Atrial Natriuretic Factor in NaCl-Sensitive and NaCl-Resistant Spontaneously Hypertensive Rats

Hongkui Jin, Yiu-Fai Chen, Ren-Hui Yang, and Suzanne Oparil

Our previous studies demonstrated that chronic dietary NaCl supplementation is associated with significant increases in plasma atrial natriuretic factor in Wistar-Kyoto (WKY) rats but not in NaCl-sensitive spontaneously hypertensive rats (SHR-S). The current study tested the hypotheses that 1) acute volume-induced atrial natriuretic factor release is impaired in SHR-S compared with control NaCl-resistant SHR (SHR-R) and WKY rats maintained on basal (1%) NaCl diets; 2) dietary NaCl supplementation (8% NaCl for 2 weeks) alters acute volume-dependent atrial natriuretic factor release in these strains; and 3) replacement of the deficiency in circulating atrial natriuretic factor seen in NaCl-supplemented SHR-S can reverse the NaCl-sensitive component of hypertension. SHR-S and control SHR-R and WKY rats were placed on 1% or 8% NaCl diets at age 7 weeks; 2 weeks later, right atrial pressure and plasma atrial natriuretic factor were measured in conscious rats before and after acute volume expansion (7, 20, and 60 ml/kg, 5% dextrose, for 1 minute). The slopes of the right atrial pressure x plasma atrial natriuretic factor linear regression for the SHR-S fed both 1% and 8% NaCl were significantly shallower (p<0.01) than those of 1% NaCl-fed SHR-R or WKY rats. Dietary NaCl supplementation did not alter right atrial pressure in any strain and blunted acute volume-induced atrial natriuretic factor release in WKY rats, but not in SHR-S or SHR-R, suggesting the dietary NaCl-induced elevation in plasma atrial natriuretic factor levels in WKY rats may be related to impaired clearance, as well as enhanced release, of the peptide. The plasma levels of exogenous atrial natriuretic factor required to abolish the NaCl-induced pressor effect in SHR-S were 12-fold greater than endogenous plasma atrial natriuretic factor levels in 8% NaCl-fed WKY rats, suggesting that impairment of atrial natriuretic factor release does not play a major role in the pathogenesis of NaCl-sensitive hypertension in SHR-S. (Hypertension 1989;14:404-412)

Atrial natriuretic factor (ANF), a family of peptide hormones isolated from mammalian atria, has potent natriuretic, diuretic, vasodilator, sympathetic, and renin- and aldosterone-suppressing activities.1-10 ANF is involved in the regulation of volume and electrolyte balance and blood pressure.1-10 However, the pathophysiological role of ANF in the development or maintenance of systemic hypertension is unclear.

Data concerning the effects of acute administration of ANF on blood pressure in the spontaneously hypertensive rat (SHR) are conflicting. Depressor responses to bolus injection or infusion of ANF have been reported to be greater11-14 or equivalent15-17 in SHR to those observed in normotensive control rats. Further, elimination of endogenous ANF by autoimmunization has been shown not to affect the rate of development or the severity of hypertension in SHR.18 The SHR studied in this report were maintained on normal NaCl diets throughout, and the NaCl sensitivity of their hypertension was not assessed.

Acute volume loading and atrial stretch are potent stimuli of ANF release,19,20 but the effects of chronic dietary NaCl loading on ANF release in the rat are less clear.21-23 Natriuresis in response to acute intravenous volume expansion was inhibited in autocrine normotensive rats, but natriuresis produced by chronic oral salt loading was not sup-
pressed in these animals. Moreover, the role of circulating ANF in setting blood pressure and volume levels in SHR fed diets of varying NaCl content is poorly understood.

Our previous studies have demonstrated that NaCl-sensitive SHR (SHR-S) from Taconic Farms (IBU3 colony, Germantown, New York) exhibit significant increases in blood pressure and sympathetic outflow when fed a high NaCl diet. In contrast, NaCl-resistant SHR (SHR-R) from Charles River Breeding Laboratories (Kingston, New York) and normotensive control Wistar-Kyoto (WKY) rats do not respond to dietary NaCl loading with either a pressor effect or an enhancement in sympathetic nervous system activity. We recently found that dietary NaCl supplementation (8% NaCl for 2 weeks) produced a significant increase in plasma ANF levels in WKY rats, but not in SHR-S, suggesting an impairment in NaCl-induced ANF release in SHR-S.

