Salt Induces Myocardial and Renal Fibrosis in Normotensive and Hypertensive Rats

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Background—The detrimental effects of high dietary salt intake may not only involve effects on blood pressure and organ hypertrophy but also lead to tissue fibrosis independently of these factors.

Methods and Results—The effect of a normal (1%) or high (8%) sodium chloride diet on myocardial and renal fibrosis was assessed by quantitative histomorphometry in spontaneously hypertensive rats (SHRs) and normotensive Wistar-Kyoto rats (WKYs). The effect of salt on transforming growth factor-β1 (TGF-β1) gene expression was assessed by Northern blot hybridization. A high-salt diet from 8 to 16 weeks of age resulted in increased blood pressure and left ventricular hypertrophy in both WKYs and SHRs. Marked interstitial fibrosis was demonstrated in the left ventricle (LV), glomeruli, and renal tubules and in intramyocardial arteries and arterioles but not in the right ventricle. The collagen volume fraction increased significantly after high-salt diet in the LV, intramyocardial arteries and arterioles, glomeruli, and peritubular areas in both WKYs and SHRs. In the kidneys, glomerular and peritubular type IV collagen was also increased. There was overexpression of TGF-β1 mRNA in the LV and kidneys in both rat strains after a high-salt diet (all P<0.001).

Conclusions—High dietary salt led to widespread fibrosis and increased TGF-β1 in the heart and kidney in normotensive and hypertensive rats. These results suggest a specific effect of dietary salt on fibrosis, possibly via TGF-β1-dependent pathways, and further suggest that excessive salt intake may be an important direct pathogenic factor for cardiovascular disease. (Circulation. 1998;98:2621-2628.)

Key Words: sodium • diet • collagen • hypertension • growth substances

Despite numerous clinical and experimental studies, controversies as to the effect of dietary salt intake on blood pressure remain.1,2 The lack of consensus on the relationship between salt and blood pressure makes public health advice to lower dietary salt intake difficult to sustain. Although most studies have emphasized that the pathogenic effects of salt are via its ability to elevate blood pressure,3 it has recently become evident that salt may have other effects that lead to tissue injury, such as promoting organ hypertrophy.2 Indeed, in the experimental context, high dietary salt leads to left ventricular hypertrophy (LVH) without significantly elevating blood pressure,4,5 and clinical studies have shown that high salt intake is a powerful and independent determinant of LVH.6

In experimental studies, accumulation of myocardial interstitial collagen has been demonstrated in various models of LVH, including in renovascular hypertension, after angiotensin II or aldosterone infusion, and in aging spontaneously hypertensive rats (SHRs).78 The importance of salt per se as a mediator of tissue fibrosis is further suggested from studies in which, despite aldosterone infusion, salt deprivation prevented collagen deposition in intramural coronary arteries.9 Fibrosis is an important component of the vascular remodeling process, and perivascular fibrosis of the intramyocardial arteries has been commonly observed in various models of vascular injury, such as hypertension. However, whether high dietary salt intake–induced LVH is accompanied by myocardial fibrosis is unknown.

In the kidney, the effect of salt per se on renal structure, such as glomerular and peritubular fibrosis, has not been reported. This may have important clinical implications in the genesis of chronic glomerulosclerosis and tubulointerstitial fibrosis, which ultimately lead to end-stage renal failure.10 Cytokines, especially transforming growth factor-β1 (TGF-β1), have been shown to play a pivotal role in promoting fibrosis at various sites, including the kidney and blood vessels.11 Overexpression of TGF-β1 has been observed in various models of progressive renal injury and cardiovascular disease. It is therefore probable that TGF-β1 plays a role in dietary salt–induced organ hypertrophy and fibrosis.
This study investigates the possibility that the detrimental effects of salt intake may occur via effects on tissue fibrosis, a process that has been implicated as a major pathway to organ failure.12,13 The hypothesis that high dietary salt intake induces myocardial and renal fibrosis was tested in both SHRs and their normotensive counterpart, the Wistar-Kyoto rat (WKY). In addition, the possibility that this fibrosis may involve the prosclerotic cytokine TGF-β, was examined.

Methods

Experimental procedures were performed according to the National Health and Medical Research Council guidelines for animal experimentation.

