Beta2-adrenergic receptor polymorphisms and salbutamol-stimulated energy expenditure

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IT IS WELL DOCUMENTED that both environmental and genetic factors are involved in the onset and progression of obesity in humans. Severe obesity appears to have a particularly strong genetic component and is polygenic in nature (1). An increasing number of polymorphisms is assumed to be associated with obesity and has been described in literature (1). Despite intense effort, the pathways underlying these associations with obesity remain elusive. This is largely due to the complexities circumventing the process of developing obesity, which include age of onset; polygenic inheritance; genetic heterogeneity; incomplete penetrance; unknown mode of action of disease alleles; effect of ethnicity, age, gender, and the interaction with environmental factors, such as diet, physical activity, or smoking status.

Of all contributing factors, the components of the sympathetic nervous system are of interest because this system, in particular its β-adrenergic component, is involved in the control of energy metabolism and expenditure (2, 3). The β-adrenergic system is involved in the control of energy metabolism and expenditure. The β₂-adrenergic receptor (β₂-AR) gene shows polymorphisms that have been associated with obesity in several studies. In vitro and in vivo studies suggest differences in β₂-AR-mediated function between these polymorphisms. The aim of this study was to investigate the influence of genetic variation in codon 16 of the β₂-AR gene on energy metabolism in humans.

Thirty-four subjects were recruited [Gly16Gly (n = 13), Gly16Arg (n = 16), or Arg16Arg (n = 5)]. The β₂-AR was stimulated with two doses of salbutamol (50 and 100 ng/kg fat-free mass per minute) after blockade of the β₂-adrenergic receptors with atenolol. Energy expenditure and plasma substrate and hormone concentrations were measured.

The increase in energy expenditure (ΔEE) was significantly different among groups in which the Arg16Arg group showed the lowest increase (P < 0.05 vs. Gly carriers). In a multiple regression model, variations in the increase in nonesterified fatty acid concentration during salbutamol infusion (partial r = 0.51) and the polymorphism contributed significantly to the variation in ΔEE. Thirty-five percent of the variation in ΔEE was explained by these two factors.

We conclude that subjects with the Arg16Arg polymorphism of the β₂-AR gene have a reduced thermogenic response to β₂-adrenergic stimulation. Although this relatively small study needs confirmation, the findings support a role for this polymorphism in the development and maintenance of overweight and obesity. (J Clin Endocrinol Metab 90: 2301–2307, 2005)
study (32 men and two women, aged 45 ± 0.8 yr, BMI 27.8 ± 0.8 kg/m²). In part (n = 14) they were recruited from an existing cohort that has been described previously (13), in which the polymorphisms in the β2-AR were known; in part they were newly recruited by advertisement (n = 20). The subjects did not use medication. Physical characteristics of the subjects are summarized in Table 1.

### Experimental design

One week before the experimental day, subjects came to the laboratory after an overnight fast, and body composition was determined by hydrostatic weighing with simultaneous lung volume measurements (Volugraph 2000, Mijnhardt, Bunnik, The Netherlands). Body composition was calculated according to the equation of Siri (19).

Subjects were asked to refrain from strenuous exercise during 24 h before the experiment. After an overnight fast, subjects arrived at the laboratory by bus or car to minimize activity before the measurements. On arrival, a cannula was inserted into a forearm vein of each arm. One cannula was used for the infusion of drugs and the other cannula for the sampling of blood. Next, indirect calorimetry measurements were started with a ventilated hood system with the subject in recumbent position and continued for the remainder of the experiment.

The study consisted of three study periods of 45 min. Before the first period, subjects received a priming dose of 50 µg/kg fat-free mass (FFM) atenolol (β1-adrenergic receptor antagonist) (Tenormin, Zeneca, Ridderskerk, The Netherlands) in 5 min, after which a continuous infusion of 1.2 µg/kg FFM per minute atenolol was started for the remainder of the experiment. After 45 min atenolol infusion, subjects additionally received consecutive infusions of 50 and 100 ng/kg FFM per minute salbutamol (Ventolin, GlaxoWellcome, Zeist, The Netherlands). Each infusion period lasted 45 min. After 30 and 45 min of each study period, a blood sample was taken.

