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Mini review

Effects of *interleukin-1beta* polymorphisms on brain function and behavior in healthy and psychiatric disease conditions

Shih-Jen Tsai[a,b,*]

[a] Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan
[b] School of Medicine, National Yang-Ming University, Taipei, Taiwan

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ABSTRACT

A high level of Interleukin-1beta (IL1B), a key mediator of inflammation, is expressed in the brain, particularly in the hippocampus, which plays a pivotal role in memory and mood regulation. In the brain, IL1B exerts a myriad of effects such as neuronal proliferation, differentiation, apoptosis, and long-term potentiation. Considering its pleiotropic effects in the brain, IL1B has been implicated in the pathogenesis of various psychiatric disorders as well as cognitive function in normal individuals. Thus, *IL1B* has been considered a candidate gene for the study of psychiatric diseases as well as brain function in normal individuals. The polymorphisms of *IL1B* have been described in relation to various expression levels in response to stimulation. This review describes previous studies on the genetic effects of *IL1B,* which relate it to psychiatric diseases such as major depressive disorder, bipolar disorder, schizophrenia, and Alzheimer's disease, as well as cognitive function in normal individuals. Although many reports have indicated a possible role of the genetic effects of *IL1B* or its phenotypes in psychiatric diseases, some reports were unable to confirm these findings. IL1B release is mediated by an inflammatory response or psychological stress, leading to a cascade of immune reactions involving numerous immune components. To further explore the genetic effects of *IL1B* on mental diseases and brain function, gene–gene and gene–environment interactions should also be considered.

Contents

1. Introduction

Interleukin-1 beta (IL1B), a member of the interleukin-1 family, is a potent pro-inflammatory cytokine and plays a crucial role in several inflammatory and autoimmune diseases. IL1B is mainly produced by blood monocytes and tissue macrophages [1,2]. Increased peripheral IL1B production has been reported in patients

* Corresponding author at: Department of Psychiatry, Taipei Veterans General Hospital, No. 201, Shih Pai Road, Sec. 2, 11217, Taipei, Taiwan.
E-mail address: tsai610913@gmail.com (S.-J. Tsai).

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with various inflammatory and autoimmune diseases, infections, cancers, and trauma [3–5]. In addition to peripheral tissue, an immunocytochemical study in rats reported that IL1B is widely distributed in the brain, particularly in the hippocampus and hypothalamus [6]. In the brain, IL1B is synthesized and released mainly by the microglia and astrocytes [7,8]. In 1998, Schneider et al. first demonstrated that the expression of *IL1B* increases substantially during long-term potentiation (LTP) of synaptic transmission, which is a synaptic strengthening process that has been implicated in learning and memory [9]. Subsequent animal studies have indicated that physiological levels of IL1B promote LTP and memory formation [10], whereas high levels of IL1B can act on hippocampal neurons to inhibit synaptic strengthening and LTP [11,12].

Peripheral proinflammatory cytokines such as IL1B can also exert their effects on the brain. These effects probably occur through two different routes. The neural route is represented by the primary afferent neurons and the humeral route involves diffusion of the cytokines from the blood to the brain through the circumventricular organs and the choroid plexus [13].

In humans, *IL1B* is located on chromosome 2q14. Its expression is modified by several genetic polymorphisms in its regulatory region. In 1992, Pociot et al. identified a functional biallelic (C/T) polymorphism in the promoter region (position 511) (rs16944) of *IL1B* [14]. An *IL1B* allele dosage effect of this single nucleotide polymorphism (SNP) on secretory capacity was observed after lipopolysaccharide (LPS) stimulation in vitro. In the study, the *IL1B*-511T homozygous individuals secreted significantly more IL1B than the heterozygous individuals did. However, the heterozygous individuals secreted significantly more IL1B than the *IL1B*-511C homozygous individuals did [14]. This *IL1B* C-511T polymorphism has been shown to be associated with various diseases, including systemic sclerosis [15], gastric cancer [16], chronic obstructive pulmonary disease [17], and chronic periodontitis [18]. In addition to the *IL1B* C-511T SNP, other common SNPs within the *IL1B* promoter region might affect promoter function. The *IL1B* C-1473T (rs1143623) SNP lies within a binding site in the promoter region for proteins belonging to the GATA transcription factor family, and the minor allele exhibits enhanced protein binding. This SNP was associated with gastric cancer in the Korean population [19]. A study on *IL1B* G-31A (rs1143627) involving a single SNP analysis indicated that the *IL1B*-31A allele reduced promoter activity more than the *IL1B*-31G allele did, and the SNPs *IL1B* C-511T and *IL1B* G-31A are essentially in complete linkage disequilibrium (LD) in all populations [20]. The *IL1B* C-3737T (rs4848306) SNP was reported to be functional [20] and associated with the risk of colorectal cancer in a Danish case-cohort study [21].

