Correction of diet-induced hyperglycemia, hyperinsulinemia, and skeletal muscle insulin resistance by moderate hyperleptinemia

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Buettner, Roland, Christopher B. Newgard, Christopher J. Rhodes, and Robert M. O'Doherty. Correction of diet-induced hyperglycemia, hyperinsulinemia, and skeletal muscle insulin resistance by moderate hyperleptinemia. Am. J. Physiol. Endocrinol. Metab. 278: E563–E569, 2000.—Human obesity and high fat feeding in rats are associated with the development of insulin resistance and perturbed carbohydrate and lipid metabolism. It has been proposed that these metabolic abnormalities may be reversible by interventions that increase plasma leptin. Up to now, studies in nongenetic animal models of obesity and in human obesity have concentrated on multiple injection therapy with mixed results. Our study sought to determine whether a sustained, moderate increase in plasma leptin, achieved by administration of a recombinant adenovirus containing the leptin cDNA (AdCMV-leptin) would be effective in reversing the metabolic abnormalities of the obese phenotype. Wistar rats fed a high-fat diet (HF) were heavier (P < 0.05), had increased fat mass and intramuscular triglycerides (mTG), and had elevated plasma glucose, insulin, triglyceride, and free fatty acids compared with standard chow-fed (SC) control animals (all P < 0.01). HF rats also had impaired glucose tolerance and were markedly insulin resistant, as demonstrated by a 40% reduction in insulin-stimulated muscle glucose uptake (P < 0.001). Increasing plasma leptin levels to 29.0 ± 1.5 ng/ml (from 7.0 ± 1.4 ng/ml, P < 0.001) for a period of 6 days decreased adipose mass by 40% and normalized plasma glucose and insulin levels. In addition, insulin-stimulated skeletal muscle glucose uptake was normalized in hyperleptinemic rats, an effect that correlated closely with a 60% (P < 0.001) decrease in mTG. Importantly, HF rats that received a control adenovirus containing the β-galactosidase cDNA and were calorically matched to AdCMV-leptin-treated animals remained hyperglycemic, hyperinsulinemic, insulin resistant, and maintained elevated mTG. We conclude that a gene-therapeutic intervention that elevates plasma leptin moderately for a sustained period reverses diet-induced hyperglycemia, hyperinsulinemia, and skeletal muscle insulin resistance, and that these improvements are tightly linked to leptin-induced reductions in mTG.

Obesity is a metabolic disorder characterized by weight gain, increased adiposity, insulin resistance, perturbed carbohydrate and lipid metabolism, and in many cases the development of non-insulin-dependent diabetes mellitus (2, 3, 7). Administration of leptin corrects the metabolic abnormalities of the ob/ob mouse, which lacks the adipocyte hormone (17, 21, 24), whereas hyperleptinemia in the normal rat reduces plasma and tissue lipids and increases insulin sensitivity (1, 5, 26). On the basis of these observations it has been proposed that leptin therapy may be effective in the treatment of human obesity.

To date, studies on the efficacy of leptin therapy in nongenetic animal models of obesity and in human obesity have concentrated on multiple injection therapy, with mixed results. Thus in high fat fed (HF) animals, a widely used model of obesity, intraperitoneal delivery of recombinant leptin reduces food intake and weight gain (4, 8). However, these studies did not address the ability of leptin therapy to reverse the metabolic abnormalities associated with high fat feeding. Human trials have reported weight loss in response to delivery of leptin by injection (7), but the losses have generally been minor compared with the weight of those individuals before the initiation of leptin therapy. Leptin injection therapy may be complicated by the short half-life of the peptide in the circulation (16, 31). Thus a more effective therapy may require a sustained, steady-state increase in leptin levels. Indeed, a recent study has demonstrated the greater effectiveness of sustained leptin increases over intraperitoneal leptin delivery in decreasing food intake and weight gain in the ob/ob mouse (16).

We have demonstrated previously that sustained, moderate hyperleptinemia can be achieved in normal rats by use of a recombinant adenovirus gene delivery system (5, 19). In the present study we have used this system to induce hyperleptinemia in the HF rat and tested the effects of this gene-therapeutic intervention on the metabolic abnormalities associated with obesity. The results demonstrate that hyperglycemia, hyperinsulinemia, and skeletal muscle insulin resistance are corrected by a sustained, moderate increase in plasma leptin.

