

Complement, Kinins, and Hereditary Angioedema: Mechanisms of Plasma Instability when C1 Inhibitor is Absent

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Abstract Plasma of patients with types I and II hereditary angioedema is unstable if incubated in a plastic (i.e., inert) vessel at 37 °C manifested by progressively increasing formation of bradykinin. There is also a persistent low level of C4 in 95 % of patients even when they are symptomatic. These phenomena are due to the properties of the C1r subcomponent of C1, factor XII, and the bimolecular complex of prekallikrein with high molecular weight kininogen (HK). Purified C1r auto-activates in physiologic buffers, activates C1s, which in turn depletes C4. This occurs when C1 inhibitor is deficient. The complex of prekallikrein-HK acquires an inducible active site not present in prekallikrein which in Tris-type buffers cleaves HK stoichiometrically to release bradykinin, or in phosphate buffer auto-activates to generate kallikrein and bradykinin. Thus immunologic depletion of C1 inhibitor from factor XII-deficient plasma (phosphate is the natural buffer) auto-activates on incubation to release bradykinin. Normal C1 inhibitor prevents this from occurring. During attacks of angioedema, if factor XII auto-activates on surfaces, the initial factor XIIa formed converts prekallikrein to kallikrein, and kallikrein cleaves HK to release bradykinin. Kallikrein also rapidly activates most remaining factor XII to factor XIIa. Additional cleavages convert factor XIIa to factor XIIb and factor XIIb activates C1r enzymatically so that C4 levels approach zero, and C2 is depleted. There is also a possibility that kallikrein is generated first as a result of activation of the prekallikrein-HK complex by heat shock protein 90

released from endothelial cells, followed by kallikrein activation of factor XII.

Keywords C1-Inhibitor · Complement · Bradykinin · Kininogen · Factor XII · Prekallikrein · Kallikrein

Introduction

The pathogenesis of hereditary angioedema (HAE) relates to instability of plasma due to low functional *C1 inhibitor* (C1-INH) leading to uncontrolled production of *bradykinin* [1]. An analogous scenario leads to activation of the early steps of the classical complement pathway. Although activation of complement does not produce a vasoactive peptide that could be considered to be pathogenic, it allows for ready diagnosis of types I or II HAE even if a family history of swelling is not present. Thus 95 percent of patients have a low *C4* level even when asymptomatic. Although there is no obvious marker for activation of the *bradykinin*-forming cascade when swelling is not evident, incubation of the plasma in vitro, even in the absence of a surface capable of initiating activation of factor XII, leads to generation of *kallikrein* activity [2] and *bradykinin* formation [1, 2].

The activation of complement and the *bradykinin*-forming cascade is dependent on the ability of *C1-INH* to stabilize both the first component of complement (particularly *C1r*) [3, 4], and the *prekallikrein high molecular weight kininogen* (HK) complex [5], and to inhibit *factor XII* (*FXII*) auto-activation [6]. In this review we will present the evidence that *C1-INH* is requisite for these in vitro functions and discuss how each contributes to the onset of attacks of angioedema when its functional levels are below 35 percent of normal [7].

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Complement Activation Role in the Diagnosis of Types I/II HAE

