Association Analysis of the Adenosine A1 Receptor Gene Polymorphisms in Patients with Methamphetamine Dependence/Psychosis

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Abstract: Several lines of evidence suggest that the dopaminergic nervous system contributes to methamphetamine (METH) dependence, and there is increasing evidence of antagonistic interactions between dopamine and adenosine receptors in METH abusers. We therefore hypothesized that variations in the A1 adenosine receptor (ADORAI) gene modify genetic susceptibility to METH dependence/psychosis. In this study, we identified 7 single nucleotide polymorphisms (SNPs) in exons and exon-intron boundaries of the ADORA1 gene in a Japanese population. A total of 171 patients and 229 controls were used for an association analysis between these SNPs and METH dependence/psychosis. No significant differences were observed in either the genotypic or allelic frequencies between METH dependent/psychotic patients and controls. A global test of differentiation among samples based on haplotype frequencies showed no significant association. In the clinical feature analyses, no significant associations were observed among latency of psychosis, prognosis of psychosis, and spontaneous relapse. These results suggest that the ADORA1 gene variants may make little or no contribution to vulnerability to METH dependence/psychosis.

Keywords: Single nucleotide polymorphism, SNP, variation, human, Japanese, MAP, abuse, dopamine.

INTRODUCTION

Methamphetamine (METH) is a psychomotor stimulant with high liability for abuse, and METH abuse has become a very serious social problem in Japan [1]. Chronic METH abusers have been shown to have persistent dopaminergic deficits [2, 3]. Amphetamines are thought to produce their stimulant effects mainly via the dopaminergic system [4, 5], although other systems may also be involved. Dopamine D1 and D2 receptors form heterodimeric complexes with adenosine A1 and A2a receptors respectively, which modulate their responsiveness [6-9], suggesting that responses to amphetamines may also depend on adenosinergic function.

Several lines of evidence suggest that adenosine A1 receptors play a role in inhibiting the effects of METH. Adenosine receptor antagonists potentiate the effects of lower METH doses and substitute for the discriminative stimulus effects of METH [10, 11]. Adenosine receptor agonists protect against METH-induced neurotoxicity, and amphetamine-induced stereotypy and locomotor activity, and reduce the acquisition of conditioned place preference induced by amphetamine [12-15]. These results suggest that adenosine A1 receptors play important roles in the expression of METH-induced neurotoxicities and behaviors.

To date, however, there has been no association analysis between A1 adenosine receptor (ADORAI) gene variants and drug addiction. The purpose of this study was (1) to identify novel sequence variants in all coding exons as well as exon-intron boundaries of the ADORA1 gene in Japanese, and (2) to investigate whether these polymorphisms and/or haplotypes were associated with METH dependence/psychosis.

MATERIALS AND METHODS

Subjects

One-hundred seventy-one unrelated patients with METH dependence/psychosis (138 males and 33 females; mean age 37.5±12.0 years) meeting ICD-10-DCR criteria (F15.2 and F15.5) were used as case subjects; they were outpatients or inpatients of psychiatric hospitals. The 229 control subjects (119 males and 110 females; mean age 41.2±12.3 years) were mostly medical staff members who had neither per-
sonal nor familial history of drug dependence or psychotic disorders, as verified by a clinical interview. All subjects were Japanese, born and living in the northern Kyushu, Setouchi, Chukyo, Tokai, and Kanto regions. This study was approved by the ethical committees of each institute of the Japanese Genetics Initiative for Drug Abuse (JGIDA), and all subjects provided written informed consent for the use of their DNA samples for this research [16]. After informed consent was obtained, blood samples were drawn and genomic DNA was extracted by the phenol/chloroform method.

