Interactions of Plasma Kallikrein and Cl-INH with Normal and Dysfunctional Cl-Inhibitor Proteins From Patients With Hereditary Angioneurotic Edema: Analytic Gel Studies

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Purified preparations of normal Cl-inhibitor (Cl-INH) formed high mol wt complexes with plasma kallikrein that were stable during sodium dodecyl sulfate (SDS)-gel electrophoresis, but most of the dysfunctional Cl-INH proteins isolated from plasma of patients with type II hereditary angioneurotic edema (HANE) did not. Two of eight dysfunctional Cl-INH proteins were cleaved to lower mol wt forms that were not seen following the reaction of normal Cl-INH with equimolar amounts, or less, of plasma kallikrein. Only the higher mol wt component of normal Cl-INH (106,000 mol wt) appeared to form a stable complex with the plasma kallikrein, whereas both the 106,000 and 96,000 mol wt forms made stable complexes with Cls. When a preparation of normal Cl-INH containing a homogeneous single band of Cl-INH was exposed to Cls or kallikrein, a "doublet" form evolved in which the heaviest band was in the original position of native Cl-INH; Cls cleavage provided a second band of 96,000; and cleavage by kallikrein, a second band of 94,000 mol wt. We conclude that dysfunctional Cl-INH proteins from plasma of persons with type II hereditary angioneurotic edema have impaired interactions with plasma kallikrein and are heterogeneous with respect to these interactions. Moreover, the requirements for the formation of stable complexes between normal Cl-INH and plasma kallikrein differed from those for stable complex formation with Cls. The doublet form of Cl-INH, which purified preparations frequently demonstrate, may be due to prior cleavage by Cls or kallikrein.

C-INHIBITOR (Cl-INH) from normal serum blocks the activities of the activated first component of complement, Cl, and its Cls and Clf subunits; activated forms of Hageman factor (factor XIIa); activated plasma thromboplastin antecedent (factor XIIa); plasmin; and plasma kallikrein.1 Persons with hereditary angioneurotic edema (HANE) are deficient in serum Cl-INH activity, but from 15% to 30% of those affected have Cl-INH in their serum that contains normal antigenic determinants but is dysfunctional in that it fails to inhibit preparations of Cl or Cls normally.5 This has been called type 2 HANE. Recent studies of purified preparations of eight dysfunctional Cl-INH proteins from affected members of kindred with type II HANE revealed that each dysfunctional Cl-INH varied in its capacity to inhibit purified preparations of activated Hageman factor, plasma kallikrein, plasmin, and Cls subunit.6 The dysfunctional Cl-INH proteins also varied from one another in their ability to inhibit any one of these plasma proteases.8 Analysis of the interactions of Cl-INH proteins with plasmin and Cls in sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis confirmed the evidence of heterogeneity obtained in functional studies, since some formed covalent complexes with Cls and plasmin and some were degraded by these enzymes. The studies reported here demonstrate that there is heterogeneity among dysfunctional Cl-INH proteins with regard to SDS-polyacrylamide gel analysis of their interactions with plasma kallikrein. When normal Cl-INH reacted with plasma kallikrein, only the higher mol wt form (106,000) appeared to form a stable complex with plasma kallikrein, which was visible in SDS-polyacrylamide gels. In addition, two dysfunctional Cl-INH proteins not previously examined were cleaved by Cls.

MATERIALS AND METHODS

Plasma was obtained from normal persons and persons with type II HANE, whose dysfunctional proteins were previously characterized,4 after informed consent was given by the donors. Plasma was separated by plasmapheresis and immediately mixed with benzamidine (0.1 M) and EDTA, 0.1 mol/L, final concentrations.

