Sodium-Potassium Pump Activity in Reduced Renal-Mass Hypertension

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SUMMARY We have previously reported that ouabain-sensitive 86Rb uptake, a measure of Na⁺-K⁺ pump activity, is decreased in blood vessels of animals with several low renin, and probably volume-dependent models of hypertension likely due to the action of a circulating sodium transport inhibitor. In this paper we summarize a detailed study of these and other related parameters in a model known to be volume expanded, reduced renal-mass hypertension in rats. We measured cardiovascular muscle cell Na⁺-K⁺ pump activity in control normotensive and experimental hypertensive reduced renal-mass rats, assayed supernates of boiled plasma from these rats for presence of a circulating Na⁺ transport inhibitor and studied the effects of anteromedial third ventricle (AV3V) lesions and central sympathectomy (by intraventricular injection of 6-hydroxydopamine) on development of reduced renal-mass hypertension, and on vascular Na⁺-K⁺ pump activity and level of circulating Na⁺ transport inhibitor(s). We also measured the effect of dietary sodium restriction on development of reduced renal-mass hypertension, cardiovascular muscle cell Na⁺-K⁺ pump activity and level of the circulating Na⁺ transport inhibitor. Compared to the normotensive control rats, the experimental hypertensive rats had increased extracellular fluid volume, decreased plasma renin activity, increased level of a circulating Na⁺ transport inhibitor, decreased vascular Na⁺-K⁺ pump activity (even after in vitro chemical sympathectomy) and decreased cardiac microsomal Na⁺-K⁺-ATPase activity. Pump suppression and development of hypertension were temporally associated. Both AV3V lesions and central sympathectomy prevented development of reduced renal-mass hypertension, inhibition of vascular Na⁺-K⁺ pump activity, and appearance of a circulating Na⁺ transport inhibitor. Withdrawal of saline reversed reduced renal-mass hypertension as well as vascular pump suppression and increased levels of a circulating pump inhibitor. These data support the hypothesis that inhibition of cardiovascular muscle cell Na⁺-K⁺ pump activity by a circulating Na⁺ transport inhibitor that is released from or influenced by the AV3V area of the brain plays an important role in the mechanism of some types of low renin experimental hypertension. (Hypertension 5 (suppl 1): I-94-I-100, 1983)

KEY WORDS • Na⁺-K⁺ pump • four-fifth nephrectomy • AV3V lesion • central sympathectomy • reversal of hypertension

We have previously reported that ouabain-sensitive 86Rb uptake, a measure of Na⁺-K⁺ pump activity, is decreased in blood vessels of animals with several low renin, presumably volume-expanded, models of experimental hypertension. These include dogs with one-kidney, one-wrap hypertension and rats with one-kidney, DOCA-salt hypertension and one-kidney, one clip hypertension.

We have also shown that Na⁺-K⁺-ATPase activity of cardiac microsomes is decreased in these rat models of hypertension. Furthermore, we have shown that supernates of boiled plasma from one-kidney, one-wrap hypertensive dogs and one-kidney, one clip hypertensive rats inhibit Na⁺-K⁺ pump activity when applied to tail arteries from normal rats. Because acute suppression of cardiovascular muscle cell Na⁺-K⁺ pump activity, by ouabain, for example, causes increased cardiac contractility, increased peripheral resistance, increased blood vessel responsiveness to vasoactive agents, and increased arterial blood pressure particularly if diuresis cannot occur, we have hypothesized that suppressed Na⁺-K⁺ pump activity by a circulating Na⁺ transport inhibiting agent may be responsible for the development and maintenance of hypertension in these animals.
Interestingly, Buggy et al. have shown that electrolytic lesions of the anteroventral third ventricle (AV3V) region of the brain in rats prevents and reverses one-kidney, renal and one-kidney, DOCA-salt hypertension. Haeusler et al. have shown that central sympathectomy by intraventricular injection of 6-hydroxydopamine prevents the development of one-kidney, one clip and one-kidney, DOCA-salt hypertension in rats. These are all models in which we find decreased vascular Na\(^+\)-K\(^+\) pump activity.

