Atrial Natriuretic Factor in Dahl Rats
Atrial Content and Renal and Aortic Responses

RUDOLF M. SNAJDAR AND JOHN P. RAPP

SUMMARY Inbred Dahl salt-sensitive rats had a higher content of atrial natriuretic factor by bioassay in their atria than did inbred Dahl salt-resistant rats. This finding was true both in young 1- to 2-month-old rats, when blood pressure differences between strains were small, and in 7-month-old rats, when blood pressure differences were marked. Atria from salt-sensitive rats had more atrial natriuretic factor than did atria from salt-resistant rats when the rats were fed either low (0.3% NaCl) or high (8% NaCl) salt diet, but a high salt diet suppressed the atrial content of atrial natriuretic factor equally in both strains. In young, prehypertensive salt-sensitive rats, intravenous injections of atrial natriuretic factor caused significantly less natriuresis and diuresis than in salt-resistant rats (p < 0.05). As the rats aged and salt-sensitive rats became markedly hypertensive, the strain responses to atrial natriuretic factor were reversed, that is, the salt-sensitive rats became more sensitive to atrial natriuretic factor than did the salt-resistant rats. Aortic vascular smooth muscle response to contraction with KCl was equally inhibited in both strains by atrial extracts or atriopeptin II. Thus, the salt-sensitive rat renal hyporesponsiveness to atrial natriuretic factor was not associated with a generalized hyporesponsiveness of vascular tissue to atrial natriuretic factor. It is argued that salt-sensitive rats could have two defects relating to atrial natriuretic factor, one involving hyporesponsive kidneys and another involving decreased release of atrial natriuretic factor from the atria.

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KEY WORDS • atrial natriuretic factor • genetic hypertension • salt-sensitive rats

Atrial myocytes contain a peptide (or peptides) with natriuretic and diuretic activity. Several closely related active peptides have been isolated, and their sequence determined. The atrial natriuretic factor (ANF) is believed to play a role in the control of renal water and sodium excretion, and it may be involved in the development of various forms of hypertension.

Most of the work in this area has been directed at elucidating the structure of ANF and its normal physiological control of sodium excretion, but there are also a few reports concerning its relevance in various cardiovascular pathophysiological states, including one article on Dahl rats. In this study, we have evaluated developmental patterns of renal and vascular responsiveness to ANF in inbred Dahl salt-sensitive rats and inbred Dahl salt-resistant rats. Data on the effect of salt feeding on atrial content of ANF in Dahl rats are also given.

Materials and Methods

Inbred strains of Dahl rats that were developed in our laboratory were used. The strain designations for these inbred Dahl rats are S/JR for salt-sensitive rats and R/JR for salt-resistant rats. For simplicity the inbred Dahl rats will be referred to in the text by their generic symbols, S and R respectively. Male Long-Evans and Sprague-Dawley rats weighing 250 to 300 g (Charles River Breeding Laboratory, Wilmington, MA, USA) were used as bioassay rats. Rats were fed a standard laboratory diet, which contains 1% NaCl (Wayne Rodent Blox Continental Grain Co., Chicago, IL, USA), except in experiments for which special low salt (0.3% NaCl) or high salt (8% NaCl) diets (Teklad, Madison, WI, USA) were used. Blood pressures were obtained by the tail cuff method with the rats under light ether anesthesia, at least 3 days before animals were to be used. Hearts were collected from CO2-killed adult Dahl S, Dahl R, or Sprague-Dawley rats and rinsed in phosphate buffered saline. Both atria and the apex of the hearts were removed, blotted dry, and pooled separately. Extracts were prepared by homogenizing the tissue in 10 mM phosphate buffered saline, pH 7.4 (1:2.5 wt/vol). The homogenate was then placed into a boiling water bath for 10 minutes, after which it was cen...
trifuged at 25,000 g for 30 minutes at 4 °C. The resulting supernatant was aliquoted and frozen at −20 °C until tested. Total protein was determined by the method of Lowry et al. 11

