RAPID COMMUNICATION

Effects of glucocorticoids and of growth hormone on serum leptin concentrations in man

Kaspar Berneis, Susanne Vosmeer and Ulrich Keller
Departments of Research and of Internal Medicine, University Hospital Basel, Switzerland


Recent data suggest an involvement of the ob gene and its product leptin in the regulation of body fat. To assess the effects of glucocorticoids and growth hormone (GH) on serum leptin and body fat, 30 normal subjects received methylprednisolone (0.5 mg · kg⁻¹ · day⁻¹) per os for 7 days and 15 subjects received in addition sc injections of GH (0.15 IU · kg⁻¹ · day⁻¹) twice daily (combination group). Serum leptin levels increased both in the glucocorticoid group (p < 0.02) and in the combination group (p < 0.002). When body fat was estimated by bioelectrical impedance analysis it decreased during combined treatment and remained unchanged in the glucocorticoid group. Plasma insulin concentrations increased in both groups. Resting energy expenditure (indirect calorimetry) increased in the combination group and remained unchanged in the glucocorticoid group. The finding of increased serum leptin concentrations during treatment with glucocorticoid and GH suggests that serum leptin is regulated by glucocorticoids, possibly though changes in insulin secretion, independently of changes of body fat mass.

Ulrich Keller, Departments of Research and of Internal Medicine, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland

It has been suggested recently that the ob gene (1) is involved in the regulation of body fat (2). Serum concentrations of leptin, the gene product of the ob gene, were demonstrated to be correlated with body fat in rodents and in lean and obese humans (3, 4). Daily intraperitoneal injection of ob/ob mice with leptin lowered their body weight, percentage body fat and food intake (2) and suppressed their feeding (5).

It has been reported that ob mRNA is up- or down-regulated by an increase or decrease of insulinemia, respectively (6–8). Administration of glucocorticoids induced adipose tissue ob gene expression in rats and resulted in reduced food intake and decreased body weight gain (9). Because administration of glucocorticoids and growth hormone (GH) affect both plasma insulin concentrations (10) and body fat (11, 12), the present study was performed to assess the effects of glucocorticoids and the combination of glucocorticoids and GH on serum leptin and insulin concentrations and on body fat content in normal subjects.

Subjects and methods

Written informed consent was obtained from 34 healthy young men aged 25.4 ± 0.7 years with a body mass index of 22.7 ± 0.4 kg/m².

The study protocol was reviewed and approved by the ethical committee of the Basel University Hospital.

After a 12-h overnight fast, three blood samples were obtained in intervals of 30 min before (day 1) and during hormonal treatment (day 7). Plasma was rapidly obtained by refrigerated centrifugation (4°C) and stored at –70°C until later assay. Before and during treatment body weight and body composition (BIA, bioelectrical impedance apparatus: Data Input, Frankfurt, Germany) were recorded, and energy expenditure was determined by indirect calorimetry using a ventilated hood metabolic monitor (Deltatrac II™ MBM-200, Datex, Helsinki, Finland). Thirty subjects received methylprednisolone (0.5 mg · kg⁻¹ · day⁻¹) per os; Urbasone®, Hoechst, Germany) divided into three equal daily doses during days 1–7. Fifteen subjects also received, after random allocation, sc injections of GH (0.15 IU/kg/day; Genentropin®, Pharmacia, Stockholm Sweden) twice daily at 08.00 h and 20.00 h on days 1–7. Four subjects received no hormonal treatment and served as controls. Serum leptin was measured using a human leptin RIA kit (HL-81K) (Linco Research, Inc.; St Charles, MO). Plasma concentrations of insulin were measured using a radioimmunoassay kit (CIS Insik-5 (P2796); Sorin Biomedica, Italy).

Repeated measures ANOVA, Student’s paired t-tests or Wilcoxon signed rank tests (for non-parametric distributions) (Statview®, Abacus Concepts Inc., Berkeley, CA) on a Power Macintosh 7100/80 were used to detect differences between and within the two groups. A
regression model of simple order was used to determine the relation between serum leptin concentrations and plasma insulin and between plasma insulin concentrations and percentage of body fat. A polynomial regression model of second order was used to detect a relationship between percentage body fat and serum leptin concentrations.

