Body Weight Reduction, Sympathetic Nerve Traffic, and Arterial Baroreflex in Obese Normotensive Humans

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Background—Previous studies have shown that sympathetic cardiovascular outflow is increased in obese normotensive subjects and that this increase is associated with a baroreflex impairment. The purpose of this study was to determine whether these abnormalities are irreversible or can be favorably affected by body weight reduction.

Methods and Results—In 20 obese normotensive subjects (age, 31.3±1.7 years; body mass index, 37.6±0.9 kg/m², mean±SEM), we measured beat-to-beat arterial blood pressure (Finapres technique), heart rate (ECG), postganglionic muscle sympathetic nerve activity (microneurography at a peroneal nerve), and venous plasma norepinephrine (high-performance liquid chromatography) at rest and during baroreceptor stimulation and deactivation induced by increases and reductions of blood pressure via stepwise intravenous infusions of phenylephrine and nitroprusside. Measurements were repeated in 10 subjects after a 16-week hypocaloric diet with normal sodium content (4600 to 5000 J and 210 mmol NaCl/d) and in the remaining 10 subjects after a 16-week observation period without any reduction in the caloric intake. The hypocaloric diet significantly reduced body mass index, slightly reduced blood pressure, and caused a significant and marked decrease in both muscle sympathetic nerve activity (from 50.0±5.1 to 32.9±4.6 bursts per 100 heart beats, *P < .01*) and plasma norepinephrine (from 356.2±43 to 258.4±29 pg/mL, *P < .05*). This was associated with a significant improvement in the sensitivity of the baroreceptor heart rate (+71.5±11%, *P < .01*) and muscle sympathetic nerve activity (+124.5±22%, *P < .001*) reflex. Total body glucose uptake also increased significantly (+60.8±12.0%, *P < .05*), indicating an increase in insulin sensitivity. All variables remained unchanged in subjects not undergoing caloric restriction.

Conclusions—In obese normotensive subjects, a reduction in body weight induced by a hypocaloric diet with normal sodium content exerts a marked reduction in sympathetic activity owing to central sympathoinhibition. This can be due to the consequences of an increased insulin sensitivity but also to a restoration of the baroreflex control of the cardiovascular system with weight loss. (Circulation. 1998;97:2037-2042.)

Key Words: obesity ■ nervous system, autonomic ■ reflex ■ diet

Several lines of evidence exist that sympathetic activity is increased in obesity. First, in obese normotensive and hypertensive subjects, plasma norepinephrine concentrations are greater than in lean control subjects.1-4 Second, the spillover rate of norepinephrine from sympathetic nerve terminals (assessed by infusion of tritiated norepinephrine) is increased in obese compared with lean individuals in whom body weight is normal.5,6 Third, sympathetic nerve traffic to skeletal muscle circulation is twice as large in normotensive subjects with a body mass index >35 kg/m² than in normotensive subjects with a body mass index <25 kg/m².7,8,11 Evidence also exists that dietary-induced reductions in body weight are accompanied by a reduction in plasma norepinephrine1,2,8 and muscle sympathetic nerve traffic.9 However, these results have been obtained in essential hypertensive individuals and/or by diets that included a restriction of sodium intake, ie, under conditions in which sympathetic activity may be affected by factors other than the body weight reduction per se.10,11 In the present study, we measured muscle sympathetic nerve traffic and plasma norepinephrine in obese normotensive subjects before and after a hypocaloric diet with normal sodium content. The primary aim of the study was to establish the effect of body weight reduction on sympathetic activity without the confounding factors existing in previous studies. Additional aims, however, were to determine the peripheral or central nature of the sympathetic deactivation possibly caused by loss of body weight and whether an improvement in the baroreceptor sympathetic reflex was involved. This results because this reflex is impaired in obesity,7 and its improvement has been shown to lead to sympathoinhibition in other diseases.12

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Methods

Population
The present study included 20 obese subjects (14 men, 6 women) with a body mass index from 30 to 45 kg/m² and an age from 22 to 41 years. Ten subjects (age, 29.3 ± 3.0 years) were placed on a low-calorie diet and sodium intake (210 mmol/d sodium chloride), which allowed body weight to remain almost unchanged from the screening visit (difference never >1%). In the subjects placed on the dietary program, the second experimental session was performed after 16 weeks of a hypocaloric diet (4600 to 5000 J/d), while the remaining 10 subjects (age, 33.2 ± 3.3 years) were given no dietary prescription and used as control subjects. The subjects, who were assigned to the low-calorie or unchanged diet on a sequential basis, were recruited if they had (1) normal blood pressure values (≤140/85 mm Hg) on repeated sphygmonanometric measurements, (2) no family history of hypertension, (3) no physical or laboratory evidence of major cardiovascular or noncardiovascular diseases, and (4) no dietary or pharmacological treatment of obesity at recruitment. No subject was a cigarette smoker, and none had a history of more than occasional alcohol consumption.

