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Association between *Taq*I A dopamine D_2 receptor polymorphism and therapeutic response to bromperidol: a preliminary report

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Abstract The relationship between *Taq*I A dopamine D_2 receptor (DRD_2) polymorphism and therapeutic response to bromperidol, a selective dopamine antagonist, was investigated in 30 acutely exacerbated schizophrenic inpatients. Patients were treated with bromperidol 6–18 mg/day for 3 weeks. Clinical symptoms were evaluated by the Brief Psychiatric Rating Scale (BPRS) before and 3 weeks after the treatment. The *Taq*I A genotypes were determined with the PCR method. There was no significant difference in the percentage improvement of total BPRS or 5-subgrouped symptoms (positive, negative, anxiety-depression, excitement and cognitive symptoms) after the 3-week treatment between the patients with A1 alleles (n=18) and those with no A1 allele (n=12). Although the present study is preliminary, it is suggested that the *Taq*I A DRD_2 polymorphism is not associated with therapeutic response to bromperidol in schizophrenic patients.

Key words Bromperidol · Schizophrenia · *Taq*I A DRD_2 polymorphism · Therapeutic response

Introduction

The human dopamine D_2 receptor (DRD_2) gene contains a *Taq*I restriction fragment length polymorphism, creating the A1 and A2 alleles [3]. Studies using postmortem brain [5, 6] and positron emission tomography (PET) [5] showed that the subjects with one or two A1 alleles had lower DRD_2 density than those without this allele. Functionally, the A1 allele has been associated with diminished dopaminergic activity and reduced glucose metabolism in the brain regions with abundant dopamine receptors [6]. Therefore, the *Taq*I A DRD_2 polymorphism may be one of the important markers for the DRD_2 density and function.

We previously studied the relationship between the *Taq*I A DRD_2 polymorphism and therapeutic response to nemonapride, a potent and highly selective dopamine D_2-like receptors antagonist [8], in schizophrenic patients [9]. The patients with A1 alleles showed higher improvement than those with no A1 allele, suggesting that the *Taq*I A DRD_2 polymorphism is related to therapeutic response to nemonapride possibly by modifying the efficiency of DRD_2 antagonism of the drug.

Bromperidol is a close structural analogue of haloperidol. An in vitro study [8] has suggested that bromperidol has potent antagonistic effects for DRD_2 similar to nemonapride. This similarity in pharmacological properties between the two drugs suggests that the *Taq*I A DRD_2 polymorphism is also related to therapeutic response to bromperidol. Therefore, we examined the relationship between the *Taq*I A DRD_2 polymorphism and therapeutic response to bromperidol in schizophrenic patients.

Subjects and methods

The subjects were 30 acutely exacerbated Japanese schizophrenic inpatients who fulfilled the DSM-IV criteria for schizophrenia. None had received any medication for at least one month. The detailed characteristics of the patients are shown in Table 1. This study was approved by the Ethics Committee of Hirosaki University Hospital, and written informed consent to participate in this study was obtained from the patients and their families.

The patients were randomly allocated to one of the three different doses, i. e., 6 mg/day (n=11), 12 mg/day (n=11) or 18 mg/day (n=8), of

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Tab. 1 Comparisons of demographic data, clinical characteristics, drug factors and percentage improvement scores after the treatment between the patients with A1 alleles and those with no A1 allele

	Patients with A1 alleles (n=18)	Patients with no A1 allele (n=12)	p value
Mean age (±SD), year	39.1 (±13.0)	33.7 (±13.0)	0.271
Sex, No. (%)			
Male	8 (44.4)	7 (58.3)	0.710
Female	10 (55.6)	5 (41.7)	
Duration of illness (±SD), month	122.1 (±94.8)	126.0 (±123.3)	0.921
Age at onset (±SD), year	29.1 (±9.4)	23.2 (±4.6)	0.055
Pre-treatment BPRS score (±SD)			
Total	24.7 (±7.5)	26.2 (±5.8)	0.561
Positive	8.1 (±3.1)	9.9 (±2.4)	0.090
Negative	4.6 (±3.1)	4.2 (±2.0)	0.665
Anxiety-depression	4.8 (±3.1)	5.4 (±2.5)	0.589
Excitement	4.7 (±2.4)	4.6 (±1.7)	0.864
Cognitive	2.4 (±2.6)	2.1 (±2.0)	0.686
Mean daily dose of bromperidol (±SD), mg	12.0 (±4.6)	10.5 (±5.2)	0.427
Plasma bromperidol concentration, ng/ml	7.0 (±3.4)	5.3 (±2.8)	0.164
Concomitant drugs, No. (%)			
Biperiden	8 (44.4)	5 (41.7)	1.000
Flunitrazepam	14 (77.8)	12 (100.0)	0.130
% improvement score after the treatment (±SD)			
Total	54.1 (±29.9)	60.8 (±32.6)	0.568
Positive	56.0 (±40.5)	65.3 (±38.0)	0.535
Negative	44.7 (±42.7)	42.8 (±51.9)	0.912
Anxiety-depression	55.4 (±44.9)	39.3 (±52.1)	0.389
Excitement	58.7 (±54.3)	76.1 (±31.2)	0.346
Cognitive	60.0 (±77.1)	92.6 (±22.2)	0.232

