L-Arginine Administration Normalizes Pressure Natriuresis in Hypertensive Dahl Rats

Ami Patel, Scott Layne, Dennis Watts, Kent A. Kirchner

A blunted pressure-natriuretic response characterizes hypertension in the Dahl salt-sensitive rat. Long-term L-arginine administration prevents hypertension in these animals. To determine if long-term L-arginine corrects the pressure-natriuretic response, we gave salt-sensitive rats on an 8% sodium diet L-arginine or vehicle daily for 3 weeks. Identically treated salt-resistant rats served as controls. After 3 weeks, acute pressure-natriuresis curves were determined. To control for hypertension-induced renal damage, we also examined pressure natriuresis in salt-sensitive rats after short-term L-arginine. Baseline mean arterial pressure was 158±3 mm Hg in vehicle-treated salt-sensitive rats and 127±3 mm Hg in chronically L-arginine-treated salt-sensitive rats. During alterations in perfusion pressure, renal blood flow was autoregulated in all groups. Glomerular filtration rate was autoregulated in salt-resistant rats and L-arginine-treated salt-sensitive rats but fell with decreasing pressure in vehicle-treated salt-sensitive rats. Sodium excretion was greater (P<.05) in L-arginine-treated than in vehicle-treated salt-sensitive rats and did not differ from salt-resistant rats at 100, 125, and 158 mm Hg. The slope of the pressure-natriuresis relation was greater (P<.05) in chronically L-arginine-treated than in vehicle-treated salt-sensitive rats. L-Arginine had no effect on natriuresis in salt-resistant rats. Thus, long-term L-arginine administration normalizes pressure-natriuretic responses in salt-sensitive rats. The effect is not due to the prevention of renal damage and is specific to the salt-sensitive strain. The mechanism may in part result from improvement in autoregulation of glomerular filtration rate. (Hypertension. 1993;22:863-869.)

KEY WORDS • rats, Dahl • endothelium-derived relaxing factor • nitric oxide • blood pressure • natriuresis • homeostasis

Abnormal renal sodium handling is a frequent finding in salt-induced hypertension in humans and in some hypertensive animal models such as the Dahl salt-sensitive (DS) rat.1-4 A consistent observation in salt-sensitive hypertension is that at equivalent renal perfusion pressure (RPP), salt-sensitive hypertensive subjects excrete sodium less efficiently than their salt-resistant normotensive counterparts.1-4 In the DS rat the abnormal relation between RPP and urinary sodium excretion is of renal origin1 and is present before the development of hypertension.2,5,6 Thus, this abnormality may participate in the development of hypertension in these animals. Recently, Chen and Sanders7 observed that enhanced nitric oxide synthesis occurs in normotensive and salt-resistant (DR) rats treated with vehicle or L-arginine chronically were examined for comparison.

Methods
Male DS and DR rats (Harlan Sprague Dawley Inc, Indianapolis, Ind) were maintained on tap water and standard rodent chow (20 μmol/L sodium per gram of L-arginine in DS rats would be through improvement in the blunted relation between RPP and sodium excretion that usually characterizes these animals. The L-arginine effect could occur through alterations in endothelium-derived nitric oxide activity or other as yet unidentified mediators. The current study was designed to examine whether long-term administration of L-arginine to DS rats of the inbred Rapp strain improves the pressure-natriuresis relation in these animals. DS rats receiving the vehicle for L-arginine, DS rats receiving L-arginine acutely, and salt-resistant (DR) rats treated with vehicle or L-arginine chronically were examined for comparison.

