Insulin resistance induced by hydrocortisone is increased in patients with abdominal obesity

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Darmon, Patrice, Frédéric Dadoun, Sandrine Boullu-Ciocca, Michel Grino, Marie-Christine Alessi, and Anne Dutour. Insulin resistance induced by hydrocortisone is increased in patients with abdominal obesity. Am J Physiol Endocrinol Metab 291: E995–E1002, 2006. First published June 13, 2006; doi:10.1152/ajpendo.00654.2005.—Glucocorticoids hypersensitivity may be involved in the development of abdominal obesity and insulin resistance. Eight normal weight and eight obese women received on two occasions a 3-h intravenous infusion of saline or hydrocortisone (HC) (1.5 μg·kg−1·min−1). Plasma cortisol, insulin, and glucose levels were measured every 30 min from time−30 (min) to time+240. Free fatty acids, adiponectin, and plasminogen activator inhibitor-1 (PAI-1) levels were measured at time−30, time+180, and time+240. At time+240, subjects underwent an insulin tolerance test to obtain an index of insulin sensitivity (KITT). Mean+30–240 cortisol levels were similar in control and obese women after saline (74 ± 16 vs. 75 ± 20 μg/l) and HC (235 ± 17 vs. 245 ± 47 μg/l). The effect of HC on mean+180–240 insulin, mean+180–240 insulin resistance obtained by homeostasis model assessment (HOMA-IR), and KITT was significant in obese (11.4 ± 2.0 vs. 8.2 ± 1.3 mU/l, P < 0.05; 2.37 ± 0.5 vs. 1.64 ± 0.3, P < 0.05; 2.81 ± 0.9 vs. 3.22 ± 1.02%/min, P < 0.05) but not in control women (3.9 ± 0.6 vs. 2.8 ± 0.5 mU/l, 0.78 ± 0.1 vs. 0.49 ± 0.1; 4.36 ± 1.1 vs. 4.37 ± 1.2%/min). In the whole population, the quantity of visceral fat, estimated by computerized tomography scan, was correlated with the increment of plasma insulin and HOMA-IR during HC infusion (∆mean+180–240 insulin (r = 0.61, P < 0.05), ∆mean+180–240 HOMA-IR (r = 0.66, P < 0.01)). The increase of PAI-1 between time+180 and time+240 after HC was higher in obese women (+25%) than in controls (+12%) (P < 0.05), whereas no differential effect between groups was observed for free fatty acids or adiponectin. A moderate hypercortisolism, equivalent to that induced by a mild stress, has more pronounced consequences on insulin sensitivity in abdominally obese women than in controls. These deleterious effects are correlated with the amount of visceral fat.

glucocorticoid hypersensitivity; visceral obesity; metabolic effects of hydrocortisone

MOST OF THE FEATURES of the metabolic syndrome, such as increased abdominal fat deposition, arterial hypertension, dyslipidemia, and altered glucose tolerance, are found in patients diagnosed with Cushing’s syndrome or treated chronically with synthetic glucocorticoids. Furthermore, cortisol excess leads to hepatic and extrahepatic insulin resistance (2). Thus increased glucocorticoids activity may play a key role in the development of central obesity and in the state of insulin resistance found in common obesity (4). An increase of cortisol production has been described in obesity and linked to chronic stress, either through increased exposure and/or hypersensitization (44). However, increased metabolic clearance appears to counterbalance excessive production, so that normal plasma cortisol levels are generally found in obese subjects (30). Rather than a persistent excess of circulating cortisol, recent data suggest an involvement in obesity of increased peripheral actions of cortisol related to changes of intracellular metabolism and/or glucocorticoid sensitivity. Indeed, elevated glucocorticoid receptor concentrations and local regeneration of cortisol from cortisone driven by the 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD-1) could play a pivotal role by amplifying local glucocorticoid action (49, 50). Remarkably, recent data show that visceral adipose tissue substantially contributes to the splanchnic production of cortisol, which can counteract insulin actions in the liver (1, 3). Differences in glucocorticoid intratissue metabolism leading to increased local exposure to cortisol might explain the paradox of the presence in the metabolic syndrome of Cushing’s features despite normal plasma cortisol. Such a local hypercortisolism may be responsible for increased adipocyte differentiation (21) and free fatty acids (FFA) release, which can contribute to insulin resistance (5). In addition, glucocorticoids may also regulate the synthesis and secretion of various adipokines that may influence insulin sensitivity (18). Indeed, glucocorticoids were found to inhibit both the expression of the gene of the insulin-sensitizing hormone adiponectin and its secretion in isolated human adipose tissue (13, 20). In addition, glucocorticoids increase plasminogen activator inhibitor-1 (PAI-1) gene expression in adipose tissue (19, 33). Elevated plasma levels of PAI-1 have been found in patients with obesity, insulin resistance, and cardiovascular diseases (23, 48); moreover, PAI-1 excess has been shown to induce insulin resistance in adipocytes (27). To date, there is no study describing the existence of differential effects of glucocorticoids on insulin sensitivity in normal weight and obese patients. We hypothesized that obese subjects show increased tissue sensitivity and increased metabolic responses to moderate rises of plasma cortisol, similar to those seen in response to everyday stressors. To test this hypothesis, we compared the metabolic responses, i.e., changes of insulin sensitivity and variations of FFA, adiponectin, and PAI-1 plasma levels, of obese women with abdominal obesity and lean controls, to a moderate induced hypercortisolism, equivalent to that evoked by a mild physical or psychological stress.
Materials and Methods

