Renorenal Reflexes Present in Young and Captopril-Treated Adult Spontaneously Hypertensive Rats

Ulla C. Kopp and Lori A. Smith

In normotensive Sprague-Dawley rats and Wistar-Kyoto (WKY) rats stimulation of renal mechanoreceptors or chemoreceptors by increasing ureteral pressure or renal pelvic perfusion with 0.9 M NaCl results in a contralateral inhibitory renorenal reflex response with contralateral diuresis and natriuresis. However, in 14–15-week-old spontaneously hypertensive rats (SHR) renal sensory receptor stimulation failed to elicit a contralateral inhibitory renorenal reflex response. The present study was performed to examine whether the lack of a renorenal reflex response in SHR was related to elevated arterial pressure by studying the responses to renal sensory receptor stimulation in 5–6-week-old SHR and in 12–16-week-old SHR that had been treated with captopril from 3 weeks of age to prevent the development of hypertension. In 5–6-week-old SHR, mean arterial pressure was 113±3 mm Hg. Graded increases of ureteral pressure of 15 and 29 mm Hg resulted in graded increases in ipsilateral afferent renal nerve activity of 57±22% and 120±38%. Contralateral urinary sodium excretion increased from 0.26±0.06 to 0.35±0.07 μmol/min/g and from 0.36±0.08 to 0.46±0.11 μmol/min/g, respectively. In captopril-treated SHR, mean arterial pressure was 109±3 mm Hg. Increasing ureteral pressure by 34 mm Hg increased ipsilateral afferent renal nerve activity 65±21% and contralateral urinary sodium excretion from 1.28±0.24 to 1.53±0.30 μmol/min/g. Similar results were produced by renal chemoreceptor stimulation. It is concluded that renal sensory receptor stimulation results in a contralateral inhibitory renorenal reflex response in 5–6-week-old SHR and in SHR treated with captopril to prevent the development of hypertension. These results suggest that the previously demonstrated lack of a renorenal reflex response to renal sensory receptor stimulation in hypertensive SHR is related to the maintenance of hypertension. (Hypertension 1989; 13:430–439)
of the renorenal reflexes suggests that an attenuation in the renorenal reflex control of renal function would result in a smaller decrease or possibly an increase in ERNA leading to renal water and sodium retention. Thus, the lack of a renorenal reflex response to renal sensory receptor stimulation in adult SHR may contribute to the hypertension by promoting excess renal water and sodium retention.

Accumulating evidence indicates that the renal nerves contribute to the pathogenesis of hypertension in SHR. Peripheral sympathetic nerve activity and, in particular, renal sympathetic nerve activity is enhanced in SHR. Renal denervation delays the development of hypertension. The delay in the development of hypertension is associated with a greater percentage of ingested sodium excreted by renal denervated SHR. The eventual development of hypertension correlates with reinnervation of the kidney and increased renal sodium retention. Furthermore, both the arterial and cardiopulmonary baroreceptor reflexes are impaired in SHR. These observations, taken together with those of our previous study in SHR, suggest that the defect in the reflex control of ERNA in SHR is diffuse and involves aortic and cardiac baroreceptors as well as renal sensory receptors.

The present study was undertaken to examine whether the lack of a renorenal reflex response in SHR is related to increased arterial pressure. Renal MR and CR stimulation were performed in 5-6-week-old SHR in which arterial pressure is only slightly elevated compared with age-matched normotensive WKY control rats and in 12-16-week-old SHR treated with the converting enzyme inhibitor captopril (The Squibb Institute for Medical Research, Princeton, New Jersey) from 3 weeks of age to prevent the development of hypertension.

Materials and Methods

The study was performed on two groups of rats. The first group consisted of untreated 5-6-week-old SHR (average age 38±1 days) (Cardiovascular Center, University of Iowa College of Medicine, Iowa City, Iowa) weighing 121±4 g. Age-matched WKY rats (Cardiovascular Center, University of Iowa College of Medicine) (39±1 days old) weighing 122±3 g were used as controls. The second group consisted of 12-16-week-old SHR (average age 99±4 days) (Cardiovascular Center, University of Iowa College of Medicine) weighing 280±10 g and treated with captopril from 3 weeks of age to 12-16 weeks of age to prevent the development of hypertension. Age-matched WKY rats (Cardiovascular Center, University of Iowa College of Medicine) (92±4 days old) weighing 267±10 g were similarly treated and used as controls. Captopril was administered via the drinking water at a concentration ranging from 0.3 to 0.6 mg/kg depending on the rats' age and weight to achieve a daily intake of 100 mg/kg/day. The dose of captopril ingested averaged 102±2 mg/kg/day in SHR and 108±2 mg/kg/day in WKY rats. The water was made slightly acidic (pH=5) to stabilize captopril.

