A Renin Inhibitor from Rabbit Kidney

CONVERSION OF A LARGE INACTIVE RENIN TO A SMALLER ACTIVE ENZYME

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ABSTRACT

Renin in extracts of frozen rabbit kidney exists in two forms: active (molecular weight about 37,000) and inactive (molecular weight about 55,000) renin. The inactive form becomes active after exposure to pH 2.5 at 4°C. If extracts are chromatographed on DEAE cellulose, the inactive renin dissociates into active renin plus a renin inhibitor (molecular weight about 13,000). The inhibitor recombines with active renin if the two are incubated together at 37°C. The inhibitor is destroyed by acid treatment at pH 2.5 at 4°C. We conclude that the activation of inactive renin is due to destruction of the inhibitor by acid. The inactive material may be a renin proenzyme or a storage form of active renin combined with inhibitor.

KEY WORDS
renin pressor response proenzyme renin activation molecular weight of renin membrane-bound renin

Extracts of rabbit kidney contain an active and an inactive form of the enzyme renin (1). Inactive rabbit renin has a molecular weight of around 55,000, and active renin has a molecular weight of around 37,000. When a solution of inactive rabbit renin is acidified to pH 2.5, its pressor activity increases and its molecular weight becomes similar to that of active rabbit renin. A slow-acting renin is also present in extracts of pig kidney (2). It is not present in extracts of rabbit kidney. When a solution of inactive rabbit renin is treated with acid at pH 2.5, its pressor activity becomes active after exposure to pH 2.5 at 4°C. If extracts are chromatographed on DEAE cellulose, the inactive renin dissociates into active renin plus a "renin-binding protein," when it is chromatographed on DEAE cellulose. The inactive renin from the rabbit kidney may be similar to the slow-acting renin from the pig kidney.

The present experiments were carried out in an attempt to characterize the inactive renin from rabbit kidney and to study its activation.

Methods

Kidney Extracts.—Kidneys were obtained from male or female New Zealand white rabbits. The rabbits were anesthetized with sodium pentobarbital, and their kidneys were excised and stored frozen. The kidney cortex was extracted as previously described (1). Extracts for DEAE cellulose chromatography were made in 0.005M sodium phosphate buffer, pH 7.0, using 3 ml buffer/g kidney cortex.

Buffers.—Buffer solutions were boiled and made up to volume in boiled, cooled distilled water. Phosphate-saline buffer contained 0.05M NaH2PO4/Na2HPO4, 0.1M NaCl, and 2.0 g/liter of neomycin sulfate, pH 5.0–7.4. Glycine-HCl buffer contained 0.05M glycine/HCl and 0.1M NaCl, pH 1.5–4.0.

Standard Renin.—Standard renin was prepared by a modification of the method of Lever et al. (3). Rabbit kidneys were minced in 0.9% saline and allowed to stand at 4°C for 48 hours. The slurry was centrifuged at 2,000 g for 30 minutes, the supernatant fluid was decanted, and the precipitate was washed with half of the original volume of saline, and the washings were added to the supernatant fluid. All subsequent operations were carried out at 4°C. The extract was acidified to pH 2.5 and allowed to stand for 7–16 hours. The pH was adjusted to 7.4, the precipitate was centrifuged off, and 40 g/100 ml of solid (NH4)2SO4, was added to the supernatant fluid. After standing overnight, the precipitate was centrifuged off, dissolved in distilled water, and equilibrated with 0.05M sodium phosphate buffer, pH 7.0. The renin solution was applied to a DEAE cellulose column in the 0.005M sodium phosphate buffer, pH 7.0. The column was washed with starting buffer and then with 0.05M sodium phosphate; finally, the renin was eluted with 0.25M sodium phosphate buffer, pH 7.0. The column was washed with starting buffer and then with 0.05M sodium phosphate; finally, the renin was eluted with 0.25M phosphate-saline buffer, pH 6.0. The renin was dialyzed against distilled water, freeze-dried, dissolved in phosphate-saline buffer, pH 7.4, and stored frozen. One unit of renin was capable of producing angiotensin at a rate of 100 ng/ml hour⁻¹ in the standard incubation mixture of Lever et al. (3).

