Control of Rat Renal Vascular Resistance during Alterations in Sodium Balance

PAUL A. JOHNSTON, DAVID B. BERNARD, NANCY S. PERRIN, LEONARD ARBEIT, WILFRED LIEBERTHAL, AND NORMAN G. LEVINSKY

SUMMARY Renal perfusion pressure (RPP), total renal blood flow (RBF), and renal vascular resistance (RVR) were comparable in groups of rats placed on high (HS) or low sodium (LS) diets for several weeks (HS, RVR = 16.4 ± 0.6; LS, RVR = 17.4 ± 0.6 mm Hg/ml per min). However, urinary kallikrein excretion was significantly lower in HS (0.31 ± 0.05U/min) than LS rats (0.98 ± 0.09U/min; P < 0.001).

Studies reported here were performed to test the hypothesis that parallel changes in the kallikrein-kinin system act to modify the vasoconstrictor effect of changes in the renin-angiotensin system in rats on varying sodium diets. In LS rats, saralasin, a competitive antagonist of angiotensin II (AII) reduced RVR from 17.4 ± 1.1 to 12.7 ± 1.1 mm Hg/ml per min (P < 0.005), and captopril, a converting enzyme (kininase II) inhibitor, reduced RVR from 17.1 ± 1.0 to 10.8 ± 0.7 mm Hg/ml per min (P < 0.005). Captopril failed to reduce RVR when given to LS rats pretreated with saralasin, indicating that AII inhibition probably is the mechanism of action of captopril in LS rats. Aprotinin, a kallikrein inhibitor, increased RVR from 17.5 ± 0.5 to 20.8 ± 0.9 mm Hg/ml per min in LS rats. Kinin infusion failed to reduce RVR in LS rats, but decreased RVR from 21.2 ± 1.7 to 17.6 ± 1.0 mm Hg/ml per min in aprotinin-treated LS rats. Therefore, resistance to the vasodilator effect of kinins in LS rats probably is due to functionally maximal endogenous kinin levels. In HS rats, saralasin failed to reduce RVR, but captopril reduced RVR from 15.6 ± 0.9 to 12.3 ± 1.0 mm Hg/ml per min (P < 0.025). Since aprotinin blocked this effect of captopril, it was probably due to potentiation of kinins by inhibition of kininase II. In HS rats, aprotinin alone had no effect on RVR, whereas kinin infusion reduced resistance from 17.8 ± 1.6 to 13.5 ± 1.6 mm Hg/ml per min (P < 0.005). From these data we concluded that kinins and AII both exert significant control over RVR in LS, but not HS rats. The balance between these hormones may act to stabilize RVR during wide variations in sodium intake. Circ Res 48: 728-733, 1981

IT IS NOW well established that the renin-angiotensin system is stimulated by reduction of dietary sodium intake (Granger et al., 1972; Flamhaembaum and Hamburger, 1974; Fray et al.; 1977; Kimbrough et al., 1977). Under these conditions, angiotensin II (AII), a potent vasoconstrictor component of this hormone system, which is produced locally within the kidney, has been shown to be an important factor regulating renal vascular resistance (RVR) (Freeman et al., 1973; Mimran et al., 1974; Warren and Ledingham, 1975; Arndshorst and Finn, 1977; Hall et al., 1977; Hollenberg et al., 1977; Kimbrough et al., 1977; Gavras et al., 1978, 1979). However, several studies in the rat and dog demonstrate that variations in sodium intake do not affect RVR appreciably (Arndshorst and Finn, 1977; Fagard et al., 1978; Steiner et al., 1979). These observations suggest that the vasoconstrictor effect of AII may be antagonized in some manner during reduced sodium intake. The kidney also produces kinins, potent renal vasodilator substances. Several studies have demonstrated that dietary sodium restriction stimulates the urinary excretion of kallikrein, the enzyme responsible for generating kinins (Margolius et al., 1974; Johnston et al., 1976; Levy et al., 1978; Arbeit et al., 1979). It seemed possible therefore, that renal kinin formation, may also be stimulated by sodium restriction and modulate the effect of AII.