### Measurements

Whole-body EE and respiratory exchange ratio (RER) were measured by indirect calorimetry, using an open-circuit ventilated hood system. In the study a homemade system, which is based on the analysis system for respiration chambers, which has been described previously (20), was used. The volume of air drawn through the hood was measured by a dry-gas meter (Schlumberger, Dordrecht, The Netherlands), and the composition of the in- and outflowing air was analyzed by a paramagnetic O2 analyzer (Servomex, Crowborough, UK) and an infrared CO2 analyzer (Hartmann and Braun, Frankfurt, Germany). The airflow rate and the O₂ and CO₂ concentrations of the in- and outflowing air were used to compute O₂ consumption and CO₂ production online through an automatic acquisition system connected to a personal computer. EE was calculated according to the formula proposed by Weir (21). EE and RER values were averaged over the last 15 min of each period. The reproducibility of the measurement was within 5% as described before (22).

### Table 1. Subject characteristics of groups with different polymorphisms at codon 16 of the β2-adrenergic receptor gene (mean ± SEM)

<table>
<thead>
<tr>
<th>Gly16Gly</th>
<th>Gly16Arg</th>
<th>Arg16Arg</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 13)</td>
<td>(n = 16)</td>
<td>(n = 5)</td>
</tr>
<tr>
<td><strong>Gender (M/F)</strong></td>
<td>12/1</td>
<td>16/0</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>83.6 ± 4.3</td>
<td>87.0 ± 3.5</td>
</tr>
<tr>
<td><strong>Height (m)</strong></td>
<td>1.73 ± 0.03</td>
<td>1.78 ± 0.02</td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
<td>46.9 ± 1.4</td>
<td>45.5 ± 1.3</td>
</tr>
<tr>
<td><strong>Fat percentage (%)</strong></td>
<td>28.0 ± 2.6</td>
<td>27.4 ± 1.8</td>
</tr>
<tr>
<td><strong>Fat mass (kg)</strong></td>
<td>23.9 ± 2.7</td>
<td>24.6 ± 2.4</td>
</tr>
<tr>
<td><strong>FFM (kg)</strong></td>
<td>59.6 ± 3.0</td>
<td>62.4 ± 1.7</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>27.8 ± 12</td>
<td>27.7 ± 13</td>
</tr>
<tr>
<td><strong>HOMA index</strong></td>
<td>2.25 ± 0.52</td>
<td>2.15 ± 0.33</td>
</tr>
</tbody>
</table>

a Significantly different between Arg16Arg and Gly16Arg (P < 0.05).

b Tendency for difference between Arg16Arg and Gly16Gly (P = 0.06).

Total carbohydrate and fat oxidation were calculated using stoichiometric equations (23):

- Total fat oxidation (grams per minute) = 1.695 VO₂ (liters per minute) – 1.701 VCO₂ (liters per minute).
- Total carbohydrate oxidation (grams per minute) = 4.585 VCO₂ (liters per minute) – 3.226 VO₂ (liters per minute).

Substrate oxidation was expressed as percentage of the contribution to total EE (1 g fat = 37.8 kcal and 1 g carbohydrate = 16.9 kcal).

Heart rate was monitored by conventional electrocardiography. Blood pressure was measured three times by an automated blood pressure device (OMRON 705CP, Hamburg, Germany) during the last 5 min of each study period. The means of these three measurements were used for further analysis.

### Analytical methods

Genomic DNA of the subjects was extracted from leukocytes by digestion with proteinase K followed by phenol/chloroform extraction. Determination of the polymorphism was performed using a PCR restriction fragment length polymorphism analysis as described before (23).