On the day of the experiment, the rats were anesthetized with intraperitoneally administered pentobarbital sodium (50 mg/kg) (Nembutal, Abbott Laboratories, North Chicago, Illinois) and maintained with an intravenous infusion of 10 mg/kg/hr. Catheters were placed in the femoral artery for continuous blood pressure recordings (Statham transducer P23Db, Gould, Oxnard, California) and in the femoral vein for inulin and pentobarbital sodium infusion. Inulin, administered only to the 12-16-week-old rats, was given initially as a bolus injection (30 mg) followed by an infusion at a rate of 1.5 mg/min in combination with pentobarbital sodium in isotonic saline. Isotonic saline was infused throughout the experiment at 15 μl/min in the 5-6-week-old rats and 50 μl/min in the 12-16-week-old rats. The left kidney was exposed by a flank incision and a 20–25-cm-long PE-10 catheter was inserted into the right ureter for collection of urine. The dead space of the catheter was in the range of 7–10 μl. Heart rate was recorded with a linear cardiotachometer (Beckman 9857B, Schiller Park, Illinois) triggered by the arterial pressure waveform. All recordings were made on a Beckman R-611 Dynograph recorder.

Renal Mechanoreceptor Stimulation

Renal MR stimulation was performed by increasing ureteral pressure by elevating a 50-cm-long ureteral catheter (PE-10 in 5-6-week-old rats and PE-60 in 12-16-week-old rats) inserted into the left ureter and filled with the rat's own urine. Ureteral pressure was recorded with a P23Db Statham transducer connected to the ureteral catheter by a T-tube connector.

Renal Chemoreceptor Stimulation

In 5-6-week-old rats an angled 30-gauge needle connected to a PE-10 catheter was placed in the ureter close to the pelvis with the tip of the needle in the renal pelvis. The position of the needle was secured by application of Wacker Sil-Gel 604. A PE-10 catheter was placed in the ureter with its tip ending 4–5 mm below the needle to ensure complete drainage of the perfusion. The needle did not interfere with the ipsilateral renal excretory function as reflected by similar basal urinary sodium excretion from the ipsilateral and contralateral kidney, 0.64±0.23 and 0.60±0.23 μmol/min/g, respectively (n=20, NS). The renal pelvis was perfused via the needle with 0.9 M NaCl at 25 μl/min, a perfusion rate previously shown not to affect ureteral pressure. In 12-16-week-old rats renal CR were stimulated by a retrograde ureteropelvic perfusion with 0.9 M NaCl as previously described. A PE-60 catheter was inserted into the left ureter with its tip extending 1–2 mm beyond the tip of the
PE-60 catheter. This technique allowed complete drainage of the effluent. Similar to the 5–6-week-old rats, the renal pelvis was perfused at 25 μL/min.

Recording of Renal Nerve Activity
With the use of a stereoscopic dissecting microscope, one renal nerve branch was isolated at the angle between the aorta and the left renal artery. Recordings from multifiber preparations were made by placing the renal nerve on a bipolar silver wire (Cooner Wire, Chatsworth, California) electrode. The electrode was fixed to the renal nerve with Wacker Sil-Gel 604. The signals were led via a high impedance probe (Grass H1P511, Quincy, Massachusetts) to a bandpass amplifier (Grass P511) with a high frequency cutoff at 3,000 Hz and low frequency cutoff at 30 Hz. The signals were amplified 10,000–50,000 times. The output of the bandpass amplifier was continuously displayed on an oscilloscope (Tektronix 5113, Beaverton, Oregon) with audio monitoring and fed into a voltage integrator (Beckman 9873B). Renal nerve activity was integrated over 1-second intervals. Assessment of renal nerve activity was done by its pulse-synchronous rhythmicity and its reduction by loading of the high pressure arterial baroreceptors via an intravenous injection of a pressor dose of norepinephrine (2 μg).

After identification and verification of renal nerve activity, the renal nerve was sectioned proximal to the electrode for recording of ipsilateral ARNA. Background noise level was assessed by crushing the decentralized renal nerve bundle peripheral to the recording electrode. The integrated background noise level was subtracted from the integrated total signal in μV·sec per 1-second interval or μV·sec/1 sec. In 10 rats the integrated background noise level after crushing of the nerve was 0 μV·sec/1 sec. In the remaining 34 rats the integrated total signal to background noise ratio averaged 6±1; it did not differ between groups.

Experimental Procedure
Approximately 1.5 hours were allowed to elapse between the end of surgery and the start of the experiment.

In 5–6-week-old SHR (n=7) and WKY rats (n=9) the experimental protocol consisted of two 10-minute experimental periods during which ureteral pressure was increased by 15±1 mm Hg and 27±1 mm Hg (n=16), respectively. Each experimental period was preceded by a 20-minute control period and followed by a 20-minute recovery period. In an additional two SHR and three WKY rats, 5–6 weeks old, only one experimental period was performed during which ureteral pressure was increased by 15 mm Hg. In another group of 5–6-week-old SHR (n=11) and WKY rats (n=9), renal CR stimulation was performed during the experimental period. Urine was collected during each control, experimental, and recovery period.

In a separate group of five 5–6-week-old SHR, average age 37±1 days, the left kidney was denervated after the first control, experimental, and recovery period. All visible renal nerves were cut, and the left renal artery was carefully stripped. After stabilization the control, experimental, and recovery periods were repeated. Right ureteral pressure was increased by 30 mm Hg during both experimental periods. Renal nerve activity was not measured in this group of rats.

In 12–16-week-old captopril-treated SHR (n=7) and WKY rats (n=8), the experimental protocol consisted of two 20-minute experimental periods during which renal MR and CR stimulation were performed in random order. Each experimental period was preceded by a 20-minute control period and followed by a 20-minute recovery period. In another three captopril-treated SHR and one captopril-treated WKY rat, only one experimental period was performed during which renal MR were stimulated in SHR and CR in WKY rats. Urine was collected in 20-minute periods with arterial blood samples taken at the end of each period. Blood was replaced with equal amounts of saline.

