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Short Communication

Genetic Variation of the MAO B Gene is Related to Shorter Reaction Times in Alcohol Dependent Patients

Petra Netter[1]*, Christian Montag[2], Martin Reuter[3,4], Melanie Baars[5] and Bernd Gallhofer[6]

[1]*Department of Psychology, University of Giessen, Germany*
[2]*Department of Molecular Psychology, University of Ulm, Germany*
[3]*Department of Psychology, University of Bonn, Germany*
[4]*Center for Economics and Neuroscience, University of Bonn, Germany*
[5]*Department of Psychiatry, University of Tübingen, Germany*
[6]*Department of Psychiatry, University Clinic of Giessen/Marburg, Germany*

***Corresponding author**
Petra Netter, Department of Psychology, University of Giessen, Otto-Behaghel-Strasse 10, FD-35394 Giessen, Germany, Tel: 49 641 9926065; Fax: 49 6421 67250; E-mail: petra.netter@psychol.uni-giessen.de

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Abstract

Introduction: Both low levels of platelet monoamine oxidase B (MAO B) and polymorphisms of the MAO A gene coding for MAO A activity have been found to be associated with alcoholism and violent or impulsive aggression, while associations of these variables with the polymorphism of the MAO B gene coding for MAO B activity have hardly been reported. Therefore the present study tries to investigate if the polymorphism rs1799836 of the MAO B gene located on intron 13 of chromosome X is associated with alcohol dependence, and if possible associations between aggression related personality traits and the MAO B polymorphism are different in patients and controls.

Method: In a small pilot study including 60 male alcohol dependent patients and individually matched healthy controls, personality questionnaire scores on aggression and impulsivity and reaction times in a Go/NoGo task as a measure of impulsive behavior were obtained and genotypes A and G for the single nucleotide polymorphism on the MAO B gene (rs1799836) were determined.

Results: The ratios of A and G carriers in patients and controls were both equivalent to ratios in Caucasian populations and not statistically different between groups. Aggression and impulsivity scores were not statistically different between genotypes, but significantly faster reaction times were observed in G-as compared to A-genotype participants exclusively in the patient group (p=.016).

Discussion: Although no association between the polymorphism of the MAO B gene and alcohol dependence was observed, and the association with aggression failed to reach statistical significance, it is noteworthy that faster reaction times in carriers of the G allele were exclusively observed in alcohol dependent patients and not in controls This might be explained by the possible effects of the investigated polymorphism on brain dopamine levels modified by alcohol dependence.

Conclusions: The study provides a hypothesis for a novel functional significance of the MAO B gene associated with alcohol dependence.

ABBREVIATIONS

MAO B: Monoamine Oxidase B; DA: Dopamine; SNP: Single Nucleotide Polymorphism; SEM: Standard Error of the Mean, ANOVA: Analysis of Variance

INTRODUCTION

Low levels of the enzyme monoamine oxidase B (MAO B) in plasma, which is mainly responsible for degradation of dopamine; have been found to be associated with alcohol dependence [1-3] and with personality traits related to alcoholism, like violent aggression and impulsivity, in non-psychopathological samples [2-6]. Similarly, the genetic variant of the monoamine oxidase A (MAO A) gene coding for lower MAO enzyme activity has frequently been reported to be associated with aggression [7], antisocial personality disorder and impulsive overt anger [8,9] and alcoholism [10,11]. But most publications analyzing the impact of the MAO B gene (coding for MAO B activity) in relation to alcoholism and/or aggression, are either based on psychopathological samples like schizophrenics [12] or suicidal

patients [9] or females [11]. So far, no direct single effects of the MAO B gene on alcoholism or antisocial behavior could be observed [12-14]. But since associations between personality traits and MAO A gene polymorphisms have frequently only been observed in subsamples like antisocial alcoholics or females with childhood abuse [11] or suicidal males [9], it seemed promising to compare the associations between aggression related personality traits and the MAO B polymorphism in alcohol dependent patients and healthy controls.

The genetic single nucleotide polymorphism (SNP rs1799836) of the MAO B gene located on intron 13 of chromosome X has been claimed to be related to MAO B activity [15]. The SNP is defined by an exchange of adenine to guanine resulting in the two alleles A and G. Since the MAO B gene is located on the X chromosome which is single in males, A and G also represent the two possible genotypes in male samples.

