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Effects of renal denervation on the sodium excretory actions of leptin in hypertensive rats

Daniel Villarreal, Garry Reams, and Ronald H. Freeman

Departments of Internal Medicine and Physiology, University of Missouri, and Harry S. Truman Memorial Veterans' Hospital, Columbia, Missouri, USA

Effects of renal denervation on the sodium excretory actions of leptin in hypertensive rats.

Background. Previous studies from this laboratory have reported a marked attenuation of the renal responses to pharmacologic doses of synthetic murine leptin infused in the spontaneously hypertensive rat (SHR) model compared with normotensive Sprague-Dawley and lean Zucker rat models.

Methods. In the present study, the hemodynamic and renal excretory effects of an intravenous bolus administration of pharmacologic doses of synthetic murine leptin were examined in groups of anesthetized SHR with unilateral nephrectomy and renal denervation or sham-denervation of the remaining kidney.

Results. In the SHR with acute renal denervation ($N = 8$), an intravenous bolus of 1600 μg/kg of leptin produced a significant twofold to fourfold elevation in sodium excretion but did not increase natriuresis in the sham-denervated group ($N = 6$). Chronic renal denervation of one-week duration ($N = 8$) was associated with qualitatively and quantitatively similar increases of sodium excretion in response to leptin administration. Mean arterial pressure remained unchanged in all groups after the administration of leptin.

Conclusions. Collectively, these results are interpreted to suggest that the blunted natriuretic and diuretic responses to leptin observed in the SHR with intact renal nerves may be partially explained by the antinatriuretic effect of an enhanced baseline efferent renal sympathetic activity and/or leptin's stimulation of the sympathetic nervous system.

Leptin, the product of the *ob* gene, is a recently isolated peptide-hormone primarily secreted by adipocytes that has been implicated in the regulation of food intake and thermogenesis [1, 2]. It has been suggested that this hormone functions as a messenger for adipose tissue and acts on the hypothalamus to reduce food intake in a negative feedback manner [1–4]. Leptin circulates in several animal species, including rats and humans, and its plasma levels correlate with body fat content. Interestingly, other than obesity, it has been reported that circulating levels of leptin are elevated in patients with essential hypertension [5].

The leptin receptor is a member of the extended class I cytokine receptor family having multiple splice variants [1, 2, 4]. The *ob*-Ra variant has been postulated to transport leptin across the blood–brain barrier. *Ob*-Rc and *ob*-Rd have been implicated in the clearance of leptin from the circulation, and the *ob*-Re variant is a putative soluble receptor. The *ob*-Rb variant encodes a receptor with a long intracellular domain, which is essential for intracellular signal transduction [6–8]. High tissue levels of leptin receptor gene expression occur in the lung, moderate levels in the kidney, and low levels in the heart, brain, spleen, liver, and muscle [8–10]. Expression of the extracellular domain of the leptin receptor *ob*-R and the short splice variant *ob*-Ra has been shown in many peripheral tissues [11]; however, the long splice variant *ob*-Rb was detectable primarily in the adrenal gland and the kidney [12].

Emerging information indicates that the functions of leptin are much more extensive than those of an anti-obesity hormone. Leptin also affects several neuroendocrine mechanisms and regulates multiple hypothalamic-pituitary axes [4]. In addition, accumulating evidence suggests that a regulatory role of leptin may extend to other organs and biological functions, including the cardiovascular and renal systems. Within the rat kidney, in situ hybridization of the ob-Rb receptor occurs over the inner zone of the medulla and pyramid, appearing to be associated with collecting tubules and ducts [10]. Also, immunohistochemical studies have disclosed intense leptin labeling in the apical membrane and cytoplasm of inner medullary collecting duct cells, with only weak staining found in the rest of the collecting ducts and tubules [13]. More recently, studies from independent laboratories have demonstrated that exogenous leptin produces a natriuresis in anesthetized, normotensive rats when infused intravenously [14] or directly into the renal

