Effects of angiotensin infusion on renal function in the unanesthetized rat

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Effects of angiotensin infusion on renal function in the unanesthetized rat. Am. J. Physiol. 213(5): 1205-1208. 1967.—Renal clearances were performed on unanesthetized rats before, during, and after the intravenous infusion of varying doses of angiotensin. Blood pressure increase was linearly related to the log of the dose. Low doses of angiotensin, 20 ng/kg per min, significantly decreased sodium excretion and GFR. At higher doses, 80-1,000 ng/kg per min, sodium excretion was greatly elevated despite diminished GFR. If the rats were infused with 5% glucose or 75 mM NaCl, this natriuretic response was abolished. Potassium excretion, in all animals at all dose levels, was decreased. The decrement in potassium excretion was not related to sodium excretion, but did correlate well with both GFR and RPF reductions. We conclude that no species difference exists between rat and dog as regards the effects of angiotensin on renal function.

angiotensin and sodium excretion; sodium and potassium excretion; renal hemodynamics

Previous investigators have reported that the administration of renin or angiotensin consistently increased sodium excretion in rat (6, 8, 19, 23, 24) and rabbit (1, 3, 11, 13, 21). In contrast, renin and angiotensin have been reported to be either natriuretic or antinatriuretic in dog and human (15, 27). Recent studies have clearly demonstrated that the directional change of sodium excretion induced by angiotensin in the dog is, in large part, determined by the dose infused (5, 9, 10, 12, 15, 25). The primary aim of the present study was to investigate the possibility that the rat also demonstrates this type of dose response. In addition the effects of altering the salt and water balance on the response was studied.

METHODS

All experiments were performed on unanesthetized rats which had catheters surgically implanted in the jugular vein, carotid artery, and bladder, as previously described (18). Except for one group (see protocol 3 below), the rats were fed a standard rat chow (Rockland Laboratory animal diet). Inulin clearance was used as a measure of glomerular filtration rate, and the clearance of C14-labeled para aminohippuric acid (PAH) as the renal plasma flow (RPF). Arterial blood pressure was continuously monitored in most experiments by connecting a pressure transducer to the carotid catheter and recording with an appropriate recorder. Experimental protocols were as follows:

1) Saline-loaded group. These animals were infused with isotonic saline at 1 ml/min until a volume equal to 2.5% body wt was administered. A priming dose of inulin and C14-labeled PAH was given, followed by a sustaining infusion of saline containing inulin and PAH at 0.108 ml/min. Thirty minutes was allowed for equilibration before clearances were measured. Each clearance period was 10 min in duration. Arterial blood was obtained from the carotid catheter 1 min before the midpoint of each period. Urine drained freely from the bladder catheter into a graduated centrifuge tube. At the end of the second control period, angiotensin was added to the infusion. One hour later, two additional periods were obtained and the infusion changed to one without angiotensin. After 45 min, two final clearances were obtained. Renal function was measured before, during, and after administration of different doses of angiotensin.

2) Water diuresis. Five percent glucose in water was infused at 1 ml/min until a volume equal to 2.5% body wt was administered. A priming dose of inulin and C14-labeled PAH was given, followed by a sustaining infusion of saline containing inulin and PAH at 0.108 ml/min. Thirty minutes was allowed for equilibration before clearances were measured. Each clearance period was 10 min in duration. Arterial blood was obtained from the carotid catheter 1 min before the midpoint of each period. Urine drained freely from the bladder catheter into a graduated centrifuge tube. At the end of the second control period, angiotensin was added to the infusion. One hour later, two additional periods were obtained and the infusion changed to one without angiotensin. After 45 min, two final clearances were obtained. Renal function was measured before, during, and after administration of different doses of angiotensin.

3) Low-sodium diet plus 0.5 isotonic saline. These rats were on a low-sodium diet (Nutritional Biochemicals) for 21 days prior to use, and were treated as in protocol 2 except that 0.5 isotonic saline was infused instead of 5% glucose in water.

RESULTS

Figure 1 shows the changes in blood pressure as a function of the dose of angiotensin in saline-loaded
animals (protocol 1). All doses resulted in an increase in the mean arterial blood pressure. Over the range studied the change in blood pressure appeared to be linearly related to the log of the dose.

The effects on GFR and Na excretion were quite different. In Fig. 2 are plotted the mean changes in GFR and Na excretion for the same group of animals (all in protocol I). None of the measured parameters in the control periods were significantly different between groups. With doses greater than 10 ng/kg per min, GFR was significantly reduced except in the dose range, 80–100 ng/kg per min. Na excretion was dose dependent in that at low doses (10 ng/kg per min), no significant change in excretion was found. At 20 ng/kg per min, Na excretion significantly decreased below that during the control periods. At higher doses sodium excretion increased; natriuresis occurring at doses of 80 ng/kg per min or greater.

