Short- and Long-Term Neuroadrenergic Effects of Moderate Dietary Sodium Restriction in Essential Hypertension

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Background—In essential hypertension, marked restrictions in dietary sodium intake cause in the short-term period an increase in muscle sympathetic nerve traffic (MSNA) and a baroreflex impairment. The present study was set out to assess on a long-term basis the neuroadrenergic and reflex effects of moderate sodium restriction.

Methods and Results—In 11 untreated mild to moderate essential hypertensive patients (age 42.0 ± 2.6 years, mean$\pm$SEM), we measured beat-to-beat blood pressure (Finapres), heart rate (ECG), and MSNA (microneurography) at rest and during stepwise intravenous infusions of phenylephrine and nitroprusside. Measurements were performed at regular sodium intake, after 1 and 8 weeks of low-sodium diet (80 mmol NaCl/d), and repeated again at regular sodium intake. After 1 week, urinary sodium excretion was markedly reduced. This was accompanied by a slight blood pressure reduction, no heart rate change, and a significant increase in plasma renin activity, aldosterone, and MSNA ($+23.0\pm4.6\%$ $P<0.05$). Whereas baroreflex heart-rate control was unchanged, baroreflex modulation of MSNA was reduced by $46.8\pm5.1\%$ ($P<0.01$). At the end of the 8-week low-sodium diet, the neurohumoral and baroreflex responses were similar to the ones after 1 week of the dietary intervention. All changes disappeared when regular sodium diet was restored.

Conclusions—Thus, a moderate dietary sodium restriction triggers a sympathetic activation and a baroreflex impairment. Maintenance of low-sodium diet for several weeks does not attenuate these adverse adrenergic and reflex effects. (***Circulation***. 2002;106:1957-1961.)

Key Words: hypertension ■ sodium ■ nervous system, sympathetic ■ nervous system, autonomic ■ baroreceptors

S everal studies have shown that in essential hypertensive patients, a marked restriction in dietary sodium intake is accompanied by a clear-cut reduction in blood pressure (BP) but also by a sympathetic activation, as documented by an increase in urinary norepinephrine levels, plasma norepinephrine concentrations, norepinephrine spillover from the renal circulation, and efferent postganglionic sympathetic nerve traffic to the skeletal muscle vascular district.[1–6] Evidence has also been provided that under this circumstance there can be an impairment in the baroreceptor modulation of vagal and sympathetic cardiovascular outflow,[6–8] leading to a 2-fold conclusion. First, in hypertension, a marked reduction in dietary sodium content additionally enhances the sympathetic hyperactivity characterizing several patients with a high BP state,[5,9–12] thereby aggravating its undesirable cardiovascular, metabolic, and hemorheologic effects.[13,14] Second, this occurs at least in part because of the impairment of a reflex mechanism of fundamental importance both for restraining sympathetic tone and for maintaining BP homeostasis.[15]

Whether a more moderate restriction in dietary sodium intake triggers neuroadrenergic and reflex alterations similar to the ones seen during a marked sodium restriction is less certain. Because in most previous studies the dietary intervention was short lasting, it is also uncertain whether this popular nonpharmacological antihypertensive approach is accompanied by the above alterations just in its early phase or on a more chronic basis. This is because several studies have confined the dietary manipulation to a few days only. It is also because in more long-term studies sympathetic activation usually has been quantified by urinary or plasma norepinephrine values, ie, on variables that may increase because of a reduced tissue clearance triggered by a sodium-dependent reduction in blood volume and flow rather than by a greater secretion from the sympathetic nerve terminals.[16] The present study was aimed at addressing these two issues by examining in hypertensive individuals both the short- and the long-term effects of a moderate restriction in sodium intake on muscle sympathetic nerve traffic (MSNA) as directly quantified by

microneurography and MSNA and heart rate (HR) responses to arterial baroreceptor stimulation and deactivation.

