Purification and Some Properties of Two Proteinases from *Crotalus adamanteus* Venom That Inactivate Human α₁-Proteinase Inhibitor*†,

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Two proteinases (proteinases I and II) have been purified from *Crotalus adamanteus* venom to the stage of electrophoretic homogeneity and proteinase II has been crystallized. The proteinases differ slightly in molecular weight and amino acid composition. Both are metalloenzymes requiring Zn²⁺ or Ca²⁺, or both; neither requires thiol compounds for activation. The proteinases are free of esterolytic activity against benzoyl-L-arginine ethyl ester and benzoyl-L-tyrosine ethyl ester. Proteinase II cleaves the oxidized B chain of insulin at the bonds Phe₁⁻Val₂, His₁₀⁻Leu₁₄, Ala₁₄⁻Leu₁₆, Leu₁₆⁻Tyr₁₆, and Tyr₁₆⁻Leu₁₇. Digestion of polyl-lysine by proteinase II liberates products ranging from dodecapeptides to hexapeptides.

Proteinases I and II catalytically inactivate human plasma α₁-proteinase inhibitor (54,000 daltons). Electrophoretic analysis of the reaction of proteinase II with α₁-proteinase inhibitor reveals that an inactivated peptide of 4,000 daltons is released. The gradual disappearance of the native inhibitor results in the corresponding loss of inhibitory activity against trypsin and chymotrypsin.

The occurrence of proteinases in various snake venoms and their effects on such physiological processes as blood coagulation and hemorrhage are well documented and have recently been reviewed (1). However, no reports regarding the action of venom proteinases on human α₁-proteinase inhibitor have appeared. The present paper is based upon the observations(1) that α₁PI had no inhibitory effect on proteinases of crude *Crotalus adamanteus* venom, and that α₁PI was in fact enzymatically inactivated by the venom. The ability to inactivate α₁PI from human blood describes a previously unknown physiological role for certain snake venom proteinases: namely, weakening or destroying one of the principal natural defense mechanisms regulating endogenous serine-type proteinases.

Limited proteolysis of α₁PI resulting in formation of an inactive, modified inhibitor and release of a small peptide has been shown when the inhibitor forms a stoichiometric complex with bovine β-trypsin (2), elastase (3, 4), or porcine trypsin (5, 6). The size of the peptides released from α₁PI varied from 2200 daltons with elastase (4) to 8000 daltons with trypsin (5).

Inactive α₁PI can also result from enzymatic digestion of the inhibitor molecule with no complex being formed. Loss of α₁PI activity was observed after exposure of the inhibitor to lyophilized supernatants of broths in which *Pseudomonas aeruginosa* or *Proteus mirabilis* had been cultured (7). The loss was attributed to an enzymatic activity in the culture supernatant. Inactivation of α₁PI via limited proteolysis by the thiol proteinases, papain and cathepsin B, has recently been reported (8). Electrophoretic analysis showed a decrease in the molecular weight of α₁PI from 53,000 to 47,000 and the release of a peptide.

The present report describes the purification, composition, and some properties of two isoenzymes, referred to as proteinases I and II, from *C. adamanteus* venom. Both proteinases inactivate α₁PI. Proteinase II hydrolyzes α₁PI by limited proteolysis at a single region of the inhibitor molecule, releasing inactive fragments of 50,000 and 4,000 daltons.

**EXPERIMENTAL PROCEDURES**

**Materials**—Venom of *Crotalus adamanteus* (Lot CASOS-172) was obtained from Miami Serpentarium, hide powder azure was from Calbiochem, casein from Mann Research Laboratories, Bio-Gel P-150, Bio-Rex 70, and Dowex 50-X2 were purchased from Bio-Rad Laboratories; Sephadex G-25 and sulfo-propyl (SP)-Sephadex C-25 were from Pharmacia; DE52 cellulose was from Reeve Angel. Oxidized chain B of insulin, ovalbumin, and poly-L-lysine (type VII-B) were obtained from Miami Serpentarium, hide powder azure was from Calbiochem, and bovine trypsin, chymotrypsin, chymotrypsinogen, and soybean trypsin inhibitor were from Worthington. Fluorescamine was from Roche. Human α₁PI was prepared as previously described (9), except that a final chromatography on DE52 at pH 6.5 was incorporated (10). The active α₁PI was pooled, adjusted to pH 8.0, and dialyzed against 5 mM sodium phosphate, pH 8.0. The material was concentrated with an Amicon UM-10 membrane, and aliquots were used immediately or lyophilized.