In the current study, we extended our investigation of the role of ANF in NaCl-sensitive hypertension in SHR-S by: 1) direct measurement of acute ANF release in response to volume expansion in SHR-S and control SHR-R and WKY rats; 2) direct assessment of the effects of chronic dietary NaCl supplementation on acute volume-dependent ANF release in these three strains; and 3) testing whether replacement of the deficiency in circulating ANF seen in NaCl-supplemented SHR-S can reverse the NaCl-sensitive component of hypertension in this model. We hypothesized that acute volume-induced ANF release would be impaired in SHR-S compared with SHR-R and WKY rats on both basal and high NaCl intakes. Further, we predicted that the NaCl-induced increment in blood pressure seen in SHR-S could be abolished by infusion of exogenous ANF in doses that would increase plasma ANF to levels comparable with those seen in WKY rats fed a high NaCl diet. Our results demonstrated that: 1) there was an alteration in the right atrial pressure/ANF relation in SHR-S compared with SHR-R and WKY rats on a basal NaCl intake, but this did not affect circulatory levels of ANF; 2) chronic dietary NaCl supplementation led to blunting of acute volume-induced ANF release in WKY rats, but not in either SHR strain; 3) the increase in plasma ANF levels in chronically NaCl-loaded SHR-S produced by infusion of ANF in doses sufficient to abolish the NaCl-induced increment in blood pressure was 14-fold greater than the difference in endogenous plasma ANF levels between normal and high NaCl-fed WKY rats. Thus, impaired ANF release does not appear to account for NaCl-sensitive hypertension in SHR-S; and 4) dietary NaCl supplementation was associated with an exaggerated depressor response to ANF in SHR-S compared with SHR-R and WKY rats, suggesting that ANF receptor or clearance mechanisms, in addition to release mechanisms, may be altered in NaCl-sensitive hypertension.

**Materials and Methods**

Male SHR-S of the Okamoto strain (IBU3 colony) and normotensive control WKY rats were obtained from Taconic Farms at 7 weeks of age. Male SHR-R were obtained from Charles River Breeding Laboratories at the same age. All rats were maintained four per cage at constant humidity (60±5%), temperature (24±1°C), and 12-hour light/dark cycle (6:00 AM–6:00 PM). Three days after arrival, half of the rats in each group (SHR-S, SHR-R, or WKY rats) were placed on an 8% NaCl diet (ICN Biochemicals Purina chow with 8% NaCl, Costa Mesa, California), and the other half remained on the basal 1% NaCl diet (Ralston Purina diet 5001, St. Louis, Missouri). Food and water were available ad libitum throughout the study. Systolic blood pressure was measured twice weekly in conscious, prewarmed, restrained rats by the tail-cuff method using an electrosphygmomanometer and physiograph recorder (Narco Bio-Systems, Houston, Texas). The median of five successive measurements was used as the estimate of blood pressure. Body weight was determined on the same day.

In the initial set of experiments, effects of acute volume expansion on ANF release were compared in SHR-S, SHR-R, and WKY rats fed 1% or 8% NaCl diets. Twelve days after initiation of the special diets, rats were anesthetized with ether. Polyethylene cannulas (PE-10 fused to PE-50) filled with heparin-saline solution (50 units/ml) were implanted into the abdominal aorta through the right femoral artery for recording of right atrial pressure. Catheter position was identified by the pressure tracing during the cannulation. All cannulae were exteriorized subcutaneously at the back of the neck. After catheter implantation, all rats were housed individually.