Renin Assays.—Renin was assayed by measuring the blood pressure response of a rat to a direct injection of the substance (4). The pressor response to a sample was bracketed between the responses to injections of standard renin.

Activation of Inactive Renin.—A 0.5-ml sample of extract was dialyzed to pH 2.5 for 24 hours at 4°C and then dialyzed back to pH 7.4 over 16–24 hours. Any precipitate was centrifuged off before the sample was assayed. The amount of active and inactive renin in an extract was calculated as follows: units renin/ml without acidification = units active renin/ml, and units renin/ml after acidification = units active renin/ml + units renin/ml that have been activated. If one unit of inactive renin yields one unit of active renin, then units inactive renin/ml = units renin/ml after activation — units renin/ml at pH 7.4.
Protein.—Protein was assayed by a micro-Biuret method (5).

DEAE Cellulose Chromatography.—DEAE cellulose (Whatman) was equilibrated with 0.005 M sodium phosphate buffer, pH 7.0, and packed in a 22 × 1.0-cm column. Then 5 ml of rabbit kidney extract in the same buffer was applied, and the column was washed with sodium phosphate buffer, pH 7.0. Renin was eluted by one of two procedures. For schedule A 250 ml of 0.2 M sodium phosphate buffer, pH 8.0, was used for elution, and for schedule B 250 ml of 0.075 M sodium phosphate buffer, pH 7.0, followed by 250 ml of 0.2 M sodium phosphate buffer, pH 6.0, was used. The effluent from each wash was dialyzed against distilled water, freeze-dried, and taken up in 5.0 ml of phosphate-saline buffer, pH 7.4.

For large-scale preparation of renin and inhibitor, a DEAE cellulose column 2.8 × 78 cm was loaded with 80 ml of kidney extract. It was washed with starting buffer, then with one column volume of 0.075 M sodium phosphate buffer. A gradient of 1 liter of 0.075 M sodium phosphate buffer, pH 7.0, in the mixing chamber and 1 liter of 0.3 M sodium phosphate buffer, pH 6.0, in the reservoir was applied; 16.0-ml fractions were collected.

G100 Sephadex Chromatography.—A 1.5 × 25-cm column of G100 superfine Sephadex in phosphate-saline buffer, pH 7.4, was packed and calibrated with Blue Dextran, bovine serum albumin, α-chymotrypsinogen, and myoglobin (6); 1.2-ml fractions were collected.

Results

Extraction of Renin from Kidneys.—The extraction of renin from fresh and frozen kidneys was compared. In eight rabbits, one kidney was extracted immediately and the other kidney was frozen and then extracted. The amounts of active and total renin obtained are shown in Table 1. Extracts from frozen kidneys contained significantly (P < 0.01) more renin than did extracts from fresh kidneys. Thus, freezing and thawing facilitates the extraction of renin, as others have reported (7). The mean percent of inactive renin in extracts of fresh kidneys was significantly higher than that in extracts of frozen kidneys. To see if freezing and thawing activated inactive renin, some inactive renin that had been partially purified by DEAE cellulose and G100 Sephadex chromatography was assayed several times before and after freezing. It contained 14.8 ± 2.2 units/ml of active renin before freezing and 13.2 ± 1.5 units/ml after freezing; this difference was not significant. Therefore, it seems that the higher percent of active renin in extracts from frozen kidney is not due to activation of inactive renin by freezing and thawing. Freezing releases enzymes from intracellular organelles such as lysosomes and zymogen granules (8, 9). Possibly, extracts of fresh kidney contain some renin that is membrane bound and inaccessible to substrate. To test this hypothesis, two extracts of fresh kidney were made and assayed before and after freezing. The renin concentrations were 13.5 units/ml and 10.0 units/ml, respectively, before freezing and 22.5 units/ml and 27.0 units/ml, respectively, after freezing. The apparent increase in renin concentration cannot be due to activation of the large inactive renin, because this entity is unaffected by freezing and thawing. Thus, the increase is probably caused by the release of membrane-bound active renin after freezing. Extracts of frozen kidneys were used in all of the subsequent experiments reported in this paper.

