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Pathophysiology of Hereditary Angioedema

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The genetic deficiency of the C1 inhibitor is responsible for hereditary angioedema (HAE), which is a disease transmitted as an autosomal dominant trait. More than 200 point mutations in the C1 inhibitor gene have been found to be associated with HAE. Patients with this disease suffer from recurrent angioedema, which is mediated by bradykinin derived from activation of the contact system. This system is physiologically controlled at several steps by the C1 inhibitor. In this review, we describe known mechanisms for the development of angioedema in patients with C1 inhibitor deficiency.

The Genetics of Hereditary Angioedema

William Osler first comprehensively described the clinical picture of hereditary angioedema (HAE) in 1888[1] and, acknowledging the severity of the disease, urged the community to search for a scientific solution. In 1963, Donaldson and Evans discovered that HAE was caused by a genetic deficiency of the C1 inhibitor (C1-INH).[2] Other forms of HAE have since been described, but the pathogenesis of those diseases remains obscure. This review will therefore focus on HAE that develops as a result of C1-INH deficiency.[3] C1-INH is a serine protease inhibitor (SERPIN), which controls different proteases involved in the complement, kinin/contact, fibrinolytic, and coagulation systems.[4] Similar to other SERPINs, C1-INH consists of α-helices and β-sheets, as well as an exposed mobile reactive center loop that is cleaved upon contact with a target protease. This reaction results in the formation of a stable, covalent bond. Protease binding causes dramatic conformational changes in C1-INH, which crushes the protease against its lower pole resulting in inactivation of the enzyme.[5] Mutations in C1-INH disrupt the structure of the protein, but oftentimes these changes cannot be detected in plasma or, when a mutated C1-INH is present, has no functional activity. These two situations account for the genetic variants of HAE described by Rosen et al. They found that all patients have low functional plasma levels of C1-INH: most of the times with antigenic deficiency (HAE type I), and in 20% of affected subjects with normal or elevated antigenic levels (HAE type II).[6]

The genetic transmission of HAE as an autosomal dominant trait was first described in 1917.[7] Discovery and subsequent sequencing of the C1-INH gene (SERPING1)[8,9] confirmed that the disease occurs when one of the two alleles is mutated.[10,11] Rare homozygous C1-INH deficient patients have also been described.[12–14] The presence of one mutated allele affects mRNA transcription and protein secretion, which eventually leads to C1-INH plasma levels ranging from 10% to 30% of normal.[15] The mechanisms that prevent the remaining wild-type allele from generating C1-INH plasma levels around 50% remain unknown. Patients with HAE catabolize C1-INH faster than normal subjects,[16] but concomitant downregulation of the normal allele may also occur, at least with some mutations.[17–19] Most mutations that cause HAE are point mutations resulting in single amino acid substitutions.[10] Independent families rarely possess identical mutations. More than 200 different mutations have been associated with HAE, and only one protein polymorphism resulting in an amino acid substitution not associated with a disease state has been described to date.[20] Moreover, no correlation between genotype and clinical phenotype has been found.

Mechanisms of Edema Formation

Patients with genetic deficiency of C1-INH constantly present increased activation of the classical complement pathway with depletion of C4 and, to a lesser extent, of C2.[21,22] Measurement of these parameters may help in the laboratory diagnosis of HAE. Patients with this condition have lifelong C1-INH deficiency and episodic, localized subcutaneous and/or submucosal angioedema. It was originally proposed that complement activation may play a principle role in the pathogenesis of these symptoms, but this was later discredited.[23–27] It is known that minor local trauma, stress, and other events may trigger angioedema, and it is now well established that bradykinin (BK) is the principal mediator of symptoms of C1-INH deficiency.[28,29]

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Accordingly, specific inhibition of BK-B2 receptors can revert angioedema.[30]