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were placed in the right carotid and femoral arteries to
arteries were used to examine both long- and short-term effects
containing 5% polyfructosan (Inutest, Laevosan Gesellschaft, Linz, Austria) and 1% L-arginine. Ligatures were then loosely placed
were also placed in the jugular veins for intravenous
blood pressures were obtained by tail-cuff plethysmography. All animals were housed according to institutional
Guidelines, and the studies were approved by the Institutional Animal Care and Use Committee of the University of Mississippi Medical Center. Baseline systolic blood pressures were obtained by tail-cuff plethysmography. Animals were placed on a
thermostatically controlled animal table, and body temperatures were maintained at 37°C with a servo-activated controller (Vestavia Scientific Co, Vestavia Hills, Ala). After tracheostomy, PE-50 polyethylene catheters were placed in the right carotid and femoral arteries to allow for continuous measurement of mean arterial pressure above and below the renal arteries. Catheters were also placed in the jugular veins for intravenous infusions. A flanged PE-50 polyethylene catheter was placed in the bladder for urine collection. The aorta was exposed through a midline abdominal incision, and ultramicro clamps were placed above and below the renal arteries. Ligatures were then loosely placed around the superior mesenteric and celiac arteries.
From the start of surgery, isonitotic Ringer's solution containing 5% polyfructosan (Inutest, Laevosan Gesellschaft, Linz, Austria) and 1% L-arginine hydrochloride (PAH) was administered through the right jugular venous catheter at a rate of 1.2 mL/h and maintained throughout the study. To compensate for the reduction in plasma volume attendant on abdominal surgery, rats received a 1.2 mL/100 g body wt infusion of 5% albumin–Ringer's solution during the surgical procedure. Additionally, all rats received an infusion of 154 mmol/L sodium chloride containing 1% bovine serum albumin at a rate of 100 µL/min throughout the surgical period. After completion of the surgical procedure, a 15-minute surgical recovery period was allowed. Two protocols were used to examine both long- and short-term effects of L-arginine on renal function and sodium excretion. Protocol 1 examined the effects of long-term L-arginine administration in DS and DR rats. In this protocol, group 1 DS rats (n=12) received daily intraperitoneal injections of the vehicle for L-arginine administration (0.15 mol/L NaCl) and 8% sodium chow for 3 weeks. Group 2 DS rats (n=6) received daily intraperitoneal injections of the hydrochloride salt of L-arginine in a dose of 300 mg/kg body wt per day (Sigma Chemical Co, St Louis, Mo) for 3 weeks. The last dose of L-arginine was administered approximately 16 hours before study. Group 3 DR rats (n=6) received the vehicle for L-arginine. Group 4 DR rats (n=4) received daily intraperitoneal L-arginine injections as described above. In protocol 2, the short-term effects of L-arginine on DS rats were examined. All DS rats in this protocol had received intraperitoneal injections of L-arginine vehicle and 8% sodium chow for 3 weeks before study. Group 5 DS rats (n=6) received intravenous L-arginine in a 300 mg/kg load and then 1 mg/kg per minute initiated after the surgical recovery period and continued throughout the short-term study. The L-arginine was added to the infusion of 154 mmol/L NaCl and 1% bovine serum albumin. Group 6 DS rats (n=8) received intravenous D-arginine in a similar manner. Group 7 DS rats (n=6) received intravenous L-arginine as described above and also received the inhibitor of nitric oxide synthase Nω-nitro-L-arginine-methyl ester (L-NAME) as a 3 µg/kg load and then 1 µg/kg per minute.
After a 40-minute stabilization period, RPP was reduced to approximately 30 mm Hg below baseline values by tightening of the aortic clamp above the renal arteries. RPP was approximately 100 mm Hg in groups 1, 2, 4, and 5 and approximately 125 mm Hg in groups 1, 6, and 7. After a 15-minute equilibration period, urine was collected over a 40-minute experimental period. Plasma samples were obtained at the beginning and end of the experimental period. The red cells were suspended in a small amount (400 µL) of saline and returned to the animal. In groups 1, 6, and 7 the aortic clamp was tightened further to reduce RPP to 100 mm Hg. After a 15-minute equilibration period, a 40-minute clearance was again performed. Plasma samples were obtained as described above. The aortic clamp was then released, allowing RPP to return to baseline values. After a 15-minute equilibration period, urine and blood samples were collected as described above. RPP was then increased approximately 25 mm Hg above baseline values by tightening of the aortic clamp below the renal arteries. Urine and blood were again collected over a 40-minute interval. To assure that the order of collection did not influence the findings, the order of pressure adjustment was varied in some rats from each group.

Analytic Techniques

Urine flow rate was determined by change in weight of preweighed vials. Inulin concentration in urine and plasma was determined by the diphenylamine method of Walser et al. Sodium concentration in urine and plasma samples was determined using a flame photometer (model 943, Instrumentation Laboratories, Lexington, Mass). The concentration of PAH in plasma and urine was determined according to the method of Waugh and Beall.

