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Angiotensin II-mediated renal vasoconstriction amenable to α_1-adrenoceptor blockade

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Abstract

Renal adrenergic interactions of intravenously and intrarenal arterially administered angiotensin II were studied in the anesthetized rabbit. Systemic arterial blood pressure and left renal blood flow were monitored. Bolus doses of angiotensin II, 50 and 100 ng/kg given intravenously, caused an immediate reduction in renal blood flow followed by a more sustained vasoconstrictor response. Prazosin, 5 μg/kg/min, infused intrarenal arterially, decreased both components of the reduced renal blood flow, suggesting adrenergic contribution to the response. Renal denervation reduced significantly the immediate response to angiotensin II without affecting the sustained response; administration of prazosin after denervation caused a further decrease in the response. Left adrenalectomy had no significant effect on the angiotensin II-induced renal blood flow response, ruling out the possible contribution of adrenal catecholamine release via the adrenal rete. In animals that had undergone renal denervation and left adrenalectomy, the renal blood flow response to intrarenal arterial injection of subpressor doses of angiotensin II (5 and 10 ng/kg) was reduced by the infusion of prazosin. It is concluded that angiotensin II-induced renal vasoconstriction is contributed to by adrenergic actions dependent in part on intact renal nerves, but also by a component not requiring an intact nerve supply.

Keywords: Renal blood flow; Catecholamine release; Angiotensin II; Renal nerve; Prazosin; α-Adrenoceptor

1. Introduction

There is a long history of the interaction of the pressor peptide, angiotensin II, with the sympathetic nervous system. Angiotensin II activates the sympathetic nervous system by stimulation of specific brain areas (Ferrario et al., 1972; Simpson, 1981; Hartle et al., 1982; Fink et al., 1987), and also acts peripherally by facilitating release of norepinephrine from adrenergic nerve terminals (Zimmerman, 1978). One of the most important sites of physiologic action of angiotensin II is the renal vascular bed, upon which the peptide has an extremely potent direct vasoconstrictor action exerted mainly on the glomerular arterioles. However, central and peripheral sympathetic effects may also contribute to the renal vasoconstrictor action of angiotensin II. Infusion of angiotensin II into either the brain ventricular system or vertebral artery has been shown in some investigations to increase renal sympathetic nerve activity (Aars, 1972; Fukiyama, 1972; Tobey et al., 1983; Dorward and Rudd, 1991), but when given intravenously the pressor-induced activation of the baroreflex appears to negate this effect (Matsumura et al., 1989).

Evidence for a peripheral sympathetic effect of angiotensin II in the kidney derives mainly from studies conducted in the dog. Intrarenal arterial infusion of a range of doses of angiotensin II was shown to potentiate the renal vasoconstrictor response to electrical stimulation of the renal nerves (Zimmerman et al., 1972), and a higher dose was found to facilitate the release of norepinephrine into the renal venous outflow during nerve stimulation (Zimmerman and Gisslen, 1968; Carriere et al., 1980). Others found that an angiotensin converting enzyme inhibitor decreased

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the norepinephrine release evoked by low frequency renal nerve stimulation, suggesting adrenergic facilitation by endogenous levels of angiotensin II (Hayashi et al., 1991).

The observation of a dependence of the renal vasoconstrictor response to angiotensin II in the dog on an intact renal innervation suggested catecholamine release by the peptide (McGiff and Fasy, 1965). An actual increase in plasma norepinephrine caused by angiotensin II in the absence of electrical stimulation of sympathetic nerves has been observed by some investigators, but is considered to occur only with high doses of the peptide (Reid, 1992). However, it is conceivable that the renal vascular bed is particularly prone to release catecholamines through an action of angiotensin II.

The present investigation was begun as a result of an observation made in this laboratory that intrarenal arterial infusion of the α_1-adrenoceptor antagonist, prazosin, attenuated the renal vasoconstrictor response to angiotensin II in anesthetized rabbits. Because this finding is suggestive of renal catecholamine release by angiotensin II, we wished to further examine this adrenergic effect. Experiments were done to determine if this effect of angiotensin II required an intact renal nerve supply, was dependent on the adrenal medulla, or occurred in the renal vessels themselves.