Renal nerve activity was measured and averaged over each control, experimental, and recovery period and expressed in percent of its first control value.

Analytical Procedure
Plasma and urinary sodium concentrations were determined with a flame photometer (model I43, Instrumentation Laboratories, Lexington, Massachusetts). Plasma and urine samples were analyzed for inulin by an anthrone method. Urinary clearance of inulin was used for measurement of glomerular filtration rate. Values of glomerular filtration rate, urine flow rate, and urinary sodium excretion are expressed as per gram kidney weight.

Statistical Analysis
The effects of renal MR and CR stimulation were evaluated by comparing the experimental value with the average of the control and recovery period values. Friedman two-way analysis of variance, Wilcoxon matched-pairs, signed-rank test, Walsh test, and Mann-Whitney U test were used. A significance level of 5% was chosen. Data in text, tables, and figures are expressed as mean±SEM.

Results
Spontaneously Hypertensive Rats and Wistar-Kyoto Rats, 5–6 Weeks Old
The results are shown in Figures 1–4. In SHR (n=25) basal mean arterial pressure and heart rate were 113±3 mm Hg and 382±13 beats/min, respectively, and were slightly higher (p<0.01) than those observed in WKY rats (n=21), which averaged 96±3 mm Hg and 331±11 beats/min, respectively. Similarly, basal urinary sodium excretion was greater in SHR than in WKY rats, 0.59±0.17 and 0.23±0.52.


**Kopp and Smith**

Renorenal Reflexes Present in Normotensive SHR

---

**Renal Mechanoreceptor Stimulation - SHR, 38±1 days old**

- **Figure 1.** Effects of increasing ureteral pressure by 15 mm Hg (left panel) and 29 mm Hg (right panel) on mean arterial pressure (MAP), ipsilateral afferent renal nerve activity (ARNA), contralateral urine flow rate (V), and urinary sodium excretion (UNaV) in 38±1-day-old spontaneously hypertensive rats (SHR).

- MAP (mmHg)
- Ipsilateral ARNA % of Control
- Contralateral V µl/min/g
- Contralateral UNaV µmol/min/g
- Ipsilateral Ureteral Pressure mmHg

- **Control**
- **Experimental**
- **Recovery**

<table>
<thead>
<tr>
<th>MAP (mmHg)</th>
<th>Ipsilateral ARNA % of Control</th>
<th>Contralateral V µl/min/g</th>
<th>Contralateral UNaV µmol/min/g</th>
<th>Ipsilateral Ureteral Pressure mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>120</td>
<td>100</td>
<td>15</td>
<td>0.2</td>
<td>30</td>
</tr>
<tr>
<td>100</td>
<td>150</td>
<td>0</td>
<td>1.2</td>
<td>150</td>
</tr>
<tr>
<td>300</td>
<td>250</td>
<td>25</td>
<td>2.5</td>
<td>250</td>
</tr>
<tr>
<td>350</td>
<td>250</td>
<td>30</td>
<td>3.0</td>
<td>350</td>
</tr>
</tbody>
</table>

- C, control; E, experimental; R, recovery.

- **p<0.05**
- **p<0.01**

---

**Renal Chemoreceptor Stimulation - SHR 39±1 days old**

- **Figure 2.** Effects of retrograde ureteropelvic perfusion with 0.9 M NaCl on mean arterial pressure (MAP), ipsilateral afferent renal nerve activity (ARNA), contralateral urine flow rate (V), and urinary sodium excretion (UNaV) in 39±1-day-old spontaneously hypertensive rats (SHR).

- MAP (mmHg)
- Ipsilateral ARNA % of Control
- Contralateral V µl/min/g
- Contralateral UNaV µmol/min/g

- **Control**
- **Experimental**
- **Recovery**

<table>
<thead>
<tr>
<th>MAP (mmHg)</th>
<th>Ipsilateral ARNA % of Control</th>
<th>Contralateral V µl/min/g</th>
<th>Contralateral UNaV µmol/min/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>130</td>
<td>110</td>
<td>9</td>
<td>0.2</td>
</tr>
<tr>
<td>110</td>
<td>80</td>
<td>0.7</td>
<td>1.4</td>
</tr>
<tr>
<td>90</td>
<td>60</td>
<td>0.6</td>
<td>1.8</td>
</tr>
<tr>
<td>70</td>
<td>40</td>
<td>0.5</td>
<td>2.2</td>
</tr>
<tr>
<td>50</td>
<td>30</td>
<td>0.4</td>
<td>2.6</td>
</tr>
</tbody>
</table>

- **n=11 p<0.001**

---

**Renal CR stimulation** increased ipsilateral ARNA 51±14% (p<0.001) from a baseline value of 131±54 µV·sec/1 sec in SHR (Figure 2). During the 60-minute equilibration period preceding the first control period contralateral urine flow rate was stable (less than 10% variation between successive 20-minute collections) and averaged 7.5±2.3 µl/min/g, which was not different from that in the first 20-minute control period, 7.3 µl/min/g. Contralateral urine flow rate decreased to 9.1±2.0 µl/min/g during the 20 minutes after the cessation of the renal pelvic perfusion. Contralateral urinary sodium excretion increased from 1.1±0.4 to 1.4±0.5 µmol/min/g (p<0.001) during renal CR stimulation and remained elevated, 1.46±0.47 µmol/min/g, 20 minutes after the end of

