Interactions Between Leptin and the Human Sympathetic Nervous System

Nina Eikelis, Markus Schlaich, Anuradha Aggarwal, David Kaye, Murray Esler

Abstract—Results from animal experimentation suggest a 2-way interaction between leptin and the sympathetic nervous system, with leptin causing sympathetic activation and conversely, with the sympathetic system exercising regulatory feedback inhibition over leptin release. We have now tested this hypothesis in humans. In the absence of results from leptin infusions, to test for sympathetic stimulation of leptin release, we sought a quantitative naturalistic linkage of sympathetic activity with leptin plasma concentration across a broad range of leptin values in men of widely differing adiposity. Renal norepinephrine spillover was correlated with plasma leptin ($r=0.628$, $P<0.01$), but other measures of sympathoadrenal function did not. To test for sympathetic and adrenomedullary inhibition of leptin release, we studied clinical models of high sympathetic tone, heart failure, and essential hypertension, in which lowered plasma leptin levels might have been expected but were not found; a model of low sympathetic activity, pure autonomic failure, in which plasma leptin level was normal (6.1±1.2 vs 12.8±3.1 ng/mL in healthy subjects); and a clinical model of reduced epinephrine secretion, healthy aging, in which plasma leptin level again was normal (5.7±1.1 ng/mL vs 4.0±0.9 ng/mL in men $>60$ years and $<35$ years, respectively). Paradoxically, leptin concentration was elevated in heart failure, caused entirely by reduced renal clearance of leptin release, 142.0±30.5 mL/min, compared with 56.9±18.9 mL/min ($P<0.05$). These results provide some support for the view that leptin stimulates the sympathetic nervous system, at least for renal sympathetic outflow, but do not confirm the concept of regulatory feedback inhibition of leptin release by the sympathetic nervous system. (Hypertension. 2003;41:667–672.)

Key Words: leptin ■ nervous system, sympathetic renal ■ heart failure ■ hypertension, essential ■ autonomic nervous system ■ aging ■ obesity

Leptin, a 16-kDa peptide derived principally from white adipose tissue, is believed to serve an “adipostat” function, being released in proportion to fat cell mass. Although extra-adipocyte sites of leptin production are well documented, it is the leptin released by adipocytes and circulating in plasma that is thought to regulate fat mass by acting within the brain to reduce food intake and stimulate thermogenesis. Activation of the sympathetic nervous system by leptin is the primary mechanism mediating this increase in energy expenditure. Leptin administered intravenously, intracerebroventricularly, and into hypothalamic nuclei in rodents has been demonstrated to increase the sympathetic outflow to the kidneys, adipose tissue, and the skeletal muscle vasculature and the neural traffic to the adrenal.

Although leptin gene expression in white adipose tissue and circulating leptin plasma concentration are both strongly correlated with adiposity, which, along with gender, is the dominant long-term determinant of leptin gene expression and release, important short-term regulators of leptin synthesis and release have been identified. Important among these might be the sympathetic system, which has been suggested to be a key regulatory inhibitor of leptin production, mediating, for example, the reduction of leptin synthesis accompanying exposure to cold. An inhibitory effect on leptin synthesis and release has been demonstrated for the catecholamines, norepinephrine (NE), and epinephrine, and for isoproterenol, both in adipocyte cell cultures and in intact experimental animals. Thus, there seems to be a 2-way interaction between leptin and the sympathetic nervous system, perhaps constituting a regulatory feedback loop, with leptin acting within the hypothalamus to cause activation of central sympathetic outflow and stimulation of adrenal medullary release of epinephrine and, conversely, with the sympathetic nervous system inhibiting leptin release from white adipose tissue.

It should be mentioned, however, that evidence supporting such a dual interaction of leptin and the sympathetic nervous system drawn from clinical sources is often absent or paradoxical. The effect of leptin infusions on sympathetic nervous activity in humans has not been studied to this point. Although the high plasma leptin levels of human obesity are often accompanied by sympathetic nervous activation, this sympathetic stimulation does not involve all outflows, sparing the sympathetic nerves directed to the heart, whereas the
stimulation of epinephrine secretion expected with high leptin levels is not seen in obesity.15,16 The most direct evidence for catecholaminergic inhibition of leptin release in humans, reduction of plasma leptin levels during infusion of isoproterenol, alternatively might perhaps be attributable to an increase in leptin clearance by the kidneys4,17 because of the drug’s increasing renal blood flow.18

In the present study, we have further tested the nature of the human leptin-sympathetic nervous link by measuring arterial plasma leptin concentrations in clinical models of increased (cardiac failure, essential hypertension) or reduced (pure autonomic failure [PAF]) sympathetic tone, in which modified catecholaminergic inhibition of leptin release might be expected. Given that definitive results from leptin infusions in humans are lacking, to test for a possible direct stimulation of the sympathetic nervous system by leptin, we sought a naturalistic linkage between regional sympathetic activity and plasma leptin concentration across a broad range of leptin values present in men of widely differing adiposity.

