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Changes in Immunological Expressions in Schizophrenia and Their Relationships to the Psychopathological Therapy: A Review

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Abstract: Schizophrenia is a debilitating psychiatric disorder characterized by disturbances in perception, cognition, emotion, and behaviour. While traditionally viewed as a disorder of neurodevelopmental and neurochemical origin, emerging evidence suggests that dysregulation of the immune system may contribute to its pathophysiology. This review critically examines the current literature on changes in immunological expressions in schizophrenia and their relationships to psychopathological therapy. We discuss findings from studies investigating alterations in cytokine levels, immune cell function, and the presence of autoantibodies in individuals with schizophrenia. Furthermore, we explore potential mechanisms underlying these immunological abnormalities and their interactions with neurobiological pathways implicated in schizophrenia. Additionally, we review evidence on the effects of psychopharmacological and psychosocial interventions on immunological markers in schizophrenia and their implications for treatment outcomes. Finally, we identify key gaps in the literature and propose directions for future research aimed at elucidating the complex interplay between immunological dysregulation and psychopathological manifestations in schizophrenia, with the ultimate goal of informing the development of novel therapeutic approaches targeting both neurobiological and immunological mechanisms.

Keywords: Schizophrenia, Immunological dysregulation, Psychopathological therapy, Autoantibodies, Cytokine

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Introduction

Schizophrenia is known as a chronic mental disorder with distortions in thought, perception and behaviour. The disease is frequently seen in the young adults involving psychological, social, vocational disabilities during the productive years of an individual's life (Kooyman and Walsh, 2011). Nowadays, humans are constantly being encountered with the physical trauma, psychological stress, infectious agents, and noxious chemicals. Fortunately they have also

evolved with a combating mechanism- inflammatory response. But the harmful effects of inflammation are observed in many infectious and autoimmune diseases. Inflammation in CNS can be either neuroprotective or neurodegenerative. As an example, multiple sclerosis (inflammatory disease of CNS) shows chronic and relapsing course which is also observed in Schizophrenia (Arneth, 2017). The concept of 'smoldering inflammation' says that inflammation of CNS can drive the process of the disease towards both the chronic and acute phases. A close interaction between the CNS and the peripheral immune system during chronic inflammation are seen which involves activation of microglial cells, and activation of pattern recognition receptors (TLR , RIG)(Deerhake *et al.*, 2019) . Activation of microglia is also involved causing neuronal destruction by secreting anti-inflammatory and pro-inflammatory cytokines like IL2, IL6, IL8, TNFα, IFNγ, respectively. IL-2 levels act in an opposite manner with other inflammatory factors like IFN-γ which results in an imbalance between Th1-Th2 arms.

On other hand, researches have shown that impaired blood-brain barrier (BBB) plays a major role in psychosis. If BBB is more permeable to inflammatory molecules and immune cells which can act as disease modifiers in genetically predisposed persons with neurotransmitter systems, also contribute to disease (Brown, 2011). If lymphocytes are present outside blood vessels or in brain parenchyma, then it is a clear sign of neuroinflammation or vascular disorder, same as in the case of multiple sclerosis, viral CNS infections or ischemic stroke. Slight increase in lymphocyte densities is also found in the hippocampus of schizophrenic patients. The presence of higher concentrations of lymphocytes is considered as a marker of blood-brain barrier dysfunction.

Long-term antipsychotic treatment can cause a motor syndrome which consists of involuntary and hyperkinetic movements, called tardive dyskinesia. The development of this disease includes dopamine super-sensitivity and gamma aminobutyric acid deficiency (GABA), dysfunction of serotonin and glutamate receptor, oxidative stress and neuroinflammation (Bishnoi *et al.*, 2008). A number of cytokine receptors present in neurons and glial cells depict that change in levels of cytokines directly affect neurons and brain activity. On other hand, certain cytokine overloaded oxidative stress can influence the neurotransmitter metabolism like dopaminergic system by the activation of immune system. Other than CD4+ T lymphocytes, monocytes and macrophages also produce IL-2 in less amount which plays a critical role in dopamine system. It has been reported that schizophrenic patients who have developed TD have higher IL-2 concentrations compared to patients without TD. IL-6, a multiple cytokine, released from peripheral immune cells of monocytes and macrophage act as a mediator of peripheral acute phase responses and also plays a pivotal role in T cell and B cell activation or proliferation. IL-8 which is a chemokine has the same source of production like IL-2. Chemokines acts in the directional migration of the leukocytes during normal and inflammatory phase by forming a complex recruiting other adhesion molecules, cytokines and proteases. Some studies have shown that there is an increase in IL-8 levels in schizophrenic patients (An *et al.*, 2015).

Innate immune system components in pathogenesis of schizophrenia (*Table 1*)

Glial Cells: Both oligodendrocytes and astrocytes, the major subclasses of glial cells, are seen to get altered in psychotic disorders.

Oligodendrocytes: Oligodendrocytes (OL) are mainly responsible for myelination and the maintenance of white matter. Through some *in vivo* brain imaging and post-mortem studies it has been seen that dysfunction in development of oligodendrocytes, location and myelination capacity can cause white matter abnormalities which may lead to psychosis. From the histological study of a schizophrenic brain, reduced histological myelin staining intensity has been

