapine is superior and preferable to first-generation and second-generation antipsychotics.[189] Even among patients with moderate disease, clozapine is superior to second-generation antipsychotics.[184]

Investigating the relationship between biopsychological findings and clinical symptoms of schizophrenia could lead to the development of new pharmacological therapies.[185] In small-scale trials, treatment with NMDAR agonists such as glycine, D-alanine, D-serine, and D-cycloserine was successful. However, in a larger placebo-controlled study, the results for glycine and D-cycloserine were negative.[184]

Since it is an inflammatory disease, using an anti-inflammatory agent to treat schizophrenia may be effective and helpful. Studies on anti-inflammatory factors such as antioxidants, omega-3 fatty acids, minocycline,
and hormonal therapies have shown significant effects in reducing patients' overall symptoms.[7]

Janus kinase inhibitors are safe and effective treatments for rheumatoid arthritis, psoriasis, and inflammatory bowel disease, and may be a promising treatment option for schizophrenia.[7]

Immunotherapy

Immunosuppressive methods include the use of nonsteroidal anti-inflammatory drugs (NSAIDs) (To modulate inflammatory processes), antioxidants, nutrients, vitamins, plant products that inhibit pro-inflammatory processes, and the use of antipsychotic drugs. These drugs can exert anti-inflammatory effects or, in particular cases, like clozapine, would boost poor inflammatory responses and biological factors with specific immune mediators, such as cytokines.[188]

Currently, all antipsychotic drugs approved for the treatment of schizophrenia are anti-dopaminergic agents that in many patients can show varying degrees of therapeutic resistance. Therefore, there is great motivation to explore and identify other effective treatments for schizophrenia.

Treatment with anti-inflammatory agents can be associated with improving the symptoms of psychopathology, and this indicates the

pathophysiological role of inflammation in patients with schizophrenia.[190]

CRP is an acute-phase protein that is synthesized by the liver in response to inflammation and its expression is induced by cytokines, particularly IL-6.[191] This protein can be a very important screening marker for the diagnosis of inflammation in patients with schizophrenia and is suitable for immunotherapies that target IL-6.[7]

Using the antagonist of TNF-α may improve symptoms of treatment-resistant depression in patients with high inflammatory markers.[190] Baseline levels of inflammatory markers in the blood may predict responses to anti-inflammatory therapeutic agents and immunotherapy.[191,192]

In cases where schizophrenia is associated with common immune-related disorders such as autoimmunity, treatments such as cortisone pulse therapy, intravenous immunoglobulins, plasmapheresis, the use of human monoclonal antibodies (such as rituximab), or effective immunosuppressants (such as cyclopean) can be effective.[193]

Monoclonal antibodies have many anti-inflammatory properties compared to other anti-inflammatory agents.[190] The major advantage of monoclonal antibody immunotherapy over anti-inflammatory agents such as NSAIDs is that NSAIDs can have non-specific and off-target effects (e.g., non-immune), but monoclonal antibodies have no off-target effects and only affect specific inflammatory cytokines. NSAIDs have stronger anti-inflammatory properties than other immune modulators such as monoclonal antibodies.[191-194]

NSAIDS, immunotherapy with antibodies, anti-rheumatic agents, neuro-steroids, antioxidants, tetracycline antibiotics, and statins are not considered the key treatments for schizophrenia, but clinical trials have shown that they can play a role in adjunctive therapy in schizophrenia.[195] Experiments have shown that adjunctive therapy with NSAIDs or other anti-inflammatory agents may be associated with improved psychological pathology in patients with schizophrenia.[194]

In cases of resistance to antipsychotic drugs, corticosteroids may be used in combination with plasma exchange or intravenous immunoglobulin, which reduces serum antibody levels and palliates the pathological symptoms in patients.[196]

Monoclonal antibodies also function by directly neutralizing cytokines or cytokine receptors or other molecules involved in the immune system and thus suggest a pathophysiological role for inflammation in schizophrenia.[194,195]

Considering that STAT3 is one of the transcription factors in Th17 cells and the activation of Th17 leads to the recruitment of neutrophils and neutrophilic inflammation. On the other hand, inflammation has been seen in schizophrenic patients. So STAT3 pathway inhibition through inhibition of differentiation to Th17 and inhibition of inflammation is also an important approach to schizophrenia immunotherapy[192] (Table 1).

