

Intrarenal Role of Angiotensin II

HOMEOSTATIC REGULATION OF RENAL BLOOD FLOW IN THE DOG

By Ronald H. Freeman, James O. Davis, Stephen J. Vitale, and J. Alan Johnson

ABSTRACT

The analogue, 1-sarcosine-8-alanine-angiotensin II, a specific competitive antagonist of the vascular action of angiotensin II in the rat, blocked the decrease in renal blood flow after a single intrarenal injection of angiotensin II but not after an injection of norepinephrine in normal dogs, in a sodium-depleted dog, and in a dog with thoracic vena caval constriction. Infusion of the analogue at $0.2 \mu\text{g}/\text{kg min}^{-1}$ into the renal artery consistently increased renal blood flow and decreased renal resistance in both sodium-depleted dogs and dogs with vena caval constriction but did not alter these functions in normal dogs. In five sodium-depleted dogs, renal blood flow increased from an average control value of $196 \pm 5 \text{ ml}/\text{min}$ to 222 ± 11 and $246 \pm 12 \text{ ml}/\text{min}$ after 20 and 40 minutes of antagonist infusion ($P < 0.01$ and $P < 0.005$, respectively); renal resistance fell from $0.71 \pm 0.03 \text{ mm Hg}/\text{ml min}^{-1}$ to 0.62 ± 0.06 and $0.54 \pm 0.03 \text{ mm Hg}/\text{ml min}^{-1}$ ($P < 0.005$ for the 40-minute value). In five dogs with vena caval constriction, renal blood flow increased from $143 \pm 16 \text{ ml}/\text{min}$ to 178 ± 23 and $190 \pm 19 \text{ ml}/\text{min}$ after 20 and 40 minutes of analogue infusion ($P < 0.02$ and $P < 0.005$, respectively); renal resistance fell from $0.90 \pm 0.14 \text{ mm Hg}/\text{ml min}^{-1}$ to 0.73 ± 0.14 and $0.64 \pm 0.10 \text{ mm Hg}/\text{ml min}^{-1}$ ($P < 0.01$ and $P < 0.02$, respectively). Mean arterial blood pressure was not altered significantly by the analogue when it was infused at $0.2 \mu\text{g}/\text{kg min}^{-1}$. Infusion of the analogue at $2.0 \mu\text{g}/\text{kg min}^{-1}$ decreased arterial blood pressure and renal resistance and increased renal blood flow in five sodium-depleted dogs and in three dogs with vena caval constriction. These observations suggest an important intrarenal role for angiotensin II in the homeostatic regulation of renal blood flow in sodium-depleted dogs and in dogs with vena caval constriction.

KEY WORDS
renal resistance

angiotensin II analogue
sodium depletion

angiotensin II antagonist
vena caval constriction

Recent evidence indicates that the renin-angiotensin system participates in the maintenance of arterial blood pressure in dogs subjected to thoracic inferior vena caval constriction or to sodium depletion (1, 2). A specific competitive antagonist of angiotensin II, 1-sarcosine-8-alanine-angiotensin II, significantly depresses mean arterial blood pressure and aldosterone secretion rate in these dogs when it is infused intravenously despite a concomitant increase in plasma renin activity; however, the antagonist has no appreciable influence on arterial blood pressure or plasma renin activity in normal dogs. Pals and his associates (3) were first to demonstrate that this angiotensin II analogue acts as a competitive antagonist of angiotensin II on vascular smooth muscle in the rat and the rabbit, and Brunner et al. (4) used the analogue to show that angiotensin II is involved in the pathogenesis of experimental two-kidney Goldblatt hypertension in the rat.

In the studies of steroid secretion mentioned above (1, 2), adrenal blood flow increased, reflecting the decrease in vascular resistance caused by the angiotensin II antagonist. Since renal blood flow is decreased in dogs with vena caval constriction and in sodium-depleted dogs, it has been hypothesized that endogenous angiotensin II combines with specific receptors in the renal vascular bed to effect an elevation in renal resistance and to help maintain arterial blood pressure in the presence of a reduced cardiac output. To evaluate this hypothesis, the competitive antagonist of angiotensin II, 1-sarcosine-8-alanine-angiotensin II, was infused into the renal artery of normal and sodium-depleted dogs and of dogs with thoracic vena caval constriction. In addition, the ability of this antagonist to eliminate the intrarenal vascular actions of exogenous angiotensin II amide (Hypertensin, Ciba) or norepinephrine was evaluated.