Resins used to purify Cl-INH proteins and the enzymes used in these experiments included SP Sephadex C-50, DEAE-Sephadex A-50, DEAE-Sephadex C-50, CM-Sephadex C-60, DEAE-activated Sepharose 4B, Sephacryl S-200 superfine, and Sephadex G-150, all of which were obtained from Pharmacia Fine Chemicals, Piscataway, NJ. Hydroxyapatite (HTP) was obtained from Bio-Rad Laboratories, Richmond, CA; Aca 54 Ultrogel from LKB Instruments (Bromma, Sweden via Rockville, MD). Polyacrylamide was obtained from Eastman Kodak, Rochester, NY; soybean trypsin inhibitor from Worthington Chemical, Freehold, NJ; benzamidine and L-lysine hydrochloride from Matheson, Coleman and Bell, Norwood, OH; sodium dodecyl sulfate (SDS) from Fisher Chemical, Norwood, OH; and BRJ-33 from Calbiochem-Behring, La Jolla, CA. Conjugates of lysine-Sepharose and soybean trypsin inhibitor-Sepharose were prepared using the instructions provided by the manufacturer for conjugating materials with Sepharose.

Cl-INH was isolated from normal plasma according to the method of Harrison,7 using either Sephacryl S-200 or Sephadex...
G-150 for gel filtration. The C1-INH prepared by this method was usually a homogeneous single band in SDS analytic gel electrophoresis, but some preparations demonstrated two closely approximated bands.8,9 Recoveries were as high as 70% of that in the starting plasma.

Plasma kallikrein was isolated according to the procedure of Nagase and Barrett,18 which was modified to include a second step in affinity chromatography with SBTI-Sepharose following chromatography on Ultrogel A C54. In addition, immune adsorption on a column of Sepharose-antihuman IgG was used to remove contaminating immunoglobulins at the end of the purification. This kallikrein was homogeneous in SDS analytic gel electrophoresis when freshly prepared, or a doublet, and had a specific activity of approximately 176 units of coagulant activity per milligram of protein. In determining the specific activity of plasma kallikrein preparations, a coagulation assay was used1 in which one unit of activity is defined arbitrarily as the amount in 1.0 mL of pooled normal human plasma. During storage at −30°C, autodigestion products formed of 67,000 and lower mol wt. Cleavage products of less than 52,000 mol wt, induced by cleavage by factor XIIa, have been shown to have reduced ratios of coagulation to amidolytic activity.12

C1S was prepared by the method of Bing and his colleagues13,14 and gave a homogeneous single band in SDS-analytic polyacrylamide gel electrophoresis when freshly prepared. This material had a specific activity of over 1,000 U/mg of protein.1 Some degradation of the C1S used has occurred in the present studies, providing lower mol wt bands visible in stained gels (see figures) after EDTA was removed during gel filtration.

SDS-polyacrylamide gel analyses were performed using a Hoefer Vertical Gel Electrophoresis system and was carried out either in 7.5% polyacrylamide, according to the method of Laemmli15 or in gradient gels prepared using a modification of this method in which a gradient of 7.5% to 12.5% (wt/vol) acrylamide was prepared as reported previously.8 Gel-bond (FMC, Marine Colloids Division, BioProducts, Rockland, ME) was inserted between the glass plates into which the gels were poured for vertical electrophoresis to stabilize the gels. After adding SDS, the mixtures were incubated at 37°C for another 30 minutes, instead of boiling, to avoid aggregation of proteins. Electrophoresis was carried out at 3 to 3.5 V/cm for 18 hours at room temperature or until the tracking dye was within 1 to 2 cm of the bottom of the gel when gradient polyacrylamide gel was used. When a single concentration of polyacrylamide gel was used, electrophoresis was carried out at 4°C until the tracking dye was near the bottom of the gel. After staining with 0.25% Coomassie brilliant blue, the gels were fixed in mixtures of 33% methanol, 15% trichloroacetic acid, and 3% sulfosalicylic acid for 30 minutes, followed by washing in an aqueous mixture of 5% acetic acid and 16% glycerol overnight.

