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The role of pro-inflammatory cytokines in the neuroinflammation and neurogenesis of schizophrenia

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ABSTRACT

Schizophrenia is a serious mental illness with chronic symptoms and significant impairment in psychosocial functioning. Although novel antipsychotics have been developed, the negative and cognitive symptoms of schizophrenia are still unresponsive to pharmacotherapy. The high level of social impairment and a chronic deteriorating course suggest that schizophrenia likely has neurodegenerative characteristics.
Inflammatory markers such as pro-inflammatory cytokines are well-known etiological factors for psychiatric disorders, including schizophrenia. Inflammation in the central nervous system is closely related to neurodegeneration. In addition to pro-inflammatory cytokines, microglia also play an important role in the inflammatory process in the CNS. Uncontrolled activity of pro-inflammatory cytokines and microglia can induce schizophrenia in tandem with genetic vulnerability and glutamatergic neurotransmitters. Several studies have investigated the possible effects of antipsychotics on inflammation and neurogenesis. Additionally, anti-inflammatory adjuvant therapy has been under investigation as a treatment option for schizophrenia. Further studies should consider the confounding effects of systemic factors such as metabolic syndrome and smoking. In addition, the unique mechanisms by which pro-inflammatory cytokines are involved in the etiopathology of schizophrenia should be investigated. In this article, we aimed to review (1) major findings regarding neuroinflammation and pro-inflammatory cytokine alterations in schizophrenia, (2) interactions between neuroinflammation and neurogenesis as possible neural substrates for schizophrenia, and (3) novel pharmacological approaches.

Contents

Abbreviations: Th1, type 1 T helper cells; Th2, type 2 T helper cells; CNS, central nervous system; BBB, blood–brain barrier; IL-2, interleukin-2; IL-12, interleukin-12; IL-10, interleukin-10; IL-4, interleukin-4; IL-6, interleukin-6; TNF-α, tumor necrosis factor alpha; IFN-γ, interferon gamma; CSF, cerebrospinal fluid; TGF-β, transforming growth factor beta; Th17, type 17 T helper cell; PolyI:C, polyriboinosinic-polyribocytidilic acid; RNA, Ribonucleic acid; IL-8, interleukin-8; SVZ, subventricular zone; SGZ, subgranular zone; DISC-1, Disrupted-in-schizophrenia 1; mRNA, messenger RNA; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; TNF-R1, TNF-α receptor 1; TNF-R2, TNF-α receptor 2; HPA, hypothalamus-pituitary-adrenal; gp130, glycoprotein 130; LTP, long-term potentiation; NMDA, N-methyl-D-aspartate; LIF, leukemia inhibitory factor; NRG-1, neurergulin-1; SNPs, Single nucleotide polymorphisms; IL-3, interleukin-3; sIL-2R, soluble IL-2 receptor; COX-2, cyclooxygenase-2; IDO, indolamine 2,3-dioxygenase; CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness; CRP, C-reactive protein; COX-1, cyclooxygenase-1; KYNA, kynurenic acid; MDD, major depressive disorder; MAPK, mitogen-activated protein kinase.

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1. Introduction

Schizophrenia is a chronic, debilitating mental disorder with a heterogeneous symptomatology which includes delusions, hallucinations, negativism, and cognitive deficits (Green, 1996). Although many etiological factors remain to be elucidated, interactions between genetic susceptibility and environmental stressors in the early stages of life are important in the development of schizophrenia (Harrison and Weinberger, 2005; McDonald and Murray, 2000). Several neuroimaging studies have also suggested that neurodegeneration is involved in the development of schizophrenia. Cortical gray matter loss has been shown to be associated with childhood-onset schizophrenia (Thompson et al., 2001). Hypofunctioning in the frontal regions during working-memory-related tasks has also been observed in the dorsolateral prefrontal cortical region in the brains of those with schizophrenia (Carter et al., 1998). Along with genetic and neurodegenerative factors, inflammation has been also regarded as a major causative and/or mediating factor for schizophrenia (Fan et al., 2007). In this article, we aimed to review the roles of cytokines on neuroinflammation and neurogenesis and, consequently, on the development of schizophrenia.

2. Inflammation in schizophrenia

2.1. The immune response and cytokines

Inflammation, the first reaction of the immune response, is a complex response of the host to tissue injury such as infection or physical insult (Nathan, 2002). The main function of inflammation is to restore host homeostasis by recovering from the damage. Because the collateral effects of the inflammatory processes can be harmful to the host, they should be rapid, specific, and self-limited. Immune reactions are categorized as either innate or adaptive responses. Innate immunity is mainly comprised of circulating effector cells such as mast cells, phagocytes, natural killer cells, and microglia. The main role of innate immunity is to quickly eliminate pathogens in a non-specific manner and to initiate an adaptive immune response by stimulating antigen-specific T and B lymphocytes. Adaptive immunity specifically recognizes and remembers pathogens. T helper cells play an important role in mediating the adaptive immune response. It has been suggested that naïve T helper cells mature into type 1 T helper cells (Th1) or type 2 T helper cells (Th2) in response to specific types of cytokines (D'Elios and Del Prete, 1998; Mosmann et al., 1986; Seder and Paul, 1994). A cytokine is composed of small glycoproteins that mediate signal communications among various immune and neuronal cells during the immune response. Cytokines are produced by peripheral immunocompetent cells, glial cells, and neurons (Woodroofe, 1995). Th1 cells are known to be involved in cellular immunity against intracellular bacteria and viruses and in autoimmune diseases such as multiple sclerosis and rheumatoid arthritis. In contrast, Th2 cells manage humoral immunity against extracellular parasites and allergic reactions.

