ORIGINAL

No association of the Trp 64 Arg mutation of the β3-adrenergic receptor gene with obesity, type 2 diabetes mellitus, hyperlipidemia, and hypertension in Japanese patients with schizophrenia

Takamasa Nagano#, Yukihiko Matsuda#*, Tetsuya Tanioka**, Takaoki Yoshioka, Tadashi Hiroi, Kenichi Yoshikawa, Ken-ichiro Okabe, Kyoko Osaka**, Isao Nagamine**, and Yoichiro Takasaka

*Division of Psychiatry, Hosogi Unity Hospital, Kochi, Japan, *Division of Internal Medicine, Hosogi Unity Hospital, Kochi, Japan, and **Department of Community and Psychiatric Nursing, School of Medical Sciences, The University of Tokushima, Tokushima, Japan*

Abstract Objective : This study was conducted to address the question of whether the β3-adrenergic receptor gene mutation (Trp 64 Arg) is associated with metabolic disease in Japanese patients with schizophrenia.

Methods : In a cross-sectional study, 89 participants were grouped into three genotypes. The 64 Arg allelic frequency in patients with or without metabolic disease was analyzed. Anthropometrics variables and biochemical parameters were compared among the genotypes.

Results : The 64 Arg allele, which had a frequency of 0.22, was not associated with obesity, type 2 diabetes mellitus, dyslipidemias, or hypertension. No significant differences among the genotypes were found in current age, age at diagnosis with schizophrenia, body mass index, waist-hip ratio, plasma glucose, plasma insulin, triglycerides, free fatty acids. Patients with the 64 Arg allele had greater 24-h excretion of norepinephrine than those lacking the variant (p=0.019).

Conclusion : The 64 Arg allelic mutation is not associated with obesity, type 2 diabetes mellitus, lipid metabolism dysfunction, or hypertension in Japanese patients with schizophrenia.

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Keywords *: schizophrenia, β3-adrenergic receptor polymorphism, obesity, metabolic disease, Trp 64 Arg allele*

INTRODUCTION

The β3-adrenergic receptor (β3-AR) predominantly locates in adipose tissue in humans and transmits catecholamine signals, resulting in lipolysis and thermogenesis (1, 2). Lipolysis of triglycerides supplies free fatty acids to other organs as an energy source, and thermogenesis is important to maintain body temperature. In the first reports of a β3-AR mutation in humans, the replacement of 64 Trp with 64 Arg, is closely associated with obesity and early-onset diabetes (3, 4). Several subsequent reports show that the frequency of the 64 Arg allele mutation varies in different ethnic groups : Inuit, Pima Indians, and Japanese have a relatively higher frequency of the mutation, in that order (3-10). Some investigators report that the muta-

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#Both authors should be equally designated as senior authors.
Address correspondence and reprint requests to Yukihiko Matsuda, M.D., Ph.D., Division of Internal Medicine, Hosogi Unity Hospital, 100 Nishi-machi, Kochi-shi, Kochi 780-8535, Japan and Fax : +81-88-825-0915.

tion is associated with obesity and type 2 diabetes mellitus (3-7, 11-13), but others report little association (14-23).

Antipsychotic drugs are beneficial for patients with chronic schizophrenia to suppress their psychotic symptoms, but those medications are often accompanied by weight gain and obesity (24, 25). Obesity is closely linked with the development of type 2 diabetes mellitus, hyperlipidemia, and hypertension, which are known to contribute to potentially lethal stroke and cardiovascular disease (26-28). Therefore, obesity is a serious issue for patients who must take long-term medication.

In this cross-sectional study in inpatients receiving chronic medication for schizophrenia, we investigated the relations between the 64 Arg allelic mutation of β3-AR and metabolic diseases including obesity to determine whether metabolic disease in schizophrenic patients is attributed to the administration of antipsychotic drugs, or the β3-AR mutation, or both.

PATIENTS AND METHODS

Patients

Eighty-nine patients with schizophrenia (49 men and 40 women) in the Hosogi Unity Hospital participated in this cross-sectional study. All patients had been treated with antipsychotic drugs for more than 6 months.

