

Pathogenesis of Hereditary Angioedema



The Role of the Bradykinin-Forming Cascade

Allen P. Kaplan, MD^{a,*}, Kusumam Joseph, PhD^b

KEYWORDS

• Factor XII • Prekallikrein • Kininogen • Bradykinin • Angioedema

KEY POINTS

- Attacks of swelling in types I and II hereditary angioedema (HAE) are due to overproduction of bradykinin.
- HAE types I and II are caused by mutations in the gene encoding C1 inhibitor (C1-INH) so that patients are functionally deficient.
- C1-INH blocks plasma kallikrein and the 2 molecular forms of activated factor XII, enzymes requisite for bradykinin formation and stabilizes the prekallikrein-high molecular kininogen complex.
- Therapies for types I and II HAE include C1-INH replacement, inhibition of the enzyme kallikrein, and blockade at the bradykinin B-2 receptor.

INTRODUCTION

Hereditary angioedema (HAE) represents a prototypic disorder in which episodic swelling, that is, angioedema, is dependent on the generation of bradykinin. In contrast with the ingestion of inhibitors of angiotensin-converting enzyme, which cause accumulation of bradykinin owing to impaired degradation, all forms of HAE in which the pathogenesis is understood, seem to be due to overproduction of bradykinin. The first described entity is C1 inhibitor (C1-INH) deficiency,¹ in which absent or dysfunctional C1-INH lessens inhibition of key enzymes required for bradykinin formation. Decades later, a novel form of HAE was described in which C1-INH levels are normal.^{2,3} About one-third of the latter cases (but varies greatly worldwide) have a mutation in factor XII,^{4,5} which leads to an increased rate of factor XII activation and augmented bradykinin formation. There is no genetic abnormality or mechanistic

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^a Department of Medicine, Medical University of South Carolina, 171 Ashley Avenue, Charleston, SC 29425, USA; ^b Department of Biochemistry and Molecular Biology, Medical University of South Carolina, 173 Ashley Avenue, Charleston, SC 29425, USA

* Corresponding author. 17 Logan Street, Charleston, SC 29401.

E-mail address: Kaplana@musc.edu

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rationale involving the remaining two-thirds of subjects, although indirect evidence, for example, response to agents that are effective in other types of HAE, suggest that this entity also depends on bradykinin production. Those lacking any defined mutation are distinguished from idiopathic angioedema by a clear family history of recurrent angioedema. This review addresses the major pathophysiologic mechanisms operative in HAE of each type.

THE ROLE OF C1 INHIBITOR IN COMPLEMENT ACTIVATION

C1-INH was named because it inhibited the activated form of the first component of complement.⁶ More specifically, it inhibits activated C1r and activated C1s of the C1 complex. The formula of C1 is actually C1q (C1r)₂ (C1s)₂.⁷ C1q is the key structure to which immune complexes bind and consists of 6 globular heads and a lengthy collagen-like tail. Two molecules each of C1r and C1s bind to the collagen tail in calcium-dependent reactions. Thus, chelation of calcium by EDTA disrupts C1 and activation cannot proceed. When immune complexes bind to C1, C1r is initially activated by a conformational change (C1r*) and the 2 C1r* digest each other to yield C1r̄, which is cleaved and fully active.⁸ C1r̄ digests C1s to C1s̄ and C1 and C1s digests its 2 substrates, C4 and C2 (Fig. 1) to yield C4a (anaphylatoxin) and C4b and C2a and C2b, respectively. The labile component of the C1 complex is clearly C1r because, when purified, it autoactivates and autodigests to C1r̄ (Fig. 2).⁸ When the entire C1 complex is purified, it too autoactivates, but much more slowly than purified C1r and the autoactivation phenomenon is inhibited by the C1-INH; that is, the complex is stabilized.⁹ When an immune complex activates C1, each C1r̄ and each C1s̄ binds irreversibly to C1-INH to yield (C1r̄)₂ - (C1-INH)₂ and (C1s̄)₂ (C1-INH)₂ so that 4 C1-INH molecules are “used up.”