Animals for bioassay of ANF in atrial extracts were anesthetized with sodium pentobarbital, and the femoral vein was cannulated. Phosphate buffered saline was used for maintenance intravenous infusion at a rate of 11 μl/min as well as a vehicle for test material injected as a bolus through the same cannula. The bladder was cannulated through a small suprapubital incision with PE-50 tubing (Clay Adams, Parsippany, NJ, USA). The tubing was tied in place. It was important to keep light tension on the cannula with another suture to prevent occluding the cannula by the pressure of the bladder wall against the end of the cannula. The rats were kept warm with a warming light. After an equilibration of at least 30 minutes, urine was collected for two 10-minute control periods before intravenous injection of sample and for at least three consecutive 10-minute periods after sample injection. Urine volume was determined by gravimetry, and sodium excretion was determined by flame photometry. In some experiments the Long-Evans bioassay rats received multiple injections with a 40- to 60-minute rest interval between each injection to allow the urine volume to return to a steady, baseline value. The order of test material was varied to eliminate bias.

To examine the sensitivity of S and R vasculature to ANF, we looked at the ability of the synthetic peptide atriopeptin II (Peninsula Labs, Belmont, CA, USA) to inhibit KCl-induced contraction of S and R thoracic aortas. Aged-matched young female S and R rats (1-2 mo old) were killed by cervical dislocation. Thoracic aortas were quickly removed and placed into physiological salt solution (118 mM NaCl, 4.7 mM KCl, 12.5 mM NaHCO₃, 1.2 mM KH₂PO₄, 1.2 mM MgSO₄, 2.5 mM CaCl₂, 11 mM glucose). The aorta was dissected free of fat and connective tissue while it was submerged in the physiological salt solution. Two (1 S, 1 R) 5 mm long rings of thoracic aorta were placed in the same 50-ml muscle chamber containing the physiological salt solution at 37 °C. The physiological salt solution was bubbled with 95% O₂, 5% CO₂, which adjusted the pH to 7.3. Tissue was allowed to equilibrate for 90 minutes under 2.5 g of tension, after which KCl was added in a stepwise fashion to the bathing solution in the presence or absence of atriopeptin II. Atriopeptin II was added 5 to 8 minutes before the addition of KCl. The KCl-induced responses were allowed to reach maximum tension at each concentration before the next dose of KCl was added. Cumulative dose-response curves were thus obtained. Similar experiments were performed with a pooled atrial extract replacing the atriopeptin II. Tension developed was measured with a force displacement transducer (model FT .03, Grass Instruments, Quincy, MA, USA) and a Grass polygraph (model 79D) recorder.

At the end of contractions the aortic rings were blotted dry, weighed, and measured. The cross-sectional area was determined according to the method of

<table>
<thead>
<tr>
<th>Injection</th>
<th>No. of tests</th>
<th>Urine volume (μl/10 min)</th>
<th>Sodium excretion (μEq/10 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>10</td>
<td>65 ± 8.8</td>
<td>5.8 ± 1.3</td>
</tr>
<tr>
<td>Atrial extract</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75 μl</td>
<td>7</td>
<td>119 ± 23.5</td>
<td>13.5 ± 7.7</td>
</tr>
<tr>
<td>150 μl</td>
<td>13</td>
<td>461 ± 63.0</td>
<td>78.2 ± 13.2</td>
</tr>
<tr>
<td>300 μl</td>
<td>8</td>
<td>968 ± 96.5</td>
<td>153.4 ± 9.3</td>
</tr>
</tbody>
</table>

Values are means ± se.

Greenberg and Bohr. 14 Tension developed by aortic rings was expressed as milligrams per square millimeter of cross-sectional area.

One-way and two-way analyses of variance and t tests were performed on an Olivetti 6060 minicomputer (Dallas, TX, USA) using software obtained from Olivetti. A probability of less than 0.05 was considered significant.

Results

When Long-Evans male bioassay rats were given pooled atrial extract, increases in urinary sodium and water excretion were dose dependent, which is in agreement with the well-known report by deBold. 2 In our bioassay, rats responded in a dose-dependent fashion when 75 to 300 μl of atrial extract was injected (Table 1). Urine volume and sodium excretion increased markedly during the first 10 minutes after bolus injection of atrial extracts and essentially returned to preinjection levels within 30 minutes after injection, as has been shown repeatedly by others. 1,15-18 Similarly prepared extracts from the ventricles or vehicle alone had no significant effect on urine volume or sodium excretion.

