Cardiorenal abnormalities associated with high sodium intake: correction by spironolactone in rats

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Cordaillat, Magali, Caroline Rugale, Daniel Casellas, Albert Mimran, and Bernard Jover. Cardiorenal abnormalities associated with high sodium intake: correction by spironolactone in rats. Am J Physiol Regul Integr Comp Physiol 289: R1137–R1143, 2005. First published May 26, 2005; doi:10.1152/ajpregu.00154.2005.—Reversal by the mineralocorticoid receptor antagonist spironolactone of cardiac and renal abnormalities, associated with long-term (since weaning) administration of a high (2 and 8% NaCl chow, HS2 and HS8) sodium diet, was assessed in Sprague-Dawley rats. At the age of 5 mo, spironolactone (20 or 100 mg/kg, gavage) or placebo were given for 14 days to HS2 and HS8 rats. A group fed a regular diet (0.8% NaCl, NS) remained untreated. High sodium intake had no detectable effect on blood pressure; however, cardiac mass index and cross-sectional area of the carotid artery, as well as albuminuria, were increased only in the HS8 group compared with the control group on NS diet. In addition, a marked reduction in glomerular filtration rate (by 40%), associated with a nonproportional fall in renal plasma flow (thus resulting in a decrease in filtration fraction), was observed only in the HS8 group. No change in cardiac and renal fibrosis was detected. Production of the reactive oxygen species (ROS) by aortic tissue was increased in HS8 rats, whereas ROS production by the heart was unaffected. Only the high dose of spironolactone was effective, as it markedly reversed the cardiac hypertrophy and renal hypofiltration associated with the HS8 feeding. The changes were observed in the absence of any effect on systemic blood pressure and production of ROS. These observations favor aldosterone’s role in the deleterious effects of marked and prolonged increases in sodium intake.

spironolactone; renal function; reactive oxygen species; cardiac hypertrophy

In addition to its widely debated effect on blood pressure, chronic variation of sodium intake has been reported to modulate the cardiovascular morphology in human and experimental models. In animal studies, dietary sodium restriction has been shown to prevent the development of cardiac hypertrophy in renovascular (13) and ANG II-induced hypertension (14), independently of blood pressure. Reversal of cardiac hypertrophy was achieved by 6 wk on a low-sodium diet in 2-kidney, one-clip hypertensive rats (17). Administration of a diet containing 8% sodium chloride for more than 4 wk was associated with the development of left ventricular hypertrophy, cardiac fibrosis, and an increase in collagen content (10, 23).

Because an increase in systemic pressure associated with high sodium was not consistently observed, it was suggested that a direct effect of sodium may underlie the increased sensitivity of target organs to blood pressure. Interestingly, in a cohort of normotensive subjects and never-treated patients with essential hypertension, it was recently demonstrated that increasing dietary sodium (as estimated by 24-h natriuresis), enhanced the slope of the relationship between left ventricular mass index or albuminuria and systolic blood pressure (5).

These findings are in favor of a blood-pressure-independent effect of sodium that could function as a prohypertrophic factor. As demonstrated by Takeda et al. (19), an increased activity and tissue synthesis of aldosterone was observed in normotensive rats fed a high-sodium diet for 8 wk after weaning. In addition, the mineralocorticoid receptor antagonist spironolactone was shown to prevent the development of left ventricular hypertrophy and fibrosis induced by 8-wk feeding of adult Wistar rats with an 8%-NaCl diet (9). These findings prompted us to evaluate the possible reversal by spironolactone of the already established cardiac and renal consequences of long-term administration of a high-sodium diet. Two high-salt (2 and 8% NaCl) diets were proposed since weaning for 19 wk, so the rats were durably and only exposed to the high-salt protocol.

METHODS

Experiments were conducted in 70 male Sprague-Dawley rats. Immediately after weaning and until the age of 5 mo, rats were fed the normal sodium diet (NS containing 150 mmol Na+/kg of chow, i.e., 0.8% NaCl) or a high-sodium diet containing either 460 or 1,370 mmol of Na+/kg, i.e., 2% (HS2) and 8% (HS8) of NaCl. Potassium content of diets was 223 mmol/kg of chow.

At the age of 5 mo, rats were placed in individual metabolic cages for 2 wk. Animals fed HS2 and HS8 diets were then treated by the aldosterone antagonist spironolactone, given by gavage (between 9 and 10 AM) at doses of 20 or 100 mg·kg⁻¹·day⁻¹ for 14 days (n = 8 in each group). The low and high doses were in the range of those used previously in rats fed a high-sodium diet (9) or after myocardial infarction (18). One group of 8 rats fed the NS diet was treated with the high dose of spironolactone. Three groups of 10 rats receiving arabic gum (1 ml/kg body wt by gavage) served as control groups.

