Sodium Pump Activity in Arteries of Dahl Salt-Sensitive Rats

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SUMMARY Decreased activity of the electrogenic sodium pump of vascular smooth muscle has been reported in several forms of experimental hypertension and may play an important role in basic disease mechanisms. It has been proposed that such pump suppression may characterize volume-expanded forms of hypertension. The present investigation tested this latter hypothesis. Sodium pump activity was assessed in vitro in sodium-loaded tail artery and thoracic aorta freshly excised from Dahl salt-sensitive (S) and salt-resistant (R) rats on low (0.4%) or high (8%) NaCl diets for 5 to 7 weeks. Rubidium (\(^{86}\)Rb) uptake in the absence (total uptake) and presence (ouabain-insensitive uptake) of 1.0mM ouabain was measured and ouabain-sensitive uptake (nmole/mg dry weight/10 min) was calculated. In S rats, salt feeding was accompanied by elevation of arterial pressure, cardiac hypertrophy, increases of 20% to 30% in total blood volume, and increases in the ouabain-sensitive, ouabain-insensitive, and total uptakes in the aorta, but no significant change in uptakes in the tail artery. However, ouabain-sensitive uptake in the tail artery of all S rats exceeded that in R rats. There was no evidence of a decrease in vascular sodium pump activity accompanying hypertension in either artery. Therefore, the results of this study provide no evidence in support of the hypothesis that pump suppression in vascular smooth muscle characterizes volume-expanded forms of hypertension. It is unlikely that the observed increases in vascular pump activity in S rats reflected intracellular sodium concentrations higher than those in the control rats. Rather, increases in the numbers of pump molecules or in their turnover rate are probably involved. (Hypertension 3: 306-312, 1981)

KEY WORDS. • arterial hypertension • tail artery • aorta • Na,K-ATPase • salt-dependent hypertension • volume-expanded hypertension • genetic hypertension • plasma volume • blood volume • extracellular fluid volume

In certain forms of arterial hypertension, potassium vasodilation is attenuated,\(^{1,3}\) the ouabain-sensitive component of rubidium uptake by vascular smooth muscle is decreased,\(^1,4\) and myocardial Na, K-ATPase activity is reduced.\(^5\) Based on this evidence, Overbeck\(^1\) and Overbeck et al.\(^4\) proposed that, in hypertension, the activity of the sodium pump in the sarcolemma of cardiovascular muscle cells may be depressed. Reduced pump activity might account for several manifestations of hypertension,\(^4,5\) including the increased arteriolar resistance, reduced venous compliance,\(^6,7\) and increased myocardial contractility.\(^8\)

Noting that most of the evidence for depressed pump activity was obtained from animals with volume-expanded forms of hypertension\(^6,10\) (e.g., one-kidney, one-wrapped renal;\(^4\) one-kidney, one clipped renal), Haddy and Overbeck\(^11\) later proposed that this defect may be unique to volume-expanded hypertension. Additional preliminary evidence from Haddy's laboratories\(^12\) has been presented in support of this hypothesis.

It was the purpose of the present investigation to test this hypothesis further. There is presumptive evidence that hypertension in Dahl salt-sensitive rats is accompanied by volume expansion and mediated by a humoral factor.\(^13,14\) Therefore, we studied sodium pump activity in arteries obtained from Dahl salt-sensitive and salt-resistant rats receiving diets varying in sodium content. We also measured body fluid volumes in these rats.
Methods

In vitro measurements of sodium pump activity were made in the ventral tail artery and thoracic aorta samples obtained from four groups of rats: 1) salt-sensitive rats (S_L) on low (0.4%) NaCl diet; 2) salt-sensitive rats (S_H) on high (8%) NaCl diet; 3) salt-resistant rats (R_L) on low NaCl diet; and 4) salt-resistant rats (R_H) on high NaCl diet.

Male S and R rats, aged 5 to 10 weeks, body weights 80 to 290 g (mean ± SEM: 163 ± 7 g), were obtained from the colonies of Dr. J. P. Rapp. Average ages of S and R rats were comparable. The S rats were randomly divided into the two appropriate groups, as were the R rats, and maintained thereafter on the low or high NaCl diet. Body weights and tail systolic blood pressures (by the tail cuff method under light ether anesthesia) were measured in all rats weekly. Arterial tissue was obtained from these rats 5 to 7 weeks after beginning the diet. All S_H rats had elevated arterial pressures (>150 mm Hg) at the time tissue was obtained; in most cases the S_H rats had elevated arterial pressures for 4 weeks.

