Review
Pregledni članak

Med Jadert 2024;54(3):203-212
DOI: https://doi.org/10.57140/mj.54.3.7

The role of Toll-like receptors in the etiopathogenesis and treatment of schizophrenia: a literature review

Uloga Toll-like receptora u etiopatogenezi i liječenju shizofrenije: pregled literature

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Summary

In this review paper, we present current theories about the inflammatory etiopathogenesis of schizophrenia. We mentioned the biopsychosocial etiological model of the disease and stressed the importance of neuroinflammation and neurodegeneration in its biological basis.

We searched the literature about innate immunity, Toll-like receptors, inflammation, and neurodegeneration, and we summarized their role in the etiopathogenetic mechanisms of schizophrenia. We also found studies on available antipsychotics that can regulate the expression of Toll-like receptors and modulate innate inflammatory mechanisms. Despite the effective properties of antipsychotics in reducing psychotic symptoms, their role in inflammatory mechanisms remains imprecise and under-researched.

More specific information about how antipsychotics affect neuroinflammation could lead to the development of a wider range of possible drugs that could keep inflammatory processes working properly and improve mental abilities and, ultimately, the quality of life.

Key words: anti-psychotics, immunity, inflammation, neurodegeneration, schizophrenia

Sažetak

U ovom preglednom radu predstavili smo aktualne teorije o upalnoj etiopatogenezi shizofrenije. Spomenuli smo biopsihosocijalni etiološki model bolesti i naglasili važnost neuroinflamacije i neurodegeneracije u njezinoj biološkoj osnovi.

Pretražili smo literaturu o urođenoj imunosti, Toll-like receptorima, upali i neurodegeneraciji, te smo saželi njihovu uloga u etiopatogenetskim mehanizmima shizofrenije. Također smo pronašli i studije o dostupnim antipsihoticima koji mogu regulirati ekspresiju Toll-like receptora i modulirati urođene upalne mehanizme. Unatoč učinkovitim svojstvima antipsihotika u smanjenju psihotičnih simptoma, njihova uloga u upalnim mehanizmima ostaje neprecizna i nedovoljno istražena.

Specifičnije informacije o tome kako antipsihotici utječu na neuroinflamaciju mogu dovesti do razvoja šireg raspona mogućih lijekova koji bi mogli održati ispravnima upalne procese, poboljšati mentalne sposobnosti, a u konačnici i kvalitetu života.

Ključne riječi: antipsihotici, imunitet, upala, neurodegeneracija, shizofrenija

Introduction

Schizophrenia is a severe mental disease that affects a large number of people around the world. According to the World Health Organization, about 24 million people worldwide have this disease, which

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Received/*Primljeno*/ 2024-02-09; Revised/*Ispravljeno* 2024-05-31; Accepted/*Prihvaćeno* 2024-06-11

is about 0.32% of the total world population.[1] The etiology of schizophrenia has not been clarified at the moment. However, many studies show a possibility of multiple factors that confirm the biopsychosocial etiopathogenetic model presented as a combination of genetic vulnerability, impacts from the environment, and various psychological factors.[2] It is assumed that the beginning of this disease dates back to the fetal period. Exposure to infectious diseases, traumas, or dangerous substances during pregnancy can trigger inflammatory reactions that alter fetal brain development, which continues later through synaptogenesis and a flawed disorder of neural connections.[3]

There are many descriptions of a connection between infection, long-term inflammation of the central nervous system (CNS), and schizophrenia. For example, signs of schizophrenia have been observed in cases of encephalitic, viral central nervous system infections caused by the herpes simplex virus, measles, and autoimmune disorders such as lupus erythematosus and scleroderma.[4] The immune system plays a significant role in brain development and the pathophysiology of neurodegenerative diseases such as Alzheimer's, Parkinson's, and multiple sclerosis, as well as in the etiopathogenesis of psychiatric disorders such as schizophrenia, depression, and bipolar affective disorder. Neuroinflammation in neurodegenerative disorders is a pathophysiological mechanism that could explain the pathophysiology of schizophrenia, which involves an innate immune response through the Toll-like receptors (TLRs).[5]

