Arterial Pressure and Exaggerated Natriuresis in Spontaneously Hypertensive Rats

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SUMMARY We tested the hypothesis that the exaggerated natriuretic response of spontaneously hypertensive rats (SHR) to intragastric volume expansion may be independent of the sustained level of arterial pressure. The SHRs were treated for 10 days with guanethidine S0, 25 mg/liter, and hydralazine HCl, 80 mg/liter, in drinking water. Mean arterial pressure (MAP) in conscious treated SHRs (T-SHR) was 130 ± SE 9 mm Hg vs 193 ± 3 mm Hg in untreated (U-) SHR (p < 0.001). An intragastric (i.g.) saline load (2% body weight) produced increases in absolute sodium excretion (Δ UNaV) by T- and U-SHR of 2.25 ± 0.85 and 2.45 ± 0.46 nEq/min, respectively (p > 0.5). However, the increase in fractional sodium excretion (FE Na) by T-SHR (Δ 0.89 ± 0.33%) was significantly less than that of U-SHR (Δ 2.16 ± 0.40%, p < 0.005), owing to a small increase in glomerular filtration rate (GFR) by T-SHR (Δ 0.28 ± 0.08 ml/min, p < 0.01). The difference in FE Na between T- and U-SHR was not affected by spironolactone. Acute drug-induced normotension in other SHR abolished the natriuresis; but, when coupled with intravenous volume expansion to 5% of body weight, the response was restored. Hydrostatic pressure in surface proximal tubules and peritubular capillaries of anesthetized T-SHR was not significantly different from that in U-SHR, nor was it significantly altered after intravenous volume expansion to 2% of body weight. It is unlikely, then, that elevated arterial pressure, per se, mediated the exaggerated natriuretic response of SHR to 2% i.g. saline-loading. Additionally, the natriuretic response of T-SHR to i.g. saline-loading may have been preserved, at least in part, by expansion of extracellular fluid volume caused by the prolonged reduction of MAP. (Hypertension 3: 386-394, 1981)

KEY WORDS • sodium excretion • hypertension • Wistar-Kyoto • micropuncture • extracellular fluid volume

THE natriuretic response of conscious, unrestrained spontaneously hypertensive rats (SHR) to an acute intragastric (i.g.) saline load (approximately 2 ml of 0.9% NaCl/100 g of body weight) is exaggerated in comparison to the response of normotensive Wistar-Kyoto rats (WK).1 The difference in response may result from a difference in mineralocorticoid-mediated sodium reabsorption between the two strains (greater in the WK),1 and not from the hypertension in the SHR.

Other investigators have examined the natriuretic responsiveness of SHR and WK to acute saline loads. Beierwaltes and Arendshorst4,4 observed no difference in natriuretic responsiveness between conscious4 and anesthetized4 SHR and WK after i.v. volume expansion (3% BW with 0.9% NaCl). Similarly, Mullins and Banks8 and Vandewalle et al.8 were unable to detect a difference in sodium excretion between anesthetized female SHR and WK after volume expansion with isotonic* or hypertonic* saline (4% to 5% of BW). These investigators suggested that hypertension may not necessitate exaggerated natriuresis in SHR. DiBona and Rios,4 on the other hand, examined the natriuretic responsiveness of male anesthetized SHR and WK to 10% BW volume expansion with isotonic saline. The natriuretic response of the SHR was approximately 65% greater than that of the WK, and the authors attributed the outcome of the experiments to the elevated blood pressure in the SHR. Other data suggest that the difference in the natriuretic responsiveness to saline-loading between SHR and WK may be related to the volume of the saline challenge.8 Intravenous volume expansion of 2% BW or more was associated with apparent suppression of the difference in mineralocorticoid activity between SHR and WK and, with that, elimination of the
difference in natriuresis. These results may explain why other investigators have not observed the exaggerated natriuresis in SHR vs WKY after mild volume expansion (3% to 5% of BW), but they do not explain the findings of DiBona and Rios.7

A direct relationship between arterial pressure and urinary sodium excretion, that is, pressure natriuresis, is a clearly documented phenomenon.8-10 However, this relationship was demonstrated with acute alterations of arterial and renal perfusion pressure, and may not be germane to a study of sodium excretion in chronic hypertension. The present studies were designed, therefore, to examine renal sodium-handling in a model of chronic hypertension, and to test the hypothesis that the exaggerated natriuretic response of SHR to i.g. saline-loading may be independent of elevated arterial pressure.