Methods

The present study included a total of 27 never-treated male outpatients with mild or moderate essential hypertension, ie, with diastolic BP between 95 and 109 mm Hg on repeated sphygmomanometric measurements, no history or physical or laboratory evidence of cardiovascular disease or major target organ damage, such as congestive heart failure, coronary heart disease, stroke, peripheral artery disease, renal insufficiency, or echocardiographic left ventricular hypertrophy, and no major noncardiovascular diseases. However, because in 11 patients compliance to sodium restriction was poor and in 5 patients MSNA recording (see below) was unsatisfactory, the study was successfully completed in 11 subjects. These subjects had a body mass index <25 kg/m^2, an age ranging from 29 to 51 years (mean$\pm$SEM, 42.0$\pm$2.6 years), a sedentary lifestyle, no smoking habits, and no history of excessive alcohol consumption. The ethics committee of our institution approved the protocol of the study. The patients agreed to participate in the study after explanation of its nature and purpose.

Dietary Regimens and Measurements

In each patient, 4 experimental sessions were sequentially carried out. The first session was performed after 1 week of regular (220 mmol NaCl/d) sodium diet; the second and third sessions, respectively, after 1 week and 8 weeks of moderately low-sodium (80 mmol sodium chloride pro die) diet, and the fourth session after 1 additional week of regular sodium diet. Both the regular and the moderately low-sodium diets were designed to contain 100 mmol potassium pro die and to be isocaloric, ie, to contain 50% carbohydrates, 18% proteins, and 32% fats.

Patients were asked to continue their usual daily activities during the entire period of the study (10 weeks). In each individual, 24-hour urinary sodium and potassium excretion, electrolytes plasma concentration, BP (sphygmomanometry, 3 measurements in the sitting position), HR (palpatory method), and body weight were measured after the initial week of regular sodium intake, after the first, third, fifth, and eighth week of the moderately low-sodium diet, and after the final week in which regular sodium intake was restored.

During the 4 experimental sessions, the following additional measurements were obtained: (1) beat-to-beat BP through a finger photoplethysmographic device (Finapres 2300, Ohmeda) capable of providing accurate and reproducible systolic and diastolic values[6,12,17]; (2) beat-to beat HR through a cardiotachometer triggered by the R wave of an ECG lead; (3) respiration rate through a strain-gauge pneumograph, positioned at the midchest level; (4) plasma renin activity and aldosterone (radioimmunoassay),[18,19] norepinephrine, and epinephrine (high-pressure liquid chromatography)[20] on a venous blood sample taken from an antecubital vein; and (5) multiunit recording of efferent postganglionic MSNA, obtained from a microelectrode directly inserted in the right or left peroneal nerve posterior to the fibular head, as previously described.[5,6,12,17] Integrated nerve activity was monitored by a loudspeaker, displayed on a storage oscilloscope (model 511A, Tektronix), and recorded together with BP, HR, and respiratory rate on an ink polygraph. The muscle nature of MSNA was assessed according to the criteria outlined in previous studies,[5,6,12,17] and the recording was considered acceptable if the signal-to-noise ratio exceeded a value of 3. Under baseline conditions, MSNA was quantified as bursts per minute, bursts per 100 heartbeats, and integrated MSNA (bursts per minute times mean burst amplitude expressed in arbitrary units). Quantification of MSNA by this integration was shown to be highly reproducible, ie, to differ by only 3.8% when assessed on the same tracing on 2 separate occasions by a single investigator.[17]

Baroreceptor modulation of MSNA and HR was studied by incrementally infusing in an antecubital vein phenylephrine (0.3, 0.6, and 0.9 μg/kg per minute) and nitroprusside (0.4, 0.8, and 1.2 μg/kg per minute), respectively, each dose infusion lasting 5 minutes. Mean BP (diastolic plus one third of pulse pressure), MSNA, and HR values were averaged for the 5 minutes before infusion and for the 5 minutes of each dose infusion. The percent change in integrated MSNA and the absolute change in HR in relation to the mean BP change was calculated for each dose of vasoactive drugs infused and averaged for the 3 doses of phenylephrine and nitroprusside. The latter was used as an overall index of baroreflex sensitivity for a BP range from above to below baseline.

A cold pressor test was performed by immersion of the hand contralateral to that used for BP measurements in iced water (3°C) for 2 minutes. Mean BP, HR, and integrated MSNA were averaged for the 5 minutes before the immersion and compared with the average values during the maneuver.

