Lipid deposition in rats centrally infused with leptin in the presence or absence of corticosterone

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Lipid deposition in rats centrally infused with leptin in the presence or absence of corticosterone. Am J Physiol Endocrinol Metab 281: E809–E816, 2001.—The aim of the present study was to assess whether the glucocorticoid corticosterone (Cort) modulates the effects of leptin on food intake and lipid deposition. Rats were subjected to a 6-day intracerebroventricular infusion of leptin and were either sham-adrenalectomized (Sham-ADX) or ADX and supplemented with 0 (C0), 40 (C40), or 80 mg (C80) of Cort. Investigation of potential peripheral sites of interaction of leptin and Cort included liver and plasma triglyceride (TG) content and lipoprotein lipase (LPL) activity in adipose and muscle tissues. The study confirmed the respective anorectic and orexigenic effects of leptin and Cort and revealed that the leptin-induced reduction in food intake was dampened by the high dose of Cort replacement. Such an interaction did not, however, extend to body and adipose tissue weights, which were lowered by leptin infusion independently of the Cort status. Leptin and ADX significantly reduced liver TG content and triglyceridemia, whereas Cort replacement significantly increased these variables. Central infusion of leptin also lowered plasma insulin levels, accompanied by a reduction in LPL activity of storage tissues (inguinal and epididymal white adipose tissue, 2- and 3-fold, respectively). In contrast, leptin infusion increased LPL activity in oxidative tissues (soleus and vastus lateralis muscles, 3- and 4-fold, respectively). Cort replacement prevented the ADX-induced fall in epididymal LPL activity but failed to do so in leptin-infused rats. The study demonstrates that, whereas the anorectic effect of leptin is dampened by high physiological plasma levels of corticosterone, leptin can produce its effects on body weight, lipid transport and accumulation, and adipose and muscle LPL activity in the absence or presence of an intact hypothalamic-pituitary-adrenal axis.

LEPTIN, THE ENCODING PRODUCT of the ob gene, likely plays a role in the regulation of energy balance. Secreted mainly by adipose tissue in proportion to its mass, leptin reduces energy deposition by decreasing food intake and by stimulating thermogenesis, thereby preventing fat accretion (7, 20, 25, 30, 36). In addition to the anorectic action on energy balance, leptin also influences a number of peripheral physiological processes, including insulin secretion, glucose transport, lipoprotein lipase (LPL) activity, and hypothalamic-pituitary-adrenal (HPA) activity (for review, see Ref. 49).

Glucocorticoids, especially corticosterone, whose levels are positively associated with fat accretion and obesity (8, 13), have been hypothesized to be potential modulators of the anorectic effects of leptin (51). Because leptin and corticosterone are two competitors in the regulation of energy balance, the questions that arise are whether the effects of leptin are reduced when corticosterone is present or whether they are accentuated by the absence of corticosterone. A recent study has reported that the effects of peripherally administered leptin on food intake and body weight of adrenalectomized rats were reversed by co-administration of corticosterone at a dose comparable to stress-induced production (45). It has also been reported that a single intracerebral injection of leptin reduced food intake for several subsequent days in adrenalectomized, but not in intact, rats, an effect that was prevented by peripheral administration of the type II glucocorticoid receptor agonist dexamethasone (53). These findings support the notion that glucocorticoids constitute part of the mechanisms by which leptin exerts its action on feeding. Contrastingly, a systematic investigation of a possible interaction of leptin and corticosterone by use of chronic subcutaneous infusion of the hormones in intact and adrenalectomized rats demonstrated that leptin could produce its effects on energy and fat gains in absence of an intact hypothalamic-pituitary-adrenal (HPA) axis (2). Using a similar approach, we have demonstrated the absence of any leptin-corticosterone interaction in the control of food intake and thermogenesis in genetically obese ob/ob mice (3). These findings are not unexpected, because leptin is very effective in ob/ob mice, despite the fact that they display hypercorticosteronemia (29), suggesting that high levels of corticosterone do not blunt the...
effects of leptin. Thus divergent conclusions have been drawn from studies on acute central administration and chronic peripheral infusion of leptin regarding the involvement of glucocorticoids in the effect of leptin on energy metabolism. Whether the HPA status interferes with leptin action when the hormone is chronically administered into the brain remains unknown. The assessment of such a possibility constituted the main objective of the present study.