The present study was designed to evaluate whether interaction between AII and kinins, might be consequential in determining RVR. To evaluate this, we studied the effects of altering the activity of these hormone systems in rats maintained on high and low sodium diets. From the results of this study we concluded that the degree of renal vascular tone in rats on varying sodium diets is dependent, in part, on the balance between AII and kinins.

Methods

Two groups of Charles River CD rats weighing 270 ± 9 g (220–350 g) were studied. The first group (HS) was allowed free access to normal laboratory chow and drank 1% saline ad lib. In addition, each rat in this group received 5 mg of desoxycorticosterone acetate (DOCA) per week in a single subcutaneous injection. The second group of animals (LS) was fed low Na⁺ chow (Purina laboratory rat
chow, 9 μEq/g) and drank distilled water. Sodium intake for the high salt group was about 24 mEq/day, and for the low salt group approximately 100 μEq/day. The rats remained on their respective diets for at least 3 weeks prior to study. The rats that received DOCA were studied at least 1 week after the final injection.

On the morning of the study, the animals were anesthetized, intraperitoneally, with ketamine hydrochloride (100 mg/kg) and inactin (25 mg/kg). Supplemental doses of inactin were given as needed. Body temperature was maintained between 37 and 38°C. Isotonic saline was infused continuously through a jugular vein catheter at 0.03 ml/min. Renal perfusion pressure (RPP) was monitored continuously through a catheter placed in the left femoral artery and attached to a strain gauge transducer and recorder. Blood flow in the left renal artery (RBF) was measured continuously with a flow probe (EP model, 401.5) connected to a squarewave electromagnetic flowmeter (Carolina Medical Electronics, model 501). Calibration of the probe system has been described previously (Johnston et al., 1979). Zero blood flow was determined periodically by completely occluding the renal artery distal to the probe.

Perfusion pressure, RBF, and RVR (RVR = RPP/RBF) were assessed during an initial control period in both HS and LS rats. Following control measurements, various inhibitors or vasoactive agents were administered intravenously. [Sar1, Ala2]angiotensin II (saralasin), a competitive inhibitor of AI (Castellion and Fulton, 1979), was diluted in isotonic saline and infused at 3-4 μg/kg per min. The converting enzyme inhibitor, D-3-mercapto-2-methylpropionyl-L-proline (captopril), which inhibits the conversion of angiotensin I (AI) to AI, and blocks the catalbolid of kinins (Ondetti et al., 1977), was diluted in isotonic saline and given as a bolus of 250 μg every 30 minutes. Aprotinin (Boehringer-Mannheim), which inhibits serine esterases, among them kallikrein (Werle et al., 1973), was diluted in isotonic saline and given as a bolus of 17 X 10⁶ kallikrein inhibitory units (KIU)/min followed by a maintenance of 150 KIU/min (Kramer et al., 1979). Kinins (bradykinin, ICN Pharmaceuticals, or kallidin, Protein Research Foundation) were infused at a rate of 4-5 μg/kg/min. Indomethacin, a non-steroidal inhibitor of prostaglandin synthetase, was diluted in a Na₂CO₃ buffer (0.2% Na₂CO₃, 0.88% NaCl, pH 8), and given as a bolus of 2 mg/kg followed by a maintenance of 2 mg/kg per hr. An interval of 45 minutes was allowed for equilibration after infusion of any of these agents was begun before additional hemodynamic assessments were made. Perfusion pressure and RBF values in each rat are a mean of at least three determinations made 10 minutes apart.

To evaluate the effect of alterations in dietary sodium intake on renal kallikrein activity, we measure urinary kallikrein excretion in separate groups of HS and LS rats. Urinary kallikrein activity was determined by the amidase method of Chung et al. (1979). Briefly, 5 μl of rat urine were incubated for 60 minutes with 45 μl of distilled water and 50 μl of substrate (Pro-Phe-Arg-[³H]benzylamide) in a 0.2 m Tris-HCl buffer at pH 9.5. The rate of hydrolysis of the substrate, determined from release of radiolabeled benzylamide, is a specific measure of the amount of kallikrein activity in urine. A unit of kallikrein activity (U) is defined as the percent of the total substrate hydrolyzed by 1 ml of urine in 1 minute of incubation.

