Hereditary angioedema: a current state-of-the-art review, III: mechanisms of hereditary angioedema

Alvin E. Davis III, MD

Objective: To review the available evidence on the pathophysiologic mechanism of episodes of edema in hereditary angioedema (HAE).

Data Sources: MEDLINE and PubMed were searched using the following keywords: *hereditary angioedema*, *C1 inhibitor*, *complement system*, *contact system*, and *bradykinin*.

Study Selection: Studies were selected based on their relevance to the pathophysiologic features of HAE.

Results: Early studies from the 1970s and 1980s disagreed as to whether the symptoms in HAE were mediated via complement or contact system activation. Studies have demonstrated that, in vitro, in C1 inhibitor (C1-INH)–deficient plasma, only contact system activation results in generation of a vascular permeability enhancing factor. Furthermore, individuals who express a variant C1-INH that is a normal inhibitor of contact system proteases but is deficient in the ability to inactivate complement system proteases do not develop angioedema. The blood of patients with HAE, during attacks, contains elevated levels of cleaved high-molecular-weight kininogen and bradykinin. Last, C1-INH-deficient mice develop increased vascular permeability that is mediated via contact system activation.

Conclusions: Hereditary angioedema attacks are mediated by bradykinin generated via contact system activation. The specific factors that trigger attacks remain unclear.

Ann Allergy Asthma Immunol. 2008;100(Suppl 2):S7–S12.

INTRODUCTION

Although hereditary angioedema (HAE) was described earlier, its hereditary nature was first clearly recognized in 1888 by Sir William Osler,[1] who also provided the first complete, detailed, clinical description of this autosomal-dominant inherited disease. The explanation for this inheritance pattern is that people with HAE are heterozygous for deficiency of C1 inhibitor (C1-INH). Donaldson and Evans[2] were the first to recognize that C1-INH was deficient in the plasma of patients with HAE. Complete deficiency of C1-INH in humans has not been observed. Simple absence of expression from one allele, with resulting decreased expression of C1-INH in the plasma, is referred to as type 1 HAE, whereas expression of a dysfunctional C1-INH protein and decreased levels of normal protein is type 2 HAE.

The mechanism of edema formation in HAE has remained somewhat controversial until relatively recently. The controversy, in a sense, began with the initial observation by Landerman and colleagues[3] that the plasma of patients with HAE was deficient in plasma kallikrein inhibitory capacity. When Donaldson and Evans[2] showed that deficiency of C1-INH resulted in HAE, the only known function of C1-INH, inactivation of C1, had been described only 6 years earlier.[4] Later studies demonstrated that C1-INH inactivates C1r and C1s, the protease subcomponents of C1.[5] The role of C1-INH in regulation of contact system activation, via inactivation of plasma kallikrein and factor XIIa, was accomplished during the 1970s and 1980s.[5] Because C1-INH regulated both systems, the question became, "Which system is responsible for the generation of symptoms?" Over the next 3 decades, a number of studies were published that supported either complement or contact system mediation. The accumulated data strongly indicate that the primary (and likely the only) mediator of symptoms is bradykinin. However, the specific biochemical triggers that initiate angioedema remain ill defined.

THE BIOLOGICAL FUNCTION OF C1-INH

C1-INH is the only serine protease inhibitor that plays a significant role in regulation of complement activation. It is the primary regulator of classic pathway activation via inactivation of C1r and C1s (Table 1).[5] It also regulates lectin pathway activation via inactivation of a C1s-like protease known as mannan-binding lectin–associated protease 2 (MASP2), which is activated after binding of mannan-binding lectin to a microorganism surface.[6] α_2-Macroglobulin also is able to inactivate MASP2.[6] However, the relative contributions of C1-INH and α_2-macroglobulin toward lectin pathway regulation have not been determined. C1 inhibitor also

Affiliation: CBR Institute for Biomedical Research, Harvard Medical School, Boston, Massachusetts.

Disclosure: The author has served as a consultant to each of the companies that are developing therapies for HAE: Jerini, Dyax, Lev Pharmaceuticals, Pharming, and CSL Behring.

Funding Sources: This study was supported by grants HD22082 and AI057366 from the National Institutes of Health.

Received for publication August 29, 2007; Received in revised form September 17, 2007; Accepted for publication September 17, 2007.

Table 1. The Contribution of C1-INH to Protease Inhibition in Plasma

Protease	% of plasma inhibitory capacity provided by C1-INH
Complement system	
C1r	100
C1s	100
MASP2	[a]
Contact system	
Plasma kallikrein	42–84
Coagulation factor XIa	47
Coagulation factor XIIa	90
Fibrinolytic system	
Tissue plasminogen activator	[b]
Plasmin	[b]

Abbreviations: C1-INH, C1 inhibitor; MASP2, mannan-binding lectin–associated protease.

[a] Undetermined, probably the primary inhibitor; α_2-macroglobulin may play some role.

