



Interaction effects between COMT and BDNF polymorphisms on boredom susceptibility of sensation seeking traits

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ABSTRACT

Sensation seeking is a temperament associated with willingness to take risks to obtain arousal. We investigated the relationship between the polymorphisms of the COMT Val158Met and BDNF Val66Met and sensation seeking traits. The Sensation Seeking Scale (SSS) and genotyping were performed in 277 Korean healthy volunteers (165 males, 112 females). Multivariate analysis of covariance was used to test the association between the COMT and BDNF functional polymorphisms and dimensions of sensation seeking, namely, disinhibition, boredom susceptibility, experience seeking and thrill/adventure seeking. No main and interaction effects of the COMT and BDNF on SSS were observed for total subjects. However, in females, a significant gene–gene interaction effect on the boredom susceptibility of SSS was shown. Among females with COMT Met present genotype (Val/Met + Met/Met), subjects with BDNF Met absent genotype (Val/Val) had significantly higher boredom susceptibility than subjects with BDNF Met. The effects of BDNF Val66Met polymorphism on boredom susceptibility of sensation seeking traits could be modulated by COMT Val158Met polymorphism in female.

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1. Introduction

Sensation seeking, defined as ‘seeking varied, novel, complex and intense sensations and experiences, irrespective of the adverse consequences’, is one of the fundamental human temperaments believed to have a biological basis that is expressed as a need for physiological arousal, novel experience, and a willingness to take risks to obtain arousal (Zuckerman, 1990). This trait is associated with a variety of risk behaviors such as sexual risk behaviors, gambling and risky driving (Hoyle et al., 2000). Low sensation seekers have a tendency to reveal greater anxiety for risk activities. It has been known that sensation seeking traits are strongly determined by genetic factors (Koopmans et al., 1995).

It is commonly known that dopamine plays an important role on the brain functions that are related to approach and reward (Hoebel et al., 2007). The higher level of sensation seeking traits was suggested to be associated with a lower dopamine turnover and a higher sensitivity to dopamine in the postsynaptic receptor (Cloninger, 1986). In a rat model of human sensation seeking, rats which respond highly to novelty exhibit elevated release of accumbal dopamine (Blanchard et al., 2009). More particularly, drug seeking behaviors and related personality traits, such as responding to novelty are

believed to be mediated via neuromodulatory action of dopamine in the prefrontal cortex of rats (Zhu et al., 2007).

One of the key enzymes that are involved in dopamine neurotransmission is catechol-O-methyltransferase (COMT). It plays a major role in the inactivation of dopamine in the synaptic cleft and thus has an impact on dopamine level in the prefrontal cortex. A single nucleotide polymorphism (SNP) in the human COMT gene (472G>A) resulting in a valine (Val) to methionine (Met) amino acid substitution (Val158Met, rs4680), reduces the activity of the enzyme to one quarter of that encoded by the Val allele and thereby impacts cortical dopamine level (Lachman et al., 1996). Thus, the Met allele of COMT Val158Met is supposed to have higher dopamine level in prefrontal areas whereas the Val allele is supposed to have lower dopamine level. The low-activity Met allele showed the linear effects on prefrontal function with a dose dependent manner, in which Met/Met genotype was associated with better performance on executive cognition tasks (Egan et al., 2001). In addition, COMT Val158Met has been implicated in many psychiatric conditions including substance dependence, anxiety disorder, bipolar disorder, and attention deficit hyperactivity disorder (ADHD) (Hosak, 2007). A previous study in the Korean population showed females with Met/Met homozygotes of the COMT Val158Met have a significantly lower tendency for harm avoidance (Kim et al., 2006), which is known to be negatively related to sensation seeking. Furthermore, a recent genetic study on the sensation seeking traits demonstrated the association between the COMT Val158Met polymorphism and the sensation seeking traits only in females (Lang et al., 2007).

