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Abstract

The “complement system” is one of the effector pathways of the immune system against microorganisms and tumor cells. The complement system can be activated through three major pathways: classical, lectin, and alternative. The sequential activation through the generation of complex enzymes from inactive zymogens produces a cascade in which a capable enzyme generates a large number of active downstream molecules.

C1 inhibitor (C1-INH) is a serine protease inhibitor (serpin) that regulates the following closely interrelated proteolytic pathways: complement system, coagulation system, contact system, and fibrinolysis system. The absence or malfunction of C1-INH results in the presence of attacks of angioedema (AE) due to uncontrolled activation of the contact system, with the generation of bradykinin (BK), a vasoactive peptide released from high-molecular-weight kininogen (HMWK). Some drugs that inhibit the catabolism of BK have been implicated in the development of AE. These include angiotensin-converting enzyme inhibitors (ACEIs), dipeptidyl peptidase IV (DPP-IV) inhibitors, aminopeptidase P (APP) inhibitors, and neutral endopeptidase (NEP) inhibitors.

We describe in this chapter the biochemistry pathways implicated in the pathophysiology of bradykininergic angioedema (BK-AE) and the role of the complement system in the prototype of BK-AE, in hereditary angioedema with C1-INH deficiency (C1-INH-HAE), and also in acquired angioedema with C1-INH deficiency (C1-INH-AAE).

Keywords: acquired angioedema, aminopeptidase P, angioedema, angiotensin-converting enzyme, bradykinin, C1 inhibitor, carboxypeptidase, complement system, contact system, dipeptidyl peptidase-IV, endothelin-converting enzyme-1, factor XII, fibrinolysis system, hereditary angioedema, neutral endopeptidase
1. Introduction: definition of angioedema and differentiation between histaminergic and bradykininergic angioedema

The term “angioedema” (AE) is defined as localized and transient subcutaneous and/or submucosal swelling (which may affect the gastrointestinal, respiratory, or genitourinary tract) [1, 2]. It occurs when there is vasodilation with consequent increase in capillary permeability and extravasation of fluid into the interstitial space [2, 3]. A variety of inflammatory mediators have been described that can lead to this process, such as histamine, prostaglandins, leukotrienes, and bradykinin [4]. The most frequent type of AE is produced by histamine release, as a consequence of mast cell activation, and is called “histaminergic angioedema.”

It includes allergic reactions, but also idiopathic AE in the context of chronic spontaneous urticaria [5]. Histaminergic AE can be associated to urticaria [6], is usually erythematous, warm, and pruritic, and is responsive to treatment with antihistamines [7]. The clinical expression of urticarial lesions is mainly a consequence of inflammation and edema of the upper dermis, whereas swellings are located in the deep dermis and even in the subcutaneous tissue.

Another important type of AE is produced by an increase in bradykinin (BK). This AE type is non-erythematous, non-pruritic, cold, non-responsive to antihistamines and urticaria is not associated [7]. This subgroup is known as bradykininergic angioedema (BK-AE).

2. Classification of bradykinin-mediated angioedema (BK-AE)

BK-AE comprises several entities (Table 1). In recent years, there has been a dramatic increase in knowledge about this condition, particularly on the role of BK as the “final common mediator.” The Spanish Study Group for Angioedema due to C1-inhibitor deficiency was established in 2007 within the Committee of Immunology of the Spanish Society of Allergology and Clinical Immunology (SEAIC). However, such was the progress in the understanding of the pathophysiology of different types of BK-AE that this group’s name quickly changed to “Spanish Study Group on Bradykinin-Induced Angioedema” (SGBA).

BK-AE is mainly classified into two subtypes depending on whether or not there is a functional deficiency of C1 esterase inhibitor, better known as C1 inhibitor (C1-INH) (Table 1) [8]. Another common way to classify BK-AE is hereditary angioedema (HAE) and acquired angioedema (AAE) [8]. There are two forms of AE with C1-INH deficiency, a hereditary form (C1-INH-HAE) and an acquired form (C1-INH-AAE).

Among the forms of AE with no functionally active C1-INH deficiency are hereditary angioedema with normal C1-INH (nC1-INH-HAE), with/without mutation in the F12 gene that encodes coagulation factor XII (FXII-HAE/U-HAE) or acquired AE associated with drugs that inhibit the metabolic pathways of BK, angiotensin-converting enzyme inhibitors (ACEi-AAE).
Other drugs that inhibit the catabolism of BK have been implicated in the development of AE. These include dipeptidyl peptidase IV (DPP-IV) inhibitors, aminopeptidase P (APP) inhibitors, neutral endopeptidase (NEP) inhibitors, and others.

