Effect of angiotensin II antagonist infusion on autoregulation of renal blood flow

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ABE, YOUICHI, TAKETOSHI KISHIMOTO, AND KENJIRO YAMAMOTO. Effect of angiotensin II antagonist infusion on autoregulation of renal blood flow. Am. J. Physiol. 231(4): 1267-1271. 1976.—The role of the renin-angiotensin system in the autoregulation of renal blood flow was examined in the anesthetized dog. The angiotensin II antagonist, [l-sarcosine, 8-isoleucine]angiotensin II, was continuously infused into the renal artery at rates of 1 and 3 μg/min, and renin secretion rate and intrarenal distribution of blood flow as well as total renal blood flow were measured during acute reductions in renal perfusion pressure within and below the range of autoregulation. Renal autoregulation and redistribution of blood flow by pressure reduction were not disturbed by the angiotensin II antagonist. This result does not provide any evidence for a primary role of the renin angiotensin system in renal autoregulation. Redistribution of blood flow by pressure reduction occurred independently of the renin-angiotensin system. It might depend on the differences in the resting tone among the zones.

There are many theories that have been advanced to explain the mechanism of autoregulation of renal blood flow (RBF) and glomerular filtration rate. The participation of the renin-angiotensin system in the regulation of single-glomerular filtration rate and perfusion rates was proposed by Thurau and Scherermann (27), but its importance in the autoregulation of total RBF is in doubt. Autoregulation has been found to persist during an infusion of angiotensin II (14), but conflicting results have been reported in the renin-depleted dog (5, 13). Recently, Anderson et al. (3) reported that the intravenous infusion of an angiotensin II antagonist did not impair autoregulation.

The distribution of renin and cortical blood flow in the renal cortex is not homogeneous; both decrease from the outer to the inner cortex (10, 16, 26). Accordingly, there may be a closer relationship between renin secretion and intrarenal blood flow distribution than total RBF. We have previously demonstrated that a reduction of renal arterial pressure within the range of autoregulation changed distribution of intrarenal blood flow to the deep cortex and simultaneously increased renin secretion (2). The flow redistribution might relate to the renin secretion or to the autoregulation of RBF.

If the renin-angiotensin system is responsible for renal autoregulation, an infusion of an angiotensin II antagonist into the renal circulation should modify renal autoregulation and flow redistribution. The purpose of this study was to examine renin secretion rate, intrarenal cortical blood flow distribution, and total RBF in control and after an angiotensin II antagonist ([l-sarcosine, 8-isoleucine]angiotensin II) in dogs during acute reductions in renal perfusion pressure within and below the range of autoregulation.

Methods

Mongrel dogs weighing 14-18 kg were anesthetized with intravenous pentobarbital sodium at a dose of 30 mg/kg and were then given additional doses as required during the experiment. The left kidney was exposed through a retroperitoneal flank incision. The kidney was denervated by division of all visible nerve fibers and sharp dissection of tissue connected to the renal hilum cephalad to the renal artery. RBF was measured by an electromagnetic flowmeter (Nihonkoden MF-25). Renal arterial pressure was considered equal to the aortic pressure measured at the level of the renal artery. An adjustable aortic clamp was placed above the left renal artery. Systemic arterial blood was collected from the right brachial artery, and the renal venous blood was collected via a cannula introduced through the left spermatic or ovarian vein.

An intravenous infusion of 0.9% saline, 4.0 ml/min, was started after anesthesia. A 23-gauge needle was introduced into the left renal artery proximal to the flow probe for infusions of 0.9% saline solution and of an angiotensin II antagonist at a rate of 0.5 ml/min.

Experiments were divided into the following three groups, A, B, and C:

Group A. To determine the effectiveness of the intrarenal infusion of the angiotensin II antagonist ([l-sarcosine, 8-isoleucine]angiotensin II, Daiichi Seiyaku Co., Tokyo) in inhibiting the vasoconstrictor effect of exogenous angiotensin II, angiotensin II (0.1 μg), angiotensin I (0.2 μg), and norepinephrine (1 μg) were injected into the renal artery before and during antagonist infusions at rates of 1, 3, and 10 μg/min, respectively.

Group B. The effects of the angiotensin II antagonist (1 μg/min) on renal autoregulation and on the intrarenal distribution of blood flow were evaluated. In seven dogs, renal perfusion pressure was altered in steps as indicated in Fig. 2 before and during antagonist infusion, and pressure-flow measurements were obtained. In the same dogs the intrarenal hemodynamics were measured at control pressure and after 5 min constric-
tion of the renal artery before antagonist infusion. In another six dogs, microsphere injections were performed at control pressure, and before and after 5 min constriction of the renal artery during infusion of the angiotensin II antagonist respectively.

