Regulation of Forearm Lipolysis in Different Types of Obesity

In Vivo Evidence for Adipocyte Heterogeneity

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Abstract

Forearm and systemic adipose tissue free fatty acid (FFA) release was measured in eight nonobese, six lower-body obese, and eight upper-body obese women under basal, hyperinsulinemic, and hypoinsulinemic conditions to determine whether forearm fat is regulated in a similar manner as whole body fat. Results: Adipose tissue palmitate release was greater from forearm than whole body (5.97±0.75 vs. 3.84±0.34 μmol · kg fat^{-1} · min^{-1}, respectively, $P < 0.005$, $n = 22$ subjects). Systemic palmitate release, relative to fat mass, was significantly ($P < 0.01$) greater in nonobese than upper-body obese, and upper-body obese than lower-body obese women, and forearm adipose tissue palmitate release followed the same pattern. Hyperinsulinemia suppressed systemic and forearm lipolysis to similar degrees, however, hypoinsulinemia consistently increased systemic palmitate flux without increasing forearm palmitate release. These results confirm the heterogeneity of adipose tissue in an in vivo model and emphasize the need to consider which adipose tissue depots are responsible for the differences in systemic FFA flux in obese and nonobese humans. (*J. Clin. Invest.* 1991. 87:187–193.). Key words: body composition • body fat distribution • free fatty acids • insulin • [1-^{14}C]palmitate

Introduction

Upper-body obesity is more likely to result in adverse health consequences than lower body obesity (1, 2). The reasons for these differences are unknown; however, the increased free fatty acid (FFA) availability in upper body obesity (3) could contribute to the hypertriglyceridemia (4) and insulin resistance (5, 6) seen in this condition. This greater FFA flux could result from either accelerated lipolysis in specific adipose tissue depots or from all body fat equally. Plasma FFA concentrations correlate best with abdominal adipocyte lipolysis in vitro (7); thus, increased amounts of upper body fat could be primarily responsible for the increased FFA flux in upper body obesity.

Upper-body and lower-body adipocytes differ in several respects. Physiologic catecholamines increase lipolysis in fat cells from arm (8), omental (9), and abdominal subcutaneous depots (9, 10), but not those from gluteal/thigh regions (8–10). This phenomena likely results from a combination of increased β-adrenergic and decreased α_2-adrenergic (antilipolytic) sensitivity of upper-body fat cells compared with lower-body fat cells (10). In addition, abdominal adipocytes are sensitive to insulin in vitro (11), whereas gluteal adipocytes show little (12) or no (13) antilipolytic response to insulin. Whether anatomically separate adipose tissue depots have different lipolytic rates or responses to insulin in vivo, however, is unknown.

The following studies were designed to determine whether differences in adipose tissue lipolytic properties are present in vivo. Basal, insulin-suppressed and insulin-withdrawn FFA release from forearm fat was compared with total body FFA release. Forearm and body fat mass were quantified to allow comparisons relative to fat content. In addition, three groups of women with different adipose tissue lipolytic rates were included in order to directly compare upper-body extremity adipose tissue FFA release. The results confirm that heterogeneity of adipose tissue lipolysis does occur in vivo.

Methods

Subjects. Informed, written consent was obtained from 14 healthy, moderately obese (body mass index 30–36 kg/m^2) premenopausal women and eight nonobese premenopausal women. The obese women were selected such that six had waist/hip ratios < 0.76 and eight had waist/hip ratios > 0.85 (14). The waist circumference was measured at the natural (smallest) waist with the subject in the supine position, and the hip measurement was made at the maximum circumference with the subject standing with their feet together. All women had maintained a stable weight for > 2 mo before the study and were instructed to consume > 200 g of carbohydrate daily for at least 2 wk before the study. To determine whether upper body extremity (forearm) adipose tissue lipolysis differs between obese individuals with different systemic lipolytic rates upper-body obese and lower-body obese women were intentionally selected to have different palmitate flux values. One of the obese women participated in a previous study (3) and others were recruited during participation in ongoing studies of body fat distribution. A summary of the subjects' clinical characteristics, serum lipids, and body composition is given in Table I.