Additional data from our laboratory indicate that acute extracellular fluid volume expansion of dogs and rats stimulates release of a humoral Na\(^+\) transport inhibiting agent which suppresses \(^{86}\)Rb uptake when applied to tail arteries from normal rats. Since the volume status of the hypertensive animals previously reported to show decreased Na\(^+\)-K\(^+\) pump activity is uncertain, the role of volume in release of a Na\(^+\) transport inhibiting agent in these animals is not clear. Therefore, in the present investigation, a low renin model of hypertension with documented volume expansion, the reduced renal-mass model, was studied in detail.

The purpose of this study was to determine whether: 1) the reduced renal-mass model is, in fact, a low renin, volume-expanded model of hypertension; 2) cardiovascular muscle cell Na\(^+\)-K\(^+\) pump activity is decreased in rats with reduced renal-mass hypertension; 3) decreased pump activity in these animals is accompanied by the appearance of a humoral Na\(^+\) transport inhibiting agent; 4) decreased pump activity and development of hypertension are temporally associated; 5) the AV3V lesion or central sympathectomy influences the development of reduced renal-mass hypertension, decreased vascular Na\(^+\)-K\(^+\) pump activity, and appearance of a humoral Na\(^+\) transport inhibitor; and 6) the hypertension can be reversed by reducing sodium intake and also to determine what effect this has on cardiac and vascular muscle cell Na\(^+\)-K\(^+\) pump activity and appearance of a humoral Na\(^+\) transport inhibitor.

### Methods

#### Preparation of Reduced Renal-Mass Rats and Measurements of Renin Activity, Fluid Volumes, Pump Activity, and Supernate Activity

Control-normotensive and experimental-hypertensive reduced renal-mass rats were prepared according to methods previously described. Briefly, all rats underwent subtotal nephrectomies in which 70% to 80% of the renal mass was removed. All rats consumed a low sodium (0.02%) diet, and control rats drank distilled water while experimental rats drank a 1% NaCl solution. After 4 weeks of sustained hypertension in the experimental rats (systolic blood pressure > 140 mm Hg) and after a similar time interval in the paired normotensive control animals, blood was collected by decapitation in some rats for measurement of plasma renin activity. Others were anesthetized with sodium pentobarbital for measurement of plasma volume, extracellular fluid volume (sodium thiocyanate or \(^1^{4}\)C inulin), vascular ouabain-sensitive and insensitive \(^{86}\)Rb uptakes, cardiac microsomal Na\(^+\)-K\(^+\)-ATPase activity, and plasma Na\(^+\) transport inhibiting activity. In some animals hematocrits and supernatant electrolyte concentrations were also measured.

Plasma renin activity was measured by radioimmunoassay using the first 3 ml of trunk blood according to the method of Haber et al. A Becton-Dickinson radioimmunoassay kit was used (Becton-Dickinson, Orangeburg, New York).

The Evans blue dilution method of Wang was used for plasma volume determinations and the sodium thiocyanate dilution method of Elkinton and Taffel was used for measurement of extracellular fluid volume in the same animals, as previously described. In another group of animals, extracellular fluid volume was measured using a \(^{41}\)C inulin method similar to that of Addanki et al., modified as previously described.

Ouabain-sensitive and insensitive \(^{86}\)Rb uptakes were measured in freshly excised tail arteries using our standard technique. In some animals ouabain-sensitive and insensitive \(^{86}\)Rb uptake by tail arteries were measured following acute in vitro sympathectomy of the vessels with 6-hydroxydopamine plus phentolamine according to the method of Aprigliano and Herrms-meyer. Na\(^+\)-K\(^+\)-ATPase activity was measured in microsomes of left ventricular myocardium according to our standard technique.

Normal rat tail arteries were incubated in supernates of boiled plasma for measurement of Na\(^+\) transport inhibiting activity as previously described. Due to the small quantity of supernate obtained from each animal, only total or ouabain-insensitive \(^{86}\)Rb uptake was measured in each assay.

In some pairs of animals, ouabain-sensitive and insensitive \(^{86}\)Rb uptake by tail arteries were measured at weekly intervals for 5 weeks following subtotal nephrectomy to determine whether there is a temporal association between suppression of vascular Na\(^+\)-K\(^+\) pump activity and the development of hypertension.

