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Abstract

Several lines of evidence suggest that oxidative stress plays a role in the mechanisms of action of methamphetamine (MAP) in the human brain. Given the role of glutathione S-transferases (GSTs) in the protection against oxidative stress, genes encoding the GSTs have been considered as candidates for association studies of MAP abuse. This study was undertaken to investigate the role of the functional polymorphism of GSTP1 gene exon 5 (Ile105Val) in the pathogenesis of MAP abuse. Genotyping for GSTP1 gene polymorphism exon 5 (Ile105Val) in 189 MAP abusers and 199 normal controls was performed by polymerase chain reaction (PCR)-restriction fragment length polymorphism. Association between GSTP1 gene polymorphism and clinical features (prognosis of psychosis (transient-type and prolonged-type), spontaneous relapse (positive and negative), and poly-substance abuse) of MAP abusers was evaluated. Significant differences in the frequency of both alleles ($p = 0.026$, odds ratio: 1.70, 95% confidence intervals (CI) 1.06-2.72) and genotypes ($p=0.029$) between MAP abusers and controls were detected. In particular, a significant difference in both genotype frequency ($p=0.013$) and allele frequency ($p=0.014$, odds ratio: 1.84, 95% CI 1.13-2.97) between MAP abusers with psychosis (transient-type and prolonged-type) and controls was detected. Our findings suggest that the polymorphism (Ile105Val) on exon 5 of the GSTP1 gene may contribute to a vulnerability to psychosis associated with MAP abuse in

Japanese population.

KEY Words: Methamphetamine; Psychosis; Drug abuse; Genetic factor; Polymorphism

Introduction

Abuse of methamphetamine (MAP) is a growing problem worldwide. Some lines of evidence suggest that both environmental and genetic factors might contribute to drug abuse vulnerability [Cami and Farre, 2003; Rawson et al., 2002; Merikangas et al., 1998; Kendler et al., 2000; Uhl et al., 2002]. It is well known that MAP induces a strong psychological dependence, and that repeated further consumption of MAP results in psychotic states, the symptoms of which resemble those of the paranoid type of schizophrenia [Sato et al., 1983; Sato et al., 1992].

Positron emission tomography (PET) imaging studies of the brains of MAP abusers have demonstrated that the density of dopamine (DA) transporters is significantly decreased in the caudate/putamen of MAP abusers [Volkow et al., 2001; Sekine et al., 2001]. Such findings suggest that the long-term use of MAP leads to the damage of dopaminergic neurons in the human brain. It has been shown that MAP-induced neurotoxicity in the brain requires the involvement of striatum DA and also involves mechanisms associated with oxidative stress, further suggesting that oxidative stress in dopaminergic pathways might be implicated in MAP-induced neurotoxicity [Cadet et al., 2003]. There are a number of papers demonstrating the neuroprotective effects of glutathione or its related compounds on MAP- or DA-induced neurotoxicity [Choi et al., 2002; Fukami et al., 2004; Hashimoto et al., 2004; Shimizu et al.,

2002]. In addition, it is also well known that dopaminergic pathways in the mesocorticolimbic systems can play an important role in drug reward [Kalivas, 2002]. Therefore, polymorphisms in genes that regulate dopaminergic pathways may contribute to interindividual differences as regards a vulnerability to drug abuse [Koob and LeMoal, 1997].

The glutathione S-transferases (GSTs: EC 2.5.1.18) belong to a family of multifunctional enzymes that catalyze the conjugation of reduced glutathione with electrophilic groups of a wide variety of compounds including carcinogens, environmental contamination, and products of the oxidative process [Mannervik 1985; Hayes and Strange, 2000; Smythies and Galzigma, 1998]. Because of their important role in the cellular defense against oxidative stress, GSTs are of interest in the context of association studies of MAP abuse. The genes encoding three classes of GSTs, i.e., GSTM (mu, chromosome 1p13.3), GSTP (pi, chromosome 11q13), and GSTT1 (theta, chromosome 22q11.2), are known to be polymorphic [Stucker et al., 2002; De Roos et al., 2003; Kelada et al., 2003; Wang et al., 2003; Watson et al., 1998]. Recently, we reported an association between GSTM1 gene deletion and female MAP abusers, suggesting that GSTM1 gene deletion may contribute to a vulnerability to MAP abuse in Japanese subjects [Koizumi et al., 2004]. Furthermore, it has been reported that genetic polymorphisms of GSTP1 exon 5 (rs947894, Ile105Val (A>G)) and exon 6 (rs1799811, Ala114Val (C>T)) have functional relevance to the GST gene product resulting in reduced GST enzyme activity

(~30%) [Watson et al., 1998; Board et al., 1989; Zimniak et al., 1994; Ali-Osman et al., 1997]. Taken together, such findings appear to suggest that individuals with these variant GSTP1 genotypes which result in reduced GSTP1 enzymatic activity may be at greater risk of MAP abuse. In order to verify the potential role of the GSTP1 gene in the pathogenesis of MAP abuse, we analyzed a polymorphism of the GSTP1 gene in subjects with a diagnosed MAP-related disorder.

