Differences in Mechanisms between Weight Loss-Sensitive and -Resistant Blood Pressure Reduction in Obese Subjects

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This study was conducted to clarify the mechanisms involved in the sensitivity for blood pressure (BP) reduction in response to weight loss. In particular, we focused on the contributions of sympathetic nervous system activity and fasting plasma leptin and insulin levels to BP levels during weight loss in obese subjects with weight loss-sensitive and -resistant BP reduction. Sixty-one young, obese untreated hypertensive men (HT) and 52 obese normotensive men (NT) were enrolled in a weight loss program consisting of a low caloric diet and aerobic exercise over a 24-week period. At entry and at week 24, body mass index (BMI), BP, plasma norepinephrine (NE), leptin and insulin were measured. Successful weight loss and BP reduction were respectively defined as a more than a 10% reduction in BMI or mean BP from baseline at week 24. More than 60% of subjects in either group successfully achieved weight loss by this definition. The percentage of subjects who successfully achieved BP reduction was higher (64%) among those subjects who achieved weight loss than among those who did not (22%). Plasma NE level at entry in subjects who failed to achieve BP reduction despite weight loss was significantly higher than that in subjects who succeeded in BP reduction. Plasma leptin and insulin levels were similar between subjects with and without BP reduction. In addition, the absolute decrement and percent decrement in plasma NE in subjects who succeeded in BP reduction were significantly greater than those in subjects who failed to reduce their BP. Absolute and percent decrements in plasma leptin and insulin were similar in both groups. These results suggest that individuals who are resistant to weight loss-induced BP reduction have more sympathetic overactivity both at the outset of and during weight loss. (*Hypertens Res* 2001; 24: 371–376)

Key Words: hypertension, family history of obesity, sympathetic nervous system, leptin, insulin

Introduction

It has been well documented through cross-sectional surveys of the general population that obesity contributes to the development of hypertension (1–3). Several lines of evidence, both epidemiological and experimental, point to a close interrelationship among the heightened sympathetic nervous system activity, hyperleptinemia, hyperinsulinemia and arte-

rial hypertension (4–8) that accompany obesity (9–16). In a recent study, we reported that the mechanisms involved in weight gain-sensitive BP elevation were different than those involved in weight gain-resistant BP elevation in subjects who gained weight over 12 months (13). Heightened sympathetic activity as determined by high plasma norepinephrine (NE) levels was the dominant factor for BP elevation with weight gain in both normotensive and hypertensive subjects. Although the association between obesity and hypertension

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has been firmly established, the underlying mechanisms of the blood pressure (BP) elevation in obesity-related hypertension remain unclear. The WHO/ISH guidelines (17), the JNC VI (18) and the Hypertension Optimal Treatment (HOT) study (19) all recommend that weight loss should be regarded as an essential component of any treatment program for obesity and hypertension. There have been reports that suppression of sympathetic nervous activity (10–13, 20, 21), hyperinsulinemia (22, 23) and hyperleptinemia play a role in BP reduction accompanying weight loss. One method of evaluating mechanisms of weight loss-induced BP reduction is the serial measurement of the relevant parameters during a longitudinal weight loss study. In most individuals, however, reduction in BP is quite sensitive to changes in weight, with weight gain being accompanied by a rise in BP, and weight loss by a fall in BP. But not all people with high blood pressure or obesity have this sensitivity.

The goal of the present study was to clarify the mechanism responsible for the difference in sensitivity to BP reduction in response to weight loss. For this purpose, we evaluated the contributions made to weight loss-induced BP reduction by family history of obesity, sympathetic nervous activity, and plasma insulin and leptin levels in a cohort of obese normotensive and obese hypertensive men during a 24-week weight loss regimen. We postulated that the contributions of a family history of obesity, sympathetic activity, and fasting plasma leptin and insulin levels would contribute the different BP responses to weight loss.

Methods

Subjects

Sixty-one obese, untreated hypertensive men (age, 35 ± 3 years; BMI, 28.1 ± 0.6 kg/m²; BP, 171 ± 6 / 106 ± 5 mmHg) and 52 obese normotensive men (age, 34 ± 4 years; BMI, 27.9 ± 0.6 kg/m²; BP, 131 ± 5 / 83 ± 4 mmHg) were enrolled in the study. The two study groups were matched in age and BMI at entry and none of the subjects had diabetes (HbA1c > 6.0%) or serious illness, and none were taking antihypertensive agents or other medications. All the hypertensive participants in the present study preferred to control their BP by means of lifestyle changes rather than by taking antihypertensive agents. Normal BP was defined as the mean of three supine readings of $\leq 140/90$ mmHg. Hypertension was defined as the mean of three supine reading of $\geq 160/95$ mmHg. A positive family history of obesity (FHOB+) was defined as at least one parent having obesity (BMI > 27.0 kg/m²) documented by medical records or by direct body weight measurements in the parents. FHOB– was defined as both parents being nonobese (≤ 27.0 kg/m²). Informed consent was obtained from each subject as approved by the Ethics Committee of Osaka University Medical School.