2. Materials and methods

Experiments were conducted with the approval of the University of Minnesota Animal Care Committee. New Zealand White rabbits weighing 2.8–3.2 kg, fed rabbit chow, and allowed free access to water were studied. Rabbits were anesthetized with 30 mg/kg of sodium pentobarbital injected into a marginal ear vein. Two polyethylene 50 catheters were placed in the jugular vein for infusion of anesthetic and drug administration. A steady state of anesthesia was maintained throughout the experiment by the continuous intravenous infusion of sodium pentobarbital at 6–8 mg/kg/h, and the trachea was cannulated to allow spontaneous unimpeded respiration. The left carotid artery was cannulated with polyethylene 190 tubing that was connected to a Statham P23AA pressure transducer (Gould-Statham, Oxnard, CA, USA) for recording systemic arterial blood pressure.

The left renal artery was exposed through a retroperitoneal flank incision, and to provide better exposure of the renal hilum the rabbit was raised on a stand with a clamp connected to a spinous process. Renal blood flow was monitored with a precalibrated blood flow probe (5.5 mm in circumference, Carolina Medical Electronics, King, NC, USA) placed on the renal artery and connected to a Carolina electromagnetic flowmeter. The flow probe was zeroed, and about 5–10 min allowed for stabilization of blood pressure and renal blood flow. A 31 gauge needle, 5 mm in length, attached to polythylene 10 tubing was inserted into the renal artery for intrarenal arterial drug administration. After another stabilization period, blood pressure and renal blood flow were recorded on a Grass polygraph (Grass Instruments Co., Quincy, MA, USA).

In some experiments (groups I, III, and IV) the renal innervation was untouched, while in others the renal nerves were stimulated to evaluate the degree of α_1-adrenoceptor blockade or sectioned as in group II. Nerve stimulation was conducted by placing a small silver bipolar electrode around the left renal nerves and connecting the leads to a Grass stimulator (model S9). Square wave pulses, 8V in intensity and 1 ms in duration, were applied at frequencies of 2 and 4 Hz for a duration of 30 s. Renal denervation was accomplished by sectioning the nerves traversing the left renal artery and applying 80% phenol to the fatty hilar tissue through which other renal nerves pass.

To test the selectivity and specificity of prazosin, we studied its effect on renal vasoconstrictor responses to norepinephrine, 0.3 μg intrarenal arterially, and BHT-920, a specific α_2-adrenoceptor agonist (Kobinger and Pichler, 1981), at 5 and 40 μg intrarenal arterially.

2.1. Experimental protocols

Group I (n = 11)

The effect of α_1-adrenoceptor blockade on the renal vasoconstrictor response to high (maximally effective) doses of angiotensin II injected intravenously was determined in six experiments. After stabilization of blood pressure and renal blood flow, angiotensin II in doses of 50 and 100 ng/kg was administered as bolus injections with an interval of 10 min between injections. Five to 10 min after the control responses to angiotensin II were elicited, the α_1-adrenoceptor antagonist, prazosin, was infused intrarenal arterially at the dose of 5 μg/kg/min for 18–20 min, and the two doses of angiotensin II were repeated during the continued infusion of prazosin. Responses to a low dose, 10 ng/kg, of angiotensin II were elicited in five experiments and a protocol using prazosin as above was employed.

Group II (n = 5)

These experiments were conducted in a similar fashion as those of group I; however, renal denervation was performed instead of administering the adrenergic blocking agent. Responses to angiotensin II were evoked before and after denervation. Prazosin was also infused intrarenal arterially after denervation to ascertain whether α_1-adrenoceptor blockade produced an

additional effect on the responses to angiotensin II in the denervated kidney.

