Leptin and the Renin-Angiotensin-Aldosterone System

To the Editor:

Shek et al recently reported in a very detailed study that chronic leptin infusion in rats increased mean arterial blood pressure. However, the mechanism of leptin-induced hypertension is unclear and may involve both central and peripheral actions. While the sympathoexcitatory action of leptin is well established and may be a major factor mediating its hypertensive effect,1,2 the role of leptin in another major regulator of blood pressure, the renin-angiotensin-aldosterone system, has yet to be defined. Shek et al provide the first data on renin and aldosterone levels after leptin treatment in vivo.3 Whereas renin levels were unchanged, aldosterone tended to decrease at higher doses. In accordance with these findings, previous studies have shown that infusion of leptin caused natriuresis and diuresis.3 The authors suggest that reduced plasma aldosterone levels may be due to reduced potassium intake associated with leptin-induced anorexia. We suggest that a more likely explanation is a direct effect of leptin on the adrenal cortex. We have previously demonstrated in primary adrenal cell cultures that leptin can directly inhibit adrenocortical steroid production and the mRNA expression of cytochrome P450 enzymes.4 Therefore, leptin can chronically depress steroid production at the level of the adrenal, which is in line with the in vivo data reported in this study. In addition, our preliminary data demonstrate a slight increase in plasma renin activity in rats chronically treated with leptin (0.12 mg/kg per day IP over 7 days). In treated animals, we observed a trend toward increased plasma renin activity in rats chronically treated with leptin (0.12 mg/kg per day IP over 7 days). In treated animals, we observed a trend toward increased plasma renin activity (leptin-treated, 9.3±1.0 (n=7); vehicle-treated, 6.9±0.60; P=0.15). The renin increase may have been due to increased sympathetically mediated activity. The results of our study and those of Shek et al suggest that leptin may influence the mineralocorticoid axis and perhaps participate in the hypertension observed with human obesity.

In addition, the hyperleptinemia that occurs in critically ill patients’ may contribute to the hyperreninemic hypoaldosteronism that is found in a substantial percentage of these patients.5 The effects of leptin on the mineralocorticoid axis in humans need to be studied directly.

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Response

We appreciate the interest of Drs Bornstein and Torpy in our recent study which demonstrated that chronic elevation of plasma leptin concentration, to levels similar to those found in obesity, increased mean arterial pressure in rats.1 Drs Bornstein and Torpy raise two issues in their letter. (1) They suggested that the slight reductions in plasma aldosterone measured in our studies might be due to a direct inhibitory effect of leptin on the adrenal glomerulosa cells, and (2) they proposed that “leptin may influence the mineralocorticoid axis and perhaps participate in the hypertension observed with human obesity.”

On the basis of their novel observation that leptin inhibits adrenocortical cortisol production,2 Drs Bornstein and Torpy suggest that a direct effect of leptin on the adrenal gland may explain the decreased plasma aldosterone and corticosterone concentrations observed during chronic leptin infusion in our studies. However, it is important to note that Bornstein and Torpy studied the acute effects of leptin on cortisol secretion rather than aldosterone or corticosterone. Aldosterone and corticosterone secretion often do not change in parallel with cortisol. For example, potassium, one of the most powerful regulators of aldosterone and corticosterone secretion, has little effect on cortisol secretion. We are not aware of any evidence that leptin chronically reduces aldosterone secretion via a direct effect on the adrenal gland. In fact, recent studies by Malendowicz et al3 suggest that leptin may directly increase aldosterone and corticosterone production by rat zona glomerulosa cells. Thus, it is questionable whether a direct effect of leptin on the adrenal glands could account for the decrease in plasma aldosterone concentration observed in our studies. On the other hand, there is substantial support for our suggestion that decreased potassium intake, associated with the effect of leptin to reduce food intake, could account for a chronic reduction in aldosterone secretion. Many previous studies indicate that reducing potassium intake significantly decreases mineralocorticoid secretion.4 In our experiments, food intake (and therefore potassium intake, since all of the daily intake of potassium was provided in the food) was reduced by 65% to 70% at the higher rate of leptin infusion, which also decreased plasma aldosterone and corticosterone concentrations by 30% to 50%. However, direct testing of this possibility would require studies in which potassium intake was maintained constant during chronic leptin infusion.

With regard to the second point raised by Drs Bornstein and Torpy, we agree that our studies suggest a possible role for leptin in obesity hypertension. However, it is unlikely that decreased mineralocorticoid secretion contributes to leptin-induced hypertension; reduced plasma aldosterone and corticosterone would tend to blunt, rather than mediate, the hypertensive effects of leptin.

Our study provides a small step toward elucidating the role of leptin in obesity hypertension. The possibility that leptin is an important regulator of energy balance is widely appreciated, but the role of leptin in mediating the cardiovascular, renal, and endocrine changes associated with increased adiposity is still unclear and deserves further study.