Methods

The hypothesis that the sympathetic nervous system and epinephrine exert an inhibitory control over leptin release was tested in humans by measuring arterial plasma leptin concentrations in clinical models of high sympathetic tone, heart failure, and essential hypertension; in a model of reduced sympathetic activity, PAF, sympathetic tone, in which modified catecholaminergic inhibition of leptin release might be expected. Given that definitive results from leptin infusions in humans are lacking, to test for a possible direct stimulation of the sympathetic nervous system by leptin, we sought a naturalistic linkage between regional sympathetic activity and plasma leptin concentration across a broad range of leptin values present in men of widely differing adiposity.

Characteristics of these clinical groups are summarized in the Table. Participation in the study was allowed after written, informed consent was obtained and with the approval of the Alfred Hospital Ethics Review Committee.

Subject Characteristics and Plasma Leptin Levels

<table>
<thead>
<tr>
<th>Healthy</th>
<th>CHF</th>
<th>EH</th>
<th>PAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, F/M</td>
<td>6/56</td>
<td>9/61</td>
<td>7/19</td>
</tr>
<tr>
<td>Age, y</td>
<td>45.1±2.1</td>
<td>55.0±0.9*</td>
<td>44.2±2.7</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.8±0.6</td>
<td>27.6±0.5</td>
<td>28.8±1.2</td>
</tr>
<tr>
<td>Total NE spillover, ng/min</td>
<td>435.8±29.2</td>
<td>961.9±92.4*</td>
<td>566.8±60.4*</td>
</tr>
<tr>
<td>Leptin concentration, ng/mL</td>
<td>7.7±0.8</td>
<td>11.5±1.2*</td>
<td>12.9±2.4*</td>
</tr>
</tbody>
</table>

CHF indicates congestive heart failure; EH, essential hypertension; PAF, pure autonomic failure; BMI, body mass index; and NE, norepinephrine.

Excluded from the study. Overweight subjects had been weight stable (±1 kg) for at least 2 months before the study.

Heart Failure

The 70 patients with cardiac failure (61 men, 9 women) had impaired left ventricular systolic function (ejection fraction 23%±8%) attributable to either coronary artery disease or primary cardiomyopathy. Given the severity of their heart failure, all were maintained on their therapy during the study.

Essential Hypertension

The 26 patients with hypertension (19 men, 7 women) constituted a consecutive series of consenting patient volunteers who were carefully evaluated to exclude secondary hypertension. Average clinic blood pressure in all exceeded 150 mm Hg systolic, 90 mm Hg diastolic, or both. None had accelerated hypertension, diabetes, clinical coronary artery disease, heart failure, a history of stroke, renal insufficiency, or average clinic blood pressure exceeding 200 mm Hg systolic or 125 mm Hg diastolic. Most were previously unmedicated; if they had been on prior therapy, all antihypertensive drugs were stopped a minimum of 6 weeks before the research testing. Dietary sodium intake and caloric intake in the obese were unrestricted at the time of the study.

Pure Autonomic Failure

The 5 patients (2 men, 3 women) with PAF (idiopathic sympathetic nerve degeneration)20–22 had severe postural hypotension (mean fall in systolic blood pressure on standing, 76 mm Hg) and demonstrable postganglionic sympathetic degeneration. Sympathetic nerve recording sites could not be identified with microneurography, and release of NE from the heart was near zero, 0.4±0.6 ng/min (normal, 11.0±4.0 ng/min; mean±SEM).20–22

Aging

Aging was used as a clinical model of reduced epinephrine secretion23 to test whether reduced adrenal medullary function led to loss of restraint on leptin release.24 From the pool of 62 healthy volunteers, comparisons in epinephrine secretion and plasma leptin concentration were made between 11 men >60 years old and 15 men <35 years old. To avoid any confounding influence of high sympathetic activity in the older men,23 analysis was confined to those with total NE spillover values no greater than 1 SD above the group mean present in younger men.

