Clin Auton Res (2007) 17:112–114
DOI 10.1007/s10286-007-0403-6

RESEARCH LETTER

$\alpha_{2\beta}$ adrenoreceptor 301–303 deletion polymorphism in polycystic ovary syndrome

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Received: 1 June 2006
Accepted: 5 February 2007
Published online: 16 March 2007

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Abstract $\alpha_{2\beta}$ adrenoreceptor 301–303 deletion polymorphism does not influence basal metabolic rate, insulin resistance or weight gain in Greek women with polycystic ovary syndrome.

Key words polycystic ovary syndrome · body weight · obesity · insulin resistance · basal metabolism · adrenoreceptor polymorphism · autonomic nervous system

Introduction

Polycystic ovary syndrome (PCOS), the most common hormonal reproductive problem in women of childbearing age, is associated with high blood pressure, weight gain and type II diabetes [5, 8, 9, 11]. These are known risk factors in coronary heart disease [4], a disease that is hereditary. A 301–303 deletion polymorphism of the $\alpha_{2\beta}$ adrenergic receptor is associated with reduced agonist-promoted desensitization [9, 11] and has been linked to low basal metabolic rate and gain weight [3, 10]. This raises the question of whether $\alpha_{2\beta}$ adrenergic receptor polymorphism is present in PCOS.

Materials and methods

Subjects

A total of 112 Greek women with PCOS (age; mean ± SEM 24.0 ± 1.0, range 18–42 years; mean body mass index, 26.7 ± 1.6 kg/m^2) and 114 healthy women (age; mean 27.0 ± 1.0, range 21–43 years; mean body mass index 19.1 ± 1.0 kg/m^2) were recruited.

The diagnosis of PCOS was based on the revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome [1, 7]. All controls were regularly menstruating.

Methods

A standard Oral Glucose Tolerance Test (OGTT) with 100 g glucose was carried out and insulin resistance was assessed by determining the fasting insulin levels, the fasting glucose/insulin ratio, the

CAR 403

HOMA and QUICKI indexes as well as the AUC for the OGTT derived glucose values. Body composition was determined by bioelectrical impedance. BMR was measured by indirect calorimetry as previously described [2] and expressed as kilocalories per day. Each subject's BMR was adjusted for fat-free mass, fat mass, sex and age using the equation: adjusted BMR = (group mean BMR) + (measured BMR − predicted BMR) [6]. For each subject, the predicted BMR was obtained by substituting the individual lean body mass, fat mass, sex and age in the linear regression equation generated by the data of all patients.

Genotyping

Genomic DNA was extracted by a commercial kit (Nucleospin Blood QuickPure, Macherey-Nagel, Düren, Germany). A fragment of the $\alpha_{2\beta}$ adrenoceptor gene encompassing the polymorphic glutamate repeat was amplified by the polymerase chain reaction (PCR), as previously described [3]. Oligonucleotide primers were synthesized by MWG-Biotech AG, Ebersberg, Germany.

Association analyses

The genotype frequency distributions were tested for Hardy–Weinberg equilibrium and compared by χ^2 tests. The adjusted BMR was compared between genotype groups by one-way ANOVA. The main effects of genotype on BMI, and insulin resistance were evaluated by multivariate analysis of variance (MANOVA). All statistical procedures were performed using SPSS 11.0 for Windows (SPSS, Inc., Chicago, IL, USA). All data are expressed as mean ± SEM unless otherwise stated.

Results

The α_{2B} genotype frequencies in the control group were 73 (64.00%) Glu^{12}/Glu^{12}, 36 (31.60 %) Glu^{12}/Glu^{9} $\kappa\alpha_1$ 5 (4.40%) Glu^{9}/Glu^{9} and in women with PCOS 68 (60.70%) Glu^{12}/Glu^{12}, 41 (36.60%) Glu^{12}/Glu^{9} $\kappa\alpha_1$ 3 (2.70%) Glu^{9}/Glu^{9}. There were no statistically significant differences between patients and controls. Allelic frequency was 182 (79.80%) for the Glu^{12} and 46 (20.20%) for the Glu^{9} in the control group and 177 (79.00%) for the Glu^{12} and 47 (21.00%) for the Glu^{9} in the women with PCOS.

The adjusted BMR of 73 patients (48 Glu^{12}/Glu^{12} and 25 Glu^{12}/Glu^{9}) was compared for the α_{2B} adrenoreceptor genotypes.

