Leptin treatment markedly increased plasma adiponectin but barely decreased plasma resistin of ob/ob mice

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First published May 4, 2004; 10.1152/ajpendo.00488.2003.—Adiponectin (ApN) and leptin are two adipocytokines that control fuel homeostasis, body weight, and insulin sensitivity. Their interplay is still poorly studied. These hormones are either undetectable or decreased in obese, diabetic ob/ob mice. We examined the effects of leptin treatment on ApN gene expression, protein production, secretion, and circulating levels of ob/ob mice. We also briefly tackled the influence of this treatment on resistin, another adipocytokine involved in obesity-related insulin resistance. Leptin-treated (T) obese mice (continuous sc infusion for 6 days) were compared with untreated lean (L), untreated obese (O), and untreated pair-fed obese (PF) mice. Blood was collected throughout the study. At day 3 or day 6, fat pads were directly analyzed (mRNA, ApN content) or cultured for up to 24 h (ApN secretion). The direct effect of leptin was also studied in 3T3-F442A adipocytes. Compared with L mice, ApN content of visceral or subcutaneous fat and ApN secretion by adipose explants were blunted in obese mice. Accordingly, plasma ApN levels of O mice were decreased by 50%. Leptin treatment of ob/ob mice increased ApN mRNAs, ApN content, and secretion from the visceral depot by 50–80%. Leptin also directly stimulated ApN mRNAs and secretion from 3T3-F442A adipocytes. After 6 days of treatment, plasma ApN of ob/ob mice increased 2.5-fold, a rise that did not occur in PF mice. Plasma resistin of T mice was barely decreased. Leptin treatment, but not mere calorie restriction, corrects plasma ApN in obese mice by restoring adipose tissue ApN concentrations and secretion, at least in part, via a direct stimulation of ApN gene expression. Such a treatment only minimally affects circulating resistin. ApN restoration could, in concert with leptin, contribute to the metabolic effects classically observed during leptin administration.

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solved in 5 mM sodium citrate (pH 4) and administered for 6 (or 3) days to T mice as a continuous subcutaneous infusion (20 μg/day) via an osmotic minipump. Although food intake was normalized at constant delivery of the lower amount of the hormone, this dosage was found to be necessary to normalize metabolic parameters, hyperthermia, and uncoupling protein expression in ob/ob mice (23). The minipump (Alzet model 2001; Alza, Palo Alto, CA) was implanted in the interscapular region of mice under light anesthesia. Mice from the other groups received pumps filled with vehicle. Unlike other animals fed ad libitum, PF mice received a restricted amount of food similar to that spontaneously ingested by T mice; this amount was adjusted daily and administered in two rations (one-third at 1000 and two-thirds at 2200). At the beginning of the study, the groups of ob/ob mice were matched for body weight and fed blood glucose (see Fig. 1). They were also matched, as seen a posteriori, for fed plasma insulin and adiponectin levels sampled on day 0 (see Figs. 1 and 2).

Body weight and food intake were measured daily. On several occasions, tail vein blood was collected from fed mice (between 0800 and 0900). At the end of the experiment, the mice were killed by decapitation (between 0800 and 1000), and larger blood samples were also saved. Pairs of visceral (intrapерitoneal-retrovesical) and subcutaneous (inguinal) white fat pads and interscapular brown adipose tissue were immediately removed and either frozen in liquid nitrogen and stored at −70°C or immediately used for ex vivo studies (adipose tissue culture).

The University Animal Care Committee approved all procedures.

**Culture of adipose explants and 3T3-F442A adipocytes.** Small fragments of mouse visceral and inguinal adipose tissue (2–3 mm³; explants) were prepared and cultured in MEM with Earle’s salts, supplemented with 0.5% BSA and antibiotics as described (15). It proved necessary to culture 400-mg adipose tissue for 24 h to obtain detectable amounts of ApN secreted into medium by fat from obese mice. These experimental conditions were therefore extended to all groups of mice. ApN secretion was linear for ≤24 h in each group. Aliquots of medium were saved during the culture and stored at −20°C.