Obesity

Drawn from the pool of 62 volunteers, a subset of 19 obese but otherwise healthy participants with a body mass index (BMI) ≥28 were compared with 21 matching lean volunteers with a BMI <26. We investigated whether measures of regional sympathetic activity and epinephrine secretion were interrelated with plasma leptin concentrations across the broad range of accompanying leptin values. This was done to test for a possible direct stimulation of the sympathetic nervous system by leptin, which might be expressed as a quantitative linkage of regional sympathetic activity with plasma leptin concentrations.

Subject Characteristics

Healthy Volunteers

Sixty-two lean or obese but otherwise healthy volunteers (56 men, 6 women) were recruited from the general community for the study. All underwent a thorough clinical screening, which included clinical evaluation and serum biochemistry measurements to exclude hepatic and renal dysfunction. Respondents with a history of cardiovascular disease, diabetes, long-term medication use, blood pressure >140/85 mm Hg, or an alcohol intake of >2 standard drinks per day were excluded from the study. Overweight subjects had been weight stable (±1 kg) for at least 2 months before the study.

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Pharmacological Procedures for Changing Sympathetic Activity

Nitroprusside Infusion
Nitroprusside (David Bull), a direct-acting vasodilator, was infused intravenously in 11 patients with cardiac failure to reflexly increase sympathetic activity and to test for sympathetically mediated reduction in leptin release. Nitroprusside was administered into a peripheral vein at an initial rate of 0.5 µg·kg⁻¹·min⁻¹. The infusion rate was increased at 5-minute intervals, titrated to achieve a stable reduction in arterial systolic blood pressure of 20 mm Hg or a minimum systolic pressure of 90 mm Hg. Measurements of sympathetic activity and arterial plasma leptin concentration were made with blood pressure stable, after a mean total infusion time of ~1 hour.

Clonidine Infusion
Clonidine (Boehringer-Ingelheim), a centrally acting inhibitor of sympathetic outflow, was administered to 9 patients with cardiac failure through a peripheral vein in sequential doses of 0.1 µg/kg, 0.25 µg/kg, and 1 µg/kg, each dose being infused over 15 minutes, with a 20-minute delay before the next dose. Measurements of sympathetic activity, arterial plasma leptin concentration, and renal plasma flow were made after a mean total dosing time of ~90 minutes.

Measurement of Plasma Catecholamine Kinetics
Whole-body, renal, and cardiac NE spillover rates were determined as measures of sympathetic activity. Subjects were infused with levo-7-3H-norepinephrine (New England Nuclear; specific activity, 12 to 20 Ci/mmol) at a rate of 0.6 to 0.8 µCi/min. At steady state, whole-body NE spillover to plasma was determined by using isotope dilution. Epinephrine secretion rates were determined similarly by isotope dilution. Regional NE spillover from the heart and kidneys was calculated from the venoarterial plasma NE concentration difference across the organ in question, the fractional extraction of radiolabeled NE occurring in transit across that organ, and regional plasma flow. Coronary sinus plasma flow was derived from thermodilution blood flow measurements and the hematocrit, whereas renal plasma flow was determined from the clearance of infused p-aminophenylisocyanide.

Central Venous Catheter Procedure
The study was performed with the subjects at supine rest. A 21-gauge cannula was introduced percutaneously under local anesthesia into the brachial or radial artery of either arm for blood sampling and pressure monitoring. In the same arm, an 8.5F-gauge introducer sheath was inserted percutaneously into the median antecubital vein. Venous catheterization was performed through this sheath. The coronary sinus and a renal vein were reached by passing a guidewire through this antecubital vein at an initial rate of 0.5 g/kg, each dose being infused over 15 minutes, with a 20-minute delay before the next dose. Measurements of sympathetic activity, arterial plasma leptin concentration, and renal plasma flow were made after a mean total dosing time of ~90 minutes.