Tissues from two R_L and R_H rats were processed simultaneously, as were tissues from the two S rats. The two rats were anesthetized with pentobarbital (60 mg/kg i.p.). The ventral tail artery, and then the descending thoracic aorta, were gently and rapidly excised (by D.D.K.) from each rat. These specimens were placed in Krebs-Henseleit solution (NaHCO_3, 27.2 mM; NaCl, 118.0 mM; KH_2PO_4, 1.0 mM; KCl, 4.8 mM; MgSO_4 • 7H_2O, 1.2 mM; CaCl_2 • 2H_2O, 1.25 mM; and glucose, 11.1 mM) at 27°C bubbled with 95% O_2, 5% CO_2 (pH 7.4), and gently and rapidly (<5 minutes) cleaned of adventitia and blood, and opened longitudinally. Then rubidium (^{86}Rb) uptakes were immediately measured by procedures similar to those previously reported by Overbeck et al.

In brief, the arteries from the two rats were placed in K+-free Krebs-Henseleit solution (NaHCO_3, 27.2 mM; NaCl, 117.0 mM; NaH_2PO_4 • H_2O, 1.0 mM; MgSO_4 • 7H_2O, 1.2 mM; CaCl_2 • 2H_2O, 1.25 mM; and glucose, 11.1 mM) at 0–2°C for 5 minutes of sodium-loading. Next, the arteries were incubated for 10 minutes at 37°C in a O_2-CO_2 bubbled K+-free Krebs-Henseleit solution containing "cold" RbCl, 4 mM, plus trace amounts of ^{86}RbCl (New England Nuclear). For this incubation, each artery was divided in half; one-half was incubated in the medium without ouabain and the other half incubated in the medium with added ouabain (1.0 mM). Tissues were then washed three times (total time, 15 to 20 seconds) with O° C K+-free Krebs-Henseleit containing 4 mM "cold" RbCl, blotted with tissue paper to remove surface fluid, weighed, and placed in a crystal scintillation counter to determine ^{86}Rb uptake. The tissue was then dried at 100°C for 24 hours and reweighed. The ^{86}Rb uptake was calculated as nmole/mg of dry weight/10 min and also as nmole/mg of dry weight/10 min. Ouabain-sensitive uptake was calculated as the difference between the ^{86}Rb uptake without (total uptake) and with (ouabain-insensitive uptake) ouabain.

Analysis of variance was used for statistical analysis; if the F test was significant (p < 0.05), group means were compared by treatment contrasts.

In some rats from each group (R_L = 6; R_H = 5; S_L = 7; S_H = 6), blood urca nitrogen (autoanalyzer), serum creatinine (autoanalyzer), and sodium and potassium (flame photometer) concentrations were measured.

It is possible that depleted cell-energy stores in freshly excited vascular tissue might reduce pump activity. Therefore, ^{86}Rb uptakes of freshly excised tail artery and aorta from 24 additional normotensive control rats (body weights 350 to 450 g) were measured after preincubating the tissues for 0, 60, 120, or 180 minutes in 37°C Krebs-Henseleit solution bubbled with O_2-CO_2. procedures that should return energy stores (and tissue ion contents) toward normal levels. We then sodium-loaded the tissues for 5 minutes and incubated them with ^{86}Rb, using methods identical to those described above. Analysis of variance and treatment contrasts were also used to analyze these data.

So that intracellular sodium concentrations would not be rate-limiting in our measurements of ^{86}Rb uptake, it may be seen by the above description that we subjected these freshly dissected tissues to 5 minutes of sodium-loading in K+-free Krebs-Henseleit solution at 0–2°C. To further validate this procedure, we studied the effects of more prolonged sodium-loading in 19 additional R rats (body weights 269 ± 5 g) that had been maintained on a normal salt diet since birth. In freshly dissected (by D.D.K.) sodium-loaded tail artery and thoracic aorta from six of these rats, we measured total ^{86}Rb uptake, and, in sodium-loaded tissue from another four rats, we measured ouabain-insensitive uptake, using procedures identical to those described above. We used a paired experimental design: each artery was divided in half, half was loaded for 5 minutes and half for 60 minutes. Methods used for the 5-minute sodium-loading were identical to those described above. The K+-free Krebs-Henseleit solution was also used for the prolonged sodium-loading, but the temperature was maintained at 37°C to further promote sodium-potassium interchange. We used Student's t test for paired replicates to compare uptakes in arterial segments loaded for minutes with those in the corresponding segments loaded for 60 minutes.

