Whole body and abdominal lipolytic sensitivity to epinephrine is suppressed in upper body obese women

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Horowitz, Jeffrey F., and Samuel Klein. Whole body and abdominal lipolytic sensitivity to epinephrine is suppressed in upper body obese women. Am J Physiol Endocrinol Metab 278: E1144–E1152, 2000.—We measured whole body and regional lipolytic and adipose tissue blood flow (ATBF) sensitivity to epinephrine in 10 lean [body mass index (BMI): 21 ± 1 kg/m²] and 10 upper body obese (UBO) women (BMI: 38 ± 1 kg/m²; waist circumference >100 cm). All subjects underwent a four-stage epinephrine infusion (0.00125, 0.005, 0.0125, and 0.025 µg·kg·fat-free mass⁻¹·min⁻¹) plus pancreatic hormonal clamp. Whole body free fatty acid (FFA) and glycerol rates of appearance (Ra) in plasma were determined by stable isotope tracer methodology. Abdominal and femoral subcutaneous adipose tissue lipolytic activity was determined by microdialysis and ¹³⁵Xe clearance methods. Basal whole body FFA Ra and glycerol Ra were both greater (P < 0.05) in obese (449 ± 31 and 220 ± 12 µmol/min, respectively) compared with lean subjects (323 ± 44 and 167 ± 21 µmol/min, respectively). Epinephrine infusion significantly increased FFA Ra and glycerol Ra in lean (71 ± 21 and 122 ± 52%, respectively; P < 0.05) but not obese subjects (7 ± 6 and 39 ± 10%, respectively; P = not significant). In addition, lipolytic and ATBF sensitivity to epinephrine was blunted in abdominal but not femoral subcutaneous adipose tissue of obese compared with lean subjects. We conclude that whole body lipolytic sensitivity to epinephrine is blunted in women with UBO because of decreased sensitivity in upper body but not lower body subcutaneous adipose tissue.

lipolysis; catecholamine; adipose tissue blood flow; stable isotopes; pancreatic clamp
Table 1. Characteristics of the study subjects

<table>
<thead>
<tr>
<th></th>
<th>Lean</th>
<th>Obese</th>
</tr>
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<tbody>
<tr>
<td>Weight, kg</td>
<td>56.9 ± 1.7</td>
<td>98.6 ± 1.7*</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>20.9 ± 0.4</td>
<td>37.6 ± 0.7*</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>27.1 ± 1.5</td>
<td>52.1 ± 0.7*</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>15.5 ± 1.1</td>
<td>51.3 ± 1.2*</td>
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<tr>
<td>Fat-free mass, kg</td>
<td>41.4 ± 1.3</td>
<td>47.4 ± 0.9*</td>
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Values are means ± SE. BMI, body mass index. *Significantly different from lean value, P < 0.05.

search Center (GCRC) Scientific Advisory Committee of Washington University School of Medicine.

Experimental protocol. Subjects were admitted to the GCRC at Washington University School of Medicine in the evening before the day of the study. At 1900 on the day of admission, subjects ingested a standard meal (55% carbohydrate, 30% fat, and 15% protein) containing 12 kcal/kg body wt for obese subjects and 12 kcal/kg body wt for lean subjects and 12 kcal/kg adjusted body wt for obese 30% fat, and 15% protein) containing 12 kcal/kg body wt for subjects ingested a standard meal (55% carbohydrate, 30% fat, and 15% protein) containing 12 kcal/kg body wt for lean subjects and 12 kcal/kg adjusted body wt for obese subjects and 12 kcal/kg adjusted body wt for obese subjects

At 0 min, a four-stage epinephrine infusion was started. Epinephrine (Lederle Laboratories, Chicago, IL) was infused for 30 min at 0.00125 µg·kg FFM⁻¹·min⁻¹ (Epi-1), 0.005 µg·kg FFM⁻¹·min⁻¹ (Epi-2), 0.0125 µg·kg FFM⁻¹·min⁻¹ (Epi-3), and 0.025 µg·kg FFM⁻¹·min⁻¹ (Epi-4) in discrete stages separated by a 30-min period without epinephrine infusion to reestablish basal epinephrine concentration and lipolytic rates (Fig. 1). Ascorbic acid (0.5 mg/ml; Abbott Laboratories, Chicago, IL) was added to the epinephrine infusate to prevent degradation.