So the present pilot study aims to investigate, if the two alleles A and G of the MAO B polymorphism are a) differently distributed among alcohol dependent patients and healthy controls, and b) (differently) associated with levels of aggression and impulsivity, i.e., if possible associations are due to the genetic disposition for alcohol dependence or to related personality dimensions.

METHOD

Participants

A pilot study was started to test these questions in a small group of alcohol dependent males and healthy controls. Patients were recruited maximally 10 days after detoxification from two hospitals (Psychiatric University Clinic and Vitos Hospital Giessen) and two further institutions for post withdrawal psychotherapy in the city of Giessen, Germany. Participants had to be males beyond the age of 18 years and to fulfill the criteria of alcohol abuse according to ICD-10 diagnosed by an experienced psychiatrist. Furthermore, patients suffering from any other drug dependence or from schizophrenia, schizotypal or delusional disorders according to ICD-10 as well as those treated with MAO inhibitors were excluded. Furthermore, patients had to be free from drugs like benzodiazepines and antidepressants used during and after treatment of withdrawal. The resulting 60 male patients (age range 27-69 years, mean: 47.9+/-9.0 years) were individually matched for age and level of education with healthy controls. N= 47 healthy controls could be obtained for individual matching according to age and educational level. They were individually approached by the experimenters at sports clubs, the agency for employment, and recruited from personal acquaintances and the department staff they were checked for not having ever been exposed to psychiatric or psychotherapeutic treatment. Age and educational level in this sample were statistically almost identical with those in the total patient sample. (Age range 26-68 years, mean 48,3 +/-9.5 years). All participants gave informed consent and were rewarded with 20 Euro. The study was approved by the ethics committee of the Medical Faculty of the University of Giessen, Germany.

Methods and procedure

The complete experimental procedure lasted about two hours. First, blood samples for molecular genetic analysis of the rs1799836 polymorphism of the MAO B gene were drawn and self-report personality questionnaires had to be filled in. Aggression was assessed by the Freiburg Aggression Scale (FAF), [16] consisting of five subscales (spontaneous aggression, reactive aggression, irritability, inhibition of aggression, openness = lie scale). The subscale of spontaneous aggression (19 items) was selected for detailed analysis, because it best represents violent aggression. *Impulsivity* was measured by the Impulsiveness scale I7 [17] which comprise items referring to lack of emotional and cognitive control and premature acts of behaviour (17 items). Behavioural measures of impulsivity were obtained by a modified version of the Go/NoGo task described by Fillmore [18]. Participants have to react as fast as possible to the symbol Y (Go-item) on a computer screen and not to respond to the NoGo symbol 0 presented in random order of 40 each. Number of responses to NoGo-items (false alarms = commission errors) indicates impulsive premature responding, and reaction times measured as an average across the 40 Go-items were recorded, since decision times had been shown to be shorter in impulsive individuals [19].

Genetic analyses

DNA was extracted from whole blood samples. Automated purification of genomic DNA was conducted by means of the Mag NA Pure® LC system using a commercial extraction kit (MagNA Pure LC DNA isolation kit; Roche Diagnostics, Mannheim, Germany). Genotyping of MAO-B rs1799836 single nucleotide polymorphism (SNP) (an adenine to guanine transition in intron 13 of the MAO-B gene located on the X-chromosome) was performed by real time polymerase chain reaction using fluorescence melting curve detection analysis by means of the Light Cycler System (Roche Diagnostics, Mannheim, Germany).

The primers and hybridization probes used (TIB MOLBIOL, Berlin, Germany) were as follows: forward primer: 5'- CTCTTA-TACCACAGGAGAAAGACC -3'; reverse primer: 5'- CATGCAGGATC-TGAAATGAA -3'; sensor [G] hybridization probe: 5'- AATAG-CAAAAGCGACACCATCTT –fluoresce in-3': anchor hybridization probe: 5'-LCRed640- CTAATCTGCTCCCTAAAGGACTAAGTAAC-TG-phosphate 3'.

Statistical evalution

Differences in distribution of genotypes between patients and controls were tested by Chi^2 test, and associations of questionnaire and behavioural measures (Go/NoGo task) with genotypes were analysed separately for each variable first by two-factorial analyses of variance (ANOVA) to test for general effects of groups and genotypes and their possible interactions and additionally by one-way ANOVAs in each of the two samples separately.

