Mechanism of Acid-Activation of Renin: Role of Kallikrein in Renin Activation

WILLA A. HSUEH, M.D., ELAINE J. CARLSON, B.S., AND MONICA ISRAEL-HAGMAN, B.S.

SUMMARY Dialysis of plasma to pH 3.3 and then pH 7.5 is a method commonly used to activate plasma inactive renin. Endogenous plasma kallikrein has been shown to participate in activation during neutral dialysis. The present studies demonstrate that plasma inactive renin is fully activated following dialysis to pH 3.3 at 10°C. Activation by low pH is a reversible process when followed by titration to a pH greater than 4.0. The rate of reversal of acid activation increases with increasing pH and temperature, reaching a maximum at pH 7.0 and 37°C. The disappearance of activated renin is not due to its destruction, because dialysis back to pH 3.3 fully restores activation. A preparation of renin zymogen devoid of active renin also shows complete reversal of activation. The K_m of acid-activated renin is the same as that of endogenous active renin. Acid-activated renin (untreated by protease) elutes with an apparently greater Stokes radius than non-acid-treated inactive renin on Sephadex G-100. Once reversal of acid activation occurs, renal or plasma kallikrein has no effect on renin. However, once kallikrein acts on acid-activated renin, activation is no longer reversible.

These data can explain the mechanism of acid activation of renin and the contribution of plasma kallikrein to renin activation in vitro. At low pH, inactive renin appears to undergo a conformational change such that the active site is accessible. Acid may unfold the renin molecule, as suggested by an increase in Stokes radius following acid dialysis. Kallikrein may then cleave a small peptide that permanently maintains acid-activated renin in an active state. Thus, renin zymogen must be in an active conformation such as that induced by acid to be "acted upon" by kallikrein, suggesting that other factors, in addition to renal kallikrein, may be involved in renin activation in vivo. (Hypertension 3 (suppl I): I-22-I-29, 1981)

KEY WORDS acid activation · kallikrein · renin · plasma · zymogen

A zymogen of renin isolated from normal human plasma may be a precursor of the physiologically active form of the enzyme.1,2 Of the total plasma renin, 30% to 98% exists in the inactive form; this percentage is dependent on sodium intake,3 the presence of renal disease,4 and other factors.5,6 The apparent molecular weight (mw) of renin zymogen determined by gel filtration is 55,000,7 larger than that of active renin in human plasma or kidney, 40,000 to 48,000. Pulse labeling studies have demonstrated that the kidney synthesizes 55,000 mw prorenin, which is converted intrarenally to a 40,000 mw form.7 Whether the kidney releases large molecular weight renin into the circulation is unknown.

Renal kallikrein may be an in vivo activator of renin.8 Dialysis of plasma to pH 3.3 and then to 7.5, a method frequently used to activate plasma renin,8,10 is dependent upon endogenous plasma kallikrein, which is enzymatically active during neutral dialysis.11 Renal kallikrein can activate renin only if plasma is first dialyzed to pH 3.3 or if kallikrein activation is performed in the cold.8 Although low pH destroys plasma kallikrein inhibitors,11 acid dialysis also alters inactive renin in such a manner as to facilitate its activation by kallikrein.12

In the present study, we investigate the effect of acid treatment on plasma inactive renin. The results further define the mechanism and reversible nature of acid activation of renin, and elucidate the role of plasma or glandular kallikrein in renin activation in vitro. These observations suggest that multiple steps are involved in the in vivo activation of renin.

Methods

Plasma was obtained from five normal volunteers, who were ambulatory and on normal sodium intake. Blood was collected into chilled tubes containing EDTA, centrifuged within 15 minutes at 1000 G, and the plasma frozen at -20°C.
The active renin concentration is the measurement of renin in untreated samples, and the active plus inactive renin concentration is the measurement of renin in samples treated by methods (described below) to activate renin. After addition of nephrectomized sheep plasma containing angiotensinogen and angiotensinase inhibitors, samples were incubated at pH 7.5 at least four times, for periods between 6 minutes and 3 hours, to ensure linearity of angiotensin I (AI) generation. The slope of the plot of AI concentration as a function of time represents renin concentration. The AI generated was measured by radioimmunooassay.

