The COMT Val158Met polymorphism is associated with novelty seeking in Czech methamphetamine abusers: Preliminary results

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Abstract

OBJECTIVES: Measurable traits of human personality may mark the predisposition to psychopathology. Increased novelty seeking plays an important role in the pathogenesis of substance abuse. Novelty seeking, one of the fundamental traits of the human temperament, is related to dopamine. Catechol-*O*-methyltransferase (COMT) is essential for dopamine inactivation. The aim of our study was to assess whether the COMT gene Val158Met functional polymorphism in patients dependent on methamphetamine is related to their novelty seeking score.

METHODS: Patients dependent on methamphetamine who had been treated at the Addiction Treatment Unit in Nechanice in 2004 and 2005 agreed to participate in the investigation. We administered the Temperament and Character Inventory (TCI) questionnaire, assessed their novelty seeking score and analysed their DNA samples for COMT Val158Met genotype.

RESULTS: The subjects were thirty-seven Czech Caucasians (women N=10) dependent on methamphetamine with an average age of 23.6±3.8 years. We found a significantly higher mean novelty seeking score among the patients with the Met allele (Met/Met homozygotes + Val/Met heterozygotes; N=28) than in nine Val/Val homozygotes (27.4 vs 24.1; p=0.042, Two-Sample T-Test).

CONCLUSION: The Met allele of the COMT gene Val158Met polymorphism is associated with low COMT enzyme activity and high endogenous dopamine synaptic levels in the prefrontal cortex. This leads to a decrease in dopaminergic neurotransmission in nucleus accumbens and a need for an increased activity to stimulate it. Novelty seeking behavior corresponds with this need.

ORIGINAL ARTICLE

Abbreviations

COMT - Catechol-O-methyltransferase
DNA - Deoxyribonucleic acid
DRD4 - Dopamine D4 receptor
DSM-IV - Diagnostic and Statistical Manual of Mental Disorders, 4th edition
Met - Methionine
NS - Novelty seeking
N.S. - Not significant
S.D. - Standard deviation
TCI - Temperament and Character Inventory
TPQ - Tridimensional Personality Questionnaire
Val - Valine

Introduction

Individuals dependent on substances typically exhibit predisposing personality traits including novelty seeking and antisocial behavior [7]. Novelty seeking (NS) is well defined as a fundamental biobehavioral trait of temperament [3]. At present, it is assessed by the Temperament and Character Inventory (TCI) [17].

NS is characterized by exploration, changeability, excitability, hotheadedness, and extravagance as opposed to frugality, stoicism and loyalty. According to Cloninger´s biobehavioral theory [2], novelty seeking relates to dopaminergic neurotransmission.

The first investigations were focused on assessing the relationship of temperamental traits and dopamine receptor genes. The association between the dopamine D4 receptor (DRD4) gene exon III polymorphism and novelty seeking was reported in 1996 [1, 6]. Later, the meta-analysis of 21 studies provided support for a small positive link between NS and long repeats (>5 tandem repeats) of the DRD4 polymorphism [16].

The essential enzyme for dopamine inactivation is Catechol-*O*-methyltransferase (COMT). The differences in COMT activity are three- to four-fold and depend on the COMT gene Val158Met polymorphism (Val/Val vs Met/Met homozygotes) [12].

The aim of our study was to assess whether the COMT gene Val158Met polymorphism in patients treated for dependence on methamphetamine is related to their novelty seeking score.

Subjects and methods

Patients dependent on methamphetamine (DSM-IV Code 304.40) who had been treated in the Addiction Treatment Unit in Nechanice in 2004–2005 agreed to participate in the investigation. We assessed their novelty seeking score by the TCI questionnaire during the treatment programme. The participants did not have any withdrawal symptoms at the time of assessment.

DNA was extracted from peripheral white blood cells using standard procedures. The analyses were performed on MegaBACE 1000 capillary-array genetic analyzer (Amersham Biosciences, Sunnyvale, CA). We conducted the COMT gene Val158Met genotyping using Cycling Gradient Capillary Electrophoresis [13] and polymerase chain reaction.

The study was approved by the local Ethics Committee. We used the NCSS 2004 statistical software to test demographic differences among subjects with individual genotypes (Mann-Whitney Test for age, Fisher´s Exact Test for gender distribution), and the association between the novelty seeking score and the COMT gene Val158Met polymorphism in these patients (Two-Sample T-Test). We did not analyse any other associations of the COMT polymorphism in order to avoid multiple testing.

