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A functional polymorphism in the interleukin-1beta and severity of nicotine dependence in male schizophrenia: A case-control study

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ABSTRACT

Previous studies have shown that the functional 511C/T polymorphism in the IL-1beta-gene may be implicated in the susceptibility for schizophrenia. Moreover, recent studies suggested that IL-1 participates in the progression of lung disease in smokers, which are overrepresented in schizophrenia. We aimed to investigate the possible relationship between the *IL-1beta-511*C/T polymorphism and smoking behavior in schizophrenia versus healthy controls in a Chinese population. The *IL-1beta-511C/T* polymorphism was genotyped in 638 male patients with chronic schizophrenia (smoker/never-smoker = 486/152) and 469 male controls (smoker/never-smoker = 243/226). The cigarettes smoked per day, the Heaviness of Smoking Index (HSI) and the Fagerstrom Test for nicotine dependence (FTND) were assessed. Patients were also rated on the Positive and Negative Syndrome Scale (PANSS). The results showed no significant differences in genotype and allele distribution between patients and controls, and between smokers and never-smokers in either the patient or control group. However, in patients, smokers with the C/C genotype had significantly higher HSI ($p < 0.005$) and FTND ($p < 0.05$) scores than smokers with the T/T genotype, without significant differences in controls. Furthermore, there was a linear positive correlation between the number of C alleles and the HSI ($p < 0.005$) in patients. Our findings suggest that the *IL-1beta-511*C/T polymorphism may not be related to schizophrenia or smoking status in Chinese individuals, but may affect the severity of nicotine dependence among male smokers with schizophrenia.

1. Introduction

Smoking rates among patients with schizophrenia are significantly higher than in the general population, as well as compared to other severe mental illnesses (de Leon and Diaz, 2005). Furthermore, smokers with schizophrenia may smoke more heavily and extract more nicotine from each cigarette (Williams et al., 2005). Cigarette smoking or nicotine may serve as a form of self-medication to reduce some side effects of antipsychotic medications, and may alleviate negative symptoms and/or cognitive deficits in patients with schizophrenia (Kumari and Postma, 2005; Leonard et al., 2007; Mobascher and Winterer, 2008; Winterer, 2010). Using nicotine to 'self-medicate' may explain the lower motivation and the greater difficulty during smoking cessation efforts in individuals with schizophrenia (Tsoi et al., 2010). However, chronic cigarette smoking in people with schizophrenia has

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been reported as an important contributing factor to the higher morbidity and mortality (Lichtermann et al., 2001).

It is generally accepted that many of the deleterious effects of cigarette smoke on human health may be due to its adverse effects on the immune system by altering the humoral and cellular immunity and the levels of certain cytokines (Sopori et al., 1998, 2002). Cigarette smoking has been reported to suppress the production of human proinflammatory IL-1beta (IL-1β), IL-2, interferon-gamma, and TNF-alpha *in vitro* (Ouyang et al., 2000). The experimental animal models showed immunosuppressive properties of nicotine by depressing the primary and secondary immune response of the lungs, lymph nodes, and spleen (Sayers and Drucker, 1999). Reduced production of the proinflammatory cytokines IL-1β, IL-6 and TNF-alpha by alveolar macrophages has also been demonstrated in smokers in the general population (Chen et al., 2007). Moreover, chronic smoking has been associated with a decreased number of Th1 cells and increased Th2-cells with subsequently higher levels of the anti-inflammatory cytokines IL-4, IL-5 and IL-10 secreted by Th2-cells (McCrea et al., 1994; Sopori and Kozak, 1998). Although the effect of smoking on the immune system has been studied extensively, unfortunately, conflicting results have been reported. For example, an increase in the secretion of pro-inflammatory cytokines in smokers has also been reported (George et al., 1997; Sopori and Kozak, 1998).

Schizophrenia is associated with various abnormalities in the immune system (Muller et al., 1999; Muller and Schwarz, 2006; Altamura et al., 2013). Recently, numerous studies have reported changes in cytokines, cytokine receptors and cytokine activity modifiers in the blood and cerebrospinal fluid (CSF) of patients with schizophrenia. For example, a meta-analysis by Potvin et al. (2008) found an increase in *in vivo* peripheral levels of IL-1 receptor antagonist (IL-1RA), sIL-2R, and IL-6 and a decrease in *in vitro* IL-2 secretion in patients with schizophrenia. A more recent meta-analysis by Miller et al. (2011) found significant increases in macrophage derived cytokines IL-1β, IL-6, and TNF-alpha, as well as of Th1-derived cytokines IFN-gamma and IL-12 in patients with first-episode psychosis. Also, a meta-analysis of genome wide association study (GWAS) datasets identified variants of genes involved in the immune response that are significantly correlated with a schizophrenia diagnosis (Ripke et al., 2011). Taken together, these results suggested that smoking may contribute to immune abnormalities implicated in the pathogenesis of schizophrenia.