Metabolic parameters. Three days before and during the entire period of treatment, body weight, and food and water consumption, as well as urinary excretion of water, sodium, potassium, and creatinine were measured daily. Tail-cuff pressure (Narco Biosystems) and urinary excretion of albumin were determined before and at the end of the treatment period.

Estimation of renal function in anesthetized rats. At the end of the treatment period, rats were anesthetized with pentobarbital sodium (60 mg/kg body wt ip), and blood was sampled (75 µl) for measurement of serum concentrations of sodium, potassium, and creatinine. Two hours after the last administration of treatments, renal function was estimated in anesthetized animals, and only in the three vehicle groups and HS2 and HS8 groups treated by the high dose (100 mg/kg) of spironolactone. Clearances of ⁹⁹ᵐTC-diyethyleneetriaminopentaacetic acid (DTPA; glomerular filtration rate) and ¹³¹Iorthiodihippurate (OIH; effective renal plasma flow) were measured as previously

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reported (4). After completion of four 20-min urine collections, renal extraction of both tracers was determined by sampling blood from the abdominal aorta close to the renal artery and the renal vein. Animals were then killed by an intra-arterial injection of pentobarbital sodium, and both kidneys were removed and weighed.

Cardiovascular morphology and production of reactive oxygen species. At the end of renal function determination, the heart was removed and weighed for the calculation of heart weight index (mg/g of body weight). The thoracic aorta was removed, cleaned of adherent fat, and washed in an ice-cold bicarbonate buffer. Production of superoxide anion (O$_2^-$) by cardiac and thoracic aorta tissues was measured by a chemiluminescence technique using lucigenin, as previously described (14). Aortic production of hydrogen peroxide (H$_2$O$_2$) was also determined using luminol and horseradish peroxidase (14). The carotid artery was fixed in formalin (10%) at a constant pressure of 120 mmHg and cross-sectional area (mm$^2$) was measured on hematoxylin-colored slices (20-μm thickness).

All procedures were designed in accordance with French law and institutional guidelines for the care and use of laboratory animals and approved by the local ethics committee for animal experimentation.

Renal and cardiac histology. Five rats from the untreated NS and HS8% groups and 5 rats from the HS2% group treated with the high dose of spironolactone were prepared for cardiac and renal histology evaluation. The left kidney was perfusion-fixed with 10% buffered formalin, as previously described (2). Concomitantly, the heart was removed and the left ventricle was immersed in formalin 10%. Tissue samples were blocked in paraffin wax after alcohol dehydration and 3-μm-thick sections were stained with 0.1% Sirius red for collagen fibrosis and mounted in Eukitt medium. Sections of left ventricles and kidneys were examined on a blind fashion. Slides of left ventricle and kidneys were examined by a chemiluminescence technique using lucigenin, as previously described (14). Aortic production of hydrogen peroxide (H$_2$O$_2$) was also determined using luminol and horseradish peroxidase (14). The carotid artery was fixed in formalin (10%) at a constant pressure of 120 mmHg and cross-sectional area (mm$^2$) was measured on hematoxylin-colored slices (20-μm thickness).

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Table 1. Influence of dietary sodium diets of the experimental parameters in untreated rats

<table>
<thead>
<tr>
<th>Regimen</th>
<th>NS</th>
<th>HS2</th>
<th>HS8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final body weight, g</td>
<td>516±11</td>
<td>508±8</td>
<td>458±8*</td>
</tr>
<tr>
<td>Body weight gain, g/14 days</td>
<td>24±9</td>
<td>27±2</td>
<td>9±10*</td>
</tr>
<tr>
<td>Food consumption, g/day</td>
<td>23±1</td>
<td>25±1</td>
<td>22±1</td>
</tr>
<tr>
<td>Water intake, ml/day</td>
<td>35±2</td>
<td>50±2*</td>
<td>92±5*</td>
</tr>
<tr>
<td>Urine volume, ml/day</td>
<td>16±2</td>
<td>31±2*</td>
<td>72±4*</td>
</tr>
<tr>
<td>Water balance, ml/day</td>
<td>18±2</td>
<td>18±1</td>
<td>20±2</td>
</tr>
<tr>
<td>Sodium excretion, mmol/day</td>
<td>1.5±0.2</td>
<td>8.9±0.3*</td>
<td>23.2±2.1*</td>
</tr>
<tr>
<td>Potassium excretion, mmol/day</td>
<td>3.0±0.4</td>
<td>3.4±0.1</td>
<td>2.2±0.1*</td>
</tr>
<tr>
<td>Albuminuria, mg/day</td>
<td>0.62±0.19</td>
<td>0.43±0.08</td>
<td>1.91±0.55*</td>
</tr>
</tbody>
</table>