Activation of Renin in Kidney Extracts by Acidification.—Samples of rabbit kidney extract were dialyzed against buffers of various levels of pH for 24 hours at 4°C and then dialyzed back to pH 7.4 before being assayed. Figure 1 shows that the optimum pH for activation was 2.5. The increase in renin pressor activity after activation over that at pH 7.4 was significant by a paired t-test (P < 0.01).

To determine the rate of activation, portions of an extract were assayed and then dialyzed to pH 7.4, pH 4.0, or pH 2.5 at 4°C for 16-24 hours before being reassayed. Figure 2 shows the renin concentration in the samples after 0-24 hours of dialysis at acid pH. When an extract was dialyzed against buffer at pH 2.5 at 4°C, the extract reached pH 3.0 after 2 hours and pH 2.5 at 5 hours. A rise in the amount of renin was noted at 5 hours, probably because some activation occurs at pH 3.0 (Fig. 1). Maximum activation of renin was reached at 10 hours (P < 0.05 compared with 0-hour samples), and no loss of renin was noted at 24 hours. A 24-hour dialysis at pH 2.5 and 4°C was therefore chosen as the standard activation procedure. No activation occurred at pH 4.0 either at 4°C or at 37°C. Prolonged incubation at pH 2.5 and 37°C destroyed renin pressor activity. Samples of kidney extract were equilibrated to pH 2.5 over 24 hours at 4°C, then warmed at 37°C for various times before

### Table 1

| Total and Active Renin in Eight Extracts of Fresh and Frozen Kidney from the Same Rabbits and in Several Assays on One Preparation of Partially Purified Inactive Renin |
|-------------------------------|------------------------|
| Total renin (units/ml) | Active renin (units/ml) |
| Fresh kidney | 41.1 ± 9.1 | 5.8 ± 1.5 |
| Frozen kidney | 102.6 ± 45.0 | 71.3 ± 22.9 |
| Fresh inactive renin | 101.4 ± 14.6 | 14.8 ± 2.2 |
| Frozen inactive renin | 112.5 ± 22.0 | 13.2 ± 1.5 |

All values are means ± SE.
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Means ± SE of renin (units/ml) in six kidney extracts dialyzed to various levels of pH at 4°C and then dialyzed back to pH 7.4 and assayed. The optimum pH for activation was 2.5.

being brought back to pH 7.4 and assayed. The results suggested that the half-life of renin at pH 2.5 and 37°C is about 1 hour.

Activation of Renin by DEAE Chromatography.—Boyd (2) has shown that elution of pig kidney renin from DEAE cellulose with relatively low molarity buffers results in the recovery of “fast-acting” renin only. If the column is then washed with buffer of higher molarity a “renin-binding” material is eluted; this material converts fast-acting renin to the slow-acting form.

Rabbit kidney extract was chromatographed on DEAE cellulose with 0.2M buffer, pH 6.0, according to schedule A. Both active and inactive renin was eluted. The same extract was also chromatographed at the same time with buffer of lower molarity according to schedule B. In five experiments, only active renin was eluted in the 0.075M wash, pH 7.0. Recoveries indicated that activation had taken place on the column as shown by the experiment reported in Table 2. If inactive renin is split into active renin plus an inhibitor during chromatography, the inhibitor should be present in the 0.2M wash, pH 6.0, of schedule B.

Inhibition of Renin by an Eluate from the DEAE Cellulose Column.—In four experiments, 64.4 units of standard renin in 0.1 ml were mixed with 0.9 ml of the 0.2M wash, pH 6.0, of schedule B at 4°C. The protein concentration in the samples of eluate ranged from 4.0 to 7.6 mg/ml. The mixture was incubated at 37°C, and samples were taken for assay at 0, 1, and 2 hours. A control tube contained renin in buffer alone. Figure 3 shows that a significant drop in renin pressor activity occurred in the sample tube after 1 hour of incubation. If this drop is due to combination of the renin with a renin inhibitor, it should be reversed when the renin mixture is activated. Figure 3 also shows that this reversal occurred: acidification restored the renin activity in the sample tube. Next, dilutions of inhibitor were incubated with 25.8 units of standard renin for 1 hour at 37°C in a total volume of 0.55 ml; the samples were then assayed. Figure 4 shows that the greater the amount of inhibitor in the mixture, the greater the inhibition of renin. The maximum inhibition obtained was 73%; complete inhibition of the renin pressor response was not obtained in this experiment.