Experiments were performed to determine the adequacy of saralasin and captopril to block the renal vascular effects of AI. AI (100-200 ng/min, iv) caused an increase in RPP of 32.1 ± 6 mm Hg (n = 8), and a fall in RBF of 1.6 ± 0.2 ml/min (n = 4) in HS rats. The same doses of AI resulted in a rise in RPP of 21.5 ± 3 mmHg (n = 9), and fall in RBF of 1.2 ± 0.2 ml/min (n = 5) in LS rats. Captopril blocked 93 ± 3% of this effect on RPP in four HS rats and 96 ± 2% in five LS rats. Captopril also blocked 100 ± 1% of the effect of angiotensin I on RBF in two HS and two LS rats. Saralasin blocked 80 ± 5% of the angiotensin I effect on RPP in four HS rats, and 80 ± 2% of the effect in four LS rats. Saralasin inhibited the effect of AI on RBF by 90 ± 3% in four LS rats, and 75 ± 1% in three HS rats.

Additional experiments were performed to determine the effectiveness of the dose of aprotinin used in the physiological experiments as a blocker of renal kallikrein activity. Urinary kallikrein activity, which was measureable in both HS (n = 5) and LS (n = 6) rats before treatment, could not be measured during aprotinin infusion.

Data are reported as mean ± se. In those groups of animals given a single treatment, the differences observed were evaluated by Student's t-test for paired data. In those groups which underwent multiple drug treatment, the differences observed were first tested by a multiple treatments ANOVA. If the F ratio was found to be significant (P < 0.05), individual means were then tested by Student's t-test for paired data (Snedecor and Cochran, 1967).

**Results**

In five rats (three HS, two LS), RBF and RVR were observed for at least 1 hour without any experimental intervention. Initially, RBF was 6.2 ± 0.3 ml/min and—after 1 hour—remained unchanged at 5.9 ± 0.3 ml/min. The mean change in RVR was 1.12 ± 0.64 mm Hg/ml per min (not significant). In addition, three of the rats were observed for 2 hours. No significant change in RBF or RVR was observed in this subsequent time period.

Table 1 summarizes our observations of RPP, RBF, and RVR in rats on high and low sodium intake. There were no significant differences between the two groups with regard to any of these factors. Urinary kallikrein excretion was signifi-
Table 1  Renal Hemodynamics of Rats on High and Low Salt Diets

<table>
<thead>
<tr>
<th>Diet</th>
<th>RPP (mm Hg)</th>
<th>RBF (ml/min)</th>
<th>RVR (mm Hg/ml per min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High salt (n = 26)</td>
<td>104 ± 3</td>
<td>6.5 ± 0.2</td>
<td>16.4 ± 0.6</td>
</tr>
<tr>
<td>Low salt (n = 33)</td>
<td>106 ± 2</td>
<td>6.1 ± 0.2</td>
<td>17.4 ± 0.4</td>
</tr>
</tbody>
</table>

Data are mean ± SE.

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Table 2 summarizes the effect of pharmacological alterations in the renin-angiotensin and kallikrein-kinin systems on the hemodynamics of the HS rats. Competitive inhibition of AII with saralasin significantly reduced RPP and RVR, and significantly increased RBF. Treatment with captopril which, in addition to blocking conversion of AI to AII, also reduces the catabolism of kinins, significantly reduced RVR. The magnitude of this reduction was statistically equivalent to that caused by saralasin. An additional group of HS rats was first treated with saralasin and subsequently with captopril. Captopril failed to reduce RVR further in these rats. These observations suggested that both saralasin and captopril were acting to reduce RVR in HS rats by antagonism of AII. The ability of captopril to reduce kinin degradation does not appear to contribute to its ability to reduce RVR in HS rats.

Low sodium rats were also treated with aprotinin to inhibit the kallikrein-kinin system (Table 2). Aprotinin treatment significantly reduced RBF and elevated RVR. In addition, RVR of LS rats was not altered by exogenous infusion of kinins. From these observations, we hypothesized that the failure of the renal vasculature to respond to kinin administration was due to the fact that endogenous kinin levels were maximal under conditions of reduced sodium intake. To test this hypothesis further, one additional experiment was performed. Low sodium rats first were treated with aprotinin to inhibit endogenous kinin formation; then kinins were administered. Under these circumstances, exogenous kinin infusion significantly reduced RVR.