Previous studies of plasma from these patients have indicated that attacks are marked by signs of activation of the contact system.[31,32] This system is comprised of a substrate, high molecular weight kininogen (HK), and two zymogens, plasma prekallikrein (PPK) and factor XII (FXII). The system is closely linked to intrinsic coagulation (FXI and onward) and kinin generation pathways (Fig. 1).[33] *In vitro* activation of the contact system is used to measure activated partial thromboplastin time (aPTT), while the best characterized event associated with its *in vivo* activation is angioedema due to C1-INH deficiency. It has been shown that the increase in BK plasma levels during attacks is due to local production of BK as a result of inappropriate activation of systems controlled by C1-INH.[34,35] However, the molecular events triggering angioedema remain unclear, and the reasons for the extreme variability in symptom recurrences among patients and within the same subject from time to time are unknown. Since increased generation of BK appears to be critical for angioedema formation, specific emphasis has been placed on the study of HK, which is the substrate that releases BK when it is cleaved at two sites by plasma kallikrein (PK).[36] The cleaved form of HK remains in plasma after protease cleavage, and measurement of this form has shown that the breakdown product not only increases during attacks, but also correlates with disease severity.[37] It is known that BK release is the final event of contact system activation, and that activation begins when the two zymogens of this system, FXII and PPK, are proteolytically cleave into FXIIa and PK to acquire enzymatic activity, respectively. These two enzymes reciprocally act on their zymogens through a positive feedback loop to generate BK efficiently. Binding to a negatively charged surface changes the conformation of FXII, which attains limited proteolytic activity and becomes increasingly susceptible to cleavage by PK and FXIIa.[38] Small amounts of FXIIa have the capacity to cleave more of its own precursor to produce efficient contact activation.[39] The mechanisms for *in vitro* activation of the contact system by negatively charged surfaces are well established. The process begins with the formation of FXIIa, which in turn generates the active enzymes PK and FXIa that eventually form BK and thrombin. However, the sequence of events that occurs *in vivo* is less clear, and pathways of contact activation that skip FXII and begin with PPK and/or PK have been described. Membrane-expressed enzyme prolylcarboxypeptidase (PRCP) and/or the protein HSP90 can directly activate prekallikrein bound to endothelial cell surfaces.[40,41] PPK itself has enzymatic activity that can initiate PK generation and contact activation under specific circumstances.[42] Based on these findings, a FXII-independent mechanism of contact activation initiating symptoms in HAE patients has been suggested.[43] Experimental results have shown that FXII may pivot contact system activation *in vivo* similar to the mechanism observed *in vitro*, suggesting that the enzymatic activity of FXII may initiate contact activation.[33,44] Moreover, other studies have shown that FXII can be activated *in vivo* by substances such as platelets polyphosphates and heparin-activated mast cells, thus ensuring efficient activation of the contact system.[45,46] Thus, it is possible that these mechanisms of contact activation specifically contribute to angioedema formation.[47]

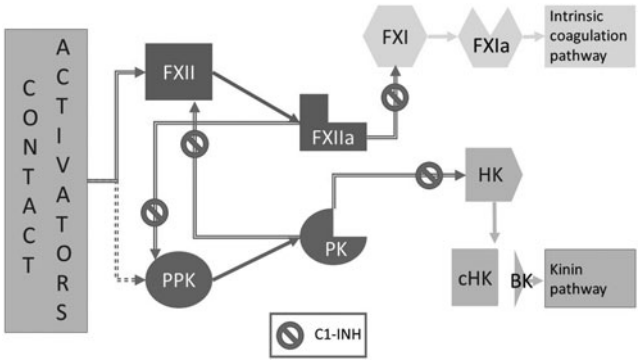

FIG. 1. Schematic representation of the mechanism of activation of the contact system. In the presence of contact system activators (see text for details), the zymogens Factor XII (FXII) and/or possibly plasma prekallikrein (PPK) are converted into active enzymes FXIIa and plasma kallikrein (PK), respectively. These enzymatic forms reciprocally activate their zymogens and thus generate a positive feedback loop. In the presence of sufficient amounts of active enzyme, FXIIa generates active Factor XI (FXIa), which initiates the intrinsic coagulation pathway. PK proteolyzes high molecular weight kininogen (HK) at two sites thus generating cleaved HK (cHK) and the nonapeptide bradykinin in the kinin pathway. C1 inhibitor (C1-INH) controls the system by intervening at several locations.

