Current perspectives

Angioedema attacks in patients with hereditary angioedema: Local manifestations of a systemic activation process

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Hereditary angioedema (HAE) caused by a deficiency of functional C1-inhibitor (C1INH) becomes clinically manifest as attacks of angioedema. C1INH is the main inhibitor of the contact system. Poor control of a local activation process of this system at the site of the attack is believed to lead to the formation of bradykinin (BK), which increases local vasopermeability and mediates angioedema on interaction with BK receptor 2 on the endothelium. However, several observations in patients with HAE are difficult to explain from a pathogenic model claiming a local activation process at the site of the angioedema attack. Therefore we postulate an alternative model for angioedema attacks in patients with HAE, which assumes a systemic, fluid-phase activation of the contact system to generate BK and its breakdown products. Interaction of these peptides with endothelial receptors that are locally expressed in the affected tissues rather than with receptors constitutively expressed by the endothelium throughout the whole body explains that such a systemic activation process results in local manifestations of an attack. In particular, BK receptor 1, which is induced on the endothelium by inflammatory stimuli, such as kinins and cytokines, meets the specifications of the involved receptor. The pathogenic model discussed here also provides an explanation for why angioedema can occur at multiple sites during an attack and why HAE attacks respond well to modest increases of circulating C1INH activity levels because inhibition of fluid-phase Factor XIIa and kallikrein requires lower C1INH levels than inhibition of activator-bound factors. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

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Hereditary angioedema (HAE) resulting from a deficiency in the function of the plasma protein C1-inhibitor (C1INH) becomes clinically manifest as repeated attacks of angioedema in subcutaneous or submucosal tissues at various anatomic sites.[1-3] These attacks typically worsen over 24 hours and last for 2 to 5 days. Attacks can be lethal when located in the submucosal tissue of the larynx,[4] cause severe morbidity when located in the mucosa of the gastrointestinal tract,[5] or result in disability when subcutaneous edema impairs function of the extremities.[6] The frequency and locations of attacks vary widely among patients with HAE and often occur without any obvious trigger.

C1INH is a serine protease inhibitor (Serpin) that controls Factor XIIa, kallikrein, and Factor XIa of the contact system and activated C1s-, C1r-, and mannan-binding lectin–associated proteases of the complement system. Therefore C1INH deficiency leads to uncontrolled activation of the complement and contact systems and generation of vasoactive peptides. Indeed, patients with HAE have ample evidence for increased activation of both systems.[7-11] Complement activation does not correlate with clinical symptoms of HAE and also occurs in asymptomatic patients.[7-9] Therefore the main vasoactive peptide mediating angioedema in patients with HAE is derived supposedly from the contact system (ie, bradykinin [BK]).[11-13] Indeed, a BK receptor antagonist restores abnormal vasopermeability in C1INH-deficient mice[14] and attenuates HAE attacks.[15]

Angioedema during attacks of HAE results from a local increase in vasopermeability in the affected tissue. Activation of the contact system leading to generation of BK, which mediates this increase, is believed to be a local process as well.[3,16,17] However, several observations in patients with HAE are difficult to understand from a local activation process as the trigger for angioedema attacks; that is, swellings often occur at multiple sites during one attack[18] and can be preceded by muscle aches, rash, and fatigue.[19,20] Rather, these observations suggest systemic activation of the contact system as the precipitating event. Here we discuss how a systemic activation process of the contact system can result in localized angioedema attacks in patients with HAE. According to this model, localization of angioedema is determined through local expression of the involved receptors for vasoactive peptides on the endothelium. This new pathogenic model might better explain some clinical and biochemical observations in patients with HAE.

Abbreviations used
BK: Bradykinin
B1R: Bradykinin receptor 1
B2R: Bradykinin receptor 2
C1INH: C1-inhibitor
CPM: Carboxypeptidase M
CPN: Carboxypeptidase N
FXI: Factor XI
FXII: Factor XII (Hageman factor)
FXIIa: Activated Factor II
HAE: Hereditary angioedema
HK: High-molecular-weight kininogen
PK: Prekallikrein

THE CONTACT SYSTEM

The contact system consists of the proteins Factor XII (FXII), prekallikrein (PK), high-molecular-weight kininogen (HK), and Factor XI (FXI).[21,22] FXI connects the contact system to coagulation and will not be discussed further here. The term contact system refers to the fact that the system becomes activated on contact of blood with negatively charged surfaces, such as glass.[23] Other *in vitro* activators of the contact system include kaolin, celite, and dextran sulfate.[24] *In vivo* activators include inorganic polyphosphate released from platelets,[25,26] mast cell–derived heparin,[27] nucleosomes exposed on neutrophil extracellular traps,[28] fibrin clots,[29] collagen,[30] and misfolded proteins.[31]