Blood sampling. Blood samples were obtained at −165, −160, −155, and −150 min (basal), at −15, −10, −5, and 0 min (hormonal clamp baseline or “Pre-Epi”), and every 5 min during each 30-min epinephrine infusion stage (Epi-1, Epi-2, Epi-3, and Epi-4; Fig. 1). These samples were used to assess lipid kinetics and plasma hormone concentrations during basal conditions, the hormonal clamp baseline period, and each stage of epinephrine infusion.

Microdialysis. Four microdialysis probes (3-cm loop probes; BioAnalytical Systems, West Lafayette, IN) were placed in the subcutaneous adipose tissue under local anesthesia. Two probes were placed in the abdominal region, ~3 cm lateral to the umbilicus, and two probes were placed in the femoral region, ~25 cm above the patella. Before insertion, the probes were flushed overnight (~16 h) with Ringer solution (with 2.5 mM glucose added) to remove any residual glycerol. Throughout the study, the probes were perfused with the same
solution at a rate of 2 µl/min. Microdialysis samples were not collected for at least 3 h after insertion to avoid any influence of trauma due to probe placement. Microdialysis samples were collected during the 15-min period immediately before Epi-1 and during each epinephrine infusion (Fig. 1).

ATBF measurement. Abdominal and femoral subcutaneous ATBF was measured by the \(^{133}\)Xe clearance technique (28). At least 60 min before the first epinephrine infusion (during the hormonal clamp) \(^{133}\)Xe dissolved in 0.1 ml of normal saline were slowly injected over 60 s into abdominal and femoral subcutaneous adipose tissue. A cesium iodide detector (Oakfield Instruments, Eynsham, UK) was placed directly over the injection sites and was secured to the skin by tape. The decline in \(^{133}\)Xe was determined by collecting 10-s counts (36) beginning 15 min before Epi-1 and throughout each epinephrine infusion (Fig. 1).

Measurement of gas exchange. The rates of oxygen consumption and carbon dioxide production were measured during the basal period and during the hormonal clamp before the first epinephrine infusion (Fig. 1) by using a Vmax-29 metabolic cart (SensorMedics, Yorba Linda, CA).

Analytical procedures. Plasma insulin concentration was measured by RIA (16). Plasma catecholamine concentrations were determined by a radioenzymatic method (38). Glycerol concentration in the microdialysis samples was measured by a fluorometric method (9). Plasma glycerol concentration was determined by gas chromatography-mass spectrometry (GC-MS) and by adding \([2-\text{\textsuperscript{13}C}]\) glycerol to plasma as an internal standard. Plasma FFA concentrations were quantified by gas chromatography and by adding heptadecanoic acid to plasma as an internal standard.

Plasma glycerol and palmitate tracer-to-tracee ratios (TTR) were determined by GC-MS using an MSD 5971 system (Hewlett-Packard, Palo Alto, CA) with a capillary column (19, 33). Acetone was used to precipitate plasma proteins, and hexane was used to extract plasma lipids. The aqueous phase was dried by speed-vac centrifugation (Savant Instruments, Hoddesdon, UK). The residue was dissolved in hexane and added to 30 ml of water to give a concentration of 10 ml/g for both plasma and converted to their methyl esters with iodomethane. FFAs were isolated from plasma and converted to their methyl esters with iodomethane. Ions at m/z 253, 254, and 257. FFAs were isolated from plasma and converted to their methyl esters with iodomethane. Ions at m/z 270.2 and 271.2, produced by electron impact ionization. Glycerol TTR was determined by selectively monitoring ions at mass-to-charge ratio (m/z) 253, 254, and 257. FFAs were isolated from plasma and converted to their methyl esters with iodomethane. Ions at m/z 270.2 and 271.2, produced by electron impact ionization, were selectively monitored.