To test whether the effects of the kallikrein-kinin system in LS rats were mediated by enhanced prostaglandin synthesis, we treated 10 LS rats with indomethacin. There was no significant effect on RPP (114 ± 2 to 106 ± 3 mm Hg), RBF (5.8 ± 0.3 to 5.3 ± 0.3 ml/min), or RVR (20.0 ± 1.0 to 20.8 ± 1.7 mm Hg/ml per min).

Table 3 summarizes the effect of alterations in the renin-angiotensin and kallikrein-kinin systems on renal hemodynamics of HS rats. Saralasin and

Table 2  Effect of Alterations in Renin-Angiotensin and Kallikrein-Kinin Systems on Renal Hemodynamics of Low Sodium Rats

<table>
<thead>
<tr>
<th>RPP (mm Hg)</th>
<th>RBF (ml/min)</th>
<th>RVR (mm Hg/ml per min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>105 ± 3</td>
<td>5.9 ± 0.3</td>
</tr>
<tr>
<td>Saralasin</td>
<td>88 ± 5‡</td>
<td>7.1 ± 0.3‡</td>
</tr>
<tr>
<td>(n = 7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>101 ± 5</td>
<td>6.2 ± 0.3</td>
</tr>
<tr>
<td>Captopril</td>
<td>74 ± 4‡</td>
<td>6.9 ± 0.3</td>
</tr>
<tr>
<td>(n = 7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>100 ± 2</td>
<td>5.4 ± 0.1</td>
</tr>
<tr>
<td>Saralasin</td>
<td>93 ± 6</td>
<td>6.2 ± 0.3†</td>
</tr>
<tr>
<td>Saralasin + captopril (n = 4)</td>
<td>89 ± 6</td>
<td>6.0 ± 0.3‡</td>
</tr>
<tr>
<td>Control</td>
<td>99 ± 3</td>
<td>5.7 ± 0.2</td>
</tr>
<tr>
<td>Aprotinin</td>
<td>95 ± 3</td>
<td>4.7 ± 0.3‡</td>
</tr>
<tr>
<td>(n = 15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>106 ± 6</td>
<td>6.8 ± 0.4</td>
</tr>
<tr>
<td>Kinin (n = 4)</td>
<td>108 ± 8</td>
<td>6.7 ± 0.4</td>
</tr>
<tr>
<td>Control</td>
<td>103 ± 4</td>
<td>6.0 ± 0.4</td>
</tr>
<tr>
<td>Aprotinin</td>
<td>99 ± 4</td>
<td>4.9 ± 0.4†</td>
</tr>
<tr>
<td>Aprotinin + kinin (n = 7)</td>
<td>102 ± 4</td>
<td>5.9 ± 0.3§</td>
</tr>
</tbody>
</table>

Data are mean ± SE.

* P < 0.05 vs. control; † P < 0.025 vs. control; ‡ P < 0.005 vs. control; § P < 0.05 vs. aprotinin-treated rats.
### Table 3  Effect of Alterations in the Renin-Angiotensin and Kallikrein-Kinin Systems on Renal Hemodynamics of High Sodium Rats

<table>
<thead>
<tr>
<th></th>
<th>RPP (mm Hg)</th>
<th>RBF (ml/min)</th>
<th>RVR (mm Hg/ml per min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>104 ± 5</td>
<td>6.0 ± 0.5</td>
<td>15.9 ± 1.2</td>
</tr>
<tr>
<td>Saralasin</td>
<td>97 ± 6</td>
<td>5.8 ± 0.4</td>
<td>17.2 ± 1.6</td>
</tr>
<tr>
<td>Control</td>
<td>94 ± 5</td>
<td>6.8 ± 0.4</td>
<td>15.6 ± 0.9</td>
</tr>
<tr>
<td>Captopril</td>
<td>92 ± 4*</td>
<td>7.8 ± 0.6*</td>
<td>12.3 ± 1.0*</td>
</tr>
<tr>
<td>Control</td>
<td>90 ± 4</td>
<td>5.8 ± 0.3</td>
<td>15.7 ± 0.7</td>
</tr>
<tr>
<td>Aprotinin</td>
<td>82 ± 7</td>
<td>5.2 ± 0.3</td>
<td>15.9 ± 1.4</td>
</tr>
<tr>
<td>Aprotinin + captopril</td>
<td>80 ± 7</td>
<td>5.3 ± 0.5</td>
<td>15.1 ± 1.5</td>
</tr>
<tr>
<td>Control</td>
<td>102 ± 5</td>
<td>6.0 ± 0.6</td>
<td>17.8 ± 1.6</td>
</tr>
<tr>
<td>Kinin</td>
<td>91 ± 6</td>
<td>7.0 ± 0.7†</td>
<td>13.5 ± 1.6†</td>
</tr>
</tbody>
</table>