**Determination of Proteolytic Activity**—During the purification of proteinases I and II, column fractions were routinely assayed with hide powder azure (11). Each tube contained 15 mg of substrate, 3 ml of 0.05 M sodium glycinate, 2 mM ZnCl₂, pH 10, and 1 ml of enzyme solution. The mixture was incubated 1 h at 37°C and filtered through Whatman No. 1 paper, and absorbance at 595 nm was read against a blank. Under these conditions, the increase in A₅₉₅ from 0.1 to 0.25 was proportional to the amount of enzyme. One unit of activity was the amount of enzyme producing ΔA₅₉₅ of 1.0/min. Specific activity was activity per 1.0 A₅₉₅ unit of enzyme solution.† The E₂₈₀ at 280 nm of crystalline proteinase II was 8.8.

Caseinolytic activity was determined essentially by the method of Kunitz (12), using 0.05 M sodium glycinate, 2 mM ZnCl₂, pH 10. The

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*Abbreviations used: α₁PI, human α₁-proteinase inhibitor (previously referred to as α₁-trypsin inhibitor or α₁-antitrypsin); SDS, sodium dodecyl sulfate; Temed, N,N,N',N'-tetramethylethylenediamine.

†This work is dedicated to the memory of Dr. Beatrice Kassell.

‡One A₅₉₅ unit of protein is defined as that amount which, if dissolved in 1 ml and read in a 1-cm light path at 280 nm, will show an absorbance of 1.
enzyme solution contained 10 times the amount of enzyme that was used for the hide powder azure method. Incubation time was for 1 h at 37°C. Under these conditions, the increase in A280 from 0.1 to 0.3 was proportional to the amount of enzyme.

Homogeneity and Composition of Proteinases I and II—Electrophoresis on polyacrylamide gels was performed at pH 9.4 (14), and in SDS (14). Amino acid analyses were performed according to Moore and Stein (15); tryptophan was determined spectrophotometrically (16); sulfhydryl content was determined according to Edman (17), and half-cystine was determined as cysteic acid on performic acid-oxidized samples (18).

Substrate Specificity—The oxidized B chain of insulin (50 mg) was incubated with proteinase II (0.5 mg) for 16 h at 37°C in 0.1 M bicarbonate, pH 10, and the reaction was stopped by addition of 0.5 ml of glacial acetic acid. Undigested B chain was removed by gel filtration on Sephadex G-25 in 10% acetic acid. The digestion peptides were separated on Dowex 50-X2 (19), hydrolyzed for 22 h, and analyzed for amino acid composition with a Beckman 120B analyzer.

Poly-L-lysine and poly-l-arginine (1 ml of a 1% solution in 0.05 M bicarbonate, pH 10) were incubated for 16 h with 100 mg of proteinase II and the reaction ended with 0.1 ml of glacial acetic acid. The reaction products were separated on a Bio-Gel P-2 column (0.9 x 100 cm) using 10% acetic acid. Eluted protein was determined fluorometrically (20) using an Amino filter fluorometer. Samples (25 μl) were added to 2 ml of 0.1 M phosphate, pH 6.8, and 0.5 ml of fluorescamine (0.1 mg/ml in acetone) was rapidly introduced with constant mixing (Vortex).

