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

JEFFREY F. HOROWITZ AND SAMUEL KLEIN
Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri 63110

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 8 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·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 133Xe clearance methods. Basal whole body FFA Ra and glycerol Ra were both greater (P < 0.05) in obese (449 ± 6 and 167 ± 21 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.

Epinephrine is the major plasma hormone that stimulates lipolysis of adipose tissue triglycerides. In lean persons, the lipolytic threshold to epinephrine is low, and a progressive increase in circulating epinephrine causes a progressive increase in lipolysis (14). Although persons with upper body obesity (UBO) have higher whole body basal lipolytic rates than lean persons, studies performed in vivo have found that their lipolytic response to epinephrine is blunted (7, 24). However, these in vivo findings are confounded by hyperinsulinemia associated with obesity, which could attenuate the lipolytic response to epinephrine (6). In addition, these studies did not evaluate whether regional differences in the lipolytic response to epinephrine exist in vivo between lean and obese subjects.

Epinephrine is also an important regulator of adipose tissue blood flow (ATBF), which modulates fatty acid delivery from adipose tissue into the systemic circulation. Simultaneous increases in lipolysis and ATBF may be advantageous by enhancing the removal of free fatty acid (FFA) released during lipolysis from the interstitial space and preventing local accumulation of FFA (10, 37). In lean persons, basal ATBF is lower in femoral than in abdominal subcutaneous fat depots (11). In addition, abdominal basal ATBF is lower in obese than in lean persons, whereas femoral ATBF is similar in both groups (11, 20). It is possible that regional and adiposity-related differences in vascular ß-adrenergic sensitivity may explain these differences in ATBF. However, regional ATBF sensitivity to epinephrine has not been evaluated in lean and obese persons.

The principal purpose of the present study was to evaluate whole body and regional lipolytic and ATBF sensitivity to a physiological range of plasma epinephrine concentrations in lean and UBO women. A pancreatic hormonal clamp (27) was used to eliminate differences in plasma insulin concentration between lean and obese groups and to prevent epinephrine-stimulated insulin secretion (14). In addition, the hormonal clamp allowed us to evaluate the influence of basal hyperinsulinemia on lipid metabolism in women with UBO.

METHODS

Subjects. Ten women with UBO [body mass index (BMI) >32 kg/m2; >40% body wt as fat; waist-to-hip ratio >0.85; waist circumference >100 cm] and eight lean women (BMI <24 kg/m2; <30% body wt as fat) participated in this study (Table 1). Fat mass (FM) and fat-free mass (FFM) were determined by dual-energy X-ray absorptiometry (Hologic QDR 1000W). Although all women were premenopausal, obese women (37 ± 2 yr old) were older than the lean women (26 ± 3 yr old; P < 0.05). All subjects were considered to be in good health after a comprehensive medical examination, which included a history and physical examination, blood tests, and an electrocardiogram. Obese subjects had normal glucose tolerance based on a 2-h oral glucose tolerance test. No subjects were taking any medications, and all were weight stable for at least 2 mo before the study, which was performed within the first 2 wk of the follicular phase of their menstrual cycle. Written informed consent was obtained before participation in the study, which was approved by the Human Studies Committee and the General Clinical Re-
Table 1. Characteristics of the study subjects

<table>
<thead>
<tr>
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<th>Lean</th>
<th>Obese</th>
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<tr>
<td>Weight, kg</td>
<td>56.9 ± 1.7</td>
<td>98.6 ± 1.7*</td>
</tr>
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<td>BMI, kg/m²</td>
<td>20.9 ± 0.4</td>
<td>37.6 ± 0.7*</td>
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<td>Body fat, %</td>
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<td>52.1 ± 0.7*</td>
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<td>Fat mass, kg</td>
<td>15.5 ± 1.1</td>
<td>51.3 ± 1.2*</td>
</tr>
<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 lean subjects and 12 kcal/kg adjusted body wt for obese subjects (adjusted body wt = [actual body wt - ideal body wt] × 0.25). Therefore, this meal contained ~700 and ~800 kcal for lean and obese subjects, respectively. At 2230, subjects ingested a liquid formula snack containing 80 g carbohydrate, 12.2 g fat, and 17.6 g protein (Ensure; Ross Laboratories, Columbus, OH). After this snack, the subjects fasted until completion of the study.

The following morning, a stable isotope infusion protocol was performed to evaluate lipolytic rates under basal conditions and during a four-stage epinephrine infusion with a pancreatic hormonal clamp (Fig. 1). Catheters were inserted in a forearm vein of each arm for isotope and hormone infusion and in a radial artery for blood sampling. At ~0800 (~240 min) a primed (1.5 µmol/kg), constant (0.10 µmol·kg⁻¹·min⁻¹) infusion of [1,1,2,3,3-2H]glycerol (99% APE; Cambridge Isotopes) bound to human albumin (Cen-1.7*teon LLC, Kankakee, IL) was started and continued for the next 450 min by using a calibrated syringe pump (Harvard Apparatus, Natick, MA). At ~210 min, a constant infusion (0.04 µmol·kg⁻¹·min⁻¹) of [1-¹³C]palmitate (98% APE; Cambridge Isotopes, Andover, MA) was started and continued for the next 60 min to assess basal plasma FFA kinetics. Palmitate tracer infusion was restarted at ~60 min and was continued throughout the remainder of the study.