The first component of complement consists of a calcium-dependent complex of *C1q*, *C1r*, and *C1s* with a molar ratio of 1:2:2 respectively. The globular heads of *C1q* form the binding sites for immune complexes [8] while the collagen-like tail binds (*C1r*)₂ and (*C1s*)₂ and it is the latter interactions that require calcium ion. Thus binding of calcium ion by anticoagulants such as EDTA leads to dissociation of *C1r* and *C1s* from *C1q*, so that complement activation via the classical cascade is not possible. *C1-INH* inhibits the activated forms of *C1r* and *C1s*, typically designated by a bar above, i.e., *C1r̄* and *C1s̄* [9]. When activation is initiated by immune complexes, binding to the globular heads induces a conformational change in the collagen-like tail, the result of which is that each molecule of *C1r* attacks its *C1r* neighbor resulting in two molecules of *C1r̄*. This requires expression of an active site in *C1r* prior to any enzymatic cleavage [3, 4]. The next step involves cleavage of a critical bond within a disulfide bridge such that the single chain *C1r* is converted to a two-chain *C1r̄* with the active site present in its light chain. Evidence for the presence of an active site within the single chain *C1r* is provided by the fact that when *C1r* is purified, it is intrinsically unstable and on incubation in buffer at 37 °C is converted to the two-chain *C1r̄*. This is shown in Fig. 1 and is a key observation originally made by Zicardi [3, 4]. Addition of *C1-INH* prevents this auto-activation and accounts for the stabilization of the *C1 complex* in human plasma. The next step in *C1* activation is activation of *C1s* to *C1s̄* by *C1r̄* by an analogous cleavage in which a single chain *C1s* is cleaved within a disulfide bridge to yield a 2-chain *C1s̄*. *C1s̄* is also inhibited by *C1-INH*. Normally *C1s̄* cleaves both *C4* and *C2* to generate the *C4bC2a* enzyme requisite for *C3* cleavage. However in

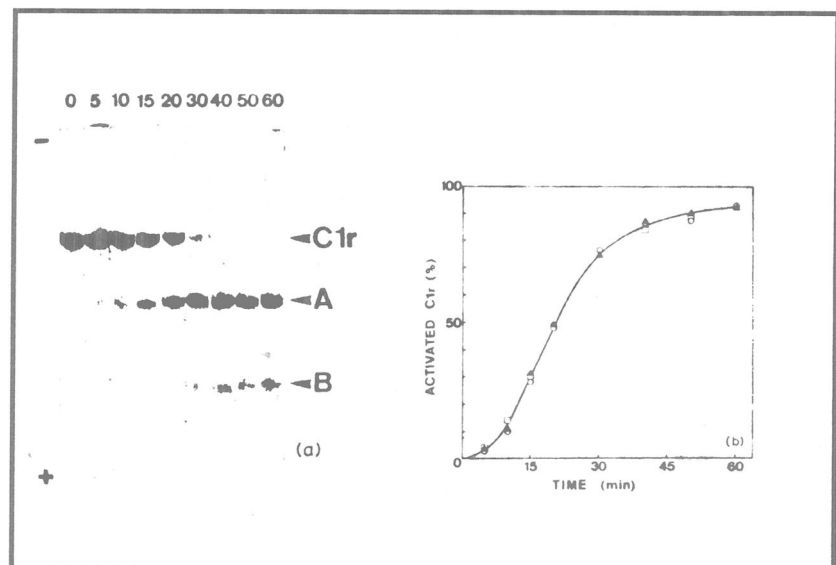
the absence of an immune complex or other potent activator of *C1*, only partial activation is noted in HAE patients. *C4* is the “favored” substrate of *C1s* and synthesis of *C4* does not adequately compensate, thus patients with HAE have a low *C4* level at baseline [7]. When there is an attack of swelling, there is further activation of *C1*, *C4* levels approach zero, and *C2* levels diminish [10].

Thus in the absence of *C1-INH*, one has to presume a small amount of *C1* activation (both *C1r̄* and *C1s̄*) to account for diminished levels of *C4*. The complement-specific functions of *C1-INH* lacking in HAE types I/II are: (1) stabilization of *C1r* by interaction with its active site, (2) inhibition of *C1r̄*, and (3) inhibition of *C1s̄*.

Historical Perspective of the Complement vs. the Bradykinin-forming Cascade, as Pathogenic in Types I/II HAE

C1-INH was shown to be deficient in patients with HAE by Donaldson and Evans in 1963 [11]. The observation was made soon after the discovery of the inhibitor by Irwin Lepow [12] and demonstration that it inhibits activated *C1r* and *C1s*. It was assumed that activation of complement would lead to production of a vasoactive peptide that would be responsible for the increased vascular permeability leading to angioedema. Such a peptide was reported in 1977 [13]; it was called *C2-kinin* because it was formed by a two-step process in which *C2* is activated to *C2a* and *C2b* fragments and further cleavage of *C2a* by *plasmin* would produce the *C2-kinin* peptide [13]. Production of the peptide appeared to be linked to *factor XII (FXII)* activation [14] and *FXII* was known to initiate intrinsic coagulation, *bradykinin* formation, and fibrinolysis (*plasmin* generation). A role for *FXII* in all steps of the