Two days after implantation, the femoral arterial and right atrial catheters were connected to pressure transducers (model CP-01, Century Technol. Co., Inc., Inglewood, California), and mean arterial pressure (MAP), right atrial pressure, and heart rate (HR) were recorded continuously (Grass model 7 polygraph, Grass Instr. Co., Quincy, Massachusetts) in conscious unrestrained rats. MAP, right atrial pressure, and HR were allowed to stabilize for 60 minutes before rats were challenged with acute volume expansion (7, 20, and 60 ml/kg 5% dextrose over 1 minute i.v.). Each rat received all three volumes of dextrose in random order. Each volume expansion experiment was done on a separate day. On each of the 3 days, a stimulated (immediately after the respective acute volume expansion) blood sample (0.7 ml) for circulating ANF was withdrawn. The blood withdrawn was immediately replaced with an equal volume of whole rat blood from a pool.
of normotensive Sprague-Dawley donor animals. To assess the relation between acute volume expansion, right atrial pressure, and plasma levels of ANF, right atrial pressure was continuously monitored on each day during the volume expansion experiment.

Blood was placed in iced tubes containing 1.5 mg EDTA and 1 trypsin-inhibitor unit of aprotinin. Plasma was separated by centrifugation at 4°C, and plasma samples were stored at −80°C until radioimmunoassay (RIA) for ANF.

A second set of experiments examined the effect of exogenous ANF on MAP in SHR-S, SHR-R, and WKY rats fed 1% or 8% NaCl diets. Twelve days after initiation of the special diets, rats were instrumented with femoral artery and vein cannulas, as previously described. Two days after implantation, tubing was connected to the femoral arterial cannula for blood sampling. At least 1 hour was allowed to pass before 1.0 ml blood was collected from conscious, unrestrained, resting animals for ANF determination. The blood withdrawn was immediately replaced with an equal volume of 0.9% saline. Twenty-four hours later, MAP and HR were recorded continuously through the arterial cannula in conscious, unrestrained rats, as previously described. After a stable MAP was obtained, rat ANF-(1–28) (Bachem, Inc., Torrance, California) was infused intravenously in a dose of 0.06 μg/min for 30 minutes. Preliminary study had shown that this dose of ANF (infusion at 0.06 μg/min for 30 minutes) reduced MAP by 20 mm Hg at a flow rate of 10 μl/min. The 8% NaCl diet did not influence HR significantly in any experimental group. There was no significant difference in basal SBP before initiation of the special diets between the 1% and 8% NaCl groups, SHR-S (144.4±4.1 vs. 144.8±2.7 mm Hg), SHR-R (138.0±4.4 vs. 139.3±2.8 mm Hg), or WKY rats (117.2±3.2 vs. 115.0±3.6 mm Hg). After 2 weeks on the special diets, SHR-S fed 8% NaCl had significantly greater MAP than SHR-S fed 1% NaCl (Table 1); both SBP and MAP in the 8% NaCl group averaged 20 mm Hg more than in the 1% NaCl group (p<0.02 and p<0.01, respectively). In contrast, SBP and MAP in the SHR-R (151.2±2.7 vs. 155.2±4.1 mm Hg for SBP in 1% NaCl vs. 8% NaCl groups, NS; 138.8±4.8 vs. 142.5±4.2 mm Hg for MAP in 1% NaCl vs. 8% NaCl groups, NS) and the WKY rats (123.9±2.0 vs. 119.4±2.1 mm Hg for SBP in 1% NaCl vs. 8% NaCl groups, NS; 108.8±4.2 vs. 110.6±3.8 mm Hg for MAP in 1% NaCl vs. 8% NaCl groups, NS) showed no change in response to dietary NaCl supplementation (p>0.2 for SBP, p=0.5 for MAP). The 8% NaCl diet did not influence HR significantly in any experimental group.

Body weights of WKY rats were significantly greater than those of SHR-S and SHR-R on both 1% and 8% NaCl diets. There was no difference in body weight between the 1% and 8% NaCl groups within each strain.

