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Effects of Sodium Supplementation during Energy Restriction on Plasma Norepinephrine Levels in Obese Women*

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ABSTRACT. We tested whether sodium restriction would counteract the decrease in sympathetic nervous system activity usually associated with marked energy restriction. The effects of two levels of energy restriction, with different sodium intakes, on plasma norepinephrine (NE) levels while supine and in response to standing were studied. Twenty-two healthy normotensive obese female subjects (body mass index, 34 ± 1 kg/m^2; weight, 90 ± 2 kg) followed one of three 3-week protocols: 1) total fasting with 80 mmol/day NaCl, 2) a very low energy diet (VLED) containing 1.7 MJ, 93 g protein, and 90 mmol Na/day, with an additional 60 mmol/day NaCl supplement, or 3) total fasting without NaCl (0 Na fast). At the end of the baseline isocaloric diet and of total fasts or VLED, pulse, blood pressure, and plasma NE were measured after 4 h of recumbency and 5 and 10 min after assuming the upright posture. These measurements were repeated after 1 L physiological saline was infused into the 0 Na fast subjects. Cumulative negative sodium balance was observed only in the 0 Na fasting subjects. Supine blood pressure decreased from baseline with fasting, but not with the VLED. The decreases in systolic pressure and increases in heart rate on standing observed with all diets were greatest with the 0 Na fast. Supine plasma NE (*vs.* baseline value) declined ($P < 0.05$) with the VLED, remained unchanged with the Na supplemented fast, but increased with the 0 Na fast ($P < 0.05$). The upright plasma NE values were highest in the 0 Na fast subjects, but lower after the saline infusion as well as in the subjects on the VLED. Thus, the decrease in NE due to energy restriction with normal sodium intake was counteracted by moderate sodium restriction, and levels increased with zero sodium intake. Therefore, sodium depletion can override the suppressive effect of energy restriction and, instead, increase the activity of the sympathetic nervous system, as reflected by plasma NE. (*J Clin Endocrinol Metab* **73:** 975–981, 1991)

THE INTAKES of both energy and sodium have been reported to alter plasma norepinephrine (NE) concentrations and the activity of the sympathetic nervous system (SNS). Indeed, energy restriction in the presence of constant sodium intake is associated with a reduction in the plasma NE concentration in obese subjects (1–4) and animals (5, 6), whereas salt restriction results in increases in plasma NE concentration in humans (7–10). NE turnover in a variety of tissues has been shown to fall with sodium-supplemented fasting and rise with overfeeding in rats (5, 11). Studies of whole body NE kinetics report increases in the NE appearance rate in response to overeating (12) and decreases with sodium-supplemented semistarvation in normal weight (12) and obese (13) subjects. In contrast, when sodium intake is restricted along with energy, increases in both NE appearance and clearance rates accompanied by higher arterial NE levels have been observed (13), whereas limiting sodium intake while providing sufficient energy is associated with a decrease in the NE clearance rate only, accompanied by increases in plasma NE levels that are explained by a fall in the volume of distribution of NE (10).

The decrease in SNS activity induced by Na-supplemented underfeeding (12, 14) has been related to the decrease in resting metabolic rate seen with weight reduction (15), the fall in mean supine arterial pressure (3, 4, 16, 17), and the concomitant development of orthostatic hypotension (16). We have also shown in obese subjects (18) that significant decreases in recumbent and standing mean arterial blood pressures occur after 14 days of total fasting without Na supplementation; however, the plasma NE levels during both supine and upright postures became significantly elevated.