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artery [15], suggesting a potential role of this hormone in the regulation of sodium-volume balance. Importantly, however, these natriuretic and diuretic effects are markedly blunted in the spontaneously hypertensive rat (SHR) [12] and Koletsky hypertensive rat model (abstract; Correia et al, *Am J Hypertens* 11:22a, 1998). Although the factors that attenuate the renal responses to leptin in experimental hypertension are unclear, one possible counter-regulatory natriuretic mechanism could involve the enhanced efferent renal sympathetic nerve activity (ERSNA) characteristic of these genetic hypertensive rat strains. In addition, studies by Haynes et al recently demonstrated that synthetic murine leptin produced a significant dose-related elevation in efferent sympathetic nerve activity to kidney, adrenal gland, brain, adipose tissue, and hind limb of the normal rat [16]. It is possible that this elevation in leptin-induced renal sympathoactivation could contribute to promote antinatriuresis and could attenuate the tubular sodium excretory actions of leptin. Thus, the present study was designed to evaluate the hypothesis that blockade of renal sympathetic activity with acute and chronic renal denervation enhances the renal sodium excretory actions of synthetic murine leptin in the SHR.

METHODS

Animal models

Spontaneously hypertensive rats with body weights between 250 and 330 g were utilized (Charles Rivers, Wilmington, MA, USA). All animals were housed in individual cages in a room on a 12-hour light/dark cycle and were maintained on a regular rat chow diet (Purina, St. Louis, MO, USA) for at least seven days before the study. Tap water was available ad libitum. The animal care provided during these studies met institutional guidelines.

Acute renal denervation experiments

All experiments were performed in the postabsorptive state at least 18 hours after the last meal. On the day of the acute experiment, anesthesia was induced with Inactin (100 mg/kg intraperitoneally; Andrew Lockwood & Associates, Sturtevant, WI, USA). Under sterile conditions, the left kidney was approached retroperitoneally via a flank incision, and the renal vessels were stripped of all visible nerves and were painted with a 10% phenol solution. It is well established that this denervation procedure reduces renal cortex norepinephrine content by >95%, consistent with complete renal denervation [17]. Sham acute denervation consisted of identical anesthetic and all surgical procedures, but the renal nerves were left intact. Following the denervation or sham procedure, a tracheostomy was performed to facilitate respiration, and polyethylene catheters (PE-50) were inserted into the carotid artery for the measurement of blood pressure and the jugular vein for infusion of solutions. Finally, via a ventral midline incision, a right nephrectomy was performed, and the urinary bladder was exteriorized and cannulated for collection of urine. The arterial catheter was connected by a Statham P23Db strain gauge pressure transducer (Oxnard, CA, USA) to a Hewlett Packard 7714-041A Recorder (St. Louis, MO, USA) for continuous mean arterial pressure (MAP) monitoring. After the completion of the surgical procedures, saline infusion was started at a sustained rate of 25 μL/min and was continued for the duration of the experiment. Subsequently, 15 minutes of an equilibration interval was observed in all groups of rats. Immediately after, in the renal denervated SHR, either synthetic murine leptin (PeproTech, Rock Hill, NJ, USA) at 1600 μg/kg ($N = 8$) or saline vehicle ($N = 8$) was infused over 30 seconds into the jugular vein. The two SHR groups of sham acute denervation were similarly treated with leptin at the same dose ($N = 6$) or vehicle ($N = 6$). In all of the renal-denervated and sham-denervated groups, following an additional 30-minute equilibration interval, two 45-minute experimental periods (E_1 and E_2) were obtained. Urine was collected for each entire period and assayed for sodium concentration with flame photometry. The present pharmacologic dose and type of leptin were selected based on previous studies [12] and preliminary experiments indicating a maximal natriuresis in normal Sprague-Dawley rats with no effect on sodium excretion in the SHR with intact renal nerves.

Chronic renal denervation experiments

Under anesthesia with ketamine [200 mg/kg intramuscularly (IM)] and xylazine (2.6 mg/kg IM), the left kidney was approached retroperitoneally via a flank incision, and renal denervation was produced as described previously in this article. Following the denervation procedure, the rats recovered from anesthesia, and one week was allowed prior to the terminal experiment. On the day of the acute experiment and in the postabsorptive state, anesthesia was induced with Inactin (100 mg/kg intraperitoneally; Andrew Lockwood & Associates). A tracheostomy was performed, and catheters were inserted into the carotid artery and jugular vein. Finally, a right nephrectomy was performed, and the urinary bladder was exteriorized and cannulated as previously described. After the completion of all surgical procedures, saline infusion was started at a rate of 25 μL/min and was continued for the duration of the experiment. Similar to the acute denervated series, a 15-minute equilibration period was observed. Immediately after, the animals were infused with either 1600 μg/kg of leptin ($N = 8$) or a saline vehicle ($N = 8$). Following an additional 30-minute equilibration interval, two 45-minute experimental periods (E_1 and E_2) were obtained. Urine was

