Effects of Angiotensin Inhibition and Renal Denervation in Two-Kidney, One Clip Hypertensive Rats

RICARDO RADEMACHER, KATHLEEN H. BERECEK, AND DAVID W. PLOTH

SUMMARY Neural and angiotensin-mediated influences that alter hemodynamic and excretory behavior of the nonclipped kidney of two-kidney, one clip hypertensive rats were assessed by sequential acute surgical denervation of the nonclipped kidney and intravenous infusion of converting enzyme inhibitor (SQ 20881), 3 mg/kg-hr. Normal and two-kidney, one clip hypertensive rats (0.2-mm silver clip on the right renal artery 3-4 weeks before study) were prepared to allow study of each kidney. Mean arterial blood pressure of two-kidney, one clip hypertensive rats fell significantly from control values of 149 ± 6 to 135 ± 6 mm Hg after denervation of the nonclipped kidney. Despite this decrease in arterial pressure, the nonclipped kidney exhibited significant increases in glomerular filtration rate (from 1.00 ± 0.08 to 1.24 ± 0.08 ml/min), sodium excretion (from 88 ± 39 to 777 ± 207 nEq/min), fractional sodium excretion (from 0.06 ± 0.02 to 0.54 ± 0.14%), and urine flow rate (from 3.7 ± 0.5 to 8.2 ± 1.1 µl/min). A significant decrease in glomerular filtration rate (from 1.12 ± 0.07 to 0.85 ± 0.08 ml/min) with no change in excretory function was observed for the clipped kidney following denervation of the nonclipped kidney. Intravenous addition of converting enzyme inhibitor significantly increased renal blood flow (from 7.0 ± 1.3 to 10.6 ± 1.5 ml/min) and sodium excretion (from 777 ± 207 to 1384 ± 425 nEq/min) for the nonclipped kidney; blood pressure decreased from 135 ± 6 to 123 ± 4 mm Hg, and renal vascular resistance decreased significantly (from 22 ± 3 to 13 ± 2 mm Hg · min/ml). In normal rats acute surgical denervation of one kidney resulted in reductions in arterial pressure and ipsilateral increases in urine flow rate and sodium and potassium excretion that were of smaller magnitude than those observed in the denervated kidney of the two-kidney, one clip hypertensive rats; sodium excretion decreased slightly in the untouched, innervated kidney. Addition of converting enzyme inhibitor produced a further increase of sodium excretion in both kidneys. Renal hemodynamics were not altered in either kidney throughout the experiment. These results suggest that renal neural influences, in addition to angiotensin-mediated effects, contribute to the altered hemodynamic and excretory behavior of the nonclipped kidney of the two-kidney, one clip hypertensive rat. 

KEY WORDS • angiotensin • renal hypertension • renal nerves • angiotensin converting enzyme inhibition

RECENTLY, the role of renal nerves in the regulation of renal function has been the subject of much interest. Studies from a number of laboratories have shown that the withdrawal of sympathetic nerve activity, achieved through surgical or pharmacological denervation, is accompanied by an increase in sodium excretion by the kidney. 1,2 This increased sodium excretion is associated with variable renal hemodynamic responses. 1,3 Most of the studies assessing the effects of renal denervation have focused on changes in tubule absorptive function by identifying specific segments of the nephron responsive to removal of neural influences under different experimental conditions 1,2 or have examined the changes in glomerular hemodynamic function in response to renal denervation. 5,7 These previous experiments, however, generally have not assessed possible interactions between renal nerves and other regulatory systems that contribute to the control of renal hemodynamic or excretory function. One such system, the renin-angiotensin system, has been demonstrated to play an important role in the regulation of glomerular and tubular function during normal conditions and in a number of different pathophysiological settings. 8

We have shown previously that the renin-angioten-
sin system plays an important role in the pathophysiology of renal vascular hypertension by contributing to altered renal hemodynamic and excretory function in this experimental model. 8-10 The purpose of the present study was to assess the interaction of renal nerves and the renin-angiotensin system on renal hemodynamic and excretory function observed in two-kidney, one clip (2K1C) hypertension. Neural and angiotensin interactions that influence renal hemodynamics and salt and water excretion were assessed by sequential removal of renal sympathetic nerve activity by acute surgical denervation and by the removal of angiotensin II activity, achieved by inhibition of converting enzyme activity. To compare the influence of these systems with those observed under normal conditions, additional studies were done in normal rats.