Assay of Plasma Catecholamines
Blood samples for the estimation of catecholamines were transferred immediately to ice-chilled tubes containing EGTA and reduced glutathione and centrifuged at 4°C, and the plasma was stored at -80°C before assay. Plasma catecholamine concentrations were determined by high-performance liquid chromatography with electrochemical detection. Timed collection of the eluate leaving the detection cell with a fraction collector permitted separation of 3H-labeled NE and epinephrine for counting by liquid-scintillation spectroscopy. Intra-assay variations were 4.6% for plasma NE and 6.8% for plasma epinephrine at concentrations of 150 pg/mL and 7.2% and 6.5% for 3H-labeled NE and epinephrine.

Plasma Leptin Assay
Blood was drawn into chilled tubes containing EGTA. Blood samples were centrifuged, and plasma was stored at -80°C until assay. Plasma leptin levels were measured in duplicate by radioimmunoassay (Linco Research Inc), with an intra-assay coefficient of variation of 5% and a sensitivity of 0.5 ng/mL. Renal leptin clearance was calculated as the product of the fractional extraction of plasma leptin in transit through the kidney and renal plasma flow.

Statistical Analysis
Statistical analyses were performed with SigmaStat for Microsoft Windows, version 2.03 (Jandel Scientific). Comparisons between groups were made with a Student t test. If normality or equal variance failed, a Mann-Whitney rank-sum test was done. A Student paired t test was used to compare the changes before and after treatment with nitroprusside or clonidine. For multiple comparisons, a Student-Newman-Keuls method test was performed. Data are expressed as mean ± SEM. Statistical significance was set at P < 0.05.

Results

Clinically Altered Sympathetic Activity, NE Spillover, and Epinephrine Secretion
Cardiac Failure and Essential Hypertension
NE spillover measurements established the bona fides of high sympathetic nervous activity. Total NE spillover rates were significantly higher in heart failure (961.9 ± 92.4 ng/min, P < 0.001) and essential hypertension (568.3 ± 57.9 ng/min, P < 0.05) patients than in healthy volunteers (435.8 ± 29.2 ng/min; Figure 1). Despite this sympathetic nervous activation, arterial plasma leptin concentrations were not suppressed. Perhaps unexpectedly, plasma leptin values were significantly higher in both groups, heart failure 11.5 ± 1.2 ng/mL (P < 0.01) and essential hypertension 12.9 ± 2.4 ng/mL (P < 0.05) patients, than in healthy volunteers, 7.7 ± 0.8 ng/mL (Figure 1).

The paradoxical elevation in plasma leptin concentration in heart failure patients was attributable to a substantially lower renal clearance of leptin, 56.9 ± 18.9 mL/min, compared with 142.0 ± 40.5 mL/min in healthy controls (P < 0.05), accompanying a reduced renal plasma flow in heart failure patients, 503.0 ± 70.0 mL/min versus 770.8 ± 66.6 mL/min (P < 0.05; Figure 2). Renal clearance of leptin, 40% lower in hypertensive patients than in healthy volunteers (P = 0.236), appeared to contribute to the higher plasma leptin values in hypertension also.

Sympathetic Denervation: PAF
The control group (healthy volunteers) was matched with respect to gender, age, and BMI to patients with PAF, so there were no differences between groups in subject characteristics. As expected, total NE spillover was significantly lower in PAF patients than in healthy subjects, 90.0 ± 18.6 ng/min versus 399.1 ± 64.3 ng/min (P < 0.01). The accompanying arterial plasma leptin concentrations in PAF patients were not elevated (Figure 1).

Low-Epinephrine Secretion Model: Aging
Secretion of epinephrine from the adrenal medulla was significantly reduced in older subjects, 43.8 ± 20.5 ng/min, compared with 185.1 ± 32.9 ng/min in the younger volunteers (P < 0.05; Figure 3). This did not translate into obvious loss of restraint on leptin secretion in the elderly; arterial plasma leptin concentration was marginally higher only in older subjects, 5.7 ± 1.1 ng/mL versus 4.0 ± 0.9 (P = 0.07; Figure 3).
Pharmacological Modification of Sympathetic Activity

Nitroprusside Infusion
Nitroprusside infusion to patients with heart failure resulted in further increases in the total NE spillover, from $569.1 \pm 68.1$ ng/min to $947.8 \pm 67.0$ ng/min ($P<0.001$). Plasma leptin levels, however, did not change after the administration of nitroprusside (Figure 1).