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The brain-derived neurotrophic factor (BDNF) can also be a candidate gene for the sensation seeking traits. The BDNF has a critical effect on the proliferation and differentiation of neurotransmitter systems, including the dopaminergic and serotonergic systems. In particular, BDNF was reported to be a key regulator of the release of dopamine in the mesolimbic dopaminergic system (Berton et al., 2006). The BDNF gene, located on chromosome 11p13, contains a common SNP, producing a Val to Met amino acid substitution at codon 66 (Val66Met, rs6265) which affects the activity-dependent secretion of BDNF. The Met allele of BDNF Val66Met affects impaired BDNF secretion, which may be explained by the trafficking defect of BDNF to the secreting pathway (Egan et al., 2003). The BDNF Val66Met is associated with the efficacy of long-term potentiation in hippocampus, hippocampal volume, memory performance, and various psychiatric disorders such as mood disorders (Hariri et al., 2003; Bath and Lee, 2006).

To date, although there is little evidence of direct association between BDNF gene and sensation seeking traits, some indirect evidence supporting their association has been reported. Flanagan et al. (2006) reported that subjective and physical responses induced by amphetamine were associated with BDNF Val66Met genotype, in which the Met carriers had lower levels of arousal and energy and greater increases in heart rate. The findings reflect an involvement of BDNF gene on drug seeking vulnerability. In addition, there are several studies suggesting the association between BDNF Val66Met polymorphism and anxiety-related traits, although it is still inconclusive. An animal study using rats showed that the Met allele of BDNF Val66Met polymorphism is associated with increased anxiety-related behaviors (Chen et al., 2006; Takizawa et al., 2009). Contrary to this, a recent meta-analysis shows that subjects with Val/Val genotype, compared to those with Met/Met and Val/Met display statistically significant higher neuroticism, which is a personality trait highly correlated with anxiety (Frustaci et al., 2008). Meanwhile, a recent genome-wide association study (Terracciano et al., 2008) indicated the association between BDNF Val66Met polymorphism and the extraversion of the revised NEO Personality Inventory (NEO-PI). This trait is related to an approach trait such as interest in others, need for environmental stimulation, and tendency to experience positive emotion (Terracciano et al., 2008) and correlates with sensation seeking traits (Aluja et al., 2003). Also, Itoh et al. (2004) reported that female subjects with Met/Met genotype of BDNF Val66Met had higher extraversion of NEO-PI than those with the other genotypes, although this was not found in males.

Based on these findings, the purpose of the present study was to examine the relationship between the COMT and BDNF gene polymorphisms and the level of the sensation seeking traits. Therefore, it was investigated whether the four dimensions of sensation seeking as measured by the Sensation Seeking Scale (SSS) are potentially linked to the COMT Val158Met and BDNF Val66Met functional gene polymorphisms in healthy Korean college students. The interaction effects between these two genes on the SSS were also examined.

2. Methods

2.1. Subjects

A total of 291 healthy Korean college student volunteers (male 172, female 119) were recruited through advertisements for the study. Subjects with any neurological, current or lifetime Axis I psychiatric disorders according to the DSM-IV (American Psychiatric Association, 1994) criteria were excluded. In addition, subjects with a family history of mental disorder in first-degree relatives were excluded. The study protocol was approved by the local ethics committee, and every subject gave written informed consent before participating in the study.

A subset of subjects was excluded from analysis due to the inability to obtain complete genotype results or complete responses on the questionnaire. Finally, 277 subjects with complete data sets (165 males, 112 females) were included in the final analysis. The mean age of the final sample was 23.02 years (SD = 2.35 years) for males and 22.65 years (SD = 2.44 years) for females. All participants were ethnically Korean.