We hypothesized that the previously demonstrated decreases in indices of SNS activity with energy restriction with constant sodium intake could not account for

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the decreased metabolic rate, as claimed, if simultaneous restrictions of energy and salt intake were associated with increased SNS activity (18), and yet the same metabolic responses occur. This suggested that a hierarchy of SNS responses to different stimuli occurs (probably organ and tissue specific), in which maintenance of circulatory status is more important than responses to decreased energy intake and, thus, raises the question of the importance of the SNS in energy expenditure regulation in low energy states. The authors of a recent study of a 2.5 MJ/day diet with sodium restriction arrived at a similar conclusion (13). Most earlier studies employed mild or moderate energy restriction for relatively short periods of time and did not report substantial changes in blood pressure or pulse. We wished to study diets in which ketosis-associated fluid volume losses are substantial and of sufficient duration to obtain maximal and steady state changes. Therefore, to investigate the interactions between sodium and energy intakes in determining net NE, blood pressure, and heart rate responses, we studied the effect on plasma NE (supine and standing) of total fasting with or without sodium supplementation, of an acute saline infusion during the sodium-restricted fast, and of a very low energy, all protein diet (VLED) supplemented with sodium chloride. Metabolic and nitrogen balance responses during the VLED have been reported previously (19).

Materials and Methods

Subjects and procedures

Twenty-two healthy normotensive nonsmoking female obese subjects were admitted to the Clinical Investigation Unit of the Royal Victoria Hospital. Each had been informed of the nature, purpose, and possible risks involved in each study, and written consent was obtained as prescribed by the institutional Human Ethics Committee, which had approved the protocols. The ages of all subjects ranged from 19–49 yr, with a mean of 31.9 ± 2.1 (±SEM) yr. The average weight was 90 ± 2 kg, and the average body mass index 33.7 ± 1.1 kg/m^2. All subjects had normal fasting and postprandial plasma glucose concentrations and were free from clinical and laboratory evidence of hepatic, renal, pulmonary and cardiovascular disease, diabetes, and gout. All had normal electrocardiograms. During the study they were confined to the sedentary life of the hospital ward with no other exercise performed, apart from ambulation within the unit.

All subjects began with an isocaloric baseline 80 mmol/day Na liquid formula diet (Ensure, supplemented in some with Polycose, both from Ross Laboratories, Montreal, Quebec, Canada) for 4–7 days based on the calculated resting metabolic rate × 1.5, according to the Harris-Benedict equation (20). Subsequently, one of three 21-day diet protocols was followed. Group 1 subjects underwent total fasting supplemented with 80 mmol NaCl/day. Group 2 subjects consumed a diet of 1.7 MJ (412 Cal, 90% protein, and 10% carbohydrate)/day supplemented with 60 mmol sodium chloride/day. The protein source was partially hydrolyzed gelatin fortified with L-tryptophan and D,L-methionine and containing 90 mmol sodium (total intake of 150 mmol/day; Bariatrix International, Inc., Dorval, Quebec, Canada). Group 3 subjects underwent total fasting without salt supplementation (0 Na fast). The subjects were not randomized, but the different diets were studied in an overlapping fashion over a period of 18 months.

During the VLED and fasting periods all subjects received a multivitamin-multimineral supplement (Centrum Forte, Cyanamid Canada, Inc., Montreal, Quebec, Canada) and 16 mmol potassium as KCl (Slow K, Ciba Pharmaceutical Co., Dorval, Quebec, Canada) daily. Water intake was at least 1.5 L/day. Coffee, tea, or other beverages were not allowed. After the experimental diets, the subjects were refed, as previously described (21). Vital signs were monitored twice daily; overnight-fasted serum electrolytes, calcium, phosphorus, magnesium, uric acid, liver and kidney function tests, venous blood gases, complete blood counts, as well as electrocardiograms were performed weekly.

Protocol

Studies of plasma NE were performed in the overnight-fasted state at the end of the baseline diet and on day 21 of energy restriction. A 20-gauge Cathlon iv cannula (Critikon Canada, Inc., Markham, Ontario, Canada) was inserted retrogradely into a superficial vein on the dorsum of the hand and was kept patent by a solution of heparin (10 U/mL) in saline. The hand was placed in a box at 60 C to arterialize the blood. Sampling was started after 4 h of recumbency and at least 1 h after cannulation.