Table 1: Different immune system components involved in schizophrenia

Innate immunity	Oligodendrocytes (immune cell)	Impaired myelination process
	Astrocytes (immune cell)	Problems in stabilization of glutamatergic receptors and maintenance of dopaminergic receptors.
	Microglia (immune cell)	Neurodegeneration
	TLR (pattern recognition receptor)	Loss of appetite, neurodevelopmental damage
	Interleukins (cytokines)	Cognitive impairments, panic attacks, lethargy, impaired learning and memory
Adaptive Immunity	T Cells • CD4+ Th1 T cells • CD4+ Th2 T cells • CD4+ Th17 T cells • CD8+ T cells	Activation of proinflammatory cytokines , acute psychosis.
	B Cells • IgG • IgM • IgA	Hydrolysis of myelin basic proteins, neurodegeneration, acute infection

observed. From numerous studies it has been seen that schizophrenia is associated with changes in chemical composition of myelin. The levels of myelin-associated glycoprotein (MAG), trans-ferrin, quaking 1, and 2′, 3′-cyclic nucleotide 3′-phosphodiesterase (CNP) mRNA transcripts have been seen to be reduced in the anterior cingulate cortex white matter in schizophrenia (Aberg *et al.*, 2006). Decreases in phospholipids, CNP, MAG and myelin-basic protein (MBP) expression were also detectable in other brain areas in schizophrenia through cDNA microarray, quantitative PCR, Western blot analysis (Arnold *et al.*, 1991; Barley *et al.*, 2009). Disease-linked single nucleotide polymorphisms were found for myelin oligodendrocyte glycoprotein, MAG, CNP and transferrin. From recent studies, neuregulin (NRG) turn OLs into activity-dependent mode of myelination by increasing NMDA receptor currents. Decrease in OL density not only occurs in white matter but occurs in grey matter also including cortical layer cells, cortical perineuronal and pericapillary OLs and hippocampal OLs. Decrease in the levels of perineuronal, non-myelinating OLs indicates that myelination process is disrupted and this OL level can drop up to 30% in schizophrenic patients. The reduction in OL density in chronic schizophrenia may be a consequence of neuroleptic medication because typical neuroleptic haloperidol causes reduction of myelin structural proteins and loss of OLs in adult mouse brain. From a large body of evidences, it has been concluded that there are several dozens of OL-related genes who are dysregulated in Schizophrenic patients. The dominance of "myelin-shaping" genes in the associated gene set confirms that most of the encoded proteins are involved in fatty acid and cholesterol metabolism which are known as "myelin-related" (Bayer *et al.*, 1999). Some non-myelin associated genes are also found which acts through oxidation-reduction enzyme machinery. In addition, the conformational change of ADAM2 happens which is responsible for TGFβ signaling. However, besides the down-regulated

genes, some upregulated genes are also found such as myelin-associated oligodendrocyte basic protein (MOBP), syntaxin binding protein 1 (STXBP1), prohibitin, DISC1, cyclin D1 and phosphorylated retinoblastoma protein. The over-expression of DISC1 may contribute significantly to the reduced levels of two myelin markers, CNP and MBP in schizophrenia. OLs in schizophrenia are characterized by abnormalities in dopamine and glutamate metabolism. Many gray and white matter OLs express the enzyme glutamine synthetase which is mandatory for proper glutamatergic and GABAergic neurotransmission. There is a significant upregulation of N-acetyl-aspartate (NAA) and NAA associated enzymes in psychosis. OLs are known to be vulnerable to oxidative glutamate toxicity and the changes may affect glutamatergic neurotransmission and myelin synthesis.

Astrocytes: On the other hand, astrocytes (ACs) maintain the stabilization of glutamatergic synapses. They are most numerous cells present in mammalian brain. Besides being a part of brain glue holding neurons at particular places, ACs also play important roles in brain functions, supplying neurons and OLs with substrates for energy metabolism, controlling extracellular water and electrolyte homeostasis, expressing neuromo-dulators, regulating neurotransmitter release, modulating immune responses, producing multiple trophic factors, and helping developing neurons to migrate during regulation of synapse formation. From some experimental data it is found that there is a decrease in astrocyte densities in various cortical regions, the hippocampus and the periaqueductal grey. The glial fibrillary acid protein (GFAP) mRNA has been observed at a low level in white matters due to antipsychotic treatment as ACs express dopamine receptors (Oksanen *et al.*, 2019). There are some morphological changes like increased expression of the lysosomal enzymes cathepsin B and D in swollen cortical ACs in schizophrenia patients, which may be a morphological correlation of the recent finding of up-regulated autophagy in schizophrenia. A study discovered 31 astrocyte gene sets, which have been functionally implicated for signal transduction, tyrosine kinase signaling, G protein–coupled receptor signaling, small GTPase-mediated signalling (Bernstein *et al.*, 2015).

An alteration in expression has been seen in another astrocyte-associated enzyme called glutamine synthetase by which glutamate released from neurons is taken up by ACs and converted to glutamine. This glutamine in converted to glutamate by other neurons (Koyama, 2015). Thus glutamine synthetase-expressing ACs obligates the function of glutamatergic and GABAergic synapses. So, the disturbances of the glutamatergic and GABAergic neurotransmission in schizophrenia may be the result of dysfunction of Glutamine synthetase. Decrease in levels of another enzyme called glutaminase which is involved in glutamate-glutamine cycle has been also reported. In addition, ACs also release other "gliotransmitters", including D-serine, ATP, kynurenic acid and S100B. ATP mainly influences purinergic signaling pathways, D-serine and kynurenic acid target glutamatergic and GABAergic neurotransmission by interacting with kainate receptors, metabotropic glutamate receptors, and NMDA receptors (D-serine interacts only with the latter receptor type). If mutation occurs in the human D-serine metabolizing enzymes serine racemase and D-amino acid oxidase, it add risk factors for schizophrenia. It is also observed that decrease in D-serine levels can be a consequence of extreme degradation of D-serine in schizophrenia. AC-derived kynurenic acid acts as an antagonist at NMDA and α7 nicotinic acetylcholine receptors and influences glutamate, dopamine, and acetylcholine signaling. There is an elevation found in the cerebral and CSF kynurenic acid concentrations in schizophrenia patients. This may be the result of a disease-related impairment of the kynurenic acid metabolizing enzyme kynurenine 3-monooxygenase. Increased level of S100B has been found in the body fluids of schizophrenic patients. Disease-linked S100B gene polymorphisms also have been identified. The

