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Pathophysiology of Bradykinin-Mediated Angioedema: The Role of the Complement System

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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.

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

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

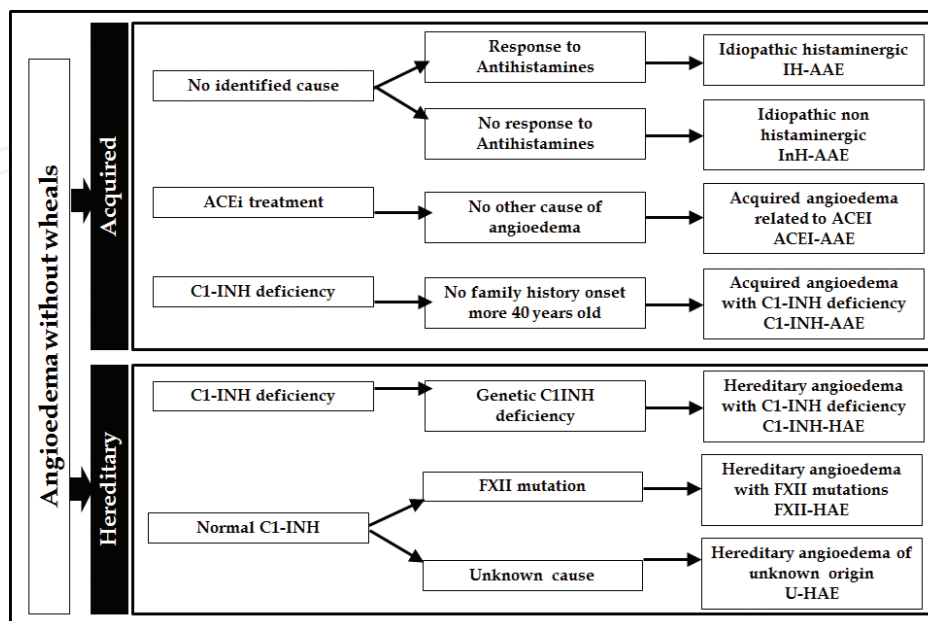


Figure 1. Classification of angioedema without wheals [7].

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) bradykinergic 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].

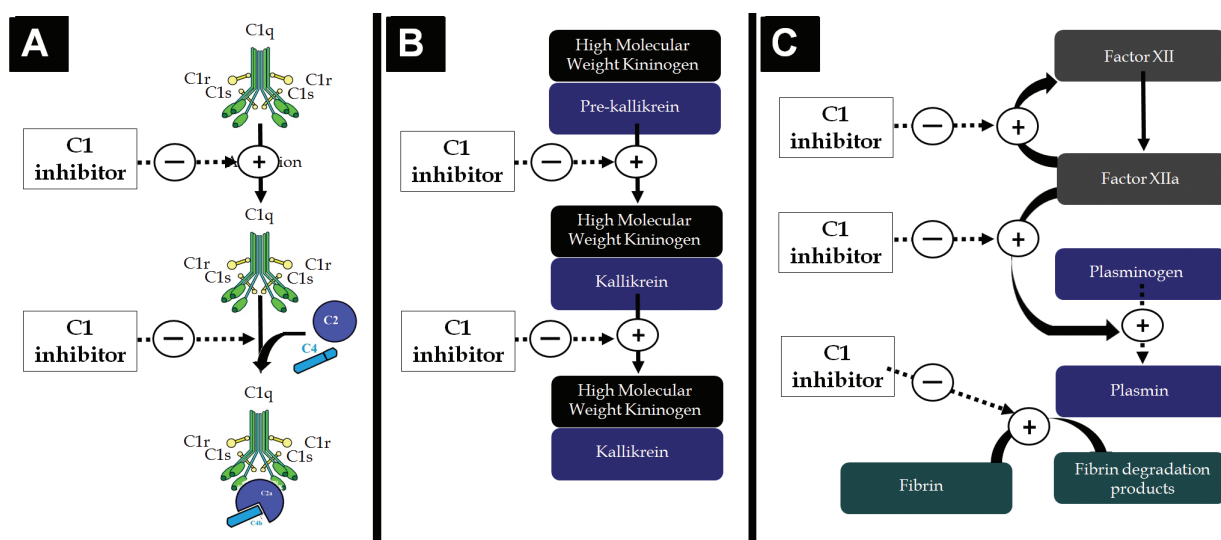


Figure 2. C1-INH regulates different pathways: (A) complement system, (B) contact system, and (C) fibrinolysis system.

