Impaired Renorenal Reflexes in Spontaneously Hypertensive Rats

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SUMMARY In normotensive Sprague-Dawley rats stimulation of renal mechanoreceptors and chemoreceptors by increasing ureteral pressure and retrograde ureteropelvic perfusion with 0.9 M NaCl results in a contralateral inhibitory renorenal reflex response with contralateral diuresis and natriuresis. Since efferent renal nerve activity is increased in spontaneously hypertensive rats (SHR) and renal denervation delays the onset of hypertension in SHR in association with increased diuresis and natriuresis, the present study was undertaken to examine whether renorenal reflexes were altered in SHR compared with normotensive Wistar-Kyoto rats (WKY). In WKY mean arterial pressure was 113 ± 2 mm Hg and remained unchanged during renal mechanoreceptor and chemoreceptor stimulation. Increasing ureteral pressure 35 mm Hg increased ipsilateral afferent renal nerve activity 4.5 ± 1.7 resets/min, decreased contralateral efferent renal nerve activity 3.2 ± 0.8 resets/min, and increased contralateral urine flow rate 33 ± 4% and urinary sodium excretion 49 ± 8%. Similarly, retrograde ureteropelvic perfusion with 0.9 M NaCl increased ipsilateral afferent renal nerve activity 2.5 ± 0.6 resets/min, decreased contralateral efferent renal nerve activity 2.4 ± 1.1 resets/min, and increased contralateral urine flow rate 39 ± 5% and urinary sodium excretion 38 ± 8%. Stimulating renal mechanoreceptors and chemoreceptors to the same extent in SHR failed to increase ipsilateral afferent renal nerve activity, decrease contralateral efferent renal nerve activity, and produce a contralateral diuresis and natriuresis. It is concluded that renorenal reflexes are impaired in SHR. Failure of ipsilateral afferent renal nerve activity to increase during renal mechanoreceptor and chemoreceptor stimulation indicates a peripheral defect at the level of the renal sensory receptors. This abnormality in the renorenal reflex control of renal function may contribute to hypertension in SHR by promoting excess sodium and water retention. (Hypertension 9: 69-75, 1987)

KEY WORDS • renal nerve activity • renal mechanoreceptors • renal chemoreceptors • spontaneously hypertensive rats

INCREASED sympathetic nervous system activity and, in particular, enhanced sympathetic neural influences to the kidney have been observed in genetic models of hypertension such as spontaneously hypertensive rats (SHR).1 In the anesthetized, young, prehypertensive SHR sympathetic activity to the kidney is elevated far more than the activity to other vascular beds.2 Lundin et al.,3 using multifiber and single-fiber recordings of efferent renal nerve activity (ERNA) in conscious and anesthetized animals, have shown that SHR have higher ERNA than their normotensive controls, Wistar-Kyoto rats (WKY). In addition, standardized mental stress results in a more pronounced increase in renal sympathetic nerve activity in association with a greater decrease in urinary sodium excretion in conscious SHR than in WKY.45 Renal denervation markedly attenuates the antinatriuretic response to stress in SHR. In further support of a role for the renal nerves in the development and maintenance of hypertension are the studies showing that renal denervation delays the development of hypertension in SHR.1 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 in renal-denervated SHR is correlated with enhanced urinary sodium retention and increasing renal norepinephrine content, suggesting renal reinnervation. Repeated renal denervation prevents full expression of hypertension in SHR.6

Previous studies in our laboratory have character-
ized renorenal reflexes in normotensive Sprague-Dawley rats. Renorenal reflexes are defined as responses occurring in one kidney in response to interventions on the same (ipsilateral) or the opposite (contralateral) kidney that are mediated by neurohumoral mechanisms. Renal mechanoreceptor (MR) and chemoreceptor (CR) stimulation in the area of the renal pelvis induced by increasing ureteral pressure and by retrograde ureteropelvic perfusion with hypertonic saline, respectively, results in an increase in ipsilateral afferent renal nerve activity (ARNA) and a decrease in contralateral ERNA that produces a contralateral diuresis and natriuresis. Thus, renal MR and CR stimulation results in a contralateral inhibitory renorenal reflex response in normotensive Sprague-Dawley rats. In preliminary studies, we have also found that the magnitudes of the increases in ipsilateral ARNA and contralateral urinary sodium excretion are related to the magnitude of renal MR stimulation.

