

Weight Gain–Induced Blood Pressure Elevation

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Abstract—This study was conducted to evaluate the mechanisms in weight gain–induced blood pressure (BP) elevation focusing, in particular, on the contributions of sympathetic nervous system activity, fasting plasma insulin, and leptin to BP levels. The study design was longitudinal with a cohort of 1897 men. BP, pulse rate, body mass index (BMI), fasting plasma norepinephrine (NE), insulin, and leptin were measured at 6 and 12 months in those 172 lean normotensive, 79 obese normotensive, 64 lean untreated hypertensive, and 38 obese untreated hypertensive men whose BMI increased >10% during the first 6 months. At entry, levels of BP, pulse rate, plasma NE, insulin, and leptin in obese subjects, regardless of BP status, were significantly greater than those in lean subjects. The levels of plasma NE, insulin, and leptin increased with weight gain in the 4 study groups. In the subjects with BP elevation, the increase in pulse rate and plasma NE was significantly greater than that in the subjects without BP elevation at both 6 and 12 months for each of the 4 study groups, although the increase in BMI was similar between the subjects with and without BP elevation. In obese but not lean subjects, whether normotensive or hypertensive, the increases in plasma insulin and plasma leptin with weight gain were greater in the subjects with accompanying BP elevation compared with the subjects without BP elevation. On the other hand, at 6 months in lean subjects, the increase in plasma insulin with weight gain in the subjects with BP elevation was actually lower than that in the subjects without BP elevation. These results suggest that weight gain–induced sympathetic overactivity is more tightly linked to weight gain–induced BP elevation than the changes in plasma insulin and leptin that also accompany weight gain. It is probable that sympathetic nervous activation with weight gain is a major mechanism of blood pressure elevation. Hyperinsulinemia and hyperleptinemia may be ancillary factors that contribute to sympathetic nervous stimulation with weight gain. (*Hypertension*. 2000;35:1135-1140.)

Key Words: obesity ■ body mass index ■ hypertension, obesity ■ investigative techniques
■ sympathetic nervous system ■ leptin ■ insulin

Obesity and obesity related–hypertension are major and growing, international health problems, described by the World Health Organization (WHO) in its “Global Burden of Disease” report.¹ Furthermore, it is well known that obesity is a leading risk factor for chronic arterial hypertension and coronary heart disease.² The plasma concentration of the adipocyte hormone, leptin, is elevated in human obesity, which is thought to represent a state of leptin “resistance.”³ Leptin has been shown to influence sympathetic nerve activity.^{4,5} Collins et al reported that leptin increased norepinephrine (NE) turnover in interscapular brown adipose tissue.³ Shek et al⁶ reported that in the animal models, chronic leptin infusion caused an increase in heart rate and blood pressure, suggesting a possible role for leptin in the development of obesity-related hypertension.

In a cross-sectional study of many of young, nondiabetic men⁷ and in weight reduction studies that lasted for 3 months,^{8,9} we reported that heightened sympathetic activity and body mass index (BMI) are interrelated. In previous epidemiological and clinical studies, heightened sympathetic activity, and higher levels of plasma leptin and insulin have

been described in normotensive and hypertensive humans.^{7,10,11} However, the precise relationships among those factors in obesity-related hypertension were not fully clarified in humans, and a causal relationship of each to blood pressure elevation has not been delineated, perhaps in part because of the deficiency of the cross-sectional design typical of those studies.

The goal of the present longitudinal study was to clarify the mechanisms of blood pressure (BP) elevation with overweight. We sequentially studied the accompaniments of spontaneous weight gain over 1 year, focusing especially on sympathetic activity and the plasma levels of insulin and leptin. It was our expectation that by prospectively studying weight gain and BP elevation in this way, any causal contribution of changed sympathetic activity, leptin, and plasma insulin to BP elevation would become evident.

Methods

Subjects

A cohort of 1897 men who worked in 1 factory, 2 companies, and 2 nursing homes in Osaka, Japan, were studied during their biannual

Received August 31, 1999; first decision October 12, 1999; revision accepted January 3, 2000.