Experimental Protocol

Six-week-old male SHRs (n = 38) and WKYS (n = 38) were used. SHRs are regularly tested with polymorphic markers to confirm their inbred status. Systolic blood pressure (SBP) was measured by the indirect tail-cuff technique (W&K recorder, model 8005). At 8 weeks of age, SHRs and WKYS were randomized to a normal-NaCl (1%) or high-NaCl (8%) rat chow (Janos Hoey Pty Ltd) for 8 weeks. At week 16, rats were placed in metabolic cages, and food and water intake, urine volume, and urinary sodium, chloride, and osmolality were measured.

Tissue and Blood Collection and Analysis

Rats were killed by decapitation, and trunk blood was collected into heparin tubes for measurement of plasma sodium, chloride, osmolality, and hematocrit and into EDTA tubes for the measurement of plasma renin activity (PRA) and atrial natriuretic peptide (ANP). The hearts and kidneys were rapidly excised and weighed. In half of the animals, the hearts were divided into right ventricle (RV) and left ventricle plus septum (LV). The heart and kidney were frozen in liquid nitrogen for later RNA extraction. In the remaining animals, the hearts were divided at the coronary plane at its ventricular equator, and fields containing vessels, artifacts, minor scars, or incomplete tissue were excluded. In the LV, 20 to 25 fields were analyzed, whereas 10 to 15 fields were analyzed for the RV. In the kidney, glomerular and tubular collagen were measured separately.

To assess fibrosis in the intramyocardial coronary arteries, LV sections were stained with Verhoeff and van Gieson’s method to delineate the internal elastic lamina of arterioles and smooth muscle of media. Cross-sectional images of coronary arteries with vessel diameter between 125 and 300 μm were selected for analysis.16 The border of the internal elastic lamina, the outer border of the tunica media, and the outer border of the tunica adventitia were traced, and the area of perivascular fibrosis was measured (Measure Software, Capricorn Scientific).

In the glomerulus, the visceral layer of Bowman’s capsule was traced, and the stained area was calculated as a percentage of glomerular area. For the cortical renal tubules, the interstitial collagen fraction was measured as in the LV, and fields containing glomeruli were excluded from analysis. In both the glomeruli and cortical tubules, 20 to 25 fields were analyzed from each kidney.

Northern Blot Hybridization for TGF-β1

RNA from the RV and LV and kidneys was extracted by the acid guanidinium thiocyanate–phenol-chloroform method.18 Hybridization was performed as previously described.19 In brief, filters were hybridized with a 985-bp cDNA probe coding for rat TGF-β1 (kind gift of Dr Qian, National Institute of Health, Bethesda, Md). The filters were then exposed to x-ray film. Discrepancies for RNA loading and transfer were corrected by rehybridization with an oligonucleotide probe for 18S rRNA. Results are expressed as the ratio of optical density of TGF-β1 to 18S.

In Situ Hybridization for TGF-β1

In situ hybridization was performed on 4-μm-thick sections of formalin-fixed, paraffin-embedded tissues as previously described.19 In brief, heart and kidney sections were dewaxed, rehydrated, and hybridized with riboprobes. Sections were washed and incubated with RNase A (150 μg/mL), dehydrated, and exposed to Kodak X-Omat autoradiographic film for 1 to 3 days. Slides were dipped in Ilford K5 nuclear emulsion, stored in a light-free box with desiccant at room temperature, immersed in Kodak D19 developer, fixed in Ilford Hypean, and stained with hematoxylin and eosin.

Immunohistochemistry

Detection of type IV collagen was performed by the avidin-biotin-enzyme complex (ABC) peroxidase method.20 Type IV collagen expression was assessed by use of a polyclonal goat anti-bovine and human type IV collagen antibody (Southern Biotechnology Associates, Inc).

Statistics

The results are presented as mean±SEM. Systolic blood pressure and body weight were compared among groups by ANOVA for repeated measures followed by post hoc analysis with Scheffé’s test and 2-way ANOVA. All the other results were analyzed by 2-way ANOVA followed by the Bonferroni test for comparison of multiple

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TABLE 1. Metabolic Caging Studies in Rats After 8 Weeks (Age 16 Weeks) On Normal-Salt (1%) and High-Salt (8%) Diets