In the remaining nine rats, we used lithium-substitution procedures similar to those developed by Friedman et al. to estimate intracellular concentrations of Na+ and K+ in freshly dissected (by D.D.K.) tail artery and thoracic aorta, sodium-loaded for 5 or 60 minutes as described above. Again, we used a paired experimental design, dividing each artery in half. Then, the sodium-loaded arterial tissue was incubated at 0–2°C for 40 minutes in a medium (LiCl, 120.0 mM; CaCl_2, 2.0 mM; MgCl_2, 1.0 mM; KCl, 5.0 mM; and 20 mM Hapes buffer adjusted to pH 7.6 with Tris base) in which extracellular sodium in the tissue is replaced by lithium. Following measurement of these tissues for 1 week in 0.75 N HNO_3, ion concentra-
tions were estimated by atomic absorption spectrophotometry. Assuming that all measured Na\(^+\) and K\(^+\) were from the intracellular components, we calculated [Na\(^+\)]\(_i\) and [K\(^+\)]\(_i\), as nmole/mg dry weight. We again used Student's t test for paired replicates to compare [Na\(^+\)]\(_i\) and [K\(^+\)]\(_i\) in arterial segments loaded for 5 minutes with those in corresponding segments loaded for 60 minutes.

Finally, in an additional nine SL, nine SH, 10 RL, and 10 RH on diet for 5 to 7 weeks, we estimated body fluid volumes by indicator-dilution: plasma volume by \(^{125}\)I-labelled human serum albumin (Mallinckrodt), and extracellular fluid volume by \(^{38}\)S (Na\(^{38}\)SO\(_4\), New England Nuclear). Preliminary experiments in six SL, four SH, seven RL, and seven RH indicated no significant differences in the 2-hour plasma disappearance rate of labelled albumin.

We used the following methods for measurement of body fluid volumes. Volumes were measured at the same time of day in each group to control for diurnal variation. With the rat under ether anesthesia, both kidneys were excised by flank incision. Then, approximately 0.05µCi \(^{125}\)I-labelled human serum albumin and 0.05µC Na\(^{38}\)SO\(_4\) were injected intravenously in 100 µl saline, with a flush of 0.3 ml saline. For standards, identical injections were made into volumetric flasks and diluted. To facilitate complete mixing of the labels, the rats were allowed to recover from the anesthesia. Then, exactly 1 hour after the injections were administered, the rats were decapitated and trunk blood collected for hematocrit and isotope isotopes were administered, the rats were decapitated for hematocrit and isotope.

The 

\textbf{Results}

Mean values (± SEM) of body weights, final tail systolic blood pressures, heart-weight-to-body-weight ratios, serum creatinine, Na\(^+\), K\(^+\), and blood urea nitrogen are presented in Table 1. Analysis of variance revealed that the SL rats had significantly higher blood pressures and heart weight/body weight ratios than all other groups of rats studied. Blood pressures of SL rats, compared to R rats, were also significantly increased. Serum creatinine, sodium, and potassium concentrations remained within normal ranges, and there were no significant differences between the groups. Blood urea nitrogen, however, rose slightly in RH and SH rats.

Table 2 presents the mean values (± SEM) of \(^{86}\)Rb uptakes in the tail artery and thoracic aorta from these same rats. As indicated, analysis of variance revealed that the ouabain-sensitive component of \(^{86}\)Rb uptake in the tail artery was elevated in S rats as compared to R rats. However, high NaCl intake did not significantly alter the ouabain-sensitive \(^{86}\)Rb uptakes by the tail artery within either strain (p > 0.5). There was not even a trend toward a decreased ouabain-sensitive uptake. Because the ouabain-insensitive component was essentially similar among the four groups.

Table 1.

