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Intrarenal Vascular Effects of [Des-Asp^1]Angiotensin I and Angiotensin III in the Dog

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SUMMARY **We determined the effects of direct renal intra-arterial injections of [des-Asp^1]angiotensin I (0.2–3.2 μg) and angiotensin III (0.00625–0.1 μg) on renal blood flow in 10 dogs anesthetized with pentobarbital. Both [des-Asp^1]angiotensin I and angiotensin III caused dose-dependent decreases in renal blood flow. The decreases in ipsilateral renal blood flow occurred in the absence of alterations in systemic arterial pressure and flow to the contralateral kidney, suggesting that the response was a local event. The renovascular responses to [des-Asp^1]angiotensin I were greatly attenuated during the intravenous administration of SQ 20881, a synthetic peptide that competitively inhibits angiotensin converting enzyme, SQ 20881 did not alter the vasoconstrictor responses to angiotensin III, angiotensin II, or norepinephrine. [Ile^7]Angiotensin III (an angiotensin III antagonist) abolished decreases in renal blood flow produced by [des-Asp^1]angiotensin I, angiotensin II, angiotensin III, and angiotensin I, whereas the response to norepinephrine was unchanged. These results suggest that the decrease in renal blood flow produced by [des-Asp^1]angiotensin I is due to its local enzymatic conversion to angiotensin III. About 7% of [des-Asp^1]angiotensin I is converted to angiotensin III during one transit through the kidney.** ***Circ Res 44:666–671, 1979***

IT HAS BEEN demonstrated recently that [des-Asp^1]angiotensin II (angiotensin III) is as potent as angiotensin II in decreasing renal blood flow, and it was hypothesized that the local production of angiotensin III occurs at the level of the renal arteriolar receptor (Freeman et al., 1975). Data are available to support the existence of two pathways for the generation of angiotensin III: the first from angiotensin II by the cleavage of the N-terminal aspartic acid through the action of aminopeptidases (Glenner et al., 1962; Regoli et al., 1963), and the second from the nonapeptide [des-Asp^1]angiotensin I by the cleavage of the C-terminal dipeptide histidyl-leucine through the action of angiotensin converting enzyme (Tsai et al., 1975).

The present experiments assessed the ability of the kidney to form angiotensin III by the second pathway. The effects of [des-Asp^1]angiotensin I and angiotensin III on renal blood flow were examined in the presence and absence of a synthetic nonapeptide, SQ 20881 (Pyr-Trp-Pro-Arg-Pro-Glr-Ile-Pro-Pro), that inhibits angiotensin converting enzyme (Ferreira et al., 1970a, 1970b; Cushman et al., 1971; Ondetti et al., 1971; Schaeffer et al., 1971; Yang et al., 1971). Experiments also were performed in the presence and absence of [Ile^7]angiotensin III, an angiotensin III antagonist (Peach, 1977). The results suggest that the renal vasoconstrictor effects of [des-Asp^1]angiotensin I are due to its local enzymatic conversion to angiotensin III. About 7% of [des-Asp^1]angiotensin I is converted to angiotensin III during one transit through the renal vasculature.

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Methods

Experiments were performed on 10 mongrel dogs of either sex (9–13 kg) anesthetized with sodium pentobarbital (25 mg/kg, iv). Dogs were maintained on a normal diet (Nutrena) and tap water ad libitum. Femoral artery blood pressure was monitored with a pressure transducer (Statham P23Db) and recorded on a polygraph (Grass). A femoral vein was cannulated for the administration of drugs and additional anesthetic. All dogs were ventilated mechanically with a respirator (Harvard) and were paralyzed by the intravenous administration of gallamine (0.2 mg/kg). Minute volume ventilation was selected by reference to the nomogram of Kleinman and Radford (1964). The dogs were given heparin (300 IU/kg, iv) at the beginning of each experiment.