Materials. [1-^{14}C]palmitate (Research Products International Corporation, Mount Prospect, IL) was prepared for intravenous infusion as a 0.3% albumin in 0.9% NaCl solution as previously described (15). Human regular insulin (Eli Lilly & Co., Indianapolis, IN), recombinant DNA human growth hormone (Genentech Inc., South San Francisco, CA), and somatostatin (Bachem Inc., Torrence, CA) were used in these studies.

Methods. Plasma palmitate concentration and specific activity (SA)[1] were determined by high-performance liquid chromatography (16) using [$^2H_{31}$]palmitate as an internal standard (17). Plasma insulin (18), glucagon (19), and growth hormone (20) were determined by radioimmunoassay. Plasma glucose concentrations were determined by glucose analyzer (Yellow Springs Instrument Co., Yellow Springs, OH).

Forearm blood flow was measured with venous occlusion plethysmography (21, 22) with a capacitance plethysmograph (Utterly Fantas-

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1. *Abbreviations used in this paper:* DPX, dual-energy x-ray absorptiometry; LBM, lean body mass; SA, specific activity.

tic Instruments, Monterey, CA). Forearm plasma flow was calculated by multiplying forearm blood flow by (1 − hematocrit/100).

Body composition was determined by body potassium counting and tritiated water space (23) in addition to dual-energy x-ray absorptiometry (DPX, Lunar Radiation Corp., Madison, WI) (24). DPX uses the same principles as dual-photon absorptiometry (25) to estimate bone mineral calcium and the percentage of fat and lean body mass, (LBM), in nonbone tissue. The entire subject and the forearm to be studied were scanned separately. Forearm volume was determined by water displacement, and the forearm bone volume (calculated from grams of bone mineral calcium) (26) was subtracted to estimate forearm nonbone tissue. The fat content was calculated by multiplying the volume of forearm nonbone tissue (grams) by the fractional fat content obtained from the DPX. Each forearm scan was done twice: once with the palm flat on the scanning table and once with the hand perpendicular to the table. Mean values from both scans were used for the calculations. Calibration of the DPX was confirmed every 1–2 wk with a series of four phantoms composed of a range (4–61% fat) of known quantities of fat and lean (25) (kindly provided by the research and development section of the George A. Hormel Company, Austin, MN).

Protocol. Each subject was admitted to the Mayo Clinic General Clinical Research Center the evening before the first study and given a standard evening meal. The following morning, after an overnight fast, an 18-gauge infusion catheter was placed in a forearm vein and kept patent by controlled infusion of 0.9% NaCl (20 ml/h). In the same arm a radial artery catheter was placed for blood sampling purposes. Mixed venous forearm blood from the contralateral arm was sampled via an 18-gauge catheter placed antegrade in an antecubital vein such that the tip was 1–2-cm proximal to the antecubital crease. This position was chosen on the basis of a preliminary study which confirmed that the PO_2 of the blood at this site is above that known to predict preferential blood flow to muscle. A 0.9% solution of NaCl was infused between blood samples to maintain catheter patency.

At 0730 hours (0 min) a continuous infusion of [1-^{14}C]palmitate (~ 0.2 μCi/min) was begun and continued until 1300 hours (330 min). At 90 min a primed, continuous infusion of insulin was begun (0.15 mU · kg LBM^{-1} · min^{-1} in nonobese and 0.25 mU · kg LBM^{-1} · min^{-1} in obese subjects) and was continued until 210 min. These insulin infusion rates were chosen to achieve partial suppression of FFA flux in each subject. Infusions of somatostatin (0.14 μg · kg LBM^{-1} · min^{-1}) and growth hormone (5 ng · kgLBM^{-1} · min^{-1}) were then administered from 210 to 330 min. From 90 to 330 min, 50% dextrose was infused as needed to maintain each subject's plasma glucose concentration at the values observed from min 0 to 90. The study intervals 0–90 min, 90–210 min, and 210–330 min are subsequently referred to as baseline, hyperinsulinemia, and hypoinsulinemia, respectively. Owing to technical problems the hypoinsulinemic study interval was not completed in two upper body obese women.

