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 $C1\bar{r}$, which is cleaved and fully active.[8] $C1\bar{r}$ digests C1s to $C1\bar{s}$ 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 $C1\bar{r}$ (**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 $C1\bar{r}$ and each $C1\bar{s}$ binds irreversibly to C1-INH to yield $(C1\bar{r})_2$ - $(C1\text{-}INH)_2$ and $(C1\bar{s})_2$ $(C1\text{-}INH)_2$ 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 $C1\bar{s}$ is depleted. C4 levels are low in 95% of patients[10]; 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

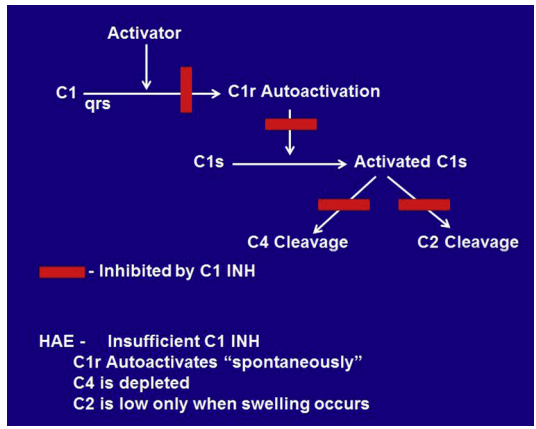

Fig. 1. The activation mechanism for the first component of complement leading to diminished levels of C4 and C2 in patients with hereditary angioedema (HAE). C1-INH, C1 inhibitor.