PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 179, 147–154 (1985)

Renin Release from Nonclipped Kidneys of 2K-1C Hypertensive Rats (42076)

JOHN R. DIETZ

Department of Physiology, University of South Florida College of Medicine, Tampa, Florida 33612

Abstract. This study examined renin release and renal function of the nonclipped kidney of 2K-1C rats (HYPER) with hypertension of 3 to 4 weeks duration. Kidneys from uninephrectomized rats (UN) served as controls. The kidneys were removed and perfused *in vitro* and renin release was compared under basal conditions and then under stimulated conditions using (a) a 50 mm Hg reduction in perfusion pressure (LP), (b) β-receptor stimulation with isoproterenol (ISOP), or (c) perfusion with a low calcium solution (LCa). Basal perfusate flow, glomerular filtration rate, urine flow, sodium excretion, and basal renin release were all lower in HYPER kidneys than UN kidneys. UN kidneys showed striking increases in renin release with all three stimuli employed. HYPER kidneys showed a significant but attenuated response to ISOP and showed no detectable response to LP or LCa. Renin content of HYPER kidneys was found to be 28% of the renin content of UN kidneys. The results show that chronic hypertension leads to increased renal vascular resistance, reduced glomerular filtration, and reduced solute excretion in the nonclipped kidney. The results suggest that a reduction in renin content plays a major role in the reduced rates of basal renin release and the attenuated renin responses to a number of stimuli observed in this experimental model.

The application of a constricting clip to the renal artery of one kidney results in a relative hypotension in that kidney, and renal function is reduced. In the 2K-1C rat, the nonclipped kidney undergoes compensatory hypertrophy with vasodilitation and increased glomerular filtration rate (1). Renin release from the clipped kidney is increased (2) and the increased circulating renin and angiotensin II result in systemic hypertension (3). Over a period of 3 to 4 weeks the increase in systemic blood pressure produces a number of dramatic changes in the nonclipped kidney including increased renal vascular resistance, reduced glomerular filtration rate (GFR), and reduced sodium excretion (4–6).

Renin release from the nonclipped kidneys appears to be reduced (2, 7) but the mechanism for this reduction is unclear. Since angiotensin II is elevated in these hypertensive animals, angiotensin II may reduce renin release from the nonclipped kidneys via a negative feedback mechanism (8). The elevation in systemic arterial pressure could inhibit renin release via the renal baroreceptor or macula densa or could inhibit renin release by acting indirectly to reduce renal sympathetic nerve activity (9). Renin content in the nonclipped kidneys of 2K-1C hypertensive rats appears to be lower than normal (2, 7). This could account, at least in part, for a reduced rate of renin release from the nonclipped kidneys. Rostand *et al.* (4) recently compared nonclipped kidneys of 2K-1C rats with hypertension of 3 to 4 weeks' duration with kidneys of normotensive rats by perfusing both groups of kidneys in the isolated state at similar perfusion pressures. Their findings show that the kidneys from hypertensive rats exhibit increased renal vascular resistance due to vascular smooth muscle cell hypertrophy with arteriolar narrowing. This condition could conceivably reduce the ability of the renal baroreceptor to stretch or reduce stretch with changes in perfusion pressure (10), which might contribute to the low rate of renin release observed in this experimental model.

The purpose of the present study was to examine renal function and renin release from the nonclipped kidney of 2K-1C rats and to study some of the mechanisms which might contribute to the reduced rate of renin release from kidneys exposed to a chronic elevation in arterial blood pressure. Kidneys of 2K-1C rats and uninephrectomized control rats were perfused *in vitro* at similar perfusion pressures in order to avoid possible extrarenal neural and humoral effects.

It has been previously reported that basal

0037-9727/85 $1.50

renin release is reduced in incubated slices from nonclipped kidneys of 2K-1C hypertensive rats (2, 7). This study, however, examines renal function, basal renin release, and stimulated renin release of functioning kidneys perfused *in vitro*. This allows one to observe the effects of stimuli, such as changes in perfusion pressure on renin release in order to evaluate the integrity of the renal vascular receptor in kidneys exposed to a chronic elevation in arterial pressure.