Materials and Methods

Observations are reported for normal and 2K1C hypertensive rats weighing 255 ± 7 and 209 ± 9 g, respectively (range, 180–300 g), at the time of study. The hypertensive animals were prepared 3 to 4 weeks before the study by placing a U-shaped silver clip with an internal diameter of 0.2 mm on the right renal artery of Sprague-Dawley male rats weighing 80 to 100 g at the time of clipping (Charles River Breeding Laboratories, Wilmington, MA, USA) under pentobarbital anesthesia (5 mg/100 g body weight i.p.). All animals were fed commercial rat chow (Agway, Syracuse, NY, USA) containing sodium, 0.5 mM/g chow and were allowed tap water ad libitum.

Rats were anesthetized and prepared for clearance studies on a thermostatically controlled heated table. Animals were anesthetized with pentobarbital sodium (5 mg/100 g body weight i.p.) and maintained with 0.5-mg i.v. bolus injections every 30 minutes. Surgical preparation included insertion of a tracheal cannula and cannulation of the right external jugular vein with a multilumen cannula for infusion of inulin, p-aminohippurate (PAH), drugs, and supplemental anesthetic. A cannula placed in the left femoral artery allowed blood sampling and measurement of blood pressure with a Statham P23DC transducer (Gould-Statham Instruments, Hato Rey, Puerto Rico), which was recorded on a Grass polygraph (Model P7; Quincy, MA, USA). The left kidney was isolated through a flank incision and placed in a Lucite cup to expose the left ureter, which was cannulated proximally with a PE-50 polyethylene catheter; the distal left ureter was occluded with a ligature. The urinary bladder was cannulated with a polyethylene tube (PE-90) through an abdominal incision to allow simultaneous collections of urine samples from the right kidney.

At the beginning of the operation an intravenous infusion of a solution containing polyfructosan (Inu-test; Laevosan-Gesselchaft, Linz, Austria), 10 g/dl, and PAH (Merck Sharp & Dohme, West Point, PA, USA), 2 g/dl, in 0.9% NaCl was initiated at a rate of 0.01 ml/min. A second infusion of 0.9% NaCl at 0.01 ml/min was also started, giving a total infusion rate of 1.2 ml/hr. After completion of the operation, 40 minutes was allowed for the animal to reach a steady state and two control period urine collections of 30 minutes each were initiated. Blood samples were taken at the midpoint of each clearance period.

Following the control periods, acute renal denervation of the left kidney of normal rats and the nonclipped kidney of 2K1C hypertensive rats was performed by stripping the renal artery of its adventitia and coating the remaining covering tissue with a solution of 10% phenol in absolute alcohol. During application of phenol, the kidney and adjacent tissues were carefully protected from exposure to the chemical. Forty minutes later, two or more 30-minute denervation-clearance periods were completed.

After the collection of urine and blood samples for the denervation periods, a solution containing converting enzyme inhibitor (CEI; teprotide; E.R. Squibb & Sons, Princeton, NJ, USA) was infused intravenously at a rate of 3 mg/kg·hr. The infusion of CEI replaced the saline infusion at the same volume rate. After initiating administration of CEI, 40 minutes was allowed to achieve a new steady state and to allow washout of urinary dead spaces. Urine samples for two to three additional clearance periods of 30 minutes each were then collected. The ability of this dose of CEI to block conversion of angiotensin I to angiotensin II in 2K1C hypertensive rats was tested by determining the pressor responses to bolus intravenous doses of 25 and 50 ng of angiotensin I administered before and during CEI administration. The pressor response observed for 25 ng of angiotensin I before blockade of converting enzyme, a 16 ± 0.8 (SEM) mm Hg increase of systemic blood pressure, was abolished during the infusion of CEI. The response to 50 ng of angiotensin I was reduced by 85% from a 46.5 ± 0.8 mm Hg increase in blood pressure before CEI to a 7.1 ± 0.9 mm Hg increase during administration of CEI (n = 12 animals).