2.2. Peripheral cytokines

Numerous studies have investigated alterations in peripheral cytokines in schizophrenia (Kim, 2005; Kim and Maes, 2003; Stober et al., 2009). Although the CNS is isolated from the peripheral immune system by the blood–brain barrier (BBB), it is possible for cytokines to invade the CNS under normal physiological conditions (Banks, 2005). For example, activated maternal pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 can invade the fetal CNS through various pathways (Banks, 2006). The possible mechanisms by which cytokines cross the BBB are saturable transport (Banks et al., 1989; Osburg et al., 2002), disruption of the BBB (Quagliarello et al., 1991), and through circumventricular organs that lack the BBB (Buller, 2001). Pro-inflammatory cytokines produced by chronically activated macrophages and T-lymphocytes have been reported as immunological findings in schizophrenia (Smith and Maes, 1995). Subsequent studies suggested that Th1 cytokines such as interleukin-2 (IL-2) and interleukin-12 (IL-12) are decreased in schizophrenia (Kim et al., 1998), whereas Th2 cytokines such as interleukin-10 (IL-10) are increased (Kim et al., 2002; Maes et al., 2002). Based on the dichotomous concept of an adaptive immune response, the Th1/Th2 imbalance hypothesis was suggested (Schwarz et al., 2001).

The higher prevalence of rheumatoid arthritis, a so-called Th1 disease, in control subjects versus subjects with schizophrenia is also regarded as support for the Th1/Th2 imbalance hypothesis (de la Fontaine et al., 2006; Eaton et al., 1992; Gorwood et al., 2004). However, other studies have reported inconsistent results regarding the polarization of Th2 in schizophrenia. (Hinze-Selch and Pollmacher, 2001; Kim et al., 2000, 2004, 2005; Na and Kim, 2007). Furthermore, two recent meta-analyses have reported that the evidence for the Th1/Th2 hypothesis as related to schizophrenia is insufficient. (Miller et al., 2011; Potvin et al., 2008). For example, levels of the Th2 cytokine interleukin-4 (IL-4) were not increased in patients with first onset or acute exacerbation of schizophrenia (Miller et al., 2011), or showed non-significant alterations (Potvin et al., 2008). IL-10, another Th2 cytokine, was even shown to be decreased in acutely relapsed inpatients (Miller et al., 2011). However, another study found that levels of pro-inflammatory cytokines are consistently increased in patients with schizophrenia. Yet another study reported that pro-inflammatory cytokines such as interleukin-6 (IL-6), IL-12, tumor necrosis factor-α (TNF-α), IL-1β, and interferon-γ (IFN-γ) are increased in the blood and cerebrospinal fluid (CSF) in first onset and acute relapse patients with schizophrenia (Miller et al., 2011). The results of several recent studies have supported the role of pro-inflammatory cytokines in schizophrenia. A post-mortem study reported that an inflammation-related gene is over-expressed in schizophrenia (Saetre et al., 2007). Another study found that IL-1β is significantly increased in the CSF of those with schizophrenia compared to healthy volunteers (Soderlund et al., 2009).

There are several important issues to address in interpreting the observed differences in peripheral cytokines in schizophrenia. First, the dichotomous categorization of T helper cells into Th1 and Th2 has become increasingly blurred. Most cytokines are produced and regulated by various intrinsic and extrinsic factors as well as by Th1 and Th2 cells. Additionally, novel Th cell categories have been suggested, such as regulatory T cells for TGF-β (McGuirk and Mills, 2002) and type 17 T helper cells (Th17) for interkeukin-17 (IL-17) and IL-10 (Acosta-Rodriguez et al., 2007; Korn et al., 2009; Romagnani et al., 2009). For example, rheumatoid arthritis, previously thought of as a Th1-shifted disease, has been recently suggested to be a Th17 immune response (Niu et al., 2012; Sarkar and Fox, 2010). Second, elevated peripheral cytokine levels are not necessarily associated with inflammation of the CNS, and are subject to numerous clinical and systemic factors such as obesity (Dandona et al., 1998; Weisberg et al., 2003) and glucose intolerance (DeMarco et al., 2010; Esposito et al., 2002). The approximate prevalence of the metabolic syndrome in the general population and in those with schizophrenia is 15.1–23.7% (Ford et al., 2002; Gu et al., 2005) and 22.2–60.0%, (Kang et

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