\textbf{β₁- and β₂-Adrenoceptor-Mediated Thermogenesis and Lipid Utilization in Obese and Lean Men*}

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\textbf{ABSTRACT}

The aim of this study was to elucidate the roles of the β₁- and the β₂-adrenoceptors in thermogenesis and lipid utilization in obesity. The β₁-adrenoceptor study was performed in 9 obese and 10 lean men and consisted of 4 30-min periods during which subjects received consecutive infusions of 0, 3, 6, and 9 µg/kg fat-free mass (FFM)-min dobutamine. Energy expenditure, lipid oxidation, and plasma nonesterified fatty acids (NEFA) and glycerol concentrations are impaired during epinephrine (5, 19) or isoprenaline (7) infusion. Others only found an impaired thermogenic response when very obese men were compared with very lean men (20) or only during overfeeding (18). More evident are the differences in lipid utilization between obese and lean subjects. During epinephrine (5, 19) or isoprenaline (7) infusion, the increase in lipid oxidation is reduced in overweight men. Furthermore, their increases in plasma nonesterified fatty acids (NEFA) and glycerol concentrations are impaired during epinephrine (5, 21) or isoprenaline (7) infusion. Only Katzeff \textit{et al.} (17) reported an opposite finding, e.g. that the increases in plasma glycerol and NEFA concentrations in response to norepinephrine infusion were proportional to the total fat mass of each individual and therefore were greater in the obese. Until now, it has been unclear which β₂-adrenoceptor subtype is responsible for the impaired responses of thermogenesis and lipid utilization.

The aim of the present studies was to elucidate the roles of β₁- and β₂-adrenoceptors in thermogenesis, lipid oxidation, and lipolysis in obese and lean men.

\textbf{Subjects and Methods}

\textbf{Subjects}

Fourteen obese and 15 lean male volunteers participated in these studies. Six obese and 6 lean men participated in both studies within a time frame of 9 ± 2 months. The physical characteristics of the subjects, grouped per study, are summarized in Table 1. All subjects were in good health as assessed by medical history and physical examination and were weight stable for at least 6 months. Furthermore, both obese and lean subjects spent no more than 2 h a week in organized sports activities. The study protocols were reviewed and approved by the ethics committee of Maastricht University, and all subjects gave informed consent before participating in the tests.
Experimental design

Subjects were studied in the morning after an overnight fast. They came to the laboratory by car or bus to minimize the amount of physical activity before the test. On arrival, a cannula was inserted into a forearm vein of each arm. One cannula was used for the infusion of drugs, and one cannula was used for the sampling of blood. Next, ventilated hood measurements were started with the subject in supine position and continued for the remainder of the experiment. At the end of each study period, a blood sample was taken. Room temperature was kept at 21–23 °C.

The β₁-adrenoceptor study consisted of four study periods. After a 30-min baseline measurement, subjects received consecutive infusions of 3, 6, and 9 μg/kg fat-free mass (FFM)/min dobutamine (Dobax, Byk, Zwanenburg, The Netherlands), each dose for 30 min. The β₂-adrenoceptor study consisted of three study periods. At the start of the experiment, subjects received a priming dose of 50 μg/kg FFM atenolol (β₁-adrenoceptor antagonist, Tenormin, Zeneca Pharmaceuticals, Ridderkerk, The Netherlands) in 5 min, after which a continuous infusion of 1.2 μg/kg FFM-min atenolol was started for the remainder of the experiment. After a 45 min baseline measurement, subjects additionally received consecutive infusions of 50 and 100 ng/kg FFM-min salbutamol (Ventolin, GlaxoWellcome, Zeist, The Netherlands), each infusion for 45 min.

Clinical methods

Body density was determined by hydrostatic weighing with simultaneous lung volume measurement (Völugraph 2000, Mijnhardt, Bunnik, The Netherlands). Body composition was calculated according to the equation of Siri (22).

Whole body energy expenditure and respiratory exchange ratio (RER) were measured by indirect calorimetry, using an open-circuit ventilated hood system. In the β₂-adrenoceptor study, a homemade system was used (23). The volume of air drawn through the hood was measured by a dry gas meter (Schlumberger, Dordrecht, The Netherlands), each dose for 30 min. In the β₁-adrenoceptor study, energy expenditure and RER were measured by an Oxycon (Mijnhardt, Bunnik, The Netherlands). The composition of the in- and out-moving air was measured by a dry gas meter (Schlumberger, Dordrecht, The Netherlands), each dose for 30 min.