Methods. The experiments were conducted in male Sprague–Dawley rats weighing 140–180 g at the time of the initial surgery. They were fed a standard rat chow and had free access to water throughout the course of the study. Systolic blood pressure was measured every 3 to 4 days by the tail-cuff technique (11) with baseline measurements taken prior to renal artery clipping, sham clipping, or nephrectomy.

2K-1C hypertension, nephrectomy, and sham operation. The rats were anesthetized with sodium pentobarbital (50 mg/kg) and the left kidney was approached via a flank incision. In one group of animals (2K-1C) a solid silver clip with a gap of 0.23 mm was placed on the left renal artery. In a second group the left kidney was exposed in the same fashion but no clip was applied. These sham-operated animals served as one control series. In a third group of animals the left kidney was removed. This group served as an additional control group since the right kidneys would undergo many of the same adaptive changes seen initially in the right kidneys of the clipped animals when the function of the left kidney is compromised (1). All of the experiments reported here were performed $3\frac{1}{2}$ to 4 weeks after clipping or nephrectomy.

Measurement of renin content. The right kidney of 24 rats (8 in each group) was removed at $3\frac{1}{2}$ to 4 weeks after the initial surgery and prepared for measurement of renin content (12). The kidneys were decapsulated, passed through a 240 μM sieve, and suspended in 100 ml of distilled water. The suspension was frozen and thawed four times and a 0.1-ml aliquot was added to 0.9 ml of pooled plasma from a nephrectomized dog for later determination of renin activity.

Isolated perfused kidneys. Kidneys were prepared for isolated perfusion using the method of Nishiistutsuji-Uwo *et al.* (13). The rats were anesthetized with sodium pentobarbital (50 mg/kg). The right kidney was exposed via an abdominal incision and the ureter cannulated with polyethelene tubing (PE-10). The mesenteric artery and right adrenal artery were ligated and cut and the abdominal aorta and inferior vena cava were ligated below the origin of the right renal artery and vein. Loose ligatures were placed around the aorta and vena cava proximal to the origin of the renal artery and vein. The aorta was cannulated just below the right kidney with a blunted 16-gauge needle connected to the perfusion apparatus. With the onset of perfusion, the aorta was ligated and cut proximal to the kidney and the vena cava was cut both proximal and distal to the kidney. The kidney was gently removed, suspended in a funnel, and covered with Parafilm. The renal venous effluent was passed from the funnel to the perfusion reservoir through a timing cylinder, used to measure renal flow. The perfusate was recirculated. Perfusion pressure was measured at the level of the aorta using a pressure gauge and perfusion pressure was adjusted by a clamp in a low resistance parallel circuit. The kidneys were perfused at a constant perfusion pressure of 100 mm Hg unless otherwise stated. A stabilization period of 15–20 min was allowed before beginning the experiments. Samples at perfusate were taken directly from the reservoir at the beginning and end of each time period for measurement of inulin and renin activity.

The perfusate was a perfluorochemical emulsion (FC-43, Green Cross) containing perfluorotributylamine as an oxygen carrier (20%), hydroxyethylstarch (3%), and glucose (0.18%). Electrolytes were added in the following (mM) concentrations: Na^+, 130; K^+, 4.5; Ca^{2+}, 2.5; Mg^{2+}, 1.2; Cl^-, 117; HCO_3^-, 25. Urea and aldosterone were added to the standard perfusate in concentrations of 28 g/100 ml and 200 ng/100 ml, respectively. Also, [*carboxyl*-^{14}C]inulin (New England Nuclear) was added (1 μCi/100 ml) for measurement of GFR. The perfusate was gassed throughout the experiments with 95% O_2, 5% CO_2. The final pH of the perfusate was 7.40. The perfusion experiments were carried

out in a Plexiglas box at a constant temperature of 38°C.

Series I: Time control. Kidneys from six normal intact rats weighing 275 to 350 g were perfused as described above for three 20-min periods at a constant pressure of 100 mm Hg.