Protocol

The weight loss program consisted of a low caloric (1,200 kcal/day, 55% carbohydrates, 20% protein and 25% fat) and low sodium diet (7g NaCl/day) and aerobic exercise, *e.g.*, swimming, walking, jogging, or gym exercise, at least 1 h a day. Diet and exercise compliance were monitored according to the subjects' own records every 2 weeks. After subjects had fasted for 12 h overnight, BMI, blood pressure (BP) and pulse rate were determined. After the subjects had rested for 30 min in the supine position in a quiet room, venous blood was taken to determine blood glucose, plasma insulin, leptin and norepinephrine (NE) levels. Measurements were made at entry and at week 24. Supine BP was measured three times and then averaged. BP and pulse rate were measured with an automated sphygmomanometer (TM-2713; A&D, Tokyo, Japan) which was standardized against a mercury sphygmomanometer. In the present study, BP was measured in the supine position because samples for plasma NE were also collected in this position. Plasma NE was measured after separation by high performance liquid chromatography using the fluorometric method (intraassay CV = 2.1% at 1 pmol/ml; interassay CV = 3.6% at 1 pmol/ml; sensitivity = 0.010 to 20 ng/ml). Plasma immunoreactive insulin was measured by a standard radioimmunoassay method (insulin RIABEAD II; Dinabott, Tokyo, Japan; intraassay CV = 1.9% at 10 μ U/ml; interassay CV = 2.2% at 10 μ U/ml; sensitivity = 0.75 to 300 μ U/ml). Plasma leptin was measured by radioimmunoassay (human leptin RIA kit; Linco Research Inc., St. Charles, USA; intraassay CV = 5.0% at 10 ng/ml; interassay CV = 4.5% at 10 ng/ml; sensitivity = 0.5 to 100 ng/ml). Blood glucose was measured by auto-analyzer (Hitachi-7050; Hitachi, Tokyo, Japan).

Statistical Analyses

Values are shown as the means $\pm$ SD. Changes in variables within each group and differences among groups were examined by two-way analysis of variance (ANOVA). When significant, Dunnett's test was used to determine whether the differences between the means at entry and at week 24 were significant among groups. The chi-square test was used to statistically compare the success rates of weight and BP reduction and the prevalence of a positive family history of obesity. Values of $p < 0.05$ were considered to indicate statistical significance.

Results

When weight loss was defined as a more than 10% reduction in BMI from the baseline at week 24, 63% of NT and 64% of HT subjects succeeded in achieving weight loss (Fig. 1, top). When BP reduction was defined as a more than 10% reduction in mean BP from baseline at week 24, the rate of BP reduction was higher in subjects who succeeded in weight

Fig. 1. Prevalence of success in weight loss ($\geq 10\%$), BP reduction ($\geq 10\%$) and a positive family history of obesity in obese normotensive subjects (left) and obese hypertensive subjects (right).

Fig. 2. Plasma norepinephrine level (top panel), fasting plasma leptin level (middle panel) and fasting plasma insulin level (bottom panel) at entry (week 0) and week 24 in obese normotensive subjects with weight loss ($\geq 10\%$, left column) and in obese hypertensive subjects with weight loss ($\geq 10\%$, right column). $\downarrow$ BP: subjects with BP reduction ($\geq 10\%$); BP+: subjects without BP reduction ($< 10\%$); * $p < 0.05$ vs. normotensives.

loss than in subjects who failed (Fig. 1, middle). The subjects who failed to achieve BP reduction despite successful weight loss had a significantly higher prevalence of FHOB+ compared with subjects who succeeded in BP reduction (80% in NT without BP reduction, 35% in NT with BP reduction, $p < 0.05$; 94% in HT without BP reduction, 21% in HT with BP reduction, $p < 0.01$) (Fig. 1, bottom).

Mean BP levels and BMI at entry were similar between subjects who succeeded in achieving weight loss and subjects who failed to achieve weight loss in both the NT and HT study groups. In addition, the percent reduction rates in BMI from baseline at week 24 were similar between NT and HT subjects or between subjects who succeeded and those who failed to achieve BP reduction (data not shown). There were no significant differences in food intake, physical activity or weight loss between the groups with weight loss-sensitive BP reduction and those with weight loss-resistant BP reduction throughout the study (data not shown).