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leptin. The reversal of skeletal muscle insulin resistance is strongly correlated to a decrease in muscle triglyceride levels.

MATERIALS AND METHODS

Animal care and maintenance. Male Wistar rats were purchased from Charles River, at a weight of 150–175 g. After arrival, rats were caged individually with free access to water and either a high-fat diet (HF diet, 45% of calories from fat, Harlan Teklad, Madison WI, TD 96001) or standard rat chow diet (SC diet, 11% of calories from fat, Harlan Teklad), except where indicated below, and food intake and body weight were recorded on a daily basis. Animals were held on a 12:12-h light-dark cycle.

Experimental design. After 6 wk of a HF or SC diet, animals were anesthetized with pentobarbital sodium (50–100 mg/100 g body wt ip) between 9 and 10 AM. Samples of the medial part of the right gastrocnemius muscle were rapidly excised and frozen in liquid nitrogen and used to gain a representative measure of hindlimb muscle triglyceride levels. Blood samples were collected into EDTA-rinsed vials for analysis of plasma variables. Solei muscles were excised, and basal and insulin-stimulated 2-deoxyglucose uptake was measured as described below. Mesenteric, perirenal, and epididymal fat pads were excised, patted dry of excess fluid, and weighed. Additional groups of 6-wk HF- or SC-fed animals received recombinant adenovirus containing either the rat leptin cDNA (AdCMV-leptin) (5) or the Escherichia coli β-galactosidase gene (AdCMV-βGal) (10). Where indicated, food intake in control groups was matched to animals receiving AdCMV-βGal. HF-fed or SC-fed animals were infused with 1 × 10^12 viral particles in 200–250 µl PBS into a tail vein via a 22-gauge catheter as previously described (28).

To reduce immunologic responses to the infused viruses, animals were treated with 15 mg·kg^-1·day^-1 cyclosporin A (Calbiochem, La Jolla, CA) intraperitoneally one day before the virus infusion, on the infusion day, and on the following day. Rats were also treated with 1.5 mg·kg^-1·day^-1 methylprednisone (Pharmacal Upjohn) intramuscularly on the same days. Four to five hours before the virus infusion, an extra injection of 3 mg/kg prednisone was given intramuscularly. No immunosuppression occurred for the five remaining days after an experiment. Six days after administration of the recombinant adenoviruses, blood samples were taken, solei and right medial gastrocnemius muscles were excised to measure 2-deoxyglucose uptake and triglyceride levels, respectively, and fat pads were isolated.

Oral glucose tolerance tests and measurement of insulin-stimulated skeletal muscle glucose uptake. Oral glucose tolerance tests were begun at 9:00 AM after an overnight fast. The rats were weighed, and a whole blood sample was taken from the capillary bed of the tail tip. Two grams of glucose/kg body wt were administered orally by gavage in a 40% glucose solution. Whole blood samples were taken 30, 60, 90, and 120 min after the gavage. Glucose values were measured in the samples with a HemoCue glucometer (HemoCue AB, Angelholm, Sweden). 2-Deoxyglucose uptake was measured in whole rats soleus muscles by use of a modification of previously described methods (9, 29). Briefly, muscles were quickly excised with animals under pentobarbital anesthesia, weighed, mounted onto stainless steel clips, and subjected to a series of incubations in modified Krebs-Ringer-Henseleit (KRH) buffer (118.4 mM NaCl, 1.19 mM KCl, 1.19 mM MgSO4, 4.76 mM KH2PO4, 2.49 mM NaHCO3, 1.2 mM CaCl2, 0.1% fat-free BSA) with additions, as described below, at 29°C in a shaking metabolic waterbath and under 95% O2-5% CO2. The muscles were first incubated in KRH buffer containing 8 mM glucose and 32 mM mannitol for 30 min and then in KRH buffer containing 40 mM mannitol for 10 min. They were transferred to KRH buffer containing 39 mM [14C]mannitol (44 Ci/mmol) and 1 mM 2-deoxy-[3H]glucose (50 Ci/mmol) for 30 min in the presence or absence of insulin at a final concentration of 1 µU/ml. The muscles were then hydrolyzed at 70°C for 1 h in 1 N NaOH. A 200-µl aliquot was assayed for radioactivity in scintillation cocktail, and 2-deoxyglucose uptake was calculated as nanomoles of 2-deoxyglucose per microliters intracellular water per hour.