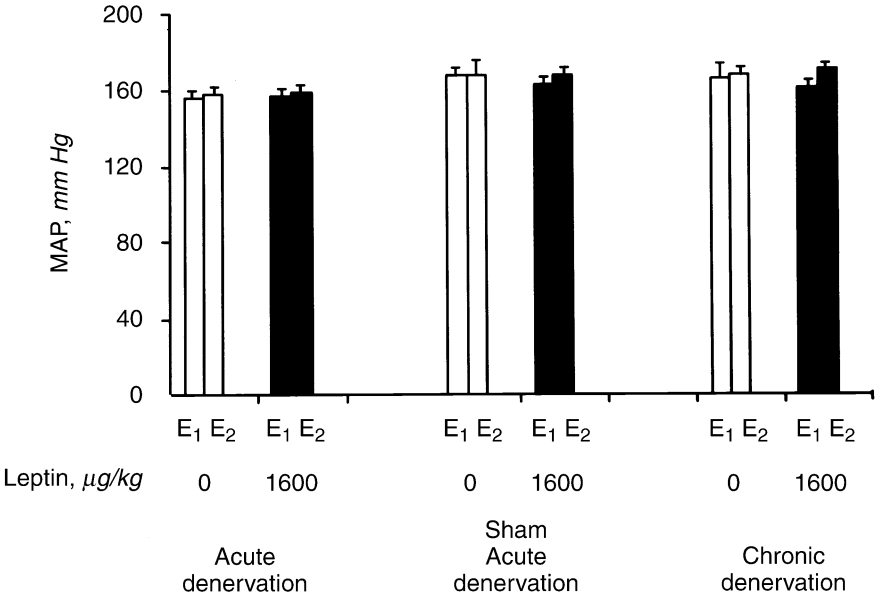

Fig. 1. Effects of leptin on mean arterial pressure (MAP) in spontaneous hypertensive rats (SHRs) with acute denervation ($N = 8$ for each group), sham acute denervation ($N = 6$ for each group), and chronic denervation ($N = 8$ for each group). Symbols are: (□) vehicle (0 dose); (■) leptin (1600 μg/kg). Values are means ± SEM. E_{1-2} are experimental periods of 45 min each.

collected for each period and assayed for sodium concentration, as described earlier.

Statistical analysis

Group data were expressed as mean ± SEM. Between appropriate groups, data were analyzed using analysis of variance (ANOVA) with a two-factor, mixed-design and LSD as post hoc test [18]. A difference was considered statistically significant when $P < 0.05$.

RESULTS

Body weights of the SHRs ranged between 250 and 330 g and were not different among the six experimental groups ($P > 0.05$). In the acute denervated series, body weights of the SHR-leptin ($N = 8$) and SHR-saline vehicle ($N = 8$) were 286 ± 7 and 277 ± 8 g, while in the SHR sham-leptin ($N = 6$) and the SHR sham-saline vehicle ($N = 6$) were 294 ± 8 and 290 ± 6 g, respectively. In the chronic denervated series, body weights were 297 ± 8 g for the leptin group ($N = 8$) and 300 ± 7 g for the saline vehicle rats ($N = 8$).

The experimental data for arterial pressure, urinary sodium excretion and urine flow rate are presented in Figures 1, 2 and 3. The data shown in Figure 1 demonstrate that in the vehicle control groups (0 dose), acute renal denervation did not produce significant changes in MAP compared with the sham-denervated group. However, in the same vehicle control groups (0 dose), urinary sodium excretion appeared elevated following acute renal denervation compared with the sham-denervated group (Fig. 2), and this increase in sodium excretion approached statistical significance ($P = 0.07$). Similarly, in these two groups, urinary flow rate was significantly elevated twofold following acute renal denervation compared with the sham-denervated rats (Fig. 3). Systemic hemodynamic and renal excretory functions were not altered ($P > 0.05$) in the vehicle control group (0 dose) with chronic renal denervation compared with the vehicle treated sham-denervated group (Figs. 1–3).