The atrial content of ANF was compared between S and R rats raised on normal laboratory chow at two ages: 1 to 2 months old and 7 months old. Long-Evans bioassay rats received two intravenous injections of 200 μl of atrial extract (equivalent to 4 atria or 0.6 mg of protein) derived from the S and R rats. The order of injection (S or R) was varied to eliminate any bias; the second injection was given approximately 45 minutes after the first. Figure 1 shows the results of the bioassay of these atrial extracts. Atrial extracts from S rats caused a significantly (by paired t tests) greater increase in urinary volume (p < 0.05) and sodium excretion (p < 0.05) than did R atrial extracts (see Figure 1). This finding was true when the S and R rats supplying the atria for bioassay were 1 to 2 months of age as well as when the atria were taken from 7-month-old rats. In the younger rats blood pressure differences between strains were slight but statistically different (S = 113 ± 2.9 mm Hg, R = 103 ± 2.1 mm Hg; p < 0.01 by t test). For the old rats blood pressure differences were massively and statistically different (S =
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Figure 1. The 10-minute urinary volume and sodium excretion of Long-Evans bioassay rats after intravenous injection of 200 µl of pooled atrial extract from 1- to 2-month-old or 7-month-old Dahl salt-resistant (R) and salt-sensitive (S) rats raised on normal rat chow. Seventeen assays were performed on extract from young rats, and 12 assays were performed on extract from older rats. Means ± se are shown. All urine volumes and sodium excretions showed significant (p < 0.05) strain differences by paired t tests in comparing the effects of S and R atrial extracts.

234 ± 7.1 mm Hg, R = 130 ± 2.3 mm Hg; p < 0.001 by t test).

The effect of varying dietary salt intake on the atrial content of ANF was evaluated in S and R rats. A set of female weanling (4 wk old) S and R rats was randomly divided and given either a high salt (8% NaCl) or a low salt (0.3% NaCl) diet for 1 month. Rats were then killed, and the atria were pooled for each experimental group and extracted. Ten Long-Evans male bioassay rats each received four randomized injections of 200 µl of atrial extract (approximately 0.5 mg of protein, equivalent to 3.5 atria) derived from S or R rats on high or low salt diets. From our pilot studies it was determined by analysis of variance that four sequential injections of a pooled atrial extract into a bioassay rat did not significantly (p > 0.1) alter the urinary volume or sodium responses (Table 2). Atrial extracts from S rats again showed more natriuretic and diuretic activity than did R atrial extracts (p < 0.05; 2 × 2 factorial analysis of variance), and these strain differences were seen regardless of dietary salt (Figure 2). Increased dietary salt decreased the natriuretic and diuretic activity of atrial extracts (p < 0.05; 2 × 2 factorial analysis on data in Figure 2). The increased content of ANF in S atria relative to that from R atria did not change with intake of salt (i.e., the interaction in the 2 × 2 factorial analysis of variance was not significant; p > 0.5). The blood pressures for the rats used in Figure 2 were 124 ± 3.0 mm Hg in R rats fed a low salt diet, 121 ± 3.0 mm Hg in R rats fed a high salt diet, 138 ± 4.4 mm Hg in S rats fed a low salt diet, and 175 ± 3.3 mm Hg in S rats fed a high salt diet.

Table 2. Response of Long-Evans Test Rats to Repeated 200-µl Injections of Atrial Extract

<table>
<thead>
<tr>
<th>Atrial extract injected</th>
<th>Urine volume (µl/10 min)</th>
<th>Sodium excretion (µEq/10 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st 200 µl</td>
<td>543 ± 72.9</td>
<td>99 ± 14.0</td>
</tr>
<tr>
<td>2nd 200 µl</td>
<td>586 ± 48.4</td>
<td>103 ± 7.3</td>
</tr>
<tr>
<td>3rd 200 µl</td>
<td>455 ± 27.9</td>
<td>72 ± 4.8</td>
</tr>
<tr>
<td>4th 200 µl</td>
<td>535 ± 60.7</td>
<td>84 ± 11.3</td>
</tr>
</tbody>
</table>

Values are means ± se.