Cardiovascular morphology

<table>
<thead>
<tr>
<th></th>
<th>NS</th>
<th>HS2</th>
<th>HS8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart weight index, mg heart wt/g body wt</td>
<td>2.49±0.06</td>
<td>2.65±0.04</td>
<td>2.90±0.06*</td>
</tr>
<tr>
<td>Carotid cross-sectional area, mm$^2$</td>
<td>0.128±0.006</td>
<td>0.136±0.007</td>
<td>0.143±0.011*</td>
</tr>
<tr>
<td>Kidney weight index, mg kidney wt/g body wt</td>
<td>6.28±0.13</td>
<td>6.41±0.12</td>
<td>7.66±0.16*</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>127±5</td>
<td>128±5</td>
<td>127±6</td>
</tr>
<tr>
<td>GFR, μl/min−1·g kidney wt−1</td>
<td>1126±100</td>
<td>1180±82</td>
<td>694±117*</td>
</tr>
<tr>
<td>RPF, ml/min−1·g kidney wt−1</td>
<td>4.4±0.4</td>
<td>4.6±0.4</td>
<td>3.6±0.5</td>
</tr>
<tr>
<td>FF, %</td>
<td>26±2</td>
<td>26±1</td>
<td>19±1*</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SE. Rats were fed the regular normal sodium (NS) or the high sodium (HS2 and HS8) diets from weaning to 5 mo of age (n = 10 in each group). HS2, high-salt (2%) diet; HS8, high-salt (8%) diet; NS, normal salt diet; GFR, glomerular filtration rate; RPF, renal plasma flow; FF, filtration fraction. *P < 0.05 vs. the NS group.
Albuminuria was log-transformed before comparison between groups. HS2, and HS8 untreated groups. Plasma sodium and potassium between the NS, comparison was significantly reduced only in rats fed the HS8 diet. Table 1, body weight gain during the 2-wk period of comparison was still observed when GFR was adjusted to body weight or extraction of DTPA. The decrease in GFR of the HS8 group was 40% in the HS8 group. In addition, a slight increase in serum creatinine and a decrease in creatinine clearance were observed in HS8 compared with the NS group (serum creatinine of 50 ± 2 vs. 42 ± 1 μmol/l, and creatinine clearance of 520 ± 40 vs. 720 ± 40 μl-min⁻¹ g⁻¹, respectively). Renal plasma flow fell nonsignificantly in the HS8 group, and as a consequence, filtration fraction was deeply reduced in the HS8 rats. This observation was confirmed by a similar reduction in the renal extraction of DTPA. The decrease in GFR of the HS8 group was still observed when GFR was adjusted to body weight or expressed as unadjusted values.

The production of superoxide anion by the heart was similar in all groups, whereas aortic superoxide anion and hydrogen significantly increased only in the HS8 group. Urinary excretion of albumin was increased only in the HS8 group compared with the NS group.

Although kidney weight, renal function, and albumin excretion were unaffected by the HS2 diet, GFR was reduced by ~40% in the HS8 group. In addition, a slight increase in serum creatinine and a decrease in creatinine clearance were observed in HS8 compared with the NS group (serum creatinine of 50 ± 2 vs. 42 ± 1 μmol/l, and creatinine clearance of 520 ± 40 vs. 720 ± 40 μl-min⁻¹ g⁻¹, respectively). Renal plasma flow fell nonsignificantly in the HS8 group, and as a consequence, filtration fraction was deeply reduced in the HS8 rats. This observation was confirmed by a similar reduction in the renal extraction of DTPA. The decrease in GFR of the HS8 group was still observed when GFR was adjusted to body weight or expressed as unadjusted values.

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peroxide generation was increased only in rats fed the 8% NaCl diet (Table 1).