Methods

Twenty-two female mongrel dogs weighing 14–25 kg were used in this study. With the exception of those dogs undergoing sodium depletion, each dog received a

From the Department of Physiology, University of Missouri School of Medicine, Columbia, Missouri 65201.

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diet which provided 65 mEq of sodium and 55 mEq of potassium daily. Water was available ad libitum. The dogs were housed individually in metabolism cages, and urine samples were collected each morning for the determination of daily sodium excretion in the sodium-depleted dogs and in the dogs with vena caval constriction. The dogs were fed in the late afternoon; all experiments were performed with the dogs in the postabsorptive state. Four different experiments were conducted to determine the effects of the angiotensin II antagonist.

EXPERIMENT 1: EFFECTS OF THE ANGIOTENSIN II ANTAGONIST DURING INTRARENAL INFUSION OF ANGIOTENSIN II AND NOREPINEPHRINE IN NORMAL DOGS

The five normal dogs used in this experiment were maintained for several days on the standard diet of 65 mEq of sodium and 55 mEq of potassium per day. On the morning of the experiment, each dog was anesthetized with sodium pentobarbital (30 mg/kg, iv). A catheter (Fr 8 polyvinyl chloride) was placed in the right femoral artery, and the tip was advanced into the abdominal aorta for the continuous measurement of mean arterial blood pressure via a Sanborn P23Db pressure transducer and a Sanborn 7700 recorder. The left kidney was exposed via a flank incision, and a noncannulating electromagnetic flow probe (Carolina Electronic Instruments) was placed on the left renal artery for the continuous measurement of renal blood flow. A 22-gauge hypodermic needle was inserted into the left renal artery distal to the flow probe, and an 0.9% saline infusion was begun at 0.6 ml/min. The dog was allowed to recover from surgery for approximately 1 hour before the experiment was started. Observations were made to establish the control levels of renal blood flow and arterial blood pressure, and the responses to three doses (1 ng/kg, 6 ng/kg, and 12 ng/kg) of synthetic angiotensin II amide (Hypertensin, Ciba) were measured; the angiotensin II was injected into the left renal artery via the 22-gauge hypodermic needle. In addition, three of the dogs received norepinephrine (50 ng/kg) intrarenally after the last response to angiotensin had been recorded. The angiotensin II and the norepinephrine were administered as single injections in a constant volume of 5 ml of 0.9% saline. Recovery periods of 10–15 minutes were allowed between injections. Ten minutes after the last injection of angiotensin II or norepinephrine, the infusion of 0.9% saline was discontinued and the infusion of the angiotensin II antagonist, 1-sarcosine-8-alanine-angiotensin II,¹ was initiated at 0.6 ml/min. The concentration of the antagonist in the infusate was adjusted to achieve a constant rate of infusion (2.0 $\mu\text{g}/\text{kg min}^{-1}$). Fifteen minutes after the initiation of antagonist infusion, injections of angiotensin II and norepinephrine were repeated under conditions identical to those during saline infusion. Ten minutes after the injection of norepinephrine, the infusion of the angiotensin II antagonist was discontinued and the infusion of 0.9% saline was begun again. To ensure an adequate

recovery from the effects of the angiotensin II antagonist, a recovery period of 90–120 minutes was observed following cessation of antagonist infusion. After observations during this recovery period, injections of angiotensin II and norepinephrine were repeated again. The values for blood pressure and renal blood flow presented in the results were those recorded at the time of maximal response, which occurred approximately 20 seconds after injection of angiotensin II or norepinephrine.

In addition, the effects of the antagonist on the renal vascular response to exogenous angiotensin II and norepinephrine were studied in one sodium-depleted dog and in one dog with vena caval constriction. In these two dogs, the angiotensin II antagonist was evaluated in a manner identical to that used in the normal dogs.