Fig. 1 Time course of auto-activation and auto-digestion of purified *C1r* upon incubation in buffer. *Left*: auto-digestion of *C1r* to yield a heavy chain and light chain that are disulfide linked. The samples are reduced prior to SDS gel electrophoresis. *Right*: evolution of activity reflecting conversion of *C1r* to *C1r̄*. Figure taken from [4]



process made sense although the steps connecting *FXII* to *bradykinin* formation, intrinsic fibrinolysis, or complement activation were not yet known. However distinction of *C2-kinin* from *bradykinin* was important and this was done by *trypsin* cleavage, which destroyed the *C2-kinin* activity (bioassay employing smooth muscle or uterine contraction) but had no effect on *bradykinin*. Further, injection of activated *C1* into human or guinea pig skin [15, 16] led to wheal formation, i.e., increased vascular permeability, which was augmented if *C1-INH* was absent, suggesting *C2-kinin* formation. The fact that any injection activates the plasma *bradykinin*-forming cascade was not addressed, although injection into guinea pigs lacking *C2* lead to diminished wheal formation [15] which seemed consistent with a contribution of a *C2-kinin*. The fact that a *C2-kinin* was not purified during the next few years plus advances in understanding the molecular mechanism leading to *bradykinin* formation, as well as its inhibition by *C1-INH*, created a need to more clearly distinguish *C2-kinin* from *bradykinin*. *C1-INH* was shown to inhibit plasma *kallikrein* by Gigli [17] in 1970. Then *C1-INH* was found to inhibit the activated forms of *FXII* [18] so that the functions of *C1-INH* were clearly as critical to limit *bradykinin* formation as for inhibition of *C2-kinin* production.

At this point activated *FXII* (factor *XIIa* or factor *XII_f*) had been shown to directly convert *prekallikrein* to *kallikrein* [19, 20], and digestion of *HK* by *kallikrein* would generate *bradykinin* [21]. *FXII* auto-activation by initiating surfaces was demonstrated by Silverberg et al [22], which was followed by rapid feedback activation of *FXII* by the *kallikrein* initially produced [23, 24]. The surface was shown to render *FXII* a substrate for enzymes and disproved the notion that *FXII* becomes an active enzyme as a result of a conformational change upon binding [25]. Thus reciprocal activation takes place with initiating surfaces, i.e., *FXIIa* (*XII_f*) converts *prekallikrein* to *kallikrein* while *kallikrein* activates *FXII* to produce *FXIIa* (initially) followed by *FXII_f* [26] by two subsequent cleavages [27, 28]. *Prekallikrein* was shown to circulate as a 1:1 molar complex with *HK* [28]. All of the aforementioned enzymatic steps are inhibited by *C1-INH* [29]. Curd et al. employed an induced blister model and demonstrated excessive *kallikrein* within the blisters of patients with HAE when compared to normal [30]. The blister induction is a traumatic process employing a combination of suction and heat which by itself readily activates the *bradykinin*-forming cascade. The demonstration of increased *kallikrein* in this model corroborated in vitro studies demonstrating that *C1-INH* inhibits *kallikrein* and presumably *FXIIa* which converts *prekallikrein* to *kallikrein*. But the controversy regarding *C2-kinin* vs. *bradykinin* was not addressed until Fields et al. [1] sought to reproduce the original experiments leading to the discovery of *C2-kinin*. They could not do so. Activation of *C1* followed by cleavage of *C4* and *C2* and addition of *plasmin* did not produce any kinin. However incubation of

HAE plasma in plastic at 37 °C, i.e., in the absence of any activator of *FXII* lead to progressive generation of *bradykinin* as the time of incubation increased. The authors concluded that existence of a *C2-kinin* could not be corroborated and that *bradykinin* is the key vasoactive peptide. Those findings regarding *C2* were confirmed by Smith and Kerr in 1985 [31]. Thus *C2* is not cleaved by any known enzyme or combination of enzymes to release a kinin-like molecule. Although a 25 amino acid sequence within *C2b* (residues 199–223) obtained as a synthetic peptide, has permeability enhancing activity on injection into guinea pig skin, a similar peptide is found within the amino acid sequence of human albumin.