We obtained approval for this study from the Ethical Committee of our institution. Before study enrollment, patients and their guardians were fully informed of the purpose of the study, and written informed consent was obtained in accordance with the Declaration of Helsinki.

Methods

After anthropometrics measurement before the morning meal, body mass index (BMI : body weight [kg]/ height squared [m^2])and waist-hip ratio were calculated. Blood pressure was measured during bed rest in the morning. Blood samples were collected after at least a 9-hrs fast. To obtain serum, an aliquot of the sample was placed in an empty plastic tube, and to obtain plasma the remainder of the sample was placed in a tube containing ethylenediamine-tetraacetic acid. Plasma glucose (normal range, 70-110mg/dl), serum cholesterol (130-220mg/dl), and serum triglycerides (50-150 mg/dl) were determined as routine laboratory tests in our hospital. Other data including plasma insulin (normal range, 2.3-15.1μU/ml) and free fatty acid (0.01-0.90 mEq/L) levels were outsourced to Mitsubishi Kagaku BCL Co. Ltd (Kochi, Japan) which also determined the presence of the β3-AR polymorphism using polymerase chain reaction-restriction fragment length-polymorphism analysis with endonuclease Mva I digestion. For analysis of catecholamines in urine, 24-h urine was collected in a bottle containing 20ml of 6 N hydrochloride, and aliquots of urine were subjected to high-performance liquid chromatography.

Diagnostic criteria

Obesity was defined as a BMI of 25 or greater according to the criteria of the Japan Society for the Study of Obesity (28). Diabetes mellitus was defined as a fasting plasma glucose level greater than 125mg/dl according to the criteria of diabetes of the Japan Diabetes Society (29). The homeostasis model assessment-insulin resistant (HOMA-IR) index, which is a conventional index of insulin resistance, was calculated using the following formula : HOMA-IR = fasting plasma glucose (mg/dl)×fasting plasma insulin (μIU/ml)/405 (30). Hypercholesterolemia and hypertriglyceridemia were defined as serum cholesterol and triglyceride levels greater than 220mg/dl and 150mg/dl, respectively. Hypertension was defined as blood pressure higher than 139 mmHg systolic, 89 diastolic, or both (31).

Statistical analysis

Analysis of variables for quantitative values among the three genotypes was performed utilizing two-tailed one-way analysis of variance with multiple comparison tests with Fisher's PLSD, and the two-tailed unpaired t-test. Two-tailed χ^2 tests were performed for the association of 64 Arg allelic mutation with obesity, type2 diabetes, hyperlipidemia, and hypertension. All analyses were conducted using StatView version 5.0 software (SAS Institute Inc., Berkley, CA, USA) and a p value of less than 0.05 was considered statistically significant.

RESULTS

Frequency of 64 Arg allele

The overall frequency of the 64 Arg allele was 0.22 (Table 1) ; of the 89 patients, 6.7% were homozygous, 32.6% were heterozygous, and 60.7% lacked the mutation. The 64 Arg allelic frequency in men (0.24) was slightly, but not significantly, higher than that in women (0.19). The frequency of the 64 Arg allelic mutation in patients with metabolic disease including obesity, diabetes

Table 1. Frequency of the Trp 64 Arg allelic mutation of the β3-adrenergic receptor gene in patients with schizophrenia.

	n	Frequency of Arg allele
Overall	89	0.22
Metabolic disease		
Obesity	30	0.16
Diabetes mellitus	15	0.14
Hypercholesterolemia	22	0.12
Hypertrigylceridemia	30	0.10
Hypertension	23	0.17
No. of concomitant metabolic diseases		
0	41	0.30
1≤ (1, ≥2)	48(23, 25)	0.15(0.22, 0.11)

Table 2. Gender distribution and frequency of metabolic disease among the β3-adrenergic receptor genotypes.