---

**Note:** (p<0.001) indicates statistically significant differences.
Table 1. Effects of Renal Mechanoreceptor Stimulation Before and After Contralateral Renal Denervation on Mean Arterial Pressure and Contralateral Renal Excretion in 37±1 Day-Old Spontaneously Hypertensive Rats

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before DNX</th>
<th>Control</th>
<th>After DNX</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>103±3</td>
<td>105±3</td>
<td>99±4</td>
<td>97±4</td>
</tr>
<tr>
<td>V (μl/min/g)</td>
<td>5.3±1.0</td>
<td>7.2±1.2*</td>
<td>9.6±1.9†</td>
<td>7.9±1.3</td>
</tr>
<tr>
<td>U\textsubscript{Na}V (μmol/min/g)</td>
<td>0.41±0.10</td>
<td>0.52±0.09*</td>
<td>0.85±0.33†</td>
<td>0.67±0.25</td>
</tr>
</tbody>
</table>

Values are mean±SEM; n=5 rats. Control, average of control and recovery values bracketing ↑ UP periods; DNX, denervation; ↑ UP, increasing ureteral pressure by 30±2 mm Hg; MAP, mean arterial pressure; V, urine flow rate; U\textsubscript{Na}V, urinary sodium excretion.

*Significantly different from control; p<0.05.
†Significantly different from control value before DNX; p<0.05.

the renal pelvic perfusion. Mean arterial pressure was unchanged.

As shown in Table 1, denervation of the contralateral kidney increased basal contralateral urine flow rate and urinary sodium excretion and abolished the contralateral diuresis and natriuresis produced by increasing ureteral pressure by 30±2 mm Hg. Mean arterial pressure was unaffected by renal denervation.

In WKY rats, increasing ureteral pressure by 15±1 and 26±2 mm Hg increased ipsilateral ARNA 22±11 (p<0.02) and 29±9% (p<0.01), respectively, from a baseline value of 92±28 μV · sec/1 sec (Figure 3). During the 60-minute equilibration period preceding the first control period contralateral urine flow rate averaged 3.5±0.6 μl/min/g, which was not different from that in the control period, 3.9±0.6 μl/min/g. Contralateral urine flow rate increased to 4.9±0.9 μl/min/g (p<0.01) during increased ureteral pressure of 15 mm Hg and remained elevated during the first 20-minute recovery period and the second 20-minute control period, 5.1±1.0 and 5.4±1.6 μl/min/g, respectively. The increase in contralateral urine flow rate to 6.5±2.0 μl/min/g during increased ureteral pressure of 26 mm Hg did not reach statistical significance. Contralateral urinary sodium excretion increased from 0.27±0.08 to 0.38±0.13 μmol/min/g (p<0.01) during increased ureteral pressure of 15 mm Hg and remained elevated during the following 40 minutes. The increase from 0.46±0.24 to 0.65±0.34 μmol/min/g produced by increasing ureteral pressure 26 mm Hg did not reach statistical significance. Mean arterial pressure was unchanged.

Renal CR stimulation increased ipsilateral ARNA 34±9% from a baseline value of 89±33 μV · sec/1 sec (p<0.01) (Figure 4). Basal contralateral urine flow rate averaged 4.3±0.8 μl/min/g during the 60-minute equilibration period before the first control period, which was not different from that in the control period, 4.0±0.5 μl/min/g. Contralateral urine flow rate increased to 5.7±1.2 μl/min/g (p<0.05) during the renal CR stimulation period and remained elevated, 5.1±0.6 μl/min/g, during the 20-minute period after the end of the renal CR stimulation period. Contralateral urinary sodium excretion increased from 0.18±0.05 to 0.29±0.07 μmol/min/g (p<0.05) during renal CR stimulation and remained elevated after cessation of the renal pelvic perfusion with 0.9 M NaCl. Mean arterial pressure was unaffected.

Captopril-Treated Spontaneously Hypertensive Rats and Wistar-Kyoto Rats, 12-16 Weeks Old

The results are shown in Figures 5 and 6. In captopril-treated SHR, basal mean arterial pressure was 109±3 mm Hg, which was slightly higher than that in similarly treated WKY rats (97±2 mm Hg, p<0.01). In prior studies from this laboratory, untreated SHR and WKY rats of similar age range

![Figure 3](http://hyper.ahajournals.org/)

**Figure 3.** Effects of increasing ureteral pressure by 15 mm Hg (left panel) and 26 mm Hg (right panel) on mean arterial pressure (MAP), ipsilateral afferent renal nerve activity (ARNA), contralateral urine flow rate (V), and urinary sodium excretion (U\textsubscript{Na}V) in 41±1-day-old Wistar-Kyoto (WKY) rats. C, control; E, experimental; R, recovery.
Renal Chemoreceptor Stimulation - WKY 37±2 days old
Pelvic Perfusion, 0.9M NaCl