The etiology and pathophysiology of schizophrenia

Schizophrenia seems to be not a single disease but a whole spectrum of disorders with abnormalities in perception of reality, opinion, emotions, and behavior. Although the exact cause of this disorder is unknown, various studies show that it is a state of complex etiology and pathophysiology depending on many psychological, biological, and environmental factors.[6] Various psychological factors, including stress, trauma, and addiction, have been associated with the onset and worsening of schizophrenia symptoms. Much genetic research has resulted in evidence to suggest that individuals with a family predisposition to schizophrenia are at greater risk of developing psychotic disorders.[7]

The environment can also have a significant impact. Various environmental factors have been found to contribute to the prenatal risk of schizophrenia, including viral, bacterial, and parasitic infections; complications during fetal and perinatal development; exposure to stress or trauma; and the misuse of various psychoactive substances.[8] Consequently, these harmful factors can cause changes in neural connections with the manifestation of symptoms of schizophrenia, which are clinically seen in impaired abilities of perception, thought, and behavior.[9] The anti-inflammatory properties of antipsychotics, the therapeutic effects of anti-inflammatory substances, and the genetic, biochemical, and immunological discoveries indicate that inflammation plays a significant role in schizophrenia.[4] Activation of microglia, production of inflammatory factors, and damage to neural connections are associated with the onset and development of psychotic symptoms. TLRs could be involved in these complex processes as part of the innate immune response, which triggers neuroinflammation.[5]

Toll-like receptors

The host's innate immune system is the primary defense against infectious antigens, but tissue damage from noninfectious etiology factors can also trigger an inflammatory response. This system is evolutionarily preserved in various species, from the wine fly to mammals. Compared to the acquired immunity that develops specifically against each infection, the innate immune system's response is considered stereotypical and nonspecific. TLRs play a crucial role in this type of immunity.[10] TLRs belong to the group of pattern recognition receptors (PRRs). They are responsible for detecting molecular samples associated with pathogens, known as pathogen-associated molecular patterns (PAMPs), or with molecular patterns related to tissue damage, known as damage-associated molecular patterns (DAMPs).[11] So far, 13 species of Toll-like receptors have been found in mammals, and 10 have a functional role in humans. The first member of this receptor family, which was discovered in humans, is TLR4. It can recognize lipopolysaccharide (LPS) obtained from the outer membrane of Gram-negative bacteria as a ligand, and its role so far has been most explored in the pathophysiology of schizophrenia.[12] Some TLRs are located on the cell surface, and some are on the endosomal surface within the cell. The cell membranes contain TLR1, 2, 4, 5, and 6. The remaining receptors, TLR3, 7, 8, 9, and 10, are on the endosomal membrane.[13,14] In Table 1, we summarized their characteristics.

In tissue damage,the primary role of TLRs is to initiate the inflammatory process, manage the pain system, preserve the central nervous system, and

Table 1 Toll-like receptors and their characteristics
Tablica 1. Toll-like receptori i njihove karakteristike

Receptor	**Location** *Lokacija*	**Ligand**		**Main role** *Glavna uloga*
		Pathogen-associated molecular pattern *Molekularni uzorak povezan s patogenima*	**Damage-associated molecular pattern** *Molekularni uzorak povezan s oštećenjem*	
TLR1	Cell surface *Površina stanice*	Peptidoglycan *Peptidoglikan* Lipopolysaccharide *Lipopolisaharid*	Unknown *Nepoznat*	Bacterial infection recognition *Prepoznavanje bakterijske infekcije*
TLR2	Cell surface *Površina stanice*	Lipoproteins *Lipoproteini*	Hyaluronic acid *Hijaluronska kiselina* High-mobility group box 1 protein *Grupa 1 proteina visoke mobilnosti* S100 proteins *S100 proteini* Heat shock proteins *Proteini toplinskog šoka*	Immune activation and inflammation *Imunološka aktivacija i upala*
TLR3	Endosomes *Endosomi*	Double-strained DNA from viruses *Dvostruka DNA iz virusa*	Double-strained DNA from damaged cells *Dvostruka DNA iz oštećenih stanica* Mitochondrial DNA *Mitohondrijska DNA*	Viral infection recognition *Prepoznavanje virusne infekcije*
TLR4	Cell surface *Površina stanice*	Lipopolysaccharide *Lipopolisaharid*	Heat shock proteins *Proteini toplinskog šoka* S100 proteins *S100 proteini* Fibrinogen Hyaluronic acid *Hijaluronska kiselina*	Bacterial infection recognition *Prepoznavanje bakterijske infekcije* Tissue damage recognition *Prepoznavanje oštećenja tkiva* Pain modulation *Modulacija boli*
TLR5	Cell surface *Površina stanice*	Flagellin *Flagelin*	Unknown *Nepoznat*	Bacterial infection recognition *Prepoznavanje bakterijske infekcije*
TLR6	Cell surface *Površina stanice*	Diacyl lipoprotein *Diacil-lipoprotein*	Unknown *Nepoznat*	Bacterial infection recognition *Prepoznavanje bakterijske infekcije*
TLR7	Endosomes *Endosomi*	Single-strained RNA from viruses *Jednostruka RNA iz virusa*	Endogenous RNA *Endogena RNA*	Viral infection recognition *Prepoznavanje virusne infekcije*