Methods

Series I: Saline-Loading Experiments

Experiment A: Effect of Chronic Drug-Induced Normotension in SHR on Urinary Responses to an Intragastric Saline Load

The effect of drug-induced normotension on the urinary response of conscious male SHR (age 12-16 weeks) to an i.g. saline load (2 ml of 0.9% NaCl/100 g BW) was determined. Normotensive WKYs were similarly studied. (Both SHR and WKY, derived from National Institutes of Health stock, were purchased from Laboratory Supply Company, Indianapolis, Indiana.) All rats were housed in plastic containers (3 rats per container) and had free access to food (Purina chow, 0.3% Na) and water. Treated animals received guanethidine and hydralazine (CIBA Company), 25 mg/kg sc daily, and 80 mg/liter, respectively, in their drinking water for 10 days; control rats received tap water. The drinking habits of the treated rats were not detectably affected by the presence of the drugs in the water.

The effectiveness of the drug treatment was assessed in a pilot study involving two groups of eight SHR each. The rats were placed in 16 metabolism cages. Eight rats were given tap water to drink, the others received water containing the antihypertensive drugs. Systolic blood pressure (tail cuff) was measured on Days 1, 5, 7, 9, and 12 in the protocol. Body weight was measured on Days 1, 9, and 12, and urinary sodium excretion was monitored daily. These rats were not studied in the saline-loading protocols.

The saline-loading studies were conducted in additional rats on the 10th day of drug treatment. Up to six rats per group were studied per week. On Day 9, each animal was anesthetized with pentobarbital sodium (50 mg/kg i.p.), and polyethylene catheters were placed in a carotid artery and a jugular vein, and exteriorized at the nape of the neck. The urinary bladder was catheterized via the urethra. Each experiment was conducted on the day after surgery. For the experiment, each animal was placed in a perforated Lucite tube, which facilitated the measurement of arterial pressure (Stentor monitor via Statham 23 Db transducer), the infusion of intravenous fluid (polyfructosan 2.5% in 0.9% NaCl, 0.05 ml/min), and the collection of urine samples. The rats, though unable to turn around, were not immobilized. After the completion of 2 120-minute control urine collections, the i.g. saline load was administered into the stomach from a syringe via a blunted stainless steel tube. Urine was collected during three additional 60-minute collection periods, and samples of arterial blood were collected at the midpoint of each period.

Forced immobilization of SHR and WKY causes activation of the sympathoadrenal medullary system in both strains, only somewhat more so in the SHR.20 Immobilized rats experience sustained elevations of plasma catecholamines.20 Although the rats in the present studies were not totally immobilized, they were restrained, and activation of the sympathoadrenal medullary system may have affected the present results.

Arterial blood pressure, sodium excretion, and glomerular filtration rate (GFR polyfructosan clearance,) were continuously monitored. Average values were calculated for the two control periods and the three experimental periods, and were compared by paired $t$ analysis. Where appropriate, comparisons between groups were made by group $t$ analysis.16

Experiment B: Effect of Acute Drug-Induced Normotension on the Urinary Response of SHR to an Intragastric Saline Load

Untreated male SHRs were subjected to all procedures as described above except the antihypertensive regimen. Immediately after administration of the i.g. saline load, the rats were given an intravenous injection of hydralazine HCl and guanethidine SO4, 40 and 12 mg/kg, respectively. Urinary and blood collection procedures and data analysis were as described previously in the chronic drug experiments (Experiment A).

Experiment C: Effect of Spironolactone on the Urinary Response of SHR to an Intragastric Saline Load During Chronic Treatment with Antihypertensive Drugs

Eight T-SHR and eight untreated controls were prepared for saline-loading experiments as already described. Spironolactone, dissolved in 0.9% NaCl, was administered intravenously (5 mg/kg) 1 hour prior to starting the control urine collection periods, and again immediately after the i.g. saline load had been given. The remainder of the experiment was conducted as described above.

