Chronic Leptin Infusion Increases Arterial Pressure

Eugene W. Shek, Michael W. Brands, John E. Hall

Abstract—Plasma leptin concentration is increased in hypertensive obese humans, but whether leptin contributes to the increased arterial pressure in obesity is not known. In this study, we tested whether chronic increases in leptin, to levels comparable to those in obesity, could cause a sustained increase in arterial pressure and also the importance of central nervous system (CNS) versus systemic mechanisms. Five male Sprague-Dawley rats were implanted with chronic nonoccluding catheters in the abdominal aorta and both carotid arteries for CNS infusion, and five other rats were implanted with an abdominal aorta catheter and femoral vein catheter for intravenous (IV) infusion. After 7 days of control, leptin was infused into the carotid arteries or femoral vein at 0.1 µg/kg/min for 5 days and 1.0 µg/kg/min for 7 days, followed by a 7-day recovery period. The carotid artery and IV infusions of leptin at 1 µg/kg/min significantly increased plasma leptin levels, from 1.2±0.4 ng/mL to 91±5 ng/mL and from 0.9±0.1 ng/mL to 94±9 ng/mL, respectively, but there was no significant increase in either group at the low dose. Food intake also did not change at the low dose but decreased by approximately 65% in the carotid group and 69% in the IV group after 7 days of the 1 µg/kg/min infusion. Mean arterial pressure (MAP) increased slightly at the low dose only in the carotid group, but there was not statistically significant. At the higher dose, however, MAP increased significantly from 86±1 mm Hg to 94±1 mm Hg in the carotid group and from 87±1 mm Hg to 93±1 mm Hg in the IV group. Heart rate also increased significantly in both groups at 1 µg/kg/min leptin infusion. Fasting blood glucose and insulin levels decreased significantly at 1 µg/kg/min in both the carotid artery group (−10.5% and −82.5%, respectively) and the IV group (−13.6% and −80.4%, respectively). All variables returned to control levels after leptin infusion was stopped. These results indicate that chronic increases in circulating leptin cause sustained increases in arterial pressure and heart rate and are consistent with a possible role for leptin in obesity hypertension. (Hypertension. 1998;31[part 2]:409-414.)

Key Words: leptin ■ hypertension ■ sympathetic nervous system ■ blood pressure ■ heart rate ■ food intake

Increased circulating leptin, the peptide product of the "obese gene," has been suggested to contribute to increased blood pressure in obesity by activation of the sympathetic nervous system. Leptin production is increased in obese animals and humans and correlates positively with body mass index. Because leptin binding sites have been found in regions of the brain that are also important in cardiovascular control, there is reason to suspect that leptin could affect cardiovascular function through its CNS effects. Supporting this possibility is the observation by Haynes and colleagues, who recently demonstrated that acute intravenous (IV) infusion of leptin increased sympathetic nerve activity to the kidney, the adrenal, and the brown adipose tissue in anesthetized Sprague-Dawley rats. However, leptin has also been shown to cause macrosegregation and diuresis following bolus IV infusion. Thus, leptin may have multiple actions on the SNS and the kidney that, in some circumstances, could have opposite effects on arterial pressure regulation. Moreover, it is not known which of these effects, if any, can be sustained and exert long-term effects on cardiovascular and renal function.

The aim of this study, therefore, was to determine whether increases in circulating leptin, to levels similar to those found in obesity, cause sustained changes in cardiovascular, renal, and neurohumoral function. Furthermore, we investigated the role of CNS versus systemic mechanisms by comparing the chronic effects of carotid artery and IV leptin infusion on control of arterial pressure and renal function.

Methods

Animal Surgery

Male Sprague-Dawley rats (n=10) weighing approximately 350 to 400 g were used in this study. The protocol was approved by the Institutional Animal Care and Use Committee of University of Mississippi Medical Center and conformed to the National Institute of Health Guide for the Care and Use of Laboratory Animals. Under pentobarbital sodium (30 mg/kg, intraperitoneally), anesthesia and aseptic conditions, a laparotomy was performed, and a nonocclusive polyvinyl catheter was inserted into the abdominal aorta, distal to the kidneys, through a puncture made with a 20-gaauge needle tip. The insertion point was sealed with cyanoacrylate adhesive, and the catheter was externalized through the lateral abdominal wall. In the carotid artery infusion group (n=5), nonocclusive polyvinyl catheters were placed orthograde in both common carotid arteries via a midventral neck incision for continuous intracarotid infusion of vehicle or leptin into the cerebral circulation. In the rat, the carotid arteries provide most of the blood supply to the hypothalamus and
Experimental Protocol

A venous catheter was inserted into the vena cava via the left femoral vein for continuous IV infusion of vehicle or leptin. All incisions were infiltrated with penicillin G procaine and Sensorcane, and all catheters were routed subcutaneously to the scapular region and exteriorized through a polypropylene button that was implanted subcutaneously.