When C1-INH is absent or dysfunctional, as is the case for types I and II HAE, respectively, the stabilization of C1 is lessened such that C1 is partially activated and C4, the preferred substrate of C1s̄ is depleted. C4 levels are low in 95% of patients¹⁰; thus, it is a good (but not perfect) biomarker for the likelihood of types I or II HAE in patients with recurrent angioedema. When suspected, blood levels of C1-INH are typically drawn at the same time and quantitated both as a protein and

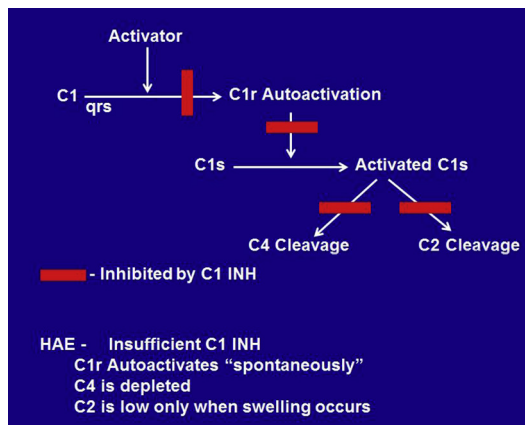


Fig. 1. The activation mechanism for the first component of complement leading to diminished levels of C4 and C2 in patients with hereditary angioedema (HAE). C1-INH, C1 inhibitor.

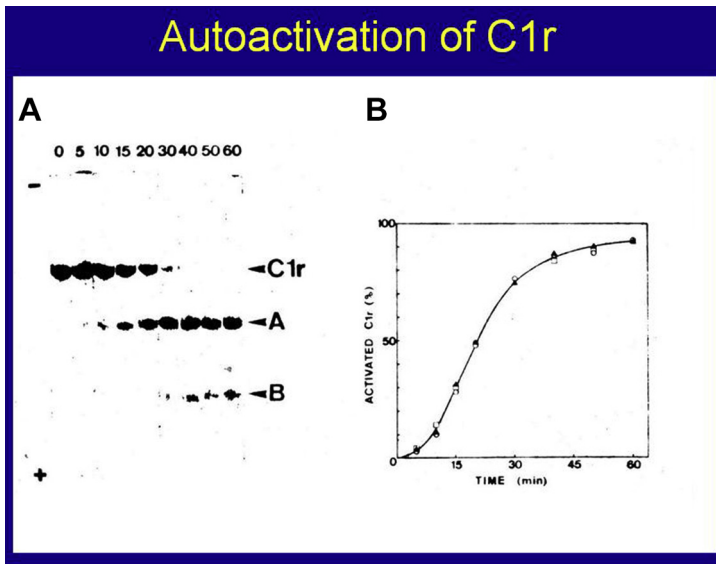


Fig. 2. Autoactivation of purified C1r. A 1-hour time course (*left*) demonstrating cleavage of C1r within a disulfide bridge as assessed by reduced SDS gel electrophoresis to yield as (A) heavy chain and (B) light chain. The time course of activity (ie, activated C1r) is shown on the right. (From Arlaud GJ, Villiers CL, Chesne S, et al. Purified proenzyme C1r. Some characteristics of its activation and subsequent proteolytic cleavage. *Biochimica et Biophysica Acta* 1980;616:119.)

functional level. In type I patients (85% of C1-INH deficiency), both are low, whereas type II patients (15% of C1-INH deficiency) have a normal or even elevated protein level, but a functional level that is just as low as type I patients. In general, the difference is in the nature of the mutation. Type I subjects tend to have deletions, insertions, or duplications that disrupt transcription and the partial polypeptide is degraded or not secreted. Type II patients usually have an amino acid substitution that affects function, although the protein is secreted normally. In either case, the mutation typically affects only 1 gene, so the disorder transmits as an autosomal-dominant change. Homozygous mutations are very rare. Because there is 1 unaffected gene, one might expect a blood level of 50% C1-INH in all patients. However, functional levels typically range from a few percent to about 35%, a range in which attacks of angioedema are seen. It seems that transcription of the normal gene is inhibited (transinhibition)¹¹ at the messenger RNA level. In addition, functional C1-INH will be further depleted by binding to enzymes whose activity it controls.¹²