These studies suggest that in normotensive Sprague-Dawley rats the renorenal reflexes may play a role in the renal regulation of body fluid volume, with each kidney exerting a tonic inhibition of the neural outflow to the opposite kidney. In support of this hypothesis are the studies in rats showing that unilateral renal denervation results in an increase in contralateral ERNA that produces a contralateral antidiuresis and antinatriuresis.

In view of the contributions of altered efferent renal sympathetic nerve activity to renal sodium handling and the development of hypertension in SHR, the present study was undertaken to examine renorenal reflex responses to renal MR and CR stimulation in SHR.

**Materials and Methods**

The experiments were performed on 20 male SHR and 26 male WKY (Harlan Sprague-Dawley, Indianapolis, IN, USA) that were 14 to 15 weeks of age and weighed 276 to 378 g (mean, 320 g) and 252 to 367 g (mean, 303 g), respectively. Anesthesia was induced with intraperitoneally administered pentobarbital sodium (Nembutal; Abbott Laboratories, North Chicago, IL, USA), 50 mg/kg, and maintained with intraperitoneally administered pentobarbital sodium solution (Abbott Laboratories) by an infusion at a rate of 1.5 mg/min in combination with pentobarbital sodium in isotonic saline at 50 μl/min. Postmortem renal nerve activity was performed to expose the left kidney. Catheters were inserted into both ureters for collection of urine.

**Renal Mechanoreceptor Stimulation**

A 50-cm-long catheter (PE-60) was inserted into the left or right ureter. Ureteral pressure was increased 30 to 38 mm Hg (mean, 34 mm Hg) by elevating the ureteral catheter above the kidney level, as previously described. Ureteral pressure was recorded with a P23Db Statham transducer connected to the ureteral catheter by a T tube connector.

**Renal Chemoreceptor Stimulation**

Renal CRs were stimulated by a retrograde ureteropelvic perfusion with 0.9 M NaCl, as previously described. A PE-60 catheter was inserted into the left or right ureter with its tip ending at the renal pelvis. A PE-10 catheter was then placed inside the PE-60 catheter with its tip extending 1 to 2 mm beyond the tip of the PE-60 catheter. This technique allowed complete drainage of the effluent. The renal pelvis was perfused at 25 μl/min, a perfusion rate previously shown not to increase ureteral pressure, which was recorded with a Statham P23Db transducer connected to the ureteral catheter by a T tube connector.

**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 renal artery. Recordings from multifiber preparations were made by placing the renal nerve on a bipolar silver wire (Cooner Wire, Chatsworth, CA, USA) electrode. The signals were led by a high impedance probe (Grass HIP511, Quincy, MA, USA) to a bandpass amplifier (Grass P511) with high frequency cutoff at 3000 Hz and low frequency cutoff at 30 Hz. The signals were amplified 10,000 to 50,000 times. The output of the bandpass amplifier was fed to an oscilloscope (Tektronix 5113, Beaverton, OR, USA) and fed into a resetting voltage integrator (Beckman 9873B). Assessment of renal nerve activity was done by its pulse-synchronous rhythmicity and its abolition by loading of the high-pressure baroreceptors by an intravenous injection of a pressor dose of norepinephrine (2.5 μg). Previous studies in our laboratory assessing renal nerve activity by voltage integration and spike counting in the same rat have yielded identical findings (U.C. Kopp, L. Smith, G.F. DiBona, unpublished results, 1986). After identification and verification of renal nerve activity, the renal nerve was sectioned and the distal part was placed on the electrode for recording of ARNA. For recording of ERNA, the central part of the sectioned renal nerve was placed on the electrode. Following cutting of the renal nerve, the electrode was fixed to the renal nerve with Wacker Sil-Gel 604. Postmortem renal nerve activity was recorded for 30 to 45 minutes after the rat was killed as a measure of background noise; this value was subtracted from all values of renal nerve activity.
In seven WKY and five SHR ipsilateral ARNA and contralateral ERNA were measured in the same rat; ARNA was recorded from the left renal nerve, and contralateral ERNA from the right renal nerve. In these rats, the PE-60 catheter was inserted into the left ureter for renal MR stimulation and the PE-10 catheter was inserted into the right ureter for urine collection. In the remaining 19 WKY and 15 SHR ipsilateral ARNA and contralateral ERNA were recorded in separate experiments. In those rats in which ipsilateral ARNA was being recorded from the left renal nerve, the PE-60 catheter was inserted into the left ureter for renal MR stimulation and the PE-10 catheter was inserted into the right ureter for urine collection. In those rats in which contralateral ERNA was being recorded from the left renal nerve, the PE-60 catheter was inserted into the right ureter for renal MR or CR stimulation and the PE-10 catheter was inserted into the left ureter for urine collection.

