Role of Chloride in Angiotensin II-Induced Salt-Sensitive Hypertension

Yuji Sato, Etsuro Ogata, and Toshiro Fujita

The present study investigated the effect of the anion accompanying sodium on the development of angiotensin II-induced hypertension in rats and the role of the sympathetic nervous system and extracellular fluid volume in its mechanism. Hypertension was induced by intraperitoneal infusion of angiotensin II (125 ng/min) for 12 days via miniosmotic pump. High dietary intake of sodium chloride significantly augmented the angiotensin II-induced hypertension (mean blood pressure on day 13, 165±6 versus 142±6 mm Hg, p<0.05), but equimolar sodium loading provided as sodium citrate failed to enhance angiotensin II hypertension (140±6 mm Hg). Plasma norepinephrine concentration in the conscious, resting state increased with sodium chloride loading in angiotensin II-infused rats (594±42 versus 312±37 pg/ml, p<0.01), but it remained unchanged with sodium citrate loading (324±23 pg/ml). Correspondingly, maximum response to hexamethonium bromide, a ganglion blocker, was greater in sodium chloride-loaded angiotensin II rats (77.7±4.6 mm Hg) than that in angiotensin II (59.7±5.1 mm Hg) or in sodium citrate-loaded angiotensin II (57.7±4.2 mm Hg) rats. Moreover, extracellular fluid volume, measured as Na\textsuperscript{+}\textsubscript{2}SO\textsubscript{4} space, increased in sodium chloride-loaded angiotensin II rats (427±18 ml/kg body wt) as compared with that in angiotensin II rats (375±15 ml/kg body wt) but not when compared with volume in sodium citrate-loaded angiotensin II (389±7 ml/kg body wt) rats. These results suggest that the full expression of salt (sodium chloride) sensitivity in angiotensin II hypertension depends on high dietary intake of both sodium and chloride and that the increased sympathetic nervous system activity might be involved in the increased salt sensitivity of blood pressure in angiotensin II hypertension, possibly through decreased renal function for sodium excretion. (Hypertension 1991;18:622-629)

Angiotensin II (Ang II) is one of the body’s most powerful regulators of sodium excretion, operating through extrarenal mechanisms as well as intrarenal mechanisms. The regulation of sodium excretion by Ang II is closely linked with arterial pressure control and volume homeostasis through the renal pressure-natriuresis mechanism: chronic infusion of physiological amounts of Ang II, in which Ang II is inappropriately elevated, causes increased arterial pressure (hypertension) so that the kidney “escapes” the potent antinatriuretic action of Ang II and sodium excretion returns to normal via the pressure-natriuresis mechanism. In addition, when sodium intake is raised concomitant with Ang II infusion, a larger increase in blood pressure is required to maintain sodium balance. This observation indicates that Ang II-induced hypertension is a type of salt-sensitive hypertension, but the precise mechanisms for the pathogenesis of Ang II-induced salt-sensitive hypertension are still unknown.

Several investigators reported that in two animal models of salt-sensitive hypertension, Dahl salt-sensitive (DS) rats or deoxycorticosterone acetate (DOCA)-salt hypertensive rats, blood pressure did not increase when dietary sodium was supplemented as nonchloride sodium salts. The evidence suggests that the anion administered with sodium has an important impact on the salt sensitivity of blood pressure. Correspondingly, we have recently demonstrated that a high dietary intake of sodium chloride significantly augmented the Ang II-induced hypertension in rats, but equimolar sodium loading provided as sodium citrate failed to enhance Ang II hypertension. These observations suggest that Ang II-induced hypertension is salt-sensitive hypertension, as mentioned above, and they provide a novel opportunity to elucidate the role of chloride in Ang II-induced salt-sensitive hypertension.

In the present studies, therefore, we conducted extracellular fluid volume (ECFV) and sympathetic nervous system (SNS) activity measurements in sodium chloride or sodium citrate loading in Ang...
II-infused rats and SNS activity in the manifestation of salt-sensitive hypertension. Also, to evaluate the possibility that failure of selective sodium loading to produce hypertension might be related to a hypotensive effect of the diet itself, blood pressure and SNS activity responses to sodium chloride or sodium citrate loading in normotensive Sprague-Dawley rats were compared.