Subjects. This study was approved by the local committees for ethics. Informed consent was obtained from all subjects. Sixteen normally cycling women of an age ranging from 20 to 50 yr, with no endocrine, cardiovascular, hepatic, or systemic disease, were investigated: eight normal weight controls [body mass index (BMI) 21.2 ± 1.7 kg/m², waist circumference 69.4 ± 6.0 cm] and eight women with abdominal obesity (BMI 39.8 ± 8.0 kg/m², waist circumference 108.8 ± 11.9 cm). None of them was taking corticoids, psychotropic drugs, or oral contraceptive. The surface of abdominal total, subcutaneous, and visceral fat was assessed by computed tomography (CT) using a single cross-sectional scan at the level of L4-L5 as previously described (22). Table 1 summarizes the clinical characteristics of control and obese subjects and the results of the CT scan.

Experimental design. All subjects were admitted at 7:00 AM on two occasions in random order separated by 15 days. They had been fasting for at least 10 h before admission. On admission, a cannula was inserted into a forearm vein of each arm. One cannula was used for venous blood sampling and the other one for hydrocortisone infusion. Differences between means were assessed (11006_P<0.05) 0.05. All data are presented means ± SD. Statistical analysis was performed using the StatView analysis program. The unpaired Student’s t-test was used to test differences between control and obese subjects. The Wilcoxon rank sum test was used to test differences for differences during and/or after saline or hydrocortisone infusion in controls and obese subjects. When appropriate, data were analyzed using repeated-measures ANOVA, and Pearson’s correlations were performed to identify a possible relationship among the assessed variables. P < 0.05 was considered significant.

Results

Baseline biological characteristics. Table 2 summarizes the biological characteristics of control and obese subjects at baseline on the day of saline infusion. As expected, fasting glucose, insulin, HOMA-IR, triglycerides, and FFA concentrations were significantly higher and HDL cholesterol and adiponectin levels lower in obese than in control subjects. Basal PAI-1 level tended also to be higher in obese than in control patients (P = 0.07). There was no difference in plasma cortisol levels at 8:30 AM (time0) between controls and obese subjects.

Cortisol levels after infusion of saline or hydrocortisone. On the day of saline infusion, plasma cortisol concentrations decline across time in both groups, reflecting the physiological circadian rhythm of cortisol. After saline infusion, mean30–240 plasma cortisol levels were similar in control and obese sub-

Table 1. Clinical characteristics of control and obese subjects at baseline

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects (n = 8)</th>
<th>Obese Subjects (n = 8)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>32.0 ± 10.3</td>
<td>41.1 ± 6.4</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>21.2 ± 1.7</td>
<td>39.8 ± 8.0</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>69.4 ± 6.0</td>
<td>108.8 ± 11.9</td>
<td>P &lt; 0.0001</td>
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<td>Waist-to-hip ratio</td>
<td>0.87 ± 0.05</td>
<td>1.01 ± 0.14</td>
<td>P &lt; 0.0001</td>
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<tr>
<td>Total abdominal fat, cm²</td>
<td>209.9 ± 104.0</td>
<td>803.7 ± 200.6</td>
<td>P &lt; 0.0001</td>
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<tr>
<td>Subcutaneous fat, cm²</td>
<td>164.2 ± 76.7</td>
<td>608.3 ± 121.3</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Visceral fat, cm²</td>
<td>45.8 ± 31.7</td>
<td>195.1 ± 84.8</td>
<td>P &lt; 0.0005</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>116 ± 12</td>
<td>134 ± 9</td>
<td>P &lt; 0.005</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>67 ± 7</td>
<td>77 ± 7</td>
<td>P &lt; 0.05</td>
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</table>

