Effect of High and Low Sodium Intake on Norepinephrine Turnover in the Cardiovascular Tissues and Brain Stem of the Rabbit

TOSHIYUKI TANAKA, M.D., AKIRA SEKI, M.D., AND JUN FUJI, M.D.

SUMMARY To assess the relationship between sympathetic nerve function and sodium intake, we examined norepinephrine (NE) turnover in several cardiovascular tissues and the brain stem of rabbits maintained for 3 weeks on high (86 mEq), normal (14 mEq), and low (0.2 mEq/day) sodium diet. None of the diets changed the blood pressure significantly. Plasma renin activity became high in the low sodium group and low in the high sodium group at the end of the treatment. NE turnover was measured from the rate of decline of tissue NE concentration after administration of α-methyl-p-tyrosine. Variation of sodium intake exerted opposite effects on NE turnover in the periphery and in the central nervous system; increasing sodium intake caused an increase in NE turnover in the thoracic aorta, mesenteric vein, and left ventricle, and a decrease in the hypothalamus, midbrain, and pons medulla. But in the mesenteric artery and abdominal aorta it was not affected by dietary sodium manipulation. The results show the varying influence of sodium balance on the central and peripheral noradrenergic neuron activity. (Hypertension 4: 294-298, 1982)

KEY WORDS • norepinephrine turnover • cardiovascular tissues • brain stem • dietary sodium

SODIUM intake and the sympathetic nerves are major factors implicated in hypertension. There are mutual interactions between these two factors; sodium excretion is modified by the activity of sympathetic nerves,1-3 and sympathetic nerve activity is modified by sodium balance. A number of studies have demonstrated that plasma levels and urinary excretions of norepinephrine (NE) are altered by sodium loading or deprivation both in human subjects4-10 and in experimental animals.11-18 Turnover of tissue NE is also affected by concomitant administration of sodium and deoxycorticosterone (DOC), in the heart and other peripheral organs16-18 or in the brain stem18,19 of the rat.

In the present study we investigated the effect of high and low sodium intake on NE turnover in several cardiovascular tissues and the brain stem of the rabbit in an attempt to delineate further the relation of activity of sympathetic nerve and central noradrenergic neuron to sodium balance.

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Methods

Male New Zealand white rabbits weighing 2.0 to 2.5 kg were divided into three groups: a high sodium (HS) group (n = 15); a normal sodium (NS) group (n = 16); and a low sodium (LS) group (n = 15). Rabbits in the three groups were fed for 3 weeks on 200 g of special diet made of soybeans containing 86 (HS group), 14 (NS group), and 0.2 (LS group) mEq sodium chloride per 200 g. Since potassium has been shown to influence NE turnover,20 potassium chloride was supplemented in the diet to give a final content of 21 mEq/200 g. The values of sodium for the NS group and potassium in the diet were chosen to equal the electrolyte contents in the standard diet for rabbits in our laboratory (Japan Clea, CR1) which provides 14 mEq sodium and 21 mEq potassium each day. Tap water was given ad libitum. Body weight and blood pressure were recorded every week, the latter being measured by an indirect method21 in the central ear artery, which was dilated by an application of a small amount of xylol to the tip of the ear.

During the last 7 days of dietary treatment, each rabbit was housed in a metabolic cage and daily urine volume was measured. A portion of the urine was stored at 4°C for determination of sodium and potassium concentration. The next morning after comple-
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Table 1 summarizes the body weight, blood pressure, hematocrit, and serum sodium and potassium concentration of the three groups of rabbits maintained on different sodium intake. There was no significant change in body weight and blood pressure during the treatment with high, normal, or low sodium diet. The hematocrit and serum sodium concentration were not different among the three groups at the end of treatments. Serum potassium concentration was slightly higher in the LS group than in the NS and HS groups.

Daily urinary sodium and potassium excretion and PRA are depicted in figure 1. The average values for the 7-day period in the metabolic cage on any of the diets were taken to represent the daily electrolyte excretion for each rabbit. Sodium output was significantly different among the groups whereas the potassium output was the same; PRA was higher in the LS group and lower in the HS group than in the NS group.

Figure 2 shows the decline in tissue NE concentration after blockade of NE synthesis with α-MT. The rate constant of NE turnover and the levels of significance tested by analysis of covariance are summarized in table 2. In general, treatment with different sodium diets had opposite influences on NE turnover in the cardiovascular tissues and central nervous system, namely, increasing sodium intake caused elevation of NE turnover in the thoracic and whole aorta, mesenteric vein, and left ventricle, and caused reduction of NE turnover in the hypothalamus, midbrain, and pons medulla. NE turnover in the abdominal aorta and mesenteric artery was not affected by variation of sodium intake.