BRADYKININ IS THE MEDIATOR OF SWELLING IN HEREDITARY ANGIOEDEMA TYPES I AND II

Although patients have a low C4 level at baseline, the C2 level is normal. However, when attacks of angioedema occur, C4 levels decrease further and C2 is depleted,¹³ indicating that there is further activation of C1, apparently in the absence of immune complexes. Donaldson and coworkers¹⁴ suspected that a vasoactive peptide might be liberated from complement, that is, C2 in particular, to cause angioedema and called the product C2 kinin. They reported that when C2 is activated to C2a and C2b, the C2a is further digested by plasmin to release the kinin.¹⁴ A number of

observations seemed to corroborate this view. For example, the intradermal injection of activated C1 (or C1s) led to a wheal, that is, an increase in vascular permeability, that was lessened in the absence of C2.¹⁵ In addition, the smooth muscle contractile activity of plasmin-derived C2 kinin was destroyed by digestion with trypsin, which has no effect on bradykinin.¹⁴ Nevertheless, after decades passed, no such peptide was identified. Curd and colleagues¹⁶ demonstrated that the concentration of plasma kallikrein, a bradykinin-forming enzyme, in induced blisters of HAE patients (C1-INH deficiency) was greater than observed in normal controls. This corroborated earlier evidence that C1-INH inhibits plasma kallikrein¹⁷ so that increased activity is observed with C1-INH deficiency, but did not address activation of the cascade in patients' plasma or the C2 kinin controversy. In 1983, Fields and colleagues¹⁸ reported that activation of C1, C4, and C2 followed by plasmin digestion of failed to produce any kinin based on contractile activity. Further, they noted that plasma of HAE patients incubated at 37°C in the absence of an activator of the bradykinin-forming cascade, produced bradykinin seemingly spontaneously with progressively increasing levels during the time course. They concluded that bradykinin and not C2 kinin is the mediator of the swelling. It is difficult, in retrospect, to explain the findings that suggested a "C2 kinin," but one issue relates to the assay used for contractile activity. We found the estrus rat uterus, used originally, to have an unstable baseline and that contractions could be induced simply by disturbing the suspension bath with buffer. A guinea pig ileum strip was stable and reproducible results were obtained. Further, injecting any substance into human skin (eg, C1) will activate the bradykinin cascade, although a lesser response with C2 deficiency cannot be explained. The inability to generate a kininlike molecule from C2 was confirmed soon thereafter,¹⁹ but additional support for bradykinin as the mediator of HAE took much longer.

Shoemaker and colleagues²⁰ reported that the only kinin that could be generated in HAE plasma was bradykinin and that plasma deficient in C2 behaved normally, in contradistinction to earlier reports. Thus, the results reported by Fields and colleagues²⁰ were confirmed, albeit with a differing methodology. Deficient plasma was used instead of purified C2 and bradykinin was measured by radioimmunoassay (developed in the ensuing decade) rather than bioassay. Next, a family was described in which C1-INH seemed deficient based on inhibition of C1 but had normal function as an inhibitor of bradykinin-forming enzymes. The result was that there was no angioedema in any family member,²¹ again demonstrating that abnormal complement activation is not the answer. Nussberger and colleagues²² measured bradykinin levels in HAE patients during acute attacks of angioedema and demonstrated elevated levels at the site of swelling demonstrating bradykinin as the *in vivo* mediator, which also suggested that its initial production is a localized process. A rat model of C1-INH deficiency led to an increase in vascular permeability that could be reversed by deleting the B2 bradykinin receptor.²³ The final observation was that icatibant, which binds to the bradykinin B2 receptor and inhibits bradykinin reactivity rapidly, reverses attacks of angioedema in HAE patients²⁴ and a plasma kallikrein inhibitor has similar efficacy.²⁵

