Sodium restriction prevents cardiac hypertrophy and oxidative stress in angiotensin II hypertension

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Rugale, Caroline, Sandrine Delbosc, Jean-Paul Cristol, Albert Mimran, and Bernard Jover. Sodium restriction prevents cardiac hypertrophy and oxidative stress in angiotensin II hypertension. Am J Physiol Heart Circ Physiol 284: H1744–H1750, 2003. First published December 5, 2002; 10.1152/ajpheart.00864.2002.—The influence of a low-sodium (LS) diet was assessed on the cardiac and renal alterations and pro-oxidant effect associated with a 10-day infusion of angiotensin II (200 or 400 ng·kg⁻¹·min⁻¹, osmotic pumps). Tail-cuff pressure (TCP), albuminuria, and renal blood flow were determined at the end of the experiments. Heart weight index (HWI) and production of superoxide anion (O₂⁻) by the left ventricle and H₂O₂ by the aorta was measured with the use of bioluminescence. Although the final TCP was similar in LS and normal sodium (NS) rats infused with high and low doses of angiotensin II, respectively, the increase in HWI was prevented by the LS diet. Sodium restriction reduced the rise in albuminuria without a change in the renal effect of angiotensin II. The increased production of O₂⁻ and H₂O₂ observed in NS rats was abrogated in LS rats. The beneficial influence of dietary sodium restriction on target organ damage induced by angiotensin II is independent of arterial pressure reduction and possibly related to attenuation of the prooxidant effect of the peptide.

heart weight; albuminuria; reactive oxygen species; renal hemodynamic

THE DEVELOPMENT OF cardiac hypertrophy results from the interaction between several factors, including elevated arterial pressure, angiotensin II (ANG II), and sodium intake. Although blood pressure is an important determinant of cardiac mass (8), ANG II may directly increase protein synthesis and cause myocyte hypertrophy, as reported in cultured cardiac myocytes isolated from chicks (2) and neonatal rats (34). In vivo long-term administration of an initially subpressor dose of ANG II, a model that mimics the development of human hypertension, induces a gradual rise in blood pressure associated with a cardiac hypertrophy (7, 14, 17). However, ANG II might increase cardiac mass independently of arterial pressure. This was suggested by the presence of cardiac hypertrophy in rats infused with a nonpressor dose of the peptide (4, 37) or in rats infused with a pressor dose of ANG II and concomitantly treated by hydralazine (7, 37).

The concentration of sodium ion in vitro or dietary sodium intake in vivo may modulate cardiac mass. In cultured neonatal rat myocardial myoblasts, cellular protein content and cell size increased when sodium concentration of the medium was augmented (15). In vivo, a high-sodium intake increased cardiac mass in normotensive rats (46) and exacerbated cardiac hypertrophy in hypertensive rats (12). In humans, sodium intake (assessed by urinary sodium excretion) and the left ventricular mass index were positively correlated in hypertensive and normotensive subjects (9). Conversely, a low-sodium (LS) intake prevents cardiac hypertrophy associated with two-kidney, one-clip Goldblatt hypertension (5, 26, 32, 36, 41) and ANG II hypertension (27). The beneficial effect of dietary sodium restriction on cardiac mass may parallel the change in arterial pressure (5, 41) or can be independent of arterial pressure reduction (26, 27, 32).

Aside from a direct effect on arterial pressure and cardiac mass, ANG II and sodium intake may alter the cardiovascular system through an increased production of reactive oxygen species (19). ANG II induces an overexpression of cytosolic proteins involved in the activation of NAD(P)H oxidase of vascular endothelial and smooth muscle cells (13, 43) and favors the production of reactive oxygen species, such as superoxide anion (O₂⁻), H₂O₂, and hydroxyl radical (43). On the other hand, an important link between sodium intake and oxidative stress was suggested by the high vascular oxidative activity of normotensive rats fed a high-salt diet and the reversal by reactive oxygen species scavengers of altered responsiveness to acetylcholine associated with high-salt intake (21).

In the present study, we tested the hypothesis that severe and chronic dietary sodium restriction may reduce the prooxidant effect of ANG II and prevent the development of cardiac and renal alterations associated with long-term infusion of the peptide. The dose of ANG II was doubled in sodium-restricted rats to obtain a level of hypertension similar to that achieved in sodium-replete rats infused with the low dose of the...
peptide. The present results indicate that cardiac hypertrophy, albuminuria, and hyperproduction of reactive forms of oxygen associated with ANG II hypertension are prevented by dietary sodium restriction independently of arterial pressure reductions.