**Group C.** At two doses of antagonist, 1 μg/min (in six dogs) and 3 μg/min (in four dogs), plasma renin activity in systemic arterial and renal venous blood, and renin secretion rate were examined at the following periods: 1) control, 2) reduced pressure within the autoregulatory range, 3) recovery, 4) intrarenal infusion of the antagonist, and 5) pressure reduction during continued infusion of the antagonist. To standardize the procedure, the blood samples used for determining renin release were always obtained after 5 min constriction and the clamp was released immediately after sampling.

**Analytical procedures.** Distribution of cortical blood flow was determined with radioactive microspheres (3M Company, St. Paul, Minn.) by the technique described in a previous paper (16). The renal cortex was cut parallel to the surface into four zones of equal thickness. Four cortex zones were analyzed for individual isotope counts, and the perfusion rate of each zone was calculated. The volume of each cortex zone was approximated by calculations based on the formula for an ellipsoid. The volume of the individual cortex zone, expressed as percent of total renal volume, was for zone 1, 27.0; zone 2, 21.9; zone 3, 17.3; zone 4, 12.2.

Plasma renin activity was determined by radioimmunoassay according to the technique described by Stockgigt et al. (25) and is expressed as angiotensin I formed during 3 h incubation per milliliter of plasma. Renin secretion rate was calculated by multiplying the difference between renal venous and arterial plasma renin activity by the renal plasma flow (RPF: RPF = (1 - hematocrit) × RBF).

The mean and standard error of significance was determined by the Student paired- and nonpaired- t test.

**RESULTS**

**Effectiveness of intrarenal infusion of angiotensin II antagonist.** The intrarenal arterial infusions of the angiotensin II antagonist ([Sar"-Ile"-angiotensin II] (6) at doses of 1, 3, and 10 μg/min resulted in a biphasic response in RBF without any significant change in the systemic blood pressure. At a low dose of antagonist (1 μg/min) the initial transient reduction of RBF lasting about 3-5 min appeared soon after the beginning of infusion (Fig. 1). RBF recovered a preinfusion level within 5 min after the start of infusion. The antagonist infusion at a dose of 10 μg/min blocked completely a vasoconstrictor effect of angiotensin II (0.1 μg) and partially that of norepinephrine (1 μg) which was administered into the renal artery. At low and medium doses of the antagonist, angiotensin II (0.1 μg) and angiotensin I (0.2 μg) were still completely blocked, but norepinephrine was not. Therefore, in the experiments described below, low and medium doses (1 and 3 μg/min) of antagonist with less agonistic activity were used for the specific blocking of angiotensin II.

**Effects of angiotensin II antagonist on renal autoregulation and intrarenal distribution of blood flow.** Figure 2 shows the pressure-flow relation with and without the angiotensin II antagonist (1 μg/min) in seven dogs. All control dogs showed a complete autoregulation of blood flow between perfusion pressures of 70 and 125 mmHg. RBF was decreased immediately following infusion of the angiotensin II antagonist into the renal artery and then returned to its control levels within 5 min as previously mentioned. Prior to infusion of the antagonist, 0.1 μg of angiotensin II decreased RBF by 60%; the same dose of angiotensin II did not alter RBF after infusion of the antagonist. By the stepwise decrement of renal arterial pressure during the antagonist infusion, RBF was still maintained until 75 mmHg of renal arterial pressure and then decreased as the pressure was reduced. The pressure-flow relations were not affected by infusion of the antagonist of angiotensin II (Fig. 2).

The flow rate of each zone differed significantly from that of the other three at normal pressure (Fig. 3A). A reduction of the pressure to the lower limit of autoregulation, 76 mmHg, showed changes in flow rates among zones, i.e., flow rate of the outer zone decreased significantly and that of the inner zones increased. The angiotensin II antagonist infusion into the renal artery at a dose of 1 μg/min resulted in a slight decrease of total
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RBF, but it did not affect the intrarenal distribution of blood flow. However, the pressure reduction to 75 mmHg during the antagonist infusion resulted in a marked redistribution of blood flow from the outer cortex to the inner cortex (Fig. 3B). Total RBF was auto-regulated fairly well. The zonal distribution during pressure reduction was not significantly affected by angiotensin II antagonist infusion.

