



Literature Review

Neuroinflammation in Schizophrenia

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Abstract

Schizophrenia is a chronic debilitating mental illness. In many aspects, the neuropathology of schizophrenia is closely associated with neuroinflammation, especially microglial activation. Microglial hyperactivity, which is characterized by the predominant release of proinflammatory cytokines serves as the basis of the neuroinflammation hypothesis in schizophrenia. The enhanced inflammatory induce neuronal susceptibility to oxidative stress and trigger, glutamatergic synaptic dysregulation, especially in the mesolimbic and mesocortical pathways. Many *in vitro* studies, *in vivo* animal evidence, *post-mortem examinations*, neuroimaging evaluations with Positron Emission Tomography (PET), anti-inflammatory and antipsychotic use converge upon the central role of microglial activation and proinflammatory cytokines as common of features schizophrenia.

INTRODUCTION

Schizophrenia is a chronic brain disease whose underlying pathophysiology remains elusive. The anatomical structure and functioning of the living human brain can be studied using indirect techniques, whereas direct microscopic and molecular characterization can be achieved using only human post mortem brain tissue [1]. Associations between psychiatric diseases and immune system dysfunctions have been postulated more than 100 years ago and have remained a matter of discussion ever since [2]. While several studies since then have not supported these findings, more recent studies suggest that different types of glia may play a role in the pathology of schizophrenia [1]. The hypothesis that the neuroimmune system plays a role in the pathogenesis of different psychiatric disorders, including schizophrenia, has attained increasing interest over the past years [2].

IMMUNE-RELATED HYPOTHESIS ON SCHIZOPHRENIA: EARLY CLINICAL FINDING

Immune-related theories about the etiology of schizophrenia have grown in popularity, implying that inflammation and autoimmunity may play a role in the pathogenesis of schizophrenia in some patients. Furthermore, genetic studies have repeatedly found links between schizophrenia and unique immune parameters, implying that genetically susceptible people are more likely to develop schizophrenia as a result of inflammation and immune components influencing the brain. Increased levels of cytokines and inflammation markers have been found in people with schizophrenia, among other immune changes. In studies of patients with schizophrenia, abnormalities of the blood-brain barrier have been discovered, along with symptoms of central nervous system (CNS) inflammation. Some infections that affect the mother during pregnancy are known to affect the fetus or newborn's growth or development, including the brain. *Toxoplasma gondii*, rubella virus, cytomegalovirus (CMV), and herpes simplex viruses, collectively known as the TORCH agents, are the most well-known agents with such teratogenic properties. Neurogenesis and neuronal migration in the developing cortex are largely complete by birth in terms of neurodevelopmental processes. The postnatal phase is marked by rapid development, which is mainly characterized by glial cell proliferation and differentiation, synapse formation, and myelination, with the human brain reaching 90–95% of its adult volume by the age of two. Mednick *et al.* stated in their seminal article published in 1988 that offspring of pregnant women who were exposed to the 1957 influenza A virus outbreak in Helsinki had a higher risk of developing schizophrenia than offspring of women who were pregnant during years when the same flu strain was not present in the population. Furthermore, multiple reports showed the incidence of post-influenza psychosis and schizophrenia-like symptoms shortly after the 1917 influenza pandemic [2]. The genome-wide association study (GWAS), which established a genetic basis for schizophrenia, conducted a large-scale meta-analysis with 36,989 cases and 113,075 controls, resulting in the identification of 100 schizophrenia-related loci, indicating that genes in the calcium signalling pathway are crucial. *CACNA1C* and *CACNA1* are the

signalling proteins in question [3]. Large-scale GWAS studies have consistently implicated chromosome 6 in the HLA region as the most important genome-wide association with schizophrenia in GWAS studies of schizophrenia patients [2]. The immune hypothesis is based on the idea of a genetic disturbance that causes a chain reaction, increasing the risk of psychosis. The seminal paper describing 108 genetic "hits" for schizophrenia also found a significant correlation between genes involved in immune function. As Pouget explained in his review article, this sparked interest in immune-related genes and schizophrenia [3].