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health checkup at 6 months and 12 months. The following subjects were excluded from the study: 125 over age 50 years and 57 with diabetes mellitus (HbA1c >6.0%). In addition, 209 subjects were excluded from the study because they were taking medications; for example, 193 subjects with antihypertensive agents, 54 subjects with lipid lowering agents, 37 subjects with uric acid-lowering agents, 24 subjects with medications for liver dysfunction, and 21 subjects with antiarrhythmic agents or digitalis. The subjects were divided into 3 groups on the basis of the BMI tertile at entry (BMI range was from 16.5 to 33.6 kg/m²); lowest (lean, 22.2 kg/m² or less), middle (between 22.2 and 27.9 kg/m²), and heaviest (obese, 27.9 kg/m² or more). After the exclusions, 721 lean normotensives, 186 obese normotensives, 154 lean untreated hypertensives, and 97 obese untreated hypertensives were recruited from the cohort.

Because the goal of the present study was to evaluate the mechanisms of weight gain-related BP elevation, only the subjects whose BMI increased $\geq 10\%$ during the first 6 months and whose BMI remained or increased further during the next 6 months were enrolled. This occurred in 172 lean normotensives (mean \pm SD, at entry period, age 37 \pm 3 years, BMI 21.2 \pm 0.7 kg/m², BP 119 \pm 6/76 \pm 5 mm Hg), 79 obese normotensives (age 39 \pm 5 years, BMI 29.2 \pm 1.1 $\ast\ast$ kg/m², BP 127 \pm 7/78 \pm 5 mm Hg, $\ast P < 0.05$, $\ast\ast P < 0.01$ versus the values in lean subjects), 64 lean untreated hypertensives (age 39 \pm 4 years, BMI 20.9 \pm 1.1 kg/m², BP 148 \pm 6/96 \pm 6 mm Hg), and 38 obese untreated hypertensives (age 37 \pm 6 years, BMI 28.9 \pm 0.8 $\ast\ast$ kg/m², BP 154 \pm 5/102 \pm 4 mm Hg, $\ast\ast P < 0.01$ versus the values in lean subjects) who were enrolled in this study.

Normotension was defined as a supine mean reading of <140/90 mm Hg at ≥ 3 measurements. Hypertension was defined as a supine mean reading of $\geq 140/90$ mm Hg at ≥ 3 measurements. Informed consent was obtained from each subject as approved by the Ethics Committee of Osaka University Medical School.

Measurements

After an overnight fast of >12 hours, BMI, waist-to-hip circumference ratio, BP, pulse rate, and venous blood sampling for measurements of plasma insulin, leptin, and NE levels were obtained after a rest of 30 minutes in the supine position in a quiet room. Measurements were made at entry, at month 6, and at month 12. BP was measured >3 times and was averaged. Those who had a wide variability in BP were asked to repeat measurements on >3 separate visits to exclude chance variation.

BP and pulse rate were measured with an automated sphygmomanometer (TM-2711 or TM-2713, A&D), which was standardized against a mercury sphygmomanometer. Plasma NE was measured after separation by high-performance liquid chromatography by the fluorometric method (intra-assay CV=2.1%; interassay CV=3.6%; sensitivity=0.06 to 120 nmol/L), and plasma immunoreactive insulin was measured by a standard radioimmunoassay method (insulin RIABEAD II, Dinabott: intra-assay CV=1.9%; interassay CV=2.2%; sensitivity=0.75 to 300 μ U/mL). Plasma leptin was measured by radioimmunoassay (human leptin RIA kit, Linco: intra-assay CV=5.0%, interassay CV=4.5%, sensitivity=0.03 to 6 nmol/L). Blood glucose was measured by an autoanalyzer (Hitachi-7050).

Statistical Analyses

Values are shown as mean \pm SD. Changes in variables within each group and differences among groups were examined by 2-way ANOVA. When significant, the Dunnett test was used to determine whether the differences of the mean at month 6 and at month 12 from values at entry period were significant among groups. Multiple linear regression analyses were used to examine relationships among variables using changes in mean BP at month 6 and at month 12 as a dependent variable in the 4 study groups combined to evaluate the role of the parameters in weight gain-induced changes in BP. Statistical analyses to compare the prevalence of BP elevations were performed by the χ^2 test. Values of $P < 0.05$ were considered significant.