Receptor	Location *Lokacija*	Ligand		Main role *Glavna uloga*
		Pathogen-associated molecular pattern *Molekularni uzorak povezan s patogenima*	**Damage-associated molecular pattern** *Molekularni uzorak povezan s oštećenjem*	
				Neurodegeneration *Neurodegeneracija*
TLR8	Endosomes *Endosomi*	Single-strained RNA from viruses and bacteria *Jednostruka RNA iz virusa i bakterija*	Endogenous RNA *Endogena RNA*	Bacterial and viral infection recognition *Prepoznavanje bakterijske i virusne infekcije* Neurodevelopment *Neurorazvoj* Neurodegeneration *Neurodegeneracija*
TLR9	Endosomes *Endosomi*	CpG-DNA fragments from viruses, bacteria, and protozoa *CpG-DNA fragmenti iz virusa, bakterija i praživotinja*	Genomic DNA from necrotic and apoptotic cells *Genomska DNA iz nekrotičnih i apoptotskih stanica*	Infection recognition *Prepoznavanje infekcije* Neuroplasticity *Neuroplastičnost*
TLR10	Endosomes *Endosomi*	Unknown *Nepoznat*	Unknown *Nepoznat*	Anti-inflammatory *Protuupalni*

maintain the organism's internal stability, whether the stimulus is caused by molecular samples associated with damage or exogenous ligands associated with pathogens.[15] They trigger an inflammatory response through the synthesis of cytokines, interferon, and chemokines such as interleukin 1 (IL-1), IL-6, and tumor necrosis factor-alpha (TNF-α).[16] TLRs can recognize different PAMPs. TLR4 specifically recognizes ligands derived from gram-negative bacteria. TLR1, 2, 5, and 6 can identify specific regions of other bacterial species, while TLR3, 7, 8, and 9 specifically recognize genetic material from the viruses.[14] The ligand of TLR10 is unknown, and this type of receptor is different from other TLRs in its function because it has anti-inflammatory effects.[13] In addition to PAMPs, TLRs can also recognize DAMPs, which are naturally found in the body during tissue damage,such as heat shock proteins (HSPs), high-mobility group box 1 protein (HMBG1), S100 proteins, hyaluronic acid, fibrinogen, and broken parts of genetic materials.[5,17]

Toll-like receptor expression in schizophrenia

The potential immunological mechanisms in the etiopathogenesis of schizophrenia were observed in the 1920s after the pandemic of Spanish flu. Some patients showed symptoms of psychosis after the flu, although they had been mentally healthy before the pandemic.[18] Subsequently, the notion of virus-induced psychosis became widely accepted, along with a multitude of additional diseases caused by bacteria and parasites that have the possibility of causing psychotic symptoms, especially after fetal infection during pregnancy. Examples of infectious agents associated with the development of schizophrenia are the herpes simplex virus (HSV), the Epstein-Barr virus (EBV),[19]*Treponema pallidum*,[20] and *Toxoplasma gondii*.[21] Recent research shows that the immune system and its various components, including cytokines, C-reactive protein, chemokines, and antibodies, may play a role in determining vulnerability to schizophrenia.[22] Studies have identified different features of Toll-like receptors in patients with schizophrenia compared to healthy control groups. In Table 2, we summarized the features of TLRs in patients with schizophrenia.