Notably, in the seven sequenced exons of *IL1B*, only one SNP was identified in the coding region. The well-described synonymous *IL1B* C3954T SNP (rs1143634, +3954 from the transcriptional start site) has previously been reported to be functional. Furthermore, the *IL1B* 3954TT individuals has been reported to produce 4-fold higher amounts of IL1B than individuals with the *IL1B* 3954CC genotype [14]. Similarly, another study reported a significant increase in the plasma levels of IL1B in *IL1B* 3954TT carriers [22].

Compelling evidence suggests that mental disorders, including major depressive disorder (MDD), bipolar disorder (BD), schizophrenia, and Alzheimer's disease (AD), can be considered to be neuroinflammatory disorders [23,24]. An increase in the inflammatory response to a psychosocial stressor or oxidative stress may trigger the microglia and lead to a marked increases in IL1B levels [25,26]. IL1B, which is overexpressed in the brain, is a major component of the inflammatory pathway. It is considered an attractive candidate for studies on brain function in healthy individuals as well as those on various mental disorders. This study reviews genetic studies on the role of *IL1B* in mental disorders, such as MDD, BD, schizophrenia, and AD, as well as brain function in normal individuals. In this study, a systematic search was performed for *IL1B* genetic studies on mental disorders by using the PubMed database up to March 1, 2017. Additional information from reference lists of published articles was also obtained. The following keywords were used for searching: ((interleukin-1 beta) OR (IL1b) OR (IL-1b) OR (IL-1β) OR (interleukin-1b)) AND ((polymorphism) OR (mutation) OR (variant) OR (variation) OR (genotype) OR (genetic)) AND (schizophreni* OR (bipolar disorder) OR manic OR mania OR depress* OR Alzheimer* OR dementia OR suicide OR cognit* OR imaging). These literature searches were limited to English language articles. All original observational studies investigating the association between *IL1B* polymorphisms and risks of mental disorders were selected. Additionally; manual searches for related articles were also performed.

2. Genetic studies on *IL1B* in major depressive disorder

Inflammation, stress, and depression are closely interrelated. Increasing evidence indicates that interleukin-mediated communication pathways between the immune system and the brain are involved in MDD pathogenesis [27]. Of the numerous interleukins, IL1B is one of the most studied in relation to MDD. Animal and clinical studies have reported the crucial role of IL1B in MDD and the action of antidepressant drugs (Table 1). Animal studies have reported that intracerebroventricular or peripheral administration of IL1B to rats produced depressive-like symptoms, including anorexia, disturbed sleep patterns, anhedonia, and endocrine variations, which are often associated with stress and anxiety [28,29]. The symptoms induced by IL1B administration were attenuated using antidepressant treatment [30,31]. In clinical studies, an increase in the levels of IL1B in the blood and cerebrospinal fluid (CSF) of patients with MDD has been reported [32,33]. CSF IL1B levels have been found to be correlated with the age of MDD onset, duration of illness, and severity of depression [32,34]. A similar finding was also reported in geriatric patients with MDD [35].

The aforementioned findings indicate that *IL1B* is an appropriate candidate in genetic and pharmacogenetic studies on MDD. In 2003, we studied the association between the *IL1B* C-511T polymorphism and MDD in 157 outpatients with MDD and 112 controls. In the study, the associations were negative, which suggested that the *IL1B* C-511T polymorphism was not a major factor contributing to MDD susceptibility [36]. However, we found that patients with MDD who were carriers of the *IL1B*-511TT

Table 1
Evidence supporting the role of interleukin-1 beta (IL1B) in the pathogenesis of major depression.

	References
Immune system alterations in stress reaction and in MDD.	[27]
Intracerebroventricular or peripheral IL1B administration produced depressive-like symptoms in rats.	[28,29]
The depressive-like symptoms induced by IL1B in rats can be attenuated by antidepressant treatment.	[30,31]
An increase in IL1B levels in cerebrospinal fluid (CSF) or serum in MDD.	[32,33]
CSF or serum IL1B levels were correlated with the age of MDD onset, duration of illness, and severity of depression.	[32,34]