Defining Variants of the ADORA1 Gene

Initially, DNA samples from 16 METH dependent/psychotic patients were used to identify nucleotide variants within the ADORA1 gene (GenBank accession no. AC105940). Exon numbers were based on the report by Ren and colleagues [17]. Exons 1A, 1B, 2, 3 and exon-intron boundaries were amplified by polymerase chain reaction (PCR) using a thermal cycler (Astec, Fukuoka, Japan), and the products were sequenced in both directions using BigDye terminators (Applied Biosystems, Foster City, CA) by an ABI Genetic analyzer 3100 (Applied Biosystems). The primer sequences used in this study are shown in Table 1.

Genotyping of IVS1A+182 (rs56298433) was performed by PCR amplification using 2F-2R primers followed by restriction enzyme Nla III digestion. Genotyping of Exon2+363 (rs10920568) was performed by PCR amplification using 4F-4R primers followed by sequencing with the same primers. IVS2+35826 (rs5780149) was performed by PCR amplification using 5F-9R primers followed by sequencing with 7F and 7R primers. Genotyping of Exon3+937 (rs6427994), Exon3+987 (rs41264025), and Exon3+1064 (rs16851030) was performed by PCR amplification using 5F-9R primers followed by sequencing with 7F and 7R primers.

Patient Subgroups

For the clinical category analysis, the patients were divided into two subgroups by three different clinical features. (A) Latency of psychosis from first METH intake: less than 3 years or more than 3 years. The course of METH psychosis varied among patients, with some patients showing psychosis sooner after the first METH intake, as previously reported [16, 18]. Because the median latency was 3 years, this time point was used as the cutoff in defining the two groups. (B) Duration of psychosis after the last METH intake: transient (<1 month) or prolonged (≥1 month). Some patients showed continuous psychotic symptoms even after METH discontinuation, as previously reported [16, 18]. Patients with the transient type showed a reduction of psychotic symptoms within one month after the discontinuation of METH consumption and the beginning of treatment with neuroleptics. Patients with the prolonged type showed a psychotic symptoms continued for more than one month even after the discontinuation of METH consumption and the beginning of neuroleptic treatment. (C) Spontaneous relapse: present or not. It has been well documented that once METH psychosis has developed, patients in the remission phase are liable to spontaneous relapse without reconsumption of METH [16, 18].

Statistical Analysis

The Hardy-Weinberg equilibrium of genotypic frequencies in each SNP was tested by the chi-square test. The level of statistical significance was set at α = 0.05. The allelic and genotypic frequencies of the patient and control groups were compared using the chi-square test. Haplotype frequencies were calculated by the Arlequin program available from http://anthropologie.unige.ch/arlequin [19]. Locus by locus linkage disequilibrium (LD) was evaluated by D' and r², which were calculated by the haplotype frequencies using the appropriate formula in the Excel program. A global test of differentiation among samples based on haplotype frequencies was also performed by the Arlequin program.

RESULTS

Analysis of the ADORA1 Gene Variants

To identify polymorphisms in the ADORA1 gene, exons 1A, 1B, 2, and 3, and exon-intron boundaries were analyzed using genomic DNA from Japanese METH dependent/psychotic subjects. Seven SNPs were identified (Table 2). Five out of seven of these SNPs were previously reported by Deckert [20]. In the two SNPs, the frequencies of the minor

