Progress in Neuro-Psychopharmacology & Biological Psychiatry 51 (2014) 119–125

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Gene × gene × gender interaction of BDNF and COMT genotypes associated with panic disorder

Yoshiaki Konishi [a], Hisashi Tanii [a,*], Takeshi Otowa [b], Tsukasa Sasaki [c], Mamoru Tochigi [d], Tadashi Umekage [e], Eishi Motomura [a], Takashi Shiroyama [a], Hisanobu Kaiya [f], Yuji Okazaki [g], Motohiro Okada [a]

[a] Department of Psychiatry, Division of Neuroscience, Graduate School of Medicine, Brain Science and Animal Model Research Center (BSAM), Mie University, Mie, Japan
[b] Department of Neuropsychiatry, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[c] Laboratory of Health Education, Graduate School of Education, The University of Tokyo, Tokyo, Japan
[d] Department of Psychiatry, Teikyo University School of Medicine, Tokyo, Japan
[e] Division for Environment, Health and Safety, The University of Tokyo, Tokyo, Japan
[f] Research Center for Panic Disorder, Nagoya Mental Clinic, Aichi, Japan
[g] Department of Psychiatry, Tokyo Metropolitan Matsuzawa Hospital, Tokyo, Japan

ARTICLE INFO

Article history:
Received 8 November 2013
Received in revised form 29 January 2014
Accepted 29 January 2014
Available online 4 February 2014

Keywords:
BDNF
COMT
Gender
Gene × gene × gender interaction
Panic disorder

ABSTRACT

Genetic and gender differences are among the factors that have a role in the etiology of panic disorder (PD). It is thought that PD is related to neurotransmitter pathways, such as brain-derived neurotrophic factor (BDNF) and catechol-O-methyltransferase (COMT), both of which are involved in the regulation of the monoamine mechanism. We examined the interactions of BDNF, COMT and gender differences in terms of personality characteristics in PD. The subjects were 470 patients (178 men, 292 women) with a DSM-IV diagnosis of PD, and 458 healthy controls (195 men, 263 women). The subjects were further clinically characterized using the Revised NEO Personality Inventory (NEO-PI-R) and State-Trait Anxiety Inventory (STAI). COMT Val158Met polymorphisms (rs4680) and BDNF Val66Met (rs6265) polymorphisms were genotyped using allelic discrimination by a real-time PCR assay. A multivariate analysis of covariance (MANCOVA) was performed with STAI and NEO-PI-R scores as the dependent factor, gender and genotyping groups (BDNF and COMT) as fixed factors, and the covariate of age in the PD and healthy control groups. Post hoc MANCOVA tests were conducted to evaluate COMT × BDNF interactions. An interaction of BDNF × COMT × gender was confirmed in the PD group by MANCOVA on STAI scores and NEO-PI-R Neuroticism and Extraversion scores, whereas no association of such interactions was observed in the healthy controls. The anxiety sensitivity of the COMT Met + BDNF Val/Val carriers was higher than that of the COMT Val/Val + BDNF Val/Val carriers by post hoc MANCOVA. A significant BDNF × COMT × gender interaction was observed in the PD patients but not in the controls. Our findings partly demonstrated the involvement of a gene × gene × gender interaction in the pathogenesis of PD.

1. Introduction

Panic disorder (PD) is an anxiety disorder characterized by frequent, unexpected panic attacks and anticipatory anxiety. Epidemiological studies have detected gender differences in the symptomatology of PD. Women are affected with PD approximately twice as often as men, and experience more panic symptoms than men do (Crowe et al., 1983). Female patients with PD are more likely to have respiratory symptoms (shortness of breath, feeling smothered, choking, difficulty swallowing) and faintness during panic attacks (Weissman, 1993).

It has been suggested that genetic factors may influence vulnerability to PD, as many current patients have a relative with the disorder (Crowe et al., 1983; Hettema et al., 2001; Weissman, 1993). Several genes related to neurotransmission and neurotrophic systems may contribute to the genetic variation of PD-related traits, and they may modify the phenotypic expression of pathologic anxiety. One plausible genetic risk factor involves brain-derived neurotrophic factor (BDNF), a protein hypothesized to limit or repair the damage caused by stress, and catechol-O-methyltransferase (COMT) (Domschke et al., 2007), both of which has been investigated as the typical gene polymorphisms related to anxiety disorders such as panic disorder.