Proteolytic Inactivation of α1PI and Electrophoretic Analysis of the Reaction Products Native α1PI (1.56 mg) was incubated at 23°C with proteinase I or II (5 μg) in 5 mM sodium phosphate, 2 mM CaCl₂, pH 8.0, in a final volume of 250 μl. The molar ratio of inhibitor to proteinase was approximately 100:1. Aliquots (50 μl) were withdrawn at various times; a portion of this (5 μl) was added to 5 μl of buffer containing 0.01 M EDTA to end the reaction, and assayed for inhibitory activity against trypsin (21) or chymotrypsin (22). The remainder of each aliquot (30 μl) was added to 3.0 ml of 10% SDS and 20 μl of Teemed. Just prior to the electrophoresis, portions (10 μl) of this reduced material were treated with 2 μl of fluorescamine (5 mg/ml in acetic acid). A control experiment using α1PI denatured by heating at 100°C for 45 min was also performed.

Vertical slab gel electrophoresis was carried out in a Hoefer apparatus using glass plates cleaned with Kodak Photo Flo 600. Gel slabs containing linear gradients from 10 to 30% of polyacrylamide were formed by mixing light and heavy gel solutions from a gradient mixing apparatus with a Buchler Polystantic pump. The light solution contained 6.5 ml of acrylamide/bisacrylamide (20%/0.5%), 6.5 ml of 0.25 M Tris-HCl, pH 8.0, 0.2% SDS, 20% sucrose, and 20 μl of Teemed. The heavy solution contained 6.5 ml of acrylamide/bisacrylamide (80%/0.2%), 30 ml of 0.05 M Tris-HCl, pH 8.0, 0.2% SDS, 40% sucrose, and Teemed. Just prior to starting the gradient, 30 μl of ammonium persulfate (40 mg/ml of H₂O) were added to each solution. After the gradient was completed, the gel slab was overlayed with 0.3 ml of H₂O. Polymerization occurred in about 90 min. The amounts given are sufficient to cast one gel 1.5 mm thick. Stacking solution was formed from 1 ml of the light gel solution, 4 ml of electrophoresis buffer (0.125 M Tris-HCl, pH 8.0, containing 0.1% SDS), 10 μl of Teemed, and 0.1 ml ammonium persulfate and layered onto the gel slab to a height of 0.5 cm.

For molecular weight determinations of the reaction products, the same gel system was used, but fluorescamine labeling prior to electrophoresis was not employed. Instead, the slab was stained with Coomasie brilliant blue and calibrated according to Weber et al. (14) using human serum albumin, ovalbumin, soybean trypsin inhibitor, pancreatic trypsin inhibitor (Kunitz), and oxidized B chain of insulin as standards.

RESULTS

Purification and Homogeneity of Enzyme—Venom (5 g) was dissolved in 80 ml of 0.05 M Tris-HCl, pH 8.0, containing 0.2 M NaCl. The small amount of insoluble material, if any, was centrifuged off. The solution was charged on a Bio-Gel P-150 column and eluted as shown in Fig. 1. The protein from the third peak contained a high amount of hide powder azure activity, some caseinolytic activity, and rapidly inactivated α1PI. Inactivation of α1PI by proteinases in Peak I from the P-150 column (Fig. 1, tubes 40 to 70) was also observed. However, the specific activity of the pooled Peak I was lower than that of crude venom, and no further purification was attempted. The second protein peak from Bio-Gel P-150 (Fig. 1, tubes 80 to 106), which contains all the venom proteinases active on fibrinogen and benzoyl-L-arginine ethyl ester (23, 24), was devoid of α1PI inactivating activity.

The pooled third peak from Step 1 (tubes 110 to 130) was dialyzed overnight against 6 liters of 0.05 M glycine buffer, pH 6.5, adsorbed on a SP Sephadex column, and eluted as shown in Fig. 2. Two protein peaks (I and II) appeared. Both were active on hide powder azure and casein, and both inactivated α1PI. Each peak was pooled, and the material was dialyzed against the starting buffer and rechromatographed separately (data not shown). The active material was then dialyzed against 0.05 M sodium borate, pH 8.0, containing 2 mM CaCl₂ and stored at −18°C. Activity was stable for at least 6 months under these conditions.