Calculations. A plateau in substrate concentration and disappearance rate, and subject characteristics between lean and obese groups. A Student's t-test for independent samples was used to test the significance of differences in lipid kinetics and plasma hormone concentrations between lean and obese groups. A two-way ANOVA (anatomical site × epinephrine dose) with Tukey's post hoc analysis was used to test the significance of differences in ATBF and regional lipolysis between abdominal and femoral adipose tissue in both groups. A Student's t-test for independent samples was used to test the significance of differences in fat oxidation, nonoxidative fatty acid disposal rate, and subject characteristics between lean and obese subjects. A value of P < 0.05 was considered to be statistically significant. All data are expressed as means ± SE.

RESULTS

Plasma hormone concentrations. Mean basal plasma insulin concentration was more than twofold greater in obese than in lean women (22.3 ± 3.0 and 9.0 ± 1.0 µU/ml, respectively; P < 0.05). During the baseline period of the hormonal clamp, plasma insulin concentration decreased to similar values in both obese and lean groups before epinephrine infusion (4.1 ± 0.3 and 4.4 ± 0.5 µU/ml, respectively) and remained low for the remainder of the study in both groups (Fig. 2A). The graded epinephrine infusion resulted in a progressive increase in plasma epinephrine concentration, which was identical in obese and lean subjects (Fig. 2B). Plasma norepinephrine concentration was not affected by epinephrine infusion and remained at basal values throughout the study (0.94 ± 0.11 and 1.13 ± 0.12 nM for obese and lean, respectively; P = not significant).
Whole body glycerol and FFA kinetics. Basal FFA $R_a$ and glycerol $R_a$ were greater in obese compared with lean subjects ($P < 0.05$; Table 2). However, basal FFA and glycerol $R_a$ expressed relative to FM were approximately twofold greater in lean than obese subjects ($P < 0.05$). Basal FFA and glycerol $R_a$ expressed relative to FFM were slightly greater in obese than lean subjects, but the differences were not statistically significant.

During the baseline period of the hormonal clamp, FFA $R_a$ and glycerol $R_a$ increased significantly above basal values in obese ($P < 0.05$) but not lean subjects (Table 2). However, despite this large increase in lipolytic rate during the hormonal clamp in obese women, FFA and glycerol $R_a$ per kilogram FM remained lower in obese compared with lean subjects ($P < 0.05$).

Epinephrine infusion increased FFA $R_a$ and glycerol $R_a$ above hormonal clamp baseline values in lean ($P < 0.05$) but not obese women (Fig. 3). Expressed relative to FM, FFA $R_a$ and glycerol $R_a$ were one-half to one-third as great in obese compared with lean subjects ($P < 0.05$; Fig. 4). However, despite the relatively large increase in lipid kinetics in lean subjects during epinephrine infusion, total glycerol $R_a$ and FFA $R_a$ relative to FFM remained higher in obese than lean subjects throughout the study ($P < 0.05$; Fig. 5).

Regional glycerol kinetics. The multistage epinephrine infusion increased glycerol release from abdominal and femoral subcutaneous adipose tissue in lean and obese subjects (main effect for epinephrine $P < 0.05$). However, the increase in abdominal adipose tissue glycerol release was blunted in obese compared with lean subjects ($P < 0.05$; Fig. 6A). In contrast, femoral adipose tissue lipolytic activity during epinephrine infusion was similar in lean and obese subjects (Fig. 6B). In lean but not obese subjects, the increase in glycerol release was greater in abdominal than femoral subcutaneous adipose tissue during the final two stages of epinephrine infusion (Epi-3: 0.52 ± 0.13 vs. 0.23 ± 0.08; Epi-4: 0.67 ± 0.15 vs. 0.18 ± 0.08 µmol·100 g$^{-1}$·min$^{-1}$, respectively; both $P < 0.05$).