Blood samples for the determination of nonesterified fatty acids (NEFAs), glycerol, glucose, and insulin were preserved with sodium-EDTA and those for norepinephrine and epinephrine with heparin plus glutathione (1.5% wt/vol). Blood samples were immediately centrifuged for 10 min at 800 × g at 4 C. Plasma was rapidly frozen in liquid nitrogen and stored at −70 C until further analysis. Plasma NEFA concentration was measured with the NEFA C kit (99475409, Wako, Neuss, Germany), plasma glycerol concentration was measured with a glycerol kit (142870, Boehringer, Mannheim, Germany), and plasma glucose concentration was measured with a glucose kit (UniKit III, 07367204, Roche, Basel, Switzerland). All on a Cobas Far chromium analyzer (Roche Diagnostics, Basel, Switzerland). Plasma insulin level was determined with a double-antibody RIA (Insulin RIA 100, Pharmacia, Uppsala, Sweden).

The homeostasis model assessment (HOMA) index was calculated according to Matthews et al. (24) using baseline plasma glucose and baseline plasma insulin levels. Plasma norepinephrine and epinephrine levels were determined by HPLC with electrochemical detection according to the method of Alberts et al. (25) using a ClinitPrep kit (Recipe, Munich, Germany).

### Data analysis

All data are presented as mean ± sem. Data for EE were adjusted for FFM for group comparison (26). The change (Δ) in EE induced by the highest dose of salbutamol (100 ng/kg FFM per minute) was calculated by subtracting baseline EE from the EE at 100 ng/kg FFM per minute salbutamol. Changes in the other variables were calculated the same way.

One-way ANOVA with repeated measurements was used to analyze the effects of salbutamol administration in the total group of subjects and the three polymorphism groups. Differences among the codon 16 polymorphism groups at baseline and in response to salbutamol administration were analyzed by one-way ANOVA. Post hoc pairwise comparisons were made using Bonferroni correction.

### Results

**Responses to salbutamol infusion in the whole group**

Table 2 shows changes in all parameters studied at baseline and during administration of increasing doses of salbutamol for the whole group of subjects. EE, heart rate, plasma norepinephrine, and NEFA and glycerol concentrations...
showed statistically significant increases (at least $P < 0.05$). Plasma epinephrine concentrations were significantly lower during salbutamol infusion ($P < 0.01$). No statistically significant changes in RER, blood pressure (BP), plasma glucose, lactate, and insulin were found.

**Baseline values and responses to salbutamol infusion in the β2-AR codon 16 polymorphism groups**

Baseline EE adjusted for FFM was similar in all polymorphism groups ($4.89 \pm 0.14$, $4.89 \pm 0.06$, and $4.92 \pm 0.23$ kJ/min for Gly16Gly, Gly16Arg, and Arg16Arg, respectively, NS). There was a significant difference in the increase in EE (ΔEE) among groups (ANOVA, $P < 0.05$) (Fig. 1). Post hoc analysis showed that the response was significantly different between the Arg16Arg and the Gly16Arg groups ($P < 0.05$) and between Arg16Arg and Gly carriers ($P < 0.05$).

At baseline RER did not differ among groups, nor did ΔRER ($P = 0.41$) (Fig. 2). Fat oxidation at baseline was not significantly different among groups ($54.4 \pm 3.4$, $55.7 \pm 3.2$, and $44.6 \pm 3.3\%$ of total EE for Gly16Gly, Gly16Arg, and Arg16Arg, respectively, $P = 0.25$) nor was carbohydrate oxidation ($47.0 \pm 3.9$, $45.6 \pm 3.9$, and $57.9 \pm 7.0\%$ of total EE for Gly16Gly, Gly16Arg, and Arg16Arg, respectively, $P = 0.25$).

During salbutamol infusion, plasma NEFA levels (Fig. 3) and norepinephrine levels (Fig. 4) increased significantly in all polymorphism groups ($P < 0.05$), with no significant difference among groups. Plasma concentrations of NEFAs, glycerol, glucose, insulin, and epinephrine changed significantly in the Gly16Gly and Gly16Arg groups ($P < 0.01$) but not in the Arg16Arg group; however, the responses to salbutamol infusion did not differ among groups. Plasma lactate levels were significantly higher at baseline and during salbutamol in the Arg16Arg group, compared with the Gly carriers (ANOVA, $P < 0.05$), but the lactate response to salbutamol infusion did not differ among groups (Fig. 3).