Figure 2 shows the mean plasma NE (top), leptin (middle) and insulin (bottom) levels at entry (week 0) and week 24 in subjects who succeeded in achieving weight loss. The groups were further subdivided according to the success ($\geq 10\%$) or failure ($< 10\%$) in achieving mean BP reduction. The plasma NE levels at entry and at week 24 in subjects who failed to achieve BP reduction were significantly higher than those in subjects who succeeded in achieving BP reduction (Fig. 2, top). Plasma leptin and insulin levels were similar between subjects with and without BP reduction in either period (Fig. 2, middle and bottom). Plasma NE levels in subjects who failed to achieve BP reduction decreased slightly, but not significantly, following weight loss, whereas plasma NE in subjects who succeeded in achieving BP reduction decreased significantly in both the NT and HT study groups. Plasma leptin and insulin decreased significantly following weight

Fig. 3. Percent changes from baseline (entry) at week 24 in plasma norepinephrine level (top panel), fasting plasma insulin level (middle panel) and fasting plasma leptin level (bottom panel) in obese normotensive subjects with weight loss ($\geq 10\%$, left column) and obese hypertensive subjects with weight loss ($\geq 10\%$, right column). $\downarrow$ BP: subjects with BP reduction ($\geq 10\%$); BP $\rightarrow$: subjects without BP reduction ($< 10\%$).

loss regardless of BP reduction, but these decreases were similar between subjects with and without BP reduction.

Figure 3 shows the percent changes in plasma NE (top), leptin (middle) and insulin (bottom) levels from baseline at week 24 in subjects who succeeded in achieving weight loss. Subjects who succeeded in achieving BP reduction had a significantly greater percent decrease in plasma NE compared with subjects who failed to achieve BP reduction. Percent decreases in plasma leptin and insulin levels were similar between subjects with and without BP reduction in both the NT and HT study groups.

In all subjects, the absolute changes in plasma NE from entry period to 24 weeks correlated with the absolute changes in plasma insulin ($r=0.29$, $p<0.05$) and with the absolute changes in plasma leptin ($r=0.35$, $p<0.05$).

Discussion

The present study was designed to clarify the mechanisms of weight loss-sensitive and weight loss-resistant BP reduction in obese subjects, focusing on the relative contributions of a

family history of obesity, and on plasma levels of NE as an index of sympathetic activity, plasma leptin and plasma insulin levels in response to weight loss and change in BP. The main findings were as follows: a positive family history of obesity appeared to lessen the chance of BP reduction from weight loss, thus contributing to a resistance to weight loss-induced BP reduction. In addition, subjects who were resistant to weight loss-induced BP reduction had more sympathetic overactivity both at the outset of and during weight loss as manifested by a smaller percent decrease from baseline in plasma NE levels following weight loss. Decreases in plasma insulin and leptin levels with weight loss were similar between subjects with and without BP reduction, so these parameters appear to play a lesser role in weight loss-induced BP reduction. Thus, suppression of heightened sympathetic activity, and not hyperinsulinemia or hyperleptinemia, might be the major neurohormonal mechanism in weight loss-induced BP reduction, and these differences appear to be genetic.

Previously, we reported that normotensive subjects whose BP increased with weight gain over 10 years had more sympathetic overactivity prior to the start of the BP elevation, so that sympathetic nervous overactivity is definitively the initial event in the genesis of hypertension, followed by changes in insulin and leptin that come on as hypertension further develops (13). In addition, Hirose *et al.* reported the effects of body weight control on blood pressure in lean-to-obese young Japanese individuals in a 3-year follow-up study (24). In that study, the authors found a positive correlation between changes in body weight and changes in heart rate only in the obese and mildly obese male subjects.

In our previous, 12-month weight loss study in which some subjects received pharmacological treatment with a calcium channel blocker or an ACE inhibitor, we found that BMI, BP, plasma NE, leptin and insulin decreased significantly in the weight loss groups independent of pharmacological treatment (20). Moreover, the decreases in BP, plasma NE, leptin and insulin levels were greater in subjects who succeeded in achieving weight loss than in subjects who failed to lose weight despite the pharmacological agents.

The decrease in plasma NE appeared to initiate these events accompanied by a more delayed reduction in plasma leptin and insulin. These findings further support our hypothesis that normalization or suppression of heightened sympathetic activity is the initiator in BP reduction during weight loss. In this study, we also noted that more than 35% of the total subjects failed to achieve weight loss when the definition of weight loss was a more than 10% reduction in BMI at month 6. Other previous results from our groups (21, 23) have also demonstrated an early relationship between falls in plasma NE and insulin levels during weight loss and are in accordance with the above hypothesis. We previously reported that, in subjects participating in a 12-month weight loss regimen, the heightened sympathetic activity was reduced prior to any BP reduction, followed by a reduction in hyper-