Recently, there has been consideration that des-arg⁹-bradykinin, a bradykinin metabolite that retains the ability to increase vascular permeability could contribute to the angioedema of HAE types I and II. Des-arg⁹-bradykinin is generated by digestion of bradykinin by carboxypeptidase N in plasma²⁶ and carboxypeptidase M on the surface of vascular endothelial cells.²⁷ It binds to B1 receptors rather than B2 receptors and B1 receptors, although not constitutively present, are induced by endothelial cell stimulants such as the cytokines interleukin 1 and tumor necrosis factor α . An animal model²⁸ and theoretic considerations²⁹ indicate that the des-arg⁹-bradykinin-B1 receptor interaction could contribute to the persistence of attacks of angioedema in

HAE, but we cannot yet test the hypothesis because a B1 receptor antagonist that could be used clinically is not available. Des-arg⁹-bradykinin, like bradykinin itself, is degraded to inactive peptide fragments by angiotensin-converting enzyme.³⁰

THE PATHWAY(S) OF BRADYKININ FORMATION IN TYPES I AND II HEREDITARY ANGIOEDEMA

Bradykinin formation is typically initiated by negatively charged surfaces or macromolecules such as kaolin, glass (silicates), uric acid or pyrophosphate crystals, mast cell heparin, or platelet polyphosphate.³¹ Dextran sulfate is an example of a soluble, negatively charged polymer that leads to factor XII activation as long as the polymer size can accommodate at least 2 factor XII molecules in proximity.³² An autoactivation process occurs in which trace quantities of factor XIIa activates surface-bound factor XII to produce more factor XIIa, which is a slow process but one that accelerates with time. The second step is conversion of prekallikrein³³ to kallikrein by factor XIIa³⁴ followed by very rapid activation of remaining unactivated factor XII by kallikrein.^{35,36} Kallikrein then digests high-molecular-weight kininogen to produce bradykinin³⁷ (Fig. 3). The digestion of factor XII by kallikrein produces 2 sequential forms of activated factor XII. The first, caused by digestion of an Arg-Val bond within a disulfide bridge produces factor XIIa (molecular weight of 80,000 Kd), which activates both prekallikrein to kallikrein and factor XI to factor XIa, each of which circulates as a complex with HK.^{38,39} There is an important function of HK that relates to this binding because the rate of activation of both prekallikrein and factor XI are markedly increased,⁴⁰ which directly affects the rate of factor XII activation (ie, the rate of kallikrein formation to enzymatically activate factor XII).⁴¹ The molar ratios are 1:1 (prekallikrein-HK) and 1:2 (factor XI-(HK)₂) because factor XI circulates as a dimer. Two subsequent cleavages in close proximity produces factor XIIf (fragment, molecular weight of 28,500–30,000) usually seen as a doublet on

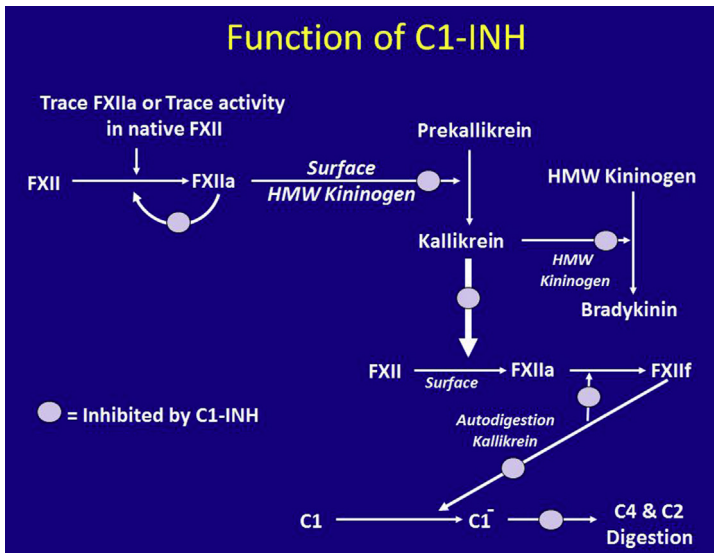


Fig. 3. Zinc-dependent binding of factor XII and HK to vascular endothelial cells. Although both bind to gC1qR, which is present in excess, there is preferential binding of factor XII to the complex of urokinase plasminogen activator receptor and cytokeratin 1, while HK binds primarily to the complex of gC1qR and cytokeratin 1. C1-INH, C1 inhibitor.