RESULTS

Association of genotypes of the MAO B polymorphism with alcohol dependence

The frequencies of the A and G genotypes in the patient and the control group are given in Table 1. In both groups the ratios are close to the ratio given for the Caucasian population which is A/G = 60/40 %.. The comparison of genotype distribution

yielded no significant difference between patients and controls (X^2 = .129, p =.720). Even when comparing controls with the exact sample of individually matched cases of patients (n= 47) resulting in n = 29 A and 18 G carriers, X^2 was far from significant (X^2 = .696, p = .464). In sum, no relationship between the MAO B polymorphism investigated and alcohol dependence could be observed.

Association of genotypes with aggression and measures of impulsivity

Table 2 shows the results obtained by analyses of variance performed for each of the dependent variables and differences of means between the genotypes in each group. To our surprise, the questionnaire score of Spontaneous Aggression, was significantly higher in controls than in patients (F1;103=5.34; p = .023), but no significant genotype or interaction effects emerged. The one-way ANOVA in the alcohol dependent sample, however, revealed slightly higher scores of aggression in carriers of the G allele, which however failed to reach significance (F1;58 = 3.32, p=.074),but did become significant when merely the 47 individually matched patients were included. (F1;45 ,p =.043),

The questionnaire score of *Impulsivity* yielded slightly, but non-significantly higher scores in the patient sample of n=60. However, no significant differences between genotypes and no genotype x group interactions could be observed either in the analysis with 60 patients (see table 2), or when analysed with the individually matched patients.

The behavioural measure of commission errors in the Go/NoGo task, due to its much skewed distribution of scores and bottom effects did not emerge as a suitable measure, (see table 2), but was in addition evaluated by the nonparametric Mann-Whitney U-test. Again, this test did not yield significant differences between groups or genotypes either (data not shown).

Reaction Times

In the Go/NoGo task, however, were not only significantly shorter in patients than in controls (F1;94 =8.42;p = .005), but also shorter in carriers of the G than of the A allele (F1;94=5.36; p = .023). This even became more evident when comparing the two groups of 47 cases each (F 1;86=5.94; p =.017). Surprisingly, the difference between A und G allele carriers observed in the total sample turned out to be only significant in the alcohol dependent group (F1; 58= 6.18; p = .016 in the sample of n = 60 (see Figure 1) and F1; 58= 6.61; p = .014 with n = 47), while in controls this difference was not significant (F1; 38=.989; p = .326).

DISCUSSION

The aim of the present study was to investigate the role of a genetic variation on the MAO B gene for alcohol dependence and related personality traits. The lack of an association between the MAO B polymorphism and alcohol dependence is in line with previous studies [11,13]. It may, furthermore, not contradict findings describing an association between low MAO B levels in platelets and alcoholism [2,3], because these findings primarily refer to persons suffering from the more criminally aggressive, mainly genetically determined early onset type 1 alcoholism according to Cloninger [1]. Although our patients were also slightly more impulsive than controls, type 1 alcoholism was evidently not represented in our sample of patients who were mostly rather characterized by reactive depression typical for type 2 alcoholics, willing to accept psychotherapeutic treatment and scoring lower than controls on the questionnaire scale of spontaneous aggression (probably in an effort to demonstrate adaptive behaviour in a clinical setting).

Table 1: Frequencies (and percentages) of genotypes in patients and controls.

	Patients	Controls	Total
A	34 (57)	25 (53)	59 (55)
G	26 (43)	22 (47)	48 (45)
Total	60 (100)	47 (100)	107 (100)
X^2 =.129, p=.720			

Associations of the polymorphism with aggression or impulsivity, as inferred from the literature concerning MAO B activity in platelets [2-6] and associations with the MAO A gene polymorphism [7-9] could not be confirmed except for the marginally higher aggression scores in genotype G in patients But significantly shorter reaction times in G allele as compared to A allele carriers were observed in the patient sample, a finding which had not been reported before. The result that although patients and controls may not differ in allelic frequencies but do differ in associations of the polymorphism with certain traits, confirms that associations between genetic variations and alcoholism or aggression could only be observed in subsamples of special vulnerability like suicidality [9]or childhood abuse [11]

