Blunted lipolytic response to fasting in abdominally obese women: evidence for involvement of hyposomatotropism[1,2]

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ABSTRACT

Background: Abdominal obesity is associated with a blunted lipolytic response to fasting that may contribute to the preservation of adipose tissue mass.

Objective: To further explore the pathophysiology of blunted lipolysis during fasting in obesity, we simultaneously measured lipolysis and distinct neuroendocrine regulatory hormones in abdominally obese and normal-weight (NW) women.

Design: Eight abdominally obese [$\bar{x}\pm$ SD body mass index (BMI; in kg/m^2): 32.1 ± 2.6] and 6 NW (BMI: 22.7 ± 1.5) women were studied during the last 8 h of a 20-h fast. The glycerol appearance rate and the serum and plasma concentrations of insulin, leptin, cortisol, and growth hormone were measured regularly.

Results: At 13 h of fasting, the mean (±SD) glycerol appearance rate corrected for fat mass was greater in NW women than in obese women (7.2 ± 1.0 and 5.1 ± 0.6 $\mu mol \cdot kg^{-1} \cdot min^{-1}$, respectively; $P = 0.001$). After a 20-h fast, lipolysis increased to 8.9 ± 1.5 $mmol \cdot kg^{-1} \cdot min^{-1}$ in NW women (23%), whereas it did not change significantly in obese women (−2%). Fasting decreased insulin concentrations by ≈ 30% in both groups, but it did not induce significant changes in leptin concentrations. Mean cortisol concentrations and urinary catecholamine excretion were comparable in both groups. However, mean plasma growth hormone concentrations were higher in NW women than in obese women (1.81 ± 0.98 compared with 0.74 ± 0.52 mU/L; $P = 0.046$). The relative change in lipolysis tended to correlate with mean plasma growth hormone concentrations ($r = 0.515$, $P = 0.059$).

Conclusion: Abdominal obesity-associated hyposomatotropism may be involved in the blunted increase in lipolysis during fasting. *Am J Clin Nutr* 2003;77:544–50.

KEY WORDS Lipid metabolism, somatotropin, starvation, lipolysis rate, obesity, women

INTRODUCTION

Glycogen stores are depleted rapidly during energy deprivation, rendering adipose tissue the most important source of energy. The products of lipolysis, fatty acids and glycerol, are of primary importance as energy substrate and gluconeogenic precursor, respectively.

Both basal lipolysis and fasting-induced lipolysis are different in normal-weight (NW) and abdominally obese humans. Specifically, basal lipolysis per kilogram of fat mass is lower, whereas the rate of whole-body lipolysis is higher in obese humans. Lipolysis clearly increases during energy restriction in NW subjects, whereas the increase appears to be blunted in abdominal obesity (1, 2). The mechanism responsible for this metabolic difference among abdominally obese and NW humans has not yet been fully elucidated. It appears important to unravel the pathophysiology of this phenomenon, because blunted lipolysis during fasting may contribute to the preservation of fat mass.

Several hormones are involved in the complex neuroendocrine control of the metabolic adaptation to fasting. Insulin strongly stimulates fat storage by inhibiting hormone-sensitive lipase (HSL; EC 3.1.1.3) and by stimulating lipoprotein lipase (EC 3.1.1.34). Plasma insulin concentrations decline in response to energy restriction (3), which allows lipolysis to occur virtually without any time delay (4, 5). Catecholamines powerfully promote HSL activity while inhibiting that of lipoprotein lipase (6). Although plasma concentrations of norepinephrine and epinephrine will increase only slightly during a short-term fast in humans, catecholamine-mediated lipolysis is enhanced through an increase in adipose tissue β-adrenoceptor sensitivity (1, 7).