SDS gels, which readily converts prekallikrein to kallikrein,³³ but retains only minimal ability to activate factor XI because the surface binding site is lost. Factor XII_f is also the form of activated factor XII that activates the C1r subcomponent of complement⁴² (see Fig. 3), which occurs during episodes of angioedema. At that time, C4 levels decrease further, often toward zero, and C2 levels diminish.¹³ The plasma enzymes inhibited by C1-INH are the activated forms of C1r and C1s, both activated forms of factor XII (factor XII_a and factor XII_f; alternative nomenclature used is α factor XII_a and β factor XII_a, respectively), plasma kallikrein, coagulation factor XI_a, and MASP I and MASP II of the lectin complement pathway. It is of interest that activated MASP I is elevated during attacks of HAE, which may relate to the severity of the clinical presentation⁴² and MASP I can directly cleave HK to release bradykinin.⁴³ Its contribution to the actual pathogenesis of attacks is not yet clear. The fibrinolytic enzyme plasmin destroys C1-INH³⁶ and could contribute to pathogenesis by lowering C1-INH levels even further.

VASOPERMEABILITY OWING TO BRADYKININ

Bradykinin stimulates endothelial cell B2 receptors to cause vasodilatation and increase vascular permeability. Like histamine, the receptor density is most prominent along small venules. The effect is rapid but downregulated by internalization of the B2 receptor.⁴⁴ Vasodilators such as nitric oxide and prostacyclin and/or PGE₂ are secreted secondarily. The resultant effect is to stimulate adherens junctions between endothelial cells. The major protein of adherens junctions is VE cadherin (cadherins create zipper-like structures), which becomes phosphorylated at specific tyrosine residues and it is then internalized, ubiquitinated, and eliminated. This leads to reversible opening of adherens cell junctions and plasma leakage.^{45,46} In animal models, point mutations in these tyrosine residues inhibits bradykinin-induced vascular permeability. Phosphorylation of myosin light chain also can lead to retraction of actomyosin to open intercellular gaps.

The second bradykinin receptor, B-1, is not normally present, but is induced by inflammatory stimuli such as interleukin 1. Its ligand is a cleavage product of bradykinin, namely, des arg⁹ bradykinin (C-terminal arginine has been removed), which can then function similarly to bradykinin. The B-1 receptor is not internalized readily; thus, its effects can be longer lasting and it possesses ligand-independent constitutive activity.⁴⁷ It has been suggested that its stimulation might relate to the location or duration of attacks of swelling.^{28,29} Unfortunately, we do not have B-1 receptor antagonists that would allow one to test that possibility. Icatibant is a selective B-2 receptor antagonist with efficacy for acute episodes.

ASSEMBLY AND ACTIVATION OF THE BRADYKININ-FORMING CASCADE ON ENDOTHELIAL CELLS

The components of the plasma bradykinin-forming cascade bind to vascular endothelial cells⁴⁸ and in a zinc-dependent reaction. Binding involves the globular receptor for C1q (gC1qR),⁴⁹ which is present in excess, as well as bimolecular complexes of cytokeratin 1 with either gC1qR or with the urokinase plasminogen activator receptor.⁵⁰ Fig. 4 depicts the binding of factor XII and HK to each cell surface molecular complex.

