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Review

Role of microglia disturbances and immune-related marker abnormalities in cortical circuitry dysfunction in schizophrenia

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ABSTRACT

Studies of genetics, serum cytokines, and autoimmune illnesses suggest that immune-related abnormalities are involved in the disease process of schizophrenia. Furthermore, direct evidence of cortical immune activation, including markedly elevated levels of many immune-related markers, have been reported in the prefrontal cortex in multiple cohorts of schizophrenia subjects. Within the prefrontal cortex in schizophrenia, deficits in the basilar dendritic spines of layer 3 pyramidal neurons and disturbances in inhibitory inputs to pyramidal neurons have also been commonly reported. Interestingly, microglia, the resident immune-related cells of the brain, also regulate excitatory and inhibitory input to pyramidal neurons. Consequently, in this review, we describe the cytological and molecular evidence of immune activation that has been reported in the brains of individuals with schizophrenia and the potential links between these immune-related disturbances with previously reported disturbances in pyramidal and inhibitory neurons in the disorder. Finally, we discuss the role that activated microglia may play in connecting these observations and as potential therapeutic treatment targets in schizophrenia.

Contents

1. Introduction

Multiple lines of evidence from biomarker, genetic and epidemiological studies have converged to indicate an important role of immune-related abnormalities in the disease process of schizophrenia (Horvath and Mirnics, 2014). For example, higher levels of proinflammatory cytokines have been consistently reported in the peripheral serum of individuals with schizophrenia (Goldsmith et al., 2016; Miller et al., 2011; Potvin et al., 2008). Furthermore, variants in immune-related genes that associate with a higher risk for schizophrenia have been identified across multiple, large scale genome-wide association studies (Purcell et al., 2009; Ripke et al., 2011; Shi et al., 2009; Stefansson et al., 2009). In addition, individuals with schizophrenia have a higher rate of autoimmune illnesses, and individuals with autoimmune illness have a higher frequency of psychotic symptoms (Benros et al., 2014a; Benros et al., 2014b). Prenatal exposure to maternal immune activation, such as maternal exposure to infectious disease during pregnancy, is

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also associated with a higher risk of offspring developing schizophrenia later in life (Brown and Derkits, 2010). Recent studies have also reported direct evidence of marked elevations in transcript levels for multiple immune-related markers, including proinflammatory cytokines, in the prefrontal cortex of individuals with schizophrenia (Fillman et al., 2013; Volk et al., 2015).

Immune-related disturbances may be directly involved in the pathophysiology of cortical circuitry dysfunction in the illness. Deficits in basilar dendritic spines of deep layer 3 pyramidal neurons, a primary source of excitatory input, have been reported in the prefrontal cortex in schizophrenia (Glantz and Lewis, 2000; Konopaske et al., 2014). In addition, alterations in the CDC42 and ARP2/3 pathways, which regulate the actin cytoskeleton within dendritic spines, have been reported in pyramidal neurons in the prefrontal cortex in schizophrenia (Datta et al., 2015; Hill et al., 2006; Ide and Lewis, 2010). Furthermore, disturbances in inhibitory neurons have been consistently reported in the prefrontal cortex across large cohorts of schizophrenia subjects, including deficits in transcript levels for the GABA synthesizing enzyme glutamate decarboxylase (GAD67) (Akbarian et al., 1995; Curley et al., 2011; Duncan et al., 2010; Guidotti et al., 2000; Straub et al., 2007; Volk et al., 2000). In addition, lower mRNA levels for the calcium-binding protein parvalbumin, which is expressed by a distinct neuronal population that provides perisomatic inhibitory input to pyramidal neurons, have also been widely replicated in the prefrontal cortex in schizophrenia (Fung et al., 2010; Hashimoto et al., 2003; Mellios et al., 2009; Volk et al., 2012). Interestingly, recent evidence has found that microglia, the resident immune-related cells located in brain parenchyma, regulate excitatory inputs to spines and inhibitory inputs to the soma of pyramidal neurons (Chen et al., 2014; Paolicelli et al., 2011; Schafer et al., 2012; Sekar et al., 2016; Stevens et al., 2007; Trapp et al., 2007; Tremblay et al., 2010; Wake et al., 2009). Thus, activated microglia may represent a central node that connects the findings of cortical immune activation with disturbances in excitatory and inhibitory inputs to cortical pyramidal neurons.

Consequently, this review describes the peripheral serum, genetic and epidemiological evidence linking immune system abnormalities to schizophrenia. Cellular and molecular evidence of cortical immune activation and its potential impact on cortical circuitry function in schizophrenia are also discussed. Evidence that activated microglia may impact pyramidal neuron dendritic spine density and inhibitory neuron function in schizophrenia is presented as well. Finally, ideas for future directions for investigating the role of activated microglia in cortical circuitry dysfunction in schizophrenia, and the potential impact on discovering novel treatment targets, are presented.