Regional ATBF. Epinephrine infusion increased abdominal and femoral ATBF in both lean and obese subjects (main effect for epinephrine $P < 0.05$). The increase in abdominal ATBF was blunted in obese compared with lean subjects ($P < 0.05$; Fig. 7A), whereas the increase in femoral ATBF was similar in lean and obese groups (Fig. 7B). Compared with abdominal ATBF, the increase in femoral ATBF in response to epinephrine was blunted in lean subjects; femoral ATBF was significantly lower than abdominal ATBF during the final two stages of epinephrine infusion (Epi-3: 4.4 ± 0.6 vs. 6.4 ± 0.7; Epi-4: 4.4 ± 0.6 vs. 7.4 ± 0.5 ml·100 g$^{-1}$·min$^{-1}$, respectively; both $P < 0.05$). In obese subjects, abdominal and femoral ATBF were similar during each stage of epinephrine infusion.

Fat oxidation. Basal FAO tended to be greater in obese than in lean subjects, but the difference was not statistically significant ($P = 0.24$; Table 3). During the

Table 2. Basal and hormonal clamp baseline fatty acid and glycerol kinetics

<table>
<thead>
<tr>
<th></th>
<th>Lean Basal</th>
<th>Hormonal clamp baseline</th>
<th>Obese Basal</th>
<th>Hormonal clamp baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFA $R_a$</td>
<td>$323 ± 44$</td>
<td>$376 ± 60$</td>
<td>$449 ± 31^*$</td>
<td>$782 ± 55^+$</td>
</tr>
<tr>
<td>µmol/min</td>
<td>µmol/kg</td>
<td>µmol/min</td>
<td>µmol/kg</td>
<td>µmol/min</td>
</tr>
<tr>
<td>FM$^{-1}$·min$^{-1}$</td>
<td>$21.8 ± 3.6$</td>
<td>$25.2 ± 4.6$</td>
<td>$8.8 ± 0.6^*$</td>
<td>$15.2 ± 1.0^+$</td>
</tr>
<tr>
<td>$R_a$</td>
<td>$167 ± 21$</td>
<td>$173 ± 22$</td>
<td>$220 ± 12^*$</td>
<td>$329 ± 28^+$</td>
</tr>
<tr>
<td>µmol/min</td>
<td>µmol/kg</td>
<td>µmol/min</td>
<td>µmol/kg</td>
<td>µmol/min</td>
</tr>
<tr>
<td>FM$^{-1}$·min$^{-1}$</td>
<td>$11.2 ± 1.7$</td>
<td>$11.7 ± 1.8$</td>
<td>$4.3 ± 0.2^*$</td>
<td>$6.4 ± 0.5^+$</td>
</tr>
</tbody>
</table>

Values are means ± SE. FFA, free fatty acid; $R_a$, rate of appearance; FM, fat mass; FFM, fat-free mass. *Significantly different from lean, $P < 0.05$. †Significantly different from basal value, $P < 0.05$. 

Fig. 2. Average plasma insulin (A) and epinephrine (B) concentrations during basal conditions, hormonal clamp baseline, and each stage of epinephrine infusion in lean (●) and obese (○) subjects. *Significantly different from lean subjects, $P < 0.05$. †Significantly different from basal value, $P < 0.05$.
baseline period of the hormonal clamp, FAO increased above basal values in both groups (P < 0.05). In obese subjects, the increase in FAO (−50 µmol/min) was much less than the increase in FFA Ra (−350 µmol/min). Therefore, the rate of nonoxidative fatty acid disposal almost tripled in obese women (P < 0.05) and was more than fourfold greater than that observed in lean women (P < 0.05; Table 3). In lean subjects, the increase in FAO (−60 µmol/min) was similar to the increase in FFA Ra (−60 µmol/min), so nonoxidative fatty acid disposal did not change.