This model system led to new considerations regarding contact activation. Particularly noteworthy is that attachment of factor XII alone to the surface does not lead to significant activation,⁵¹ but if the HK–prekallikrein complex binds, it activates without factor XII being present. This led to a series of observations, some in the fluid phase, and some requiring surface binding, as summarized in Fig. 5 and Box 1. First, incubation of prekallikrein with HK in equimolar amounts in a nonphosphate buffer (eg, HEPES buffer) leads to stoichiometric cleavage of HK.⁵² Prekallikrein has no active

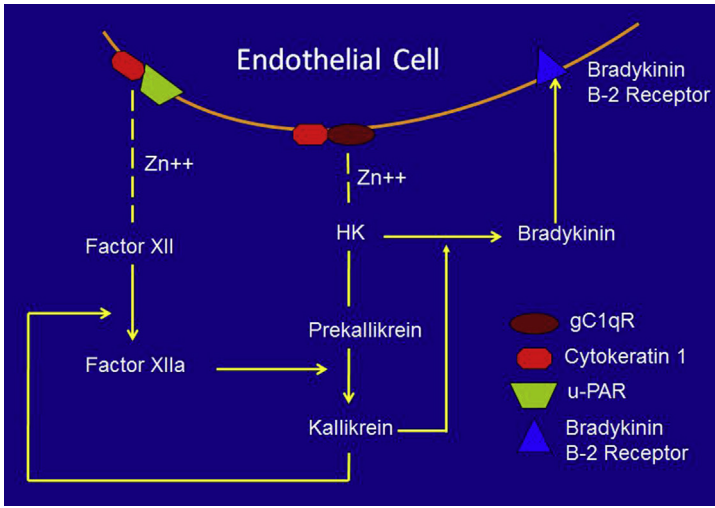


Fig. 4. Formation of bradykinin in hereditary angioedema, including the enzymatic steps inhibited by C1 inhibitor.

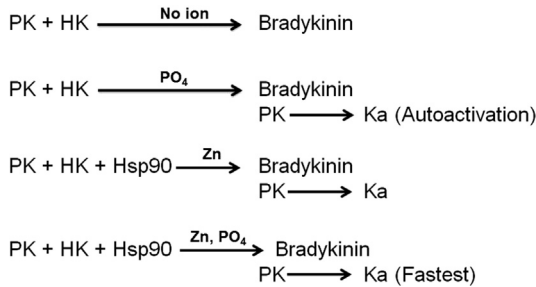


Fig. 5. In vitro reactions observed with the prekallikrein-HK complex. HSP90, heat shock protein 90 Ka, kallikrein.

Box 1
Characteristics of PK-HK activity

1. PK is not an enzyme; the complex, however, is.
2. PK stoichiometrically cleaves HK in nonphosphate buffer and remains as PK. But plasma is phosphate based.
3. PK-HK autoactivates in phosphate buffer so PK becomes kallikrein and HK is cleaved.
4. Hsp90 + #2 → kallikrein.
5. Hsp90 accelerates #3.

site! Thus, we propose an induced site in prekallikrein upon binding to HK followed by HK cleavage to produce bradykinin. The evidence against even a trace of kallikrein being present is: (1) The reaction is indeed stoichiometric; for example, 5 molecules of prekallikrein bound to 50 molecules of HK cleaves only 5 HK. Kallikrein would cleave all of it. (2) The reaction is inhibited by corn trypsin inhibitor, which has no effect on kallikrein. (3) A peptide that prevents complex formation between prekallikrein and HK prevents any HK cleavage and the peptide has no effect on kallikrein. The situation changes in phosphate buffer (plasma buffer is phosphate). Then the prekallikrein–HK complex autoactivates and the product is kallikrein (ka) and cleaved HK as if activated factor XII were present. These stoichiometric reactions are inhibited completely in plasma by the presence of C1-INH.⁵² But what happens if C1-INH is not present, as in HAE types I and II? We know that with incubation at 37°C, kallikrein forms and bradykinin evolves without any obvious initiating surface. We then took factor XII-deficient plasma, which does not activate when initiating surfaces are added, removed C1-INH by immunoadsorption, and found that the plasma activated and generated kallikrein activity, as did HAE plasma when incubated at 37°C.⁵³ Thus, the instability of HAE plasma that led to the *in vitro* identification of bradykinin as the likely mediator of HAE attacks (and disproved the existence of C-2 kinin)¹⁸ is due to autoactivation of HK–prekallikrein and does not require factor XII.

