Glucose homeostasis in abdominal obesity: hepatic hyperresponsiveness to growth hormone action

M. M. Buijs, J. A. Romijn, J. Burggraaf, M. L. de Kam, M. Frölich, M. T. Ackermans, H. P. Sauerwein, A. F. Cohen, A. E. Meinders, and H. Pijl. Glucose homeostasis in abdominal obesity: hepatic hyperresponsiveness to growth hormone action. Am J Physiol Endocrinol Metab 287: E63–E68, 2004. First published February 17, 2004; 10.1152/ajpendo.00375.2003.—It has been suggested that (abdominally) obese individuals are hypersensitive to growth hormone (GH) action. Because GH affects glucose metabolism, this may impact glucose homeostasis in abdominal obesity. Therefore, we studied the effect of GH on glucose metabolism in abdominally obese (OB) and normal-weight (NW) premenopausal women. A 1-h intravenous infusion of GH or placebo was randomly administered to six NW [body mass index (BMI) 21.1 ± 1.9 kg/m²] and six OB (BMI 35.5 ± 1.5 kg/m²) women in a crossover design. Insulin, glucagon, and GH secretion were suppressed by concomitant infusion of somatostatin. Glucose kinetics were measured using a 10-h infusion of [6,6-2 H₂]glucose. In both groups, similar physiological GH peaks were reached by infusion of GH. GH strongly stimulated endogenous glucose production (EGP) in both groups. The percent increase was significantly greater in OB than in NW women (29.8 ± 13.3 vs. 13.3 ± 7.4%, P = 0.014). Accordingly, GH responsiveness, defined as the maximum response of EGP per unit GH, was increased in OB vs. NW subjects (6.0 ± 2.1 vs. 2.2 ± 1.5 μmol·min⁻¹·m⁻², 7.4% vs. 2.1 vs. 2.2 ± 1.5 μmol·min⁻¹·m⁻², P = 0.006). These results suggest that the liver is hyperresponsive to GH action in abdominally obese women. The role of the somatotropic ensemble in the control of glucose homeostasis in abdominal obesity is discussed.

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ABDOMINAL OBESITY IS COMMONLY ASSOCIATED with alterations in glucose homeostasis. Peripheral glucose disposal is hampered and gluconeogenesis is enhanced, whereas the total amount of glucose produced remains relatively normal, as the rate of glycogenolysis is suppressed concurrently (21, 32). The pathophysiology that underlies these anomalies has not been fully elucidated. Insulin is the central hormone in the regulation of glucose homeostasis. However, other hormonal systems may be involved as well. The somatotropic ensemble [growth hormone (GH), IGF-I, and IGF-II] exerts important effects on glucose metabolism. GH stimulates endogenous glucose production (EGP) and reduces peripheral glucose uptake (8, 29, 35), whereas IGFs have insulin-like, hypoglycemic effects (6, 19, 22). It has recently been established that GH directly induces insulin resistance of the liver, whereas its effects on peripheral glucose disposal are indirect and mediated by its lipolytic activity (37).

Abdominal obesity is associated with profound alterations of the somatotropic axis. In particular, GH secretion is considerably reduced, whereas circulating IGF-I levels are relatively normal (33, 38, 45). To reconcile these apparently paradoxical findings, it has been proposed that target tissues are hypersensitive to GH action in abdominal obesity. If this notion is correct, downregulation of pituitary GH release may be a critical event for maintenance of euglycemia in abdominally obese humans (in view of the capacity of GH to counteract insulin action).

To further explore the role of GH in the regulation of glucose homeostasis in abdominal obesity, we measured EGP and peripheral glucose disposal in response to GH administration in abdominally obese (OB) and normal-weight (NW) women. We specifically hypothesized that GH would enhance EGP to a greater extent in OB women, as can be expected if target tissues are hypersensitive to GH action in abdominal obesity. Recombinant human GH (rhGH) or placebo was infused in a crossover design. The sequence of infusion was determined by random assignment. Somatostatin was infused concomitantly to inhibit endogenous GH, insulin, and glucagon secretion. The control study was used specifically to judge the effects of GH, as many other endocrine factors that differ between OB and NW individuals (e.g., insulin, cortisol) also affect glucose metabolism.