Figure 5 shows the bioassay of standard renin and renin plus inhibitor. When combined with inhibitor, 1.3 units of renin gave a lower response than did 0.644 units of standard renin. In this example, the pressor response to renin was pro-

| Units of Renin Applied and Recovered from DEAE Cellulose Columns Eluted According to Schedule A or Schedule B |
|---------------------------------------------------------------|-------------------|-------------------|
| Applied (units) | Active renin | Inactive renin |
| Schedule A | 630 | 825 |
| Schedule B, 0.075M, pH 7.0 | 518 | 771 |
| Schedule B, 0.2M, pH 6.0 | 968 | 0 |
| % Recovery | Schedule A | 84 |
| Schedule B | 93 |
| Schedule B | 156 | 0 |

See Methods for explanation of schedules A and B.
Rabbit renin incubated with buffer (crosses) or renin inhibitor fractions (circles) from the DEAE column. Means ± se for four preparations of inhibitor are shown. The broken lines indicate the change in renin concentration after the incubated mixtures had been activated.

longed by the presence of inhibitor, but the prolongation was not observed in every rat preparation. However, the reduction in the height of the renin response by inhibitor always occurred. The rats used for the assay were anesthetized with sodium pentobarbital and may not have displayed the prolongation of response so readily as the urethane-anesthetized rats used in the study of pig renin (2).

Figure 6 shows the separation of active renin and inhibitor by gradient elution on DEAE cellulose. Fractions containing renin were pooled, dialyzed against distilled water, and freeze-dried. Fractions containing inhibitor were pooled and stored without dialysis or freeze-drying. This inhibitor preparation contained 0.2 mg protein/ml and was used in the experiments that are discussed in the next two sections.

Effect of Acidification on Renin Inhibitor.—If inactive renin consists of active renin combined with inhibitor, acid-induced activation may be due to removal of the inhibitor by the acid. To test this hypothesis, 0.5-ml portions of inhibitor were acidified to pH 2.5 by dialysis at 4°C over 24 hours and were then dialyzed back to pH 7.4 for an additional 24 hours. As a control, portions of inhibitor were dialyzed at pH 7.4 for 48 hours. In another experiment, a portion of inhibitor was acidified by the addition of a few drops of 5N HCl, allowed to stand at 4°C for 20 hours, and neutralized. The acidified inhibitor was incubated with standard renin for 1 hour at 37°C, cooled to 4°C, and then assayed. The results were compared with those obtained when the same volume of nonacidified inhibitor and renin were mixed. Inhibitor, acidified inhibitor, and renin were incubated separately with buffer as controls. A mixture of renin and inhibitor was also incubated and then activated before assay to show that the inhibition was reversed by acid treatment. Table 3 shows that acidified inhibitor had no action on renin. The same volume of nonacidified inhibitor reduced the pressor response to 27% of the control value. The inhibitor did not have a depressor action in the rat.

Production of Inactive Renin in Mixtures of Renin and Inhibitor.—Active renin and inhibitor were mixed at 4°C, warmed at 37°C for 1 hour, cooled to 4°C, and applied to the G100 Sephadex column. The effluent fractions were tested for active and inactive renin as previously described (1). The same quantity of active renin was incu-
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R R+I R

\[
\begin{align*}
\Delta \text{BP} & \quad \text{mm/Hg} \\
20 & \\
0 & \\
\end{align*}
\]

\[10 \text{ min}\]

Figure 5
Pressor response (ΔBP) to 0.644 units of standard renin (R) and to 1.3 units of renin preincubated with inhibitor solution containing 0.2 mg protein/ml (R + I).

bated with buffer and applied to the column; renin inhibitor was also chromatographed on its own. Figure 7 shows the elution of active renin, inhibitor, and the mixture of active renin and inhibitor. In the fractions from the mixture of renin plus inhibitor, some large-sized inactive renin was detected. Active renin was also present, but no inhibitor was seen. This finding suggests that some of the renin combined with inhibitor to give inactive renin. No such inactive renin was present when the mixture of active renin and buffer was chromatographed. The molecular weight of inhibitor was about 16,000 in one experiment and about 9,300 in another. The molecular weight of active renin was 38,000 and 36,000 and that of inactive renin was 62,000 and 54,000, respectively, in the two experiments. These values agreed reasonably well with those previously found for active and inactive renin. Over the past 2 years, 18 determinations of the molecular weight of active rabbit renin and 11 determinations of the molecular weight of inactive renin have been made; the means ± SE of these measurements are 37,611 ± 602 for active renin and 55,455 ± 1,131 for inactive renin.