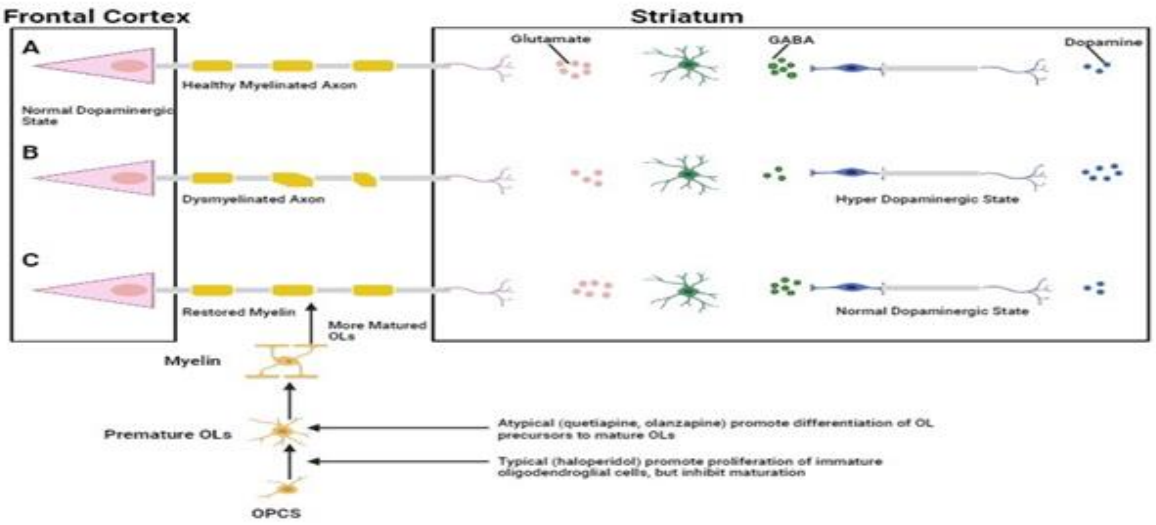

Fig. 1: Healthy myelinated axon. (A) Inhibitory neuron receives sufficient glutamatergic input from myelinated axon, and releases sufficient GABA to inhibit excess dopamine release at dopaminergic terminals. (B) Demyelinated axon. Inhibitory neuron receives insufficient glutamatergic input from unmyelinated axon, and fails to release sufficient GABA and disinhibits excess dopamine release. (C) The atypical quetiapine and olanzapine (but not the typical haloperidol) promote the maturation of OLs. Mature Ols are (possibly) able to restore impaired myelin and thereby eventually contribute to the normalization of hyperdopaminergic neurotransmission.

enzyme called Catechol-O-methyltransferase (COMT), mainly helps in brain catecholamine metabolism, has been seen to be increased in ACs of schizophrenic patients which is independent of any medications. This shows that ACs express both dopamine receptors and transporters as well as enzymes involved in monoamine metabolism. Patients with reduced monoamine oxidase-B level, found to be subjected to schizophrenia (Fig. 1).

Microglia: Microglial cells have similar regulatory functions as the dendritic cells and macrophages in peripheral tissues. Microglia plays an important role in phagocytosis of neurons undergoing apoptosis during embryonic brain development (Lampron *et al.*, 2013). In schizophrenia, the involvement of microglial cells in the regulation of synaptic structure and function links between abnormal microglia function and the schizophrenia-associated disturbances in synaptic wiring. From positron emission tomography (PET) studies several microglial markers like MHC-II, CD40, CD68 and the peripheral type benzo-diazepine receptor have been found in schizophrenic patients (Bayer *et al.*, 1999). Some HLA-DR functions have also been observed in the hippocampus and prefrontal cortex. Degeneration of microglial cells in frontal and temporal lobes have been observed in chronic schizophrenia. Microglia secrets IL-1β and IL-2 are capable of modulating catecholamine levels in the brain. So, microglial activation can inhibits neuro-transmission involving emergence of psychotic symptoms in schizophrenia. Nitric oxide (NO) produced from activated microglia influences monoaminergic activity and decreases serotonin level, also contributes in schizophrenia.

Toll like receptors: Toll like receptors (TLR) play an important role in first line of defense of immune system. They recognizes the external pathogen-associated molecular patterns (PAMPs) and detect the damage-associated molecular patterns (DAMPs) which are released as a result of tissue destruction (Medzhitov, 2001; Akira *et al.*, 2006). Activation of TLRs initiates the complex intracellular messenger cascade in immune and glial cells leading to the production of pro-

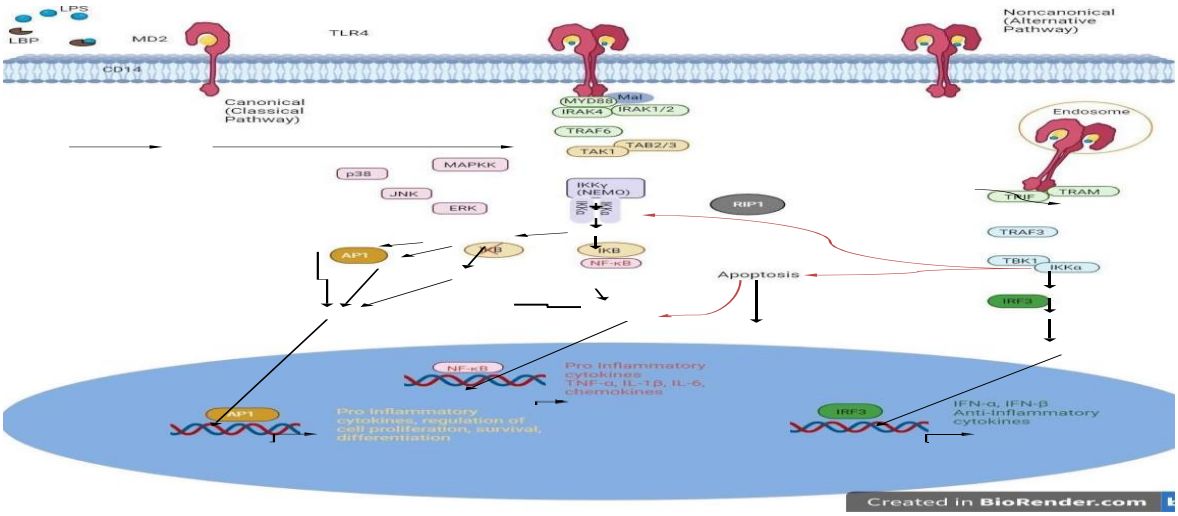

Fig. 2: TLR 4 pathway.