EXPERIMENT 2: EFFECTS OF THE ANGIOTENSIN II ANTAGONIST DURING SODIUM DEPLETION

The five dogs used in this experiment were sodium depleted by a combination of a low-sodium diet and the administration of a mercurial diuretic. Each dog received a diet which provided less than 3 mEq of sodium daily for 4 days prior to the experiment. In addition, each dog was given 2 ml of Mercurhydrin intramuscularly each day she was on the low-sodium diet. The average cumulative negative sodium balance was 131 mEq for the 4 days. On the morning of the experiment, the dog was anesthetized with sodium pentobarbital (30 mg/kg, iv). Both ureters were exposed via a suprapubic incision along the ventral midline, and they were catheterized with PE 160 tubing for continuous collection of urine samples. Catheters (Fr 8 polyvinyl chloride) were placed in the right femoral artery and vein. The left kidney was exposed and prepared as described earlier for the measurement of renal blood flow and the infusion of saline and angiotensin II antagonist. Immediately after the insertion of the 22-gauge hypodermic needle into the renal artery, a 0.9% saline infusion was begun at 0.6 ml/min. The dog was allowed to recover from surgery for 1 hour before the experiment was begun. Following this recovery period, two 20-minute urine collections were made and infusion of 0.9% saline into the renal artery was discontinued. Infusion of the angiotensin II antagonist was initiated at 0.6 ml/min, and the concentration of the antagonist was adjusted to achieve a constant rate of infusion (0.2 $\mu\text{g}/\text{kg min}^{-1}$); again, two 20-minute urine collections were made. For recovery observations, infusion of 0.9% saline was begun again and five 20-minute urine collections were obtained. Subsequently, infusion of the angiotensin II antagonist into the renal artery was begun at a rate of 2.0 $\mu\text{g}/\text{kg min}^{-1}$. Again, two 20-minute urine collections were made, and the infusion was changed to 0.9% saline. The final recovery observations consisted of three 20-minute urine collections. The values for blood pressure and renal blood flow presented in the results were those recorded at the end of each 20-minute period.

¹Generously supplied by Norwich Pharmacal Company, Norwich, New York.

EXPERIMENT 3: EFFECTS OF THE ANGIOTENSIN II ANTAGONIST DURING THORACIC VENA CAVAL CONSTRICTION

Five dogs were prepared with a chronic thoracic vena caval constriction by placing a partially constricting ligature around the inferior vena cava about 1 inch above the diaphragm under sterile conditions (5). After surgery, the dogs were returned to metabolism cages and placed on the standard diet which provided 65 mEq of sodium and 55 mEq of potassium daily. Daily output of sodium was measured to verify that the vena caval ligature was sufficiently tight to produce chronic sodium retention; all of these dogs exhibited marked retention of sodium and developed ascites. To evaluate the effects of the angiotensin II antagonist, a protocol identical to that in experiment 2 was used.

EXPERIMENT 4: EFFECTS OF THE ANGIOTENSIN II ANTAGONIST IN NORMAL DOGS

The five dogs used in this experiment were fed the standard diet of 65 mEq of sodium and 55 mEq of potassium per day for at least 4 days prior to the experiment. To evaluate the effects of the angiotensin II antagonist in these dogs, an experimental protocol identical to that in experiments 2 and 3 was followed.

Urinary sodium was measured by flame photometry. Student's *t*-test for paired observations was used to compare each experimental period with its last control and with the recovery period. Values are presented as means \pm SE.

Results

EXPERIMENT 1

Figure 1 illustrates the effects on renal blood flow of intrarenal injection of exogenous angiotensin II (1, 6, and 12 ng/kg) and of norepinephrine (50 ng/kg) before, during, and after infusion of the angiotensin II antagonist (2.0 μ g/kg min⁻¹) into the renal artery. Infusion of the antagonist abolished or almost abolished the decrease in renal blood flow elicited by injection of angiotensin II, but it had no detectable effect on the decrease in renal blood flow elicited by norepinephrine. During infusion of the angiotensin antagonist, the control level of renal blood flow appeared to be slightly higher before the 12-ng/kg injection than it was before the 1-ng/kg injection, but the difference was not significant (*P* > 0.05). During the recovery period, the responses to exogenous angiotensin II and norepinephrine were similar to those during the control period. Thus, it appears that the analogue, 1-sarcosine-8-alanine-angiotensin II, is a specific, reversible antagonist of the renal vascular action of angiotensin II in the dog.