Experimental Procedure

Approximately 1.5 hours was allowed to elapse between the end of the operation and the start of the experiment. The experimental protocol consisted of a 20-minute experimental period preceded by a 20-minute control period and followed by a 20-minute recovery period. Renal MRs or CRs were stimulated during the experimental period. In seven of the 26 WKY and five of the 20 SHR the control, experimental, and recovery periods were repeated; renal MRs were stimulated during both experimental periods. Urine was collected in 20-minute periods, and arterial blood samples were taken at the end of each period. Blood withdrawn was replaced with equal amounts of saline. Renal nerve activity was measured and averaged over each 20-minute control, experimental, and recovery period.

Renal MR stimulation was performed in nine WKY and renal CR stimulation in 17 WKY. In the seven WKY in which two periods of renal MR stimulation were performed, ipsilateral ARNA and contralateral ERNA were measured in random order. In the remaining two WKY in which renal MRs were stimulated, contralateral ERNA was measured. In the 17 WKY in which renal CRs were stimulated, ipsilateral ARNA was measured in nine WKY and contralateral ERNA in eight WKY.

Renal MR stimulation was performed in eight SHR and renal CR stimulation in 12 SHR. In the five SHR in which two periods of renal MR stimulation were performed, ipsilateral ARNA and contralateral ERNA were measured in random order. In the remaining three SHR in which renal MRs were stimulated, ipsilateral ARNA was measured in one SHR and contralateral ERNA in two SHR. In the 12 SHR in which renal CRs were stimulated, ipsilateral ARNA was measured in seven SHR and contralateral ERNA in five SHR.

Analytical Procedure

Plasma and urine sodium concentrations were determined with a flame photometer (Model 143; Instrumentation Laboratories, Lexington, MA, USA). Plasma and urine samples were analyzed for inulin by an anthrone method. Urinary clearance of inulin was used for measurement of glomerular filtration rate.

Statistical Analysis

The effects of renal MR and CR stimulation on systemic hemodynamics and renal function were evaluated by comparing the average of the values obtained in the control and recovery periods with that value obtained during the experimental period. Friedman two-way analysis of variance, Walsh test, Wilcoxon matched-pairs signed-rank test, and Mann-Whitney U test were used. A significant level of 5% was chosen. Data in text and figures are expressed as means ± SE.