Methods

This study was performed after obtaining the approval of the ethics committees of each affiliated institute of the Japanese Genetics Initiative for Drug Abuse (JGIDA). All subjects provided written informed consent for the use of their DNA samples for this study. The subjects were 189 patients (149 males and 40 females, age: 36.9 ±11.9 years (mean ± SD), age range: 18 -69 years) with MAP dependence and a psychotic disorder meeting the ICD-10-DCR criteria (F15.2 and F15.5) who were outpatients or inpatients of psychiatric hospitals of the JGIDA (Table 1). The control subjects were 199 age-, gender-, and geographical origin-matched normal controls (157 males and 42 females, age: 37.2 ± 10.5 years (mean ± SD), age range: 19-73 years), the majority of whom were with no past history and no family history of drug dependence or psychotic disorders. Diagnoses were made by two trained

psychiatrists by interview and available information including hospital records. Patients were excluded if they had a clinical diagnosis of schizophrenia, another psychotic disorder, or an organic mental syndrome as reported previously [Ujike et al., 2003]. All subjects were Japanese, born and living in restricted areas of Japan including northern Kyushu, Setouchi, Tyukyou, Toukai, and Kantou.

The patients were divided into subgroups by some characteristic clinical features (Table 1). The patients were divided by poly-substance abuse status, 55 patients abuse MAP only in their lifetime, and 116 patients abuse some other drugs besides MAP in present or past. Organic solvent was most frequently abused besides MAP, followed by marijuana. Cocaine and heroine were rarely abused in the present study. Prognosis of MAP psychosis was various among patients, and some patients showed continuous psychotic symptoms even after MAP discontinuance as previously reported [Sato et al., 1983; Sato et al., 1992]. Therefore, patients were divided into two categories of prognosis, transient-type and prolonged-type, based on duration of psychotic state after MAP discontinuance. Thus, patients with transient-type whose psychotic symptoms improves within one month after discontinuance of MAP consumption and beginning of treatment with antipsychotic drugs, and those with prolonged-type whose psychosis continues for more than one month even after discontinuance of MAP consumption and beginning of treatment. In this study, patients with transient- and prolonged-types of MAP

psychosis were 94 and 65, respectively (Table 1). It has been well documented that once MAP psychosis has developed, patients in remission state becomes reliable to spontaneous relapse without re-consumption of MAP [Sato et al., 1983; Sato et al., 1992]. It is postulated that sensitization phenomenon induced by repeated consumption of MAP should be developed in the brain of MAP psychosis patients which result in neural basis for enhanced susceptibility to relapse. Therefore, the patients were divided into two groups according to presence or absence of spontaneous relapse. The patients with and without spontaneous relapse were 62 and 111, respectively (Table 1).

Two polymorphisms on exon 5 and exon 6 of the GSTP1 gene have previously been reported. We analyzed exon 5 (rs947894, Ile105Val) of the GSTP1 gene in this study, since no minor allele frequency of the polymorphism of exon 6 (rs1799811, Ala114Val) was detected among Japanese normal subjects [Ishii et al., 1999]. Genotyping for this gene was performed by PCR-RFLP analysis. The polymorphic site in exon 5 (Ile105Val) was amplified as reported previously [Wang et al., 2003]. The primers of exon 5 of the GSTP1 gene were GSTP1-5F (5’-GTAGTTTGCCCAAGGTCAAG-3’) and GSTP1-5R (5’-AGCCACCTGAGGGGTAAG-3’). After performing PCR, a 433 bp DNA fragment was amplified for GSTP1 exon 5, followed by 2-hr digestion with BsmA I (New England Biolabs, Inc., Beverly, MA, U.S.A.). The fragments were separated on 2% agarose gel stained with

ethidium bromide. The wild-type (A/A), heterozygous genotype (A/G), and mutant genotype (G/G) yielded 2 bands (328 and 105 bp), 4 bands (328, 222, 106, and 105 bp), and 3 bands (222, 106, and 105 bp), respectively.