MICROGLIAL ACTIVATION AND SCHIZOPHRENIA

Microglia and inflammation markers

While glial involvement in schizophrenia has long been suspected, the extent to which it contributes to the disease's pathology has remained unknown. Microglia are a type of glial cell. Microglia are immune cells that originate in the central nervous system and are responsible for synaptic pruning during development as well as serving as the primary mediators of nerve inflammation [3], [4]. Microglia preserve 'a silent' phenotype in a healthy brain, in which an expanding process spreads through the local environment to detect changes in the environment. Microglia cells produce neurotrophic factors, provide axonal guidance, and control local cell proliferation at this level. Inflammatory stimuli, on the other hand, cause the cells to become activated, undergo morphological changes, and release proinflammatory cytokines [5]. Ramified microglia actively search the entire brain for bacteria or debris under normal physiological conditions. When microglia detect a danger, they rapidly change their phenotype, morphology, and function, which is known as 'microglia activation.' To facilitate migration to the pathogen site, activated microglia take on an amoeboid morphology, with swollen cell bodies and short processes. Microglia contain both neurotoxic and neuroprotective substances. As a result, some authors characterize this cell population as a two-edged sword [6]. Microglial activation has been linked to the binary activation profile of peripheral monocytes, which is characterized by M1/M2 phenotypes. TNF-, IL-6, IL-1, ROS, and glutamate are released by M1 microglia in response to inflammation, while M2-type microglia serve to overcome the inflammatory response and express IL-4, IL-13, IL-25, IL-1ra, insulin-like growth factor 1 (IGF1), BDNF, and COX1 [7]. Proinflammatory cytokines such as IL-1, IL-6, and TGF- were found to be elevated in patients with first episodes of psychosis and relapse schizophrenia, whereas successful treatment reduces these inflammatory markers. Furthermore, the meta-analysis of 16 studies published in 2018 by Wang *et al* reported that CSF levels of IL-1 β , IL-6 and IL-8 were significantly elevated in schizophrenia patients compared with controls.

Additionally, the decreased levels of the antioxidant, glutathione (GSH), have been reported in patients with acute psychosis compared with controls. Negative symptoms have been associated with low levels of GSH, and positive symptoms have been positively correlated with SOD activity [2]. Oxidative stress occurs in new-onset as well as chronic schizophrenia. Oxidative stress markers are found in peripheral blood, neutrophils, red blood cells, platelets, cerebrospinal fluid (CSF), and brain tissue [8].

Bodies of neuroimaging studies support the possible contribution of enhanced microglial activity in schizophrenia pathology. Neuroinflammation can be measured using PET with ligands for translocator protein (PK-11195), which is highly expressed by activated microglia and thus, a sensitive measure for estimating microglial activation in the CNS [9]. Studies have found greater binding of PK11195 in schizophrenia. Furthermore, another PET study using DAA1106 as the measure of pro-inflammatory microglial activation, indicated that the radiotracer binding correlated with the duration of the disease. However, it should be mentioned that the results of PET studies in schizophrenia are inconsistent [7], [10]. Stages of schizophrenia (e.g., first vs. chronic episodes), drugs, and other interfering factors may all play a role in the contradictory results [7], [10], [11]

Enhanced neuroinflammation triggers glutamate and dopamine dysregulation

Kindling, also known as "sensitization," is a mechanism in which an initial immune response to a stimulus, such as stress or infection, decreases the response threshold for subsequent responses to the same stimulus, resulting in a greater immune response or cytokine release than when the stimulus was first presented. Animal studies were used to investigate the processes underlying stress and inflammation susceptibility models, and stress was consistently linked to higher levels of proinflammatory cytokines [8], [12]

Psychotic episodes in schizophrenia are associated with inflammatory processes connected to the hypothalamic-pituitary stress-inflammatory pathways, according to this theory. Microglia and astrocytes become activated as a result of this. Interestingly, the latter is linked to increased kynurenic acid (KYNA) development in the cerebrospinal fluid and activation of the kynurenine pathway (CSF). The only recognized natural N-methyl-D-aspartate (NMDA) receptor antagonist involved in inflammatory processes is this metabolite. Because of KYNA's antagonistic impact on the glutamatergic system, dopaminergic neurons become dysregulated [13].