Series II: Isoproterenol. Nonclipped kidneys from six hypertensive rats, kidneys from six uninephrectomized rats, and the right kidney of five sham rats were perfused for two 10-min periods. Isoproterenol was added to the reservoir in a concentration of 500 n*M* after the first period.

Series III: Low perfusion. Nonclipped kidneys from six hypertensive rats, six uninephrectomized rats, and five sham rats were perfused for 10 min at 100 mm Hg and the perfusion pressure was lowered to 50 mm Hg for an additional 10 min.

Series IV: Low calcium. Nonclipped kidneys from six hypertensive rats and kidneys from six uninephrectomized rats were perfused for one 20-min period with the standard perfusate but sodium was substituted for calcium.

Analysis. Urine from the perfused kidneys was collected in preweighed tubes and urine volume was determined gravimetrically. Urine sodium and potassium concentrations were determined by flame photometry (Instrumentation Laboratories, Model 343). Urine and perfusate inulin concentrations were measured on a liquid scintillation counter (Tm Analytic, Model 6895) and GFR was calculated by dividing the rate of inulin excretion for a given time period by the mean perfusate inulin concentration for that time period. For measurements of perfusate renin activity 100-μl samples of perfusate containing EDTA were added to 900 μl of plasma from a nephrectomized animal to provide renin substrate for generation of angiotensin I. Perfusate samples and kidney extracts were dialyzed for 24 hr with a phosphate buffer (pH 5.3). Aliquots of 50 μl were incubated for 1 hr at 37°C in the presence of diisoprophylfluorophosphate to prevent breakdown of formed angiotensin I. Angiotensin I was measured by radioimmunoassay (14) using ^{125}I angiotensin I and antisera from New England Nuclear and angiotensin I standard from Sigma Chemical Company. Since the perfusate is recirculated measurements of renin activity reflect the cumulative renin secreted by the kidneys. To calculate renin secretion rate for a given time period the renin activity at the end and beginning of the period was subtracted, multiplied by the circuit volume, and divided by the number of minutes in the period.

Statistical evaluation. Statistical comparisons were made using either paired or unpaired *t* tests where appropriate. A *P* value of less than 0.05 was considered significant.

Results. Table I shows renal function and renin release of isolated kidneys from six normal rats perfused at a constant pressure of 100 mm Hg for three 20-min periods. The preparation is relatively stable for the 1-hr period with the exception of $U_{Na^+}\dot{V}$ which tends to increase over time. Renin release was stable during the first 40 min but tended to decrease during the last 20-min period, although not significantly. Renal flow is higher than in blood perfused kidney due to

TABLE I. RENAL FUNCTION AND RENIN RELEASE FROM ISOLATED PERFUSED KIDNEYS OF NORMAL RATS (n = 6)

	Time (min)		
	0–20	20–40	40–60
Perfusion pressure (mm Hg)	100	100	100
Renal flow (ml/min)	9.7 ± 0.5	10.4 ± 0.8	9.9 ± 0.3
GFR (ml/min)	0.33 ± 0.09	0.35 ± 0.04	0.33 ± 0.05
Urine flow (μl/min)	22 ± 4	26 ± 6	28 ± 8
$U_{Na^+}\dot{V}$ (μeq/min)	0.67 ± 0.06	0.72 ± 0.12	0.97 ± 0.16
$U_{K^+}\dot{V}$ (μeq/min)	0.12 ± 0.03	0.10 ± 0.02	0.14 ± 0.05
Renin secretion (ng AI/min)	10.6 ± 2.7	9.5 ± 1.1	6.2 ± 1.2

Note. Values are means ± SEM.

