The Neuroimmunology of Schizophrenia

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Schizophrenia (SCZ) is a polygenic, multi-factorial disorder and a definitive understanding of its pathophysiology has been lacking since it was first described more than a century ago. The predominant pharmacological approach used to treat SCZ is the use of dopamine receptor antagonists. The fact that many patients remain symptomatic, despite complying with medication regimens, emphasises the need for a more encompassing explanation for both the causes and treatment of SCZ. Recent neuro-anatomical, neurobiological, environmental and genetic studies have revived the idea that inflammatory pathways are involved in the pathogenesis of SCZ. These new insights have emerged from multiple lines of evidence, including the levels of inflammatory proteins in the central nervous system of patients with SCZ and animal models. This review focuses on aberrant inflammatory mechanisms present both before and during the onset of the psychotic symptoms that characterise SCZ and discusses recent research into adjunctive immune system modulating therapies for its more effective treatment.

KEY WORDS: Schizophrenia; Inflammation; Immune based therapies.

INTRODUCTION

Schizophrenia (SCZ) is a severe psychotic disorder affecting approximately 1% of the adult population worldwide over the average lifetime.1,2) This debilitating illness is characterised by the presence of delusions and hallucinations (positive symptoms), social withdrawal and loss of motivation (negative symptoms) and cognitive deficits.3) Historically thought of as a culmination of ‘a number of conditions which may lead to a severe disturbance of the ego’,4) SCZ is now understood to arise from a complex interplay of genetic and environmental risk factors acting across many stages of brain development.5-11) Several neurochemical and neuropathological theories have been proposed to explain the pathological processes intrinsic to SCZ, including impairments in dopaminergic,12) glutamatergic13,14) and GABAergic signalling,15,16) impaired prefrontal cortex function,17-19) aberrant neurodevelopment,20,21) stress vulnerability22) and variations in the inflammatory response.23,24)

Considering the sheer number of physiological systems implicated in the development of SCZ, it is perhaps unsurprising that decades of intense scientific and clinical investigation have only partially resolved the complex mechanisms driving the disease process. Recently, attention has increasingly focussed on the impact of a dysregulated inflammatory system on downstream cellular and molecular pathways previously implicated in the pathogenesis of SCZ.24-26) This review article focuses on the increasingly popular role of various inflammatory mediators and how a more comprehensive understanding of their contribution could improve both our understanding and treatment of SCZ.

MAIN SUBJECTS

Inflammation and the central nervous system (CNS)

A connection between inflammatory factors and the development of ‘mental maladies’ was first voiced by Esquirol upon the epidemic appearance of psychiatric disorders in 1845.27) Since then, a steady stream of patients have been described displaying symptoms suggestive of acute SCZ but also presented with, or later developed, the clinical hallmarks of multisystem encephalitis.28-32) Following the publication of a number of experimental studies over the last three decades, interest in activated inflammatory processes in SCZ has once again gained momentum.24-26,33,34) Inflammation is a complex homeo-
Table 1. Key research questions

- How specific are cytokine alterations to schizophrenia?
- When do immunological changes occur and how do they correlate to the clinical course of schizophrenia?
- Can certain immune factors act as markers for relapse?
- Should anti-inflammatory augmentation therapies be introduced into normal clinical practice?

Immune System Genetics and SCZ

SCZ is highly heritable, making genetic predisposition the most sought after risk factor for its development. As with a number of common diseases however, the inheritance pattern is complex, the penetrance of all but a small number of genes is low and a reliable biological marker is lacking. Recent, suitably large genome-wide association studies have implicated a number of genes of the immune system and their respective underlying biological pathways in psychiatric disorders.52,58) Linkage studies have identified a SNP in the interferon γ gene, a gene involved in regulating both the innate and adaptive immune response, and recently associated it with a 2 fold higher risk of paranoid SCZ.59) Differences in allele frequencies of interleukin (IL)1260) and IL1061) gene promoter variants and IL1 gene expression 62) have been found between patients with SCZ and healthy controls. Genetic studies have also found that the IL1B gene may increase the risk for SCZ63-65) and two immune response genes; colony-stimulating factor receptor-α (CSF1R-α) and IL-3-α have also been linked to SCZ.66-68) Significant upregulation of inflammatory markers IL-6, IL-8 and IL-β were found in the dorsolateral prefrontal cortex (DLPFC) of individuals with SCZ.69) Future work must focus on directly examining the additive effects of these specific immune-related SNPs as the genetic contribution and mechanisms remain far from clear.