Table 1. Primers Used in this Study

| Exon   | Forward          | Reverse          |
|--------|------------------|------------------|
| Exon1A | 1F: TGG ACT GGA TGC CTT ATG GCT TAG | 1R: GGC GCA GGA GCT GAG TGA CAA TCG |
|        | 2F: TCT CAC CCA GTA TCA CTT CCT TGT | 2R: ATC ACA TGG TAC GGC AGA GAC TCA |
| Exon1B | 3F: AAT AGG GAG AAA CGC CCC AGC CTT | 3R: AAG CAC CTG TGT GGT CAG GGA AGC |
| Exon2  | 4F: GGT AGG AGC TGC ATG TGA CAA GTG | 4R: GCA GAG TGA GGA GTG CAG CAC GAT |
| Exon3  | 5F: GGC TGT CAT GAA GCA ATG ATG AGA | 5R: CCA GCG ACT TGG CGA TCT TCA GCT |
|        | 6F: TCT ACC TGG AGG TCT TCT ACC TAA | 6R: CCC TGA AGC TCT GGA CTG CTC ATG |
|        | 7F: GTG GTC CCT CCA CTA GGA GTT AAC | 7R: ACA GGT AAT TAC ACT CCA AGG CTC |
|        | 8F: CTG ATA TTT GCT GGA GTG CTG GCT | 8R: ACA CTT GCA ACA GAG CTT CCA AAG |
|        | 9F: CCT TGC TGT CAT GTG AAT CCC TCA | 9R: CAA GAG GAA GAT GCC CAA GGG AGA |
alleles differed between our patients and those of Deckert. In the Exon2+363 (rs10920568) SNP, the G allele was present in 15.5% of our Japanese controls (Table 3) and 36.9% of the German controls [20]. In the Exon3+1064 (rs16851030) SNP, the T allele was present in 35.8% of our Japanese controls and 1.2% of the German controls [20]. These differences were suggested to be related to the difference in ethnicity between the two cohorts. One SNP, Exon2+363 (rs10920568), was a synonymous mutation (Ala to Ala) (Table 2). All the other SNPs were located either in the introns or an untranslated region in the exon 3. Two SNPs (Exon3+937 (rs6427994) and Exon3+1454 (rs11315020)) were in linkage disequilibrium (LD) in the sense that the genotypic patterns of the 16 samples examined were the same, representing Exon3+937 (rs6427994) for these two SNPs. IVS1A+182 (rs56298433), Exon2+363 (rs10920568), IVS2+35826 (rs5780149), Exon3+937 (rs6427994), Exon3+987 (rs41264025), and Exon3+1064 (rs16851030) were chosen for further analysis.

Table 2.  ADORA1 Gene Variants Found in the Japanese Population

| Location      | Variants | rs#        | SNP Name | Function |
|---------------|----------|------------|----------|----------|
| IVS1A+182     | G/T      | rs56298433 | intron   |
| Exon2+363     | T/G      | rs10920568 | 805T/G   | synonymous (Ala->Ala) |
| IVS2+35826    | T4/T5    | rs5780149  | intron   |
| Exon3+937     | A/C      | rs6427994  | 1777C/A  | untranslated |
| Exon3+987     | C/T      | rs41264025 | 1827C/T  | untranslated |
| Exon3+1064    | C/T      | rs16851030 | 1904C/T  | untranslated |
| Exon3+1454    | T/del    | rs11315020 | 2294insT | untranslated |

The nucleotide sequence of the ADORA1 gene was referenced to the NCBI nucleotide database under accession number AC105940. Exon numbers were based on the report by Ren and colleagues [17]. The column labelled rs# shows SNP numbers from the NCBI SNP database. The data in the column labelled SNP name are from the report by Deckert [20].

Table 3.  Genotypic and Allelic Distribution of the ADORA1 Gene SNPs in the METH Subjects and the Controls