In an additional small number of rats (n = 4), we evaluated the completeness of the denervation procedure by examining changes in renal blood flow (RBF) in response to a generalized sympathetic discharge induced by electrical stimulation of the locus ceruleus before and after acute renal denervation. This technique is based on the observation that RBF decreases in response to a generalized sympathetic discharge induced by electrical stimulation of the locus ceruleus in the presence of intact renal nerves. The magnitude of this renal vasoconstrictor response is related to the frequency of the locus ceruleus stimulation. Following adequate renal denervation, abolition of these renal vasoconstrictor responses would be expected. In brief, a bipolar stainless steel electrode was placed stereotaxically in the locus ceruleus of four normotensive rats.11 Animals were surgically prepared for study as already described, but, in addition, the left renal artery was isolated and a miniaturized ultrasonic flow probe driven by a pulsed Doppler device (directional pulsed
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By guest on April 13, 2017

The renal clearance of PAH was measured in duplicate. Plasma sodium and potassium concentrations were determined with a flame photometer (Model 443; Instrumentation Laboratory, Lexington, MA, USA). Timed urine samples were collected under oil; volumes were determined gravimetrically. Hematocrits were measured in duplicate.

Clearance of PAH, corrected for extraction, was used as an estimate of renal plasma flow. Extraction of PAH was determined in six normotensive rats and was found to be 0.81 ± 0.03. Measured PAH extraction for nonclipped kidneys of four hypertensive rats was 0.75 ± 0.06, an extraction ratio not different from that for normal rats (p > 0.05). The RBF was calculated from the estimated renal plasma flow and measured hematocrit according to the formula RBF = renal plasma flow/(1 − hematocrit). Filtration fraction (FF) was calculated as the ratio of glomerular filtration rate (GFR) to renal plasma flow. Total renal vascular resistance (RVR) of normal kidneys and the nonclipped kidneys of hypertensive rats was computed from calculated RBF and systemic arterial blood pressure and is expressed as mm Hg·min/ml. Calculation of RVRs for the clipped kidneys of the 2K1C hypertensive rats was not done because the renal arterial pressure distal to the clip was not measured.

Values for the responses observed for each period for each animal were averaged; the values presented for each period in the figures and text represent mean values that are derived from the average response for each animal for that period. Data are expressed as the mean ± 1 SEM. Statistical analyses were accomplished with an SAS package (general linear models procedures) on a computer. Within-group treatment effects were tested using analysis of variance with blocking; among-group comparisons were evaluated with a split plot analysis of variance technique. Duncan’s multiple range test was used to assess significance of intergroup differences for multiple period studies. In applicable instances paired statistical analysis was accomplished. Significance was accepted as a p value of less than or equal to 0.05.

Results

The effects of direct electrical stimulation of the locus ceruleus on RBF are shown in Figure 1. During conditions of intact renal nerves, frequency-dependent decreases in RBF were observed in response to stimulation of the locus ceruleus at frequencies ranging from 20 to 80 Hz. The changes of RBF were observed immediately after the initiation of central stimulation. Renal vasoconstriction reversed immediately after discontinuation of locus ceruleus stimulation. In contrast, no change in RBF was observed in response to locus ceruleus stimulation after renal denervation. Renal α-adrenergic receptors were not affected by the renal denervation procedure, as evidenced by the unaltered magnitude of renal vasoconstriction in response to phenylephrine following denervation as compared with the responses we had observed during conditions of intact renal nerves.