	Trp 64 Trp (*n*=54)	Trp 64 Arg (*n*=29)	Arg 64 Arg (*n*=6)	Trp 64 Arg +Arg64Arg (*n*=35)	Hardy-Weinberg Test p value	χ^2 test p value 2×2(2×3)*
Gender						
Male	28	17	5	22	0.33	0.307(0.320)
Female	26	12	1	13	0.78	
Adiposity						
Obese	21	8	1	9	0.82	0.199(0.384)
Nonobese	33	21	5	26	0.53	
Glucose metabolism						
Diabetes mellitus	11	3	1	4	0.28	0.271(0.508)
Nondiabetes	43	26	5	31	0.69	
Lipid metabolism						
Hypercholesterolemia	17	5	0	5	0.55	0.066(0.124)
Normocholesterolemia	37	24	6	30	0.47	
Hypertriglyceridemia	9	2	0	2	0.74	0.125(0.277)
Normotriglyceridemia	45	27	6	33	0.50	
Blood pressure						
Hypertension	16	6	1	7	0.66	0.311(0.586)
Normotension	38	23	5	28	0.57	
No. of concomitant metabolic diseases†						
0	20	17	4	21	0.89	0.034(0.015)
1≤ (1, ≥2)	34(14, 20)	12(7, 5)	2(2, 0)	14(9, 5)	0.08	

*2×2 χ^2 tests was carried out comparing the Trp 64 Trp group with the combined Arg 64 Arg and Trp 64 Arg group.
†Metabolic diseases include obesity, type 2 diabetes mellitus, hyperlipidemia, and hypertension. Two groups with and without metabolic diseases were compared for χ^2 tests.

mellitus, hypercholesterolemia, hypertriglyceridemia, and hypertension was lower than that in the overall patient population. As shown in Table2, our results satisfied with Hardy-Weinberg equilibrium test in β3-AR variations. The proportion of patients with the 64 Arg allele was not significantly greater than that in those lacking the mutation for each metabolic disease. The 64 Arg mutation was present in 51% (21 of 41) of patients with no metabolic disease, which was about twice the rate in patients with one or more metabolic diseases (29%, 14 of 48 patients). Because it has been reported that patients receiving atypical antipsychotic drugs are more susceptible to the development of metabolic disease than those receiving typical antipsychotic drugs, we analyzed the antipsychotic drug use among those with β3-AR gene variants. The patients were divided

Table 3. Distribution of patients with allelic mutations of the β3-adrenergic receptor gene mutation by medication group.

Medication group	Trp 64 Trp	Arg 64 Arg + Trp 64 Arg	No. of variants	
			Trp 64 Arg	Arg 64 Arg
Atypical antipsychotics	6	3	3	0
Typical antipsychotics	27	14*	11	3
Atypical + typical antipsychotics	21	18	15	3
χ^2 test between the variants and lack of the mutation		χ^2 =1.359, p=0.507		

into three medication groups : atypical antipsychotic drug users ; typical antipsychotic drug users ; and atypical plus typical antipsychotic drug users (Table 3). The χ^2 -test showed no significant differences in the distribution of drug usage among the genetic variants.

Association of anthropometrics variables and biochemical parameters with the 64Arg allele

The current age (mean±S.D.) of enrolled patients with the Trp64Trp, Trp 64 Arg, and Arg64Arg genotype was 53.0±13.0(range ; 22-69), 52.0±14.9(range ; 22-69), and 54.8±10.3(range ; 38-67) years, respectively. The age (mean±S.D.) at diagnosis with schizophrenia in patients with the Trp 64 Trp, Trp 64 Arg, and Arg 64 Arg genotype was 29.2±12.3(range ; 14-63), 28.3±10.7 (range ; 11-45), and 32.3±12.3(range ; 23-55) years, respectively. Neither current age nor age at diagnosis with schizophrenia differed significantly among the three genotypes.

To eliminate the interventional effect on glucose and lipid metabolism and blood pressure, we selected 71 patients who did not have and were not receiving treatment for metabolic diseases and then evaluated the effect of the 64 Arg allele on biochemical parameters (Table 4). The anthropometrics variables were not significantly different among the three genotypes. Glucose metabolism and blood pressure variables also did not differ. In terms of lipid metabolism, mean cholesterol levels were significantly lower in patients with the 64 Arg allele than in those lacking the Arg allele (p=0.046). There were no differences among the three genotypes in serum triglyceride and free fatty acid levels, but a slight tendency for mean triglyceride level to be lower in 64 Arg homozygotes was observed.