Individuals diagnosed with schizophrenia showed increased inflammatory reactions to peripheral stimulation of TLRs. IL-6 and TNF-α were released in large quantities when the blood of schizophrenia patients was exposed to TLR2 and TLR4 agonists *in vitro* relative to the control healthy group.[23]

Table 2 Features of Toll-like receptors in schizophrenia
Tablica 2. Značajke Toll-like receptora u shizofreniji

Reference/*Izvor*	**ExaminedToll-like receptors** *Istraženi Toll-like receptori*	**Features**/*Značajke*
Mantovani et al. 2019 *Mantovani i sur. 2019.*	TLR2 and 4 *TLR2 i 4*	Proinflammatory cytokines were released in high amounts in schizophrenia patients' blood when exposed to agonists of Toll-like receptors in vitro compared to healthy controls. *Proupalni citokini otpuštani su u velikim količinama u krvi bolesnika sa shizofrenijom kada su bili izloženi agonistima Toll-like receptora in vitro, u usporedbi sa zdravim kontrolnim ispitanicima.*
Muller et al. 2012 *Muller i sur. 2012.*	TLR4	Schizophrenia patients' monocytes expressed more Toll-like receptors than those of the healthy control group. *Monociti bolesnika sa shizofrenijom izražavaju više Toll-like receptora od monocita u zdravih kontrolnih skupina.*
Murphy et al. 2021 *Murphy i sur. 2021.*	TLR4	Schizophrenia patients exhibit higher levels of Toll-like receptors and proinflammatory cytokines in the prefrontal cortex. *Bolesnici sa shizofrenijom pokazuju više razine Toll-like receptora i proupalnih citokina u prefrontalnom korteksu.*
McKernan et al. 2011 *McKernan i sur. 2011.*	TLR2,4 and 8 *TLR2,4 i 8*	Stimulating the entire blood with ligands for Toll-like receptors in schizophrenia patients led to more increase of proinflammatory cytokines than in the healthy control group. *Stimuliranje cijele krvi ligandima za Toll-like receptore u bolesnika sa shizofrenijom dovelo je do većeg povećanja proupalnih citokina nego u zdravoj kontrolnoj skupini*.
Zhu et al. 2010 *Zhu i sur. 2010.*	TLR4	The lack of Toll-like receptor 4 in rats increased hippocampal nerve stem and progenitor cell proliferation and differentiation. *Nedostatak Toll-like receptora 4 u štakora povećao je proliferaciju i diferencijaciju hipokampalnih živčanih ogranaka i progenitorskih stanica.*
Prata et al. 2017 *Prata i sur. 2017.*	TLR2	Neonatal mice with Toll-like receptor stimulation had less gray and white matter, fewer hippocampus neurons, and more microglial cells. *Neonatalni miševi sa stimulacijom Toll-like receptora imali su manje sive i bijele tvari, manje neurona hipokampusa i više mikroglijalnih stanica.*
Kozlowska et al. 2019 *Kozlowska i sur. 2019.*	TLR1,2,3,4,5,6,7,8 and 9 *TLR1,2,3,4,5,6,7,8 i 9*	Schizophrenia patients express different amounts of Toll-like receptors than healthy people. *U bolesnika sa shizofrenijom eksprimiraju se različite količine Toll-like receptora nego u zdravih osoba.*
Juncal-Ruiz et al. 2020 *Juncal-Ruiz i sur. 2020.*	TLR5 and 8 *TLR5 i 8*	Decreased expression of Toll-like receptors 5 and 8 in persons with the first episode of psychosis compared to healthy control group. *Smanjena ekspresija Toll-like receptora 5 i 8 u osoba s prvom epizodom psihoze u usporedbi sa zdravom kontrolnom skupinom.*
Ademe et al. 2022 *Ademe i sur. 2022.*	TLR4	Schizophrenia patients have elevated peripheral immune system Toll-like receptor 4 expression and activity and often have gastrointestinal problems. *Bolesnici sa shizofrenijom imaju povišenu ekspresiju i aktivnost perifernog imunološkog sustava Toll-like 4 receptora i često imaju gastrointestinalne probleme.*
Kéri et al. 2017 *Kéri i sur. 2017.*	TLR2,4 and 5 *TLR2,4 i 5*	Toll-like receptor expression is increased in both unmedicated and treated patients with schizophrenia. Antipsychotic therapy upregulates Toll-like receptor 2 but downregulates Toll-like receptor 4 expression. *Ekspresija Toll-like receptora povećana je i u neliječenih i u liječenih bolesnika sa shizofrenijom. Antipsihotici povećavaju Toll-like receptor 2, a smanjuju Toll-like receptor 4 ekspresiju.*