Discussion
Rabbit kidney extracts contain both active and inactive renin. The present experiments indicate that inactive renin can be split into active renin (R) plus inhibitor (I). Renin and inhibitor will recom-

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**TABLE 3**

<table>
<thead>
<tr>
<th>Renin incubated alone</th>
<th>25.4 ± 4.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renin + inhibitor</td>
<td>7.7 ± 1.3</td>
</tr>
<tr>
<td>Renin + acidified inhibitor</td>
<td>25.0 ± 2.1</td>
</tr>
<tr>
<td>Renin + inhibitor, then activated</td>
<td>30.3 ± 3.0</td>
</tr>
<tr>
<td>Renin activated</td>
<td>29.9 ± 2.5</td>
</tr>
<tr>
<td>Inhibitor incubated alone</td>
<td>4.6 ± 0.7</td>
</tr>
<tr>
<td>Acidified inhibitor incubated alone</td>
<td>4.7 ± 0.7</td>
</tr>
</tbody>
</table>

All values are means ± SE for six experiments.

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**Figure 7**
Elution of renin inhibitor, active renin, and a mixture of renin and inhibitor from G100 Sephadex. Open bars = inhibitor, solid bars = blood pressure response in mm Hg to active renin, and hashed bars = blood pressure response to inactive renin; response to acidified fraction minus that to the same fraction before acidification. Solid circles indicate the void volume (Blue Dextran).

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The molecular weight of RI is 55,455, and R and I reaction on DEAE chromatography is:

\[
\text{RI} \xrightleftharpoons{37^\circ C} \text{R} + \text{I}
\]

The molecular weight of RI is 55,455, and R and I have molecular weights of 37,611 and 13,000, respectively.

The presence of inactive renin in human plasma was deduced by Skinner et al. (10), who suggested that the inactive form was activated by acid. Acid-induced activation of renin from human amniotic fluid and plasma (11), pig kidney (2, 12), and rabbit kidney (1) has been reported. There are several reports of multiple forms in pig in (2, 12-14) beef (15), and human (16, 17) kidneys. Different forms of the enzyme have been detected by DEAE chromatography (2, 14, 16), isoelectric focusing (12), electrophoresis (15), and gel filtration (1, 2, 17). Thus, it appears that renin from kidneys of a single species may be heterogeneous both according to electrical charge and molecular size and shape. The relationship of the various forms of renin to each other and to the phenomenon of acid-induced activation is difficult to determine, particularly since different methods of extraction and purification have been used by different workers.

Skeggs et al. (14) have shown that pig renin extracted at pH 7.5 gives a single peak, "renin 1," on DEAE cellulose chromatography. After treatment at pH 2.4, it is converted to "renin 2," which is eluted later than renin 1 and has a remarkably high specific activity. Boyd (2) has reported that his slow-acting form of pig renin is eluted ahead of the fast-acting form on DEAE cellulose chromatography and suggested that the renin 1 of Skeggs et al. is similar to his slow-acting renin. Possibly, inactive rabbit renin is analogous to renin 1 and slow-acting renin found in pig kidneys.

If pig renin is prepared at pH 4.6 instead of pH 7.5 four peaks are obtained on DEAE cellulose chromatography. Rubin (12) has shown that pig renin is activated after exposure to pH 3.7 during purification. This renin gives four bands on isoelectric focusing, but runs as a single peak of molecular weight 3.6-4.1 x 10^4 on G75 Sephadex. Four peaks are obtained on DEAE cellulose chromatography of human renin exposed to pH 4.0 during preparation (16). All of the renins have a molecular weight around 39,000. Beef renin exposed to pH 2.6 also gives four bands on electrophoresis (15). Therefore, renins differing in charge but of similar molecular weights may be obtained after acidification.