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Results

β₁-Adrenoceptor study

Baseline energy expenditure was significantly higher in obese compared with lean men (5.49 ± 0.21 vs. 4.61 ± 0.18 kJ/min; P < 0.01), but after adjustment for FFM, it was comparable between groups (obese vs. lean, 5.19 ± 0.25 vs. 5.15 ± 0.14 kJ/min adjusted for FFM; P = NS). During β₁-adrenergic stimulation, energy expenditure increased significantly (Fig. 1). RER was similar at baseline between obese and lean men (0.799 ± 0.013 vs. 0.797 ± 0.011; P = NS). RER significantly decreased during β₁-adrenergic stimulation. Lipid and carbohydrate oxidations were comparable in obese and lean subjects at baseline [lipid oxidation, 76 ± 7 vs. 66 ± 6 mg/min (P = NS); carbohydrate oxidation, 93 ± 19 vs. 77 ± 14 mg/min (P = NS)]. Lipid oxidation significantly increased and carbohydrate oxidation significantly decreased during β₁-adrenergic stimulation. The changes in energy expenditure, RER, lipid oxidation, and carbohydrate oxidation were similar in obese and lean men (Fig. 1).

At baseline, plasma NEFA and glycerol levels were similar in obese and lean men [NEFA, 542 ± 60 vs. 409 ± 46 μmol/L (P = NS); glycerol, 77.7 ± 8.2 vs. 62.6 ± 8.6 μmol/L (P = NS)]. Both groups showed similar dose-related increases in plasma NEFA and glycerol levels (Fig. 2). Baseline glucose and insulin levels were significantly higher in the obese compared with the lean group (glucose, P < 0.05; insulin, P < 0.01; Table 2). Plasma glucose levels significantly decreased and plasma insulin levels significantly increased during β₁-adrenergic stimulation with dobutamine. The changes in these parameters compared with baseline were not significantly different between groups. At baseline, plasma lactate and potassium concentrations were similar in obese and lean men. During β₁-adrenergic stimulation, plasma lactate levels remained similar, whereas plasma potassium levels showed some variation, but no dose-dependent changes in either group (Table 2).

Plasma dobutamine levels significantly increased to similar concentrations in obese and lean men (Fig. 3). Baseline norepinephrine and epinephrine levels were comparable between overweight and normal weight subjects (norepinephrine, 1.59 ± 0.35 vs. 1.47 ± 0.27 nmol/L; epinephrine, 0.19 ± 0.04 vs. 0.22 ± 0.03 nmol/L; both P = NS) and were significantly decreased in both groups during β₁-adrenergic stimulation (Fig. 3).

Baseline values for heart rate and systolic blood pressure were not significantly different between groups (Table 3), but diastolic blood pressure was significantly higher in obese men (P < 0.01). Heart rate and systolic blood pressure significantly increased, and diastolic blood pressure significantly decreased in both groups during β₁-adrenergic stimulation with dobutamine. The changes in heart rate and in systolic and diastolic blood pressure were comparable in both groups (Table 3).

β₂-Adrenoceptor study

Baseline energy expenditure was similar in obese and lean men (5.13 ± 0.16 vs. 4.97 ± 0.09 kJ/min adjusted for FFM; P = NS). During β₂-adrenergic stimulation, adjusted energy expenditure significantly increased. However, the increase in energy expenditure was significantly lower in the obese compared with the lean men. At baseline, plasma NEFA and glycerol levels were similar in obese and lean men. During β₂-adrenergic stimulation, plasma NEFA levels remained similar, whereas plasma glycerol levels showed some variation, but no dose-dependent changes in either group (Table 2).

Plasma dobutamine levels significantly increased to similar concentrations in obese and lean men (Fig. 3). Baseline norepinephrine and epinephrine levels were comparable between overweight and normal weight subjects (norepinephrine, 1.59 ± 0.35 vs. 1.47 ± 0.27 nmol/L; epinephrine, 0.19 ± 0.04 vs. 0.22 ± 0.03 nmol/L; both P = NS) and were significantly decreased in both groups during β₂-adrenergic stimulation (Fig. 3).