TABLE II. RENIN CONTENT OF NONCLIPPED KIDNEYS OF EIGHT 2K-1C HYPERTENSIVE RATS (HYPER), KIDNEYS OF EIGHT UNINEPHRECTOMIZED NORMOTENSIVE RATS (UN), AND THE RIGHT KIDNEYS OF EIGHT SHAM-OPERATED CONTROL RATS (SHAM)

	UN	HYPER	SHAM
Renin content (μg AI/Hr)	18 ± 2	5 ± 1*	22 ± 2
Body weight (g)	342 ± 14	333 ± 7	341 ± 12
Kidney weight (g)	2.1 ± 0.2	2.1 ± 0.2	1.4 ± 0.2*,**
Systolic blood pressure (mm Hg)	115 ± 4	167 ± 7*	115 ± 5

Note. Values are means ± SEM.
* $P < 0.001$ from uninephrectomized normotensive (UN).
** $P < 0.05$ from UN and HYPER.

the lower viscosity of the fluorocarbon emulsion compared to blood (15). Na^+ reabsorption, averaged 98% of the filtered load of Na^+ throughout the period of study. It should be pointed out that renal flow in this preparation is much closer to that of the intact animal than in kidney preparations perfused with albumin containing electrolyte solutions. Furthermore, the oxygen carrying capacity of the fluorocarbon emulsion is five times greater than that of standard electrolyte perfusates and this helps preserve the ability of the isolated kidneys to transport sodium (15).

Table II compares the renin content of the nonclipped kidney of 2K-1C hypertensive rats with kidneys from uninephrectomized rats and sham-operated rats. Renin content of kidneys from hypertensive rats averaged 28% of the renin content of uninephrectomized normotensive rats ($P < 0.001$). Also shown in Table II, body weights of the three groups of animals were not significantly different. The kidney weights of both the uninephrectomized rats and nonclipped kidneys of hypertensive rats were 50% greater than kidneys of sham-operated rats ($P < 0.001$). Systolic blood pressure measured $3\frac{1}{2}$ to 4 weeks after clipping or nephrectomy averaged 52 mm Hg higher in clipped animals compared to the nephrectomized and sham-operated rats ($P < 0.001$). A comparison of basal renal function of perfused nonclipped kidneys of 2K-1C rats and uninephrectomized rats is shown in Table III. Renal flow was 39% lower in the kidneys of hypertensive rats compared to those of uninephrectomized rats when both groups were perfused at a constant pressure of 100 mm Hg ($P < 0.01$). Therefore, renal vascular resistance was higher in the kidneys from hypertensive rats. GFR, urine flow, and the rates of excretion of sodium and potassium were all significantly less in the nonclipped kidneys of hypertensive rats. Renal flow and GFR were significantly lower in kidneys from sham-operated animals compared to kidneys from uninephrectomized rats ($P < 0.05$) but were similar to the nonclipped kidney of hypertensive rats. However, when compared on the basis of kidney weight, renal function is lower in the

TABLE III. COMPARISON OF RENAL FUNCTION OF ISOLATED KIDNEYS PERFUSED AT 100 mm Hg

	UN	HYPER	SHAM
Renal flow (ml/min)	15.2 ± 1.1	9.3 ± 0.6**	9.3 ± 0.9*
GFR (ml/min)	0.45 ± 0.05	0.28 ± 0.04**	0.30 ± 0.02*
Urine flow (μl/min)	20 ± 2	16 ± 2*	21 ± 3***
$U_{Na^+}\dot{V}$ (μeq/min)	0.64 ± 0.08	0.47 ± 0.09*	0.55 ± 0.08
$U_{K^+}\dot{V}$ (μeq/min)	0.13 ± 0.03	0.09 ± 0.01*	0.14 ± 0.03***

Note. Values are means ± SEM. UN = uninephrectomized, $n = 6$; HYPER = nonclipped kidney, $n = 6$; SHAM = sham operated, $n = 5$.
* $P < 0.05$.
** $P < 0.01$ from UN.
*** $P < 0.05$ from HYPER.

nonclipped kidneys from hypertensive rats than in the other two groups. Because of this disparity in kidney weights between the groups (Table II) it would appear that kidneys of uninephrectomized rats serve as a better comparison for the hypertensive kidneys than do kidneys of sham-operated animals. Figure 1 shows the effect of isoproterenol (500 nM) on renin release from the perfused kidneys. Renin release averaged 13 ± 4 ng AI/min (period C) from kidneys of nephrectomized rats and increased to 35 ± 10 ng AI/min (period E) when the β agonist was added to the perfusion reservoir ($P < 0.05$). Renin release averaged 1 ± 1 ng AI/min from the nonclipped kidney of hypertensive rats, (period C) a value not different from 0 (undetectable from three of six kidneys). Isoproterenol increased renin release to 11 ± 4 ng/min (period E, $P < 0.05$).