<table>
<thead>
<tr>
<th>Rat group</th>
<th>Body weight</th>
<th>Blood pressure</th>
<th>Heart wt/body wt</th>
<th>Blood urea nitrogen</th>
<th>Serum creatinine</th>
<th>Serum Na(^+) (mEq/liter)</th>
<th>Serum K(^+) (mEq/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RL (g)</td>
<td>263 ± 7*</td>
<td>116 ± 2*</td>
<td>27.6 ± 0.3*</td>
<td>21.3 ± 3.5*</td>
<td>0.53 ± 0.07*</td>
<td>141.7 ± 2.5*</td>
<td>3.84 ± 0.07*</td>
</tr>
<tr>
<td>SL (g)</td>
<td>247 ± 7*</td>
<td>118 ± 3*</td>
<td>29.6 ± 0.6*</td>
<td>29.9 ± 3.2*</td>
<td>0.60 ± 0.05*</td>
<td>141.6 ± 2.7*</td>
<td>3.84 ± 0.29*</td>
</tr>
<tr>
<td>SH (g)</td>
<td>321 ± 8</td>
<td>137 ± 4</td>
<td>30.3 ± 0.4*</td>
<td>19.6 ± 0.9*</td>
<td>0.60 ± 0.04*</td>
<td>143.3 ± 0.9*</td>
<td>3.84 ± 0.05*</td>
</tr>
<tr>
<td>RH (g)</td>
<td>264 ± 13*</td>
<td>177 ± 6</td>
<td>42.0 ± 1.6</td>
<td>24.3 ± 2.3*</td>
<td>0.57 ± 0.05*</td>
<td>145.0 ± 1.1*</td>
<td>3.72 ± 0.21*</td>
</tr>
<tr>
<td>n (RL)</td>
<td>18</td>
<td>16</td>
<td>18</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (SL)</td>
<td>16</td>
<td>16</td>
<td>18</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (SH)</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (RH)</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Within each row, values sharing superscript letters are not significantly different (p > 0.05) by analysis of variance.

RL = salt-resistant rat on low sodium diet; RH = salt-resistant rat on high sodium diet; SL = salt-sensitive rat on low sodium diet; SH = salt-sensitive rat on high sodium diet.
of rats, total uptake by the tail artery reflected differences in the ouabain-sensitive component.

Analysis of variance also revealed that the ouabain-sensitive component of $^{86}$Rb uptake in thoracic aorta in $S_H$ rats was elevated, as compared to the other three groups, which did not significantly differ from each other. Thus, salt-feeding in $S$ rats, but not in $R$ rats, increased the ouabain-sensitive $^{86}$Rb uptake in the aorta. Again, total uptake reflected these differences in the ouabain-sensitive component. Ouabain-insensitive uptake, however, was also elevated in the $S_H$ rats. In both the tail artery and aorta, calculations made using wet weights resulted in similar conclusions.

Table 3 indicates that in the tail artery and aorta from normal rats there were significant decreases in total and ouabain-sensitive uptakes after 60 minutes of preincubation.

Table 4 presents the results of our study in 19 additional $R$ rats of the effects on $^{86}$Rb uptake of brief (5 minutes), as opposed to prolonged (60 minutes), tissue sodium-loading in $K^+$-free Krebs-Henseleit solution. Compared to brief loading at 0–2° C, prolonged loading of freshly excised tissue at 37° C produced apparent increases in $[\text{Na}^+]_i$ of 60% to 80%, accompanied by reduction in $[\text{K}^+]_i$. Despite these increases in $[\text{Na}^+]_i$, there were no significant changes in $^{86}$Rb uptake by the arteries (there was actually a trend toward a reduction in total uptake).

### Table 2. $^{86}$Rb Uptakes (nmole/mg dry weight/10 min; Mean ± SEM)

<table>
<thead>
<tr>
<th>Uptake</th>
<th>Rat group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R_L$</td>
</tr>
<tr>
<td>Tail artery uptake:</td>
<td></td>
</tr>
<tr>
<td>No. of rats</td>
<td>16</td>
</tr>
<tr>
<td>Total (T)</td>
<td>21.65 ± 0.64*</td>
</tr>
<tr>
<td>Ouabain-insensitive (I)</td>
<td>7.99 ± 0.26*</td>
</tr>
<tr>
<td>Ouabain-sensitive (T-I)</td>
<td>13.66 ± 0.57*</td>
</tr>
<tr>
<td>Thoracic aorta uptake:</td>
<td></td>
</tr>
<tr>
<td>No. of rats</td>
<td>16</td>
</tr>
<tr>
<td>Total (T)</td>
<td>45.88 ± 2.27a</td>
</tr>
<tr>
<td>Ouabain-insensitive (I)</td>
<td>7.09 ± 0.33a</td>
</tr>
<tr>
<td>Ouabain-sensitive (T-I)</td>
<td>38.79 ± 2.18a</td>
</tr>
</tbody>
</table>

Within each row, values sharing superscript letters are not significantly different ($p > 0.05$) by analysis of variance.