Data are means ± SD. BMI, body mass index; BP, blood pressure. P = difference between groups at baseline.
jects [74 ± 16 μg/l vs. 75 ± 20 μg/l, not significant (NS)]. Repeated blood sampling at 30-min intervals revealed that plasma cortisol levels were significantly and constantly higher after hydrocortisone (HC) than after saline infusion between time_30 and time_240 in both groups (P < 0.05; Fig. 1). After HC infusion, plasma cortisol levels at each sampling time were not different in control and in obese subjects, just as with mean_30–240 plasma cortisol level (235 ± 17 μg/l vs. 245 ± 47 μg/l, NS).

**Glucose levels after infusion of saline or HC.** After saline infusion, mean_30–240 glucose concentrations were significantly lower in control than in obese subjects (4.0 ± 0.2 mmol/l vs. 4.4 ± 0.3 mmol/l, P < 0.05). In addition, plasma glucose concentrations were significantly higher after HC than after saline infusion at time_90 and time_210 in controls and at time_150, time_190, and time_240 in obese women (P < 0.05) (Fig. 2). According to the Wilcoxon test, the effect of the 3-h infusion of HC on mean_30–240 plasma cortisol level was significant in both control (HC 4.3 ± 0.4 mmol/l vs. saline 4.0 ± 0.2 mmol/l, P < 0.05) and obese subjects (HC 4.6 ± 0.4 mmol/l vs. saline 4.4 ± 0.3 mmol/l, P < 0.05). Similar results were found when comparing areas under the curve (AUC) of glucose from time_0 to time_240 instead of the mean_30–240 values (data not shown). Moreover, the effect of HC on mean_180–240 plasma glucose level (or glucose AUC_180–240, data not shown) was also significant in both control (HC 4.5 ± 0.5 mmol/l vs. saline 4.0 ± 0.3 mmol/l, P < 0.05) and obese subjects (HC 4.7 ± 0.5 mmol/l vs. saline 4.3 ± 0.3 mmol/l, P < 0.05).

**Insulin levels after infusion of saline or HC.** After saline infusion, mean_30–240 insulin concentrations were significantly lower in control than in obese subjects (3.0 ± 1.5 mU/l vs. 9.2 ± 4.0 mU/l, respectively, P < 0.001). In addition, plasma insulin levels were significantly greater after HC than after saline infusion at time_240 in controls and at time_60, time_190, and time_240 in obese women (P < 0.05; Fig. 3). According to the Wilcoxon test, the effect of the 3-h infusion of HC on mean_30–240 plasma insulin level was significant neither in control (HC 3.8 ± 1.8 mU/l vs. saline 3.0 ± 1.5 mU/l, NS) nor in obese women (HC 11.0 ± 5.7 mU/l vs. saline 9.2 ± 4.0 mU/l, NS). Similar results were found when comparing AUC of insulin from time_0 to time_240 instead of the mean_30–240 values (data not shown). However, the effect of HC on mean_180–240 plasma insulin level (or insulin AUC_180–240, data not shown) was significant in obese (HC 11.4 ± 5.7 mU/l vs. saline 8.2 ± 3.7 mU/l, P < 0.05) but not in control women (HC 3.9 ± 1.8 mU/l vs. saline 2.8 ± 1.5 mU/l, NS; Table 3).

**HOMA-IR index after infusion of saline or HC.** As expected, mean_30–240 HOMA-IR values were significantly lower in control than in obese subjects after saline infusion (0.53 ± 0.25 vs. 1.80 ± 0.88, respectively, P < 0.001). According to the Wilcoxon test, the effect of the 3-h infusion of HC on mean_30–240 HOMA-IR values was not significant in control (HC 0.74 ± 0.38 vs. saline 0.53 ± 0.25, NS) or in obese women (HC 2.30 ± 1.37 vs. saline 1.80 ± 0.88, NS). Similar results were found when comparing AUC of HOMA-IR from time_0 to time_240 instead of the mean_30–240 values (data not shown). However, the effect of HC on mean_180–240 HOMA-IR values (or HOMA-IR AUC_180–240, data not shown) was significant in
obese (HC 2.37 ± 1.4 vs. saline 1.64 ± 0.80, P < 0.05) but not in control subjects (HC 0.77 ± 0.40 vs. saline 0.49 ± 0.24 mU/l, NS) (Table 3).