**Influence of spironolactone on changes associated with high-sodium diets.** Administration of spironolactone at the dose of 100 mg·kg⁻¹·day⁻¹ had no influence on food and water intake and urinary excretion of sodium; however, normal growth was restored in the HS8 group (25 ± 6 vs. 9 ± 10 g/14 days). The low dose of spironolactone had no effect on these parameters. Plasma sodium was not affected by spironolactone, whereas plasma potassium was slightly higher in HS2 and HS8 rats treated by the high dose of spironolactone (PK⁺ of 3.92 ± 0.07 and 3.95 ± 0.15 mmol/l, respectively) compared with their untreated control groups (see above). In NS rats, spironolactone had no significant effect on plasma concentration of sodium and potassium (147 ± 1 and 3.80 ± 0.12 mmol/l, respectively).

As depicted in Fig. 1 and Table 2, spironolactone did not affect systemic pressure; however, only the high dose markedly reversed the cardiac hypertrophy observed in the HS8 group. This observation was confirmed when the effect of spironolactone was analyzed in age- and body weight-matched HS8 and NS rats. In addition, the beneficial effect of spironolactone was reinforced by the downward shift of the relationship between body and heart weight (Fig. 2). As illustrated in Fig. 3, interstitial fibrosis of the cardiac tissue was low and similar in untreated rats fed the NS or the HS8 diet, as well as in rats fed the HS8 and receiving the high dose of spironolactone (percentage of fibrosis of 0.9 ± 0.1, 1.0 ± 0.2, and 0.6 ± 0.2%, respectively). In the cardiac tissue, perivascular fibrosis was not different in rats fed the NS diet and those fed the HS8% diet in absence or presence of spironolactone (4.0 ± 0.7, 3.9 ± 0.6, and 3.4 ± 0.8%, respectively). No cardiac effect of spironolactone was seen in the HS2 group.

The cross-sectional area of the carotid artery was strikingly reduced by spironolactone in HS2 (25%) and HS8 (45%) groups, whereas no effect was observed in the NS rats. Interestingly, the low dose of spironolactone had an intermediate effect on carotid cross-sectional area in the HS8 untreated group, P = 0.02).

No consistent effect of spironolactone on the increase in albuminuria observed in the HS8 group was afforded by spironolactone (Fig. 4). Spironolactone at the dose of 100

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**Fig. 3.** Sirius red staining of the left ventricle (A–C) and intramyocardial arteries (D–F) isolated from control NS rats (A and D) or rats fed the HS8 diet in absence (B and E) and presence (C and F) of spironolactone (100 mg·kg⁻¹·24 h⁻¹ for 14 days). Scale bar = 100 μm.
mg·kg⁻¹·day⁻¹ had no effect on renal function in the NS and HS2 groups. In contrast, in HS8 rats, spironolactone was associated with a preferential increase in GFR and filtration fraction to a value similar to NS rats (Fig. 5). In addition, serum creatinine (47 ± 3 μmol/l) was lower and creatinine clearance (640 ± 90 μl·min⁻¹·g kidney wt⁻¹) was higher in HS8 rats treated by the high dose of spironolactone compared with the untreated HS8 rats. As illustrated in Fig. 6, the percentage of abnormal glomeruli was less than 2% and non-significantly different between the NS and vehicle-treated HS8 groups. In addition, renal histology (2% of sclerotic glomeruli) was not affected by the high dose of spironolactone in rats fed the HS8 diet. No tubulointerstitial damage was detected in the three groups (score of 0 in each group). Spironolactone did not modify the kidney weight index in NS, HS2, and HS8 groups.

Treatment by the high dose of spironolactone had no effect on the production of free radicals by the heart and aortic tissues (Table 2).

DISCUSSION

In the present study, it was demonstrated that rats fed from weaning to 5 mo of age with a diet containing 8% of NaCl had significant cardiovascular hypertrophy and renal alterations, independently of major changes in systemic arterial pressure. The prohypertrophic cardiac and vascular effects of high dietary sodium, independent of blood pressure, is well documented when the amount of sodium, as well as the duration of exposure, are large enough (10, 13, 14, 19, 23). At variance with Wistar (9), Wistar Kyoto, and spontaneously hypertensive rats (23), no clear enhancement of fibrosis was detected in the Sprague-Dawley rats, despite a longer duration of high sodium feeding. Although the circulating renin activity drastically fell during high sodium intake, an enhanced activity and expression of the renin-angiotensin system were reported in cardiac (8, 19) and vascular tissue (12). On the contrary, a low-sodium diet entirely prevented the cardiac hypertrophy associated with chronic infusion of ANG II (14), thus suggesting a role for tissue ANG II in the response of the cardiovascular system to salt intake changes. In addition, the stimulation of cardiac expression of TGF-β1, directly by high dietary sodium (23) or through ANG II (7) or endothelin (20) may underlie the hypertrophic and fibrotic changes observed in rats.

