Effect of Angiotensin on Renal Function of the Dog

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Angiotensin (5 ng/kg/min and 50 ng/kg/min) was infused directly into the left renal artery of anesthetized dogs in order to examine its effects on the renal function. Urinary volume, creatinine clearance (GFR), PAH-clearance (RPF) and electrolyte excretion were decreased by infusion of angiotensin in a small dose. On the other hand, extreme reductions of urinary volume, GFR, RPF and electrolyte excretion were observed immediately after the beginning of angiotensin infusion in a large dose, and were followed by gradual increases in these parameters during the administration of angiotensin (tachyphylaxis). In four out of six cases, urinary volume and sodium excretion surpassed the control values with increased extraction fraction of sodium. These results suggested that angiotensin affected the renal function mainly through two mechanisms: Firstly, the vasoconstrictive action of angiotensin on the renovascular system causes decrease in urinary output, and secondly the direct action on the tubular system causes natriuresis.

The effect of angiotensin on the renal function varies considerably according to the species of animals and experimental conditions.1 On the dog, some previous authors reported the decrease in urinary output and electrolyte excretion by administration of angiotensin2,3 and others their increase4,5. Since the change in systemic blood pressure and endocrine factors produced by intravenous administration of angiotensin may affect the renal function, it is difficult to evaluate the direct action of angiotensin on the kidney.

The experiments to be reported here were designed to determine changes in the renal function when angiotensin-II was directly infused into the renal artery.

METHODS

Mongrel dogs of both sexes, weighing 10 to 25 kg, were anesthetized with sodium pentobarbital in 30 mg/kg. Both ureters were exposed through a midline incision, and each was catheterized with a polyethylene tubing which was passed up until its tip had entered the renal pelvis and was tied securely in place. A polyethylene catheter was inserted through the right femoral artery into the left renal artery so that the tip of the catheter entered the left main renal artery for approximately 1.5 cm. Another catheter was placed into the left femoral artery and was connected.
to an electronic manometer to record systemic blood pressure. These operations were completed at least 30 minutes before the beginning of observations.

After intravenous administration of p-aminohippurate (PAH) as a priming dose, PAH dissolved in 5% glucose solution was infused intravenously at a constant rate during the whole period of experimental observation, so that plasma levels of 1 to 4 mg/100 ml of PAH were maintained in order to estimate the rate of PAH-clearance. When the urinary output became constant, control clearance rate was estimated in the next 20 minutes.

Angiotensin II in 5% glucose solution was given using infusion pump into the renal artery at infusion rates of 5 ng/kg/min in five dogs and 50 ng/kg/min in six dogs. The amount of glucose solution administered into the renal artery was 0.5 ml/min in each of the cases. In our preliminary observation, it was proved that isotonic glucose infused at a rate of 0.5 ml/min into the renal artery had no effect on the renal function. During 30 minutes of the angiotensin infusion, the clearance was determined in consecutive three 10 minutes periods. After the completion of infusion, the recovery period clearance was determined in the next 20 minutes. The rate of creatinine clearance, urinary volume and electrolyte excretion were also estimated concurrently with a determination of PAH-clearance.

Plasma and urinary concentrations of PAH and of creatinine were estimated by using a Beckman-DB spectrophotometer and those of sodium and potassium by a flame-photometer.

Systemic blood pressure was continuously recorded by means of an electronic manometer.

**RESULTS**

Table 1 and Fig. 1 demonstrate the changes in the functions of the kidney on the infused side when angiotensin in 4 ng/kg/min was administered into the renal artery of dogs. The changes were shown in percentages of the control value. Decreases in urinary volume, sodium and potassium excretion, creatinine clearance (GFR) and PAH-clearance (RPF) were observed. Especially, decreases in sodium excretion and urinary volume were remarkable. Since reductions of GFR and potassium excretion were less than that of sodium excretion, the extraction