A study conducted by Muller et al. 2012 found that the monocytes of patients diagnosed with schizophrenia showed increased levels of TLR4 expression compared to the control group.[24] Several studies have shown that patients with schizophrenia show altered levels of proteins and mRNA for TLRs compared to people without mental disorders. The researchers studied the brains of people who died and found that mRNA levels were altered due to genes involved in innate immunity. For example, tlr4 mRNA, as well as il6, il10, and tnf-α mRNA, are increased in the prefrontal region of the brain by people with schizophrenia.[25] On the other hand, some studies confirm increased levels of DAMPs in patients with schizophrenia,as they areS100 proteins and extracellular double-strand DNA from apoptotic cells.[26,27] A study by McKernan et al. 2011 observedan increased level of IL-1, IL-6, and TNF-α when ligands for TLR2 stimulate the whole blood of people with schizophrenia than in the healthy control group. However, only the level of IL-1 was increased after the TLR4 and TLR8 stimulation. They concluded that there is a difference in the manifestation of TLRs in people with schizophrenia and the healthy population, as well as in the response of TLRs to different ligands. They supposed that immune response could vary during the various stages of the disease, and for now, there is insufficient data to determine its exact function in the etiopathogenesis of schizophrenia.[12]

Several studies have shown that TLRs are present during brain development, affecting neurons' growth and establishing synapses. Certain types of TLRs can stop the process of cortical neurogenesis and the creation of neural connections, which can lead to behavioral problems in children and the consequent development of psychotic symptoms.[28] In addition, the absence of TLR4 in rats increased the proliferation and differentiation of the nerve stem and progenitor cells in the hippocampus.[12] The stimulation of TLR2 led to a decrease in gray and white matter, a decrease in hippocampal neuronal concentrations, and an increase in the number of microglial cells in the brains of neonatal mice. Similar pathological characteristics of the brain may be observed in patients with schizophrenia.[29] The study conducted by Kozlowska et al. in 2019 concluded that individuals with schizophrenia exhibit distinct levels of peripheral blood mononuclear cell (PBMC) expression for most of the examined TLRs compared to healthy individuals. In patients with schizophrenia, TLR1,2,4,6, and 9 expressions were decreased, while TLR3 and 7 showed increased expression. The mRNA levels for TLR5 and 8 were similar in both groups and showed no significant differences.[30]

The study by Juncal-Ruiz in 2020 examined the PBMCs of people with first-episode psychosis without psychiatric medicines in therapy and compared them to those of healthy volunteers. At the beginning of the trial and after three months of antipsychotic treatment, the findings emphasized the potential involvement of TLR5 and TLR8 in the pathophysiology of psychosis. It was observed that a decreased expression of these receptors in persons with the first episode of psychosis compared to healthy volunteers, both at the beginning and after three months of therapy. Most TLRs exhibited diminished functionality, as seen by dramatically decreased intracellular levels of TNF-α in patients with schizophrenia compared to healthy volunteers. The results of this study indicate that persons with psychosis may exhibit a distinct pattern of TLR expression compared to healthy volunteers, which could vary depending on the degree of the immune/inflammatory response.[31]

Studies in animal models show that infections that occur before and during birth significantly affect the activation of the mother's immune system and oxidative stress. The activation of TLRs through infection affects the immune response in the mother and fetus and can damage brain development. These disorders can result in behavioral problems in offsprings.[15]

The inflammatory etiopathogenetic theories of schizophrenia also fit the concept of "increased digestive permeability" in neuropsychiatric diseases, which is based on elevated intestinal permeability, leading to the entry of bacteria into the blood and activation of TLR4.[17,32] Patients with schizophrenia have shown increased expression and activity of TLR4 in their peripheral immune system and often encounter gastrointestinal problems such as hypersensitivity to gluten or casein. In addition, antibodies to *Toxoplasma gondii* are usually present in these patients.[33] Modern theories that connect the digestive system to schizophrenia say that the changes in the microbiome make the intestinal barrier less effective, and that causes microorganisms or their components, such as LPS, to move from the intestines to other parts of the body, triggering the immune system's response and causing schizophrenia symptoms.[34]

Toll-like receptor expression in response to antipsychotics

Antipsychotics work by modulating the activities of neurotransmitters in the brain.[35] However, some of them may also affect the immune system by altering the activity of TLRs,[36] as we summarized in Table 3.