Similar results were obtained in one sodium-depleted dog and in one dog with vena caval constriction (Table 1). Infusion of the antagonist (2.0 μ g/kg min⁻¹) into the renal artery of these dogs consistently abolished the decrease in renal

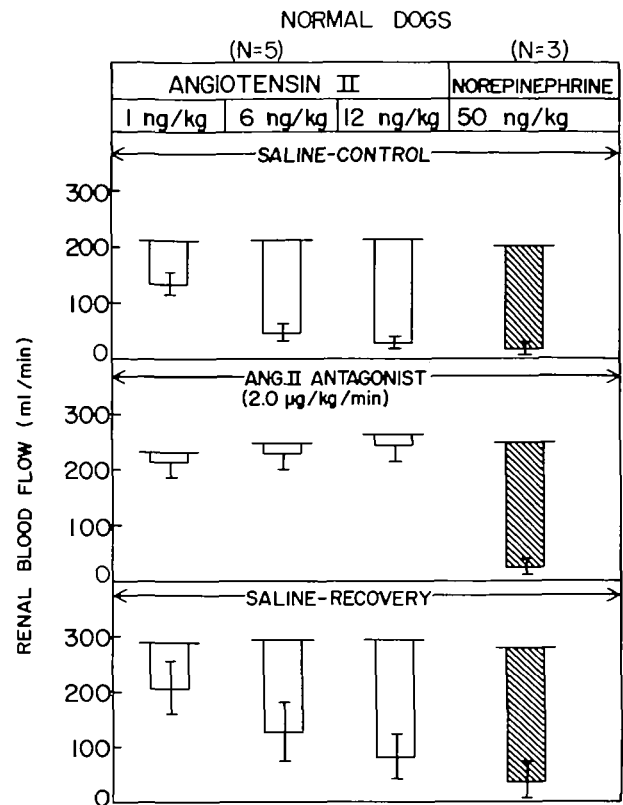


FIGURE 1

Decrease in renal blood flow to single intrarenal injections of exogenous angiotensin II and norepinephrine before, during, and after infusion of an angiotensin II antagonist, 1-sarcosine-8-alanine-angiotensin II, into the renal artery of normal dogs.

blood flow elicited by single intrarenal injections of angiotensin II, but it had no appreciable effect on

TABLE 1

Effects of Single Intra-arterial Renal Injections of Angiotensin II and Norepinephrine on Renal Blood Flow before, during, and after Intrarenal Infusion of 1-Sarcosine-8-Alanine-Angiotensin II

Treatment	Decrease in renal blood flow					
	Saline control		Analogue infusion		Saline recovery	
	(ml/min)	(%)	(ml/min)	(%)	(ml/min)	(%)
<i>Sodium-Depleted Dog</i>						
1 ng AII/kg	50	33	0	0	55	23
6 ng AII/kg	65	42	0	0	60	25
12 ng AII/kg	90	53	0	0	85	35
50 ng NE/kg	90	55	100	43	120	54
<i>Dog with Vena Caval Constriction</i>						
1 ng AII/kg	80	50	0	0	70	35
6 ng AII/kg	160	100	0	0	105	66
12 ng AII/kg			0	0	140	100
25 ng NE/kg	140	100	130	54	150	75

AII = angiotensin II and NE = norepinephrine.

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the decrease in renal blood flow elicited by norepinephrine. Although the percent decrease in renal blood flow elicited by norepinephrine was less during the antagonist infusion, the absolute values were relatively similar to control and recovery values. The percent decrease in renal blood flow during antagonist infusion was less because of a rather large increase in absolute renal blood flow.