**MATERIALS AND METHODS**

The experiments were carried out in 6 groups of 16 Sprague-Dawley rats (Iffa-Credo; L’Arbresle, France) maintained on a normal sodium (NS) or LS diet. LS rats weighed 200–220 g at the beginning of studies and NS rats were matched to obtain a similar body weight before ANG II infusion. The LS diet consisted of a sodium-free rat chow containing <5 mmol sodium/kg and distilled water as drinking fluid. The NS diet was obtained by the addition of 8.7 g NaCl/kg of the food. The sodium content of the diet was modified at least 3 wk before ANG II infusion to allow the animals to reach a new sodium balance. Rats were then placed in individual metabolic cages until the end of experiments. After a 3-day control period, ANG II (Sigma; Paris, France) was infused subcutaneously via osmotic pumps (model 2002, Alza; Palo Alto, CA) at the dose of 200 or 400 ng·kg⁻¹·min⁻¹ for 10 days in rats maintained on the NS and LS diet. Two groups of rats were infused with distilled water and served as control animals.

Before and during ANG II infusion, body weight, food and water intake, and urinary excretion of water, sodium, and potassium were measured daily in all rats. Urinary excretion of albumin and creatinine was determined before and at the end of treatment period. Tail-cuff pressure (TCP; Narco Biosystems, Houston, TX) was recorded in conscious rats before and every second day of the experimental period. On day 10 of ANG II infusion, groups were split into two subgroups of eight rats and prepared either for cardiac output and renal blood flow determination or measurement of tissue production of reactive forms of oxygen. All procedures were designed in accordance with French law and institutional guidelines for the care and use of laboratory animals.

**Cardiac output and renal blood flow.** Cardiac output and renal blood flow were evaluated in conscious rats using ⁵¹⁷⁷-Co-labeled microspheres (15 ± 1 mm diameter; New England Nuclear Research Products; Boston, MA). Three hours after implantation under ether anesthesia, the left ventricular and femoral arterial catheters were connected to a pressure transducer, and arterial pressure and heart rate were continuously recorded for 30 min. During the intraventricular injection of microspheres, blood was sampled at the rate of 0.5 ml/min for 2 min for radioactivity counting and determination of plasma concentrations of sodium, potassium, and creatinine. At the end of experiments, the heart and the kidneys were removed and weighed for radioactivity counting. The heart weight index (HWI) and kidney weight index were calculated as the ratio of the heart or kidney to body weight (BW, in mg/g) in the 96 rats included in this study.

**Detection of reactive oxygen species.** Production of O₂⁻ by cardiac tissue and H₂O₂ by the thoracic aorta was determined on freshly isolated tissue. O₂⁻ production by the left ventricle was measured after the addition of 250 μM lucigenin, a dose that does not interfere with measurements (data not shown) and used in the measurement of O₂⁻ production from cardiac muscle slices (45) and freshly minced ventricles (11). H₂O₂ production was determined on the thoracic aorta as previously described (6). Briefly, H₂O₂ production was assessed with a luminometer (model LKB 1251, Wallac; Turku, Finland) immediately after addition of phorbol 12-myristate 13-acetate to the aorta incubated for 30 min with a specific bioluminescence probe consisting of luminol and horseradish peroxidase.

**Analytical methods and statistical analysis.** Plasma and urine concentrations of sodium and potassium were measured by flame photometry (Corning), and plasma concentration of creatinine was estimated by the colorimetric method (Beckman). Creatinine clearance at the end of experiments was calculated. Urinary excretion of albumin was determined by the immunonephelometric method (33).

Results are expressed as means ± SE and were analyzed by one-factor or two-factor analysis of variance for repeated measures when appropriate. Differences between groups were assessed by the Bonferroni's test. Within-group differences were evaluated by the Student's t-test for paired values. Slopes of the linear regression between final TCP and HWI were compared with the use of Wald's test. A P value of <0.05 was considered statistically significant.

**RESULTS**

**Arterial pressure.** As depicted in Fig. 1, TCP was similar and remained stable throughout studies in the control rats fed either diet. Infusion of the low dose of ANG II induced a rise in TCP in all rats; however, the final level of TCP was significantly lower in the LS than NS rats (157 ± 3 vs. 171 ± 6 mmHg, respectively). When the high dose of ANG II was given, final TCP was slightly and not significantly lower in the LS than NS rats (178 ± 4 and 189 ± 10 mmHg, respectively). Interestingly, the final value of TCP was similar in the LS group infused with the high dose of ANG II and the NS rats infused with the low dose of ANG II (Fig. 2).

