Analysis of a functional catechol-O-methyltransferase gene polymorphism in schizophrenia: evidence for association with aggressive and antisocial behavior

Rael D. Strous\textsuperscript{a,b}, Nigel Bark\textsuperscript{c}, Sam S. Parsia\textsuperscript{c}, Jan Volavka\textsuperscript{d},
Herbert M. Lachman\textsuperscript{c,*}

\textsuperscript{a}\textit{Department of Psychiatry, Hillside Hospital-Long Island Jewish Medical Center, Glen Oaks, NY 11004, USA}
\textsuperscript{b}\textit{Harvard Medical School, Massachusetts Mental Health Centre, 74 Fenwood Road, Boston, MA 02135, USA}
\textsuperscript{c}\textit{Department of Psychiatry, Albert Einstein College of Medicine, 1300 Morris Park Ave., Bronx, NY 10461, USA}
\textsuperscript{d}\textit{Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY, USA}

Received 3 September 1996; revised 6 December 1996; accepted 20 December 1996

Abstract

We have recently characterized a functional polymorphism in the catechol-O-methyltransferase (COMT) gene that is responsible for substantial variability in COMT enzymatic activity found in humans. A common low-activity variant of the enzyme contains a methionine residue at amino acid 158 of membrane-bound COMT whereas the common high activity variant has a valine at this site. Considering the role of COMT in dopamine metabolism and the involvement of dopaminergic pathways in the pathogenesis of schizophrenia and violence, we screened 37 patients with schizophrenia to determine whether or not a behavioral association with the COMT polymorphism exists. Patients were assessed for dangerousness on the basis of a history of violent and threatening behavior, crime, cocaine and alcohol abuse, and other antisocial behaviors. We found that schizophrenic patients who were homozygous for the low activity allele were judged by their psychiatrists to be at higher risk for aggressive and dangerous behavior than those who were homozygous for the high activity allele (Kruskal–Wallis statistic = 10.43; \(P = 0.003\)). © 1997 Elsevier Science Ireland Ltd.

Keywords: Aggression; Catechol-O-methyltransferase; Polymorphism; Violence

1. Introduction

Two enzymes are important in the initial steps of metabolic transformation of catecholamines: monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT). A considerable amount of published evidence indicates that low levels of MAO may be associated with novelty seeking, substance use disorders, impulsive aggression, and other forms of deviant behavior (reviewed in Volavka, 1995). It is therefore rea-
sonable to hypothesize that low levels or low activity of COMT may also elevate the risk for deviant behavior. Somewhat surprisingly, this hypothesis has not been tested.

COMT catalyzes the S-adenosyl-L-methionine dependent methyl conjugation of catecholamine neurotransmitters and catechol drugs, thereby leading to inactivation (Axelrod and Tomchick, 1958). Because of its effect on catecholamines, COMT enzymatic activity in peripheral blood has previously been analyzed as a marker for schizophrenia, as well as for other psychiatric conditions. However, the results have been equivocal (Dunner et al., 1977; Puzynski et al., 1983; Philippu et al., 1986; Karege et al., 1987).

 Renewed interest in COMT as a modifying gene in mental illness has been stimulated recently by observations made in a condition known as velo-cardio-facial syndrome (VCFS). This is a congenital anomaly caused, in most cases, by a microdeletion on chromosome 22q11 (Scambler et al., 1992; Driscoll et al., 1993; Lindsay et al., 1995; Morrow et al., 1995). In addition to physical anomalies, an increased prevalence of psychiatric illness including schizophrenia, attention deficit hyperactivity disorder and bipolar disorder has been described (Shprintzen et al., 1978, 1992; Chow et al., 1994; Pulver et al., 1994; Papalos et al., 1996). COMT has been mapped to 22q11 and is deleted in most, if not all, patients with deletional forms of VCFS (Grossman et al., 1992; Scambler et al., 1992; Morrow et al., 1995).

 COMT activity is governed by a common polymorphism that results in substantial 3–4-fold variations in enzymatic activity (Weinshilboim and Raymond, 1977; Scanlon et al., 1979; Aksoy et al., 1993). Approximately 25% of Caucasians express a low activity form of the enzyme that is thermostable while another 25% have relatively high levels of enzymatic activity and express a heat-stable variant (Boudikova et al., 1990; Aksoy et al., 1993). We and others have recently shown that these differences are due to a G → A transition at codon 158 of membrane bound COMT, which corresponds to codon 108 of cytoplasmic COMT, leading to a valine → methionine substitution (Lotta et al., 1995; Lachman et al., 1996a).

The valine and methionine forms correspond to the high and low COMT enzyme activity variants, respectively. Recent data from our laboratory suggests that the low-activity allele may be a factor in the development of rapid cycling bipolar disorder that occurs in a subset of VCFS patients (Lachman et al., 1996b).