Blood samples were drawn, and blood pressure (using a sphygmomanometer with an appropriately sized cuff) and heart rate (by electrocardiogram monitor) were recorded while supine and 5 and 10 min after assuming the upright posture. In group 3 subjects on two occasions, at baseline and at the end of the total fast, the same protocol was repeated twice, separated by a 2-h period during which 1 L saline (154 mmol Na) was infused.

Heparinized blood was added to tubes with 10 μL of a solution that contained 100 mg EGTA/mL and 2.5 mg reduced glutathione/mL blood. Samples were kept on ice and then centrifuged at 4 C, and the plasma was immediately deproteinized with chilled 2 N perchloric acid and then frozen at −70 C until assayed for catecholamines. Heparinized blood was added to other tubes containing aprotinin (10,000 kallikrein inhibitor units/mL; Trasylol, FBA Pharmaceuticals, New York, NY) in a volume one tenth that of the added blood. These samples were cooled and centrifuged at 4 C, and aliquots of plasma were stored at −20 C. Further samples were added to oxalate-fluoride tubes for glucose determinations and to precooled tubes containing perchloric acid for ketone body measurement on the deproteinized supernatant. Urine was collected over 24-h periods and stored at 4 C. After thorough mixing of the total collected, aliquots were analyzed daily for electrolytes (K, Na, and Cl) or frozen at −20 C.

Analytical methods

Each sample was assayed in duplicate for plasma NE concentrations using the radioenzymatic technique of Sole and

Hussain (22). The supine results reported are the mean of two samples drawn 5 min apart. Plasma glucose, plasma FFA, and immunoreactive insulin were measured as previously detailed (20). Perchloric acid supernatants of whole blood were assayed for 3-hydroxybutyrate by an enzymatic microfluorometric method (cited in Ref. 19).

Statistical analysis

Data are presented as the mean and SEM. Statistical analysis was performed on a Hewlett-Packard (Sunnyvale, CA) Vectra computer using the SAS-STAT Software (SAS Institute, Inc., Cary, NC). The data were analyzed using the Waller-Duncan K-ratio *t* tests, when multiple means were compared to baseline and to each other within the same group. Analysis of variance using a repeated measures design was performed using the Primer Biostatistics (McGraw-Hill Co., Montreal, Quebec, Canada) package, with significant differences identified by the Newman-Keuls multiple range test. Student's *t* test for unpaired data was used to compare differences between groups. Results were considered significant at the $P < 0.05$ level.

Results

Weight was maintained during the baseline period. Marked weight loss (9.1 ± 0.4 kg; n = 22) was observed (Table 1). Weight loss was greater with fasting than with the VLED ($P < 0.05$; despite the somewhat higher initial weights of the group 2 subjects), and the rate of weight loss was greater ($P < 0.05$) during the first week than in subsequent weeks of treatment in all groups (Fig. 1). No untoward clinical events occurred. Liver function indices and resting electrocardiograms remained normal.

Serum Na^+ and Cl^- were not affected by treatment. Serum K^+ decreased with all diets, but significantly so only with fasting, though always remaining within the normal range. Serum CO_2 was significantly lower after the total fasting with and without sodium and did not change with the VLED (Table 2). Sodium balances were not different from zero at baseline in the three groups of subjects (not shown). The cumulative sodium losses during the total fast without sodium supplementation in the subjects of group 3 were greater ($P < 0.001$) than those of the groups of subjects supplemented with sodium, in whom balance was maintained (Table 2).

At baseline there were no significant differences among the three groups of subjects in mean recumbent systolic blood pressure or in the magnitude of the decrease in response to standing (data pooled for all groups in Table 3). Furthermore, it was not affected by the saline infusion. It decreased ($P < 0.05$) from baseline with fasting regardless of whether sodium was supplemented, but did not do so with the VLED (Table 3). It declined significantly on standing during all diets; the nadir was at 10 min. The decrease was significantly greater with the 0 Na fast (group 3) and was not affected by the saline infusion. Recumbent diastolic blood pressure decreased significantly with total fasting regardless of whether the subjects were sodium supplemented, but not with the VLED. It did not change significantly with the upright posture.