* Data are mean ± se.
* P < 0.005 vs. control; † P < 0.005 vs. control.

Aprotinin alone had no significant effect on RVR in these rats. However, captopril treatment resulted in a significant rise in RBF and fall in RVR. Kinin infusion, as well, caused a significant rise in RBF and fall in RVR in these rats. As we have demonstrated, urinary excretion of kallikrein was low relative to that in LS rats, but not completely absent. Therefore, the effect of captopril probably was due to potentiation of the kallikrein-kinin system. To test this hypothesis further, we first treated HS rats with aprotinin to reduce kinin formation to the lowest possible level (kallikrein was undetectable). In this setting, captopril failed to alter RVR (Table 3).

### Discussion

We have found that chronic alterations in dietary sodium intake have no significant effect on RBF and RVR in the anesthetized rat (Table 1). These observations are in accord with both those of Arendshorst and Finn (1977), who demonstrated little effect of dietary sodium manipulation on RBF and RVR in anesthetized rats, and those of Steiner et al. (1978), who demonstrated little effect of reduced sodium intake on single nephron blood flow, and afferent or efferent arteriolar resistance in the same species. Several investigators have made similar observations in dogs (Kimbold et al., 1977; Fagard et al., 1978). Our results also demonstrate, as in these other studies, that reduction of sodium intake enhances the effect of endogenous AI in LS rats must have been antagonized by increased activity of one or more vasodilators. Recent studies have indicated that urinary excretion of kallikrein is related inversely to the level of dietary sodium intake in humans and animals (Margolius et al., 1974; Levy et al., 1978; Arbeit et al., 1979). Our observation that urinary kallikrein excretion is higher in LS than HS rats confirms this previous work and supports the hypothesis that the kallikrein-kinin system may act as an antagonist to the vasoconstrictor effect of the renin-angiotensin system. However, the observation of an increased urinary kallikrein excretion does not constitute evidence that this increase in any way affects the renal vasculature. Moreover, kallikrein activity in urine may not reflect activity at the vascular site of action, since kidney tissue and urine contain kininases which rapidly degrade the active end product of kallikrein activity, kinin.

Our pharmacological studies, although indirect, provide evidence for a physiological role for the increased renal kallikrein-kinin activity in LS rats. First, aprotinin, a non-specific inhibitor of kallikrein, elevated RVR in LS rats (Table 2). This response to aprotinin is in keeping with the hypothesis that the kallikrein-kinin system plays a significant role in offsetting the renal vascular response to elevated AI. Second, kinin infusion failed to reduce RVR in LS rats, but lowered RVR in LS rats that had been pretreated with aprotinin. From this observation we concluded that the failure of exogenous kinins to elicit a vascular response in LS rats was due to the fact that the vascular effect of endogenous kinins was maximal on a low sodium intake. Third, in LS rats the reduction of RVR caused by captopril was statistically the same in magnitude as that caused by saralasin, and was eliminated by pretreatment with that antagonist (Table 2). From these observations, we concluded that both agents caused vasodilation only by in-
hibiting AII. If potentiation of kinins, as well as inhibition of AII, were an important mechanism in the renal vascular response of LS rats to captopril, a greater reduction in RVR would have been expected with this agent than with saralasin. In addition, saralasin should not have been able to block completely the vascular response to captopril. The likeliest explanation for the failure of kininase II inhibition by captopril to be important in this setting is that elevated endogenous kinin production already may have had a maximal effect on RVR. Based on these observations, it seems reasonable to conclude that the kallikrein-kinin system has a maximal effect on RVR during reduction in dietary salt intake, and that this vasodilator influence (elevated kinin activity) is important in offsetting the vasoconstrictor effect of an increase in the activity of the renin-angiotensin system.