#### Influence of AV3V Lesions on Development of Reduced Renal-Mass Hypertension and on Vascular Na\(^+\)-K\(^+\) Pump and Humoral Na\(^+\) Transport Inhibiting Activities

AV3V lesions and sham lesions were produced in normotensive male Wistar rats by Dr. James Buggy as previously described. Three weeks later, when lesioned rats had recovered adequate voluntary water intake (daily water intake similar to prelesion level), all rats underwent subtotal nephrectomy (70% to 80% renal mass removed), consumed a low sodium (0.02%) diet, and drank a 1% NaCl solution. Systolic blood pressure (tail plethysmography) was then monitored for 5 weeks. At the end of this 5-week period, paired sham-lesioned and AV3V-lesioned reduced renal-mass rats were anesthetized with sodium pentobarbital, tail arteries excised for measurement of ouabain-sensitive and insensitive \(^{86}\)Rb uptakes, blood col-
Influence of Central Sympathectomy on Development of Reduced Renal-Mass Hypertension and on Vascular Na\(^+\)-K\(^+\) Pump and Humoral Na\(^+\) Transport Inhibiting Activities

Normotensive male Wistar rats were centrally sympathectomized by intraventricular injections of 6-hydroxydopamine according to the method of Breese and Howard.\(^{21}\) Two weeks after the last injection of 6-hydroxydopamine, all rats underwent subtotal nephrectomy (70% to 80% renal mass removed) and consumed a low sodium (0.02%) diet. The animals were then separated into pairs. The control rat of each pair drank distilled water, while the experimental rat of each pair drank a 1% NaCl solution. Systolic blood pressure was then monitored for 5 weeks by tail plethysmography following which the animals were anesthetized with sodium pentobarbital, their tail arteries excised for measurement of ouabain-sensitive and insensitive \(^{86}\)Rb uptakes, blood collected for measurement of brain catecholamine content to determine the effectiveness of the sympathectomy. Brain catecholamine content was measured according to the electrochemical method of Felice et al.\(^{22}\) as modified by Hefti et al.\(^{23}\)

Results

Reduced Renal-Mass Hypertensive Rats

All experimental and control animals used in this study appeared healthy throughout the experiment. The saline-drinking reduced renal-mass rats became hypertensive within 1 week of subtotal nephrectomy and their systolic blood pressure was 167 ± 1 mm Hg 5 weeks after subtotal nephrectomy when plasma renin activity, body fluid volumes, and Na\(^+\)-K\(^+\) pump activity were measured. The control distilled water drinking rats remained normotensive throughout the study. Their systolic blood pressure was 116 ± 3 mm Hg 5 weeks after subtotal nephrectomy when the parameters were measured. Compared to the control rats, the experimental hypertensive rats had significantly lower plasma renin activities and hematocrits, significantly greater absolute (ml) and relative (ml/kg body weight) extracellular fluid volumes as determined with either sodium thiocyanate or \(^{14}\)C inulin and significantly greater relative (ml/kg body weight) plasma volumes.

We have previously reported that ouabain-sensitive \(^{86}\)Rb uptake by tail arteries from hypertensive rats was significantly decreased compared to uptake by tail arteries from the controls (d ± Sd: 3404 ± 418, p < 0.005, n = 10) while ouabain-insensitive uptakes (d ± Sd: 10 ± 88, p > 0.1, n = 10) were not signifi-
Na⁺-K⁺ Pump in Reduced Renal-Mass Hypertension

Na⁺-K⁺ pump in reduced renal-mass hypertension was also present after in vitro sympathectomy of the blood vessels with 6-hydroxydopamine plus phentolamine. Compared to control rats, Na⁺-K⁺ ATPase activity by microsomes prepared from the left ventricle of the hypertensive rats was significantly decreased ($p < 0.025, n = 10$).

Compared to vessels incubated in supernatants of boiled plasma of control rats, tail arteries from normal rats that were incubated in hypertensive rat supernates showed significantly decreased total $[^{86}]$Rb uptake whereas ouabain-insensitive uptakes were not different. The osmolality and the concentration of Na⁺, K⁺, Cl⁻, Ca²⁺, Mg²⁺, creatinine, BUN, and protein in the supernates from the hypertensive and control rats were not significantly different.