Results

BP elevation was defined as an increase in mean BP by $\geq 10\%$ over that measured at entry. The prevalence of BP elevation was 70% of obese subjects with weight gain and 47% of lean subjects with weight gain ($P < 0.05$) at month 6, whereas at month 12, the prevalence of BP elevation was 74% of obese subjects with weight gain and 50% of lean subjects with weight gain ($P < 0.05$). The prevalence of BP elevation was 65% in those with preexisting hypertension and 48% in normotensives ($P < 0.05$) at month 6, whereas at month 12, BP elevation occurred in 67% of hypertensives and 51% of normotensives ($P < 0.05$). (Prevalence of BP elevation in normotensive subjects versus hypertensive subjects at month 6: lean subjects, 57% versus 41%, $P < 0.05$; obese subjects, 84% versus 62%, $P < 0.05$. Prevalence at month 12: lean subjects, 60% versus 44%, $P < 0.05$; obese subjects, 84% versus 67%, $P < 0.05$).

BMI and the ratio of waist-to-hip circumference in the 4 study groups increased at month 6 and month 12 by definition. BMI and the ratio of waist-to-hip circumference at entry were similar in normotensives and hypertensives. Increases in BMI in normotensives and hypertensives and percent increases in BMI in lean subjects and obese subjects again were similar. More importantly, BMI and the ratio of waist-to-hip circumference in the 4 study groups did not differ between the subjects with and without BP elevation at any time (not shown).

On the other hand, BP levels increased significantly with weight gain in the subjects with BP elevation by definition. Not surprisingly, the BP level at entry in obese subjects was already higher than that in lean subjects (Figure 1, top). At entry, pulse rate in obese subjects was higher than in lean subjects, and pulse rate was higher in subjects with BP elevation compared with subjects without BP elevation. In addition, pulse rate increased significantly with weight gain, especially in the subjects with BP elevation (Figure 1, bottom).

Plasma NE level at entry in obese subjects was higher than that in lean subjects, and hypertensive subjects had a higher plasma NE level than normotensive subjects at entry. Plasma NE levels increased with weight gain in the 8 study groups regardless of BP elevation, but the increase in plasma NE in the subjects showing BP elevation was significantly greater than that in the subjects without BP elevation accompanying weight gain. Thus, the changes in plasma NE level were closely related with changes in BP level (Figure 2).

Plasma insulin level at entry in obese subjects was higher than in lean subjects and higher in obese hypertensives than in normotensives. Overall, plasma insulin increased similarly with weight gain in subjects either with or without BP elevation. However, in the obese hypertensive subgroup, plasma insulin increased significantly in the subjects with BP elevation, although plasma insulin did not increase with weight gain in the subjects without BP elevation (Figure 3).

The plasma leptin level in obese subjects was significantly higher than that in lean subjects regardless of BP status at entry. In lean subjects (normotensives and hypertensives), the plasma leptin level increased with weight gain, and this increase in leptin with weight gain occurred irrespective of