BPRS indicates Brief Psychiatric Rating Scale.
Probabilities were calculated by the Fisher exact test or student t-test.

bromperidol. Bromperidol was administered in two equally divided doses at 8 AM and 8 PM for 3 weeks. No other drugs were given except biperiden for extrapyramidal side effects, flunitrazepam for insomnia and sennoside for constipation.

Clinical symptoms before and 3 weeks after the treatment were assessed by the Brief Psychiatric Rating Scale (BPRS) [1], which consists of 5-subgrouped symptoms (positive, negative, anxiety-depression, excitement and cognitive symptom). The improvement after bromperidol treatment was expressed as percentage improvement, i. e., amelioration score after 3 weeks/pre-treatment score multiplied by 100. Plasma concentrations of bromperidol were measured using the high-performance liquid chromatography method [4]. The A1 and A2 alleles were determined with the PCR method [3].

Statistical analyses were performed by using the Fisher exact test and student t-test. A two-tailed *p* value of 0.05 or less was regarded as statistically significant.

Results

Three patients were homozygous for the A1 allele, 15 were heterozygous for the A1 and A2 alleles, and 12 were homozygous for the A2 allele. These patients were divided into two genotype groups; the patients with A1 alleles (n=18) and those with no A1 allele (n=12).

No significant difference was found in clinical characteristics and drug factors between the two genotype groups (Table 1). There was no significant correlation between percentage improvement in total BPRS or 5-subgrouped symptoms and doses or concentrations of bromperidol. No significant difference was found in the percentage improvement of total BPRS symptoms or any subgrouped symptoms between the two genotype groups (Table 1).

Discussion

The present results suggest that the *Taq*I A DRD_2 polymorphism does not affect therapeutic response to bromperidol. This finding is in contrast with our previous report indicating that this polymorphism affects therapeutic response to nemonapride [9]. There are two possible explanations for this discrepancy. First, the influence of *Taq*I A DRD_2 polymorphism on therapeutic response to bromperidol, if any, might be nullified by too high concentrations. According to previous reports [7], the threshold DRD_2 occupancy for optimal antipsychotic effects could be achieved even at a plasma concentration range of 1–2 ng/ml during the treatment with haloperidol, a close analogue of bromperidol. The mean plasma bromperidol concentrations of the patients with A1 allele and those with no A1 allele were 7.0 ng/ml and 5.3 ng/ml, respectively. Therefore, the possibility that the saturation of DRD_2 blockade was achieved in the majority of the patients irrespective of the genotypes cannot be excluded.

Second, the discrepant results may be attributable to the slight difference in pharmacological properties between the two drugs. Nemonapride appears to have a more selective DRD_2 antagonistic effect than bromperidol, since the $5\text{-}HT_{2A}/D_2$ affinity ratios of nemonapride and bromperidol have been reported to be 1/139 and 1/39, respectively [8]. Therefore, it is likely that the modification of DRD_2 antagonism associated with the *Taq*I A DRD_2 polymorphism has a higher impact on therapeu-

tic response to nemonapride than on that to bromperidol.

Meanwhile, in the present study, the statistical power for detecting differences between the *Taq*I A DRD_2 genotype groups was calculated to be 0.55 to detect a large effect size (0.80) according an alpha value of 5% two-tailed [2], suggesting the possibility that the negative results might be due to a small sample size. Therefore, the present results need to be replicated with a larger number of subjects.

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