The adjusted BMR was 1347.80 ± 100.40 (n = 48) Cal/day for Glu^{12}/Glu^{12} homozygotes, 1408.20 ± 130.30 Cal/day for heterozygotes (n = 25), and 1856.29 ± 973.26 (n = 2) Cal/day for Glu^{9}/Glu^{9} subjects. Thus, the mean adjusted BMR of Glu^{12}/Glu^{9} heterozygotes was 60.40 Cal/day higher than that of Glu^{12}/Glu^{12} homozygotes. Despite this trend, the differences in BMR were not statistically significant (p = 0.72) (Table 1).

MANOVA showed that the $\alpha_{2\beta}$ adrenoceptor polymorphism was not associated with the patients' BMI and insulin resistance (Table 1).

Discussion

This study showed that genotype distribution and the frequency of the $\alpha_{2\beta}$ adrenergic receptor alleles was not different in Greek women with PCOS and controls.

Genotyping of Greek women for the α_{2B} 301–303 deletion polymorphism showed that the majority of subjects were homozygous for the long receptor allele, while in the Finnish population most subjects are heterozygous [3]. In our cohort, the α_{2B} polymorphic variant was uncommon, with a Glu^{9} allelic frequency of 20.20%, compared to 45% in obese Finns. Moreover, genotype distribution and allelic frequencies did not differ between PCOS women and controls. This implies that the α_{2B} polymorphism has little impact on obesity, at least in this population of Greek women with PCOS. This view is compatible with a previous study that showed no association between the $\alpha_{2\beta}$ adrenoreceptor gene polymorphism and morbid obesity in the Greek population [10]. These studies suggest that the $\alpha_{2\beta}$ adrenoreceptor gene polymor-

Table 1 Physical and biochemical characteristics of the PCOS women according to the genotype of the $\alpha_{2\beta}$ adrenergic receptor gene polymorphism

Characteristic	Genotype			p value (by ANOVA)
	Total (n = 109)	Glu^{12}/Glu^{12} (n = 68)	Glu^{12}/Glu^{9} (n = 41)	
Age (years)	23.98 ± 5 (n = 93)	23.62 ± 0.5 (n = 61)	24.91 ± 1.2 (n = 32)	0.25
Weight (kg)	70.9 ± 17.4 (n = 92)	70.65 ± 2.18 (n = 61)	72.43 ± 3.28 (n = 31)	0.65
Height (cm)	164 ± 1.4 (n = 78)	163 ± 0.8 (n = 51)	165 ± 1 (n = 27)	0.17
BMI (kg/m^2)	26.7 ± 1.60 (n = 74)	26.64 ± 0.92 (n = 48)	27.27 ± 1.34 (n = 26)	0.7
Adjusted BMR (Cal/day)	1381.5 ± 167.9 (n = 73)	1347.8 ± 100.4 (n = 48)	1408.2 ± 130.3 (n = 25)	0.72
Fasting glucose (mg/dL)	82.13 ± 2.6 (n = 86)	81.29 ± 1.2 (n = 58)	83.82 ± 2.9 (n = 28)	0.34
Fasting insulin (μU/ml)	11.64 ± 1.8 (n = 84)	11.87 ± 1.0 (n = 57)	11.60 ± 1.5 (n = 27)	0.88
HOMA	70.43 ± 16.27 (n = 84)	67.56 ± 7.83 (n = 57)	75.31 ± 16.96 (n = 27)	0.63
QUICKI	0.350 ± 0.01 (n = 84)	0.349 ± 0.005 (n = 57)	0.352 ± 0.009 (n = 27)	0.78
AUC	13562 ± 757 (n = 84)	13177 ± 412 (n = 57)	14455 ± 673 (n = 27)	0.1
Glucose/insulin ratio	10.54 ± 2.00 (n = 84)	10.21 ± 1.00 (n = 57)	10.96 ± 2.01 (n = 27)	0.71

Data are presented as mean ± SE of the mean

phism is not associated with an increased incidence of mild or morbid obesity.

To our knowledge, this is the first study of α_{2B} adrenoreceptor 301–303 deletion polymorphism in relation to PCOS, which also took into account BMR and insulin resistance. There was no significant correlation between the $\alpha_{2\beta}$ polymorphism, BMR and insulin resistance.

The genetic determinants of BMR, insulin resistance and PCOS are largely unknown. It is possible that the α_{2B} polymorphism may have a role in the pathogenesis of the metabolic syndrome, but due to the complexity of PCOS the correlation of the polymorphism to the specific parameters of this study may be too small to be detected. The relatively small number of patients and the rarity of the Glu^9/Glu^9 genotype, imply the need for additional studies with larger cohorts in order to establish a definite conclusion.

This small study showed that the $\alpha_{2\beta}$ adrenoreceptor gene polymorphism does not determine basal metabolic rate, weight gain or insulin resistance in Greek women with PCOS. The role of 301–303 deletion polymorphism in PCOS, if any, remains unclear.

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