The differences between groups were evaluated by Fisher's exact test. The odds ratio and 95 % confidence intervals (CI) between two variables were calculated as an estimate of risk. Differences were considered significant at $p<0.05$.

Results

The frequencies of allele and genotypes in MAP abusers and controls are shown in Tables 2. The genotype distribution in both MAP abusers and controls was in the Hardy-Weinberg equilibrium. The differences in both genotype frequency (p=0.029) and allele frequency (p=0.026) between MAP abusers and controls were found to be significant (Table 2). The frequency of carrying the G allele in MAP abusers was significantly higher (p=0.026, odds ratio: 1.70, 95% CI 1.06-2.72) than that of controls.

Next, we examined the association between the clinical features of MAP abusers (i.e., prognosis of psychosis, spontaneous relapse, and poly-substance abuse) and normal controls. A significant difference in both genotype frequency (p=0.013) and allele frequency (p=0.014, odds ratio: 1.84, 95% CI 1.13-2.97) between MAP abusers with psychosis (transient-type and

prolonged-type) and controls was detected (Table 2). There was a significant difference in genotype frequency (p=0.045) between MAP abusers with transient-type psychosis and controls, and was a trend toward difference in allele frequency (p=0.052, odds ratio: 1.75, 95% CI 1.01-3.06) between MAP abusers with transient-type psychosis and controls. There was also a significant difference in both genotype frequency (p=0.028) and allele frequency (p=0.039, odds ratio: 1.96, 95% CI 1.07-3.59) between MAP abusers with prolonged-type psychosis and controls. Furthermore, a significant difference in terms of both genotype frequency (p=0.009) and allele frequency (p=0.009, odds ratio: 2.00, 95% CI 1.19-3.35) between MAP abusers with negative spontaneous relapse and controls was detected (Table 2). Moreover, there was a trend toward difference in both genotype frequency (p=0.052) and allele frequency (p=0.053, odds ratio: 1.70, 95% CI 1.00-2.88) between MAP abusers with poly-substance abuse and controls (Table 2).

Discussion

Our findings suggest that a functional polymorphism (Ile105Val) on exon 5 of the GSTP1 gene may contribute to MAP abuse vulnerability in Japanese subjects. Since a polymorphism (Ile105Val) on exon 5 has been shown to be of functional significance in terms of enzyme activity [Watson et al., 1998; Zimniak et al., 1994], individuals with the G allele

(valine) would be expected to have decreased GST detoxification. Based on the role of GSTs in the antioxidant system preventing MAP-induced neurotoxicity, variant GSTP1 genes might lead to an excess of metabolic products (e.g., DA-quinone) of the oxidative process induced by the administration of MAP, and may furthermore lead to MAP-induced neurotoxicity in the brain, including damage of the dopaminergic neurons, as compared to the products associated with the A allele (isoleucine) of GSTP1 gene. We also found that the frequency of the G allele in MAP abusers with psychosis (transient-type and prolonged-type) was significantly higher than that of controls, suggesting that this GSTP1 gene polymorphism may be associated with MAP-induced psychosis in Japanese subjects. Thus, it appears to be the case that the GSTP1 polymorphism (Ile105Val) on exon 5 may contribute to a susceptibility to MAP-induced psychosis among Japanese subjects. In contrast, we found an association between GSTP1 polymorphism (Ile105Val) and negative spontaneous relapse, whereas no association between this polymorphism and positive spontaneous relapse was detected. Taken together, it seems that GSTP1 polymorphism (Ile105Val) may be implicated in MAP-induced psychosis, but not spontaneous relapse, although further studies using a large sample are necessary.

It has been suggested that DA-quinones synthesized by auto-oxidation of DA might play a role in MAP-induced neurotoxicity in the brain, and that glutathione and GST might play a role in the detoxification against DA-quinone induced neurotoxicity [Smythies and Galzigna,

1998; LaVoie and Hastings, 1999, Whitehead et al., 2001; Shimizu et al., 2002; Asanuma et al., 2003]. Thus, DA auto-oxidation results in the formation of DA-quinones, which readily participate in nucleophilic addition reactions with sulfhydryl groups on free cysteine, glutathione, or cysteine found in proteins including DA transporters [Smythies and Galzigna, 1998; Whitehead et al., 2001]. Based on the known role of GSTs in the process of antioxidant defense, we considered the possibility that MAP abusers with the G allele of GSTP1 polymorphism were more susceptible to MAP-induced psychosis or to a spontaneous relapse of MAP abuse. In this study, we found significant differences in the distribution of genotype and allele frequencies between MAP abusers with psychosis and controls. Furthermore, we found a significant difference between MAP abusers with negative spontaneous relapse and controls. Taken together, it is likely that the polymorphism (Ile105Val) on exon 5 of the GSTP1 gene could be a risk factor for the development of MAP-induced psychosis in Japanese subjects.