Renin Activation

Acid Treatment and Neutralization by Titration

The effect of acid exposure alone was studied by dialyzing samples to pH 3.3 for 18 hours at 10°C in either 0.05 M glycine, 0.05 M citrate, or 0.05 M acetate buffer containing 0.1 M NaCl and 5 mM disodium EDTA. Samples were then neutralized with 1 M sodium phosphate buffer, pH 8.0, 0.3 ml to 0.7 ml sample, and immediately assayed.

Acid and Neutral Dialysis

Samples that had been dialyzed against pH 3.3 buffer were then dialyzed against a 0.1 M NaH₂PO₄/Na₂HPO₄ buffer containing 5 mM disodium ethylenediaminetetraacetic acid (EDTA), pH 7.5, for 18 hours at 10°C. Assay of renin following this procedure has been shown to reflect the "total" renin concentration in plasma; the percent total renin is based on this measurement.

Renal Kallikrein

Samples were treated with partially purified human renal kallikrein (2.3 IU/ml sample) at 25°C.

Pepsin

Chromatographic fractions containing inactive renin were treated with pepsin using the method of Shulkes et al., since dilution inhibits activation of renin by dialysis to pH 3.3 and then pH 7.5.

Effect of pH and Ionic Strength on Acid Activation

Plasma was dialyzed against 0.05 M glycine that had been adjusted to pH values between 2.8 and 7.5. The effect of ionic strength was tested by dialyzing plasma against the pH 3.3, 0.05 M glycine buffer containing concentrations of NaCl ranging from 0.1 to 0.4 M.

Reversibility of Acid Activation, Effect of Temperature and pH

Samples that had been dialyzed to pH 3.3 and neutralized by titration were incubated for 3 hours at 4°C, 25°C, and 37°C. Samples were then either assayed for renin activity, treated with renal kallikrein and then assayed, or redialyzed to pH 3.3 for 18 hours at 10°C and then assayed. The effect of pH was tested by titration of acid-dialyzed plasma with 1 N NaOH to pH values between 3.5 and 8.0 followed by incubation at 37°C for 2 hours. The pH of all samples was adjusted to 7.5 prior to renin assay by dialysis against the pH 7.5 phosphate buffer for 4 hours at 4°C. Since alterations in acid-activated renin occur slowly at 4°C, changes in renin activity can be attributed to incubation at 37°C.

Characterization of Acid-Activated Renin

Two ml plasma were chromatographed on a 2.5 × 85 cm column of Sephadex G-100 (Pharmacia) at either pH 7.5 or pH 3.3 and eluted with a flow rate of 12 ml/hr at 4°C. Elution was expressed as the partition coefficient, Kₘ. Recovery of active renin in the eluates is based on the active renin determined in untreated plasma, and recovery of active plus inactive renin based on total renin in the plasma.

Determination of Michaelis-Menten Constant

Sheep angiotensinogen, diluted in 0.1 M tris buffer, pH 7.5, to final concentrations between 0.05 and 0.29 μM was added to: 1) normal plasma; 2) plasma dialyzed to pH 3.3 and neutralized by titration; and 3) Medical Research Council (MRC-68-356) human renal renin. A Lineweaver-Burke plot provided the Michaelis-Menten constants, Kₘ.

Isolation of Inactive Renin from Plasma

Cibacron-blue agarose (Biorad) was used to obtain a totally inactive preparation of renin. A 18 × 1.5 cm column of cibacron-blue agarose was washed with 0.024 M sodium phosphate, pH 7.1. Normal plasma (6 ml) was dialyzed overnight against the same buffer and applied to the column which had a flow rate of 38.5 ml/hr. Proteins were eluted with a stepwise increase of NaCl in the pH 7.1 buffer of 0, 0.2, 0.5, and 2.0 M. The molarity was increased after 60 ml had been collected at each step.

Most of the active renin did not bind to cibacron-blue, although 1% eluted with albumin at 2.0 M. Inactive renin eluted at 0.5 M. These eluates were concentrated 4-fold using a Minicon CS15 (Amicon) concentrator. Activation by pepsin demonstrated an inactive renin concentration of 12.0 ng/ml/hr. No active renin was present in the preparation. The specific activity was 36 ng/ml/hr per milligram of protein, an increase of 135 times the original values in plasma.