| SNP         | Group | N   | Genotype (%) | P       | Allele (%) | P       |
|-------------|-------|-----|--------------|---------|------------|---------|
| IVS1A+182   |       | G   | G/T          | T       | 0.961      | G/T     | 0.823   |
|             |       |     | 222 (99.1%)  | 2 (0.9%)| 0 (0.0%)  | 446 (99.6%)| 2 (0.4%)| 0.333   |
|             |       |     | 166 (70.8%)  | 36 (12.1%)| 32 (19.1%)| 300 (87.7%)| 42 (13.0%)| 0.708   |
| Exon2+363   |       | T   | T/G          | G       | 0.333      | T/G     | 0.253   |
|             |       |     | 162 (94.0%)  | 16 (3.1%)| 0 (0.0%)  | 369 (85.0%)| 85 (15.5%)| 0.071   |
|             |       |     | 132 (77.2%)  | 36 (21.1%)| 3 (1.8%)  | 271 (79.2%)| 71 (20.8%)| 0.572   |
| IVS2+35826  |       | T4  | T4/T5        | T5      | 0.887      | T4/T5   | 0.071   |
|             |       |     | 150 (65.5%)  | 90 (36.1%)| 30 (13.4%)| 444 (96.9%)| 14 (3.1%)| 0.888   |
|             |       |     | 108 (63.2%)  | 55 (32.2%)| 8 (4.7%)  | 333 (97.4%)| 9 (2.6%)  | 0.222   |
| Exon3+937   |       | A   | A/C          | C       | 0.248      | A/C     | 0.248   |
|             |       |     | 2 (0.9%)     | 46 (20.1%)| 181 (79.0%)| 50 (10.9%)| 408 (89.1%)| 0.071   |
|             |       |     | 5 (2.9%)     | 38 (22.3%)| 128 (74.9%)| 48 (14.0%)| 294 (86.0%)| 0.572   |
| Exon3+987   |       | C   | C/T          | T       | 0.937      | C/T     | 0.937   |
|             |       |     | 215 (93.9%)  | 16 (6.6%) | 0 (0.0%)  | 444 (96.9%)| 14 (3.1%)| 0.888   |
|             |       |     | 162 (94.7%)  | 9 (5.3%)  | 0 (0.0%)  | 333 (97.4%)| 9 (2.6%)  | 0.572   |
| Exon3+1064  |       | C   | C/T          | T       | 0.071      | C/T     | 0.071   |
|             |       |     | 89 (38.9%)   | 116 (50.7%)| 24 (10.5%)| 294 (64.2%)| 164 (35.8%)| 0.572   |
|             |       |     | 80 (46.8%)   | 67 (39.2%)| 24 (14.0%)| 227 (66.4%)| 115 (33.6%)| 0.572   |

N: number of samples.
P: Significance values between the METH subjects and the controls.
Relationship Between the ADORA1 Gene SNPs and METH Dependence/Psychosis

Association analyses between these SNPs in the ADORA1 gene and METH dependence/psychosis were performed using DNA samples from 171 METH dependent/psychotic subjects and 214 control subjects (Table 3). Among them, the genotypes of five control samples and three METH samples could not be determined at IVS1A+182 (rs56298433). The genotypic frequencies in these SNPs were within the Hardy-Weinberg expectations. No significant differences of the genotypic and allelic distributions of these SNPs in these samples were observed. As the minor allele frequencies of two SNPs, IVS1A+182 (rs56298433) and Exon3+987 (rs41264025), were less than 5%, another four SNPs, Exon 2+363 (rs10920568), IVS2+35826 (rs5780149), Exon3+937 (rs6427994), and Exon3+1064 (rs16851030), were used for further analyses.

A global test of differentiation among samples based on haplotype frequencies was performed using the Arlequin program, but no significant association with METH dependence/psychosis was observed (P=0.590). Haplotype frequencies were estimated by the Arlequin program, and locus by locus LD was calculated by using the appropriate formula in the Excel program. Most of the SNPs in exon 2 and exon 3 were in LD, suggesting that the locus from exon 2 to exon 3 was in a LD block (Table 4).

Subcategory analyses were conducted on the clinical parameters (latency of psychosis, prognosis of psychosis, and spontaneous relapse) (Table 5). Significant differences were observed in the shorter latency of psychosis (P=0.025) at Exon3+937 (rs6427994). However, this significance disappeared after Bonferroni correction by the sub-group numbers, two (P < 0.025).