MAP  mmHg

ipsilateral ARNA 

Contralateral V  \mu l\cdot mm^{-1}\cdot g^{-1}

Contralateral U_{NaV} \mu mol\cdot min^{-1}\cdot g^{-1}

n=9  **p<0.01

C  E  R

FIGURE 4. Effects of retrograde ureteropelvic perfusion with 0.9 M NaCl on mean arterial pressure (MAP), ipsilateral afferent renal nerve activity (ARNA), contralateral urine flow rate (V), and urinary sodium excretion (U_{NaV}) in 37±2-day-old Wistar-Kyoto (WKY) rats. C, control; E, experimental; R, recovery.

had mean arterial pressure of 165±5 and 113±2 mm Hg, respectively. Basal urine flow rate and urinary sodium excretion were lower in SHR than in WKY rats, 7.4±0.8 versus 11.5±1.6 \mu l/min/g (p<0.05) and 1.12±0.27 versus 1.97±0.36 \mu mol/min/g (p<0.05), respectively. Heart rate was similar in SHR and WKY rats, 295±17 and 281±16 beats/min, respectively.

In SHR, increasing ureteral pressure by 34±1 mm Hg increased ipsilateral ARNA 65±21% (p<0.02) from a baseline value of 75±14 \mu V\cdot sec/1 sec, contralateral urine flow rate 1.1±0.4 from 8.2±0.8 \mu l/min/g (average of the control and recovery period values) (p<0.02), and urinary sodium excretion 0.25±0.09 from 1.28±0.24 \mu mol/min/g (p<0.05) in the absence of changes in contralateral glomerular filtration rate, from 0.9±0.1 to 1.0±0.1 ml/min/g (Figure 5). Similarly, renal CR stimulation increased ipsilateral ARNA 36±11% (p<0.05) and contralateral urinary sodium excretion 0.21±0.07 from 0.17±0.32 \mu mol/min/g (p<0.02). Contralateral glomerular filtration rate was unchanged, from 0.7±0.1 to 0.8±0.1 ml/min/g. Mean arterial pressure was unaffected.

In WKY rats increasing ureteral pressure by 35±2 mm Hg increased ipsilateral ARNA 35±12% (p<0.05) from a baseline value of 162±63 \mu V\cdot sec/1 sec, contralateral urine flow rate 2.0±0.5 from 13.3 \mu l/min/g (p<0.02), and urinary sodium excretion 0.44±0.09 from 2.22±0.31 \mu mol/min/g (p<0.01). Contralateral glomerular filtration rate did not change, from 1.0±0.1 to 1.0±0.1 \mu l/min/g. Similarly, renal CR stimulation increased ipsilateral ARNA 21±8% (p<0.05) and contralateral urinary sodium excretion 0.26±0.07 from 1.78±0.36 \mu mol/min/g (p<0.01). The increase in contralateral urine flow rate, 0.7±0.3 from 10.5±1.8 \mu l/min/g, did not reach statistical significance. Contralateral glomerular filtration rate remained unchanged, from 1.0±0.1 to 1.1±0.1 ml/min/g. Mean arterial pressure was unchanged.

Discussion

The results of the present study show that stimulation of renal MR and CR results in a contralateral inhibitory renorenal reflex response in 5–6-week-old SHR and in 12–16-week-old SHR treated with captopril from 3 weeks of age to the time of the study to prevent the development of hypertension. These results suggest that the previously demonstrated lack
of a renorenal reflex response to renal sensory stimulation in 14–15-week-old hypertensive SHR is related to the maintenance of hypertension. Mean arterial pressure was significantly lower in 5–6-week-old SHR than in age-matched WKY rats as previously reported, 113±3 and 96±3 mm Hg, respectively. However, mean arterial pressure was significantly lower in 5–6-week-old SHR than in 14–15-week-old untreated SHR in which mean arterial pressure averaged 165 mm Hg.2 In 5–6-week-old SHR, graded increases in ureteral pressure of 15 and 29 mm Hg resulted in graded increases in ipsilateral ARNA and a contralateral diuresis and natriuresis. The contralateral diuresis and natriuresis produced by renal MR stimulation were abolished by contralateral renal denervation. These results suggest that in 5–6-week-old SHR renal MR stimulation elicited a contralateral inhibitory renorenal reflex response.

Renal CR stimulation produced an increase in ipsilateral ARNA of 51±17% in 5–6-week-old SHR. A similar increase in ipsilateral ARNA (40±14%) was obtained in response to renal pelvic perfusion with 0.9 M NaCl at a lower rate of 13.6 μl/min in five additional SHR. These findings suggest that the effects produced by renal pelvic perfusion with 0.9 M NaCl at 25 μl/min are not related to the intrapelvic pressure–flow relation but are the result of activation of renal CR stimulation as has been previously shown in adult Sprague-Dawley rats.1 Contralateral urine flow rate and urinary sodium excretion increased during renal CR stimulation and remained elevated after cessation of renal CR stimulation.