**Cardiac mass.** As shown in Fig. 2, HWI was similarly increased by the low and high dose of ANG II in sodium-replete rats compared with their NS controls (3.48 ± 0.10 and 3.53 ± 0.11 vs. 2.97 ± 0.04 mg/g BW, respectively, P < 0.01). In the LS rats, neither the low nor the high dose of ANG II had a significant effect on HWI compared with control LS rats (2.72 ± 0.04 and 2.90 ± 0.04 vs. 2.67 ± 0.04 mg/g BW, respectively). Moreover, HWI remained lower than normotensive NS control rats in hypertensive LS rats. Of note, HWI was lower in control rats fed the sodium-free diet compared with the control NS rats (2.67 ± 0.04 vs. 2.97 ± 0.04 mg/g BW, respectively).
mg/g BW, P < 0.01). In fact, HWI was positively correlated with the final level of TCP (Fig. 3) and the slope of the regression line was lower in LS than NS rats (44.2 ± 1.12 vs. 89.9 ± 1.8 × 10^{-4} mg·g^{-1}·mmHg^{-1}, P < 0.001).

**Metabolic parameters.** Body weight was similar in all rats before ANG II infusion. Within the 10-day period of observation, body weight gain was lower in LS than NS rats. The development of ANG II hypertension was associated with a reduction of body growth in both regimens, the high dose of ANG II inhibiting weight gain in LS rats (Table 1). As shown in Table 1, food intake was similar in NS and LS rats infused with the low dose of ANG II or its vehicle. However, food consumption was reduced in both regimens when the peptide was given at the high dose.

As shown in Table 1, sodium balance increased in NS rats infused with the low dose of ANG II. When the dose of ANG II was doubled, sodium excretion was higher than intake and sodium balance became negative in NS rats. Water balance was higher in NS rats infused with the low dose of ANG II, whereas the high dose of ANG II was associated with a reduction in water balance compared with control NS rats. In the vehicle-LS rats, sodium balance was slightly negative but the sodium lost probably corresponds to the residual amount of sodium present in the LS diet. Infused at the low dose, ANG II induced a weak increase in urinary sodium excretion. Although it was reduced, body weight gain was positive, thus suggesting that there was no net loss of body sodium. When the dose of ANG II was doubled, a significant loss of sodium accompanied with a body weight arrest was observed in the LS rats. No significant change in water balance was detected in the LS rats.

The final plasma concentration of sodium was slightly lower and hematocrit was higher in LS than NS rats infused with ANG II, although significance was not achieved. Plasma concentration of potassium was higher in control LS rats compared with control NS rats. ANG II infusion had no detectable effect on this parameter in either regimen.

**Systemic and renal hemodynamics.** At the end of experiments, mean arterial pressure determined in conscious rats was similarly increased in NS and LS rats infused with ANG II (Table 2). Cardiac output and renal blood flow were lower, and total peripheral and renal vascular resistances were higher in the LS than in NS control rats, although the level of significance was not achieved. ANG II infusion was associated with a rise in total and renal resistances and with a reduction in cardiac output and renal blood flow in both sodium regimens. The systemic and renal effects of ANG II were similar for the two doses used in the present study.

Plasma concentration of creatinine and creatinine clearance were comparable in control NS and LS rats. ANG II dose dependently increased creatinine clearance in the NS rats, whereas infusion of the peptide was devoid of effect in sodium-depleted rats.

**Urinary excretion of albumin.** As depicted in Fig. 4, basal urinary excretion of albumin was similar in all groups and remained stable throughout the studies in control NS and LS rats. The marked rise in albuminuria associated with infusion of the low dose of ANG II in NS rats was prevented by sodium depletion. When the dose of ANG II was doubled, albuminuria rose in LS rats, but remained lower than their corresponding hypertensive NS rats and comparable to that obtained in the NS rats infused with the low dose of ANG II.