Table 1. Types of drugs in the treatment of schizophrenia disorder and their targets

The drug target	Possible side effects	Name of drugs	Reference
Dopamine D2 receptor **5-hydroxytryptamine 2A receptor** **Dopamine D1 receptor** **5-hydroxytryptamine 1A receptor** **Alpha-1A adrenergic receptor** **Alpha 1B adrenergic receptor** **Histamine H1 receptor** **potassium voltage-gated channel subfamily H member 2** **Dopamine D1receptor** **Dopamine D3 receptor** **Dopamine D4 receptor** **Dopamine D5 receptor** **5-Hydroxytryptamine 2C receptor** **5-Hydroxytryptamine 2 receptor** **Alpha 1 adrenergic receptors** **Alpha-2 adrenergic receptors** **Muscarinic acetylcholine receptor M1** **Muscarinic acetylcholine receptor M3** **Sphingomyelin phosphodiesterase 1** **Calmodulin** **alpha-1-acid glycoprotein** **5-hydroxytryptamine 6 receptor** **5-Hydroxytryptamine receptor 7** **Histamine H4 receptor**	Drowsiness and sleepiness, xerostomia, increased prolactin levels, glucose intolerance, postural hypotension, weight gain	Chlorpromazine (The first drug used to treat psychosis)	[197]
Dopamine D2 receptor **glutamate ionotropic receptor, NMDA 2B** **Dopamine D1 receptor** **5-hydroxytryptamine 2A receptor** **Dopamine D3 receptor** **melanin-concentrating hormone receptor 1** **Synaptic vesicular amine transporter** **5-Hydroxytryptamine 2C receptor** **Sigma non-opioid intracellular receptor 1** **Histamine H1 receptor** **m3 muscarinic acetylcholine receptor** **Alpha-1A adrenergic receptor** **Alpha-2A adrenergic receptor** **Alpha-2 adrenergic receptor** **Alpha-2C adrenergic receptor** **5-hydroxytryptamine 1A receptor** **5-hydroxytryptamine 6 receptor** **5-Hydroxytryptamine 7 receptor**	Drowsiness and sleepiness, xerostomia, galactorrhea, hypotension, tachycardia	Haloperidol	[198]
Dopamine D1 receptor **Dopamine D2 receptor** **Calmodulin**	Drowsiness and sleepiness, xerostomia, galactorrhea, hypotension, tachycardia	Perphenazine	[199]
Dopamine D2 receptor **Dopamine D1 receptor** **5-hydroxytryptamine 2A receptor**	Drowsiness and sleepiness, xerostomia, galactorrhea, hypotension, tachycardia	Thiothixene	[200]

Table 1. Continued...

Dopamine D2 receptor **Dopamine D3 receptor** **5-hydroxytryptamine 1A receptor** **5-hydroxytryptamine 2A receptor** **5-hydroxytryptamine 2C receptor** **5-Hydroxytryptamine 7 receptor** **Alpha 1 adrenergic receptors** **Histamine H1 receptor** **M1 muscarinic acetylcholine receptor**	Anxiety, constipation, dizziness, headache, insomnia, metabolic changes, nausea, vomiting	Aripiprazole	201
Dopamine D2 receptor **5-hydroxytryptamine 2A receptor**	Constipation, dizziness, headache, metabolic effects, salivation, sedation, tachycardia, weight gain	Clozapine	202
Dopamine D2 receptor **5-hydroxytryptamine A1 receptor** **5-hydroxytryptamine A2 receptor** **5-hydroxytryptamine 7 receptor**	Akathisia, Hyperprolactinemia, Metabolic changes, Nausea, Parkinsonism, Drowsiness	Lurasidone	203
Dopamine D2 receptor **5-hydroxytryptamine A2 receptor** **5-hydroxytryptamine C2 receptor** **Alpha-1A adrenergic receptor** **Histamine H1 receptor** **M1 muscarinic acetylcholine receptor**	Akathisia, constipation, dizziness, hyperprolactinemia, metabolic changes, postural hypotension, weight gain	Olanzapine	204
Dopamine D2 receptor **5-hydroxytryptamine 2A receptor** **Alpha-2A adrenergic receptor**	Hyperprolactinemia, Metabolic changes, Orthostatic hypotension, Priapism, Drowsiness, Weight gain	Paliperidone	205
Dopamine D2 receptor **5-hydroxytryptamine 2A receptor** **5-hydroxytryptamine 2C receptor** **Histamine H1 receptor** **Alpha-1A adrenergic receptor**	Restlessness, dizziness, dry mouth, headache, metabolic changes, postural hypotension, drowsiness, weight gain	Quetiapine	206
Dopamine D2 receptor **5-hydroxytryptamine A2 receptor** **Alpha-2A adrenergic receptor**	Anxiety, hyperprolactinemia, hypotension, insomnia, metabolic changes, nausea, weight gain	Risperidone	207
Dopamine D2 receptor **5-hydroxytryptamine 2A receptor** **5-hydroxytryptamine 1A receptor** **5-hydroxytryptamine 2C receptor** **NET inhibition**	Restlessness, hypotension, metabolic changes, nausea, drowsiness, tachycardia, weight gain	Ziprasidone	208
Glycine reuptake inhibitor	Because treatment with a glycine reuptake inhibitor potentially affects hematopoiesis, the level of hemoglobin and other hematopoietic parameters may be affected.	Bitopertin	188
Glutamate Receptor (NMDA) **5-Hydroxytryptamine Receptor 3** **Cholinergic Nicotinic receptor subunit UA-7** **Dopamine D2 receptor** **Ionotropic glutamate receptor, NMDA 1** **GABA (A)receptor** **Glycine receptors**	Dizziness, headache, constipation, drowsiness, and high blood pressure	Memantine	209