Group III (n = 5)

These experiments served as a time control for groups I and II. A sham-operation was carried out by exposure of the renal artery and nerve supply, but the innervation was left intact. Angiotensin II in the doses of 50 and 100 μg/kg was injected intravenously before and after sham operation, and then 0.9% saline was infused intrarenal arterially for 20 min, followed by a third series of angiotensin II injections during the infusion.

Group IV (n = 5)

This group of experiments was conducted to determine whether catecholamine release from the adrenal medulla evoked by angiotensin II might have reached the kidney through the adrenal rete (Katholi et al., 1981). After obtaining control responses to angiotensin II, the left adrenal gland was extirpated, blood pressure and renal blood flow were allowed to stabilize, and the injections of angiotensin II repeated.

Group V (n = 7)

To determine whether prazosin still depressed the response to angiotensin II, in the absence of renal neural input and the left adrenal gland, the following procedure was undertaken. In these experiments, angiotensin II was injected intrarenal arterially to produce selective renal vasoconstriction. Renal denervation was performed and the left adrenal gland was removed as described above. After stabilization of blood pressure and renal blood flow, angiotensin II (5 and 10 ng/kg) was given intrarenal arterially and shown to decrease renal blood flow, without increasing blood pressure. Prazosin was administered as in group I and the responses to angiotensin II were repeated during the prazosin infusion.

2.2. Drugs and chemicals

Prazosin and B-HT 920 were kindly supplied by Pfizer Corp. (Groton, CT, USA) and Dr. Karl Thomae (Karlsruhe, Germany), respectively. Angiotensin II and norepinephrine HCl were purchased from Sigma Chemical Co. (St. Louis, MO, USA).

2.3. Analysis of data

The response to intravenous angiotensin II appeared to be comprised of two components, a short-duration decrease in renal blood flow beginning approximately 5–6 s after injection followed by a longer-lasting component (Fig. 2). Although there may have been some overlapping of the two components, we considered them as separate to facilitate analysis of the cause(s) of the renal vasoconstriction. The short-duration component was taken as the immediate maximal decrease in renal blood flow, and the sustained component was represented by the area of the renal blood flow decrease until 4 min after the initial change in renal blood flow. Areas were measured using a planimeter. The short-duration vasoconstrictor response was expressed as a percent change from the control renal blood flow, and the percent changes, because they were not normally distributed, were subjected to square root transformation. Statistical analysis was by 1-way analysis of variance (ANOVA) with repeated measures. Dunnett's post-hoc test was applied to the mean differences after ANOVA. Values are presented as mean ± S.E.M. A P value of < 0.05 was considered statistically significant.

3. Results

The effectiveness of adrenergic blockade by prazosin was evaluated by its effect on renal vasoconstrictor responses to renal nerve stimulation. Prazosin caused a marked depression of the renal blood flow response to 2 Hz from 10 ± 2 to 2 ± 2% and 4 Hz from 33 ± 8 to 8 ± 3% ($P < 0.05$). Blockade of the α_1-adrenoceptors was verified by the attenuation of the renal vasoconstrictor response to norepinephrine with no significant effect on the responses to B-HT 920 (Table 1).

3.1. Group I – Effect of prazosin on the response to intravenous administration of angiotensin II

Bolus intravenous injection of 50 and 100 ng/kg of angiotensin II caused similar increases in blood pressure (Table 2) and decreases in renal blood flow (Figs. 1 and 2). The similar magnitude of the responses is due to a near-maximal effect on renal blood flow with these doses. Intrarenal arterial administration of prazosin had no significant effect on either the control blood pressure (Table 2) or renal blood flow (49 ± 4 to 45 ± 5 ml/min). Prazosin attenuated the angiotensin II-induced renal vasoconstrictor responses, both the short-

Table 1
Renal blood flow responses to norepinephrine and B-HT 920 before and after prazosin treatment

	Dose	Control %Δ renal blood flow	After prazosin %Δ renal blood flow
Norepinephrine ($n = 4$)	0.3 μg	−22 ± 6	−6 ± 4 [a]
B-HT 920 ($n = 5$)	5 μg	−24 ± 2	−21 ± 2
	40 μg	−38 ± 5	−37 ± 4

[a] $P < 0.05$, vs. control.