Insulin and catecholamines seem to be of primary importance for the regulation of lipolysis, but other hormones [eg, cortisol and growth hormone (GH)] are known to modulate the lipolytic process. Cortisol inhibits HSL-mediated lipolysis and promotes lipoprotein lipase activity, thereby promoting fat accumulation (8). In contrast, GH stimulates adipose tissue lipolysis by enhancing the lipolytic response to epinephrine (9, 10) or by directly increasing HSL activity in adipocytes (11). Cortisol and GH act on the lipolytic process with a delay of several hours (8), and both hormones have been shown to play a significant role in the physiologic regulation of lipolysis in humans (12, 13). Circulating GH concentrations are profoundly reduced in abdominally obese humans (14), which potentially implicates GH in the pathophysi-

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ology of the blunted lipolytic response to fasting in these persons. Moreover, leptin is involved in the metabolic and behavioral response to fasting in rodents (15). Plasma leptin concentrations decline rather quickly during a short-term fast, which potentially counteracts the lipolytic action of the earlier mentioned hormones via direct and indirect mechanisms (15, 16).

One of the difficulties in integrating all these factors is that the data are derived from multiple studies. We therefore simultaneously measured lipolysis and variables of the above neuroendocrine control system during the last 8 h of a 20-h fast in abdominally obese and NW women. We reasoned that any apparent difference in hormonal adaptation to energy restriction between obese and NW subjects may contribute to aberrant lipolysis in obese persons.

SUBJECTS AND METHODS

Subjects

Sixteen postmenopausal (follicle-stimulating hormone concentrations > 20 U/L) women—8 NW [body mass index (BMI; in kg/m^2) < 25 and fat mass < 35%] and 8 abdominally obese (BMI > 29 and fat mass > 40%)—participated in the study. The subjects were healthy, were not smokers, and were not taking any medication (including hormonal replacement therapy). They all had plasma cholesterol concentrations < 6.5 mmol/L, fasting triacylglycerol concentrations < 4.0 mmol/L, and glycosylated hemoglobin (HbA_{Ic}) concentrations < 6.7%. The subjects were weight-stable for ≥ 3 mo and did not exercise for > 3 h/wk. During the 3 d immediately before the study, the participants consumed a weight-maintaining diet containing ≥ 250 g carbohydrate. The study protocol was approved by the Medical Ethics Committee of Leiden University Medical Center. Subjects were recruited from the Center for Human Drug Research volunteer pool and by advertisements in the local media. Written informed consent was obtained from all participants.

Experimental design

The study was designed as an open observational study of 2 matched groups. After an overnight fast, the subjects were admitted to the Clinical Research Unit of the Center for Human Drug Research. They remained fasting in a semi-recumbent position until the end of the study period and were allowed only water. The subjects emptied the bladder just before the start of procedures. All urine produced during the study was collected for measurement of catecholamine and creatinine excretions.

A cannula was inserted into an antecubital vein for the infusion of isotope tracers. Another catheter, inserted in the dorsal vein of the hand of the other arm, was kept in a thermoregulated (60 °C) box and was used to sample arterialized venous blood (17). This catheter was kept patent by the infusion of 0.9% NaCl (30 mL/h). At 1000 h (after 12 h of fasting), a primed (1.6 μmol/kg), constant (0.11 $\mu mol \cdot kg^{-1} \cdot min^{-1}$), intravenous infusion of [1,1,2,3,3-$^2H_5$]glycerol (or D_5-glycerol; 98 atom percent excess; Cambridge Isotope Laboratories, Andover, MA) dissolved in saline 0.9% (18) was begun; it was continued for 8 h with the use of a calibrated pump (6000+; Sigma, St Louis). Before isotope infusion, an arterialized venous blood sample was obtained for the measurement of background isotope enrichment. During the 8-h glycerol infusion, arterialized blood samples were obtained every 20 min for the measurement of total glycerol, glycerol-specific activity, insulin, cortisol, leptin, glucose, and fatty acids and every 10 min for the measurement of GH. Indirect calorimetry using a ventilated hood (Oxycon Beta; Jaeger Toennies, Breda, Netherlands) was performed for 30 min at 11, 15, and 17 h of fasting to estimate substrate oxidation rates (19).

On another day, total body fat mass and total lean body mass (LBM) were assessed with the use of dual-energy X-ray absorptiometry (QDR 4500; Hologic Inc, Waltham, MA; 20). The scanner had a CV of 2.1% for body fat mass and of 1.0% for LBM.