DISCUSSION

The mobilization of adipose tissue lipids involves triglyceride hydrolysis and removal of released FFA by local blood vessels for delivery into the systemic circulation. Epinephrine is an important regulator of adipose tissue metabolism because it stimulates both lipolysis and ATBF (37). In the present study, we evaluated whether whole body and regional adipose tissue lipolytic and blood flow responses to a physiological range of plasma epinephrine concentrations were altered in women with UBO compared with lean women. A multistage epinephrine infusion was performed in conjunction with a pancreatic hormonal clamp to regulate plasma epinephrine concentrations while preventing the confounding influence of hyperinsulinemia associated with UBO (29) and epinephrine infusion (14). Our data demonstrate that whole body lipolytic sensitivity is blunted in women with UBO because of a decreased response to epinephrine in upper body (abdominal) but not lower body (femoral) subcutaneous fat depots. In addition, vascular sensitivity to epinephrine was blunted in abdominal but not femoral subcutaneous adipose tissue in women with UBO. These findings help explain the blunted increase in lipolysis observed in persons with UBO during physiological conditions that cause an increase in plasma epinephrine concentration.

Fig. 3. Percent increase in total free fatty acid (FFA) rate of appearance (Ra) (A) and total glycerol Ra (B) above hormonal clamp baseline values at plasma epinephrine concentrations achieved during each stage of epinephrine infusion in lean (●) and obese (○) subjects. *Significantly different from lean subjects, P < 0.05. †Significantly different from zero, P < 0.05.

Fig. 4. Total FFA Ra (A) and total glycerol Ra (B) relative to fat mass (FM) at plasma epinephrine concentrations achieved during each stage of epinephrine infusion in lean (●) and obese (○) subjects. *Significantly different from lean subjects, P < 0.05.
and a decrease in plasma insulin concentration, such as fasting (19) and exercise (25).

The mechanism responsible for the blunted adipose tissue lipolytic and vascular responses to epinephrine in persons with UBO may be related to alterations in β2-adrenergic receptor number and/or function. Adrenergic regulation of adipose tissue triglyceride lipolysis is mediated through β (stimulatory)- and α2 (inhibitory)-adrenergic receptors (40). It has been proposed that differences in the lipolytic response to catecholamines is greater in upper body than in lower body subcutaneous adipose tissue depots (15, 22, 30, 40). The major determinant for the regional differences in catecholamine-stimulated lipolysis is an increased sensitivity to β-adrenergic stimulation in upper body subcutaneous adipose tissue (15, 40) due to an increase in β2-adrenergic receptor density (40). However, increased lower body adipose tissue α2-adrenergic receptor activity may also contribute to the regional variation in lipolytic sensitivity, particularly in women (30, 40). Jensen and col-

attributed to a posttranscriptional reduction in β2-adrenergic receptor density (35). Therefore, data from in vitro studies suggest that the blunted lipolytic sensitivity to epinephrine observed in our subjects with UBO may be due to reduced β2-adrenergic receptor density, perhaps predominantly in abdominal adipose tissue.

Previous studies performed in lean subjects found that the lipolytic response to catecholamines is greater in upper body than in lower body subcutaneous adipose tissue depots (15, 22, 30, 40). The major determinant for the regional differences in catecholamine-stimulated lipolysis is an increased sensitivity to β-adrenergic stimulation in upper body subcutaneous adipose tissue (15, 40) due to an increase in β2-adrenergic receptor density (40). However, increased lower body adipose tissue α2-adrenergic receptor activity may also contribute to the regional variation in lipolytic sensitivity, particularly in women (30, 40). Jensen and col-

Fig. 5. Total FFA Ra (A) and total glycerol Ra (B) relative to fat-free mass (FFM) at plasma epinephrine concentrations achieved during each stage of epinephrine infusion in lean (●) and obese (○) subjects. *Significantly different from lean subjects, P < 0.05.