In contrast to normotensive adult Sprague-Dawley rats and captopril-treated adult SHR in which the reversible ipsilateral ARNA response to renal sensory receptor stimulation is associated with a reversible contralateral renal excretory response, the contralateral reflex responses to renal sensory receptor stimulation in young SHR were more varied. Whereas, in young SHR the reversible increase in ipsilateral ARNA produced by renal MR stimulation was accompanied with a reversible increase in contralateral urine flow rate and urinary sodium excretion, the magnitude of the response in contralateral urinary sodium excretion was not related to the magnitude of stimulation as previously shown in adult normotensive rats.3 In addition, although the increase in ipsilateral ARNA produced by renal CR stimulation was associated with an increase in contralateral urine flow rate and urinary sodium excretion, the decrease in ipsilateral ARNA after cessation of renal CR stimulation was not accompanied by a fall in contralateral urine flow rate and urinary sodium excretion. The steady-state values of contralateral urine flow rate during the 80 minutes (60-minute equilibration period plus 20-minute control period) before the start of the renal CR stimulation period argue against a rising baseline over time and suggest that the increases in contralateral urine flow rate and urinary sodium excretion were related to the increase in ipsilateral ARNA produced by renal CR stimulation. The imperfect relation between ipsilateral ARNA and contralateral renal excretory function in young SHR may be due to immature aspects of central integration of the renorenal reflexes or intrarenal neural mechanisms. Furthermore, it is possible that the contralateral urine flow rate and urinary sodium excretion would have returned to their control value if the recovery period had been prolonged in duration.

The results from the present study showing an increase in ipsilateral ARNA, contralateral urine flow rate, and urinary sodium excretion produced by renal MR and CR stimulation in 5–6-week-old SHR are in sharp contrast to the findings in 14–15-week-old hypertensive SHR in which renal MR and CR stimulation of the same magnitude failed to affect ipsilateral ARNA, contralateral ERNA, or contralateral urine flow rate and urinary sodium excretion.2 It is unlikely that the presence of a renorenal reflex response to renal MR and CR stimulation in 5–6-week-old SHR is related to the fact that the study was performed in SHR from a different colony than those in the previous study,2 since we have observed a similar lack of a renorenal reflex response to renal sensory receptor stimulation in SHR from a different colony than those in the previous study,2.
reflex response to renal MR and CR stimulation (as shown in adult SHR from Harlan Sprague-Dawley) in SHR from Charles River Laboratories (unpublished observations). The lack of an ipsilateral ARNA response to renal MR and CR stimulation (as performed in the present study) does not exclude the possibility that renal sensory receptors can be activated by renal MR and CR stimulation of a greater magnitude or by different stimuli. Our previous study in untreated adult SHR did not examine the ipsilateral ARNA response to stimulation of renal MR and CR of a greater magnitude, but it showed an increase in ipsilateral ARNA in response to renal ischemia. Of interest in this context is the study by Moss14 that showed an enhanced ipsilateral ARNA response to ischemia in SHR compared with WKY rats. The apparent discrepancy between the results from the present study and that by Moss14 may lie in the design of the experiments. To determine the steady-state renal electrophysiological and renal functional responses (clearance measurements) to increased ureteral pressure with rat urine and renal pelvic perfusion with 0.9 M NaCl the experimental period was extended to 20 minutes in our studies in adult SHR and WKY rats. In the study by Moss14 renal nerve activity was measured 1 minute before and 1 minute after the 1-minute period of renal sensory stimulation, whereas the duration of all periods (control, experimental, and recovery) was 20 minutes in our studies. There were no data reported in the study by Moss14 on the contralateral renal functional responses to the 1-minute periods of increased ureteral pressure.

Similar to our findings in 5-6-week-old SHR, graded increases in ureteral pressure of 15 and 26 mm Hg resulted in graded increases of 11±5 and 29±9% (n=9), respectively, in ipsilateral ARNA in age-matched WKY rats (p<0.02). The increases in ipsilateral ARNA produced by renal MR stimulation in SHR were of a greater magnitude than those produced in WKY rats (p<0.05). These findings may be explained by the enhanced ERNA in young SHR compared with young WKY rats,6 since previous studies in our laboratory in normotensive Sprague-Dawley rats have shown that basal ERNA has a modulatory influence on the renal sensory receptors and theirafferent renal nerve fibers and may facilitate the ARNA response to renal sensory receptor stimulation.15 The results from the present study further show that renal CR stimulation produced a rise in ipsilateral ARNA. Similar to the findings in young SHR after 80-minute steady-state urine collections, renal MR and CR stimulation resulted in an increase in ipsilateral ARNA, contralateral urine flow rate, and urinary sodium excretion. After cessation of renal sensory stimulation, ipsilateral ARNA returned to its control value, whereas contralateral urine flow rate and urinary sodium excretion remained elevated. It is likely that the failure of a prompt return of contralateral urine flow rate and urinary sodium excretion after the end of renal MR and CR stimulation is related to the young age of the WKY rats, since reversible contralateral diuretic and natriuretic responses to renal sensory receptor stimulation are obtained in adult nontreated and captopril-treated WKY rats.