A left flank incision was performed to expose the left renal artery. Blood flow to the kidney was measured by a noncannulating electromagnetic flow probe (Carolina Electronics Co.) placed around the renal artery, with care being taken not to damage the renal nerves. Distal to the flow probe a curved, 23-gauge needle attached to polyethylene tubing (PE 50) was inserted into the renal artery for the administration of drugs. The zero-flow baseline was established at the beginning of each experiment and was checked at its termination by mechanically occluding the artery distal to the flow probe. The flow probe was calibrated at the end of each experiment by cannulating the distal end of the renal artery with polyethylene tubing and diverting flow to a graduated cylinder. At all flow levels, the relationship between the output of the flow probe and the directly measured renal blood flow was linear.

In each dog, the effects of five graded doses (0.2, 0.4, 0.8, 1.6, and 3.2 μg) of [des-Asp^1]angiotensin I [0.75 μmol of peptide/mg (89% [des-Asp^1]angiotensin I); Bachem Inc.] and of five doses (0.00625, 0.0125, 0.025, 0.05, and 0.1 μg) of angiotensin III [0.98 μmol of peptide/mg (91% angiotensin III); Bachem Inc.] on renal blood flow were tested. The changes in renal blood flow were reported as a percent of maximal amplitude of change produced by a given agonist. Preliminary experiments established that these dose ranges of each agonist were approximately equipotent with regard to constrictor responses in the renal vasculature. Also evaluated were test doses of angiotensin I [0.8 μg; 0.67 μmol of peptide/mg (87% angiotensin I); Schwarz-Mann], angiotensin II [0.025 μg; 0.86 μmol of peptide/mg (90% angiotensin II); Schwarz-Mann], and norepinephrine (0.5 μg, Winthrop). All agonists were dissolved in saline and were injected in equivalent volumes (0.2 ml) into the injection catheter, after which they were rapidly flushed (3 seconds) into the renal arterial blood with 0.5 ml of saline. The injection schedule with respect to agonist and dose was randomized, and sufficient time (10 minutes), as determined in preliminary studies, elapsed between injections so that tachyphylaxis did not develop.

In two of the dogs, renal blood flow was measured simultaneously in both renal arteries. In this manner, flow to the contralateral kidney served as a control for responses that were mediated by reflexes or for recirculation of drugs injected intra-arterially into the ipsilateral kidney.

In five dogs, an abbreviated schedule of the previously mentioned doses of [des-Asp^1]angiotensin I (0.2, 0.8, and 3.2 μg), angiotensin III (0.00625, 0.025, and 0.1 μg), angiotensin I (0.8 μg), angiotensin II (0.025 μg), and norepinephrine (0.5 μg) was repeated after the intravenous administration of SQ 20881 [0.85 μmol peptide/mg (94% SQ 20881); Bachem Inc.]. A priming dose of 2.5 mg of SQ 20881 was given as a bolus, and a sustaining infusion of 5 μg/min per kg was administered for the remainder of the experiment, during which the doses of the agonists were repeated. Data obtained before and during the infusion of SQ 20881 were plotted in double-reciprocal fashion, according to the Lineweaver-Burk method (Lineweaver and Burk, 1934).

In four dogs, the abbreviated schedule of agonist doses was repeated after the administration of [Ile^7]angiotensin III [1.02 μmol of peptide/mg (91% [Ile^7]angiotensin III); Bachem Inc.]. [Ile^7]Angiotensin III was given intravenously at a rate of 2.5 μg/min per kg throughout the period, during which the doses of agonists were being repeated.

The calculation for estimating the percent conversion of [des-Asp^1]angiotensin I to angiotensin III has been described previously (DiSalvo and Montefusco, 1971). The ratio of equipotent doses of angiotensin III to [des-Asp^1]angiotensin I, with respect to percent decreases in renal blood flow (Fig. 1), was multiplied by 1.29 to estimate the percent conversion. The factor 1.29 corrects for the difference in molecular weights between [des-Asp^1]angiotensin I and angiotensin III and converts the dose ratio into a molar ratio.

Results were expressed as percent change from control renal blood flow measured immediately before injection of the agonist. The significance of differences between changes in renal blood flow caused by agonists before and after the administration of SQ 20881 or [Ile^7]angiotensin III were evaluated with Student's paired *t*-test (Zar, 1974). All results were expressed as mean ± 1 SE.