Results

Acid Activation of Renin

Dialysis of plasma to pH 3.3 at 10°C resulted in the same degree of activation of renin as dialysis to pH 3.3 and then pH 7.5 (fig. 1). Whether the pH 3.3 buffer was glycine, citrate, or acetate, activation by acid dialysis was identical. The pH of activation was 

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critical; a plot of pH vs the percent of total renin resembles a titration curve (fig. 2). If acid dialysis was performed at 25°C, full activation also occurred, while at 37°C no activation could be detected.

To demonstrate "complete" activation, plasma samples that were acid-dialyzed and neutralized by titration (fig. 3, • — •) required multiple incubation times with sheep angiotensinogen. In these samples, AI generation was linear with time only for the first hour, after which the AI production rate decreased.

If kallikrein was allowed to act on acid-activated renin either by dialysis of plasma to pH 3.3 and then pH 7.5 (○—○) or by addition of renal kallikrein to acid-treated plasma (○—●), the rate of AI generation was linear for up to 2 hours of incubation. The slope was equal to the initial slope seen in the plasma that had been only acid-treated and neutralized by titration. Therefore, the renin concentration immediately following activation was the same with all methods tested. In untreated plasma the slope, i.e., concentration of endogenous active renin, was less. Since substrate depletion and angiotensinases were not the cause of the decreased rate of AI generation in acid-dialyzed plasma, a change in the renin itself was considered.

**Reversibility of Acid Activation**

Following incubation of acid-dialyzed plasma at 25°C for 3 hours at pH 7.5, 20% of the renin activity was lost and not recovered by renal kallikrein treatment. Release dialysis to pH 3.3 also did not alter renin activity.

The effect of pH on reversal of acid activation of renin is shown in figure 5. At 37°C and a pH above 4, renin activity decreased. This decrease was maximal at pH 7.0 and then plateaued.
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Effect of Ionic Strength on Acid Activation

The effect of increasing the NaCl concentration in the pH 3.3 glycine buffer is shown in table 1. Increases of 0.10 M and 0.15 M NaCl resulted in similar activation; less was achieved with 0.20 M or 0.40 M NaCl. The higher ionic strength inhibited acid activation whether plasma was dialyzed to pH 3.3 and neutralized by titration, or dialyzed to pH 3.3 and then to pH 7.5.

Effect of Dilution on Acid Activation

As high as 1:10 dilution of plasma did not interfere with activation of plasma renin by dialysis to pH 3.3 (table 2). In contrast, previous studies have shown that dilution impairs activation of plasma renin by dialysis to pH 3.3 and then pH 7.5. These results confirm that dilution primarily affects the neutral phase of dialysis and are consistent with the mechanism of renin activation described in the following section.

Mechanism of Plasma Renin Activation by Consecutive Dialyses to pH 3.3 and pH 7.5

Changes in pH and renin activity that occur during consecutive overnight dialyses of plasma to pH 3.3, pH 7.5, and then pH 3.3 are shown in figure 6. During the initial dialysis to pH 3.3, inactive renin did not become active until the pH of the plasma was 3.3, when full activation occurred. During the neutral

Effect of Temperature on Reversal of Acid Activation

Samples were dialyzed to pH 3.3, neutralized, and incubated for 0 hour (control) or 3 hours at the indicated temperature. Aliquots were either assayed for renin immediately (white bar), treated with renal kallikrein and then assayed (black bar), or redialyzed to pH 3.3, neutralized, and assayed (hatched bar). Results expressed as average ± SEM for plasma in four normal volunteers. Active renin was 19.6% ± 5.1% of the total renin. * = p < 0.10; † = p < 0.05.