Results
Serum leptin levels increased similarly during glucocorticoid treatment (p < 0.02) and during combined administration of glucocorticoids and GH (p < 0.002) (Fig. 1). Serum leptin levels for control subjects remained unchanged (+1.3 ± 13.1% NS).

Serum leptin levels before treatment on day 1 correlated significantly with percentage of body fat estimated by BIA (p < 0.0002; r = 0.688). The percentage body fat (Table 1) remained unchanged in the glucocorticoid group, whereas it decreased in the subjects receiving GH (p < 0.001 and p < 0.0005 vs glucocorticoid group).

Plasma insulin (Table 1) levels before treatment (day 1) were correlated significantly with serum leptin levels (p < 0.0001; r = 0.683) and with percentage body fat (p < 0.05; r = 0.468). Plasma insulin levels increased significantly in both groups during treatment (p < 0.005 or less); the increase was more pronounced in the group receiving GH compared to those receiving glucocorticoids alone (p < 0.005).

Resting energy expenditure (REE) (Table 1) remained unchanged in the glucocorticoid group, whereas it increased in the subjects receiving GH (p < 0.005 vs glucocorticoid group).

Discussion
The data obtained during the baseline study demonstrated that serum leptin concentrations correlated significantly with body fat mass, estimated by BIA and plasma insulin levels, in agreement with a previous study (4). When glucocorticoids were administered in supraphysiological amounts, serum leptin levels increased after 1 week without a change of body fat mass or resting energy expenditure. The increase in serum leptin is consistent with previous data on increased ob gene expression in glucocorticoid treated rats (9). On the other hand, combined treatment with GH still resulted in an increase in serum leptin levels, although percentage body fat mass decreased and energy expenditure increased. It is possible that the decrease in percentage body fat during GH was overestimated due to changes of total body water. However, the lipolytic effect of GH is well established and a decrease of body fat during treatment with GH has been demonstrated in numerous studies (12–17).

In both groups of subjects, plasma insulin levels increased significantly. These data, and the finding that ob gene mRNA in rats is up-regulated by an increase in plasma insulin concentrations (6–8), suggest a more important role of insulin in the regulation of serum leptin than of body fat mass. In addition, the increase in glucocorticoid turnover observed in obesity (18) may also increase serum leptin concentrations in obese humans. It is possible that GH increases leptin levels either directly and/or by increasing insulin levels, thereby causing a loss of body fat. Alternatively, the marked increase in plasma insulin levels in the combination group as compared to the group receiving glucocorticoids alone was responsible for the increase in leptin secretion despite the drop of body fat mass.

In conclusion, the paradoxical finding of increased serum leptin concentrations with decreased fat mass during treatment with glucocorticoids and GH indicates a major hormonal regulation of serum leptin concentrations.

Table 1. Plasma insulin concentrations, resting energy expenditure (REE) and percentage body fat.

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucocorticoids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated fat mass</td>
<td>15.5 ± 0.7</td>
<td>16.3 ± 0.9</td>
</tr>
<tr>
<td>(percentage of body fat)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin (pmol/l)</td>
<td>46 ± 6</td>
<td>91 ± 13*</td>
</tr>
<tr>
<td>REE (kcal/24 h)</td>
<td>1699 ± 68</td>
<td>1743 ± 54</td>
</tr>
<tr>
<td><strong>Glucocorticoids + GH</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated fat mass</td>
<td>15.1 ± 0.7</td>
<td>12.5 ± 0.4b</td>
</tr>
<tr>
<td>(percentage of body fat)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin (pmol/l)</td>
<td>50 ± 4</td>
<td>347 ± 28b</td>
</tr>
<tr>
<td>REE (kcal/24 h)</td>
<td>1590 ± 59</td>
<td>1859 ± 102b</td>
</tr>
</tbody>
</table>

* p < 0.005 vs day 1 (N = 30) by ANOVA.

b p < 0.001 vs day 1 and glucocorticoid group (N = 30) by ANOVA.
Acknowledgments. Supported by Grant No. 32-39747.93 of the Swiss National Science Foundation.

References


Received June 6th, 1996
Accepted July 5th, 1996