Experiment D: Effect of Acute Drug-Induced Normotension and Volume Expansion on the Urinary Response of SHR to an Intragastric Saline Load

Five SHR were prepared for saline-loading experiments as described above except that, coincident with the administration of the inulin prime, 0.5 ml of
the guanethidine-hydralazine mixture was administered i.v. (12 and 40 µg/kg, respectively). At the same time, *w*, an intravenous infusion of isotonic saline, was started and continued until a volume equivalent to 5% of body weight had been infused (infusion times ranged from 25 to 35 minutes). Sixty minutes later, two control urine collections were obtained, after which the i.g. saline load was administered. The remainder of the experiment was conducted as described above.

Series 2: Micropuncture Experiments

Experiment E: Effect of Drug-Induced Normotension on Proximal Tubular and Peritubular Capillary Hydrostatic Pressure in SHR

The effect of the hydralazine-guanethidine treatment regimen on hydrostatic pressure in superficial proximal tubules and peritubular capillaries of SHR and WKR was determined with renal micropuncture techniques. Each week, one rat per group was prepared for micropuncture as described below. Rats were added to the groups at appropriate intervals to provide a continuous supply of animals of suitable age at the specified times.

Each rat was anesthetized with pentobarbital sodium (30 mg/kg), and catheters were placed in the trachea, carotid artery, and jugular vein. The left kidney was exposed via a flank incision, and was gently cleared of loose tissue. The left ureter was cannulated with polyethylene tubing. Sutures were placed in the skin of the back and nape of the neck, and a suture was looped around the upper incisors. These sutures were then secured on a movable horizontal rod above the rat table, suspending the rat in an upright position with its feet lightly touching a platform. Such positioning prevented the spontaneous and sustained reduction of blood pressure from hypertensive to normotensive (or hypotensive) levels in the untreated SHR, which regularly occurred when conventional surgical approaches to the kidney were utilized. The SHR that were not suspended soon became normotensive, developed respiratory difficulty, and died. However, in suspended rats, the incidence of such adverse occurrences was virtually eliminated; indeed, hypertension and normal unencumbered respiration could be restored in supine SHR simply by suspending them.

The exposed left kidney was placed in a small Lucite holder, cushioned with small bits of gauze, and bathed in warm (37°C) isotonic saline. Measurements of hydrostatic pressure in proximal tubules and peritubular capillaries were made with a servonulling technique. Each animal during three 30-minute urine collection periods. Each animal received an intravenous infusion of polyfructosan, and arterial blood pressure was continuously monitored. Average values for intratubular and intracapillary hydrostatic pressure were calculated for each rat; group means were calculated from the individual averages, and were used for statistical comparison between groups (Student’s *t* test).

Experiment F: Effect of Volume Expansion (2% and 3% of Body Weight) on Proximal Tubular and Peritubular Capillary Hydrostatic Pressure in SHR

Two groups of four SHR were prepared for micropuncture experiments as described above. Multiple measurements of intratubular and intracapillary hydrostatic pressure were made in randomly-selected tubules and capillaries in each animal during a 30-minute control urine collection period, after which isotonic saline was infused intravenously to expand the extra-cellular fluid volume by either 2% or 3% of body weight. Infusion times ranged between 20 and 30 minutes. Immediately after completion of the volume expansion, another 30-minute urine collection period was started during which additional measurements of intratubular and intracapillary hydrostatic pressure were obtained.

Analytical Methods

Polyfructosan concentration in plasma and urine was determined by an automated method for inulin. Sodium and potassium concentrations in plasma and urine were determined by flame photometry. In some cases, where data were compared between as well as within experimental groups, one-way analysis of variance was utilized.

Results

Series 1: Saline-Loading Experiments

Experiment A: Effect of Chronic Drug-Induced Normotension on Urinary Responses of SHR to an Intragastric Saline Load

Figure 1 displays the time course of the antihypertensive drug effects on systolic blood pressure, body weight, and daily sodium balance in SHR. Arterial pressure was significantly reduced by Day 5 and remained suppressed throughout the period of treatment. No significant differences between the groups with respect to body weight or daily sodium balance were observed.

Figure 2 (left and center panels) displays the data obtained in the saline-loading series of experiments. Control mean arterial blood pressure in the T-SHR and U-SHR was 130 ± 9 mm Hg and 193 ± 3 mm Hg, respectively (*p* < 0.001), and saline-loading had no detectable effect on arterial pressure in either group. Mean control rates of urinary sodium excretion for both groups of rats were not significantly different from each other, and saline-loading produced statistically significant increases in urinary sodium excretion in both groups. These responses did not differ from each other (Δ *UNaV* in untreated SHR was
Figure 1. Time course of guanethidine-hydralazine effect in SHR. Vertical lines designate one standard error of the mean.