Skeletal muscle triglycerides. Muscle triglycerides were determined as described previously (28) with slight modifications. Briefly, frozen muscle samples were first powdered under liquid nitrogen. Twenty to fifty milligrams of frozen muscle powder were then weighed into 1 ml of a chloroform-methanol mix (2:1) and incubated for 1 h at room temperature with occasional shaking to extract the lipid. After addition of 200 µl H2O, vortexing, and centrifugation for 5 min at 3000 g, the lower lipid phase was collected and dried at room temperature. The lipid pellet was redissolved in 60 µl tert-butanol and 40 µl of a Triton X-114-methanol (2:1) mix, and triglycerides were measured by means of the GPO-triglyceride kit (Sigma, St. Louis, MO) with Lintrol lipids as standards (Sigma).

Plasma measurements. Plasma triglycerides and free fatty acids were measured with kits from Sigma and Boehringer Mannheim, respectively. Plasma glucose was measured with a HemoCue glucose analyzer (HemoCue AB). Plasma leptin and insulin were measured using rat-specific RIA kits (Linco Research, St. Charles, MO).

Statistical methods. All results are expressed as means ± SE. Statistical significance was determined by an unpaired Student’s t-test by use of the statistics module of Microsoft Excel, Version 5.0 (Microsoft, Seattle, WA). Statistical significance was assumed at P < 0.05.

RESULTS

Fasting plasma variables, fat depots, and skeletal muscle triglyceride levels in the high fat fed rat. After 6 wk, marked alterations in carbohydrate and lipid metabolism were observed in HF rats compared with SC control animals (Table 1). Fasting plasma insulin, glucose, triglycerides, and cholesterol were significantly higher in HF fed rats compared with SC fed rats. Triglyceride accumulation was strongly correlated to a decrease in muscle triglyceride levels. The reversal of skeletal muscle insulin resistance is strongly correlated to a decrease in muscle triglyceride levels.

Table 1. Basal variables in SC and HF rats

<table>
<thead>
<tr>
<th>Variable</th>
<th>SC n = 7</th>
<th>HF n = 8</th>
</tr>
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<tbody>
<tr>
<td>Weight, g</td>
<td>403 ± 1.5</td>
<td>442 ± 3.3†</td>
</tr>
<tr>
<td>Food intake, kcal/day</td>
<td>95.9 ± 0.6</td>
<td>93.3 ± 0.9</td>
</tr>
<tr>
<td>Plasma</td>
<td></td>
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</tr>
<tr>
<td>Glucose, mg/dl</td>
<td>137.7 ± 4.7</td>
<td>198.4 ± 10.4‡</td>
</tr>
<tr>
<td>Triglyceride, mg/dl</td>
<td>37.0 ± 4.2</td>
<td>72.5 ± 5.2‡</td>
</tr>
<tr>
<td>Insulin, ng/ml</td>
<td>0.67 ± 0.12</td>
<td>4.39 ± 0.5‡</td>
</tr>
<tr>
<td>Leptin, ng/ml</td>
<td>0.99 ± 0.10</td>
<td>6.99 ± 0.89‡</td>
</tr>
<tr>
<td>FFA, mmol/l</td>
<td>0.222 ± 0.040</td>
<td>0.413 ± 0.06‡</td>
</tr>
<tr>
<td>Muscle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglyceride, protein µmol/g</td>
<td>46.5 ± 4.16</td>
<td>169 ± 20‡</td>
</tr>
<tr>
<td>Visceral and fat pads</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total weight, g</td>
<td>9.3 ± 0.6</td>
<td>27.3 ± 2.1‡</td>
</tr>
<tr>
<td>% Body wt</td>
<td>2.3 ± 0.06</td>
<td>6.2 ± 0.18‡</td>
</tr>
</tbody>
</table>

†Significant differences between HF and SC animals at P < 0.05 and P < 0.001, respectively.
glucose, and leptin levels were increased in HF animals by 6.5-, 1.4-, and 7.0-fold, respectively. In addition, skeletal muscle triglycerides were increased 3.6-fold, and there were marked increases in plasma triglycerides (2.0-fold), free fatty acids (1.9-fold), and visceral fat mass (2.7-fold). Finally, HF rats were significantly heavier than SC controls. Taken together, these data demonstrate that the HF rats display a metabolic profile consistent with obesity, insulin resistance, and a perturbed state of lipid and carbohydrate homeostasis.