Since the results of our present study showed the presence of a renorenal reflex response to renal sensory receptor stimulation in 5-6-week-old SHR, the next part of our study was performed to examine whether the lack of a renorenal reflex response to renal sensory stimulation in 14-15-week-old hypertensive SHR could be prevented by treating SHR from 3 weeks of age to 12-16 weeks of age with an antihypertensive agent to prevent the development of hypertension. In view of our previous findings showing that decreases in ERNA decrease the responsiveness of renal sensory receptors and their afferent renal nerve fibers to renal MR and CR stimulation,13 the converting enzyme inhibitor captopril was chosen because captopril has been previously shown to have little or no effect on peripheral sympathetic activity in SHR or hypertensive humans.16,17 Chronic oral administration of captopril for 3-6 months has been shown to reduce mean arterial pressure to normal in SHR without affecting urine flow rate or urinary sodium concentration.18 Similarly, 5 days of treatment with oral captopril reduced mean arterial pressure 30 mm Hg without affecting urinary sodium excretion.19 Okuno et al further showed that central administration of captopril attenuated the development of hypertension without affecting fluid intake or daily urinary sodium excretion. Thus, despite significant reductions in mean arterial pressure, there were no concomitant reductions in urinary water or sodium excretion. Captopril produces a decrease in vascular reactivity to exogenous vasoconstrictors and a potentiation of the baroreceptor reflex control of heart rate.20,21 In the present study captopril administered in the drinking water to SHR from 3 weeks of age to adulthood prevented the development of hypertension. In captopril-treated SHR mean arterial pressure was 109±3 mm Hg at 12-16 weeks of age, which was significantly lower than that in agematched untreated SHR, 165±5 mm Hg (p<0.01).2 In the present study captopril administered in the drinking water to SHR from 3 weeks of age to adulthood prevented the development of hypertension. In captopril-treated SHR mean arterial pressure, increased in response to renal sensory stimulation (as performed in the present study) does not exclude the possibility that renal sensory receptors can be activated by renal MR and CR stimulation of a greater magnitude or by different stimuli. Our previous study in untreated adult SHR did not examine the ipsilateral ARNA response to stimulation of renal MR and CR of a greater magnitude, but it showed an increase in ipsilateral ARNA in response to renal ischemia. Of interest in this context is the study by Moss14 that showed an enhanced ipsilateral ARNA response to ischemia in SHR compared with WKY rats. The apparent discrepancy between the results from the present study and that by Moss14 may lie in the design of the experiments. To determine the steady-state renal electrophysiological and renal functional responses (clearance measurements) to increased ureteral pressure with rat urine and renal pelvic perfusion with 0.9 M NaCl the experimental period was extended to 20 minutes in our studies in adult SHR and WKY rats. In the study by Moss14 renal nerve activity was measured 1 minute before and 1 minute after the 1-minute period of renal sensory stimulation, whereas the duration of all periods (control, experimental, and recovery) was 20 minutes in our studies. There were no data reported in the study by Moss14 on the contralateral renal functional responses to the 1-minute periods of increased ureteral pressure.

Similar to our findings in 5-6-week-old SHR, graded increases in ureteral pressure of 15 and 26 mm Hg resulted in graded increases of 11±5 and 29±9% (n=9), respectively, in ipsilateral ARNA in age-matched WKY rats (p<0.02). The increases in ipsilateral ARNA produced by renal MR stimulation in SHR were of a greater magnitude than those produced in WKY rats (p<0.05). These findings may be explained by the enhanced ERNA in young SHR compared with young WKY rats,6 since previous studies in our laboratory in normotensive Sprague-Dawley rats have shown that basal ERNA has a modulatory influence on the renal sensory receptors and their afferent renal nerve fibers and may facilitate the ARNA response to renal sensory receptor stimulation.15 The results from the present study further show that renal CR stimulation produced a rise in ipsilateral ARNA. Similar to the findings in young SHR after 80-minute steady-state urine collections, renal MR and CR stimulation resulted in an increase in ipsilateral ARNA, contralateral urine flow rate, and urinary sodium excretion. After cessation of renal sensory stimulation, ipsilateral ARNA returned to its control value, whereas contralateral urine flow rate and urinary sodium excretion remained elevated. It is likely that the failure of a prompt return of contralateral urine flow rate and urinary sodium excretion after the end of renal MR and CR stimulation is related to the young age of the WKY rats, since reversible contralateral diuretic and natriuretic responses to renal sensory receptor stimulation are obtained in adult nontreated and captopril-treated WKY rats.

Since the results of our present study showed the presence of a renorenal reflex response to renal sensory receptor stimulation in 5-6-week-old SHR, the next part of our study was performed to examine whether the lack of a renorenal reflex response to renal sensory stimulation in 14-15-week-old hypertensive SHR could be prevented by treating SHR from 3 weeks of age to 12-16 weeks of age with an antihypertensive agent to prevent the development of hypertension. In view of our previous findings showing that decreases in ERNA decrease the responsiveness of renal sensory receptors and their afferent renal nerve fibers to renal MR and CR stimulation,13 the converting enzyme inhibitor captopril was chosen because captopril has been previously shown to have little or no effect on peripheral sympathetic activity in SHR or hypertensive humans.16,17 Chronic oral administration of captopril for 3-6 months has been shown to reduce mean arterial pressure to normal in SHR without affecting urine flow rate or urinary sodium concentration.18 Similarly, 5 days of treatment with oral captopril reduced mean arterial pressure 30 mm Hg without affecting urinary sodium excretion.19 Okuno et al further showed that central administration of captopril attenuated the development of hypertension without affecting fluid intake or daily urinary sodium excretion. Thus, despite significant reductions in mean arterial pressure, there were no concomitant reductions in urinary water or sodium excretion. Captopril produces a decrease in vascular reactivity to exogenous vasoconstrictors and a potentiation of the baroreceptor reflex control of heart rate.20,21
response to renal sensory receptor stimulation in captopril-treated SHR was due to a potentiation of the renorenal reflexes by captopril, since the renorenal reflex responses to renal MR and CR stimulation in captopril-treated WKY rats were not greater than those in untreated WKY rats of similar age. These findings suggest that the presence of a renorenal reflex response to renal sensory receptor stimulation in the captopril-treated SHR was related to the prevention of the development of hypertension.