MATERIALS AND METHODS

Subjects. Six NW [body mass index (BMI) <25 kg/m²] and six OB (BMI >29 kg/m², waist circumference >88 cm) premenopausal women participated in the study (Table 1). The subjects were healthy, nonsmoking, and not taking any medication, including oral contraception. They all had plasma cholesterol <6.5 mmol/L, fasting triglycerides <1.4 mmol/L, and Hb A1C <6.7%. The subjects were weight stable for ≥3 mo and did not exercise for more than 3 h/wk. During the 3 days preceding the study, the participants consumed a weight-maintaining diet containing ≥250 g of carbohydrate. The study protocol was approved by the Medical Ethics Committee of Leiden University Medical Center. Subjects were recruited using the Center for Human Drug Research volunteer pool and using advertisements in the local media. Written informed consent was obtained from all participants after the nature of procedures was explained.

Experimental procedures. The study comprised two occasions and was performed in a randomized, placebo-controlled, and double-blind
Table 1. Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>NW (n = 6)</th>
<th>OB (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>31±11</td>
<td>39±11</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>60.2±6.7</td>
<td>18.5±4.5</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>21.1±1.9</td>
<td>35.5±1.5</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>72.5±3.5</td>
<td>67.0±7.6</td>
</tr>
<tr>
<td>Fat percentage, %</td>
<td>27.7±4.2</td>
<td>41.0±5.2</td>
</tr>
<tr>
<td>Lean body mass, %</td>
<td>69.1±4.1</td>
<td>56.5±5.2</td>
</tr>
<tr>
<td>Hb A1C, %</td>
<td>4.8±0.5</td>
<td>4.7±0.3</td>
</tr>
</tbody>
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NW, normal-weight subjects; OB, obese subjects. All variables, except age and Hb A1C, were significantly different between NW and OB subjects. Fat and lean mass percentages do not add up to 100%, because bone mass was not included in lean body mass.

Fig. 1. Study design. rhGH, recombinant human growth hormone; SRIH, somatostatin; FFA, free fatty acids.

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estimate the difference in GH exposure between both occasions (ΔGH AUC). These ΔGH AUCs were compared between the two study groups.

The mean basal levels of insulin, glucagon, IGF-I, glucose, and FFA concentrations were calculated from \( t = -46 \) to \(-32 \) min. Insulin and glucagon secretion was suppressed by somatostatin infusion. Therefore, average hormone concentrations were calculated from \( t = -2 \) to 420 min. Differences in response of plasma IGF-I, glucose, and FFA levels to GH vs. placebo were determined by subtracting the response to placebo from the response to GH administration (Δ-score) for all time points. To allow correction for differences in catecholamine exposure, urinary catecholamines released per millimole creatinine (to correct for urine concentration) were determined in both groups from urine collected throughout the occasion.

Basal EGP and peripheral glucose disposal were calculated by dividing the infusion rate of [6,6-\(^3\)H]glucose by the steady-state \( M + 2 \) enrichment of plasma glucose, which was achieved between \( t = -46 \) and \(-32 \) min (before somatostatin and GH infusion). Because metabolic nonsteady state existed between \( t = 120 \) and 420 min, Steele’s equations for non-steady-state conditions adjusted for the use of stable isotopes (44, 46) were used to calculate the response of EGP and peripheral glucose disposal (glucose \( R_d \)) to GH vs. placebo administration. The effective volume of glucose distribution was assumed to be equal to the amount of extracellular fluid. Extracellular fluid was calculated from the amount of LBM as measured by dual-energy X-ray absorptiometry (42). To compensate for nonuniform mixing, the correction factor \( P \) of the non-steady-state equations was assumed to be 0.65 (46).