2.45 ± 0.46 nEq/min, p < 0.005, and in treated SHR, Δ UₙaV was 2.25 ± 0.85 nEq/min, p < 0.05). The individual natriuretic responses of the T-SHR were more variable and less consistent than those of the U-SHR, but the responses of both T-SHR and U-SHR alike seem to have borne little relationship to the level of arterial pressure. Control GFR did not differ significantly between groups (fig. 2). In the U-SHR, the i.g. saline load did not significantly affect GFR, but in the treated SHR, GFR was significantly, albeit slightly, increased (Δ GFR 0.28 ± 0.08 ml/min, p < 0.01). Thus, the elevation of fractional sodium excretion by the T-SHR (Δ 0.89 ± 0.33%, p < 0.05), was significantly less (p < 0.05) than that for the untreated SHR (Δ 2.16 ± 0.40%, p < 0.005).

A parallel series of experiments was conducted in normotensive WKRF to control for effects of guanethidine and hydralazine on urinary sodium handling that may have been independent of their effects on arterial blood pressure. Results from these studies are shown in figure 3. Ten days of drug treatment produced no detectable differences between the treated and untreated WKRF with respect to arterial blood pressure or control urinary sodium excretion. Mean control GFR in the treated WKRF was significantly less than that in the untreated WKRF, but saline-loading had no detectable effect on GFR in either group. The mean natriuretic response of the treated WKRF to saline-loading, expressed either in absolute or fractional terms, did not differ significantly from that of the untreated WKRF.

Experiment B: Effect of Acute Drug-Induced Normotension on the Urinary Responses of SHR to an Intragastric Saline Load

The effect of a sudden, acute reduction in arterial pressure on the natriuretic response of SHR to i.g. saline-loading was evaluated. The preceding experimental protocol was repeated except that the SHR did not receive the antihypertensive drugs until immediately after the saline load had been administered (fig. 2, right panel). Control values for MAP, urinary sodium excretion, and GFR in those rats did not differ significantly from those of the U-SHR. The antihypertensive drugs produced an immediate reduction in MAP by 68 ± 13 mm Hg to 115 ± 12 mm Hg, which was not significantly different from that achieved by chronic drug treatment, and did not
significantly alter GFR. The natriuretic responsiveness of these SHR to the saline load was completely suppressed. Indeed, urinary sodium excretion was significantly reduced after administration of the saline load (Δ -0.70 ± 0.19 nEq/min, p < 0.025).

Experiment C: Effect of Spironolactone on the Urinary Responses of SHR to an Intragastric Saline Load During Chronic Treatment with Antihypertensive Drugs

Enhanced endogenous mineralocorticoid activity associated with prolonged reduction of blood pressure may have been responsible for the apparent increase in tubular sodium reabsorption that was observed after saline-loading in the T-SHR of Series 1, Experiment A. To assess this possibility, the experiment was repeated with an additional group of SHR that had received the antihypertensive drugs, except that on the day of the saline-loading experiment, each rat received spironolactone (5 mg/kg). The results of this experiment are shown in figure 4. The MAP in the hypertensive SHR (171 ± 3 mm Hg) differed significantly from that of the T-SHR (151 ± 3 mm Hg, p < 0.001) prior to administration of the saline load, but the load produced no significant alteration of blood pressure in either group. Absolute urinary sodium excretion did not differ between the groups either before or after saline-loading, but FE\textsubscript{Na} in the antihypertensive-treated SHR was increased to a lesser degree (p < 0.05) than in either the hypertensive spironolactone-treated SHR (fig. 3) or the hypertensive SHR of figure 2. As in Series 1, Experiment A, this effect was attributable to a small but consistent increase in GFR.
Experiment D: Effect of Acute Drug-Induced Normotension and Expansion of the Extracellular Fluid Volume on the Urinary Responses of SHR to an Intragastric Saline Load