Recumbent heart rates were not affected by diet or supplementation (Table 3). There was a significant increase in response to upright posture in all groups of subjects. The values reached were greatest during the total fasting without sodium and were not significantly affected by saline infusion. Notably, the Na-supplemented fast standing heart rates were significantly less than those during unsupplemented fasting.

In all groups of subjects, mean plasma glucose decreased ($P < 0.05$) from baseline, and plasma insulin followed the same pattern of change (data not shown). Blood 3-hydroxybutyrate increased markedly from baseline (0.07 ± 0.02 mmol/L) in all subject groups ($P < 0.05$); the values were significantly greater with total fasting and unaffected by sodium supplementation or saline infusion (Fig. 2). Plasma FFA increased ($P < 0.05$) from baseline with all treatments (data not shown).

Plasma NE was significantly altered by the different diet protocols and by upright posture (Fig. 3). To test for an age effect on plasma NE as a possible confounding variable, we sought a correlation between these variables and found none either supine ($r = -0.02$; $P = 0.934$) or upright ($r = 0.140$; $P = 0.579$) at baseline. This was also

TABLE 1. Subject characteristics

	Group 1 (fast, 80 mmol Na)	Group 2 (VLED, 150 mmol Na)	Group 3 (fast, 0 Na)
Dietary energy (MJ/day)	0	1.72	0
Na (mmol/day)			
Supplement	80	60	0
Diet	0	90	0
n	10	6	6
Age (yr)	28.4 ± 3.8	31.3 ± 5.0	34.8 ± 3.5
Initial wt (kg)	89.5 ± 6.3	99.9 ± 2.6	88.4 ± 3.0
Initial BMI (kg/m^2)	33.1 ± 2.3	37.3 ± 1.6	31.0 ± 0.6
Wt loss (kg)	9.8 ± 0.4	7.2 ± 0.3	10.0 ± 0.4

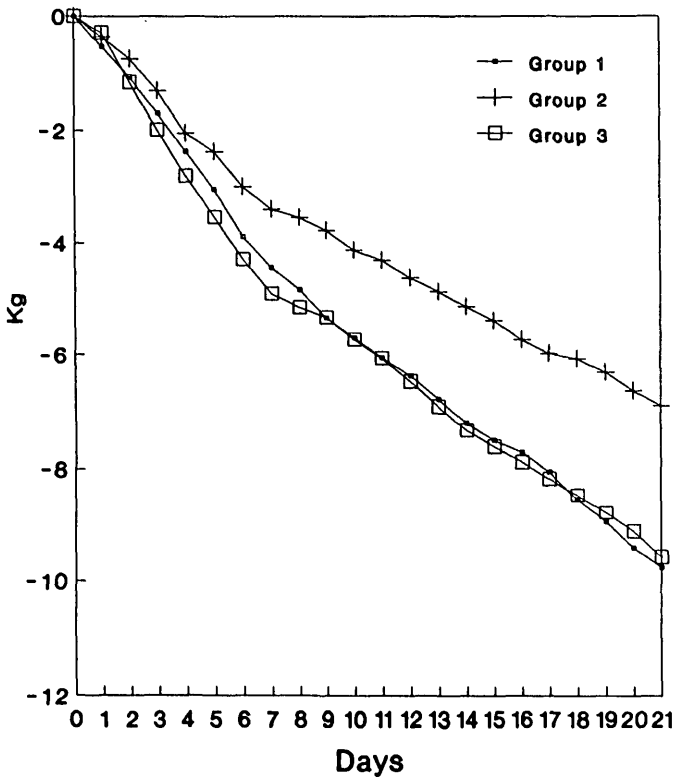

FIG. 1. Mean cumulative weight change in the three groups of subjects over the 21-day study periods. Group 1 (■—■) subjects underwent fasting with 80 mmol Na, and group 3 (□—□) subjects underwent 0 Na fasting, whereas group 2 (+—+) subjects consumed the 1.7 mJ/day all-protein diet. Time zero is taken as the weight at the end of the 4- to 7-day isocaloric formula diet period.

