Effect of Energy-Restricted Diet on Sympathetic Muscle Nerve Activity in Obese Women

Björn Andersson, Mikael Elam, B. Gunnar Wallin, Per Björntorp, and Ove K. Andersson

Twenty obese women aged 45–65 years with borderline hypertension were allocated randomly to either a group with an energy-restricted diet or to a control group. Body weight, blood pressure, urinary sodium, and urinary excretion of norepinephrine and plasma volume were recorded. Resting muscle sympathetic nerve activity was measured in the peroneal nerve by tungsten microelectrodes and expressed as bursts per minute. These measurements were repeated after 3 days of semistarvation and after a body weight reduction of 7% while each patient's weight was in a steady state. After 3 days of semistarvation, only body weight was reduced, whereas after the long-term energy intake restriction, there were reductions of body weight (79.9±3.4 versus 74.1±3.4 kg; p<0.001), diastolic blood pressure (93±3 versus 86±4 mm Hg; p=0.01), and muscle sympathetic nerve activity (49±2 versus 42±3 bursts/min; p<0.05). Other variables were unchanged. There were no changes in body weight, blood pressure, or muscle sympathetic nerve activity in the control group. We conclude that body weight decrease in obesity results in a reduction of blood pressure that is at least partially caused by a reduction of sympathetic vasoconstrictor activity. (Hypertension 1991;18:783-789)

Many studies have shown that a decrease in body weight in hypertensive patients with moderate-to-severe obesity is associated with a fall in blood pressure.1-2 The mechanisms behind the blood pressure reduction are only partially understood. Some authors have suggested that a restricted sodium intake3-4 contributes to the blood pressure decrement; others have found a fall in blood pressure without a concomitant decrease of sodium intake.5 Based on measurements of circulating norepinephrine concentrations, it has also been proposed that both the acute and the long-term reduction of blood pressure are due to a reduced sympathetic vasoconstrictor drive.6-12

In a previous study13 of obese borderline hypertensive women who had been fasting for 48 hours, we made direct recordings of sympathetic neural outflow to the vascular bed of skeletal muscle and found an essentially unchanged nerve traffic in spite of a significant blood pressure reduction. The patients were energy and sodium restricted. It has been suggested previously14,15 that salt and energy intake restriction have opposite effects on sympathetic nervous activity so that the net effect of a markedly reduced sodium intake combined with a negative energy balance may be no change or even an increased sympathetic drive (expressed as increased levels of plasma norepinephrine). Our previous results are compatible with this hypothesis.

The aim of the present study was to clarify the effect of calorie restriction on sympathetic nerve activity by measuring efferent muscle sympathetic activity in a group of obese and borderline hypertensive women before and after a short-term sodium-supplemented period of fasting and also to assess the effects of a long-term negative energy balance on plasma volume, blood pressure, and efferent vasoconstrictor tone.

Methods

Subjects

Thirty moderately obese women with borderline hypertension (diastolic blood pressure 90 mm Hg or greater on at least two occasions) aged 43–66 years and with a body mass index (BMI) (kg/m²) of 26–36 were included. The mean systolic blood pressure in the examined group at baseline was 146±3 mm Hg (mean±SEM), and the mean diastolic blood pressure was 93±2 mm Hg. None of the women were on...
a diet, and their body weights had been stable the preceding 3 months. For detailed patient characteristics, see Table 1.

Patients were not included if they had diabetes mellitus, overt cardiovascular disease, malignant disease, or hypertension necessitating drug management. In five patients who previously had been on antihypertensive medication, the drug was withdrawn at least 4 weeks before the study.

In seven women, baseline sympathetic nerve recordings failed for technical reasons and they were therefore excluded. Three women were excluded because of noncompliance. All patients gave their informed consent to the study, which was approved by the Ethics Committee of the University of Gothenburg.