Results

Injections of [des-Asp^1]angiotensin I or angiotensin III directly into the renal artery caused dose-dependent decreases in renal blood flow (Fig. 1) which were rapid in onset (2–4 seconds), attained maximal levels within approximately 10 seconds, and returned to control levels during the following 1–2 minutes. Injections of the saline vehicle pro-

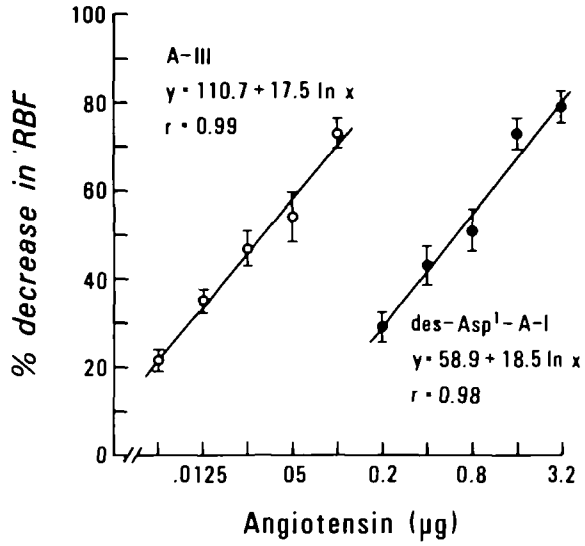

FIGURE 1 *Dose-response curves as determined by least-squares regressions for the decrease in renal blood flow caused by angiotensin III (unfilled circles) and [des-Asp¹]angiotensin I (filled circles). Each point represents the mean response of 10 dogs; vertical line represents ± 1 SE. Agonist dose is shown on a log scale.*

duced no alteration in renal blood flow. The dose-response curves for [des-Asp¹]angiotensin I and angiotensin III were parallel. Generally, angiotensin III was about 16 times more potent than [des-Asp¹] angiotensin I on a molar basis.

For each dose of [des-Asp¹]angiotensin I tested, the equipotent dose of angiotensin III can be estimated from the dose-response relationship (Fig. 1). This information allows an estimate of the amount of intrarenal conversion of [des-Asp¹]angiotensin I to angiotensin III. The calculated values for percent conversion at different doses of agonist throughout the range examined are shown in Table 1.

Decreases in renal blood flow produced by the intrarenal injection of [des-Asp¹]angiotensin I and angiotensin I were greatly attenuated during inhibition of angiotensin converting enzyme by the intravenous administration of SQ 20881 (Figs. 2 and 3). In contrast, decreases in renal blood flow produced by norepinephrine, angiotensin II, and angiotensin III were not affected by SQ 20881. Although systemic arterial pressure was not altered by the dose of SQ 20881 given, there was a significant ($P < 0.01$) increase in baseline renal blood flow. Left renal blood flow increased from 113 ± 9 ml/min before SQ 20881 injection to 164 ± 13 ml/min after the initial priming dose plus 60 minutes of the sustaining dose of SQ 20881. Lineweaver-Burk plots show that the ordinate intercepts ($1/V_{max}$) generated by [des-Asp¹]angiotensin I in the presence and absence of SQ 20881 were similar (Fig. 4). Also, it should be noted that $1/V_{max}$ was similar for both [des-Asp¹]angiotensin I and angiotensin III.

Blockade of angiotensin III receptors with [Ile⁷] angiotensin III almost abolished the renal vasoconstrictor effects produced by angiotensin I, [des-Asp¹]angiotensin I, angiotensin II, and angiotensin III (Figs. 5 and 6); however, [Ile⁷]angiotensin III did not alter the renal blood flow response to norepinephrine. As observed with intravenous administration of SQ 20881, [Ile⁷]angiotensin III had no significant effects on systemic arterial pressure. However, in contrast to SQ 20881, [Ile⁷]angiotensin

TABLE 1 *Percent Conversion of [Des-Asp¹]Angiotensin I to Angiotensin III in Renal Vasculature*

Dose of [des-Asp¹] angiotensin I tested (μg)	Estimated equivalent dose of angiotensin III (μg)*	Percent conversion of [des-Asp¹]angiotensin I to angiotensin III†
0.2	0.0093	6.00
0.4	0.0210	6.77
0.8	0.0325	5.24
1.6	0.1162	9.37
3.2	0.1563	6.30
		6.74 (mean)

* Estimated from dose-response relationship in Figure 1.
† Conversion (%) = angiotensin III (μg)/[des-Asp¹]angiotensin I (μg) × 1.29 × 100.