Table 3 Antipsychotics that can change the expression of Toll-like receptors
Tablica 3. Antipsihotici koji mogu promijeniti ekspresiju Toll-like receptora

Receptor	**Inflammation modulating agent** **Modulirajući agent upale**	**Reference/Izvor**
TLR1	No data/*Nema podataka*	No data/*Nema podataka*
TLR2	Chlorpromazine↑ *Klorpromazin*↑	Gandhi et al.2012 *Gandhi i sur.2012.*
	Clozapine↓ *Klozapin*↓	Park et al. 2015 *Park i sur. 2015.*
	Olanzapine ↑ *Olanzapin*↑	Kéri et al.2016;Da Silva et al.2017 *Kéri i sur.2016;Da Silva i sur.2017.*
	Risperidone↑ *Risperidone*↑	Kéri et al. 2016 *Kéri i sur. 2016.*
TLR3	Fluphenazine↓ *Flufenazin*↓	Zhu et al. 2010 *Zhu i sur. 2010.*
	Paliperidone↓ *Paliperidon*↓	MacDowell et al.2016 *MacDowell i sur. 2016.*
	Clozapine↓ *Klozapin* ↓	Reisinger et al. 2015/ *Reisinger i sur. 2015.*
	Olanzapine ↓ *Olanzapin*↓	Li et al. 2021 *Li i sur. 2021.*
TLR4	Paliperidone ↓ *Paliperidon*↓	MacDowell et al. 2014 *MacDowell i sur. 2014.*
	Risperidone↓ *Risperidon*↓	Kéri et al. 2016; Feiner et al. 2019 *Kéri i sur. 2016;* *Feiner i sur. 2019.*
	Olanzapine↓ *Olanzapin*↓	Kéri et al. 2016 *Kéri i sur. 2016.*
	Olanzapine↑ *Olanzapin*↑	He et al. 2020 *He i sur. 2020.*
	Fluphenazine↓ *Flufenazin*↓	Zhu et al. 2010 *Zhu i sur. 2010.*
	Chlorpromazine↑ *Klorpromazin*↑	Gandhi et al. 2012 *Gandhi i sur. 2012.*
	Clozapine↓ *Klozapin*↓	Jeon et al. 2017 *Jeon i sur. 2017.*
TLR5	No data/*Nema podataka*	No data/ *Nema podataka*
TLR6	No data/*Nema podataka*	No data/ *Nema podataka*
TLR7	Fluphenazine↓ *Flufenazin*↓	Zhu et al. 2010 Zhu i sur. 2010.
TLR8	Fluphenazine↓ *Flufenazin*↓	Zhu et al. 2010 Zhu i sur. 2010.
TLR9	Olanzapine↑ *Olanzapin*↑	Zuo et al. 2023 Zuo i sur.2023.
TLR10	No data/*Nema podataka*	No data/ *Nema podataka*

↑=Increases expression of Toll-like receptors/ ↑=*Povećava ekspresiju Toll-like receptora*
↓=Decreases expression of Toll-like receptors/↓=*Snižava ekspresiju Toll-like receptora*

In a study by McDowell et al. from 2014, TLR4 was associated with the pharmacological processes involved in the treatment of schizophrenia. Studies have shown that the antipsychotic paliperidone controls TLR4 activation in rats by reducing blood LPS levels, relieving schizophrenia symptoms, and thus stopping the presence of molecular samples associated with TLR4 activation.[37] In 2016, McDowall et al. conducted a new study that demonstrated how the immune system can be triggered before birth to induce brain damage in mice, similar to in patients with schizophrenia. They activated TLR3 using viral mimic samples injected into pregnant mice. Both adult mothers and their

infants had an activated innate signaling pathway through TLR3, proinflammatory mediators, and increased oxidative stress levels. Prolonged paliperidone injections effectively suppressed the neuroinflammatory system and oxidative stress. Furthermore, paliperidone successfully reduced the spatial working memory loss shown in this animal model of schizophrenia. Researchers found that giving young adult mice paliperidone regularly, while they were still developing and exposed to immune stimulants during pregnancy, protected them against inflammation and oxidative damage.[38]