Eleven rats each received four consecutive injections of the same pool of atrial extract. A one-way analysis of variance showed that there were no significant differences among the responses to the consecutive injections of atrial extract for either urine volume (p = 0.39) or sodium excretion (p = 0.11).
rats fed a high salt diet. A 2 × 2 factorial analysis of variance showed significant effects on blood pressure for strain (p < 0.001), diet (p < 0.001), and interaction of strain and diet (p < 0.001).

The next set of experiments was designed to determine the responses of S and R kidneys to pooled atrial extract. Male S and R bioassay rats of 1, 2, and 7 months of age were given a 100-µl bolus of pooled atrial extract, which was equivalent to 1.5 atria or 0.375 mg of protein. The S and R rats used for bioassay were maintained on standard laboratory diet. Blood pressures of the bioassay rats were obtained 3 days before rats were used for testing. The results are given in Figure 3. Control urine volume and sodium excretion of 1-month-old S and R bioassay rats were not significantly different before the injection of atrial extract. After the injection of pooled atrial extract, however, the S rats responded significantly less than the R rats, although at this age the differences were not statistically significant. At this age, the blood pressures of the S bioassay rats were markedly greater than the blood pressures of R bioassay rats, since the blood pressures of the S rats had risen above 200 mm Hg. This high blood pressure is typical of the inbred S (S/JR) strain raised on normal rat chow.

Ventricular extracts or vehicle (phosphate buffered saline) alone injected into any of the three age groups of S and R bioassay rats did not have a significant effect on urinary sodium or water excretion.

The effect of synthetic atriopeptin II on aortic responses to KCl was evaluated next. Thoracic aortas of young (1–2 mo old) female S and R rats were studied concomitantly in the same muscle bath chambers, and they were contracted with KCl in the presence and absence of atriopeptin II. Figure 4 shows the responses of aortas in absence and presence of 0.5 µg and 1.0 µg of atriopeptin II in the 50-ml muscle chamber. Two micrograms of atriopeptin II was also tested, but the responses were similar and not statistically different than the 1-µg dose, that is, 1 µg gave a maximal response. For clarity, the 2-µg dose was omitted from the graphs. Atriopeptin II inhibited KCl-induced contractions in a dose-dependent manner; increasing amounts of atriopeptin II shifted the tension response curve to the right.

The values for effective dose, 50% (ED50) were estimated graphically for each rat used in Figure 4, and the results are given in Table 3. A 2 × 3 factorial analysis of variance (2 strain × 3 doses of atriopeptin II) on the ED50 values showed a significant (p < 0.001) effect of atriopeptin II on the KCl-induced aortic contraction, which indicates that increased amounts of KCl were required to produce a half-maximal response in the presence of atriopeptin II. The differences between strains and (most importantly, as will be explained) the interaction of strain × dose of atriopeptin II were not significant in the analysis of ED50 values.

The effect of atrial extracts on thoracic aortic responses to KCl was also evaluated, but in this experiment aortas were obtained from 7-month-old female S rats.
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![Graph showing cumulative dose-response curves for the thoracic aortas of 1- to 2-month-old Dahl salt-sensitive (S) and salt-resistant (R) female rats are shown in the absence and presence of two doses of atriopeptin II per 50-ml chamber. Means ± se are shown.](image)

**Figure 4.** Cumulative dose-response curves for the thoracic aortas of 1- to 2-month-old Dahl salt-sensitive (S) and salt-resistant (R) female rats are shown in the absence and presence of two doses of atriopeptin II per 50-ml chamber. Means ± se are shown.

**Table 3.** Effect of Atriopeptin II on the Effective Dose, 50%, for KCl-Induced Contraction of Thoracic Aortas from 1- to 2-Month-Old Dahl Salt-Resistant (R) and Salt-Sensitive (S) Rats

<table>
<thead>
<tr>
<th>Strain</th>
<th>Atriopeptin II (μg/50 ml chamber)</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>19.9 ± 0.7 (27)</td>
<td>28.4 ± 0.9 (9)</td>
<td>32.2 ± 0.3 (10)</td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>17.0 ± 0.7 (27)</td>
<td>27.1 ± 2.1 (10)</td>
<td>31.3 ± 0.6 (10)</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± se.