In any consideration of the molecular events leading to episodic BK release in patients deficient in C1-INH, the role of plasmin, which is a key enzyme of the fibrinolytic cascade, should be considered. Plasmin is generated from plasminogen by physiologic activators tPA and uPA, but plasmin is also involved in contact system activation and can form kinins through the activation of kallikrein.[48] In addition, the contact system can also lead to the generation of fibrinolytic activity *in vivo*.[49] Early experiments from Virginia Donaldson's group showed that the presence of plasmin is necessary for *in vitro* generation of kinin activity in plasma from patients with HAE, and that the presence of plasmin facilitates the release of BK from HK.[24,50] Moreover, patients with HAE have increased levels of plasmin–antiplasmin complexes during attacks, and antifibrinolytic agents have been shown to be efficacious in the treatment of these patients.[51–53] Thus, although the data are not conclusive and the *in vivo* relevance of plasmin activity on the contact system remains to be defined, a role for plasmin should be carefully considered when trying to solve the puzzle of angioedema pathogenesis.

Other proteases, such as MASP-1, which is activated during episodes of angioedema, might also contribute to bradykinin production.[54] Under physiologic conditions, BK either binds specific receptors or is degraded by proteolytic enzymes comprising angiotensin-converting enzyme (ACE), aminopeptidase P (APP), neutral endopeptidase 24.11 (NEP, neprilysin), and carboxypeptidases M and N (CPM, CPN).[55] During angioedema attacks, HAE patients release large amounts of BK into their plasma, and it has been found that these patients can have up to a 10-fold increase in concentration over resting conditions.[28] Two types of receptors can bind BK: B2, which is constitutively expressed, and B1, which is induced by inflammatory stimuli (mainly IL-1β and tumor necrosis factor [TNF]-α).[56] Animal studies assessing the therapeutic efficacy of specific B2 antagonists have

shown that angioedema is predominantly dependent on stimulation of B2 receptors.[29,30] Nevertheless, experiments using a transwell model of endothelial cell permeability and intravital microscopy in animals suggest a potential role also for B1 receptors.[57] Considering that expression of these receptors requires an inflammatory stimulus and that efficiently respond to BK metabolites as well, it has been suggested that they may intervene during the late phase of the attacks and possibly extend the duration.

The receptors for BK are coupled to G-proteins, which comprise a family of intracellular signal transmitting proteins that signal through intracellular calcium mobilization, release of arachidonic acid, and stimulation of the endothelial nitric-oxide synthase (eNOS).[58] These intracellular events increase paracellular permeability opening through endothelial cell–cell junctions, which are largely composed of vascular endothelial cadherin (VE-cadherin).[59] BK has a fast and potent effect on increasing the permeability in veins by inducing the acute and generally reversible disorganization of junctional VE-cadherin through tyrosine phosphorylation, which depends on activation of the tyrosine kinase Src.[60] Bouillet et al. demonstrated that BK- and PK-mediated stimulation of a confluent endothelial cell monolayer induced a time-dependent release of soluble VE-cadherin fragments, as well as an increase in vascular permeability secondary to the disruption of cell–cell junctions. They also detected a 90 kDa VE-cadherin extracellular domain fragment in a patient's serum during the attack that was barely detectable when the attack was not occurring.[61] Moreover, Kajdacsi et al. found that markers of endothelial cell activation, including serum levels of von Willebrand factor antigen and collagen-binding activity, soluble E-selectin, and endothelin-1, were significantly increased during HAE attacks.[62] Taken together, these studies indicate that endothelial cells actively participate in angioedema attacks and may represent new potential targets for diagnosis and therapy.

Starting from Osler's solicitation to discover a scientific solution for HAE, this review has detailed studies that advance our understanding of the mechanisms leading to angioedema. Importantly, these studies have led to therapies that are already available for treatment of HAE, as well as others that are currently being assessed in clinical trials. As a consequence, the lives of patients with HAE have drastically improved. However, this review underscores the possibility of developing new diagnostic and therapeutic approaches that may be better tailored to patients. Moreover, we still face a marginal understanding of newly described forms of angioedema that await novel diagnostic and therapeutic approaches. Thus, Osler's request still remains today: science has to proceed and find solutions.

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Author Disclosure Statement

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