Dietary Regimen
In all subjects, a first experimental session was performed after 4 weeks of stable caloric diet and sodium intake (210 mmol/d sodium chloride), which allowed body weight to remain almost unchanged from the previous assessment of plasma norepinephrine was withdrawn, and blood pressure, heart rate, respiratory rate, and MSNA were averaged for the 5 minutes of each step infusion. Baroreceptor modulation of MSNA was estimated by calculating absolute changes in sympathetic bursts per minute and percent changes in sympathetic burst amplitude (integrated activity—ie, bursts per minute times mean burst amplitude expressed in arbitrary units) in relation to the changes in mean arterial pressure induced by each dose of phenylephrine and nitroprusside. It was also estimated by calculating absolute changes in heart rate in relation to the changes in mean arterial pressure induced by each dose of the vasoactive drugs. The reflex heart rate and MSNA changes in response to mean arterial pressure changes were averaged separately for the three doses of phenylephrine and nitroprusside to obtain mean baroreflex sensitivities during baroreceptor stimulation and desensitization.

The cold pressor test was performed by immersion of the hand contralateral to that used for blood pressure measurements in iced water (3°C) for 2 minutes. Hemodynamic variables and MSNA were averaged for the 5 minutes before the cold pressor test and for the 2 minutes during the cold pressor test.

Protocol and Data Analysis
The first experimental session was performed in the morning. After a light breakfast, the subject was put in the supine position and fitted with the intravenous cannulas, the microelectrodes for MSNA recording, and the other measuring devices. The blood sample for assessment of plasma norepinephrine was withdrawn, and blood pressure was measured three times by a mercury sphygmomanometer. After a 30-minute period, blood pressure, heart rate, respiratory rate, and MSNA were continuously monitored during (1) a 15-minute baseline state, (2) infusion of one vasoactive drug, (3) a second 15-minute baseline state, (4) infusion of the second vasoactive drug, (5) a 5-minute baseline state, and (6) a 2-minute cold pressor test. A 40-minute recovery period was allowed between (1) the end of the first drug infusion and the beginning of the second one and (2) the end of the second drug infusion and the performance of the cold pressor test. In half of the subjects, phenylephrine was infused first; in the other half, it was preceded by nitroprusside infusion. The second experimental session (which was also performed in the morning) followed the same protocol, including the order of the vasoactive drugs infused. The glucose clamp sessions
were performed within 1.7±1.1 days from the sessions in which MSNA was measured.

Data were calculated by a single investigator unaware of the experimental design. Baseline blood pressure, heart rate, ventilation rate, and MSNA obtained in individual subjects were averaged separately for each experimental session and expressed as mean±SEM. This was also done for body weight, body mass index, waist-to-hip ratio, plasma norepinephrine, glucose and insulin, insu-

lin sensitivity and urinary electrolytes, and responses to baroreceptor stimulation and deactivation (see above).

Comparisons between data obtained in each experimental session were made by two-way ANOVA. The Spearman analysis was used to correlate changes in different variables. A value of \( P < .05 \) was taken as the level of statistical significance.

**Results**

Table 1 shows that the 16-week hypocaloric diet with normal sodium content induced a marked and significant reduction in body weight, body mass index, and waist-to-hip ratio without significant changes in 24-hour urinary sodium excretion. Sphygomonometric and, to a lesser extent, finger beat-to-beat systolic and diastolic blood pressures were reduced, with no significant reduction in heart rate, no change in ventilation rate, a nonsignificant decrease in plasma glucose and insulin, but a significant increase in total body glucose uptake (+60.8±12.0%, \( P < .05 \)) and thus in insulin sensitivity. MSNA was significantly less after than before the hypocaloric diet, as was the case for plasma norepinephrine (Fig 1, left). The decrease in MSNA was related to the reduction in body weight and body mass index (\( r = .65 \) and \( r = .68 \), respectively; \( P < .05 \) for both) but not to the blood pressure reduction. No change in all the above variables occurred in the group of subjects in whom the caloric dietary regimen remained unchanged (Table 1 and Fig 1, right).