Table 2
Control and changes in systemic blood pressure, (in mm Hg) to angiotensin II given intravenously in groups I–IV

			Change in blood pressure Angiotensin II (μg/kg)		
			10	50	100
Group I	Control BP	118±3	–	26±1	26±2
(n = 11)	Prazosin	114±3	–	17±4	23±4
	Control BP	113±4	6±1	–	–
	Prazosin	104±6	5±1		
Group II	Control BP	110±4		18±1	19±3
(n = 5)	Denervation	106±6		16±3	23±3
Group III	Control BP	99±2		20±1	26±2
(n = 5)	Sham	94±2		25±1	22±1
	Saline	93±4		15±3	20±3
Group IV	Control BP	112±5		24±6	27±6
(n = 5)	Adrenalectomy	112±4		17±3	25±5

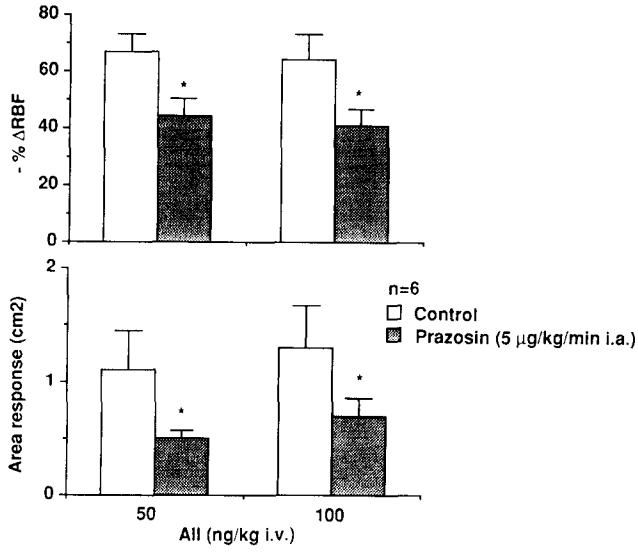

Fig. 1. Bar graph showing effect of prazosin, 5 μg/kg/min, given intrarenal arterially for 20 min on angiotensin II-induced renal vasoconstriction (group I, n = 6). The two doses of angiotensin II (50 and 100 ng/kg) were given as intravenous bolus injections before and during prazosin infusion. Renal blood flow responses to angiotensin II are expressed as percent decrease from control (−% ΔRBF), upper panel and area (cm^2), lower panel. * $P < 0.05$ vs. control.

duration and area of the response (Fig. 1). The reduction in the two components of the renal blood flow responses to angiotensin II, 50 and 100 ng/kg, by prazosin ranged between 32 and 56%, representing a substantial decrease due to α_1-adrenoceptor blockade. A tracing of a representative experiment showing the depressant effect of prazosin on the responses to these maximally effective doses to angiotensin II is shown in Fig. 2. Although prazosin also decreased the blood pressure increase produced by intravenous angiotensin II in this experiment, in the overall analysis this effect was not significant (Table 2). Not only did prazosin reduce the responses to maximally effective doses of angiotensin II, but it also reduced similarly the initial response to a low dose, 10 ng/kg, of angiotensin II given intravenously, from a 24 ± 5 to 12 ± 2% decrease in renal blood flow (n = 5, $P < 0.05$).