Insulin tolerance test after infusion of saline or HC. As expected, KITT was significantly higher in control than in obese subjects after saline infusion (4.37 ± 1.24%/min vs. 3.32 ± 1.02%/min, P < 0.05). In addition, plasma glucose levels were significantly higher after HC than after saline infusion at 1, 3, 7, 9, 11, 13, and 15 min of the insulin tolerance test in obese women but only at 7 min in controls (P < 0.05) (Fig. 2). According to the Wilcoxon test, the 3-h infusion of HC induced a significant decrease of KITT in obese (HC 2.81 ± 0.86%/min vs. saline 3.32 ± 1.02%/min, P < 0.05) but not in control subjects (HC 4.36 ± 1.10%/min vs. saline 4.37 ± 1.24%/min, NS) (Fig. 4) (Table 3). Results were similar when using comparisons of AUC (data not shown).

PAI-1 levels after infusion of saline or HC. After saline infusion, plasma PAI-1 levels decreased progressively between time 0 and time 180, and time 240 in both control (17.3 ± 12.1 ng/ml, 16.3 ± 7.9 ng/ml, and 13.2 ± 7.1 ng/ml, respectively) and obese subjects (46.8 ± 41.0 ng/ml, 29.5 ± 29.7 ng/ml, and 22.7 ± 22.8 ng/ml, respectively). The percentage of decrease between time 180 and time 240 was not different in control and in obese subjects (−19.8 ± 7.4% vs. −27.6 ± 11.2%, NS). After HC infusion, plasma PAI-1 concentrations increased between time 0 and time 180, and time 240 in both control (15.1 ± 5.9 ng/ml, 15.8 ± 8.5 ng/ml, and 17.1 ± 9.5 ng/ml, respectively) and obese subjects (26.9 ± 16.3 ng/ml, 23.4 ± 17.0 ng/ml, and 32.8 ± 36.8 ng/ml, respectively). However, the percentage of increase of plasma PAI-1 level between time 180 and time 240 was higher in obese (+25.2 ± 11.8%) than in control subjects (+11.9 ± 24.6%) (P < 0.05) (Fig. 5).

FFA levels after infusion of saline or HC. Not surprisingly, FFA levels were higher in obese subjects than in controls, at any time before or during infusion of saline or HC (P < 0.05). In addition, there was a significant increase in FFA concentrations across time during saline infusion in control (time 0 9.54 ± 1.00 mg/dl, time 180 14.62 ± 0.96 mg/dl, time 240 13.84 ± 1.46 mg/dl) and in obese subjects (time 0 17.68 ± 2.04 mg/dl, time 180 21.14 ± 1.48 mg/dl, time 240 23.09 ± 1.15 mg/dl), which may relate to the prolonged fasting state. However, there was no significant additional effect of HC infusion on FFA levels in controls (time 0 10.98 ± 2.36 mg/dl, time 180 16.02 ± 1.10 mg/dl, time 240 16.78 ± 2.70 mg/dl) or in obese subjects (time 0 18.75 ± 1.93 mg/dl, time 180 24.68 ± 3.31 mg/dl, time 240 23.00 ± 2.63 mg/dl). Moreover, at any sampling time, FFA levels were not statistically different when comparing HC vs. saline infusion in both groups.