When we compared the progressive increase in systolic blood pressure with changes in vascular Na⁺-K⁺ pump activity of the experimental rats, we found that ouabain-sensitive $[^{86}]$Rb uptake was depressed by 19% just 1 week after subtotal nephrectomy when the rats were becoming hypertensive, and ouabain-sensitive uptake remained depressed for the entire study while systolic blood pressure remained elevated. There was, however, no significant correlation between the level of arterial blood pressure and percent inhibition of ouabain-sensitive $[^{86}]$Rb uptake.

Anteroventral Third Ventricle Lesion Study

Systolic blood pressures of the sham-lesioned reduced renal-mass rats drinking saline increased progressively following subtotal nephrectomy and was $163 \pm 3$ mm Hg 5 weeks later. Systolic blood pressures of the AV3V-lesioned reduced renal-mass rats drinking saline showed only a modest increase reaching $136 \pm 3$ mm Hg 5 weeks after subtotal nephrectomy (table 1).

Ouabain-sensitive $[^{86}]$Rb uptake by tail arteries from AV3V-lesioned reduced renal-mass rats was significantly greater than that by tail arteries from the paired sham-lesioned reduced renal-mass rats, while ouabain-insensitive $[^{86}]$Rb uptakes were not significantly different (table 1).

Central Sympathectomy Study

Systolic blood pressure of the centrally sympathectomized reduced renal-mass rats drinking saline showed only a modest increase following subtotal nephrectomy and was $132 \pm 3$ mm Hg 5 weeks later. The systolic blood pressure of the distilled water drinking rats did not significantly change during the course of this study and was $118 \pm 3$ mm Hg 5 weeks after subtotal nephrectomy.

There were no significant differences in either ouabain-sensitive or insensitive $[^{86}]$Rb uptakes between tail arteries from the saline drinking or distilled water drinking rats. Also, total $[^{86}]$Rb uptakes by tail arteries from normal rats incubated in supernates from saline drinking and distilled water drinking rats were not significantly different.

Measurement of whole-brain catecholamine content showed that both norepinephrine and dopamine levels were significantly lower in brains from saline and distilled water drinking centrally sympathectomized reduced renal-mass rats compared to levels in brains from normal unoperated rats. The level of these catecholamines in the saline drinking and distilled water drinking centrally sympathectomized rats was not significantly different.

Hypertension Reversal Study

Figure 1 shows the weekly systolic blood pressures of control distilled water drinking and experimental saline drinking reduced renal-mass rats for 5 weeks following subtotal nephrectomy, and the daily systolic blood pressures of these rats for 7 days following substitution of distilled water for drinking in the experi-

### Table 1. Comparison of Blood Pressure Levels and $[^{86}]$Rb Uptake Between Sham-Lesioned and AV3V-Lesioned Rats

<table>
<thead>
<tr>
<th>Rat group</th>
<th>Systolic BP (mm Hg) 5 weeks after subtotal nephrectomy</th>
<th>Ouabain-sensitive $[^{86}]$Rb uptake by tail arteries*</th>
<th>Ouabain-insensitive $[^{86}]$Rb uptake by tail arteries*</th>
<th>Total $[^{86}]$Rb uptake by tail arteries of normal rats incubated in boiled plasma supernates*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AV3V-lesioned reduced renal-mass saline-drinking rats</td>
<td>$136 \pm 3$</td>
<td>$7304 \pm 1100$</td>
<td>$1099 \pm 232$</td>
<td>$3216 \pm 590$</td>
</tr>
<tr>
<td>Sham-lesioned reduced renal-mass saline-drinking rats</td>
<td>$163 \pm 3$</td>
<td>$4227 \pm 523$</td>
<td>$943 \pm 189$</td>
<td>$2393 \pm 630$</td>
</tr>
<tr>
<td>Number</td>
<td>10</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>$p$ comparing lesioned vs sham lesioned</td>
<td>$&lt; 0.005$</td>
<td>$&lt; 0.025$</td>
<td>$&lt; 0.05$</td>
<td>$&lt; 0.025$</td>
</tr>
</tbody>
</table>

*pmoles/mg tissue dry weight.
mental group. As expected, systolic blood pressure of the saline drinking rats progressively increased following subtotal nephrectomy, reaching 168 ± 2 mm Hg by the 5th week while the systolic blood pressure of distilled water drinking rats did not significantly change during the entire study. Just 1 day after substitution of distilled water for saline, systolic blood pressure of the experimental rats dramatically and significantly decreased. There was a further significant decrease in blood pressure by 3 days after substitution with the distilled water and from the 3rd through 7th day following the change in drinking solutions, i.e., the systolic blood pressures of the control and experimental rats were not significantly different.