### TABLE 2. Metabolic parameters at different doses of salbutamol for the whole group (n = 34)

<table>
<thead>
<tr>
<th>Salbutamol (ng/kg FFM · min)</th>
<th>0</th>
<th>50</th>
<th>100</th>
<th>$P$ value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy expenditure (kJ/min)</td>
<td>4.8 ± 0.1</td>
<td>5.1 ± 0.1</td>
<td>5.3 ± 0.1</td>
<td>0.037</td>
</tr>
<tr>
<td>RER</td>
<td>0.83 ± 0.01</td>
<td>0.85 ± 0.01</td>
<td>0.82 ± 0.01</td>
<td>0.183</td>
</tr>
<tr>
<td>Fat oxidation (% of total energy expenditure)</td>
<td>53.5 ± 2.2</td>
<td>48.5 ± 2.8</td>
<td>55.6 ± 3.2</td>
<td>0.179</td>
</tr>
<tr>
<td>Carbohydrate oxidation (% of total energy expenditure)</td>
<td>47.9 ± 2.8</td>
<td>53.6 ± 3.2</td>
<td>45.7 ± 3.5</td>
<td>0.181</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>55.9 ± 1.2</td>
<td>62.8 ± 1.2</td>
<td>71.2 ± 1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>83.9 ± 1.8</td>
<td>81.7 ± 1.7</td>
<td>78.2 ± 1.7</td>
<td>0.075</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>118.1 ± 2.0</td>
<td>118.9 ± 1.9</td>
<td>121.1 ± 1.9</td>
<td>0.532</td>
</tr>
<tr>
<td>[Norepinephrine] (ng/liter)</td>
<td>456.0 ± 20.6</td>
<td>513.3 ± 33.2</td>
<td>579 ± 32.7</td>
<td>0.014</td>
</tr>
<tr>
<td>[Epinephrine] (ng/liter)</td>
<td>33.9 ± 3.5</td>
<td>24.1 ± 2.5</td>
<td>21.8 ± 2.1</td>
<td>0.006</td>
</tr>
<tr>
<td>[NEFA] (µmol/liter)</td>
<td>366.6 ± 21.1</td>
<td>580.2 ± 30.8</td>
<td>724.9 ± 42.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>[Glycerol] (µmol/liter)</td>
<td>58.5 ± 3.7</td>
<td>84.3 ± 5.2</td>
<td>106.8 ± 7.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>[Glucose] (mmol/liter)</td>
<td>5.40 ± 0.12</td>
<td>5.36 ± 0.10</td>
<td>5.49 ± 0.10</td>
<td>0.656</td>
</tr>
<tr>
<td>[Lactate] (mmol/liter)</td>
<td>0.97 ± 0.06</td>
<td>1.00 ± 0.05</td>
<td>1.15 ± 0.05</td>
<td>0.055</td>
</tr>
<tr>
<td>[Insulin] (mU/liter)</td>
<td>10.1 ± 1.3</td>
<td>15.5 ± 1.8</td>
<td>15.2 ± 1.6</td>
<td>0.075</td>
</tr>
</tbody>
</table>

Data represent mean ± SEM.
and are highly correlated ($R^2 = 0.838$), only basal NEFAs and $\Delta$NEFAs and not basal glycerol and $\Delta$glycerol were used in the multiple regression analysis. The analysis indicated statistically significant associations of $\Delta$NEFAs and the codon 16 polymorphism as independent variables was performed subsequently. Because glycerol and NEFAs are both parameters of lipolysis and are highly correlated ($R^2 = 0.838$), only basal NEFAs and $\Delta$NEFAs and not basal glycerol and $\Delta$glycerol were used in the multiple regression analysis. The analysis indicated statistically significant associations of $\Delta$NEFAs and the codon 16 polymorphism with $\Delta$EE. No significant association with the other variables was found. The partial correlation coefficient for $\Delta$NEFAs was 0.51. The polymorphism added another 10% to the explained variance in $\Delta$EE. The whole model therefore explained 35% of the variation in $\Delta$EE (adjusted $R^2 = 0.354$, $P < 0.001$). Introducing basal and $\Delta$glycerol instead of basal and $\Delta$NEFAs into the model gave similar results, $\Delta$NEFAs being replaced by $\Delta$glycerol.