Blood sampling and biochemical analyses

Blood for the measurement of total glycerol, glycerol-specific activity, GH, cortisol, and leptin was collected in 2.7-mL lithium-heparin tubes. Fatty acids were measured in blood collected in 1.2-mL EDTA tubes. Insulin and glucose were measured in 1.2 mL serum. All blood samples were collected into chilled tubes, and heparin and EDTA samples were kept on ice. All tubes were centrifuged within 30 min of sampling (2000 × *g* at 4 °C for 10 min). Plasma, serum, and urine samples were stored at −40 °C and transported on dry ice before assay. All samples from one subject were run in the same batch.

Serum glucose and urinary creatinine were measured at the Leiden University Medical Center Clinical Chemistry Laboratory, using a fully automated system (Hitachi 747; Hitachi, Tokyo) system. Serum insulin was assayed by a radioimmunoassay (Medgenix, Fleurus, Belgium) with a detection limit of 3 mU/L. The interassay CV was 3.8–8.0%. Plasma leptin was measured by a radioimmunoassay (Linco Research, St Charles, MO), with a detection limit of 0.5 μg/L, an intra-assay CV of 3.4–8.3%, and an interassay CV of 3.0–6.2%. Plasma cortisol was assayed by a radioimmunoassay (Sorin Biomedica, Milan, Italy) with a detection limit of 25 nmol/L. The intra- and interassay precision varied from 2% to 4%. Plasma GH was measured by time-resolved fluoroimmunoassay (Delfia; Wallac, Turku, Finland) specific for the 22-kDa GH, which was used as the standard (Genotropin; Pharmacia Corp, Peapack, NJ) as calibrated against the World Health Organization First International Reference Preparation, 80/505 (to convert mg/L to mU/L, multiply by 2.6). The limit of detection was 0.03 mU/L. The intra-assay CV varied from 1.6% to 8.4% and the interassay CV from 2.0% to 9.9%. Plasma fatty acids were measured with an enzymatic colorimetric assay kit (Boehringer, Mannheim, Germany). Plasma glycerol concentrations and stable isotope tracer enrichment were measured in a single analytic run with the use of gas chromatography–mass spectrometry (Hewlett-Packard, Palo Alto, CA) as described previously (21). Catecholamines in urine were measured by an HPLC method and then by electrochemical detection.

Calculations

Glycerol concentration and enrichment data were individually smoothed by spline fitting (22), and the rate of appearance (R_a) of glycerol, as a measure of lipolysis, was calculated by the use of both smoothed and raw data. Steele's equation for non-steady state conditions adjusted for stable isotopes was used to calculate these lipolysis rates (23, 24). The effective volume of distribution of glycerol was assumed to be equal to the extracellular fluid volume as measured by dual-energy X-ray absorptiometry (25). In the case of glycerol, it is not necessary to compensate for nonuniform mixing, and so the correction factor p of the non-steady state equation was assumed to be equal to 1 (26).

TABLE 1
Characteristics of subjects in the study[1]

	Normal-weight subjects (n = 6)	Obese subjects (n = 8)
Age (y)	54.7 ± 3.1	54.8 ± 4.5
Weight (kg)	64.7 ± 13.5	86.5 ± 8.6[2]
BMI (kg/m^2)	22.7 ± 1.5	32.1 ± 2.6[3]
Waist circumference (cm)	76.3 ± 5.8	101.6 ± 10.7[2]
Body fat		
(kg)	19.5 ± 4.2	36.2 ± 5.6[3]
(%)	29.4 ± 2.1	40.9 ± 3.1[3]
Lean body mass (kg)	44.5 ± 8.8	49.6 ± 3.6

[1] $\bar{x}$ ± SD.
[2,3] Significantly different from normal-weight women: [2] $P < 0.05$, [3] $P < 0.001$.

Time profiles of lipolytic variables (lipolysis, plasma glycerol, and fatty acid concentrations) and plasma glucose concentrations were compared between the NW and obese groups by the use of values characterizing the profiles at the first hour and at the last hour of the experiment. Plasma glycerol, fatty acid, and glucose concentration data were therefore characterized by calculating the average value from 1000 to 1100 and that from 1700 to 1800. Because plasma D_5-glycerol concentrations reached steady state after 1 h of continuous infusion, average lipolysis was calculated from 1100 to 1200 and from 1700 to 1800 with the use of both raw (R_a raw) and spline-fitted (R_a-fitted) glycerol enrichment data.

