The DBH −1021 C/T polymorphism is not associated with alcoholism but possibly with patients’ exposure to life events

Short Communication

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Summary. Two DBH polymorphisms were investigated in 114 Brazilian alcoholics of European descent and 233 controls. Personality and life events were also analyzed among alcoholics. No significant differences were observed in allele or genotype frequencies between alcoholics and controls. No association was detected between the polymorphisms and personality dimensions. Carriers of the −1021 T allele presented a higher number (F = 7.49; P = 0.007) of life events. This study provides a preliminary indication that the DBH −1021 C/T polymorphism influences the exposure to life events.

Keywords: Life change, hyperactivity, alcoholism, genetics.

Introduction

Dopamine beta-hydroxylase (DBH) catalyzes the conversion of dopamine to norepinephrine. Alterations in the activity levels of DBH have been reported in several psychiatric disorders including conduct disorder and attention deficit hyperactivity disorder (ADHD) (Rogeness et al., 1989), schizophrenia (Wei et al., 1997, 1998) and psychotic depression (Cubells et al., 2002).

The DBH gene is located on chromosome 9q34 (Craig et al., 1988). The sequence comprises 22.98 kb, with 12 exons in a transcript of 2760 bp coding for a 603 aa protein (http://www.ensembl.org). Molecular markers at the DBH locus were shown to be associated with variation in plasma-DBH activity (Wei et al., 1997; Cubells et al., 1998, 2000) and with DBH cerebrospinal-fluid levels (Cubells et al., 1998). Zabetian et al. (2001) identified a functional polymorphism (−1021 C/T; NCBI dbSNP ID 1611115) that accounted for 35%–52% of the variation in plasma-DBH activity in their samples.
The DBH −1021 C/T (Zhang et al., 2004, 2005) and the DBH intron 5 TaqI (NCBI dbSNP ID 1611128; Daly et al., 1999; Roman et al., 2002) polymorphisms have been associated with ADHD. The polymorphisms are 9 Kb apart. Once ADHD predisposes to alcoholism (Biederman et al., 1998), these polymorphisms could be underlying both disorders. However, there are no positive linkage studies for alcoholism in that region, and the only association study between DBH and alcoholism resulted negative (Kohnke et al., 2002). Interestingly, the authors verified that DBH activity was significantly lower in alcoholics compared with healthy controls, independently of −1021 genotypes (Kohnke et al., 2002).

The objective of this study is to investigate association and possible influences of DBH −1021 C/T and TaqI polymorphisms on alcohol dependence, personality and life events. The reason to choose these two SNPs for analysis is the fact that the intron 5 TaqI has been associated with ADHD (Daly et al., 1999; Roman et al., 2002), while −1021 C/T is functional (Zabetian et al., 2001). Moreover, there are no previous linkage disequilibrium studies including these two polymorphisms.

### Material and methods

#### Subjects

This study is part of a series of investigations on the genetics and heterogeneity of alcoholism assessing the role of temperament and life events. A clinical sample of male patients of European descent with alcohol dependence (n = 114) was interviewed in an alcoholism treatment ward. The diagnosis followed the DSM-III-R criteria (American Psychiatric Association, 1987). The interviews were performed with the Semi-Structured Assessment for the Genetics in Alcoholism (Bucholz et al., 1994). The “Life Experiences Survey” (Sarason et al., 1978) was applied to assess life events. This scale comprises 57 items (events experienced in the last 12 months). The number of events with positive or negative psychological impact was scored. The total number of life events included the events coded as positive, negative and neutral. The Tridimensional Personality Questionary (Cloninger, 1987) measured four temperament dimensions: novelty seeking, harm avoidance, reward dependence and persistence.

The control group for allele and genotype frequencies was composed of 233 Brazilian blood donor males of European descent assessed in a blood bank. Exposure to alcohol was measured by the CAGE questionnaire (Ewing, 1984) and by inquiring about the type, quantity and frequency of alcoholic beverage consumption. The CAGE questionnaire is a combination of 4 questions for the screening (but no definite diagnosis) of alcoholism. A total of 2 or more positive answers suggests alcohol abuse or dependence. Although eight percent of the individuals sampled were possibly previous alcohol abusers, none of them was a probable alcohol dependent. All individuals sampled (patients and controls) signed an informed consent approved by the Ethics Committee of the Federal University of Rio Grande do Sul.

#### Determination of DBH genotypes

The DNA was extracted by the method of Lahiri and Nurnberger (1991). The polymorphic 5’ flanking region was amplified and the genotypes were determined following the procedures described by Kohnke et al. (2002). The polymorphic region in intron 5 was amplified and the genotypes were determined in accordance with Daly et al. (1999).

#### Statistical analysis

The analysis of Hardy-Weinberg equilibrium and comparisons between alcoholics and controls was performed using the chi-square test. Analyses of covariance removing age effects