insulinemia and hyperleptinemia (21, 25). In their study on 24 obese hypertensive subjects, Ikeda *et al.* (22) reported that a strict calorie-restricted diet for 4 weeks produced a weight loss of more than 10%. The decrease in BP after weight loss was related to suppression of sympathetic nervous activity alone and not due to suppression of hyperinsulinemia or the renin angiotensin system (22). Tuck *et al.* showed a strong correlation between fall in BP and level of NE in obese subjects on a very low caloric diet (16, 26). These subjects with weight loss but only mild BP reductions had insignificant changes in NE. Kawamura *et al.* (27) reported in an acute low calorie diet study over 2 weeks in 51 obese women that the calorie sensitive-BP reduction group was significantly younger than the calorie insensitive group. They concluded that age might predict the extent of BP reduction. In the present study, the age and BMI at entry period were matched in the study groups. Therefore, we could exclude the effects of age and BMI in our results.

We have also previously reported that, in subjects with a spontaneous weight gain over 12 months, there is an increase in sympathetic nervous system activity that induces the BP elevation with weight gain (13). Overall, the results from our longitudinal weight loss and weight gain studies suggest that changes in sympathetic nervous system activity with weight change play the initial role in weight change-induced BP changes. Additionally, other hormonal changes such as hyperinsulinemia and hyperleptinemia are secondary responses to alterations in the level of sympathetic nervous system activation. The significantly lesser degree of the solitary suppression of plasma NE in the subjects with weight loss-resistant BP reduction than in the subjects with weight loss-sensitive BP reduction provides further evidence that changes in sympathetic nervous system activity with weight loss play the initial role in weight loss-induced BP reduction.

In the present study, because weight loss was achieved by a combination of low caloric diet, mild sodium restriction and aerobic exercise, the independent effects of these measures were not clarified. It has been well demonstrated that aerobic exercise alone can suppress stimulated sympathetic activity and hyperinsulinemia even in the absence of weight reduction, and it has been concluded that the BP reduction induced by physical training is mediated by neural sympathetic mechanisms (28, 29).

It is important to note that the group of subjects who failed to achieve BP reduction despite weight loss (the weight loss-resistant BP reduction group) had a significantly higher prevalence of FHOB+ than the weight loss-sensitive BP reduction group. In addition, the subjects who failed to achieve weight loss had a significantly higher prevalence of FHOB+. These results suggest that FHOB+ status may reduce the ability of subjects to lose weight or to further reduce BP in the event that weight loss can be achieved. We have reported that lean NT subjects who were FHOB+ had higher levels of BP and plasma NE than lean NT subjects who were FHOB-, and that obese subjects who were

FHOB+ had higher levels of BP, plasma NE, leptin and insulin (29). These results suggest that in lean subjects genetically predisposed to obesity, sympathetic activation, not hyperleptinemia or hyperinsulinemia, is a mediating mechanism underlying the subsequent development of obesity. This is counterintuitive, in that higher sympathetic activity, through stimulating thermogenesis, might have been expected to prevent the development of obesity. The findings, however, concur with the recent hypothesis of Julius that genetic factors promoting sympathetic activation lead to reduced β -adrenergic responsiveness, such as predisposition to weight gain and obesity (30, 31). In the present study, we suggest that the weight loss-resistant BP reduction and higher plasma NE are linked to FHOB+ status, suggesting a genetic role in BP determination as related to body weight. Narkiewicz *et al.* (32) reported in a twin study that genetic factors are the major determinants of plasma leptin levels in humans. Further studies of longitudinal design will be needed, however, to more precisely determine the role of genetic factors, and their mechanism, in the development of obesity and associated hypertension.

In addition, Haynes *et al.* (33, 34) reported that leptin influenced sympathetic nervous activity in their leptin infusion study, and Collins *et al.* (35) reported that leptin increased NE turnover in brown adipose tissue. Shek *et al.* (36) reported that chronic leptin infusion caused an increase in both heart rate and BP. These findings might point to a role of leptin in obesity-related hypertension. In the present study, there were no significant differences in plasma leptin levels between subjects with weight loss-sensitive BP reduction and those with weight loss-resistant BP reduction, or between those who were FHOB+ and those who were FHOB-, suggesting that inheritance and SNA do not strongly affect plasma leptin levels and that plasma leptin does not affect BP.

In summary, a positive family history of obesity and sympathetic overactivity are more closely linked to weight loss-resistant BP reduction than are hyperinsulinemia or hyperleptinemia in obese subjects. Our results further suggest that in subjects genetically predisposed to obesity, sympathetic activation is a mediating mechanism underlying the development of obesity.

Abbreviations and Acronyms

BP, blood pressure; BMI, body mass index; CV, coefficient of variation; FHOB+, positive family history of obesity; FHOB-, no family history of obesity; HbA1c, hemoglobin A1c; HT, hypertensive subjects; NT, normotensive subjects; NE, norepinephrine; SNA, sympathetic nervous system activity.

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