A comparison of the data for protocols 1-3 is shown in Table 1. All rats received the same dose of angiotensin, 100 ng/kg per min, a dose which caused significant natriuresis in the saline-loaded rats. However, it is clear that angiotensin did not cause natriuresis in the rats of protocols 2 and 3. The group which was on a low-sodium diet but received 0.5 isotonic saline to promote water diuresis excreted more Na during the control periods than did the glucose-infused rats but less than the saline-loaded group. Their response to angiotensin also seemed to be intermediate; a very small rise in Na excretion of questionable significance was observed.

In all but a few rats, regardless of treatment, potassium excretion was decreased by the angiotensin infusion. The magnitude of this decrease did not correlate with that of sodium excretion (Fig. 3). In contrast there was a significant linear correlation between the changes in potassium excretion and both RPF and GFR (Fig. 4).

**DISCUSSION**

These experiments have demonstrated that sodium excretion in the unanesthetized rat is altered by angiotensin in a biphasic manner, related to dose. Low doses, 20 ng/kg per min, induced antinatriuresis, whereas higher doses caused natriuresis. The dose-response relationship appears to be virtually identical, quantitatively, for rat and dog (5, 9, 10, 12, 15). A similar study is lacking for humans, but it has been well documented that angiotensin can cause natriuresis in humans under certain conditions, namely hypertension (2, 4, 26) and edematous states (14). Therefore, although quantitative differences may exist, it is evident that all species studied manifest the same basic responses to angiotensin, i.e., antinatriuresis at low doses and natriuresis at higher doses. There is general agreement that the former is secondary to renal vasoconstriction and a reduced glomerular filtration rate. Our data are consistent with this view since GFR reduction invariably accompanied

**TABLE 1. Changes in GFR and Na excretion before, during, and after the infusion of 100 ng angiotensin/kg per min**

<table>
<thead>
<tr>
<th>Infusion</th>
<th>No. of Exps.</th>
<th>GFR, ml/min</th>
<th>Na Excretion, μM/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before infusion</td>
<td>During infusion</td>
</tr>
<tr>
<td>Glucose</td>
<td>11</td>
<td>.81±.010</td>
<td>.71±.015</td>
</tr>
<tr>
<td>½ Saline</td>
<td>3</td>
<td>.89±.027</td>
<td>.83±.016</td>
</tr>
<tr>
<td>Saline</td>
<td>4</td>
<td>.94±.16</td>
<td>.87±.07</td>
</tr>
</tbody>
</table>

Data in table are means ±1 se. * The mean is statistically different from that of the ½ saline and glucose groups, P < .05.
The antinatriuresis. There was, therefore, no evidence that angiotensin increased tubular reabsorption of sodium either directly or indirectly, via aldosterone. Moreover, this antinatriuretic effect in acute experiments has been demonstrated to be independent of aldosterone in human (28) and dog (22). It is clear from the GFR and sodium-excretion data that the natriuretic effect of larger doses represents inhibition of tubular reabsorption but the mechanism of action remains unknown.

The loss of the natriuretic response to angiotensin during water diuresis is also consistent with studies of previous investigators in rabbit (11), dog (5, 10), and rat (23). This may be related to the absolute level of GFR or to differences in the renal hemodynamic response to angiotensin. From Table 1 there is a clear relation between the control GFR and the magnitude of the natriuretic effect in acute experiments has been demonstrated to be independent of aldosterone in normal humans. What is the mechanism by which angiotensin reduced potassium excretion in these studies? The reduction in GFR may be a contributing factor, only if one accepts that a significant fraction of the filtered K+ is excreted. In the dog, it has been demonstrated that potassium excretion was not altered by GFR reduction so long as sodium excretion was maintained (7), as was the case in our experiments because of the angiotensin-induced natriuresis. It is possible that angiotensin inhibited the generally postulated distal sodium-potassium exchange mechanism; however, this concept may require revision in light of recent micropuncture studies (16, 17) which indicate a far more complex relationship between distal sodium and potassium handling than previously visualized. Finally, the highly significant correlation between the decreases in RPF and potassium excretion may indicate a close relationship between potassium influx and the delivery of potassium to the tubule via the blood.

The role of the renin-angiotensin system in blood pressure regulation and kidney function. ANGII and renal function.

REFERENCES