<table>
<thead>
<tr>
<th>Variable</th>
<th>WKYs 1% Salt</th>
<th>WKYs 8% Salt</th>
<th>SHR 1% Salt</th>
<th>SHR 8% Salt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td>274±13</td>
<td>271±11</td>
<td>298±7</td>
<td>285±5</td>
</tr>
<tr>
<td>Food intake, g/100 g BW</td>
<td>7.5±0.9</td>
<td>8.4±0.8</td>
<td>7.4±0.3</td>
<td>8.2±0.3</td>
</tr>
<tr>
<td>Urinary sodium, mmol · 100 g BW⁻¹ · min⁻¹</td>
<td>0.66±0.07</td>
<td>5.06±0.44*</td>
<td>0.70±0.06</td>
<td>4.40±0.32*</td>
</tr>
<tr>
<td>Water intake, mL/100 g BW</td>
<td>12.7±1.2</td>
<td>35.9±2.5*</td>
<td>10.9±0.9</td>
<td>34.4±1.4*</td>
</tr>
<tr>
<td>Urine volume, mL/100 g BW</td>
<td>6.4±1.0</td>
<td>27.8±2.9*</td>
<td>5.8±0.5</td>
<td>22.8±1.9*</td>
</tr>
</tbody>
</table>

*P<0.01, 8% vs 1% salt diet.
**Body Weight**

Body weight was not different among the groups at 8 weeks of age (WKY 1%, 160±5 g; WKY 8%, 169±6 g; SHR 1%, 169±8 g; and SHR 8%, 174±5 g; P=0.17). High-salt diet did not significantly affect body weight in either the hypertensive or normotensive rats, and all groups gained weight over the experimental period (Table 1).

**Systolic Blood Pressure**

SBP at 8 weeks of age was higher in SHRs than WKYs (8 weeks: WKYs, 132±2 versus SHRs, 168±2 mm Hg, P<0.001). Over the study period, SBP did not rise in WKYs on normal-salt diet (P=0.36) but increased in all other groups (P<0.001) (Figure 1). At 16 weeks of age, SBP was significantly increased in WKYs on high-salt compared with normal-salt diet (1%, 137±3 versus 8%, 154±3 mm Hg; P<0.001). However, SBP was still ∼50 mm Hg lower in the WKYs on a high-salt diet than in SHRs on a normal diet (Figure 1). In SHRs, SBP was further increased by high-salt diet (1%, 211±4 versus 8%, 246±5 mm Hg; P<0.001). At 16 weeks of age, the increase in blood pressure induced by high-salt diet was greater in SHRs than in WKYs (SHRs, 35±5 versus WKYs, 17±3 mm Hg; F=8.0, P<0.05).

**Biochemical and Hormonal Data**

The metabolic caging results at 8 weeks of age were essentially the same as at 16 weeks of age, and therefore, only data at the later time point are shown (Table 1). High-salt diet increased urinary sodium excretion, lowered urinary osmolality, and increased fluid intake and urine output in rats, with no difference between rat strains. The plasma level of sodium, chloride, osmolality, and hematocrit were not different among the groups (data not shown). High-salt diet suppressed PRA (P<0.01) and stimulated the production of ANP (P<0.01) in both SHRs and WKYs, with no difference between strains (Table 2).

**Heart and Kidney Weight**

High-salt diet induced a significant LVH in both WKYs and SHRs (P<0.0001) (Table 2). In SHRs on normal-salt diet, LV mass was increased compared with WKYs on a normal-salt diet (P<0.05), but this difference was not observed between the strains after 8 weeks of high-salt diet. Neither rat strain nor dietary salt intake had an effect on RV weight. High-salt diet induced renal hypertrophy in both WKYs and SHRs (P<0.0001). However, SHRs had significantly lower kidney weight than WKYs (P<0.0001) on both salt regimens.

**Interstitial Fibrosis of the Heart, Vessels, and Kidney**

In the LV, salt loading caused a diffuse increase in the interstitial fibrillar collagen assessed by picrosirius red staining (Figure 2). The collagen strands coursed through widened interstitial spaces and were disrupted along their course before coalescing to form the perimysium, and there was increased branching of collagen fibrils. In SHRs on high-salt diet, there were focal areas of dense collagen deposition, and the morphological changes were exacerbated compared with WKYs. Under polarized light, high-salt diet induced a generalized increase in birefringence in the myocardial interstitial tissue. Both yellow-red and green birefringence were found in these areas, indicating the presence of both thick and thin collagen fibrils.