Clonidine Infusion
Administration of clonidine to heart failure patients reduced total NE spillover from $674.1 \pm 97.6$ to $529.0 \pm 87.9$ ng/min ($P<0.001$). Renal plasma flow was measured before and after clonidine infusion. There was a significant decrease in plasma flow through the kidney after clonidine administration, from $739.2 \pm 111.4$ to $493.8 \pm 59.3$ mL/min ($P<0.05$). As a result, there was a decrease in renal leptin clearance of nearly 60%, from $123.4 \pm 26.7$ to $47.7 \pm 33.9$ mL/min ($P<0.05$). Despite this and the reduction in sympathetic nervous activity with clonidine, arterial plasma leptin concentration did not increase (Figure 1).

Does Plasma Leptin Concentration Determine Sympathetic Activity? Measurements in Lean and Obese Men
Arterial leptin concentration was significantly higher in healthy subjects with a BMI $>28$ compared with lean participants with a BMI $<26$, 12.0 $\pm$ 1.6 ng/mL versus 2.6 $\pm$ 0.2 ng/mL (Figure 2).
ng/mL ($P<0.001$). The higher plasma leptin concentration was not attributable at all to altered renal leptin clearance, which was unremarkable in obesity (Figure 4).

Plasma leptin concentration and renal NE spillover were found to be significantly correlated overall in these subjects: $r=0.628$, $P<0.01$. By applying multiple linear regression analysis with renal NE spillover as the dependent variable and plasma leptin concentration and percent body fat (calculated according to the formula of Womersley and Durnin27) as the independent variables, the prediction of NE spillover was statistically significant and stronger with leptin ($P<0.05$) than with percent body fat ($P=0.13$). Other measures of sympathoadrenal function, total and cardiac NE spillover and epinephrine secretion rate, were not correlated with plasma leptin concentration (Figure 5).

**Discussion**

An inhibitory effect on leptin synthesis and release has been demonstrated for the catecholamines, NE and epinephrine, and for isoprenaline, both in adipocyte cell cultures and in intact experimental animals.$^{11,13}$ In the present study, we further investigated the nature of the human leptin-sympathetic nervous link by measuring arterial plasma leptin concentrations in clinical models of increased (cardiac failure, essential hypertension, nitroprusside infusion) or reduced (PAF, clonidine dosing) sympathetic tone, in which modified catecholaminergic inhibition of leptin release might be expected. We also tested for a linkage between regional sympathoadrenal function, total and cardiac NE spillover and epinephrine secretion rate, were not correlated with plasma leptin concentration (Figure 5).

Our main objective was to determine whether sympathetic tone dictates leptin release. Results from previous studies suggest that the sympathetic nervous system exerts an inhibitory control over leptin production and release.$^{11,13}$ On this basis, we anticipated that patient groups with increased sympathetic nervous system activity (heart failure and essential hypertension were studied by us) would have low levels of leptin circulating in blood plasma. Sympathetic nervous activation was present in these 2 conditions, as has been well documented previously.$^{19}$ Contrary to expectation, we found that in heart failure and essential hypertension, arterial plasma leptin concentrations were significantly elevated, rather than suppressed, compared with the levels in healthy volunteers. The BMI range was similar for chronic heart failure, hypertensive patients, and healthy volunteers, probably excluding differences in body adipose mass as the mechanism, although the existence of muscle wasting and fluid retention in heart failure patients would make the BMI an unreliable measure of adiposity.

This finding that leptin plasma levels are elevated in hypertensive patients is in agreement with previous studies.$^{28,29}$ Results in heart failure patients are less consistent, with reports of both low plasma leptin concentration in chronic heart failure$^{30}$ and hyperleptinemia.$^{31}$ Contradictory results in heart failure patients in different studies may perhaps reflect differences in cohorts used. Murdoch and colleagues$^{30}$ have shown that plasma leptin concentrations were significantly lower in heart failure patients with cachexia. Richartz and colleagues$^{32}$ have reported that plasma leptin concentrations are reduced in severe heart failure, New York Heart Association (NYHA) heart failure grades III and IV, but elevated in patients with milder heart failure, NYHA grade II.

To further test for a direct effect of high sympathetic tone on plasma leptin, we measured leptin concentration in chronic heart failure patients before and after administration of the
vasodilator nitroprusside. Nitroprusside lowers arterial pressure and activates the sympathetic nervous system via the arterial baroreflex. In our studies, as expected, nitroprusside further increased sympathetic nervous activity in the heart failure patients, as manifested in a rise in total NE spillover, but plasma leptin concentration was unaltered after 60 minutes of sympathetic stimulation.