Plasma insulin and leptin concentrations were analyzed similarly to glycerol and fatty acids, because changes in these hormones will affect lipolysis immediately (27). In contrast, plasma GH and cortisol concentrations will affect lipolysis rate with a time delay by changing the sensitivity of the adipose tissue to other hormones. Therefore, these hormones were characterized by use of the average of concentrations over the full 8-h period. Moreover, as GH is secreted in a pulsatile pattern, it is not useful to compare the average of GH concentrations obtained over 2 periods of 1 h each.

Catecholamine exposure was calculated from collected urine as urinary catecholamines released/mmol creatinine to correct for differences in urine concentration. Thus, the results cannot show a possible trend in catecholamine excretion over time. However, previous studies have shown that the concentration of plasma norepinephrine and epinephrine during short-term fasting remains below the reported threshold for lipolysis (28). Changes in substrate oxidation rates expressed per kilogram of LBM from the first measurement (0900) to the last (1500) measurement were compared between the NW and obese groups.

Statistical analysis

Calculations were performed by using SPSS for Windows, version 10.0.7 (SPSS, Inc, Chicago). Between-group comparisons of basal variables were performed by using the unpaired 2-tailed Student's t test. Glycerol R_a, glycerol, fatty acids, insulin, leptin, and glucose were also analyzed after log transformation, and the results were back-transformed, yielding estimates of percentage increase. Finally, Pearson's correlation coefficient was computed to determine the relation between specific variables. $P < 0.05$ was considered significant. Data are presented as means (±SDs).

RESULTS

Subject characteristics

Two of the 8 NW subjects were excluded from analysis: 1 had severe migraine, which shortened the study by about 2 h, and 1 was nauseated and vomited several times during the experiment. This latter subject's plasma GH, cortisol, and catecholamine concentrations exceeded the means by >2 SDs. The characteristics of the 14 analyzed subjects (6 NW and 8 abdominally obese) are shown in **Table 1**.

Plasma substrate concentrations

Basal glycerol and fatty acid concentrations did not differ significantly in NW and abdominally obese subjects (**Table 2**). Short-term fasting increased plasma fatty acid concentrations from 350 ± 89 to 471 ± 103 μmol/L in the NW women and from 289 ± 87 to 384 ± 78 μmol/L in the abdominally obese women. Plasma glycerol concentrations increased in the NW subjects, but hardly changed in the obese subjects. However, the relative changes in both variables did not differ significantly between NW and obese women (Table 2). Basal serum glucose concentrations were significantly higher in the abdominally obese women than in the NW women (Table 2). Glucose concentrations were not affected by continued fasting in the NW women, but, in the obese women, they decreased from 5.6 to 4.9 mmol/L. Accordingly, the relative change in glucose concentration tended to be higher in the abdominally obese women than in the NW women (−12% and −6%, respectively, $P = 0.074$).

TABLE 2
Lipolysis and plasma hormone and substrate concentrations

	Normal-weight subjects (n = 6)		Obese subjects (n = 8)	
	12-h Fast	Percentage change[1]	12-h Fast	Percentage change[1]
		%		%
Insulin (mU/L)	7.3 ± 2.1[2]	−28	18.5 ± 8.1[3]	−33
Leptin (μg/L)	7.2 ± 1.3	−24	23.8 ± 5.1[3]	−7
Glycerol (μmol/L)	61 ± 7	25	72 ± 15	5
Fatty acids (μmol/L)	350 ± 89	35	289 ± 87	35
Glucose (mmol/L)	5.1 ± 0.3	−6	5.6 ± 0.4[3]	−12
Glycerol appearance rate (μmol·kg fat^{-1}·min^{-1})	7.2 ± 1.0	23	5.1 ± 0.6[3]	−2[3]

[1] Relative change from 12 to 20 h of fasting.
[2] $\bar{x}$ ± SD.
[3] Significantly different from normal-weight subjects, $P < 0.05$.