2.2. SNP genotyping

Subjects donated a blood sample through venipuncture, and the DNA was isolated using standard techniques. The genotyping of the functional polymorphisms of the COMT Val158Met (rs4680) and BDNF Val66Met (rs6265) was screened using single base primer extension assay, using ABI PRISM SNaPshot Multiplex kit (ABI, Foster City, CA, USA) according to the manufacturer's recommendation. The forward and reverse primer pairs used for the SNaPshot assay were 5'-ATCAACCCGACTGTGCC-3' (forward) and 5'-CTTTTCCAGGTGACAACG-3' (reverse) for the COMT and 5'-TGATGACCATCTTTTCCCTT-3' (forward) and 5'-CACTGGGAGTCCAATGC-3' (reverse) for the BDNF. The genomic DNA flanking the SNP was amplified with polymerase chain reactions (PCR) with the forward and reverse primer pairs and standard PCR reagents in 10 μ L reaction volume, containing 10 ng of genomic DNA, 0.5 pM of each oligonucleotide primer, 1 μ L of 10 \times PCR Gold buffer, 250 μ M dNTP, 3 mM MgCl₂ and 0.25 unit i-StarTaq DNA Polymerase (iNtRON Biotechnology, Sungnam, Gyeonggi-do, Korea). The PCR reactions were carried out as follows: 10 min at 95 °C for 1 cycle, and 30 cycles at 95 °C for 30 s, 55 °C for 1 min, 72 °C for 1 min followed by 1 cycle of 72 °C for 7 min. After amplification, the PCR products were treated with 1 U each of shrimp alkaline phosphatase (SAP) (Roche) and exonuclease I (USB Corporation) at 37 °C for 60 min and 72 °C for 15 min to purify the amplified products. 1 μ L of the purified amplification products were added to a SNaPshot Multiplex Ready reaction mixture containing 0.15 pMs of genotyping primer for primer extension reaction. The primer extension reaction was carried out for 25 cycles of 96 °C for 10 s, 50 °C for 5 s, and 60 °C for 30 s. The reaction products were treated with 1 U of SAP at 37 °C for 1 h and 72 °C for 15 min to remove excess fluorescent dye terminators. 1 μ L of the final reaction samples containing the extension products were added to 9 μ L of Hi-Di formamide (ABI, Foster City, CA). The mixture was incubated at 95 °C for 5 min, followed by 5 min on ice and then analyzed by electrophoresis in ABI Prism 3730 \times 1 DNA analyzer. Analysis was performed using Genemapper software (version 3.0; Applied Biosystems).

2.3. Measures

2.3.1. Sensation Seeking Scale (SSS) – V

The form V of the SSS, a 40-item forced-choice questionnaire was used to assess the sensation seeking traits (Zuckerman, 1990). The SSS reflects four factors: boredom susceptibility, experience seeking, disinhibition, and thrill/adventure seeking. Boredom susceptibility indicates a tendency to dislike routine activities, boring people, and suggests a restless reaction to a lack of stimulus variety. Experience seeking reflects the desire to seek new experiences through the senses and the mind. Disinhibition supports a tendency to seek a social hedonistic orientation with the pursuit of a sensation such as drinking or sex. Thrill/adventure seeking reflects a desire to engage in certain kinds of physical risk activities. Each factor was comprised of 10 questions. For each dichotomous choice, a score of 1 was assigned if the sensation seeking response was chosen and the total scores represented the number of sensation seeking responses.

2.4. Statistical analysis

The Hardy-Weinberg equilibrium for genotype frequencies was calculated using chi-square tests. Two-way multivariate analysis of covariance (MANCOVA) and a *post hoc* one-way analysis of covariance (ANCOVA) after inclusion of age as a covariate were conducted to examine the single and interaction effects of a COMT or BDNF genotype on total scores and the four subscales of the SSS. The data were analyzed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA), and the significance was accepted at $P < 0.05$. All tests were two-tailed. We had a sufficient power (0.8) to detect a medium effect size (Cohen's $d = 0.41$) between two main genotypes, that, as an example, corresponds to 2.40 points on total sensation seeking scores (Cohen, 1992).

3. Results

The allelic distributions of the COMT and BDNF polymorphisms were in accordance with the Hardy-Weinberg equilibrium ($\chi^2 = 0.37$ and $\chi^2 = 3.66$, respectively, all $P > 0.05$).

For the COMT polymorphism, the most prevalent genotype was Val/Val ($n = 145$, 52.3%), followed by Val/Met ($n = 108$, 39.0%), and Met/Met ($n = 24$, 8.7%). The COMT genotype distribution of the present sample was similar to previous Korean reports (Kim et al., 2006). Because the number of Met/Met homozygotes was relatively small, to increase statistical power and given the evidence of COMT activity according to genotypes of COMT (Chen et al., 2004; Takizawa et al., 2009), we grouped COMT genotypes into Val/Val homozygotes ($n = 145$) and Met carrier (Met/Met + Val/Met, $n = 132$).

For the BDNF polymorphisms, the most prevalent genotype was Val/Met ($n = 122$, 44.0%), followed by Val/Val ($n = 87$, 31.4%) and Met/Met ($n = 68$, 24.6%). The genotype distribution of the present

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