Results

Wistar-Kyoto Rats

Renal Mechanoreceptor Stimulation

The results of renal MR stimulation are shown in Figure 1. Since renal MR stimulation resulted in similar changes in contralateral urine flow rate and urinary sodium excretion, whether ipsilateral ARNA or contralateral ERNA was measured in the first part of the experiment, the data have been pooled. Basal systemic and renal hemodynamics and renal excretion did not differ during measurements of ipsilateral ARNA and contralateral ERNA. Mean arterial pressure was 117 ± 5 and 120 ± 4 mm Hg during measurements of ipsilateral ARNA and contralateral ERNA, respectively, and remained unchanged throughout the experiment. Heart rate was 298 ± 11 and 318 ± 13 beats/min during measurements of ipsilateral ARNA and contralateral ERNA, respectively, and remained unchanged throughout the experiment. Increasing ureteral pressure 35 ± 1 and 34 ± 1 mm Hg increased ipsilateral ARNA 4.5 ± 1.7 resets/min (p < 0.01) and decreased contralateral ERNA 3.2 ± 0.8 resets/min (p < 0.01), respectively. Contralateral urine flow rate increased 1.2 ± 0.1 μl·min⁻¹·g⁻¹ (30 ± 6%; p < 0.02) and 2.28 ± 0.41 μl·min⁻¹·g⁻¹ (37 ± 6%; p < 0.02) and contralateral urinary sodium excretion 0.13 ± 0.07 μmol·min⁻¹·g⁻¹ (41 ± 10%; p < 0.02) and 0.35 ± 0.11 μmol·min⁻¹·g⁻¹ (56 ± 12%; p < 0.01) during the two periods of renal MR stimulation. Contralateral glomerular filtration rate remained unchanged during the experiment.

Renal Chemoreceptor Stimulation

The results of renal CR stimulation are shown in Figure 2. Basal systemic and renal hemodynamics and renal excretion did not differ between the two groups of WKY. Mean arterial pressure was 112 ± 2 and 108 ± 4 mm Hg in the two groups of rats in which ipsilateral ARNA and contralateral ERNA, respectively, were measured and remained unchanged throughout the experiment. Heart rate was 340 ± 14 and 318 ± 17 beats/min in the two groups of rats and did not change during the experiment. Retrograde uretero-
pelvic perfusion with 0.9 M NaCl increased ipsilateral ARNA 2.5 ± 0.6 resets/min (p < 0.01) and decreased contralateral ERNA 2.4 ± 1.1 resets/min (p < 0.01). In addition, in the two groups of rats renal CR stimulation increased contralateral glomerular filtration rate 0.29 ± 0.05 ml • min⁻¹ • gr⁻¹ (31 ± 5%) and 0.11 ± 0.08 ml • min⁻¹ • gr⁻¹ (37 ± 8%), contralateral urinary flow rate 1.7 ± 0.2 µl • min⁻¹ • gr⁻¹ (39 ± 7%) and 1.8 ± 0.4 µl • min⁻¹ • gr⁻¹ (38 ± 7%), and contralateral urinary sodium excretion 0.25 ± 0.10 µmol • min⁻¹ • gr⁻¹ (38 ± 13%) and 0.12 ± 0.04 µmol • min⁻¹ • gr⁻¹ (38 ± 11%); p < 0.01 for all responses.

At the end of the experiment the capability of the renal afferent and efferent nerves to respond to other stimuli, such as i.v. injection of air or renal artery occlusion and an i.v. injection of a pressor dose of norepinephrine (2.5 µg).

Spontaneously Hypertensive Rats
Renal Mechanoreceptor Stimulation

The results of renal MR stimulation are shown in Figure 3. Basal systemic and renal hemodynamics and renal excretion did not differ during measurements of ipsilateral ARNA and contralateral ERNA. Mean arterial pressure was 164 ± 5 and 169 ± 3 mm Hg during measurements of ipsilateral ARNA and contralateral ERNA, respectively, and remained unchanged throughout the experiment. Heart rate was 297 ± 13 and 313 ± 15 beats/min during measurements of ipsilateral ARNA and contralateral ERNA, respectively, and did not change during the experiment. Basal contralateral glomerular filtration rate, urine flow rate, and urinary sodium excretion increased from 0.7 to 3.0 resets/min (n = 1) in response to renal artery occlusion. ERNA decreased from 7.3 ± 1.6 to 1.0 ± 0.4 resets/min (p < 0.01; n = 15) in response to an i.v. injection of a pressor dose of norepinephrine (2.5 µg).
and urinary sodium excretion were not significantly different from those obtained in WKY before renal MR stimulation except that basal urinary sodium excretion during measurements of ipsilateral ARNA was higher in SHR ($p < 0.05$). However, the responses to renal MR stimulation were significantly different in SHR compared with those in WKY. In SHR increasing ureteral pressure 34 ± 1 mm Hg failed to affect ipsilateral ARNA or contralateral ERNA. Similarly, contralateral urine flow rate and urinary sodium excretion remained unchanged throughout the experiment. There was a slight fall in contralateral glomerular filtration rate during the recovery period during measurements of contralateral ERNA.