Adiponectin levels after infusion of saline or HC. Plasma adiponectin levels were found to be lower in obese subjects than in controls, at any time before or during infusion of saline or HC (P < 0.05). However, there were no significant changes of adiponectin levels across time during saline or HC infusion in control (saline infusion, time 0 16.37 ± 5.32 µg/ml, time 180 14.83 ± 4.76 µg/ml; HC infusion, time 0 17.22 ± 5.18 µg/ml, time 180 18.20 ± 5.23 µg/ml, time 240 16.56 ± 5.91 µg/ml) or in obese subjects (saline infusion, time 0 10.81 ± 3.33 µg/ml, time 180 9.75 ± 2.80 µg/ml, time 240 10.33 ± 3.22 µg/ml; HC infusion, time 0 10.68 ± 3.21 µg/ml, time 180 10.20 ± 4.51 µg/ml, time 240 10.92 ± 5.20 µg/ml). Moreover, at any sampling time, adi-

<table>
<thead>
<tr>
<th>Mean180–240 Insulin, mU/l</th>
<th>Mean180–240 HOMA-IR</th>
<th>KITT, %/min</th>
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<tbody>
<tr>
<td><strong>Control subjects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>2.8 ± 1.5</td>
<td>0.49 ± 0.24</td>
</tr>
<tr>
<td>HC</td>
<td>3.9 ± 1.8</td>
<td>0.77 ± 0.40</td>
</tr>
<tr>
<td><strong>Obese subjects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>8.2 ± 3.7</td>
<td>1.64 ± 0.8</td>
</tr>
<tr>
<td>HC</td>
<td>11.4 ± 5.7</td>
<td>2.04 mg/dl</td>
</tr>
</tbody>
</table>

Data are means ± SD. HC, hydrocortisone; KITT, insulin sensitivity. P = HC vs. saline infusion.
Regression analysis. On the day of saline infusion, considering the analysis for both normal weight and obese subjects as a whole, there was a significant positive correlation between visceral fat and fasting plasma glucose ($r = 0.69, P < 0.01$), fasting plasma insulin ($r = 0.86, P < 0.0001$), HOMA-IR time0 ($r = 0.91, P < 0.0001$), and $K_{ITT}$ ($r = 0.65, P < 0.01$). Furthermore, there was a significant positive correlation between visceral fat and $\Delta_{\text{mean} 30-240}$ insulin ($r = 0.61, P < 0.05$), $\Delta_{\text{mean} 180-240}$ insulin ($r = 0.65, P < 0.01$), $\Delta_{\text{mean} 30-240}$ HOMA-IR ($r = 0.66, P < 0.01$), and $\Delta_{\text{mean} 180-240}$ HOMA-IR ($r = 0.73, P < 0.01$).

**DISCUSSION**

Our data demonstrate that a moderate hypercortisolism, equivalent to that observed in response to a mild stress, has more pronounced effects on insulin sensitivity in obese than in normal weight subjects, suggesting that, in obese subjects, glucose homeostasis shows increased sensitivity to the deleterious actions of glucocorticoids. The deleterious effect of HC on insulin sensitivity was more pronounced in obese subjects than in controls during the last hour of sampling, which followed the end of the 3-h infusion of HC. Indeed, increases in insulin concentrations and HOMA-IR values after HC were significantly greater in obese than in controls during the late in insulin concentrations and HOMA-IR values after HC were followed the end of the 3-h infusion of HC. Indeed, increases in insulin concentrations and HOMA-IR values after HC were significantly greater in obese than in controls during the late period extending from time180 to time240. Moreover, data from the insulin tolerance tests (performed at time240) showed a significant alteration of insulin sensitivity in response to HC infusion in obese but not in control subjects. Thus the harmful effects of HC on insulin sensitivity seem to be delayed and to occur at least 3 h after plasma cortisol rise. Indeed, it has been shown that the time course of the effects of the acute elevation of morning plasma cortisol on the daytime profiles of plasma glucose, serum insulin, and insulin secretion rates involves both immediate and delayed effects: the immediate effect is an abrupt inhibition of insulin secretion without change in glucose concentration, and the delayed effect is the appearance of a state of relative insulin resistance, which occurs 4–6 h after the morning rise of cortisol and probably reflects a stimulation of hepatic glucose output and a decrease in glucose disposal by peripheral tissues (36).

