SUMMARY  We studied postclamp renal artery pressure and renin release in eight conscious dogs with one-kidney Goldblatt hypertension. On normal sodium intake, intrarenal blockade of angiotensin II with Sar'-Ala₈-angiotensin II (P-113, saralasin acetate) markedly decreased postclamp renal artery pressure and increased renin release during the first 5 days after renal artery constriction. We found that 10–14 days after renal artery constriction, the maintenance of postclamp renal artery pressure and negative feedback on renin release became markedly less dependent on angiotensin II, as shown by almost no change in postclamp renal artery pressure or renin release with intrarenal blockade of angiotensin II. At this stage of our study the dogs were given a sodium diet of <5 mEq/day and we found that within 5–10 days intrarenal blockade of angiotensin II once again markedly decreased postclamp renal artery pressure and increased renin release. These observations support the concept of an angiotensin II-sodium interdependent negative feedback mechanism for renin release.

EXPERIMENTAL hypertension produced by partial constriction of the renal artery was first accomplished in 1934. 1 Renin release from the kidney was demonstrated in 1940. 2-3 Since then a great effort has been expended in defining the mechanisms controlling renin release. These mechanisms have recently been reviewed and involve both stimulation and inhibition. 4

It has been demonstrated many times in the dog that partial constriction of the renal artery to the remaining kidney of a uninephrectomized dog initially increases plasma renin activity, but after a few days the plasma renin activity returns to normal. 5-7 Thus, the dog appears to have an intrarenal mechanism for controlling the output of renin from the kidney. In the conscious dog, renal autoregulation occurs immediately after partial renal artery constriction; however, within 24 hours renal vasoconstriction is present and the postclamp renal artery pressure has returned toward normal. This increase in postclamp renal artery pressure is associated with a decrease in peripheral plasma renin activity. 5 Intrarenal infusion of vasodilators (dopamine, isoproterenol, acetylcholine, and nitroprusside) in doses small enough to decrease postclamp renal artery pressure without lowering systemic blood pressure releases large quantities of renin. This suggests that the increase in postclamp renal artery pressure within 24 hours after partial renal artery constriction produces a negative feedback effect on renin release. 8 In the first 48-hour period after partial renal artery constriction, blockade of the intrarenal renin-angiotensin system with the angiotensin-converting enzyme inhibitor SQ 20881, and with the angiotensin II antagonist, Sar'-Ala₈-angiotensin II (P-113, saralasin acetate), produces a marked decrease in postclamp renal artery pressure. Concomitantly, plasma renin activity increases markedly. 9 Converting enzyme has been found in the kidney 10 and conversion of angiotensin I to angiotensin II within the kidney 11 has been demonstrated. 12 This evidence supports the concept of an intrarenal negative feedback mechanism dependent on conversion of angiotensin I to angiotensin II within the kidney.

The present study was designed to determine whether the negative feedback mechanism on renin release is the same as the early angiotensin II-dependent mechanism in the canine chronic one-kidney Goldblatt model. We found that in the conscious dog, intrarenal vasoconstriction and the negative feedback mechanism became progressively less dependent on angiotensin II with time. By the 14th day of unilateral partial renal artery constriction very little change in postclamp renal artery pressure and peripheral renin activity occurred in response to intrarenal blockade of angiotensin II. In contrast, after sodium restriction for 5–10 days, intrarenal vasoconstriction once again became angiotensin II-dependent. Thus, there exists an angiotensin II-sodium interdependent negative feedback mechanism for renin release in the conscious dog with chronic one-kidney Goldblatt hypertension.
NEGATIVE FEEDBACK MECHANISM FOR RENIN RELEASE/Ayers et al.

Methods

Female foxhounds weighing 17-22 kg were studied. During periods of normal sodium intake the dogs received approximately 82 mEq of sodium per day. This was accomplished by giving a diet containing <5 mEq of sodium per day supplemented with 77 mEq of intravenous sodium as 0.9% sodium chloride daily. During periods of low sodium intake, the diet contained <5 mEq of sodium. The dogs were prepared surgically under pentobarbital anesthesia. The trachea was intubated and under sterile conditions a laparotomy was performed and the right kidney was removed. Teflon catheters (0.974-cm outer diameter) were placed suprarenally in the aorta and inferior vena cava through the severed right renal artery and vein. A steel wire was used to puncture the aorta and served as a guidewire to insert a Teflon catheter (0.025-cm outer diameter) into the left renal artery as previously described. A stainless steel screw clamp was placed around the base of the left renal artery. During continuous monitoring of the aortic and postclamp renal artery pressures with a P23D Statham strain gauge and Sanborn recorder, a gradient of 35-45 mm Hg was produced across the clamp. The catheters were then exteriorized through a stab wound near the right costovertebral angle and the laparotomy incision was closed.