Blood was sampled before starting the isotope infusions and assayed for plasma palmitate SA to serve as background. Arterial and forearm venous blood samples were obtained simultaneously at 10-min intervals from 60 to 90, 180 to 210, and 300 to 330 min and analyzed for plasma palmitate concentration and SA. Arterial blood was assayed for plasma insulin, glucagon, and growth hormone concentrations at these same time points. Plasma glucose concentrations were measured at 10-min intervals from min 60 to 330 to assist in determining the amount of dextrose to be infused in order to maintain euglycemia. Forearm blood flow was measured without occluding the circulation to the hand on four occasions over the final 30 min of the baseline, hyperinsulinemic, and hypoinsulinemic study intervals.

Calculations. Arterial plasma palmitate concentration and SA were relatively constant over the final 30 min of each study interval in each group (Figs. 1–3); therefore, systemic palmitate release was calculated using steady-state equations. Likewise, forearm plasma flow and venous palmitate concentration and SA were relatively constant (Figs. 1–3) during the final 30 min of each study interval. Mean values were used to calculate forearm balance data.

Uptake of palmitate by the forearm was calculated as follows:

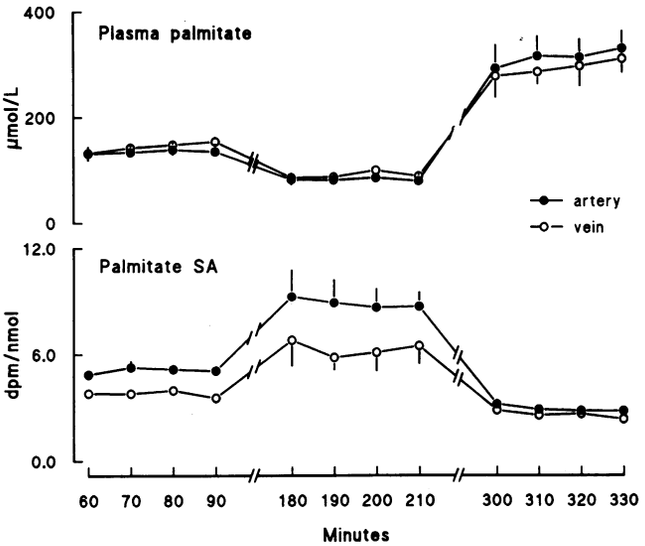

Figure 1. Arterial and mixed forearm venous palmitate concentrations and specific activities (SA) in nonobese subjects during the baseline (60–90 min), hyperinsulinemic (180–210 min), and hypoinsulinemic (300–330 min) study intervals. L, liter.

Palmitate uptake = (arterial palmitate concentrations

× forearm plasma flow)

$$\times \left(1 - \frac{\text{venous } [^{14}\text{C}]\text{palmitate concentration (dpm/ml)}}{\text{arterial } [^{14}\text{C}]\text{palmitate concentration (dpm/ml)}}\right).$$

Forearm palmitate release was calculated as:

Release = [forearm plasma flow

× (venous plasma palmitate concentration

− arterial plasma palmitate concentration)] + palmitate uptake.

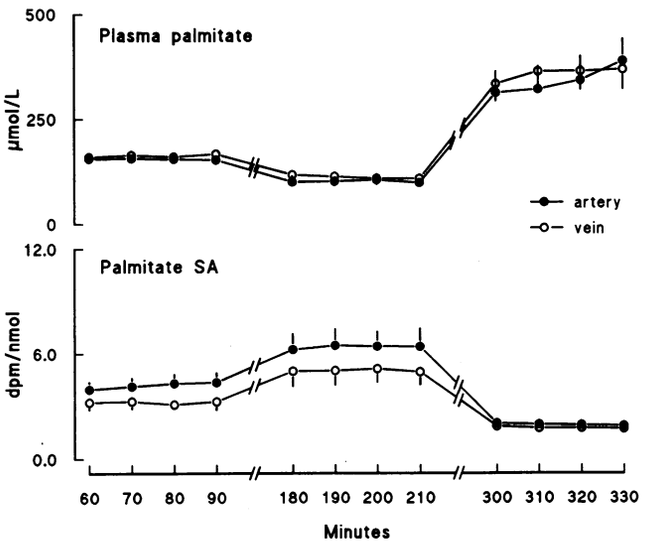

Figure 2. Arterial and mixed forearm venous palmitate concentrations and specific activities (SA) in upper body obese subjects during the baseline (60–90 min), hyperinsulinemic (180–210 min), and hypoinsulinemic (300–330 min) study intervals. L, liter.