Rats were allowed to recover from the surgery and were housed in individual metabolic cages in a quiet, air-conditioned room with a 12:12 hour light/dark cycle. In the CNS infusion group, the carotid artery catheters were connected to a syringe pump (Harvard Apparatus) via a dual-channel hydraulic swivel (Instech) mounted above the cage for continuous 24-hour infusion. The aortic catheter was filled with heparin solution (1000 USP U/mL) and plugged. For arterial pressure measurement, the aortic catheter was flushed and connected to a pressure transducer (Cobe) mounted on the cage exterior at the level of the rat. Pulsatile arterial pressure signals were sent to an analog-to-digital converter and analyzed by computer using customized software. The analog signal was sampled for 4 seconds every 15 seconds from 7:00 AM to 1:00 PM daily. In the IV-infused group, the venous catheter was connected to a syringe pump via one port of the hydraulic swivel for continuous 24-hour infusion, and the aortic catheter was connected to the transducer via the other port.

The rats received food and water ad libitum throughout the study. Sodium intake was maintained constant at approximately 3.0 mEq/d by continuous infusion of 20 mL of 0.9% saline/d, combined with feeding a sodium-deficient rat chow. In addition, 21 mL of sterile water/d was infused as a vehicle for the leptin infusion during the experimental period, yielding a total volume of 41 mL/d. This infusion began immediately after placement of rats in their metabolic cages. A minimum of 5 to 7 days were allowed for accommodation before control measurements were made. All solutions contained antibiotic (penicillin G potassium 30,000 U/d and metoclopramide 27 mg/d) and were infused through a Millipore filter (22 μm, Cathvane, Millipore).

Analytical Methods

PRA was measured by radioimmunoassay using 125I-angiotensin I from New England Nuclear and antibody from Amgen. Plasma insulin, aldosterone, and corticosterone concentrations were measured by radioimmunoassay (Diagnostic Products). Plasma leptin concentration was measured by enzyme immunoassay (Amgen Inc). Plasma protein concentration was measured by refractometry (American Optical). Urine sodium concentration was determined by using ion-sensitive electrodes (Nova). Blood glucose was measured by using an Accu-Check III blood glucose monitor (Boehringer Mannheim Corpora-

Results

Effects of Leptin Infusion on Food Intake, Arterial Pressure, and Heart Rate

Food intake did not change significantly during leptin infusion at 0.1 μg/kg/min. However, at the higher infusion rate (1 μg/kg/min), food intake decreased markedly from 20.4 ± 0.7 g/d to 7.1 ± 0.5 g/d (Fig 1). Similar to the effect of carotid artery infusion, chronic IV infusion of leptin did not affect food intake at the low dose but markedly decreased food intake from 20.4 ± 0.2 g/d to 6.2 ± 0.5 g/d at 1 μg/kg/min (Fig 1). Food intake in both carotid artery and IV infusion groups returned to control 2 days after leptin infusion was stopped.

MAP increased slightly by day 5 of carotid artery leptin infusion at 0.1 μg/kg/min, but the increase was not statistically significant (Fig 2). At the 1 μg/kg/min dose, however, MAP increased significantly, to 94 ± 2 mm Hg by the fifth day. Leptin infusion at 0.1 μg/kg/min IV did not change MAP, but, at the higher dose, raised MAP significantly from 87 ± 1 mm Hg to 93 ± 1 mm Hg (Fig 2).

Arterial pressure

Figure 1. Effect of chronic bilateral carotid artery or intravenous infusion of leptin at 0.1 μg/kg/min (5 days) and 1.0 μg/kg/min (7 days) on daily food intake in conscious normal SD rats (n=5 per group). *P<0.05 compared to control.