Inflammatory Cytokine Alterations and SCZ

Two recent meta-analyses of over 100 studies provide in vivo evidence that SCZ can be, in part, explained by an inflammatory imbalance.25,70) Potvin et al.25) found an increase in IL-1 receptor antagonist (IL-1RA), soluble IL-2 receptor (sIL-2R) and IL-6 in either the plasma or serum of patients with SCZ, regardless of clinical presentation. Conversely, Miller et al.70) found that cytokine alterations in SCZ vary with clinical status, potentially labelling specific cytokines as either ‘state’ or ‘trait’ markers. IL-1 β; IL-6, and transforming growth factor-β (TGF-β) were found to be elevated in first episode and acutely exacerbated patients and normalised with medication whereas IL-12, interferon gamma (IFNG), TNF, and sIL-2R levels remained elevated following antipsychotic treatment in acutely relapsed patients.70) These disparate findings could reflect varying patient groups, medication effects or major ‘pro-inflammatory’ confounds such as smoking, diet, stress and obesity, previously shown to significantly impact the immune system.71-75) Considering the inflammatory impact of lifestyle, medication and environmental variables, along with the added complication of other immune-mediated comorbidities,76,77) it is therefore
essential to determine how inflammation specially operates within the confines of SCZ.

**Imaging Neuronal Inflammation and SCZ**

Dilatation of the lateral ventricles in the brains of people with SCZ was first documented in the landmark study of Johnstone et al. Following this revelation more sophisticated neuroimaging studies using techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) consistently showed abnormalities in several brain structures in SCZ. It has been repeatedly shown that a population at high risk of developing SCZ display structural brain abnormalities and deficits in a number of schizotypal features that precede the onset of psychosis, for example, social withdrawal, anxiety and executive function. These studies therefore exclude the possibility that structural and functional variations are merely a result of chronic illness or treatment. It has also been shown that patients with a diagnosis of SCZ and previously exposed to high levels of IL-8 in utero have significant increases in their ventricular cerebrospinal fluid (CSF) and decreases in left entorhinal cortex and right posterior cingulate volumes, structural modifications that have been highly reproducible in SCZ research.

Functional neuroimaging has also been employed to investigate whether systemic inflammation alters neural activity associated with SCZ and other psychiatric disorders. Recent genome-wide linkage studies have started to pinpoint a number of common genetic denominators upstream of neurotransmitter release. For example, NRG1, encoding neuregulin 1, is involved in nervous system development and plasticity and has been associated with decreased activation of frontal and temporal lobe regions, increased development of psychotic symptoms and decreased premorbid IQ. The onset of SCZ has also been shown to be partly associated with polymorphisms in NRG1 and their interactions with variants of IL-1 β. A recent functional imaging study demonstrated that genetic variability at a particular locus of the IL-1 β gene correlates with differential neuronal activation in the bilateral frontal region of patients with SCZ. PET imaging has also revealed that a functional polymorphism of the IL-1 β gene is associated with decreased neuronal activity in the left DLPFC of SCZ patients during an attention task. These findings suggest that the altered expression of immune-related genes and the impact on downstream cytokines might contribute to both structural and functional brain abnormalities documented in people with SCZ.