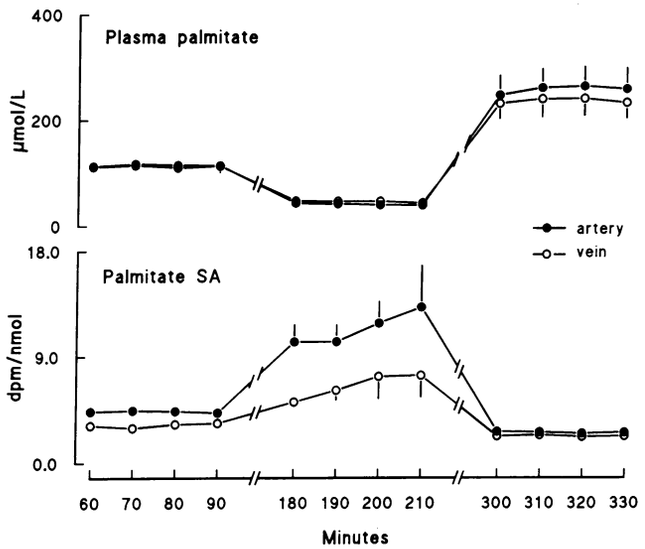

Figure 3. Arterial and mixed forearm venous palmitate concentrations and specific activities (SA) in lower body obese subjects during the baseline (60–90 min), hyperinsulinemic (180–210 min), and hypoinsulinemic (300–330 min) study intervals. L, liter.

All results are expressed as mean±SEM. Statistical comparisons between the same study periods among groups were performed using analysis of variance and subsequent nonpaired *t* test. Comparisons between one study interval and another within the same group were made using a two-tailed paired Student's *t* test.

Results

Subject characteristics (Tables I and II). The mean ages and serum cholesterol concentrations of the women in the different groups were not statistically different. Fasting plasma glucose concentrations were similar in nonobese, upper-body obese, and lower-body obese women (5.3±0.2 vs. 5.7±0.1 vs. 5.6±0.2 mmol/liter, respectively, P = NS). Women with upper-body and lower-body obesity did not differ with respect to their degree of overweight, total lean body mass, total body fat, or forearm fat content.

Table I. Subject Characteristics

	Age	Body mass index	Waist–hip ratio	Serum triglycerides
	yr	*kg/m²*		*mg/dl*
UBOb (n = 8)	40±2	33.2±0.6	0.93±0.02‡	171±41*
LBOb (n = 6)	37±2	31.8±0.6	0.74±0.01	64±14
NonOb (n = 8)	37±2	21.9±0.6	0.77±0.01	54±4
	Serum cholesterol	Lean body mass	Fat mass	Forearm fat content
	mg/dl	*kg*		*g*
UBOb (n = 8)	211±15	49.4±1.3	43.2±2.1	328±40
LBOb (n = 6)	170±8	48.8±1.2	41.4±2.4	348±45
NonOb (n = 8)	170±8	41.9±1.5*	16.7±1.6*	187±42*

Abbreviations: UBOb, upper body obese women; LBOb, lower body obese women; NonOb, nonobese women. Because waist to hip circumference ratios were not random variables between groups of obese subjects, these values are not analyzed UBOb vs. LBOb. * $P < 0.001$ cf. other groups. ‡ $P < 0.001$ cf. NonOb.