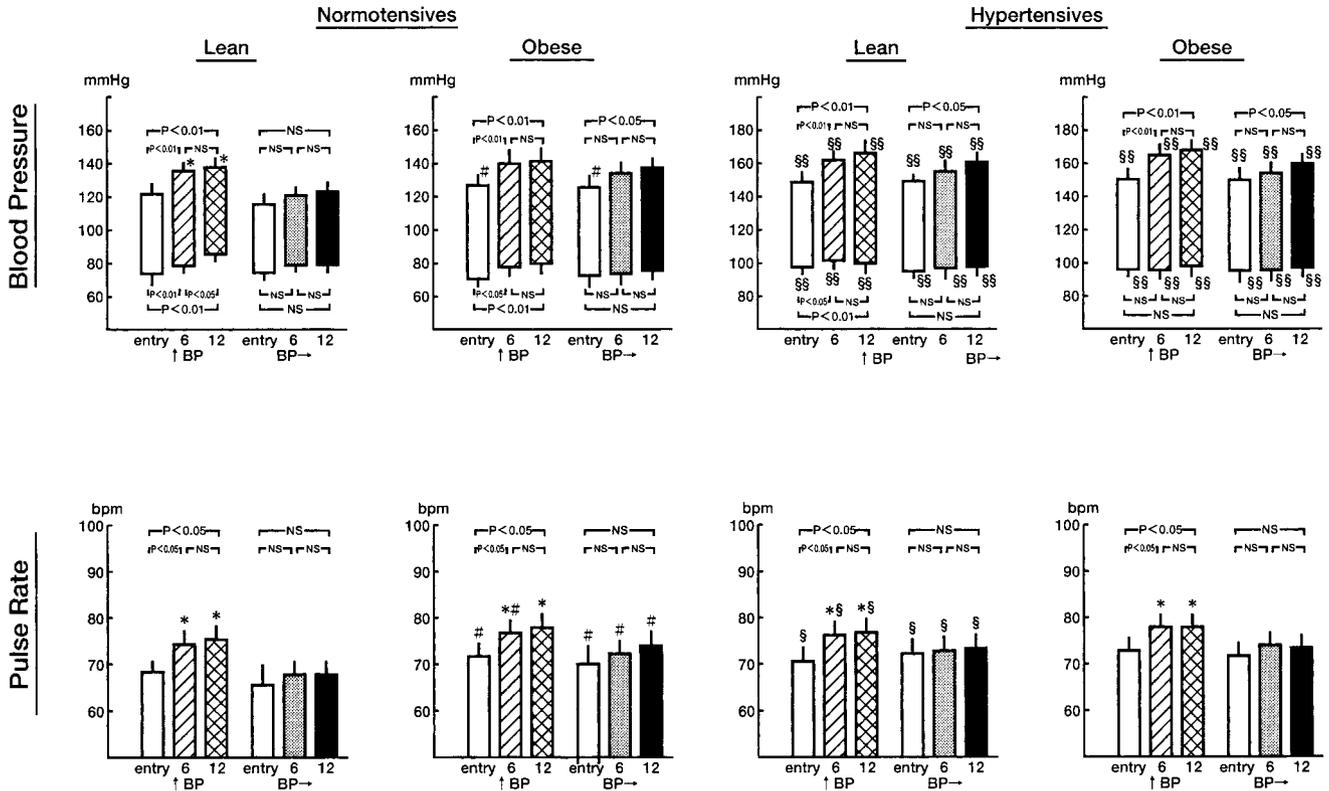


Figure 1. Blood pressure levels (top) and pulse rates (bottom) in lean normotensive subjects (left column), obese normotensive subjects (the second column from the left), lean hypertensive subjects (second column from the right), and obese hypertensive subjects (right column). ↑ BP indicates the subjects with BP elevation ($\geq 10\%$); BP→, the subjects without BP elevation ($< 10\%$); entry, at the entry period; 6, at month 6; and 12, at month 12. * $P < 0.05$ vs values in the subjects without BP elevation. # $P < 0.05$, ## $P < 0.01$ vs values in lean subjects. \$ $P < 0.05$, \$\$ $P < 0.01$ vs values in normotensive subjects.

whether BP increased. On the other hand, in obese subjects (normotensives and hypertensives) showing BP elevation with weight gain, plasma leptin levels at month 6 and month 12 were significantly higher than those in obese subjects without BP elevation accompanying weight gain, although BMI and the ratio of waist-to-hip circumference, which are

known to be closely related to plasma leptin levels, were at all times similar in obese subjects with or without BP elevation. Thus, changes in plasma leptin levels in the obese subjects related closely with BP change during weight gain (Figure 4).