**Prenatal Infection and the Risk of Adult SCZ**

A neurodevelopmental origin for at least some aspects of SCZ has received strong support in the literature over the past twenty years. Two major lines of evidence support the view that SCZ may be, in part, caused or exacerbated by inflammation triggered at an early age. First, events affecting the course of in utero neurodevelopment can have significant effects on long-term health and functioning. An inflammatory insult experienced in utero can lead to an enhanced expression of pro-inflammatory cytokines that have been previously shown to interfere with neonatal white matter development during the middle trimester of intrauterine life. A significant association has been found between high maternal levels of the pro-inflammatory cytokines TNF-α and IL-8 during pregnancy and an increased risk of the progeny developing the clinical features associated with SCZ. Epidemiological evidence suggests immune activation triggered by prenatal exposure to a range of infectious agents, such as herpes simplex virus (HSV-1), cytomegalovirus or influenza, is also associated with a heightened risk of SCZ. Exposure to HSV-1 has been linked to the presence of various structural abnormalities well documented in the brains of patients with SCZ and in those at high risk of developing psychosis. Voxel-based morphometric analyses has revealed that patients with SCZ who tested positive for antibodies to HSV-1 displayed grey matter reductions in the thalamus, cerebellum, pallidum, prefrontal cortex (PFC) and anterior cingulate cortex (ACC). These patients also performed significantly worse in neuropsychological measures of psychomotor speed, executive functioning and verbal memory. Prenatal infection and subsequent inflammatory attack on a background of genetic liability serves to further increase the risk of developing SCZ, consistent with the idea that genetic factors are necessary for inflammation to affect in utero brain development.

Second, animal models of maternal immune activation directly complements evidence suggesting that in utero infections are associated with an increased risk of developing SCZ. Experimental animal work shows that prenatal exposure to pro-inflammatory agents can be sufficient to cause apoptotic, necrotic and behavioural alterations consistent with what is observable in SCZ. Prenatal administration of poly cytidylic acid (poly-I:C), an agent capable of mimicking RNA virus exposure and immune challenge, has been shown to induce hallmark...
SCZ-like abnormalities in rodent offspring. A recent systematic review found that studies published between May 2001 and October 2011 consistently reported the development of the positive and negative dimensions of SCZ in animals treated with poly-I:C.\textsuperscript{125} In support of the neurodevelopmental model of SCZ, the progression of these symptoms were dependent on the specific gestation time window of the immune challenge.\textsuperscript{123} A more recent study reported an increase in the expression of interferon-induced transmembrane protein 3 (IFITM3) in astrocytes and notable neurodevelopmental impairments in mice following exposure to poly-I:C.\textsuperscript{124} Elevated mRNA expression levels of IFITM3 have also been routinely reported in the brains of neuropsychiatric diseases\textsuperscript{125} and IFITM proteins can be strongly induced by a number of viruses.\textsuperscript{126} Taken together, these findings serve to strengthen the argument that early, long-lasting immune insults contribute to the pathophysiology of neuronal dysfunction and SCZ. It is conceivable that maternal infection may impact negatively on later neurodevelopmental processes such as neuronal/glial cell maturation, signalling, differentiation, proliferation, and survival. The disruption of such crucial processes can lead to the thinning of cortical areas, reduced grey and white matter, and accelerated grey matter loss, potentially thereby facilitating the development of neuropsychological and neuropathological deficits associated with SCZ. It still remains unclear whether genes implicated in SCZ and environmental insults interact with pre- and postnatal levels of pro-inflammatory cytokines to increase the risk of SCZ and associated brain alterations.