In support of these studies, there is also a study on human liposarcoma cells that express TLR4. When stimulated by LPS, there was an increase in the level of proinflammatory cytokines, but when the antipsychotic risperidone was added, a minor expression of proinflammatory cytokines mRNA was observed. Similar effects risperidone could have on neuroinflammation are not surprising because the risperidone metabolite paliperidone is known to reduce neuroinflammation.[39] The study conducted by Kéri et al. in 2016 found that alterations in TLRs in individuals with schizophrenia are not specific to particular cell types. The study found that TLR5 expression went up in both untreated and treated cases of the disease, and TLR2 expression went up in response to antipsychotic treatment. No significant differences were observed between olanzapine and risperidone regarding TLR2 expression. The down-regulation of TLR4, which is connected to antipsychotic medication, exhibited an opposite change in direction compared to TLR2.[36]

Olanzapine inhibits the activation of TLR3, which is known to play a crucial role in the development of inflammatory disorders such as sepsis and rheumatoid arthritis. Thus, inhibition of TLR3 activation may have beneficial effects in preventing the development of these disorders, but it may impair the immune response to viral infections.[40] In the central nervous system, olanzapine, through TLR4, is thought to activate astrocytes in the hypothalamus and thus trigger an inflammatory cascade that increases hunger sensation and food intake, which is a widespread side effect of this very effective antipsychotic.[41] In addition to the activation of TLR4, olanzapine may also affect the activity of TLR2 and 9. The activation of TLR2 may promote a dipogenesis and insulin resistance, while TLR9 has been shown to promote inflammation and insulin resistance.[42] Chlorpromazine has also been found to stimulate an inflammatory response in peripheral cells through TLR2 and 4.[43]

A study by Zhu et al. in 2010 observed that fluphenazine directly inhibits the innate immune signaling system and the induction of neuroinflammatory processes through TLR3, 4, 7, and 8. As TLR3,7, and 8 are endosomal receptors, they stop the neuroinflammatory process; however, they go through different pathways compared to the TLR4 found on the cell surface.[10]

Some studies have shown that clozapine can inhibit the activation of TLR2, 3, and 4, reducing the production of proinflammatory cytokines.[44] Inhibition of TLR4 activation leads to both beneficial and harmful consequences. The modulation of TLR activity by clozapine has implications for the immune response to infections and inflammatory disorders. At the same time, the inhibition of TLR activation may have beneficial effects in preventing the development of sepsis and other inflammatory and neuroinflammatory disorders such as schizophrenia and Alzheimer's disease. On the other hand, it may also increase the risk of chronic inflammatory disorders by impairing tissue repair and the clearance of damaged cells. It may increase the risk of infections and malignancies associated with the long-term use of clozapine.[45,46]

The expression and activity of TLRs may vary depending on the stage of the disease and the use of antipsychoticsthat can modulate inflammatory processes. For now, we can suppose that higher cytokine levels in patients with schizophrenia are a result of changes in TLR function, which may start with damage during neurodevelopment.

Conclusion

The neurodevelopmental and neuroinflammatory theories of schizophrenia are currently an important area in the pathophysiology of mental disorders. Numerous studies have found that the expression of TLRs is associated with neurodegenerative diseases in which inflammation plays a significant role. Some studies have been conducted on the role of the immune response in schizophrenia and the association of TLRs with neuroinflammatory processes. Some of them could be more consistent and clear, possibly due to the many different tissues and parts of the body in which they were investigated. For now, the importance of TLR2 and 4 in schizophrenia is particularly emphasized, as they have been more clearly researched than other TLRs. Available evidence presenting the involvement of TLRs in the etiopathogenesis of schizophrenia remains limited and requires further research. Antipsychotics may inhibit the activity of TLRs, reducing the production of proinflammatory cytokines and improving the quality of life. However, long-term use of antipsychotics can inhibit TLR

activation and change the innate immune response. Obtaining more concrete results could increase the range of potential pharmacological approaches to maintaining the proper functioning of the inflammatory processes for optimal mental capacities and improve the overall quality of life of patients with schizophrenia.

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