Hepatic Inactivation of Renin

By Robert Heacox, B.A., Alice M. Harvey, M.D., and Arthur J. Vander, M.D.

ABSTRACT

Renin activities were measured in plasma from an artery and from the hepatic, portal, and renal veins of anesthetized dogs. A significant arterial-hepatic venous renin difference was observed during control periods and after elevation of arterial renin by stimulation of endogenous renin secretion (induced by acute salt depletion) or by infusion of exogenous renin. There was good quantitative agreement between the calculated rates of renin infusion and hepatic renin clearance. No significant arterial-portal venous renin difference was observed. Infusion of exogenous renin decreased the usual renal venous-arterial renin difference; slight net renal inactivation of renin was observed in only 2 of 12 periods. We conclude that the liver is the major site of renin inactivation.

ADDITIONAL KEY WORDS angiotensin kidney spleen pancreas chloromerodrin gastrointestinal tract sodium depletion liver function anesthetized dogs

The plasma concentration of renin is determined by the relative rates of renin release and inactivation. Yet, to date, there have been few studies concerned directly with the sites or rate of renin inactivation. The present experiments were designed to investigate this problem by measuring arteriovenous differences for renin across several vascular beds. The word "inactivation" is not meant to connote a specific mechanism, but only to indicate the finding of an arteriovenous difference in renin activity.

Methods

All experiments were performed on mongrel dogs of either sex, weighing 12 to 20 kg. They were anesthetized with sodium pentobarbital, 30 mg/kg intravenously, with supplements given as required. All infusions were administered through indwelling venous catheters; arterial blood pressure was monitored from a femoral artery. In most dogs, catheters were introduced into a jugular and femoral vein and, through a flank incision, were manipulated into a hepatic vein and renal vein, respectively. The positions of the catheters were checked manually during and at the conclusion of the experiments and verified by measuring extraction ratios for BSP and PAH for liver and kidney, respectively. In one group of 3 dogs, a catheter was introduced into the splenic or colic vein and passed into the portal vein beyond the entry of the pancreatic-duodenal and gastric veins. In 2 of these 3 experiments, the splenic vessels were ligated; in 1, they were left intact. After completion of surgery, the dogs were allowed a recovery period of 1 hr. Control blood samples were then obtained simultaneously from the various catheters, and one of the following two procedures was followed:

Procedure 1: Endogenous Renin Secretion.—Chlormerodin, 2 mg Hg/kg, was infused intravenously in 4 dogs to induce acute salt depletion and increased renin secretion (1, 2). Arterial and hepatic venous blood samples were obtained 30, 60, and 120 min later.

Procedure 2: Exogenous Renin Infusion.—In 6 dogs, after obtaining control blood samples, a priming dose of 1.5 dog units of hog renin (Nutritional Biochemicals Co.) was given intravenously and followed immediately by a continuous infusion of 0.15 dog units of renin/min. Further samples were collected after 30 and 60 min. The renin infusion was then discontinued and further samples obtained 5 and 30 min later.

All blood samples were immediately centrifuged, the plasma was removed, and erythrocytes were resuspended in an equal volume of isotonic...
saline and returned to the dog. Plasma renin activity was measured by the method of Boucher et al. (3), with the following modification: After the final phase of angiotensin separation from plasma (removal from the Dowex column with diethylamine and NH₄OH), the solution was acidified to pH 1 or less, saturated with NaCl, and extracted with 10 ml of butanol; the butanol was then removed using water suction and heating at 80°C. This modification was used only to facilitate solvent sublimation, and in no way changed the characteristics of the method as described by Boucher et al. (3). We found that the method, developed for human plasma, was applicable as described to dog plasma. Detailed validation has been published elsewhere (4); only key points will be summarized here.

1. The pressor substance measured was completely destroyed by trypsin.
2. Assayed blood from dogs 24 hr after nephrectomy had no measurable pressor activity in contrast to that from intact dogs, in which activity was always detectable.
3. Reproducibility was 5 ± 1% (mean ± SEM).
4. In vitro addition of renin to blood demonstrated that renin was always rate limiting for generation of pressor activity, and angiotensinogen was always present in excess.

In the results, plasma renin activity is expressed as nanograms of angiotensin equivalents per milliliter of original plasma.

Results

Table 1 summarizes all data for arterial and hepatic venous renin activities during all control periods and after chlormerodrin, which invariably increased renin secretion, as indicated by increased arterial renin. The data for control periods are for all dogs used in both procedures. After chlormerodrin, 60-min samples were obtained for only 3 dogs and 120-min samples for only 2 dogs. The mean hepatic venous renin concentration was significantly less than the arterial (P < .01).

Table 2 summarizes the three experiments in which exogenous renin was infused. In all experiments, after the infusion hepatic venous renin was less than arterial renin. Assuming a hepatic plasma flow of 300 ml/min (5), the calculated hepatic clearance of renin during infusion was 3,000 to 4,200 angiotensin-equivalents/min. The renin used in these experiments has previously been found...
HEPATIC INACTIVATION OF RENIN

Comparison of renin activities in arterial and portal venous plasma before and during infusion of renin in 3 dogs.

to yield an average of 3,300 angiotensin-equivalents/0.15 dog units when added to dog plasma in vitro (4); therefore there was good quantitative agreement between the rates of renin infusion and hepatic inactivation. The reason for the high control rate of renin secretion in dog 10 (Table 1) is unknown.