Protocol and Data Analysis

All experimental sessions were performed in the morning. After a light breakfast, the subject was put supine and fitted with an intravenous cannula, the microelectrodes for MSNA recording, and the other measuring devices. This was followed by withdrawal of a blood sample and a 30-minute interval. BP, HR, respiration rate, and MSNA were then continuously monitored during the following: (1) a 10-minute baseline state; (2) the infusion of one vasoactive drug; (3) a second 10-minute baseline state; (4) the infusion of the second vasoactive drug; (5) a 5-minute baseline state; and (6) a cold pressor test. In any given subject, the vasoactive drug to be infused was selected randomly at the time of the first session. A 45-minute recovery period was always allowed between the end of the first drug infusion and the beginning of the second one and between the end of the second drug infusion and the performance of the cold pressor test.

Data were calculated by a single investigator unaware of the experimental design. Baseline BP, HR, respiration rate, and MSNA obtained in individual subjects were averaged for the group as a whole, separately for each experimental session. This was done also for plasma and urinary biohumoral values and for changes in the above variables induced by vasoactive drugs and by cold pressor test. Comparisons between data obtained in each experimental session were made by 2-way ANOVA. The Spearman analysis was used to correlate changes in different variables. $P<0.05$ was taken as the level of statistical significance. Throughout the text, the symbol $\pm$ refers to the SEM.

Results

Baseline Values

The Table shows that compared with the initial regular sodium diet, moderate sodium restriction caused a reduction in 24-hour urinary sodium excretion that remained constant throughout the 8 weeks of the dietary modification. Twenty-four-hour urinary potassium excretion, serum electrolyte concentrations did not show any significant change, this being the case also for body weight and HR. Sphygmomanometric systolic and diastolic BP were slightly reduced, the reduction being statistical significant after the first week of the dietary intervention. When the regular sodium diet was restored, the altered variables returned to the control prediet values.

Figure 1 shows baseline data obtained during the 4 experimental sessions. Compared with the initial regular sodium diet, sodium restriction did not affect respiration rate. There was a short-term and a more prolonged increase in plasma renin activity and aldosterone. Supine beat-to-beat systolic and diastolic BP showed a concomitant modest reduction. Both when expressed as bursts incidence over time and as bursts incidence corrected for HR, MSNA showed a clear-cut increase after 1 week of sodium restriction (that involved 10 out of 11 patients) and was maintained unchanged when the

Baseline Hemodynamic and Humoral Variables, Body Weight, and Serum and Urinary Electrolytes With Diets Containing Different Sodium Content

Variable	Initial Regular Sodium Diet (220 mmol NaCl/d)	Moderate Sodium Restriction Diet (80 mmol NaCl/d)				Final Regular Sodium Diet (220 mmol NaCl/d)
		1st Week	3rd Week	5th Week	8th Week	
Sphygmo systolic BP, mm Hg	146.1±2.2	142.7±2.5	140.2±2.4*	139.4±2.4*	138.9±2.4*	145.5±2.3
Sphygmo diastolic BP, mm Hg	104.3±2.4	102.9±2.7	100.8±2.5*	101.3±2.4*	99.8±2.5*	104.7±2.5
Heart rate, bpm	67.3±2.1	69.1±2.4	67.9±2.6	68.8±2.5	68.4±2.4	67.8±2.3
Body weight, kg	72.7±1.9	72.5±2.0	72.3±2.2	70.8±2.3	70.4±2.3	71.5±2.0
Serum sodium, mmol/L	142.5±2.2	141.7±2.3	142.0±2.3	141.5±2.4	141.4±2.2	142.0±2.3
Serum potassium, mmol/L	4.2±0.2	4.3±0.2	4.2±0.2	4.1±0.3	4.1±0.2	4.3±0.3
24-Hour urinary sodium, mmol/d	211.5±17	75.6±18†	80.3±13†	78.8±15†	82.4±16*	218.1±19
24-Hour urinary potassium, mmol/d	62.8±4.1	65.6±6.0	66.4±11	75.7±1.3	80.0±13	61.0±5.8