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Control</th>
<th>4°C</th>
<th>25°C</th>
<th>37°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Total Renin</td>
<td>0</td>
<td>20</td>
<td>40</td>
<td>60</td>
</tr>
</tbody>
</table>

TABLE 1. Effect of NaCl Concentration on Acid Activation

<table>
<thead>
<tr>
<th>NaCl concentration</th>
<th>Total Renin ng/ml/hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH 3.3, neutralize</td>
<td>pH 3.3 — pH 7.5</td>
</tr>
<tr>
<td>0.09</td>
<td>23.9</td>
</tr>
<tr>
<td>0.15</td>
<td>20.9</td>
</tr>
<tr>
<td>0.20</td>
<td>15.8</td>
</tr>
<tr>
<td>0.40</td>
<td>12.1</td>
</tr>
</tbody>
</table>

Samples were dialyzed against pH 3.3 glycine buffer containing various NaCl concentrations and then either: 1) neutralized with 1 N NaOH and dialyzed against pH 7.5 phosphate buffer at 4°C for 4 hours, or 2) dialyzed to pH 7.5. Thus, all samples contained the same NaCl concentration prior to renin assay (see text).
dialysis, activated renin remained in the active state, and no change in activity resulted from repeat dialysis to pH 3.3. When aprotinin, 200 kallikrein inhibitor units in 10 μl, was added to 1 ml plasma to inhibit endogenous plasma kallikrein, acid-activated renin gradually lost activity as the pH increased. After 24 hours, the remaining activity was equal to the level of endogenous active renin. Repeat dialysis of pH 7.5 plasma containing aprotinin to pH 3.3 fully activated renin in a manner resembling the initial dialysis to pH 3.3.

Once kallikrein acts on acid-activated renin, activation is no longer reversed by 37°C incubation. This allowed us to determine when plasma kallikrein had acted on renin during neutral dialysis. Samples of dialysate were removed after 1, 2, 3, and 4 hours of dialysis to pH 7.5 and incubated at 37°C for 3 hours. The renin remaining in the dialysates was 30, 21, 92, and 100% of the total renin respectively, suggesting that during pH 7.5 dialysis at 10°C, plasma kallikrein stabilizes acid-activated renin in 3 hours and little reversal of acid activation occurred prior to this time.

Following dialysis of plasma to pH 3.3 at 10°C, neutral dialysis was also performed at 25°C and at 37°C. Renin remained active at 25°C, but lost activity at 37°C.

### Characterization of Acid Activated Renin

#### Kinetic Studies

Active plasma renin, plasma renin activated by dialysis to pH 3.3 only, and MRC renin all had the same Km with sheep angiotensinogen at 37°C, pH 7.5 determined by Lineweaver-Burke analysis: 0.28, 0.29, and 0.27 μM respectively.

#### Gel Filtration

When normal plasma was chromatographed on Sephadex G-100 at pH 7.5, inactive renin eluted with an apparent 55,000 mw, 60% recovery, and active renin with an apparent 48,000 mw, 80% recovery. A Haas preparation of human kidney renin eluted with a 44,000 mw, similar to that determined for pure human renin.17

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**TABLE 2. Effect of Dilution on Acid Activation**

<table>
<thead>
<tr>
<th>Dilution</th>
<th>%</th>
<th>ng/ml/hr</th>
<th>Dilution</th>
<th>%</th>
<th>ng/ml/hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1</td>
<td>100</td>
<td>11.2</td>
<td>100</td>
<td>100</td>
<td>10.4</td>
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<tr>
<td>1:4</td>
<td>93</td>
<td>10.3</td>
<td>98</td>
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<tr>
<td>1:7</td>
<td>100</td>
<td>12.0</td>
<td>100</td>
<td>11.3</td>
<td></td>
</tr>
<tr>
<td>1:10</td>
<td>100</td>
<td>13.0</td>
<td>100</td>
<td>12.0</td>
<td></td>
</tr>
</tbody>
</table>

Results expressed as % of renin in undiluted sample (1:1) treated similarly and absolute values of renin concentration (ng/ml/hr).