<table>
<thead>
<tr>
<th>Time min</th>
<th>Urine vol.</th>
<th>GFR</th>
<th>RPF</th>
<th>U&lt;sub&gt;Na&lt;/sub&gt; V</th>
<th>U&lt;sub&gt;K&lt;/sub&gt; V</th>
<th>EF&lt;sub&gt;Na&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>20</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Angiotensin 5ng/kg/min</td>
<td>10</td>
<td>45.8±18.8</td>
<td>53.8±20.1</td>
<td>153.8±12.6</td>
<td>45.3±31.2</td>
<td>49.2±19.7</td>
</tr>
<tr>
<td>Angiotensin 5ng/kg/min</td>
<td>10</td>
<td>47.7±25.6</td>
<td>55.4±20.4</td>
<td>45.6±14.0</td>
<td>48.7±35.4</td>
<td>49.1±22.2</td>
</tr>
<tr>
<td>Angiotensin 5ng/kg/min</td>
<td>10</td>
<td>49.4±21.4</td>
<td>62.5±15.8</td>
<td>146.1±12.2</td>
<td>251.2±37.2</td>
<td>60.2±22.4</td>
</tr>
<tr>
<td>Recovery</td>
<td>20</td>
<td>70.6±26.7</td>
<td>94.7±10.4</td>
<td>98.6±8.3</td>
<td>392.3±36.4</td>
<td>112.3±27.1</td>
</tr>
</tbody>
</table>
Fraction of sodium was decreased. These changes were approximately constant throughout the administration of angiotensin. The blood pressure did not change appreciably.

Table 2 and Fig. 2 show the changes in the function of the kidney on the infused side when 50 ng/kg/min of angiotensin was administered. The cessation of urinary flow observed immediately after starting the infusion was followed by gradual increase in urinary volume within 3 minutes. In four of six cases, the urinary volume during the angiotensin infusion surpassed the control value. Similar findings were obtained on sodium and potassium excretions, GFR and RPF. The extraction fraction of sodium also increased. Blood pressure rose by 20 to
**TABLE 2.** Effect of angiotensin on renal function on infused side at a large dose of 50 ng/kg/min. Mean value of six dogs ± S.D.

<table>
<thead>
<tr>
<th>Time min</th>
<th>Urine vol.</th>
<th>GFR</th>
<th>RPF</th>
<th>U_{Na} V</th>
<th>U_{K} V</th>
<th>EF_{Na}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>20</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Angiotensin 50 ng/kg/min</td>
<td>10</td>
<td>26.6 ± 14.2</td>
<td>30.9 ± 11.8</td>
<td>27.1 ± 8.4</td>
<td>38.4 ± 15.8</td>
<td>25.7 ± 8.9</td>
</tr>
<tr>
<td>Angiotensin 50 ng/kg/min</td>
<td>10</td>
<td>83.8 ± 38.6</td>
<td>89.3 ± 32.6</td>
<td>85.1 ± 31.5</td>
<td>98.8 ± 47.0</td>
<td>94.6 ± 31.8</td>
</tr>
<tr>
<td>Angiotensin 50 ng/kg/min</td>
<td>10</td>
<td>110.0 ± 42.6</td>
<td>95.4 ± 34.0</td>
<td>078.5 ± 27.1</td>
<td>95.8 ± 60.8</td>
<td>65.2 ± 21.0</td>
</tr>
<tr>
<td>Recovery</td>
<td>20</td>
<td>109.0 ± 41.2</td>
<td>233.2 ± 30.3</td>
<td>089.8 ± 33.9</td>
<td>98.5 ± 37.6</td>
<td>76.5 ± 22.8</td>
</tr>
</tbody>
</table>

Fig. 2. Changes in renal function on the infused side produced by administration of a large dose (50 ng/kg/min) of angiotensin. The peptide was infused directly into the left renal artery during 30 minutes.
Fig. 3. Effects of 5 ng/kg/min of angiotensin on renal function in a dog.
-o-o- shows renal function on infused side.
- o-o-o shows renal function on control side.

When 5 ng/kg/min of angiotensin was infused, RPF, GFR, sodium and potassium excretion and urinary output were decreased. Especially, the decreases in RPF, sodium excretion and urinary volume were prominent. Similar observations
Fig. 4. Effect of 50 ng/kg/min of angiotensin on renal function in a dog.
-o-o- shows renal function on infused side.
-.-.-. shows renal function on control side.

were reported by Louis and Doyle\textsuperscript{2} and Healy \textit{et al.}\textsuperscript{8} Mueller \textit{et al.}\textsuperscript{9} have already described that even very slight depression of GFR should cause a considerable fall in urinary excretion of sodium. Since the same mechanism seems to operate in the alteration of the renal functions in the case of angiotensin infusion, it seems possible that the slight reduction of glomerular filtration due to vasoconstrictive effect of angiotensin, \textit{i.e.}, the decrease in tubular load causes a marked decrease in excretion of sodium and water.

