Sodium Intake Alters the Effects of Norepinephrine on Blood Pressure

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SUMMARY To examine the interactions between sodium balance and the sympathetic nervous system, we studied eight normotensive men after high (800 mEq/day) and low (10 mEq/day) sodium intake. We measured blood pressure (BP), arterial, venous, and urinary norepinephrine (NE) before and during incremental infusion of NE. We found significant direct, linear relationships (p < 0.001) between the dose of NE infused and arterial and venous NE levels, and with mean arterial BP at both levels of sodium balance. In addition, the sensitivity was greater and the threshold of pressor response to NE as well as the basal concentrations of NE in arterial and venous plasma significantly lower (p < 0.05) after the high sodium period. These observations expose heretofore unrecognized qualitative and quantitative interactions between sodium balance and NE that are capable of influencing BP in man. (Hypertension 3: 650-656, 1981)

KEY WORDS • sympathetic nervous system • salt loading • pharmacodynamics

The control of arterial blood pressure (BP) is complex. Evidence suggests that sodium intake influences the BP in a variety of ways; an excess can lead to increased cardiac output, thereby increasing the BP, and an altered sodium balance can in turn alter the dose-response characteristics of vasoactive hormones. We have previously reported that large increases in dietary sodium intake can increase the BP of normotensive men. Components of the sympathetic nervous system such as plasma and urinary norepinephrine (NE) levels exhibited an incomplete reduction at increasing levels of sodium intake. Further, we observed a relationship between plasma and urinary levels of NE and BP during salt loading.

In this study we examined the effect of low and high sodium intake on the pressor responses to administered NE in normotensive men. We also examined both arterial and venous NE concentration in order to evaluate the effect of sodium balance on the pharmacodynamics of NE. These studies substantiate an important role for the state of sodium balance in the pressor response to exogenous NE. In addition, our observations further document the vascular compartmentalization of the metabolism of NE and provide information about the adaptive changes that occur in response to sodium restriction or loading.

Methods

After obtaining approval from the Indiana University Human Use and Clinical Research Center Committee, we recruited eight normotensive men by advertisement. Their ages ranged from 24 to 38 years. They had no history of serious illness or family history of hypertension. Informed consent was obtained after explanation of the procedures to be performed.

The protocol was conducted with each subject in equilibrium after low and high levels of sodium (Na) intake. The basic diet was constant throughout and consisted of 10 mEq Na, 80 mEq potassium (K), 65 g protein, 50 g fat, 280 g carbohydrate, 400 mg calcium (Ca), and 1000 mg phosphorous (P) daily. The high Na diet was identical with the exception that 290 mEq Na was added to the diet in the form of NaCl. An additional 500 mEq NaCl was given in bouillon between and with meals to attain a total Na intake of 800 mEq/day. An increase in fluid intake during the high sodium period prevented gastrointestinal symptoms. The high Na diet was identical with the exception that 290 mEq NaCl was added to the diet in the form of NaCl. An additional 500 mEq NaCl was given in bouillon between and with meals to attain a total Na intake of 800 mEq/day. An increase in fluid intake during the high sodium period prevented gastrointestinal symptoms. The high sodium diet was given for 5 days and the low sodium for 7. Each subject was randomly assigned to enter the study on either low or high Na intake. The second phase was performed after 3 to 7 days of an intervening normal diet period. Sodium homeostasis

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was documented by determination of 24-hour urinary Na excretion.

On the study day, the subject ate breakfast and lunch as usual. Liberal fluid intake was provided to ensure rapid urine flow during the study. After lunch, a venous catheter was placed in the dominant arm and subjects were recumbent during the study. A solution of 5% dextrose in water (D,W) was then administered at a rate of 45 ml/hr throughout the study. After 1 hour, a catheter was placed in the radial artery of the nondominant arm. A venous catheter for blood sampling was also placed in the nondominant arm.