Protocol
Before inclusion, the subjects were allocated randomly to receive (group 1) or not to receive (group 2) diet intervention. During a run-in period of 4 weeks, blood pressure, heart rate, and body weight were measured on four separate occasions. Furthermore, four 24-hour (starting at 7:00 AM) urinary sodium and urinary norepinephrine samples were collected. The means of the measurements of these four samples were considered the baseline values. All patients were interviewed by a dietician, and their dietary habits were recorded for 4 days.

The patients in group 1 underwent 3 days of semistarvation supervised by a dietician. At baseline (day 1), blood pressure, heart rate, body weight, and plasma volume were determined. Muscle nerve sympathetic activity was recorded. The patients were ambulatory throughout the study. On day 4, the subjects came to the laboratory in a fasting condition, and all measurements were repeated. Twenty-four-hour urinary sodium and norepinephrine samples were collected. The patients in group 2 (control group) were not given dietary advice but were instructed to maintain their usual energy intake during these 3 days. The same measurements as in group 1 were performed. Patients from the two groups were investigated in random order, and the physicians who performed the nerve recordings (M.E. and B.G.W.) were not aware of to which group the patients belonged.

After the semistarvation period, the subjects in group 1 were placed on an individually adjusted energy-restricted diet that aimed at a weight decrease of 7% of the original body weight. This level of body weight reduction was chosen since, in previous studies of similar design, weight loss of at least 5% was considered necessary to obtain a significant fall in blood pressure. Sodium intake was not restricted. The patients visited the dietician every fourth week on an average. Body weight was recorded during all visits. When the desired body weight decrement was achieved and the patient’s weight had been stable for 4 weeks (less than ±2 kg weight change), the patient came to the laboratory; body weight, blood pressure, heart rate, and plasma volume were measured. Muscle nerve sympathetic activity was recorded. Two 24-hour urinary sodium and norepinephrine samples were collected, and the mean values of these samples were used.

The patients in group 2 were given no dietary advice and were instructed to remain on a steady-state energy intake. They were reexamined after 3–5 months, a time period that was chosen as an attempt to imitate the long-term energy restriction period in group 1. One patient in group 1 failed to cope with the semistarvation diet but accomplished the long-term energy restriction. Two patients dropped out of long-term treatment because of inability to decrease their body weight.

Diet
The semistarvation diet was composed of beverages of carrot, apricot, prune, and mixed fruit juices as well as a linseed supplement that totaled about 621 kJ/24 hr with a sodium content of 3 mmol and a potassium content of 7 mmol.

To provide an unchanged sodium balance during the semistarvation period, the patients received sodium
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TABLE 2. Hemodynamic and Metabolic Variables Before and After 3 Days of Either Semistarvation (Group 1) or Unchanged Energy Intake (Group 2)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (n=10)</th>
<th>Group 2 (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>83.5±4.0</td>
<td>81.0±3.9*</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>148±4</td>
<td>147±3</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>93±2</td>
<td>87±4</td>
</tr>
<tr>
<td>Heart rate</td>
<td>72±3</td>
<td>73±4</td>
</tr>
<tr>
<td>MSA (bursts/min)</td>
<td>48±2</td>
<td>53±3</td>
</tr>
<tr>
<td>Plasma volume (l)</td>
<td>2.82±0.16</td>
<td>2.75±0.24</td>
</tr>
<tr>
<td>Urinary norepinephrine (nmol/24 hr)</td>
<td>204±14</td>
<td>302±64</td>
</tr>
<tr>
<td>Urinary sodium (mmol/24 hr)</td>
<td>168±21</td>
<td>127±20</td>
</tr>
</tbody>
</table>

Values are mean±SEM. SBP, systolic blood pressure; DBP, diastolic blood pressure; MSA, muscle sympathetic nerve activity.
*p<0.001 comparing before-after in each group.

tables (Natriumklorid 0.5 g, ACO, Solna, Sweden). The amount necessary was estimated from the sodium excretion in 24-hour urinary sodium outputs measured before the study. During the chronic energy restriction period, the mean daily energy intake was about 6,300 kJ/24 hr, consisting of about 15–20% protein, 50% carbohydrate, and 25–30% fat.