DISCUSSION

We analyzed the ADORA1 gene variations in a Japanese population and found seven SNPs in exons and exon-intron boundaries. However, no significant associations were

Table 4. Linkage Disequilibrium Mapping of the ADORA1 Gene

| SNP          | Exon2+363 (rs10920568) | IVS2+35826 (rs5780149) | Exon3+937 (rs6427994) | Exon3+1064 (rs16851030) |
|--------------|------------------------|------------------------|-----------------------|-------------------------|
| Exon2+363    |                        |                        |                       |                         |
| IVS2+35826   | 0.029                  | 0.807                  | 1.000                 | 0.676                   |
| Exon3+937    | 0.012                  | 0.030                  |                       | 1.000                   |
| Exon3+1064   | 0.014                  | 0.061                  | 0.068                 |                         |

D' and r² values for Controls are shown in the upper right and lower left, respectively.

Table 5. Genotypic Distribution of the ADORA1 Gene SNPs in Subcategorized METH Subjects

| SNP          | Exon2+363 (rs10920568) | IVS2+35826 (rs5780149) | Exon3+937 (rs6427994) | Exon3+1064 (rs16851030) |
|--------------|------------------------|------------------------|-----------------------|-------------------------|
| Genotype     | T                      | T/G                    | G                     | A                       |
| Group        | N                      | P                      | P                     | P                       |
| Control      | 229                    | 162                    | 63                    | 4                       |
| Latency of Psychosis |            |                        |                       |                         |
| <3 years     | 67                     | 48                     | 16                    | 3                       |
| ≥3 years     | 71                     | 56                     | 15                    | 0                       |
| Prognosis of Psychosis |            |                        |                       |                         |
| Transient (<1 month) | 91                  | 70                     | 19                    | 2                       |
| Prolonged (≥1 month) | 56                  | 41                     | 14                    | 1                       |
| Spontaneous Relapse |                |                        |                       |                         |
| Not present  | 104                    | 81                     | 22                    | 1                       |
| Present      | 60                     | 45                     | 13                    | 2                       |

N: number of samples.
P: Significance values between the METH subjects and the controls.
observed between these SNPs and METH dependence/psychosis in the genotypic, allelic, haplotypic or clinically subcategorized analyses.

This is the first association analysis between ADORA1 gene variants and drug addiction. We failed to find associations between the ADORA1 gene SNPs and METH dependence/psychosis. While the significant difference (P=0.025) in the shorter latency of psychosis at Exon3+937 (rs6427994) disappeared after Bonferroni correction, this may have been due to the sample size, and thus further analysis with a larger sample is warranted.

The variants we found were one synonymous SNP, two intron SNPs and four exon SNPs in the untranslated region. These SNPs are unlikely to affect receptor function because they are not non-synonymous SNPs or promoter SNPs. Because several animal studies have suggested a modulatory role of adenosine receptors for dopamine systems, it remains possible that another region in the ADORA1 gene, such as a promoter region or intron regions, contributes to the alteration of ADORA1 gene function.

Although a few association analyses of the ADORA1 gene and psychiatric diseases have been performed, no significant association has been reported between ADORA1 variants and bipolar affective disorder or panic disorder [20, 21]. As caffeine is a nonselective adenosine receptor antagonist, the association between the psychoactive effects of caffeine and gene variants of adenosine receptors have also been studied. However, the anxiogenic response to an acute dose of caffeine in healthy, infrequent caffeine users was not associated with ADORA1 gene polymorphism [22]. Interindividual variation in the anxiety response to amphetamine has also been studied in healthy volunteers, but no association was observed with ADORA1 gene variants [23]. These results suggest that the ADORA1 gene variations have little effect on psychiatric symptoms and/or personality traits.

In conclusion, our data suggest that the ADORA1 gene variants may not play a major role in the development of METH dependence/psychosis.

ACKNOWLEDGEMENTS

We thank all the subjects who participated in this study. This study was supported in part by a Grant-in-Aid for Health and Labor Science Research (Research on Pharmaceutical and Medical Safety) from the Ministry of Health, Labor and Welfare of Japan; and by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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