Other additional effects of neuroinflammatory hyperactivation are the enhanced neural oxidative stress and the activation of arachidonic acid pathways. The oxidative radicals are triggered by the activation of NMDA receptors through glutamate. Glutamate is actively taken up into astrocytes and converted into glutamine. Changes in glutamine increase calcium entry into neurons, which can contribute to excitotoxicity and alter nerve transmission via NMDA antagonism. The glutamatergic imbalance leads further to ROS and RNS, leading to DNA, protein and lipid breakdown, in situations where oxidative defences are already vulnerable [14].

Anti-inflammatory therapy in schizophrenia

The discovery that anti-inflammatory medications may help people with schizophrenia may be the most compelling evidence yet that inflammation plays a role in the disease. Inhibitors of cyclooxygenase (COX) are the subject of this overview. Celecoxib, a COX-2 inhibitor, is the most studied COX inhibitor. Patients with a disease period of fewer than two years gained from the addition of celecoxib, whereas those with a longer disease duration did not vary from the placebo community. These results indicate that COX-2 inhibitor

therapy for schizophrenic patients is most effective in the early stages of the disorder. Studies that have found little benefit to this hypothesis back up this theory. Another anti-inflammatory agent, acetylsalicylic acid (ASA), has also been shown to help people with schizophrenia. A meta-analysis of five double-blind trials of nonsteroidal anti-inflammatory drugs in schizophrenia (four celecoxib studies and one ASA study) showed that the medication had a beneficial effect on overall symptoms as well as positive and negative symptoms (four celecoxib studies and one ASA study). A meta-analysis of eight studies (six on celecoxib and two on ASA) found that patients with first psychotic episodes and stable chronic schizophrenia benefited the most from these interventions [11].

CLINICAL IMPLICATIONS OF NEUROINFLAMMATION IN SCHIZOPHRENIA

The role of glutamate dysregulation in mesolimbic systems impact positive symptoms.

Positive signs of schizophrenia are linked to dopamine hyperactivity in these downstream mesolimbic dopamine neurons [15]. However, disconnectivity in upstream glutamate neurons, i.e. weakened and hypofunctional glutamate internal GABA innervation nerves containing GABA receptors on NMDA receptors containing synapses, is thought to be the cause of this downstream impact. It's also conceivable that, through a four-neuron circuit, the disconnectivity of upstream glutamate neurons in the hippocampus leads to downstream mesolimbic dopamine hyperactivity. To control dopamine, glutamate brainstem projections interact with mesolimbic dopamine pathways in the ventral tegmental region (VTA) The cortical brainstem pathway to VTA will be overactive if the NMDA receptor on cortical GABA interneurons is hypoactive, resulting in excessive glutamate release in VTA. The mesolimbic dopamine pathway would be overstimulated, resulting in excessive dopamine release in the nucleus accumbens. The ventral hippocampus's hypofunctional NMDA receptors at glutamatergic synapses can also lead to mesolimbic dopamine hyperactivity. Glutamate released in the ventral hippocampus binds to the NMDA receptor on GABAergic interneurons, causing GABA release to be stimulated. GABA binds to glutamate receptors on glutamate pyramidal neurons that project to the nucleus accumbens, inhibiting glutamate release. The absence of glutamate in the nucleus accumbens allows normal activation of the globus pallidus-projected GABAergic neurons, which in turn allows normal activation of the GABAergic neurons in the ventral tegmental region (VTA). As a consequence, the dopamine mesolimbic pathway from the VTA to the nucleus accumbens is activated normally. The glutamatergic pathway to the nucleus accumbens would be overactive if the NMDA receptors on the ventral hippocampal GABA interneurons are hypoactive, resulting in excessive glutamate release in the nucleus accumbens. Overstimulation of GABAergic neurons projecting to the globus pallidus will result, which will prevent GABA release from the globus pallidus into the VTA. The mesolimbic dopamine pathway would be disinhibited, resulting in excessive dopamine release in the nucleus accumbens.

