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The α_{2B} and β_3 Adrenergic Receptor Genes Polymorphisms in Women with Polycystic Ovarian Syndrome (PCOS) and their Association with Insulin Resistance and Basal Metabolic Rate (BMR)

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S u m m a r y. The aim of the present study was to determine the incidence of α_{2B} and β_3 adrenergic receptors gene polymorphisms in Greek women with PCOS as well as their association with the basal metabolic rate and insulin resistance. The study included 91 Greek PCOS patients. Genotype frequencies were similar in patients and in a group of 47 normal volunteers. The patients' BMR, adjusted for fat-free mass, fat mass, sex and age, did not differ between the α_{2B} and β_3 genotypes. Moreover, the polymorphisms were not associated with the patients' BMI and insulin resistance.

INTRODUCTION

The sympathetic nervous system participates in the regulation of the basal metabolic rate (BMR) and in the pathogenesis of the obesity-related metabolic syndrome. Germline polymorphisms of adrenergic receptors are associated with low BMR and/or obesity. A deletion/insertion germline polymorphism of the α2β adrenergic receptor that is associated with reduced agonist-promoted desensitization has been linked to low BMR in obese subjects and to a predisposition of non-diabetic subjects to gain weight. The β3 adrenergic receptor polymorphism was correlated with insulin resistance, obesity, abdominal adiposity, earlier onset of obesity, diabetes and/or low basal metabolic rhythm.

METHODS

The study included 91 Greek women with PCOS with a mean age of 24±0.6 years (range: 17-39) and a mean BMI 27.41±0.83 kg/m^2 and 47 regularly menstruating women with a mean age of 34±1.0 years (range: 17-60) and a mean BMI 19.10±1.0 kg/m^2 as controls. The diagnosis of PCOS was based on the revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (1,2).

All subjects had normal thyroid, kidney and liver function and none had excessive alcohol intake. None was taking drugs known to affect BMR, blood pressure or glucose metabolism. No subject had diabetes, as evaluated by fasting serum glucose or an oral glucose tolerance test. A standard Oral Glucose Tolerance Test (OGTT) with 100 g glucose was carried out and insulin resistance was assessed by determining fasting insulin levels, the fasting glucose/insulin ratio, the HOMA and QUICKI indexes as well as the AUC for the OGTT derived insulin values. Body composition was determined by bioelectrical impedance (Body Composition Analyzer, Tanita, Tokyo, Japan). The BMR was measured by indirect calorimetry (Pulmolab EX505, Morgan Medical Ltd, Kent, U.K.) as previously described by Ferrannini (3) and expressed as kilocalories per day. Each subject's BMR was adjusted for fat-free mass, fat mass, sex and age as previously described (4), using the equation: adjusted BMR= (group mean BMR) + (measured BMR - predicted BMR). For each subject, the predicted BMR was obtained by substituting the individual lean body mass, fat mass, sex and age in the linear re-

gression equation generated by the data of all patients.

RESULTS

The α_{2B} genotype frequencies in the control group were 26 (56%) Glu^{12}/Glu^{12}, 18 (38%) Glu^{12}/Glu^{9} και 3 (6%) Glu^{9}/Glu^{9} and in women with PCOS 57 (63%) Glu^{12}/Glu^{12}, 32 (35%) Glu^{12}/Glu^{9} και 2 (2%) Glu^{9}/Glu^{9}. There were no statistically significant differences between patients and controls (p=ns). Allelic frequency was 70 (81.00%) for the Glu^{12} and 24 (19.00%) for the Glu^{9} in the control group and 146 (80.00%) for the Glu^{12} and 36 (20.00%) for the Glu^{9} in the women with PCOS.

The adjusted BMR of 63 patients (41 Glu^{12}/Glu^{12} and 22 Glu^{12}/Glu^{9}) was compared between the α_{2B} adrenoreceptor genotypes.

The adjusted BMR was 1493.7±104.5 (n=41) Cal/day (mean±standard error) for Glu^{12}/Glu^{12} homozygotes, and 1527.7±140.6 Cal/day for heterozygotes and 1654.28 ± 804 (n=10) Cal/day for Glu^{9}/Glu^{9} subjects. Thus, the mean adjusted BMR of Glu^{12}/Glu^{9} heterozygotes was 34 Cal/day higher than that of Glu^{12}/Glu^{12} homozygotes. Despite this ternd, the differences in BMR were not statistically significant (p=0.85).

MANOVA showed that the $\alpha_{2\beta}$ and β_3 adrenoceptor polymorphisms were not associated with the patients' BMI and insulin resistance.