inflammatory cytokines. There is a decrease in TLR3 and TLR5 mRNAs whereas increase in TLR4 receptors in impaired function of monocytes which leads to a low grade inflammation in schizophrenia. Enhanced TLR-dependent responses were observed where IL6 has been released at a massive rate. It has been found that LPS played a key role in TLR4 stimulation increasing the permeability of intestinal barrier resulting bacterial translocation in patients with schizophrenia. There is an evidence of pre-perinatal infections inducing maternal immune activation and inflammatory and oxidonitrosative stress which lead to neurodevelopmental damage and behavioral abnormalities in the progeny. The activation of TLRs by infection has been observed to affect the fetomaternal immune response and cause behavioral abnormalities in offsprings. Other factors including psychosocial stressors, physical inactivity, obesity, smoking, poor dental care or overall hygiene and sleep deprivation can cause inflammation leading to activation of TLRs (Khandaker *et al.*, 2015). From other experiments higher expression of TLR4 and Myeloid differentiation primary response 88 (MyD88) was found in the postmortem prefrontal cortex of schizophrenic patients. Some experiments also have shown that the NF-Kβ, which is a part of TLR4 activation, which has also increased with TLR4 concentration along with a significant decrease in the anti-inflammatory receptor PPARγ in patients with FEPS and chronic schizophrenia (García-Bueno *et al.*, 2016). On other hand higher content of MDA found in the PFC of patients with schizophrenia treated with antipsychotics compared with both antipsychotic-free patients and controls. Some SNPs like *IL6* rs1800795 and *IL1B* rs1143634, rs1927914 CC genotype which is located on 5'UTR of the TLR4 gene are strongly associated with Schizophrenia. Polymorphism of *MyD88*, *IL6* and *IL1B* along with key genes in the intracellular signaling of the TLR4 pathway as shown in Figure 2. *NFKB1* and *IRAK* play the major role in classification of patients with schizophrenia and healthy controls with high sensitivity and specificity (Fig. 2).

Interleukins: Schizophrenia has been observed to be associated with various abnormalities. *In vitro* production of cytokines in neuropsychiatric disorders suggest that these molecules may play a role in the pathogenesis of such disorders. It has been seen that cytokines are involved in pathology of schizophrenia (Baker *et al.*, 1996). A decrease in in-vitro production of IL-2 and IFN-γ, increased

serum IL-6, interleukin-1b and tumor necrosis factor (TNF)-α, increased serum IL-2 receptor, IL-6 receptor and IL1R antagonist (IL-1RA), increased CSF IL-2 level and increased serum IL-2 level (Al-Asmari *et al.*, 2014). Abnormalities in cytokine levels functions may reflect the presence of an infectious or immune activation because cytokines have many critical interactions among cells of the immune system (Chiavetto *et al.*, 2002). The peripherally applied IL-2 and IL-6 enhance catecholaminergic neurotransmission in the rat frontal cortex and hippocampus. This phenomenon indicates that these two cytokines play pivotal role in the disease. IL-6 is a pleiotropic cytokine that plays a role in the immune and acute phase response, hematopoiesis and both the development and the functioning of neurons. Elevation in serum IL-2 level in neuroleptic-free schizophrenic patients contributes to dopaminergic neurotransmission, abnormal brain morphology and autoimmune response. It has been observed that there were significant correlations between IL-2 and homovanillic acid (HVA), IL-2 and SAPS and HVA and SAPS during the acute state of illness in schizophrenia which suggest that the cytokines can modulate dopaminergic metabolism and schizophrenic symptomatology in schizophrenia. IL-2 might increase vulnerability to psychiatric abnormalities associated with the central dopaminergic processes by selectively blocking dopamine D1 or D2 receptor antagonist and IL-2 influenced extracellular dopamine levels and D2 binding in the nucleus accumbens. IL-2 could abnormally produce excessive free radicals by modulating dopamine metabolism resulting in oxidative stress and neuronal degeneration (Alonso *et al.*, 1993).

Another finding suggests that there is a decrease in serum IL6 in schizophrenic patients. IL-6 is a multiple cytokine released from peripheral immune cells of the monocyte/ macrophage lineage. They act as a mediator of peripheral acute-phase responses, and also plays a pivotal role in T- and B-cell activation or proliferation. Some neurons and microglia also produce IL6 where IL6 acts as a neurotrophic factor in the central nervous system.

Studies have shown that serum IL-8 level was significantly higher in schizophrenia patients than in normal controls. Activated T cells, endothelial cells, monocytes,and macrophages produce this chemokine called IL-8. A significant correlation was found between serum IL-6 and IL-8 in schizophrenic patients (Zhang *et al.*, 2002).

There was significant decrease in IL-10 ratio in schizophrenic patients. IL-10 protects against inflammation mediated degeneration of dopaminergic neurons in the disease (Gennarelli, 2002). So decrease in IL-10 level may alter the central dopamine function and further affect the negative symptoms. IL-10 is responsible for cognitive impairment in schizophrenia along with Alzheimer's dementia and Parkinson's disease.

Another findings suggest that serum IL-18 levels were significantly increased in chronic schizophrenic patients. IL-18 is a member of the IL-1 family who has potent proinflammatory properties, and induces the activation of Th1 cells. Elevated IL18 levels can contribute to several symptoms associated with neuropsychiatric disorders such as depression. Change in IL-18 level contributes in central and peripheral stress response, and panic attacks along with lethargy, loss of appetite, impaired learning and memory.