A summary of the purification procedure is presented in Table I. The activity at pH 10 on hide powder azure of crude venom is taken as 100%. A slight, but analytically significant, difference in specific activity between the proteinases is noticed and is presumably due to the difference in tryptophan content, since activity is calculated on the basis of A280. In order to conserve α1PI, only crude venom and pools from the column were assayed for α1PI inactivation. The specific activity of venom at pH 10 was 8.6 (proteinase I) and 110 to 120 (proteinase II) were pooled.
inactivation of human α1-proteinase inhibitor

Inactivation of Human α1-Proteinase Inhibitor

The two upper gels contained 7.5% acrylamide and were run in 0.05 M Tris/HCl, pH 8.0, with 100 μg of proteinase. All gels were stained with aniline blue black in 7% acetic acid.

Proteinase II, the more abundant of the two, was crystallized (Fig. 2). The material obtained after rechromatography on SP-Sephadex was dissolved in a small amount of 0.05 M Tris-HCl, pH 8.0. Solid ammonium sulfate was added to attain 35% saturation (200 mg/ml) followed by the dropwise addition of saturated ammonium sulfate solution every 12 h until the first sign of turbidity. The sample was then placed in the refrigerator. Crystallization started after about 4 days and was completed after a week. The specific activity of crystals remained at 56 (Table I).

Properties—The proteinases retained full activity after exposure to diisopropyl fluorophosphate, indicating that they are not of the serine type. On the other hand, EDTA completely inhibited both proteolysis of hide powder azure and inactivation of α1-P1. Of several metals that were tried as activators, the most effective were Zn^{2+} or Ca^{2+} at 2 mM concentration (Table III). Higher concentrations (10 mM) of Zn^{2+} or Ca^{2+} were inhibitory. The proteinases showed no requirement for thiol compounds for activation or for maximal activity. On the contrary, increasing amounts of reducing agents proved inhibitory, with a much lower concentration of cysteine being required for inhibition in the presence of Ca^{2+} than in the presence of Zn^{2+}. The optimal conditions for proteinase activity on hide powder azure are pH 10 and 2 mM Zn^{2+}. Table III shows data for proteinase II. Results with proteinase I are essentially identical and are not shown. The metal requirements appear similar to those reported for Leuconostoma peptidase (20) which contains 2 atoms of Ca^{2+} and 1 atom of Zn^{2+} per molecule of enzyme.

![Fig. 2. Crystals of proteinase II x 270.](https://www.jbc.org/)

![Fig. 3. Electrophoretic homogeneity of proteinases I and II. The two upper gels contained 7.5% acrylamide and 0.1% SDS. Samples (50 μg) of proteinase in 0.2 M phosphate, pH 7.2, were run at 1.5 mA/tube. The two lower gels contained 7.5% acrylamide and were run in 0.05 M Tris/glycine, pH 9.4, with 100 μg of proteinase. All gels were stained with aniline blue black in 7% acetic acid.](https://www.jbc.org/)
Specificity on Substrates of Known Structure—The amino acid compositions of the B chain peptides eluted from Dowex 50 accounted for the entire B chain. Bond cleavages by proteinase II occurred at Phe$_{2}$-Val$_{15}$, His$_{10}$-Leu$_{26}$, His$_{1}$-Leu$_{12}$, Ala$_{1}$-Leu$_{16}$, Leu$_{16}$-TyR$_{16}$, and TyR$_{16}$-Leu$_{12}$. All bands of the type X-Leu, and one of the type X-Val were cleaved. Judging from peptide recoveries, the Ala$_{1}$-Leu$_{16}$ and His$_{10}$-Leu$_{26}$ bonds were most readily attacked. No cleavages occurred in the right half of the molecule, which is in contrast to several other venom proteinases (25), but similar to the H$_{2}$-proteinase from *Trimeresurus* (27). Both polylysine and polyarginine were digested by proteinase II with the liberation of products estimated to range from dodecapeptide to hexapeptide. No free amino acids were liberated. In other tests of substrate specificity, no hydrolysis by proteinase I or II of either benzoyl-L-arginine ethyl ester or benzoyl-L-tyrosine ethyl ester was detected. Lack of activity against these substrates is also an indication that the proteinases are not contaminated by the "thrombin-like esterases" present in this venom (24). These results with the various substrates suggest that not only the nature of the amino acid, but the length of substrate determines its susceptibility to digestion by proteinase II.