Numbers in parentheses are the numbers of independent determinations of effective dose, 50% (ED₅₀), made on individual aortic rings from 10 S and 10 R rats. The ED₅₀ values are derived from the same rats used in Figure 4. A 2 x 3 factorial analysis of variance on ED₅₀ values showed significant effects caused by atriopeptin II (p < 0.001) but no significant effect of strain or strain x atriopeptin II interaction.

*μM of KCl (mean ± se) required to give a half-maximal contraction (ED₅₀) in the presence or absence of atriopeptin II.

Discussion

Phosphate buffered saline extracts of S and R atria caused an abrupt and short-lived diuresis and natriuresis after injection into a bioassay rat. However, the atrial extracts derived from S rats produced approxi-
FIGURE 5. Cumulative dose-response curves for the thoracic aortas of 7-month-old Dahl salt-sensitive (S) and salt-resistant (R) female rats are shown in the absence and presence of two doses of atrial extract per 50-ml chamber. Means ± se are shown.

TABLE 4. Effect of Atrial Extract on the Effective Dose, 50%, for KCl-Induced Contraction of Thoracic Aortas from 7-Month-Old Dahl Salt-Resistant (R) and Salt-Sensitive (S) Rats

<table>
<thead>
<tr>
<th>Strain</th>
<th>Atrial Extract (μL/50 ml chamber)</th>
<th>0</th>
<th>62</th>
<th>125</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td></td>
<td>32.7±0.7(24)</td>
<td>35.7±1.6(8)</td>
<td>46.1±2.4(8)</td>
</tr>
<tr>
<td>S</td>
<td></td>
<td>27.7±1.1(16)</td>
<td>31.9±1.9(8)</td>
<td>41.6±2.3(8)</td>
</tr>
</tbody>
</table>

Values are means ± se.

Numbers in parentheses are the numbers of independent determinations of effective dose, 50% (ED50) made on individual aortic rings from 8 S and 8 R rats. The ED50 values are derived from the data in Figure 5. A 2 × 3 factorial analysis of variance on ED50 values showed significant effects caused by strain (p < 0.001) and atrial extract (p < 0.001), but the interaction of strain × atrial extract was not significant (p > 0.9).

Values are in mM of KCl (mean ± se) required to give a half-maximal contraction (ED50) in the presence or absence of atrial extract.

Thus, a high atrial content of ANF appears to be the result of decreased demand, increased storage, and decreased synthesis of ANF. The number of atrial granules decreased after saline or deoxycorticosterone acetate treatment. Our atrial extracts from rats receiving high and low salt diets indicate that both S and R rats can respond to a high salt diet with a decrease in the atrial content of ANF. Presumably, salt feeding should increase demand for ANF and increase blood levels of ANF. Decreased atrial content of ANF with salt feeding presumably reflects a state of rapid synthesis and release, which favors decreased storage.

In the absence of data on peripheral blood levels and synthesis and secretion rates of ANF in S and R rats it is difficult to know why ANF was higher in the atria of S than in R rats. One possibility is that S but not R rats have a defective mechanism of release of ANF. If that were true, increased blood levels of ANF in S compared with those in R rats might be expected. Failure to secrete adequate ANF certainly could be important in causing hypertension in S rats by allowing a relatively increased positive sodium balance, expanded blood volume, and increased blood pressure. There is some evidence for an expanded blood volume in salt-fed S rats relative to salt-fed R rats.23

On the other hand, when prehypertensive, 1-month-old rats were challenged with atrial extract, S rats excreted significantly less sodium and water than did R rats. This finding suggests that 1-month-old S rats are relatively resistant to the effects of ANF. Of course, such end-organ hyporesponsiveness to ANF in S rats could lead to the same result as does hyposecretion of ANF in S rats (i.e., sodium and water retention, expanded blood volume, and hypertension). One important difference between the two speculations is that
with end-organ hyporesponsiveness one expects ANF blood levels in S rats to show a compensatory increase, in contrast to the decreased blood levels expected if S rats have a defect in the release of stored hormone.