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**Figure 6.** Mechanism of plasma renin activation by dialysis to pH 3.3 and pH 7.5. Top panel: Changes in pH with time. Bottom panel: Changes in % total renin with time; •• without aprotinin, ○○ with aprotinin. Results are expressed as average ± SEM for plasma from two normals assayed in duplicate. Arrow denotes when plasma kallikrein stabilized the acid-activated renin.
Because of reversal of acid activation, the same Sephadex G-100 column used for the pH 7.5 studies was run at pH 3.3 (fig. 7). The $K_{av}$ for ovalbumin, $0.309 \pm 0.009$ (average $\pm$ SEM, $n = 9$), was not altered by the change in pH. Haas renin eluted at the same $K_{av}$ as ovalbumin on both the pH 3.3 and the pH 7.5 column. Acid-activated renin eluted on the pH 3.3 column with $K_{av} = 0.220$, larger than inactive renin eluted on the pH 7.5 column, $K_{av} = 0.256 \pm 0.005$ ($n = 6$). Incubation of eluates containing acid-activated renin for 3 hours at $37^\circ$C and neutral pH reversed activation. Assay of eluates treated in this manner demonstrated a peak of active renin with $K_{av} = 0.285$ (recovery, 50%; fig. 7 A, 0—0), similar to that determined when active renin is eluted at pH 7.5 (Figure 7 B, 0—0). If following neutralization by titration eluates were immediately treated with renal kallikrein, activation was irreversible. The peak demonstrated with renal kallikrein eluted with $K_{av} = 0.216$.

**Effect of Acid on Renin Zymogen Isolated from Plasma**

When a totally inactive preparation of renin was dialyzed to pH 3.3, neutralized by titration, and immediately assayed, the renin concentration was 10.5 ng/ml/hr. Incubation at $37^\circ$C, pH 7.5 for 3 hours resulted in complete loss of activity. Repeat dialysis to pH 3.3 activated renin to the level of the initial dialysis, 10.5 ng/ml/hr.

**Discussion**

Many enzymes and peptide hormones are synthesized as inactive precursors that are proteolytically converted to their active form. In vivo conversion of these precursor forms is irreversible and serves as a more rapid control mechanism for physiologic function than control at the level of gene transcription. Studies of activation are thus important in understanding regulation of enzyme activity. A number of studies have demonstrated changes in plasma active and inactive renin levels in response to perturbations of the renin-angiotensin system, suggesting that conversion of inactive to active renin may be a modulator of active renin production. Activation of renin appears to involve proteolytic steps within the kidney, although vascular activation of renin may also be of physiologic importance.

When normal human plasma is dialyzed against either glycine, citrate, or acetate buffer, pH 3.3, inactive renin becomes active. Activation is "complete," since a similar increase in renin activity results either from dialysis of plasma to pH 3.3 and then pH 7.5, or treatment of plasma with pepsin, trypsin, or renal kallikrein. We have demonstrated that acid activation is a fully reversible process, suggesting that low pH activates renin directly rather than providing a milieu for acid protease-mediated activation. In the latter situation, reversibility of peptide bond hydrolysis would be highly unlikely. Furthermore, dilution of potential activator as much as 10-fold has no effect on acid activation.

**Figure 7**. Left: Normal human plasma run on Sephadex G-100 at pH 7.5. Untreated eluates, O—O, demonstrate active plasma renin; pepsin treated eluates •—• represent total renin. Right: Normal plasma dialyzed to pH 3.3 run on Sephadex G-100 at pH 3.3. Eluates neutralized and assayed for renin immediately; O—O eluates neutralized, incubated at $37^\circ$C for 3 hours and then assayed for renin. Solid lines represent human serum albumin, $K_{av} = 0.191$, and ovalbumin, $K_{av} = 0.309$. 

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The product of acid activation kinetically resembles active renin. The $K_m$ of renin activated by dialysis to pH 3.3 (without neutral dialysis), active plasma renin, and MRC renin for sheep angiotensinogen are the same. This value agrees with that previously published for MRC renin and for renin in diabetic plasma dialyzed to pH 3.3 and then pH 7.5. Hence, activation by dialysis to pH 3.3 does not occur by an increase in renin's affinity for substrate, but rather is due to increased production of active enzyme from an inactive pool. These results eliminate the possibility that low pH destroys a competitive inhibitor of renin but do not rule out the possibility of a non-competitive inhibitor.