Thus, at 6 months, increment in plasma NE in the subjects with BP elevation was significantly greater than that in the

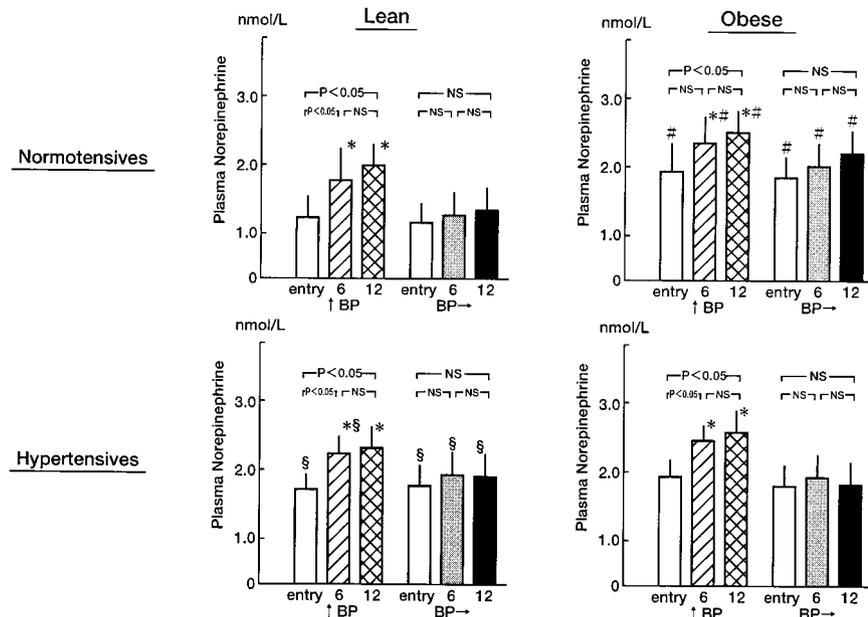


Figure 2. Supine plasma norepinephrine levels in lean normotensive subjects (top, left column), in obese normotensive subjects (top, right column), in lean hypertensive subjects (bottom, left column), and in obese hypertensive subjects (bottom, right column). ↑ BP indicates the subjects with BP elevation ($\geq 10\%$); and BP→, the subjects without BP elevation ($< 10\%$). * $P < 0.05$ vs values in the subjects without BP elevation. # $P < 0.05$, ## $P < 0.01$ vs values in lean subjects. \$ $P < 0.05$ vs values in normotensive subjects.

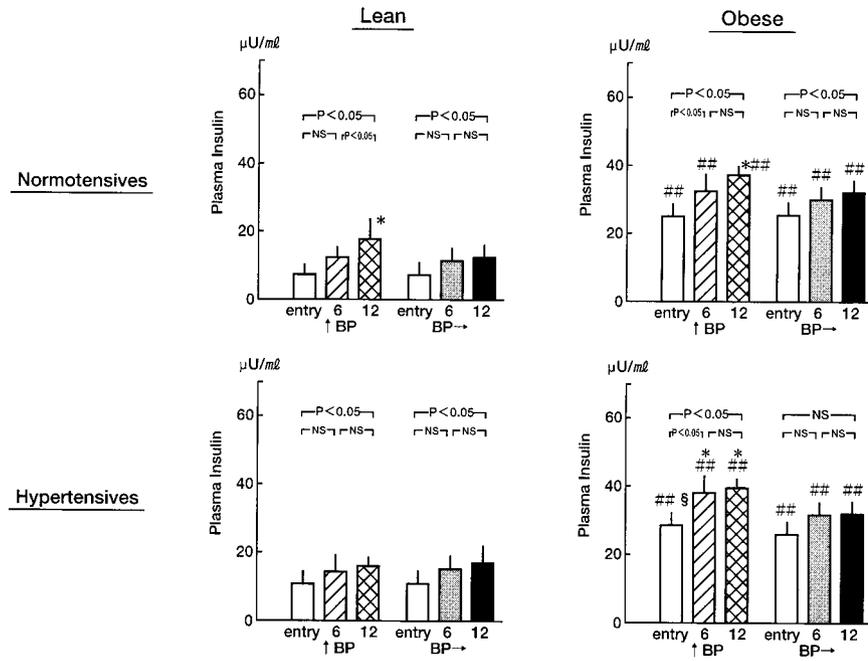


Figure 3. Fasting plasma insulin levels in lean normotensive subjects (top), in obese normotensive subjects (top, right column), in lean hypertensive subjects (bottom, left column), and in obese hypertensive subjects (bottom, right column). ↑ BP indicates the subjects with BP elevation ($\geq 10\%$); and BP→, the subjects without BP elevation ($< 10\%$). * $P < 0.05$ vs the values in the subjects without BP elevation. # $P < 0.05$, ## $P < 0.01$ vs the values in lean subjects. § $P < 0.05$ vs the values in normotensive subjects.