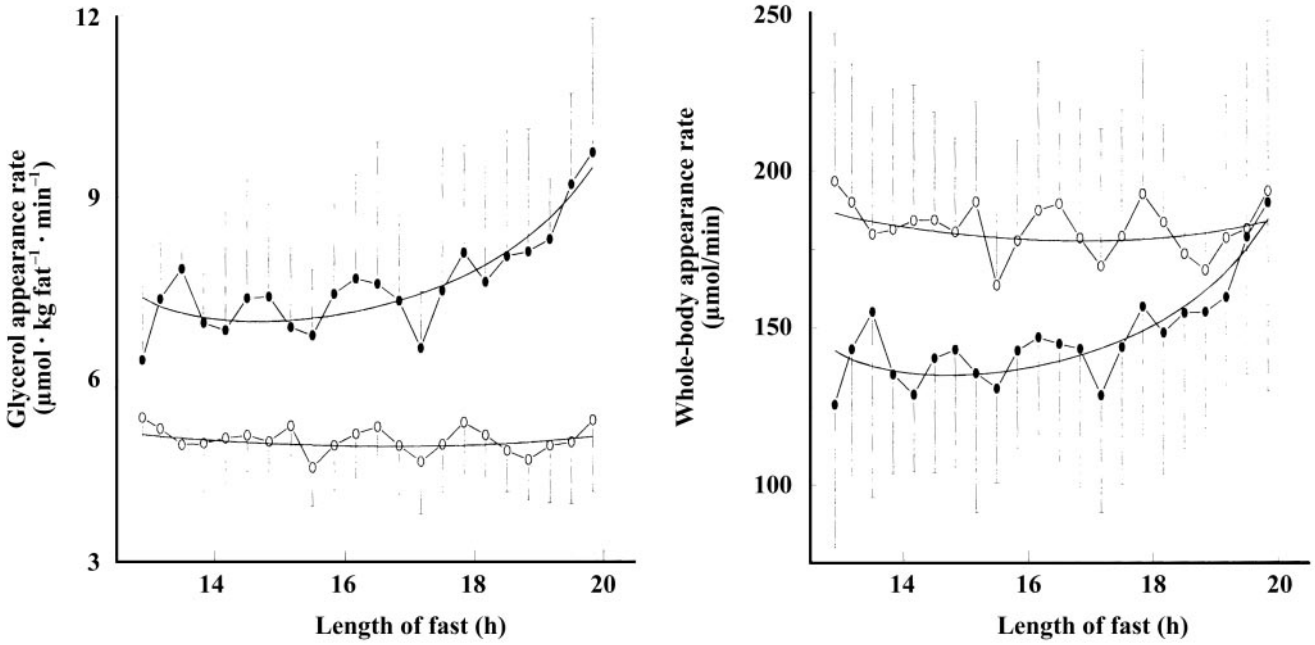

FIGURE 1. Mean (± SD) raw and fitted (—) glycerol appearance rates corrected for fat-mass profiles and whole-body glycerol appearance rates in 6 normal-weight (●) and 8 obese (○) subjects. Raw data were individually fitted before averaged values were calculated.

Glycerol kinetics

Time profiles for lipolysis are shown in **Figure 1**. Because visual inspection revealed a close association between calculated raw and fitted glycerol R_a, all calculations were done by using the fitted values. Basal lipolysis per kilogram of fat was higher in the NW women than in the abdominally obese women (Table 2). In contrast, the whole-body lipolysis rate was higher in the obese women than in the NW women (184 ± 40 and 139 ± 32 μmol/min, respectively, $P = 0.038$). Continued fasting increased lipolysis from 7.2 ± 1.0 to 8.9 ± 1.5 μmol · kg fat^{-1} · min^{-1} in the NW women, whereas it did not change in the abdominally obese women. Accordingly, the relative change of lipolysis was significantly higher in NW subjects than in obese subjects (Table 2).