**R** = salt-resistant rat on low sodium diet; **R** = salt-resistant rat on high sodium diet; **L** = salt-sensitive rat on low sodium diet; **H** = salt-sensitive rat on high sodium diet.
TABLE 4. $^{86}$Rb Uptake, $[Na^+]_i$ and $[K^+]_i$, After 5 or 60 Minutes of Sodium-Loading (Mean ± SEM)

<table>
<thead>
<tr>
<th>Intracellular ions (nmole/mg dry wt):</th>
<th>Tail artery</th>
<th>Thoracic aorta</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of rats</td>
<td>5 min loading</td>
<td>p</td>
</tr>
<tr>
<td>$[Na^+]_i$</td>
<td>9</td>
<td>61.3 ± 6.5</td>
</tr>
<tr>
<td>$[K^+]_i$</td>
<td>9</td>
<td>41.6 ± 4.0</td>
</tr>
</tbody>
</table>

$[^86]$Rb uptake (nmole/mg dry wt/10 min):

<table>
<thead>
<tr>
<th>Total uptake</th>
<th>5 min loading</th>
<th>60 min loading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tail artery</td>
<td>25.50 ± 1.59</td>
<td>(n = 5)</td>
</tr>
<tr>
<td>Thoracic aorta</td>
<td>9.28 ± 1.15</td>
<td>(n = 4)</td>
</tr>
</tbody>
</table>

Tail artery $p$'s < 0.02, < 0.01, > 0.5, > 0.05

Thoracic aorta $p$'s < 0.01, < 0.1, > 0.2, > 0.1

Finally, table 5 presents the results of measurement of body fluid volumes in R and S rats on high and low salt diet for 5 to 7 weeks. Compared to the other three groups, plasma volumes were elevated in $S_H$ rats, whether or not expressed in terms of body weight. Total blood volume, expressed in terms of body weight, was also elevated in $S_H$. This was also true (+31%) if the four $S_H$ rats with low hematocrits were omitted from the analysis, removing significant differences in hematocrits among groups. There were increases in extracellular fluid volumes, expressed in terms of body weight, in $R_H$ rats, compared to $R_L$ and $S_L$. However, in $S_H$, extracellular fluid volumes did not differ from the other three groups.

Discussion

This study was designed to test the hypothesis that decreased activity of the sarcolemmal sodium pump in cardiovascular muscle characterizes volume-expanded forms of hypertension. We tested this hypothesis in Dahl salt-sensitive (S) and salt-resistant (R) rats.

Because the pressure-natriuresis curve of kidneys of S rats is shifted toward the pressure axis, one would expect that salt-feeding would result in salt and water retention sufficient to elevate arterial pressure. The results of the present study offer evidence that such volume-expansion does, in fact, occur. On high salt diet, S rats expand their plasma and total blood volumes, the latter by 20% to 30%. However, they apparently do not expand their extracellular fluid volume with salt-feeding, suggesting changes in capillary filtration or in vascular or interstitial compliance.

In the R rats on high salt diet, in contrast to S rats, plasma and total blood volumes do not expand, but there is evidence for an increase in extracellular fluid volume. It might be speculated that the ability of these R rats to maintain normal intravascular volumes may...
be related to their resistance to salt hypertension; this protective mechanism may, in part, involve movement of retained fluid into the extravascular space.

We found the ouabain-sensitive component of the $^{86}$Rb uptake to be significantly increased in the tail artery and aortic tissue excised from these salt-sensitive rats. In the aortae, these increases accompanied the volume expansion and enhanced hypertension produced by salt-feeding. However, in the tail arteries, the increases seemed to be strain-related rather than associated with volume expansion. These differences in uptakes in the tail artery and aorta may be related to differences in their wall composition.

Hypertension also changes arterial wall composition. However, it is unlikely that the increases we found in the $^{86}$Rb uptakes in S rats are attributable to the differences in arterial wall composition associated with hypertension. In this regard, there is evidence that the proportion of fibrous tissue in the arterial walls increases in hypertension. Such changes would decrease, rather than increase, calculated uptakes expressed on a per tissue weight basis.

Similarly, it is unlikely that the increases we observed in the ouabain-sensitive $^{86}$Rb uptake can be attributed to back-diffusion of the label, i.e., diffusion of $^{86}$Rb from the cells back into the incubation medium. In the S rats, increased $[Rb^+]$, and also increased membrane permeability, if it is present in this form of hypertension, would tend to raise back-diffusion. We would expect that increased back-diffusion would reduce the net uptake.