There is, then, a paradox in the higher atrial content of ANF found in S rats. On the one hand, a high salt diet, which is expected to increase demand for ANF, lowered atrial ANF content. On the other hand, renal hyporesponsiveness to ANF, which is also expected to increase demand for ANF, was associated with higher, not lower, atrial ANF content. For this reason, we believe that there is a reasonable possibility for two genetically mediated defects relating to the ANF system in S rats. One defect should involve the kidney and its response, the other should involve the machinery for synthesis, storage, or release of ANF from the heart.

The renal hyporesponsiveness to ANF was seen only in young, prehypertensive S rats. As the rats aged and blood pressure increased, S and R renal responses to ANF became statistically nonsignificant. When the S rats were older and markedly hypertensive, the S and R renal responses were reversed: compared with R rats, the S rats were hyperresponsive to ANF. We interpret this shift to be secondary to the greatly elevated blood pressure in the S rats and the resulting effects of pressure on natriuresis and diuresis and/or the marked glomerular tubular and vascular lesions that have been shown to occur in old S rats. Older S rats also have been shown to excrete large amounts of protein in their urine as a consequence of these lesions.

There are important data from isolated perfused kidneys indicating that the relation between renal perfusion pressure and excretion of sodium and water is altered in S rats. In such experiments, at equal perfusion pressures kidneys of S rats excreted less sodium and water than did kidneys of R rats and it took a higher pressure in S than in R rats to equalize excretion rates. There is some question as to whether this phenomenon is acquired as the result of hypertension or an intrinsic primary genetic defect. In either case, this phenomenon might influence how the kidneys of S rats respond to ANF. On the other hand, nothing in this discussion excludes the possibility that the renal hyporesponsiveness of S rats to ANF resides in a defect more specific for ANF (e.g., a receptor). There is some argument as to whether ANF acts on the kidney through a direct effect on tubules or through its vasoactive properties on the kidney. Some of the atrial natriuretic peptides are known to have vasorelaxant properties. The precursor for these natriuretic peptides also contains an amino acid sequence (so-called cardiokinin) that has vasorelaxant properties but no diuretic properties. In our experiments, we tested the effect of a natriuretic peptide, which also has vasorelaxant activity (atriopeptin II), as well as crude atrial extract on aortic vascular smooth muscle. Responsiveness of S and R aortas to KCl-induced contractions was inhibited similarly by these preparations. This finding suggests that the vascular responsiveness to atrial factors are intact in S rats. It has been reported that in salt-fed S rats dilatation of renal vasculature does not occur as it does in salt-fed R rats. In our view, this could result from a failure of S rats to release enough ANF from the heart in response to salt.

Hirata et al. have reported data similar to ours on atrial content of ANF in S and R rats and renal hyporesponsiveness of nonhypertensive S rats to ANF. Their data on the effect of salt on atrial content of ANF probably are different because of differences in the dietary protocols. They found a transient increase in the atrial content of ANF in R but not in S rats, after the rats had been receiving a 4% NaCl diet for 5 days, and no change in atrial ANF content in either S or R rats after they had been fed the 4% NaCl diet for 3 months. In our experiments, an 8% NaCl diet fed for 1 month caused a significant decrease in atrial content of ANF in both S and R rats.

Recently, it was reported that spontaneously hypertensive rats have less ANF in their atria than do control Wistar-Kyoto rats. This finding is the opposite of what we found in S and R rats and is not necessarily surprising since, a priori, one does not expect the various hypertensive rat strains to have fixed the same set of genetic defects.

In comparing strains of genetically hypertensive rats with their control strain for atrial content of ANF it is necessary to extract the atria by some method. Of the several methods in current use, we chose the boiled extract, since it involves minimal manipulation and does not introduce toxic substances into the assay animal. There is evidence that the method of extraction can influence the lengths of atrial peptides obtained. It is less clear how the total ANF biological activity is influenced by extraction methods. Extraction artifacts are likely to similarly affect both strains being compared. It may be prudent, however, to qualify each strain comparison as having been attained under the conditions of a given extraction method.

In conclusion, we found that S rats contained increased amounts of ANF in their atria compared with R rats. Young S rats also were hyporesponsive to the natriuretic and diuretic effects of ANF. This phenomenon does not appear to be the result of altered responses of vascular smooth muscle to ANF. As the S rats aged and became hypertensive, they changed from being hyporesponsive to hyperresponsive to the effects of ANF on the kidney.

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