We also wished to address in the study some of the peripheral sites of action possibly involved in the combined actions of leptin and corticosterone on fat deposition. Lipoprotein lipase (LPL) mediates the intravascular disposal of lipoprotein-bound triglycerides (TG) and partly determines the distribution of their component fatty acids between storage (adipose tissue) and oxidative (muscle) tissues. Increased adipose LPL is strongly associated with fat deposition and obesity (15, 33). Among others, we have shown that the status of both the HPA axis (27) and leptin (38) impacts LPL, at least in adipose tissue. The activity of this key permissive determinant of fat deposition was therefore determined in adipose tissue and skeletal muscle.

MATERIALS AND METHODS

Animals. Fifty male Sprague-Dawley rats initially weighing 225–250 g were purchased from Charles River Canada (St-Constant, QC, Canada). All rats were cared for and handled according to the Canadian Guide for the Care and Use of Laboratory Animals, and the protocol was approved by the institutional animal care committee. The animals were individually housed in wire-bottom cages suspended above absorbent paper and were fed ad libitum a stock diet (Charles River Rodent Diet, distributed by Ralston Products, Woodstock, ON, Canada). They were subjected to a 12:12-h light-dark cycle (lights on between 0700 and 1900) and kept under an ambient temperature of 23 ± 1°C. The rats were accustomed to these conditions during a period of 7 days, after which they were subjected to the experimental treatments, which lasted for a period of 6 days.

Treatments. Animals were assigned to a 2 × 4 factorial design. Four cohorts of rats differing in their corticosterone status [sham-adrenalec tomized (Sham-ADX) rats, ADX rats without corticosterone (C0), ADX rats with 40 mg corticosterone replacement (C40), and ADX rats with 80 mg corticosterone replacement (C80)] were infused with either sterile phosphate-buffered saline (PBS) or leptin and was primed in vitro before implantation for ≥12 h at 37°C. Corticosterone was administered using 100-mg cholesterol-based pellets, which were prepared in our laboratory and contained either no corticosterone (C0), 40% (wt/wt) corticosterone (C40), or 80% corticosterone (C80). After surgery, all groups were provided with drinking water supplemented with NaCl (0.9%).

Body weight and food intake. Throughout the study, body weight and food intake were monitored every day. Food spilled on the absorbent paper placed under the cages was carefully collected, was allowed to dry, and was accounted for in the food intake calculations.

Tissue sampling. At the end of the experimental treatment, between 0800 and 1000, rats in the fed state and under general ketamine-xylazine anesthesia were perfused intracardially with 30 ml of ice-cold isotonic saline. A portion of the liver, epididymal white adipose tissue (WE), inguinal white adipose (WI), and vastus lateralis (VLM) and soleus muscle were quickly dissected out during the saline perfusion and weighed. Approximately 50 mg from each tissue were homogenized using all-glass tissue grinders (Kontes, Vine land, NJ). Adipose tissue samples were homogenized in 1 ml of a solution containing (in mmol/l) 0.25 sucrose, 10 IU/ml heparin, and 5% (vol/vol) aprotinin (Trasylol, Miles Pharmaceuticals, Rexdale, ON, Canada), pH 7.4. Muscle samples were homogenized in 1 ml of a solution containing 1 mol/l ethylene glycol, 50 mmol/l Tris-HCl, 3 mmol/l deoxycholate, 10 IU/ml heparin, and 5% (vol/vol) aprotinin (Trasylol, Miles Pharmaceuticals, Rexdale, ON, Canada), pH 7.4. Muscle homogenates were quickly frozen at −70°C. Adipose tissue homogenates were centrifuged (12,000 g for 20 min at 4°C), and the fraction between the upper fat layer and the bottom sediment was removed, diluted with 4 volumes of the homogenization solution without deoxycholate, and stored at −70°C until LPL activity measurement.