**Methods**

In all experiments, male Sprague-Dawley rats (Charles River Japan Inc., Atsugi, Japan) weighing 220–280 g were used. A miniosmotic pump (model 2002, Alza Corp., Palo Alto, Calif.) was implanted in the peritoneal cavity of Ang II-infused rats, providing Ang II ([Ileu5]-Ang II, Sigma Chemical Co., St Louis, Mo.) at an infusion rate of 125 ng/min. Control rats received a pump implant containing vehicle (saline). Rats were given ad libitum a normal rat chow (0.66% sodium chloride, Oriental Yeast Co., Tokyo), an 8% sodium chloride diet (by adding 7.34% sodium chloride to normal rat chow), or a diet containing sodium equimolar to 8% sodium chloride, provided as sodium citrate (by adding 12.3% sodium citrate to normal rat chow). Each group of rats received tap water to drink ad libitum. The animals were housed in group cages (3–4 rats/cage) and were kept in a temperature-controlled (23±1°C) and humidity-controlled (60±5%) room with a 12-hour light/dark cycle (illuminated between 6:00 AM and 6:00 PM).

**Experiment 1**

In experiment 1, the objective was to compare plasma concentration of catecholamines and Ang II. Thirty-two rats were divided into four groups after body weight measurements. Group 1 rats (n=8) received an Ang II-containing pump implant and were given a normal rat chow to eat (Ang II group). Group 2 rats (n=8) received an Ang II-containing pump implant and were fed an 8% sodium chloride diet (Ang II+NaCl group). Group 3 rats (n=8) received an Ang II-containing pump implant and were fed a sodium citrate diet (Ang II+sodium citrate group). Group 4 rats (n=8) received a vehicle-containing pump implant and were fed a normal rat chow (control group). After 12 days of each treatment, all of the rats of each group were weighed and anesthetized with pentobarbital sodium (50 mg/kg i.p.), and the femoral vein and artery were cannulated. Arterial pressure was monitored with a pressor transducer in conscious unrestrained, resting animals for 24 hours after catheter placement. After a stable mean arterial pressure was obtained (at least 30 minutes was allowed for stabilization), saralasin was infused intravenously at a rate of 9 μg/min for 30 minutes. Thereafter, 270 μg of the inhibitor was rapidly infused (within 3 minutes), and the maximum decrease in mean arterial pressure was regarded as the response to saralasin.

**Experiment 2**

In a separate experiment, to further explore the involvement of SNS activity and Ang II in the maintenance of elevated blood pressure, we measured the hypotensive responses to hexamethonium bromide (Hexamethonium, Tokyo Kasei Kogyo Co., Ltd., Tokyo), a ganglion blocker,18 or to [Sar'-Ala'-Ang II (saralasin, Peptide Institute Inc., Osaka, Japan), a specific competitive inhibitor of Ang II.19 Rats were subjected to all procedures as described for experiment 1. After 12 days of each treatment, all of the rats from each group were anesthetized with pentobarbital sodium (50 mg/kg i.p.), and the femoral vein and artery were cannulated. Arterial pressure was monitored with a pressor transducer in conscious unrestrained, resting animals for 24 hours after catheter placement. After a stable mean arterial pressure was obtained (at least 30 minutes was allowed for stabilization), saralasin was infused intravenously at a rate of 9 μg/min for 30 minutes. Thereafter, 270 μg of the inhibitor was rapidly infused (within 3 minutes), and the maximum decrease in mean arterial pressure was regarded as the response to saralasin.20 Immediately afterward, 30 mg/kg hexamethonium bromide was infused intravenously, and the maximum decrease in mean arterial pressure was regarded as the response to hexamethonium.

**Experiment 3**

In a separate experiment, ECFV was measured as the value of distribution of Na/35SO4 (New England Nuclear Corp., Boston, Mass.).21 Rats were subjected to all procedures as described for experiment 1. After 12 days of each treatment, 500,000 cpm of the tracer in 300 μl saline was injected as a bolus into the tail vein using a Hamilton microcitor syringe fitted with a disposable 26-gauge needle. Hemostasis was achieved by applying pressure with an applicator stick flap pulled over the injection site. Since preliminary study had shown that 30 minutes was the optimum equilibration period, a blood sample was taken by decapitation and was centrifuged; plasma samples were centrifuged and the serum and plasma were frozen at —40°C. Serum sodium, potassium, and chloride were measured by standard laboratory techniques. Plasma norepinephrine and epinephrine were measured using a modification of the radioenzymatic method of Dolber and Johnson (Cat-A-Kit, Upjohn, Kalamazoo, Mich.). Plasma Ang II concentration was measured by the radioimmunoassay technique. Also, plasma aldosterone concentration was quantitated by the radioimmunoassay technique using a commercial kit (Aldosterone-RiaKit, Dainabot, Tokyo).
of radioactivity. The bladder was exposed through a suprapubic incision, and its entire contents were added to an adequate volume of scintillation cocktail (Aquasol) for counting of radioactivity.