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Effect of Daytime Sleep on Blood Pressure Monitoring in HARVEST Study Results

To the Editor:

In their recent report on target organ damage in white coat and sustained stage I hypertensive subjects from the HARVEST study, Palatini et al have made a significant contribution by applying different cutoff points for normotension and by matching for ambulatory blood pressure of the normotensives and white coat hypertensives by one of the chosen values. Nevertheless, there is still one caveat. By choosing daytime instead of 24-hour ambulatory blood pressure, Palatini et al ignore the potential contribution to blood pressure load of nocturnal blood pressure. Perhaps even more important is the potential confounding effect of the siesta (daytime sleep, afternoon nap), which is not an uncommon practice in the Mediterranean area (including Italy, where the above-mentioned study took place), Latin America, and other countries. We have found that 30% of those referred for 24-hour ambulatory blood pressure monitoring follow the practice of the siesta. Inclusion of daytime-sleep blood pressure in daytime blood pressure significantly diminishes its average value. This is because during the siesta, in our and other studies, blood pressure declines to nocturnal levels. If the prevalence of the siesta is not evenly distributed among hypertensives, there may be different from the population-recruited hypertensives in having less opportunity to practice the siesta.

This caveat may be circumvented by applying corresponding 24-hour ambulatory blood pressure values instead of daytime values. Another option is reporting actual awake blood pressure values from patients’ activity diaries instead of the average daytime values, which may include those recorded during the siesta, as was done in other studies. Either of these options will eliminate the powerful effects of the siesta on daytime ambulatory blood pressure.

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Response

In response to the letter from Dr Bursztyn regarding the possible influence of afternoon sleep on the calculation of daytime blood pressure, the following data and comments are relevant.

The presence of an afternoon dip during 24-hour blood pressure monitoring, not necessarily related to the siesta, has been found in several countries, even outside the Mediterranean area or Latin America. In an analysis of a large database contributed by several countries, a profound afternoon dip was found in persons from Australia and China, and a less pronounced one in persons from France and Italy. No afternoon blood pressure decline was found in subjects studied in Belgium, Germany, Ireland, Japan, Sweden, and the United States. However, it has to be pointed out that these data were not collected from random population samples, and thus they are not truly representative for each country. Moreover, they may be influenced by the age and gender distributions of the study participants.

As far as the HARVEST study participants are concerned, it is worthwhile noting that they live in a highly industrialized area (northeast Italy) that has the lowest rate of unemployment for Italy (<5%). Persons living in this region, especially the young, are no longer used to having a siesta, as those in the southern part of Italy or other Mediterranean countries still do. Thus, it is unlikely that the results we recently obtained in a group of 18- to 45-year-old white coat hypertensive subjects are due to the impact of an afternoon nap on the calculation of daytime blood pressure.

This conclusion is reinforced by a recent analysis of the ambulatory blood pressure data in the HARVEST population. Analysis of the hourly averages showed that the lowest average blood pressure values were reached from 1 PM to 4 PM in both the white coat hypertensive subjects (cutoff point for daytime blood pressure, 130/80 mm Hg; n = 150) and the normotensive subjects (n = 95). The average of the blood pressure readings recorded during these 3 hours did not differ between the 2 groups, being 121.2 ± 9.4/72.0 ± 8.8 mm Hg in the white coat hypertensive subjects and 120.9 ± 11.9/71.8 ± 7.8 mm Hg in the normotensive subjects (P > 0.8 for both systolic and diastolic blood pressure readings). A modest decline in diastolic blood pressure was observed during this time of day in comparison with average daytime blood pressure calculated from the remaining daytime hours (1.4 mm Hg in white coat hypertensive subjects and 2.8 mm Hg in normotensive subjects), and there was virtually no change in systolic blood pressure (+0.6 and ±0.1 mm Hg, respectively). During the period of 1 PM to 4 PM, both diastolic and systolic blood pressures were well above the values recorded during nighttime (106.9 ± 8.8/65.5 ± 6.0 in white coat hypertensive subjects and 105.7 ± 10.1/63.6 ± 8.2 in normotensive subjects). Thus, even though we are unable to say how many of our study participants, if any, had an afternoon sleep, it seems unlikely that the prevalence of the siesta was unequally distributed between the groups. Therefore, the low daytime blood pressure found in the HARVEST study in the subjects with white coat hypertension cannot be ascribed to a possible effect of an afternoon nap.
As for the possible impact of a different nighttime blood pressure on the left ventricle of the normotensive and the white coat hypertensive subjects, as suggested by Dr Burzstyn we also examined 24-hour blood pressure and found no significant differences between the 2 groups. Average 24-hour blood pressure was 117.9 ± 6.5/72.3 ± 4.9 mm Hg in the white coat hypertensive subjects and 116.2 ± 10.2/71.3 ± 8.1 mm Hg in the normotensive subjects (NS).

The early afternoon is associated with a transient decline in alertness in adults, a phenomenon that may cause a short-lasting slight decrease in blood pressure in persons not taking a nap.6 A greater afternoon fall in pressure is frequently detectable in elderly subjects due to the effect of postprandial hypotension.7 The siesta (postlunch sleep) is less practiced in recent times than it used to be, especially in highly developed countries where only a short pause from work, if any, is taken after lunch. Today, the siesta is still practiced mostly in hot countries,1–3 especially during the summer. Certainly, this is not a common habit in the towns where the HARVEST study is conducted, where summer temperature ranges from 17°C to 28°C.8

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