Measurements

Body weight was measured to the nearest 0.1 kg with the subjects in their underwear. Systolic and diastolic blood pressures were measured automatically with a Nicon Colin Sphygmonanometer BP-203 model Y with a calibrated V-look cuff (Nippon Colin Ltd., Komachi-City, Japan) after the subject had rested at least 15 minutes in the supine position. Measurements were taken every minute during the nerve recordings at rest (10 minutes), and the mean value of the measurements was used. Heart rate was measured every minute from an electrocardiogram recorded by chest electrodes, and the mean value from the whole rest period was calculated.

All recordings of muscle nerve sympathetic activity were performed in the same room at the Department of Clinical Neurophysiology while the patient was in a comfortable supine position. The recording technique and display system have been described in detail previously.17-19 In summary, nerve recordings were made with tungsten microelectrodes with a tip diameter of a few microns. The electrodes were inserted manually through intact skin into a muscle nerve fascicle in the peroneal nerve at the knee. Small electrode adjustments were made until an optimal position was found for recording sympathetic impulses. Recordings 1 and 2 were made in different legs.

After amplification, the nerve signal was monitored on a storage oscilloscope (model 549, Teledtronix, Beaverton, Ore.) and a loudspeaker and also fed through an RC-integrating network (time constant 0.1 second) to obtain a mean voltage display of the nerve activity. The analog signals of both original and mean voltage neurograms were stored together with other variables on an eight-channel, FM tape recorder (Sabre VI, Sangamo, Sarasota, Fla.).

Spontaneous sympathetic activity was recorded at rest for 10 minutes, and the mean voltage neurogram was displayed on an ink jet recorder. Records were divided into 1-minute periods, and for each period all pulse synchronous bursts that could be identified by inspection of the mean voltage neurogram were marked and counted. For each 1-minute period the strength of the sympathetic activity was expressed as the number of bursts per minute,19 and the results are presented as the mean value for all 1-minute periods.

In one patient in group 1, the nerve recording after the semistarvation period failed, but a satisfactory recording was obtained after the long-term negative energy balance. In group 2 (control group), nerve recordings after 3 days failed in one patient because of technical difficulties.

The 24-hour urine samples were collected daily in bottles containing 4N HCl as preservative. Urinary sodium was measured by flame photometry and urine norepinephrine by a high-performance liquid chromatography method with an electrochemical detector.20 Plasma volume was determined by a radioiodinated serum albumin method with 125I.21

Statistics

Results are given as mean±SEM. Statistical methods used were one-factor analysis of variance (ANOVA) with repeated measurements for comparison within groups and factorial ANOVA for comparison between groups. Multiple regression analyses were performed according to Macintosh STATVIEW. All tests were two-tailed, and values of p<0.05 were regarded as statistically significant.

Results

Baseline characteristics of the participating women are shown in Table 1. There was no difference at baseline between the treatment (group 1)
and the control group (group 2) regarding blood pressure, sympathetic nerve activity, plasma volume, or anthropometric data.

Effects of Initial Semistarvation

In group 1, body weight was reduced from 83.5±4.0 to 81.0±3.9 kg (p<0.001, Table 2), but no changes in systolic blood pressure, heart rate, plasma volume, or excretion of sodium and norepinephrine were observed. There was, however, a tendency for a decrease in diastolic blood pressure (93±2 versus 87±4 mm Hg, p=0.087) and an increase in muscle sympathetic nerve activity (MSA) (48±2 versus 53±3 bursts/min; p=0.092; Figure 1A). In the control group, there were no changes in the measured variables.