Confirmation of insulin resistance induced by high fat feeding. To confirm diet-induced insulin resistance, SC and HF animals were fasted overnight and then subjected to an oral glucose tolerance test and analysis of insulin-stimulated glucose uptake in skeletal muscle (Figs. 1 and 2). Administration of a glucose bolus to HF animals resulted in whole blood glucose levels that were significantly greater than those of SC animals at all time points tested (Fig. 1). In addition, at 120 min postglucose bolus, when blood glucose had returned to baseline in the SC group, blood glucose in the HF animals had decreased only marginally from the maximum value at 60 min postglucose bolus (Fig. 1), demonstrating severe whole body glucose intolerance and implying the presence of insulin resistance. Because a major site of glucose disposal is skeletal muscle, basal and insulin-stimulated glucose uptakes were measured in the isolated soleus muscle of HF and SC animals. Basal glucose uptake was unchanged by high fat feeding; however, insulin-stimulated glucose uptake was reduced by 40% compared with that of SC animals (Fig. 2). These data demonstrate insulin resistance in skeletal muscle of HF rats.

Leptin action in the high fat fed rat. We next determined the effects of a sustained, moderate increase in leptin on the obese phenotype. Recombinant adenovirus containing the leptin cDNA was administered to both SC and HF animals, and a number of variables of leptin action were monitored (Fig. 3 and Table 2). A control HF group received an adenovirus expressing β-galactosidase, and food intake was subsequently matched to food intake in hyperleptinemic HF animals. Hyperleptinemia decreased caloric intake in both HF and SC animals (Fig. 3A), but the decrease was significantly greater in SC animals (Table 2). Cumulative weight loss induced by hyperleptinemia was significant in SC, but not in HF animals (Table 2); however, when expressed as grams lost per day, HF rats lost significant body wt from day 5 to day 6 of hyperleptinemia (Fig. 3B). Visceral fat mass was markedly decreased by hyperleptinemia in HF rats (Table 2), and the loss was substantially greater in absolute terms compared with hyperleptinemic SC and calorically matched, AdCMV-βGal-treated HF rats.

Effects of hyperleptinemia on plasma metabolic variables and skeletal muscle insulin sensitivity. We next tested the hypothesis that sustained hyperleptinemia would correct the metabolic abnormalities and skeletal muscle insulin resistance associated with diet-induced obesity. First, hyperleptinemia resulted in a reduction in plasma glucose and insulin in HF animals to levels comparable with those in SC animals (Table 3). Importantly, these effects were specific, because HF animals that received AdCMV-βGal and were caloricly matched to the hyperleptinemic HF rats remained hyperglycemic and hyperinsulinemic compared with SC and hyperleptinemic HF rats (Table 3). As previously reported (5), hyperleptinemia in SC rats also reduced plasma glucose and insulin (Table 3), an effect that was not observed in SC calorically matched animals (data not shown). These data suggest that insulin sensitivity is improved by hyperleptinemia. To evaluate this directly, we measured insulin-stimulated glucose uptake in skeletal muscle from hyperleptinemic HF and control animals. Skeletal muscle insulin sensitivity was restored in hyperleptinemic HF rats to levels that were
similar to those in SC animals (Fig. 4). It is noteworthy that treatment of HF rats with AdCMV-βGal and subsequent caloric matching to hyperleptinemic HF rats did not correct skeletal muscle insulin resistance. Finally, plasma triglycerides and intramuscular triglycerides, but not free fatty acids, were decreased in hyperleptinemic HF rats compared with HF controls (Table 3 and Fig. 5). Caloric matching of AdCMV-βGal-treated HF rats to hyperleptinemic rats also reduced plasma triglycerides and free fatty acids; however, skeletal muscle triglycerides in calorically matched animals remained at levels similar to those in HF animals fed ad libitum. Because insulin resistance was not corrected in calorically matched animals, these data suggest that the leptin-mediated reduction in skeletal muscle triglyceride stores underlies improvements in insulin action. Indeed, a comparison of tissue triglyceride levels to skeletal muscle insulin sensitivity in individual animals demonstrated a negative correlation of $r = -0.7$ (Fig. 6), lending further support to this possibility.