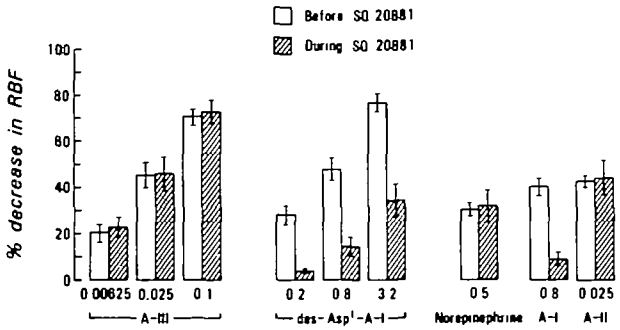

FIGURE 2 *Effects on renal blood flow of angiotensin III, [des-Asp¹]angiotensin I, norepinephrine, angiotensin I, and angiotensin II before and during the administration of SQ 20881. Responses are shown as mean ± 1 SE (n = 5).*

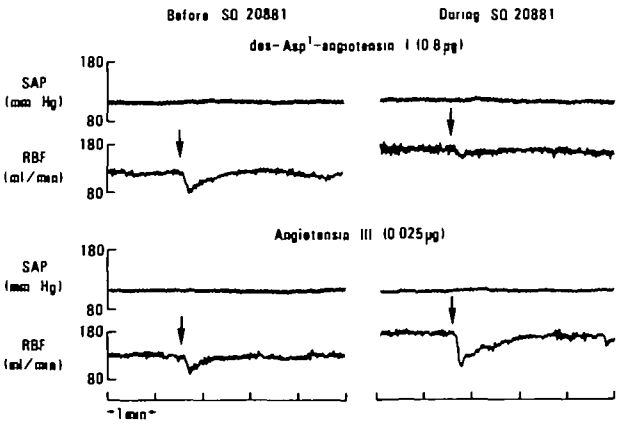

FIGURE 3 *Effects on renal blood flow (RBF) and systemic arterial pressure (SAP) of [des-Asp¹]angiotensin I and angiotensin III before and during inhibition of angiotensin converting enzyme with SQ 20881. Arrows represent agonist injection.*

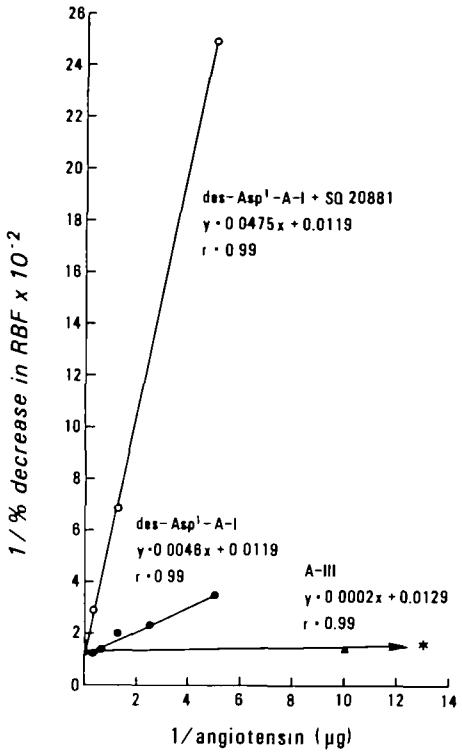

FIGURE 4 *Lineweaver-Burk plot for responses to [des-Asp¹]angiotensin I in the presence and absence of SQ 20881 and for angiotensin III. Points represent mean values (n = 5); lines represent calculated least-squares fit for equations shown. Higher doses of angiotensin III used to determine the regression line are not shown. Coordinates used for the four higher doses were: 20 μg, 0.0185; 40 μg, 0.0215; 80 μg, 0.0283; and 160 μg, 0.0461.*

III did not alter the baseline for renal blood flow.