subjects without BP elevation regardless of BMI or BP status. On the other hand, increments in plasma insulin and leptin in the subjects with BP elevation were greater than those in the subjects without BP elevation, which was only in obese subjects. More importantly, at 6 months in lean subjects (normotensives and hypertensives), increment in insulin in the subjects with BP elevation was slightly lower than that in the subjects without BP elevation. At 12 months, the increment in plasma NE in lean subjects with BP elevation was significantly greater than that in lean subjects without BP elevation. However, at 12 months, increments in plasma insulin and leptin in obese subjects with BP elevation were still significantly greater than those in obese subjects without BP elevation.

We analyzed the change in mean BP as a dependent factor in association with changes in BMI, plasma NE, insulin, and leptin as determinant factors by multiple regression analysis. At 6 months, changes in BMI ($P = 0.028$) and plasma NE ($P = 0.034$) were significant determinant factors in the change in mean BP ($R^2 = 0.072$, $F = 2.31$, $P = 0.027$). At 12 months, changes in plasma NE ($P = 0.048$), insulin ($P = 0.015$), and leptin ($P = 0.024$) were significant determinant factors ($R^2 = 0.130$, $F = 3.91$, $P = 0.0003$).

Discussion

New findings in the present study included the following: (1) Subjects with BP elevation during weight gain had a greater absolute increment in plasma NE than those with no BP increase

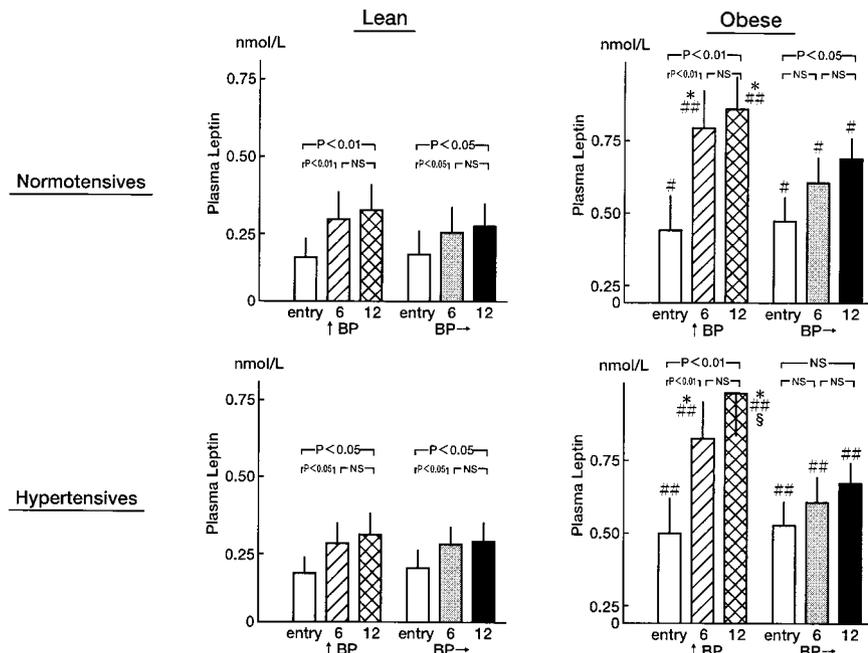


Figure 4. Fasting plasma leptin levels in lean normotensive subjects (top, left column), in obese normotensive subjects (top, right column), in lean hypertensive subjects (bottom, left column), and in obese hypertensive subjects (bottom, right column). ↑ BP indicates the subjects with BP elevation ($\geq 10\%$); BP→, the subjects without BP elevation ($< 10\%$). * $P < 0.05$ vs the values in the subjects without BP elevation. # $P < 0.05$, ## $P < 0.01$ vs the values in lean subjects. § $P < 0.05$ vs the values in normotensive subjects.