The role of glutamate dysregulation in mesocortical systems impact negative symptoms

Negative signs of schizophrenia are linked to dopamine hyperactivity in these downstream mesocortical dopamine neurons [15]. A pyramidal interneuron connects the glutamate

brainstem projection to the mesocortical dopamine pathway in the ventral tegmental region (VTA), controlling dopamine release in the prefrontal cortex. The cortical brainstem pathway to VTA will be overactive if the NMDA receptor on the cortical GABA interneuron is hypoactive, resulting in excessive glutamate release in VTA. This will result in overstimulation of brainstem pyramidal neurons, which will then suppress mesocortical dopamine neurons. It inhibits the production of dopamine in the prefrontal cortex, and is thought to be the biological basis for psychotic symptoms.

Neuroinflammation causes cognitive impairment in schizophrenia

Neuroinflammation can have indirect biological effects on cognition by hippocampus neurotrophic factor modulation. While further research into the relationship between inflammation, cognition, and neurotrophic factors is needed, there is evidence that cytokines can influence BDNF levels and behaviour. In particular, proinflammatory cytokines such as TNF- α and IL-1 β decrease BDNF expression, leading to the inhibition of long-term potentiation as the underlying mechanism of memory formation in the hippocampus. Additionally, the crosstalk between M1 microglial and hippocampal neurons via CX3C receptor 1 is known to prevent hippocampal neurogenesis [16]. The proinflammatory microglial activity also enhances kynurenine by inhibiting indoleamine 2,3-dioxygenase (IDO), the key enzyme of tryptophan/kynurenine metabolism [17]–[20]. Finally, the enhanced inflammatory state in the brain, induces the production of all the hormones produced along the hypothalamic-pituitary-adrenal (HPA) axis, which subsequently leads to glutamatergic-dopaminergic imbalance to cognitive alteration in schizophrenia [19], [20].

SUMMARY

Convergent lines of epidemiological genetic and clinical evidence indicate that the inflammatory pathway is altered in schizophrenia. Neuroinflammation has been suggested as a potential mechanism underlying these brain changes, with evidence of increased density and activation of microglia, the immune cells that inhabit the brain. Controversial evidence results in increased density of microglial cells, which act as main cells for immune defense in the brain. However, there are higher numbers of microglial cells in psychotic patients who commit suicide, and several studies report changes in the expression of surface markers associated with microglia in schizophrenia. This suggests that immunological/inflammatory factors may be relevant to the pathophysiology of psychosis.

The positive effect of anti-inflammatory medications in schizophrenia may provide the most compelling evidence that inflammation is involved in schizophrenia. The most studied COX inhibitor is the COX-2 inhibitor celecoxib

REFERENCES

- [1] M. D. Benjamin J. Sadock, M.D. Virginia A. Sadock, M.D. Pedro Ruiz, Ed., "Schizophrenia and other Psychotic Disorder," in *Kaplan & Sadock's Comprehensive Textbook of Psychiatry*, Tenth., New York: Wolters Kluwer, 2017, p. Schizophrenia and other Psychotic Disorder.
- [2] et al Khandaker GM., *Neuroinflammation and*

Schizophrenia, 44 th edit. Cambridge UK: "Springer Nature Switzerland AG 2020, 2020.