In two dogs, blood flow to both kidneys was recorded simultaneously (Fig. 7). The intravenous injection of [des-Asp¹]angiotensin I (1.6 μg) increased systemic arterial pressure and decreased flow to both kidneys. However, [des-Asp¹]angiotensin I or angiotensin III administered directly into the left renal artery resulted in the usual vasoconstriction in the ipsilateral renal vasculature but no alteration in systemic arterial pressure or in flow to the contralateral kidney.

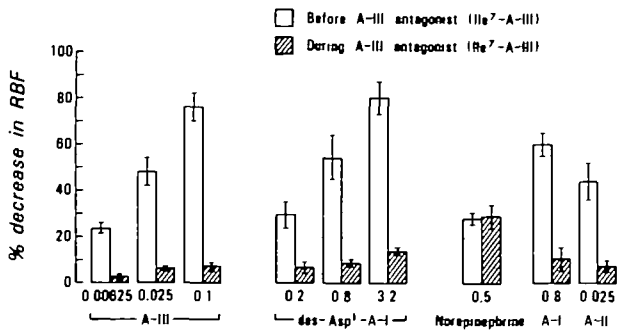

FIGURE 5 *Effects on renal blood flow of angiotensin III, [des-Asp¹]angiotensin I, norepinephrine, angiotensin I, and angiotensin II before and during the administration of [Ile⁷]angiotensin III. Responses are shown as mean ± 1 SE (n = 4).*

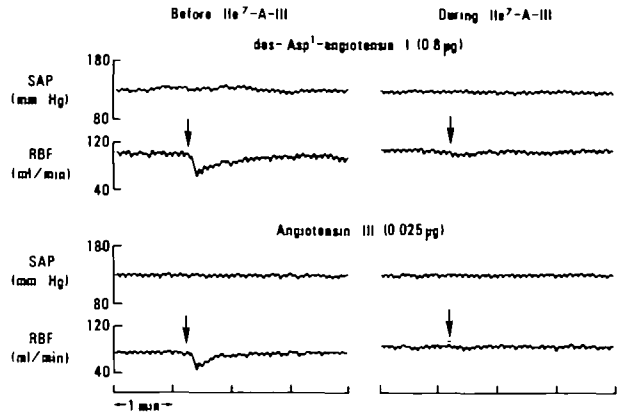

FIGURE 6 *Effects on renal blood flow (RBF) and systemic arterial pressure (SAP) of [des-Asp¹]angiotensin I and angiotensin III before and during antagonism of angiotensin III with [Ile⁷]angiotensin III. Arrows represent agonist injection.*

Discussion

The results of the present study show that (1) [des-Asp¹]angiotensin I and angiotensin III cause dose-dependent decreases in renal blood flow; (2) angiotensin III as a vasoconstrictor is 16 times more potent than [des-Asp¹]angiotensin I; (3) during inhibition of angiotensin converting enzyme with SQ 20881, vasoconstriction produced by [des-Asp¹]angiotensin I is greatly attenuated, whereas the vasoconstrictor responses elicited by angiotensin III or norepinephrine are unaltered; and (4) vasoconstriction produced by either [des-Asp¹]angiotensin I or angiotensin III is significantly reduced in the presence of angiotensin III antagonist [Ile⁷]angiotensin III, whereas constriction caused by norepinephrine is unchanged. These findings suggest that the renal vascular response to [des-Asp¹]angiotensin I is due to its intrarenal enzymatic conversion to angiotensin III. This conversion is about 7%.

The demonstration that renal vasoconstrictor responses produced by [des-Asp¹]angiotensin I were rapid in onset and occurred in the absence of significant changes in systemic arterial blood pressure shows that the responses were due to an intrarenal mechanism. Further support for this view is derived from the finding that [des-Asp¹]angiotensin I and angiotensin III, when injected directly into the left renal artery, produced no change in flow to the right kidney. Thus, the renal constrictor responses elicited by [des-Asp¹]angiotensin I and angiotensin III are not a consequence of recirculation or a reflex mechanism.