Selected Abbreviations and Acronyms

CNS = central nervous system

GFR = glomerular filtration rate

HR = heart rate

MAP = mean arterial pressure

PRA = plasma renin activity

RPF = renal plasma flow

RVR = renal vascular resistance

SNS = sympathetic nervous system
Figure 2. Effect of chronic bilateral carotid artery or intravenous infusion of leptin at 0.1 μg/kg/min (5 days) and 1.0 μg/kg/min (7 days) on mean arterial pressure in conscious normal SD rats (n=5 per group). *P<.05 compared to control.

decreased rapidly to levels below control levels after leptin infusion was stopped in both carotid artery and IV infusion groups.

Chronic carotid artery infusion of leptin at 0.1 μg/kg/min did not change heart rate significantly, but at the 1 μg/kg/min dose, HR increased from 323±4 beats/min to 355±5 beats/min by day 7 of the infusion (Fig 3). Similar to the effect of carotid artery infusion, chronic IV infusion of leptin did not affect HR at the low dose, but heart rate increased significantly at the high dose, from 305±9 beats/min during the control period to 322±10 beats/min by day 7 of the leptin infusion period (Fig 3). HR decreased rapidly in both carotid artery and IV infusion groups after leptin infusion was stopped and was significantly below control (202±5 beats/min and 284±5 beats/min, respectively) by day 3 of the recovery period.

Effects of Leptin Infusion on Renal Function

Although there was a tendency for urine volume to increase during leptin infusion at 1 μg/kg/min in both carotid artery and IV infusion groups, the increase was not statistically significant (Fig 4). There was also no significant change in urinary sodium excretion in either group during leptin infusion at 0.1 or 1 μg/kg/min (Fig 5). GFR, RPF, and RVR did not change during
Leptin-Induced Hypertension

**Figure 6.** Effect of chronic bilateral carotid artery or intravenous infusion of leptin at 0.1 μg/kg/min (5 days) and 1.0 μg/kg/min (7 days) on glomerular filtration rate (GFR), renal plasma flow (RPF), and renal vascular resistance (RVR) in conscious normal SD rats (n=5 per group). Data are expressed as percent control.

The most significant finding of this study is that chronic leptin infusion, at rates that increased plasma leptin concentrations to levels comparable to those found in obese humans, markedly reduced food intake and elevated arterial pressure and heart rate in normal rats. The tendency for arterial pressure to increase only in the carotid artery infusion group at the low dose is consistent with the possibility that the pressor effect of leptin may have a CNS component. However, the higher infusion rate produced similar increases in both plasma levels of leptin and arterial pressure.

**Humoral and Metabolic Actions of Leptin**

Food intake did not change during carotid artery or IV leptin infusion at 0.1 μg/kg/min but was decreased significantly at 1 μg/kg/min in both groups. These observations are consistent with previous studies that chronic injection of leptin in ob/ob mice, animals with deficient leptin production, significantly reduces food intake. The mechanism for leptin's effect to reduce food intake has been suggested to be suppression of hypothalamic NPY mRNA expression and NPY release, although most previous studies have used very high concentrations of leptin to demonstrate these effects. In the present study, increased circulating leptin concentration, to levels comparable to those found in obese humans, markedly reduced food intake. These observations provide further support for the concept that leptin is an important physiological regulator of energy balance.

Increased circulating leptin also markedly decreased plasma insulin concentration and modestly reduced blood glucose. Although the mechanisms responsible for leptin's effects on plasma insulin and glucose levels are not clear, a recent study by Kieffer et al indicates that there are leptin receptors located on the pancreatic β-cells, although the function of these receptors remain unclear.

**Discussion**

The most significant finding of this study is that chronic leptin infusion, at rates that increased plasma leptin concentrations to levels comparable to those found in obese humans, markedly reduced food intake and elevated arterial pressure and heart rate in normal rats. The tendency for arterial pressure to increase only in the carotid artery infusion group at the low dose is consistent with the possibility that the pressor effect of leptin may have a CNS component. However, the higher infusion rate produced similar increases in both plasma levels of leptin and arterial pressure.