Plasma determinations. At the time of killing, immediately before the beginning of the intracardial perfusion, an intracardial blood sample was taken in anesthetized rats. The collected blood was centrifuged, and the plasma was frozen at −70°C. Plasma corticosterone was determined by a competitive protein-binding assay [sensitivity, 58 pmol/l; interassay coefficient of variation (CV), 9.0%] using plasma from a dexamethasone-treated female rhesus monkey as the source of transcortin (32). Plasma leptin was determined using the rat leptin radioimmunoassay (RIA) kit provided by Linco Research (St. Charles, MO). Plasma insulin was also measured by RIA using a reagent kit from Linco Research, with rat insulin as standard. Plasma glucose was determined (glucose oxidase method) using a glucose analyzer (Beckman, Palo Alto, CA). Plasma TG were measured by an enzymatic method with a reagent kit from Boehringer Mannheim (Montreal, QC, Canada), which allowed correction for free glyco-
Erol. Plasma nonesterified fatty acid (NEFA) levels were determined enzymatically with a reagent kit from Wako Pure Chemical Industries (Richmond, VA).

**Tissue measurements.** Frozen liver samples were thawed, and total lipids were extracted and solubilized in isopropanol. TG in the lipid extracts were then quantitated using the above-mentioned reagent kit. LPL activity was measured in 100 µl of thawed adipose and muscle tissue homogenates, which were incubated under gentle agitation for 1 h at 28°C with 100 µl of a substrate mixture consisting of 0.2 M Tris-HCl buffer, pH 8.6, which contained 10 Mbg/l (carboxyl-14C) triolein and 2.52 mM cold triolein emulsified in 5% gum arabic, 10% human serum as source of apolipoprotein C-II, and either 0.2 or 2 M NaCl. Free olate released by LPL was then separated from intact triolein and mixed with Universal (New England Nuclear, Montreal, QC, Canada), and sample radioactivity was determined in an LKB rack-β liquid scintillation counter. LPL activity was calculated by subtracting non-LPL lipolytic activity determined in a final NaCl concentration of 1 M from total lipolytic activity measured in a final NaCl concentration of 0.1 M. Tissue LPL activity was expressed as microunits (1 µU = 1 µmol NEFA released/h incubation at 28°C). The interassay CV was 4.8% and was determined using bovine skin milk as a standard source of LPL. Protein content of the tissue extracts was determined by the method of Lowry et al. (26). LPL activity is expressed as specific activity of LPL (µU/g tissue protein).

**Statistical analyses.** Data are expressed as means ± SE. A 2 × 4 factorial analysis was used to evaluate the main and interaction effects of intracerebroventricular infusion (PBS and 2 µg/day leptin) and corticosterone status (Sham-ADX, ADX-C0, ADX-C40, ADX-C80). When mean variances were not homogeneous, data were log transformed before ANOVA and 2

### RESULTS

Central leptin infusion and ADX both exerted anorectic effects that were additive (Table 1). The intracerebroventricular infusion and the corticosterone status interacted significantly on food intake. Indeed, whereas leptin decreased food intake in sham-ADX, C0, and C40 groups, it failed to do so in ADX rats receiving the high dose of corticosterone (C80). Leptin infusion also decreased final body weight. In contrast to its stimulating effect exerted on food intake, corticosterone supplementation did not maintain body weight over ADX levels, nor did it significantly affect weights of WE, WI, VLM, and soleus muscle. Factorial analysis demonstrated that ICV leptin infusion significantly reduced body and tissue weights independently of the presence or absence of corticosterone, since no leptin-corticosterone interaction was observed.