3.2. Group II – Effect of renal denervation followed by prazosin on the response to intravenous administration of angiotensin II

The increments in blood pressure and the effect on renal blood flow evoked by two dose levels of angiotensin II in group II were similar to those obtained in group I (Table 2 and Fig. 3). Renal denervation had no significant effect on either basal blood pressure or on renal blood flow (51 ± 3 to 56 ± 6 ml/min). Follow-

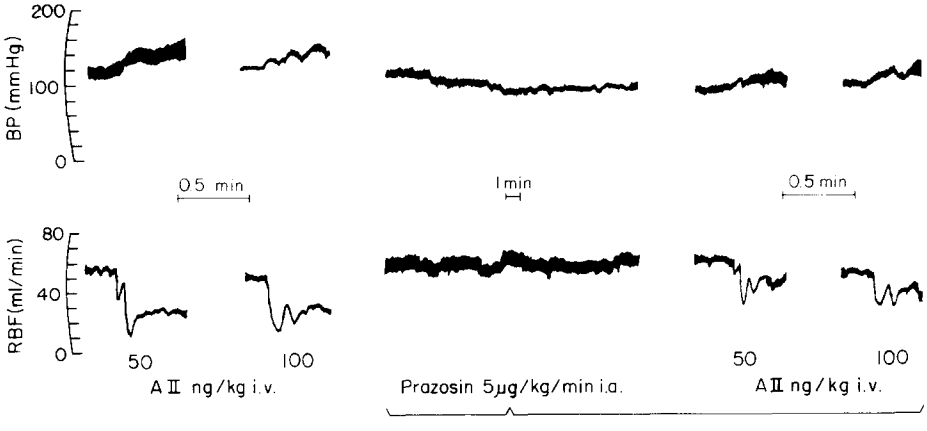

Fig. 2. Representative tracing showing a single experiment in group I. Responses to angiotensin II, 50 and 100 ng/kg, given intravenously were elicited before and during infusion of prazosin. Prazosin was infused for 18 min before repeating the angiotensin II injections. At the onset of the response to angiotensin II, the recorder paper speed was increased to 50 cm/min, as indicated by a 0.5 min time interval mark.

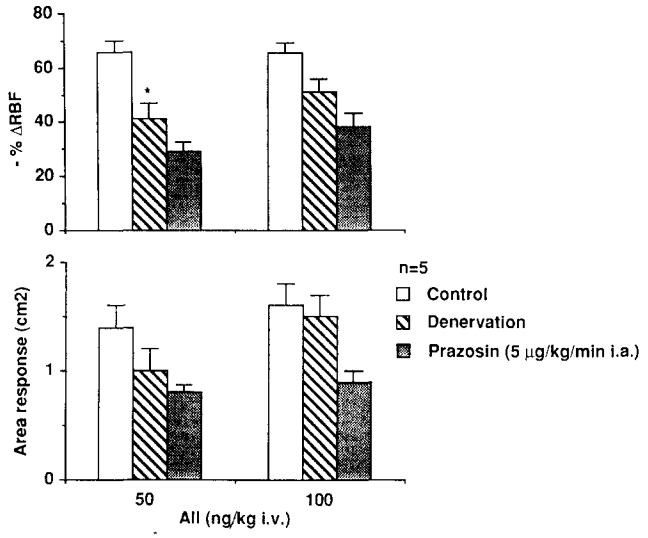

Fig. 3. Bar graph showing effect of denervation followed by prazosin infusion on angiotensin II-induced renal vasoconstriction (group II, $n = 5$). Renal denervation was performed after the control responses to angiotensin II, and the injections were repeated after stabilization of blood pressure and renal blood flow. Renal blood flow responses to angiotensin II are expressed as percent decrease from control ($-\%$ ΔRBF), upper panel and area (cm^2), lower panel. Prazosin was infused as in group I above. * $P < 0.05$ vs. control.