[b] C1-INH plays little, if any, role under normal circumstances, but small amounts of complexes with tissue plasminogen activator and plasmin may be observed in some situations (angioedema attacks, endotoxin shock, and exhaustive exercise).

inhibits alternative pathway activation by reversibly binding to C3b, which inhibits factor B binding.[6] This activity differs from inhibition of the classic and lectin pathways in that it does not involve protease inhibition. However, the potential in vivo importance of this activity remains to be determined.

C1-INH is responsible for most of the inhibition of plasma kallikrein and coagulation factor XIIa and is, therefore, the major regulator of contact system activation (Table 1).[5,6] α_2-Macroglobulin also contributes to inactivation of these pathways.[5,6] C1-INH also inactivates factor XIa and, therefore, is also involved in regulation of the intrinsic coagulation pathway. In vitro, C1-INH also inactivates several other proteases, in particular plasmin and tissue plasminogen activator (tPA).[5,6] Plasmin, in vivo, is inhibited primarily by α_2-antiplasmin; C1-INH does not play a major role in its regulation.[5,6] C1-INH may participate, to some degree, in tPA inactivation.[7] Under some circumstances, C1-INH may play a minor role in the regulation of coagulation and fibrinolysis. For example, coagulation and fibrinolytic pathway activation have been shown during HAE attacks.[8,9] It is not clear whether this indicates that C1-INH is normally involved in regulation of these pathways or if activation of coagulation and fibrinolysis may induce attacks of angioedema. In addition, small amounts of complexes with tPA and plasmin are present in plasma in endotoxin shock and during exhaustive exercise.

PATHOPHYSIOLOGIC CHARACTERISTICS OF ANGIOEDEMA ATTACKS

Attacks of angioedema in HAE are not associated with signs of inflammation, although attacks may be triggered by inflammatory conditions. There also is no indication that allergy plays a role. Although some reports initially suggested that histamine levels in the urine were elevated during HAE attacks, a later study[10] demonstrated that urinary histamine levels are not elevated. Furthermore, antihistamines are ineffective. Epinephrine also is ineffective in HAE.

C1-INH is a member of the serpin family of serine proteinase inhibitors. Serpins inactivate proteases by exposing a peptide within a surface loop that mimics the natural substrate of the protease. This sequence is recognized and cleaved by the protease, but the result, rather than release of the protease, is formation of a covalent serpin-protease complex. Therefore, the protease and the serpin are inactivated. This inactivation of the inhibitor via complex formation may be a factor in triggering episodes of angioedema. Activation of any of the several proteases that may be inactivated by C1-INH would result in inactivation and consumption of the inhibitor. If the rate of consumption exceeded the rate of synthesis, the C1-INH plasma level would decrease, which, if substantial, could result in an episode of angioedema. This consumption would be amplified if activation of 1 system induced activation of either or both of the other 2 systems (Fig 1). In vitro, factor XIIa and plasmin may activate C1, and factor XIIa or kallikrein may generate plasmin from plasminogen, but the in vivo relevance of these observations remains unclear.[11–17] Angioedema sometimes develops during therapy with recombinant tPA,[18,19] which suggests that plasmin may activate the contact system. The data suggest that this angioedema is mediated by bradykinin.[19,20] Trauma or inflammation, which commonly induce symptoms in HAE, might result in the

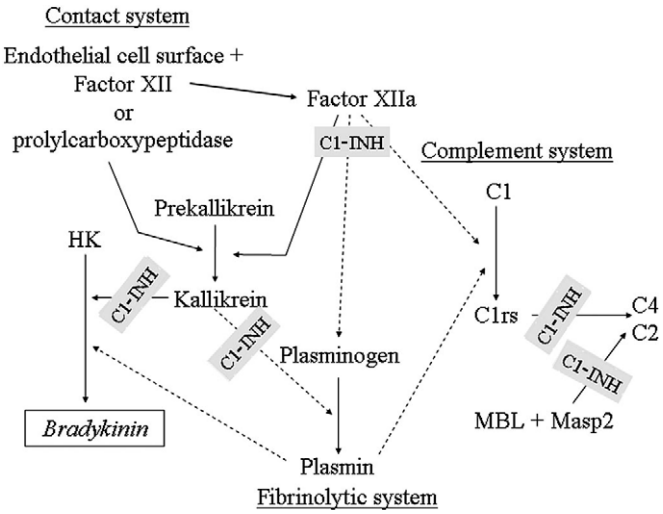

Figure 1. Potential interactions among the complement, contact, and fibrinolytic systems. Solid lines with arrows indicate reactions of defined biological relevance, and dotted lines with arrows indicate reactions that have been demonstrated in vitro but that are of unproven biological importance. C1-INH indicates C1 inhibitor; HK, high-molecular-weight kininogen; MASP2, mannan-binding lectin–associated protease 2; MBL, mannan-binding lectin.

Download English Version:

https://daneshyari.com/en/article/3193235

Download Persian Version:

https://daneshyari.com/article/3193235

Daneshyari.com