Along with progress in biochemical-molecular knowledge, much has been learned about the different pathophysiological mechanisms of the different types of AE. For example, the initial term “HAE type III or oestrogen-induced” has evolved into the term FXII-HAE due to the description in some of these patients of mutations in the F12 gene. Another example would be the recognition of antihypertensives belonging to the group of ACE inhibitors (ACEIs) as producers of AE by increased BK, secondary to the inhibition of its catabolism. This has led to classifications over time by different groups. In order to agree on a common name for all types of AE “without papules” described so far, the HAE International Working Group (HAWK), under the sponsorship of the European Academy of Allergy and Clinical Immunology (EAACI), proposed a classification of AE without wheals as seen in Figure 1 [7], with four types of AAE and three types of HAE.

<table>
<thead>
<tr>
<th>Bradykinin (BK)-mediated angioedema (AE)</th>
<th>With verified C1-inhibitor protein deficiency</th>
<th>Hereditary (C1-INH-HAE)</th>
<th>Type I (C1-INH-HAE type I)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acquired (C1-INH-AAE)</td>
<td></td>
<td>Type II (C1-INH-HAE type II)</td>
</tr>
<tr>
<td>No verified C1 inhibitor protein deficiency</td>
<td>Hereditary (related to estrogen) (HAE type III)</td>
<td>With known mutation of F12 gene (FXII-HAE)</td>
<td>Without known mutation of F12 gene (U-HAE: HAE unknown)</td>
</tr>
<tr>
<td></td>
<td>Acquired associated with angiotensin-converting enzyme (ACE) inhibitors (ACEIs) (AAE-ACEI)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Classification of different types of bradykinin-mediated AE (modified from SGBA Consensus) [9].

![Figure 1. Classification of angioedema without wheals](image-url)
However, this classification has some limitations such as the noninclusion of AE caused by non-steroidal anti-inflammatory drugs (NSAIDs), which often occurs without associated urticaria [10]. These drugs act by inhibiting the enzyme cyclooxygenase in the metabolic pathways of arachidonic acid and increasing leukotrienes.

A classification of AE according to endotypes was proposed later [11]. In this classification, three subtypes of AE were included: (1) mast cell and basophil-driven AE, (2) bradykininergic AE, and (3) idiopathic AE [11]. It has the advantage that NSAIDs induced or exacerbated AE and allergic AE are both included within the mast cell and basophil-driven AE.

3. C1-inhibitor deficiency

C1-INH is a serine protease inhibitor (serpin) that regulates the following closely interrelated proteolytic pathways: complement system, coagulation system, contact system, and fibrinolysis system [12, 13] (Figure 2). It is also known as SERPING1, belongs to the SERPIN superfamily, and is mainly synthesized in hepatocytes [9].

First, C1-INH inhibits C1r, C1s, and mannose-binding-lectin-associated serine proteases (MASP1, MASP2) in the complement system. The inhibition of C1r and C1s is the function that gives name to this protein, “C1 inhibitor.” The C1 fraction of complement, also known as C1 esterase, is the first protein of the complement system, and circulates in an inactive form. C1 esterase is activated during immunological processes, initiating the complement cascade and splitting off proteins from the classical pathway (C4 and C2) [9]. In patients with C1-INH deficiency, an increase in C1 esterase functioning produces decreased C2, C4 levels, the natural substrates of the complement C1s fraction, which diminish much more during AE attacks [9]. C3, the protein that follows C2 in the classical complement cascade, is usually normal in patients with C1-INH-HAE, since it is not controlled by C1-INH [9].

![Figure 2. C1-INH regulates different pathways: (A) complement system, (B) contact system, and (C) fibrinolysis system.](image-url)
Besides, C1-INH inhibits factor XI and thrombin in the coagulation system and tissue plasminogen activator and plasmin in the fibrinolytic system [9].

Finally, C1-INH also inhibits factor XII and kallikrein in the contact system, being the main inhibitor of the contact system and of BK formation [9]. This is the crucial action involved in AE development when C1-INH is lacking.

C1-INH deficiency can produce an activation of the four described cascades, with a final increase in BK. BK produces vascular hyperpermeability and edema formation [9].

C1-INH is the most potent inhibitor of the contact system and thus low C1-INH function can activate this system, with uncontrolled activation of FXII and increased formation of kallikrein. Kallikrein releases BK from high-molecular-weight kininogen (HMWK). The lack of C1-INH also produces an increase in plasmin through the activation of the fibrinolytic system. The split of BK from HMWK induced by kallikrein is facilitated by the presence of plasmin [9].

C1-INH is a glycoprotein with 478 amino acids. It is heavily glycosylated (approximately 30% by weight). Its apparent molecular weight on sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) is 104 kilodalton (kDa), but its calculated molecular weight is 76 kDa. It is formed by an N-terminal domain of 113 amino acids and a serpin domain of 365 amino acids [14].

The genetic study of SERPING1 gene, which codes C1-INH, has identified more than 300 different mutations causing C1-INH-HAE [7].