Table 1. Continued...

A selective COX-2 inhibitor that is able to penetrate the CNS and has been tested as a supplement in the treatment of schizophrenia.	Celecoxib has cardiovascular and gastrointestinal risks, and patients taking celecoxib need to have their liver enzymes checked.	Celecoxib	195
A common nonsteroidal anti-inflammatory drug that is much more effective at inhibiting COX-1 than COX-2	Chronic use of high doses of NSAIDs is associated with gastric side effects such as gastrorrhagia.	Aspirin	202
It acts as an antioxidant, anti-inflammatory, and anti-apoptotic agent.	Gastrointestinal side effects, dizziness, skin rash and headache	Minocycline	197
Glutamate Excitotoxicity	Mild abdominal cramps and discomfort, drowsiness, constipation, dizziness, vomiting, increased appetite, nausea, headache, dry mouth	N acetylcysteine	209
5-hydroxytryptamine 2A receptor	Vomiting and abdominal pain	MIN-101	207
5-hydroxytryptamine 3 receptor	5-HT3 receptor-regulating drugs are able to improve cognitive deficits and extrapyramidal side effects.	Ondansetron	188
Acetylcholinesterase **Neuronal acetylcholine receptor subunit alpha-7** **The muscle-type nicotinic acetylcholine receptor** **Cholinesterase**	Gastrointestinal symptoms such as nausea, vomiting, diarrhea, abdominal pain, indigestion, anorexia and weight loss	Galantamine	200
oxytocin receptor agonist	Extrapyramidal side effects	Oxytocin	195

CONCLUSION

Studies have shown abnormalities in the blood-brain barrier, innate immune system, specific immune system, and cytokine profile during schizophrenia. Changes in gene expression of the molecules involved in tight junctions, increased expression of adhesion molecules, and activation of microglia cells can play an effective role in destroying the integrity of the blood-brain barrier and increasing the permeability of brain endothelium. As a result, the disruption of the blood-brain barrier causes the passage of immune cells, inflammatory cytokines, and antibodies from the blood to the brain, which can enhance brain inflammation. In schizophrenic patients, we see an increase in Th2 and Th17 cell responses and a decrease in Th1 and Treg responses. Therefore, schizophrenia is aggravated by inflammatory responses caused by immune cells. However, some cells, such as M2 macrophages, Bregs, and Tregs can reduce immune inflammatory activity in schizophrenia. Therefore, these regulatory factors can be effective as a regulatory response against the inflammatory immune response in schizophrenia patients. Considering the contradictory results about the role of some cells such as Th17 in schizophrenia, there is a need for more studies to determine the exact function of these cells in this disease. In schizophrenic patients, the cytokine profile is inflammatory and unbalanced. These findings indicated that both pro- and anti-inflammatory cytokines can contribute to the clinical and pathophysiological features of schizophrenia.

These considerations show, that a lot of further research is necessary to clarify the role of the immune system in schizophrenia, but recent results including therapeutic progress encourage a further emphasis on this fascinating field.

STATEMENT OF ETHICS

The Ethics Committee of Shahrekord University of Medical Sciences approved this study (IR.SKUMS.REC.1401.094).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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