The systemic and renal hemodynamic responses of normal rats to denervation of the left kidney followed by addition of treatment with a converting enzyme antagonist are shown in Figure 2. Mean blood pressure for the normal rats during the control period was 122 ± 3 mm Hg. After renal denervation blood pressure decreased significantly to 108 ± 3 mm Hg, and during infusion of CEI blood pressure significantly decreased further from levels of the denervation period to 100 ± 3 mm Hg (all p < 0.05). The renal clearance and excretory responses for the same normal rats for
the same experiments are presented in Figure 3. Insignificant changes in GFR, RBF, renal plasma flow, whole kidney FF, and RVR were observed throughout the experiment. For the denervated kidney, RBF was 6.84 ± 0.86, 6.69 ± 0.53, and 7.07 ± 0.66 ml/min and renal plasma flow was 3.48 ± 0.46, 3.44 ± 0.3, and 3.81 ± 0.42 ml/min for the control, renal denervation, and CEI periods, respectively. For the same periods, GFR and FF were 0.99 ± 0.06, 1.04 ± 0.06, and 0.99 ± 0.09 ml/min and 0.31 ± 0.03, 0.32 ± 0.04, and 0.25 ± 0.02, respectively. The RVR tended to decrease following renal denervation (from 20 ± 2 to 17 ± 1 mm Hg·min/ml) and tended to decrease further during CEI infusion (to 15 ± 1 mm Hg·min/ml). However, these changes did not achieve statistical significance because of the large variation in the observations. Similar to the denervated kidney changes of GFR, renal plasma flow and FF for the innervated kidney did not achieve statistical significance. Arterial hematocrits were 50 ± 1%, 48 ± 1%, and 47 ± 1% for each of the periods, respectively.

Figures 4 and 5 summarize the observations for urine flow rate and absolute and fractional excretion of sodium and potassium for each kidney of normal rats in response to acute unilateral renal denervation and superimposed converting enzyme blockade. During the control period, absolute sodium excretion of the innervated kidney was 89 ± 27 nEq/min; after denervation of the contralateral kidney there was a slight but significant decrease of sodium excretion to 59 ± 27 nEq/min (p < 0.05). During converting enzyme blockade, sodium excretion for the innervated kidney increased to 231 ± 64 nEq/min (p < 0.05). The denervated kidney exhibited significantly increased sodium excretion: from 51 ± 24 nEq/min during the control period to 176 ± 40 nEq/min (p < 0.05) following acute denervation. An impressive natriuresis was observed for the denervated kidney during converting enzyme blockade when sodium excretion increased further to 516 ± 125 nEq/min (p < 0.05). Changes in fractional sodium excretion followed the same pattern as those observed for absolute sodium excretion for both kidneys. The absolute and fractional excretion of potassium did not change significantly for the innervated kidney in response to either intervention in these experiments. Absolute excretion of potassium was 926 ± 117 nEq/min, and fractional potassium excretion was 24 ± 3%; both values remained unchanged from control during renal denervation and CEI periods, respectively. The denervated kidney exhibited significant increases of both absolute and fractional excretion of potassium from 816 ± 123 nEq/min and 47 ± 1% during the control period to 1325 ± 123 nEq/min and 35 ± 4.1% after denervation. Subsequent blockade of converting enzyme activity resulted in no further change in the absolute or fractional excretion of
INNERVATED
Clipped, Right Kidney
Normal, Right Kidney

DENERVATED
Nonclipped, Left Kidney
Normal, Left Kidney

FIGURE 4. Responses of absolute excretion of Na⁺ (UₙaV), absolute excretion of K⁺ (UₖV), and urine flow rate (V) to sequential renal denervation (DNX) and blockade of angiotensin converting enzyme (CEI). Values are means ± SEM, and statistical notations are shown in the same format as in Figure 2.

Renal plasma flow for the clipped kidney was 2.85 ± 0.08 ml/min during the control period and remained unchanged following denervation of the nonclipped kidney and after addition of CEI. The RBF for the clipped kidney was 5.5 ± 0.1 ml/min during the control period and remained unchanged after denervation of the nonclipped kidney. The addition of CEI resulted in a small but insignificant decrease in RBF to 5.4 ± 1.0 ml/min. Data for RVR for the right, clipped kidney were not obtained. The FF decreased slightly but not significantly from 0.32 ± 0.01 during the control period in response to denervation and CEI.