Baseline values for heart rate and systolic blood pressure were not significantly different between groups (Table 3), but diastolic blood pressure was significantly higher in obese men (P < 0.01). Heart rate and systolic blood pressure significantly increased, and diastolic blood pressure significantly decreased in both groups during β₂-adrenergic stimulation with dobutamine. The changes in heart rate and in systolic and diastolic blood pressure were comparable in both groups (Table 3).

![Fig. 1. Changes in energy expenditure adjusted for FFM, RER, and lipid and carbohydrate oxidation during β₁-adrenergic stimulation with dobutamine in 9 obese (○) and 10 lean (■) men. Values are the mean ± SEM. ###, P < 0.001, by ANOVA for treatment.](image)
pared with the lean group (ANOVA for energy expenditure × group, \( P < 0.05 \); Fig. 4). At baseline, RER was similar in obese and lean men (0.838 ± 0.011 vs. 0.825 ± 0.008; \( P = \text{NS} \)). RER significantly decreased during \( \beta_2 \)-adrenergic stimulation, but the decrease was significantly larger in the lean group (ANOVA for RER × group, \( P < 0.05 \); Fig. 4). At baseline, lipid and carbohydrate oxidation were similar in obese and lean subjects [lipid oxidation, 55 ± 6 vs. 42 ± 3 mg/min (\( P = \text{NS} \)); carbohydrate oxidation, 143 ± 17 vs. 116 ± 9 mg/min (\( P = \text{NS} \))]. Lipid oxidation significantly increased during \( \beta_2 \)-adrenergic stimulation, but this increase was significantly higher in the lean group (ANOVA for lipid oxidation × group, \( P = 0.05 \)). Carbohydrate oxidation rates significantly decreased (ANOVA for treatment, \( P < 0.05 \)) during \( \beta_2 \)-adrenergic stimulation, but did not differ significantly between groups (Fig. 4).

At baseline, plasma NEFA levels were similar in obese and lean men (443 ± 21 vs. 395 ± 34 \( \mu \text{mol/L} \); \( P = \text{NS} \); Fig. 2). Baseline glycerol levels were significantly higher in the overweight compared with the normal weight group (76.5 ± 4.3 vs. 61.7 ± 4.8 \( \mu \text{mol/L} \); \( P < 0.05 \)). During \( \beta_2 \)-adrenergic stimulation with salbutamol, plasma NEFA and glycerol levels increased significantly more in the lean compared with the obese group (ANOVA for group × treatment: NEFA, \( P < 0.01 \); glycerol, \( P < 0.05 \); Fig. 2). Plasma glucose and insulin levels were significantly higher in the obese group at baseline (Table 4). Plasma glucose levels remained similar in the overweight group, but increased significantly in the normal

### Table 2. Plasma concentrations of glucose, insulin, lactate, and potassium during \( \beta_1 \)-adrenergic stimulation with dobutamine in obese and lean men

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Dobutamine (( \mu \text{g/kg FFM/min} ))</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>Obese</td>
<td>5.56 ± 0.16</td>
<td>5.31 ± 0.21</td>
</tr>
<tr>
<td></td>
<td>Lean</td>
<td>5.04 ± 0.15(^a)</td>
<td>4.86 ± 0.15</td>
</tr>
<tr>
<td>Insulin (mU/L)</td>
<td>Obese</td>
<td>14.0 ± 2.7</td>
<td>19.4 ± 4.7</td>
</tr>
<tr>
<td></td>
<td>Lean</td>
<td>6.1 ± 0.6(^b)</td>
<td>7.8 ± 1.0(^a)</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>Obese</td>
<td>1.28 ± 0.16</td>
<td>1.28 ± 0.17</td>
</tr>
<tr>
<td></td>
<td>Lean</td>
<td>0.93 ± 0.14</td>
<td>0.83 ± 0.07(^a)</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>Obese</td>
<td>4.22 ± 0.11</td>
<td>4.26 ± 0.09</td>
</tr>
<tr>
<td></td>
<td>Lean</td>
<td>4.07 ± 0.08</td>
<td>4.16 ± 0.09</td>
</tr>
</tbody>
</table>

Values are the mean ± SEM. Obese, \( n = 9 \); lean, \( n = 10 \).

\(^a\) \( P < 0.05 \), obese vs. lean, by unpaired \( t \) test.