A possibility to explain the evolution of *bradykinin* and presumably *kallikrein* formation considered at the time was that *FXII* might be unstable and auto-activate, as does *C1r*, when *C1-INH* is deficient. Many subsequent studies corroborated *bradykinin* as the mediator of HAE [32–35] but only one other study addressed the *C2-kinin* issue and that included some of the original authors of the *C2-kinin* papers. Thus Shoemaker et al. supported the conclusion of Fields et al. in which *bradykinin* was the only kinin they could identify employing HAE plasma [32]. The difference (11 years later) was that *bradykinin* was assayed by radioimmunoassay rather than bioassay, and *C2* deficient plasma was employed rather than purified *C2*. Nevertheless when *C2-kinin* persisted in being included in reviews of the pathogenesis of HAE, we published a commentary [36] emphasizing the inability to corroborate existence of *C2-kinin*, the multifaceted evidence for *bradykinin* as the mediator of HAE, and added that the prior evidence for its presence was artifactual in part, and any observed increased vascular permeability, were due to *bradykinin*.

Control of *FXII* Auto-activation by *C1-INH*

FXII (Hageman factor) deficiency was discovered by Ratnoff and Colopy [37] who demonstrated absence of a critical surface-dependent factor required to initiate the intrinsic coagulation cascade. It also appeared to be requisite for surface-dependent *bradykinin* formation [38]. *FXII* is indeed difficult to work with so that activated *FXII* (*FXIIa*) was purified and characterized prior to the native, i.e., unactivated *FXII*. First a low molecular weight form of activated *FXII* of 28.5 Kd was purified [19] which we designate as *FXII fragment* (*FXII_f*) because it could be generated by *FXIIa* cleavage with *plasmin* [20], i.e., prior to the discovery of the *kallikrein* feedback. But *FXII_f* possessed only 2–4 % of the coagulant activity of *FXIIa* (80,000 Kd; the enzyme that activates *FXI* in intrinsic coagulation), but retained full ability to convert *prekallikrein* to *kallikrein*. The first preparation of unactivated human *FXII* was reported by Cochrane and Wuepper [39] and shown to be converted to active forms called α -*FXIIa*, and β -*FXIIa* by

cleavage in plasma corresponding to *FXIIa* and *FXII_f* respectively [40]. However their proposal was that activation of *FXII* occurred either by cleavage within a disulfide bridge to produce α -*FXIIa* or cleavage outside the disulfide bridge to produce β -*FXIIa* [23]. This is in contrast to the original description of these forms, which suggested sequential cleavage, i.e., first cleavage of native *FXII* to *FXIIa* and then cleavage of *FXIIa* to factor *XII_f* [20]. Proof that the latter mechanism is the correct one was provided by Dunn et al. [26, 27]. We have therefore retained the *FXIIa*/*FXII_f* nomenclature, consistent also with coagulation nomenclature, i.e., factors *XIIa*, *XIa*, *VIIa*, and *IXa* for coagulation enzymes, since the trace clotting activity associated with factor *XII_f* is insignificant [20]. Further, the proposed cleavage to produce β -*FXIIa*, that is not preceded by cleavage within the disulfide bond [27], would not produce an active enzyme.

As *FXII* is purified and enzymes such as *kallikrein* and *plasmin* (or *prekallikrein* and *plasminogen*) are eliminated, it continues to be unstable and activates, seemingly spontaneously, to *FXIIa* and *FXII_f*. Observations such as this lead to considerations that *FXII* might auto-activate, but required purified preparations of *FXII* to test the hypothesis. Once it was clear that *FXIIa* could further cleave *FXII* to produce more *FXIIa* [41], *FXII* was formally shown to auto-activate [22]. However the process is relatively slow and the *kallikrein* feedback is responsible for the rapid burst of activity seen on contact activation [42]. Figure 2 demonstrates the consequences of *FXII* auto-activation vs. *kallikrein* activation as assessed by SDS gel electrophoresis. As *FXII* is activated, it is inactivated by fluoresceinated pro-phe-arg-chloromethylketone. The fluorescence reflects those molecules which had been activated.