RESULTS

Interactions of C1S and plasma kallikrein with normal C1-INH. When purified normal C1-INH was incubated with plasma kallikrein for as short a period as five minutes at 37°C, stable complexes between kallikrein and the inhibitor formed (Fig 1A). These complexes appear to involve the component of C1-INH of about 106,000 mol wt but not that of approximately 96,000 mol wt, even when the concentration of kallikrein was in molar excess with respect to the inhibitor (Fig 1A). In experiments not shown, complexes between the lower mol wt component of C1-INH and kallikrein in equimolar amounts or in enzyme excess failed to

![Fig 1](http://www.bloodjournal.org)
occur during incubation for as long as two hours. On the other hand, when C1 was incubated with this preparation of C1-INH, both components of the C1-INH appeared to become involved in complexes with C1 (Fig 1B). These observations suggest that there are different structural requirements for the formation of stable complexes between normal C1-INH and kallikrein than with C1s.

When a purified preparation of normal C1-INH, which was apparently homogeneous having a mol wt of 106,000, was used, it was cleaved by both C1s and kallikrein during incubation for brief periods at 37°C (Fig 2). The cleavage product had an approximate mol wt of 96,000. A major high mol wt complex formed with each enzyme and this inhibitor. The mol wt of the complex with C1s was approximately 182,000 and that with kallikrein was 185,000 (Fig 2). The C1-INH was not completely consumed in this experiment, probably because the C1s used had a lower specific activity than that used in the experiment shown in Fig 1B. In an experiment not shown here, a preparation of C1-INH, which had lost most of its activity against C1s, consisted of two lower mol wt components of approximately 95,000 and 92,000. Neither of these formed a complex with plasma kallikrein.

Interactions of plasma kallikrein with dysfunctional C1-INH. Dysfunctional C1-INH proteins from members of eight different kindred with type II HANE were purified and analyzed for their interactions with plasma kallikrein. The subjects from whom plasma was obtained were not receiving androgen therapy at the time, with the exception of one preparation from subject Da, noted below, and therefore did not have therapeutically induced increases in serum concentrations of normal C1-INH. These proteins were examined for their interactions with C1s and plasmin in work reported earlier.8 Table 1 summarizes the interactions of these proteins with kallikrein and compares them with their interactions with C1s, most of which were reported in an earlier study.8 In these studies the kallikrein and inhibitor proteins were incubated together at 37°C for 20 minutes before SDS was added, and electrophoresis was performed in SDS gels. The preparation of C1-INH from subject Bo contained a single low mol wt contaminant, and C1-INH from subject Ta contained a single unidentified high mol wt contaminant visible in SDS gel. The preparation of C1-INH from Da, which formed a stable high mol wt complex with kallikrein, was obtained when this patient had received androgen therapy and probably contained detectable amounts of normal C1-INH. It was not possible to distinguish the normal protein from some of the dysfunctional protein in these gels. Other preparations from this subject failed to form complexes stable in SDS gels.

In the experiment illustrated in Fig 3, kallikrein was incubated with the inhibitor proteins at 37°C, as above, and before electrophoresis SDS was added, and the mixtures were incubated at 37°C for 30 minutes, instead of boiling, to

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<td>% of Normal</td>
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The first column designates the abnormal C1-INH from kindred with HANE by the first two letters of the kindred name, and the second and third columns provide the levels of inhibition of C1s and kallikrein by each dysfunctional C1-INH as compared to that of the normal C1-INH, which were published earlier.8 The inhibition of C1s and kallikrein by normal C1-INH was arbitrarily determined to be 100%. The percent of inhibition provided by each dysfunctional C1-INH was calculated by dividing the reduction rate of hydrolysis of synthetic substrates by each enzyme, in nanomoles per minute per microgram of dysfunctional inhibitor, by the reduction rate in percent per microgram of normal C1-INH × 100. Each dysfunctional C1-INH was tested four to six times against each enzyme using different quantities of inhibitor.8 Kallikrein inhibition was measured with a synthetic chromogenic amide (S-2302, Kabi, Stockholm, Sweden) and inhibition of C1s by the method of Levy and Lepow,1 which employs an acridinometric titration of N-acetyl-L-tyrosine ethyl ester hydrolysis. The reduction in rate of hydrolysis in the presence of the inhibitor proteins by a preparation of C1s in units per milligram of protein was calculated. Columns 4, 5, 6, and 7 indicate whether or not complex formation occurred between C1s, kallikrein (+ = stable complexes) and each inhibitor and if the inhibitors were cleaved (–) by either enzyme.