Patients with PAF (idiopathic sympathetic nerve degeneration) and severe postural hypotension served as a reference population to investigate whether low sympathetic nervous system activity leads to escape of leptin release from sympathetic inhibition. In these patients, sympathetic nerve recording sites could not be identified with microneurography, and whole-body and cardiac releases of NE were very low.20–22 Contrary to the hypothesis that the sympathetic nervous system exerts an inhibitory control over leptin release, leptin plasma concentrations were marginally lower and certainly not increased in these patients. The central thesis, of sympathetic nervous system inhibition of leptin release, was further evaluated by using the centrally acting sympathetic nervous system inhibitor clonidine, which was administered to patients with heart failure. We found that intravenous infusion of clonidine caused the expected reduction in sympathetic nervous activity without affecting plasma leptin levels. Clonidine reduced renal plasma flow, with a resulting 40% decrease in renal plasma clearance of leptin. Despite this and the reduction in sympathetic nervous activity for ~90 minutes with clonidine, arterial plasma leptin concentration did not increase. It is perhaps problematic whether alteration of sympathetic activity of this duration, or for the slightly shorter period with nitroprusside, could be expected to modify leptin release, given that leptin responses sometimes are sluggish, as with exercise, for example. The reduction of plasma leptin concentration with isoproterenol infusion in humans, however, is prompt13 and occurs within a time frame similar to that of the clonidine and nitroprusside experiments reported here.

An inhibitory effect on leptin release by epinephrine secreted from the adrenal medulla has been claimed, with in vitro observations in humans demonstrating that epinephrine acutely regulates ob gene expression in adipocytes.24 We used healthy aging as a clinical model of reduced epinephrine secretion.23 Importantly, to avoid any confounding influence of high sympathetic activity in the older men,23 analysis excluded those with total NE spillover values >1 SD above the group mean present in men <35 years old. Despite the fact that secretion of epinephrine from the adrenal medulla was substantially reduced in older subjects, this did not translate into loss of restraint on leptin secretion in the elderly. Arterial plasma leptin concentration was similar in older and younger subjects.

It should be acknowledged that existing difficulties in matching physiological and treatment variables to some extent does undermine the “purity” of the clinical models used. Comparisons were made to avoid obvious confounding from age, gender, and adiposity, but an influence of concurrent medication on leptin release in patients with PAF (prescribed fludrocortisone) and heart failure (patients maintained on differing combinations of an angiotensin-converting enzyme inhibitor, β-adrenergic blocker, and diuretic) cannot be excluded with certainty. Similarly, perfect matching of physiological variables between the patient groups and the reference population of healthy subjects is not achievable. This was shown to be important in the heart failure patients, in whom the existing low renal blood flow elevated plasma leptin concentration by reducing renal leptin clearance.

Because circulating plasma NE concentrations derived from sympathetic nerves are in most contexts too low to have direct metabolic effects,23 2 additional key issues for interpreting the results described previously are whether the sympathetic system, in fact, innervates adipocytes in white adipose tissue, and if so, whether increases or decreases in catecholaminergic influences specific to white adipose tissue are those anticipated from the global measures of sympathetic activity, because whole-body NE spillover measurements were used as the defining categorizer of sympathetic nervous status. On the first point, direct sympathetic innervation of adipocytes does seem to exist,34 although there has previously been dispute on this point. For the second, it remains problematic whether total NE spillover values are representative of sympathetic outflow to white adipose tissue, given that sympathetic nervous responses commonly show topographic discrimination.19 Brown adipose tissue, certainly, is spared from arterial baroreflex–mediated sympathetic activation,35 such as is operative with nitroprusside infusion. Measurement of interstitial NE concentrations in adipose tissue by microdialysis, which was not done, would have been necessary to establish that changes in total-body NE spillover measurements and sympathetic tone in adipose tissue were concordant. This caveat does not apply to the PAF results, because sympathetic nerve degeneration is generalized,20 25 or to the epinephrine secretion results in the elderly.