Fig. 6. Absolute increase in regional glycerol release above hormonal clamp baseline values in subcutaneous abdominal (A) and femoral (B) adipose tissue in lean (●) and obese (○) subjects at plasma epinephrine concentrations achieved during each stage of epinephrine infusion. *Significantly different from lean subjects, P < 0.05. †Significantly different from zero, P < 0.05.
leagues (15, 22) found that lower body adipose tissue lipolysis in women did not increase at all during catecholamine infusion. In contrast, we found that, although lipolytic sensitivity was blunted in femoral compared with abdominal adipose tissue, femoral adipose tissue lipolysis nearly doubled during epinephrine infusion. The reason for the differences observed between our studies may be related to differences in study design. The lipolytic response to epinephrine infusion peaks at \( \sim 30 \) min and then declines toward baseline because of increased insulin secretion and possibly \( \beta \)-adrenergic receptor tachyphylaxis (2, 23, 26, 37). In the studies performed by Jensen and colleagues, lower body adipose tissue lipolytic rate was measured between 60 and 90 min of the catecholamine infusion and thus after completion of the peak lipolytic response. In our study, we measured femoral adipose tissue lipolysis during the first 30 min of epinephrine infusion and administered somatostatin to prevent the normal increase in insulin secretion.

Our data demonstrate that the heterogeneity in adipose tissue lipolytic sensitivity to catecholamines observed in lean persons is attenuated in persons with UBO. The cause for this blunted lipolytic sensitivity in abdominal subcutaneous adipose tissue in our obese subjects is unclear. To our knowledge, no study has evaluated adrenergic receptor density in upper and lower body subcutaneous adipose tissue in persons with UBO. However, recent evidence indicates that adipocyte \( \beta \)-receptor density is similar in both upper and lower body subcutaneous adipose tissue regions when adipocyte volume is similar (3). It is possible that the large fat cell size in abdominal subcutaneous adipose tissue in persons with UBO (35) may reduce \( \beta \)-adrenergic receptor density and lipolytic sensitivity to \( \beta \)-adrenergic stimulation.

![Average ATBF in subcutaneous abdominal (A) and femoral (B) adipose tissue in lean (●) and obese (○) subjects at plasma epinephrine concentrations achieved during each stage of epinephrine infusion.](image)

Our data demonstrate that the heterogeneity in adipose tissue lipolytic sensitivity to catecholamines observed in lean persons is attenuated in persons with UBO. The cause for this blunted lipolytic sensitivity in abdominal subcutaneous adipose tissue in our obese subjects is unclear. To our knowledge, no study has evaluated adrenergic receptor density in upper and lower body subcutaneous adipose tissue in persons with UBO. However, recent evidence indicates that adipocyte \( \beta \)-receptor density is similar in both upper and lower body subcutaneous adipose tissue regions when adipocyte volume is similar (3). It is possible that the large fat cell size in abdominal subcutaneous adipose tissue in persons with UBO (35) may reduce \( \beta \)-adrenergic receptor density and lipolytic sensitivity to \( \beta \)-adrenergic stimulation.

Stimulation of \( \beta_2 \)-adrenergic receptors in vascular smooth muscle reduces vascular tone and increases blood flow (17). ATBF sensitivity to epinephrine was blunted in the abdominal but not the femoral region of our obese subjects compared with our lean subjects. Therefore, regional ATBF sensitivity to epinephrine parallels the increase in lipolytic sensitivity. These data support the notion that the regulation of ATBF and lipolysis is coordinated to enhance the delivery of newly released FFA into plasma and to prevent local accumulation of excessive and potentially toxic FFA (10, 37). Presumably, the coordinated increase in lipolysis and ATBF by epinephrine is a consequence of \( \beta_2 \)-adrenergic stimulation, both in adipocytes and adipose tissue blood vessels. Recently, we found that lipolysis and abdominal ATBF in lean men increased in a coordinated manner at low to moderate epinephrine concentrations but not at concentrations \( > 3 \) nM, when the increase in ATBF was attenuated (18). In the present study, abdominal ATBF increased proportionately to the increase in lipolysis during all stages of epinephrine infusion in our female subjects, but plasma epinephrine concentration did not exceed 2.2 nM. However, our study does not rule out the possibility of gender-related differences in ATBF regulation by epinephrine.