Other cytokines

Tumor necrosis factor α: Besides other cytokines tumor necrosis factor-α (TNFα) plays an important role in the disease. It has been reported that gene encoding TNF-α is located within the HLA region on chromosome 6p21.3, which is susceptible to schizophrenia. Scientists have found a higher concentration of TNFα in diseased individuals than normal control. TNFα is highly polymorphic and there are many single nucleotide polymorphism (SNPs) seen. Regarding the polymorphism, mainly two promoter regions – TNFα-238 and -308 are said to be associated in previous studies. From a survey, it has been seen

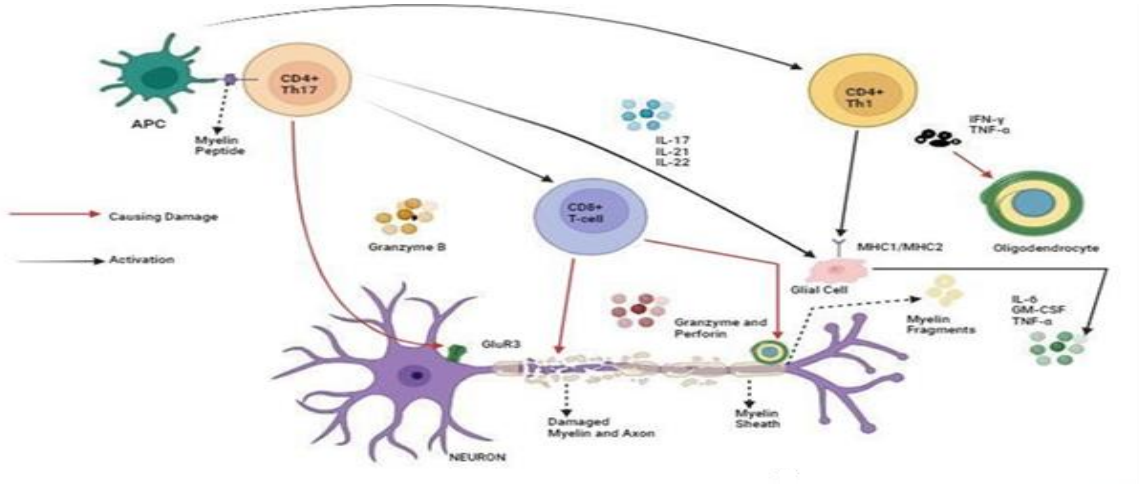

Fig. 3: T-Cells in CNS leading to Schizophrenia.

that individuals carrying the GG genotype had a higher risk of treatment resistance.

Adaptive immune system components in pathogenesis of schizophrenia

T Cells: Proinflammatory CD4+ Th1 and Th17 cells are majorly involved in the development of Schizophrenia as they release IFN-γ , TNFα and IL-17 (Baskak *et al.*, 2008). From previous studies, it has been found that both IFN-γ and IL-17 tend to escalate the immune activation by inducing the release of additional proinflammatory mediators either by augmenting antigen presentation or by affecting the viability of resident cells of CNS. It has also been reported that naive T-cells are induced to differentiate into Th17 in response to IL-6 and TGF-β. But IL-12 induces the differentiation into Th1. APCs of myeloid lineage such as microglia, produces proinflammatory cytokines like IL-6 and IL-12. Astrocytes are also involved in the secretion of proinflammatory cytokines which contributes in differentiation and activation of the Th1 and Th17 in CNS. Th1 secretes IFN-γ which is seen to activate microglia (enhancing phagocytotic activity). They present myelin antigens to T cells. Oligodendrocytes can be killed by IFN-γ directly. The antigen presenting ability of myeloid cells has been enhanced by the IFN-γ which restimulate myelin-antigen-pecific CD4 and CD8 T cells in meningeal sites. On the other hand, Th-17 cells provide defense against bacteria by secreting IL-17, IL-22 and IL-21. IL-17 has a combining ability with other cytokines, increasing the secretion of proinflammatory cytokines, chemokines, and complement proteins. These attributes of IL-17 are involved in maintaining the population of Th17 cells and also activates microglia to initiate the recruitment of lymphocyte, macrophages and neutrophils which causes inflammatory damage to the neurons by attacking the myelin sheath. In comparison to Th1 cells, Th17 cells efficiently migrate across the BBB, bind and recognize the self antigens of myelin protein and secrete high levels of IL-17. This leads to neutrophil expansion and BBB disruption. IL17A and IL-22 expressing Th17 show cytolytic activity on neurons by the secretion of granzyme B which is also involved in killing and destroy neurons by targeting the glutamate receptors i.e., GluR3. The CD8+ T cells are involved in the mechanism of killing through perforin and granzyme. They secrete IL17 and IFN-γ as a defense against inflammation as CNS is very prone to viral attacks. CD4+ T cells cause inflammation which induce the CNS resident cells (astrocytes, microglia, oligodendrocytes) to express MHC-1 molecule which in turn presents self-antigens to the CD8+ T-cells and make them an easy target for damage and demyelination (Fig. 3).

B Cells: The elevation in IL6 levels induce the B cell proliferation and differentiation in patients with

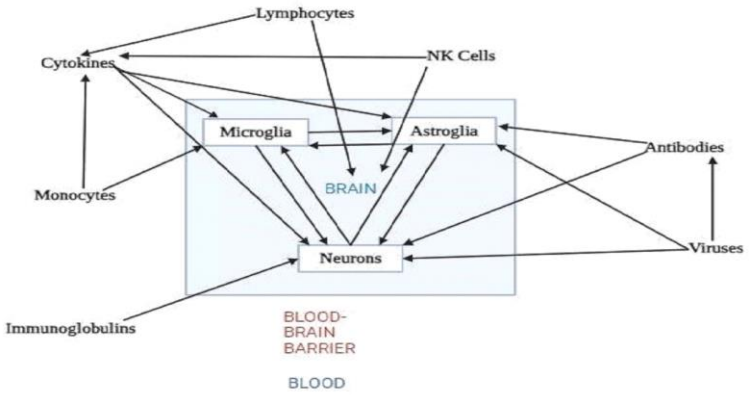

Fig. 4: Involvement of both Innate and Adaptive immune system in pathogenesis of Schizophrenia.

schizophrenia. Oligodendroglial cells produced the myelin sheath. The adult postmortem reports showed structural changes in oligodendroglia cells which reduce the concentration of myelin basic protein (MBP) in the anterior frontal cortex. Decreased expression of MBP in the gray matter of frontal cortex is a characteristic of schizophrenic patients. An increase in the level of antibodies like MBP antibodies against neuro antigens indicates the severity of clinical symptoms in schizophrenia (Maino *et al.*, 2007). There are several catalytic antibodies (abzymes). The catalytic activity of the immunoglobulins like hydrolysis of DNA, RNA, polysaccharides, and protein has also been recorded (Ermakov *et al.*, 2017). From the ELISA it has been seen that concentration of autoantibody against MBP are much higher in diseased individuals than in healthy ones. Studies have been shown that autoantibodies that binds neuroantigens in early stages of ontogenesis results in the formation of various structural anomalies in the nervous system which leads to a violation of the behavior in young individuals. The penetration of the immunoglobulins through blood-brain barrier in autoimmune disorders explained that MBP stimulates the synthesis of the antibodies to myelin components. IgGs catalyze the hydrolysis of MBP in the patients with schizophrenia (Fig. 4)(Ermakov *et al.*, 2022).