Eight consecutive 30-minute clearance periods were then conducted. The first two periods provided baseline data. L-norepinephrine bitartrate (Levophed, Winthrop, New York, New York) was infused in D,W delivered by a Harvard infusion pump into the venous catheter in the dominant arm at rates of 1, 2, 4, 8, and 15 μg/min during consecutive 30-minute periods. A final recovery period was also conducted. If mean arterial blood pressure (MAP) increased more than 25 mm Hg from control, the NE infusion rate was not increased further, and the recovery period was conducted during the next 30 minutes.

At 5, 15, and 25 minutes of each clearance period, the BP was recorded using a P23GB transducer (Statham Gould, Oxnard, California) and an Electronics for Medicine recorder (Model VR 12, White Plains, New York). Each pulse wave was measured, thus obtaining a systolic (SBP) and diastolic (DBP) determination. Mean arterial pressure (MAP) for each wave was calculated using the formula MAP = DBP + 1/3 pulse pressure. The mean and standard deviation of SBP, DBP, and MAP for all pulse waves at each recording was then used for analysis. At the midpoint of each period, venous blood was sampled for determination of Na, K, and venous NE concentrations. Arterial blood was obtained simultaneously for determination of NE concentration. Urine was obtained at the end of each period for determination of Na, K, and NE excretion. Diuresis was maintained by intravenous D,W infusion throughout the study.

We used a flame photometer (Instrumentation Laboratories, Boston, Massachusetts) for the Na and K determinations. The concentration of NE in plasma and urine was measured by a radioenzymatic assay.

The data were analyzed using repeated measures analysis of variance, two-way analysis of variance, linear regression analysis, Student’s t test, or non-parametric approaches as appropriate. The 95% confidence limits were accepted as significant. Results are expressed as mean and standard error of the mean (SEM). Threshold was determined as the dose of NE required to raise the MAP more than 1 SD above the control values.

**Results**

Table 1 presents the characteristics of the study population. The subjects excreted approximately as much Na as was in the diet during the 24 hours prior to study. The K excretion was greater on the high Na intake than on the low (p < 0.01). The subjects weighed more (p < 0.05) and had lower hematocrits (p < 0.05) after the high when compared to the low Na dietary regimen. Prior to NE infusion, the arterial concentration of NE was not different from the venous concentration at either level of Na intake. However, the mean NE concentration was higher on the low Na diet than on the high Na diet (p < 0.01) in both arterial and venous samples. In addition, the basal BP was significantly higher (p < 0.05) at the high Na intake as were the paired differences. All subjects received all five infusion rates of NE (1, 2, 4, 8, 16 μg/min) when studied during the low Na phase. However, during the high Na period, six subjects developed an increase in MAP of > 25 mm Hg with the infusion of 8 μg NE/min, and the infusion was terminated. Thus, only two subjects received 16 μg/min NE during the high Na regimen.

As the infusion rate of NE was increased, the arterial (AN) and venous (VN) norepinephrine concentration increased in an incremental linear fashion (fig. 1). The infusion rate and AN were highly correlated during both Na intakes (r = 0.96, r = 0.93, p < 0.001). There was no difference in the arterial NE concentration produced by a given infusion dose on the two Na intakes. AN was correlated with the venous level (VN) during both levels of Na intake (r = 0.89, p < 0.001) over the wide range of concentrations. It can be seen that the arterial levels were greater than the venous levels after the infusion of exogenous NE at both levels of Na intake (fig. 2). There were no significant effects of high and low Na intake on the arteriovenous NE relationships as evaluated by paired t test analyses. During NE infusion, repeated measures analysis of variance revealed that the arteriovenous differences shown in figure 2 changed significantly (p < 0.05) during both studies. Arterial NE concentration and its urinary excretion rate were directly correlated during both studies (r = 0.86, 0.93, respectively).