**Limited Proteolysis and Inactivation of αIPI**—As described under "Experimental Procedures," native αIPI was incubated with either proteinase II (Fig. 5, A and B) or proteinase I (Fig. 5, C and D). The gradual loss of inhibitory activity was monitored by assaying the remaining active αIPI against trypsin (Fig. 5, A and D) and chymotrypsin (Fig. 5, B and C). The inactivation curves, normalized to 100% of starting αIPI activity, were similar for all four variants.

Fig. 6, D to I, shows that the inactivation of native αIPI by proteinase II (cf. Fig. 5, A and B) results in the gradual decrease of intact αIPI (54,000 daltons) and the appearance and corresponding increase of inactivated αIPI (50,000 daltons) and of a peptide of 4,000 daltons. After a 4-h incubation, detectable αIPI activity against trypsin has decreased to 1.3% and against chymotrypsin to 3.9% of the starting values (Fig. 5, B and C). The band of intact αIPI visible at 4 h (Fig. 6H) corresponds to approximately 5% of the starting material. After 24 h, no αIPI activity remained, and no 54,000-dalton band is visible (Fig. 6I). The 50,000-dalton band is undiminished after incubation with proteinase I.

**Effect of metal ions on the activity of proteinase II**

The results in Table III show that the activity of proteinase II is not significantly altered by the addition of metal ions. The activity of proteinase II assayed in the presence of either Zn$^{2+}$ or Ca$^{2+}$ was found to be essentially the same as that assayed without added metal ions.

**Table III**

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Zn$^{2+}$ (2 mM)</th>
<th>Ca$^{2+}$ (2 mM)</th>
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<td></td>
<td>Concentration</td>
<td>Activity (%)</td>
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<td>Cysteine</td>
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<td>Glutathione-SH</td>
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<td>2-Mercaptoethanol</td>
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$^*$ All activities were calculated on the basis of the activity shown at pH 10 in the presence of 2 mM Zn$^{2+}$.

**Fig. 5.** Inactivation of αIPI by proteinases I and II. Aliquots of the incubation mixtures of proteinases I or II with αIPI (see "Experimental Procedures") were assayed for residual inhibitory activity toward trypsin or chymotrypsin. The zero time activity is that of a comparable aliquot prior to proteinase addition and is normalized to 100%.

**Fig. 6.** Electrophoretic analysis of the reaction between proteinase II and native αIPI shown in Fig. 5, A and B. Gel channels were charged with 1-μl aliquots. Standard proteins (0.8 μg) were: A, ovalbumin (the lower band is a contaminant); B, soybean trypsin inhibitor (upper band) and oxidized B chain of insulin (lower band). Samples (6.24 μg each) taken during the proteinase II-native αIPI reaction were: C, native αIPI (prior to proteinase); D, 15 s; E, 30 min; F, 60 min; G, 120 min; H, 240 min; I, 24 h. Samples (6.24 μg each) taken during the proteinase II-heat denatured αIPI reaction (see "Experimental Procedures") were: J, 15 s; K, 30 min; L, 60 min; M, 120 min; N, 240 min; O, 24 h. The arrow marks the location of the bromphenol blue tracking dye charged only in the extreme left and right channels. Electrophoresis was carried out in 0.125 M Tris-Cl buffer, pH 8.0, containing 0.1% SDS at 150 V for 17 h. Initial amperage (40 mA/slab) decreased to 10 mA over this period. Slabs were cooled via circulating tap water. Fluorescent bands were visualized with a Chromatovue long wave transilluminator and photographed using a combination of Kodak #2A and #3A gelatin filters.
inhibitory activity has disappeared, indicating that this species is inactive. Both cleavage products of α1PI appear resistant to further digestion, since they are still detectable after 24 h (Fig. 6, J to O) and since no intermediate molecular weight bands are observed. Full protease activity (assayed on hide powder azure) was maintained over the course of the 24-h incubation period. No bands corresponding to α2PI-protease complex were detected, a further indication of the catalytic nature of the inactivation process. The electrophoretic pattern for the inactivation of α1PI by protease I (not shown) does not differ from that observed with protease II.