Ouabain-sensitive and insensitive $^{86}$Rb uptakes by tail arteries from control and experimental rats 7 days after substitution of distilled water for saline in the experimental group are presented in figure 2. There were no significant differences in either ouabain-sensitive or insensitive $^{86}$Rb uptakes. Also, Na$^+-$K$^+$-ATPase activities by microsomes prepared from the left ventricles of these rats were not significantly different (d ± Sd: 2.76 ± 1.1, $p > 0.5$, n = 5). Total $^{86}$Rb uptakes by tail arteries from normal rats incubated in supernates prepared from those control and experimental rats were also not significantly different (d ± Sd: 317 ± 352, $p > 0.5$, n = 7).

When these parameters were measured in control and experimental rats 3 days after substitution of distilled water for saline in the experimental group, there were again no significant differences in ouabain-sensitive (d ± Sd: 2.76 ± 1.1, $p > 0.2$, n = 7) or insensitive (d ± Sd: 98 ± 200, $p > 0.5$, n = 7) $^{86}$Rb uptake by tail arteries, Na$^+-$K$^+$-ATPase activities of cardiac microsomes (d ± Sd: 1.53 ± 0.2, $p > 0.2$, n = 7) or total $^{86}$Rb uptake by normal rat tail arteries incubated in control or experimental rat plasma supernates (d ± Sd: 166 ± 237, $p > 0.5$, n = 7).

There were no significant differences in hematocrit values between control and experimental rats at 3 days ($p > 0.3$, n = 7) or 7 days ($p > 0.5$, n = 7) following substitution of distilled water for saline in the experimental group.

Membrane Potentials

The EM values recorded from vascular smooth muscle cells in tail arteries of hypertensive and normotensive animals were not different. The plasma supernates...
obtained from hypertensive rats depolarized muscle cells in tail arteries from hypertensive rats. Similarly, the plasma supernates obtained from control normotensive rats depolarized muscle cells in tail arteries from control normotensive rats.

Discussion
Reduced Renal-Mass Hypertensive Rats

These findings indicate that in reduced renal-mass rats (70% to 80% renal mass removed), increasing the sodium intake (i.e., drinking 1% NaCl solution) induces hypertension whereas restricting the sodium intake (low sodium chow with distilled water for drinking) prevents the development of hypertension. Similar findings have been reported by other investigators. Additionally, measurements of plasma renin activity, hematocrit, and body fluid volumes show that the reduced renal mass model of hypertension is a low renin, volume-expanded type of hypertension, confirming the findings of Ylitalo and Gross and Pitcock et al.

Our findings of decreased ouabain-sensitive 86Rb uptake by tail arteries and decreased Na+-K+-ATPase activity by cardiac microsomes indicate decreased cardiovascular muscle cell Na+-K+ pump activity in the hypertensive reduced renal-mass rats relative to normotensive controls. As previously noted, the inhibition of Na+-K+ pump activity in experimental rats cannot be attributed to uremia since both control and experimental animals had similar reductions in functional renal mass and, in fact, experimental rats were less uremic than controls as indicated by lower blood urea nitrogen. Our finding of decreased pump activity in reduced renal-mass hypertensive rats is in agreement with our previous findings, and those of others in several types of low-renin hypertension. Depressed vascular ouabain-sensitive 86Rb uptake has been reported in rats with one-kidney, DOCA-salt hypertension and one-kidney, one clip hypertension. Decreased cardiac microsomal Na+-K+-ATPase activity has also been reported in rats with one-kidney, DOCA-salt hypertension and in dogs with one-kidney, one clip hypertension. Additionally, supernates of boiled plasma from rats with reduced renal-mass hypertension inhibited total but not ouabain-insensitive 86Rb uptake when applied to normal rat tail arteries. Since ouabain-sensitive 86Rb uptake is calculated as the difference between total and ouabain-insensitive uptakes, this observation suggests that there is a circulating Na+ transport inhibitor in hypertensive rats which may be responsible for the decreased cardiovascular muscle cell Na+-K+ pump activity found in these animals. This finding is consistent with reports from other models of low-renin hypertension. These include one-kidney, one clip3 and one-kidney, DOCA-salt hypertensive rats as well as one-kidney, one wrap hypertensive dogs. Furthermore, our finding that decreased vascular pump activity occurs as rapidly as the hypertension develops suggests that this pump defect may in fact play a role in the genesis of the hypertension. The observation that there is no direct correlation between the level of arterial blood pressure and percent inhibition of ouabain-sensitive 86Rb uptake is understandable. There are a variety of physiologic servomechanisms which contribute to the long term regulation of arterial blood pressure and it is expected that animals will vary in their physiological sensitivity to each of these systems.