EXPERIMENT 2

The response to the angiotensin II antagonist was determined at two different rates of infusion (0.2 and 2.0 $\mu\text{g}/\text{kg min}^{-1}$) into the renal artery of sodium-depleted dogs (Fig. 2). Renal blood flow averaged 196 ± 5 (SE) ml/min during the control period and increased to 222 ± 11 and 246 ± 12 ml/min after 20 and 40 minutes of infusion of the angiotensin II antagonist at the rate of 0.2 $\mu\text{g}/\text{kg min}^{-1}$ ($P < 0.01$ and $P < 0.005$, respectively). Renal resistance decreased from 0.71 ± 0.03 mm Hg/ml min^{-1} to 0.62 ± 0.06 and 0.54 ± 0.03 mm Hg/ml min^{-1} after 20 and 40 minutes of analogue infusion, respectively ($P < 0.005$ for the 40-minute value). Arterial blood

pressure and renal sodium excretion were not significantly altered by infusion of the antagonist at this rate. Renal sodium excretion by the left kidney for the five dogs was 9 ± 5 $\mu\text{Eq}/\text{min}$ during the control periods and 11 ± 5 and 13 ± 6 $\mu\text{Eq}/\text{min}$ during the experimental periods; renal sodium excretion by the right kidney for the five dogs was 9 ± 2 $\mu\text{Eq}/\text{min}$ during the control periods and 12 ± 3 and 12 ± 3 $\mu\text{Eq}/\text{min}$ during the experimental periods. After a recovery period of 100 minutes, the rate of antagonist infusion was increased tenfold to 2.0 $\mu\text{g}/\text{kg min}^{-1}$. At this faster rate of infusion, renal blood flow increased again from 235 ± 10 ml/min to 269 ± 15 and 282 ± 17 ml/min after 20 and 40 minutes of antagonist infusion ($P < 0.005$ for both values): renal resistance decreased from 0.56 ± 0.03 mm Hg/ml min^{-1} to 0.45 ± 0.04 and 0.41 ± 0.03 mm Hg/ml min^{-1} ($P < 0.005$ for both values). Moreover, at this rate of antagonist infusion, a decrease in arterial blood pressure was observed from 130 ± 4 mm Hg to 118 ± 6 and 113 ± 4 mm Hg during infusion of the antagonist for 20 and 40 minutes ($P < 0.05$ and $P < 0.005$, respectively). During the last recovery period, arterial blood pressure increased to 127 ± 6 mm Hg, renal blood flow decreased to 254 ± 18 ml/min, and renal resistance increased to 0.51 ± 0.05 mm Hg/ml min^{-1} . Again, renal sodium excretion did not change significantly in either kidney at this faster rate of antagonist infusion.

EXPERIMENT 3

The five dogs with thoracic vena caval constriction were separated into two groups on the basis of their response to infusion of the antagonist at the higher dose of 2.0 $\mu\text{g}/\text{kg min}^{-1}$ (Table 2). However, both groups responded in a manner similar to the sodium-depleted dogs to infusion of the antagonist at the rate of 0.2 $\mu\text{g}/\text{kg min}^{-1}$. In both groups, renal blood flow increased and renal resistance decreased following infusion of the antagonist at the rate of 0.2 $\mu\text{g}/\text{kg min}^{-1}$. Arterial blood pressure and renal sodium excretion did not change significantly. For all five dogs with vena caval constriction, renal blood flow increased from 143 ± 16 ml/min to 178 ± 23 and 190 ± 19 ml/min after 20 and 40 minutes of antagonist infusion ($P < 0.02$ and $P < 0.005$, respectively); renal resistance decreased from 0.90 ± 0.14 mm Hg/ml min^{-1} to 0.73 ± 0.14 and 0.64 ± 0.10 mm Hg/ml min^{-1} after 20 and 40 minutes of antagonist infusion