The difference observed between chronically- and acutely-normotensive SHR in natriuretic responsiveness to the intragastric saline challenges may have been due to prior expansion of the extracellular fluid volume in the former caused by the prolonged reduction of blood pressure. To evaluate this possibility, i.e., saline-loading experiments were conducted in another group of seven SHR in which blood pressure had been acutely reduced to normotensive levels with the antihypertensive drug combination, but in which extracellular fluid volume had been expanded to 5% of body weight by the intravenous infusion of 0.9% saline. Data from these experiments are shown in table 1. Prior to receiving the antihypertensive drugs, the MAP in the rats of this group was 195 ± 6 mm Hg. After drug treatment and volume expansion, the MAP stabilized at 136 ± 5 mm Hg for the duration of the experiments. This value was not significantly different from the blood pressures of other groups of T-SHR in this report. As is evident from table 1, the natriuretic responses of these normotensive, volume-expanded SHR to the 2% BW i.g. saline load were variable, but natriuresis was evident in all animals and the mean response was statistically significant (p < 0.05). No consistent alteration of GFR was observed. In addition, the mean natriuretic response of this group was significantly greater than that of acutely normotensive SHR (Series 1, Experiment B, fig. 1), but not significantly different from the responses of either group of SHR in Series 1, Experiment A (fig. 1).

Series 2: Micropuncture Experiments

Experiment E: Effect of Drug-Induced Normotension on Proximal Tubular and Peritubular Capillary Hydrostatic Pressure in SHR

The effects of hydralazine and guanethidine on hydrostatic pressure in superficial proximal tubules and peritubular capillaries in SHR and WKR are summarized in table 2. The MAP in rats of both

### Table 1. Effect of Acute Drug-Induced Normotension and Expansion of the Extracellular Fluid Volume (5% BW) on the Urinary Responses of SHR to an Intragastric Saline Load (2% BW)

<table>
<thead>
<tr>
<th>Rat</th>
<th>Mean arterial blood pressure (mm Hg)</th>
<th>Urinary sodium excretion (nEq/min)</th>
<th>Glomerular filtration rate (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Saline</td>
<td>Δ*</td>
</tr>
<tr>
<td>1</td>
<td>210</td>
<td>145</td>
<td>150</td>
</tr>
<tr>
<td>2</td>
<td>180</td>
<td>120</td>
<td>145</td>
</tr>
<tr>
<td>3</td>
<td>200</td>
<td>147</td>
<td>125</td>
</tr>
<tr>
<td>4</td>
<td>185</td>
<td>127</td>
<td>110</td>
</tr>
<tr>
<td>5</td>
<td>210</td>
<td>127</td>
<td>140</td>
</tr>
<tr>
<td>6</td>
<td>210</td>
<td>130</td>
<td>140</td>
</tr>
<tr>
<td>7</td>
<td>170</td>
<td>155</td>
<td>156</td>
</tr>
<tr>
<td>Mean</td>
<td>195 ± 6</td>
<td>136 ± 5</td>
<td>138 ± 6</td>
</tr>
</tbody>
</table>

*Δ = difference between Control and Saline values.
†ns = not statistically significant.

### Table 2. Effect of Chronic Treatment with Antihypertensive Drugs on Glomerular Filtration and Renal Hydrostatic Pressures in SHR and WKR

<table>
<thead>
<tr>
<th></th>
<th>SHR</th>
<th>WKR</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>141 ± 9</td>
<td>136 ± 8</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>1.44 ± 0.33 (2)</td>
<td>1.75 ± 0.27 (2)</td>
</tr>
<tr>
<td>Pr (mm Hg)</td>
<td>14.3 ± 0.6 (11.0 - 17.7)</td>
<td>13.1 ± 0.7 (12.4 - 16.3)</td>
</tr>
<tr>
<td>Ptc (mm Hg)</td>
<td>9.6 ± 0.6 (8.5 - 13.0)</td>
<td>10.2 ± 0.5 (8.3 - 13.9)</td>
</tr>
<tr>
<td>n</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Abbreviations: MAP = mean arterial blood pressure; GFR = glomerular filtration rate (left kidney); Pr = proximal tubular hydrostatic pressure; Ptc = peritubular capillary hydrostatic pressure; n = numbe of animals per group; * denotes a statistically significant difference.

For GFR, the numbers in parentheses denote the number of animals in which GFR was measured.

Values are given as mean ± standard error. The values for Pr and Ptc are based on measurements from at least seven tubules and four capillaries per rat.
strains was comparable to that reported elsewhere in this paper, and blood pressure in T-SHR was suppressed to normotensive levels. Estimates of whole-kidney GFR showed reasonable agreement within and between strains. No statistically significant differences were detected between either group of SHR or WKR, treated or untreated, with respect to tubular or peritubular capillary hydrostatic pressure.