Although these are very preliminary findings and although associations between the MAO B polymorphism and activity of MAO B in platelets have frequently not been confirmed [20,21], a functional interpretation of our results could be based on the finding by Balciunieni et al. [22] that the G allele of the MAO B polymorphism rs1799836 was associated with lower MAO brain activity observed in post-mortem brains. This would result in higher dopamine (DA) brain levels which, among others, have been reported to be associated with both aggression [23] and speed of perception [24]. So this might provide an (admittedly speculative) functional explanation of the mechanism underlying our results. Particularly shorter reaction times in G allele carriers seem to turn out as a fairly robust association in the patient sample, because when controlling for level of education as a possible confounder by analyses of covariance, the association remained significant in the patient sample (F1;57=5.98;p=.018), while in controls inclusion of the covariate reduced the significance level even further,(p=.896)

The very small sample of the present study, of course, only provides hypotheses for further research on larger samples. Given the experimental nature of the present study, the inclusion of a patient sample and the intention of individual matching made it difficult to recruit large sample sizes as also emphazised by Montag and Reuter [25].

CONCLUSIONS

The single nucleotide polymorphism rs1799836 of the MAO B gene, although seemingly not related to the development

Table 2: Results of the two-way analyses of variance (ANOVA) with means (+/-SEM) of groups (patients (Pat) n=60; controls (Co) n=47) and genotypes (A and G) for each variable and comparisons between means of genotypes in each group by one-way ANOVAs.

Variable	Means of main effects for groups and genotypes			Means of genotypes within each group	
	Group score p	Genotype score p p int		Patients n score p	Controls n score p
Spontaneous Aggression score	Pat:**2.36**(.335) **023** Co:**3.59**(,398)	A:2.79(.359) .479 G 2.92(.466)	.164	A:34 1.80(.407) .074 G:26 **2.92**(.466)	A:25 3.78(.624) .688 G:22 3.41(.665)
Impulsivity Score	Pat:7.61(.506) .138 Co:6.47(.568)	A:7.04(.512) 1.00 G:7.04(.563)	.411	A:34 7.29(.680).222 G:26 7.92(.787)	A:25 6.79(.743) 566 G:22 6.16(.792)
Commission Errors	Pat.1.28(.222) .945 Co:1.30(276)	A: 1.36(.230) ..692 G:1.22(.296)	.132	A:34 1.56(.397)...298 G:26 1.00(.346)	A:25 1.04(.342) 334 G:22 1.56(.402)
Reaction Time (ms)	Pat.**428** (9.65) **.005** Co.**474**(11.92)	A:**470** (9.89) **.023** G:**434**(11.72)	.508	A: 34 **452**(11.97)..**016** G:26 **407**(13.96)	A:25 487(16.31) 326 G:22 461(19.55)

(n: number of cases, p int=interaction effect; bold type: p<.05)

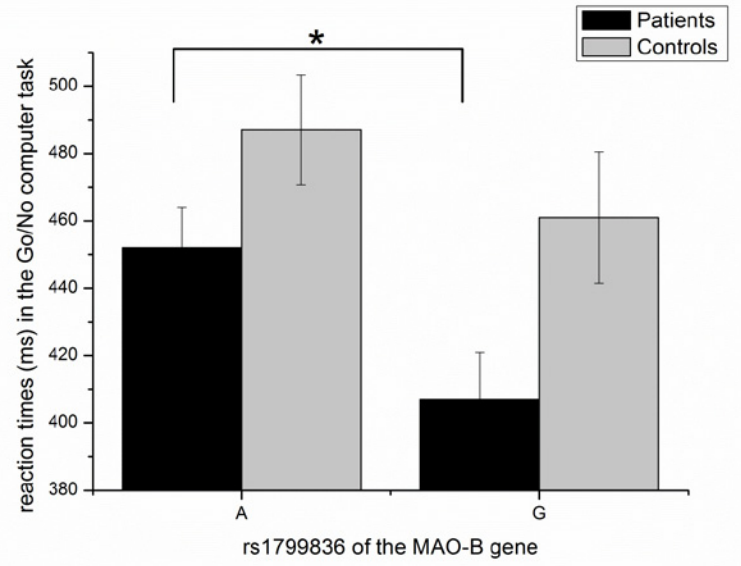

Figure 1 Reaction times (msec.) in the computer Go/NoGo task observed for carriers of genotypes A and G in male alcohol dependent patients (n= 60) and healthy matched controls (n= 47) * p=.016.

of alcohol dependence, may indicate a so for undiscovered relationship in particular to higher speed of reaction in G allele carriers which merely becomes evident in patients suffering from clinically relevant alcohol abuse, a condition possibly associated with vulnerability to higher DA brain activity resulting from G allele induced lower MAO B brain activity.

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