**Table 1:** Effects of Chronic Bilateral Carotid Artery Infusion of Leptin at 0.1 and 1.0 μg/kg/min on Plasma Leptin, Fasting Insulin (Ins), Fasting Glucose (Glu), Plasma Renin Activity (PRA), Plasma Aldosterone (Aldo), and Plasma Corticosterone (Cort)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Leptin (ng/mL)</th>
<th>Ins (μU/mL)</th>
<th>Glu (mg/dL)</th>
<th>PRA (ng Al/mL/h)</th>
<th>Aldo (ng/dL)</th>
<th>Cort (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.2±0.4</td>
<td>412±10.5</td>
<td>104±3.2</td>
<td>31±0.6</td>
<td>40.7±10.8</td>
<td>131±34.1</td>
</tr>
<tr>
<td>Leptin (0.1 μg/kg/min)</td>
<td>1.4±0.5</td>
<td>40.2±6.7</td>
<td>106±2.2</td>
<td>36±0.5</td>
<td>35.5±43</td>
<td>94.5±12.6</td>
</tr>
<tr>
<td>Leptin (1.0 μg/kg/min)</td>
<td>91.0±4.9*</td>
<td>72±1.3*</td>
<td>93.4±4.4*</td>
<td>37±0.3</td>
<td>25.1±49</td>
<td>87.3±28.1</td>
</tr>
<tr>
<td>Recovery</td>
<td>0.8±0.2</td>
<td>42.2±10.4</td>
<td>109±3.5</td>
<td>32±0.6</td>
<td>31.4±5.9</td>
<td>105.8±33.6</td>
</tr>
</tbody>
</table>

Values are mean±SE, n=5 rats

*P<0.05 compared with control, leptin (0.1 μg/kg/min), and recovery
is not known. Leptin may also decrease insulin release by stimulating α-adrenergic receptors in the pancreas via its effect on sympathetic activity. However, the finding that leptin decreased plasma glucose suggests additional effects besides a simple inhibition of insulin secretion. Another possibility is that leptin increased glucose utilization or improved insulin sensitivity in peripheral tissues, which enhanced glucose disposal in skeletal muscle and fat cells and suppressed glucose output by the liver. Thus, the decrease in plasma insulin could be a compensatory response to a fall in plasma glucose. Additional studies are needed, however, to determine how leptin affects glucose control and insulin secretion.

Leptin, at the higher dose, did not alter plasma renin activity, but corticosterone and aldosterone tended to decrease, although not significantly. The reduced plasma aldosterone levels may be related to reduced potassium intake associated with reduced food consumption.

### Arterial Pressure and Heart Rate Responses to Leptin

Previous studies have reported that arterial pressure and heart rate were not changed by acute leptin infusion. One possible explanation is that arterial pressure and heart rate were measured under anesthesia in those studies, whereas our studies were conducted in conscious rats. In addition, leptin was administered acutely in previous studies, either by a single bolus injection or by short-term infusion. Our results are consistent with those findings, because the increases in arterial pressure and heart rate were not apparent until 3 to 4 days after the leptin infusion was started. This was true even for the low infusion rate, which appeared to have a small centrally mediated effect on arterial pressure, since there was no significant change in systemic plasma leptin concentration and IV leptin infusion at this rate caused no changes in heart rate and arterial pressure. Thus, both the arterial pressure and heart rate responses to physiological increases in circulating leptin levels appear to be slow in onset.

The mechanisms by which increased circulating levels of leptin elevate arterial pressure and heart rate chronically are not entirely clear. One possible explanation is activation of the sympathetic nervous system. The finding that animals with deficient leptin production (ob/ob mice) or defective leptin receptors (db/db mice) also have decreased metabolic activity and hypothermia is consistent with the concept that leptin interacts with hypothalamic receptors to reduce food intake and activate the SNS. Furthermore, leptin has been shown to increase norepinephrine turnover in interscapular brown adipose tissue, and a recent study by Haynes and colleagues reported that acute IV infusion of leptin in rats increased sympathetic nerve activity in the adrenals, brown adipose tissue, and the kidneys.

Our finding that there was a tendency for arterial pressure to increase with low-dose carotid artery infusion suggests a possible CNS mechanism, but our studies cannot determine the precise role of CNS compared to systemic actions of leptin in chronic blood pressure regulation. Further studies are needed to determine the role of the CNS and peripheral effects of leptin in long-term blood pressure regulation.