Figure 2 shows the effect of reducing perfusion pressure on renin release in the perfused kidneys. Renin release was 9 ± 2 ng AI/min from kidneys of uninephrectomized rats perfused at 100 mm Hg and increased to 25 ± 4 when perfusion pressure was reduced to 50 mm Hg ($P < 0.01$). Renin release averaged 1 ± 1 ng AI/min from kidneys of hypertensive rats (undetectable in four of six kidneys) at a perfusion pressure of 100 mm Hg and was unchanged when perfusion pressure was reduced to 50 mm Hg. In kidneys from sham-operated animals reducing perfusion pressure from 100 to 50 mm Hg

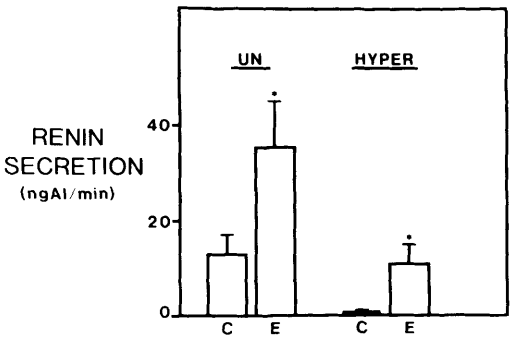

FIG. 1. Effect of isoproterenol (500 nM) on renin released from the nonclipped kidney of 2K-1C rats (HYPER) and kidneys of uninephrectomized rats (UN) perfused for two 10-min periods at 100 mm Hg. Values are means + 1 SEM. C = control period, E = experimental period in which isoproterenol was added. $n = 6$, $^*P < 0.05$ from C.

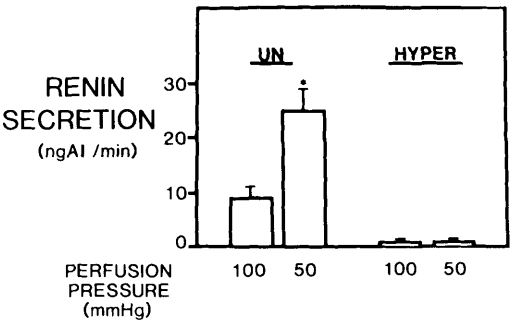

FIG. 2. Effect of low prefusion pressure on renin release from nonclipped kidneys of 2K-1C rats (HYPER) and kidneys of uninephrectomized rats (UN). Kidneys were perfused *in vitro* for two 10-min periods. Values are means + 1 SEM, $n = 6$, $^*P < 0.01$ from 100 mm Hg period.

increased renin secretion from 11 ± 2 to 30 ± 4 ng AI/min ($n = 5$, $P < 0.01$) and isoproterenol increased renin secretion from 16 ± 5 to 47 ± 9 ng AI/min ($n = 5$, $P < 0.01$). These data are not shown in the figures.

A comparison of renin release from kidneys perfused with either the normal perfusate (Ca^{2+}, 2.5 mM) or a low calcium perfusate (0.0 mM) is shown in Fig. 3. Renin release averaged 9 ± 3 ng AI/min from kidneys of uninephrectomized rats perfused at 100 mm Hg with the normal perfusate (Ca^{2+}, 2.5 mM) and 58 ± 16 ng AI/min with the low calcium perfusate ($P < 0.01$, unpaired t test). Renin release from nonclipped kidneys of hypertensive rats at a perfusion pressure of 100 mm Hg was near zero using either the normal or low calcium perfusate.