**Discussion**

The aim of the present study was to examine the influence of polymorphisms in codon 16 of the $\beta_2$-AR gene on EE and substrate oxidation during $\beta_2$-AR stimulation by infusing the $\beta_2$-AR agonist salbutamol. During salbutamol infusion subjects with the Arg16Arg variant of the $\beta_2$-AR gene showed a blunted increase in EE, and their plasma lactate levels were higher. Fat oxidation as percentage of total EE and plasma NEFA and glycerol levels did not differ among groups, nor was there a difference in response to salbutamol. Multiple regression analysis showed that the polymorphism in codon 16 of the $\beta_2$-AR gene and plasma NEFA or glycerol change but not RER change, percent body fat, BMI, age, and HOMA index were significantly associated with the change in EE.

The combined infusion of salbutamol and atenolol selectively stimulates the $\beta_2$-AR, as shown previously (27). This selective stimulation resulted in the expected increases in EE, heart rate, plasma glycerol, NEFAs, lactate, insulin, and norepinephrine concentrations and in reductions in plasma epinephrine levels and diastolic BP (27, 28). There was no clear change of RER during salbutamol infusion in this study. However, changes in RER have been inconsistent in previous studies (27, 28).

The $\beta_2$-AR gene contains the genetic code for the receptor protein. Several variants in this gene have been described in literature (14). Three of the single-nucleotide polymorphisms, at nucleotides 46, 79, and 491, lead to amino acid substitution at codons 16, 27, and 164 in the coding region of the gene and might therefore have consequences for receptor function (29). When expressed in cells, the receptors with polymorphisms at codons 16 and 27 have been associated with differences in cellular $\beta_2$-AR trafficking (30). The more rare polymorphism at codon 164 is associated with depressed functional coupling to Gs and reduced $\beta_2$-adrenergic receptor sequestration (31). Large et al. (18) showed that isolated abdominal sc fat cells from women homozygous for the Arg16 polymorphism of the $\beta_2$-AR had a 5-fold lower sensitivity for $\beta_2$-AR agonist-induced lipolysis than fat cells from women heterozygous or homozygous for Gly16, independent of percent body fat of the women. More recently it was shown that fat cells from subjects with different ho-

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**Fig. 2. RER for the codon 16 polymorphisms in the $\beta_2$-AR at baseline and during infusion of salbutamol. #, $P < 0.05$ Arg16Arg vs. Gly carriers.**
mozygous haplotypes of the \(\beta_2\)-AR gene differed about 250-fold in sensitivity to terbutaline-induced lipolysis (17). The least sensitive homozygous haplotype group in this study contained the Arg variant at codon 16 (17).

This study extends these findings and demonstrates a reduced \(\beta_2\)-AR agonist-induced thermogenic response in individuals homozygous for the Arg16 polymorphism of the \(\beta_2\)-AR gene. On the basis of changes in plasma NEFA and glycerol concentrations, we could not confirm the reduced lipolytic response to \(\beta_2\)-AR stimulation in the Arg16Arg group, which has been reported by Large et al. (18) based on \textit{in vitro} lipolysis. This might be related to the limitations of plasma NEFA concentration as a measure of lipolysis because not only lipolysis but also reesterification and NEFA oxidation affect plasma NEFA concentrations. The higher RER and plasma lactate concentrations at baseline as well as during salbutamol infusion in the Arg16Arg group suggest that their energy production relies more on carbohydrate oxidation, which would be compatible with a reduced lipolysis.