Anteroventral Third Ventricle Lesion Study

Our findings in AV3V-lesioned and sham-lesioned rats indicate that the AV3V lesion markedly attenuates the development of reduced renal mass hypertension. This observation is consistent with reports in other low-renin, presumably volume-dependent models of hypertension. AV3V lesions have been shown to prevent the development of one-kidney, DOCA-salt hypertension and one-kidney, Grollman wrap hypertension in rats and reverse one-kidney, Grollman wrap hypertension in rats.

Our results indicate that the AV3V lesion prevents inhibition of vascular Na+-K+ pump activity and appearance of a sodium transport inhibiting factor in the plasma of saline-drinking reduced renal-mass rats. This finding is similar to that reported by Bealer et al who showed that AV3V lesions prevent appearance of a natriuretic factor in the plasma of acutely volume expanded rats. Additionally, we have shown that the AV3V lesion abolishes inhibition of vascular Na+-K+ pump activity and appearance of a circulating sodium transport inhibiting factor in acutely volume expanded rats. Furthermore, Songu-Mize et al have shown that AV3V lesions not only prevent the development of one-kidney, DOCA-salt hypertension, but they also prevent inhibition of Na+-K+ pump activity in tail arteries of these rats. These studies suggest that AV3V lesions may prevent the development of certain types of experimental low-renin hypertension by interfering with the synthesis and/or release of a circulating sodium transport inhibitor that affects cardiovascular muscle cells and plays an important role in the development and maintenance of the hypertension.

Central Sympathectomy Study

Our whole-brain catecholamine measurements indicate that the sympathectomies were effective. Central sympathectomy by intracerebroventricular injection of 6-hydroxydopamine markedly attenuated the development of reduced renal-mass hypertension, prevented inhibition of vascular Na+-K+ pump activity in these animals, and prevented appearance of a circulating sodium transport inhibitor in their plasma.

The observation that central sympathectomy prevents the development of reduced renal-mass hypertension is in agreement with findings in one-kidney, one clip hypertensive and one-kidney, DOCA-salt hypertensive rats. These findings suggest that central adrenergic pathways are involved in the synthesis and/or release of a
circular Na⁺-K⁺ pump activity and plays a role in the pathophysiology of certain types of experimental low-renin hypertension.

Hypertension Reversal Study

When distilled water was substituted for the 1% NaCl drinking solution of reduced renal-mass hypertensive rats, their arterial blood pressures dramatically fell within 24 hours to levels not significantly different from those of the normotensive control rats after 3 days of distilled water drinking. Since hematocrits of the control and experimental rats were also not significantly different at 3 and 7 days after substitution of the distilled water, the fall in blood pressure appears to have been accompanied by a decrease in blood volume.

Reversal of reduced renal-mass hypertension by this maneuver was also accompanied by a reversal of cardiovascular muscle cell Na⁺-K⁺ pump inhibition and absence of assay evidence for the presence of a circulating pump inhibitor.

These findings indicate that decreasing the sodium intake of reduced renal-mass hypertensive rats reverses the hypertension. Furthermore, the mechanism by which this occurs may be by decreasing body fluid volumes that reduce the stimulus for release of a Na⁺-transport inhibitor that affects cardiovascular muscle cells and thereby contributes to the development of hypertension.

Collectively, the findings of our present study support the hypothesis that inhibition of cardiovascular muscle cell Na⁺-K⁺ pump activity by a humoral sodium transport inhibitor, whose synthesis and/or release involves the AV3V area of the brain and central adrenergic pathways, contributes to the development and maintenance of certain low-renin, presumably volume-dependent models of experimental hypertension.

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Hypertension. 1983;5:194
doi: 10.1161/01.HYP.5.2_Pt_2.194

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