It is now clear that all activated forms of *FXII* have been cleaved and that formation of *FXIIa* precedes formation of *FXII_f*. In fact, Griffin et al. [25] demonstrated that the surface bound *FXII* is a substrate and binding does not induce enzyme

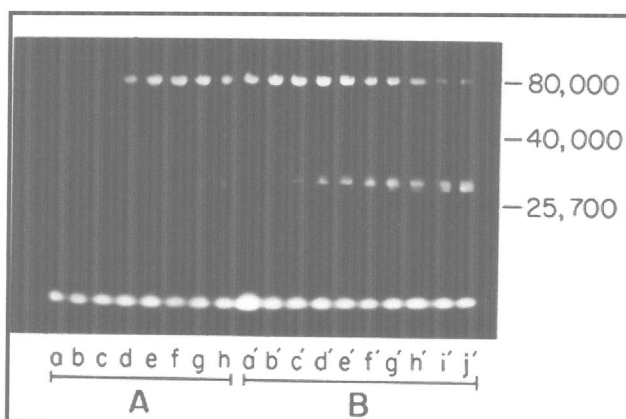


Fig. 2 Activation of *FXII* by auto-activation (a) vs. *kallikrein* (b) as assessed by SDS gel electrophoresis after active-site inhibition employing fluorescent pro-phe-arg-chloromethylketone. Time points a–h and a'–j' are from 20 s to 30 min. Figure taken from [26]

formation by a conformational change. Thus either trace amounts of *FXIIa* are always present in *FXII* preparations or native *FXII* has an active site (perhaps analogous to that of *C1r*) albeit with very low activity relative to *FXIIa* but enough to digest adjacent molecules to generate a small amount of *FXIIa* (Note, *FXIIa* activates *FXII* but *FXII_f* does not). We attempted to quantitate activity present in *FXII* but could not do so [43]. Our lower limit of detection was 0.01 % or one molecule of *FXIIa* in 10,000 of *FXII*, or *FXII* possessing 1/10,000 the activity of one *FXIIa* molecule. But we cannot rule out activity at infinitesimal levels, e.g. one part in a million or less. An important point regarding surface-dependent initiation of kinin formation in HAE is the role of *C1-INH* in *FXII* auto-activation. One such experiment is shown in Fig. 3 where the curvature reflects *FXII* auto-activation [6]. At half-normal level of *C1-INH*, the curvature is much diminished and is almost linear at normal levels. Thus, it could be shown that *C1-INH* prevents activation at this initiating step.

Instability of HAE Plasma is Due to Activity of the Prekallikrein-HK Complex

Prekallikrein binds to *HK* as a 1:1 bimolecular complex [29] and 75–80 % of *prekallikrein* circulates in a complex form [44]. *FXI* also circulates bound to *HK* [45] with a molar ratio of 1:2 (*FXI* is dimeric) but *HK* is present in excess; sufficient to bind both. However, a single *HK* molecule is bound to either *prekallikrein* or *FXI*, but not both. Schmaier et al. [46] reported that when the *prekallikrein*-*HK* complex (*HK*-*PK*) is bound to endothelial cells in the absence of *FXII*, the