Effects of Long-term Calorie Restriction

During long-term dieting (group 1), body weight decreased from 79.9±3.4 to 74.1±3.4 kg (p<0.001; Table 3). Systolic blood pressure was unchanged, whereas diastolic blood pressure was reduced from 93±3 to 86±4 mm Hg (p<0.01). MSA decreased 14% from 49±2 bursts/min at baseline to 42±3 bursts/min after the long-term energy restriction (p<0.05; Figure 1B). The decrease was even more pronounced (21%) when MSA after the initial semistarvation period was compared with the level after the long-term negative energy balance (53±3 versus 42±3 bursts/min; p<0.01; Figure 1C). Heart rate, urinary excretion of norepinephrine and sodium, and plasma volume were unchanged (Table 3).

After a mean of 4 months, the subjects in group 2 had unchanged body weight, systolic and diastolic

| Table 3. Hemodynamic and Metabolic Variables Before and After Long-term Energy Intake Reduction (Group 1) or After 4 Months of Unrestricted Energy Intake (Group 2) |
|--------------------------------------------------|------------------|------------------|------------------|------------------|
| Variable                                         | Before (n=9)     | After             | Before (n=9)     | After             |
| Body weight (kg)                                 | 79.9±3.4        | 74.1±3.4*         | 81.8±2.5         | 82.0±2.8          |
| SBP (mm Hg)                                      | 146±4           | 142±5             | 143±4           | 146±4             |
| DBP (mm Hg)                                      | 93±3            | 86±4†             | 93±2            | 94±3             |
| Heart rate                                       | 71±3            | 66±3              | 75±4            | 74±3              |
| MSA (bursts/min)                                 | 49±2            | 42±3‡             | 53±3            | 50±3              |
| Plasma volume (l)                                | 2.68±0.20       | 2.73±0.17         | 2.91±0.19       | 2.68±0.18         |
| Urinary norepinephrine (nmol/24 hr)              | 210±13          | 198±31            | 198±25          | 232±33            |
| Urinary sodium (nmol/24 hr)                      | 157±20          | 133±14            | 135±17          | 143±16            |

Values are mean±SEM. SBP, systolic blood pressure; DBP, diastolic blood pressure; MSA, muscle sympathetic nerve activity.

* p<0.001, † p<0.01, ‡ p<0.05, comparing before-after in each group.
blood pressure, heart rate, urinary excretion of norepinephrine and sodium, and plasma volume (Table 3). The level of MSA (50 ± 3 bursts/min) was unchanged compared with both the initial control value (53 ± 3 bursts/min) and the value after 3 days (52 ± 3 bursts/min).

Although both diastolic blood pressure and MSA decreased during long-term dieting, the correlation between these changes did not reach statistical significance (r = 0.56, p = 0.12). There were no correlations between changes in body weight and MSA or blood pressure during treatment.

Discussion

The main findings in the present study were significant decreases of MSA and diastolic blood pressure after long-term energy restriction and a tendency to increased MSA and decreased diastolic blood pressure after 3 days of semistarvation.

Previous reports concerning sympathetic nervous activity after energy restriction have been based on measurements of circulating norepinephrine, which has been considered an indicator of sympathetic activity. Although a correlation between plasma norepinephrine and MSA is usually found, there are exceptions, and it must be remembered that plasma norepinephrine levels are influenced not only by central sympathetic outflow but also by peripheral mechanisms such as altered release or reuptake into nerve terminals, regional blood flow, and spillover from different vascular beds.

In contrast, recording MSA has an advantage in that it gives a direct measurement of sympathetic nerve traffic. Previous studies have shown that the MSA level at rest is highly reproducible in repeated recordings over several months, which is confirmed by the control group in the present study. There is, however, also a limitation with the nerve recording method. Sympathetic outflow is differentiated and therefore, results from one sympathetic subdivision cannot be extended to other regions.

Effects of Semistarvation

Short-term fasting is known to reduce blood pressure, and it has been suggested this effect is due to a reduced sympathetic activity. However, in a previous study we found an essentially unchanged sympathetic nerve traffic despite a decrease in blood pressure after 48 hours of fasting. Our present results are similar, even if the decrease in diastolic blood pressure did not reach statistical significance.