Although the onset of the impairment of the renorenal reflexes has not been examined, the results of the present and previous studies suggest that the impairment of the renorenal reflex control of renal nerve activity may not contribute to the pathogenesis of hypertension, but rather to the maintenance of hypertension in SHR by promoting increased ERNA and renal water and sodium retention. Likewise, it has been suggested that impaired baroreceptor reflex buffering of efferent nerve activity serves as a permissive mechanism that allows arterial blood pressure to remain elevated. However, in contrast to the carotid and aortic baroreceptors, which are reset after acute increases in arterial pressure and in chronic hypertensive states, previous and present studies from our laboratory provide no evidence for acute resetting of renal MR. In further agreement with the results from the present studies are previous findings showing that the abnormal relation between the aortic baroreceptor function and arterial pressure, characteristic of adult hypertensive SHR, was not present in young SHR and in SHR chronically treated with antihypertensive agents to prevent the development of hypertension.

Although the present study was not designed to examine the specificity of the renal sensory receptors, previous studies from our laboratory in normotensive Sprague-Dawley rats have shown that increasing ureteral pressure with 0.1 M NaCl resulted in a contralateral diuresis and natriuresis of the same magnitude as that produced by elevating ureteral pressure with the rat's own urine bathing the renal pelvis. However, renal pelvic perfusion with 0.1 M NaCl at unchanged ureteral pressure failed to produce a contralateral renal excretory response. A preliminary study has further shown an increase in ipsilateral ARNA of 42±7% and contralateral urinary sodium excretion of 43±7% (n=15) in response to increases in ureteral pressure of 30 mm Hg with 0.15 M NaCl bathing the renal pelvis. Furthermore, graded increases in ureteral pressure produced by elevating the ureteral catheter filled with the rat's urine to different heights above the kidney resulted in graded increases in ipsilateral ARNA and contralateral urinary sodium excretion. In the present study the sodium concentration of the renal pelvic perfusate (0.9 M NaCl) used to demonstrate the presence of renal sensory receptors sensitive to changes in the ion concentration in the renal interstitium was similar to that previously shown to result in activation of renal CR in normotensive rats. Taken together, these studies suggest that the renorenal reflex responses to increased ureteral pressure and renal pelvic perfusion with 0.9 M NaCl are the result of stimulation of two different renal sensory receptors: a renal MR responding to an increase in ureteral pressure and unaffected by the sodium concentration of the fluid and a renal CR responding to changes in the chemical composition of the renal pelvic perfusate. Recordati et al further showed that the renal CR responding to renal pelvic perfusion with 0.9 M NaCl were activated, but to a lesser extent, by renal pelvic perfusion with NaCl at 0.5 M. The findings, together with our previous findings that showed graded renorenal reflex responses to graded increases in ureteral pressure, show that the magnitude of the responses to renal MR and CR stimulation is related to the magnitude of the stimulation. These studies in normotensive rats suggest that the renorenal reflexes play a physiological role in the renal regulation of body water and sodium. As discussed above, impaired renorenal reflexes would contribute to the enhanced ERNA characteristic of SHR and promote sodium and water retention. Although the study by Beierwaltes et al does not provide any evidence for increased positive sodium balance in SHR 9–13 weeks of age, it is well known that the pressure diuresis and pressure natriuresis curves are shifted to the right in SHR compared with WKY rats (i.e., at similar arterial pressure renal water and sodium excretion is lower in SHR than WKY rats) (e.g., Reference 28). The cause of impaired renorenal reflex responses to renal sensory receptor stimulation in adult hypertensive SHR is not known. A possible contributing factor may be the increased renal vascular resistance demonstrated in SHR, which might affect intrarenal pressure development or distribution. Of interest in this context are the recent findings by Khraibi and Knox showing an attenuated increase in intrarenal hydrostatic pressure and urinary sodium excretion in response to an increase in renal perfusion pressure compared with WKY rats. Studies on the impairment of the carotid and aortic baroreceptor reflexes in SHR have suggested membrane defects causing altered ion permeability as a possible cause for chronic resetting; whether similar changes involve the renal pelvic urothelium is not known.

In summary, the results of the present study show the presence of a renorenal reflex response to renal MR and CR stimulation in 5–6-week-old SHR and in 12–16-week-old SHR treated with captopril to prevent the development of hypertension. These results suggest that the previously demonstrated impairment of the renorenal reflex responses to renal sensory receptor stimulation in adult hypertensive SHR may contribute to the maintenance of the elevated arterial pressure in SHR rather than to its initiation.
Acknowledgments

We are grateful to Dr. Gerald F. DiBona, University of Iowa College of Medicine, Iowa City, Iowa for valuable advice. We thank The Squibb Institute for Medical Research, Princeton, New Jersey for a generous supply of captopril.

References


Key Words • renal sensory receptor stimulation • renorenal reflex response • afferent renal nerves
Renorenal reflexes present in young and captopril-treated adult spontaneously hypertensive rats.

U C Kopp and L A Smith

doi: 10.1161/01.HYP.13.5.430

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1989 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/13/5/430

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/