In the 2K1C hypertensive rats, the mean blood pressure during the control period was 149 ± 6 mm Hg (see Figure 2). After denervation of the nonclipped kidney, blood pressure decreased significantly to 135 ± 6 mm Hg (p < 0.05). During infusion of CEI blood pressure decreased significantly from levels of the renal denervation period to 123 ± 4 mm Hg (p < 0.05). As shown in Figure 3, GFR for the clipped kidney of the 2K1C hypertensive rats decreased significantly after acute denervation of the nonclipped kidney (from 1.12 ± 0.07 ml/min during the control period to 0.85 ± 0.08 ml/min following denervation; p < 0.05). During CEI infusion, GFR for the clipped kidney tended to decrease further (to 0.7 ± 0.1 ml/min), although this change was not significantly different from the level of GFR observed following denervation alone.
from 0.37 ± 0.05 during the denervation period to 0.25 ± 0.05 during the addition of CEI (p ≤ 0.05). The RVR tended to decrease throughout the course of the experiment, although these changes achieved significance only during the period of CEI infusion. Arterial hematocrits were 48 ± 1%, 46 ± 1%, and 44 ± 1% for each of the study periods, respectively.

The changes for excretory function for the nonclipped kidney of the hypertensive group are presented in Figures 4 and 5. Urine flow rate increased twofold after acute denervation (from 3.7 ± 0.5 to 8.2 ± 1.1 μl/min; p ≤ 0.05). An additional increase of urine flow to 10.8 ± 1.4 μl/min (p ≤ 0.05) was observed after converting enzyme blockade. Absolute excretion of sodium for the nonclipped kidney increased significantly from 88 ± 39 nEq/min during the control period to 777 ± 208 nEq/min following acute ipsilateral renal denervation (p ≤ 0.05) and increased further to 1384 ± 425 nEq/min after addition of systemic blockade of converting enzyme (p ≤ 0.05). Although the fraction of the filtered load of sodium that was excreted exhibited the same pattern of responses, statistically significant increases of fractional excretion of sodium were observed only in response to denervation. Fractional sodium excretion increased from 0.06 ± 0.2 to 0.54 ± 0.14% (p ≤ 0.05) in response to denervation of the nonclipped kidney, as opposed to the insignificant change to 0.81 ± 0.25% in response to the addition of converting enzyme blockade (p ≥ 0.05). Absolute and fractional excretion of potassium by the nonclipped kidney increased significantly only during the denervation period; no significant increase of potassium excretion was observed in response to addition of converting enzyme blockade. Absolute and fractional excretion of sodium and potassium and urine flow rate did not change significantly for the clipped kidney in response to denervation or the addition of CEI.

**Discussion**

It has become increasingly evident that the renal nerves probably contribute to the homeostatic control of renal function under normal conditions.\(^{14,15}\) Interruption of the spontaneous renal nerve activity by denervation of the kidney has been found to result in diuresis and natriuresis with no alterations in renal hemodynamics\(^ {14,15}\) or with small increases in RBF or GFR.\(^ 4\) Renal nerves also play an important role in the pathophysiology of many forms of experimental hypertension.\(^ {16-19}\) In some of these models of hypertension, the renin-angiotensin system contributes significantly to the initiation and maintenance of the elevated blood pressure by influencing deranged renal function.\(^ 5,9,20,21\)

One uncertainty almost always present when dealing with acute surgical denervation studies is the reliability of the renal denervation technique used.\(^ {14}\) Our approach made us feel quite confident about the adequacy of the renal denervation in these studies. When the locus ceruleus was electrically stimulated during conditions of intact renal nerves, large and significant decreases in RBF were observed in response to the resulting generalized sympathetic discharge. However, no change in RBF was observed in response to the same locus ceruleus stimulation when the kidney was previously denervated, even though the level of central stimulation was significantly higher. These observations, taken with the changes of renal function that are typical for responses following renal denervation in normal animals,\(^ {1,2}\) lead us to conclude that our renal denervation procedure was effective.