One milliliter of each standard and 1 ml of serum from each rat were counted at the same time, and the average counts per minute of the four standards were used to calculate the number of counts that had been injected in each rat; it was not necessary to correct for radioactive decay. The activity of serum samples was usually more than 10 times that of the background activity, and counting errors were usually less than 1%. Estimated ECFV, expressed as percent body weight, was calculated as follows

\[
\text{ECFV (\% body wt)} = \frac{\text{\textsuperscript{35}S injected (cpm)} + \text{\textsuperscript{35}S urine (cpm)}}{\text{\textsuperscript{35}S/ml serum (cpm)}} \times \frac{1}{\text{body wt (g)}} \times 100
\]

**Experiment 4**

In another separate experiment, we compared the effects of either high sodium chloride diet or high sodium citrate diet on basal mean arterial pressure, pressor responses to Ang II or norepinephrine, and depressor response to hexamethonium. The high sodium chloride group \((n=7)\), the high sodium citrate group \((n=7)\), or the control group \((n=7)\) of rats were fed each diet for 12 days. Rats were anesthetized with pentobarbital sodium \((50 \text{ mg/kg i.p.})\), and the femoral vein and artery were cannulated. Twenty-four hours after catheter placement, stable mean arterial pressure was recorded \((30 \text{ minutes after the start of recording})\). Graded doses of Ang II \((\text{Sigma, 6.25–100 ng/kg})\) or norepinephrine \((\text{Winthrop Labs, New York, 125–2,000 ng/kg})\) were administered intravenously by bolus injection. The order in which the two drugs were given was randomized between rats. Thereafter, 30 mg/kg hexamethonium was infused intravenously, and the maximum decrease in mean arterial pressure was regarded as the response to hexamethonium.

**Statistical Analysis**

All values are expressed as mean±SEM. Statistical significance of differences in values among groups was derived from performing an analysis of variance followed by the use of the Bonferroni method for making simultaneous multiple comparisons. A value of \(p<0.05\) was considered significant.

**Results**

**Experiment 1**

Twenty-four hours after catheter placement, mean arterial pressure was recorded (Figure 1). The rats with minipumps (control group) showed mean arterial pressure of 103±2 mm Hg. Mean arterial pressure of rats with pumps containing Ang II (Ang II group) was 142±6 mm Hg. Sodium chloride loading in the Ang II-infused rats (Ang II+NaCl group) augmented the rise in mean arterial pressure \((165±6 \text{ mm Hg})\), but sodium citrate supplementation to Ang II-infused rats (Ang II+sodium citrate group) did not augment the rise in mean arterial pressure \((140±6 \text{ mm Hg})\). There was no statistically significant difference in the levels of mean arterial pressure measured on day 13 between the Ang II and Ang II+sodium citrate groups.

There were no group differences of starting body weight or weight gain during the study (Table 1). Although serum sodium concentration was not different among four groups, potassium concentration was significantly lower in the Ang II+NaCl and Ang II+sodium citrate groups than in the other three groups. Plasma Ang II concentration was significantly increased in the three groups infused with Ang II compared with the control group. Plasma aldosterone concentration was significantly lower in the Ang II group than in the control group. Although supplementation of either sodium chloride or sodium citrate suppressed plasma aldosterone in Ang II rats, it was moderately, but not significantly, lower in sodium citrate-supplemented Ang II rats as com-
Table 1. Body Weight and Blood Variables of Rats in Control, Angiotensin II, Sodium Chloride-Supplemented Angiotensin II, and Sodium Citrate-Supplemented Angiotensin II Groups