Discussion. The results demonstrate that the nonclipped kidneys of 2K-1C hypertensive rats exhibit lower rates of renin release than kidneys of sham or uninephrectomized control rats when perfused under similar conditions. In addition, the kidneys of hypertensive rats failed to release renin in response to low perfusion pressure or low perfusate calcium. The nonclipped kidneys of 2K-1C rats showed a significant increase in renin release in response to β-receptor stimulation with isoproterenol but the absolute magnitude of the response was much less than the response to isoproterenol in perfused kidneys of sham or uninephrectomized rats. It is reasonable to suggest that in

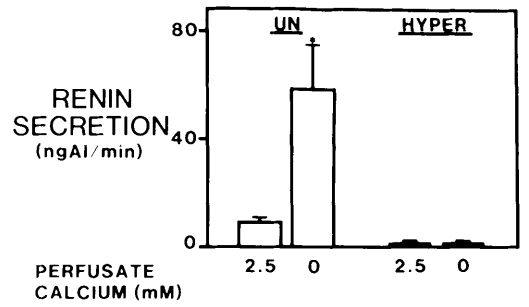

FIG. 3. Comparison of renin release in kidneys perfused at 100 mm Hg for 10 min with a perfusate containing either 2.5 or 0 m*M* calcium. Values are means + 1 SEM; UN, uninephrectomized; HYPER, nonclipped kidneys of 2K-1C rats; $n = 6$; $^*P < 0.01$ from 2.5 m*M*.

the intact animal high circulating levels of angiotensin II produced by the clipped kidney could reduce renal function (5, 17, 18) and inhibit renin release from the nonclipped kidney (8).

However, the angiotensin antagonist saralasin has no effect on renal vascular resistance in isolated perfused nonclipped kidneys (4) which suggests that the levels of angiotensin II in this preparation are very low. Therefore, an inhibitory action of angiotensin on renin release cannot explain the depressed rate of renin secretion in the isolated perfused nonclipped kidney unless chronic elevations in AII contribute to the decrease in renin content of the nonclipped kidneys. The lower renin content of nonclipped kidneys compared to the kidneys of the control rats (Table II) would appear to account for a major part of the lower rate of renin release from the hypertensive kidneys and the poor responses to the stimuli employed in the present study. DeJong (2) and Naftilan and Oparil (7) have demonstrated that renin content of the nonclipped kidneys of 2K-1C hypertensive rats is lower than normal. They have also shown that slices of nonclipped kidneys of 2K-1C rats release less renin than kidney slices from normal rats (2, 7). A direct relationship between renin content and release has also been demonstrated in isolated perfused kidneys where changes in renin content were produced by altering sodium intake (19, 20). Fray showed that sodium loading which reduced renin content to approximately 35% of the value seen in rats on a low salt diet markedly reduces basal renin release from isolated perfused kidneys (19). Also, the perfused kidneys of salt loaded kidneys failed to increase renin release in response to low perfusion pressure or isoproterenol (19) and the response to a low calcium perfusate was attenuated (21). Although the mechanism(s) for the reduced renin content by sodium loading or 2K-1C hypertension is not known it is reasonable to suggest that the reduced renin content of the nonclipped kidney of 2K-1C hypertensive rat is a major contributing factor to the reduction in basal renin release observed in the present study. It should be pointed out that the absolute magnitude of the renin response to β-receptor stimulation with isoproterenol (Fig. 1) is proportional to the renin content of the two groups of kidneys (Table II).

This also demonstrates that the nonclipped kidneys of 2K-1C rats are capable of releasing renin under some conditions. The complete lack of any detectable renin response to low perfusion pressure or low perfusate calcium in nonclipped kidneys suggests that factors other than reduced renin content may contribute to the reduced rate of renin release. One possible explanation can be derived from the work of Rostand *et al.* (4). They showed that isolated perfused nonclipped kidneys of 2K-1C rats with hypertension of 3- to 4-weeks duration exhibit an increased renal vascular resistance and reduced GFR. Histological studies revealed vascular hypertrophy and arteriolar narrowing in the nonclipped kidneys. They also found that basal renin release from isolated perfused nonclipped kidneys was very low at a perfusion pressure of 100 mm Hg (4). The present study in perfused kidneys was carried out under conditions similar to those in their study and the data presented here on renal function of the nonclipped kidneys of 2K-1C rats (Table III) support their findings (4). Based on these studies an additional mechanism to account for the lack of a renin response to low perfusion pressure in the nonclipped kidney of 2K-1C rats can be proposed. Since the renal vascular receptor functions as a stretch receptor (10) the vascular hypertrophy observed in the nonclipped kidneys might modify the ability of the receptor to stretch or reduce stretch with changes in perfusion pressure. Thus, the ability of the isolated perfused kidney to release