There are classically two main types of AE due to C1-INH deficiency: hereditary (C1-INH-HAE) and acquired (C1-INH-AAE). In turn, two types of C1-INH-HAE [9] have been described; in patients with type I (85%) there is decreased antigenic C1-INH (consequently resulting in decreased functional activity); type II (15%) is characterized by normal C1-INH levels with decreased functional C1-INH (the molecule being dysfunctional) [9]. The acquired subtype is characterized by low levels of either antigenic and/or functional C1-INH, associated in most cases with B-cell lymphoproliferative disorders.

Hereditary or acquired deficiency of C1-INH is characterized by recurrent episodes of circumscribed, non-itchy AE in submucosal or subcutaneous locations. AE attacks can be triggered by estrogens, trauma, infection, or stress.

4. What is the complement system?

The “Complement System” is one of the effector pathways of the immune system against microorganisms and tumor cells, consisting of about 30 molecules, part of the complement factors enhance “inflammation” and “phagocytosis,” producing lysis of cells and microorganisms. The sequential activation through the generation of complex enzymes from inactive zymogens produces a cascade in which a capable enzyme generates a large number of active downstream molecules. Very strict regulation of downstream activation processes can be expected to restrict such activation to the foci where it started, thereby
Both receptors belong to the superfamily of receptors that have seven transmembrane domains coupled to G proteins, differing both in primary structure, expression, and regulation of their tissue distribution [85, 86].

Two types of G protein-coupled receptors have been found that bind to BK mediating its response in pathophysiological conditions. To summarize, there are stimulatory G proteins (Gs and Gq) and inhibitory G proteins (Gi). Gs binds to GTP and activates adenylate cyclase, increasing the amount of intracellular cAMP. Gi binds to GTP and inactivates adenylate cyclase, indirectly reducing the amount of intracellular cAMP. Gq binds to GTP and activates PLC, increasing the amount of DAG, IP, and intracellular Ca++. Transduction pathways stimulated by kinins have been extensively investigated in endothelial cells, where BK1 interacts with Gq and Gi proteins, using the same signaling pathways as BK2 (Figure 10).

BK2 binds to G proteins and activates phospholipases A₂ and C. The kinin-induced increase in phospholipase C (PLC) causes it to act on their specific substrate, phosphatidylinositol biphosphate (PIP₂), hydrolyzing it generating the two metabolites: inositol triphosphate (IP₃) and diacylglycerol (DAG). IP₃ binds to a specific receptor (IP₃R) in the endoplasmic reticulum facilitating the release of intracellular Ca++. IP₃, possibly together with its metabolite, IP₄, can regulate calcium channels of the plasma membrane allowing the entry of extracellular calcium into the cell [87, 88]. The other metabolite of PIP₂ hydrolysis, DAG, is responsible for the activation of protein kinase C (PKC) [89, 90]. PKC consists of one polypeptide chain with two functional domains: (a) a hydrophobic domain for binding to the cell membrane and (b) a hydrophilic domain, which possesses catalytic function. PKC at cellular rest is found in an inactive form in the cytosol, but once stimulated by DAG together with Ca²⁺ ions it translocates to the cell membrane to exert its function of protein kinase in serine and threonine.
amino acids. BK has been shown to activate a Ca\(^{2+}\)-dependent PKC and PKC not dependent on this ion, as well as atypical isoforms [91]. The stimulation of phospholipase A\(_2\) (PLA\(_2\)) releases arachidonic acid from membrane phospholipids [92], which can be metabolized in the form of powerful inflammatory mediators.

In addition, BKR2 transitorily promotes phosphorylation of tyrosine from tyrosine kinases such as MAP kinase ("mitogen-activated protein kinase"), as well as the activation of the JAK/STAT pathway. Activated BKR2 interacts directly with nitric oxide synthase (NOS) resulting in nitric oxide (NO) [93].

9. Conclusions

C1-INH-HAE is a rare inherited disorder, characterized by recurrent AE attacks in various regions of the body. C1-INH-AAE is an acquired disease usually due to the presence of anti-C1-INH autoantibodies. The lack of C1-INH leads to inappropriate activation of the kallikrein-kinin system and release of BK, a vasoactive mediator.

nC1-INH-HAE is another inherited form of AE, with no C1-INH deficiency, but a probable increase in BK formation due to mutation in exon 9 of F12 gene with subsequent hyperactivability.

BK (common final mediator of BK-AE) is a linear nonapeptide (with sequence Arg1-Pro2-Pro3-Gly4-Phex5-Ser6-Pro7-Phex8-Arg9) produced endogenously in humans and other mammals as a result of the proteolytic activity of kallikrein on kinogens.

Some drugs that inhibit the catabolism of BK have been implicated in the development of AE. These include ACEIs, DPP-IV inhibitors, APP inhibitors, and NEP inhibitors.

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