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Control (n=8)</th>
<th>Angiotensin II (n=8)</th>
<th>Angiotensin II+NaCl (n=8)</th>
<th>Angiotensin II+Na citrate (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>248±7</td>
<td>247±6</td>
<td>245±7</td>
<td>248±6</td>
</tr>
<tr>
<td>Day 12</td>
<td>306±8</td>
<td>298±7</td>
<td>280±9</td>
<td>283±7</td>
</tr>
<tr>
<td>Serum variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium (mmol/l)</td>
<td>145.0±1.3</td>
<td>144.1±1.1</td>
<td>145.1±1.1</td>
<td>143.6±0.9</td>
</tr>
<tr>
<td>Potassium (mmol/l)</td>
<td>4.8±0.2</td>
<td>4.9±0.2</td>
<td>3.6±0.3*</td>
<td>3.7±0.3*</td>
</tr>
<tr>
<td>Chloride (mmol/l)</td>
<td>99.4±1.1</td>
<td>97.1±1.2</td>
<td>96.4±2.5</td>
<td>77.2±3.2*</td>
</tr>
<tr>
<td>Plasma variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiotensin II (pg/ml)</td>
<td>21.6±2.8</td>
<td>129.3±16.7*</td>
<td>132.5±17.1*</td>
<td>119.2±20.6*</td>
</tr>
<tr>
<td>Aldosterone (ng/dl)</td>
<td>22.2±3.2</td>
<td>227.4±52.1*</td>
<td>63.2±10.4</td>
<td>18.0±2.5*</td>
</tr>
<tr>
<td>Corticosterone (ng/ml)</td>
<td>639±31.8</td>
<td>633±63.3</td>
<td>603±41.9</td>
<td>588±44.7</td>
</tr>
</tbody>
</table>

*p<0.05 vs. control group.

As shown with sodium chloride–supplemented Ang II rats (18.0±2.5 versus 63.2±10.4 ng/ml, 0.05<p<0.1).

As shown in Figure 2, plasma norepinephrine concentration was not different between the control and Ang II groups (335±34 versus 312±37 pg/ml), but it was significantly increased in the Ang II+NaCl group (594±42 pg/ml). However, sodium citrate supplementation to the Ang II-infused rats did not increase plasma norepinephrine concentration (324±23 pg/ml). Moreover, plasma epinephrine concentration tended to be higher (but not statistically significant) in the Ang II+NaCl group compared with that in the other three groups, and plasma total catecholamine (norepinephrine+epinephrine) concentrations were markedly (p<0.01) increased in the Ang II+NaCl group (1,026±131 pg/ml) compared with that in the other three groups (control, 505±47; Ang II, 527±72; Ang II+sodium citrate, 547±38 pg/ml).

Experiment 2

Moreover, we examined blood pressure responses to saralasin or hexamethonium. Rats were prepared as in experiment 1. The rats of the control group showed mean arterial pressure of 107±2 mm Hg. Mean arterial pressure of the Ang II group was significantly (p<0.01) increased to 143±4 mm Hg. Sodium chloride loading in the Ang II-infused rats further increased (p<0.01) mean arterial pressure (166±4 mm Hg), but the sodium citrate load did not (139±4 mm Hg). These results are consistent with those in experiment 1. As shown in Figure 3, depressor response to saralasin was not different among the three Ang II-infused groups (Ang II, -26.7±4.2; Ang II+NaCl, -31.6±4.6; Ang II+sodium citrate, -29.4±5.3 mm Hg), which is consistent with the data of plasma Ang II concentrations mentioned above. However, maximum response to hexamethonium was greater in sodium chloride–loaded Ang II rats (−77.7±4.6 mm Hg) compared with that in the control (−49.0±2.1 mm Hg), Ang II (−59.7±5.1 mm Hg), or Ang II+sodium citrate groups (−57.7±4.2 mm Hg). There was no significant difference in

![Figure 2](http://hyper.ahajournals.org/) Bar graphs show plasma norepinephrine (NE) and epinephrine (E) concentrations in rats treated with each regimen. Group 1 received saline-containing pump implant and normal rat chow (control); group 2 received angiotensin II–containing pump implant and normal rat chow (A II); group 3 received angiotensin II–containing pump implant and 8% sodium chloride diet (A II+NaCl); and group 4 received angiotensin II–containing pump implant and sodium diet equimolar to 8% sodium chloride, provided as sodium citrate (A II+Na citrate).
postganglionic blockade mean arterial pressure in the four groups of rats (Figure 3).