Neurochemical Changes

Dopamine belongs to catecholamine family. Dysfunction of dopamine results in pathology of Schizophrenia (Brisch *et al.*, 2014). In rodent models interactions between dopamine and various non-dopamine receptors, such as N-methyl-d-aspartate (NMDA)-, AMPA-, GABA(A)-, and nicotinic receptors are seen (Bogerts *et al.*, 1983). Dopamine receptors are G-protein-coupled receptors and can be divided into D(1), D(2), D(3) and D(4)-receptors. There is an decrease in D1 receptors in prefrontal cortex whereas an increase in the parieto-temporal cortex in patients. It has also been found that there is an increase in D2 receptors in prefrontal cortex in patients with schizophrenia.

There are four types of dopaminergic pathways in brain. They are – (i) Nigrostriatal Dopamine Pathway, (ii) Mesolimbic Dopamine Pathway, (iii) Mesocortical Dopamine Pathway,and (iv) Tuberoinfundibular Dopamine Pathway.

The Mesolimbic Pathway is mainly involved in Schizophrenia. In this pathway:

- This starts from ventral tegmental area and ends into the nucleus accumbens in the limbic system.
- Positive psychotic symptoms are carried out by the hyperactivity of dopamine.

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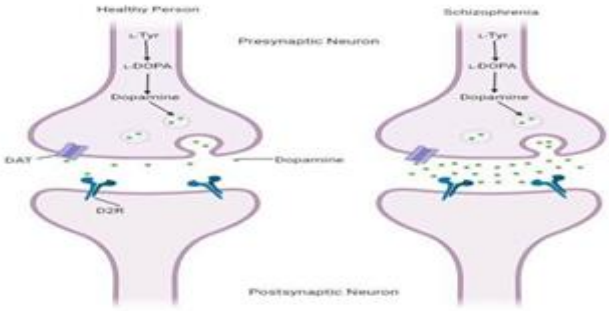

Fig. 5: Dopamine concentration in healthy person and Schizophrenic patients.

- Antipsychotics can block D2 receptors through this pathway resulting a reduce in pleasure feeling (Burt *et al.*, 1977).
- Individuals with schizophrenia have a higher tendency of smoking because nicotine enhances dopamine in reward pathway.
- Antagonists of D2 treats positive psychotic symptoms.

In case of humans the polymorphism in the gene encoding catechol-O-methyltransferase, an enzyme involved in the degradation of dopamine, is associated with hypoactivity of prefrontal dopaminergic neurons in schizophrenia. Studies have found that DRD2-antagonism can prevent DRD1-mediated potentiation of N-Methyl-d-aspartate (NMDA) responses in the prefrontal cortex (Wang *et al.*, 2012). Schizophrenic patients have been diagnosed with the expression levels of tyrosine hydroxylase (TH), the enzyme that catalyzes the first (and limiting) step in the biosynthesis of dopamine, and have found heterogeneous results, supporting either dopaminergic hyperactivity or hypoactivity (Fig. 5).

Dopaminergic Alterations in Schizophrenia

- There is an increase in DRD3 and DRD5 in peripheral blood T cells, results in neurogenesis.
- Increase in percentage of CD4+ T-cells expressing the DRD4 and DRD2 in medicated schizophrenic patients, results in adaptation of psychological stress.
- Reduction in Treg levels in patients, results in Production of IFN-g that stimulates GABAergic inhibitory neurons.
- Increased percentage of CD8+ T-cells expressing DRD4 in medicated schizophrenic patients compared to controls, results in neurogenesis and cognition problems.
- Increased hippocampal microglial cells, results in Synaptic pruning.

Neurochemical Regulation on Immune System

Dopaminergic Regulation of T Cell

The effect of Dopamine on T cells depends on -- concentration of dopamine, types of T cell and their activation status, number of dopamine receptors being expressed. The expression of dopamine receptors also depends on some subsets of T-cells as sources of dopamine. In human Tregs can synthesize and release dopamine which shows negative feedback on their activity. Another evidence has been found where follicular helper T (TFH) cells synthesize and store dopamine and they are released upon antigen-recognition to stimulate DRD1- signaling on B-cells as a costimulatory signal to induce antibody production (Vidal and Pacheco, 2020). Studies have shown that the stimulation of D1- like dopamine receptors induce the differentiation of

naive CD4+ T-cells toward a Th2 phenotype and attenuates the regulatory activity of Tregs. The DRD3 stimulation increases IFN-g production and concomitantly decreases IL-4 and IL-10 release, along with an exacerbated expression of the activation marker CD25. The DRD3-signalling in CD4+ T-cells helps in the expansion of the Th17lineage. The DRD5 stimulates CD4+ T-cells which potentiates TCR-signaling favoring a stronger T-cell activation. In Teff DRD5 signaling favors the acquisition of the Th17- lineage, whereas Tregs increase the potency of their suppressive activity. DRD3-stimulation on CD8+ T- cells potentiates IFN-y transcription and increases their integrin mediated adhesion to fibronectin and intercellular adhesion molecule 1 (ICAM-1), synergizes lymphocytes migration toward inflammatory chemokines. Alterations in physiological dopamine levels or the expression of dopamine receptors exhibits strong changes in behavior of T cells.