Values are shown as mean±SEM in 11 subjects.
*$P<0.05$; †$P<0.01$ vs initial regular sodium diet.

dietary manipulation was prolonged to 8 weeks. This was the case also for plasma norepinephrine and epinephrine levels, although the epinephrine increase was significant only after 1 week of sodium restriction. All changes disappeared after the final restoration of the regular sodium intake.
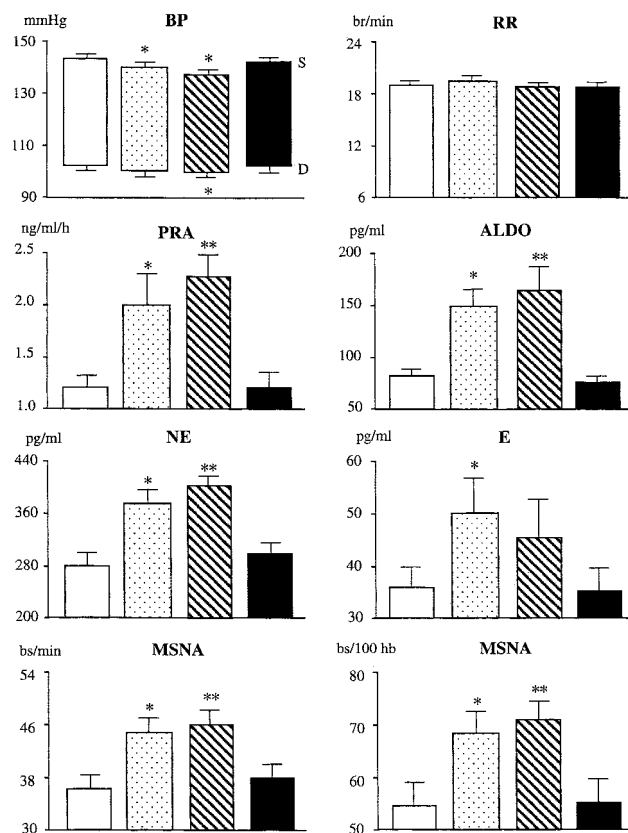

Figure 1. Mean (±SEM) values of systolic (S) and diastolic (D) BP, respiration rate (RR), plasma renin activity (PRA), plasma aldosterone (ALDO), plasma norepinephrine (NE), plasma epinephrine (E), and MSNA, expressed as bursts/min (bs/min) and as bursts/100 heartbeats (bs/100 hb) during regular (open bars), moderately low (first week: dotted bars; eighth week: dashed bars), and again regular (closed bars) sodium diet. Asterisks (**$P<0.01$) refer to the level of statistical significance between data obtained during regular and moderately low-sodium diets.

Baroreflex Responses

As shown in Figure 2, during the initial regular sodium diet, the stepwise infusion of phenylephrine caused a progressive increase in mean BP, a progressive decrease in HR, and a progressive reduction in MSNA, whereas the stepwise infusion of nitroprusside had opposite effects. This was the case also during the early and late experimental sessions performed during dietary sodium restriction. However, whereas the magnitude of the reflex HR changes was slightly and nonsignificantly reduced, the magnitude of the reflex MSNA changes induced by the different doses of vasoactive drugs was always clearly and significantly less than that observed during the preceding regular sodium diet. Similar findings were obtained for the overall sensitivity of the baroreceptor-MSNA reflex, which was reduced by 46.8±4.1% and 51.4±5.2% during the early and late phases of sodium restriction, respectively. The attenuation of the baroreflex modulation of MSNA disappeared when regular sodium diet was restored.

During the regular sodium diet, cold pressor test caused an increase in mean BP (+11.0±2.4 mm Hg), HR (+9.8±1.7 bpm), and MSNA (+61.4±9%). For each variable, the increase was similar at the first (+11.8±2.6 mm Hg, +10.5±1.8 bpm, and +76.7±12%) and at the eighth (+10.3±2.5 mm Hg, +11.3±2.0 bpm, and +75.3±13%) weeks of the moderately low-sodium diet as well as at the restoration of the regular sodium diet (+11.5±2.5 mm Hg, +11.5±2.4 bpm, and +66.0±10%).

