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Clinical studies of neuroinflammatory mechanisms in schizophrenia

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ABSTRACT

Schizophrenia is a pervasive neurodevelopmental disorder that appears to result from genetic and environmental factors. Although the dopamine hypothesis is the driving theory behind the majority of translation research in schizophrenia, emerging evidence suggests that aberrant immune mechanisms in the peripheral and central nervous system influence the etiology of schizophrenia and the pathophysiology of psychotic symptoms that define the illness. The initial interest in inflammatory processes comes from epidemiological data and historical observations, dating back several decades. A growing body of research on developmental exposure to infection, stress-induced inflammatory response, glial cell signaling, structural and functional brain changes and therapeutic trials demonstrates the impact that inflammation has on the onset and progression of schizophrenia. Research in animal models of psychosis has helped to advance clinical and basic science investigations of the immune mechanisms disrupted in schizophrenia. However, they are limited by the inability to recapitulate the human experience of hallucinations, delusions and thought disorder that define psychosis. To date, translational studies of inflammatory mechanisms in human subjects have not been reviewed in great detail. Here, we critically review clinical studies that focus on inflammatory mechanisms in schizophrenia. Understanding the neuroinflammatory mechanisms involved in schizophrenia may be essential in identifying potential therapeutic targets to minimize the morbidity and mortality of schizophrenia by interrupting disease development.

1. Introduction

Schizophrenia is a disabling psychiatric disorder that affects an estimated 250 million people across the world at some point in their life (van Os and Kapur, 2009). Delusions, hallucinations, disorganized thinking and cognitive impairment are hallmarks of schizophrenia. Schizophrenia is a disease with no cure and long-term individual, family and societal costs. Suicide rates of those suffering from schizophrenia approach 10–15% (Rossler et al., 2005). Significant discoveries related to early identification, early treatment and stabilization with medications have led to more extensive research and a better long-term prognosis for schizophrenic patients.

Schizophrenia is likely the most researched of the neuropsychiatric diseases with an advanced scientific understanding of the genetic, environmental, molecular and physiologic contributing factors (Insel, 2011; Jaaro-Peled et al., 2009a; Muller and Schwarz, 2010; van Os and Kapur, 2009). However, there remains insufficient knowledge regarding the primary origin and subsequent progression of the disease. This may be due in part to the complexity of the illness and logistical challenges of studying psychotic symptoms in human subjects. Given the ability to manipulate neurotransmitter signals, animal models have been critical in determining that inflammatory signatures and cytokine signaling are precursors to psychosis. The collective literature in animal models appears to mimic the progressive nature of the clinical syndrome of schizophrenia, with exposure to pathogens in-utero and then development of aberrant pathology and clinical/behavioral symptoms emerging in adolescence or early adulthood. However, animal models have limitations in being able to recapitulate positive and negative symptoms of psychosis. The need for translational approaches in clinical schizophrenia investigations, the difficult nature of experimental design, and the clinical morbidity and mortality of the disease have generated research interest in new hypotheses that address the etiological process of schizophrenia in human subjects, cells and tissue and subsequently help lay the foundation for new therapies.

Historically, the pathophysiology of schizophrenia has been linked to abnormal neurodevelopment and deficits in dopamine. While the dopamine hypothesis has defined schizophrenia for

Abbreviations: CNS, central nervous system; COX, cyclooxygenase; CSF, cerebrospinal fluid; EAAT2, excitatory amino acid transporter 2; GWAS, genome-wide association study; HLA, human leukocyte antigen; IFN, interferon; IL, interleukin; KYP, kynurenine pathway; LPS, lipopolysaccharide; MRS, magnetic resonance spectroscopy; MHC, major histocompatibility complex; NAC, N-acetylcysteine; iNOS, inducible nitric oxide synthase; NK, natural killer; NMDA, N-methyl D-aspartate; NSAID, non-steroidal anti-inflammatory agents; PET, positron emission tomography; Polyl:C, polyriboinosinic–polyribo-cytidylic acid; RA, rheumatoid arthritis; ROS, reactive oxygen species; SLE, systemic lupus erythematosus; SNP, single nucleotide polymorphism; TGF, transforming growth factor; Th, T helper; TNF, tumor necrosis factor; TSPO, translocator protein.

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many years, a growing number of research investigations and scientific curiosity have developed around the immune system and the role of neuroinflammation in precipitating psychotic symptoms in a subset of patients with psychosis (Drexhage et al., 2010; Miller et al., 2011; Potvin et al., 2008; Upthegrove et al., 2014). These studies provide a detailed review of the theories and mechanisms that support a role for inflammation in schizophrenia. Since the 1980s the immune hypothesis of schizophrenia has emerged as a theory unified by data from human developmental, molecular imaging and therapeutic trial techniques. The consensus is that alterations in the immune system and neuroinflammation lead to progressive brain changes in schizophrenia (Fudenberg et al., 1983; Stevens, 1983). Epidemiologic, developmental, neuropathological and neuroimaging observations have further advanced clinical and neuroscience investigations in support of neuroinflammatory pathways in psychiatric illness.