### Table 2. Effects of 6 days of hyperleptinemia or caloric matching on weight, food intake, and visceral fat mass in HF and SC animals

<table>
<thead>
<tr>
<th></th>
<th>SC-Lep</th>
<th>HF-Lep</th>
<th>HF-βGal-CM</th>
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<tbody>
<tr>
<td></td>
<td>n=5</td>
<td>n=9</td>
<td>n=6</td>
</tr>
<tr>
<td><strong>Weight loss</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beginning weight, g</td>
<td>415.5 ± 8.2</td>
<td>431.9 ± 14.9</td>
<td>458.3 ± 14.0</td>
</tr>
<tr>
<td>End weight, g</td>
<td>381.6 ± 9.5</td>
<td>419.6 ± 15.4</td>
<td>447.92 ± 14.2</td>
</tr>
<tr>
<td>Total weight loss, %</td>
<td>8.2 ± 1.0</td>
<td>2.8 ± 0.7</td>
<td>2.3 ± 0.2</td>
</tr>
<tr>
<td>Calorically matched to HF-Lep</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Food intake, days 2–6 kcal/day</strong></td>
<td>35.45 ± 1.6</td>
<td>42.61 ± 2.7*</td>
<td></td>
</tr>
<tr>
<td><strong>Visceral fat depots, at day 7</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total weight, g</td>
<td>5.6 ± 0.4</td>
<td>15.2 ± 1.5</td>
<td>23.7 ± 1.4</td>
</tr>
<tr>
<td>Total loss, g</td>
<td>3.7 ± 0.4</td>
<td>12.1 ± 1.5</td>
<td>3.6 ± 1.4</td>
</tr>
<tr>
<td>% lost†</td>
<td>40 ± 5</td>
<td>44 ± 6§</td>
<td>20 ± 2</td>
</tr>
</tbody>
</table>

HF-Lep, HF rats administered recombinant adenovirus containing leptin cDNA (AdCMV-leptin); SC-Lep, SC rats administered AdCMV-leptin; HF-βGal-CM, HF rats administered adenovirus expressing β-galactosidase (AdCMV-βGal) and calorically matched to HF-Lep. All results are expressed as mean ± SE. *Significant differences between HF-Lep and HF-βGal-CM (P < 0.05), †Significant difference between HF-Lep and HF-βGal-CM (P < 0.01), §Compared to fat pad mass of HF animals.

### DISCUSSION

The ability of leptin administration to reverse metabolic abnormalities in the ob/ob mouse (17, 21, 24) and improve insulin action in normal animals (1, 5, 26) has led to the proposal that leptin may serve as an effective therapy for human obesity. However, a number of questions remain unanswered in this regard. First, it is not clear that increasing plasma leptin levels will be sufficient to correct the metabolic abnormalities associated with obesity, principally insulin resistance and perturbed lipid and carbohydrate metabolism. Second, leptin therapy involving multiple injections has had mixed results both in animal models of obesity and in human trials, and this suggests that alternative strategies such as sustained increases in plasma leptin should be considered. The current study addressed these questions in the HF rat, a model of obesity that...
displays a metabolic phenotype similar to that in human obesity.

Previous studies in the HF obese model demonstrated that leptin administration can alter food intake and weight gain (4, 8) but did not address the capacity of leptin to correct the obese phenotype. This is an important question, because correction of the metabolic abnormalities of obesity with leptin has been demonstrated only in the ob/ob mouse, a model that lacks endogenous leptin. Thus the current study extends previous observations of leptin action in obesity by demonstrating in a nongenetic model that hyperglycemia, hyperinsulinemia, and skeletal muscle insulin resistance are corrected by a sustained, moderate increase in plasma leptin mediated by recombinant adenovirus administration. It is important that we do not observe a similar correction of insulin action or plasma variables in HF animals that received a control adenovirus expressing β-galactosidase and were calorically matched to the HF hyperleptinemic animals.