the case within each group. At baseline, mean supine plasma NE values did not differ significantly among groups. The overall mean NE increased ($P < 0.05$) from 1.28 ± 0.1 nmol/L supine to 2.8 ± 0.3 nmol/L after standing for 5 min and to 2.7 ± 0.2 nmol/L after 10 min. Supine plasma NE was significantly higher (1.76 ± 0.2 nmol/L; group 3) as an effect of the total fast without sodium, whereas it did not change when the total fast was supplemented with sodium (1.48 ± 0.21 nmol/L; group 1). In contrast, it was significantly lower with the VLED (0.89 ± 0.09 nmol/L). Although recumbent plasma NE was higher with the sodium-restricted fast, after saline infusion it was no longer significantly higher than the baseline mean or the mean of group 1.

There was a significant increase in plasma NE in response to upright posture after 5 and 10 min in all groups (Fig. 3). The mean values reached were significantly higher during the total fast without sodium than during the sodium-supplemented fast, the VLED, and the baseline diet. After saline was infused into the fasted (group 3) subjects, the plasma NE values reached while standing were significantly lower ($P < 0.05$) than those observed before the infusion.

Discussion

The desired end points of energy restriction with and without sodium restriction were achieved. In addition, the unsupplemented fasted subjects showed marked alterations in the cardiovascular variables measured. No net Na loss was found in the supplemented fasting subjects over the 21 days. Sodium chloride supplementation had no measurable effect on the metabolic adaptation to fasting, as assessed by urine nitrogen or ketone bodies, plasma glucose, insulin, FFA (data not shown), or blood ketone bodies. We had previously found that sodium chloride supplements greater than 80 mmol/day were not tolerated for more than a few days by totally fasted subjects. Therefore, the subjects receiving the VLED allowed us to maintain a high sodium intake in a setting with sufficient energy restriction to produce an equivalent fat loss as with fasting (20), although with less

TABLE 2. Cumulative Na balance and serum electrolytes and CO_2 in response to treatment

	Group 1 (fast, 80 mmol Na)	Group 2 (VLED, 150 mmol Na)	Group 3 (fast, 0 Na)
Na balance (mmol)	+30 ± 45	+10 ± 9	−594 ± 24[a]
Serum Na^+ (mmol/L)			
Baseline	139.8 ± 0.5	141.0 ± 0.6	141.2 ± 0.3
Posttreatment	141.0 ± 0.7	141.8 ± 0.5	141.4 ± 0.7
Serum Cl^- (mmol/L)			
Baseline	106.4 ± 0.9	106.3 ± 1.0	105.8 ± 0.8
Posttreatment	108.0 ± 1.4	105.8 ± 1.0	106.2 ± 0.9
Serum K^+ (mmol/L)			
Baseline	4.07 ± 0.13	4.35 ± 0.15	4.36 ± 0.05
Posttreatment	3.64 ± 0.11[b]	4.08 ± 0.12	3.70 ± 0.08[b]
Serum CO_2 (mmol/L)			
Baseline	22.0 ± 0.6	24.6 ± 0.7	26.6 ± 2.2
Posttreatment	16.4 ± 1.5[b]	22.2 ± 0.4	18.4 ± 0.2[b]

[a] $P < 0.001$ *vs.* all other groups.
[b] $P < 0.05$ *vs.* baseline.