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**TABLE 2. Relative Organ Weight and Hormonal Data in Rats on Normal-Salt (1%) and High-Salt (8%) Diet**

<table>
<thead>
<tr>
<th>Variable</th>
<th>WKYs</th>
<th>SHRs</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>1% Salt</td>
<td>8% Salt</td>
</tr>
<tr>
<td>Relative LV mass, mg/100 g BW</td>
<td>245±5</td>
<td>296±10*</td>
</tr>
<tr>
<td>Relative RV mass, mg/100 g BW</td>
<td>70±5</td>
<td>72±6</td>
</tr>
<tr>
<td>Relative kidney mass, mg/100 g BW</td>
<td>729±9</td>
<td>797±14*</td>
</tr>
<tr>
<td>Plasma renin activity, nmol/L</td>
<td>1.96±0.23</td>
<td>0.21±0.04*</td>
</tr>
<tr>
<td>Ang I · L⁻¹ · h⁻¹</td>
<td></td>
<td></td>
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<tr>
<td>Plasma ANP, pmol/L</td>
<td>19.4±1.7</td>
<td>36.6±3.6*</td>
</tr>
</tbody>
</table>

*P<0.01, 8% vs 1% salt diet.
†P<0.05, ‡P<0.01, SHRs vs WKYs.

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*Figure 1. Change of blood pressure in rats on normal-salt (1%) and high-salt (8%) diet from 8 to 16 weeks. All rats except WKYs on 1%-salt diet had a significant increase in blood pressure over time. Systolic blood pressure at 16 weeks of age was significantly different between the 4 groups by ANOVA. WKYs+1%-salt diet; ▲, SHR+1%-salt diet; WKYs+8%-salt diet; and ●, SHRs+8%-salt diet.*
thin collagen fibers, respectively, which contributed to the development of interstitial fibrosis. In the LV, high dietary salt significantly increased the amount of interstitial fibrosis, measured as the collagen volume fraction in both SHRs and WKYs ($P < 0.01$, Table 3). There was also a significant difference in LV fractional collagen volume between rat strains ($P < 0.01$). SHRs had increased collagen volume fraction in the RV compared with WKYs. No effect of salt intake was observed on this parameter in the RV.

High-salt diet induced fibrosis in the intramyocardial arteries and arterioles in both WKYs and SHRs ($P < 0.01$) to a similar extent (Table 3 and Figure 3). SHRs had increased fibrosis at this site compared with WKYs on a normal-salt diet ($P < 0.001$).

High-salt diet in both WKYs and SHRs increased glomerular and tubular interstitial collagen volume fraction (Figure 4, Table 3). SHRs had increased glomerular and tubular interstitial fibrosis compared with WKYs on a normal-salt diet. 

![Figure 2. Picrosirius red staining of LV under light microscopy (magnification ×100). A, WKYs +1%-salt diet; B, WKYs +8%-salt diet; C, SHRs +1%-salt diet; and D, SHRs +8%-salt diet. There was increased amount and branching of collagen fibers in both WKYs and SHRs on high-salt diet. Interstitial space was expanded, and there was dense crisscrossing of collagen network in SHRs on high-salt diet.](image-url)

<table>
<thead>
<tr>
<th>Variable</th>
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<th>SHRs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1% Salt</td>
<td>8% Salt</td>
</tr>
<tr>
<td>Collagen volume fraction, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV</td>
<td>3.0±0.3</td>
<td>4.0±0.4$^*$</td>
</tr>
<tr>
<td>RV</td>
<td>4.9±0.5</td>
<td>5.9±0.4</td>
</tr>
<tr>
<td>Intramyocardial arteries</td>
<td>5.4±0.9</td>
<td>10.7±1.2</td>
</tr>
<tr>
<td>Glomerulus</td>
<td>12.3±0.7</td>
<td>18.0±1.2$^*$</td>
</tr>
<tr>
<td>Renal tubule</td>
<td>3.2±0.3</td>
<td>5.1±0.7$^*$</td>
</tr>
<tr>
<td>Collagen type IV, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glomerulus</td>
<td>9.3±0.7</td>
<td>15.4±0.8$^*$</td>
</tr>
<tr>
<td>Renal tubule</td>
<td>5.6±0.5</td>
<td>8.4±0.5$^*$</td>
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$^*$ $P < 0.01$, 8% vs 1% salt diet.
† $P < 0.01$, SHRs vs WKYs.
diet. Type IV collagen assessed immunohistochemically in the kidney showed the same pattern of changes as described with picrosirius red staining (Table 3).