BDNF Met carriers may play a crucial role in increased sensitivity to anxiety, and persons with the Met/Met carriers polymorphism may be

Abbreviations: BDNF, brain-derived neurotrophic factor; COMT, catechol-O-methyltransferase; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; HA, harm avoidance; MANCOVA, multivariate analysis of covariance; Met, methionine; MINI 24, Mini International Neuropsychiatric Interview 5.0.0; NEO-PI-R, NEO Inventory; PCR, polymerase chain reaction; PD, panic disorder; PTSD, posttraumatic stress disorder; SPSS, Statistical Package for Social Science; STAI, The State-Trait Anxiety Inventory; Val, valine.

* Corresponding author at: Department of Psychiatry, Division of Neuroscience, Graduate School of Medicine, Brain Science and Animal Model Research Center (BSAM), Mie University, 2-174, Edobashi, Tsu, Mie, Japan. Tel.: +81 59 231 5018; fax: +81 59 231 5208.
E-mail address: h-tanii@clin.medic.mie-u.ac.jp (H. Tanii).

0278-5846/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pnpbp.2014.01.020

more sensitive to the stress-induced down-regulation of BDNF (Elzinga et al., 2011). The symptoms of Met/Met carriers tended to be more serious compared to those of Val/Val or Val/Met carriers (Monteleone et al., 2006). COMT Val158Met polymorphisms have been associated with "worrier" (Met allele) tendencies based on findings that the Met allele has been broadly associated with anxiety-related phenotypes (Domschke et al., 2004; McGrath et al., 2004). Studies of personality traits in anxiety disorders have clarified a relationship between neuroticism (Ormel et al., 2004) and extraversion (Jylha et al., 2009). Another recent study reported that resilience was influenced by COMT and BDNF polymorphisms in male — but not female — healthy college students (Kang et al., 2013). Resilience was reported to be negatively associated with neuroticism, and positively related to extraversion in young healthy adults (Campbell-Sills et al., 2006).

Regarding gene–gene interaction with anxiety disorder, associations between BDNF and dopamine receptor 3 gene polymorphism have been shown in bipolar disorder comorbid with anxiety disorder (Chang et al., 2013). Hemmings et al. (2013) reported that the interaction of BDNF Val66Met and DRD2 Taq1A polymorphisms influences posttraumatic stress disorder (PTSD) symptom severity. An interaction of promoter variants of the cannabinoid receptor 1 gene (CNR1) and 5-HTTLPR affects the anxious phenotype (Lazary et al., 2009).

From the viewpoint of pharmacogenomics and gene–gene interactions, an association between polymorphisms in serotonin transporter (SLC6A4) and serotonin receptor 2A (HTR2A) genes was reported to predict treatment response to venlafaxine XR in generalized anxiety disorder (Lohoff et al., 2013). In addition Lee et al. (2013) reported a significant interaction effect for the Val/Val carriers of the BDNF Val66Met polymorphism and the Met carriers of the COMT Val158Met polymorphism in a comparative study between patients with bipolar II disorder without anxiety disorder and controls.

With regard to the gender difference observed in PD, several studies have investigated BDNF and COMT as representative polymorphisms. Shalev et al. (2009) reported that in male subjects, BDNF Val/Val homozygotes showed a greater increase in salivary cortisol than Val/Met heterozygotes. In female subjects, the opposite trend was observed; that is, the Val/Val homozygotes had the lowest increase (Shalev et al., 2009). The female subjects also displayed significantly lower platelet BDNF levels compared to the males. Lommatzsch et al. (2005) found that platelet BDNF levels changed during the menstrual cycle. The 196G/A (Val66Met) polymorphism of the BDNF gene was revealed to be significantly associated with the severity of binge eating behavior in women with bulimia nervosa or other binge eating disorders.

It has been suggested that the role of gender in the relationship between the COMT gene and personality may be due to an interaction between estrogen and COMT activity (Harrison and Tunbridge, 2008). An earlier study showed that women with high estrogen levels had lower COMT activity (Briggs and Briggs, 1973). Estrogen was reported to inhibit COMT mRNA expression and reduce its activity (Jiang et al., 2003; Xie et al., 1999). COMT plays an important role in metabolizing catechol estrogens, thereby lowering their levels (Creveling, 2003). Thus, gender differences may interact with the COMT gene to affect personality.