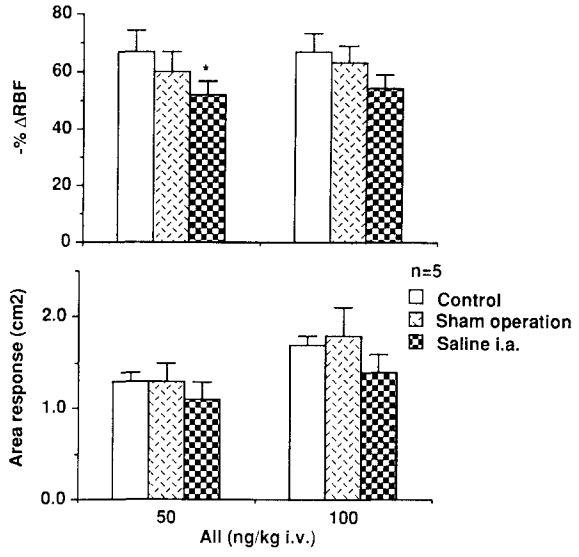

Fig. 4. Bar graph showing results of control experiments (group III, $n = 5$) in which sham operation and intrarenal arterial infusion of saline were substituted for renal denervation and intrarenal prazosin infusion. Renal blood flow responses to angiotensin II are expressed as percent decrease from control ($-\%$ ΔRBF), upper panel and area (cm^2), lower panel.

ing denervation, the short-duration renal blood flow response to the low dose but not the high dose of angiotensin II was significantly decreased. Denervation had no significant effect on the area of the renal blood flow response. The administration of prazosin to the denervated kidney decreased the short duration response and area of the response as in group I; however, the data obtained with prazosin in group II will be interpreted with caution as will be explained below.

3.3. Group III – Effect of sham operation and vehicle on response to intravenous administration of angiotensin II

The basal blood pressure (Table 2) and renal blood flow remained stable (43 ± 2 to 48 ± 4 ml/min) for the duration of these experiments attesting to a steady baseline hemodynamic state. Reproducibility of the angiotensin II responses was also noted by the consistent blood pressure and renal blood flow effect before and after the sham operation (Fig. 4). When the injections of angiotensin II were repeated after the sham operation during saline infusion the response to the higher dose was unchanged, but there was a small decrease (23%) in the lower dose response. Thus, statistical comparisons of responses before and after interventions were made only between the control and a single repeat injection after an intervention to avoid the small degree of tachyphylaxis noted in these experiments.

3.4. Group IV – Effect of left adrenalectomy on response to intravenous administration of angiotensin II

Left adrenalectomy had no significant effect on basal blood pressure (Table 2), renal blood flow (39 ± 4 to

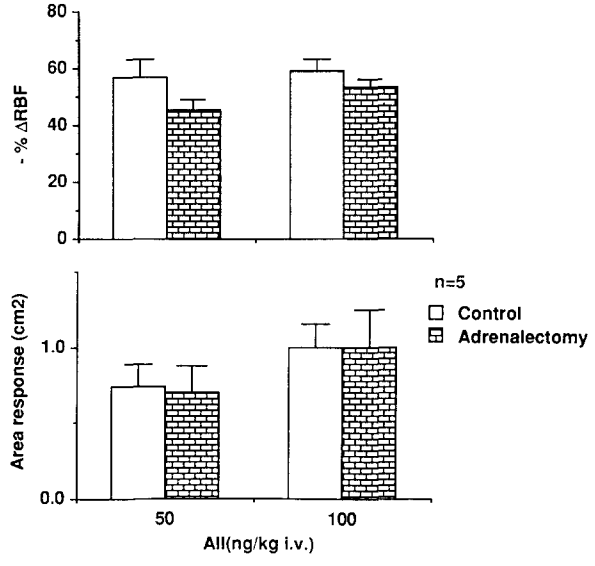

Fig. 5. Bar graph showing effect of unilateral adrenalectomy on angiotensin II-induced renal vasoconstriction (group IV, $n = 5$). Left adrenal gland was removed after the control reponses to angiotensin II, and the injections were repeated after stabilization of blood pressure and renal blood flow. Renal blood flow responses to angiotensin II are expressed as percent decrease from control ($-\%$ ΔRBF), upper panel and area (cm^2), lower panel.