**Table 1. Characteristics of the Population on the Day of Testing (mean ± SEM)**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Low intake (10 mEq Na)</th>
<th>High intake (80 mEq Na)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UN (mEq/24 hr)</td>
<td>19.9 ± 4.6</td>
<td>795.8 ± 28.6*</td>
</tr>
<tr>
<td>Uv (mEq/24 hr)</td>
<td>61.4 ± 6.6</td>
<td>159.4 ± 6.7*</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>83.5 ± 6.5</td>
<td>86.0 ± 6.3†</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>42.5 ± 1.7</td>
<td>38.4 ± 1.4†</td>
</tr>
<tr>
<td>Basal arterial NE concentration (μg/ml)</td>
<td>192 ± 35</td>
<td>86 ± 17*</td>
</tr>
<tr>
<td>Basal venous NE concentration (μg/ml)</td>
<td>234 ± 63</td>
<td>107 ± 16*</td>
</tr>
<tr>
<td>Basal MAP (mm Hg)</td>
<td>92.2 ± 3.0</td>
<td>94.5 ± 3.6†</td>
</tr>
<tr>
<td>Change in basal MAP (mm Hg)</td>
<td>—</td>
<td>3.41 ± 1.66†</td>
</tr>
</tbody>
</table>

*p < 0.01 compared to 10 mEq Na intake.  †p < 0.05 compared to 10 mEq Na intake.
FIGURE 1. Responses of plasma norepinephrine (NE) (top panel), pulse rate (middle panel), and mean arterial blood pressure (MABP) (bottom panel) before, during, and after NE infusion while on low (left) or high (right) sodium intake are compared. Only two subjects received the 16 μg/min rate while on high sodium intake. The NE increments depicted are nonlinear.

FIGURE 2. Response of mean arterial blood pressure (MABP) to norepinephrine (NE) infusion during high sodium intake (solid circles) compared to that on low sodium intake (open circles). Only two subjects received 16 μg/min infusion on high sodium intake, and therefore data are not presented. The NE increments are nonlinear.
The MAP and pulse changed in opposite directions during NE infusion and the recovery period of both studies (fig. 1). The relationship between MAP and arterial NE concentration is shown in figure 3. The \( A_{NE} \) was directly correlated with MAP during both 10 mEq (\( r = 0.76, p < 0.001 \)) and the 800 mEq (\( r = 0.63, p < 0.001 \)) Na intakes. Since the slopes of the equations were different (\( p < 0.01 \)), the BP was greater for a given \( A_{NE} \) after the high Na than on the low Na diet. In addition, the BP was directly correlated with the NE infusion rate (\( r = 0.79, r = 0.59, p < 0.001 \)) and with the dose of NE if expressed on a body weight basis (\( \mu g/kg/min \)) (\( r = 80, r = 0.84, p < 0.001 \)).

The magnitude of the BP change at each of the four lower infusion rates (excluding 16 \( \mu g/min \)) was significantly greater after the high Na diet (\( p < 0.05 \)) than during low Na diet for all subjects when compared by paired \( t \) test. In addition, the threshold of significant BP response occurred at 1 \( \mu g/min \) in all but one subject (2 \( \mu g/min \)) after the high Na diet, while after low Na intake individual thresholds ranged from 1 to 4 \( \mu g/min \). These differences were significant (\( p < 0.05 \)) when evaluated by the nonparametric sign test for paired data. Figure 4 depicts the incremental change in MAP from control at each infusion rate in the two studies. When these data were analyzed by paired test, significant differences (\( p < 0.05 \)) were again observed.

The correlation between \( A_{NE} \) and MAP was different during the infusion periods when compared to the control periods. No correlation existed during control periods on the 10 mEq study day; however, during infusion periods, \( A_{NE} \) and MAP were directly correlated (\( r = 0.51, p < 0.05 \)). In contrast, on the 800 mEq Na intake, the MAP was correlated with \( A_{NE} \) during both control (\( r = 0.76, p < 0.001 \)) and infusion periods (\( r = 0.61, p < 0.001 \)). The relationship between \( V_{NE} \) and BP was also examined. These two variables interacted significantly (\( p < 0.01 \)) during both control and infusion periods on 10 mEq Na intake (\( r = 0.84, r = 0.71 \)) and during the 800 mEq Na intake (\( r = 0.75, r = 0.46 \)). The plasma concentrations of Na and K were unaltered by Na intake or NE infusion.