\(^b\) \( P < 0.01 \), obese vs. lean, by unpaired \( t \) test.

**Fig. 2.** Changes in plasma NEFA and glycerol concentrations during \( \beta_1 \)-adrenergic stimulation with dobutamine in 9 obese (○) and 10 lean (■) men (left panels) and during \( \beta_2 \)-adrenergic stimulation with salbutamol in combination with atenolol in 10 obese (○) and 11 lean (■) men (right panels). Values are the mean ± SEM. ###, \( P < 0.001 \) (by ANOVA for treatment). *, \( P < 0.05 \); **, \( P < 0.01 \); ***, \( P < 0.001 \) (by unpaired \( t \) test, obese vs. lean).
weight group during $\beta_2$-adrenergic stimulation. Plasma insulin levels increased significantly more in the obese compared with the lean group during salbutamol infusion. Baseline lactate and potassium concentrations were similar in both groups. Lactate levels significantly increased, and potassium levels significantly decreased during $\beta_2$-adrenergic stimulation, but remained comparable between groups (Table 5).

Plasma salbutamol concentrations increased to a similar level in obese and lean men during both infusion periods.
Baseline norepinephrine levels were comparable between overweight and normal weight subjects (2.57 ± 0.16 vs. 2.36 ± 0.16 nmol/L; P = NS), but baseline epinephrine levels were significantly higher in the lean group (0.13 ± 0.02 vs. 0.22 ± 0.03 nmol/L; P < 0.01). Norepinephrine levels increased similarly in both groups during β₂-adrenergic stimulation. Epinephrine levels decreased significantly in both groups during β₂-adrenergic stimulation, but the decrease was significantly higher in the lean group (Fig. 3).

Baseline values for heart rate and systolic and diastolic blood pressure were not significantly different between obese and lean men (Table 5). Heart rate significantly increased, systolic blood pressure remained similar, and diastolic blood pressure significantly decreased in both groups during β₂-adrenergic stimulation with salbutamol. The changes in heart rate and systolic and diastolic blood pressure were similar in obese and lean men (Table 5).

**Table 4.** Plasma concentrations of glucose, insulin, lactate, and potassium during β₂-adrenergic stimulation with salbutamol in obese and lean men

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Salbutamol (ng/kg FFM/min)</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>Obese</td>
<td>5.64 ± 0.18</td>
<td>5.56 ± 0.17</td>
</tr>
<tr>
<td></td>
<td>Lean</td>
<td>4.89 ± 0.12</td>
<td>4.96 ± 0.15</td>
</tr>
<tr>
<td>Insulin (mU/L)</td>
<td>Obese</td>
<td>11.8 ± 2.4</td>
<td>17.2 ± 4.0</td>
</tr>
<tr>
<td></td>
<td>Lean</td>
<td>5.0 ± 0.4</td>
<td>6.8 ± 0.8</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>Obese</td>
<td>1.06 ± 0.11</td>
<td>1.12 ± 0.11</td>
</tr>
<tr>
<td></td>
<td>Lean</td>
<td>0.86 ± 0.13</td>
<td>0.98 ± 0.08</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>Obese</td>
<td>4.32 ± 0.01</td>
<td>4.32 ± 0.07</td>
</tr>
<tr>
<td></td>
<td>Lean</td>
<td>4.21 ± 0.07</td>
<td>4.29 ± 0.08</td>
</tr>
</tbody>
</table>

Values are the mean ± SEM. Obese, n = 10; lean, n = 11.

* P < 0.05, obese vs. lean, by unpaired t test.

# P < 0.01, obese vs. lean, by unpaired t test.

**Discussion**

The aim of the present studies was to examine the roles of the β₁- and the β₂-adrenoceptor in thermogenesis and lipid utilization in obese and lean men. During β₁-adrenergic stimulation with dobutamine, no differences were found in the changes in energy expenditure and lipid utilization between groups. During β₂-adrenergic stimulation with salbutamol, obese subjects had a reduced increase in energy expenditure; a reduced decrease in RER, suggesting a blunted increase in
lipid oxidation, and lipolysis in the obese responsible for the impaired responses in thermogenesis, with dobutamine, but after incubation with isoprenaline or salbutamol to investigate $\beta_2$-adrenoceptor specific changes in lipid utilization. Addition of the $\beta_2$-adrenoceptor antagonist atenolol prevented simultaneous $\beta_2$-adrenergic stimulation, but did not affect $\beta_2$-adrenoceptor-specific changes. Therefore, in the current study salbutamol was given in combination with atenolol to investigate $\beta_2$-adrenoceptor specific changes in thermogenesis and lipid utilization.