Heart rate also increased significantly with chronic carotid artery and IV leptin infusion at 1 μg/kg/min. Although leptin receptor mRNA has been shown to be expressed in the heart, the physiological role of this receptor remains to be determined. Leptin could increase heart rate by increasing cardiac sympathetic activity or by withdrawal of parasympathetic tone. A recent study in our laboratory, for example, demonstrated that the increased heart rate associated with 5 weeks of a high-fat diet in dogs was due mainly to decreased cholinergic activity. However, additional studies are required to determine the contribution of sympathetic and parasympathetic mechanisms in mediating leptin’s effect on heart rate.

### Renal Effects of Leptin

Previous acute studies have shown that infusion of leptin at high doses caused natriuresis and diuresis. For example, Jackson and Le reported that intrarenal leptin injection at 30 μg/min caused a twofold increase in urine volume and sodium excretion in normal rats. Reams et al also reported that bolus IV injection of leptin at 400 μg/kg significantly increased urine volume and sodium excretion in normotensive Sprague-Dawley rats, although natriuresis was not observed in spontaneously hypertensive rats.

In the present study, we found no significant changes in sodium excretion or urine volume during chronic infusion of leptin at a rate that produced physiological increases in plasma leptin concentration. However, the absence of significant changes in sodium excretion in our study does not necessarily imply that leptin had no effect on renal function. In fact, IV leptin infusion significantly decreased RPF and increased RVR. Moreover, the observation that leptin did not increase sodium excretion, despite raising arterial pressure, provides evidence that leptin, infused IV or via the carotid arteries, shifted the renal-pressure natriuresis relationship to higher.

---

### Table 2: Effects of Chronic Intravenous Infusion of Leptin at 0.1 and 1.0 μg/kg/min on Plasma Leptin, Fasting Insulin (Ins), Fasting Glucose (Glu), Plasma Renin Activity (PRA), Plasma Aldosterone (Aldo), and Plasma Corticosterone (Cort)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Leptin (ng/mL)</th>
<th>Ins (μU/mL)</th>
<th>Glu (mg/dL)</th>
<th>PRA (ng AI/mL/h)</th>
<th>Aldo (ng/dL)</th>
<th>Cort (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.9±0.1</td>
<td>52±6.10</td>
<td>113±35</td>
<td>3.8±0.5</td>
<td>458±6.5</td>
<td>1376±20.2</td>
</tr>
<tr>
<td>Leptin (0.1 μg/kg/min)</td>
<td>2.3±0.7</td>
<td>39±1.09</td>
<td>113±2.4</td>
<td>3.6±0.6</td>
<td>369±5.9</td>
<td>1180±35.8</td>
</tr>
<tr>
<td>Leptin (1.0 μg/kg/min)</td>
<td>94±0.9*</td>
<td>10±2.3*</td>
<td>103±2.6*</td>
<td>3.4±0.4</td>
<td>23.6±7.7</td>
<td>106±38.7</td>
</tr>
<tr>
<td>Recovery</td>
<td>0.7±0.1</td>
<td>53.8±15.8</td>
<td>114±0.3</td>
<td>4.0±0.3</td>
<td>35.4±10.4</td>
<td>116.2±26.8</td>
</tr>
</tbody>
</table>

*P<0.05 compared with control, leptin (0.1 μg/kg/min), and recovery
Leptin-Induced Hypertension

blood pressures. In the absence of an impaired pressure
naturess, increased arterial pressure would tend to increase
renal sodium and water excretion. Whether this effect of
leptin to shift pressure nauresses is due to direct renal action or
to other effects, such as sympathetic stimulation, is still unclear
In summary, our studies demonstrated that leptin, at phys-
ological concentration, markedly decreased food intake and
plasma mrsulin, supportmg the concept that leptin plays an
important role in regulating energy balance. Our studies also
indicate that increases in circulating leptin concentration, to
levels similar to those found in obesity, significantly elevate
arterial pressure and heart rate, findings suggesting a possible
role for leptin in obesity hypertension. Further studies are
needed, however, to determine the precise role of the CNS
and peripheral effects of leptin in long-term blood pressure
regulation in obesity.

Acknowledgments

We thank Dr Mans J Smith, Jr for the radioimmunoassays and Dr
Margery Nicolson (Amgen Inc) for the enzyme immunoassay used in
these experiments. We also thank Amgen Inc for supplying the
murine leptin.