**Discussion**

It is well recognized that the state of Na balance and the sympathetic nervous system plays important roles in the control of arterial pressure. These effects on BP have been shown to be both direct and indirect. As an example, it has been shown that dietary Na loading can increase pressure in normotensive men associated with an increase in cardiac output.\(^4\) In addition, the state of Na balance is known to influence the responsiveness to vasoactive substances such as angiotensin II and NE in experimental animals.\(^8-10\) The activity of pressor systems such as the renin-angiotensin axis and, to a less well-defined degree, sympathetic nervous activity, are influenced by the state of Na balance.\(^10-18\) In humans, the interactive effect of Na and the sympathetic nervous system in influencing BP has not been carefully explored. Our earlier observations showed that plasma and urinary levels of NE were not suppressed as effectively by dietary Na loading as was plasma renin activity (PRA),\(^6,8\) and suggested that sympathetic function

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**Figure 3.** Relationship between arterial norepinephrine concentration and mean blood pressure (MABP).
might be involved in the homeostatic responses to the Na loads.6 The results of the present study demonstrate that the state of Na balance does indeed influence the BP response to exogenous NE in normal men and provide new information regarding the interactions between the level of Na balance, the sympathetic nervous system, and BP.

In the present study we were able to discern a small but significant increase in basal MAP after the high compared to the low Na diet. As demonstrated in figures 1 and 3, the state of Na balance also altered the threshold and magnitude of the BP response to exogenous NE. A significant increase in response was discernible in all but one subject at the 1 μg/min infusion rate during the high Na phase but required as much as 4 μg/min to produce a significant BP increase in all subjects during the low Na diet. While such an effect of Na on the sensitivity of response to NE has not previously been shown in normal man, similar observations have been made with another pressor agent, angiotensin II.17 Several factors could account for this differential sensitivity induced by a high Na diet. The reciprocal relationships observed between changes in BP and pulse rate seen during NE infusion in both studies documents the intact nature of the baroreceptor reflex. An increase in the number, affinity, or type (α 1, α 2) of sympathetic receptor sites induced by the level of Na balance or by changes in BP could have altered the sensitivity to NE, but these aspects were not evaluated in the current study. However, we did examine another aspect of sympathetic function that also could have influenced the vascular response, namely, arterial and venous NE concentrations.

High dietary Na intake was associated with a decrease in both basal arterial and venous NE concentrations when compared to those seen after the low Na diet (table 1). These observations are in accord with a substantial body of evidence indicating that Na loading decreases sympathetic tone. Efferent renal nerve activity has been reported to decrease with volume expansion.18 It has been suggested that this effect is mediated by an increase in pressure sensed in the atriæ,19 carotid body, or aorta.17 Tissue NE content18 as well as the concentrations in plasma and urine6,19,19,19,19 have been shown to vary inversely with the Na balance and volume status. Some investigators have identified changes in catecholamine metabolism induced by potassium loss31 which can be seen with large sodium loads.2 Thus, alterations in the rate of NE metabolism induced by the changes in Na and/or K balance may be responsible for the observations in the present study.

Other investigators have observed that simultaneous sampling of arterial and venous NE concentrations showed no differences,21,21 as our subjects demonstrated in the basal samples, or lower values in arterial blood.21 We have previously reported that the sampling site may be important in the interpretation of plasma NE measurements.6 The concepts of vascular compartmentalization of vasoactive substances proposed by Vane4 influenced our approach to the evaluation of the relationships among NE infusion, arterial, and venous NE concentrations, and the pressor responses examined in the present study.

With infusion of NE, a dose-related increase in arterial NE concentration was noted, as shown in figure 1. No significant differences in the arterial concentrations achieved were seen at the two levels of dietary Na intake (several subjects did not receive the highest infusion rate during high Na intake). However, venous NE concentrations did not increase to the same degree as those seen in arterial plasma (figures 1 and 2). Arteriovenous differences have been seen by other investigators24 and may be related to changes in local uptake, release, or metabolism of NE. Since the fractional extraction of NE during passage through the capillary bed is thought to be constant, the clearance of NE across this bed should not be influenced by the rate of NE infusion.