IL-1β is a pleiotropic cytokine that is produced predominantly in the periphery by activated immune cells, contributing to inflammation, cell growth, and tissue repair (Vamvakopoulos et al., 2002; Hanninen et al., 2008). Several lines of evidence suggest that the pro-inflammatory cytokine IL-1β is implicated in the etiology and pathophysiology of schizophrenia. For example, abnormal blood, cerebrospinal fluid concentrations and *in vitro* production of IL1 and IL1 receptor antagonist have been detected in patients with schizophrenia (Maes et al., 1996; Toyooka et al., 2003), although studies investigating peripheral levels of IL-1β in patients with schizophrenia have reported inconsistent results (Xu and He, 2010). However, the most recent study reported elevated serum IL-1β levels, but not in leukocyte gene expression analyses in first-episode psychosis patients, suggesting that elevated serum IL-1β levels are not related with the peripheral blood immune cells but may derive from cytokine-producing cells (Di Nicola et al., 2013). Kowalski et al. (2001) reported that the release of IL-1β by peripheral monocytes was increased before treatment and then normalized with antipsychotic medication in patients with schizophrenia. Recently, Liu et al. (2010) reported that IL-1β was over expressed in the peripheral blood of paranoid patients with schizophrenia.

The *IL1β* gene is located within an *IL-1* gene cluster, spanning 400 kb on chromosome 2q.14, a region that linkage studies have identified as increasing susceptibility for schizophrenia (Lewis et al., 2003; Ng et al., 2009). The *IL-1β* gene has a single nucleotide polymorphism (SNP) in the promoter region at position -511 (-511C/T, rs16944) (Hanninen et al., 2008), which has been shown to produce an impact on the levels of *IL-1* gene complex (Hulkkonen et al., 2000) and which is also involved in the regulation of IL-1β expression (Chen et al., 2006). A number of association studies have suggested that genetic variability at *IL1β* might be strongly implicated in the susceptibility to schizophrenia, specifically the -511C/T polymorphism (Katila et al., 1999; Zanardini et al., 2003; Papiol et al., 2004; Rosa et al., 2004; Hanninen et al., 2008; Mata et al., 2006; Shirts et al., 2006; Sasayama et al., 2011; Borkowska et al., 2012), although other studies did not replicate this result (Meisenzahl et al., 2001; Betcheva et al., 2009; Chowdari et al., 2001; Yang et al., 2003; Saiz et al., 2006). Two recent meta-analyses provided support for a significant association of the *IL-1β*-511C/T polymorphism with schizophrenia (Allen et al., 2008; Xu and He, 2010); however, one most recent meta-analysis does not support a role for *IL-1β* in schizophrenia susceptibility (Shibuya et al., 2014).

It is well known that cigarette smoking is a main and definite risk factor for lung cancer, and the majority of lung cancers are associated with tobacco smoking. A number of molecular epidemiological studies have been conducted to examine the association between *IL1β* and cancer susceptibility (Zienolddiny et al., 2004; Lind et al., 2005; Asada et al., 2006; Wu et al., 2010), suggesting that *IL1β* may contribute to lung cancer progression. Moreover, haplotypes of *IL1β* and of the naturally occurring IL-1RA are different in smokers with rapidly declining lung function than in smokers with normal lung function, suggesting that IL-1 participates in the progression of lung disease in smokers (Joos et al., 2001; Wu et al., 2010). On the other hand, increasing evidence demonstrates the association between *IL1β* and addiction. A previous study showed that *IL1β*-31C/T was associated with smoking in Japanese (Hamajima et al., 2001), although the same group did not confirm the association between the smoking habit and the *IL1B*-31C/T polymorphism in Japanese Brazilians (Uno et al., 2002). Another study has shown that the *IL-1β*-511C/T gene polymorphism was associated with susceptibility to alcoholism in Spanish men (Pastor et al., 2005). Furthermore, this finding was confirmed by a more recent study, showing that *IL-1β* single nucleotide polymorphisms at position -511 and -31, were associated with dependence to alcohol as well as to opioids in two separate populations (Liu et al., 2009a). These results suggest that *IL-1β* gene polymorphisms are associated with altered risk of smoking, alcohol or opioid dependence.

The main purpose of the present study, therefore, was to investigate the possible relationship between the *IL1β*-511C/T polymorphism and smoking behavior in patients with schizophrenia versus healthy controls in a Chinese population. Because smoking is substantially more common among Chinese men than Chinese women with schizophrenia (Zhang et al., 2010), and since there are gender differences in smoking behaviors (de Leon and Diaz, 2005), we included only male subjects.

2. Methods

2.1. Subjects

We recruited 638 male schizophrenia inpatients from Beijing Hui-Long-Guan hospital, a Beijing-city-owned psychiatric hospital, and HeBei Province Veteran Psychiatric Hospital in BaoDing city,