Table II. Plasma Hormone Concentrations

	Insulin		
	Baseline	Hyperinsulinemia	Hypoinsulinemia
		pM	
UBOb (n = 8)	120±29*	157±40‡	23±5‡
LBOb (n = 6)	72±13	128±20‡	22±2‡
NonOb (n = 8)	45±7	70±8*‡	21±2‡
	Glucagon		
		pg/ml	
UBOb	163±12	145±10	120±10‡
LBOb	147±12	132±12	108±6‡
NonOb	160±11	145±10	120±6‡
	Growth hormone		
		ng/ml	
UBOb	1.5±0.3	1.1±0.2	1.2±0.2
LBOb	1.7±0.4	1.0±0.4	1.2±0.2
NonOb	7.6±1.4*	4.7±1.8	2.0±0.2*‡

Abbreviations are as in Table I. Values from UBOb subjects during hypoinsulinemia are from six subjects (see text).
* $P < 0.05$ cf. other groups.
‡ $P < 0.05$ cf. baseline.

The serum triglyceride concentrations were greater in upper body obese women ($P < 0.001$) than lower-body obese or nonobese women, whose concentrations were not different from each other. Nonobese women had less body fat ($P < 0.001$) and fat-free mass ($P < 0.01$) than either group of obese women. Forearm fat content was less ($P < 0.001$) in nonobese women than lower-body obese or upper-body obese women. The baseline plasma insulin concentrations were greater in upper body obese women ($P < 0.001$) than nonobese or lower-body obese women, whereas plasma growth hormone concentrations were greatest in nonobese women ($P < 0.05$). Baseline plasma glucagon concentrations were not statistically different.

Plasma hormone concentrations. During the insulin infusion, plasma insulin concentrations increased in each group of subjects (Table II) with no significant changes in plasma glucagon or growth hormone concentrations. During the somatostatin infusion plasma insulin concentrations decreased to comparable values in each group of subjects. Because glucagon was not infused (27) during the somatostatin infusion, plasma glucagon concentrations decreased in all three groups ($P < 0.05$). Plasma growth hormone concentrations were greater in nonobese women than either group of obese women.

Systemic palmitate kinetics. Upper-body obese women were intentionally selected to have greater palmitate release relative to lean body mass (Table III) compared with the other two groups. Likewise, total palmitate flux and plasma concentrations were slightly increased in this group. During the hyperinsulinemic study interval palmitate flux decreased ($P < 0.05$) in each group, but remained highest in upper-body obese

Table III. Palmitate Kinetics

	Systemic palmitate kinetics								
	Baseline			Hyperinsulinemia			Hypoinsulinemia		
	Concentration	Total flux	Flux/LBM	Concentration	Total flux	Flux/LBM	Concentration	Total flux	Flux/LBM
	μM	$\mu mol/min$	$\mu mol \cdot kg\ LBM^{-1} \cdot min^{-1}$	μM	$\mu mol/min$	$\mu mol \cdot kg\ LBM^{-1} \cdot min^{-1}$	μM	$\mu mol/min$	$\mu mol \cdot kg\ LBM^{-1} \cdot min^{-1}$
UBOb ($n = 8$)	155±9	139±8	2.8±0.2	103±13‡	97±10*‡	2.0±0.2*‡	334±57‡	258±32*‡	5.0±0.5‡
LBOb ($n = 6$)	115±9	102±5	2.1±0.2	42±10‡	44±8‡	0.9±0.2‡	259±38‡	184±24‡	3.8±0.5‡
NonOb ($n = 8$)	133±14	86±3	2.1±0.2	81±12‡	53±5‡	1.3±0.1‡	314±36‡	159±15‡	3.8±0.3‡

	Forearm kinetics					
	Baseline		Hyperinsulinemia		Hypoinsulinemia	
	Release	Uptake	Release	Uptake	Release	Uptake
	$\mu mol/min$					
UBOb	1.58±0.30	1.23±0.25	1.04±0.27‡	0.68±0.21‡	1.12±0.54	1.50±0.52
LBOb	1.45±0.26	1.57±0.28	0.92±0.36	0.66±0.27‡	1.06±0.20	2.06±0.57
NonOb	1.23±0.28	0.93±0.11	0.82±0.12	0.56±0.09‡	0.68±0.11‡	1.06±0.23

Abbreviations are as in Table I. Because baseline palmitate flux values (per kilogram LBM) between groups were not random variables (see text), baseline systemic palmitate kinetics between groups were not analyzed. Values from UBOb subjects during hypoinsulinemia are from six subjects (see text). * $P < 0.05$ cf. other groups. ‡ $P < 0.05$ cf. baseline.

women. The hypoinsulinemia created by somatostatin infusion resulted in an 80–86% increase ($P < 0.001$) in palmitate flux in each group. Although total palmitate flux during hypoinsulinemia was greater ($P = 0.02$) in upper-body obese women than lower-body obese or nonobese women, when corrected for lean body mass these differences were no longer statistically significant ($P = 0.06$ vs. nonobese, $P = 0.12$ vs. lower-body obese).