Differences between EGP, glucose \( R_d \), and glucose concentration in response to GH vs. placebo administration were calculated by subtracting the placebo response from the GH response (Δ-score) for each time point. Maximum Δ-scores and maximum percent increase compared with basal values were determined in NW and OB women. Tissue responsiveness to the effect of GH on EGP, defined as the maximum change in EGP per unit GH, was calculated by dividing the maximum Δ-score by the ΔGH AUC.

**Statistics.** Basal values, maximum Δ-scores, and responsiveness estimates were compared between the two groups by means of ANOVA with group (NW vs. OB) as factor. Comparisons of Δ-scores between NW and OB subjects, with data obtained at subsequent time points, were made by an ANOVA for repeated measurements with time and group as factors, the interaction time \( \times \) group, and prevalues as covariate, using SAS software v. 8.1 for Windows (SAS Institute, Cary, NC). Because Δ-scores are used, significance of the factor time indicates a difference between GH and placebo treatment. A significant group effect indicates a different level of response of NW and OB subjects. A significant interaction indicates a different reaction to GH treatment for the OB compared with the NW subjects. No post hoc tests were performed. Data are presented as means ± SD. A \( P \) value of \(<0.05\) was considered statistically significant.

**RESULTS**

**Hormone concentrations.** Plasma GH peak concentrations in response to GH infusion were similar in NW and OB subjects (49.8 ± 10.4 vs. 45.1 ± 5.6 mU/L; Fig. 2). Because somatostatin infusion suppressed GH secretion completely in both NW and OB women, ΔGH AUC was not different between groups (NW: 52.4 ± 11.1 mU\( \cdot \)h\(^{-1}\)·LBM\(^{-1}\); OB: 48.0 ± 6.5 mU\( \cdot \)h\(^{-1}\)·LBM\(^{-1}\)). Basal insulin concentration was significantly lower in NW compared with OB women (6.1 ± 2.5 vs. 13.5 ± 4.4 mU/L, \( P = 0.005 \)), whereas basal glucagon level was similar in both groups (NW: 120 ± 41 ng/L; OB: 136 ± 35 ng/L, \( P > 0.05 \)). In all studies, somatostatin infusion suppressed insulin levels to values below the assay detection limit (<3 mU/L). Plasma glucagon concentration was slightly decreased to a similar extent in both groups (NW: 106 ± 40 ng/L; OB: 114 ± 42, \( P > 0.05 \)).

Norepinephrine concentration in urine did not differ between OB and NW groups, during either GH or placebo administration. Although urinary epinephrine concentration tended to be higher in NW than in OB women (3.2 ± 0.9 vs. 2.1 ± 1.5 nmol/mmol creatinine, \( P = 0.052 \)), the difference between GH and placebo conditions was similar in both groups (−0.4 ± 0.8 vs. −0.5 ± 1.4 nmol/mmol creatinine, \( P = 0.878 \)).

**Glucose kinetics.** Basal glucose concentration was 4.7 ± 0.3 and 4.8 ± 0.2 mmol/l in NW and OB subjects, respectively. Overnight postabsorptive EGP was higher in OB than in NW subjects (959 ± 121 vs. 774 ± 97 µmol/min, \( P = 0.015 \)), but expressed per kilogram of LBM the values did not differ between OB and NW women (16.6 ± 1.9 vs. 18.3 ± 1.3 µmol·kg\(^{-1}\)·min\(^{-1} \), \( P > 0.05 \)).