Our study suggests that it is the $\beta_2$-adrenoceptor that is responsible for the impaired responses in thermogenesis, lipid oxidation, and lipolysis in the obese in vitro. In in vitro studies, similar results are found in relation to lipolysis. Glycerol release from sc abdominal fat cells from normal weight and overweight women was similar after incubation with dobutamine, but after incubation with isoprenaline or terbutaline, glycerol release was reduced in fat cells from the obese. This appeared to be due to a significant reduction in cell surface density of $\beta_2$-adrenoceptors, although messenger ribonucleic acid (mRNA) levels were similar in both groups (29). In another study, lean subjects with low isoprenaline sensitivity, as measured by in vitro sc abdominal fat cell lipolysis, appeared to have lower $\beta_2$-adrenoceptor number and mRNA level compared with lean subjects with high isoprenaline sensitivity, whereas $\beta_1$-adrenoceptor number and mRNA levels were similar in both groups (30). Both studies suggest that the $\beta_2$-adrenoceptor is responsible for the reduced $\beta_2$-adrenoceptor-mediated increase in lipolysis, which is in line with our findings.

Further evidence for a role of the $\beta_2$-adrenoceptor in the etiology of obesity is provided by two recently found polymorphisms in the $\beta_2$-adrenoceptor that are associated with obesity. The Arg$^{16}$Gly polymorphism in the $\beta_2$-adrenoceptor is associated with obesity in Japanese women (31). In a group of Swedish women, this mutation is not associated with obesity, but fat cells from women homozygous for Arg$^{16}$ showed a 5-fold lower agonist sensitivity for $\beta_2$-adrenoceptors than women heterozygous or homozygous for Gly$^{16}$ (32). The Gln$^{27}$Glu polymorphism is associated with obesity in Japanese males and females (31, 33). Swedish women homozygous for Glu$^{27}$ had an average fat mass excess of 20 kg and approximately 50% larger fat cells than women homozygous for Gln$^{27}$. However, no significant association with changes in $\beta_2$-adrenoceptor function was observed, as assessed by in vitro fat cell lipolysis experiments (32). Obesity in Swedish males tends to be negatively associated with the Gln$^{27}$Glu polymorphism (34). As we did not determine $\beta_2$-adrenoceptor polymorphisms, it is unknown whether the impaired responses in thermogenesis and lipid utilization found in our obese group are associated with one or both of the above-mentioned polymorphisms. Until now, no associations between polymorphisms in the $\beta_1$-adrenoceptor and obesity have been reported.

The reduced increases in thermogenesis and lipid oxidation during $\beta_2$-adrenergic stimulation in the obese might also be explained by the reduced increase in NEFA in blood. The amount of NEFA presented to skeletal muscle occurred in the obese. Moreover, others found that obese women have a decreased capacity to oxidize substrates

### Table 5. Heart rate and systolic and diastolic blood pressures during $\beta_2$-adrenergic stimulation with salbutamol in obese and lean men

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Salbutamol (ng/kg FFM-min)</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>Obese</td>
<td>58</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>Lean</td>
<td>53</td>
<td>59</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>Obese</td>
<td>121</td>
<td>119</td>
</tr>
<tr>
<td></td>
<td>Lean</td>
<td>113</td>
<td>117</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>Obese</td>
<td>90</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>Lean</td>
<td>82</td>
<td>80</td>
</tr>
</tbody>
</table>

Values are the mean $\pm$ SEM. Obese, n = 10; lean, n = 11.
and have increased glycolytic and anaerobic capacities, as measured by the activities of several key enzymes in skeletal muscle biopsies (37, 38). This suggests that lipid oxidation and thermogenesis are impaired in the obese independently from NEFA availability. Our \( \beta_1 \)-adrenoceptor study and the study using lipid heparin infusion (35) show that similar increases in thermogenesis and lipid oxidation occur in obese and lean men for a certain increase in plasma NEFA concentration, and therefore do not support these findings.