Blood pressure decreased after acute unilateral renal denervation in normal rats. These results were consistent in every animal subjected to renal denervation and quite unexpected, insofar as most previous studies have reported no change in blood pressure following acute surgical denervation.\(^ {1,2}\) It should be noted, however, that blood pressure either tended to decrease or actually did decrease following denervation in several of these earlier reports.\(^ {2,3}\) It is very unlikely that the removal of the normally rather low prevailing activity of the renal sympathetic nerves\(^ 22\) should have any major impact on blood pressure. Although the reason for these relatively larger decreases of blood pressure in our studies is not clear, it may originate in differences in the volume status of animals. The hydropenic state and relative volume contraction of the animals in our study may have contributed to the decreases of blood pressure observed in response to denervation. Further, the effects of anesthesia would be expected to accentuate responses that could be the result of increased activity of the renin-angiotensin system or the sympathetic nervous system attributable to hydropenia. Blood pressure decreased further after converting enzyme inhibition with SQ 20881, a result consistent with previous reports from our and other laboratories.\(^ 9,10\)

In agreement with the results reported by others in the rat, we observed no changes in RBF, renal plasma flow, GFR, FF, and RVR after acute renal denervation in normal rats.\(^ {1-3}\) Treatment with a CEI superimposed on the denervation was not followed by any significant vasodilation or increase in GFR. This last observation was quite surprising in that we previously have observed that blockade of converting enzyme activity in normal rats results in significant increases in RBF and GFR during conditions of intact innervation of the normal kidney.\(^ {23}\) Our results agree with a recent publication by Pelayo and Blantz,\(^ 7\) who demonstrated that the infusion of captopril to previously renal denervated normal hydropenic rats was followed by no change in GFR.

Acute denervation of the left kidney of normal rats resulted in significant diuresis and natriuresis, findings consistent with the results of previous studies.\(^ {1-3}\) The unique feature of the present experiments is that the kidney responded with an increased excretion of sodium and water after denervation, even though blood pressure was decreased. The addition of blockade of converting enzyme activity resulted in a significant additional natriuresis in the presence of a further decrease of systemic blood pressure.
The innervated kidney of these normal animals showed a small but significant decrease in sodium excretion after denervation on the contralateral side, in agreement with previous reports.\textsuperscript{1,3} Sodium excretion by the innervated kidney increased significantly following systemic blockade of the renin-angiotensin system. The results of these experiments appear to dissociate the effects of renal nerves and angiotensin II on sodium conservation in the same animal. Under conditions of similar systemic blood pressure, the removal of renal nerve activity or the application of CEI had directionally similar effects in the denervated kidney: to increase sodium excretion. On the other hand, in the kidney with intact renal nerves these influences seemed to have directionally opposite effects: renal denervation resulted in conservation of sodium, probably through a reflex increase in sympathetic activity after contralateral denervation,\textsuperscript{1} and blockade of generation of angiotensin II resulted in increased excretion of sodium. Although less likely, it is also possible that these observations are the result of a denervation-induced decrease in renin-angiotensin system activity within the denervated kidney. The intravenous administration of CEI would interfere with generation of angiotensin II in the systemic circulation and its effects in both the denervated and innervated kidneys.

In the 2K1C hypertensive rats, acute denervation of the nonclipped kidney resulted in a 25% increase in GFR. Urine flow rate and absolute sodium excretion also increased markedly following denervation. These increases in filtration rate and excretory function occurred in spite of a contemporaneous, significant decrease in blood pressure. Although the filtered load of sodium was increased modestly following denervation of the kidney, the larger magnitude of the ninefold increase of fractional excretion of sodium is consistent with the suggestion that the renal nerves exert direct tubular effects to stimulate sodium absorption.

Several lines of evidence have suggested that neurogenic mechanisms may participate in the development or established phase (or both) of renovascular hypertension. These include elevated plasma catecholamines,\textsuperscript{24} accentuated reduction in blood pressure after ganglionic blockade,\textsuperscript{25,26} reversal or prevention of hypertension by destruction of selective regions in the anterior hypothalamus,\textsuperscript{27,28} reduction in blood pressure by injection of angiotensin antagonists intracerebroventricularly,\textsuperscript{29} depletion of central catecholamine stores,\textsuperscript{30} maintenance of an inappropriately high neurogenic vasoconstrictor tone,\textsuperscript{31} and lowering of blood pressure following denervation of the clipped kidney.\textsuperscript{32} Our results indicate that neurogenic influences mediated through renal nerves play a role in modulating renal function and probably contribute to the altered hemodynamic and absorptive behavior of the nonclipped kidney of 2K1C hypertensive rats. Further, these results suggest a possible mechanism by which neural influences could contribute to the development and perhaps the early maintenance phases of renovascular hypertension: by contributing to the maintenance of a reduced filtered load of sodium and an increased level of renal tubular absorption of sodium. In effect this mechanism could contribute to the development of hypertension by altering the basic relationships of the pressure—sodium natriuresis phenomenon, as suggested by the general hypothesis of the pathophysiology of hypertension of Guyton et al.\textsuperscript{33} However, the present experiments do not permit us to determine if this denervation natriuresis is a direct result of removal of neural influences or an indirect result of the intervention, possibly related to some intrarenal or other compensatory mechanism in response to denervation.