2. Peripheral serum, genetic, and epidemiological evidence of immune abnormalities in schizophrenia and relevance for cortical circuitry dysfunction in the disorder

2.1. Peripheral serum and cerebrospinal fluid evidence of immune activation in schizophrenia

Multiple meta-analyses have confirmed the presence of higher cytokine levels in the peripheral serum of individuals with schizophrenia (Goldsmith et al., 2016; Miller et al., 2011; Potvin et al., 2008). Serum levels of proinflammatory cytokines such as IL-1β, IL-6, IL-8, and TNF-α have been reported to be elevated in individuals at all stages of the illness including first episode psychosis, acute relapse, and later in life (Goldsmith et al., 2016; Miller et al., 2011). Furthermore, a preliminary analysis from the North American Prodrome Longitudinal Study that included individuals at high risk for schizophrenia found evidence that elevated levels of IL-1β and IL-8, in combination with alterations in other immune- and inflammation-related markers, were associated with a higher risk of developing psychosis (Perkins et al., 2015). Treatment with antipsychotic medications can also partially ameliorate the elevated levels of some cytokines such as IL-1β and IL-6 in individuals with schizophrenia (Goldsmith et al., 2016). However, acute treatment with antipsychotic medications has also been associated with elevated levels of other cytokines, such as IL-12, in schizophrenia (Goldsmith et al., 2016). Thus, exposure to antipsychotic medications, in particular clozapine (Roge et al., 2012), may have a more complicated pattern of immunomodulatory effects on circulating cytokine levels in the disorder (Goldsmith et al., 2016). In addition, a recent meta-analysis reported elevated serum levels of C-reactive protein, an indicator of inflammation, in individuals with schizophrenia (Fernandes et al., 2016), and elevated C-reactive protein levels have been associated with more severe psychotic symptoms (Fernandes et al., 2016) and cognitive impairment (Dickerson et al., 2007; Johnsen et al., 2016) in the disorder. Furthermore, deficits in verbal fluency were reported in a subset of schizophrenia subjects with elevated peripheral cytokine mRNA levels (Fillman et al., 2016).

However, the relevance of higher peripheral serum cytokine levels and other indicators of inflammation to the underlying disease process in the brains of individuals with schizophrenia remains unclear for several reasons. First, the presence of cytokine buffering systems in the serum, such as soluble receptors and transmembrane proteins that inhibit the effects of IL-6 and TNF-α (Calabrese and Rose-John, 2014; Wolf et al., 2014), may mitigate the inflammatory effects of elevated peripheral serum cytokine levels on brain function in schizophrenia. Second, elevations in IL-1β and IL-6 levels have also been reported in the cerebrospinal fluid of individuals with schizophrenia (Garver et al., 2003; Sasayama et al., 2013; Schwieler et al., 2015; Soderlund et al., 2009). These findings suggest that small elevations in peripheral serum cytokine levels may instead be an indicator of, and may be possibly attributable to, elevated cytokine levels in the brains of individuals with schizophrenia, which is a topic that is discussed in greater detail below. Studies that quantify cytokine levels both in the peripheral serum and in the brains of the same schizophrenia subjects are needed to test this hypothesis. Finally, meta-analyses have also found elevated levels of several cytokines, such as IL-6 and TNF-α, in the peripheral serum of subjects with bipolar disorder (Goldsmith et al., 2016; Modabbernia et al., 2013) and major depressive disorder (Goldsmith et al., 2016; Hiles et al., 2012). Furthermore, exposure to multiple acute and chronic forms of stress has been reported to result in elevated levels of peripheral serum cytokines, including IL-6 and IL-1β, in subjects without psychiatric illness (Gouin et al., 2012; Maes et al., 1998; Steptoe et al., 2007). These findings raise the question of whether higher peripheral cytokine levels in individuals with schizophrenia, bipolar disorder and major depressive disorder may be attributable to stress-related factors associated with having a severe psychiatric illness.

2.2. Links between immune-related genes and schizophrenia

Genome-wide association studies (GWAS) of thousands of individuals with schizophrenia and unaffected individuals have consistently found that genetic variants of immune-related genes have a strong association with elevated risk for the disorder. In particular, multiple single nucleotide polymorphisms (SNPs) that were most strongly associated with schizophrenia are located in the extended major histocompatibility complex (MHC) region spanning several megabases on chromosome 6p (Purcell et al., 2009; Ripke et al., 2011; Shi et al., 2009; Stefansson et al., 2009). The association between the MHC region and schizophrenia risk has been reported to be partially attributable to allelic variants in the complement component 4 (C4) gene (Sekar et al., 2016), though this novel finding awaits replication. These allelic variants can affect C4 expression levels in human brain, and higher C4 mRNA levels have been reported in multiple cortical regions in schizophrenia (Sekar et al., 2016).

Recent evidence suggests that the C4 gene may be relevant for cortical circuitry dysfunction in schizophrenia. C4 is an important component of the classical complement cascade which is involved in synaptic pruning across adolescence (Schafer et al., 2012; Stevens et