renin in response to low perfusion pressure might be impaired. This is analogous to the situation where a vasodilator, such as paparerine, blocks the renin response to low perfusion pressure in the nonfiltering kidney (22). In the present study, the experiments with the low calcium perfusate were used to test this hypothesis. There is substantial evidence that stimuli for renin release such as low perfusion pressure act by reducing intracellular calcium of the juxtaglomerular cells (23). Cellular calcium ions may act as a common pathway by which the intrarenal receptors exert their effect on renin secretion (24). Based on this hypothesis, lowering perfusate calcium concentration should stimulate renin secretion by a mechanism which is dependent on renin stores but not dependent on the integrity of the vascular stretch receptor.

When kidneys of uninephrectomized normotensive rats were perfused with a low calcium perfusate renin secretion was sixfold greater than renin release from kidneys perfused with a 2.5 m*M* solution (Fig. 3) while the nonclipped kidneys of 2K-1C hypertensive rats failed to release significant amounts of renin in response to the low calcium perfusate. Although it is likely that the changes in the renal vasculature observed in the nonclipped kidney of 2K-1C hypertensive rats would result in some change in the ability of the baroreceptor to stimulate renin secretion these results suggest that a reduction in renin content of the nonclipped kidneys is the major contributing factor to the depressed rate of renin release observed in the present study. The fact that isoproterenol produced a significant increase in renin secretion in the nonclipped kidneys while low calcium gave no response might also suggest that chronic hypertension leads to changes in calcium permeability in the juxtaglomerular cells.

It is interesting that both salt loading (20, 21) and renal hypertension (2, 7) can result in reductions in renin content of the kidneys. Although the exact mechanisms responsible for these reductions are unclear, the mechanisms are apparently much different in the two experimental situations. In the 2K-1C rat arterial pressure and plasma renin activity are markedly elevated at least 6 weeks after clipping while plasma volume may be normal or slightly decreased (25). The reduction in renin content in the nonclipped kidney apparently results from the chronic overperfusion of the nonclipped kidney since the renin content of the clipped kidney is normal (2, 7). It would be interesting to see if sodium depletion in 2K-1C rats would result in an increase in renin content of the nonclipped kidney and improve the responsiveness of the renal vascular receptor to changes in perfusion pressure. These studies are important in determining the contribution of the nonclipped kidney to the development and maintenance of hypertension in this experimental model.

The author acknowledges the expert technical assistance of Mr. William Fay and Ms. Sheryl Brenner. This study was supported by the Suncoast Chapter of the American Heart Association, Florida Affiliate.