Previous investigations in our laboratory and in the laboratories of others have demonstrated that the renal hemodynamic and excretory alterations for the nonclipped kidney during the intermediate phase of the hypertension in this model are reversed by angiotensin antagonists.\textsuperscript{5,10} These observations suggested that the altered behavior of the nonclipped kidney is largely dependent on the effects of angiotensin.\textsuperscript{8} This conclusion does not contradict the possibility that renal nerves also contribute greatly to the altered excretory function of the nonclipped kidney. In our experiments addition of blockade of angiotensin converting enzyme resulted in a further significant vasodilation, natriuresis, and diuresis by the previously denervated kidney. These results most likely represent an unmasking of major, persistent vasoconstricting and antinatriuretic effects of angiotensin II on the nonclipped kidney in the absence of neurogenic influences. From these observations it would seem that both the renal sympathetic nervous system and the renin-angiotensin system might contribute in parallel to the derangements of renal function observed in the nonclipped kidney of the 2K1C Goldblatt rat during the initial and intermediate phases of hypertension. The present experiments do not allow any quantitative estimates of the relative contributions of renal nerves and the renin-angiotensin system to renal hemodynamics or to sodium conservation under the conditions of our study.

The only significant alteration of renal function exhibited by the clipped kidney after denervation of the nonclipped side was a decrease in GFR. Renal hemodynamics and renal excretory function for the clipped kidney were not materially changed throughout the remainder of the experiment. It is possible that the decreases in blood pressure following denervation of the nonclipped kidney and systemic administration of CEI could have masked or prevented detection of direct effects resulting from contralateral denervation or angiotensin blockade on the clipped kidney.\textsuperscript{8}

A comparison of the results observed in normotensive and 2K1C hypertensive rats indicates that the responses in excretory behavior following sequential removal of neurogenic activity and systemic blockade of the renin-angiotensin system were qualitatively similar. In both groups acute denervation and blockade of angiotensin II converting enzyme resulted in increases of sodium excretion, even in the presence of contemporaneous decreases in blood pressure. It also appears that in normotensive and hypertensive rats the effects of renal nerves and angiotensin II on sodium
reabsorption are mediated, at least in part, through parallel mechanisms. In contrast to the similarity of neurogenic and angiotensin II influences on sodium absorption in normal and hypertensive rats, the renal hemodynamic responses of the two groups were quite different. In normal rats renal denervation resulted in no change in renal hemodynamics; in 2K1C hypertensive rats acute denervation was followed by a significant increase in GFR and a moderate vasodilatation. These observations suggest that the neural vasoconstrictor tone of the nonclipped kidney may be increased relative to normal, in agreement with recent data of Faber and Brody indicating an inappropriately high neurogenic tone in the initial phase of renovascular hypertension. Converting enzyme inhibition after denervation resulted in further decreases of renal vascular resistance and increases of renal blood flow, suggesting that additional vasoconstriction in the nonclipped kidney was the result of angiotensin-mediated influences.

In summary, our results suggest that to the extent that they can be inhibited separately, renal sympathetic nerve activity and angiotensin II contribute to the regulation of sodium excretion by the kidney through mechanisms that appear to be independent in both normotensive and 2K1C hypertensive rats. The results of this study also suggest that neural influences, in addition to angiotensin-mediated effects, contribute to altered hemodynamic and excretory behavior of the nonclipped kidney of the 2K1C hypertensive rat and, through this mechanism are important to the pathophysiology of the initiation or maintenance (or both) of hypertension in this model.

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