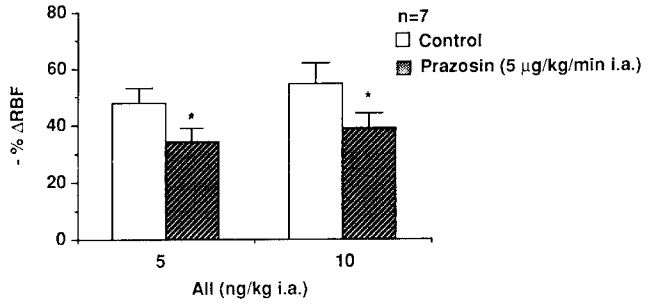

Fig. 6. Bar graph showing effect of prazosin on angiotensin II-induced renal vasoconstriction (group V, $n = 7$). The left adrenal gland was extirpated and the kidney denervated prior to the control angiotensin II injections. The two doses of angiotensin II (5 and 10 ng/kg) were given intrarenal arterially instead of intravenously before and during prazosin infusion. Renal blood flow responses to angiotensin II are expressed as percent decrease from control (−% ΔRBF). $^{*}P < 0.05$ vs. control.

43 ± 5) or on the renal vasconstrictor responses elicited by intravenous administration of angiotensin II (Fig. 5).

3.5. Group V – Effect of prazosin on the response to intrarenal arterial administration of angiotensin II after left adrenalectomy and renal denervation

Basal blood pressure (Table 2) and renal blood flow (43 ± 3 ml/min) in group V was similar to that in the other four groups of rabbits. Because the response to the intrarenal arterial injection of angiotensin II appeared as a single component, only the maximal change in renal blood flow was analyzed. Prazosin caused a reduction in both renal blood flow responses to angiotensin II which amounted to decreases of approximately 29% (Fig. 6).

4. Discussion

Intravenous administration of bolus doses of angiotensin II in the anesthetized rabbit produced renal vasoconstriction, a portion of which was amenable to α_1-adrenoceptor blockade. The effect of prazosin was specific since the response to norepinephrine, an α_1-adrenoceptor agonist, was blocked, but not that to the specific α_2-adrenoceptor agonist, B-HT 920.

Renal vasoconstrictor responses to angiotensin II were characterized by a short-duration maximal fall in renal blood flow followed by a more sustained decrease in renal blood flow. In order to analyze these responses, the maximal change in renal blood flow and area of the renal blood flow response were measured. More than a single mechanism appears to contribute to the renal blood flow response, and these will be discussed in the context of the experimental protocols conducted.

4.1. Effect of prazosin on angiotensin II-induced renal vasoconstriction (group I)

Prazosin in the dose administered was effective in producing α_1-adrenoceptor blockade as judged by marked suppression of vasoconstrictor responses to renal nerve stimulation at frequencies of 2 and 4 Hz. Prazosin also attenuated the renal response to angiotensin II. Both the short-duration and area of the renal vasoconstrictor response to angiotensin II were affected, indicating adrenergic involvement in both components of the response. In order to rule out a time trend or tachyphylaxis, the sham experiments (group III) were conducted. In those experiments, the magnitude of the renal vasoconstrictor response was reproducible after repeated administration, thus it can be concluded that pharmacological blockade was responsible for attenuating the response to angiotensin II. After a third series of injections, there was some decrease in the lower dose angiotensin II response suggesting tachyphylaxis, making comparisons between control and the third series of responses less reliable. Based on the attenuation of the short-duration and area of response by prazosin, an adrenergic interaction was suggested to contribute to both components of the renal blood flow response to angiotensin II.

4.2. Effect of renal denervation on angiotensin II-induced renal vasoconstriction (group II)

Acute renal denervation also depressed the short-duration component of the renal blood flow response, indicating that this component depended in part on the renal nerves; there also appeared to be some nonneural involvement since the short-duration response was not totally abolished by denervation or prazosin. The absence of total blockade may be explained by an overlapping of an adrenergic neural effect and direct vasoconstrictor action of angiotensin II.