Dopaminergic Regulation of Microglia

Microglial cells reside in the CNS and they are exposed to dopamine released by dopaminergic neural circuits of the CNS. Upon inflammatory stimulation of microglial cells, DRD2 levels are induced and expressions are changed. High dopamine levels attenuate the inflammatory activation of microglia by reducing the release of nitric oxide and decreasing the extent of phagocytosis. The cAMP-mediated degradation of the NLRP3 inflammation is induced by DRD1 signaling, thus exerting a potent anti-inflammatory effect. The microglial complement-dependent signaling pathway mediates elimination of D1-like receptors in the nucleus accumbens of adolescent male, leading to the development of social behavior changes in male rats. DRD2 signaling also triggers the anti-inflammatory effects on microglial cells. The high-dopamine levels exhibit the down-regulation of angiotensin II released by astrocytes. It also induces the upregulation of the anti-inflammatory molecules in astrocytes and attenuates inflammatory behavior in microglial cells.

Alternate Neurochemical Models and Their Interactions with Dopamine

Glycine reduces the release of dopamine by modulating DAT-type transporters in the prefrontal cortex and striatum by NMDA-stimulated GABA-release and GABAB-receptor activity. In prefrontal cortex, there is an increase in number of GABA-cells expressing D1 receptors. Neurotensin inhibits dopamine discharge, which increases glutamate release and activates GABA pathway resulting in subsequent increase in glutamate transport in pre-frontal cortex (Corkrum *et al.*, 2020). Zotepine increases the extracellular levels of noradrenaline, dopamine, glutamate, and GABA. This GABA interacts with acetylcholine by constraining its excitatory contribution to cholinergic interneurons, which are decreased in the striatum of diseased individuals.

In mid brains, dopamine neurons release serotonin. It is very important during combined drug treatment where the antipsychotics include 5-HT1A receptor agonists or antagonists, 5-HT2A receptor antagonists, 5-HT2c receptor inverse or partial agonists or neutral antagonists, 5-HT6 receptor antagonists, and 5-HT7 receptor antagonists. Antipsychotics like clozapine and aripiprazole possess 5- HT-1A agonist and induce neurogenesis resulting in increase in dopamine level in prefrontal cortex. The drug called asenapine increases the dopamine and glutamate levels in various subcortical regions. A range of dopamine/serotonin, glutamate/serotonin, and acetylcholine/serotonin interactions activate receptors and signaling molecules in response to antipsychotic drugs. Stress in the patients with schizophrenia also causes elevation in dopamine level. This cannot be counteracted by reducing the activity of GABAA receptor complex. Cannabis has been found to be inducing hyperdopaminergic and hypo glutaminergic activities in individuals. Cannabis mainly increases the dopamine level in nucleus accumbens (Fig. 6).

Cytokine alteration during treatment with antipsychotic drugs (Fig. 7)

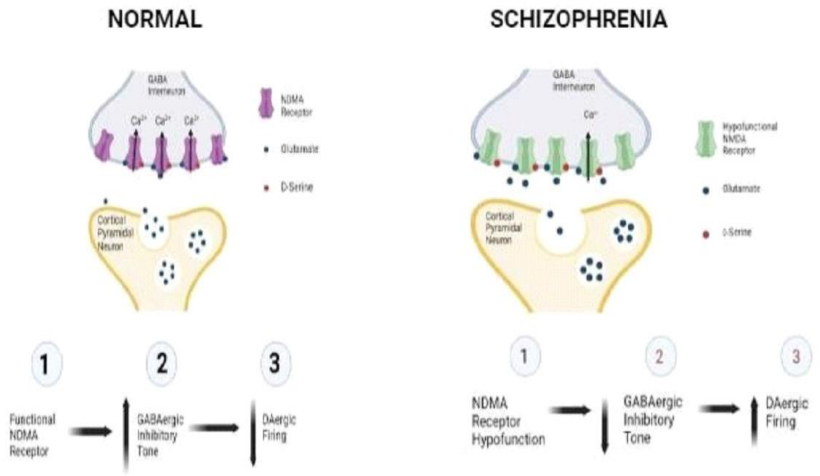

Fig. 6: Interactions between dopamine and glutamate neurotransmission in normal and schizophrenic patient.

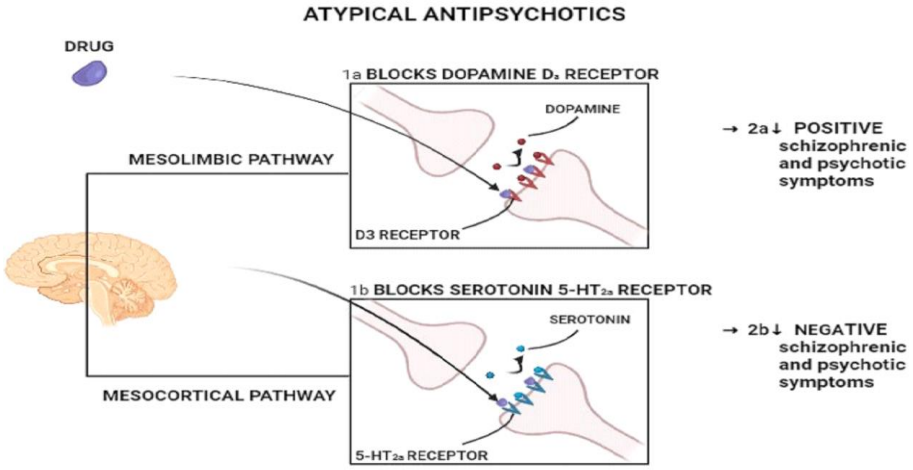

Fig. 7: Mode of action of atypical antipsychotics.

Haloperidol: It is atypical antipsychotic drug which is widely used for of the mentioned disease. Previous studies suggest that it has a potential to normalize the higher serum levels of IL2. It also inhibits mitogen-stimulated IL2 production. Simultaneously it also decreased the homovanillic acid levels. It normalizes the increased secretory activity of monocytes. The LPS stimulated production of IL10 and TGFβ are enhanced by haloperidol.