Our results show the pronounced metabolic effects of a moderate transient excess of glucocorticoids in abdominal obesity. Although the isolate increase of plasma cortisol levels that results from infusing HC is far from being equivalent to the whole neuroendocrine response to an innate stress, these data provide a potential pathophysiological link between a chronic exposure to psychosocial stressors and deleterious metabolic consequences, emphasizing the potential role of stress in the pathophysiology of obesity. Indeed, if, in abdominally obese subjects, the sole moderate increase of cortisol that results from our experimental paradigm is powerful enough to induce alterations of insulin sensitivity, deleterious consequences may be even greater when cortisol increase is associated with the sympathetic activation produced by stressful events. Several studies have previously demonstrated that the neuroendocrine stress axis is activated in patients with the metabolic syndrome (42). Psychosocial and socioeconomic handicaps provide an environment in which stress reactions are expected to be frequent and have been shown to be strongly associated with abdominal obesity and with the risk of coronary heart disease (9, 10, 16). Self-reported social anxiety is also associated with increased waist-to-hip ratio (26). Moreover, in patients with abdominal obesity, the level of perceived stress exposure reported by the patients appears to correlate positively to an increased response of cortisol to stress, suggesting that a high exposure to stressors leads to a sensitization of the hypothalamic-pituitary-adrenal axis (44). Repeated stresses, increased cortisol response to stress, and increased deleterious metabolic effects of glucocorticoid may exacerbate the disorders of the metabolic syndrome in a vicious circle. In the current work, we chose to infuse a dose of 1.5 g·kg$^{-1}$·min$^{-1}$ of HC during 3 h to mimic the moderate hypercortisolism evoked by everyday stressors, according to data derived from previous studies (40, 41). Our goal was achieved, and we obtained a mild hypercortisolism both in controls and in obese women (mean plasma cortisol 30–240 235 ± 17 μg/l and 245 ± 47 μg/l, peak plasma cortisol 277 ± 10 μg/dl at time150 and 314 ± 23 μg/dl at time180, in controls and obese subjects, respectively). Such plasma cortisol concentrations are equivalent to those seen during exposure to a mild physical or psychological stress or during a prolonged endurance exercise (11), making our protocol relevant to assess the cortisol-driven effects of everyday stressors. Several authors have shown previously that HC infusion at the dose of 2.0 μg·kg$^{-1}$·min$^{-1}$ induces a rise of plasma cortisol up to 370–420 μg/dl, levels that are seen after exposure to a major stress (34, 51). Indeed, such an intense hypercortisolism induces marked insulin resistance (40, 41) but may not be as relevant to mimic the cortisol response to the frequent moderate stresses of everyday life. For the first time, our data show that a moderate hypercortisolism is sufficient to induce deleterious effects on glucose metabolism, especially in obese women, and suggest that moderate stresses, leading to modest cortisol responses, may have worse metabolic consequences in obese than in normal weight subjects.

We have also shown that a moderate hypercortisolism induces an elevation of circulating PAI-1 levels that is significantly greater in obese than in control subjects. This greater increase of PAI-1 probably also results from an increased local sensitivity of PAI-1-producing tissues to glucocorticoid action. Indeed, we and others (19, 33) have already demonstrated that the PAI-1 gene is expressed in adipose tissue and hepatocytes, where its expression is regulated by insulin and glucocorticoids. The enhanced elevation of PAI-1 after a rise of plasma cortisol can contribute to the cardiovascular complications of obesity. Indeed, PAI-1 is the primary inhibitor of fibrinolysis. An increase of PAI-1 concentration in the circulation leads to a state of hypofibrinolysis, which impairs the removal of thrombi from the vascular system. Furthermore, the relevance of PAI-1 is not limited to the thrombotic process. Elevated levels of plasma PAI-1 have been found in obesity and insulin resistance and appear to predict future risk for the development of both type 2 diabetes and cardiovascular diseases (23, 48).

Our study was not designed specifically to elucidate the mechanisms by which an excess of cortisol may deteriorate insulin resistance in humans and more specifically in abdominally obese subjects. Nevertheless, some of our results may provide some interesting clues. Numerous data support the deleterious effects of increased FFA release from visceral
adipose tissue on insulin action, especially in abdominally obese subjects (5). Accordingly, we found increased plasma FFA levels in the group of insulin-resistant obese subjects compared with those found in controls. Moreover, the administration of cortisol, leading to plasma concentrations in the upper physiological range, has been shown to increase lipolysis (14, 15), and hyperresponsiveness of obese subjects to the lipolytic effect of HC may represent a possible mechanism leading to the exaggerated insulin resistance found in the obese group in response to HC infusion. However, our data do not support such a hypothesis. An increase of plasma FFA levels was found along with time, during saline and HC infusion in both obese and control subjects, that may relate to the continuation of the fast. However, no further increase of plasma FFA was seen after HC infusion compared with saline infusion. The lack of a specific effect of HC infusion on FFA plasma levels may relate to the fact that FFA release may be already maximally stimulated by the fasting state and/or to the fact that glucocorticoids exert variable effects on lipolysis (14), depending on the dose and on the metabolic status, especially the level of insulin inhibition. Nevertheless, we cannot exclude a transient, short-lasting effect of HC infusion on FFA release, since we did not measure FFA during the early period of HC/saline infusion because a late increase was expected (15). Nor can we exclude local effects of HC on specific adipose tissue depots (45), which could remain undetectable in peripheral venous blood.