Although acid-activated renin closely resembles the endogenous active enzyme, acid activation is fully reversible in a manner dependent on temperature and pH. In every normal plasma studied, the maximal decrease in renin concentration associated with reversal occurs to the level of the endogenous active renin (about 20% of the total renin) measured in undialyzed plasma. The apparent loss of activation at a higher pH is not caused by destruction of renin because redialysis to pH 3.3 restores enzyme activity to the level seen following the initial acid dialysis. This behavior describes inactive renin in plasma or in a semipurified preparation that contains no measurable active renin. The data are consistent with a pH-dependent conformational change in inactive renin. At pH 3.3, activation of renin is accompanied by an apparent increase in Stokes' radius, demonstrated by a decrease in $K_m$. We suggest that at this critical pH the tertiary structure of renin is altered so as to permit access to its previously unexposed active site. A plot of activation vs pH resembles a titration curve with $pK_a$ of 3.6. Activation may involve protonation of a carboxy-terminal amino acid, which has a $pK_a$ of about 3.5. Ionic strength effects (NaCl concentration greater than 0.2 M impairs acid activation) further support a conformational change. At a pH above 4.0, acid-activated renin returns to an inactive state, but can be reactivated by reexposure to pH 3.3. The conformation of several enzymes is altered by pH and coincides with enzyme activity. A common example is $\delta$-chymotrypsin, which is stabilized in its active conformation by a salt bridge. At high pH, the salt bridge becomes deprotonated, resulting in loss of enzyme activity. The absence of dilution effects seems to preclude dissociation and reassociation of active renin with a low-molecular-weight noncompetitive inhibitor as an explanation of reversible acid activation. Furthermore, activation is still reversible following separation by dialysis or gel filtration of acid-activated renin from a possible inhibitor. Clear documentation of a conformational change will require purification of inactive renin.

Reversal of acid activation at neutral pH can be prevented by kallikrein. Once reversal has occurred, however, kallikrein cannot activate plasma inactive renin, unless the renin itself is first acid-treated. At low pH, inactive renin unfolds, exposing its active site. Both renal kallikrein and plasma kallikrein have the same effect, which is to maintain acid-activated renin in an active form. The effect is accompanied by an apparent decrease in Stokes radius, so that the molecular weight of the activated renin again appears to be 55,000. Cleavage of a peptide by kallikrein may permanently prevent renin from returning to its inactive conformation.

No in vitro methods of activation have converted inactive renin of an apparent 55,000 mw to endogenous active renin of an apparent 40,000 mw. Hence, the mechanism we have described in vivo may be unrelated to in vivo mechanisms. A large molecular weight active renin has been described in vivo, however, in the plasma of diabetics with nephropathy and hyperkalemia, in smaller amounts in the plasma of normal subjects on a high sodium diet, in a normal plasma pool, and in cadaver kidney from subjects without prior renal disease. It is possible that the large molecular weight active renin may represent one step of several necessary in the conversion of big inactive renin to normal active renin. Furthermore, more than one enzyme may be required in this conversion. Preparathyroid hormone, for example, requires both a trypsin-like enzyme and a carboxypeptidase-B-like enzyme for conversion to parathyroid hormone.

Events that occur during activation of renin by the conventional method of dialysis to pH 3.3 and then pH 7.5 are as follows. During dialysis to pH 3.3:

1) Plasma renin is fully activated; 2) inhibitors of plasma kallikrein are destroyed; and 3) plasma prekallikrein is converted to kallikrein. Reversal of renin activation is slow during dialysis to pH 7.5 at 10°C, and within 3 hours plasma kallikrein has stabilized the acid-activated renin in an active form. At 37°C, pH 7.5, reversal of acid activation occurs at a faster rate, which prevents kallikrein from stabilizing renin. Hence, if dialysis to pH 7.5 is performed at 37°C, no activation can be demonstrated.

A previous study by Atlas, et al. suggested that acid activation is a two-stage process, whereby 30% of the plasma inactive renin was activated during acid dialysis and 70% during the neutral phase of dialysis. These observations appear contradictory to the present report, but can be explained by the reversible nature of acid activation. In the study of Atlas et al. following acid dialysis and titration to pH 5.7, human substrate was added and the mixture incubated at 37°C, pH 5.7, for 1 hour. Reversible activation occurs under these conditions, but could not be recognized without determining linearity of AI generation. Thus, only 30% of plasma inactive renin appeared to be activated during the acid phase of dialysis. Therefore, an initial rate of AI generation must be used to determine the renin concentration following an activation procedure.

In summary, these studies have shed light on the mechanism of acid and kallikrein "activation" of renin in vitro. Whether the activation of kallikrein on renin represents a physiologic link between the renin-angiotensin and kallikrein-kinin systems in vivo remains unknown.
Acknowledgments

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