*With molar excess of enzyme only (2:1).
We have not detected cleavage fragments of less than 96,000 mol wt in SDS gels when normal CT-INH has been exposed to Cl. The interactions of each of these Cl-INH proteins with Cl and kallikrein are compared in Table I.

DISCUSSION

When normal C1-INH, which was a doublet in SDS-polyacrylamide gel electrophoresis, was incubated with kallikrein and then subjected to electrophoresis in the same gel system, a major high mol wt complex of about 185,000 to 190,000 mol wt could be visualized (Fig 1A), but only the component of C1-INH having a mol wt of approximately 106,000 formed stable complexes with kallikrein. The lower

Fig 3. Each purified dysfunctional C1-INH protein is indicated by the first two letters of the kindred name, shown at the top of the gel, describing its electrophoretic behavior following preliminary incubation with one or more quantities of purified plasma kallikrein (K). Lane 1 (A) contained proteins (m) of known mol wt, indicated to the left. The gels contained concentrations of polyacrylamide graded continuously of from 7.5% at the top of the gel to 12.5% at the bottom (anode). The amounts of kallikrein and of C1-INH proteins were: (A, B) C1-INH At and Bo, 31 μg; kallikrein, 30 μg (lane 3) and 60 μg (lane 4); Lane 1, (B), kallikrein alone, 30 μg. (C): C1-INH Mo, 28 μg (lanes 2 to 4); kallikrein, 30 μg (lane 3) and 60 μg (lanes 1 and 4). Although a somewhat higher mol wt band was generated in mixtures of C1-INH At and kallikrein, low mol wt fragments were not found. Possibly the complex contained a cleavage fragment of C1-INH At and kallikrein (panel 1). A low mol wt band in the C1-INH Bo preparation (panel 2, lane 2) is an unidentified contaminant, reported earlier. Although C1-INH Bo failed to form a stable complex with kallikrein, it was cleaved by the enzyme (lane 4). There was no apparent interaction between C1-INH Mo and kallikrein (panel 3).

Fig 4. Comparison of electrophoretic behavior of dysfunctional C1-INH At, Bo, and Za with Cls in SDS polyacrylamide gels of 7.5% concentrations (ungraded). C1-INH was used in molar excess with respect to Cls: C1-INH At in an amount of 22.5 μg; C1-INH Bo (lanes 4, 5), 25 μg, and Za (lanes 7, 8), 55 μg. C1s, 7.5 μg in all mixtures. The anode is down. Even though C1-INH At was clearly cleaved into lower mol wt fragments by Cls, two high mol wt complex bands stable in SDS were also formed. C1-INH Bo, which failed to interact with kallikrein in the experiment in Figure 3, did form a small amount of stable complex with Cls. C1-INH Za and C1s formed two high mol wt bands, but the source of the two bands is not clear.

avoid aggregation of proteins. After electrophoresis, C1-INH from subject At appeared to form a lower mol wt complex than would be predicted with plasma kallikrein (Fig 3, lane 3 and 4, panel 1). In contrast, C1-INH from Bo was cleaved into multiple visible lower mol wt cleavage fragments during incubation with kallikrein but did not form a stable, higher mol wt complex (Fig 3, panel 2). C1-INH from subject Mo apparently failed to interact with the kallikrein, even in excess (Fig 3, panel 3). C1-INH Da also exhibited lower mol wt cleavage fragments when incubated with a molar excess of kallikrein (not shown). Thus under comparable conditions the dysfunctional proteins were heterogeneous in their susceptibility to cleavage by kallikrein. In earlier studies, C1-INH We formed a complex with kallikrein and was also readily cleaved by this protein. This protein was also cleaved by plasma kallikrein but only into a single cleavage product of approximately 96,000 mol wt.