The baroreflex data are shown in Fig 2. The progressive increase in mean arterial pressure induced by phenylephrine was accompanied by a progressively greater bradycardia and sympathoexcitation. During both baroreceptor stimulation and deactivation, the sensitivity of the baroreceptor heart rate and MSNA reflex was related to resting MSNA values (baroreceptor stimulation, \( r = .65 \) and \( r = .74 \) for heart rate and MSNA, respectively, \( P < .05 \) for both; baroreceptor deactivation, \( r = .68 \) and \( r = .75 \) for heart rate and MSNA, respectively, \( P < .05 \) for both). Compared with the initial condition, all reflex responses were greater after the subjects maintained the hypocaloric diet (Fig 2, left); thus, the baroreflex sensitivities were increased during both baroreceptor stimulation and deactivation (Table 2). During both baroreceptor stimulation and deactivation, the increase in the sensitivity of the baroreflex modulation of heart rate and MSNA was related to the MSNA reduction induced by body weight loss (baroreceptor stimulation, \( r = .64 \) and \( r = .72 \) for heart rate and MSNA respectively, \( P < .05 \) for both; baroreceptor deactivation,

![Figure 1. Muscle sympathetic nerve activity (MSNA) expressed as bursts (bs)/100 heart beats (hb) and plasma norepinephrine values (NE) before (B, open bars) and after 16 weeks (16 weeks, hatched bars) of hypocaloric normosodic diet (left) or before (B, open bars) and after 16 weeks (16 weeks, hatched bars) of unchanged caloric intake (right). Data are shown as mean±SEM. n=10 for each group. *P<.05; **P<.01.](http://circ.ahajournals.org/doi/abs/10.1161/01.CIR.98.10.2039?ut=converge)
Sympathetic Activity and Body Weight Reduction

Figure 2. Changes in heart rate (ΔHR, expressed as beats per minute [b/min]) and muscle sympathetic nerve activity (ΔMSNA, expressed as bursts per minute [bs/min]) and percent integrated activity (% IA) in response to changes in mean arterial pressure (ΔMAP, mm Hg) induced by stepwise intravenous nitroprusside and phenylephrine infusions. Solid lines refer to HR and MSNA changes observed under baseline conditions; dashed and dotted lines refer to HR and MSNA changes observed after 16 weeks of either reduced caloric intake (left) or unchanged caloric intake (right). Data are mean ±SEM. n=10 for each group. *P<.05; **P<.01.

r=.66 and r=.78 for heart rate and MSNA, respectively, \(P<.05\) and \(P<.01\). No relationship was found, however, between any such baroreflex improvement and the blood pressure effect of body weight reduction. Baroreflex modulation of heart rate and MSNA was unchanged in the control subjects undergoing no dietary modification (Table 2 and Fig 2, right).

The cold pressor test caused an increase in mean arterial pressure, heart rate, and MSNA. In the group undergoing the hypocaloric diet with normal sodium content, the increase was similar before and after body weight reduction (mean arterial pressure, +11.2±2.8 versus +12.4±3.1 mm Hg; heart rate, +9.4±1.8 versus +10.1±1.9 bpm; MSNA, +67.7±12% versus +73.1±10.8% integrated activity [% IA]). This was also the case in the control group (mean arterial pressure, +10.2±3.1 versus +10.7±3.3 mm Hg; heart rate, +10.5±2.1 versus +9.7±1.6 bpm, and MSNA, +71.5±10.2% versus +75.4±12.8% IA).

Discussion

In our obese normotensive subjects, plasma norepinephrine was 356.2±43 pg/mL and MSNA was 50.0±5.1 bursts per 100 heart beats, thereby displaying values much greater than those found in age-matched, lean normotensive individuals. After a 16-week hypocaloric diet with normal sodium content, however, body weight was effectively reduced, and this reduction was accompanied by plasma norepinephrine and MSNA levels that were markedly less than the original values (a reduction of 28.4% and 35.5%, respectively). This provides evidence that the sympathetic activation that accompanies obesity is reversible when the overweight condition is corrected by dietary treatment. This can be obtained through central sympathetic suppression in the absence of any concomitant change in dietary sodium intake.