Forearm palmitate kinetics. Total forearm plasma flow during the baseline study interval was similar in upper-body obese, lower-body obese, and nonobese women (41±5 vs. 48±5 vs. 36±5 ml/min, respectively, P = NS). Forearm plasma flow remained relatively constant in these three study groups during the hyperinsulinemic (41±4, 43±7, and 36±5 ml/min, respectively) and the hypoinsulinemic (35±4, 41±5, and 27±5 ml/min, respectively) study intervals.

Forearm palmitate uptake was not significantly different between the three study groups during the baseline, hyperinsulinemic, or hypoinsulinemic study intervals (Table III). Hyperinsulinemia decreased plasma palmitate concentrations and forearm palmitate uptake similarly in each group. Although plasma palmitate concentrations increased dramatically during the hypoinsulinemic study interval, palmitate uptake by forearm did not increase significantly.

Total forearm palmitate release during the baseline interval was not significantly different between the three groups and represented ~ 1.3% of systemic palmitate release. When corrected for the forearm and whole body fat content, baseline release (all subjects, $n = 22$) was greater ($P < 0.005$) from forearm fat than from total body fat (5.79±0.75 vs. 3.84±0.34 $\mu mol \cdot kg\ fat^{-1} \cdot min^{-1}$, respectively). Similar trends were seen in each group (Table IV). Forearm adipose tissue palmitate release, when expressed per unit fat mass, was greater in nonobese women than lower-body obese ($P < 0.05$) or upper body obese women ($0.10 > P > 0.05$). Because of the selection criteria for obese subjects systemic palmitate release per kilogram of fat mass was greater ($P < 0.01$) in upper-body obese women than lower-body obese women by ~ 28%. Although not statistically different, palmitate release per kilogram of forearm fat was also 27% greater in upper-body obese women than lower-body obese women.

Hyperinsulinemia reduced systemic palmitate release by 40%, 56%, and 28% in nonobese, lower-body obese, and upper-body obese women, respectively, with comparable decrements in forearm palmitate release (34%, 39%, and 33%, respectively) (Table III). When the data from all 22 subjects was analyzed, forearm adipose tissue palmitate release during hyperinsulinemia remained greater than total body adipose tissue palmitate release (3.90±0.58 vs. 2.33±0.25 $\mu mol \cdot kg\ fat^{-1} \cdot min^{-1}$, $P < 0.005$).

In contrast, hypoinsulinemia changed forearm and systemic palmitate release in opposite directions. Systemic palmitate flux was greater during hypoinsulinemia than during the baseline (Tables III and IV), while forearm palmitate release was less (0.93±0.17 vs. 1.34±0.16 $\mu mol \cdot min^{-1}$, $P < 0.05$, $n = 20$ subjects). This decrease in forearm palmitate release was not equally apparent in each group, however, with a statistically significant ($P < 0.05$) reduction in nonobese women, but not in lower-body obese ($P = 0.14$), or in upper-body obese ($P = 0.92$) women.

Table IV. Adipose Tissue Lipolysis

	Palmitate release					
	Baseline		Hyperinsulinemia		Hypoinsulinemia	
	Total fat	Forearm fat	Total fat	Forearm fat	Total fat	Forearm fat
	$\mu mol \cdot kg\,fat^{-1} \cdot min^{-1}$					
UBOb (n = 8)	3.2±0.2‖	5.2±0.9‡	2.3±0.2‖	3.5±1.0	6.2±0.9§	4.5±2.1
LBOb (n = 6)	2.5±0.2‖	4.1±0.6*§	1.1±0.2‖	2.5±0.8‡§	4.4±0.4§	2.9±0.5
NonOb (n = 8)	5.5±0.5‖	8.2±1.4‡	3.3±0.4‖	5.4±0.9*	10.0±1.2	5.1±1.4*

Abbreviations are as in Table I. Because forearm release of palmitate was compared between study intervals in Table III, these values are not reanalyzed here. Values from UBOb subjects during hypoinsulinemia are from six subjects (see text). * $P < 0.05$ cf. total fat palmitate release same study interval. ‡ $0.10 > P > 0.05$ cf. total fat palmitate release same study interval. § $P < 0.05$ cf. nonobese same study interval. ‖ $P < 0.05$ cf. other groups same study interval.