**Glial Cell Activation and SCZ**

The release of cytokines in the CNS is mediated by glial cells - the ‘house-keeping’ cells of the brain. Microglia, supportive glial cells acting as resident macrophages and antigen-presenting cells within the CNS, are involved in the clearance of infection or cellular debris, thus playing a critical role in both neuronal repair and protection.\textsuperscript{127,128} One approach used in the study of the neuropathology of SCZ has involved examination of microglial and astrocytic activity. It has recently emerged that microglia may play a part in mediating and modulating inflammatory processes in the CNS of patients with SCZ.\textsuperscript{127-130} Increased densities of immunoreactive microglia have been reported in the brains of SCZ patients,\textsuperscript{131-136} findings recently confirmed in temporolimbic grey matter using PET imaging and an activated microglial ligand.\textsuperscript{135,136} However, this finding is not consistent and cannot be complicated in affected individuals using post-mortem immunohistochemical techniques.\textsuperscript{137-147} Perhaps microglial activation associated with active psychosis is short-lived and therefore difficult to detect. Other complicating factors relate to the inclusion of older patients within such studies, as aging is known to lead to increased microglial activity.

Abnormal astrocyte functions have also been implicated in the pathogenesis of SCZ. Analogous to microglia, astrocytes serve as immunocompetent cells and secrete a wide array of chemokines and cytokines to maintain CNS homeostasis.\textsuperscript{142} The proliferation of astrocytes (gliosis) can be considered a normal cellular process within the CNS, but can also serve as an indicator of a pathological process if persistent and present without explanation. In order to evaluate the functionality of astrocytes, astrocytic markers detected in the CSF and serum have been measured. A reliable indicator used in a number of studies is S100B, a small calcium binding astrocytic protein implicated in the regulation of both neuronal/glial proliferation and innate immune response.\textsuperscript{143-146} It has been demonstrated that the levels of serum S100B are significantly higher in drug naive patients with SCZ compared to healthy controls.\textsuperscript{145,147} It is important to note, however, that the upregulation of S100B by astrocytes and oligodendrocytes has also been noted in a number of neurodegenerative disorders,\textsuperscript{148} S100B expression has been associated with other neural cell types\textsuperscript{149} and its expression can be affected by confounding factors, such as obesity and diabetes.\textsuperscript{149-151} As with many other implicated pathways, the involvement of glial reactivity and its contribution to the immune signature of SCZ awaits further validation in drug-naive, or minimally medicated first-episode patients with SCZ.

**SCZ, Autoimmune Diseases and Autoantibodies**

A positive association between several autoimmune diseases present in the endocrine, neurologic and vascular systems, and SCZ is well documented in the literature.\textsuperscript{152} A variety of autoantibodies with cross-reactivity against specific brain regions and antigens linked to neurotransmission have also been described in the sera of patients with SCZ.\textsuperscript{23,153} It is well established that N-methyl-D-aspartate (NMDAR) hypofunction and downstream dysfunctional cortical-subcortical circuitry exists as one of the most persuasive models for SCZ.\textsuperscript{154,155} Healthy volunteers given NMDA antagonists such as ketamine display symptoms and cognitive deficits routinely observed in SCZ patients.\textsuperscript{156-158} Studies showing an increase in the
concentration of antibodies directed against NMDARs, and other neurotransmission receptors implicated in SCZ, provide an important link between immune abnormalities and altered neurotransmission. It has now been suggested that the NMDAR antibody interferes with glutamatergic signalling by selectively decreasing the number of NMDAR clusters in the postsynaptic density. In fact, prominent psychiatric symptoms such as psychosis, catatonia-like symptoms and dyskinesias in patients with encephalitis, can be triggered by IgG serum and CSF antibodies that are directed against extracellular epitopes of the NR1a subunit of NMDARs. Recent studies found that approximately 5-10% of SCZ cases were associated with serum and CSF autoantibodies to the NMDAR encephalitis can be triggered by IgG serum and CSF autoantibodies to the NMDAR. Importantly, the repertoire of antibody subtypes in SCZ has now been shown to differ from NMDAR encephalitis, potentially revealing a novel method to reaffirm the diagnosis of SCZ and provide more effective immunomodulatory treatment strategies.

