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Research paper

Interactions between the vascular endothelial growth factor gene polymorphism and life events in susceptibility to major depressive disorder in a Chinese population

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ABSTRACT

Background: Recent studies suggest that vascular endothelial growth factor (VEGF) is involved in the development of major depressive disorder. The aim of this study is to investigate the interaction between vascular endothelial growth factor (VEGF) polymorphism (+405 G/C, rs2010963) and negative life events in the pathogenesis of major depressive disorder (MDD).

Methods: DNA genotyping was performed on peripheral blood leukocytes in 274 patients with MDD and 273 age-and sex-matched controls. The frequency and severity of negative life events were assessed by the Life Events Scale (LES). A logistics method was employed to assess the gene-environment interaction (G × E).

Results: Differences in rs2010963 genotype distributions were observed between MDD patients and controls. Significant G × E interactions between allelic variation of rs2010963 and negative life events were observed. Individuals carrying the C alleles were susceptible to MDD only when exposed to high-negative life events.

Conclusions: These results indicate that interactions between the VEGF rs2010963 polymorphism and environment increases the risk of developing MDD.

1. Introduction

Major depressive disorder (MDD) is a common, severe and life-threatening psychiatric illness and is one of the leading causes of disability in the world (Kessler et al., 2006; Baune et al., 2007; Minelli et al., 2011); however, to date, its pathogenesis remains unknown.

Increasing evidence demonstrates that dysregulation of neurotrophic factors plays an important role in the pathophysiology of depression. The neurotrophic hypothesis of MDD implicates that stress decreases the level of neurotrophic factors in limbic brain structures, while antidepressants have an opposing effect, thus underlying the pathophysiology and treatment of MDD (Schmidt and Duman, 2007; Krishnan and Nestler, 2008; Greene et al., 2009; Serafini et al., 2014).

Vascular endothelial growth factor (VEGF) has been extensively described as an angiogenic and mitogenic factor produced by endothelial cells (Ferrara et al., 2003). Recent studies found that VEGF contributed to hippocampal neurogenesis (Jin et al., 2002; Ruiz de Almodovar et al., 2009), and displayed neuroprotective effects against stress-related neuronal injury (Storkebaum et al., 2004). In addition, studies indicated that electroconvulsive seizures increased hippocampal VEGF expression (Newton et al., 2003; Altar et al., 2004) and that these increased VEGF levels in hippocampus were essential for exerting the effects associated with antidepressant drugs (Segi-Nishida et al., 2008; Warner-Schmidt and Duman, 2008; Greene, Banasr et al., 2009; Fournier et al., 2012). Taken together, the above studies suggest that VEGF may be involved in the pathophysiology and potential treatment of MDD.

The VEGF gene is located on chromosomal region 6p21.3 and

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includes eight exons and seven introns (Elfving et al., 2014). VEGF +405 G/C (rs2010963) is a polymorphism located within the VEGF 5-untranslated promoter region, and has been extensively explored in association studies due to the highest frequency of the VEGF gene in this area (Young et al., 2004). In addtion, a significant correlation has been found between VEGF +405 G/C and VEGF protein production (Watson et al., 2000). Studies have found that VEGF +405 G/C is associated with psoriasis (Wu et al., 2010; Lee and Song, 2015; Bozduman et al., 2016), lung cancer (Liu et al., 2015), type 1 diabetes mellitus (Del Bo et al., 2006), and Graves' disease (Vural et al., 2012). To the best of our knowledge, there is no study regarding the relationship of the VEGF +405 G/C polymorphism and MDD.

Although genetic predisposition accounts for 31–42% of MDD cases (Sullivan et al., 2000), environmental factors also a play crucial role in the pathogenesis of MDD. Growing evidence have indicated that stress plays an important role in the pathology of major depressive disorder (Bale, 2006; Binder and Nemeroff, 2010). Negative life events are known to be one of the most common stressors and include health problems, interpersonal relationship problems, unemployment, and a variety of other negatively related occurrences. A large body of evidence has indicated that MDD patients experienced more stressful life events than healthy controls, indicating that negative life events are associated with MDD (Kraaij et al., 2002; Kendler et al., 2003; Rice et al., 2003; Fisher et al., 2012).

Therefore, to study the interactions between environmental factors and genetic factors is essential for clarifying the pathogenesis of MDD. However, to date, it remains unknown whether VEGF gene polymorphisms are associated with MDD via interactions with environmental factors. The aim of the present study was to explore the interaction between VEGF +405 G/C and negative life events in a Chinese population and to determine whether this interaction is involved in the pathophysiology and therefore, potential treatment of MDD.