TABLE 3. Blood pressure and heart rate responses

Group	Systolic blood pressure (mm Hg)			Diastolic blood pressure (mm Hg)			Heart rate (beats/min)		
	Supine	Standing		Supine	Standing		Supine	Standing	
		5 min	10 min		5 min	10 min		5 min	10 min
Baseline (all subjects)	117 ± 2	113 ± 2	107 ± 3[a]	77 ± 1	81 ± 2	78 ± 3	72 ± 2	90 ± 2[a]	86 ± 3[a]
1 (fast, 80 mmol Na)	102 ± 3[b]	94 ± 2[b]	89 ± 5[a]	73 ± 2[b]	76 ± 2	70 ± 3	71 ± 1	94 ± 4[a,c]	87 ± 4[a,c,d]
2 (VLED, 150 mmol Na, 60 mmol NaCl)	114 ± 3	107 ± 6[c,e]	96 ± 3[a,c]	73 ± 3	76 ± 4	71 ± 3	65 ± 2	97 ± 6[a]	102 ± 3[a,c]
3 (fast, 0 Na)									
Preinfusion	102 ± 2[b]	86 ± 6[a,b]	77 ± 5[a,b]	69 ± 4[b]	75 ± 3	69 ± 3[b]	69 ± 3	115 ± 6[a,b]	127 ± 4[a,b]
Postinfusion	102 ± 3[b]	87 ± 7[a,b]	86 ± 7[a,b]	64 ± 3[b,f]	68 ± 2		70 ± 2	104 ± 8[a,b]	118 ± 5[a,b]

[a] $P < 0.05$ *vs.* supine.
[b] $P < 0.05$ *vs.* baseline.
[c] $P < 0.05$ *vs.* fast 0 Na, preinfusion.
[d] $P < 0.05$ *vs.* all other diet or fasting treatments.
[e] $P < 0.05$ *vs.* fast with 80 mmol Na.
[f] n = 2.

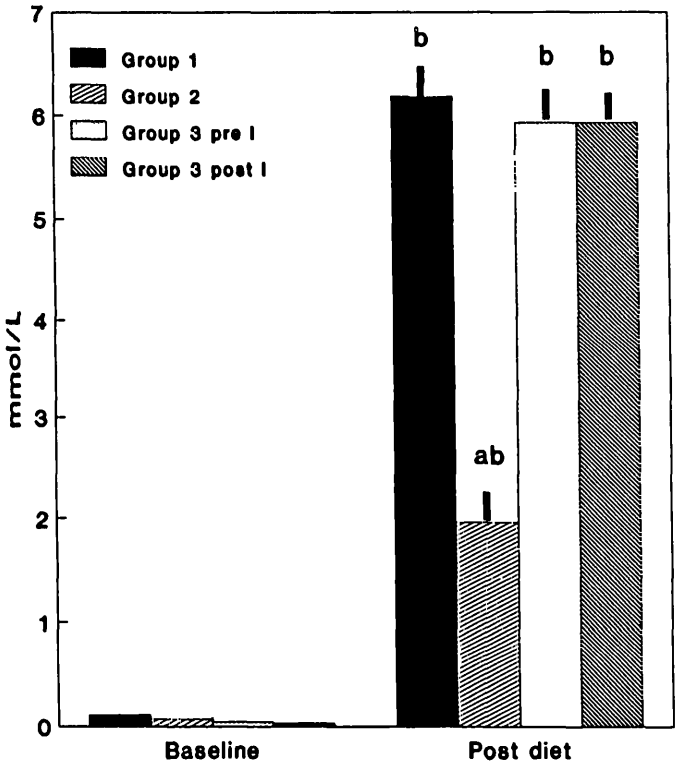

FIG. 2. Blood 3-hydroxybutyrate concentrations at the end of the baseline isocaloric diet, after 21 days of the 1.7 MJ/day protein diet (group 2), and after total fasts (group 1, 80 mmol Na; group 3, 0 Na). In group 3 subjects, values are given both before (pre I) and after (post I) the infusion of 1 L saline. Data are presented as the mean ± SEM. a, $P < 0.05$ *vs.* values in subjects of the total fast groups (groups 1 and 3); b, $P < 0.05$ *vs.* baseline value for the same group.

