Flow Responses to Angiotensin in Innervated and Denervated Kidneys* (33410)

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The renal vasoconstrictor action of angiotensin is reported to be due to: a direct action on vascular smooth muscle, or a peripheral interaction with the sympathetic nervous system and a central autonomic component. The evidence regarding the relative significance of each component is conflicting. Zimmerman (1) reported no consistent central component of the renal vasoconstrictor response to angiotensin administered into the carotid or vertebral artery. He did, however, find that intrarenal infusion of angiotensin potentiated the response to stimulation of the renal sumpathetic nerves. Since this effect could be elicited without a vasoconstrictor effect of angiotensin, this action appears to be independent of the vasoconstrictor action of angiotensin. McCubbin *et al.* (2) reported that a peripheral sympathetic interaction with subpressor doses of angiotensin could result in hypertension.

McGiff and Fasy (3) suggested that the renal vasoconstrictor response to angiotensin is mediated through central and direct peripheral actions upon the sympathetic nervous system. They reported that denervation of the kidneys abolished the renal vasoconstrictor response to intravenous angiotensin and reduced the response to intra-arterial angiotensin. In contrast to these results, we observed (4) an increased sensitivity to angiotensin in the excised kidney perfused with the dog's own blood. Similarly, Korner *et al.* (5) observed an increased sensitivity to angiotensin in the denervated kidney of a rabbit. The present investigation was undertaken to study the relative contributions of these peripheral and central components to the renal vascular response to angiotensin.

Methods. Seven mongrel dogs (20–24 kg) were anesthetized with morphine (3 mg/kg) subcutaneously and chloralose (100 mg/kg) intravenously. Left and right renal blood flows were measured simultaneously in all animals except one, in which only left renal flow could be obtained satisfactorily. A Statham (M-4000) electromagnetic flowmeter was used. Flow sensors (3–4 mm diameter) were selected to fit snugly the renal arteries. Zero flow was determined at regular intervals by momentarily occluding the renal arteries distal to the magnet. Flow calibrations were made after each experiment by perfusing and catching timed samples of blood from an isolated segment of the carotid artery.

Mean systemic arterial blood pressure was measured from a branch of the left femoral artery using a Statham strain gage. Mean flow and pressure were recorded on an Offner oscillograph. The vagi were cut in all animals.

Changes in left renal flow in response to intrarenal artery (IRA) angiotensin (0.01 and 0.02 μg/kg of body wt.) were recorded before and after denervation of this kidney. The appropriate dose was selected to produce comparable flow responses and less than a 5% change in mean arterial pressure. Angiotensin was given through a catheter (1 mm o.d.) introduced through the femoral artery and advanced so that the tip extended about 5 mm into the left renal artery. The placement of this catheter caused no detectable reduction in renal blood flow. After obtaining the control responses this kidney was denervated.

Denervation consisted of stripping the renal artery, vein, and ureter. In all but one case

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TABLE I. Average Flow Responses (± SEM) to IRA Angiotensin (0.01–0.02 μg/kg of body wt.) in Seven Dogs Before and Following Left Renal Denervation.

Condition	Base level	Change (%)
Predenervation (19)[a]		
Mean arterial blood pressure (mm Hg)	122 ± 8	< +2
Left renal flow (ml/min)	168 ± 6	−40 ± 5
Left renal resistance (P/F)	0.777 ± 0.05	+91 ± 19
Left renal denervation (35)		
MABP	113 ± 2	< +1
LRF	172 ±10	−49 ± 3
LR resistance	0.753 ± 0.06	+119 ± 11
Bretylium (36)[b]		
MABP	112 ± 6	< +2
LRF	145 ±12	−48 ± 3
LR resistance	0.954 ± 0.07	+120 ± 14

[a] Number of responses in parentheses.
[b] In four dogs.

these structures were then painted with concentrated phenol. Application of phenol was without effect on the results. The denervation procedure took about 20 min. Care was taken to keep the innervation of the right kidney intact. The flow response to bilateral carotid artery occlusion was used as a test for denervation. Carotid occlusion increased mean blood pressure from an average level of 112 to 174 mm Hg. Flow in the denervated kidney increased parallel with pressure in response to carotid occlusion while either a decrease or no change in flow was observed in the innervated kidney.

Simultaneous flow changes in both left and right renal arteries to intravenous (i.v.) angiotensin (0.05 and 0.1 μg/kg) were recorded before and following denervation of the left kidney. The dose was selected to produce comparable pressure and flow responses.

Angiotensin-amide (Hypertensin-Ciba) was made up in Locke's solution in concentrations of 1 and 10 μg/ml. Bretylium tosylate (5–10 mg/kg i.v.) was given in four animals.

The analog data were digitized at 6-sec intervals using a Benson-Lehner Oscar and decimal converter system. The mean pressure–mean flow ratio was calculated at each point using a CDC 3600 computer. The maximal changes in pressure, flow, and resistance are presented.

Results. The average maximal changes in pressure, flow, and renal resistance (mean pressure/mean flow) in response to intra-arterial angiotensin are shown in Table 1. Denervation of the kidney caused little or no change in renal flow or resistance. The average change in flow or resistance in response to angiotensin (IRA) was not significantly ($p > .05$) different from control following denervation of the kidney. In the seven experiments, the renal response to angiotensin was slightly reduced in one case, increased in two experiments and not changed by denervation in the other four.