**Production of reactive oxygen species.** \( \text{O}_2^- \) production by the left ventricle was similar in the NS and LS control rats (0.24 ± 0.01 and 0.25 ± 0.01 mV/mg tissue, Fig. 3). Relationship between heart weight index and the final TCP in rats fed a NS diet or submitted to the severe dietary sodium restriction.
respectively). In the NS rats, \(O_2^-\) production increased by \(\sim50\%\) for the both doses of ANG II. This rise in \(O_2^-\) production was totally blocked in rats fed the LS diet. \(H_2O_2\) production by aorta segments was comparable in the NS and LS control rats (0.59 ± 0.02 and 0.58 ± 0.03 mM/mg tissue). In the NS rats, \(H_2O_2\) production increased by 60–70% with both doses of ANG II. Again, the rise in \(H_2O_2\) production associated with ANG II infusion was abrogated in rats fed the LS diet (Fig. 5).

**DISCUSSION**

In the present study, it was demonstrated that severe dietary sodium restriction prevented the development of cardiac hypertrophy associated with ANG II, despite the achievement of a similar level of hypertension obtained by adjusting the dose of the peptide infused. In addition, the ANG II-induced rise in albuminuria was blunted in sodium-restricted rats. Interestingly, the increase of reactive oxygen species production by the heart and aorta in rats infused with ANG II was also prevented by prior dietary sodium restriction.

Prevention by sodium restriction of the increase in cardiac mass was accompanied by a slight attenuation of ANG II hypertension compared with rats fed the regular sodium diet. The reduced responsiveness to the peptide may be related to a downregulation of ANG II type 1 receptors (1) and/or unopposed vasodilatation mediated by the type 2 receptors, as reported in normotensive rats (35). Although we cannot exclude the involvement of blood pressure changes in the prevention of cardiac hypertrophy by sodium restriction, several reports favor the hypothesis of a pressure-independent influence of dietary sodium removal on cardiac mass. In two-kidney, one-clipped hypertension, a severe sodium restriction prevented cardiac growth in the absence of significant antihypertensive influences (23, 32). In ANG II hypertension, cardiac hypertrophy was also prevented without a change in blood pressure in rats submitted to a moderate sodium restriction (27).

In addition, dietary sodium restriction initiated during the established phase of renovascular hypertension had no effect on blood pressure but reversed cardiac hypertrophy (36). In the present study, the dose of ANG II was doubled (400 ng kg\(^{-1}\) min\(^{-1}\)) in sodium-depleted rats to achieve a similar level of hypertension in both sodium regimen groups. In these conditions of similar development and final level of hypertension and higher ANG II infusion rate, sodium restriction still precluded the increase in cardiac mass. In addition, the kidney weight index was similar in all groups, thus suggesting that the effect of the low sodium intake specifically affected cardiac growth. Although we cannot exclude its involvement in the cardiac effect of the

### Table 1. Influence of sodium diet on body weight, sodium and water balance, and serum electrolytes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Sodium Diet</th>
<th>Low-Sodium Diet</th>
<th>ANG II</th>
<th>ANG II</th>
<th>ANG II</th>
<th>ANG II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vehicle</td>
<td>200 ng kg(^{-1}) min(^{-1})</td>
<td>400 ng kg(^{-1}) min(^{-1})</td>
<td>Vehicle</td>
<td>200 ng kg(^{-1}) min(^{-1})</td>
<td>400 ng kg(^{-1}) min(^{-1})</td>
</tr>
<tr>
<td>Body weight before ANG II</td>
<td>296 ± 4</td>
<td>304 ± 9</td>
<td>307 ± 7</td>
<td>298 ± 5</td>
<td>305 ± 9</td>
<td>298 ± 3</td>
</tr>
<tr>
<td>Body weight gain, g/10 days</td>
<td>42 ± 3</td>
<td>27 ± 5(\text{a})</td>
<td>10 ± 4(\text{a})†</td>
<td>19 ± 3*</td>
<td>11 ± 3(\text{a})‡</td>
<td>-5 ± 4(\text{a})‡</td>
</tr>
<tr>
<td>Food intake, g/24 h</td>
<td>28.0 ± 0.3</td>
<td>26.4 ± 0.7</td>
<td>24.2 ± 1.1</td>
<td>26.0 ± 0.9</td>
<td>23.9 ± 1.2</td>
<td>19.2 ± 1.2(\text{a})‡</td>
</tr>
<tr>
<td>Cumulative balance per 10 days</td>
<td>Sodium, μmol</td>
<td>9,732 ± 818</td>
<td>-1,176 ± 4,208(\text{a})</td>
<td>-69 ± 11</td>
<td>-181 ± 38</td>
<td>-259 ± 41</td>
</tr>
<tr>
<td></td>
<td>Water, ml</td>
<td>199 ± 13</td>
<td>256 ± 16(\text{a})</td>
<td>136 ± 28*</td>
<td>177 ± 12</td>
<td>188 ± 26</td>
</tr>
<tr>
<td>Serum concentration</td>
<td>Sodium, mmol/l</td>
<td>132 ± 2</td>
<td>137 ± 2</td>
<td>136 ± 3</td>
<td>133 ± 1</td>
<td>131 ± 2</td>
</tr>
<tr>
<td></td>
<td>Potassium, mmol/l</td>
<td>3.53 ± 0.14</td>
<td>3.29 ± 0.13</td>
<td>3.26 ± 0.34</td>
<td>3.87 ± 0.12</td>
<td>4.03 ± 0.32\‡</td>
</tr>
<tr>
<td></td>
<td>Hematocrit</td>
<td>46.1 ± 0.8</td>
<td>46.8 ± 0.8</td>
<td>47.5 ± 1.5</td>
<td>48.9 ± 0.8</td>
<td>48.4 ± 2.2</td>
</tr>
</tbody>
</table>