Experiment 3

As shown in Figure 4, Na$_2^{35}$SO$_4$ space was increased in the Ang II+NaCl group ($427 \pm 18$ ml/kg body wt) as compared with the control ($377 \pm 8$ ml/kg body wt) or Ang II ($375 \pm 15$ ml/kg body wt) groups, but it was not increased in the Ang II+sodium citrate group ($389 \pm 7$ ml/kg body wt).

Experiment 4

Neither the high sodium chloride (100±4 mm Hg, $n=7$) nor the high sodium citrate (102±3 mm Hg, $n=7$) diet affected mean arterial pressure in the control group (fed normal rat chow) rats (100±3 mm Hg, $n=7$). Also, pressor responses to Ang II or norepinephrine were not different in the three groups of rats (Figure 5). Moreover, depressor response to hexamethonium did not differ among the three groups (control, $-42.6 \pm 1.8$; NaCl, $-42.8 \pm 2.6$; sodium citrate, $-43.0 \pm 3.3$ mm Hg).

Discussion

We observed that sodium chloride loading augmented the development of Ang II hypertension but that sodium citrate loading did not. Also, sodium chloride loading in Ang II-infused rats increased both ECFV and SNS activity but sodium citrate loading did not. Furthermore, in normotensive control rats, neither sodium chloride nor sodium citrate affected resting blood pressure, pressor responses to Ang II or norepinephrine, or the vasodepressor response to hexamethonium. These results suggest that full expression of salt-induced blood pressure increase might be intimately related to the combination of volume expansion and increased SNS activity, which might be manifested only in situations of the chronic coexistence of Ang II and sodium chloride.

Our experiments were performed using subcutaneous infusion of 125 ng/min [Ileu$^5$]-Ang II; plasma concentrations of Ang II were approximately 100–150 pg/ml. These levels could almost certainly cover the physiological and pathophysiological ranges but not the pharmacological ones. In the current studies, Ang II-infused rats had a moderate increase in blood pressure without increases in ECFV and SNS activity. According to normal ECFV, Hall et al.
demonstrated, in their experiments with dogs chronically infused with Ang II, that Ang II might be primarily responsible for the tendency toward sodium and water retention that occurs until arterial pressure increases enough to achieve sodium and water balance. In turn, increased arterial pressure would normally cause natriuresis through the pressure-natriuresis mechanism, resulting in the restoration of increased ECFV to the control level.\(^{23}\) It should be noted that in our early study,\(^{13}\) systolic blood pressure of Ang II--infused rats, measured by the tail-cuff method at 4-day intervals, had reached a plateau by day 8. In the present study, therefore, it was suggested that Ang II--infused rats had no apparent increase in ECFV measured on day 12, despite a sustained increase in plasma aldosterone. According to normal SNS activity in Ang II rats, there are several evidences supporting it: administration of the sympatholytic agent did not attenuate the sodium-retaining or hypertensive actions of Ang II.\(^{26}\) Moreover, norepinephrine overflow in the kidney, an index of renal sympathetic nerve activity, was not increased in Ang II--infused dogs.\(^{27}\) Finally, the present finding that there was no significant difference in postsaralasin blood pressure levels between control rats (108±4 mm Hg) and Ang II--infused rats (115±6 mm Hg) but that the difference was still significantly higher in sodium chloride-supplemented Ang II rats (136±6 versus 108±4 mm Hg, \(p<0.01\)) suggested that other factors than the direct vascular action of Ang II are less important in the maintenance of blood pressure in Ang II--treated rats as compared with sodium chloride-supplemented Ang II rats. This is compatible with the present data, which indicate that either ECFV measured by isotope dilution method or SNS activity measured by plasma norepinephrine concentration and vasodepressor response to hexamethonium were normal in Ang II--treated rats, but both indexes were significantly increased in Ang II+NaCl rats.