regardless of prior BMI or BP status. (2) In obese subjects, greater increments were observed during weight gain in plasma leptin and insulin levels in the obese subjects with BP elevation than in those without BP elevation. In lean subjects with BP elevation, the rise in insulin with weight gain at 6 months was actually lower than that in lean subjects without BP elevation. At 12 months, it was noted that even in lean subjects with weight gain, the increments in plasma insulin and leptin tended to be greater in the subjects with BP elevation than in the subjects without BP elevation, which is similar to what was observed in obese subjects. These results suggest that heightened sympathetic activity plays an important role in weight gain-induced BP elevation. By analogy, we infer that in stable obesity, with accompanying hypertension, a similar mechanism is also operating.

Hypertensive patients in the present study were untreated and all of the subjects were men, because it is well known that some antihypertensive agents influence plasma NE, insulin, and leptin levels¹² and that there are gender differences in plasma leptin level. The extent of the spontaneous weight gain in our cohort is perhaps surprising, but it is representative of public health records of body weight change in Japan and typical of the amazing increase in the prevalence of obesity in industrialized countries over the past 10 years.¹

Grassi et al¹³ reported that by using microneurography at the peroneal nerve, the baseline muscle sympathetic nerve activity in obese normotensive subjects was twice that seen in lean control subjects. It was concluded that even in the absence of any BP alteration, human obesity is characterized by a marked sympathetic activation, possibly because of an impairment of reflex sympathetic restraint. The authors speculated that another possible factor is an enhancement of sympathetic drive caused by an increase in levels of circulating insulin, angiotensin II, or both. Rumantir et al¹⁴ reported, using NE spillover methods, that an absence of suppression of the cardiac sympathetic outflow seen in normotensive obese individuals may be important in obesity-related hypertension. Increases in renal sympathetic activity in obesity may be a necessary cause for the development of hypertension in obese individuals. Previously, we also reported that at the entry point in a weight reduction study^{8,9} and in a cross-sectional study,⁷ plasma NE as well as fasting plasma insulin and leptin were significantly higher in obese subjects (normotensives and hypertensives) than in lean subjects. In the present study, obese subjects had higher levels of plasma NE, pulse rate, and BP at entry as well as greater changes during weight gain in those parameters, suggesting that stimulated sympathetic activity caused by obesity plays an important role in obesity-related hypertension.

A strength of the present study was its longitudinal design, which allowed sequential measurement of weight, BP, and possible determinants of BP increase. In our results, the absolute increments in pulse rate and plasma NE during weight gain in the subjects with BP elevation was significantly greater than in the subjects without BP elevation, regardless of prior BMI or BP status. In addition, the elevation in BP was concordant with increases in pulse rate and plasma NE, suggesting that stimulated sympathetic activity is the primary initiator of BP elevation during weight gain.

The renin-angiotensin system, especially angiotensin II, have also been hypothesized to be etiologically relevant in obesity-

related hypertension¹¹; however, we did not measure angiotensin II, plasma renin activity, or plasma aldosterone concentration in the present study. Thus, we cannot discuss their relevance to weight gain-induced BP elevation.

Epidemiological and clinical studies document a relationship between BP, obesity, and hyperinsulinemia.¹⁵⁻¹⁸ Some investigators have reported that chronic administration of insulin might contribute to a sympathetically mediated increase in BP in animal models of obesity hypertension.^{19,20} On the other hand, it has been reported that insulin administered acutely causes vasodilation and does not increase BP in animal or humans models.²¹⁻²⁴ Infusion of insulin in subjects with established insulin resistance, such as obese subjects, produces vasoconstriction rather than vasodilation.^{25,26} Thus, data regarding the effects of chronic exogenous administration of insulin and the resultant hyperinsulinemia on BP are controversial, perhaps because insulin has dual actions, both pressor and depressor. With higher insulin concentrations, the pressor action of insulin might predominate, as suggested by the study of Rowe et al.²³ With more severe insulin resistance that attends android obesity or more severe hypertension, the balance between pressor and depressor actions of insulin could be altered in favor of a pressor action. Additionally, chronic trophic actions of insulin might promote structural vascular changes contributing to hypertension.