When 50 ng/kg/min of angiotensin were infused, the changes were quite different from the results observed in the cases of infusion with small dose of angiotensin. Extreme oliguria in the very beginning of infusion was followed by gradual increase of urinary volume. Four of six cases showed that the urinary volume
in the later period of angiotensin infusion surpassed the control value. In the remaining two cases, however, a similar pattern to that observed in the 5 ng/kg/min infusion was demonstrated. Therefore, we considered that there was individual difference in the sensitivity to the diuretic action of angiotensin.

What is the mechanism of natriuresis in the cases of infusion with large amount of angiotensin? Healy et al.8 and Louis and Doyle7 reported inhibitory action of angiotensin on the sodium reabsorption in the tubule basing upon their experiments in dogs with intravenous infusion of large amount of angiotensin. Langford10 using Sperber chicken preparation and Vander11 by the stop-flow method observed the natriuretic effect of angiotensin, which was attributed to its direct action on the renal tubule. We also consider that the natriuresis is possibly due to the direct action of angiotensin on the renal tubule, because there are cases in which sodium excretion higher than the control value is observed even when GFR and RPF have recovered their control level and also because extraction fraction of sodium is constantly high in association with diuresis. The possible involvement of endocrine factors, e.g., antidiuretic hormone and aldosterone, was thought to be negligible in the present experiments, because the change of urinary volume or sodium excretion did not occur in the contralateral control kidney.

In the present experiments, we have observed that a large amount of angiotensin caused a temporary oliguria followed by a gradual increase of urinary volume, and RPF changed in proportion to the change of urinary volume. This seems to show that the vasoconstrictive action of angiotensin lasts for only two to five minutes after the start of infusion of a large dose of angiotensin.

It has been reported that tachyphylaxis to the pressor effect of the peptide was observed only when a large amount of angiotensin was infused.12 Since the tachyphylaxis is the result of decreased sensitivity of the vascular system to angiotensin, the same phenomenon can be also expected in the renovascular system when a large amount of angiotensin was administered directly into the renal artery. Antidiuresis in the cases of administration of small amount of angiotensin can be understood on the basis of absent tachyphylaxis and of tubular preponderance due to acute reduction of glomerular filtration.

The present results suggested that angiotensin might affect the renal function mainly through two mechanisms. First, its vasoconstrictive action to the renovascular system causes a decrease in urinary volume and sodium excretion through the reduction in tubular load. Since the extreme vasoconstrictive effect produced by administration of a large amount of angiotensin lasts only a few minutes (tachyphylaxis), RPF and GFR gradually return to the initial level. On the other hand, when a small amount of angiotensin is administered, the tachyphylaxis is not observed and the reduction of RPF and GFR is maintained during the angiotensin infusion. The second mechanism is the direct action of angiotensin on the tubular cells. Natriuresis during the administration of a large amount of angiotensin can be explained by its inhibitory action on the tubular reabsorption of sodium. We consider that these two mechanisms may operate
independently. In the cases of infusion with small dose of angiotensin, the increase in sodium reabsorption due to vasoconstrictive effect of the peptide overcomes the inhibitory action on the tubular transport of sodium, because no tachyphylaxis is observed with small dose infusion of angiotensin and furthermore, the most effective factor for sodium excretion is the change in the tubular load. On the other hand, in the cases of a large amount of angiotensin, GFR and RPF gradually returned to their control level during angiotensin administration (tachyphylaxis). So, the vasoconstrictive factor, i.e., a change in the tubular load, can be negligible. Natriuresis may develop as a result of the inhibition of tubular sodium reabsorption.

The mechanism responsible for the inhibition of tubular reabsorption of sodium by administration of angiotensin is still unknown. Leyssac et al.\textsuperscript{13} demonstrated that angiotensin reduced the rate of tubular sodium transport in \textit{in vitro} experiments. But a similar diuretic effect was also observed by administration of tyramine and adrenaline.\textsuperscript{14} We consider that the natriuretic action may be a common property of these pressor agents rather than specific to angiotensin. Although natriuresis in angiotensin administration may be due to inhibition of tubular transport of sodium by the peptide, we cannot exclude the possibility that changes in intrarenal circulation are able to cause a reduction of tubular reabsorption of sodium and water.

\textbf{Acknowledgment}

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\textbf{References}