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Interleukin 18 and cognitive impairment in first episode and drug naïve schizophrenia versus healthy controls

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ABSTRACT

Alterations in the inflammatory and immune systems have been documented to occur from the earliest stages of schizophrenia, and have been associated with neurodevelopmental changes. Cognitive impairment is a core feature in the pathology of schizophrenia, and recent studies showed a significant increase in serum IL-18 in schizophrenia, and a putative role of IL-18 in neuroprogression and thus neurocognitive defects. The purpose of this study was to examine the association of IL-18 with cognitive deficits in schizophrenia. We recruited 77 first episode and drug naïve schizophrenic patients and 75 healthy control subjects and examined the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and serum IL-18 in both groups. Schizophrenic symptoms were assessed using the positive and negative syndrome scale (PANSS). We found that IL-18 levels were non-significantly higher in patients than controls (206.0 ± 92.9 pg/ml vs 193.2 ± 41.8 pg/ml, $p = 0.28$). Cognitive scores on the RBANS and nearly all of its five subscales (all $p < 0.05$) except for the Visuospatial/Constructional index ($p > 0.05$) were significantly lower in schizophrenic patients than normal controls. For the patients, IL-18 was positively associated with the Visuospatial/Constructional domain of cognitive deficits in schizophrenia. Our findings suggest that cognitive deficits occur during the acute stage of a schizophrenic episode, and IL-18 may be involved in Visuospatial/Constructional deficits of these patients.

1. Introduction

In recent decades, prenatal infection and subsequently altered immuno-inflammatory, oxidative and nitrosative stress (O and NS) pathways have shown a significant role in schizophrenia (Smith and Maes, 1995; Anderson and Maes 2013) as neuroprogressive processes in the neurodevelopmental hypothesis of schizophrenia (Brown and Derkits, 2010). Such changes render the offspring prone to subsequent second hits from additional factors that are active during adolescence, contributing to both the emergence and progression of disease manifestations in schizophrenia (Anderson et al., 2013; Miller et al., 2013). Thus, interactions between early brain damage and abnormal development in adolescence are explained in this "2-hit" model (Keshavan, 1999; Keshavan and Hogarty, 1999). According to this model, the occurrence of abnormal development exists during two critical time points (i.e., early brain development and adolescence), eventually developing a full-blown schizophrenic disorder (Keshavan, 1999; Anderson et al., 2013).

Cytokines play an important role during neurodevelopment and in central nervous system (CNS) functions at all stages (Gaulden and Reiter, 2008). Indeed, besides their various roles in the peripheral immune system, cytokines have been recognized to exert a number of essential neurodevelopmental effects, including neuronal induction, proliferation, migration and survival (Deverman and Patterson, 2009; Jonakait, 2007). An increase of cytokines, following maternal infection, may alter the immune status of the brain, causing abnormal cell development with subsequent brain damage (Brown and Derkits, 2010). Numerous studies have shown that activation of the peripheral innate immune system induces production of cytokines within the brain that can have deleterious effects on cognition including interleukin-1β (IL-1β), IL-6, and tumor necrosis-α (TNF-α) (Chen et al., 2008; Dantzer et al., 2008; Sparkman et al., 2006; Yirmiya and Goshen, 2011). Inflammatory

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cytokines can negatively affect hippocampal function by directly impairing long-term potentiation (LTP) (Lynch, 2002; Pickering and O'Connor, 2007), and by inhibiting neurotrophins (Tong et al., 2008), which are important for neuronal survival/function, synaptic plasticity and memory formation (Minichiello, 2009; Poo, 2001; Tyler et al., 2002).

IL-18, previously termed IFN-γ-inducing factor, is a member of the IL-1 family of pro-inflammatory cytokines. The biological effects of IL-18 binding to the IL-18 receptor include induction of Th1 and Th2 helper T-cell responses and cytotoxic activity by natural killer cells, in addition to propagation of intrinsic and extrinsic pathways of apoptosis (Chandrasekar et al., 2004; Dinarello and Fantuzzi, 2003; Nakanishi et al., 2001). Based on recent experimental and clinical studies, IL-18 is also a presumed 'key' cytokine in the central nervous system (CNS), controlling two distinct immunological regulatory pathways of cytotoxic and inflammatory responses under neuropathological conditions (Felderhoff-Mueser et al., 2005). The active form of IL-18 induces signal transduction by binding to its receptor, which is expressed in a variety of brain regions including the hippocampus, the hypothalamus and the cerebral cortex (Wheeler et al., 2003, 2000). In addition, microglia and astrocytes can produce IL-18 (Das et al., 2008; Jeon et al., 2008). Therefore, IL-18 and its receptors are important modulators of immune responses in the CNS where they participate in neuroinflammatory and neurodegenerative processes but also influence homeostasis and behavior (Alboni et al., 2011).