In a previous study on obese normotensive individuals, we found the baroreceptor modulation of heart rate and MSNA to be blunted and suggested a baroreflex impairment as a possible cause of the obesity-related sympathetic activation. This possibility is in line with the present findings that (1) before a low-calorie diet, resting MSNA was related to the sensitivity of the baroreflex modulation of MSNA and heart rate and (2) after a dietary-induced reduction in body weight, baroreflex modulation of MSNA and heart rate was improved to a degree related to the concomitant reduction in resting MSNA. It is thus reasonable to keep the hypothesis alive that the changes in sympathetic activity associated with body weight modifications have a reflex origin. This is certainly neither specific for body weight reduction, nor is it the only mechanism involved, however. First, baroreflex sensitivity has also been found to be related to resting MSNA in congestive heart failure. Second, a reduction in nutrient intake has been shown to exert a direct sympathoinhibitory

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group With Reduced Caloric Intake (n=10)</th>
<th>Group With Unchanged Caloric Intake (n=10)</th>
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<td>Control 16th wk</td>
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MSNA indicates muscle sympathetic nerve activity; HR, heart rate; MAP, mean arterial pressure; PHE, phenylephrine; NTP, nitroprusside; and IA, integrated activity. Values shown are mean ±SEM.

*P<.05, †P<.01 vs control conditions.
effect. Third, plasma insulin and insulin resistance are reduced by body weight reduction, as also was clearly evident in our patients. It should also be emphasized that in the induction of sympathetic activation, reflex and metabolic mechanisms may reinforce each other because, while insulin causes sympathetic activation possibly through an impairment of the baroreceptor function, sympathetic activation can induce insulin resistance and hyperinsulinemia.

Several other findings of our study deserve to be mentioned. First, after the reduction in body weight, not only baroreceptor modulation of sympathetic activity but also baroreceptor modulation of heart rate were improved. Because baroreceptor modulation of heart rate depends to a large extent on the vagus, this means that the baroreflex control of both autonomic divisions involved in cardiovascular regulation is favorably affected by correction of body overweight. Second, the hemodynamic and sympathetic responses to the cold pressor test were unaffected by body weight reduction and were not different from those usually found in lean individuals. Thus, this intervention does not modify all neural cardiovascular influences; rather, its effect is specifically limited to the baroreflex. Third, the weight loss obtained in our obese subjects was capable of reducing MSNA to values comparable to those reported for lean individuals, although the body weight remained higher than normal. This should not be taken as evidence that sympathetic activation is a feature of only a marked rather than a more modest increase in body weight, when normotensive subjects are considered, because (1) evidence from other studies indicates that even in normotensive subjects with mild obesity, an increase in sympathetic activity can be detected and (2) a reduction in nutrient intake per se may exert a sympathoinhibitory effect that normalizes sympathetic activity even when body fat remains somewhat abnormal.

Our study has some limitations. First, after loss of body weight, our obese subjects showed a blood pressure reduction, which might have altered sympathetic activity per se. However, the blood pressure reduction was small (particularly when quantified by finger blood pressure measurements), presumably because blood pressure was normal in the predict condition. Furthermore, no relationship was found between the dietary-induced changes in plasma norepinephrine and MSNA and the concomitant blood pressure changes. Finally, and more importantly, the blood pressure reduction might have reflexly increased sympathetic activity, thereby blunting a sympathoinhibitory effect of body weight loss that would have been even greater than that observed. Second, the mechanisms responsible for the baroreflex improvement after weight loss are not explained by our data. However, because body weight loss had no effect on the MSNA and heart rate responses to the cold pressor test, it is likely that factors specifically affecting the central and/or afferent portion of the baroreflex arch are involved. In the afferent portion, an increased distensibility of the large arteries where the baroreceptors are located might play a role because obesity is accompanied by an increased large artery wall stiffness. Third, because microneurography allows only sympathetic nerve activity to be recorded in skeletal muscle districts, no evidence is available from our study as to what extent the central sympathoinhibition induced by body weight loss also involves visceral districts. We can speculate, however, that this is the case because the reduction in sympathetic nerve traffic was quantitatively similar to the reduction in plasma norepinephrine, although the latter cannot be taken strictly as a balanced marker of sympathetic activity throughout the body because the contributions of some districts (including the skeletal muscle ones) may prevail over others.

Finally, our study has clinical implications because removal of the sympathetic activation by loss of body weight may eliminate a factor that may possibly be involved in the high prevalence of hypertension, congestive heart failure, ischemic heart disease, and sudden death typical of obesity. We can also speculate, however, that the suppression of sympathetic activity associated with correction of an overweight condition does not have an entirely favorable significance because in obese subjects a sympathetic activation may favor energy consumption and thus oppose a further body weight increase, its suppression by body weight loss thus predisposing to a weight regain.

References


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