However, these fluid-phase observations were actually preceded by studies of the activation of HK–prekallikrein bound to endothelial cells. The cell surface reactions were carried out in nonphosphate buffers so that prekallikrein is stable even if HK becomes cleaved. With time, endothelial cells secrete a substance(s) that converts prekallikrein to kallikrein within the complex. Two groups identified 2 differing molecules capable of doing this. One is heat shock protein-90 (HSP-90), a “stress” protein that has phosphatase activity but no proteolytic site (see [Fig. 5](#) and [Box 1](#)).⁵⁴ The other is prolylcarboxypeptidase, which produces angiotensin 1-7 from angiotensin II.⁵⁵ Its mechanism resembles that of HSP-90 in that it acts stoichiometrically, does not activate prekallikrein unless it is bound to HK, and is inhibited by corn trypsin inhibitor. Prolylcarboxypeptidase is an exopeptidase apparently functioning, in this instance, as an endopeptidase, and its active site is said to be necessary for conversion of prekallikrein–HK to kallikrein. HSP-90 has no proteolytic active site, which raises questions about a requirement for any active site other than that within prekallikrein–HK. Regardless, the HSP-90 mechanism seems clear. It forms a trimolecular complex with HK–prekallikrein that requires zinc ion and binds primarily to the HK.⁵⁶ In nonphosphate buffer, the prekallikrein is converted stoichiometrically to kallikrein; that is, the amount of kallikrein formed is directly proportional to the ratio of HSP-90 to the complex of HK–prekallikrein. The activation of the HK–prekallikrein complex by HSP-90 is inhibited by C1-INH or corn trypsin inhibitor. In a phosphate milieu, in which HK–prekallikrein generates kallikrein anyway, the addition of HSP-90 increase the activation rate. Most recently, we have demonstrated that the addition of HSP-90 directly to normal plasma activates prekallikrein to kallikrein and generates bradykinin,⁵³ so as to override the inhibitory effect of C1-INH on prekallikrein–HK.

Issues raised by these observations are as follows.

- (1) Could attacks of HAE begin at the endothelial cell surface with activation of HK–prekallikrein first and then activate factor XII by the kallikrein thus produced?
- (2) If HK–prekallikrein has an active site controlled by the presence of C1-INH, when an initiating factor XII binding surface is added, does activation start by factor XII autoactivation followed by the kallikrein feedback, as is generally believed, or could the site in HK–prekallikrein cleave and activate surface-bound factor XII first?

Regarding the first possibility, we have demonstrated that interleukin 1, tumor necrosis factor α , and estrogen all stimulate HSP-90 secretion by endothelial cells,⁵⁵ reminiscent of hormone and infectious influences on attacks of angioedema in HAE types I and II.

HEREDITARY ANGIOEDEMA WITH NORMAL C1 INHIBITOR: NEW FORMS OF HEREDITARY ANGIOEDEMA

This entity was described by Bork and colleagues² and Binkley and Davis³ as a hereditary form of HAE with normal functional C1-INH that is strikingly prominent in women and strongly dependent on estrogen. A subpopulation of patients (perhaps one-third, depending on the country or region) has a mutation at threonine 309 with replacement by lysine (most commonly) or arginine. There are also rare cases of deletions, insertions, and duplications.^{57,58} The lysine substitution eliminates an O-carbohydrate attachment site so that the mutant protein is somewhat less in molecular weight and visible on SDS gels as a doublet.⁵⁹ Because it is a “dominant” gene defect, most are heterozygotes with a 50/50 mix of normal and mutant proteins. Rare homozygous mutations have been reported.⁶⁰ At first, it was reported that incubation of plasma with low concentrations of dextran sulfate (in contrast with the typical amount used, eg, 10 $\mu\text{g/mL}$) leads to augmented activation of the entire cascade. This was attributed to the absent carbohydrate⁵⁹ and enhanced autoactivation of factor XII was assumed. Next, it was found that replacement of threonine with lys or arg yields a new plasmin cleavage site and the addition of plasmin leads to an increased rate of mutant factor XII activation relative to normal factor XII.⁶¹ A coordinated event follows because cleavage at this site does not activate factor XII, but the product, a lower molecular weight factor XII (about 35 Kd) is cleaved and activated at the usual Arg-Val