In sodium citrate--loaded Ang II rats, serum chloride concentration was markedly decreased, whereas potassium concentration was also decreased as in sodium chloride--loaded Ang II rats. Moreover, sodium citrate loading could cause relative alkalosis as demonstrated in human subjects,\(^{28}\) although we did not measure arterial pH or bicarbonate levels. These circumstances were also observed in the salt-sensitive hypertensive rats given the sodium bicarbonate and sodium ascorbate diets.\(^{8,10}\) However, in the absence of hypokalemic alkalosis by addition of a mixture of non–chloride-containing sodium salts (including phosphate, bicarbonate, aspartate, and glycinate), selective sodium loading failed to increase arterial pressure.\(^{8,10}\) Thus, the lack of the chloride anion probably accounts for the failure of sodium citrate to raise blood pressure in salt-sensitive hypertension.\(^{14,29}\)

It is well known that a salt-induced blood pressure rise in salt-sensitive hypertensive animals and humans is associated with increased ECFV.\(^{2,7,25,30}\) Studies of selective sodium loading also implicated volume mechanisms in the pathogenesis of salt-sensitive hypertension: In DOCA-salt rats, ECFV (inulin space) is expanded by dietary sodium chloride loading but not by selective sodium loading.\(^{10}\) Similarly, Kurtz et al\(^ {11}\) have recently reported that blood pressure was increased by a high sodium chloride intake but not by equimolar sodium loading provided as sodium citrate in five salt-sensitive essential hypertensive men. In their study, plasma volume was increased by high sodium chloride intake but not by high sodium citrate intake. These evidences\(^ {10,11,21}\) suggest that a sodium citrate load could excrete urinary sodium more rapidly than a sodium chloride load, resulting in the inhibition of volume expansion. Although the mechanism for sodium citrate--induced natriuresis is still unknown, it might be attributable partly to lower plasma aldosterone in sodium citrate--supplemented Ang II rats than in sodium chloride-supplemented Ang II rats. Alternatively, it might be related to metabolic alkalosis induced by sodium citrate. Recently, Sharma et al\(^ {28}\) demonstrated that sodium chloride loading not only increased blood pressure but also decreased arterial pH in young salt-sensitive normotensive subjects, whereas sodium citrate loading did not alter blood pressure with metabolic alkalosis. Furthermore, they speculated that the abnormality of renal acid–base regulation
might be involved in sodium chloride-induced rise in blood pressure and the concomitant metabolic acidosis in salt-sensitive subjects, but metabolic alkalosis with sodium citrate could normalize the abnormal renal sodium handling, leading to natriuresis. This suggests that sodium chloride loading in salt-sensitive humans and animals would cause sodium retention with the resultant blood pressure increase, whereas sodium citrate load would not induce sodium retention, resulting in the absence of blood pressure rise. However, there is still some possibility that the differences of ECFV in sodium citrate- and sodium chloride-fed animals are related to an altered volume of distribution rather than to a difference in sodium excretion since we did not measure sodium balance.

In contrast to sodium citrate-loaded Ang II rats, sodium chloride loading in Ang II rats was associated with increased SNS activity. Of course, the increased SNS activity could cause the rise in blood pressure with salt loading by increasing vascular resistance. If it is the case in the kidney, it might cause sodium retention and thus increase blood pressure. There is a considerable body of evidence suggesting that the increased renal SNS activity may play an important role in salt-induced blood pressure rise through sodium retention. Katholi et al. and Cowley and Lohmeier demonstrated that chronic intrarenal infusion of norepinephrine resulted in sustained hypertension via sodium retention, whereas chronic intravenous infusion failed to produce sustained hypertension because of pressure natriuresis. Although we did not measure renal SNS activity directly, it may be speculated that sodium chloride-induced augmentation of Ang II hypertension in our studies might be attributed to the increased renal SNS activity, which causes impaired renal function for sodium excretion. Conversely, sodium citrate loading in Ang II-infused rats did not produce volume expansion or increased SNS activity, with no further increase in blood pressure. Thus, the chloride ion plays an important role in sodium chloride-induced potentiation of hypertension by modulating the renal function curve for sodium excretion, possibly through the changes in renal SNS activity. Coexistence of two major hypertensinogenic factors, volume expansion, and the increased SNS activity might, therefore, contribute to the continuous elevation of blood pressure in sodium chloride-loaded Ang II rats, as in DOCA-salt hypertensive rats.

In conclusion, we found that sodium chloride loading in Ang II-infused rats potentiated the hypertension associated with volume expansion and increased SNS activity, whereas sodium citrate loading did not. At present, the precise mechanism for the pathogenesis of salt-sensitive hypertension is not clear, but impaired response of SNS to volume expansion might be primarily important in the development of Ang II-induced salt-sensitive hypertension.

References


**Key Words**: sympathetic nervous system • sodium • chloride • angiotensin II