Effects of pressure reduction on renin secretion before and during angiotensin II antagonist infusion. At normal pressure the mean plasma renin activities (PRA) of the systemic arterial and renal venous blood were 9.0 ± 2.7 and 11.3 ± 3.5 ng/ml, respectively (Table 1). A reduction of the pressure to 75 mmHg resulted in increases in PRA and renin secretion rate along with a redistribution of blood flow from the outer cortex to the inner cortex. Fifteen minutes after release of aortic constriction, PRA and renin secretion rate almost returned to the control level. Twenty minutes after infusion of the low dose (1 µg/min) of angiotensin II antagonist, renin secretion rate decreased slightly from 9.2 ± 2.2 to 3.4 ± 1.3 ng/g·min, and it was statistically significant (P < 0.05). Pressure reduction during infusion of the angiotensin II antagonist resulted in marked increases in the renal venous and systemic arterial PRA, and the renin secretion rate significantly increased from 3.4 ± 1.3 to 84.2 ± 18.0 ng/g·min (P < 0.05). Intrarenal infusion of a medium dose (3 µg/min) of antagonist resulted in a qualitatively similar response to that seen at low dose (Table 2). The effect of pressure reduction on renin secretion rate was not modified by the infusion of the angiotensin II antagonist.

DISCUSSION

Renal autoregulation is a well-established physiological phenomenon which maintains blood flow and filtration rate relatively constant over a wide range of perfusion pressure through changes in resistance of the preglomerular vessels (1, 20, 21). Alterations in the renin-angiotensin system may be viewed either as the initiator or the consequence of renal autoregulatory efficiency (8, 19). In support of the former view, Brech et al. (5) and Kaloyanides et al. (13) reported that renal autoregulation of blood flow was abolished in the dog renin-depleted by a high sodium intake and deoxycorticosterone (DOCA). During reductions of renal perfusion pressure in the lower autoregulatory range, a redistribution of RBF could be observed from the outer cortical to the inner cortical juxtamedullary compartments (5). In contrast, Kishimoto et al. (15) reported a close correlation between renin secretion and redistribution of blood flow with complete autoregulation of total RBF during renal venous occlusion. These results raise a question concerning participation of the renin-angiotensin system in
the autoregulation of RBF and in the redistribution of blood flow. In the present study, we have demonstrated that a reduction of renal arterial pressure within the autoregulatory range caused a significant increase in renin secretion and a redistribution of cortical blood flow from the outer to the inner cortex. A pressure reduction during angiotensin II antagonist infusion resulted in a redistribution of blood flow, which was identical to that noted during the pressure reduction, and a marked increase in renin secretion. Moreover, the autoregulatory response of RBF was significantly changed by the angiotensin II antagonist. If the generation of angiotensin II was essential for the efficiency of renal autoregulation, the angiotensin II antagonist should have precluded the maintenance of RBF with a reduction in renal perfusion pressure. Anderson et al. (3) have previously reported that the reduction of renal perfusion pressure to 100 mmHg was not associated with changes in renin secretion and intrarenal distribution of blood flow (2), but that only at the lower limit of autoregulation an increase in renin secretion rate and a redistribution of blood flow were observed. These findings suggest that the renin-angiotensin system does not participate in autoregulation; autoregulation occurs independently of the renin-angiotensin system.

In renal tissue, local formation of angiotensin II is possible only in the presence of both renin substrate and converting enzyme. The conversion of exogenous angiotensin I to angiotensin II during passage through the kidney has been demonstrated by Oparil et al. (18) and Franklin et al. (7). But our studies on the radioimmunologic determination of endogenous angiotensins I and II in the arterial and renal venous blood during pressure reduction have indicated that production of angiotensin II was negligible as compared with that of angiotensin I in one renal circulation (unpublished data). Recently, Itskovitz and McGiff (11) reported that angiotensin I, instead of angiotensin II, was a regulatory factor in renal hemodynamics, and that infusions of angiotensin I in the presence or absence of converting enzyme inhibitor selectively diminished the inner cortical fraction of RBF without affecting the outer cortical fraction. However, in the present study the effect of angiotensin I on RBF was completely blocked by the infusion of angiotensin II antagonist (Fig. 1), and the infusion of antagonist did not affect the intrarenal distribution of blood flow. The redistribution of blood flow by the pressure reduction was seen with and without angiotensin II antagonist infusion despite the high levels of angiotensin I and renin activity on the renal venous blood in both experimental conditions (Table 1). Gagnon et al. (9) reported that renal autoregulation was maintained in the infused kidney despite the continuous infusion of a converting enzyme inhibitor. Antagonist infusion resulted in a slight decrease of renin secretion rate. This inhibition of renin secretion might be dependent on its agonistic activity, since angiotensin infusion inhibited renin secretion (4). These different effects may be attributed to differences in the selective ability of receptors in vascular smooth muscle and in the self-inhibitory system of renin secretion or in the release system of renin. Johnson and Davis (12), Steele and Lowenstein (23), and Slick et al. (22) reported that the administration of the Sar\(^1\)-Ala\(^8\) analogue of angiotensin II stimulated the release of renin in sodium-depleted rabbits and in the chronic caval dog, and that the antagonist also blocked the pressor effect of angiotensin II infusion. The present results that showed failure to stimulate renin release by pressure reduction might depend on the different analogue of angiotensin II or the experimental condition: innervation or the route of administration into the renal artery. The differences