Basal, resting right atrial pressure was significantly greater in both 1% NaCl- and 8% NaCl-fed SHR-S (5.2±0.8 mm Hg, n=8 and 6.0±0.5 mm Hg, n=8, respectively) than in SHR-R (1.5±0.7 mm Hg, n=8) (Table 1). Right atrial pressure in both 1% NaCl- and 8% NaCl-fed SHR-S after 20 and 60 ml/kg volume expansion was significantly greater than in WKY rats or SHR-R.
TABLE 1. Effects of NaCl Supplementation for 2 Weeks in NaCl-Sensitive and NaCl-Resistant Spontaneously Hypertensive Rats and Wistar-Kyoto Rats

<table>
<thead>
<tr>
<th>Group</th>
<th>SBP (mm Hg)</th>
<th>MAP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>Body wt (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHR-S</td>
<td>162.5±6.3*</td>
<td>144.6±2.5*</td>
<td>376.3±12.5</td>
<td>212.8±3.5*</td>
</tr>
<tr>
<td></td>
<td>(9)</td>
<td>(8)</td>
<td>(8)</td>
<td>(9)</td>
</tr>
<tr>
<td>SHR-R</td>
<td>151.2±2.7*</td>
<td>138.8±4.8*</td>
<td>370.8±10.0</td>
<td>203.7±4.1*</td>
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<tr>
<td></td>
<td>(10)</td>
<td>(9)</td>
<td>(9)</td>
<td>(10)</td>
</tr>
<tr>
<td>WKY</td>
<td>123.9±2.0</td>
<td>108.8±4.2</td>
<td>377.5±8.0</td>
<td>226.8±4.1</td>
</tr>
<tr>
<td></td>
<td>(9)</td>
<td>(8)</td>
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1% NaCl

<table>
<thead>
<tr>
<th>SBP (mm Hg)</th>
<th>MAP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>Body wt (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHR-S</td>
<td>162.0±3.6††</td>
<td>163.8±3.9</td>
<td>370±13.1</td>
</tr>
<tr>
<td></td>
<td>(9)</td>
<td>(8)</td>
<td>(8)</td>
</tr>
<tr>
<td>SHR-R</td>
<td>155.4±2.9*</td>
<td>142.5±4.2</td>
<td>388.0±10.8</td>
</tr>
<tr>
<td></td>
<td>(10)</td>
<td>(10)</td>
<td>(10)</td>
</tr>
<tr>
<td>WKY</td>
<td>119.4±2.1</td>
<td>110.6±3.8</td>
<td>363.3±10.0</td>
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<td></td>
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<td>(9)</td>
<td>(9)</td>
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</table>

8% NaCl

<table>
<thead>
<tr>
<th>SBP (mm Hg)</th>
<th>MAP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>Body wt (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHR-S</td>
<td>203.7±4.1*</td>
<td>212.8±3.5*</td>
<td>207.2±2.7*</td>
</tr>
<tr>
<td></td>
<td>(9)</td>
<td>(8)</td>
<td>(9)</td>
</tr>
<tr>
<td>SHR-R</td>
<td>203.7±4.1*</td>
<td>212.8±3.5*</td>
<td>207.2±2.7*</td>
</tr>
<tr>
<td></td>
<td>(10)</td>
<td>(10)</td>
<td>(10)</td>
</tr>
<tr>
<td>WKY</td>
<td>226.8±4.1</td>
<td>233.8±3.6</td>
<td>233.8±3.6</td>
</tr>
<tr>
<td></td>
<td>(9)</td>
<td>(9)</td>
<td>(9)</td>
</tr>
</tbody>
</table>

Results represent mean±SEM. Number of rats is shown in parentheses. SBP, systolic blood pressure; MAP, mean arterial pressure; HR, heart rate; SHR-S, spontaneously hypertensive rats (SHR) NaCl-sensitive strain; SHR-R, SHR NaCl-resistant strain; WKY, Wistar-Kyoto rats.

*p<0.05 compared with respective values of WKY rats; †p<0.05 compared with respective values of 1% NaCl-fed control group; ‡p<0.05 compared with respective values of SHR-R and WKY rats.

fed either diet. However, the slopes of the curves relating right atrial pressure to volume expansion were not significantly different among the six subgroups (Figure 1). The 8% NaCl diet did not significantly alter either resting or post-volume expansion right atrial pressure in any strain. Acute volume expansion significantly increased (p<0.01, ANOVA) plasma ANF concentration in a dose-dependent manner in all six subgroups (Table 2). The volume x plasma ANF interactions were not significantly different among the six subgroups.