Persons with UBO have greater basal whole body lipolytic rates than lean persons (19, 24, 29). The results of the present study suggest that the increase in
lipolysis is probably caused by adipose tissue insulin resistance rather than enhanced sensitivity to catecholamines. However, persons with UBO are not completely resistant to the antilipolytic effect of insulin, and basal hyperinsulinemia may be an important mechanism for preventing even higher lipolytic rates from occurring. We found that, when plasma insulin concentrations were decreased in our obese subjects to match those found in our lean subjects during the hormonal clamp baseline period, whole body glycerol and FFA $R_d$ increased to values double those of our lean subjects. Therefore, basal hyperinsulinemia, which helps normalize plasma glucose concentrations in obese persons, also helps control lipolytic activity.

Excessive lipolytic rates, in conjunction with liver and muscle uptake of FFA that is not oxidized, may be a principal contributor to the metabolic abnormalities found in persons with UBO (4, 34). We found basal nonoxidized fatty acid disposal to be $>50\%$ greater in obese than lean subjects. Reducing plasma insulin concentration during the baseline period of the hormonal clamp caused similar increases in FFA $R_d$ and FAO in our lean subjects. However, the increase in FFA $R_d$ during the baseline period of the hormonal clamp did not cause an equivalent increase in FAO in our obese subjects. It is likely that the marked increase in lipolysis and FFA availability overwhelmed the capacity for FAO during resting conditions. Moreover, the difference in nonoxidative fatty acid disposal rates between lean and obese subjects was probably greater than our estimated values. Our calculation of nonoxidized fatty acid disposal underestimated the true disposal rate because a portion of fatty acids derived from intramuscular, intra-abdominal, and plasma triglycerides might be oxidized without entering the circulation and would not be detected by tracer infusion. Compared with lean persons, persons with UBO have greater intramuscular triglyceride stores (34), intra-abdominal fat (31), and plasma triglyceride concentrations (24) and presumably greater rates of undetected FFA release.

We attempted to minimize the confounding influence of alterations in insulin secretion and simplify subject participation by performing a multistage epinephrine infusion with a pancreatic hormonal clamp on one day. However, this experimental design may have some limitations. First, the decrease in plasma insulin concentration during the pancreatic hormonal clamp may have affected the lipolytic response to epinephrine in our obese subjects. The pancreatic hormonal clamp allowed us to match plasma insulin concentrations in lean and obese subjects and to evaluate the effect of different plasma epinephrine concentrations on lipolysis and ATBF independently of changes in plasma insulin that normally occur during epinephrine infusion. The rate of insulin infusion was chosen to maintain euglycemia and basal lipolytic rates in our lean subjects. Therefore, the relative decrease in plasma insulin concentration was much greater in our obese than in our lean subjects. The marked decline in circulating insulin in the obese group may have caused maximal stimulation of lipolysis and may have prevented further increases in lipolytic rate during epinephrine infusion. However, during the hormonal clamp baseline period, glycerol and FFA $R_d$ expressed relative to body FM were one-half as great in the obese than in the lean group, suggesting additional capacity for lipolysis. Second, infusing epinephrine in four discrete stages on the same day might reduce the lipolytic response to epinephrine during the later stages because of tachyphylaxis (2). However, Divertie et al. (8) found that lipolytic rates were not different when a four-stage sequential epinephrine infusion with pancreatic hormonal clamp was performed on a single day compared with when the same epinephrine infusions were performed on four separate days.

In summary, whole body lipolytic sensitivity to epinephrine was blunted in women with UBO compared with lean women, due in large part to reduced lipolytic sensitivity in abdominal subcutaneous adipose tissue. Additionally, although basal lipolytic activity is elevated in women with UBO, the presence of hyperinsulinemia prevents basal lipolysis from increasing to very high rates. Therefore, reduced adipose tissue lipolytic sensitivity to epinephrine in conjunction with basal hyperinsulinemia has beneficial effects by limiting excessive rates of lipolysis and FFA release into the systemic circulation.

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REFERENCES

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