In response to somatostatin infusion, EGP, glucose \( R_d \), and plasma glucose concentrations initially decreased and subsequently increased in both NW and OB women. Administration of GH profoundly affected these somatostatin-induced changes of glucose metabolism in both groups: the decline of EGP and glucose \( R_d \) was blunted and the subsequent rise of EGP, glucose \( R_d \), and plasma glucose levels was enhanced (Fig. 3). Although GH had a significant impact on all three parameters \((P < 0.0001)\), the effects on glucose \( R_d \) and plasma glucose levels were not different between both groups (time \( \times \) group effect, \( P > 0.05 \)). However, EGP was affected differently in NW and OB women: OB subjects had significantly greater maximum Δ-scores (289 ± 125 vs. 104 ± 59 µmol/min, \( P = 0.008 \), or 4.8 ± 1.6 vs. 2.4 ± 1.4 µmol·kg LBM\(^{-1}\)·min\(^{-1} \), \( P = 0.020 \)) and percent increase of EGP (29.8 ± 11.3 vs. 13.3 ± 7.4%, \( P = 0.014 \)) than NW subjects. Accordingly, tissue responsiveness, expressed as the maximum Δ-score of
EGP per unit GH, was higher in OB than in NW subjects (6.0 ± 2.1 vs. 2.2 ± 1.5 μmol·min⁻¹·mU⁻¹·l⁻¹, P = 0.006, or 0.10 ± 0.03 vs. 0.05 ± 0.04 μmol·kg⁻¹·LBM⁻¹·min⁻¹·l⁻¹, P = 0.032).

Additional effects. Basal plasma IGF-I and IGFBP-3 levels in NW subjects were similar to those in OB subjects (IGF-I: 15.8 ± 6.4 vs. 12.3 ± 5.8 nmol/l; IGFBP-3: 101.8 ± 28.8 vs. 108.8 ± 17.2 nmol/l). Overnight-fasting FFA concentrations were similar in NW and OB women (451 ± 174 vs. 429 ± 149 μmol/l). Plasma FFA levels rapidly increased during somatostatin infusion. GH administration induced a significant further rise of FFA levels that was similar in both groups (time effect, P = 0.0033; time × group effect, P > 0.05).

DISCUSSION

We aimed to establish the in vivo responsiveness of glucose metabolism to GH action in abdominal obesity. To this end, we measured postabsorptive glucose kinetics in response to plasma GH peaks of similar (physiological) heights in abdominally obese and normal-weight women. Fasting plasma glucose levels were similar in normal-weight and obese women. Also, basal EGP and peripheral glucose disposal did not differ between the two groups. Plasma glucose concentrations rose significantly in response to GH administration in both groups. Hyperglycemia was brought about by a considerable increase of EGP, which was significantly more marked in abdominally obese than in normal-weight women. Concomitantly, GH increased peripheral glucose uptake in both groups. In absolute terms, the rise was greater in abdominally obese compared with normal-weight women. However, if corrected for differences in LBM, the effect of GH on peripheral glucose disposal did not significantly differ between obese and normal weight women.

These results indicate that GH has a greater impact on EGP in abdominally obese than in normal-weight women. As ~80–95% of glucose is produced by the liver after an overnight fast (31), we infer that hepatocytes of abdominally obese humans are exquisitely GH sensitive. This inference is in line with previous observations indicating that concentrations of IGF-I and IGFBP-3 in plasma are normal in the face of profoundly reduced circulating GH in abdominal obesity (33). Also, in the present study, plasma IGF-I and IGFBP-3 concentrations were similar in abdominally obese and normal-weight women. In addition, the concentration of GH-binding protein in plasma, which reflects the number of cell surface GH receptors (24), is increased and positively correlated with indexes of abdominal fat mass in obese humans (17, 39, 41). Collectively, these data strongly suggest that the liver (and thereby EGP) is hypersensitive to GH action in abdominal obesity, perhaps through upregulation of the number of hepatic GH receptors. Because insulin promotes GH receptor expression in hepatocytes (3, 25), it is conceivable that hyperinsulinemia induced by chronic
overnutrition, sedentary lifestyles, and/or insulin resistance explains this phenomenon.