Excretion of catecholamines

In the analysis of urinary catecholamine excretion, patients with obesity, diabetes mellitus, dyslipidemia, and hypertension were excluded, because those metabolic diseases and the medication administered might influence catecholamine metabolism and thus yield misleading data. Among 14 patients selected, none were

Table 4. Biochemical data (mean±S.D.) in patients not receiving medication for metabolic disease by Arg allelic group.

	Trp 64 Trp (n=42)	Trp 64 Arg (n=24)	Arg 64 Arg (n=5)	ANOVA p value
Anthropometrics				
BMI (kg/m^2)	23.9±4.4	22.4±4.1	21.2±5.4	0.255
Waist-hip ratio	0.93±0.10	0.90±0.11	0.92±0.09	0.447
Glucose metabolism				
Plasma glucose (mg/dl)	88.7±16.0	85.1±9.8	86.2±9.0	0.591
Plasma insulin (μIU/ml)	7.6±6.0	6.2±4.3	4.6±2.4	0.365
HOMA-IR	1.7±1.5	1.3±1.0	1.0±0.5	0.337
Lipid metabolism				
Cholesterol (mg/dl)	188.7±33.9*	168.6±33.4	168.0±14.1	0.046
Triglycerides (mg/dl)	101.9±52.8	83.2±34.9	75.4±23.3	0.193
Free fatty acids (mEq/l)	0.46±0.27	0.39±0.22	0.47±0.27	0.534
Blood pressure				
Systolic(mmHg)	117.6±18.8	119.6±14.7	111.6±15.6	0.640
Diastolic (mmHg)	71.5±10.7	70.8±10.0	69.6±9.0	0.907

*p=0.02(Trp 64 Trp vs. Trp 64 Arg), multiple comparison with Fisher's PLSD.

Table 5. Catecholamine excretion (mean±S.D.) in 24-h urine by β3-adrenergic receptor genotype.

	Trp 64 Trp (n=8)	Trp 64 Arg (n=6)	Test for equal variance F value	Two-tailed unpaired t-test t value	p value
Epinephrine (normal ; 1−23 μg/day)	9.3±5.1	17.2±10.1	0.250	1.911	0.080
Norepinephrine (normal ; 29−120 μg/day)	95.6±42.1	155.5±39.2	1.154	2.714	0.019

64 Arg homozygotes, 6 were 64 Arg heterozygotes, and 8 lacked the Arg allele (Table 5). Those with the Arg allele tended to have higher 24-h excretion of epinephrine compared with those lacking the mutation. Twenty-four hour excretion of norepinephrine was significantly greater (p=0.019) in patients with the Arg allele than in those lacking the mutation. There were no significant differences among the genotypes in age, sex, BMI, waist-hip ratio, fasting plasma glucose level, HOMA-IR, serum triglyceride level, serum cholesterol level, and systolic and diastolic blood pressure (data not shown).

DISCUSSION

The frequency (0.22) of the 64 Arg allele in 89 patients with schizophrenia was similar to that reported in the literature for the general Japanese population, less than that in Pima Indians and Inuit, but higher than that in American Caucasians, Europeans, and Scandinavian (3-23). The equivalent frequency of the mutation in patients with schizophrenia as compared with the general Japanese population and lack of difference in the age at diagnosis among the β3-AR genotypes indicate that the 64 Arg allele mutation does not contribute to the occurrence of schizophrenia or influence age at onset of schizophrenia.

