Effects of Angiotensin on Canine Renal Blood Flow[1] (34706)

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McGiff and Fasy, in 1965, reported that the efficacy of angiotensin in reducing renal blood flow was markedly attenuated in acutely denervated kidneys, or in the kidneys of dogs treated with either reserpine or guanethidine (1). These results suggested that the renal vasoconstrictor action of angiotensin was dependent on an intact sympathetic vasomotor innervation. In contrast, Geller and Kendrick recently reported that the renal vasocontrictor action of angiotensin was unaltered, or slightly enhanced, in chronically denervated kidneys, and suggested that the efficacy of angiotensin in reducing renal blood flow was largely independent of an intact vasomotor innervation (2).

In the present study, renal blood flow responses to angiotensin were examined in dogs with innervated kidneys, innervated kidneys treated with lidocaine, innervated but reserpinized kidneys, and in dogs with chronically denervated kidneys. Results obtained in this study are consonant with the findings reported by Geller and Kendrick suggesting that the renal vascular action of angiotensin is largely independent of renal vasomotor innervation.

Methods. Nineteen dogs of either sex, weighing 15–20 kg, were anesthetized with sodium pentobarbital (20–25 mg) 30–60 min after subcutaneous injection of morphine sulfate (3 mg/kg). The animal breathed spontaneously throughout the experiment.

Catheters were inserted via the right femoral artery and vein so that tips were close to the heart, and central venous and arterial pressures were monitored with Statham P23AC transducers. The left renal artery was exposed through a retroperitoneal incision. A noncanulating electromagnetic flow sensor was fitted around the renal artery to measure renal blood flow (Statham, Medicon Model K-2000). Occlusion of the renal artery distal to the flow sensor was used to establish the zero flow base line, which was checked at the end of each experiment. All recordings were made on a Grass Model 5 polygraph.

Angiotensin (CIBA) was dissolved in saline, and the bolus was injected (1 ml) into the renal artery through a 25-gauge needle. The angiotensin dose schedule was randomized, and 10–15 min elapsed between successive injections. The maximum change in blood flow induced by angiotensin was expressed as percentage of control renal blood flow measured just before drug injection. The Student's t test was used to evaluate responses statistically (3).

In 3 dogs, responses to angiotensin were studied before and after intra-arterial injection of lidocaine (300 mg). Responses in 5 chronically denervated kidneys were also studied. In one dog, renal denervation was performed by autotransplanting the left kidney to the right iliac region. In this procedure, the peripheral end of the left renal artery was anastomosed to the central end of the right external iliac artery, and the renal vein was anastomosed to the right external iliac vein. The ureter was left intact, but stripped of its innervation. In four additional dogs, the left kidney was denervated by severing all of its connections except for the artery, vein, and ureter which were stripped of innervation. These dogs were used for terminal experiments 14–21 days following surgery.

Three dogs with innervated kidneys were treated with reserpine (0.5 mg/kg of body

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wt, subcutaneously) 24 hr prior to study to deplete neural stores of catecholamines (4).

Results. Renal blood flow reponses in innervated, reserpinized, and in chronically denervated kidneys are summarized in Fig. 1. In all cases, the magnitude of renal vasoconstriction induced by angiotensin increased with dosage. For the most part, no significant differences in response were noted among the different kidney preparations. For example, renal blood flows in response to 0.1 μg of angiotensin were 65% $\pm$ 7 SE of control (innervated), 58% $\pm$ 4 SE of control (reserpinized), and 57% $\pm$ 7 SE of control (chronically denervated). However, with 0.5 μg of angiotensin,the blood flow response in denervated kidneys was significantly greater than in either innervated ($p < 0.001$), or reserpinized kidneys ($p < 0.001$).

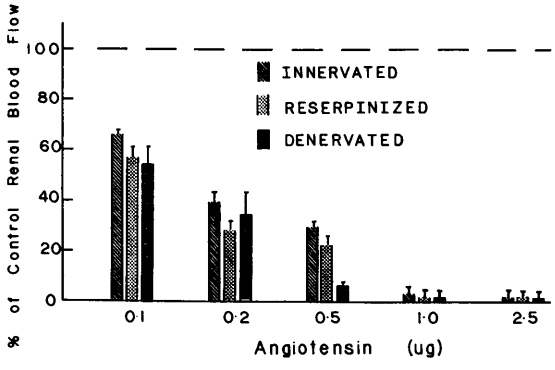

FIG. 1. Renal blood flow responses to intra-arterial injections of angiotensin: (--) control blood flow. Mean responses to varying doses are shown for 7–12 dogs with innervated kidneys, 3 reserpinized dogs (0.5 mg/kg of body wt), and 4 dogs with chronically denervated kidneys. Small vertical bars represent $\pm$1 SE. No significant difference between angiotensin responses in innervated, reserpinized, or denervated kidneys was noted except with 0.5 μg of angiotensin.