Analysis of Data

Determination of the concentration of inulin, PAH, and sodium in blood and urine and urine flow rate permitted calculation of glomerular filtration rate (GFR), PAH clearance, and urinary sodium excretion rate according to standard expressions. Renal blood flow (RBF) was calculated from PAH clearance, renal PAH extraction, and hematocrit as described previously. A value for PAH extraction of 85% was assumed. This is consistent with values measured in Sprague-Dawley rats by several investigators and confirmed in our laboratory. Urinary excretion data, RBF, and GFR were all expressed per gram kidney weight.

To examine the effects of L-arginine on the autoregulation of GFR in DS rats, the autoregulatory index was calculated by the method of Semple and de Wardener according to the following expression:

\[
\text{GFR Autoregulatory Index} = \frac{\text{GFR}_2 - \text{GFR}_1}{\text{GFR}_1} \times \frac{\text{RPP}_2 - \text{RPP}_1}{\text{RPP}_1}
\]
S Control
SL-Arg
R Control
RL-Arg
• (X.05 v» S Control
f p<05 vs Prs Wgh Sodium Pressure
7 14 21
Days on 8H Sodum Intake

Fig 1. Plot shows systolic blood pressures determined by tail-cuff plethysmography in Dahl salt-sensitive (S) and salt-resistant (R) rats maintained on 8% sodium diet and treated with daily injections of L-arginine (L-Arg) or its vehicle (Control).

As there was no difference in GFR between acutely and chronically L-arginine–treated DS rats, data from groups 1 and 5 were combined for this calculation. For the calculation of autoregulatory index, it was assumed that RPP was acutely lowered from the higher pressure (RPP1) to the lower pressure (RPP2) in one increment. Statistical significance between values determined at various perfusion pressures within a single animal was determined with analysis of variance for repeated measures followed by Bonferroni’s T test. Statistical significance between groups was determined with one-way analyses of variance and Bonferroni’s T test.

Results
Tail-Cuff Pressures During 8% Sodium Intake
Systolic pressures measured by impedance plethysmography were 133±15 mm Hg in conscious DS rats and 132±3 mm Hg in conscious DR rats (P=NS) before initiation of the high-sodium diet (Fig 1). After 1 week of the 8% sodium intake, systolic pressure had increased (P<.05) to 158±9 mm Hg in DS rats receiving L-arginine vehicle and remained elevated for the 3-week interval. DS rats begun on 8% sodium intake and given daily injections of L-arginine (group 2) had no increase in systolic pressure above baseline values during the 3-week interval. Systolic pressures in group 2 rats were lower (P<.05) than DS rats treated with L-arginine vehicle at 1, 2, and 3 weeks after initiation of the 8% sodium intake. Systolic pressures were unchanged after initiation of the high-sodium diet in DR rats. Daily L-arginine injections had no effect on blood pressure in DR rats (group 4).

Hemodynamic Parameters in Anesthetized Dahl Rats
Mean arterial pressure at the conclusion of the surgical recovery period was 161±1 mm Hg in group 1 rats and 125±3 mm Hg in group 2 rats (P<.05) (Table). Mean arterial pressures at the conclusion of the surgical recovery period were 125±1 mm Hg in group 3 and 129±3 mm Hg in group 4 (P=NS). Mean arterial pressure did not change in any of these four groups over the 40-minute stabilization period.

The short-term intravenous administration of L-arginine to hypertensive DS rats (group 5) reduced mean arterial pressure from 155±3 to 125±3 mm Hg (P<.05) by the start of the first experimental period. The short-term intravenous administration of D-arginine to hypertensive DS rats (group 6) had no effect on mean arterial pressure (162±2 to 162±2 mm Hg, P=NS). Short-term administration of L-arginine combined with L-NAME had no effect (P=NS) on mean arterial pressure in hypertensive DS rats (group 7).

Hemodynamic Parameters and Sodium Excretion in Dahl Rat Groups at Poststabilization Period Renal Perfusion Pressures