The kidney plays an important role in human leptin metabolism, because leptin is removed from the circulation primarily by the kidneys.4–17 A contribution of reduced renal clearance to elevated plasma leptin concentration in renal failure has been assumed,36 but otherwise this issue has been little studied. The explanation for the paradoxical elevation in plasma leptin concentration in heart failure patients does seem to primarily lie in their lower renal clearance of leptin, largely attributable to their reduced renal plasma flow. Renal clearance of leptin, 40% lower in hypertensive patients than in healthy volunteers, appeared to contribute to the higher plasma leptin values in hypertension also, although in this case, additional factors must be operating to cause their plasma leptin levels to be nearly 60% higher than those in a control group. Arterial leptin concentrations, as expected, were significantly higher in the otherwise-healthy overweight subjects. These higher plasma leptin concentrations were not attributable at all to renal leptin clearance, which was unremarkable in obesity.

Leptin administered intravenously, intracerebroventricularly, and into hypothalamic nuclei in rodents has been demonstrated to increase the sympathetic outflow to the kidneys, adipose tissue, and the skeletal muscle vasculature and the neural traffic to the adrenal medulla.7–9,37 The effect of leptin infusions on sympathetic nervous activity in hu-
mans, however, has not been studied to this point. Mechanisms other than those involving leptin, specifically hyperinsulinemia46 and obstructive sleep apnea,39 have been claimed to be the cause of the sympathetic activation characterizing obesity. Given this uncertainty, to test for a possible direct stimulation of the sympathetic nervous system by leptin, which would constitute the efferent limb of the proposed feedback leptin–sympathetic regulatory loop, we sought a naturalistic linkage between regional sympathetic activity and plasma leptin concentration across a broad range of leptin values present in men of widely differing adiposity.

Arterial leptin concentrations, as expected, were significantly higher in otherwise-healthy overweight men. Of measures of the sympathoadrenal function quantified, total, cardiac, and renal NE spillover and epinephrine secretion rate, only renal NE spillover was correlated with plasma leptin concentration. By applying multiple linear regression analysis with renal NE spillover as the dependent variable and plasma leptin concentration and percent body fat as the independent variables, the prediction of NE spillover was stronger with leptin than with percent body fat. These findings do, perhaps, suggest that hyperleptinemia may be the prime mover underlying the neural pathophysiology of obesity, having a parallel in the pattern of sympathetic stimulation noted in human obesity,40 namely, activation of renal sympathetic outflow and efferent sympathetic nerves to the skeletal muscle vasculature (not measured here by us), but with sparing of the neural outflow directed to the heart and the adrenal medulla. It should be mentioned, however, that in a previous investigation of leptin-sympathetic nervous relationships, which included patients with obesity-related hypertension who were not included here,16 we found a weaker and statistically nonsignificant relationship between plasma leptin concentration and renal NE spillover only.

Therefore, the link that we find between the sympathetic nervous system and leptin plasma concentration is, at best, only suggestive, and more compelling results will be needed to definitively document such a relationship and to establish leptin as the driving force in the renal sympathetic activation of obesity and obesity-related hypertension. Future studies investigating the proposed feedback leptin–sympathetic nervous system regulatory loop in humans should include patients with obesity-related hypertension who were not included here,16 which would constitute the efferent limb of the proposed feedback loop in humans, previously documented in experimental animals (not measured here by us), but with sparing of the neural outflow directed to the heart and the adrenal medulla.

Perspectives
Although the importance of leptin as an antiobesity factor in rodents seems well established, its contribution to human energy balance is uncertain. There are fundamental differences between rodents and humans in mechanisms of thermogenesis, perhaps primarily because of the importance of brown adipose tissue in the former. We find no support for the presence of a regulatory leptin–sympathetic nervous feedback loop in humans, previously documented in experimental animals, in which leptin activates central sympathetic outflow and the sympathetic nervous system inhibits leptin release. An earlier hypothesis of obesity causation was that weight gain in obesity is caused in part by sympathetic nervous underactivity and reduced secretion of epinephrine by the adrenal medulla reducing thermogenesis and contributing to a positive energy balance. The findings here and elsewhere of normal epinephrine secretion rates in obesity accompanied by activated sympathetic activity in some sympathetic outflows argue strongly against this, perhaps weakening the case for the development and clinical use of β-adrenergic agonists as thermogenic antiobesity drugs. Leptin is rather rapidly cleared from plasma by the kidneys. Our findings in heart failure of reduced renal clearance of leptin, thus elevating its plasma concentration, illustrate that the plasma concentration of leptin and its release rate are not strictly equivalent, with the high plasma leptin levels reported in renal failure providing another example of this phenomenon.

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References


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