**Experiment F: Effect of Volume Expansion (2% and 3% of Body Weight) on Proximal Tubular and Peritubular Capillary Hydrostatic Pressures in SHR**

Hydrostatic pressures in superficial proximal tubules and peritubular capillaries of SHR were measured before and after the intravenous infusion of isotonic saline to a volume of 2% or 3% of body weight. The results of these experiments are summarized in table 3. Expansion of extracellular fluid volume caused no statistically significant alteration of systemic arterial pressure or of intratubular or peritubular capillary hydrostatic pressure in either group, although in the 3% volume expansion group an upward trend was apparent.

**Discussion**

These data support in several ways the hypothesis that the exaggerated natriuresis in the SHR is independent of elevated arterial blood pressure. First, chronic drug-induced suppression of arterial pressure in SHR by some 65 mm Hg (Series 1, Experiment A) did not significantly affect the natriuretic response of these rats to an i.g. saline load. If the response was principally a function of elevated arterial pressure, it should have been suppressed during drug treatment. Second, expansion of the extracellular fluid volume to 2% and 3% of body weight (Series 2, Experiment F) did not significantly elevate hydrostatic pressure in superficial proximal tubules or peritubular capillaries of SHR, although a clear upward trend was evident with 3% expansion. Since a 2 ml/100 g body weight i.g. saline load produces a volume expansion that is closer to 1% of body weight than to 2%, owing to incomplete intestinal absorption of the saline, the possibility that the i.g. saline load in the present experiments caused elevation of tubular and capillary hydrostatic pressures seems remote. Third, in spite of a difference in arterial pressure of 43 mm Hg between the hypertensive and normotensive SHR of Series 2, Experiment E, neither proximal tubular pressure nor peritubular capillary pressure differed significantly between the groups (table 2). Moreover, the hydrostatic pressures in the microvasculature and tubules of both groups of SHR did not differ significantly from those in WKR. Admittedly, these micropuncture data were variable, and group sizes were small. Nevertheless, other investigators have reported that intratubular and peritubular capillary hydrostatic pressures in SHR are either the same as, or slightly lower than those in WKR, that renal vascular resistance is high, and that renal hemodynamics in SHR are not compromised by acute alterations of arterial pressure. Thus, the exaggerated natriuretic response of the SHR to i.g. saline-loading cannot be explained by elevated renal perfusion pressure per se. In contrast, elevated renal microvascular pressures have been reported in salt-sensitive hypertensive rats and have been proposed as a contributing factor in the exaggerated natriuresis. As yet, however, elevated

### Table 3. Effect of Expansion of the Extracellular Fluid Volume on Hydrostatic Pressure in Proximal Tubules and Peritubular Capillaries in SHR

<table>
<thead>
<tr>
<th>Rat</th>
<th>Proximal tubule pressure (mm Hg)</th>
<th>Capillary pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Expansion</td>
</tr>
<tr>
<td>1</td>
<td>16.2 ± 0.4* (11)</td>
<td>15.7 ± 0.4 (6)</td>
</tr>
<tr>
<td>2</td>
<td>20.5 ± 0.8 (11)</td>
<td>19.8 ± 1.0 (10)</td>
</tr>
<tr>
<td>3</td>
<td>22.7 ± 2.2 (8)</td>
<td>27.3 ± 1.3 (11)</td>
</tr>
<tr>
<td>4</td>
<td>14.8 ± 1.4 (16)</td>
<td>12.6 ± 1.4 (12)</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>18.6 ± 1.9</td>
<td>18.9 ± 3.2</td>
</tr>
<tr>
<td>Difference ± SE</td>
<td>0.3 ± 1.5</td>
<td>-0.5 ± 1.2</td>
</tr>
<tr>
<td>p</td>
<td>na</td>
<td>na</td>
</tr>
</tbody>
</table>