Renal Chemoreceptor Stimulation

The results of renal CR stimulation are shown in Figure 4. Basal systemic and renal hemodynamics and renal excretion did not differ between the two groups of SHR. Mean arterial pressure was 162 ± 11 and 167 ± 12 mm Hg in the two groups of rats in which ipsilateral ARNA and contralateral ERNA, respectively, was measured and remained unchanged throughout the experiment. Heart rate was 371 ± 11 and 377 ± 16 beats/min in the two groups of rats and did not change during the experiment. Basal contralateral glomerular filtration rate, urine flow rate, and urinary sodium excretion were not different from those obtained in WKY before renal CR stimulation. In SHR, however, retrograde ureteropelvic perfusion with 0.9 M NaCl failed to affect ipsilateral ARNA or contralateral ERNA. Similarly, contralateral glomerular filtration rate, urine flow rate, and urinary sodium excretion remained unchanged throughout the experiment.

At the end of the experiment the capability of the afferent and efferent renal nerves to respond to other stimuli, such as an i.v. injection of air or renal artery occlusion and an i.v. injection of a pressor dose of norepinephrine (2.5 μg), was tested in eight and 12 rats, respectively. Ipsilateral ARNA increased from 1.1 ± 0.5 to 3.8 ± 1.0 resets/min ($n = 3$) in response...
to an i.v. injection of air and from 4.9 ± 0.8 to 14.9 ± 3.2 resets/min (p < 0.05; n = 5) in response to renal artery occlusion. Contralateral ERNA decreased from 9.3 ± 1.4 to 2.3 ± 0.8 resets/min (p < 0.01; n = 12) in response to an i.v. injection of norepinephrine.

Discussion

The results of this study demonstrate that in normotensive WKY renal MR and CR stimulation each produce a contralateral inhibitory renorenal reflex response with contralateral diuresis and natriuresis. The afferent limb is increased ipsilateral ARNA, and the efferent limb is decreased contralateral ERNA. In contrast, in SHR, renal MR and CR stimulation of the same magnitude as in WKY failed to affect ipsilateral ARNA, contralateral ERNA, or contralateral urine flow rate and urinary sodium excretion.

In WKY, increasing ureteral pressure 35 mm Hg or retrograde ureteropelvic perfusion with 0.9 M NaCl increased ipsilateral ARNA, decreased contralateral ERNA, and increased contralateral urine flow rate and urinary sodium excretion without affecting mean arterial pressure or heart rate. These findings are in agreement with our previous findings in normotensive Sprague-Dawley rats, in which renal MR and CR stimulation of the same magnitude as in the present study resulted in similar contralateral renal responses in the absence of changes in mean arterial pressure, heart rate, contralateral renal blood flow, or contralateral glomerular filtration rate. In the present study, the effects of renal sensory receptor stimulation on inulin clearance were somewhat variable in the different groups of rats. Whereas contralateral inulin clearance was not affected by increasing ureteral pressure, it was increased by retrograde ureteropelvic perfusion with 0.9 M NaCl. With the increase in urine flow rate above the nondiuretic control level and the relatively short and consecutive urine collection periods without equilibration intervals, it may be that the increase in inulin clearance reflects a washout of inulin rather than a true increase in glomerular filtration rate. In support of this view are our previous studies showing no or variable nonsignificant increases in contralateral inulin clearance during renal CR stimulation.7 8