Fig. 6, J to O reveals that heat-denatured α1PI is digested by protease II more extensively than is native α1PI. However, major bands of 50,000 and 4,000 daltons appear. Apparently, the same region in α1PI is most sensitive to proteolytic attack in both the native and denatured inhibitor. The 50,000-dalton fragment of denatured α1PI appears rather resistant to proteolytic digestion judging from the amount remaining after 24 h (Fig. 6O). As expected (since the heat denaturation conditions were deliberately rigorous), numerous intermediate molecular weight bands are also apparent, indicating random cleavages in the denatured α1PI molecule.

From the results shown in Figs. 5 and 6, it was concluded that incubation of α1PI with protease II resulted in the catalytic inactivation of the inhibitor by limited proteolysis.

**DISCUSSION**

Venoms from snakes of the families Crotalidae and Viperidae are known to possess a variety of proteases which react with plasma proteins (28). Among these are the "thrombin-like esterases" which convert fibrinogen to fibrin (29, 30), the protease from Russell's viper venom which converts Factor X to Factor Xa (31), and the protease from Agkistrodon rhodostoma which inactivates bradykinin (32). The examples cited all involve limited proteolysis of a specific plasma protein.

The results reported in the present paper extend the interaction of venom proteases with another class of plasma proteins, namely, the plasma proteinase inhibitors. The inactivation of α1PI by venom protease II proceeds in a fashion similar to that reported for papain and α1PI (8). These authors observed catalytic inactivation of α1PI with papain and stoichiometric inactivation with liver cathespin B1, both of which are thiol proteases. The results with venom proteases I and II indicate that the catalytic inactivation of α1PI can also be accomplished by metallicproteinases which in this case are not of the serine type and do not require thiol compounds for activation.

Calculation of molecular weights prior to fluorescamine labeling in the same gel system shown in Fig. 6 (see "Experimental Procedures") shows that intact α1PI of 54,000 is converted by protease II to inactivated α1PI of 50,000. Within the range of variation expected for the gel system used (14), these values are comparable to those reported for α1PI inactivated by papain (8).

The molecular weight value for the peptide released calculated by reference to the oxidized B chain of insulin is 4,000 (Fig. 6). In other experiments (not shown) employing different polyacrylamide gradients, the peptide consistently migrated above the oxidized D chain and well below the 6,500-dalton pancreatic trypsin inhibitor (Kunitz). The molecular weight for the peptide calculated in these gel systems was again 4,000. Since calculation from SDS gels of molecular weights for small peptides is subject to greater variation than that for larger proteins (14, 30), the possibility cannot be excluded that the peptide released from α1PI by venom protease II may differ slightly from that reported for trypsin and papain (5, 8).

The comparison of the inactivation of native α1PI with that of heat-denatured α1PI (Fig. 6) indicates that no peptides of less than 4,000 daltons are released from native α1PI, whereas several peptides smaller than 4,000 daltons are detectable as products of digestion of denatured α1PI. The fact that no bands other than the 50,000- and 4,000-dalton bands are detectable after 24 h of digestion of native α1PI (Fig. 6I) implies that a single sensitive region has been digested by the venom protease to catalytically inactivate the inhibitor.

The mechanism of α1PI inactivation follows the general pattern for limited proteolysis (34). Selective bond cleavage occurs in an exposed segment of the native α1PI molecule, while random cleavage of internal portions of the molecule is observed when heat-denatured α1PI is incubated with protease II (Fig. 6, J to O).

The detailed mechanism of the catalytic inactivation of α1PI by venom proteases remains to be demonstrated. The inactivation process apparently does not enhance the effectiveness of C. adamanteus proteases or esterases, since these enzymes are not inhibited by α1PI. However, the catalytic mechanism (as opposed to stoichiometric enzyme-inhibitor complex formation) would enable small amounts of venom proteases to rapidly inactivate large quantities of circulating α1PI.

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