**TGF-β₁ mRNA Expression**

High-salt diet increased expression of LV TGF-β₁ mRNA in both WKYs and SHRs (1.5 and 1.4 times, respectively, *P*<0.01), with no interstrain difference (Figure 5, Table 4). In the RV, there was no difference in TGF-β₁ mRNA expression with respect to either salt diet or rat strain (Table 4). There was evidence of TGF-β₁ gene expression associated with mononuclear cells and fibroblast-like cells within the myocardium in salt-loaded rats (Figure 6A). TGF-β₁ mRNA was also detected in the medial layer of intramyocardial vessels. This was most clearly evident in rats fed a high-salt diet (Figure 6B). SHRs had significantly higher renal TGF-β₁ mRNA levels than WKYs (*P*<0.01), and high-salt diet induced renal TGF-β₁ mRNA expression in both WKYs and SHRs (2 and 1.7 times, respectively, *P*<0.001) (Figure 5, Table 4).

**Discussion**

The results of this study have important implications with regard to dietary salt. High dietary salt intake was confirmed to raise blood pressure and cause LVH. Of particular significance, however, was the finding that salt promotes fibrosis in the LV, intramyocardial arteries, and kidney, not only in SHRs but also in WKYs. These changes were associated with overexpression of TGF-β₁.

The present study highlights the detrimental effect of salt at 3 important sites. First, there was evidence not only of LVH but also of intramyocardial fibrosis. The development of cardiac interstitial fibrosis has important prognostic implications, because it forms the structural basis of abnormal myocardial stiffness that leads to ventricular diastolic and systolic dysfunction and ultimately symptomatic cardiac failure. Second, there was evidence of fibrosis of intramyocardial arteries, a process that is thought to play a major pathogenic role in retarding the capacity of the coronary circulation to dilate in response to an increased LV load. Finally, there was evidence of widespread renal fibrosis, a process that has been shown not only to lead to renal impairment but also to further elevate blood pressure. This could potentially create a vicious circle, with progressive renal fibrosis and ultimately end-stage renal failure. It is of interest that in the RV, increased mass was observed in the hypertensive strain and was not influenced by salt intake. The difference in response between the LV and RV suggests that local rather than circulating factors are responsible for the fibrosis at these sites.

Salt loading was associated with evidence of increased circulating volume, as shown by an increase in ANP levels and suppression of PRA. There was no change in hematocrit,
but this may be a less sensitive marker of circulating volume status than ANP.

In both WKYs and SHRs, salt loading led to widespread tissue fibrosis. It should be noted that there was only a modest increase in systolic blood pressure in WKYs (17 mm Hg), this level being ≈50 mm Hg lower than observed in SHRs. Despite this large difference in blood pressure, WKYs on a high-salt diet had a degree of fibrosis similar to that of SHRs on a normal diet. This suggests that although blood pressure is a major determinant of tissue fibrosis, salt appears to play an important and direct role in aggravating the effects induced by hypertension.

Cytokine overexpression is an important humoral mediator of fibrogenesis. Previous studies have shown that TGF-β1, a fibrogenic cytokine, is linked to myocardial fibrosis in stroke-prone SHRs as well as in ventricular remodeling after acute myocardial infarction in rats. In the kidney, TGF-β1 has been shown to be involved in glomerulosclerosis and tubulointerstitial fibrosis in various models, such as diabetes. In this study, we have demonstrated that high-salt diet induces the overexpression of TGF-β1 mRNA in the hearts and kidneys of both WKYs and SHRs. In the kidney, the changes in the degree of fibrosis paralleled the changes in TGF-β1 gene expression, consistent with TGF-β1 playing an important role in renal fibrosis. By contrast, in the LV, despite SHRs having more fibrosis than WKYs, there was no difference in TGF-β1 gene expression. This would suggest that in the heart, other proclerotic factors, as yet poorly delineated, are also involved in the genesis of fibrosis in the LV.

The novel finding that overexpression of TGF-β1 is associated with salt-induced myocardial and renal fibrosis carries important clinical implications, not only in the understanding of the detrimental effect of salt to the cardiovascular system but also in the design of therapeutic maneuvers against tissue fibrosis. Indeed, in other forms of renal fibrosis and extracellular matrix accumulation, various approaches have been implemented, including the use of TGF-β1 antagonists. Furthermore, some investigators have suggested that TGF-β1 rather than blood pressure should be considered the target for preventing renal fibrosis.