Body weight reduction during short-term fasting is due mainly to dehydration. Reduced intravascular fluid volume may cause the initial blood pressure fall by reducing venous return and cardiac output. Under such circumstances it is possible that unloading of arterial or low-pressure receptors would activate the sympathetic vasoconstrictor system as a compensatory mechanism to preserve blood pressure. In addition, a reduced sodium intake per se has been shown to increase both MSA and plasma norepinephrine in borderline hypertensive and normotensive subjects.

In the present study, sodium intake was unchanged and therefore this factor would not influence MSA, which may explain why the changes in sympathetic nerve activity (and blood pressure) were small.

Effects of Long-term Energy Restriction

The decrease of resting MSA after the long-term negative energy balance provides direct support for the hypothesis that the blood pressure decrement is caused by a reduction of sympathetic nervous traffic. The underlying mechanisms are unclear. It has been proposed that a low carbohydrate intake suppresses sympathetic activity whereas overfeeding with carbohydrates or dietary fat causes an increased sympathetic drive both in humans and rats. In the present study, the subjects were given a diet that was reduced in dietary fat, but the carbohydrate intake was roughly unchanged compared with steady-state conditions. It is unclear whether the reduction of fat might have influenced the sympathetic nerve traffic.

Decreased insulin sensitivity and hyperinsulinemia have been suggested to be one mechanism linking obesity to hypertension. An independent correlation between plasma insulin and blood pressure in hypertensive patients with both normal body weight and overweight has been reported in several studies. It has also been shown that insulin infusion increases sympathetic nervous activity in the absence of changes in blood glucose and accordingly there might be an association between obesity with accompanying hyperinsulinemia, hypertension, and the sympathetic nervous system. This could not be evaluated in the present study since insulin was not assessed.

In previous reports, severe energy intake restriction (1,260–1,680 kJ/24 hr) caused reduction of blood pressure independent of sodium intake, whereas more moderate energy restriction (5,040 kJ/24 hr) failed to decrease blood pressure unless sodium intake was restricted. However, contradictory to the results of the latter study, Reisin and coworkers demonstrated a fall in blood pressure in patients with only a moderately negative energy balance independent of sodium intake. Our data are in agreement with the findings of Reisin et al since a mild calorie restriction (about 6,300 kJ/24 hr) leads to a significant blood pressure decrease in spite of an unchanged sodium balance. Thus, even a moderate energy restriction is sufficient to achieve a fall in blood pressure independent of sodium intake. However, our results do not exclude the possibility of an additive effect of sodium restriction superimposed on a negative energy balance.

As mentioned above, reduced intravascular fluid volume may contribute to the fall in blood pressure during severe short-term energy restriction. However, several reports indicate that also after long-term negative energy balance, weight loss re-
sults in a contracted blood volume, leading to a decreased cardiac output and lowered blood pressure. We failed to show any contraction of plasma volume in spite of a reduced blood pressure. This may be due to a difference in study design, diet composition, and patient compliance compared with previous studies. On the other hand, our results are consistent with the findings in a previous study in which obese men with mild hypertension on an energy-reduced diet had unchanged plasma volume although weight and blood pressure were decreased.

Studies of resting MSA in essential hypertension have given varying results. In early reports on established hypertension, MSA was found to be normal, but in a recent study, MSA was increased. Similarly, in borderline hypertension two studies showed an increase and another did not. The explanation for the divergent findings may be the large interindividual differences in MSA and the increase in MSA that normally occurs with age. In summary, we conclude that the blood pressure reduction observed after a long-term moderate energy restriction is associated with, and probably caused by, a reduction of sympathetic vasoconstrictor drive as measured here by direct-nerve recordings of the effrent muscle sympathetic activity.

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**KEY WORDS** • obesity • sympathetic nervous system • blood pressure • microneurographyobesity
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