Our finding that angiotensin III produces pronounced vasoconstriction in the kidney confirms results obtained by other laboratories (Freeman et al., 1975, 1976, 1978). The demonstration that [des-

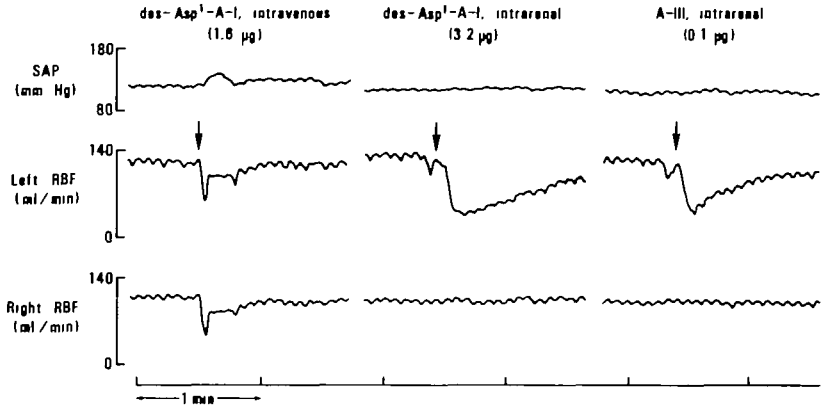

FIGURE 7 *Effects on simultaneously measured left and right renal blood flow (RBF) and systemic arterial pressure (SAP) of [des-Asp¹]angiotensin I and angiotensin III when administered intravenously or intrarenally into the left renal artery. Arrows represent agonist injection.*

Asp¹]angiotensin I causes vasoconstriction by its intrarenal conversion to angiotensin III is a new observation. Freeman et al. (1978) have shown that the intravenous administration of [des-Asp¹]angiotensin I and angiotensin III produced qualitatively similar effects on renal blood flow and renal function. However, their study did not differentiate between a local intrarenal effect of [des-Asp¹]angiotensin I and an effect from its conversion to angiotensin III, which could have occurred during passage through the pulmonary circulation. That pronounced pulmonary conversion likely occurred is supported by the finding of the present study that angiotensin III is 16 times more potent than [des-Asp¹]angiotensin I when given intrarenally, whereas Freeman et al. (1978) found that angiotensin III was only three times more potent than [des-Asp¹] angiotensin I when given intravenously.

Formation of angiotensin III from injected [des-Asp¹]angiotensin I may occur in blood during the time required for transit from the site of injection to the site of action in the renal vasculature. This is not likely because the activity of the angiotensin converting enzyme in dog blood is too low to permit extensive conversion in the 2–4 seconds that elapsed between the injection of [des-Asp¹]angiotensin I into the renal artery and the onset of the renal vasoconstriction (Oparil et al., 1970; Yang et al., 1971).

Renal vasoconstriction produced with [des-Asp¹] angiotensin I could result from its direct interaction with vascular smooth muscle or from the local enzymatic conversion to angiotensin III or from both mechanisms. Accordingly, SQ 20881 could inhibit responses to [des-Asp¹]angiotensin I by preventing interaction between [des-Asp¹]angiotensin I and vascular smooth muscle or by inhibiting angiotensin converting enzyme. Either mechanism is consistent with the finding that SQ 20881 did not alter responses to angiotensin III. Ample evidence exists showing that SQ 20881 inhibits angiotensin converting enzyme in vitro and in vivo (Cushman et al., 1971; DiSalvo et al., 1973; Ondetti et al., 1971; Yang et al., 1971). Because data bearing on interaction between SQ 20881 and [des-Asp¹]angiotensin I are lacking, it is presumed in this study that the effects of SQ 20881 are due primarily to inhibition of angiotensin coverting enzyme. Constrictor responses to [des-Asp¹]angiotensin I that persist in the presence of SQ 20881 could result partly from incomplete inhibition of angiotensin converting enzyme or from a small amount of vasoactivity that [des-Asp¹]angiotensin I may possess or from both mechanisms.