Immune system dysfunction may result in part from prenatal exposure to a maternal infection of cerebral insult from *Toxoplasma gondii*, *Cytomegalovirus*, Chlamydia, influenza or other infectious agents that generate an immune response (Ellman et al., 2009; Khandaker et al., 2014b; Smesny et al., 2010). The subsequent cytokine cascade is thought to alter neuronal development before the illness is clinically expressed (Chew et al., 2013; Hagberg et al., 2012; Jaaro-Peled et al., 2009b). More recent developmental studies using schizophrenia patients and tissues have clarified this initial observation and shown that the inflammatory response, not necessarily the disease pathogen, alters the developmental trajectory of neurons (Meyer et al., 2010; Miller et al., 2011). Immune-related genes have also been linked to aberrant immune signaling in schizophrenia (Jia et al., 2010; Stefansson et al., 2009).

In response to infection, stress-induced inflammation appears to lead to psychopathological symptoms. In animal behavioral studies, an increased release of cytokines is suggested to mediate a cascade that "desensitizes" the immune system. This leads to changes in cellular proliferation, which further increases proinflammatory cytokines downstream. Cytokines are also important in the immune mechanisms of schizophrenia, as they activate the kynurenine pathway — an alternate route for tryptophan metabolism that leads to long-term changes in glutamatergic function, trophic support and synaptic function (Fig. 1). Glia cells in the form of astrocytes and microglia further support the role of the immune system. Microglia in particular act as cytokine sensors and serve as the key regulatory cells of the immune system in the central nervous system (CNS). Structural, molecular and functional changes in microglia were noted in post-mortem schizophrenia patients who completed suicide (Radewicz et al., 2000; Steiner et al., 2008b, 2011b; Wierzba-Bobrowicz et al., 2005). However, investigations using immunohistochemical markers have not consistently reported glial cell changes across all studies (Matthews and Harrison, 2011). Inflammatory mediators, through microglia and kynurenine metabolism, provide a related link to glutamate, dopamine and downstream reactive oxygen species as markers of oxidative stress in the pathophysiology of schizophrenia (Flatow et al., 2013; Kohen and Nyska, 2002; Muller, 2014; Swerdlow et al., 2009).

We conducted a critical review of the literature for articles on PubMed involving clinical studies and the search terms, schizophrenia and inflammation. We then assessed the data related to immune modulation of schizophrenia in either human tissue, cells or patients with schizophrenia. We selected articles where the primary language was English and then critically reviewed the multidisciplinary, translational research in schizophrenia subjects and subjects with non-affective psychosis. We discuss and analyze these investigations and identify potential therapeutic targets that may mitigate the debilitating effects of the disease and lead to a better-long term prognosis for patients.

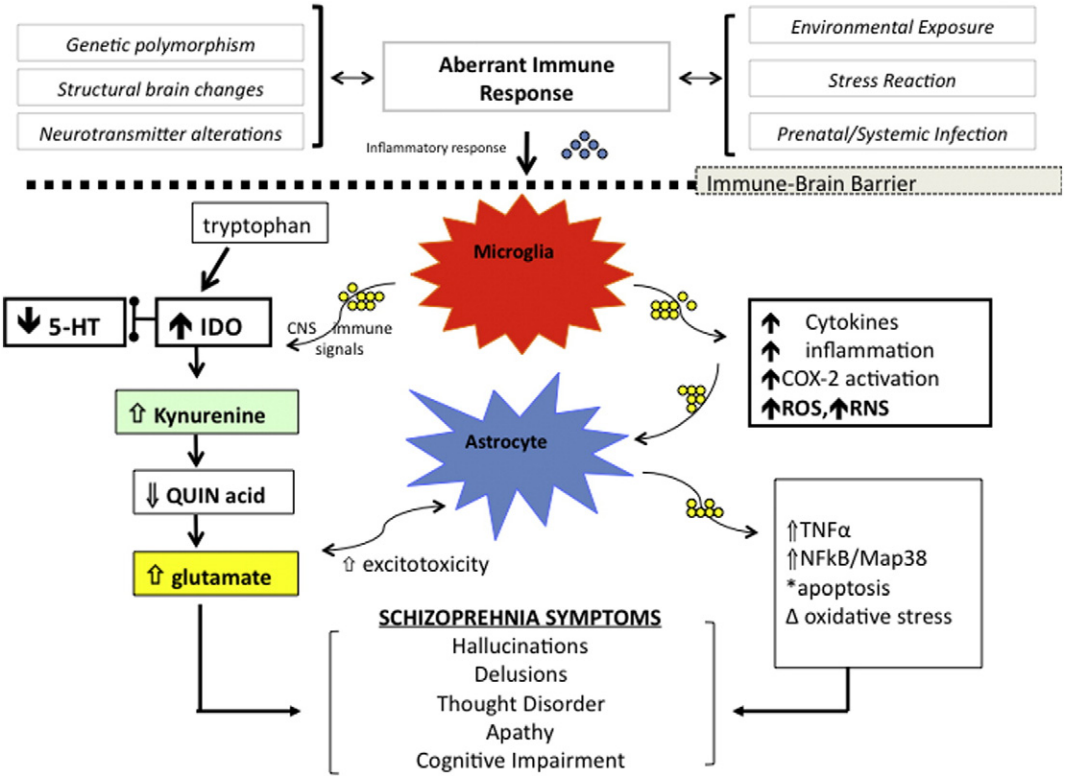

Fig. 1. Neuroinflammatory mechanism involved in schizophrenia and linked through kynurenine pathway (CRP — C-reactive protein; IDO — indoleamine 2,3-dioxygenase; 5-HT — serotonin; RNS — reactive nitrogen species; ROS — reactive oxygen species).