Correlations

The MSNA increase (bursts corrected for HR) induced by sodium restriction was significantly related to the concomitant increase in plasma norepinephrine both after 1 and 8 weeks ($r=0.55$, $P<0.01$ and $r=0.47$, $P<0.02$, respectively). A significant relationship was also seen between the MSNA increase and the attenuation of the baroreflex sensitivity seen at the first and eight weeks of the dietary intervention ($r=0.51$, $P<0.02$ and $r=0.46$, $P<0.04$). On the other hand, no relationship was seen between the sodium restriction-related increase in MSNA and the concomitant changes in plasma renin activity, plasma aldosterone, 24-hour urinary
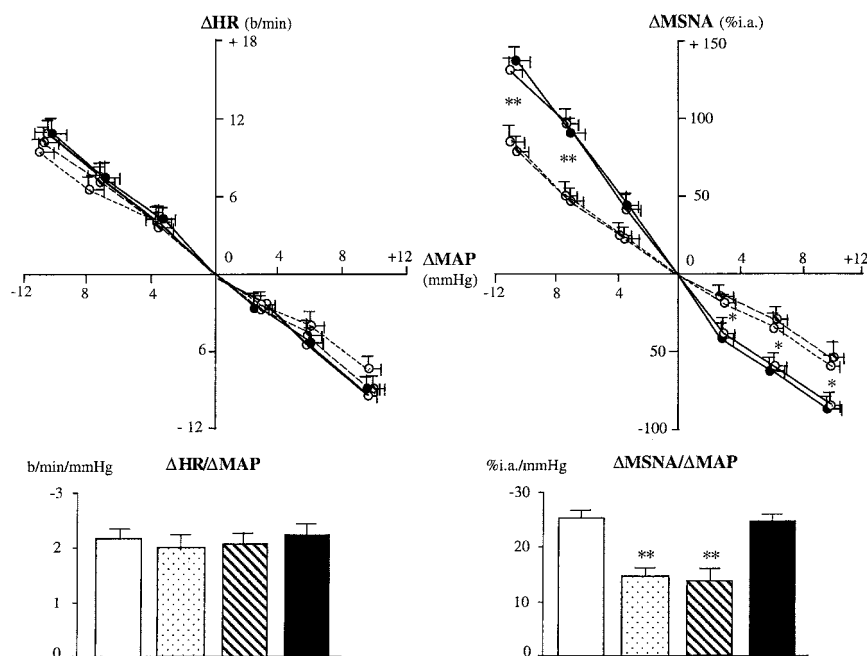
Figure 2. Top, Plots showing changes in heart rate (ΔHR), expressed as beats per minute (b/min), and in MSNA (ΔMSNA), expressed as percent integrated activity (% i.a.), accompanying stepwise increases and reductions in mean arterial pressure (ΔMAP), induced by intravenous infusion of phenylephrine or nitroprusside during regular (continuous lines, open symbols), moderately low (first week: dotted lines, eighth week: dashed lines), and again regular (continuous lines, closed symbols) sodium diet. Asterisks (*$P<0.05$, **$P<0.01$) refer to the statistical significance between responses observed at each step. Bottom, Average values of baroreflex sensitivity for HR (left) and MSNA (right) during regular (open bars), moderately low (first week, dotted bars; eighth week, dashed bars), and again regular (closed bars) sodium diet. Asterisks (**$P<0.01$) refer to the level of statistical significance between data obtained during regular and moderately low-sodium diets.

sodium excretion, and plasma epinephrine (r never >0.31, $P=$NS). This was the case also for the MSNA or the norepinephrine increase and the change in systolic or diastolic BP (r never >0.27, $P=$NS).