In all six subgroups, the increase in plasma ANF levels after acute volume expansion was positively correlated with increments in right atrial pressure (Figure 2). The slopes of the right atrial pressure x plasma ANF linear regression curves for SHR-S fed both 1% and 8% NaCl were significantly shallower (p<0.01; unpaired Student’s t test of the slopes after linear regression) than those for 1% NaCl-fed WKY rats and SHR-R. Dietary NaCl supplementation significantly reduced (p<0.05) the slope of the right atrial pressure x plasma ANF curve in WKY rats but not in SHR-S or SHR-R.

ANF infusion produced dose-dependent reductions in MAP in all experimental groups (Figure 3). The depressor response to ANF in 8% NaCl-fed SHR-S was significantly greater than in 1% NaCl-fed SHR-S when expressed as either absolute change (p<0.01) or percent change (p<0.05) (Table 3). In contrast, there was no significant difference in the depressor effect of ANF between 1% and 8% NaCl groups of SHR-R or WKY rats (Table 3). ANF infusion also caused dose-dependent decreases in HR (Table 3). There was no significant difference in the bradycardic response to ANF among SHR-S, SHR-R, and WKY rats fed the same diet, or between 1% and 8% NaCl rats within the same strain.

The time course of the effects of ANF infusion on MAP and HR is shown in Figures 4 and 5. Depressor and bradycardic responses appeared almost immediately after the intravenous infusion of ANF was begun (0.3 μg/min). Maximal effects were achieved at 20–24 minutes of infusion. A significant difference in the depressor effect of ANF between the 1% and 8% NaCl groups was observed in SHR-S, but not in SHR-R or WKY rats.

Dietary NaCl supplementation was associated with a significant increase in endogenous plasma ANF levels in WKY rats but not in SHR-S or SHR-R (Figure 6). After 2 weeks of the 8% NaCl diet, SHR-S and SHR-R had significantly lower basal ANF levels than did WKY rats fed the same diet. No significant difference in endogenous plasma ANF was found between 8% NaCl-fed SHR-S and SHR-R or among WKY rats, SHR-R, and SHR-S fed the 1% NaCl diet.

The 8% NaCl diet (for 2 weeks) was associated with a 19.2 mm Hg increase in MAP in SHR-S (Table 1). Infusion of ANF (0.06 μg/min for 30
TABLE 2. Effects of Volume Expansion on Plasma Atrial Natriuretic Factor Levels

<table>
<thead>
<tr>
<th>Group</th>
<th>Type of diet</th>
<th>Volume (ml/kg)</th>
<th>0</th>
<th>7</th>
<th>14</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHR-S</td>
<td>1% NaCl</td>
<td></td>
<td>66±18 (8)</td>
<td>147±27 (8)</td>
<td>248±32 (7)</td>
<td>456±60 (6)</td>
</tr>
<tr>
<td>SHR-S</td>
<td>8% NaCl</td>
<td></td>
<td>65±11 (9)</td>
<td>187±16 (7)</td>
<td>211±22 (6)</td>
<td>434±78 (6)</td>
</tr>
<tr>
<td>SHR-R</td>
<td>1% NaCl</td>
<td></td>
<td>98±15 (8)</td>
<td>192±44 (6)</td>
<td>259±38 (7)</td>
<td>596±90 (8)</td>
</tr>
<tr>
<td>SHR-R</td>
<td>8% NaCl</td>
<td></td>
<td>83±9 (8)</td>
<td>164±24 (7)</td>
<td>313±65 (7)</td>
<td>508±28 (6)</td>
</tr>
<tr>
<td>WKY</td>
<td>1% NaCl</td>
<td></td>
<td>66±9 (7)</td>
<td>134±24 (6)</td>
<td>317±68 (7)</td>
<td>618±102 (7)</td>
</tr>
<tr>
<td>WKY</td>
<td>8% NaCl</td>
<td></td>
<td>150±23 (7)*</td>
<td>158±21 (8)</td>
<td>344±68 (7)</td>
<td>517±102 (6)</td>
</tr>
</tbody>
</table>