### Table 1. Effects of pressure reduction on plasma renin activity and renin secretion rate with and without angiotensin II antagonist

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Renal Perfusion Pressure, mmHg</th>
<th>Renal Blood Flow, ml/g · min</th>
<th>Plasma Renin Activity, ng/ml</th>
<th>Renin Secretion Rate, ng/g · min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>139 ± 6</td>
<td>3.16 ± 0.17</td>
<td>9.0 ± 2.7</td>
<td>11.3 ± 3.5</td>
</tr>
<tr>
<td>Pressure reduction</td>
<td>76 ± 2</td>
<td>3.15 ± 0.18</td>
<td>20.7 ± 3.8*</td>
<td>74.2 ± 6.2*</td>
</tr>
<tr>
<td>Recovery</td>
<td>138 ± 6</td>
<td>3.21 ± 0.18</td>
<td>12.5 ± 2.8</td>
<td>17.3 ± 3.8</td>
</tr>
<tr>
<td>Angiotensin II antagonist, 1 μg/min</td>
<td>141 ± 7</td>
<td>3.15 ± 0.20</td>
<td>9.3 ± 1.0</td>
<td>11.1 ± 1.5†</td>
</tr>
<tr>
<td>Pressure reduction with angiotensin II antagonist, 1 μg/min</td>
<td>75 ± 2</td>
<td>3.23 ± 0.20</td>
<td>22.6 ± 3.8†</td>
<td>65.7 ± 5.4*</td>
</tr>
</tbody>
</table>

*All values are means ± SE. A, systemic arterial blood; V, renal venous blood. Comparison was made between intervention and previous intervention: *P < 0.01, †P < 0.05.

### Table 2. Effects of pressure reduction on renin secretion rate with and without angiotensin II antagonist

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Renal Perfusion Pressure, mmHg</th>
<th>Renal Blood Flow, ml/g · min</th>
<th>Renin Secretion Rate, ng/g · min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>132 ± 5</td>
<td>2.22 ± 0.17</td>
<td>6.6 ± 1.8</td>
</tr>
<tr>
<td>Pressure reduction</td>
<td>75 ± 2</td>
<td>3.14 ± 0.18</td>
<td>118.3 ± 13.7*</td>
</tr>
<tr>
<td>Recovery</td>
<td>131 ± 7</td>
<td>3.17 ± 0.27</td>
<td>8.1 ± 1.9</td>
</tr>
<tr>
<td>Angiotensin II antagonist, 3 μg/min</td>
<td>134 ± 7</td>
<td>3.11 ± 0.20</td>
<td>6.6 ± 3.0</td>
</tr>
<tr>
<td>Pressure reduction with angiotensin II antagonist, 3 μg/min</td>
<td>74 ± 3</td>
<td>3.08 ± 0.17</td>
<td>114.7 ± 10.3*</td>
</tr>
</tbody>
</table>

*All values are means ± SE. Comparison was made between intervention and previous intervention: *P < 0.05
in innervation might explain the failure of angiotensin II antagonist to enhance renin release during reduced perfusion pressure. In addition, the possibility remained that angiotensin II antagonism was not complete at reduced pressure so that the negative feedback loop of angiotensin II on renin secretion rate was not interrupted. However, the administered dose of angiotensin II antagonist was shown to block the renal vasoconstrictor effect of doses of exogenous angiotensin II greater than the anticipated circulating levels in these experimental conditions. In our laboratory, concentrations of angiotensin II in renal venous plasma are 50–80 pg/ml at control pressure and 120–240 pg/ml at reduced pressure. If RPF was 100 ml/min, the rate of angiotensin II entering and leaving the kidney at reduced pressure would be 24 ng/min. The infused dose of angiotensin II antagonist was capable of blocking the renal vasoconstrictor effect of angiotensin II (100 ng injection: 100 ng/2–3 s) that was 4–80 times these calculated amounts.

The present study has demonstrated that the efficiency of renal autoregulation and redistribution of blood flow by pressure reduction are not disturbed by an angiotensin II antagonist. This result does not provide any evidence for a primary role of the renin-angiotensin system in renal autoregulation. Redistribution of blood flow by pressure reduction within the autoregulatory range occurred independently of the renin-angiotensin system, and since such redistribution was seen also with other vasodilator stimuli such as acetylcholine and bradykinin infusions (17, 24), it might depend on the differences in the resting tone among the zones.

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REFERENCES