It has been well documented that renal prostaglandins have a very complex relationship with the renin-angiotensin and kallikrein-kinin systems (Levinsky, 1979); they may stimulate both systems, and probably mediate some of the biological effects of kinins. Recently, Stahl et al. (1979) have demonstrated that the PGE2 content of rabbit renal tissue is elevated by dietary sodium restriction. In the present study we explored the possibility that an increase in prostaglandin activity might be involved in control of RVR in LS rats. When LS rats were treated with indomethacin, RVR remained unchanged. This observation suggests that if prostaglandin synthesis is increased in LS rats it does not affect RVR directly, and does not mediate the effect of endogenous kinin synthesis. It also suggests that increased prostaglandin synthesis is not the stimulus for increased kinin production in LS rats. However, our studies are limited in scope; the dose of indomethacin we used has been shown to block only about 70% of prostaglandin synthesis in dog (Zambraski and Dunn, 1979), and blockade of prostaglandin synthesis might decrease the renin-angiotensin and kallikrein-kinin systems proportionately. Therefore, although lack of effect of indomethacin is against a key role for prostaglandins in control of renal vascular tone in LS rats, a firm conclusion is not possible.

Our observations are also consistent with the hypothesis that elevation of dietary sodium intake, which suppresses AII, suppresses the kinin effect on renal vascular tone as well. As in other studies in rats (Arendshorst and Finn, 1977; Steiner et al., 1978), dogs (Freeman et al., 1973), and humans (Hollenberg et al., 1977, 1979), we observed that saralasin had no significant effect on RVR in HS rats. We also observed that aprotinin had no significant effect on RVR of HS rats, suggesting that the kallikrein-kinin system does not significantly influence vascular tone under these conditions. Also consistent with low endogenous kinin activity is the marked renal vasodilator effect of kinins (Table 3) in HS rats. Although kinins appear to be suppressed to low levels which do not influence RVR in HS rats, endogenous synthesis is not completely absent. We found that urinary kallikrein activity in HS rats, while reduced to one-third that in LS rats, was readily measurable. In HS rats captopril decreased RVR, presumably because it elevated kinins to physiologically effective levels by inhibiting degradation. This explanation is supported by our observation that captopril had no effect in HS rats treated with aprotinin (Table 3). Arendshorst and Finn (1977) report that SQ20881, another kininase II inhibitor, had no effect on RVR in HS rats. Except for small variations in experimental design and the use of a different kininase II inhibitor, we cannot readily explain the discrepancy in results.

These pharmacological studies provide the first evidence that variation in the activity of the kallikrein-kinin system is a physiologically important determinant of RVR during variations in sodium intake. Unfortunately, at the present time there are no specific inhibitors of kinins or kallikrein similar to saralasin or captopril. Therefore, our conclusions are based on somewhat indirect data. Nevertheless, these observations coupled with the measurement of elevated urinary excretion of kallikrein in LS rats provide strong evidence that parallel changes in AII and kinins are one mechanism for maintaining the constancy of RVR in anesthetized rats despite changes in dietary sodium intake.

Unlike the data from rats, studies in rabbits (Mimran et al., 1974; Warren and Ledingham, 1975), humans (Hollenberg et al., 1971) and some studies in dogs (Freeman et al., 1973; Gavras et al., 1978; Oliver and Cannon, 1978) indicate that RVR does not remain constant as dietary sodium intake is varied. In these studies, RVR is about one-third higher on a low sodium than on a high sodium diet. Kallikrein activity of kidney or urine varies inversely with dietary sodium in dogs and humans as in rats (Levinsky, 1979). Thus, the increased activity of the kallikrein-kinin system appears unable to antagonize completely the increased activity of the renin-angiotensin system. It is possible that the increased kallikrein-kinin activity in these species on a low sodium diet partly antagonizes the effect of accelerated AII production, but appropriate experiments in these species are needed to clarify this point.

In conclusion, our results indicate that the variations in renal kallikrein activity, which were observed as dietary salt intake was varied, have an important role in setting renal vascular tone and stabilizing RVR over a wide range of sodium intake. The kallikrein-kinin system may be particularly important in preventing excessive vasoconstriction by AII on low sodium intake.

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References


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