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

preventing possible tissue damage [15, 16]. This set of molecules, those involved in the activation and the regulators (distinguishing between “triggers” —those able to bypass control systems—and “nontriggers”), is called the “complement system.” The need for both “amplification” and “regulation” with strict control gives an idea of the complexity of the “Complement System.”

5. Description of the complement system:

5.1. Alternative pathway of the “complement system”

We begin with the description of this pathway, which although referred to as “alternative” is phylogenetically older than the “classical pathway.” It does not require the presence of antibodies (Abs) for activation, thus constituting an important defense in the early stages of infection, when there are no significant amounts of Ab synthesized. Continuously “at rest,” it operates at a low level, and it is amplified in the presence of certain factors. So we can differentiate as follows:

(a) Alternative pathway “resting,” “idle,” or “pacemaker”

- (1) In normal plasma conditions (absence of infection), the internal thioester bond of the C3 fraction is spontaneously hydrolyzed in a low ratio with a water molecule (H_2O) forming the complex $C3(H_2O)$, also referred to as “C3i” (“tick-over” or “idle” activation) (**Figure 3**).
- (2) $C3(H_2O)$ or “C3i”: It binds to factor B, forming the $C3(H_2O)B$ complex, also referred to as “C3iB.” Factor B is equivalent to the C2 factor of the classical pathway detailed later.
- (3) The D factor acting on the $C3(H_2O)B$ complex, breaking fraction B and generating subproducts B1 and C3iBb.
- (4) The C3iBb complex acts as a “C3 convertase” in fluid phase cleaving C3 into C3a and C3b*.
- (5) The “C3b*” in fluid phase is hydrolyzed by water inactivating it. However, if by some chance the “C3b*” bonds covalently to an external surface (“recognition of the strange”), the “amplification of the alternative pathway” would occur. It is said that “C3b*” does not start this amplification within the body due to regulatory proteins that prevent it, such as the following:
 - a. Factor H binds to C3b*, attaching to the cytoplasmic membranes.
 - b. Factor I breaks the C3, displacing Factor H that returns intact to serum (would be ready to start its action again).
 - c. Factor I inactivates the free C3b bound to the cytoplasmic membrane itself (iC3b).
 - d. Factor I cleaves iC3b into C3c (small fragment in solution) and C3dg (inactive larger fragment bound to membrane).

(b) “Amplification” of the alternative pathway (“positive feedback loop”)

- (1) The “C3b*” binds covalently to an external surface (“recognition of the strange”) that amplifies in such a way that many C3b molecules anchor (**Figure 3**).
- (2) The membrane-bound C3b binds to Factor B, forming the C3bB complex.
- (3) Factor D (with serine protease activity) acts on C3bB, breaking the bound “B,” releasing Ba and forming the active C3bBb complex.
- (4) The C3bBb complex (with C3 convertase activity in Bb) is quickly dissociated, unless it is stabilized by binding to the host Factor P (also called “properdin”), forming the stable complex C3bBbP (the C3 convertase bound to alternative pathway membrane).
- (5) The C3bBb complex produces rupture of numerous C3 molecules, whose C3b fragments bind near the same membrane-bound convertase.
- (6) Such “feedback loop” is also activated by the C4b2a complex (C3 convertase) of the classical complement pathway.