As noted above, gender differences in BDNF and COMT have been investigated by many researchers, but the potential interaction of BDNF, COMT and gender is not clear, and no definitive results were obtained in the studies of the relationship between PD and BDNF and COMT We suspected that it would be worthwhile to investigate the gender differences between PD and healthy controls from the viewpoint of gender × genotype interaction. Based on previous studies, we hypothesized that the gene–gene interaction of BDNF Met66 allele and COMT Met158 allele would predispose PD individuals to higher anxiety sensitivity, and would show a gender difference.

The aim of our study was to explore the possible association between the gender-specific characteristics of PD-related anxiety traits and two functional polymorphisms of the BDNF and COMT genes. This study focused particularly on a gene × gene interaction of BDNF and COMT.

2. Methods

2.1. Subjects

The study subjects were 470 PD patients (178 men and 292 women) and 458 healthy controls (195 men and 263 women). The study was explained to all subjects prior to their participation, and they each provided written informed consent to participate. In the healthy control group, the inclusion criteria were as follows: drug-free, no previous diagnosis of a psychiatric disorder, and no family history of psychiatric disorder. We excluded individuals with a history of major physical illness, neurological disorder, alcohol abuse, substance abuse, or loss of consciousness due to head injury. The healthy control subjects were screened for the presence or absence of a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) axis I disorder using the Japanese version of the Mini International Neuropsychiatric Interview 5.0.0 (MINI, 24) (Otsubo et al., 2005).

All of the patients with a DSM-IV diagnosis of PD were outpatients at the Nagoya Mental Clinic in Japan, and were diagnosed by at least two doctors. The MINI is a structured interview used to assess psychiatric illness. Screenings were completed for psychiatric illnesses including PD. Agoraphobia was found in 65.8% ($n = 192$) of the female patients and 51.7% ($n = 92$) of the male patients. Depression was found in 33.5% ($n = 98$) of the female patients and 27.5% ($n = 49$) of the male patients. Bipolar disorder was found in 16.1% ($n = 47$) of the female patients and 11.2% ($n = 20$) of the male patients. Most of the 470 patients were on medication and took antidepressants ($n = 401$), anxiolytics ($n = 357$), or a mood stabilizer including antipsychotic drugs ($n = 160$). Most of the patients were being treated with an antidepressant drug such as a serotonin reuptake inhibitor, and the average imipramine equivalent was 74.4 ± 3.2 mg (standard error: SE) (Bollini et al., 1999).

This study was approved by the institutional ethics committees of the Mie University Graduate School of Medicine and the Warakukai Nagoya Mental Clinic.

2.2. Psychological tests

Psychological tests were administered to the participants by questionnaire and by interview. The questionnaire was used to collect clinical information including basic data on family members with PD and genetic factors. The collected data included gender, age, height, weight, blood type, birthplace, growth history, body weight at birth, marital status, drinking habits, smoking habits, menstruation, medical health history, family medical history, and disease under treatment. The questionnaire concerned the individual's experience with PD, including symptoms of first panic attack, frequency of attacks, and avoidance during the previous month of situations in which a panic attack might occur.

The State-Trait Anxiety Inventory (STAI) was administered to all of the subjects The STAI has 20 questions to assess state anxiety, and 20 for trait anxiety (Nakazato and Mizuguchi, 1982; Spielberger et al., 1983). "Trait anxiety" represents stable individual differences in the propensity for anxiety, and refers to a tendency to respond to life situations with "general" anxiety. The Revised NEO Personality Inventory (NEO-PI-R) was also administered to all of the subjects The NEO-PI-R is a standard instrument for measuring the personality traits of individuals over a wide range of ages, from the elderly to the young (Costa and McCrae, 1992; Shimonaka, 1997). The inventory is based on a five-factor model of character: Neuroticism (N), Extroversion (E), Openness to Experience (O), Agreeableness (A), and Conscientiousness (C). The subjects responded to the 240 items on a 5-point scale.