ICV leptin infusion blunted endogenous levels of plasma leptin, especially in ADX animals and in rats supplemented with corticosterone (4-fold, 12-fold, and 5-fold reduction in C0, C40, and C80 groups, respectively; Fig. 1A). The corticosterone status significantly impacted plasma leptin, which rose with increasing corticosteronemia. As expected, removal of the adrenals through ADX significantly reduced plasma corticosterone levels (Fig. 1B). Corticosterone replacement dose-dependently increased corticosteronemia in both PBS- and leptin-infused rats. A decrease in plasma glucose was observed after intracerebroventricular leptin infusion, which was accentuated by ADX, whereas corticosterone replacement tended to maintain glycemia to sham-ADX levels (Fig. 1D). The leptin-induced decrease in glycemia was accompanied by a sixfold reduction in insulinemia, which was not significantly affected by the corticosterone status (Fig. 1C).

The ICV infusion and corticosterone status exerted main but no interactive effects on plasma and liver TG content. Leptin infusion reduced plasma TG sevenfold independently of corticosterone levels, and ADX animals displayed significantly lower triglyceridemia than sham-ADX animals (Fig. 2A). Liver TG content, an index of long-term liver TG synthetic activity, was reduced by leptin (Fig. 2B). ADX also reduced liver TG content, which was increased dose dependently by corticosterone supplementation. Plasma NEFA levels, which partly determine rates of liver TG synthesis, were altered neither by leptin nor by the corticosterone status (data not shown).