Hormonal clamp. At ~150 min of the study, a pancreatic hormonal clamp was initiated by infusing somatostatin (0.17 µg·kg⁻¹·min⁻¹; Bachem Feinchemikalien, Bubendorf, Switzerland), insulin (0.08 mU·kg⁻¹·min⁻¹; Novo Nordisk Pharmaceuticals, Princeton, NJ), and growth hormone (0.00375 µg·kg⁻¹·min⁻¹; Genentech, San Francisco, CA; Fig. 1). Plasma glucose concentration was monitored every 10 min between ~150 and ~15 min, and 20% dextrose was infused as needed between ~150 and ~60 min to maintain baseline blood glucose concentration. By ~60 min, euglycemia was maintained in all subjects without infusing dextrose. Therefore, dextrose was not infused during the last 4.5 h (~60 to 210 min) of the hormonal clamp.

Epinephrine infusion. At 0 min, a four-stage epinephrine infusion was started. Epinephrine (Lederle Laboratories, Chicago, IL) was infused for 30 min at 0.000025 µg·kg⁻¹·min⁻¹ (Epi-1), 0.005 µg·kg⁻¹·min⁻¹ (Epi-2), 0.0125 µg·kg⁻¹·min⁻¹ (Epi-3), and 0.025 µg·kg⁻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, ~150, 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 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

![Fig. 1. Schematic diagram of the isotope infusion study protocol. ATBF, adipose tissue blood flow; Epi, epinephrine.](http://ajpendo.physiology.org/)

Downloaded from http://ajpendo.physiology.org/ by 10.220.33.6 on June 24, 2017
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 was 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 [2-13C]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, Holtsville, NY). Heptadecanoic acid (HFB) anhydride was used to form an HFB derivative of glycerol, and ions were produced by electron impact ionization. Glycerol TTR was determined by selectively monitoring ions at mass-to-charge ratios (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 TTR was achieved during basal and hormonal clamp baseline periods. Therefore, glycerol and palmitate rates of appearance (Ra) in plasma and disappearance (Ro) from plasma during these time periods were calculated using Steele's equation for steady-state conditions (39). Total glycerol and palmitate R0 during each 30-min epinephrine infusion were calculated as the area under the R0 vs. time curve by using the non-steady-state equation of Steele (39). The effective volume of distribution was estimated to be 240 ml/kg for glycerol and 50 ml/kg for palmitate. FFA kinetics were calculated by dividing palmitate kinetics by the ratio of plasma palmitate to total plasma FFA concentration. The TTR and concentration data were smoothed by spline fitting (41). Nonoxidative fatty acid disposal was calculated as FFA Ra determined by isotope tracer infusion minus fatty acid oxidation (FAO; determined by indirect calorimetry; see Ref. 13).

Subcutaneous ATBF was calculated from $^{133}$Xe disappearance (28)

$$\text{ATBF} = -k \cdot \lambda \cdot 100 \cdot (\text{ml} \cdot 100 \text{ g adipose tissue}^{-1} \cdot \text{min}^{-1})$$

where k is the rate constant of the $^{133}$Xe monoexponential washout curve, and $\lambda$ is the adipose tissue-blood partition coefficient for $^{133}$Xe. The values for k were determined experimentally as (ln $y_2$ - ln $y_1$)/(t2 - t1), where $y_1$ and $y_2$ were the counting rates at times t1 and t2, respectively. The value for $\lambda$ was assumed to be 10 ml/g (42) for all subjects. It has been suggested that $\lambda$ might vary with adiposity (5). However, direct measurement of $\lambda$ by Jansson and Lonnroth (21) determined that 10 ml/g was a reasonable estimate for both lean and obese subjects.

An index of regional glycerol release was estimated using the Fick principle

$$\text{regional glycerol release} = (V - A) \times \text{ATBF} \left( \frac{\text{µmol} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}}{100 \text{ ml}} \right)$$

where A and V are the arterial and venous glycerol concentrations, respectively. Arterial and venous glycerol concentration was approximated using the equation

$$V = \left( I - \left( L - e^{PSATBF} \right) \right) + A$$

where $I$ is the intracellular glycerol concentration (calculated from microdialysis glycerol concentration), and PS is the permeability-surface area product for glycerol (assumed to be 5 ml · 100 g$^{-1}$ · min$^{-1}$ (32)). We did not directly measure glycerol recovery but used an estimated recovery of 30% for all subjects (20). Therefore, our calculation of regional glycerol release should be considered qualitative rather than absolute. Although the principal factors that affect recovery (perfusion flow rate, properties of the dialysis membrane, and properties of the compound being analyzed; see Ref. 1) were the same in both groups, recent evidence suggests that the relative recovery of glycerol may depend on local adiposity (12). Based on these data, the relative recovery in our obese subjects might be as much as 25% lower than in our lean subjects. However, a reduction in glycerol recovery of this magnitude would not affect our conclusions regarding regional lipolysis in lean and obese women.