Mouse 3T3-F442A preadipocytes were grown at 37°C in 5% CO₂ in basal medium (i.e., DMEM with 1 g/l glucose containing 10% FCS, 8 mg/l biotin, and antibiotics) (38). Two days after confluence, cells were induced to differentiate in induc- 

**Northern blot analysis and real-time PCR.** Total RNA from adipose tissue was subjected to Northern blot analysis (21). The cDNA probes for mouse ApN and TNF-α have been described elsewhere (15, 43). The cDNA probe for mouse resistin was obtained after RT-PCR on total RNA from mouse adipose tissue (sense primer 5’ TTCCTGTCCCTGAACTGC

3’ and antisense primer 5’ TGGAACACGCTCACCT 3’). After hybridization with the radiolabeled probes (15), optical densities (OD) of the mRNA bands on the autoradiograms and of 18S rRNA on the membranes were quantified by scanning densitometry. Levels of specific mRNA were expressed relative to those of 18S rRNA.

ApN mRNAs from 3T3-F442A adipocytes were measured by real-time PCR. Total RNA (2 μg) was reverse transcribed using oligo(dT) primers and Superscript II Reverse Transcriptase (Life Technologies, Leek, The Netherlands). Total RNA equivalents (40 ng) were amplified with iQ Syber Green Supermix (Bio-Rad Laboratories, Brussels, Belgium) containing 300 nM of each specific primer by use of the iCycler iQ Real Time PCR Detection System (Bio-Rad). The primers designed for ApN were 5’ GCGAGATGCGACTCTGTGA 3’ (sense) and 5’ CTTTGCTCTGATCTATTC 3’ (antisense), and those for rat were cyclophilin 5’ ACCCCACGGTGTTCTTC 3’ (sense), and those for rat were cyclophilin 5’ TGCCCTCTCTTACCTC 3’ (antisense). The threshold cycles (Ct) for ApN and cyclophilin were measured in separate tubes and in duplicate. The amount of ApN mRNA, normalized to cyclophilin mRNA, was expressed relative to the respective control culture condition and calculated as 2^{-ΔΔCt}}, (13).

**Quantification of ApN and resistin.** ApN concentrations were measured in plasma, culture medium, or homogenized adipose tissue samples (15). Aliquots from plasma (0.5 μl), medium (30 μl, Western blot; 100 μl, RIA), or tissue homogenates (2.5- to 10-μg protein) were analyzed by Western blot, as described (15), or by RIA (Linco Research, St. Charles, MO). There was a close correlation between absolute ApN levels obtained by both methods (P < 0.0001). Two species of ApN were detected on Western blots (15): one that migrates like recombinant ApN as a 30-kDa band (immature form), and the other found in plasma and in culture medium that migrates as a 32-kDa band (mature, posttranslationally modified form) (see Figs. 2 and 3D). In adipose tissue homogenates, both forms of ApN could be detected (see Fig. 3C).

Resistin levels were measured in duplicate on diluted (1:5) plasma samples using an ELISA kit (Phoenix Pharmaceuticals, Belmont, CA). These results were confirmed by a mouse resistin RIA kit (Linco).

**Other analytical procedures.** Blood glucose was measured using a glucometer (Elite, Bayer, Brussels, Belgium). Plasma insulin, corticosterone, total cholesterol, and triglyceride levels were determined as described (5, 44). Protein concentrations in tissue homogenates were measured by the Bradford method.

**Statistical analysis.** Results are given as means ± SE for the indicated number of mice. Multiple comparisons were carried out by ANOVA or by repeated-measures ANOVA followed by the Newman-Keuls test, and comparisons between two conditions were by unpaired or paired Student’s t-test or by a nonparametric test when appropriate. Differences were considered statistically significant at P < 0.05.