Results represent mean±SEM. Atrial natriuretic factor levels are in picograms per milliliter in SHR-S, SHR-R, and WKY fed 1% and 8% NaCl diets for 2 weeks. Number of rats is shown in parentheses. SHR-S, spontaneously hypertensive rats (SHR) NaCl-sensitive strain; SHR-R, SHR NaCl-resistant strain; WKY, Wistar-Kyoto rats.

*p<0.05 compared with the other five groups by analysis of variance.

Discussion

In the current study, there was an alteration (flattening of the regression line) in the right atrial pressure/ANF relation in SHR-S compared with SHR-R and WKY rats fed both high and basal NaCl diets. This did not result in reductions in circulating levels of ANF after volume expansion in SHR-S compared with the other strains, however. Chronic (2 weeks) dietary NaCl supplementation did not alter the sensitivity of ANF release in response to acute volume expansion in either SHR strain, but did blunt the response in WKY rats. This finding suggests that the failure of both SHR strains to increase circulating ANF levels when subjected to dietary NaCl supplementation is related to the genetics of the SHR or to hypertension, per se, rather than to NaCl sensitivity. The dose of exogenous ANF required to abolish the NaCl-induced increase in MAP of SHR-S under our experimental conditions produced a 19-fold increase in plasma ANF levels, but plasma ANF levels were elevated only 2.3-fold after chronic dietary NaCl supplementation in WKY rats. Taken together, the data suggest that impairment of ANF release does not play a major role in the pathogenesis of NaCl-sensitive hypertension in SHR-S.

ANF release is regulated mainly by atrial distension secondary to a variety of stimuli, including volume loading. Recent studies in vivo showed that atrial stretch is the principal determinant of ANF release in open chest anesthetized dogs. Further, studies of the response of plasma ANF to acute volume expansion with saline in young and adult SHR versus WKY rats demonstrated that for a given increase in right atrial pressure, less ANF was released in SHR than in WKY rats. In the current study, right atrial pressure both before and after acute volume expansion was significantly higher in SHR-S than in SHR-R or WKY rats on either diet. This probably reflects a state of chronic volume expansion in SHR-S maintained on either basal or high NaCl intake. Alternatively, it is possible that the atria of SHR-S may be less distensible than those of SHR-R or WKY rats. The slopes of the linear regression curves for the right atrial pressure×plasma ANF relation were significantly

FIGURE 2. Plots showing correlation between right atrial pressure and plasma levels of atrial natriuretic factor or peptide (ANP) after acute blood volume expansion. SHR-S, spontaneously hypertensive rats (SHR) NaCl-sensitive strain; WKY, Wistar-Kyoto rats; SHR-R, SHR NaCl-resistant strain.
shallower for SHR-S fed either diet than for either SHR-R or WKY rats on 1% or 8% NaCl. Thus, for a given increase in right atrial pressure, smaller amounts of ANF were released in SHR-S than in SHR-R or WKY rats in either diet condition and that more atrial stretch (i.e., a higher right atrial pressure) was required to elevate circulating ANF levels in SHR-S than in SHR-R or WKY rats.

Dietary NaCl supplementation significantly reduced the slope of the right atrial pressure x plasma ANF curve in WKY rats but not in either hypertensive strain. This was unaccompanied by any NaCl-induced change in resting right atrial pressure. Despite this, circulating ANF levels doubled in NaCl-supplemented WKY rats compared with WKY rats fed a basal diet. The finding of elevated plasma ANF in the presence of blunted acute release mechanisms in 8% NaCl-fed WKY rats suggests impairment in ANF clearance in this situation. Further study is needed to test this hypothesis directly. Our finding of elevated plasma ANF in WKY rats fed 8% NaCl confirms numerous previous demonstrations that acute or chronic NaCl loading causes significant increases in plasma ANF levels in normotensive rats, suggesting that NaCl loading induces release of ANF from the atria into the circulation. This effect has generally been attributed to volume expansion with resultant atrial stretch, although an independent effect of the sodium ion per se or of other neurohumoral factors cannot be ruled out.