It is reported that the frequency (18 %) of the G allele in Asians such as Taiwanese is lower than that in African-American (42 %) and European-American (33 %)[Watson et al., 1998]. The frequency of (8 %; our study) of the G allele in Japanese control subjects is significantly (x^2=13.3, p=0.0003) lower than that (18 %) of Taiwanese, suggesting the ethnic difference between Asians and European- and African-Americans for the polymorphism

(Ile105Val) on exon 5 of GSTP1. Therefore, it may be of interest to examine the association between the GSTP1 gene polymorphism and methamphetamine abusers in European- and African-Americans. If replication studies are confirmed, the polymorphism (exon 5 Ile105Val) of GSTP1 would be only the known specific mechanism by which genetic variation leads to a risk for the development of MAP-induced psychosis. Interestingly, our recent PET study demonstrated that the antioxidant N-acetyl-L-cysteine (a precursor for glutathione synthesis) could attenuate significantly the reduction of DA transporter in monkey striatum after repeated administration of MAP [Hashimoto et al., 2004]. In addition, we reported that N-acetyl-L-cysteine attenuated hyperlocomotion, development of sensitization, and neurotoxicity after administration of MAP [Fukami et al., 2004], suggesting that N-acetyl-L-cysteine would be a suitable drug for treatment of MAP abuse. As described in Introduction, it is likely that endogenous antioxidant glutathione plays a role in the behavioral changes and neurotoxicity associated with MAP abuse. Taken together, our findings may shed light on some of the neurobiological mechanisms and pathways that lead to the development of MAP abuse, and could thereby facilitate the development of novel treatments and prevention strategies for MAP abuse.

In conclusion, our findings indicate that a polymorphism (exon 5 Ile105Val) of the GSTP1 gene may contribute to a vulnerability to MAP abuse among Japanese subjects.

Furthermore, it is likely that this polymorphism (exon 5 Ile105Val) of the GSTP1 gene could be a risk factor for the development of MAP-induced psychosis in Japanese subjects.

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Table 1. Characteristics of control subjects and MAP abusers.

Variable	Controls	Abusers	p Values
Sex, M/F	157/42	149/40	0.989*
Age, mean ± SD, y	37.2 ± 10.5 (19-73)	36.9 ± 11.9 (18-69)	0.813**
Prognosis of Psychosis			
Transient type		94	
Prolonged type		65	
Spontaneous Relapse			
Positive		62	
Negative		111	
Poly-substance Abuse			
No		55	
Yes		116	

*The comparison between 2 groups was performed using the x^2 test.

**The comparison between 2 groups was performed using the t test.

Table 2. Genotype and allele frequencies of the GSTP1 exon 5 gene polymorphism in controls and MAP abusers

Ile105Val (A>G) rs947894	n	Genotype AA	AG	GG	p	Allele A	G	p
Control	199	167 (83.9 %)	32 (16.1 %)	0 (0 %)		366 (92.0 %)	32 (8.0 %)	
Abuser	189	144 (76.2 %)	41 (21.7 %)	4 (2.1 %)	0.029*	329 (87.0 %)	49 (13.0 %)	0.026*
Prognosis of Psychosis (n=159)					0.013*			0.014*
Transient	94	71 (75.5 %)	21 (22.3 %)	2 (2.1 %)	0.045*	163 (86.7 %)	25 (13.3 %)	0.052
Prolonged	65	48 (73.8 %)	15 (23.1 %)	2 (3.1 %)	0.028*	111 (85.4 %)	19 (14.6 %)	0.039*
Spontaneous Relapse								
Positive	62	50 (80.6 %)	11 (17.7 %)	1 (1.6 %)	0.255	111 (89.5 %)	13 (10.5 %)	0.463
Negative	111	81 (73.0 %)	27 (24.3 %)	3 (2.7 %)	0.009**	189 (85.1 %)	33 (14.9 %)	0.009**
Poly-substance Abuse								
No	55	44 (80.0 %)	9 (16.4 %)	2 (3.6 %)	0.065	97 (88.2 %)	13 (11.8 %)	0.254
Yes	116	87 (75.0 %)	28 (24.1 %)	1 (0.9 %)	0.052	202 (87.1 %)	30 (12.9 %)	0.053

*P<0.05, **P<0.01 as compared to control (Fisher's exact test)