This study shows that the codon16 polymorphism has a significant effect on the salbutamol-induced thermogenic response, independent of the change in NEFAs. The explanation for this effect is not directly apparent from our study. It could be that the \(\beta_2\)-AR-stimulated muscle and liver glycogen breakdown is also affected by the polymorphism, thus resulting in differences in carbohydrate substrate availability and oxidation (4).

It is not surprising that the study revealed a correlation between the change in NEFAs and the thermogenic response because we and others have previously shown an increase in EE during the infusion of a triglyceride emulsion, which elevates plasma NEFA levels (28, 32–34), although this is not found in all studies (35, 36), which may be related to differences in patient populations and study design. In addition, part of the increase in EE induced by dobutamine, a \(\beta_1\)-adrenergic agonist, can be blocked by inhibiting lipolysis with nicotinic acid (37).

Previous studies have suggested that the \(\beta_2\)-AR is involved in the reduced \(\beta_2\)-AR-mediated increase in lipolysis (5, 38, 39), lipid oxidation, and thermogenesis (5) in obese compared with lean individuals. This study suggests that variations in the lipolytic response to \(\beta_2\)-adrenergic stimulation are associated with variations in the thermogenic response. BMI and fat percentage were negatively correlated with \(\Delta\)NEFA in our study (\(P < 0.01\) and \(P = 0.06\), respectively),

---

**FIG. 3.** Plasma NEFA concentration (micromoles per liter), plasma glycerol concentration (micromoles per liter), plasma glucose concentration (millimoles per liter), and plasma lactate concentration (millimoles per liter) for the codon 16 polymorphisms in the \(\beta_2\)-AR at baseline and during infusion of salbutamol. *\(P < 0.05\) vs. baseline; #, \(P < 0.05\) Arg16Arg vs. Gly carriers.
which supports these earlier findings. Whether the association between these variations in $\beta_2$-AR-mediated $\Delta$NEFA and the variation in body fat are completely independent of the codon 16 polymorphism remains to be determined, but as discussed above, no association between the polymorphism and the response of plasma NEFAs or glycerol was found in this study. Other factors that might have influenced the lipolytic response are age, insulin sensitivity, $\alpha_2$-adrenergic receptor sensitivity and other polymorphisms in the $\beta_2$-AR gene or other genes associated with lipolysis. Aging is known to reduce $\beta$-adrenergic sensitivity (40). The Arg16Arg group tended to be slightly, although not significantly ($P = 0.11$), younger than the other two groups. This difference in age would only tend to reduce the difference in responsiveness between the polymorphism groups. It is therefore unlikely that the differences in thermogenic sensitivity among groups are due to age differences. HOMA index as a measure for insulin sensitivity was different among polymorphism groups (Table 1) and correlated with $\Delta$EE but did not significantly contribute to the multiple regression model. As to be expected, the HOMA index was also associated with fat mass.

Subjects carrying the Arg16Arg polymorphism were all carriers of the Gln27Gln polymorphism of the $\beta_2$-AR gene. Of the Gly16Gly carriers, one subject had the Gln27Gln polymorphism and seven had the Gln27Glu polymorphism. Subjects with the Arg16Gly polymorphism were either Gln27Gln ($n = 7$) or Gln27Glu ($n = 9$). Limiting the analysis to the Gln27 homozygotes ($n = 13$) revealed the same difference in thermogenic response between Gly16 carriers ($n = 8$) and Arg16Arg carriers ($n = 5$) as in the total group. It is therefore unlikely that the polymorphism at codon 27 was responsible for the differences in thermogenic response between the Arg16Arg subjects and the Gly16 carriers.

We conclude that subjects with the Arg16Arg polymorphism of the $\beta_2$-AR have a reduced thermogenic response to $\beta_2$-adrenergic stimulation. Although this relatively small study needs confirmation, the findings support a role for this polymorphism in the development and maintenance of overweight and obesity, as suggested by association studies (12, 17, 18, 41).

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**References**


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