Since prazosin decreased the area of the response to angiotensin II, but denervation did not, this suggested an additional adrenergic contribution to the sustained component of the response. We surmised that angiotensin II either released norepinephrine from renal adrenergic nerve terminals (McGiff and Fasy, 1965) or sensitized the vascular smooth muscle to circulating catecholamines (Day and Moore, 1976; Povolny et al., 1977). Because the sustained effect was unchanged after denervation, this component of the angiotensin II response was not due to a central effect or facilitation of transmitter release, mechanisms requiring an intact renal nerve supply.

4.3. Effect of left adrenalectomy on angiotensin II-induced renal vasoconstriction (group IV)

Because catecholamine release appeared to explain, at least in part, the sustained component of the renal

blood flow response to angiotensin II, liberation of catecholamine from the adrenal medulla was considered. One pathway for such an effect was the adrenal rete, which allows passage of catecholamines from the adrenal gland directly into the kidney (Katholi et al., 1981). However, the absence of an effect of left adrenalectomy on the renal blood flow response to angiotensin II in group IV negated this possibility. A more likely possibility is that angiotensin II releases norepinephrine from the renal adrenergic nerves, a tyramine-like effect. Such a mechanism would need to be confirmed by additional experiments.

4.4. Effect of prazosin on response to angiotensin II after left adrenalectomy and renal denervation (group V)

Renal vasoconstriction elicited by intrarenal arterial administration of angiotensin II was reduced by prazosin. Thus, with the potential release of catecholamines from the adrenal medulla eliminated and in the absence of renal neural input, there remained an adrenergic contribution to the effect of angiotensin II, and this appears due to catecholamine release from renal adrenergic nerve terminals. This effect may be responsible for the sustained component of the response to intravenous administration of angiotensin II.

Our results indicating a neural cause of the short-duration component of the response to intravenous injected angiotensin II are compatible with the study of Aars in anesthetized rabbits (Aars, 1972), showing a transient increase in renal sympathetic nerve activity due to angiotensin II given by the intravenous route. At variance with these findings was the lack of evidence of any increase in renal nerve activity in conscious rabbits given an intravenous infusion of angiotensin II (Matsumura et al., 1989). Disagreement between the results of these studies can be attributed to the difference in the doses of angiotensin II administered. Probably relatively high doses, high dose infusion in the Aars investigation and bolus doses in the present study, are required to evoke renal sympathetic nerve firing. As referred to in the Introduction, angiotensin II acts at various central sites, which when stimulated increase peripheral sympathetic nerve activity. Assuming that the short-duration response that we have observed and the above are due to central stimulation, this adrenergic component requires an intravenous bolus dose of angiotensin II to be evoked.

It is, however, not possible to separate a central stimulatory from a peripheral adrenergic facilitating effect based on the present study. It is quite possible that the mechanism of angiotensin II to enhance adrenergic transmitter release came into play during the short-duration response. This action of angiotensin II has been shown to be particularly prominent in the renal vascular bed (Zimmerman et al., 1972), and is a good candidate for providing an explanation for the short-duration response. This initial effect was only a minor part of the overall renal vasoconstriction produced by intravenous angiotensin II, since the area of response was not significantly decreased after denervation. The overall adrenergic contribution to the renal vasoconstrictor effect of angiotensin II is, however, important in this species. Quantitative examination of the decrease in the angiotensin II-evoked vasoconstrictor response by prazosin (Figs. 1 and 2) reveals that the adrenergic contribution and the direct contribution (effect after prazosin) to the response are about equal.

Because bolus doses of angiotensin II were used in the present study to allow detection of the initial short-duration response, it is difficult to know whether this dual adrenergic contribution to angiotensin II-induced renal vasoconstriction is physiologically relevant in the rabbit. That an adrenergic effect also occurred with the low dose of angiotensin II suggests that it is not solely a high dose effect. It is safe to conclude that beside the potent direct renal vasoconstrictor action of angiotensin II, i.e. the effect on the vascular smooth muscle, the peptide has the capacity to trigger an adrenergic action dependent on intact renal nerves, and also an adrenergic component not requiring an intact nerve supply.

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