The results obtained in response to i.v. angiotensin are presented in Table II. Denervation of the left kidney did not greatly alter the level of renal flow or the flow responses of either kidney to angiotensin. Similarly, bretylium (5–10 mg/kg) had no significant ($p > .05$) effect on the renal response to angiotensin in either the innervated or denervated kidney. The control flow responses in the right kidney were consistently greater than those in the left. This may possibly be explained by the presence of the catheter in the left renal artery. However, the catheter did not appear to reduce the level of left renal flow. The changes in renal resistance in response to the i.v. angiotensin probably are poor indices of the active changes in

TABLE II. Average Pressure and Flow Responses (± SEM) to i.v. Angiotensin (0.05–0.10 μg /kg of body wt.) in Six Dogs Before and Following Left Renal Denervation.

Condition	Base level	Change (%)
Predenervation (15)[a]		
Mean arterial blood pressure (mm Hg)	124 ± 8	+23 ± 3
Left renal flow (ml/min)	180 ± 11	−37 ± 8
Right renal flow (ml/min)	174 ± 16	−52 ± 5
Left renal resistance (P/F)	0.708 ± 0.05	+141 ± 43
Right renal resistance (P/F)	0.769 ± 0.07	+234 ± 57
Left renal denervation (25)		
MABP	112 ± 3	+20 ± 2
LRF	162 ± 13	−48 ± 3
RRF	149 ± 6	−48 ± 5
LR resistance	0.830 ± 0.08	+137 ± 15
RR resistance	0.807 ± 0.03	+191 ± 44
Bretylium (22)[b]		
MABP	126 ± 4	+32 ± 4
LRF	164 ± 13	−48 ± 3
RRF	142 ± 7	−51 ± 5
LR resistance	0.893 ± 0.08	+146 ± 23
RR resistance	0.883 ± 0.03	+196 ± 41

[a] Number of responses in parentheses.
[b] In four dogs.

vascular tone, since both renal flow and systemic pressure are changing. It should be remembered that the resistance values presented are peak values and do not necessarily coincide with the peaks of the flow or pressure response. The area under the response curves was calculated to determine whether the peak responses were representative of the overall effects observed. In all cases, these areas paralleled the data presented.

Discussion. Bickerton and Buckley (6) have described in dogs an effect of angiotensin on central autonomic structures as well as a direct peripheral action on vascular smooth muscle. A central effect of i.v. angiotensin resulting in peripheral vasoconstriction has also been reported in man (7–9). Reports of peripheral interactions of angiotensin with the sympathetic nervous system are numerous. Zimmerman (10) found that denervation of the hindquarters of dogs reduced the vascular action of angiotensin. Similar results were obtained by Laverty (11) in the rat. Angiotensin is reported to facilitate the vacular response to sympathetic stimulation in the cutaneous (12) and mesenteric (13) vascular beds, to release catecholamines from the adrenal medulla (14, 15) and to enchance the pressor response to tyramine (13). McCubbin *et al.* (2) reported that long-term infusion of subpressor amounts of angiotensin results in sustained arterial hypertension presumably by an action on the sympathetic nervous system.

The renal vasoconstrictor action of angiotensin has been related to the integrity of the sympathetic nervous system. McGiff and Fasy (3) reported that the response of the renal vascular bed to angiotensin is reduced or abolished by either renal denervation, spinal cord transection, and by bretylium, guanethidene, and other autonomic blocking agents. They suggest that the renal vascular response to angiotensin is determined by central and direct peripheral actions upon the sympathetic nervous system. Zimmerman (1) reported that angiotensin infusion facilitates the vasoconstrictor response to renal nerve stimulation by a mechanism that is apparently not dependent upon the renal vasoconstrictor action of angiotensin. He was, however,

unable to demonstrate a central sympathetic action of angiotensin on the renal vascular bed.

The results of the present experiments support the evidence presented by Zimmerman that a central sympathetic effect of angiotensin on the renal vascular bed is unlikely in a physiological situation. Renal denvervation by destruction of the renal nerves had no effect on the response to IRA angiotensin. Bretylium, which depletes and then blocks norepinephrine release from sympathetic nerve endings, did not alter the response to angiotensin in either the innervated or denervated kidney. This suggests that angiotensin exerts a direct vasoconstrictor action on renal vascular smooth muscle rather than an indirect one through interactions with the renal sympathetic nerves.

Intravenous administration of angiotensin produced equivalent flow responses in the innervated or denervated kidney. If angiotensin exerted a significant effect upon the renal vascular bed through an action on a central nervous component, then the response in the innervated kidney should differ from the response in the denervated one.

The differences between our results and those of McGiff and Fasy (3) may possibly be explained by the differences between the preparations. They measured flows in the renal vein with a rotameter. The kidney was denervated by transection of the renal artery and then perfused with blood from the carotid artery.

We observed the perfused excised kidneys of dogs to be more sensitive to angiotensin (4). Korner *et al.* (5) observed similar sensitization in the denervated kidneys of the rabbit. Although we made no quantitative study of the increased sensitivity to angiotensin, we found the dose required to produce a comparable pressure increase in perfused excised kidneys to be about one-tenth to one-fifth of the dose in the innervated perfused kidneys. In the present study, renal denervation caused sensitization to angiotensin in only two of the seven animals and then not to the degree we found in the excised kidneys perfused at a constant rate. We have no explanation for these differing results.

Summary. The renal vasoconstrictor response to angiotensin was not altered by renal denervation or by bretylium. This suggests that the action of angiotensin on renal vascular smooth muscle is mainly a direct action rather than an indirect one involving a peripheral or central autonomic component.

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