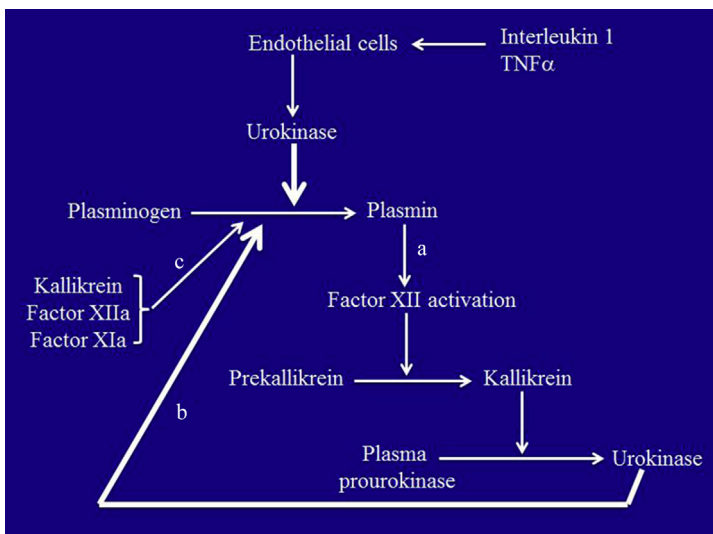


Fig. 6. Extrinsic and intrinsic sources of urokinase and/or plasmin, which may be critical for enzymatic activation of mutant factor XII in a subpopulation of patients with hereditary angioedema (HAE) and normal C1 inhibitor (type 3). ^a Important for activation of mutant factor XII (HAE with normal C1 inhibitor). ^b Major pathway for “intrinsic” activation of fibrinolysis. ^c Minor pathway for “intrinsic” activation of fibrinolysis; each enzyme is a weak plasminogen activator. TNF α , tumor necrosis factor α ,

bond by either kallikrein or plasmin (Coen Maas, personal communication 2016). Both cleavages occur considerably faster than the rate of activation of normal factor XII; hence, enhanced activity is seen. Activation of factor XII by plasmin is not new; it was reported in 1971 by Kaplan and Austen³⁴ at a time when the activated forms of factor XII were first discovered. The product of the plasmin activation of mutant factor XII most closely resembles factor XII_f,³³ which lacks the surface binding site and activates prekallikrein readily with minimal activity on factor XI.

The source of plasmin could be exogenous for example, by secretion of urokinase or tissue plasminogen activator within tissues and diffusion into plasma, or generated through the intrinsic fibrinolytic cascade within plasma. The latter is relatively weak and it is unclear whether sufficient plasmin is generated in that fashion, particularly when all antifibrinolytic inhibitors are present. To that end, we have observed that interleukin 1 and tumor necrosis factor α , in the endothelial cell experiments as described, cause secretion of urokinase along with HSP-90, but not tissue plasminogen activator.⁵⁶ A proposed scheme by which enzymes of the fibrinolytic pathway can lead to bradykinin formation, particularly in HAE with factor XII mutation, is shown in Fig. 6. Further, subpopulations of HAE and normal C1-INH, with or without the factor XII mutation, have strikingly low levels of plasminogen activator inhibitor-2,⁶² one of the plasma inhibitors of urokinase. Further work is in progress to define this subpopulation, but those with very low PAI-2 may have enhanced fibrinolysis and factor XII activation if urokinase is the initiating agonist.

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