The dogs were maintained on 83 mEq of sodium per day beginning with the day of surgery. All experiments were performed while the dogs were awake in a canvas sling, which allowed them either to stand or lie down. They were calm and comfortable in this position. All blood samples were collected from the aortic catheter for measurement of plasma renin activity. The angiotensin II antagonist, Sar1-Ala8-angiotensin II, was infused directly into the renal artery while the aortic pressure was monitored. The initial infusion dose was 0.5 μg/kg per min. The mean aortic pressure was monitored continuously during the infusion and the postclamp renal artery pressure was monitored at 5-minute intervals. The initial dose was infused into the renal artery for 30 minutes, and then increased by 0.5 μg/kg per min increments until a barely detectable decrease was noted in the aortic pressure. At this time a marked decrease in postclamp renal artery pressure was present in periods I and III (see Results). An aortic blood sample for determination of plasma renin activity was obtained after 30 minutes of infusion at the highest dose level used. Sar1-Ala8-angiotensin II infusion then was discontinued and the postinfusion aortic and postclamp renal artery pressures were monitored. The maximum dose of Sar1-Ala8-angiotensin II given intrarenally was 2.0 μg/kg per min.

Intrarenal infusion of Sar1-Ala8-angiotensin II was repeated twice weekly until there was only a small decrease in postclamp renal artery pressure with little renin release in face of complete angiotensin II blockade. The dogs were then changed to a low sodium diet containing <5 mEq of sodium per day, and a Sar1-Ala8-angiotensin II infusion was given into the renal artery twice weekly until there was a marked decrease in postclamp renal artery pressure. At this time a significant increase in peripheral plasma renin activity occurred. The dogs were then recy-
tional cycles of normal or low sodium intake, ending on the 45th day of study.

Eight dogs were studied through the initial normal sodium cycle. This normal sodium cycle was divided into an early period (period I), in which postclamp renal artery pressure dropped markedly and plasma renin activity increased after intrarenal angiotensin II blockade (0–5 days after renal artery constriction) and a chronic period (period II), 10–22 days after renal artery constriction, in which there was little decrease in postclamp renal artery pressure or increase in plasma renin activity with blockade of intrarenal angiotensin II. Between days 5 and 10 intermediate changes in postclamp renal artery pressure and renin release were found with intrarenal infusion of Sar'–Ala8-angiotensin II. The low sodium cycle (period III) was completed by six dogs.

During period I (Fig. 2) intrarenal angiotensin II blockade with Sar'–Ala8-angiotensin II in eight conscious one-kidney Goldblatt hypertensive dogs produced a decrease in postclamp renal artery pressure from 90 ± 6.6 mm Hg to 52 ± 6.3 mm Hg (P < 0.01). Plasma renin activity increased from 7.8 ± 4.4 ng/ml per hour to 36.8 ± 6.8 ng/ml per hour (P < 0.01). Mean aortic pressure was not significantly changed by intrarenal infusion of Sar'–Ala8-angiotensin II (132 ± 4.5 vs. 127 ± 3.8 mm Hg, P > 0.3).

At 10–22 days after renal artery constriction (period II, Fig. 3) the postclamp renal artery pressure of dogs on normal sodium intake remained nearly the same with blockade of intrarenal angiotensin II. However, the small decrease of 5 ± 1.3 mm Hg from 99 ± 7.2 mm Hg to 94 ± 7.8 mm Hg was significant, P < 0.01. Aortic pressure was not changed significantly (138 ± 5.3 vs. 131 ± 4.2 mm Hg, P > 0.3) by intrarenal Sar'–Ala8-angiotensin II. Plasma renin activity was also not affected by Sar'–Ala8-angiotensin II infusion (3.4 ± 1.8 to 10.5 ± 6.4 ng/ml per hour, P > 0.3).

Six dogs survived period II and were started on a low sodium diet (period III). Intrarenal vasoconstriction was restored to an angiotensin II-dependent state within 5–10 days, as manifested by a decrease in postclamp renal artery pressure and increase in plasma renin activity with intrarenal angiotensin II blockade (Fig. 4). Postclamp renal artery pressure decreased from 98 ± 8.9 to 64 ± 9.6 mm Hg (P < 0.01). Plasma renin activity increased from 10.8 ± 5.5 to 48.5 ± 18.3 ng angiotensin I/ml per hour (P < 0.05). Aortic pressure was not changed significantly by angiotensin II blockade (134 ± 6.8 vs 132 ± 7.6 mm Hg, P > 0.3).
Three of the dogs completed two additional cycles of normal and low sodium intake, and the same angiotensin II-sodium interdependent vasoconstriction was demonstrated.

Discussion

The stimuli controlling the release of renin have been extensively studied and recently reviewed. The most important mechanisms which stimulate renin release are (1) the pressure-sensing mechanism, (2) the quantity or concentration of sodium presented to the macula densa in the distal convoluted tubule, (3) stimulation of the juxtaglomerular apparatus directly by the adrenergic neurotransmitter, norepinephrine, and (4) serum sodium and potassium concentrations.