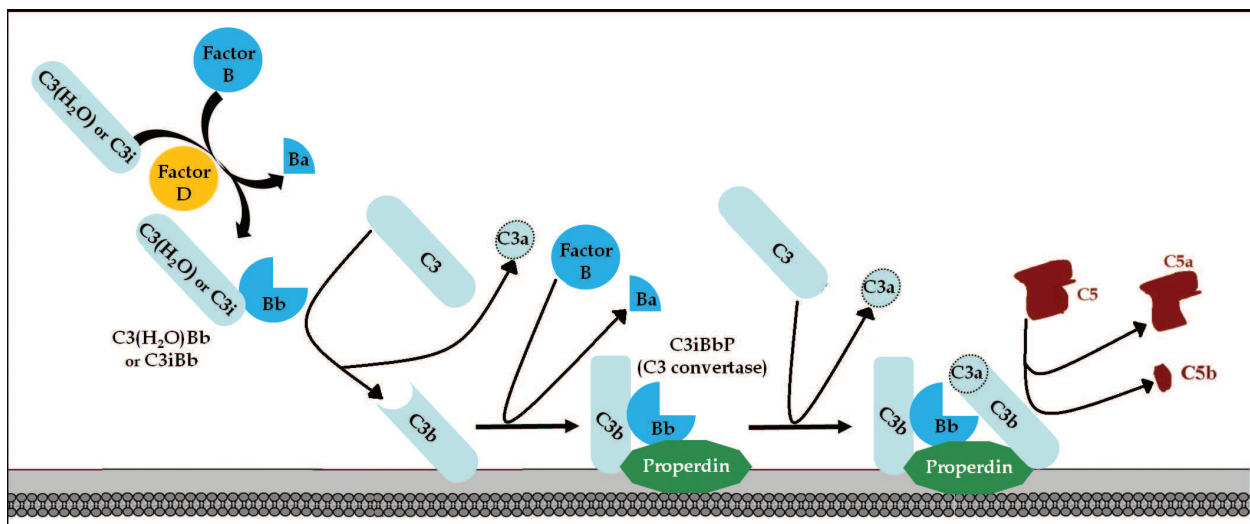


Figure 3. Alternative pathway activation of the complement system.

5.2. Classical pathway of the “complement system”

1. Activation of the complement system via the classical pathway requires the formation of the antigen-antibody complex (Ag-Ab), being the Ab of the subisotypes IgM, IgG1, IgG2, or IgG3. This interaction gives rise to conformational changes in the Fc fragment of immunoglobulin (Ig) generating an attachment site for the C1 fraction in the C_γ2 domain (constant part “2” of the IgG heavy chain) or the C_μ3 domain (constant part “3” of the IgM heavy chain).