Thus, the increased ouabain-sensitive $^{86}$Rb uptake we observed in the arteries from S rats probably reflects elevated activity of the sodium pump of the sarcolemma of the vascular smooth muscle cells. In this regard, it is important to note that in this study we found no evidence at all for decreases in pump activity in this form of volume-expanded hypertension. Hadley's laboratory has recently reported preliminary data confirming these results. Thus, studies by both laboratories appear not to support the hypothesis we proposed in 1976. Other evidence suggests that decreases in pump activity are not unique to volume-expanded forms of hypertension. Overbeck et al. found attenuated vasodilatory responses to intraarterial infusions of $K^+$ in a significant proportion of patients with uncomplicated essential hypertension. There is little evidence that uncomplicated essential hypertension is accompanied by volume expansion; most investigators report that decreased plasma volume characterizes such patients.

Activity of the membrane sodium pump is a function of the concentration of intracellular sodium. There was evidence for this relationship in our preincubation experiments; we observed a significant decrease in $^{86}$Rb uptake after 60 minutes of preincubation in a medium designed to replenish cell energy stores and restore normal levels of intracellular ions. Although we did not measure intracellular ion concentrations, the decreases in pump activity with increasing incubation time probably reflected decreases occurring in $[Na^+]$. These preincubation studies also provide evidence that cell energy stores in our freshly excised arterial tissues were not rate-limiting for pump activity, a possibility that has been suggested.

With regard to this relationship of intracellular sodium and pump activity, it is possible that the increases in pump activity we observed in tissues from the S rats reflected levels of $[Na^+]$, that were higher than those in control rats, even though identical methods of tissue excision and sodium-loading were used. This implies that levels of intracellular sodium in tissue from the control groups may have been sufficiently low to be rate-limiting for the pump. We tested this possibility by correlating $^{86}$Rb uptake in arterial tissue from control rats with measured $[Na^+]$. Our results indicate that intracellular sodium concentrations in freshly dissected arterial tissue from control rats subjected to our brief sodium-loading procedures are ample and are not rate-limiting for pump activity. Thus, the increases we observed in the activity of the arterial sodium pump in the S rats appear to be real.

Although hypertension in the salt-fed S rats is characterized by volume expansion, it is also related to genetic influences that are indicated by the mild, but significant, hypertension developing in these rats even on a low NaCl diet. Thus, at least a portion of the hypertension in Dahl S rats may be similar to that in other forms of genetic hypertension in rats, such as SHR. Increasing evidence indicates that the activity of the sodium pump in vascular smooth muscle in SHR may also be elevated. It has been proposed that such elevation in pump activity in SHR may be secondary to abnormalities in cell-membrane ion permeability, increasing intracellular sodium concentrations; it would be interesting to have similar studies done of vascular smooth muscle membrane permeability in Dahl S rats. In this regard, we found increases in the ouabain-insensitive component of $^{86}$Rb uptake in the aorta of S rats on high salt diet. However, we may not draw any conclusions from this particular measurement about ion permeability of the membrane, because this component also reflects nonspecific binding and $^{86}$Rb in interstitial fluid.

We feel that it is unlikely that the increased pump activity in the S rats on high salt diet reflects intracellular sodium concentrations elevated above those in the control rats, because further elevation of $[Na^+]$, in our control rats by 60% to 80% did not increase pump activity. Thus, other explanations must be sought for the increases we observed in vascular sodium pump activity in the S rats. Likely possibilities include one or a combination of the following: 1) more pump molecules per unit sarcolemma; 2) more sarcolemma per unit tissue weight; or 3) a faster turnover rate of a normal complement of pump molecules (not, apparently, related to $[Na^+]$, or $[K^+]$). A faster turnover rate might reflect the effects of altered vascular wall concentrations of prostaglandin or other substances that may affect pump activity.

Finally, it must be considered that the arteries we studied in these rats may not be representative of resistance vessels. This is especially true of the aorta.
Furthermore, we studied arteries in vitro under conditions of near-maximal pump activity, rather than in vivo at normal resting levels of pump activity. Thus, the present studies have by no means excluded the possibility that the activity of the sodium pump in sarcolemma of resistance vessels in vivo in hypertensive S rats is unchanged or even decreased. This possibility, which is clearly more difficult to investigate, requires further study.

Acknowledgments

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