- [3] P. F. Buckley, "Neuroinflammation and Schizophrenia," *Curr. Psychiatry Rep.*, vol. 21, no. 8, pp. 19–21, 2019, doi: 10.1007/s11920-019-1050-z.
- [4] N. Müller, E. Weidinger, B. Leitner, and M. J. Schwarz, "The role of inflammation in schizophrenia," *Front. Neurosci.*, vol. 9, no. OCT, 2015, doi: 10.3389/fnins.2015.00372.
- [5] A. G. Dietz, S. A. Goldman, and M. Nedergaard, "Glial cells in schizophrenia: a unified hypothesis," *The Lancet Psychiatry*, vol. 7, no. 3, pp. 272–281, 2020, doi: 10.1016/S2215-0366(19)30302-5.
- [6] L. J. De Picker, M. Morrens, S. A. Chance, and D. Boche, "Microglia and brain plasticity in acute psychosis and schizophrenia illness course: A meta-review," *Front. Psychiatry*, vol. 8, no. NOV, pp. 1–14, 2017, doi: 10.3389/fpsy.2017.00238.
- [7] L. E. Laskaris *et al.*, "Microglial activation and progressive brain changes in schizophrenia," *Br. J. Pharmacol.*, vol. 173, no. 4, pp. 666–680, 2016, doi: 10.1111/bph.13364.
- [8] I. López-González, R. Pinacho, È. Vila, A. Escanilla, I. Ferrer, and B. Ramos, "Neuroinflammation in the dorsolateral prefrontal cortex in elderly chronic schizophrenia," *Eur. Neuropsychopharmacol.*, vol. 29, no. 3, pp. 384–396, 2019, doi: 10.1016/j.euroneuro.2018.12.011.
- [9] P. S. Bloomfield *et al.*, "Microglial activity in people at ultra high risk of psychosis and in schizophrenia: An [11C]PBR28 PET brain imaging study," *Am. J. Psychiatry*, vol. 173, no. 1, pp. 44–52, 2016, doi: 10.1176/appi.ajp.2015.14101358.
- [10] T. R. Marques *et al.*, "Neuroinflammation in schizophrenia: meta-analysis of in vivo microglial imaging studies," *Psychol. Med.*, vol. 49, no. 13, pp. 2186–2196, 2019, doi: 10.1017/S0033291718003057.
- [11] M. Norbert, "Inflammation in Schizophrenia: Pathogenetic Aspects and Therapeutic Considerations," no. April, pp. 1–10, 2018, doi: 10.1093/schbul/sby024.
- [12] C. C. Watkins and S. Ramsay, "Clinical studies of neuroinflammatory mechanisms in schizophrenia," 2015, doi: 10.1016/j.schres.2015.07.018.
- [13] S. Najjar, S. Pahlajani, V. De Sanctis, J. N. H. Stern, A. Najjar, and D. Chong, "Neurovascular Unit Dysfunction and Blood–Brain Barrier Hyperpermeability Contribute to Schizophrenia Neurobiology: A Theoretical Integration of Clinical and Experimental Evidence," *Front. Psychiatry*, vol. 8, no. May, 2017, doi: 10.3389/fpsy.2017.00083.
- [14] B. Pedraz-Petrozzi, O. Elyamany, C. Rummel, and C. Mulert, "Effects of inflammation on the kynurenine pathway in schizophrenia - A systematic review," *J. Neuroinflammation*, vol. 17, no. 1, pp. 1–17, 2020, doi: 10.1186/s12974-020-1721-z.
- [15] "Psychosis and Schizophrenia," in *Stahl's Essential psychopharmacology*, 2013.
- [16] S. A. Kusuma and Y. Setiawati, "LITERATURE REVIEW: COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA," vol. 9.
- [17] J. Kindler *et al.*, "Dysregulation of kynurenine metabolism is related to proinflammatory cytokines, attention, and prefrontal cortex volume in schizophrenia," *Mol. Psychiatry*, vol. 25, no. 11, pp. 2860–2872, 2020, doi: 10.1038/s41380-019-0401-9.

[18] H. Noyan *et al.*, “Association of the kynurenine pathway metabolites with clinical, cognitive features and IL-1 β levels in patients with schizophrenia spectrum disorder and their siblings,” *Schizophr. Res.*, vol. 229, pp. 27–37, 2021, doi: 10.1016/j.schres.2021.01.014.

[19] E. Nanou and W. A. Catterall, “Calcium Channels, Synaptic Plasticity, and Neuropsychiatric Disease,” *Neuron*, vol. 98, no. 3, pp. 466–481, 2018, doi: 10.1016/j.neuron.2018.03.017.

[20] C. Fourier, G. Singhal, and B. T. Baune, “Neuroinflammation and cognition across psychiatric conditions,” pp. 1–12, 2019, doi: 10.1017/S1092852918001499.