**RESULTS**

Initial body weights and daily food consumption of ob/ob mice were about twofold higher than those of L mice (Fig. 1A). Except for a decrease in food consumption that occurred immediately after surgery in all groups of mice, these parameters remained rather stable in L and O mice throughout the
In contrast, leptin-treated mice presented a progressive decrease in body weight (about −15% at day 6) and a persistent and marked reduction in food intake. PF mice behaved similarly: their body weight and food intake paralleled those of T mice. Weights of brown adipose tissue from the interscapular region and white fat pads from two depots were heavier in O than in L mice (on the average ~4-fold for brown fat and ~13-fold for white fat; Table 1). As described (23), leptin treatment caused a marked decrease in brown adipose tissue weight, likely as a result of enhanced sympathetic tone (45). Both leptin and calorie restriction reduced inguinal (34), but not retrovesical, fat mass of obese mice (Table 1).

Obese mice were hyperglycemic and hyperinsulinemic compared with lean mice (Fig. 1B). Leptin treatment resulted in a normalization of plasma glucose and insulin levels, which decreased to values similar to those of L mice from the 6th or the 3rd day onward. Mere calorie restriction in PF mice also decreased to values similar to those of L mice from the 6th or 3rd day onward. Likewise, leptin, but not pair-feeding, normalized the hypercholesterolemia that otherwise occurred in O mice. Treatment with the adipokine also attenuated plasma triglycerides (Table 1).

ApN circulates as a 32-kDa isof orm in plasma of the four groups of mice (Fig. 2). Initial plasma ApN concentrations were 50% lower in ob/ob mice than in lean mice. These levels remained fairly stable in O and L mice during the experiment. Leptin treatment for 6 days induced a 2.5-fold rise in circulating ApN that actually exceeded L values, whereas no changes otherwise occurred in O mice. Treatment with the adipokine also attenuated plasma triglycerides (Table 1).

ApN mRNA levels were measured in several adipose tissue sites. In brown adipose tissue, the ApN gene was not affected by 10.2210.33.5 on June 12, 2017 http://ajpendo.physiology.org/ Downloaded from
ApN concentrations were expressed as OD per milligram of tissue (not shown).

ApN secreted in medium by adipose explants from mice of the four groups was measured after 24 h of culture (Fig. 3D). Only the 32-kDa species (mature isoform) was secreted by either lean or ob/ob explants. The pattern of ApN secretion paralleled that of overall tissue ApN. Depot-specific differences in secretion were observed in L mice (P < 0.05 between regions). In addition, ApN secretion was markedly suppressed in both depots of O mice (by 70% and 50% in visceral and inguinal fat, respectively; P < 0.05 or less). Eventually, leptin treatment partially restored ApN secretion in visceral fat (65% increase compared with O values), whereas calorie restriction was without effect.

Because TNF-α is involved in obesity-related insulin resistance and is known to downregulate ApN secretion (17, 36), we examined whether the correction of circulating ApN levels brought about by leptin was explained by changes in TNF-α. TNF-α mRNA levels were measured in visceral and inguinal fat of the four groups of mice (Table 2). In lean mice, TNF-α mRNA levels were expressed more in visceral than in inguinal fat. Compared with L mice, the TNF-α gene was overexpressed in inguinal fat of O mice (4.5-fold). However, leptin treatment or calorie restriction did not modify TNF-α mRNA abundance (whether expressed per 18S rRNA or mg tissue) in any depots at any time (data not shown (day 3) and Table 2 (day 6)).

To assess whether leptin directly affected ApN gene expression, this adipocytokine was added to the culture medium of fully differentiated 3T3-F442A adipocytes for 6 days. After 24 h of culture, leptin increased ApN gene expression and secretion by 200 and 50%, respectively (Fig. 4).