In each experiment, renin infusion reduced the renal venous-arterial renin difference, but in only 2 of 12 collection periods was the venous-arterial difference negative. The rise in mean arterial blood pressure produced by the renin infusion was 5 to 10 mm Hg.

Figure 1 summarizes all data for the 3 dogs in which hepatic portal venous and arterial blood samples were analyzed for renin during renin infusion. It is evident that no significant arterio-portal venous difference was observed.

Discussion

These data demonstrate that the liver is a major site of renin inactivation. The relative constancy of the ratio, (arterial-hepatic venous renin difference)/(arterial renin concentration), indicates that hepatic renin inactivation occurs normally at control levels of renin secretion and increases directly with the concentration of renin in arterial blood when secretion increases. These were all acute experiments and provide no data concerning possible chronic changes in hepatic inactivation rates. Moreover, the mechanism of inactivation cannot be determined from these data. Braun-Menendez et al. (6) have previously reported that the disappearance of intravenously injected renin from plasma was delayed in hepatectomized dogs, although at lower doses of renin, heptectomy did not alter the disappearance rate. However, the lower doses were still very large and their relevance for renin inactivation at physiological plasma concentrations is uncertain. Moreover, the disappearance of renin after injection

<table>
<thead>
<tr>
<th>Dog</th>
<th>Period</th>
<th>Renal vein</th>
<th>Artery</th>
<th>Hep. vein</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Control</td>
<td>15.0</td>
<td>10.5</td>
<td>11.0</td>
</tr>
<tr>
<td></td>
<td>Renin; 30 min</td>
<td>23.2</td>
<td>22.3</td>
<td>13.3</td>
</tr>
<tr>
<td></td>
<td>Renin; 60 min</td>
<td>25.0</td>
<td>25.3</td>
<td>15.2</td>
</tr>
<tr>
<td></td>
<td>Recovery; 30 min</td>
<td>14.8</td>
<td>11.1</td>
<td>9.6</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>16.0</td>
<td>10.5</td>
<td>8.7</td>
</tr>
<tr>
<td></td>
<td>Renin; 30 min</td>
<td>20.0</td>
<td>25.5</td>
<td>11.0</td>
</tr>
<tr>
<td></td>
<td>Renin; 60 min</td>
<td>41.9</td>
<td>38.1</td>
<td>18.2</td>
</tr>
<tr>
<td></td>
<td>Recovery; 30 min</td>
<td>18.2</td>
<td>15.7</td>
<td>10.5</td>
</tr>
<tr>
<td>9</td>
<td>Control</td>
<td>50.1</td>
<td>41.0</td>
<td>14.5</td>
</tr>
<tr>
<td></td>
<td>Renin; 30 min</td>
<td>27.9</td>
<td>26.7</td>
<td>12.7</td>
</tr>
<tr>
<td></td>
<td>Renin; 60 min</td>
<td>24.2</td>
<td>21.3</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td>Recovery; 30 min</td>
<td>36.2</td>
<td>23.5</td>
<td>12.1</td>
</tr>
</tbody>
</table>
of a single large amount might be related to nonspecific binding of renin by vascular tissue (7-9) rather than to true inactivation. It was for this reason that we chose to study renin inactivation during continuous exogenous infusion or endogenous secretion; under these steady-state conditions any vascular binding should be constant and would not contribute to arterio-venous differences.

This study also eliminates several other organs as important sites of inactivation. The lack of an arterial-portal venous difference indicates lack of inactivation by the spleen, pancreas, and gastrointestinal tract. The decreased renal venous-arterial renin difference produced by exogenous renin is consistent with the fact that angiotensin inhibits renin release (10); the failure to find consistent or significant negative renal venous-arterial differences suggests that the kidney is not a major site for renin inactivation. This is consistent with previous demonstrations that injection of large quantities of urinary renin (6), that acute nephrectomy did not alter the half-life of injected renin (11), and that the pressor responses to renin injected into the renal artery or femoral vein were identical (12). On the other hand, the presence of renin in urine has been demonstrated (13), and it is certainly possible that urinary excretion and uptake by renal tissue constitute minor sources of renin loss from the blood. In our study, no effort was made to study the possibility of inactivation of renin by the heart, lung, or limbs. Previous investigations have indicated their lack of importance; neither the heart, lungs, nor perfused leg of a heart-lung preparation inactivated renin added to the blood during 1 to 2 hr of perfusion (6); and in humans there was no limb arterial-venous renin difference (14). Finally, the good agreement in our experiments between total renin infused and total hepatic inactivation (within the limitations of the calculations described above) indicates that the liver is the major, if not sole, site of renin inactivation. Elucidation of the mechanism and control of this process awaits future investigation. It is evident, however, that changes in plasma renin in diseases such as cirrhosis and congestive failure may reflect, in part, changes in the rate of renin inactivation.

References
Hepatic Inactivation of Renin
ROBERT HEACOX, ALICE M. HARVEY and ARTHUR J. VANDER

Circ Res. 1967;21:149-152
doi: 10.1161/01.RES.21.2.149

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1967 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/21/2/149

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/