The large inactive renin in rabbit kidneys may be a renin zymogen. Many proteolytic enzymes are synthesized as an inactive zymogen which is then split by limited proteolysis to give the active enzyme. For instance, pepsinogen (molecular weight 42,000) breaks down autocatalytically below pH 5.0 to give pepsin (molecular weight 35,000) plus several peptides, one of which can act as a pepsin inhibitor (18). If the inactive renin of molecular weight 55,000 is a renin zymogen, the primary effect of acidification would be to stimulate a limited proteolysis to give active renin plus peptide. The peptide might then act as a renin inhibitor. In this case, the reaction should be written:

\[
\text{"Reninogen"} \xrightarrow{\text{R + I}} \xrightarrow{\text{RI}}
\]

since the initial proteolysis is irreversible. Some evidence for the existence of a renin zymogen is provided by the fact that amniotic fluid renin can be activated by proteolytic enzymes (19). Also, a large form (molecular weight 60,000) of renin has been found by Day and Luetscher (17) in the plasma and tumor tissue of a patient with Wilms' tumor. After acidification, this renin becomes more active, although the tumor enzyme still has a molecular weight of 60,000 after acidification during the purification procedure. Normal human renal renin shows two peaks on G75 chromatography, corresponding to molecular weights of 43,000 and 38,000. Renin from the tumor may be a prohormone analogous to the proinsulin secreted by insulinomas.

However, the large inactive rabbit renin may not be a renin zymogen. Renin may be synthesized in the active form and stored in association with an inhibitor. In this case the inhibitor would be similar to the Kunitz trypsin inhibitor that is stored with trypsinogen in the pancreas (20). It would not be joined to renin by a peptide bond, so activation need not involve proteolysis. The inhibitor may not be a peptide. A lysophospholipid inhibitor can be extracted from dog kidneys (21), but it is probably different from the rabbit kidney inhibitor which is water soluble and of relatively high molecular weight. The rabbit inhibitor may not even be synthesized in the kidney but could be blood-born material similar to the protease inhibitors found in serum (22). Since about 50% of renal renin is inactive, however, this possibility seems unlikely. The presence of inactive renin in the kidney makes sense from a teleological point of view.
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view. Active renin with its potent vasoconstrictor effect must be a dangerous material for the kidney to store in bulk. Storage in an inactive form would be a protective device similar to that employed with the digestive proteases.

These different hypotheses have different physiological implications. If renin is synthesized as a zymogen, the level of active renin would be affected by the rate of synthesis, the rate of release, and the rate of activation of the zymogen. If inhibitor is synthesized independently of renin, the level of active renin would be affected by factors that control production of inhibitor as well as those that control renin production.

The mechanism of renin activation in the intact animal is unknown. It may take place in the kidney, possibly during release of the enzyme from a zymogen granule. Alternatively, inactive renin may be released, and activation may take place in the bloodstream or the blood vessel walls. Boyd (2) reports that slow-acting renin is released from pig kidneys. Renin in human plasma can be activated by acid (11), indicating that some inactive renin may be present. However, hormones such as insulin (23) are normally released in the active form.

When the inhibitor is incubated with renin and the mixture injected into a rat, the pressor effect of the inhibitor is reduced. It is possible that inhibitor injected into an animal with abnormally high renin levels, e.g., with a renal artery clip (24), may reduce the blood pressure. Single injections of inhibitor into a normal rat do not cause a depressor response.

Many enzymes in crude tissue extracts are apparently inactive until the extract is frozen. These enzymes are bound in organelles such as mitochondria and lysosomes and are inaccessible to substrate until they are released from the organelle by freezing and thawing. Renin is stored in the granules of the juxtaglomerular apparatus (25). If extracts are made from fresh kidney, assayed, frozen, and reassayed, some increase in renin pressor activity is noted. This increase is probably due to the fact that the extracts contain some renin which is bound to granules and is therefore inaccessible to substrate. On freezing, this bound enzyme would be released. The increase could not be due to activation of the inactive renin with a molecular weight of 55,000 since the pressor activity of partially purified inactive renin is not altered by freezing.

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