It has been suggested that fibroblast activation and proliferation are responsible for the overproduction of TGF-β1 and collagen synthesis in the heart and kidney of hypertensive rats. In addition, infiltration and clustering of inflammatory cells, especially macrophages, is associated with myocardial fibrosis or vascular lesions in genetically hypertensive rats. In this study, TGF-β1 messenger mRNA was localized to areas of interstitial fibrosis associated with inflammatory and fibroblast-like cells. Furthermore, TGF-β1 gene expression was detected at sites of fibrosis and was most evident in intramyocardial arteries from SHRs fed a high-salt diet.

It has been suggested that salt may promote and increase the response to vasoconstrictors. Therefore, it is possible
that salt facilitates the profibrogenic effect of vasoactive hormones, such as angiotensin II and endothelin, even in the context of no change or a reduction in the levels of these vasoactive hormones. It has been clearly shown in cultured vascular smooth muscle and mesangial cells that certain hormones are fibrogenic, primarily by TGF-β₁-dependent mechanisms. These in vitro studies are consistent with the view that tissue fibrosis can occur independently of increases in systemic blood pressure.

It has been clearly demonstrated in patients with arterial hypertension that there is structural remodeling of intramyocardial coronary arterioles. These changes include increased media wall/lumen ratio and fibrosis. This fibrosis is considered to be a major factor in impairing the vasodilator capacity of coronary vessels in hypertensive subjects. This phenomenon of salt promoting perivascular fibrosis in both WKYs and SHRs suggests that the deleterious effect of salt should not be confined to the context of hypertension. Indeed, perivascular fibrosis has been observed in other states associated with increased cardiovascular risk, including diabetes and LVH induced by aortic banding.

It is of interest that several therapeutic maneuvers that promote urinary sodium excretion have been reported to reduce perivascular fibrosis. These include dihydropyridine calcium channel blockers and diuretics. Furthermore, salt restriction has been shown to be renoprotective despite

**Figure 5.** Northern blot of TGF-β₁ mRNA expression in LV (A) and kidney (B). Gene expression was increased in both WKYs and SHRs on high-salt (8%) diet for 8 weeks. In kidney, SHRs had a higher level of TGF-β₁ gene expression than WKYs on same salt diet. 18S ribosomal RNA was used as housekeeping gene.

**Figure 6.** In situ hybridization for TGF-β₁ mRNA in myocardium (A) and intramyocardial vessels (B) from SHRs on 8%-salt diet. TGF-β₁ mRNA was localized to mononuclear and fibroblast-like cells within myocardium (A) and to media of intracoronary arterioles (B). Magnification ×400.

**TABLE 4.** TGF-β₁ mRNA Expression in Rats on Normal-Salt (1%) and High-Salt (8%) Diet

<table>
<thead>
<tr>
<th>Variable</th>
<th>WKYs</th>
<th>SHRs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1% Salt</td>
<td>8% Salt</td>
</tr>
<tr>
<td>TGF-β₁ mRNA expression (TGF-β₁ to 18S)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV</td>
<td>0.99±0.14</td>
<td>1.47±0.14*</td>
</tr>
<tr>
<td>RV</td>
<td>1.22±0.04</td>
<td>1.16±0.09</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.47±0.05</td>
<td>0.94±0.14*</td>
</tr>
</tbody>
</table>

*P<0.01, 8% vs 1% salt diet.
†P<0.01, SHRs vs WKYs.
minimal effect on blood pressure. Therefore, it is possible that these therapies confer organ protection via attenuation of sodium-dependent pathways.

Our data confirm earlier studies that showed that a high salt intake exacerbated blood pressure in SHR and caused an increase in LVH. In addition, this study demonstrates that high dietary salt significantly raises systolic blood pressure and causes LVH in normotensive rats. This result differs slightly from the findings of Frohlich et al. and Yuan and Leenen, in which high dietary salt caused LVH in WKY but did not increase blood pressure, and contrasts with the study by Kreutz et al., who reported no change in blood pressure or LVH in WKYs with high salt. The lower salt concentration, which did not increase blood pressure, and contrasts with the study of Frohlich et al. and Yuan and Leenen, slightly from the findings of Frohlich et al. and Yuan and Leenen. We thank Richard Gilbert for advice and Melinda D. Rockell and Donna Paxton for their assistance with biochemical assays.

Acknowledgments
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