Interestingly, administration of the highest dose (100 mg·kg⁻¹·day⁻¹) of spironolactone for 2 wk to the rats with already established hypertrophic cardiovascular changes was associated with complete reversal of left ventricular and large vessel hypertrophy. The lack of major changes in blood pressure and potassium handling suggests that these factors have a minor role in the deleterious effects of high sodium intake, as well as in the beneficial influence of spironolactone. Although it was not measured in the present study, plasma aldosterone
decreased (6, 19) while cardiac production of aldosterone and aldosterone synthase activity and expression (CYP11B2 mRNA) approximately doubled in response to high sodium intake in normotensive rats (19). In a study conducted in rats aged from 5–6 wk and fed an 8% NaCl diet for 4 or 8 wk, only the high dose (80 mg·kg\(^{-1}\)·day\(^{-1}\) in drinking water) of spironolactone fully prevented left ventricular hypertrophy and fibrosis, as well as an increase in cardiomyocyte cross-sectional diameter (9). Assuming that spironolactone mainly acts through the blockade of aldosterone actions, the present results and those of Lal et al. (9) suggest that aldosterone is involved in the development and persistence of deleterious cardiovascular effects from excessive sodium intake. The lack of influence of spironolactone on cardiovascular morphology in the rats fed the regular sodium diet suggests that aldosterone is involved in the cardiovascular remodeling only for an excessive sodium intake.

Among factors that may participate in the cardiovascular alterations associated with high sodium intake is an enhanced production of reactive oxygen species (ROS), as reported in the microvessels of striated muscle isolated from normotensive rats fed a high (7%)-salt diet for 4–5 wk (11). In addition, an increase in oxidative stress equated with 8-isoprostane levels and hydrogen peroxide excretion was observed in adult rats fed a 10% NaCl diet for 2 wk (22). In the present study, generation of free radicals by aortic tissue, but not the hypertrophied left ventricle, was slightly increased (by \(-20\%\)) only in rats fed the HS8 diet. This observation suggests that increased production of ROS may be involved in the chronic effect of salt. The lack of effect of spironolactone on ROS generation, despite correction of target organ damage, suggests that reversal of excessive generation of free radicals by the heart and aorta is not required for a favorable effect of spironolactone. In contrast, spironolactone prevented the increase in aortic production of ROS in chronic ANG II, as well as aldosterone-infused rats (21).

At variance with the lack of consistent change in GFR after short-term high-salt administration (16), GFR decreased in the rats fed the HS8 diet. The concomitant fall in filtration fraction suggests a preferential constriction of the preglomerular arteriole. Although an effect of anesthesia on GFR cannot be excluded, the lower value of creatinine clearance is in favor of an influence of the HS regimen on glomerular filtration. Because no increase in renal fibrosis or obvious alteration of glomeruli and renal tubules was evidenced, changes in renal function were hardly related to structural alterations of the kidneys. The enhanced albuminuria by the HS8% diet may be related to a reduced tubular catalbolism of albumin or a decrease in the proximal tubular reabsorption of albumin rather than an increase in transglomerular passage. Early and long-term exposure of rats to a high-sodium diet may explain the decrease in GFR and enhanced albuminuria through an increase in TGF-\(\beta\) production (23). Although feeding adult Lewis rats for 13 wk with a high-sodium diet did not have an effect on blood pressure and renal histology (mainly no mesangial expansion), moderate albuminuria did develop (15), thus suggesting that albuminuria may precede consistent renal structural changes. Of interest, GFR and filtration fraction returned to values similar to normal animals, whereas resistance of excessive albuminuria to spironolactone was observed. Beside changes in tubular handling of proteins, the resistance of albuminuria to spironolactone observed in our study may be related to a too-short (2 wk) exposure to the drug, thus the possibility of a poor effect on intrarenal alterations.

In addition to the favorable effect of spironolactone on the cardiac and renal functional alterations associated with high dietary sodium given from weaning to 5 mo of age, an important finding of the present study was that long-term salt loading resulted in a 40% deterioration in GFR. It cannot be excluded that after a shorter period of a high-salt diet, GFR could be elevated, or at least unchanged. Obviously, time-course studies assessing the renal functional and histological changes associated with high-salt feeding since weaning are needed. An interesting concept of “sodium glomerulopathy” was recently proposed by Aviv et al. (1) to explain the high prevalence of renal injury associated with salt-sensitive essential hypertension in humans.

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