### Table 1. Food intake and final body and adipose and muscle tissue weights

<table>
<thead>
<tr>
<th>Cort Status</th>
<th>Infusion</th>
<th>Food Intake, g/day</th>
<th>Final Body Wt</th>
<th>WE Wt</th>
<th>WI Wt</th>
<th>VLM Wt</th>
<th>Soleus Wt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham-ADX</td>
<td>PBS</td>
<td>22.1 ± 1.0a</td>
<td>326.3 ± 5.5</td>
<td>1.3 ± 0.04</td>
<td>1.07 ± 0.07</td>
<td>1.0 ± 0.03</td>
<td>0.126 ± 0.006</td>
</tr>
<tr>
<td>C0</td>
<td>Leptin</td>
<td>10.9 ± 0.9b</td>
<td>286.4 ± 8.2</td>
<td>1.04 ± 0.21</td>
<td>0.53 ± 0.07</td>
<td>0.86 ± 0.08</td>
<td>0.121 ± 0.006</td>
</tr>
<tr>
<td>C40</td>
<td>PBS</td>
<td>14.0 ± 1.5b</td>
<td>301.7 ± 9.0</td>
<td>1.0 ± 0.07</td>
<td>0.80 ± 0.09</td>
<td>0.97 ± 0.03</td>
<td>0.123 ± 0.006</td>
</tr>
<tr>
<td>C80</td>
<td>Leptin</td>
<td>4.4 ± 0.6c</td>
<td>253.5 ± 13.0</td>
<td>0.61 ± 0.11</td>
<td>0.45 ± 0.08</td>
<td>0.94 ± 0.04</td>
<td>0.108 ± 0.006</td>
</tr>
<tr>
<td></td>
<td>PBS</td>
<td>18.3 ± 1.7c</td>
<td>313.8 ± 5.6</td>
<td>1.38 ± 0.06</td>
<td>1.05 ± 0.12</td>
<td>1.0 ± 0.07</td>
<td>0.121 ± 0.003</td>
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<tr>
<td></td>
<td>Leptin</td>
<td>7.5 ± 1.0d</td>
<td>248.1 ± 6.9</td>
<td>0.42 ± 0.11</td>
<td>0.39 ± 0.05</td>
<td>0.83 ± 0.04</td>
<td>0.097 ± 0.011</td>
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<tr>
<td></td>
<td>PBS</td>
<td>17.0 ± 3.3e</td>
<td>307.7 ± 8.0</td>
<td>1.42 ± 0.09</td>
<td>0.94 ± 0.12</td>
<td>0.87 ± 0.05</td>
<td>0.134 ± 0.005</td>
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<tr>
<td></td>
<td>Leptin</td>
<td>12.0 ± 0.8f</td>
<td>249.9 ± 8.2</td>
<td>0.69 ± 0.22</td>
<td>0.51 ± 0.14</td>
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<td>0.102 ± 0.004</td>
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<td></td>
</tr>
<tr>
<td>Leptin (L)</td>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.03</td>
<td>0.0002</td>
</tr>
<tr>
<td>Corticosterone (C)</td>
<td></td>
<td>0.0004</td>
<td>0.01</td>
<td>0.31</td>
<td>0.35</td>
<td>0.46</td>
<td>0.14</td>
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<tr>
<td>Interaction (L × C)</td>
<td></td>
<td>0.01</td>
<td>0.68</td>
<td>0.21</td>
<td>0.39</td>
<td>0.35</td>
<td>0.19</td>
</tr>
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Data represent means ± SE of 5–6 animals per group of food intake and final body and adipose and muscle tissue weights (g) after a chronic ivc infusion for 6 days with PBS or leptin (2 µg/day) in rats differing in their corticosterone status (sham-adrenalectomized (Sham-ADX), ADX without corticosterone (Cort; C0), ADX with 40% corticosterone replacement (C40), and ADX with 80% corticosterone replacement (C80)). WE, epididymal white adipose tissue; WI, inguinal white adipose tissue; VLM, vastus lateralis muscle. * Means in this column not sharing the same superscript are significantly different from each other (P < 0.05).
Figure 3 illustrates the effects of intracerebroventricular leptin infusion and corticosterone status on tissue LPL specific activities. Intracerebroventricular leptin infusion significantly reduced LPL activity in WE and WI by two- and threefold, respectively (Fig. 3, A and B), whereas ADX alone reduced LPL only in the WE depot. The intracerebroventricular infusion and corticosterone status interacted on WE LPL activity. The interaction stemmed from the fact that the lowering effect of leptin infusion and ADX were not additive and that corticosterone replacement prevented the ADX-induced, but not the leptin-induced, fall in WE LPL. In contrast, leptin significantly increased LPL activity in VLM and soleus muscle four- and threefold, respectively (Fig. 3, C and D), independently of the corticosterone status. Corticosterone replacement in ADX animals significantly stimulated soleus LPL activity in both PBS- and leptin-infused animals.

**DISCUSSION**

The present study demonstrates that, whereas the anorectic effect of centrally infused leptin is dampened by increasing doses of corticosterone, the ability of leptin to reduce body weight, fat deposition, and LPL activity in white adipose tissue, plasma and liver TG levels, glycemia, and insulinemia is not influenced by corticosterone levels within the physiological range. In fact, leptin even decreased adipose LPL activity to a greater extent in ADX rats treated with the highest dose of corticosterone used in the study (WE, 3-fold and WI, 4-fold decrease) than it did in nonsupplemented ADX rats (WE, no change and WI, two-fold decrease). In addition, leptin increased muscle LPL activity, and this effect was also not reduced by corticosterone, further supporting the notion that glucocorticoids are not
inhibitory to leptin action on peripheral lipid metabolism.