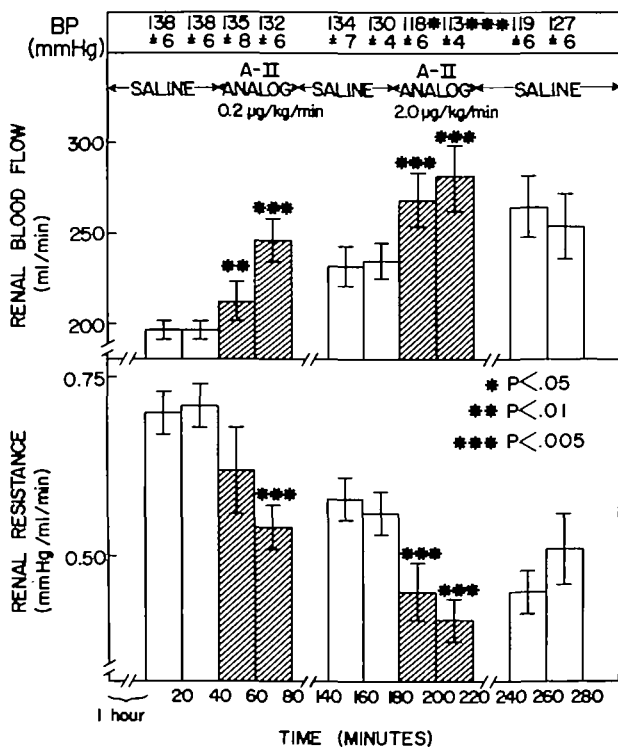


FIGURE 2

Changes in renal blood flow, renal resistance, and arterial blood pressure (BP) in sodium-depleted dogs before, during, and after infusion of an angiotensin II antagonist, 1-sarcosine-8-alanine-angiotensin II, into the renal artery at two different rates. Values are means \pm SE, and $n = 5$.

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TABLE 2

Arterial Blood Pressure, Renal Blood Flow, Renal Resistance, and Sodium Excretion by the Experimental Kidney before, during, and after Intrarenal Infusion of 1-Sarcosine-8-Alanine-Angiotensin II into Dogs with Vena Caval Constriction

	Saline infusion		Analogue infusion (0.2 $\mu\text{g}/\text{kg min}^{-1}$)		Saline infusion		Analogue infusion (2.0 $\mu\text{g}/\text{kg min}^{-1}$)		Saline infusion					
	20 min	40 min	60 min	80 min	100 min	120 min	140 min	160 min	180 min	200 min	220 min	240 min	260 min	280 min
	Group A (N = 8)													
BP (mm Hg)	126 \pm 9	126 \pm 9	124 \pm 10	120 \pm 13	122 \pm 13	121 \pm 12	108 \pm 15	105 \pm 14	122 \pm 11	120 \pm 8				
RBF (ml/min)	123 \pm 16	129 \pm 23	157 \pm 34	178 \pm 31	164 \pm 33	158 \pm 34	208 \pm 41	217 \pm 42	186 \pm 21	182 \pm 22				
RR (mm Hg/ml min^{-1})	1.12 \pm 0.23	1.05 \pm 0.20	0.87 \pm 0.20	0.72 \pm 0.15	0.81 \pm 0.16	0.84 \pm 0.18	0.56 \pm 0.15	0.53 \pm 0.15	0.67 \pm 0.09	0.68 \pm 0.09				
E _{Na} ($\mu\text{Eq}/\text{min}$)	3 \pm 1	3 \pm 2	4 \pm 2	11 \pm 9	9 \pm 7	5 \pm 3	10 \pm 5	4 \pm 2	7 \pm 2	8 \pm 1				
	Group B (N = 2)													
BP (mm Hg)	112 \pm 12	112 \pm 16	110 \pm 14	107 \pm 17	119 \pm 11	118 \pm 14	86 \pm 14	81 \pm 9	115 \pm 15	110 \pm 10				
RBF (ml/min)	166 \pm 4	165 \pm 5	209 \pm 9	207 \pm 13	189 \pm 13	198 \pm 2	153 \pm 31	123 \pm 33	215 \pm 25	221 \pm 19				
RR (mm Hg/ml min^{-1})	0.67 \pm 0.07	0.69 \pm 0.12	0.53 \pm 0.10	0.51 \pm 0.05	0.63 \pm 0.12	0.60 \pm 0.07	0.57 \pm 0.03	0.69 \pm 0.11	0.54 \pm 0.01	0.50 \pm 0.01				
E _{Na} ($\mu\text{Eq}/\text{min}$)	2 \pm 0	2 \pm 0	2 \pm 0	1 \pm 0	3 \pm 1	2 \pm 0	1 \pm 1	0.3 \pm 0.3	3 \pm 1	5 \pm 1				

Values are means \pm SE. BP = arterial blood pressure, RBF = renal blood flow, RR = renal resistance, E_{Na} = sodium excretion. See text for explanation of groups A and B.