Administration of leptin did not produce any changes in the arterial pressure within any group of rats compared with the corresponding vehicle control groups (Fig. 1). Also, there were no significant changes in the heart rate of these animals (data not shown). Similar to our previous studies, leptin did not produce any changes in urinary sodium and volume excretion in the sham-denervated animals compared with the corresponding vehicle-infused group (Figs. 2 and 3). However, acute denervation was associated with twofold to fourfold increases in urinary sodium excretion following leptin infusion compared with the corresponding vehicle-infused acute denervated group (Fig. 2). Similar, although less marked responses in the urinary flow rate were observed following leptin administration in the acute denervated group compared with its corresponding vehicle control group (Fig. 3). Finally, leptin produced quantitatively similar significant increases in urinary sodium and urinary volume excretion in the chronic denervated rats compared with the corresponding vehicle control animals (Figs. 2 and 3).

DISCUSSION

Recent investigations [12, 14, 15] have suggested that among its multiple biological actions, the adipocyte-derived hormone leptin can promote sodium excretion in the normal [14, 15] but not the genetically hypertensive

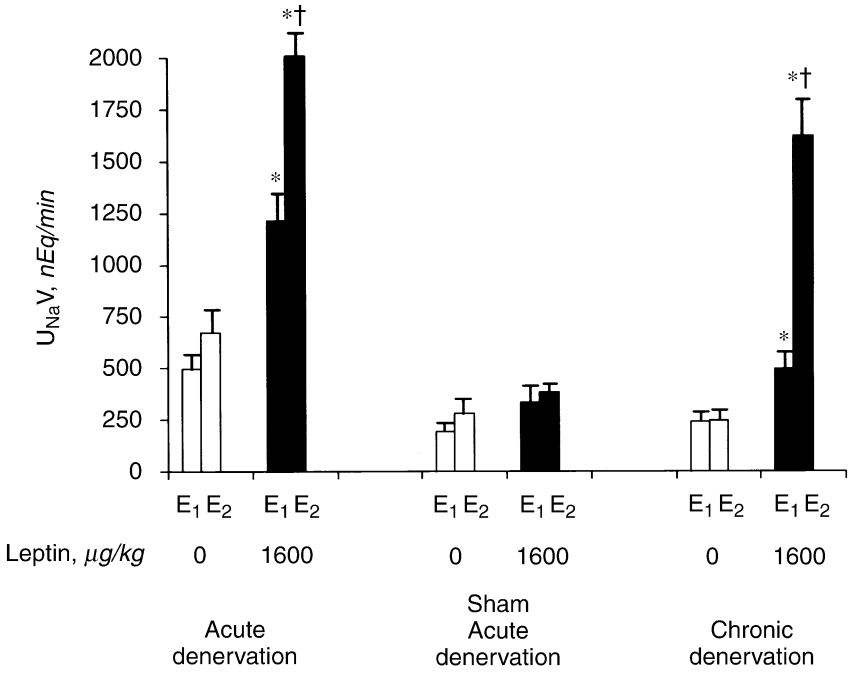

Fig. 2. Natriuretic ($U_{Na}V$) effects of leptin in SHRs with acute denervation ($N = 8$ for each group), sham acute denervation ($N = 6$ for each group), and chronic denervation ($N = 8$ for each group). Symbols are: (□) vehicle (0 dose); (■) leptin (1600 μg/kg). Values are means ± SEM. E_{1-2} are the experimental periods of 45 minutes each. *$P < 0.05$ vs. the corresponding period at 0 dose within each experimental series; †$P < 0.05$ vs. E_1.