Increasing evidence indicates that IL-18 may have a role in neurodegenerative disorders. For example, in the plasma, the levels of IL-18 were significantly elevated in patients with Alzheimer's Disease (AD), vascular dementia, and mild cognitive impairment compared to control groups (Malaguarnera et al., 2006; Ozturk et al., 2007). Furthermore, IL-18 levels from peripheral blood mononuclear cells (PBMC) were greater in AD patients than healthy control, and those IL-18 levels showed a significant correlation with cognitive decline (Bossu et al., 2008). This correlation was similar to the elevation described for other systemic pro-inflammatory cytokines associated with cognitive impairment (Baune et al., 2008; Yaffe et al., 2003). Interestingly, another recent study showed that after cardiopulmonary bypass (CPB), serum concentrations of IL-18, but not SC5b-9, were significantly different between patients with and without neurocognitive dysfunction. Moreover, serum IL-18 concentrations significantly increased in patients with neurocognitive dysfunction, suggesting a potential role for IL-18 as a serum marker for predicting neurocognitive dysfunction after CPB (Kumar et al., 2007). Taken together, these data indicate that IL-18-related inflammatory pathways may participate in pathogenic processes leading to cognitive dysfunction and dementia (Alboni et al., 2010).

There are now a number of indications that alteration in the immune system may be involved in the pathogenesis of schizophrenia (Ganguli et al., 1993; Muller et al., 1999). Numerous studies have reported changes in cytokines and cytokine receptors in schizophrenic patients (Muller et al., 2011). Two recent meta-analyses have supported the cytokine imbalance and activated macrophage hypothesis of schizophrenia (Potvin et al., 2008; Miller et al., 2011). Recently, several studies have explored the relationship between IL-18 and schizophrenia. For example, (Tanaka et al., 2000) found significantly increased serum IL-18 levels in schizophrenic patients. (Reale et al., 2011) reported significantly higher levels of constitutively and LPS-induced IL-18 released by peripheral blood mononuclear cells (PBMC) of schizophrenic patients compared with healthy controls. More recently, (Shirts et al., 2008) used a pathway-oriented approach to evaluate six genes mediating IL18 function (IL-18, IL18BP, IL18R1, IL18RAP, IL12B, and IL12A) in schizophrenia in a Caucasian population. They found that five SNPs in four genes were associated with schizophrenia. However, a most recent study did not find two promoter polymorphisms −137 G/C (rs187238) and −607 C/A (rs1946518) of IL-18 to be associated with schizophrenia in a Chinese population (Liu et al., 2011). Our recent study showed that serum IL-18 was significantly higher, and positively correlated with the general psychopathology subscore of the Positive and Negative Syndrome Scale (PANSS) in chronic schizophrenic patients (Xiu et al., 2012). Taken together, these studies may provide the initial evidence that IL-18 signaling may be involved in the pathophysiology of schizophrenia.

Schizophrenia is a psychiatric disorder characterized by cognitive deficits in the domains of executive function, working memory, attention and memory (Condray and Yao, 2011; Harvey et al., 2004; Palmer et al., 2009; Sharma and Antonova, 2003). Disturbances in cognition appear to be core features of the illness (Goff et al., 2011; Harvey et al., 2004). They can occur before the onset of the other symptoms of schizophrenia (Harvey, 2009), and generally persistent during the course of the schizophrenic illness (Irani et al., 2011; Rajji and Mulsant, 2008). These impairments have an important impact on social functioning, occupational functioning and the capacity for independent living in the community (Keefe, 2008). However, cognitive deficits are generally not responsive to currently available pharmacological treatments (Barch, 2010; Gallety, 2009; Goff et al., 2011). The pathophysiological mechanisms underlying these cognitive deficits are also unclear.

Based on the cognitive deficits of schizophrenia and the close relationship between IL-18 and cognitive dysfunction, as well as the important role of IL-18 in the pathophysiology of schizophrenia, it would be of interest to explore the association between cognitive impairments and IL-18 in schizophrenia.

2. Methods

2.1. Subjects

Seventy-seven (male, 40 and female, 37) drug-naïve first episode Chinese Han patients were followed for 3 months as inpatients after admission to Beijing Huilongguan hospital, a Beijing-city owned psychiatric hospital in order to establish a DSM-IV diagnosis of schizophrenia using the Structured Clinical Interview for DSM-IV (SCID). Their clinical subtypes were: paranoid, 42 (54.5%), undifferentiated, 29 (37.7%); disorganized 6 (7.8%). The patients had a mean age of 29.2 ± 9.6 years (range: 16–49 years), and a mean education of 12.2 ± 3.7 years. Two psychiatrists who had simultaneously attended a training session in the use of the positive and negative syndrome scale (PANSS) before this study start assessed the patients on the PANSS. After training, the psychiatrists maintained a correlation coefficient greater than 0.8 for the PANSS total score at repeated assessments. Mean scores on the PANSS were: positive subscore, 25.6 ± 6.0; negative subscale, 18.0 ± 7.3; general psychopathology subscale, 37.8 ± 10.5 and total PANSS Score, 82.4 ± 17.4.

Seventy-five healthy volunteers (male, 43 and female, 32) were recruited by advertisements in the local community. The controls had a mean age of 28.7 ± 9.1 years and a mean education of 11.7 ± 3.7 years. They were matched for gender, age and education with the above first-episode schizophrenic patients. Current mental status and personal or family history of any mental disorder were assessed using unstructured interviews. No control subject presented a personal or family history of psychiatric disorder.

All subjects were Han Chinese from the Beijing area. They were in good physical health, and any subjects with medical illnesses or drug and alcohol abuse/dependence were excluded. The Institutional Review Board for the Beijing Huilongguan hospital approved the research protocol, and all subjects provided written informed consent.