($P < 0.01$ and $P < 0.02$, respectively). Renal sodium excretion by the left experimental kidney for the five dogs was $3 \pm 1 \mu\text{Eq}/\text{min}$ during the control period and 3 ± 1 and $7 \pm 5 \mu\text{Eq}/\text{min}$ during the experimental periods; sodium excretion by the right control kidney for four of the five dogs was $9 \pm 2 \mu\text{Eq}/\text{min}$ during the control period and 12 ± 3 and $12 \pm 3 \mu\text{Eq}/\text{min}$ during the experimental periods.

At the faster rate of antagonist infusion ($2.0 \mu\text{g}/\text{kg min}^{-1}$), however, a difference in response occurred between the two groups. In three dogs (group A, Table 2), the results were similar to those obtained in the sodium-depleted dogs; renal blood flow increased, renal resistance decreased, arterial blood pressure decreased, and sodium excretion did not change significantly in either kidney. In the other two dogs (group B), arterial blood pressure and renal blood flow decreased precipitously, and renal resistance increased following infusion of the antagonist at $2.0 \mu\text{g}/\text{kg min}^{-1}$; in both of these dogs arterial blood pressure fell more than 30 mm Hg after infusion of the antagonist for 40 minutes. Sodium excretion was unchanged in either kidney.

EXPERIMENT 4

Infusion of the angiotensin II antagonist at either $0.2 \mu\text{g}/\text{kg min}^{-1}$ or $2.0 \mu\text{g}/\text{kg min}^{-1}$ into the renal artery of normal dogs produced no significant change in any of the parameters studied (Fig. 3). Renal sodium excretion declined progressively throughout the experiment on both kidneys, and the changes were apparently not influenced by the angiotensin II antagonist.

Discussion

Recent experiments of Pals et al. (3) have demonstrated that 1-sarcosine-8-alanine-angiotensin II is a specific competitive antagonist of the vascular action of angiotensin II in both the rat and the rabbit. The present study (experiment 1) indicated that this antagonist blocked the renal vasoconstrictor action of exogenous angiotensin II amide but not that of norepinephrine in normal dogs, in a sodium-depleted dog, and in a dog with vena caval constriction. Although the chemical and structural form of canine angiotensin II is unknown, it is probable that the endogenous canine angiotensin II and the synthetic angiotensin II interact with the same specific vascular receptors. Sodium-depleted dogs and dogs with vena caval constriction are known to have increased plasma renin activity (6, 7); therefore, the angiotensin II antagonist

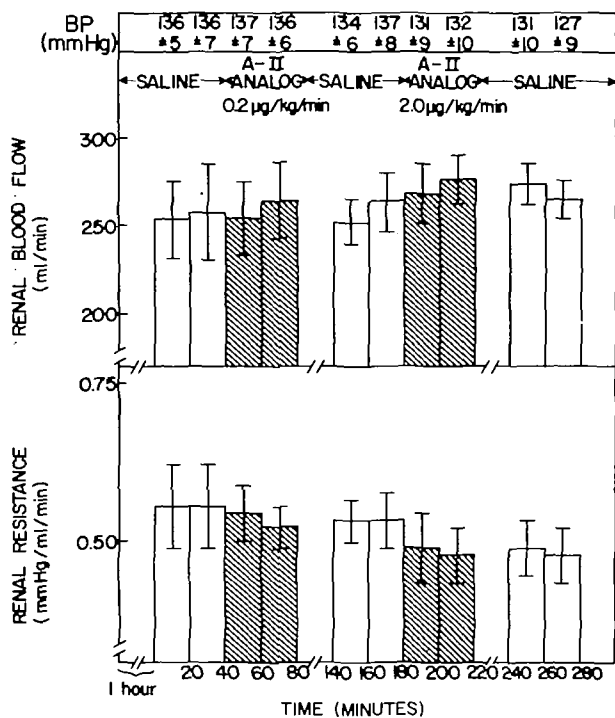


FIGURE 3

Changes in renal blood flow, renal resistance, and arterial blood pressure (BP) in normal dogs before, during and after infusion of an angiotensin II antagonist, 1-sarcosine-8-alanine-angiotensin II, into the renal artery at two different rates. Values are means \pm SE, and $N = 5$.

might have affected renal resistance and renal blood flow in the present experiments by competitively displacing endogenous angiotensin II from its specific renal vascular receptors. A direct action of the angiotensin analogue on renal arteriolar smooth muscle or an action releasing norepinephrine from sympathetic nerve endings seems unlikely, since no changes in renal blood flow were observed in normal dogs.