<table>
<thead>
<tr>
<th>Rat Group</th>
<th>Surgical Recovery MAP, mm Hg</th>
<th>Poststabilization MAP, mm Hg</th>
<th>RBF, mL/min</th>
<th>CIN, µL/min</th>
<th>U_{Na}, (µmol/L)/min</th>
<th>Fe_{Na}, %</th>
</tr>
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<tbody>
<tr>
<td>Protocol 1</td>
<td></td>
<td></td>
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<tr>
<td>Group 1 (n=12)</td>
<td>161±1</td>
<td>160±1</td>
<td>5.89±0.51</td>
<td>845±56</td>
<td>4.67±0.46</td>
<td>3.72±0.40</td>
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<tr>
<td>Group 2 (n=6)</td>
<td>125±3*</td>
<td>127±3</td>
<td>6.69±0.33</td>
<td>996±136</td>
<td>7.05±1.37</td>
<td>5.15±1.28</td>
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<tr>
<td>Group 3 (n=6)</td>
<td>125±1*</td>
<td>125±1</td>
<td>6.94±0.52</td>
<td>1221±167</td>
<td>8.98±1.64</td>
<td>4.71±0.49</td>
</tr>
<tr>
<td>Group 4 (n=4)</td>
<td>129±3*</td>
<td>129±3</td>
<td>7.48±2.10</td>
<td>1036±93</td>
<td>8.70±0.92</td>
<td>5.39±0.46</td>
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<td>Protocol 2</td>
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<tr>
<td>Group 5 (n=6)</td>
<td>155±3</td>
<td>125±3</td>
<td>6.73±1.25</td>
<td>985±82</td>
<td>6.39±0.58</td>
<td>4.27±1.10</td>
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<tr>
<td>Group 6 (n=6)</td>
<td>162±2</td>
<td>162±2</td>
<td>5.60±0.56</td>
<td>856±63</td>
<td>4.33±0.64</td>
<td>3.76±0.96</td>
</tr>
<tr>
<td>Group 7 (n=6)</td>
<td>157±3</td>
<td>157±3</td>
<td>5.33±0.99</td>
<td>974±114</td>
<td>4.73±0.42</td>
<td>3.26±0.31</td>
</tr>
</tbody>
</table>

MAP indicates mean arterial pressure; RBF, renal blood flow; CIN, inulin clearance; U_{Na}, absolute urinary sodium excretion; and Fe_{Na}, fractional urinary sodium excretion. RBF and renal values are per gram kidney weight. Values are mean±SEM; n=number of animals studied.

*P<.05 vs group 1.
†P<.05 vs surgical recovery.
There were no differences in RBF among any of the experimental groups when compared at their poststabilization period RPP values (Table). RBF during alterations in RPP in groups 1, 2, and 3 is shown in Fig 2. There were no significant changes in RBF elicited in any of these groups in the range of RPP values examined. RBF in groups 4 through 7 was also unchanged (P=NS) over the range of perfusion pressures examined (data not shown). Inulin clearances were likewise not different among any of the experimental groups when examined at each group’s poststabilization period RPP (Table). Inulin clearance during alterations in RPP in groups 1, 2, and 3 is shown in Fig 3. Reducing RPP to 100 mm Hg in group 1 rats induced a significant (P<.05) reduction in inulin clearance. No significant changes in inulin clearance were elicited during alterations in RPP in DS rats chronically treated with l-arginine (group 2) or in DR rats (group 3). Inulin clearance was also unchanged in group 4 rats at all perfusion pressures examined (data not shown). In protocol 2, there were no significant changes in inulin clearance in DS rats given l-arginine acutely (group 5). Inulin clearance was 1063±152 μL/min per gram kidney weight at 157 mm Hg and 1014±197 μL/min per gram kidney weight at 100 mm Hg in this group. Inulin clearance fell from 856±63 μL/min per gram kidney weight at 162 mm Hg to 614±121 μL/min per gram kidney weight at 101 mm Hg in group 6 and from 974±114 μL/min per gram kidney weight at 158 mm Hg to 616±114 μL/min per gram kidney weight at 100 mm Hg in group 7. These changes did not reach statistical significance. GFR autoregulatory index was lower (P<.05) in l-arginine-treated DS rats than in vehicle-treated DS rats over both ranges of RPP (Fig 4).