In the present study, fasting plasma insulin was significantly higher in obese subjects at all times than in lean subjects, and plasma insulin level increased with weight gain in the 4 study groups regardless of prior BMI, BP levels, and BP elevation. In only the obese subjects (both normotensives and hypertensives) was the increment in plasma insulin with weight gain greater in the subjects with BP elevation than in the subjects without BP elevation. In lean subjects with BP elevation, the increment in plasma insulin with weight gain at 6 months was actually lower than that in the lean subjects without BP elevation. BP change with weight gain was more closely linked to sympathetic activation than hyperinsulinemia. Previously, we showed in a longitudinal study that lasted over 10 years²⁷ in initially non-obese normotensives that in the absence of weight gain, stimulated sympathetic tone preceded significant BP elevation, followed by the subsequent emergence of hyperinsulinemia. These results and the multiple regression analyses in the present study suggested that stimulated sympathetic activity appeared to be the initial event in hypertension that developed in lean subjects, followed by hyperinsulinemia. These results are in accordance with the notion that prolonged and stimulated sympathetic activity actually causes hyperinsulinemia.^{2,28}

It has been well documented in epidemiological and clinical studies that plasma leptin levels are higher in obese subjects.^{7-10,29} In the present study, obese subjects had a significantly higher level of plasma leptin regardless of BP status. In addition, in obese subjects, there was a greater increase in plasma leptin with weight gain in the subjects with accompanying BP elevation compared with the subjects without BP elevation. This relation of leptin to BP increase with weight gain was absent in lean subjects. Two important factors that influence leptin levels, ie, gender and age, were not confounders here. The former factor can be discounted because all subjects were men, whereas age matching excluded the latter. Similar to insulin changes with weight gain, BP increase accompanying weight

gain was more closely linked to sympathetic activation than leptin increase. Weight gain-induced hyperleptinemia appears closely related to stimulated sympathetic activity and BP elevation in obese subjects but not in lean subjects. In addition, multiple regression analyses in the 4 study groups combined indicates that changes in BMI and plasma NE are significant determinants of mean BP elevation at 6 months, whereas changes in plasma NE, insulin, and leptin are determinants at 12 months. These results suggest that sympathetic hyperactivity is a factor in weight gain-induced BP elevation at all times, whereas increments in plasma insulin and leptin during weight gain are associated with BP elevation only in the later, chronic phase.

Recently, Haynes and colleagues⁴ studied the effects of intravenous infusion of leptin on regional sympathetic nerve activity in Sprague-Dawley rats. Leptin increased sympathetic nerve activity to brown adipose activity, kidney, adrenals, and hindlimb,³⁰ confirming the results of studies measuring NE turnover. The sympathetic effects of leptin occurred in the absence of changes in plasma glucose or insulin and had a rather regional pattern than a systemic effect, such as the influence on insulin, suggesting that sympathoexcitatory actions of leptin were independent of insulin. In the present study, it was noted that in only the obese subjects were increases in plasma leptin and plasma NE with weight gain linked. A relation between leptin and plasma NE was not identified in lean subjects. Recent measurements of cardiac and renal sympathetic tone in lean and obese humans also fail to document an important role for leptin in determining sympathetic tone in humans.¹⁴

In conclusion, weight gain stimulates sympathetic activity, underlies the resultant BP elevation regardless of prior weight or BP status, and probably contributes to hyperinsulinemia. In obese humans, weight gain appears to induce an elevation in plasma insulin level that precedes the elevation in plasma leptin. Whether elevated plasma leptin stimulates sympathetic activity in humans is problematic; the available evidence is largely negative. In contrast, in lean subjects, weight gain leads to the stimulation of sympathetic activity, with lesser effects on plasma insulin and leptin. The sympathetic activation is closely linked to BP increase with weight gain in lean men, but changes in insulin and leptin are not. Further studies, involving such things as the measurements of sympathetic activity during infusion of leptin, are needed to determine the more precise role and relations between sympathetic activity, insulin sensitivity, and hyperinsulinemia and the effects of leptin in BP regulation in obesity.

Acknowledgment

The authors would like to thank Prof Murray D. Esler for his thorough review of and his constructive comments on this research and manuscript.

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