Adjunctive Immune Modulation Therapies

Despite potentially fatal side effects, clozapine remains the most effective antipsychotic drug used in the treatment of SCZ. Immunologically mediated mechanisms have been attributed to the development of some of its more serious side effects, including agranulocytosis, myocarditis, and serositis. Data from both in vivo and in vitro studies suggest that clozapine exerts significant immunomodulatory actions on a number of cytokines, possibly resulting in a long-term normalisation of IL-6 levels. It is conceivable that clozapine is so successful in treating the treatment resistant positive symptoms of SCZ, and to a lesser extent the negative symptoms, because of its immunomodulatory effects. However, due to its potentially harmful effects on neutrophil levels together with the limited efficacy of a large proportion of current antipsychotic treatments, new immune-focused therapeutic strategies have been investigated. One of the major disabilities affecting the quality of life of people with SCZ, and left largely untouched, and possibly exacerbated by current antipsychotics, is the set of negative symptoms. Negative symptoms include social withdrawal, self-neglect and apathy and their severity can act as a major predictor of patient functioning. Several studies aimed at alleviating particularly the negative symptoms of SCZ have focussed on the anti-inflammatory, neuroprotective and antioxidant effects of a well-tolerated and widely available tetracycline antibiotic, minocycline. Minocycline can cross the BBB and has been shown to exert neuroprotective effects on models of ischaemic injury and Parkinson’s disease by reducing the infarct size and increasing survival of hippocampal neurons, respectively. Randomised controlled trials of minocycline in patients with early-phase SCZ showed significant treatment effects on negative symptoms and in general outcome. Minocycline may also elicit a marked acute antipsychotic effect in a subset of patients. It is likely that prompt treatment of neuronal inflammation will lead to an improvement in the quality of life and potentially delay the progression of SCZ; however, it remains unclear as to whether the therapeutic effects of minocycline are mediated by neuroprotective and/or anti-inflammatory actions.

Steroids are effective treatments for a variety of autoimmune and inflammatory conditions, for example Systemic Lupus Erythematosus (SLE) and Wegner’s Granulomatosis, but can result in alterations in mood, dementia and psychosis. Steroids are therefore a double edged sword, forcing researchers to turn to another class of molecules that counteract the effects of inflammatory mediators without inducing psychiatric effects. A recent meta-analysis on the use of non-steroidal anti-inflammatory drugs (NSAIDs) as useful therapeutic strategies in SCZ suggests a promising avenue for further investigation. A very recent review of 26 double-blind randomised controlled trials looking at the efficacy of a number of anti-inflammatory agents on symptom severity in patients with SCZ found that aspirin had beneficial effects. Together, these results provide further support for a neuroinflammatory (co)etiology and suggest that NSAIDs could be used as a relatively easy and early intervention therapy to minimise deficits and possibly even the neuro-structural and -functional abnormalities associated with the progression of SCZ. More studies using anti-inflammatory agents as augmentation therapies need to be carried out, especially those that may also impact on the metabolic syndrome, like statins.

SUMMARY AND OUTLOOK

Despite tremendous scientific and pharmacological advances, identification of the target pathology of SCZ remains a major challenge. Nevertheless, what remains abundantly clear after decades of research is that a single locus of dysfunction within the brains of SCZ patients cannot be responsible for the spectrum of symptoms that arise during the course of illness. The fact that antipsychotics provide only a partial answer together with a
leap in our understanding of the immune system has re-awakened an interest in one of the most persistent, enduring themes of research into the pathophysiological signature of SCZ. Substantial evidence from both human and animal studies suggests an association between increased levels of inflammatory cytokines, altered immune-related gene expression and SCZ, along with structural brain alterations associated with the disorder. Future clarification of cytokine and microglial signalling profiles, expression and distribution, all features of an over-active immune system, will help to elucidate how these factors are capable of giving rise to SCZ. Further understanding of gene—environment interactions will also accelerate the identification of novel genetic variants that are relevant to SCZ, all features of an over-active immune system and their involvement in SCZ.

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