2. The C1 fraction of the complement system is composed of five subunits: a "C1q" subunit (stem with six helical arms, three copies of a fundamental unit in a "Y," which in turn consists of two groups of three chains each together form a triple helix), two C1r subunits (arranged resting on the two arms of C1q), and two C1s subunits (arranged resting on the two arms of C1q, whose catalytic domains are arranged toward the center), stabilized by the Ca^{++} cation.
3. The C1q fraction is capable of binding to the Fc region of immunoglobulins provided they form part of immunocomplexes, such that
 - a. It can bind to two or more IgG molecules through the $\text{C}\gamma_2$ domain when bound to the same Ag molecule (several IgG molecules are part of the same immunocomplex). IgG has only one binding site per molecule, so at least two IgG molecules are necessary to activate the complement system.
 - b. It can bind to two or more $\text{C}\mu_3$ domains of different pentameric IgM subunits. The free pentameric IgM is "flat" but on binding to Ag, the Fab arms adopt angles with the Fc portions (in the "staple" configuration), and then C1q can bind to different monomers of the same pentameric IgM. The IgM exposes more adhesion sites when it is in "staple" configuration, explaining why the IgM is more likely to activate the complement system.
4. Binding of multiple domains of the same C1 complex induces a conformational change that activates a "C1r" molecule by autocatalysis, which in turn activates the other "C1r" molecule. Once activated, the two "C1r" molecules exert hydrolysis of both C1s molecules to be activated, which is when they possess serine esterase activity.
5. The binding of several globular domains of the same C1 complex appears to induce a conformational change in this, which involves the activation of a C1r molecule by autocatalysis; in turn, this activated C1r activates the other C1r molecule. The two active molecules exert C1r hydrolysis of the two C1s, whereby they are activated: the two active C1s possess serine esterase activity (**Figure 4**).
6. C1s has two substrates: C2 and C4. Note at this point the regulatory role of the C1 inhibitor (C1-INH) molecule. A deficiency in this would result in uncontrolled activation of C1s acting on C2 and C4, with the consequent decrease in the levels of these two complement fractions that is apparent in patients with C1-INH-HAE:
 - a. C1s bind to C4, producing two fragments: C4a (small fragment that diffuses into the plasma) and C4b (large fragment that binds to the membrane of the "target cell"). The C4a fraction is an "anaphylotoxin" that has importance later in this chain.
 - b. C1 finds a binding site on C4b, and like everything around C1s is cleaved into two fragments: C2a (large fragment attached to C4b) and C2b (small fragment that diffuses into the plasma).
7. The C4bC2a complex (formed by the C2a and C4b bond) is called "C3 convertase" since it activates C3 in fragments C3a and C3b (**Figure 5**):

- a. The intact C3 fraction has a very stable internal thioester bond between a cysteine and a glutamine (product of posttranslational modification) whose half-life is close to 600 h.
 - b. The C4bC2a complex catalyzes the proteolytic cleavage of C3 near the amino terminus of the α chain, with generation of the C3a and C3b fraction*.
 - c. The unstable C3b* component has the very unstable thioester bond, whose half-life is only 60 μ s because it is susceptible to nucleophilic attack (this is due to the negative charge of sulfur ($-S^-$), while carbon remains as carbonyl group ($-C^+=O$)).
 - d. A nearby nucleophilic group belonging to protein or cell surface carbohydrate reacts with the electrophilic C3b* carbonyl group, resulting in covalent bond (by $-CO-O-$) between the C3b and the cell surface.
 - e. The C3a fraction is an “anaphylotoxin” that will be important later in this chain.
 - f. Note that it is able to generate “tens” of C3b fragments, which is why this step is considered an “amplifier.” However, not all “C3b” generated participate in the complement pathway since a portion diffuses into the plasma functioning as an “opsonizing agent.”
8. The C3b fraction binds to C4bC2a, forming the C4b2aC3b complex, called “C5 convertase,” as the portion of the C3b fraction of this complex binds to C5, hydrolyzing it into C5a and C5b. The C5a fraction is an “anaphylotoxin” that will be important later in this chain. The C5b fraction is a key element for the formation of the membrane “attack complex” (Figure 3). This step is already part of the “final common lytic pathway” between the “classical pathway” and “lectin pathway.”