2. Methods

2.1. Subjects

Subjects consisted of 274 patients and 273 healthy controls. Both patients and controls were Chinese Han origin inhabitants of northern China.

The MDD group consisted of 82 males and 192 females (age: mean, 41.08; S.D., 12.27; range, 20–59), and all patients underwent a structured interview by two experienced psychiatrists using the Diagnostic and Statistical Manual of Mental Disorders (fourth edition, DSM-IV) to confirm MDD. The severity of depression was evaluated by a Chinese version of the 24-item Hamilton Rating Scale of Depression (HRSD-24). Patients with a minimum score of 21 were included in the study. Patients with other comorbid axis-I disorders, a family history of genetic disease, neurological diseases and those who received antidepressant medication within 4 weeks were excluded from the study.

The control group included 79 males and 194 females (age: mean, 41.2; S.D., 11.2; range, 20–57). All subjects were recruited from the Physical Examination Center in the First Affiliated Hospital of Harbin Medical University. The Structured Clinical Interview for DSM- IV (SCID) was employed to exclude psychiatric diseases, neurological illness, and alcohol or drug abuse. Controls were matched for age, sex and level of education with the MDD patients. The study was approved by the Ethics Committee of the Harbin Medical University and all subjects gave their written consent.

2.2. Assessment of negative life events

The Life Events Scale (LES), which has been validated in a Chinese population, was employed to assess negative life events (Yang and YL, 1999). The LES, a 48-item questionnaire consists of three factors: family life (28 items), work (13 items), and social and other aspects (7 items). Negative life events include among others, bereavement, divorce, serious illness, housing and financial crises, unemployment, work pressure and relationship problems with colleagues. The scores for positive and negative life events were determined by interviewers to yield a total life events score. The scale evaluated four aspects of life events: time of occurrence (absent = 1; more than one year ago = 2; within the past year = 3; and chronic = 4), character (good = 1; bad = 2), influence on mood (absent = 1; mild = 2; moderate = 3; severe = 4; and extreme = 5), and duration of influence (≤ 3 months = 1; 3–6 months = 2; 6–12 months = 3; and > 12 months = 4). The 75% percentile (a score of 2) was employed as a cutoff value for high and low level negative life events.

2.3. DNA extraction and genotyping

Genomic DNA was extracted from collected venous blood samples using the AxyPrep Blood Genomic DNA Miniprep Kit (Axygen, Union City, CA, USA) and the SNPs (rs2010963) of the VEGF gene were selected for subsquent studies. The primers used for PCR amplification were designed using Primer 5.0 software, and the specificity of potential primer was checked using the Basic Local Alignment Search Tool (BLAST) provided by the National Center for Biotechnology Information. The primers for amplifying the VEGF rs2010963 fragments were 5′ TTGCTCTACTTCCCCAAATCA 3′ (forward) and 5′ TGTCCGTCAGCGCGACTGGTC 3′ (reverse). Analyses of SNPs was performed using SNaPshot according to the manufacturer's instructions.

2.4. Statistical analysis

The SPSS package (version 20.0 for Windows) was used for data analyses. Chi-square (χ^2) goodness-of-fit test was performed to test the Hardy-Weinberg equilibrium (HWE) for the genotypic distribution of SNP. The χ^2 test was employed to compare SNP genotype and allele frequencies between MDD patients and controls. Multiple logistic regression analysis was performed to analyze gene × environment interactions. All tests were two-sided, and statistical significance was set at $P < 0.05$.

3. Results

3.1. Demographic data of study subjects

There was no significant difference between MDD patients and control subjects in sex, age and level of education ($P > 0.05$; see Table 1).

Table 1
Demographic data of MDD group and control group.

	MDD (n = 274)	Control (n = 273)	χ^2	p
Sex			0.064	0.800
Male	82(29.93%)	79(28.94%)		
Female	192(70.07%)	194(71.06%)		
Age			2.385	0.496
16–30	63(22.99%)	60(21.98%)		
31–40	44(16.06%)	55(20.15%)		
41–50	75(27.37%)	63(23.08%)		
> 50	92(33.58%)	95(34.79%)		
Education			7.288	0.121
Primary school	61(22.26%)	65(23.81%)		
Junior school	76(27.74%)	74(27.11%)		
Senior school	75(27.37%)	52(19.05%)		
Junior college	28(10.22%)	34(12.45%)		
College	34(12.41%)	48(17.58%)		