Besides ApN, we examined whether leptin treatment of obese mice could also influence resistin, another adipocytokine, which is believed to play a role in the pathogenesis of the obese insulin-resistant syndrome (Table 2). In lean mice, resistin mRNA levels exhibited a depot-specific pattern of expression similar to that of ApN and TNF-α. As reported (32, 39, 51), resistin mRNA levels were decreased in visceral fat of O mice. Leptin treatment for 6 days markedly suppressed resistin gene expression in both depots of ob/ob mice (60–70% compared with O values), whereas mere calorie restriction induced a smaller decrease (~25%) in the visceral depot only (Table 2). Differences between all groups were amplified further when data were expressed per milligram of adipose tissue (not shown). The effect of leptin on resistin mRNA levels was not detected at day 3 (not shown). As expected for a cytokine inducing insulin resistance, plasma resistin levels were ~25% higher in O mice than in L mice. Leptin treatment for 6 days tended to slightly decrease plasma resistin levels (11% compared with O values; P = 0.099), whereas pair-feeding was ineffective.

**DISCUSSION**

Leptin treatment, but not mere calorie restriction, reverses low circulating ApN levels in ob/ob mice, at least in part by restoring ApN concentrations and secretion in the visceral depot.

Plasma ApN levels were reduced in leptin-deficient ob/ob mice, as described in leptin-resistant db/db mutants (36, 52). Concomitantly, ApN mRNA levels were downregulated in...
Fig. 3. Effects of leptin treatment on ApN gene expression (A and B), tissue levels (C), and secretion (D) from fat of ob/ob mice. Visceral and inguinal adipose tissues of L, O, T, and PF mice were sampled after 6 days, except for A (3 days). Tissues were either stored for subsequent measurements of ApN mRNA or ApN content (A-C) or directly cultured to allow determination of ApN secretion (D). A and B: ApN mRNA levels were quantified by scanning densitometry of autoradiographic signals from Northern blots, normalized for 18S rRNA bands. Results were then expressed as % of values obtained in visceral fat of L mice. Representative blots, with 10 μg total RNA loaded on each lane, are shown in insets. C: tissue ApN levels were determined by Western blotting (a representative blot is shown). Aliquots of tissue homogenates (10 μg protein) were loaded on each lane, and density of ApN bands was scanned. Data were calculated as optical density (OD) units normalized for aliquote protein content. ApN levels were then expressed as % of values obtained in visceral fat of L mice. D: ApN secreted by adipose explants was measured in medium after 24 h of culture. Equal volumes (30 μl) of culture medium were loaded on each lane. Only the 32-kDa species of ApN was detected on Western blots (see inset). ApN levels were calculated as ng/mg adipose tissue and then expressed as % of values obtained with visceral explants of L mice. Absolute values of ApN secretion in L controls were 2.2 ± 0.1 ng/mg adipose tissue. Results are means ± SE for 3–4 mice per group (3rd series) in A, for 11 L, 9 O, 13 T, and 7 PF mice in B (animals selected at random from the first 2 series), 6–7 mice per group in C (animals from the 1st series), and 3, 4, 6, and 7 mice in D (second series). +P < 0.05 for T vs. O mice, *P < 0.05 for T vs. PF mice, #P < 0.05 for O vs. PF mice. Each parameter of O, T, or PF mice was significantly different from the respective value of L mice (except for visceral depot in A). Depot-specific differences (visceral vs. inguinal) were also statistically significant for each parameter of L mice.

visceral fat [Fig. 3B and as previously reported (25, 37)] but were upregulated in subcutaneous fat. However, when data were expressed per milligram of adipose tissue, ApN mRNAs dropped in both depots of ob/ob mice and were closely related to low tissue ApN content and ApN secretion. Although attenuated by enlarged fat mass, these reductions, together with other variables such as expanded circulating volume (54), could contribute to lower circulating ApN levels in ob/ob mice. As far as the relative contribution of tissue ApN to systemic levels is concerned, comparisons within the different groups of obese mice may be more straightforward because more variables are controlled (fat mass, plasma volume, and the like).

In agreement with acute (48-h) fasting (19, 55), calorie restriction imposed on ob/ob mice for 6 days did not alter circulating ApN levels. By contrast, chronic dietary restriction for 4–8 mo resulted in elevated plasma ApN in normal mice (2) and obese humans (53).