Statistical analysis. A two-way ANOVA (subject phenotype × epinephrine dose) with Tukey’s post hoc analysis 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 $P \leq 0.05$ 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 groups (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).
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 \( \mu \text{mol} \cdot 100 \text{g}^{-1} \cdot \text{min}^{-1} \), 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

![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, \( P < 0.05 \).

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

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<th>Lean Hormonal clamp baseline</th>
<th>Obese Hormonal clamp baseline</th>
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<tr>
<td></td>
<td>Basal</td>
<td>Basal</td>
</tr>
<tr>
<td>FFA ( R_a ) ( \mu \text{mol} \cdot \text{min}^{-1} )</td>
<td>232 ± 44</td>
<td>376 ± 60</td>
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<td></td>
<td>( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} )</td>
<td>449 ± 31</td>
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<td>FM ( R_a ) ( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} )</td>
<td>21.8 ± 3.6</td>
<td>25.2 ± 4.6</td>
</tr>
<tr>
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<td>8.8 ± 0.6*</td>
<td>15.2 ± 1.0*</td>
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<td>FFM ( R_a ) ( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} )</td>
<td>8.0 ± 1.2</td>
<td>9.3 ± 1.6</td>
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<td>9.5 ± 0.6</td>
<td>16.2 ± 1.2*</td>
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<tr>
<td>Glycerol ( R_a ) ( \mu \text{mol} \cdot \text{min}^{-1} )</td>
<td>167 ± 21</td>
<td>173 ± 22</td>
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<tr>
<td></td>
<td>120 ± 12*</td>
<td>329 ± 28*</td>
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<td></td>
<td>4.3 ± 0.2*</td>
<td>6.4 ± 0.5*</td>
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<td>4.1 ± 0.6</td>
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<td>4.7 ± 0.3</td>
<td>7.0 ± 0.6*</td>
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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, \( P < 0.05 \).
baseline period of the hormonal clamp, FAO increased above basal values in both groups ($P$, $0.05$). In obese subjects, the increase in FAO ($50 \mu$mol/min) was much less than the increase in FFA $R_d$ ($350 \mu$mol/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 ($60 \mu$mol/min) was similar to the increase in FFA $R_d$ ($60 \mu$mol/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 ($R_a$; A) and total glycerol $R_a$ (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 $R_a$ (A) and total glycerol $R_a$ (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, $P < 0.05$. 

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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 \( \beta_2 \)-adrenergic receptor number and/or function. Adrenergic regulation of adipose tissue triglyceride lipolysis is mediated through \( \beta \)-(stimulatory)- and \( \alpha_2 \)-(inhibitory)-adrenergic receptors (40). It has been proposed that differences in the lipolytic response to catecholamines in obese compared with lean subjects is due to variations in the functional balance between \( \beta \)- and \( \alpha_2 \)-adrenergic receptors in adipose tissue (30, 31). Reynisdottir et al. (35) found that lipolytic sensitivity to norepinephrine was suppressed in fat cells obtained from women with UBO, whereas lipolytic sensitivity to \( \beta_1 \)- and \( \alpha_2 \)-adrenergic receptor agonists was the same in fat cells obtained from lean and UBO subjects. The reduced lipolytic sensitivity to catecholamines was attributed to a posttranscriptional reduction in \( \beta_2 \)-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 \( \beta_2 \)-adrenergic receptor density, perhaps predominantly in abdominal subcutaneous 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 \( \beta \)-adrenergic stimulation in upper body subcutaneous adipose tissue (15, 40) due to an increase in \( \beta_2 \)-adrenergic receptor density (40). However, increased lower body adipose tissue \( \alpha_2 \)-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.](image)

![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.](image)
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 ~30 min and then declines toward baseline because of increased insulin secretion and possibly β-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 β-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 β-adrenergic receptor density and lipolytic sensitivity to β-adrenergic stimulation.

Stimulation of β2-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 β2-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

Table 3. Basal and hormonal clamp baseline fat oxidation and nonoxidative fatty acid disposal rates

<table>
<thead>
<tr>
<th></th>
<th>Lean</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>Hormonal clamp baseline</td>
</tr>
<tr>
<td>Fatty acid oxidation, µmol/min</td>
<td>212±41</td>
<td>278±30†</td>
</tr>
<tr>
<td>Nonoxidative fatty acid disposal, µmol/min</td>
<td>112±41</td>
<td>112±39</td>
</tr>
</tbody>
</table>

Values are means ± SE. *Significantly different from lean, P < 0.05. †Significantly different from basal value, P < 0.05.
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 Ra 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 Ra and FAO in our lean subjects. However, the increase in FFA Ra 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 may underestimate 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 Ra 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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Address for reprints requests and other correspondence: S. Klein, Washington Univ. School of Medicine, 660 S. Euclid Ave., Box 8127, St. Louis, MO 63110-1093.

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