What do these observations mean for the role of the somatotropic axis in the regulation of glucose homeostasis in (abdominal) obesity? The data allow the construction of a concept that can explain many findings concerning the somatotropic axis in obesity that have been reported to date. A positive energy balance, as a consequence of overnutrition in relation to physical activity, induces hyperinsulinemia to maintain euglycemia (16, 36). Hyperinsulinemia, in turn, upregulates the number of GH receptors (3, 9, 25, 34) and thereby enhances IGF-I secretion (10). Simultaneously, insulin blunts IGFBP-1 production (10) to increase free IGF-I (2, 20), which cooperates with insulin to control blood glucose levels (6, 22). Stimulation of IGF-I production through upregulation of hepatic GH receptors may therefore contribute to maintenance of glucose homeostasis in response to (chronic) overnutrition. However, enhanced responsiveness of the liver to GH action in the face of normal circulating GH levels also stimulates EGP (present study). It may therefore be of crucial importance for proper control of the plasma glucose concentration in (abdominally) obese humans that IGF-I feeds back on the somatotropic hypothalamic-pituitary ensemble to inhibit GH release. Thus hyposomatotropism accompanying (abdominal) obesity (38, 45) may serve to blunt EGP and thereby preclude hyperglycemia. In addition, hyposomatotropism blunts lipolysis (11) and thereby promotes insulin action in muscle (37) and fat depo- sition in (abdominal) adipose tissue to adequately adapt fuel flux to a positive energy balance. In keeping with this concept, it has been reported that obese type 2 diabetic patients produce almost twice as much GH as weight-matched nonobese controls (18).

EGP rapidly decreased and subsequently increased during somatostatin infusion in both groups of subjects. This biphasic action of somatostatin on glucose production is in accord with previous literature (14, 23, 43). Somatostatin simultaneously suppresses insulin and glucagon secretion. The rapid decline of EGP following somatostatin infusion is considered to result from the persistent and temporarily less opposed (by glucagon) state of EGP re-estimation in (abdominal) adipose tissue to adequately adapt fuel flux to a positive energy balance. In keeping with this concept, it has been reported that obese type 2 diabetic patients produce almost twice as much GH as weight-matched nonobese controls (18).

Plasma FFA concentrations are known to affect hepatic glucose metabolism by stimulation of gluconeogenesis and inhibition of glycogenolysis (13, 15). We measured FFA levels in peripheral blood, and these did not change differentially in response to GH vs. placebo infusion in obese and normal-weight women. However, portal FFA flux in response to GH administration may have been much higher in the abdominally obese than in the normal-weight women. If this, obviously undetectable, phenomenon actually occurred, it is likely to have contributed to the observed difference in EGP between the two groups.

It is likely that hyperresponsiveness to GH action as observed in the present study holds only for the liver, as GH responsiveness of other target tissues appears to be normal in abdominal obesity. In previous studies, we found that abdominally obese women are as sensitive as their normal-weight controls with respect to the lipolytic and anabolic actions of GH (11, 12). Accordingly, Leung et al. (25) demonstrated that insulin upregulates GH receptors in a hepatoma cell line, whereas GH action in osteoblasts (as a model for extrahepatic tissue) was downregulated by both insulin and IGF-I (26). Thus insulin appears to affect GH receptor number in a tissue-specific manner. Therefore, although hyposomatotropism may be instrumental in the control of glucose homeostasis in abdominal obesity, it may render other tissues GH deficient.

Although (sub)chronic GH administration is known to inhibit insulin-mediated peripheral glucose uptake (7, 8, 29), most likely as a sequel to its lipolytic activity (37), [although other studies have suggested that GH impairs glucose disposal directly (30)], GH administration significantly increased glucose disposal in the present study. Moreover, plasma FFA levels increased in response to GH infusion, which also hampers insulin-mediated glucose uptake (28). To reconcile these apparently paradoxical findings, it is important to emphasize that we did not measure the effect GH on insulin-mediated glucose disposal. In fact, our study design kept insulin at low circulating levels by infusion of somatostatin. At basal insulin levels, more than 60% of peripheral glucose disposal is insulin independent and is driven by mass action of plasma glucose levels (4). Plasma glucose levels rose by virtue of the effect of GH on EGP in the present study, which consequently may have increased glucose disposal.

In conclusion, the present study documents hyperresponsiveness of the liver to the stimulatory impact of GH on EGP in abdominally obese humans. We propose that hyperinsulinemia and the profound alterations of the somatotropic ensemble that accompany abdominal obesity are critical for proper control of glucose homeostasis in response to caloric overload.

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