This study was supported by National Heart, Lung, and Blood
Institute Grant HL-51971

References

1 Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM
Positional cloning of the mouse obese gene and its human homologue
Nature 1994,372 425-432
2 Hopkins PN, Hunt SC, Wn JI, Williams GH, Williams RR. Hyper-
tension, dyslipidemia, and insulin resistance: links in a chain or spokes on
a wheel? Can J Cardiol 1996,7 241-253
3 Considine RV, Sinha MK, Heiman ML, Kriaucynas A, Stephen TW,
Neyce MR, Ohannesian JP, Marco CC, McKee IJ, Baure TL, Caro JF
Serum immunoreactive-leptin concentrations in normal-weight and obese
4 Tartaglia LA, Dembski M, Weng X, Deng N, Culpapper J, Devos R,
Richards GJ, Campfield LA, Clark FT, Deech J, Muir C, Sanker S,
Mozaffaty A, Moore RJ, Matsuoka JS, Mays GG, Woolf EA, Mounce CA,
Tepper RJ Identification and expression cloning of a leptin receptor.
OB-R. Cell 1995,83 1263-1271
5 Haynes WG, Morgan DA, Walsh SA, Mark Al., Sivitz W1. Leptin
increases sympathetic nerve activity to brown adipose tissue and kidney
FASEB J 1997,11(3) A4
6 Jackson EK, Li P. Human leptin may function as a durence/nauress
Hypertension 1996,38 617
7 Wellens D, Wouters L, Ngkamp FP, De Jong W. Distribution of the blood
flow supplied by the vertebral artery in rats: anatomical, functional and
pharmacological aspects. Experientia 1976,32 85-87
8 Berger EY, Farber SJ, Earle DP Jr. Comparison of the constant infusion and
urine collection techniques for the measurement of renal function. J Clin
Invest 1948,27 710-719
9 Dunnet CW New tables for multiple comparisons with a control. Bio-
metrics 1964,20 482-491
10 Drumherr JL, Kille DL. Computational Handbook of Statistics. Glenview, Ill
Scott, Foreman, 1987 18-145
11 Halaas JL, Gasparra KS, Maffei M, Cohen SL, Chart BT, Rabenowitz D,
Lalome RL, Butley SK, Friedman JM. Weight-reducing effects of the
plasma protein encoded by the obese gene. Science 1995,269 543-546
12 Polleymounter MA, Cullen MJ, Baker MB, Rhecht R, Wnten D, Boone T,
Collins E. Effects of the obese gene product on body weight regulation
in ob/ob mice. Science 1995,269 540-543
13 Campfield LA, Smith FJ, Guste Y, Devos R, Burt P. Reombinant
mouse ob protein evidence for a peripheral signal linking adiposity and
14 Stephen TW, Brunnsk M, Bristow PK, Bue-Velkesy JM, Burgett SG,
Craft L, Hare J, Hoffmann J, Huang HM, Kriacynnas A, MacKellar W,
Rosteck PA Jr, Schoner B, Smith D, Tinsley FC, Zhang XY, Heimmi M
The role of neuropeptide Y in the antilobesity action of the obese gene
product Nature 1995,377 530-532
15 Kieffer TJ, Heller RS, Habener JF. Leptin receptors expressed on pan-
creatic beta cells. Biochem Biophys Res Commun 1996,224(2) 522-527
16 Reams G, Villareal D, Tazabon A, Freeman RH, Knoblich P. Renal
effects of leptin in normotensive and spontaneously hypertensive rats
FASEB J 1997,11 A798
17 Collins S, Kuhn CM, Petro AE, Swedk AG, Chrumpk BA, Surwit RS
parasympathetic control of heart rate in obese dogs. Am J Physical 1995,
269 H629-H637
19 Guyton AC. Arterial Pressure and Hypertension. Philadelphia, W B Saunders,
1980 87-99
20 Hall JE, Brands MW, Shek EW. Central role of the kidney and abnormal
fluid volume control in hypertension. J Hypertension 1996,10 625-639
Chronic Leptin Infusion Increases Arterial Pressure
Eugene W. Shek, Michael W. Brands and John E. Hall

Hypertension. 1998;31:409-414
doi: 10.1161/01.HYP.31.1.409

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on
the World Wide Web at:
http://hyper.ahajournals.org/content/31/1/409

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally
published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not
the Editorial Office. Once the online version of the published article for which permission is being requested
is located, click Request Permissions in the middle column of the Web page under Services. Further
information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/