Activation of the contact system starts with activation of FXII, which subsequently converts PK into kallikrein. Kallikrein has 2 substrates (Fig 1): it reciprocally activates additional FXII and cleaves HK to yield BK and cleaved HK. Notably, reciprocal activation of FXII and PK endows the contact system with an all or nothing–like behavior during activation.[32,33] Alternatively, when bound to HK, PK can autoactivate. Autoactivation can be accelerated by heat shock protein 90, which can be secreted by endothelial cells.[34] Another possible PK activator is prolylcarboxypeptidase expressed by endothelial cells.[35] Once PK is activated, the reciprocal FXII activation will amplify contact system activation. In addition, activated Factor II (FXIIa) and kallikrein can also activate some complement and fibrinolytic factors and mediate cross-talk between the contact, complement, and fibrinolytic systems.[34,36-38]

A main biologically active peptide generated during contact activation is BK. BK is a nonapeptide cleaved from HK by kallikrein. The sequence of BK starts and ends with arginine.[38] In biological fluids BK is rapidly processed by several peptidases. The N-terminal Arg^1-Pro^2 bond is cleaved by aminopeptidase P,[39] whereas at the C-terminal, BK is processed by enzymes that cleave either the Pro^7-Phe^8 bond or the C-terminal Phe^8-Arg^9 bond. These enzymes are subdivided into 2 groups: kininase II and kininase I. The kininase II enzymes, to which angiotensin-converting enzyme and neprilysin belong, cleave the Pro^7-Phe^8 bond. The kininase I enzymes cleave the Phe^8-Arg^9 bond. Carboxypeptidase N (CPN) and carboxypeptidase M (CPM) are, among others, kininase I enzymes.[40,41] Removal of the C-terminal arginine by kininase I enzymes yields *des*Arg^9-BK. BK, its degradation products, and its receptors are reviewed elsewhere.[42]

In addition to BK, another kinin can be generated from HK but also from low-molecular-weight kininogen: Lys-BK, also known as kallidin. This is a decapeptide with an additional lysine at the N-terminus compared with BK. In addition, Lys-BK is processed by carboxypeptidases to yield Lys-*des*Arg^9-BK.[42] BK, Lys-BK, and their metabolites, *des*Arg^9-BK and Lys-*des*Arg^9-BK interact with the G-coupled protein receptors bradykinin receptor 1 (B1R) and bradykinin receptor 2 (B2R) on endothelial cells to regulate vasopermeability.[42,43]

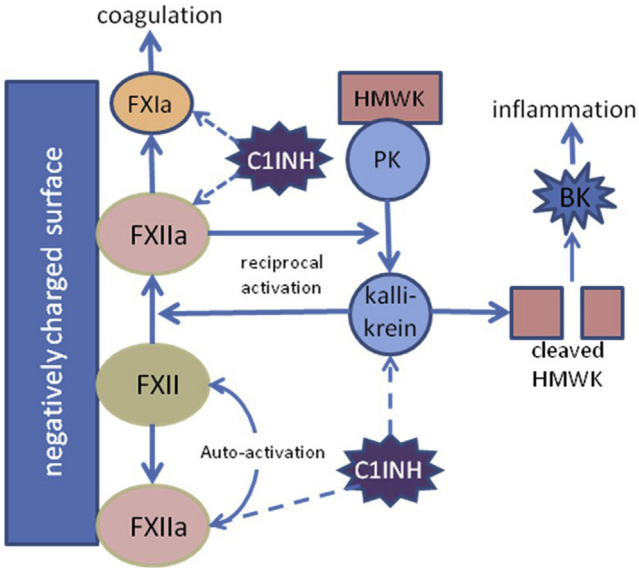

FIG 1. The contact system of coagulation. Activation of the system is triggered when FXII becomes activated on binding to an activator. *Solid arrows* indicate activation, and the *dotted line* indicates inhibition. Note the reciprocal activation of FXII and PK and the inhibition of all contact system proteases by C1INH. *HMWK*, High-molecular-weight kininogen.

Notably, several other proteases that are inhibited by C1INH can cleave BK or related peptides from HK, such as factor seven activating protease and mannan-binding lectin–associated protease.[44,45] The role of these proteases in the generation of BK *in vivo* is currently unknown and will not be discussed further here.

INVOLVEMENT OF THE CONTACT SYSTEM IN PATIENTS WITH HAE

C1INH is the major inhibitor of FXIIa and kallikrein in the circulation.[46-49] Hence decreased C1INH levels result in poor control of contact activation in the circulation. In other words, reciprocal activation of FXII and PK at low levels of C1INH will require less FXIIa than at normal C1INH levels. Thus C1INH deficiency will allow profound activation of the contact system on generation of minute amounts of FXIIa. At a physiologic concentration, C1INH will prevent such reciprocal activation by small amounts of FXIIa because it rapidly inactivates FXIIa and kallikrein (Fig 1).

There is ample evidence for involvement of the contact system in HAE attacks. First, during attacks, circulating levels of cleaved HK, as well as BK, are increased, whereas levels of contact system proteins, such as FXII, PK, and HK, are decreased.[10,12,13,17,50-54] Moreover, patients with HAE have increased kallikrein-dependent enzymatic activity in plasma during attacks.[55,56] Second, mutations of the FXII gene are associated with angioedema in the absence of C1INH deficiency, supporting a key role of FXII in mediating angioedema attacks.[57,58] Finally, drugs that inhibit kallikrein[59] or block the