Values are means ± SE. \(\text{a}\)\(P < 0.05\) vs. corresponding vehicle group; †\(P < 0.05\) vs. corresponding 200 ng kg\(^{-1}\) min\(^{-1}\) ANG II group; ‡\(P < 0.05\) vs. corresponding normal sodium groups (diet effect).

### Table 2. Influence of sodium diet on hemodynamics in ANG II or vehicle-treated animals at end of experiments

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal Sodium Diet</th>
<th>Low-Sodium Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vehicle</td>
<td>200 ng kg(^{-1}) min(^{-1})</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>111 ± 2</td>
<td>134 ± 3(\text{a})</td>
</tr>
<tr>
<td>Cardiac output, ml min(^{-1}) kg(^{-1})</td>
<td>399 ± 37</td>
<td>212 ± 24(\text{a})</td>
</tr>
<tr>
<td>Peripheral resistance, mmHg min(^{-1}) ml(^{-1})</td>
<td>0.29 ± 0.03</td>
<td>0.68 ± 0.07(\text{a})</td>
</tr>
<tr>
<td>Renal blood flow, ml min(^{-1}) g(^{-1})</td>
<td>7.4 ± 0.2</td>
<td>4.9 ± 0.3(\text{a})</td>
</tr>
<tr>
<td>Renal resistance, mmHg(^{-1}) ml min(^{-1}) g(^{-1})</td>
<td>15 ± 1</td>
<td>28 ± 5(\text{a})</td>
</tr>
<tr>
<td>Serum creatinine, μmol/l</td>
<td>35.4 ± 0.4</td>
<td>33.3 ± 1.8</td>
</tr>
<tr>
<td>Creatinine clearance, μl min(^{-1}) g KW(^{-1})</td>
<td>337 ± 24</td>
<td>483 ± 28(\text{a})</td>
</tr>
<tr>
<td>Kidney weight index</td>
<td>7.99 ± 0.12</td>
<td>8.09 ± 0.16</td>
</tr>
</tbody>
</table>

Values are means ± SE. KW, kidney weight. \(\text{a}\)\(P < 0.05\) vs. corresponding vehicle group; †\(P < 0.05\) vs. corresponding 200 ng kg\(^{-1}\) min\(^{-1}\) ANG II group; ‡\(P < 0.05\) vs. corresponding normal sodium groups (diet effect).
LS diet, the lower rate of body growth had probably only a minor role, if any. With the use of a similar protocol, cardiac hypertrophy induced by the low dose of ANG II was almost totally prevented (HWI was $3.16 \pm 0.07, n = 12$) in rats fed the LS diet supplemented with a minimal amount of sodium ($\sim 700 \mu$moles per day) that allows normal body weight gain (B. Jover, C. Rugale, and A. Mimran, unpublished observations). Interestingly, cardiac mass index was also reduced by sodium restriction in normotensive rats. A comparable finding was previously reported in sham-operated rats of the two-kidney, one-clip hypertension (5). In fact, the slope of the linear correlation between cardiac mass index and arterial pressure was blunted by dietary sodium restriction as illustrated in Fig. 3. Therefore, sodium intake appears as an important modulator of cardiac mass independently of the level and changes of arterial pressure.