**Sodium Excretion in Dahl Rats**

Absolute and fractional urinary sodium excretion were not statistically different among rat groups when examined at their poststabilization period RPP values (Table). Absolute and fractional urinary sodium excretion during alterations in RPP in groups 1, 2, and 3 are shown in Fig 5. Reductions in RPP resulted in significant (P<.05) reductions in both absolute and fractional urinary sodium excretion in all experimental groups. Increases in RPP resulted in significant (P<.05) increases in absolute and fractional urinary sodium excretion in all groups. The slope of the linear regression line relating sodium excretion and RPP over the range of pressures for which comparable data were available (100 to 158 mm Hg) was significantly greater (P<.05) in group 2 than in group 1 rats (161±33 versus 74±9 nmol/L per minute per gram kidney weight per millimeter of mercury) and not different from the slope observed in group 3 rats (123±48 nmol/L per minute per gram kidney weight per millimeter of mercury). Absolute urinary sodium excretion during alterations in RPP in groups 5, 6, and 7 are shown in Fig 6. Changes in RPP resulted in significant (P<.05) changes in urinary sodium excretion in all groups. The slope of the regression line relating sodium excretion and RPP was significantly greater (P<.05) in group 5 than in group 6 (143±39 versus 55±12 nmol/L per minute per gram kidney weight per millimeter of mercury). The slope of the regression line relating absolute urinary sodium excretion and RPP was not different between group 2 and group 5 nor between groups 1, 6, and 7.

**Discussion**

The current study confirms the previous report of Chen and Sanders that (1) long-term l-arginine admin-
Fig 5. Plots show effect of change in renal perfusion pressure on absolute (top) and fractional (bottom) urinary sodium excretion rate in vehicle-treated (group I) and L-arginine–treated (group II) Dahl salt-sensitive rats maintained on 8% sodium intake for 3 weeks. Effect in vehicle-treated Dahl salt-resistant (group III) rats is shown for comparison. An increase in renal perfusion pressure resulted in significant increases in urinary sodium excretion within each group examined (not designated to avoid clutter). *P<.05 vs value at comparable perfusion pressure in group II; #P<.05 vs value at comparable perfusion pressure in group III.

Fig 6. Plot shows effect of change in renal perfusion pressure on absolute urinary sodium excretion rate in Dahl salt-sensitive rats receiving short-term infusions of L-arginine (group V), D-arginine (group VI), or the combination of L-arginine and Nω-nitro-L-arginine-methyl ester (group VII). *P<.05 vs group VI; #P<.05 vs group VII.

The finding that prevention of hypertension in DS rats is associated with enhancement of the pressure-natriuresis response would have been predicted from the relation between urinary sodium excretion, RPP, and the development of hypertension proposed by Guyton and associates.18 According to this hypothesis, elevations in blood pressure leading to sustained hypertension result, at least in part, from the fact that kidneys which excrete sodium less efficiently than normal require a higher perfusion pressure to maintain sodium balance. This hypothesis is consistent with observations that kidneys from prehypertensive DS rats when compared with those from DR rats have an attenuated natriuretic response to short-term sodium loading.2,5,6 For an agent such as L-arginine to prevent hypertension during constant sodium intake, the reduction in arterial pressure must be associated with an improvement in renal sodium excretion. Otherwise, the fall in RPP would reduce renal sodium excretion and eventually restore arterial pressure to hypertensive levels. The observation that daily administration of L-arginine to DS rats maintained on a high-sodium intake prevented the development of hypertension over the 3-week study period implies that an improvement in the pressure-natriuresis relation must have occurred. The finding that a similar improvement in the pressure-natriuresis relation could be produced by the short-term administration of L-arginine to hypertensive DS rats demonstrates that the response in chronically treated DS rats did not result simply from prevention of hypertension-induced structural kidney damage.

How L-arginine alters the pressure-natriuresis relation in DS rats remains to be determined. Roman3 has previously shown that the slope of the relation between sodium excretion and RPP was lower in outbred DS rats than DR rats before the onset of hypertension. In that study DS rats could not maintain GFR consistent when RPP was lowered. In the current study the slope of the pressure-natriuresis relation in DS rats treated chronically with L-arginine was greater than that observed in vehicle-treated DS rats and not different from that observed in DR rats. Long-term administration of L-arginine to DS rats also prevented the fall in GFR observed in vehicle-treated DS rats during reductions in RPP. This was also reflected in the lower autoregulatory index in L-arginine–treated DS rats. Thus, one factor in the improved pressure-natriuresis relation observed in L-arginine–treated DS rats could be improvement in the ability to regulate GFR. On the other hand, when examined at equivalent RPP values, DS rats have greater chloride (and presumably sodium) reabsorption in the loop of Henle than DR rats.4,5 Greater sodium transport has also been reported in inner medullary collecting duct response characteristic of renal sodium handling in the DS rat. In fact, the magnitude of the pressure-natriuretic responses observed in L-arginine–treated DS rats was not different from that observed in DR rats. Furthermore, the observation that long-term administration of L-arginine did not alter the pressure-natriuresis relation in DR rats demonstrates that the L-arginine effect in Dahl rats is specific to the salt-sensitive strain and not a general response to L-arginine per se. The salutary effect of L-arginine in DS rats can be prevented by the concomitant administration of an inhibitor of nitric oxide synthase, L-NAME.