Results

The informed consent for the assessment and the data for analyses were obtained from 37 patients of Caucasian origin (10 women), who had been dependent on methamphetamine for 5.8 years (S.D. 3.0) on average. Their mean age was 23.8 years (S.D. 3.8), ranging from 19–30 years old.

The groups of patients based on their genotype alone or combined (Val/Val, Val/Met, Met/Met, Val/Val+ Val/Met, Val/Met+Met/Met) did not significantly differ from each other in age (p=N.S., Mann-Whitney Test) or gender distribution (p=N.S., Fisher's Exact Test).

We found the presence of the Met allele (Met/Met homozygotes + Val/Met heterozygotes; N=28) associated with a significantly higher mean novelty seeking score as compared to the absence of this allele (Val/Val homozygotes; N=9) (27.4 vs 24.1; p=0.042, Two-Sample T-Test). We also observed a trend towards a significant association of the Val allele (Val/Val homozygotes + Val/Met heterozygotes; N=25) with a lower mean novelty seeking score in comparison with the absence of the Val allele (Met/Met homozygotes; N=12) (25.7 vs 28.6; p=0.052, Two-Sample T-Test).

The results are summarized in Table 1.

Discussion

Our data in a small sample of methamphetamine dependent patients show a significant association of the Met allele at the COMT Val158Met polymorphism with a high novelty seeking score in TCI. The presence of the Val allele corresponds to a lower NS scores among the tested individuals.

The COMT activity in the prefrontal cortex accounts for more than 60% of the metabolic degradation of dopamine [10]. Activated dopamine D1 receptors in the medial prefrontal cortex suppress dopamine release in the nucleus accumbens in rats [5]. D1 receptor antagonist SCH 23390 microinjected into infralimbic prefrontal cortex significantly enhances extracellular dopamine activity in the nucleus accumbens. These findings are supported by other studies as well [9, 14]. The Met allele of the COMT gene Val158Met polymorphism, related to a low COMT enzyme activity and consequently high prefrontal dopamine level, decreases dopaminergic activity in the nucleus accumbens. This results in a need to

Table 1. The COMT Val158Met genotypes and TCI novelty seeking scores in a Czech sample of methamphetamine abusers.

COMT Val158Met genotype	Val/Val N=9	Val/Met N=16	Met/Met N=12	Val/Val+Val/Met combined N=25	Val/Met+Met/Met combined N=28
Age median (years) (Min-Max)	22 (19–30)	22.5 (20–32)	22 (20–31)	22 (19–32)	22 (20–32)
Male/female ratio	5/4	14/2	8/4	19/6	22/6
TCI novelty seeking score (Mean ± S.D.)	24.1±4.2	26.6±4.3	28.6±3.6	25.7±4.3	27.4±4.1
P value (TCI novelty seeking score differences)	N.S.	N.S.	N.S.	P=0.052*	P=0.042**

N.S. = not significant
* versus Met/Met genotype (Two-Sample T-Test)
** versus Val/Val genotype (Two-Sample T-Test)

stimulate subcortical dopamine transmission. Increased novelty seeking behavior serves this purpose.

Tsai et al. [18] investigated TPQ (Tridimensional Personality Questionnaire) personality traits, COMT gene Val158Met and DRD4 gene exon 3 polymorphisms in a population of 120 healthy young Chinese females. The results of this analysis revealed that the COMT polymorphism was significantly associated with novelty seeking (p=0.017). The highest NS score was found in Val/Val homozygotes versus the lowest value measured in Met/Met homozygotes (19.0 vs 15.2). The findings do not agree with our results. The explanation for the disagreement can be a variable prevalence of the COMT Val allele among various ethnic groups: 50% in Caucasians and 75% in the Chinese [15]. Also, novelty seeking scores in healthy subjects are different from scores of NS in methamphetamine abusers [8].

Novelty seeking correlates negatively with age [4], and a large age span among the subjects would lead to bias. Novelty seeking is also a gender-sensitive personality trait, which has generally lower scores in women [11]. The subjects in our investigation were young and made a comparatively homogenous group in terms of age and gender distribution.

The serious limitation of our finding is the small sample size, which increases the probability of false positive results. The reported association is meant as a signal to continue and needs the support of a sufficiently powered study. We recruit more patients to continue the assessments.

Our understanding of the neurobiological underpinnings of addictive behavior in the pathogenesis of methamphetamine dependence may be potentially useful for therapy.

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