Plasma hormone concentrations

Baseline serum insulin concentrations were significantly higher in the abdominally obese women than in the NW women (Table 2). During the short-term fast, serum insulin concentrations declined from 7.3 ± 2.1 to 5.3 ± 1.8 mU/L in the NW women and from 18.5 ± 8.1 to 12.4 ± 6.0 mU/L in the obese women. The relative changes were not different in NW and obese subjects (Table 2). At 20 h of fasting, insulin concentration was still twice as high in the obese women as in the NW women. Adrenaline, noradrenaline, and dopamine excretion in urine did not differ significantly between the NW women and the obese women (3.4 ± 2.3 and 3.7 ± 2.3, 17.4 ± 9.4 and 18.1 ± 5.2, and 128 ± 69 and 153 ± 26 nmol/mmol, respectively). Basal leptin concentrations were higher in the obese women than in the NW women (Table 2). Although the relative decline of leptin concentration during fasting tended to be greater in the NW women than in the obese women, the difference did not reach significance (Table 2). After the 20-h fast, plasma leptin concentrations were still 4 times as high in obese subjects as in lean subjects. Average plasma cortisol concentration did not differ significantly between NW and obese subjects (270 ± 114 and 287 ± 73 nmol/L, respectively; $P = 0.755$). In contrast, mean plasma GH concentration was significantly higher in the NW women than in the obese women (**Figure 2**). Illustrative pulsatile plasma GH concentration profiles for an NW subject and an abdominally obese subject are shown in **Figure 3**. The relative change in glycerol R_a tended to correlate with total exposure to plasma GH in the group as a whole ($r = 0.515$, $P = 0.059$). There was no correlation between the relative change in glycerol R_a and the (relative) change in any other hormone we measured.

Substrate oxidation rates

Basal lipid and carbohydrate oxidation rates per kilogram of LBM did not differ between groups. Lipid oxidation increased by 0.57 mg · kg^{-1} · min^{-1} in the NW women and by 0.43 mg · kg^{-1} · min^{-1}

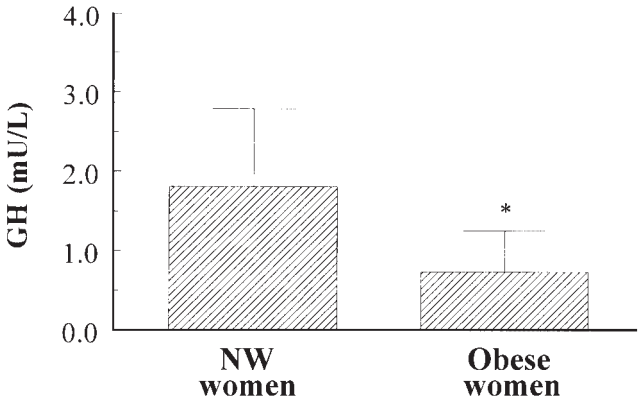

FIGURE 2. Mean (± SD) growth hormone (GH) concentrations between 12 and 20 h of fasting in 6 normal-weight (NW) and 8 obese women. *Significantly different from normal-weight women, $P < 0.05$.