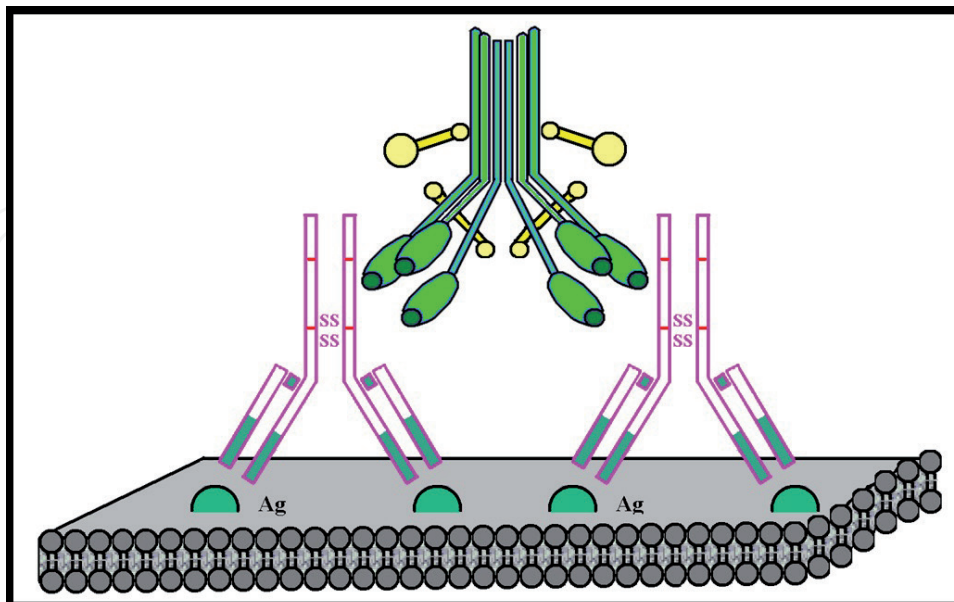


Figure 4. Classical pathway activation of the complement system, showing the binding of the C1q subunit to the Ig Fc, which is bound in turn to the cell membrane.

5.3. Lectin pathway of the “complement system”

The lectin pathway is a third way of complement system pathway activation different from the classical activation of C2 and C4 fractions (**Figure 6**). It starts with the action of the “mannan-binding protein” (MBP), which is structurally very similar to the C1q fraction (hexamers with 18 identical polypeptide chains coiled in groups of 3) and can bind two C1r subunits and two C1s subunits. However, it brings its own serine protease (called MASP) with 40% homology to C1r or C1s. MBP binds preferentially to the ends of mannose, fucose, and glucosamine of glycoproteins or polysaccharides present in the bacterial membrane. In a similar manner as described in the “classical pathway” with C1q2r2s complex, when MBP binds to carbohydrates it undergoes a conformational change, which in turn activates the serine protease (MASP). Activated MASP acts sequentially on C2 and C4 fractions to produce the “C3 convertase of the classical pathway.”

MASP-1 has been recently shown to cleave bradykinin from HMWK [17] and its levels, together with the complex MASP1-C1-INH, have been related to disease severity in C1-INH-HAE [18].

5.4. Common final pathway of the “complement system”

The three activation pathways of the complement system (the classical pathway, the alternative pathway, and the lectin pathway) converge in a common final lytic pathway. The C5b, C6, C7, C8, and C9 fractions participate in the final lytic complement pathway and form a molecular structure known as “membrane attack complex” (MAC) (**Figure 7**).