The data on the behavioral effects of this polymorphism led us to explore a possible relationship between the codon 108/158 polymorphism, bipolar disorder, and schizophrenia. The results of this exploratory study were largely negative and will be reported elsewhere. Serendipitously, one of us (HL) noted that the polymorphism appeared to be related to patients’ aggressive or threatening behavior. The exploratory study was not designed to specifically investigate such behaviors, but Risk Assessment for Dangerousness (RAD) forms that are routinely filled out by ward psychiatrists were available in a subset of patients.

The data provided in the forms were studied in relation to the patients’ genotype in order to test the hypothesis that the low activity COMT variant is associated with dangerous behaviors.

2. Methods

2.1. Subjects

The subjects were 37 inpatients hospitalized at the Bronx Psychiatric Center (BPC) whose diagnosis of schizophrenia was based on DSM-III-R criteria. All subjects were judged to have the mental capacity to give written consent, which was provided prior to participation. There were 32 males and five females. Reflecting approximately the racial composition of the Bronx Psychiatric Center inpatients, there were 14 Hispanics, 12 Caucasians, and 11 African-Americans. Their average age was 40.6 ± 8.5 years. The 37 patients in this study were part of a larger schizophrenia study involving two psychiatric facilities that will be reported elsewhere. The BPC patients represented a distinct subgroup of chronic inpatients who had previously been assessed for aggression and dangerous behavior (see below). There was no patient selection. Everyone
diagnosed with schizophrenia at BPC who was genotyped for the COMT polymorphism was included in this study.

2.2. Assessment of dangerousness

This assessment was done by the admitting psychiatrist and ward chief (NB) using the RAD. The RAD is a 16-item inventory that describes the patient’s lifelong history of deviant behaviors. These behaviors include past ownership of weapons, causing bodily harm to another person in an assault, threats, substance abuse, and violent crime. Following completion of the RAD, the admitting psychiatrist determined whether the patient was at low, medium or high risk for dangerous behavior. The admitting psychiatrists were not aware of the patients’ genotypes.

In order to understand how the psychiatrists arrived at the trichotomous classification of risk, we inspected the individual item data in the RAD. This inspection suggested that four items largely accounted for the risk classification: (1) history of causing bodily harm; (2) history of violent crime; (3) alcohol and/or cocaine abuse; and (4) history of threatening behavior. A table summarizing the findings is available on request.

The assessment of dangerousness was not done for the purpose of research. The RAD is a clinical tool whose reliability and validity have not been formally tested. However, the behaviors covered by the RAD are generally recognized as associated with (or predictive of) violence in schizophrenic patients; ample supportive evidence is reviewed elsewhere (Volavka, 1995).

2.3. Analysis of COMT genotype

The COMT genotype was determined by Restriction Fragment Length Polymorphism (RFLP) analysis as previously described in detail (Lachman et al., 1996). DNA was extracted from peripheral blood leukocytes obtained from 10 ml of anticoagulated blood and genotyped blind to aggression score. Briefly, a 210-bp PCR product was generated using the primers 5’-CTCATCACCACACCATCGAGATCAA and 5’-GATGACCCTGG-GTGATAGTGGG (nucleotides 1881–1900 and 2071–2090, GenBank accession number z26491, and Bertocchi et al., 1991; Lundstrom et al., 1991; Tenhunen et al., 1994). When codon 108/158 is ATG (methionine, low activity form), a recognition signal for the restriction enzyme Nla III is generated. Radiolabelled PCR product (10 μl) was treated with 5 units of Nla III for 3 h at 37°C and a 2-μl aliquot (in loading buffer) was separated by electrophoresis through an 8% non-denaturing acrylamide gel.

2.4. Statistical analysis

A Kruskal–Wallis test was applied to test the association between the trichotomous (ordinal) risk classification and the trichotomous genotype. Fisher exact probability test was used for analyses of nominally classified variables (race).

3. Results

The relationship between the genotype and risk is displayed in Table 1. Inspection of Table 1 indicates that the val/val, but not the met/met genotype is associated with low risk; the opposite was true for high risk. Five out of seven patients with the val/val genotype were considered to be low risk, and none were high risk. By contrast, all seven patients with the met/met genotype were judged to have either a high or medium risk. The relationship is highly statistically significant (Kruskal–Wallis statistic = 10.43; P = 0.003).

It is possible that the results were confounded by demographic factors (Table 2). The average age of the val/val and met/met homozygotes was, respectively, 42.1 ± 9.3, and 33.4 ± 5.4 years (t = 2.15, d.f. = 12, P = 0.053, unpaired t-test,

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Kruskal–Wallis statistic = 10.43; P = 0.003 (exact). Val is the high activity allele, and met is the low activity allele.
two-tailed). There was also a slightly elevated frequency of met/met homozygotes among Ca-
casians compared with African-Americans, who showed a slightly elevated frequency of the val/val genotype, similar to the findings in Caucasian, African and African-American controls (unpublished observations, Spielman and Weinshilboum, 1981; Daniels et al., 1996; Lachman et al., 1996). However, there was no significant difference when allele frequencies were analyzed (Table 2, Fisher’s exact test, two-sided: Caucasian vs. African-American, $P = 0.38$; Caucasian vs. Hispanics, $P = 0.59$; African-American vs. Hispanics, $P = 0.58$).