Unlike mere calorie restriction, leptin treatment for 6 days strikingly increased plasma ApN levels of ob/ob mice. This was accompanied by a partial restoration of tissue ApN concentrations and secretion that occurred in a depot-specific manner, as reported for thiazolidinediones (10). This restoration was preceded by a rise in ApN mRNA levels. Although the increases in adipose tissue ApN mRNA, content, and secretion were substantial (~50–80% of untreated O or PF values), these changes (per g tissue) may appear relatively small compared with values of L mice. However, they could be involved in the correction of plasma ApN, as obese T mice still preserved a large excess of ApN-producing white fat mass (see Table 1). The rise in ApN mRNA triggered by leptin was transient: detected at day 3, but no longer at day 6 of treatment. One may raise the possibility that the (over)correction of plasma ApN observed in T mice had exerted a negative feedback on its own mRNA levels at day 6. Alternatively, pulsatile, rather than continuous, administration of leptin (7) could be required to produce a sustained rise in the mRNA levels. As in humans (19), in our mice, acute leptin treatment (~58 h) did not affect plasma ApN levels. Yet, changes in ApN mRNA levels may already have occurred, as shown in our study.

Several mechanisms could theoretically contribute to leptin-induced stimulation of ApN mRNA levels. First, reduced fat
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Table 2. Effects of leptin treatment on TNF-α and resistin mRNAs in visceral and inguinal fat and on plasma resistin levels in ob/ob mice

<table>
<thead>
<tr>
<th>Adipose tissue mRNAs</th>
<th>Lean Mice L</th>
<th>ob/ob Mice O</th>
<th>ob/ob Mice T</th>
<th>ob/ob Mice PF</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inguinal</td>
<td>19.7±1.5*</td>
<td>62.0±16.3†</td>
<td>80.3±6.5†</td>
<td>58.8±6.5†</td>
</tr>
<tr>
<td>Visceral</td>
<td>100.0±12.6</td>
<td>97.4±20.7</td>
<td>88.5±13.6</td>
<td>97.6±11.9</td>
</tr>
<tr>
<td>Resistin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inguinal</td>
<td>31.5±2.4*</td>
<td>35.7±4.3</td>
<td>14.7±2.2†‡§</td>
<td>34.7±2.9</td>
</tr>
<tr>
<td>Visceral</td>
<td>100.0±3.5</td>
<td>48.2±2.9†‡§</td>
<td>14.9±1.8†‡§</td>
<td>35.7±2.8†‡ §</td>
</tr>
<tr>
<td>Plasma resistin levels, ng/ml</td>
<td>7.1±0.6</td>
<td>8.9±0.4†‡</td>
<td>8.0±0.3</td>
<td>9.0±0.7†</td>
</tr>
</tbody>
</table>

Sampling and measurements were made at end of study (day 6). mRNA levels were quantified by Northern blot analysis, normalized for 18S rRNA bands and then expressed as % of results obtained in visceral fat of L mice. Plasma resistin levels were measured by ELISA, mRNA values are means ± SE of 14, 4, 6, and 7 mice of the second series, and plasma resistin levels are means ± SE of 6 mice/group. †P ≤ 0.05 vs. the other respective fat depot; †P ≤ 0.05 vs. L; †‡§P ≤ 0.05 vs. O; †‡§P ≤ 0.05 vs. PF [ANOVA or t-test (plasma resistin)].