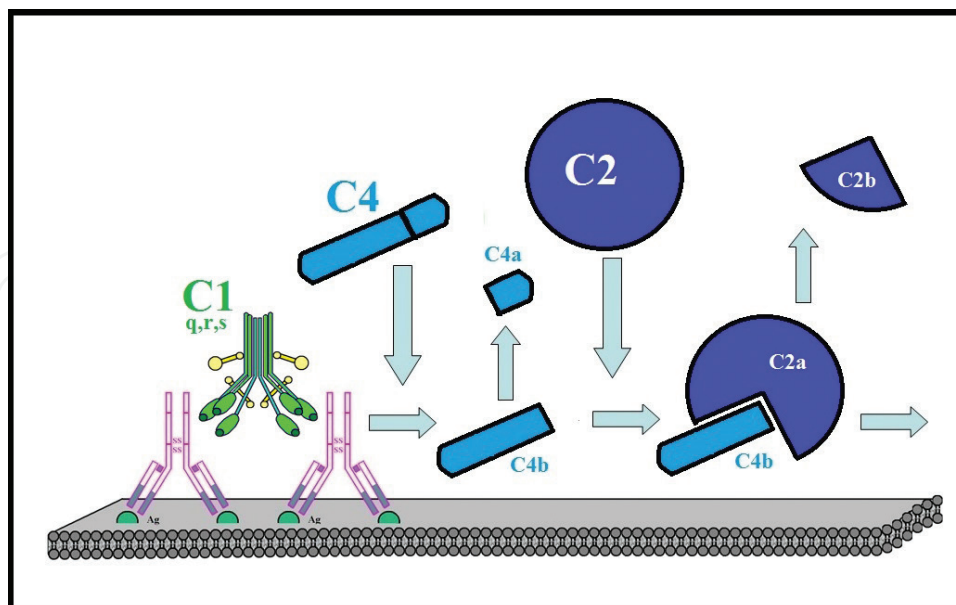


Figure 5. Classical pathway for the activation of the complement system, where the formation of the C1qrs complex until the formation of the C3b molecule can be observed.

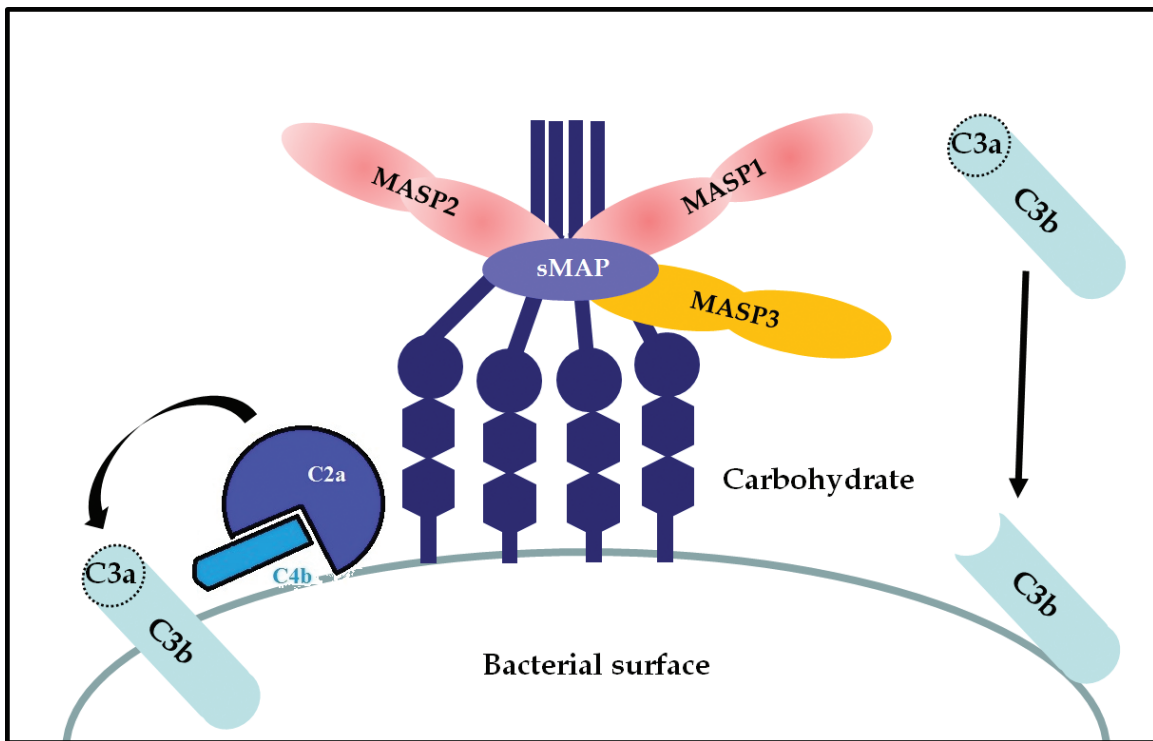


Figure 6. Lectin pathway for the activation of the complement system.