Mean arterial pressure was significantly higher in SHR than in WKY (165 ± 5 vs 113 ± 2 mm Hg; p < 0.01). Since renal nerve activity was measured with multifiber preparations, no attempts were made to compare baseline ARNA and ERNA between the different groups of rats, since the magnitude of renal nerve activity in each animal is dependent on factors such as overall number of nerve fibers as well as electrode placement.16 17 However, the responses within each animal to an intervention designed to reflexly alter renal nerve discharge rates are faithfully reflected by multifiber renal nerve recordings. In SHR, neither increasing ureteral pressure 34 mm Hg nor retrograde ureteropelvic perfusion with 0.9 M NaCl affected ipsilateral ARNA, contralateral ERNA, urine flow rate, or urinary sodium excretion. Thus, in SHR renal MRs and CRs were unresponsive to the same stimuli that elicited clear responses in WKY. Basal urine flow rate and urinary sodium excretion were variable in both SHR and WKY and did not differ between the two groups with the exception that urinary sodium excretion was higher in the group of SHR in which ipsilateral ARNA was measured during renal MR stimulation. Thus, it is unlikely that the differences in the responses to renal MR and CR stimulation between WKY and SHR could be explained by differences in basal urine flow rate and urinary sodium excretion. Moreover, the lack of responses of ARNA and ERNA to increasing ureteral pressure or retrograde ureteropelvic perfusion with 0.9 M NaCl in SHR could not be explained by some nonspecific generalized unresponsiveness of the nerves (e.g., dissection damage), since ARNA increased in response to i.v. injection of air or renal artery occlusion and ERNA decreased in response to an i.v. injection of a pressor dose of norepinephrine, as tested at the end of the experiment. Furthermore, the responses of afferent and efferent renal nerves to these tests of responsiveness were not different in SHR and WKY.

Taken together, the results of the present study suggest that renorenal reflexes are impaired in SHR. The findings that increasing ureteral pressure and retrograde ureteropelvic perfusion with 0.9 M NaCl failed to increase ipsilateral ARNA in SHR indicate a peripheral defect at the level of the renal sensory receptors as a cause for the attenuated renorenal reflex responses. In view of previous studies indicating that renorenal reflexes can be initiated by renal MR stimulation of a much smaller magnitude than that applied here and that unilateral renal denervation results in a contralateral excitatory response10 11 in normotensive Sprague-Dawley rats, renorenal reflexes may be thought to play an important physiological role in the control of ERNA and, thus, renal regulation of total body sodium and water. In agreement with this view, the results from the present study suggest that the impairment of renorenal reflexes in SHR may contribute to the enhanced renal function in SHR,3 thus favoring renal water and sodium retention and potentially contributing to the hypertension. In this context, it is to be recalled that total withdrawal of ipsilateral ARNA, as occurs with unilateral renal denervation, results in an increase in contralateral ERNA that produces a decrease in contralateral urine flow rate and urinary sodium excretion in normotensive Sprague-Dawley rats.10 11

In analogy with the findings in the present study is the considerable evidence supporting the view that both the arterial and cardiopulmonary baroreceptor reflexes are impaired in SHR.18 The afferent neural discharge response of the aortic baroreceptors to increased pressure is attenuated in SHR compared with WKY.19 Similarly, Thoren et al.20 showed that elevation of left atrial pressure resulted in an attenuated afferent neural discharge response of the atrial baroreceptors in SHR. In addition to these studies showing a defect at the level of the aortic and atrial baroreceptors
in SHR, there is also a central abnormality in the baroreceptor reflex control of efferent sympathetic nerve activity.21 The results of these studies taken together with the findings of the present study suggest that the defect in the reflex control of efferent (renal) sympathetic nerve activity in SHR is diffuse and involves aortic and cardiac baroreceptors as well as renal sensory receptors.

In summary, the results of the present study demonstrate that renal MR and CR stimulation in WKY results in a contralateral inhibitory renorenal reflex response similar to that previously observed in Sprague-Dawley rats.78 In SHR, however, similar renal MR and CR stimulation failed to elicit a renorenal reflex response due, at least in part, to a peripheral defect at the level of the renal sensory receptors. Since the results of previous studies in Sprague-Dawley rats suggest that renorenal reflexes play a physiological role in the control of ERNA and renal regulation of total body sodium and water, the attenuated renorenal reflex response in SHR would enhance ERNA, favor sodium and water retention, and thus potentially contribute to hypertension in SHR.

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