Beside changes in pressure overload, the beneficial effect of dietary sodium restriction on cardiac mass may be related to a reduction of preload of the heart. In sodium-replete rats, infusion of the low dose of ANG II was associated with an increase in sodium and water balances. Interestingly, such changes did not occur in the LS rats, thus suggesting that prevention of the increase in circulating volume may participate in the beneficial influence of dietary sodium removal on cardiac structure. When given at the high dose, ANG II was associated with a reduction of water balance and achievement of a negative sodium balance in sodium-replete rats. Such a loss of sodium may represent a malignant form of hypertension, or, more likely, it may reflect the activation of the pressure-natriuresis mechanism, which is altered in ANG II hypertension (38). Despite this sodium wasting state, cardiac hypertrophy developed in NS rats but not in LS rats, a finding that does not favor a major role for preload changes in the antihypertrophic effect of sodium restriction in the present model. In addition, it was previously reported that severe sodium restriction prevented the development of cardiac hypertrophy in two-kidney, one-clip hypertension without change in sodium and water balances (32).

Together with the increase in arterial pressure and cardiac mass, both doses of ANG II induced a marked rise in urinary albumin excretion as well as glomerular filtration rate, equated with creatinine clearance, in rats fed the NS diet. Previous studies have implicated an increase in glomerular capillary pressure in the proteinuria associated with ANG II hypertension (25) and 5/6 nephrectomy (18). Severe dietary sodium restriction, a maneuver devoid of effect on hypertension and renal vasoconstriction, prevented both the proteinuric effect and hyperfiltration associated with infusion of the low dose of ANG II in the present study. When the dose of ANG II was doubled, albuminuria rose in rats fed the sodium-free diet without change in glomerular filtration rate. However, albuminuria was lower in sodium-depleted than in sodium-replete rats infused with a high dose of ANG II. These results do not favor a major role of the blunting of hyperfiltration in the beneficial effect of dietary sodium restriction on proteinuria. Similar prevention of proteinuria by dietary sodium restriction was previously described in uninephrectomized spontaneously hypertensive rats (3) and 5/6 nephrectomy model (10). In the latter studies (3, 10), it was clearly shown that reduction in glomerular pressure determined by micropuncture or arterial

![Fig. 4. Urinary excretion of albumin (UAlbV) determined before (basal) and at the end (final) of the 10-day period of ANG II infusion to rats fed the NS or LS diet. *P < 0.05 compared with the corresponding vehicle group.](#)

![Fig. 5. Production of superoxide anion (A) by the left ventricle and H$_2$O$_2$ (B) by the aorta determined at the end of the 10-day period of ANG II infusion to rats fed the NS or the LS diet. *P < 0.05 compared with the corresponding vehicle group.](#)
pressure did not account for the beneficial effect of sodium restriction.

The beneficial effects of dietary sodium restriction are probably multifactorial with complex interactions between various systems such as the renin-angiotensin-aldosterone system, the sympathetic nervous system, endothelin, prostaglandins, or the nitric oxide system. Besides the hormonal systems, the redox status of the cell has been evoked as a potential mechanism of the cardiovascular alterations associated with hypertension and/or high-sodium intake. It was demonstrated that reactive oxygen species are responsible for the functional changes in the microcirculation of rats fed a high-salt diet (20, 21). In Dahl salt-sensitive rats, it was reported that the antioxidant capacity was reduced in rats on a normal sodium diet and worsened when salt intake was increased (22). However, the influence of a reduced intake of sodium on oxidative stress has not been investigated. The major goal of the present study was to evaluate the effect of dietary sodium restriction on the stimulation by ANG II of the production of reactive oxygen species in the heart and arterial wall of hypertensive rats. As previously described, ANG II infusion was associated with a rise in the production of reactive forms of oxygen (19, 42). A prominent finding of our study is the complete prevention of the prooxidant effect of the octapeptide in rats fed the sodium-restricted diet. Particularly, sodium restriction prevented the hyperproduction of $O_2^\cdot$ by the left ventricle even for the high dose of ANG II. Whether the reduction of oxidative stress is a cause or a consequence of the absence of cardiovascular remodeling cannot be unequivocally evoked from the present experiments. A growing body of evidence points to the free radicals production as one of the major factors involved in cardiovascular and renal alterations associated with ANG II hypertension. Treatment with superoxide dismutase (SOD) reduced spontaneous tone of aorta isolated from rats infused with ANG II (39) and SOD (19) or SOD mimetic (29, 30) blunted hypertension induced by ANG II in rats. Inhibition of the HMG-CoA reductase with various statins was reported to be an additional approach to dietary sodium restriction. Particularly regarding the target organ damage of arterial hypertension.

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