Few studies have examined the relationships between plasma NE concentration and BP during NE infusion. In the present study we observed a significant relationship between arterial and venous NE concentrations and BP. Most important, as shown in figure 3, the slope of this relationship was significantly influenced by Na balance, becoming much steeper after high Na intake. In addition, these studies have shown...
that the state of Na balance alters the threshold of pressor responsiveness to NE, an observation that may have physiological and pathophysiological significance. While previous investigators have observed a relationship between graded infusion of NE and increases in BP in normal man, they have not reported the correlation of the latter with arterial plasma NE levels or the influence of Na balance on the threshold and sensitivity of pressor responses. The studies of Silverberg et al. did not provide data on BP responses at NE infusion rates between 0.1 and 5.0 \( \mu \text{g}/\text{min} \), but their data suggest that the threshold of BP response occurred at venous NE levels exceeding 1800 \( \mu \text{g}/\text{ml} \). Such levels were observed in our subjects only at infusion rates of 16 \( \mu \text{g}/\text{min} \), yet significant BP responses were seen at much lower infusion rates (and plasma NE concentrations) and were influenced by Na balance. It is of interest that while hypertensive subjects have been shown to have increased pressor responses to administered NE, the state of Na balance has not been previously examined as a factor influencing such responses in man. In these previous studies, which utilized concentrations of NE in venous plasma, the investigators were unable to observe a correlation with BP over the range of infusion doses. Our ability to discern a similar relationship between venous concentrations and BP may be additionally ascribed to an increased methodologic specificity and sensitivity, to the wider range of infusion rates utilized in the present study, or to careful control of Na balance as compared with the earlier observations.

It could be argued that the plasma NE concentrations achieved during this study were supra-physiologic and thus the ambient NE levels normally seen could not influence arterial pressure significantly. However, a variety of studies have reported plasma NE concentrations as high as 2000 \( \mu \text{g}/\text{ml} \) during normal activity such as standing, exercise, cold exposure, cigarette smoking, or volume depletion, and levels achieved at the lower end of the range of NE infusion rates used in our study and associated with significant increases in arterial pressure. Indeed, a recent study has focused on the issue that NE may act as a hormone under such circumstances. In that study, venous NE concentrations approaching 2 \( \mu \text{g}/\text{ml} \) were required before a pressor effect could be discerned. In our present study, pressor responses were seen at much lower levels of venous NE and were influenced by Na balance. During high Na intake, a significant increase in pressure was seen in all but one subject at the lowest infusion rate (1 \( \mu \text{g}/\text{min} \)) while on the low Na phase every subject responded with a significant increase in pressure at rates of 4 \( \mu \text{g}/\text{min} \) or lower. Such infusion rates produced arterial NE concentrations similar to those reported for active humans. Thus, our present study provides additional support for the oft-disputed concept that circulating concentrations of NE may influence the BP, particularly when Na intake is high.

Vane has emphasized that many vasoactive hormones are compartmentalized within the circulation, that is, they are released, transported through a portal of the circulatory system, exert their biological effect, and are metabolized or degraded there. Our demonstration of different plasma concentrations of NE in simultaneously obtained arterial and venous blood samples during infusion (figs. 1 and 2) further substantiates that concept. Arterial NE concentration defines the pharmacologically active circulating level at the arteriolar vasoconstrictor sites. Arterial NE increased more during NE infusion than did venous NE in the present study.

These studies have provided new information concerning the interactions between Na balance and the biological effects of NE infusion in humans. Enhancement of the pressor effect of NE was seen (fig. 4) after high Na intake, as were differences in arterial and venous plasma concentrations of NE before and after exogenous administration. The direct effects of NE on Na excretion also displayed contrasting patterns of response depending on the state of Na balance. The observations suggest that identical levels of activation of the sympathetic nervous system may have a greater impact on arterial pressure in the Na repleted state than during Na depletion while basal levels of sympathetic activity are higher during Na depletion. We conclude that important interactions exist between sodium intake, sympathetic nervous system activity, norepinephrine metabolism, and blood pressure responses to norepinephrine. These interactions may be of pathophysiological importance in the development or maintenance of hypertension.

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