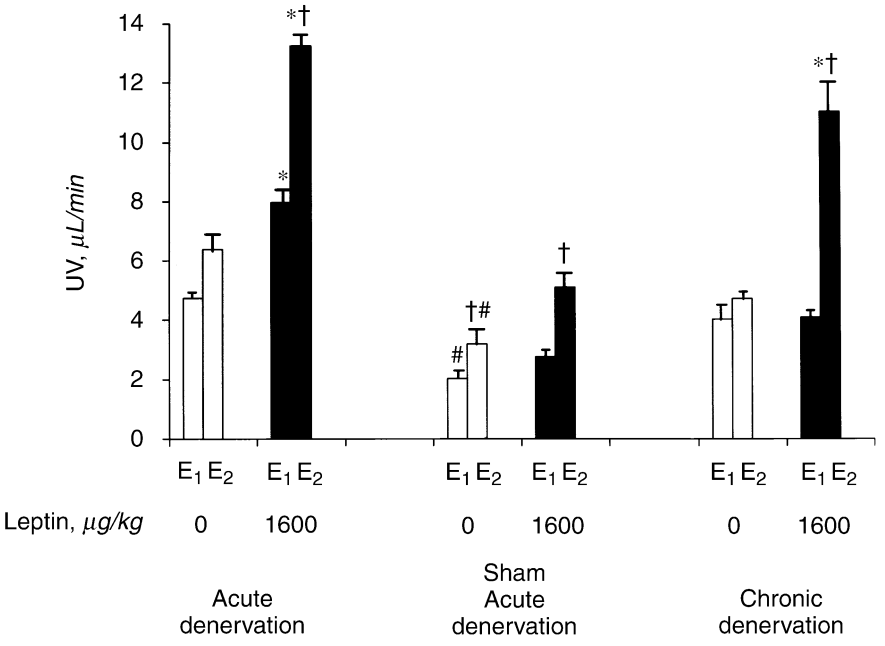

Fig. 3. Diuretic (UV) effects of leptin in SHRs with acute denervation ($N = 8$ for each group), sham acute denervation ($N = 6$ for each group), and chronic denervation ($N = 8$ for each group). Symbols are: (□) vehicle (0 dose); (■) leptin (1600 μg/kg). Values are means ± SEM. E_{1-2} are experimental periods of 45 minutes each. *$P < 0.05$ vs. the corresponding period at 0 dose within each experimental series; †$P < 0.05$ vs. E_1; #$P < 0.05$ vs. the corresponding period at 0 dose of the acute denervation group.

rat [14]. The present study confirms these findings and extends these previous observations to indicate that the attenuated natriuretic response to leptin administration in the SHR is mediated, at least in part, by an enhanced baseline efferent renal sympathetic nerve activity (ERSNA) characteristic of this hypertensive model and/or by a leptin-induced stimulation of ERSNA [16].

Leptin is a circulating polypeptide protein produced by an adipocyte-specific gene [1, 2, 4]. It regulates energy balance by binding to receptors in the hypothalamus leading to alterations in food intake, temperature, and energy expenditure [1–4]. Adipose tissue leptin mRNA and serum leptin levels directly correlate with the amount of body fat, and considerable information indicates that leptin is a signaling factor for the regulation of body weight [19–21]. Leptin has also been shown to increase norepinephrine turnover in thermogenic brown adipose tissue, suggesting that increased sympathetic ac-

tivity may, in part, modulate its action [16]. In addition, leptin-induced elevations in sympathetic activity have been demonstrated in nonthermogenic tissue, specifically the kidney [16].

In the last four years, three independent laboratories have reported natriuresis and diuresis with either intrarenal [15], intravenous [14], or intraperitoneal [12] infusions of leptin in normal anesthetized [14, 15] and conscious [12] rats. In these previous studies [14, 15], the administration of leptin had no effect on arterial pressure, heart rate, renal blood flow, glomerular filtration rate, or potassium excretion. The increased fractional excretion of sodium observed in these investigations suggests a tubular mechanism for leptin-induced natriuresis in normotensive animals. Although renal binding sites for leptin in the medulla and cortical collecting duct of rat kidney have been reported [10], the cellular mechanisms promoting sodium excretion are not clear.