Discussion

These study results provide strong evidence that regional variations in human adipose tissue lipolysis occur in vivo, supporting and extending the observations of Arner et al. (28). Relative to the quantity of adipose tissue, forearm fat released greater amounts of FFA than body fat as a whole, suggesting either inherent differences in arm fat cells (8), or the forearm hormonal milieu. Forearm palmitate release was measured in three groups of women selected to have different whole-body adipose tissue lipolytic rates. In each group forearm adipose tissue palmitate release more closely approximated their systemic palmitate flux than it did a generic forearm lipolytic rate common to the three groups. Mild hyperinsulinemia suppressed forearm and systemic lipolysis to similar degrees, suggesting that forearm adipose tissue retains the insulin responsiveness of upper-body fat (11). Despite this, somatostatin-induced hypoinsulinemia did not increase forearm FFA release as it did from nonforearm adipose tissue depots. Thus, hypoinsulinemia permits accelerated lipolysis in a heterogeneous manner in vivo.

The conclusion that forearm adipose tissue is more lipolytically active than total body adipose tissue is dependent upon the measurement accuracy of plasma palmitate concentration and SA, forearm blood flow, and adipose tissue mass. The accuracy and precision of the palmitate concentration and specific activity assay is known to be excellent (16, 17). In this study capacitance plethysmography provided forearm blood flow and FFA release values similar to those observed in previous reports in which blood flow was measured using dye dilution techniques (29, 30). A DPX (24) was used to measure forearm fat content. This technique employs the same principles as dual-photon absorptiometry, a method that provides excellent results when compared with other, independent measures of body fat in humans (25). If forearm fat content in these subjects was systematically underestimated by ~ 50%, forearm adipose tissue lipolysis would equal total body adipose tissue lipolysis. This magnitude of error is inconsistent with results observed by us and others (24, 25) for this technique. In addition, the percentage of forearm fat found in the present study (~ 18% in nonobese women and ~ 25% in obese women) is actually greater than the usually quoted figure (26). Thus, the conclusion that forearm adipose tissue is more lipolytically active than total body adipose tissue on a weight basis appears sound.

The present study, while confirming that forearm adipose tissue exhibits lipolytic differences compared with nonforearm adipose tissue, cannot distinguish whether this results from its peripheral versus central or upper body versus lower body characteristics. The latter hypothesis is supported by the finding of catecholamine responses from arm adipocytes in vitro (8), and the finding of insulin responsiveness in the forearm adipose tissue in the present study, a characteristic of upper-body fat cells (11). In addition, studies from our laboratory have demonstrated lipolytic differences in lower-body (leg) and upper-body fat (31). Basal upper-body palmitate release in these unselected upper-body obese, lower-body obese, and nonobese women in that study is similar to basal forearm palmitate release observed in the comparable groups in the present study (M. L. Martin and M. D. Jensen, unpublished data). Thus, forearm adipose tissue may be a model for the study of upper body adipose tissue in vivo, however, further studies will be needed to more directly test this hypothesis.

Nonobese, upper-body obese, and lower-body obese women with markedly different lipolytic rates per unit fat mass were intentionally selected for these experiments. This study design permits the comparison of upper-body extremity adipose tissue lipolysis among the different groups in relationship to total body adipose tissue lipolytic rates. If there was no intrinsic difference in upper-body extremity adipocytes between individuals, forearm adipose tissue palmitate release (per unit fat mass) should be similar in each group. Instead, forearm adipose tissue lipolysis was greatest in nonobese women, least in lower-body obese women, and intermediate in upper-body obese women, a pattern identical to that observed for total body fat. If forearm fat is representative of upper body fat, these results suggest that factors in addition to the quantity of upper body fat are important in determining systemic lipolysis.