The increased skeletal muscle insulin sensitivity induced by hyperleptinemia in HF rats is associated with decreases in muscle triglyceride levels. It is noteworthy that muscle triglycerides remained elevated and insulin resistance was maintained in HF animals calorically matched to HF hyperleptinemic animals, whereas plasma variables of lipid metabolism (free fatty acids and triglycerides) were similar in the two groups. A comparison of muscle triglyceride levels with muscle insulin-stimulated glucose uptake demonstrated a strong negative correlation (r = −0.7). Of interest in this regard is the clustering of insulin-"sensitive" groups (SC, hyperleptinemic SC and hyperleptinemic HF) and insulin-"resistant" groups (HF and AdCMV-βGal-treated, calorically matched HF). Although these observations do not demonstrate a mechanistic link between tissue triglycerides and insulin sensitivity, a number of other studies have demonstrated a close relationship between perturbed lipid metabolism and insulin resistance (see Ref. 15 for review). Moreover, recent studies in rat and humans (12, 18, 20, 22) have demonstrated a similar relationship between insulin sensitivity and skeletal muscle triglyceride depots. In the Zucker diabetic fatty rat, increases in tissue triglycerides occur in parallel with the development of the insulin resistance characteristic of this model (13), whereas insulin resistance does not develop when pharmaceutical interventions are used that reduce or prevent muscle triglyceride accumulation during a high fat diet or in genetic models of obesity (14, 27). Although the mechanistic link between triglyceride accumulation and insulin resistance remains to be defined, lipids have been implicated in altering elements of the insulin signaling pathway (11, 33) and are known to regulate fuel disposal (23, 25, 32).
Additional studies are required to determine the mechanisms underlying leptin-mediated increases in muscle insulin sensitivity.

Given that a subset of obese patients will likely be amenable to leptin therapy, much as some insulin-resistant type II diabetics respond to insulin therapy, an important consideration will be the method of leptin delivery. Injection therapy and more sustained increases in plasma leptin have been proposed as treatment methods. In humans, weight loss after injection therapy has been minor compared with the starting weight of the subjects (7). In animal models of obesity, a diminished (8) or absent (30) response to peripherally injected leptin has been reported. These effects may be explained by increases in plasma leptin levels that are transitory, thus compromising the efficiency of leptin action. Indeed, a recent study (16) in the ob/ob mouse demonstrated that intraperitoneally injected leptin was undetectable in plasma only 3 h after injection, having reached a peak value of 335 ng·ml⁻¹·h⁻¹ after injection. This study also demonstrated that intraperitoneal injection of leptin was less effective at promoting decreases in food intake and weight gain compared with the effects of a sustained increase in plasma leptin. Concern about temporary increases in leptin levels was circumvented in the current study by use of a gene-therapeutic intervention that resulted in a sustained moderate increase in leptin. This strategy is clearly effective, because a quite modest increase in leptin from 7 to 29 ng/ml had a substantial impact on fuel homeostasis. However, additional studies are required to determine whether therapeutic strategies that maintain constant elevated leptin levels will be an effective therapy in the treatment of human obesity.

This study and others (4, 6, 8, 30) have demonstrated that diet-induced obesity is associated with elevated plasma leptin levels, but with accelerated weight gain and normal or increased caloric intake, leading to speculation that animals on high fat diets are leptin resistant. The data in the present study demonstrate that, if present, leptin resistance can be overcome by an intervention that sustains a moderate increase in plasma leptin. Concern about temporary increases in leptin levels was circumvented in the current study by use of a gene-therapeutic intervention that resulted in a sustained moderate increase in leptin. This strategy is clearly effective, because a quite modest increase in leptin from 7 to 29 ng/ml had a substantial impact on fuel homeostasis. However, additional studies are required to determine whether therapeutic strategies that maintain constant elevated leptin levels will be an effective therapy in the treatment of human obesity.

HF hyperleptinemic animals. Given that leptin resistance has been proposed to play a role in the pathogenesis of obesity, it is important that the nature and extent of leptin resistance in the HF rat be defined.

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