Interaction of Cls with dysfunctional C1-INH. When dysfunctional C1-INHs from At, Bo, and Za were examined in 7.5% polyacrylamide gels, C1-INH At formed two high mol wt complexes with Cls, and lower mol wt cleavage fragments evolved (Fig 4, lane 2). C1-INH Bo and Za also formed high mol wt complexes with Cls, whereas neither did so with kallikrein. The mol wt of the major C1-INH Za complex with Cls was lower than that formed with C1-INH Bo but about the same as the lighter complex between C1-INH At and Cls. Cleavage of dysfunctional C1-INH Ta and We by Cls was observed in studies reported earlier.

We have not detected cleavage fragments of less than 96,000 mol wt in SDS gels when normal C1-INH has been exposed to Cls. The interactions of each of these C1-INH proteins with Cls and kallikrein are compared in Table I.
mol wt band in the C\textsubscript{I}-INH preparation (approximately 96,000) did not do so (Figs 1A and 2). When increasing amounts of C\textsubscript{I} were incubated with the same preparation of C\textsubscript{I}-INH before electrophoresis in graded concentrations of polyacrylamide, both the lower and higher mol wt components of C\textsubscript{I}-INH formed a stable complex with C\textsubscript{I}\textsubscript{s} (Fig 1B). Therefore the 96,000 mol wt component of normal C\textsubscript{I}-INH apparently contained structural requirements for stable complex formation with C\textsubscript{I}s but not with kallikrein. Both enzymes could generate the doublet C\textsubscript{I}-INH from a preparation containing a homogeneous single band of protein (Fig 2). Exposure to kallikrein appeared to generate a lower mol wt cleavage fragment than that generated by C\textsubscript{I}\textsubscript{s} (Figs 1A and 1B), as if kallikrein degraded the protein further than did C\textsubscript{I}s. Van der Graaf and his associates also found that a plasma kallikrein preparation, or its light chain failed to form complexes with a lower mol wt form (94,000) of C\textsubscript{I}-INH,\textsuperscript{14} which may be the same as the lower mol wt C\textsubscript{I}-INH seen in the present studies. The fact that some preparations of C\textsubscript{I}-INH, which are isolated by the method of Harrison,\textsuperscript{9} are in a doublet form implies that the protein may have had contact with C\textsubscript{I}s or kallikrein in vivo, for isolation was carried out in the presence of exogenous inhibitors aimed at preventing cleavage of C\textsubscript{I}-INH in vitro. One of us (Harrison), however, has found only a single band of C\textsubscript{I}-INH antigen in freshly drawn normal plasma using a monoclonal antibody (MoAb) to C\textsubscript{I}-INH in an electroimmunofixation procedure. Harpel and Cooper\textsuperscript{17} identified a plasmin-generated cleavage fragment of normal C\textsubscript{I}-INH that was initially functional but lost activity without evidence of a further loss in mol wt. Zuraw and Curd recently reported that an inactive fragment of 94,000 mol wt could be released from normal C\textsubscript{I}-INH in plasma when kallikrein was activated.\textsuperscript{17a}

The interactions of dysfunctional C\textsubscript{I}-INH proteins with plasma kallikrein were heterogeneous, and only two of these formed complexes with kallikrein that were stable during electrophoresis in graded concentrations of polyacrylamide containing SDS. Each of these (C\textsubscript{I}-INH At and Za) had reduced inhibitory properties directed against the amidolytic activity of plasma kallikrein in studies previously reported\textsuperscript{8} (Table 1). Therefore the complexes visualized in these studies may not be associated with effective inhibition of kallikrein by the C\textsubscript{I}-INH proteins. Dysfunctional C\textsubscript{I}-INH We also had reduced inhibitory properties directed against C\textsubscript{I}s but formed visible complexes with C\textsubscript{I}s (Table 1). C\textsubscript{I}-INH Bo was cleaved by the plasma kallikrein into multiple lower mol wt fragments of less than 90,000 mol wt (Fig 3). In earlier studies C\textsubscript{I}-INH We was exceedingly susceptible to plasmin cleavage.\textsuperscript{8} These observations reinforce the evidence of structural heterogeneity of these dysfunctional proteins. It is likely that point mutations account for many of the alterations in dysfunctional C\textsubscript{I}-INH proteins,\textsuperscript{18} but in at least one instance (C\textsubscript{I}-INH Ta) there is an insertion in a high mol wt cyanogen bromide fragment\textsuperscript{19} and in another (C\textsubscript{I}-INH We) a deletion as well as an insertion.\textsuperscript{20}