In contrast with the findings of the present study, basal lipolysis from upper-body adipocytes in vitro has been found to be less than or equal to that in lower-body adipocytes (7–10). Differences in endogenous catecholamine (8–10) effects on lipolysis between upper and lower body fat cells may account for the greater FFA release from forearm adipose tissue compared with total body adipose tissue. The β-adrenergic stimulatory effects of physiologic catecholamines predominate in upper body adipocytes (9), while the α_2-adrenergic inhibitory effects are equally important in lower body adipocytes (9, 10). Recent in situ studies of the adrenergic regulation of abdominal and

gluteal adipose tissue lipolysis confirm the presence of regional differences in vivo (28). Resting adrenergic tone might account for the differences seen in the present study by selectively increasing FFA release from upper body extremity fat. These results underscore the difficulty in extrapolating in vitro results to the in vivo situation unless careful consideration of the local environment is taken into consideration.

Hyperinsulinemia suppressed lipolysis in forearm and total-body adipose tissue similarly, but hypoinsulinemia did not permit the expected increase in forearm lipolysis as it did systemic lipolysis. Although the etiology of this discrepancy is not known, failure to increase forearm blood flow may have contributed to this effect. Increased FFA concentrations can inhibit lipolysis (32), and either increased FFA delivery or decreased removal of locally produced FFA may have inhibited forearm lipolysis. Whether the modest blood flow reductions observed were caused by local vasoconstriction secondary to high FFA/albumin ratios (33), a direct effect of the somatostatin, or hypoinsulinemia itself is unknown. Failure to increase forearm blood flow also might theoretically result in an apparent decrease in FFA release because of preferential adipocyte reesterification of unlabeled FFA present in the periadipocyte extracellular fluid. Why this would affect forearm adipose tissue more so than other depots is not known. Clearly, in vivo hormonal changes may not affect all fat cells in the expected manner because of the complex changes in their environment.

It is important to note that although FFA flux is generally related to lean body mass (3, 34), the tissues known to consume FFA as a metabolic fuel, this report has extensively expressed palmitate release per unit fat mass. This was done in order to allow the comparison of adipose tissue lipolysis from different body fat stores within the same individual and to compare these relationships between groups of subjects with different lipolytic rates. When reporting systemic FFA kinetic data in studies of obesity from a perspective of fuel metabolism it would still appear best to express FFA availability relative to lean body mass.

It is not possible to directly compare the effects of insulin on systemic lipolysis between the three groups of subjects in this study because of the different plasma insulin concentrations obtained during the hyperinsulinemic study interval. Somatostatin infusion, however, resulted in similar plasma insulin concentrations and similar proportional increases in palmitate flux in each group. During hypoinsulinemia palmitate flux remained greater in upper-body obese women than the other two groups, perhaps related to the greater baseline palmitate flux. Thus, insulin withdrawal resulted in similar increments in lipolysis independent of adipose tissue stores, with lower-body obese and nonobese women continuing to remain similar, and upper-body obese women maintaining a greater total palmitate release. If basal insulin availability is the only factor restraining lipolysis, FFA flux might increase in proportion to adipose tissue stores during insulin withdrawal. Local inhibition of lipolysis by adenosine (35) or FFA themselves (32) may restrain lipolysis during hypoinsulinemia and prevent excessive FFA release even when fat mass is increased by two- to threefold.

In summary, these studies have demonstrated for the first time differences in adipose tissue lipolytic rates in different tissue beds in vivo. The findings are consistent with in vitro data if the variable of adrenergic effects on upper and lower body fat cells (8–10) are taken into account. Forearm adipose tissue palmitate release varied in proportion to systemic adipose tissue palmitate release. Although forearm adipose tissue responds to hyperinsulinemia in much the same manner as total-body adipose tissue, hypoinsulinemia, when created by somatostatin infusion, does not permit increased mobilization of forearm adipose tissue fatty acids. These results support the concept of inherent regional differences in human adipocytes and suggest the need to consider that different adipose tissue beds may contribute to abnormal regulation of lipolysis in certain disease states.

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