Intracerebroventricular infusion of leptin decreased circulating levels of leptin, possibly by reducing adipose tissue mass, as well as those of insulin, perhaps through reduced secretion due to a leptin-mediated activation of the sympathetic nervous system (31). In fact, central injection of leptin may represent a potent stimulator of the sympathetic nervous system, which has been reported to inhibit leptin secretion via a β-adrenergic mechanism (50). The reduction in insulinemia caused by leptin infusion could also have contributed to reduce circulating levels of leptin, insulin being a stimulator of leptin secretion (4, 6). In contrast to the effects of intracerebroventricular infusion of leptin, peripheral administration of corticosterone increased circulating levels of leptin. This effect, which is consistent with previous findings (11, 23, 28, 46), occurred without being associated with significant effects of corticosterone on fat mass. That glucocorticoids can exert a direct effect on leptin synthesis has been previously reported (6, 12).

We have previously reported a lack of significant interaction between leptin and corticosterone on food intake in studies that had used somewhat lower doses (≤30%) of corticosterone (2, 3). In the present study, a significant interaction of leptin and corticosterone on food intake was observed with higher doses of corticosterone (≥80%), which nevertheless resulted in plasma hormone concentrations within the range of its circadian rhythm (40). Such a dampening of the anorectic effect of leptin by high levels of circulating corticosterone agrees with the study of Solano and Jacobson (45) in mice and that of Zakrzewska et al. (53) in dexamethasone-treated ADX rats given a single intracerebroventricular injection of leptin. Taken together, these findings support the notion that corticosterone counteracts the anorectic effect of leptin when the glucocorticoid reaches sufficiently high plasma levels.

The ability of corticosterone to antagonize leptin action on food intake did not extend to body and adipose tissue weights, which were lowered by leptin as efficiently in the presence or absence of corticosterone. In fact, examination of the data of Table 1 shows that leptin even tended to reduce body and adipose weight relatively more strongly in intact and corticosterone-supplemented rats than in nonsupplemented ADX animals. The observation that leptin can exert its effects on energy balance in the presence of corticosterone is consistent with the fact that leptin is very efficient at inhibiting fat deposition in ob/ob mice (7, 20, 36), which exhibit very high levels of corticosterone (29) and an enhanced sensitivity to the action of glucocorticoids (48). The present findings on body and fat gain, which are also consistent with those of previous studies carried out in this laboratory (2, 3), are, however, at least partly at variance with those of Solano and Jacobson (45), who reported that corticosterone can prevent the effect of leptin on both food intake and fat deposition, and with the finding of Zakrzewska et al. (53), which showed a complete reversal of leptin-induced body weight loss in ADX rats by dexamethasone. It is noteworthy that, in the study of Solano and Jacobson, corticosterone was effective at blocking the effect of leptin on fat deposition only when provided at a high dose, equivalent to stress-induced production, which did not, however, block the reducing effect of leptin on neuropeptide Y expression and circulating levels of insulin. These results could indicate that corticosterone compensates for the effects of leptin through some pathways that are independent of those modulated by leptin, a notion supported by the robust effects of ADX...
on energy balance in animal models such as the db/db mouse that totally lack responsiveness to leptin (43). In addition, it must be pointed out that Solano and Jacobson, in agreement with our results, reported an effect of leptin on carcass fat that was stronger in ADX mice treated with a moderate dose of corticosterone than in ADX mice not supplemented with glucocorticoids. This effect on fat deposition occurred in corticosterone-supplemented animals without any marked reduction in their food intake (45), suggesting that leptin may, as we suggested earlier (3), strongly act on thermogenesis in the presence of corticosterone, which is a strong inhibitor of the activity of brown adipose tissue in rodents (18, 47). The fact that, in the present study, the corticosterone-associated reduction in the efficiency of leptin to reduce food intake was not reflected in body or adipose gain strongly suggests that leptin retained its thermogenic action in the presence of corticosterone. This concept is further supported by our previous finding of a strong stimulatory action of peripheral leptin infusion on uncoupling protein-1 expression in brown adipose tissue, which was not affected by the corticosterone status (3). Hence, it appears that circulating corticosterone higher than the physiological levels reached in the present study (45), or glucocorticoid receptor agonists more potent than the natural hormone (53), are needed to overwhelm the strong thermogenic action of leptin. It is conceivable that the independent central signaling pathways of leptin and glucocorticoids may converge at the level of distal effectors regulating energy balance and that supraphysiological levels of one hormone may come to overwhelm the actions of the other.