4. Discussion

These preliminary data suggest that the COMT functional polymorphism may modify impulsive, aggressive, and dangerous behavior in schizophrenics. Although a number of studies suggest that reduced serotonergic transmission is implicated in impulsive-aggressive behavior (Pucilowski and Kostowski, 1980; Siever and Trestman, 1993; Mehlman et al., 1994; Miczek et al., 1994; Saudou et al., 1994; Virkkunen et al., 1994, 1995; New et al., 1996), the preliminary data reported here suggest that catecholamines may also play a role. This is consistent with the finding that $\beta$-adrenergic antagonists have an ameliorating effect on aggressive behavior in schizophrenics as well as in patients with organic brain syndrome (Mattes, 1985; Sorgi et al., 1986). Also, aggressive behavior induced in isolated mice by tricyclic antidepressants is reduced by noradrenergic denervation (Matsumoto et al., 1995). There is also evidence that the dopamine precursor L-DOPA increases aggressive behavior in rodents (Eichel, 1979). Since serotonergic and dopaminergic systems directly interact in the limbic system, it is reasonable to propose that both neurotransmitter pathways could have an effect on impulsive-aggressive behavior.

Recent observations regarding MAO-A may also be relevant as far as a role for catecholamines in impulsive-aggressive behavior is concerned. There is a report of a rare mutation in the X-linked MAO-A gene that is associated with low-normal intelligence, loss of impulse control and criminality in male members of an affected
pedigree (Brunner et al., 1995). Also, MAO-A null mice display increased aggressive behavior (Cases et al., 1995). However, since MAO-A has a direct effect on serotonin as well as catecholamine metabolism, it is difficult to determine which of these major neurotransmitter systems is responsible for the effects on impulsive aggression.

We have recently detected an association between the low activity COMT allele and the development of bipolar spectrum disorder, in particular rapid cycling bipolar disorder, found in patients with VCFS (Persico et al., 1995; Lachman et al., 1996). Although aggressive behavior has not been reported in these patients, there are anecdotal reports that children and adolescents with VCFS have impaired impulse control (R. Goldberg and D.F. Papulos, personal communication). It is interesting to note that the dangerous behavior exhibited by high risk met/met homozygotes was characterized by impulsive actions that included jumping through the window of a moving train, assaultive behavior when teased, and fire setting when stressed. Consequently, it is possible that this genotype may impart a risk for impulsive and/or aggressive behavior in subgroups of patients with severe neuropsychiatric disorders.

Cloninger (1987) defined three dimensions describing personality variants: harm avoidance, novelty seeking, and reward dependence. These trait dimensions are measured by his Tridimensional Personality Questionnaire (TPQ). Aggression and impulsiveness (measured by the Multidimensional Personality Questionnaire) are positively related to novelty seeking, whereas impulsiveness is negatively related to harm avoidance (Cloninger, 1987). These traits are under partial genetic control mediated, at least to some extent, by dopamine receptors (Van Tol et al., 1992; Campion et al., 1994; Benjamin et al., 1996; Cloninger et al., 1996; Ebstein et al., 1996). Although we did not administer the TPQ, the impulsive and aggressive behavior observed in our met/met homozygotes suggests high novelty seeking and low harm avoidance.

Although the data reported here are potentially of great interest, the results have to be viewed with caution for several reasons. First, the total number of patients homozygous for the two COMT alleles was relatively small. Second, there was an 8.7-year difference in the mean age between the two homozygous groups, a value that barely failed to achieve statistical significance. It is possible that the apparent correlation between the COMT genotype and risk for dangerous behavior could be due to the lower age of met/met homozygotes since aggressive behavior is inversely correlated with age. On the other hand, the questionnaire used to estimate the risk addressed the lifetime history of deviant behaviors, not just the recent past. Third, there is a possibility that the relationship between the genotype and the risk interacts with race; this was not possible to test formally in a sample of this size. However, considering that Caucasian mentally ill individuals do not, as a group, display increased aggressive and violent behavior compared with other ethnic groups (Volavka, 1995), it is very unlikely that the observed difference between the COMT genotype and aggressive behavior is due to population stratification. Fourth, the evaluation of risk in this preliminary study was based on an instrument that was designed for clinical use rather than as a research tool. Finally, aggressive behavior occurring in the hospital was not ascertained in this study; such data would be difficult to obtain retrospectively with any degree of reliability. These shortcomings have been corrected in a larger study that is underway. However, independent replication by other investigators will be most significant. If confirmed, these findings could have significant diagnostic and therapeutic implications.

Acknowledgements

H.M.L. is supported by a grant from the Carmel Hill Fund. The authors appreciate the participation of the patients in this study.

References