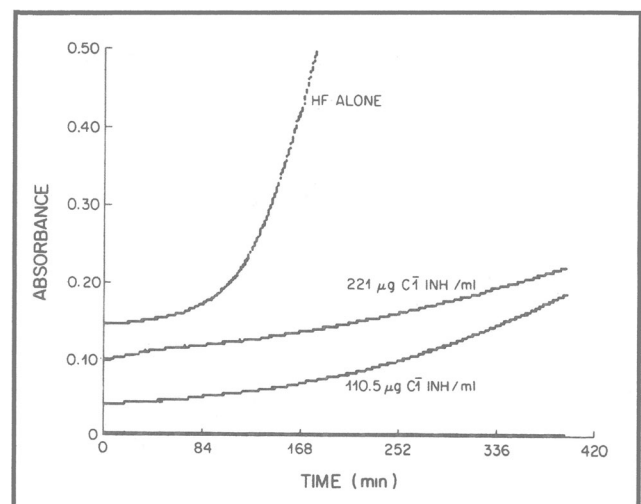


Fig. 3 Inhibition of *FXII* (*HF*) auto-activation by *C1-INH*. *FXII* (10 µg/ml) is incubated in a glass test tube with pro-phe-arg-p-nitroanalide and the evolution of a yellow color at 405 nm is plotted against time. A control curve without additional *C1-INH* is compared to a mixture of *FXII* with half-normal *C1-INH* (110.5 µg/ml) or normal *C1-INH* (221 µg/ml). Figure taken from [6]

prekallikrein is easily converted to *kallikrein* [47]. We corroborated this observation and when we isolated the factor responsible for this effect, it was identified as *heat-shock protein-90* (*HSP 90*) [48]. *HSP 90* has been reported to have phosphatase activity but no proteolytic activity so *HK-PK* appeared to auto-activate when bound to *HSP 90*. Consistent with this is the observation that a 1:1:1 trimolecular complex forms and the conversion of *HK-PK* to *kallikrein* is directly proportional to the *HSP 90* input. Thus the reaction is stoichiometric.

Other observations are that zinc ion is required for binding/activation, and that *HSP 90* will not activate *prekallikrein* unless it is bound to *HK* [48]. Thus it is very different from activation of *prekallikrein* by *FXIIa* of *FXII*. First, for in vitro studies an optimal factor *XIIa/prekallikrein* ratio is 1:50 rather than 1:1 and the presence of *HK* does increase that rate of *prekallikrein* activation by *FXIIa* (the cofactor function of *HK*) [49, 50] but activation may proceed without *HK* being present. When studying *HSP 90* activation, the control was *HK-PK* incubated with buffer. As expected, there was no conversion of *prekallikrein* to *kallikrein*. However, with prolonged incubation (1–2 h.) all the *HK* was cleaved and there was no *kallikrein* contaminating the *prekallikrein* preparation [5]. It appeared that binding of *prekallikrein* to *HK* induces an active site in *prekallikrein* which cleaves *HK*. This cleavage is inhibited not only by *C1-INH*, but also by *corn trypsin inhibitor* (*CTI*) which has no inhibitory activity on *kallikrein* [51]. Thus when *CTI* is added to plasma (rather than purified enzymes) as a *FXIIa* inhibitor [2], one is also inhibiting the site within the *HK-PK* complex. Buffers make a difference in what is observed as final products of this reaction. If we use Tris buffer, *HK* is cleaved to release *bradykinin* and *prekallikrein* is stable. If we do the same reactions in phosphate buffers, *HK-*

PK auto-activates, i.e., *prekallikrein* is converted to *kallikrein* and *HK* is cleaved [2]. *CTI* inhibits this reaction as well suggesting that it is the induced active site in *prekallikrein* that auto-activates and auto-digests to produce *kallikrein*. Here the products are the same as seen with *HSP 90*, but if we add *HSP 90*, the rate of *kallikrein* formation is more rapid. A summary of these reactions and the product(s) of each is shown in Table 1.

Since all the aforementioned reactions are demonstrable in the absence of *FXII* we compared the behavior of normal plasma with that of HAE plasma. Fig. 4a shows the original bioassay demonstrating the increasing formation of *bradykinin* as HAE plasma is incubated at 37 °C. Fig. 4b shows the same experiment assessed by SDS gel electrophoresis demonstrating conversion of *prekallikrein* to *kallikrein*. Normal plasma, incubated identically, does not generate *kallikrein* or *bradykinin*. Although a surface that might activate factor XII was not added, the process could still be due to *FXII* instability or auto-activatability when *C1-INH* is absent. We therefore took factor XII-deficient plasma, which does not activate on prolonged incubation, nor could it be activated on addition of kaolin or dextran sulfate, and removed *C1-INH* by immunoabsorption. As shown in Figs. 5 and 6, *prekallikrein* is converted to *kallikrein* [2]. Thus the instability of HAE plasma that lead to the identification of *bradykinin* as the mediator of HAE, proceeds independently of *FXII* and reflects activation of *HK-PK* in a phosphate containing milieu, i.e., plasma.