Three dysfunctional C\textsubscript{I}-INH proteins were examined for their interactions with preparations of C\textsubscript{I}s, since these had not been tested earlier (Fig 4). One, C\textsubscript{I}-INH At, was cleaved by C\textsubscript{I}s (Fig 4), and high mol wt complexes were seen, while two others (C\textsubscript{I}-INH Bo and Za) also formed a high mol wt complex with C\textsubscript{I}s but were not cleaved when examined under the same conditions of incubation and electrophoresis. C\textsubscript{I}-INH Za formed a stable complex with C\textsubscript{I}s (Fig 4) but not with kallikrein, but it inhibited C\textsubscript{I}s to a lesser degree (19% of normal) than kallikrein (64% of normal) in earlier studies.\textsuperscript{8} In this instance, the complex between this C\textsubscript{I}-INH and C\textsubscript{I}s, the C\textsubscript{I}s does not appear to be inhibited; this is reminiscent of our earlier studies in which noninhibitory complexes between plasmin and some of these dysfunctional C\textsubscript{I}-INH proteins (We, Da, Za, and Ri) were identified.

These studies point to the possibility that the C\textsubscript{I}-INH found in normal plasma may have more than one point of interaction with plasma kallikrein, some of which are defective in dysfunctional C\textsubscript{I}-INH proteins. Since most of the dysfunctional C\textsubscript{I}-INH proteins did not form complexes of sufficient stability to be visible in the SDS gels but did provide measurable degrees of inhibition in work previously reported,\textsuperscript{4} complexes were probably formed but were dissociated during the procedures used for electrophoretic examination of complexes. Some of the inhibitory activities measured may have been due to trace amounts of normal C\textsubscript{I}-INH not distinguished from the dysfunctional forms in these electrophoretic analyses. It is likely that the binding affinity of most of the dysfunctional C\textsubscript{I}-INH proteins for plasma kallikrein is considerably less than that of normal C\textsubscript{I}-INH, and, with two exceptions, significant amounts of covalently linked complexes were apparently not formed.

Serine proteases cleave inhibitors before forming functionally inhibited complexes.\textsuperscript{21-24} Salveson and his associates\textsuperscript{24} recently identified cleavage of normal C\textsubscript{I}-INH by a preparation of C\textsubscript{I}s, comparable to that used in the present experiments, by defining the amino acid sequence of a portion of the cleavage fragment released from the carboxy-terminal side of the reactive site of C\textsubscript{I}-INH. Weiss and Engel\textsuperscript{25} reported that heparin could enhance cleavage of C\textsubscript{I}-INH by C\textsubscript{I}s. In our experiments a homogeneous preparation of normal C\textsubscript{I}-INH (mol wt approximately 106,000) was cleaved by C\textsubscript{I}s and kallikrein, forming a doublet of which the mol wt of the lighter component was 96,000. Bing and Canar\textsuperscript{26} have identified a 90,000 to 92,000 mol wt fragment that could be generated by plasmin. Neither C\textsubscript{I}s nor kallikrein appeared to release a similar fragment in their experiments or those reported here. It is possible that some fragments of C\textsubscript{I}-INH of much lower mol wt may have been released from C\textsubscript{I}-INH protein during their interactions with kallikrein but were not detected because the heavily glycosylated portions of the molecule may not bind to protein stains.

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Interactions of plasma kallikrein and C1-s with normal and dysfunctional C1(-)-inhibitor proteins from patients with hereditary angioneurotic edema: analytic gel studies

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