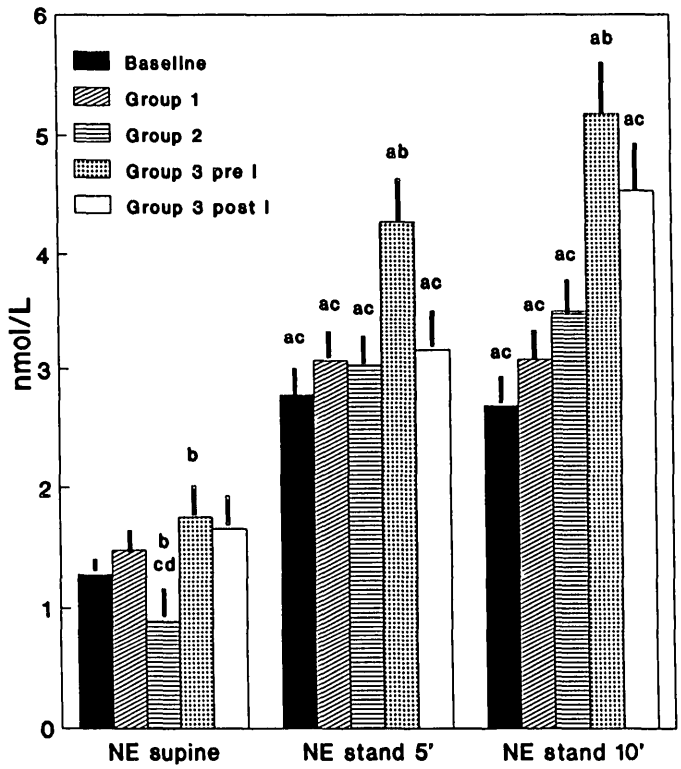

FIG. 3. Plasma NE concentrations in the supine position and 5 and 10 min after assuming the upright posture in the subjects of groups 1 (fast plus 80 mmol Na), 2 (1.7-MJ diet), and 3 (0 Na fast). Pooled data for all subjects at the end of the baseline diet are presented, and in group 3, data are shown before (pre I) and after (post I) the infusion of 1 L saline. Data are presented as the mean ± SEM. a, $P < 0.05$ *vs.* the corresponding supine value of the same group; b, $P < 0.05$ *vs.* the response at the same time point for the baseline diet; c, $P < 0.05$ *vs.* group 3 (pre I); d, $P < 0.05$ *vs.* group 3 (post I).

ketosis.

Fasting was associated with a decrease in systolic blood pressure, both supine and standing, compared to baseline values; the lowest values were observed during fasting without salt supplementation. Salt restriction induces volume depletion, lowers blood pressure, and stimulates a SNS response to increase peripheral vascular resistance

and cardiac output to maintain blood pressure (23, 24). Volume depletion, as suggested by the negative sodium balance in the nonsupplemented fasting group 3 subjects, was indeed associated with the highest observed plasma NE levels, comparable to values previously found (18, 24). Rapid sodium administration attenuated the markedly greater plasma NE rise with standing. However, blood pressure, recumbent or upright, did not differ from preinfusion values. It is possible that the amount infused was insufficient to affect the blood pressure response (24). However, the standing heart rates were highest with the unsupplemented fast and were decreased by sodium supplementation.