An increase in renal blood flow was associated with the intravenous infusion of SQ 20881. This increase in flow might indicate a role of the renin-angiotensin system in the local regulation of renovascular resistance. However, SQ 20881 also potentiates the actions of bradykinin, mainly by preventing its enzymatic degradation (Ferreira et al., 1970a; Greene et al., 1972). Thus, the renal vasodilation may have been due to potentiation of locally formed or circulating bradykinin. In support of this view is the finding that [Ile⁷]angiotensin III had no effect on baseline renal blood flow at a dose that almost abolished the responses to angiotensin I, [des-Asp¹] angiotensin I, angiotensin II, and angiotensin III.

The finding that [Ile⁷]angiotensin III inhibits the renovascular constrictor response to both [des-Asp¹]angiotensin I and angiotensin III supports the hypothesis that the responses of [des-Asp¹]angiotensin I result from formation of angiotensin III and subsequent stimulation of angiotensin III receptors. Because [Ile⁷]angiotensin III did not antagonize constrictor responses to norepinephrine, the blockade effects of [Ile⁷]angiotensin III appear to be specific for angiotensin peptides. [Ile⁷]angiotensin III also blocked the constrictor responses elicited by angiotensin I and angiotensin II, which suggests that the renal vasculature does not show a preferential receptor affinity for the octapeptide or the heptapeptide. However, such preferential affinity has been demonstrated for the adrenal cortex and the systemic arterioles (Sarstedt et al., 1975; Peach, 1977).

Double-reciprocal plots of decreases in renal blood flow obtained with [des-Asp¹]angiotensin I and angiotensin III in the presence and absence of SQ 20881 permit examination of the mechanism of

SQ 20881 inhibition and agonist-receptor interactions (Lineweaver and Burk, 1934; Goldstein et al., 1968). It is recognized that applicability of Lineweaver-Burk analysis to in vivo systems is limited, and the assumptions implicit in such analysis have been discussed previously (DiSalvo et al., 1971). However, Lineweaver-Burk plots do provide insight into mechanisms of agonist and antagonist action (Goldstein et al., 1968). The analysis suggests a predominately competitive type of enzyme inhibition, because calculated K_S values obtained in the presence and absence of SQ 20881 were different, but ordinate intercepts ($1/V_{max}$) were similar. Presumably, angiotensin III formed in the kidney from exogenously administered [des-Asp^1]angiotensin I interacts with the same vascular receptors that interact with exogenously administered angiotensin III. This inference agrees with the observation that the ordinate intercepts ($1/V_{max}$) for both [des-Asp^1] angiotensin I and angiotensin III were similar and is further evidence that the effects of [des-Asp^1] angiotensin I are consequent to its conversion to angiotensin III. In further corroboration with the view that [des-Asp^1]angiotensin I and angiotensin III are acting through an identical mechanism (that is, interaction with the same receptor) is the observation that the dose-response lines for [des-Asp^1] angiotensin I and angiotensin III are parallel (Goldstein et al., 1968).

Our data allow a limited assessment of angiotensin I conversion. Figure 2 shows that 0.8 μg of angiotensin I and 0.025 μg of angiotensin II were equally potent; this yields an estimated 3.9% conversion of angiotensin I to angiotensin II during one transit through the kidney. Our estimate of angiotensin I conversion agrees closely with that reported by other laboratories. The data of DiSalvo et al. (1971) and Aiken and Vane (1972) indicate that the renal vascular responses elicited by the renal arterial injection of angiotensin I are probably due to its intrarenal conversion to angiotensin II, and their estimates of conversion are 4% and 2.3%, respectively.

The intrarenal conversion of [des-Asp^1]angiotensin I to angiotensin III was about 7% during one passage through the renal vasculature, suggesting that such local conversion may be importantly involved in the regulation of renal blood flow and renal function, especially because angiotensin III and angiotensin II have equally potent effects on renal blood flow and renal function (Freeman et al., 1975, 1976).

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