DISCUSSION

The results of the present study showed no significant difference between PCOS women and controls with regard to genotype distribution and the frequency of the $\alpha_{2\beta}$ and β_3 receptor alleles.

Genotyping of Greek women for the α_{2B} polymorphism showed that the majority of subjects were homozygous for the long receptor allele, while in the Finnish population most subjects are heterozygous (5). In our cohort, the α_{2B} polymorphic variant was uncommon, with a Glu^{9} allelic frequency of 20%, compared to 45% in obese Finns. Moreover, genotype distribution and allelic frequencies did not differ between PCOS women and controls. Taken together, these findings imply that the overall impact of the α_{2B} polymorphism on morbidly obese Greek patients is not likely to be great.

The above conclusion is compatible with a previous study (6), which showed that there is no correlation between the $\alpha_{2\beta}$ adrenoreceptor gene polymorphism and morbid obesity in Greek patients. Concerning the Greek population and taking into consideration that PCOS is related to mild obesity this polymorphism does not appear to be important in relation to both mild and morbid obesity.

The β3 adrenoceptor is the prime receptor that mediates thermogenesis and lipolysis in brown and white adipose tissue.

It is noteworthy that in Greece in a study of women with gestational diabetes no association has been found due to the extremely low incidence (7%) of the b3 gene polymorphism in the Greek population (1). Furthermore, no association of the β3 polymorphism with the polycystic ovaries syndrome (PCOS) has been documented among different ethnic groups (8,9). In this study, the incidence of the β3 polymorphism in women with PCOS was the same as that obtained by a previous study from normal Greek women (1).

In this study we also examined the possible relation of the three α_{2B} adrenoreceptor genotype groups with BMR and insulin resistance as part of the metabolic syndrome. No significant correlation between the $\alpha_{2\beta}$ and β_3 polymorphism BMR and insulin resistance was found for all indices used to determine insulin resistance (fasting glucose, fasting insulin, HOMA QUICKI, AUC for glucose).

The genetic determinants of BMR, insulin resistance and PCOS are largely unknown. It is possible that the α_{2B} and β_3 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. To our knowledge, this is the first study of α_{2B} and β_3 adrenoreceptor gene polymorphism in relation to PCOS, taking also into account BMR and insulin resistance. According to the results of the present study there is no major functional significance of the $\alpha_{2\beta}$ and β_3 adrenoreceptor gene polymorphism in PCOS. Of course, the relatively small number of patients in the present study as well as the rarity of the Glu^{9}/Glu^{9} genotype, makes clear that additional studies with larger cohorts are required in order to establish a clear conclusion.

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Table 1
Physical and biochemical characteristics of the PCOS women according to the genotype of the α_{2B} adrenergic receptor gene polymorphism. Data are presented as mean±standard error of the mean

Characteristic	Genotype			
	Total (n=89)	Glu^{12}/Glu^{12} (n=57)	Glu^{12}/Glu^{9} (n=32)	p value (by ANOVA)
Age (years)	24±0.6 (n=81)	24±0.6 (n=53)	25±1.3 (n=28)	0.48
Weight (kg)	72.5±2 (n=76)	71.8±2.6 (n=48)	73.6±3.5 (n=28)	0.68
Height (cm)	164±1 (n=65)	163±1 (n=41)	165±1 (n=24)	0.18
BMI (kg/m^2)	27.41±0.83 (n=65)	27.41±1.02 (n=41)	27.42±1.43 (n=24)	1.0
Adjusted BMR (Cal/day)	1505.6±83.2 (n=63)	1493.7±104.5 (n=41)	1527.7±140.6 (n=22)	0.85
Fasting glucose (mg/dL)	83.4±1.4 (n=72)	82.2±1.2 (n=49)	85.9±3.4 (n=23)	0.31
Fasting insulin (μU/mL)	13.6±1.3 (n=72)	14.2±1.8 (n=48)	12.3±1.7 (n=24)	0.51
HOMA	66.94±8.66 (n=72)	64.55±9.12 (n=48)	71.70±18.81 (n=24)	0.70
QUICKI	0.347±0.005 (n=72)	0.346±0.006 (n=48)	0.348±0.010 (n=24)	0.86
AUC	13896±402 (n=71)	13414±482 (n=47)	14838±697 (n=24)	0.09
Glucose/Insulin ratio	10.24±1.06 (n=72)	9.98±1.14 (n=48)	10.76±2.26 (n=24)	0.73