The 64 Arg allelic mutation is associated with weight gain, obesity, and difficulty in losing weight in obese patients(4-7). Most patients treated with antipsychotic drugs are at risk of weight gain and obesity(24-27). We therefore assumed that obesity would be prevalent in patients with both the Arg allelic mutation and antipsychotic drug use. In our study, however, the prevalence of obesity in the Arg allele group (25.7%, 9 of 35 patients) was evidently lower, but not significantly, than that in patients lacking the mutation (38.9%, 21 of 54 patients). Antipsychotic drug-related metabolic disease including obesity, diabetes, hyperlipidemia, and hypertension are reported more frequently in atypical antipsychotic drug users than in typical antipsychotic drug users (25, 26). Then, we expected that antipsychotic drug users with β3-AR mutation would be subjected to and accumulate metabolic diseases. On the contrary, our data showed that patients complicated with metabolic diseases showed significantly lower frequency of the mutation. This might be associated with relatively lower BMI followed by lower plasma glucose, insulin and lipids levels. These results could not be explained by the facts reported so far in which patients with the mutation had shown positive relations or no relations to the presence of various metaboloic diseases. We have no data why β3-AR mutation are related to low frequency of metabolic disease complications in schizophrenic patients with antipsychotic drugs. The data from our study showed no differences in the distribution of the three types of antipsychotic drug users among the 64 Arg genotypes. In addition, no cumulative complications of metabolic disease in patients with the 64 Arg allele were noted. These findings confirmed that various metabolic diseases accompanying recent treatment for schizophrenia are not associated with the 64 Arg allele mutation of β3-AR. However, the possibility remains that phenotypic changes resulting from the Arg allele mutation require a longer time to become prominent (4, 13) or are disturbed by the cumulative effects of various antipsychotic drugs for more than half year.

The 64 Arg allele was first reported to be associated with (the visceral type of) obesity and early-onset non-insulin dependent diabetes (3, 4). Some researchers found no significant differences in glucose and insulin levels among individuals with the variants and those lacking the mutation (4, 11-15). Our data in patients with the 64 Arg alleles did not support an association with either visceral obesity or hyperglycemic hyperinsulinemic diabetes. However, some reports showed a significant difference in 2-h glucose or insulin levels, in insulin area under the curve after the 75-g glucose-loading test, or in insulin sensitivity in the euglycemic glucose clamp test (4, 32-34). Although we did not conduct those tests for insulin sensitivity (resistance), we determined HOMA-IR, which is a conventional insulin resistance marker, and demonstrated no significant differences between patients with and without the Arg allele mutation.

Lack of lipolysis is a primary functional disability in individuals with the 64 Arg allelic mutation of β3-AR, resulting in moderate storage of triglycerides in adipose tissue and little free fatty acid supply to the blood circulation as an energy source for peripheral sites (35). Our results, however, indicated no significant decrease in serum triglyceride levels or in serum free fatty acid levels in patients with the 64 Arg allelic mutation. Although mean serum triglyceride levels showed a tendency to decrease in those with the mutation, they remained within the normal range. These results suggest that factors other than β3-AR can regulate lipolysis of triglycerides in adipose tissues. As reported in a β3-AR knockout mice experiment (35), it is possible that β1-and β2-AR can participate in lipolysis to compensate for the loss of β3-AR function (35, 36).

Among 14 patients in our present studies without metabolic disease who were receiving no medication for those metabolic diseases, 24-h urinary excretion of norepinephrine was increased in those with 64 Arg allele variants. We speculate that a feedback-induced increase against the lack of response of β3-AR or a compensatory reaction for hypotension induced by α-AR blockage by antipsychotic drugs could cause the increase in norepinephrine excretion.

The results of our cross-sectional study in Japanese patients receiving antipsychotic drugs for schizophrenia suggest that the 64 Arg allelic mutation of β3-AR is not positively associated with the development of metabolic diseases such as obesity, type 2 diabetes mellitus, hyperlipidemia, and hypertension.

Our study had some limitations. The number of patients enrolled was small and they were from a single ethnic group. A large-scale study should be conducted in Japan and other countries to confirm our data. Furthermore, some participants may have metabolic diseases caused by some antipsychotic drugs, so this can affect the result of the frequency of β3-AR mutation. We could not determine the specificity of the relationship of individual antipsychotic drugs including its total dosage and treatment period to the β3-AR 64 Arg allelic mutations. Because of above reasons, our study may be preliminary one.

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