In contrast to the aforementioned studies indicating natriuretic/diuretic actions of acute leptin infusions is a recent investigation in normal, conscious Sprague-Dawley rats [22]. In this study with continuous leptin infusion at a dose of 1 μg/kg/min either directly into the carotid artery or intravenously for seven days, there was appetite suppression and a marked reduction in food intake of approximately 65 to 70%. The leptin plasma levels achieved averaged 94 ± 9 ng/mL, which fall within the endogenous circulating levels reported in obese humans [22]. It is important to note that in these animals, sodium intake was maintained constant by the continuous intravenous administration of sodium chloride in an approximate dose of 3 mEq/day, but potassium was not supplemented. In both groups of rats, MAP significantly increased 6 to 10 mm Hg during leptin infusion. Although there was a tendency for an elevation in urine flow, sodium excretion remained unchanged, in spite of the increases in arterial pressure. The reasons for the absence of a natriuresis are unclear, but as noted earlier, may imply an antinatriuretic effect of leptin-induced sympathetic nervous system activation, which was also considered to be responsible for the elevation in arterial pressure [16, 22]. Also, it is pertinent to point out that these animals were in marked negative potassium balance [22], and this effect could have influenced the absence of leptin-induced natriuresis [23]. Indeed, previous studies in animals and humans have demonstrated that chronic dietary potassium restriction is associated with significant sodium and chloride retention [23]. Although the mechanisms for this phenomenon are not clear, Gallen et al have suggested that an adaptive response to potassium restriction is an increase in Na^+, K^+, $2Cl^-$ reabsorptive cotransport in the thick ascending limb [23]. More recently, studies in rats have suggested that a low potassium diet produces intrarenal hypoxia with reductions in nitric oxide and prostaglandin E_2, which favor salt retention and blood pressure elevation (abstract; Suga et al, *J Am Soc Nephrol* 10:356A,1999).

Unlike previous observations in the normotensive Sprague-Dawley rat and the lean Zucker rat, acute leptin-induced natriuresis and diuresis have been reported to be attenuated in the obese Zucker rat and in the SHR models [14]. The mechanisms for the impaired natriuretic response to leptin observed in these rat strains are not known. Recently, a deficit in the biologically-active leptin receptor has been demonstrated in the obese Zucker rat that leads to hypothalamic leptin resistance [24], and it is possible that a similar mechanism could be implicated in the attenuated natriuresis observed in the SHR. However, a similar leptin receptor deficit and/or hypothalamic leptin resistance alterations in the SHR have not been reported. Thus, it is likely that other antinatriuretic/antidiuretic mechanisms modulate or prevent the renal responses to leptin in the SHR. As has been reported previously, these mechanisms do not appear to implicate the renin-angiotensin-aldosterone axis [14].

One potential factor that could have contributed to the attenuation of acute leptin-induced natriuresis in the SHR is an increased sympathetic nerve activity. In the context of the present study and relevant to the regulation of body-fluid volume and pressures, it is pertinent to point out that enhanced ERSNA has been demonstrated to exert antinatriuresis by a variety of direct and indirect renal mechanisms [25]. Not only does the SHR have characteristic elevations in ERSNA [26], but more importantly, recent studies have clearly indicated that leptin markedly enhances sympathetic nerve activity to various organs in the rat, including the kidney [16]. Thus, the present data are consistent with the suggestion that elevated baseline ERSNA and/or potential leptin-induced increases in ERSNA may have enhanced tubular sodium reabsorption and, thereby, attenuated the renal tubular actions of leptin to promote natriuresis in the SHR model. The results clearly indicate that both acute and chronic renal denervation permitted a robust natriuretic response to leptin, which was not obtained in the sham-denervated SHR animals with their renal nerves intact.

In the normal rat, the potential effects of renal denervation on the sodium excretory actions of leptin are unclear. However, considering that leptin-induced sympathoactivation may promote antinatriuresis and attenuate the tubular actions of the hormone [16, 22], it is also possible that pharmacological or surgical blockade of ERSNA in normal animals could enhance leptin's sodium excretory effects. Thus, as is the case with other natriuretic hormones such as atrial natriuretic peptide [27], an elevated renal sympathetic nerve activity, regardless of its cause, would be expected to attenuate the saluretic actions of leptin.

In summary, the composite results of the current inves-

tigation suggest that the blunted natriuretic and diuretic responses to the acute pharmacologic infusion of synthetic leptin in the SHR may be partially explained by an enhanced baseline and/or leptin-induced increased renal sympathetic activity. The relevance of endogenous leptin on renal excretory function is yet to be clearly determined. While leptin is clearly an important circulating signal for body weight homeostasis, it now appears to be a potential salt-excreting factor and may function pathophysiologically as a common link to obesity and hypertension. To this end, leptin's overall effects on renal sodium excretion will reflect both direct natriuretic and indirect antinatriuretic actions. Modulation of responsivity to leptin at renal and/or neural sites may also differ under various conditions to determine the overall magnitude of leptin-induced urinary sodium excretion.

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Reprint requests to Daniel Villarreal, M.D., 1E65 Health Sciences Center, One Hospital Drive, Columbia, Missouri 65212, USA.
E-mail: villarreald@health.missouri.edu

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