An important new finding of the present study is the effect of 1-sarcosine-8-alanine-angiotensin II on renal resistance and renal blood flow. In both sodium-depleted dogs and dogs with vena caval constriction, infusion of the angiotensin II antagonist into the renal artery at $0.2 \mu\text{g}/\text{kg min}^{-1}$ consistently decreased renal resistance and increased renal blood flow. At the higher infusion rate of $2.0 \mu\text{g}/\text{kg min}^{-1}$, the same directional changes in renal resistance and renal blood flow occurred in the sodium-depleted dogs and in three of the five dogs with vena caval constriction. The recovery values after each of the two dose levels of the antagonist (Fig. 2 and Table 2) were higher than

the preceding control values, because insufficient time was allowed for disappearance of the antagonist. Infusion of the antagonist into the renal artery of normal dogs at either dose had no effect on resistance or blood flow. These observations strongly suggest that angiotensin II plays an important role in the maintenance of renal arteriolar smooth muscle contractility and in the control of renal blood flow in certain pathophysiological states.

Also, the results agree with the earlier finding and interpretation (1, 8) that sodium-depleted dogs and dogs with thoracic caval constriction have a reduced pressor response to exogenous angiotensin II, because available smooth muscle receptor sites are occupied by endogenous angiotensin II which is present in large amounts. Recently, Hollenberg, et al. (9) have found that normal human subjects on a sodium-restricted diet are much less sensitive to angiotensin II, as judged by a reduction in renal blood flow, than are subjects on a normal sodium intake.

In two of the five dogs with vena caval constriction, infusion of the angiotensin II antagonist into the renal artery at $2.0 \mu\text{g}/\text{kg min}^{-1}$ produced no change or an elevation in renal resistance and a fall in renal blood flow. However, in both dogs arterial blood pressure fell more than 30 mm Hg to values of 90 mm Hg and 72 mm Hg, respectively. Hypotension of this magnitude reflexly activates the sympathetic nervous system to increase sympathetic outflow to the renal vascular bed. In this manner, the effects of the angiotensin II antagonist on the renal vasculature could have been overcome and even reversed in these two dogs.

Infusion of the antagonist into the renal artery at $2.0 \mu\text{g}/\text{kg min}^{-1}$ in the other three dogs with vena caval constriction and in the sodium-depleted dogs also produced a significant fall in arterial blood pressure. These data agree with those of previous studies (1, 2) in which the intravenous infusion of the angiotensin II antagonist at $6.0 \mu\text{g}/\text{kg min}^{-1}$ significantly reduced arterial blood pressure. Because both sodium-depleted dogs (10) and dogs with vena caval constriction (5) have decreased cardiac output and increased total peripheral resistance, the results of the present study and the previous observations strongly suggest that angiotensin II plays an important functional role in elevating total peripheral resistance and maintaining arterial blood pressure in pathophysiological states of decreased cardiac output.

Renal sodium excretion failed to change significantly during intrarenal infusion of the antagonist.

The effects of angiotensin II on renal sodium excretion are both dose and species dependent and are highly variable (11). The present data give no indication that angiotensin II plays an intrarenal role in regulating sodium excretion in normal or sodium-depleted dogs or in dogs with vena caval constriction.

The present study provides evidence that the angiotensin II analogue, 1-sarcosine-8-alanine-angiotensin II, which Pals et al. (3) demonstrated to be a specific competitive antagonist of angiotensin II in the rat and the rabbit, is a specific antagonist of angiotensin II in the dog also. Moreover, the present study suggests an important intrarenal role for angiotensin II in the maintenance of a high renal resistance in dogs with vena caval constriction and in sodium-depleted dogs. Since the changes occurring in sodium depletion are only one step removed from the physiological changes associated with altered sodium intake, it seems likely that angiotensin II is involved in the homeostatic regulation of renal blood flow.

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