The reduced increase in plasma NEFA and glycerol concentrations and the consequent reduced increases in lipid oxidation and thermogenesis during \( \beta_2 \)-adrenergic stimulation might be explained not only by a defect in the \( \beta_2 \)-adrenoceptor or the pathways it mediates, as stated above, but also by the slightly higher increase in insulin concentration in the obese, because insulin inhibits lipolysis. As the obese group was insulin resistant according to their high baseline insulin levels, the impact of this higher increase is difficult to interpret. Comparing the \( \beta_1 \) with the \( \beta_2 \)-adrenoceptor study, the increases in plasma insulin level were almost identical between studies (obese vs. lean, \( \beta_1 \) study, 8.7 \pm 3.5 vs. 4.4 \pm 0.8 mU/L; \( \beta_2 \) study, 6.0 \pm 1.0 vs. 3.5 \pm 0.8 mU/L), whereas the increases in NEFA and glycerol levels, lipid oxidation, and thermogenesis were only impaired in the \( \beta_2 \)-adrenoceptor study. Furthermore in \textit{in vitro} lipolysis tests, \( \beta_2 \)-adrenoceptor-mediated lipolysis was reduced in fat cells from the obese, although no insulin was present in the incubation medium (29, 30). These data suggest that the impaired increases in plasma NEFA and glycerol concentration were not due to the slightly higher increase in plasma insulin concentration in the obese during \( \beta_2 \)-adrenergic stimulation. However, as changes in insulin concentration and not in insulin action were measured, repeating the experiment during a hyperinsulinemic clamp can only provide direct evidence for a role of insulin in the blunted responses in the obese. Two other studies investigated the role of insulin in epinephrine-induced thermogenesis. One study showed that epinephrine induced energy expenditure independently from insulin concentrations (39), whereas the other study found an inhibitory effect of insulin (40).

Aging is also known to reduce the sensitivity for catecholamines and thus for \( \beta \)-adrenoceptor agonists (41, 42). In our \( \beta_2 \)-adrenoceptor study, obese and lean subjects were of similar age, but in the \( \beta_1 \)-adrenoceptor study, the obese group was slightly, but significantly, older than the lean one. However, as our groups differed by only 5 yr in age, whereas subjects in studies on the effect of aging commonly differ by more than 30 yr of age, we believe that the difference in catecholamine sensitivity between our subjects was only minor and therefore did not influence the interpretation of our data.

The impaired responses to \( \beta_2 \)-adrenergic stimulation may be caused by differences in norepinephrine kinetics. Studies with tritiated norepinephrine have shown that norepinephrine appearance rates are similar (43, 44) or higher (45, 46) and norepinephrine clearance rates are similar (17, 45, 46) or lower (18) in subjects with a greater fat mass. This suggests that basal sympathetic nervous system activity may be chronically increased in the obese. As a consequence, \( \beta \)-adrenoceptors may become desensitized and/or down-regulated, resulting in reduced sympathetic nervous system responses during additional \( \beta_2 \)-adrenergic stimulation, as shown in this and other studies (5, 7, 15, 16, 19–21). With regard to our study, it is unclear why this desensitization and/or down-regulation would only affect the \( \beta_2 \)-adrenoceptor and not the \( \beta_1 \)-adrenoceptor.

The question remains of whether the impaired responses during \( \beta_2 \)-adrenergic stimulation are a cause or a consequence of obesity. Blaak et al. (47) showed that \( \beta \)-adrenoceptor-mediated thermogenesis tended to increase after weight loss. This suggests that the impaired sympathetic nervous system response is a consequence of the obese state. On the other hand, Astrup et al. (48) showed that glucose-induced increases in energy expenditure and norepinephrine levels improved in obese subjects after 30-kg weight loss, but were still lower than those in control subjects. Furthermore, Blaak et al. (47) showed that \( \beta \)-adrenoceptor-mediated increases in arterial NEFA concentration and muscle NEFA uptake remained impaired after weight reduction. This suggests that a defective sympathetic nervous system may be a primary factor leading to the development of obesity rather than a secondary factor resulting from the obese state.

In conclusion, our studies suggest that \( \beta_1 \)-adrenoceptor-mediated thermogenesis and lipid utilization are similar in obese and lean men, but \( \beta_2 \)-adrenoceptor-mediated increases in energy expenditure, lipid oxidation, and lipolysis are impaired in the obese.
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Acknowledgments

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References