No difference in NE concentration was noted in the brain stem among the three groups (table 3). In the

### Table 1. Body Weight, Blood Pressure, Hematocrit, and Serum Electrolytes in Rabbits Fed a High (HS), Normal (NS), or Low Sodium (LS) Diet

<table>
<thead>
<tr>
<th></th>
<th>HS</th>
<th>NS</th>
<th>LS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>2.5 ± 0.1</td>
<td>2.4 ± 0.1</td>
<td>2.3 ± 0.1</td>
</tr>
<tr>
<td>After treatment</td>
<td>2.5 ± 0.1</td>
<td>2.4 ± 0.1</td>
<td>2.3 ± 0.1</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>101 ± 3</td>
<td>100 ± 3</td>
<td>100 ± 4</td>
</tr>
<tr>
<td>After treatment</td>
<td>101 ± 2</td>
<td>99 ± 2</td>
<td>89 ± 7</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>40.3 ± 0.9</td>
<td>40.8 ± 0.5</td>
<td>41.4 ± 1.3</td>
</tr>
<tr>
<td>Serum Na (mEq/liter)</td>
<td>141 ± 1</td>
<td>142 ± 1</td>
<td>142 ± 2</td>
</tr>
<tr>
<td>Serum K (mEq/liter)</td>
<td>4.3 ± 0.1*</td>
<td>4.2 ± 0.1†</td>
<td>4.6 ± 0.1</td>
</tr>
<tr>
<td>n</td>
<td>15</td>
<td>16</td>
<td>15</td>
</tr>
</tbody>
</table>

Each value is the mean ± SEM.
* p < 0.05 compared with LS.
† p < 0.01 compared with LS.
FIGURE 1  Amounts of urinary sodium and potassium and plasma renin activity (PRA) in rabbits fed on high salt (HS, n = 15), normal salt (NS, n = 16), or low salt (LS, n = 15) diet. Differences in the amount of urinary sodium: p < 0.001 for HS vs NS, NS vs LS, and HS vs LS. Differences in PRA: p < 0.05 for HS vs NS, p < 0.005 for NS vs LS; p < 0.001 for HS vs LS.

TABLE 2. Rate Constant of Norepinephrine Turnover in Tissues of Rabbits Fed a High (HS), Normal (NS), or Low Sodium (LS) Diet, and p Values for Significance of Difference

<table>
<thead>
<tr>
<th>Rate constant (hr⁻¹)*</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HS vs NS</td>
</tr>
<tr>
<td>Thoracic aorta</td>
<td>0.167 ± 0.039</td>
</tr>
<tr>
<td>Abdominal aorta</td>
<td>0.132 ± 0.033</td>
</tr>
<tr>
<td>Whole aorta</td>
<td>0.159 ± 0.037</td>
</tr>
<tr>
<td>Mesenteric artery</td>
<td>0.071 ± 0.018</td>
</tr>
<tr>
<td>Mesenteric vein</td>
<td>0.171 ± 0.051</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>0.125 ± 0.027</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>0.106 ± 0.024</td>
</tr>
<tr>
<td>Midbrain</td>
<td>0.138 ± 0.023</td>
</tr>
<tr>
<td>Pons medulla</td>
<td>0.146 ± 0.026</td>
</tr>
</tbody>
</table>

* Each value is the mean ± SEM calculated from the data depicted in figure 2.  † Each p value was derived from F test based on analysis of covariance.  ns = not significant.

TABLE 3 Norepinephrine (NE) Concentration in Tissues of Rabbits Fed a High (HS), Normal (NS), or Low Sodium (LS) Diet