Our finding that plasma levels of ANF do not differ significantly among conscious, freely moving SHR-S, SHR-R, and WKY rats fed a basal (1%) NaCl diet confirms previous studies. These results contrast with reports that ANF levels are significantly increased in SHR compared with WKY rats when the rats are anesthetized or blood is collected by decapitation. Plasma ANF data obtained from anesthetized or decapitated rats must be interpreted with caution because various anesthetics and different methods of blood collection alter plasma levels of ANF.

In the current study, infusion of ANF produced dose-dependent depressor effects in all experimental groups; this effect was exaggerated in NaCl-loaded SHR-S compared with all other groups. The depressor effect appeared so rapidly (5 minutes) after initiation of the ANF infusion that it is unlikely to be secondary to an ANF-related natriuresis/antinatriuresis effect.
diuresis. One possible explanation for the enhanced depressor response to ANF in NaCl-loaded SHR-S is that sensitivity to the sympatholytic effect of ANF is greater in the state of enhanced sympathetic tone seen in this model. We have previously shown that SHR-S fed high NaCl diets display increased blood pressure in association with increased peripheral sympathetic nervous system activity and enhanced peripheral vascular tone, as evidenced by an exaggerated depressor response to ganglion blockade.45 There is growing evidence that ANF inhibits both sympathetic outflow from the central nervous system and norepinephrine release from sympathetic nerve terminals in the periphery.6-8 Thus, we have considered the possibility that the enhanced depressor effect of ANF in NaCl-supplemented SHR-S is related to an increased sympatholytic action. Although preliminary experiments in our laboratory failed to reveal a reduction in circulating norepinephrine or epinephrine levels after chronic infusion of ANF into NaCl-supplemented SHR-S, this does not completely rule out a sympatholytic action of the peptide.46 More recent data suggest that intravenous administration of ANF is associated with a significant reduction in lumbar sympathetic nerve activity in the SHR-S.47 Further study is needed to determine the role of this sympatholytic effect of ANF in modulating NaCl-sensitive hypertension.

The current observation that ANF caused dose-dependent decreases in HR is consistent with other reports that ANF produces a significant bradycardia in conscious WKY rats, SHR, DOCA-treated, and two-kidney, one clip rats, and normotensive dogs.14,48,49 Since atropine reverses the ANF-induced bradycardia, it has been suggested that ANF slows HR by increasing cardiac vagal efferent activity.14 Alternatively, infusion of ANF could lead to cardiac sympathoinhibition through excitation of chemosensitive cardiac vagal afferents. Vagal efferent activity would then predominate.14
In conclusion, the current study demonstrated that the slope of the regression line relating plasma ANF levels to right atrial pressure after acute volume expansion was reduced in SHR-S compared with SHR-R and WKY rats. This effect was specific to the strain and independent of diet. Chronic dietary NaCl supplementation was associated with increased (doubling) circulatory ANF levels in WKY rats but not in either SHR strain. This occurred in the absence of NaCl-induced alterations in right atrial pressure and despite blunting of acute volume-induced ANF release in WKY rats suggesting that the chronic dietary NaCl-induced elevation in plasma ANF levels in WKY rats is related to impaired clearance, as well as enhanced release, of ANF.

The depressor response to exogenous ANF was increased (doubling) in dietary NaCl-loaded SHR-S compared with the other strain and diet groups, but exogenous ANF fully reversed the NaCl-sensitive component of hypertension in SHR-S only at pharmacological levels. This suggests that the deficiency (compared with WKY rats) in circulating ANF in NaCl-supplemented SHR does not play a major role in the NaCl-sensitive hypertension.

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KEY WORDS • blood pressure • atrial natriuretic factor • NaCl sensitivity • NaCl-induced hypertension • spontaneously hypertensive rat
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