Differential effects of HC in abdominally obese and control subjects on the plasma level of the insulin-sensitizing hormone adiponectin could also participate in the more deleterious effect of HC infusion on insulin sensitivity seen in our obese group. Indeed, it has been recently shown that an intravenous bolus of 25 mg of HC induces an acute transient decrease of plasma adiponectin levels in healthy volunteers (17), and it could be hypothesized that such a decrease may be amplified in obese subjects. Not surprisingly, we found lower plasma adiponectin levels in obese subjects than in controls, both before and during infusion of saline or HC. However, we did not observe an HC-induced decrease of adiponectin in normal weight controls or in obese subjects. This discrepancy with the former study may relate to the twofold lower plasma cortisol level obtained after the HC infusion used in our study compared with that induced by an acute bolus of 25 mg. Thus it seems unlikely that the effects of HC infusion on insulin sensitivity that we describe here are induced by changes of adiponectin. Nevertheless, we cannot exclude a transient, short-lasting effect of HC infusion on plasma adiponectin, since we did not measure adiponectin during the early period of HC/saline infusion. Last, the greater increase of PAI-1 seen in obese subjects after HC infusion compared with that seen in normal weight subjects may participate in the differential effect of HC on insulin sensitivity. Indeed, it has been shown recently that PAI-1, alongside its major involvement in the fibrinolytic process, may also affect insulin signaling at the cellular level (27).

Under our experimental conditions, we have evidenced that the effects of HC on insulin sensitivity were more pronounced in patients with visceral obesity. We also showed that the quantity of visceral fat was positively correlated with the increment of mean plasma insulin and mean HOMA-IR during HC vs. saline infusion. This phenomenon could be due to an increased local glucocorticoid sensitivity. It is well established that glucocorticoid receptor expression in visceral fat is up-regulated, leading to an amplification of glucocorticoid signaling (8, 38, 39). In addition, some polymorphisms of the glucocorticoid receptor gene appear to be associated with obesity, hypertension, and insulin resistance (43). Increased glucocorticoid sensitivity may also occur in obese patients through an increased cortisol reactivation in adipose tissue. Indeed, the significance of local glucocorticoid metabolism has been well established in rodent adipose tissue, where the enzyme 11β-HSD-1 can regenerate active glucocorticoids from inactive 11-keto-glucocorticoids. In both genetic (Zucker rats) and diet-induced models of rodent obesity, an increase of 11β-HSD-1 mRNA and activity has been evidenced in omental adipose tissue, with a subsequent increase of local glucocorticoid receptor activation (7, 29). Moreover, 11β-HSD-1 knockout mice have a “cardioprotective” metabolic phenotype and resist the deleterious effect of a high-fat diet on glyceremia (25). Oppositely, transgenic mice with a selective overexpression of 11β-HSD-1 in adipose tissue have increased corticosterone levels in adipose tissue and develop metabolic disturbances that faithfully replicate the metabolic syndrome, suggesting that increased 11β-HSD-1 activity in adipose tissue may represent a molecular etiology of visceral obesity and associated metabolic complications (31). However, the role of local glucocorticoid metabolism is not clearly established in human obesity. Numerous studies report that 11β-HSD-1 activity and mRNA levels are increased in subcutaneous and visceral adipose tissue of obese patients (35, 37). Moreover, it has been shown that, in both Pima Indian and Caucasian obese subjects, increased expression of 11β-HSD-1 in subcutaneous adipose tissue is associated with abdominal adiposity, elevated fasting glucose, and insulin resistance (24, 28).

In conclusion, we demonstrated that a moderate hypercortisolism equivalent to that induced by a mild stress has more pronounced effects on insulin sensitivity and on PAI-1 plasma levels in women with abdominal obesity than in normal weight women. The degree of these cortisol-induced deleterious metabolic effects appears to be correlated with the quantity of visceral fat. Our results emphasize the potential role of stress in the pathophysiology of obesity.

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