Conclusions

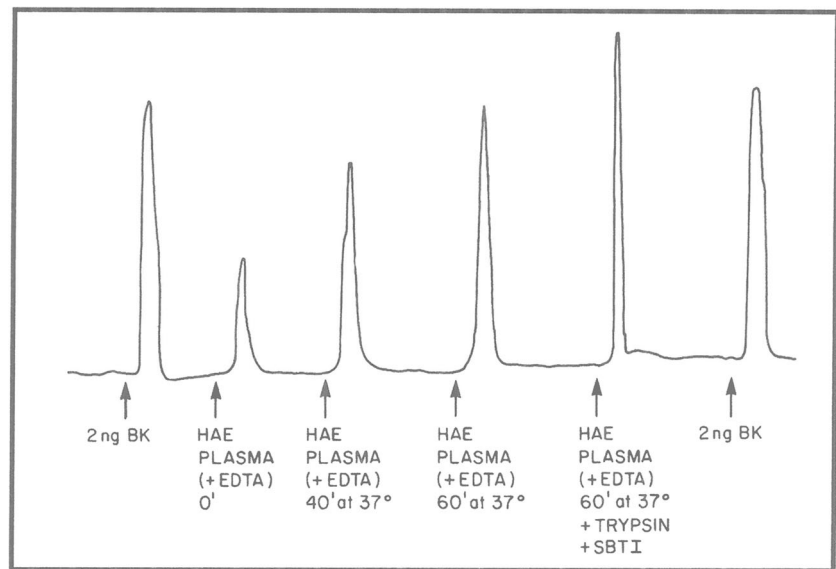
1. Auto-activatability of *C1r* within macromolecular *C1* causes the low *C4* in types I and II HAE.

Table 1 Activation reactions of the *prekallikrein-HK* complex

1. Prekallikrein-HK	(-) phosphate	→ HK cleavage
2. Prekallikrein-HK	(+) phosphate	→ HK cleavage, Prekallikrein autoactivation
3. Prekallikrein-HK	(+) Hsp90, (+) Zn	→ HK cleavage, Prekallikrein activation
4. Prekallikrein-HK	(+) phosphate (+) Hsp90	→ HK cleavage, Prekallikrein autoactivation
5. Prekallikrein-HK	(+) phosphate, (+) Zn (+) Hsp90	→ Augmented Prekallikrein autoactivation

Reaction 4 is the same as 2 because of the absence of zinc

Fig. 4 A bioassay (contraction of guinea pig ileum) for *bradykinin* demonstrating progressive formation as HAE plasma is incubated at 37 °C over time. Two ng/ml standard *bradykinin* contractions are shown at the beginning and end of the experiment demonstrating no change in sensitivity. *Trypsin* did not destroy the activity (tested at 60 min) as originally reported for *C2-kinin*. Taken from [1]



2. Experiments that disproved the existence of *C2-kinin* also demonstrated seemingly spontaneous formation of bradykinin.