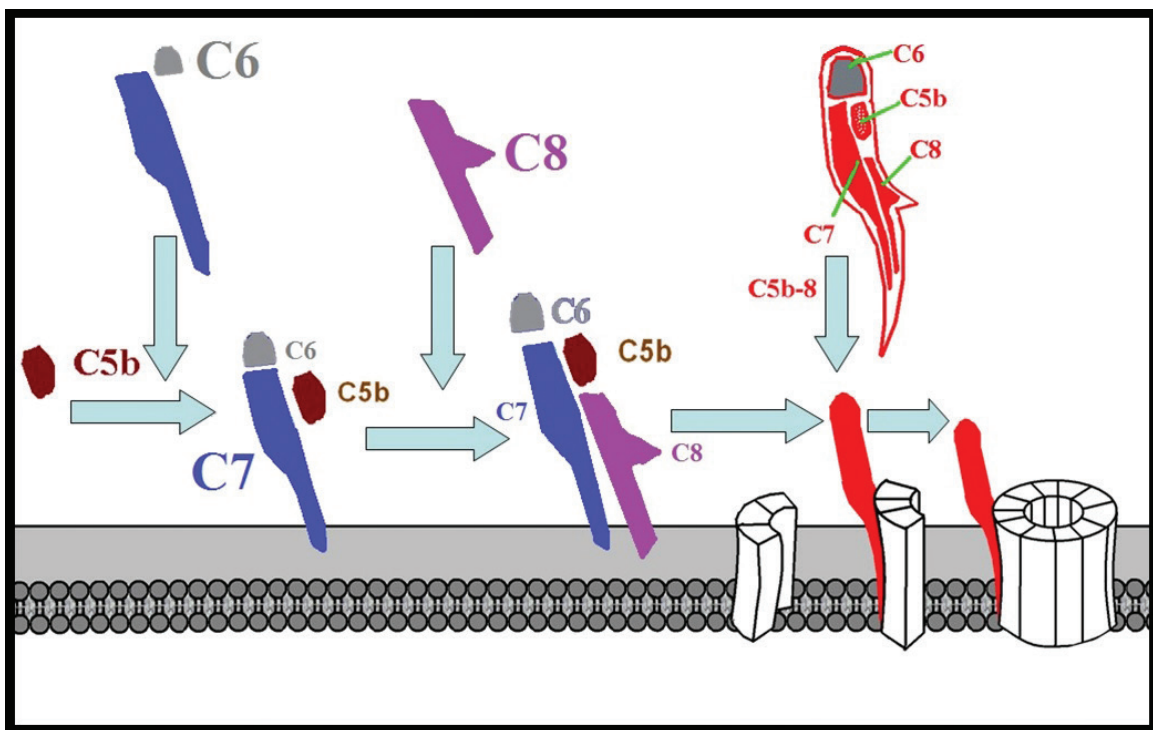


Figure 7. Major events in the lytic pathway cell membrane leading to the C9 polymerization and pore formation in the cell membrane.

MAC insertion into the cytoplasmic membrane causes an intercellular-extracellular communication pore with consequent ion exchange leading to cell death. The sequential steps are as follows:

1. As already mentioned, the final stage of the three activation pathways is common and consists in the formation of the “C5 convertase” that breaks the C5 fraction and triggers the appearance of the “membrane attack complex” (MAC). The steps at every pathway are as follows:
 - a. The “classical pathway”: the C4b2aC3b complex catalyzes the cleavage of C5 into C5a and C5b.
 - b. The “lectin pathway”: the C4b2aC3b complex catalyzes the cleavage of C5 into C5a and C5b.
 - c. The “alternative pathway”: a covalent attachment of a “new” C3b that forms part of the “C3 convertase,” forming the C3bBb3b complex.
2. C5b binds to the cytoplasmic membrane hydrophilic region.
3. C5b binds to C6, forming the C5bC6 complex.
4. C5bC6 binds to C7, forming C5bC6-7 complex, which has already hydrophobic regions that are capable of penetrating into the inner section of the lipid bilayer.
5. C5bC6-7 binds to C8, forming C5bC6-7-8 complex, which is capable of forming a 10 Armstrong pore capable of destroying erythrocytes but not able to destroy nucleated cells.
6. C5bC6-7-8 binds to about 14 C9 units to form the C5b-C6-7-8-poli9 complex (or MAC), which is capable of forming a 70–100 Armstrong pore by contacting the intracellular with the extracellular medium with the subsequent ion and water exchange, leading to cell death.