When the renal artery is partially constricted, the renal vascular bed responds immediately by vasodilating, thereby maintaining normal blood flow over a wide range of pressure (autoregulation). Renin release by the kidney is linear over the pressure range of autoregulation. Autoregulation can be blocked by papaverine at the level of the afferent arteriole. This suggests that the intrarenal pressure-sensing mechanism is a vascular phenomenon within 24 hours after partial renal artery constriction, postclamping renal artery pressure increases toward normal and renal blood flow decreases significantly. Vasodilation by the renal resistance vessels is paralleled by a decrease in plasma renin activity.

In one study, renal blood flow initially decreased following renal artery stenosis, but after 8 days returned steadily to near normal levels. This was attributed to the development of collateral circulation. Blockade of intrarenal angiotensin II with Sar-^Ala^-angiotensin II or blockade of angiotensin II formation with SQ 20881 results in a marked decrease in post-clamping renal artery pressure and a marked increase in peripheral plasma renin activity. Converting enzyme has been demonstrated to be present within the kidney, and the intrarenal conversion of angiotensin I to angiotensin II exists. These observations support the concept of an intrarenal negative feedback mechanism controlling renin release from the kidney. Pertinent also is the fact that while the kidney with a stenotic artery responds to changes in aortic pressure the aortic pressure level associated with renin release is markedly higher than in the normal dog. The "reset" upward of the renal baroreceptor for renin release in renovascular hypertension is probably influenced by renal arteriolar vasoconstriction as described in the current experiments as well as by the process of renal artery constriction itself.

The negative feedback on renin release in one-kidney dog renovascular hypertension may be due to a direct effect of angiotensin II on the juxtaglomerular apparatus or to the increase in the postclamping renal artery pressure brought about by the renal arteriolar vasoconstriction. The decrease in plasma renin activity with infusion of angiotensin II and angiotensin III suggests that the negative feedback effect may be direct. However, intrarenal infusion of vasodilators such as dopamine, acetylcholine, nitroprusside, and isoproterenol in doses too small to decrease peripheral arterial pressure markedly decrease post-clamping renal artery pressure and increase renin release. In normal dogs and dogs in balance on a low sodium intake, intrarenal blockade of angiotensin II and converting enzyme results in an approximately 2-fold rise in peripheral plasma renin activity without change in renal perfusion pressure. In the present experiment, a 4- to 5-fold increase in peripheral plasma renin activity occurred in the acute phase and in the chronic phase during low sodium intake, suggesting that the associated decrease in postclamping renal artery pressure provides an additional stimulus for renin release. It has been demonstrated that a change in perfusion pressure is a major stimulus for renin release. Therefore, it is highly probable that the reverse, an increase in post-clamping renal artery pressure and possibly an increase in pressure at the level of the afferent arteriole, has a strong negative feedback effect on renin release.

The present experiments show that the initial renal arteriolar vasoconstriction is dependent on intrarenal angiotensin II, but after a few days there is progressively less renin release and less decrease in postclamping renal artery pressure with angiotensin II blockade. Within 2 weeks the amount of renin released with angiotensin II blockade is not significant. Sodium restriction reverses this process so that renal vasoconstriction and the negative feedback mechanism are again angiotensin II-dependent. This study demonstrates a renin angiotensin II-sodium independent mechanism controlling post-clamping renal artery pressure and renin release. The basic characteristics of the sodium dependency are not clear. It is not evident from this study how the arteriolar smooth muscle distal to a clamp reacts to a change in dietary sodium intake and possibly total body sodium content. Whether these same mechanisms are operative in the two-kidney renovascular hypertension model is unknown.

The decrease in plasma renin activity from the acute phase to the chronic phase of hypertension in the one-kidney Goldblatt hypertensive dog raises the question of whether the decrease was due to renal renin depletion. There are many studies which show that renal renin content is near normal in one-kidney Goldblatt hypertension in both the dog and the rat. In the rat and dog with two kidney Goldblatt hypertension the kidney with the stenosed artery is increased, the contralateral kidney has a decreased renin content. In addition the kidney with renal artery constriction is capable of responding to appropriate stimuli by augmentation of renin release, convincing evidence that renin depletion is not present. In the present experiment there is a period of about 5 days after the plasma renin activity returns to normal after renal artery stenosis that angiotensin II blockade results in the release of large quantities of renin from the kidney, thus demonstrating that during this period the decreased plasma renin activity is due to negative feedback rather than to renal renin depletion.

The clinical significance of the angiotensin II-sodium independent negative feedback mechanism remains to be clarified. It may regulate the amount of renin released in response to partial obstruction of the renal vascular bed, thus determining the quantity of circulating renin and
perhaps also the severity of the hypertensive process. This mechanism may also determine, at least in part, the spectrum of plasma renin activity in patients with essential hypertension.

References
Intrarenal renin-angiotensin-sodium interdependent mechanism controlling postclamp renal artery pressure and renin release in the conscious dog with chronic one-kidney Goldblatt hypertension.

C R Ayers, R E Katholi, E D Vaughan, Jr, R M Carey, H M Kimbrough, Jr, M R Yancey and C L Morton

doi: 10.1161/01.RES.40.3.238

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1977 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/40/3/238