In laboratory rodents, except perhaps in the ob/ob mouse, intracerebroventricular infusion of leptin appears much more efficient in altering energy balance than the peripheral administration of the hormone (this study and Refs. 19 and 52). In the present study, intracerebroventricular infusion of leptin induced a reduction in body weight that was accompanied by a decrease in lipid deposition in all adipose depots assessed. In contrast, leptin only mildly affected the deposition of lean mass. As discussed above, the energy deficit led to by brain infusion of leptin was probably accounted for by both a reduction in food intake and an increase in thermogenesis (21, 30, 42).

Centrally infused leptin reduced glycemia, insulinemia, and triglyceridemia, as previously reported (1, 10, 44), as well as liver TG content. These effects remained robust in the presence of corticosterone, which otherwise exerted independent, opposite effects on these variables except insulinemia. The reduction in growth of adipose tissue in leptin-treated rats was accompanied by a marked decrease in LPL activity in adipose tissues and an increase in muscle LPL activity. These findings indicate that leptin favors the routing of circulating TG toward oxidative rather than storage tissues through the tissue-specific modulation of LPL activity. It is unlikely that the reduction in leptin levels per se after leptin infusion had any significant impact on LPL activity. Recent in vitro studies have indeed demonstrated that, in isolated adipocytes and muscle cells, leptin has no direct effect on glucose transport, LPL activity, and insulin action (39). The effects of leptin treatment on tissue LPL activity may have instead been caused by some of the concomitant metabolic changes. In agreement with previous findings (17, 22, 34), leptin infusion led to a marked reduction in insulinemia, which could have largely contributed to the reduction in adipose tissue LPL and increase in muscle LPL, insulin being a key modulator of the tissue-specific activity of the enzyme (5, 16, 37). The fact that insulinemia was positively correlated with LPL activity in WE (r = 0.42, P = 0.005) and WI (r = 0.62, P = 0.0001) and inversely correlated with LPL in VLM (r = −0.56, P = 0.0001) and soleus muscle (r = −0.39, P = 0.009) supports this concept. In addition, the possible contribution of a leptin-induced activation of the sympathoadrenal system (24, 41) must be considered, because the latter exerts tissue-specific actions on LPL that oppose those of insulin (14) and which are congruent with those of leptin infusion observed in the present study. On the other hand, whereas corticosterone replacement prevented the ADX-induced fall in LPL activity in EW of PBS-infused rats, as reported earlier by us (13, 27), it failed to do so in leptin-treated animals. These effects of leptin and corticosterone on adipose LPL are congruent with those on adipose weight and are likely related to the concomitant alterations in the hormonal modulators of adipose LPL discussed above.

In summary, the present study revealed that the ability of ICV leptin to reduce food intake was dampened in the presence of corticosterone, whereas leptin reduced body weight, fat deposition, and LPL activity in white adipose tissue, plasma and liver TG levels, glycemia, and insulinemia regardless of the corticosterone status. Lipid deposition and metabolism in intact and corticosterone-supplemented rats did not respond to a lesser extent to leptin than in ADX rats, as demonstrated by the strong effects of leptin on adipose mass, adipose and muscle LPL activity, and plasma and liver TG in the presence of corticosterone. These results support the view that, when present at concentrations within the physiological range, corticosterone may not be at the origin of a decreased leptin action on body weight and adiposity observed in several forms of obesity. The findings, obtained in rats infused long-term centrally with leptin, confirm earlier studies (2, 3), which showed that peripherally administered leptin and physiological levels of corticosterone do not interact on adiposity and thermogenesis, and extend this concept to variables of lipid metabolism.

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