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cells from prehypertensive DS rats compared with DR rats. Thus, long-term L-arginine administration could directly reduce tubular sodium reabsorption in DS rats irrespective of perfusion pressure. This is suggested in the current study from the observation that the difference in fractional sodium excretion between L-arginine- and vehicle-treated DS rats was greatest at the RPP at which inulin clearances were nearly equivalent (Figs 3 and 5). Consistent with this possibility are observations that short-term intravenous administration of large doses (3 to 20 mg/kg per minute) of L-arginine produces natriuresis in Sprague-Dawley rats and alters pressure natriuresis in spontaneously hypertensive rats. Natriuresis has been reported during short-term infusions of other amino acids or amino acid mixtures as well. Thus, it could be argued that the effects of L-arginine in DS rats occur solely through its action as a diuretic agent. In this regard, thiazides have been known to prevent hypertension in DS rats for some time. Although no data in the current study directly address this issue, it should be pointed out that the natriuretic effects of 20 mg/kg per minute L-arginine are dissipated within 90 minutes of the infusion being discontinued. This makes it unlikely that the improvement in pressure natriuresis observed 16 hours after the final L-arginine injection in chronically treated DS rats was solely the result of the actions of L-arginine as a diuretic. Additionally, the observation that sodium excretion rates were not different between DR rats chronically treated with L-arginine and vehicle-treated DR rats suggests that the effects of L-arginine were not solely related to its action as a diuretic. It is also unlikely that the L-arginine effect resulted from change in acid-base status or increased chloride load associated with the use of the L-arginine HCl salt. Blood pressure and the pressure-natriuresis relation were not different between DR rats treated with L-arginine or vehicle chronically, and short-term administration of D-arginine HCl to DS rats had no effect on either blood pressure or the pressure-natriuresis relation (Table, Fig 6).

The biochemical link between L-arginine, blood pressure, and sodium excretion is uncertain from the present study. Chen and Sanders have reported that the antihypertensive effect of both short- and long-term L-arginine administration in DS rats was associated with significant elevation in urinary cyclic GMP excretion. They postulated that L-arginine prevents hypertension in DS rats by increasing nitric oxide production. Administration of guanidine-substituted L-arginine analogues that inhibit nitric oxide synthase has been shown to blunt the pressure-natriuretic response in the dog and Wistar-Kyoto rats. These agents also alter transport-dependent oxygen consumption in inner medullary collecting duct cells and increase absolute proximal tubule reabsorption in vivo. Based on findings that increased dietary sodium intake stimulates urinary cyclic GMP excretion and urinary excretion of the decomposition products of nitric oxide, Shultz and Tolins have proposed that the endogenous nitric oxide system is important for the renal adaptation to increased dietary sodium intake. Although activity of the nitric oxide system was not directly measured in the current study, L-NAME prevented the antihypertensive effect and improvement in pressure natriuresis produced by L-arginine administration to DS rats. This finding, coupled with the previous observation that L-arginine stimulates urinary cyclic GMP excretion in DS rats, would be consistent with the hypothesis that the effect of L-arginine to improve pressure natriuresis in DS rats is mediated through a change in nitric oxide activity. Confirmation of this hypothesis and elucidation of the renal mechanisms involved will require additional studies.

In summary, the current study demonstrates that the prevention of hypertension observed during long-term administration of L-arginine to DS rats on a high-salt intake is associated with a significant improvement in the abnormal pressure-natriuretic response usually observed in these rats. This effect does not occur in D-arginine-treated DS rats, nor does L-arginine alter the pressure-natriuresis relation in DR rats. This improved pressure-natriuresis relation in DS rats appears to occur through improvement in the autoregulatory control of GFR and perhaps direct effects on tubular sodium transport as well. Whether these responses are the mechanism for the prevention of hypertension in DS rats exposed to a high-sodium intake remains to be determined.

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**References**


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