Jung *et al.* (3) have explained the reduction in blood pressure during energy-restricted diets with constant salt intake by a concomitant fall in plasma NE, an argument not applicable to our subjects of group 1, since supine plasma NE did not decrease. The hypotensive effect of energy deficits has also been attributed to a fall in blood volume (4). This being the case, one might predict either a compensatory rise, or at least a maintenance of NE levels, as we have observed. The supplement of 80 mmol sodium/day during fasting although associated with significantly lower ($P < 0.005$) weight loss with 0 Na on day 8 than fasting (5.4 ± 0.2 *vs.* 4.6 ± 0.1 kg) was insufficient to prevent the early fall in blood volume (occurring in the first 8 days) that would explain the hypotensive effect of the energy deficit (4) and the maintenance of NE levels during fasting. It would also explain the worst case we observed, resulting from volume loss associated with zero energy and sodium intake, in which NE concentrations were the highest, yet apparently unable to maintain normal blood pressure responses despite the marked tachycardia. Indeed, it is probable that some initial sodium and fluid volume losses with any substantial energy (and especially carbohydrate) restriction would occur even with greater sodium supplementation. This is suggested by the considerably greater weight losses in the first 8 days compared with later in all groups of subjects of the present study.

Since certain of the responses measured result from the interaction of NE with its receptors, the states of such receptors and the possible effects of obesity *per se* and of diets upon them need to be considered as well. Cignarelli *et al.* (13) also showed increased SNS activity in obese subjects (increased NE appearance and clearance by a nonradioactive NE infusion method, and increased arterial NE and urinary excretion) with combined energy (2.51 MJ/day) and sodium (9 mmol/day) restrictions compared to that with energy restriction alone. They found decreased β-adrenergic receptor numbers on circulating mononuclear cells, suggesting that if such responses also occurred on other cells, they would be consistent with decreased peripheral sensitivity to catecholamines (25).

Stimulation with standing would be expected to require a greater response from the SNS if blood pressure is to be maintained in presence of sodium depletion. This may explain in part the lower blood pressure observed in response to standing in group 3 subjects. Such increases in plasma NE during sodium restriction in the human have been explained by a decrease in the MCR due to a fall in the volume of distribution (10, 26), which might render the use of plasma NE as an indicator of SNS activity less valid, especially since changes in specific circulatory beds may not be reflected in the total blood volume that is sampled. However, it has also been explained by increases in the apparent release rate of NE (27). Using the data of published studies, we have found a significant direct linear correlation between reported rates of NE appearance and plasma NE, in settings where both energy and sodium were restricted (n = 4; means of 8 subjects; r = 0.993; $P = 0.007$) (13), where sodium intakes were modified (n = 3; means of 80 subjects; r = 0.998; $P = 0.042$) (27), or where sodium intake was modified and responses to upright position evaluated (n = 4 groups of subjects; r = 0.989; $P = 0.01$) (10). This suggests that in the type of study we report, plasma NE values may be related to NE release rates.

The response to VLED was characterized by significantly lower supine and lesser increments in plasma NE levels, associated with smaller postural declines in systolic blood pressure than those during fasting. In the study of another all-protein ketogenic diet (16), the greater lowering of systolic blood pressure could be explained by the Na intake being 54 mmol/day, one third that of the present study. Others (28, 29) have demonstrated significant reductions in blood pressure in the obese during weight reduction regardless of salt intake. Thus, other factors are likely to play a role in blood pressure regulation during weight reduction, including plasma renin, aldosterone, and others.

We conclude that combined energy and sodium restriction prevented the decrease in plasma NE associated with energy restriction in the presence of a maintained sodium intake, and that marked restriction of both is associated with increased plasma NE. Although we recognize it to be desirable and are currently measuring [^{3}H]NE turnover in such states, our results indicate that the activity of the sympathetic nervous system, as reflected by circulating NE, responds to both sodium and energy restrictions, with sodium suggested to be the dominant modulator when both are restricted simultaneously. The metabolic indicators assessed in this study as well as the weight losses after the initial week suggested that sodium intake had little effect on the overall metabolic response. This being the case (unless there are decreases in sympathetic tone in territories receiving

innervation that selectively affects thermogenesis that are not reflected in plasma NE), the present results suggest that NE may not be a central regulator of the metabolic responses to VLED or fasting.

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