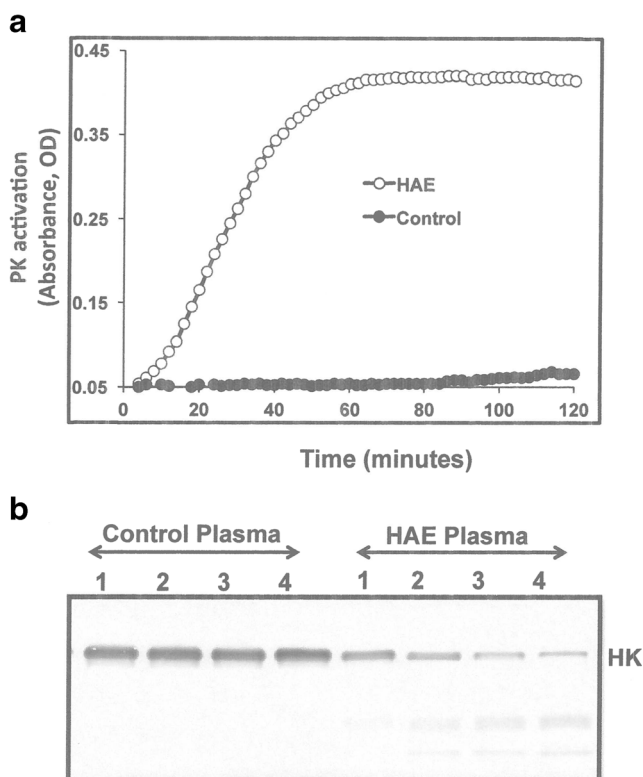


Fig. 5 **a** The same experiment as in Fig. 4, however the conversion of *prekallikrein* to *kallikrein* is quantitated by cleavage of pro-phe-arg-nitroanalide and monitored at 405 nm. HAE plasma is compared to normal plasma. **b** The same experiment as in Fig. 5a except cleavage of *high molecular weight kininogen* (HK) is monitored by reduced SDS gel electrophoresis. Control plasma (*left*) and HAE plasma (*right*). Progressive cleave of HK is seen only in the HAE plasma

3. *FXII* auto-activation is inhibited by *C1-INH* but an active site within native *FXII* has never been demonstrated, so that the inhibition is probably due to interaction with *FXIIa* to prevent cleavage of native *FXII*.

4. The *prekallikrein*-HK complex possess activity inhabitable by *corn trypsin inhibitor* (CTI). It appears to be induced on binding of *prekallikrein* to HK and is responsible for the instability of HAE plasma (types I/II) where *C1-INH* is deficient. This is demonstrable in the complete absence of *FXII*.

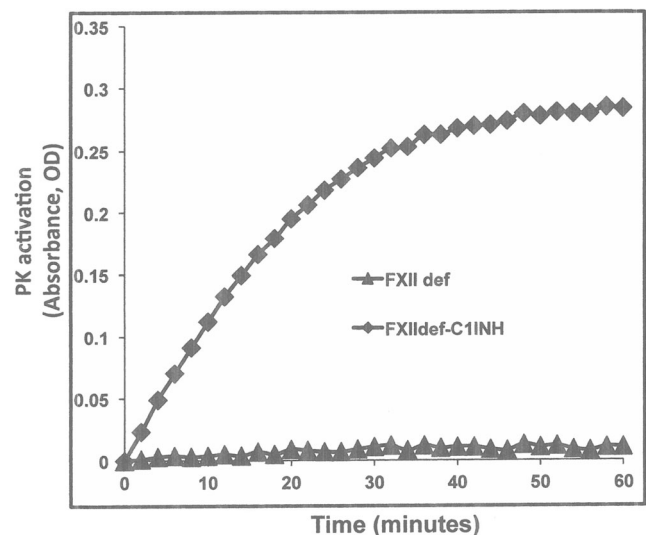


Fig. 6 Activation of *FXII*-deficient plasma by removal of *C1-INH*. A time course of *kallikrein* formation was assessed by incubation of plasma with pro-phe-arg-p-nitroanalide. Activation of *FXII*-deficient plasma that is also deficient in *C1-INH* was compared to *FXII*-deficient plasma with normal *C1-INH*. The *C1-INH* was removed by immunoadsorption with IgG antiC1-INH and addition of an equal amount of normal IgG was employed for the control sample. Reproduced from [2]

recently, we have incubated HSP 90 with normal plasma, and converted prekallikrein to kallikrein to liberate bradykinin (unpublished observation). Thus it is possible to activate the bradykinin-forming cascade by direct interaction with factor XII leading to auto-activation and the kallikrein feedback (Fig. 7a), or to activate HK-PK first and recruit factor XII secondarily (Fig. 7b). Once the latter reaction occurs, the process becomes indistinguishable from events that begin with factor XII activation. Future studies will attempt to distinguish among these possible initiating mechanisms.

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