Mass per se could contribute. Fat mass exerts a negative feedback on its own ApN production (22). However, only T, but not PF, mice exhibited a rise in ApN levels despite similar body weight loss. Moreover, the effect of leptin occurred specifically in the visceral-retrovesical depot, whose weight did not change. Second, enhanced insulin sensitivity could be involved. Several pieces of evidence suggest that, besides being a potential effect (2, 52), increased insulin action could also be a causative factor of elevated plasma ApN (14). However, plasma ApN levels were unchanged in PF mice (this study) or in type 2 diabetic mice receiving metformin (10) despite improved glucose homeostasis. Third, changes in TNF-α might play a role. TNF-α has been found to inhibit ApN mRNA and secretion (17, 36), but this mechanism may also be excluded. Unlike thiazolidinediones (36), leptin did not suppress TNF-α mRNA in any adipose depots of obese mice. Fourth, enhanced sympathetic tone could be a potential factor. Many effects of leptin on adipocyte gene expression are centrally mediated through stimulation of the adrenergic sympathetic pathway (11, 12). Although acute exposure to β-adrenergic agonists decreased ApN mRNA levels (15, 16), longer treatment of rats (6 days) increased ApN mRNAs while exerting its expected regulation on other fat genes (55). Moreover, ApN mRNAs were decreased in denervated fat pads of rats (our unpublished data). Fifth, reversal of hypercorticosteronemia might play a part. Leptin, but not mere calorie restriction, suppresses the release of glucocorticoids (this study, and Refs. 4 and 47). Dexamethasone has been found to downregulate ApN mRNA in vitro (17, 22). Conversely, adrenalectomy increased ApN mRNA and plasma ApN in ob/ob mice (37). Thus indirect sympathetic or hormonal changes, such as attenuation of hypercorticosteronemia, may contribute to raise ApN mRNA in leptin-treated ob/ob mice. Additional mechanisms may also participate. Sixth, a direct action of leptin on adipocytes and ApN gene expression is likely to be involved. Convincing evidence that leptin acts directly on peripheral targets, including adipocytes, where it may modulate the expression of several genes, has been provided. Leptin induced gene expression of the angiogenic factor (angiopoietin-2), peroxisome proliferator-activated receptor-α, and enzymes involved in energy dissipation in cultured adipocytes (6, 8, 50). Such a direct action of leptin is further supported by our in vitro experiments in 3T3-F442A adipocytes. Thus leptin added to the medium increased ApN mRNA and secretion after 24 h of culture. Conversely, it has been recently reported that adipocyte-selective reduction of leptin receptors by antisense RNA resulted in diminished ApN gene expression (26). Besides quantitative changes in ApN levels, qualitative changes may also occur in our obese mice. The distribution of circulating oligomeric complexes of ApN may be altered in obesity, resulting in impaired protein activity. This altered distribution has been corrected after weight loss in obese patients or thiazolidinedione treatment in db/db mice (30, 42). Further work will be necessary to assess whether such a correction also takes place in our study and could participate in the improved insulin sensitivity of PF or T mice. Although leptin markedly increased absolute levels of plasma ApN, it did not decrease, or only marginally decreased,
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circulating resistin levels. Despite halved mRNA levels in one fat depot, plasma levels of resistin were elevated in ob/ob mice. This may result from enlarged resistin-producing adipose tissue mass (49) and additional resistin production by nonadipose tissue (mainly white blood and mononuclear cells, splenocytes, and pituitary gland) (35, 39, 40). Resistin is indeed involved in insulin resistance and in other inflammatory processes (35).

Unlike acute fasting (29, 48), calorie restriction for 6 days barely affected resistin parameters. In contrast, leptin treatment for the same period blunted resistin mRNA levels in both depots of obese mice. Accordingly, plasma resistin levels tended to be slightly decreased in leptin-treated mice. In humans, acute administration of leptin did not alter plasma resistin (33). In our study, the decrease of circulating resistin, if any, was tiny compared with the drop in mRNA levels. This could be explained by the contribution of nonadipose tissues to systemic resistin levels and/or by compensatory mechanisms acting at a step distal to the mRNA in adipose tissue of obese mice. Both processes could ultimately limit the profound negative effect of leptin on resistin mRNA in fat tissues.

The decrease in plasma adiponectin associated with obesity suggests that an obesity-related factor or process participates in the downregulation of ApN synthesis. Our study proposes that leptin deficiency or resistance to its action (as seen in the common forms of human obesity) may contribute. On the other hand, our work underscores the potential confounding role of ApN during leptin treatment. Because leptin and ApN share several metabolic properties (enhanced insulin sensitivity, fatty acid oxidation, thermogenesis, and weight loss), some of the effects classically attributed to leptin may be indirectly mediated or amplified by a rise in ApN levels. The slight decrease in resistin levels could enhance insulin sensitivity further.


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