1. Göthberg G, Folkow B. "Structural autoregulation" of blood flow and GFR in the two renal vascular beds from two-kidney, one-clip renal hypertensive rats, as compared with kidneys from uni-nephrectomized and intact normotensive rats. Acta Physiol Scand **118**:141–148, 1983.
2. DeJong W. Release of renin by rat kidney slices; relationship to plasma renin after desoxycorticosterone and renal hypertension. Proc Soc Exp Med **130**: 85–88, 1969.
3. Davis JO. The pathogenesis of chronic renovascular hypertension. Circ Res **40**(5):439–444, 1977.
4. Rostand SG, Lewis D, Watkins JB, Huang W, Navar LG. Attenuated pressure natriuresis in hypertensive rats. Kidney Int **21**:330–338, 1982.
5. Huang W, Ploth DW, Navar LG. Angiotensin-mediated alterations in nephron function in Goldblatt hypertensive rats. Amer J Physiol **243**(12):F553–F560, 1982.
6. Ploth DW, Roy RN, Huang W, Navar LG. Impaired renal blood and cortical pressure autoregulation in contralateral kidneys of Goldblatt hypertensive rats. Hypertension **3**:67–74, 1981.
7. Naftilan AJ, Oparil S. Effects of sodium intake and Goldblatt hypertension on renin release in rat kidney slices. Amer J Physiol **240**(9):F501–F507, 1981.
8. Shade RE, Davis JO, Johnson JA, Gotshall RW, Spielman WS. Mechanism of action of angiotensin II and antidiuretic hormone on renin secretion. Amer J Physiol **224**:926–929, 1973.
9. Davis JO, Freeman RH. Mechanisms regulating renin release. Physiol Rev **56**:1–56, 1976.
10. Fray JCS. Stretch receptor model for renin release with evidence from perfused rat kidney. Amer J Physiol **231**(3):936–944, 1976.

11. Pfeffer JM, Pfeffer MA, Frohlich ED. Validity of an indirect tail-cuff method for determining systolic arterial pressure in unanesthetized normotensive and hypertensive rats. J Lab Clin Med **78**(6):957–962, 1971.
12. Blendstrup K, Leyssac PP, Poulsen K, Skinner SL. Characteristics of renin release from isolated superfused glomeruli in vitro. J Physiol **246**:653, 1975.
13. Nishiistutsuji-Uwo JM, Ross BO, Krebs HA. Metabolic activities of the isolated perfused rat kidney. Biochem J **103**:852–862, 1967.
14. Sealey JE, Laragh JH, Gerten-Barnes J, Accto RM. The measurement of plasma renin activity in man. In: Laragh JH, ed. Hypertension Manual. New York, Dunn-Donnelly, p621, 1974.
15. Franke H, Mályusz M, Runge D. Improved sodium and PAH transport in the isolated fluorocarbon-perfused rat kidney. Nephron **22**:423–431, 1978.
16. Bello-Reuss E, Colindres RE, Pastoriza-Munoz E, Mueller RA, Gottschalk CW. Effects of acute unilateral renal denervation in the rat. J Clin Invest **56**: 208–217, 1975.
17. Huang W, Ploth DW, Navar LG. Effects of saralasin infusion on bilateral renal function in two-kidney, one-clip Goldblatt hypertensive rats. Clin Sci **62**: 573–579, 1982.
18. Ichikawa I, Ferrone RA, Duchin KL, Manning M, Dzau VJ, Brenner BM. Relative contribution of vasopressin and angiotensin II to the altered renal microcirculatory dynamics in two-kidney Goldblatt hypertension. Circ Res **53**:592–602, 1983.
19. Fray JCS. Mechanism of increased renin release during sodium deprivation. Amer J Physiol **234**: F376–F380, 1978.
20. Nakane H, Nakane Y, Corvol P, Menard I. Sodium balance and renin regulation in rats: Role of intrinsic renal mechanisms. Kidney Int **17**:607–614, 1980.
21. Fray JCS. Stimulation of renin release in perfused kidney by low calcium and high magnesium. Amer J Physiol **232**(4):F377–F382, 1977.
22. Witty RT, Davis JO, Johnson JA, Prewitt RL. Effects of papaverine and hemorrhage on renin secretion in the non-filtering kidney. Amer J Physiol **221**:1666–1671, 1971.
23. Fray JCS. Stimulus-secretion coupling of renin: Role of hemodynamics and other factors. Circ Res **47**: 485–492, 1980.
24. Fray JCS, Lush DJ, Valentine AND. Cellular mechanisms of renin secretion. Fed Proc **42**:3150–3154, 1983.
25. Sen S, Smeby RR, Bumbus FM, Turcotte JG. Role of renin-angiotensin system in chronic renal hypertensive rats. Hypertension **1**:427–434, 1979.

Received November 5, 1984. P.S.E.B.M. 1985, Vol. 179.
Accepted January 28, 1985.