<table>
<thead>
<tr>
<th>NE concentration (µg/g)</th>
<th>HS</th>
<th>NS</th>
<th>LS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracic aorta</td>
<td>0.95 ± 0.09*</td>
<td>0.85 ± 0.05†</td>
<td>0.66 ± 0.06</td>
</tr>
<tr>
<td>Abdominal aorta</td>
<td>0.43 ± 0.05</td>
<td>0.45 ± 0.04</td>
<td>0.47 ± 0.06</td>
</tr>
<tr>
<td>Whole aorta</td>
<td>0.77 ± 0.07</td>
<td>0.71 ± 0.04</td>
<td>0.59 ± 0.05</td>
</tr>
<tr>
<td>Mesenteric artery</td>
<td>9.75 ± 0.55</td>
<td>11.18 ± 0.59*</td>
<td>8.48 ± 0.70</td>
</tr>
<tr>
<td>Mesenteric vein</td>
<td>5.37 ± 0.87</td>
<td>4.90 ± 0.69</td>
<td>3.91 ± 0.47</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>3.18 ± 0.25</td>
<td>3.59 ± 0.20†</td>
<td>2.80 ± 0.10</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>1.69 ± 0.08</td>
<td>1.80 ± 0.11</td>
<td>1.72 ± 0.07</td>
</tr>
<tr>
<td>Midbrain</td>
<td>0.28 ± 0.02</td>
<td>0.30 ± 0.01</td>
<td>0.31 ± 0.01</td>
</tr>
<tr>
<td>Pons medulla</td>
<td>0.41 ± 0.03</td>
<td>0.47 ± 0.02</td>
<td>0.44 ± 0.02</td>
</tr>
<tr>
<td>n</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

Each value is the mean ± SEM.  *p < 0.025 compared with LS.  †p < 0.05 compared with LS.  ‡p < 0.005 compared with LS.
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periphery, sodium restriction reduced NE concentration in the thoracic aorta, mesenteric artery, and left ventricle. Sodium loading produced a slight increase in NE concentration in the thoracic aorta.

Discussion

Previous studies have shown that sodium loading as well as restriction lowers the NE concentration in cardiovascular tissues.19,20 NE turnover in tissues, which is a better index of NE neuron activity, has also been shown to be affected by alteration in sodium balance. In DOC-sodium hypertension of the rat, NE turnover is increased in the heart, spleen, and intestine,16-18 while it is decreased in the brain stem.16,19 although a direct pharmacological action of DOC itself superimposed on the effect of sodium cannot be excluded in this situation. Sodium depletion by restriction of intake plus administration of diuretics reduces NE turnover in the heart.21

In our present study, the rate of NE turnover was compared in three groups of rabbits fed on high, normal, or low sodium diet alone without using sodium-retaining steroids or diuretic agents. Results reveal that alterations in sodium intake exerted opposite effects on NE turnover in the cardiovascular tissues and brain stem; in the thoracic aorta, mesenteric vein, and left ventricle the rate of NE turnover was elevated by increasing sodium intake while in the hypothalamus, midbrain, and pons medulla, it was reduced. No significant change in NE turnover was observed in the abdominal aorta and mesenteric artery. These results indicate that sodium loading and deprivation have variable influences on NE neuron activity in the cardiovascular system and brain stem.

Are the changes in NE turnover in the cardiovascular tissues and brain stem independent phenomena? Or is the change in the periphery secondary to that in the central nervous system? To these questions, Nakamura et al.,18 using a ganglion blocking agent, and van Ameringen et al.,19 using cervical transection, have shown that NE turnover in the periphery returns to normal after interruption of the neural connection to the central nervous system, while NE turnover in the central nervous system remains decreased in DOC-sodium hypertensive rats. From these findings they have suggested that the primary dysfunction is a decrease in activity of the sympathoinhibitory noradrenergic neurons in the brain stem, which is reflected in a decrease in NE turnover, and that this leads to enhancement of the peripheral sympathetic neuron activity. This explanation may apply to our results also, since the effects of sodium on NE turnover in the brain stem and in the periphery for the HS group in our study was in the same direction as that observed in DOC-sodium hypertension.

The process whereby alteration in NE turnover is produced in the central nervous system is unclear. Alteration in extracellular sodium or potassium concentration has been shown to affect NE release from sympathetic neurons,22,23 but serum sodium and potassium concentrations were not grossly changed in this study. In speculation, one of several factors might mediate the change in sodium balance and NE turnover. It might be a derangement of intracellular electrolyte concentrations, or a change in the renin-angiotensin system which modulates the NE secretion through presynaptic receptors,24 or a mechanism involving angiotensin II, α1-noradrenergic, or opiate receptors, which are known to be modified by the sodium ion.25-28 Further studies of this problem are needed.

Neither high, normal, nor low sodium diet affected blood pressure significantly. In this respect, it should be mentioned that alteration in NE turnover was observed only in the aorta, mesenteric vein, and left ventricle, and not in the mesenteric artery. The lack of change in blood pressure may be attributed, in part, to the fact that the changes in sympathetic tone were restricted to the capacitance vessels and heart whereas the activity of the sympathetic neurons in arteries contributing to vascular resistance remained unchanged. Accordingly, when one investigates a relationship between NE kinetics and blood pressure control, it is important to examine the peripheral arteries as well as the heart.
Acknowledgments

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