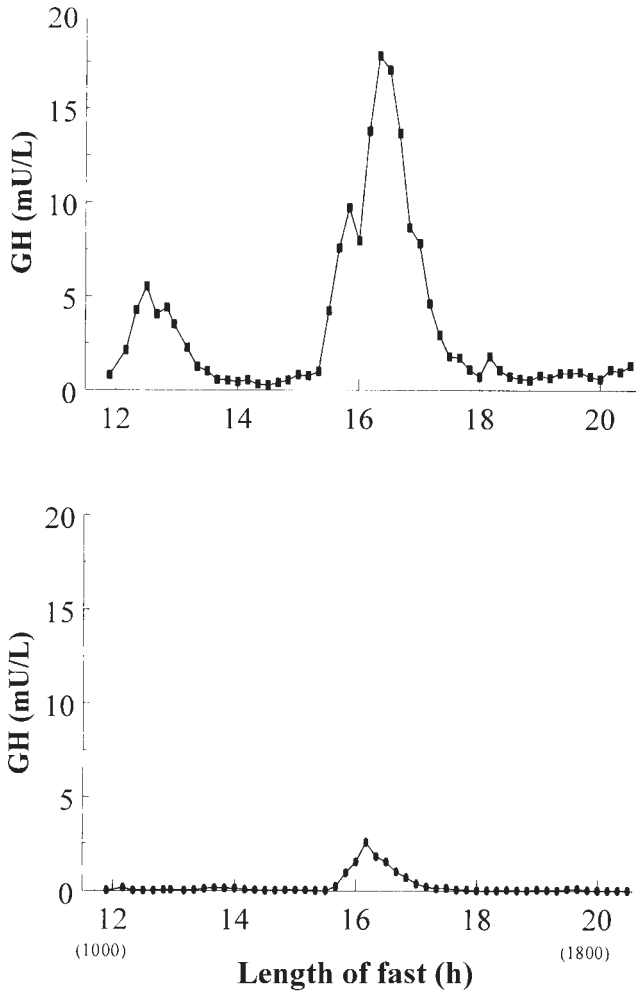

FIGURE 3. Illustrative profiles of pulsatile plasma growth hormone (GH) concentrations in a normal-weight (NW) subject (top) and an abdominally obese subject (bottom). The NW woman had a BMI of 22.1, a percentage body fat of 28.0%, and a waist circumference of 71.5 cm. The obese subject had a BMI of 33.4, a percentage body fat of 44.6%, and a waist circumference of 100.0 cm. The two subjects were of similar age (58 and 57 y, respectively).

in the abdominally obese women during prolonged fasting. Carbohydrate oxidation decreased by 1.28 $mg \cdot kg^{-1} \cdot min^{-1}$ in the NW women and by 0.92 $mg \cdot kg^{-1} \cdot min^{-1}$ in the obese women during the same period. There were no significant differences in the degree of change of lipid and carbohydrate oxidation between the groups.

DISCUSSION

Fasting induces a controlled chain of metabolic changes to meet the energy requirements of the body. For one, lipolysis is enhanced to provide fatty acid as a fuel and glycerol as a precursor for gluconeogenesis. The present study showed that basal lipolysis per kilogram of fat mass was significantly lower in abdominally obese women than in NW postmenopausal women. Moreover, lipolysis increased between 13 and 20 h of fasting in the NW women, but not in the obese women. Lipolysis is governed by a complex neuroendocrine control system with insulin and catecholamines as the major hormones. Their activity to affect the lipolytic process is modulated by several other hormones. All but one of the measured components of this complicated system behaved similarly during the fast in both groups. The only component that appeared to differ was GH: its plasma concentration was significantly lower in obese women than in NW women. Moreover, the relative change of lipolysis during the fast tended to correlate with average GH exposure in our subjects, but not with the relative change in any other regulatory hormone. We infer that the diminished GH availability is involved in the blunted lipolytic response to a short-term fast in abdominally obese persons.

GH affects lipolysis in various ways. It indirectly promotes the lipolytic response to epinephrine by increasing adipocyte β-adrenoceptor number and sensitivity (9, 10, 29). In addition, GH stimulates HSL activity in adipocytes directly (11). Adipocytes of obese humans and experimental animals are unequivocally characterized by a reduced β-adrenoceptor number and sensitivity (6, 30, 31). In accordance, the lipolytic response to epinephrine in vivo is suppressed in (abdominally) obese humans (30, 32). Plasma catecholamines per se do not reach the threshold concentrations that are necessary to stimulate lipolysis during a short-term fast in humans (28, 33). However, the reduction of insulin concentrations during fasting allows β-adrenoceptor–mediated lipolysis to occur. A reduced β-adrenoceptor number or sensitivity may then blunt the lipolytic response to energy restriction. In view of the effects of GH on adipocyte adrenoceptors, it is conceivable that hyposomatotropism contributes to the diminished β-adrenoceptor number or sensitivity in (abdominally) obese humans. The study of Yang et al (34), in which catecholamine-induced lipolysis was shown to be enhanced by GH restoration in hypophysectomized rats, corroborates this concept. Therefore, our data support the notion that obesity-associated hyposomatotropism contributes to diminished basal lipolysis per unit of fat mass and the blunted lipolytic response to short-term fasting in abdominally obese humans.