**Expansion to 3% of body weight**

<table>
<thead>
<tr>
<th>Rat</th>
<th>Proximal tubule pressure (mm Hg)</th>
<th>Capillary pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>9.5 ± 0.6 (10)</td>
<td>13.7 ± 1.7 (3)</td>
</tr>
<tr>
<td>6</td>
<td>14.8 ± 3.0 (6)</td>
<td>18.4 ± 1.0 (12)</td>
</tr>
<tr>
<td>7</td>
<td>18.2 ± 0.4 (14)</td>
<td>25.8 ± 1.8 (9)</td>
</tr>
<tr>
<td>8</td>
<td>18.9 ± 0.8 (12)</td>
<td>19.7 ± 1.1 (13)</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>15.4 ± 2.2</td>
<td>19.4 ± 2.5</td>
</tr>
<tr>
<td>Difference ± SE</td>
<td>4.1 ± 1.4</td>
<td>2.1 ± 0.7</td>
</tr>
<tr>
<td>p</td>
<td>na</td>
<td>na</td>
</tr>
</tbody>
</table>

Parentheses indicate the number of measurements per animal.
renal micropressures during saline-loading in the salt-sensitive rat have not been reported. Moreover, the exaggerated natriuretic response to i.g. saline-loading of the Dahl strain of salt-sensitive rats occurs prior to the onset of hypertension, suggesting that if the response is mediated by elevated intrarenal pressure, renal microvascular pressures may be higher than normal in prehypertensive Dahl rats. In SHR, on the other hand, the onset of the exaggerated natriuresis occurs within 3 to 6 weeks after the onset of arterial hypertension.

Although saline-loading did not produce differences in absolute sodium excretion between control and “normotensive” SHR, the renal responses of the rats did differ qualitatively. That is, GFR was uniformly increased in the “normotensive” SHR after saline-loading in two independent experiments (Series 1, Experiments A and C), but not in the hypertensive SHR. Therefore, fractional sodium excretion was enhanced to a significantly lower extent in the “normotensive” SHR by saline-loading, indicating that tubular sodium reabsorption must have been enhanced in the normotensive SHR. The enhancement would offset the increase in filtered sodium load thereby preserving the natriuretic response. The explanation for this response is obscure, but it is unlikely to have been due to increased mineralocorticoid activity associated with the sustained reduction of blood pressure since spironolactone did not enhance the natriuresis in the T-SHR of Series 1, Experiment C.

Arendshorst and Beierweltes have suggested that “... kidneys of SHR require a higher arterial pressure than kidneys of WKY to excrete a given amount of salt and water.” This connotation of an intrarenal resetting of the relationship between arterial pressure and sodium excretion is based on these authors’ observation that, in SHR, an acute reduction of renal perfusion pressure of approximately 40 mm Hg blunted the natriuretic response of the rats to volume expansion with isotonic saline (3% of body weight). Acute reductions of renal perfusion pressure do indeed reduce renal natriuretic responsiveness, as confirmed in this and in other reports, but the present results belie the notion that the natriuretic responsiveness of the SHR kidney is a direct function of the sustained level of blood pressure.

The natriuretic responsiveness of the dog kidney to saline-loading is increased by mineralocorticoid-induced salt and water retention. Moreover, drug-induced normotension causes salt and water retention. Thus, the similarity of the natriuretic responses of the hypertensive and “normotensive” SHR of Series 1, Experiment A may have resulted from upward adjustment of total body sodium and extracellular fluid volume caused by drug-induced reduction of arterial pressure in the T-SHR. Support for this possibility comes from the results of Series 1, Experiment D. In those experiments, volume expansion (5% of body weight), superimposed on acute blood pressure reduction in one group of SHR, was associated with a significantly greater natriuretic response to the i.g. saline load than occurred in the group that experienced an acute reduction of blood pressure, but no expansion of extracellular fluid volume (Series 1, Experiment B). In addition, the results of Experiment B, in which the natriuretic response of SHR to saline-loading was abolished by acute blood pressure reduction, are compatible with this possibility since no significant fluid retention could have occurred over the short course of that experiment. On the other hand, the body weight and sodium balance data of Figure 1 do not support the volume expansion hypothesis; but body weight and urinary sodium balance are not particularly sensitive indices of body fluid volume. Indeed, expansion of the extracellular fluid volume by 5% in a 250 g rat requires the retention of 12.5 ml of isotonic fluid, or 1.75 mEq Na. If it is assumed that net sodium retention occurred over a period of 5 to 10 days, only 0.2 to 0.4 mEq would have to be retained each day, and the detection of such small differences between groups of rats would be difficult. The differences would be even less readily discernible if volume expansion of less than 5% occurred. Thus, volume expansion of less than 5% BW could have been responsible for maintaining the natriuretic responsiveness of the normotensive SHR.

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