Clozapine: It is an atypical antipsychotic which is significantly associated with the risk of agranulocytosis. From the previous data it has been seen that the plasma level of sIL-2R was increased by clozapine. The binding of sIL-2R inactivates IL2 resulting into immunosuppression. It has a significant effect on IL6 also. TNFα has been seen to be increased by clozapine. As TNFα has a resistance on insulin production, the side-effects of these TNF system have been observed during clozapine treatment. IL18 levels were decreased whereas IL10, IL1Ra and TGFβ production were increased. The leptin levels were reported to be increased during the therapy. The serum levels of ghrelin which is an appetite inducer, are seen to be increased. Clozapine also alters the secretion of granulopoietic factors.

Olanzapine: This relatively new atypical antipsychotic increases the plasma levels of sTNF-R p55 and p75. Increased appetite and weight gain

were commonly seen during the treatment as a result of increased leptin levels. There is an abnormal regulation of ghrelin has been reported in the olanzapine-treated patients.

Risperidone: This atypical antipsychotic decreases the serum levels of IL2, IL6, TNFα and IFN-γ. On the other hand, it increases the plasma levels of IL10 and IL12. It also increases the leptin levels, resulting in weight-gain (Drzyzga *et al.*, 2006).

Chlorpromazine: This typical antipsychotic shows potential immuno-modulatory activity. It suppresses the delayed type hypersensitivity (Type IV) after administration. It inhibits NK cell activities and antibody-dependent cell-mediated cytotoxicity in a dose-dependent manner. The levels of TNFα were decreased along with IL1β and IL2. The LPS stimulated production of IFNγ was down-regulated. In contrast anti-inflammatory cytokine IL10 were increased which shows the involvement of chlorpromazine against endotoxic shock. The TGFβ levels were also increased whereas IL4 concentration were decreased.

Immunosuppression by antipsychotic drugs

Several studies have shown the immunosuppressive activity of antipsychotic drugs. Some drugs have been seen to lower the serum levels of pro-inflammatory cytokines like TNFα, IL1, IL6 (Borovcanin *et al.*, 2013). Chlorpromazine was reported to amplify the anti inflammatory capacity of serum by increasing the release of Th2, IL10. A prolonged treatment with this drug may cause development of autoantibodies resulting in a shift towards Th2 type cytokine production. Activation of Th1 subpopulation of lymphocytes inhibited IL10 resulting in down regulation of proinflammatory response.

Administration of haloperidol reduced IL1β and TNFα delivering a positive effect upon rheumatoid arthritis. Moreover, it has been observed that plasma levels of IL6 and sIL-6R were reduced during treatment. sIL-6R has an inhibitory effect on IL6 activity which leads to immunosuppression.

Therapeutic Approaches by stabilizing Immune system parameters

Oligodendrocytes as drug target: In schizophrenia dysregulation of oligodendrocytes are found with evidence of inflammatory infiltration and microglial activation. Since inflammatory/immune processes are thought to be the primary reason of developing schizophrenia, thus normalizing immunological imbalances may be helpful in treating the disease. For instance, the oligodendrocytes collected from the diseased individuals are restored and recovered experimentally by stabilizing the immunoglobulin Fc receptor gamma/Fyn signaling. An antibiotic called Minocycline can suppress oligodendrocytes damage from y-interferon stimulated microglia. The combination of anti-inflammatory substances with traditional antipsychotics exhibits functional recovery of oligodendrocytes. Growth factors like insulinlike growth factors (IGFs) I and II are promising candidate substances because they play an important role in regulation of development and repair of oligodendrocytes. From recent studies use of dopamine receptor agonists and antagonists have been recommended for the oligodendrocyte therapy in schizophrenia.

Astrocyte directed therapy: Astrocytes are the main part of the glutamatergic-dopaminergic dysregulation in schizophrenia. The neuroleptics are seen to have a positive influence on the disturbed astrocyte metabolism in schizophrenia by binding to astrocyte dopamine receptors and thereafter interacting with a wide range of cell compounds. As the glutamine synthase expression is less in schizophrenic patients, administration of lithium will be effective to increase the enzyme level. The antipsychotic called clozapine enhances the D-serine from astrocytes in hippocampal area. Astrocytes also contributes in immunocompetence of the CNS via their expression of class II MHC antigens and the production of inflammatory cytokines such as interleukin-ip (IL-1 beta), TNF-a and interleukin-6 (IL-6). Dysregulation of any of them can be treated with anti-inflammatory agents like cyclooxygenase-2 inhibitors.

Microglia in anti-inflammatory therapy: The increased level of proinflammatory cytokines are the key interest of the therapy and have gone through trials using TNFα antagonist etanercept (EnbrelTM). The minocycline can modulate the microglial activation which is detrimental for adult neurogenesis by suppressing the proinflammatory complexes. Minocycline suppresses the release of IL10, TNFα by blocking the nuclear translocation of nuclear factor 'kappa-lightchain-enhancer' of activated B-cells (NF-kappa B)(Bishnoi *et al.*, 2008). The inhibitors of cyclooxygenase-2 (COX-2) is an inducible enzyme and are used a potential anti-inflammatory (Akhondzadeh *et al.*, 2007). They are found to be increased in MPS cells including microglia.

Conclusion

Assembling the information on immunological and immunopathological research in Schizophrenia shows that inflammation caused by any infection or virus attack or autoimmune processes play an important role in the pathogenesis of the said disease. As the dysfunction of immune components are seen to play a major role, by normalizing their concentrations and activities will be a way to cure the disease. Along with behavioral therapy, Cognitive Behavioral Therapy (CBT), counselling, immunotherapy can be done to improve the brain functioning. From recent researches it has been seen that COX-2 inhibitors are effective as anti-inflammatory therapy in the disease. However, intensive researches are needed to find whether the immune-therapy may one day replace current anti-psychotics which possess too much side-effects.

Ethical Statement

This is a review article hence no Ethical Approval needed.

Author Contributions

Each author has contributed equally to the study's planning, analysis, writing, and editing. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

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