Our data are in accordance with previous reports showing reduced plasma GH concentrations in obesity (35, 36), particularly the abdominal type (14), and an attenuated increase in lipolysis during a short-term fast in upper-body obese subjects compared with the increase in NW subjects (2). However, these phenomena were never studied simultaneously within the same subjects, although the importance of GH in the regulation of lipolysis has been shown in humans (37). Other authors have offered a different explanation for the blunted lipolytic response in obesity. Horowitz et al (2) suggested that the distinct lipolytic responses of obese women and NW women during a short-term (22-h) fast related to a slight but significant difference in the decline of plasma insulin concentrations (20% and 32%, respectively). Their notion was supported by a significant correlation between the relative increase of glycerol R_a and relative decrease of plasma insulin. Our data do not confirm these findings. The relative decline in insulin concentrations during fasting was of the same order of magnitude in NW and obese women in our study (28% and 33%, respectively). Moreover, there was no correlation ($r = -0.072$) between the relative decline in serum insulin and the increase in glycerol R_a in our subjects. However, as discussed above, we do believe that the decrement of serum insulin concentrations is instrumental in the regulation of lipolysis during brief fasting in humans: it particularly allows β-adrenoceptor–mediated

lipolysis to occur. Because the relative decline in insulin was similar in obese subjects and in NW subjects in our study, the blunted fasting-induced lipolysis in obese persons is probably attributable to reduced adipocyte β-adrenoceptor number and sensitivity in these subjects. Alternatively, it is conceivable that the fact that absolute insulin concentrations remained elevated in obese women throughout the experiment prevented lipolysis from increasing in these subjects. Insulin's inhibiting effect on lipolysis is much more potent than that of any other hormone, and the height of the circulating insulin concentration obviously affects its action in target tissues. Our study design did not allow disentanglement of these distinct inferences.

Considering prolonged (96-h) instead of short-term (24-h) fasting, it has been shown that the lipolysis rate increases during a 4-d fast in NW humans (7) and that this increase is persistently blunted in obese individuals (1). Interestingly, in keeping with these findings, the sensitivity of adipose tissue to β-adrenergic receptor-mediated lipolysis increases during a long-term fast in NW humans (7), which does not appear to be the case in obese individuals (1). In addition, fasting induces insulin resistance in adipose tissue to allow lipolysis to increase even further (7). The mechanisms underlying these phenomena are unclear at present (7, 38). Pituitary GH secretion is considerably enhanced after 4 d of fasting in NW humans (39), whereas this increase is blunted in obese subjects (40, 41). Considering the above mentioned effects of GH on adipocyte β-adrenoceptor–mediated lipolysis and the fact that GH antagonizes insulin action (42), it is conceivable that the rise of plasma GH concentrations in response to energy restriction plays a critical role in the physiology of the phenomena in NW humans. Obesity-associated hyposomatotropism may then explain the blunted increase in lipolytic sensitivity during a (prolonged) fast in obese humans.

Although the rate of lipolysis per unit of fat mass was lower in the abdominally obese women in our study than in the NW women, the whole-body lipolysis rate was higher in the obese women than in the NW women during the entire study period (Figure 1). Therefore, the attenuated increase in lipolysis in the abdominally obese women did not compromise fatty acid availability as a source of energy. What useful purpose may blunted lipolysis serve in abdominally obese humans? It may protect against untoward effects of inappropriately elevated plasma fatty acid concentrations that potentially accompany enlarged adipose tissue stores. Fatty acids may damage pancreatic β-cells (43) and reduce insulin sensitivity of skeletal muscle (44). The portal vein directs all venous drainage of visceral adipose tissue toward the liver. Therefore, upper-body fat storage in particular will be accompanied by a large portal fatty acid flux, which may damage the liver and activate neuroendocrine systems to cause hypertension and insulin resistance (45). Hyposomatotropism accompanying fat accumulation in combination with hyperinsulinemia and other adaptations to an abdominal obese state may serve to dampen lipolysis and thereby protect against the toxic effects of fatty acids (44). However, as an adverse sequel, a reduced rate of lipolysis per unit of fat mass potentially promotes the retention of body fat.

In summary, basal lipolysis per unit of fat mass is lower in abdominally obese women than in NW women, and the lipolytic response to a short-term fast is blunted in these obese subjects. The results of this study suggest that the hyposomatotropism associated with abdominal obesity is involved in the physiology of these metabolic features. Blunted lipolysis induced by energy restriction did not compromise fatty acid availability as a fuel in obese women, because the whole-body lipolysis rate was higher in abdominally obese women than in NW women. In fact, hyposomatotropism may serve to prevent an untoward increase in plasma fatty acid concentrations in upper-body obese humans. However, as an adverse sequela, reduced lipolysis per unit of fat mass in abdominally obese women may contribute to the preservation of adipose tissue mass.

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