Renal flow responses to angiotensin in dogs with and without prior treatment with reserpine are also presented in Table I, together with data from another series of experiments in which constrictor responses to direct nerve stimulation were tested with and without reserpinization. The dose of reserpine used was sufficient to abolish responses to nerve stimulation, but the drug did not attenuate constrictor responses to angiotensin.

The renal vasoconstrictor response to angiotensin (0.2 μg), as shown in Table II, was unaltered by lidocaine. The amount of lidocaine used (300 mg) was sufficient to block renal vasoconstriction during direct renal nerve stimulation, but had no effect on responses to intra-arterially injected norepinephrine (3 μg).

Discussion. The constrictor action of angiotensin, in the present study, appeared to be entirely independent of an intact renal vasomotor innervation. Renal vasoconstrictor activity of angiotensin was equally effective in innervated, reserpinized, and chronically denervated kidneys (Fig. 1). Similarly, inhibition of renal nerve excitability with lidocaine did not alter vascular sensitivity to angiotensin (Table II). These results contrast with those reported by McGiff and Fasy (1), but agree with recent studies reported by Geller and Kendrick (2).

McGiff and Fasy concluded that the renal vascular action of angiotensin was dependent on an intact renal vasomotor innervation and suggested that the critical factors involved were neural stores of norepinephrine, and possibly some sort of cholinergic mechanism.

TABLE I. Effect of Reserpine on Vasoconstrictor Responses in Innervated Kidneys.

Stimulus	No reserpine		Reserpine treated	
	No. of dogs	(% of control)[a]	No. of dogs	(% of control)[a]
Nerve stimulation[b]	4	0	3	95 $\pm$ 1
Angiotensin, 0.1 μg	10	65 $\pm$ 7	3	58 $\pm$ 4
1.0 μg	12	3 $\pm$ 2	3	3 $\pm$ 3

[a] Values are means $\pm$ 1 SE.

[b] 10 cps, 20 V, 2-msec pulse duration.

TABLE II. Effect of Lidocaine on Vasoconstrictor Responses in Innervated Kidneys.

Stimulus	% of control renal blood flow[a]		
	Before lidocaine	After lidocaine[b] 0–10 min	After lidocaine[b] 15–25 min
Nerve stimulation[c]	0	92 ± 2	0
Angiotensin (0.2 μg)	40 ± 5	41 ± 7	41 ± 3
Norepinephrine (3.0 μg)	44 ± 2	50 ± 8	48 ± 8

[a] Mean responses ± 1 SE, from 4 dogs.
[b] 300 mg, ia.
[c] 10 cps, 20 V, 2-msec pulse duration.

Evidence in support of the hypothesis included attenuation of constrictor responses following attempts at acute denervation, inhibition of norepinephrine release, and depletion of neural norepinephrine stores. Attempts at acute renal denervation, however, were performed either by transection of the renal artery, or of the cervical spinal cord. It is possible that the surgical trauma in these procedures decreased vascular sensitivity to angiotensin. Depletion of norepinephrine stores was achieved by an extensive reserpinization (2.4 mg/kg of body wt) over a 4-day period. However, reduced vascular sensitivity to angiotensin could be due to other causes, since extensive and prolonged reserpinization produces effects other than norepinephrine depletion (4, 5). Finally, although a few responses to intra-arterial injections were studied, most were recorded during intravenous infusions of angiotensin, and renal blood flow responses were therefore complicated by systemic response.

In the present study, kidneys were chronically denervated, and reserpinization, though mild (0.5 mg/kg of body wt, 24 hr prior to study), was sufficient to eliminate responses to renal nerve stimulation. Furthermore angiotensin was always injected intraarterially.

Geller and Kendrick also worked with chronically denervated dog kidneys, in a study designed to test the influence of background sympathetic activity, altered by carotid sinus perfusion, on constrictor responses to angiotensin (2). Their data indicated that renal constrictor responses to angiotensin were not altered by chronic denervation, although this was not their principal concern. The present study, however, addressed to this specific point, demonstrated conclusively that an intact innervation is not required for angiotensin constrictor effects in the canine kidney.

Summary. Changes in canine renal blood flow in response to intra-arterial injections of angiotensin were studied in innervated and chronically denervated kidneys under a variety of conditions. In all cases, angiotensin decreased renal blood flow. Angiotensin was equally effective in reducing renal blood flow in innervated kidneys, reserpinized kidneys, kidneys treated with lidocaine, and in chronically denervated kidneys. These results suggest that the renal vasoconstrictor action of angiotensin is largely independent of an intact renal vasomotor innervation.

1. McGiff, J. C., and Fasy, T. M., J. Clin. Invest. 44, 1911 (1965).

2. Geller, R. G., and Kendrick, J. E., Circ. Res. 20, 321 (1967).

3. Goldstein, A., "Biostatistics: An Introductory Text," p. 34. Macmillan Co., New York (1964).

4. Nickerson, M., *in* "The Pharmacological Basis of Therapeutics" (L.S. Goodman and A. Gilman, eds.), p. 546. Macmillan Co., New York (1965).

5. Thorp, R. H., and Cobbin, L. B., "Cardiac Stimulant Substances," p. 180. Academic Press, New York (1967).

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