Discussion

Our study shows that in hypertensive patients, a moderate reduction in sodium intake (80 mmol/d) is accompanied by a clear-cut increase ($+23\%$) in sympathetic outflow to the skeletal muscle district. It also shows that this increase is not limited to the initial phase of this nonpharmacological intervention but persists unchanged for several weeks thereafter. Thus, sympathetic activation is triggered not only by a drastic but also by a moderate hyposodic diet, under which circumstance the activation takes place rapidly and does not show any attenuation with time. This allows us to conclude that a sympathoexcitatory effect is likely to be a characteristic, though undesirable, feature of a nonpharmacological approach commonly used as first-line antihypertensive treatment.

Our study also provides an insight into the mechanisms involved in the sympathetic hyperactivity induced by moderately restricting sodium intake. First, the clear-cut increase in plasma renin activity accompanying this therapeutic intervention did not bear any relationship with the increase in MSNA, suggesting that the well-known ability of angiotensin II to stimulate the sympathetic nervous system[21,22] played no major role. Second, the MSNA increase did not bear any relationship with the concomitant increase in plasma aldosterone, suggesting that the sympathostimulating influence of this humoral substance[22,23] was also not involved. Third, and more importantly, the sodium intake restriction used in the present study was associated with a persistent attenuation of the MSNA responses to baroreceptor stimulation and deactivation. Furthermore, there was a significant correlation between the reduction in baroreflex sensitivity and the concom-

itant MSNA increase both in the initial and in the later phase of this nonpharmacological intervention, with no concomitant impairment, however, of the MSNA responses to cold pressor test. This implies that reducing sodium intake persistently and rather specifically impairs a reflex of fundamental importance for BP homeostasis also when the reduction is not drastic, as reported in previous animal and human studies,[24–27] but just moderate. It additionally implies that the sympathostimulating effect of a moderate sodium restriction may originate from a reduced ability of this reflex to restrain sympathetic tone, thereby also supporting a role of the baroreflex not only in buffering short-term alterations in MSNA but also in determining its long-term steady-state level. This of course does not rule out the participation of additional mechanisms not tested in the present study. Sodium restriction, for example, causes insulin resistance[28]; this may result from sympathetic activation[29] but in turn also favors it through sympathoexcitatory influence of the increased insulin levels.[30,31] It also causes a reduction of central venous pressure,[6] which may lead to sympathoactivation via unloading of cardiopulmonary receptors.[15]

Several other findings of our study deserve to be mentioned. First, the increase in MSNA induced by moderately restricting sodium intake was accompanied by an increase in plasma norepinephrine, to which it was significantly related. This implies that the latter is not attributable to a reduced tissue clearance but to a true increase in sympathetic outflow.[16] It also implies that this increase probably involves districts other than the skeletal muscle one. Visceral districts are presumably involved because in our patients sodium restriction also increased plasma epinephrine, although less sustainedly than plasma norepinephrine, and a drastic reduction in sodium intake has been reported to cause in man an increase in renal norepinephrine spillover.[4] Whether the heart is also involved is impossible to conclude from our data, because, although sodium restriction is not accompanied by

tachycardia, resting HR is a very insensitive marker of adrenergic drive.[32] Second, at variance from the baroreceptor-sympathetic reflex, the moderate reduction in sodium intake used in the present study was not accompanied by any initial or later impairment of the baroreceptor-HR reflex. We can speculate this to result from the fact that in mild or moderate hypertension (the condition addressed in our study), the baroreceptor-MSNA reflex is preserved whereas the baroreceptor-HR reflex is already impaired,[6] thus limiting the chance of an additional impairment to be detected. Another possibility is that vagal influences on the sinus node (on which the baroreflex modulation largely depends) are less sensitive to sodium restriction than adrenergic influences, which play only a minor role at cardiac level. Third, our results have a clinical implication, because the persistent sympathoexcitatory effect of sodium restriction may hamper the BP-lowering effects of this intervention, thereby being involved in its overall small hypotensive effects[33] as well as in the BP unresponsiveness or increase it shows in a number of individuals,[33,34] and aggravate the sympathetic hyperactivation already present in essential hypertension, thus enhancing its undesirable hemodynamic, metabolic, and structural consequences.[13,14] We can speculate that this may account, at least in part, for the recently reviewed adverse association between dietary sodium restriction or low sodium serum concentration and cardiovascular mortality.[35]

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