6. Complement disorders

Complement disorders have been traditionally linked to immunodeficiency and associated with severe or frequent infections. More recently, complement has been recognized for its role in inflammation, autoimmune disorders, and vision loss [19]. The identification of hereditary and acquired complement deficiencies in humans has led to a better understanding of the biologic importance of the complement system in immunity and autoimmune disease (**Table 2**).

Complement protein	Gene (chromosome)	Effects of deficiency (commonly associated infections)
C1q	1p36.12 (A, B, and C chains)	Immune-complex disease Meningitis, pneumonia, sepsis (<i>Streptococcus pneumoniae</i> , <i>Neisseria meningitidis</i>)
C1r	12p13.31	Meningitis, pneumonia, sepsis (encapsulated bacteria)

Complement protein	Gene (chromosome)	Effects of deficiency (commonly associated infections)
C1s	12p13.31	Meningitis, pneumonia, sepsis (encapsulated bacteria)
C1-INH	11q11-q13.1	C1-INH-HAE
C2	6p21.33	Immune-complex disease Meningitis, osteomyelitis, pneumonia, sepsis (<i>Staphylococcus aureus</i> , <i>Streptococcus pneumoniae</i> , <i>Neisseria meningitidis</i>)
C3	19p13.3	Respiratory tract infections (<i>Haemophilus influenzae</i> , <i>Streptococcus pneumoniae</i> , <i>Streptococcus pyogenes</i> , <i>Neisseria meningitidis</i>)
C4	6p21.33 (Rodgers blood group and Chido blood group)	Immune-complex disease Meningitis, pneumonia, sepsis (encapsulated bacteria)
C5	9q33.2	SLE-like symptoms Meningitis, sepsis (<i>Neisseria meningitidis</i>)
C6	5p13.1	SLE-like symptoms MPGN Meningitis, sepsis (<i>Neisseria meningitidis</i>)
C7	5p13.1	Scleroderma, rheumatoid arthritis, and an SLE-like syndrome Meningitis, sepsis (<i>Neisseria meningitidis</i>)
C8	1p32.2 (alpha chain) 1p32.2 (beta chain) 9q34.3 (gamma chain)	Meningitis, sepsis (<i>Neisseria meningitidis</i>)
C9	5p13.1	Meningitis, sepsis (<i>Neisseria meningitidis</i>)
Factor D	19p13.3	Meningitis (<i>Neisseria meningitidis</i>)
Factor H	1q31.3	Recurrent pyogenic infections (<i>Haemophilus influenzae</i> , <i>Streptococcus pneumoniae</i> , <i>Neisseria meningitidis</i>)
Factor I	4q25	Recurrent pyogenic infections (<i>Haemophilus influenzae</i> , <i>Streptococcus pneumoniae</i> , <i>Neisseria meningitidis</i>)
Factor P (properdin)	Xp11.23	Meningitis (<i>Neisseria meningitidis</i>)
MBL (or MBP)	10q11.2-q21	Respiratory tract infections
MASP2	1p36.22	Respiratory tract infections
CD59 (or MAC-IP, MAC-IP, protectin)	11p13	Autoimmune-like conditions including paroxysmal nocturnal hemoglobinuria
DAF (or CD55)	1q32.2	Autoimmune-like conditions including paroxysmal nocturnal hemoglobinuria

C1-INH-HAE = hereditary angioedema with C1 inhibitor deficiency; CD59 = cluster of differentiation 59; MAC-inhibitory protein (MAC-IP), membrane inhibitor of reactive lysis (MIRL) or protectin; DAF = complement decay-accelerating factor; MASP2 = manna-binding lectin serine protease 2 (also called mannan-binding protein-associated serine protease 2); MBL = mannose-binding lectin (also called mannose-binding protein or mannan-binding protein (MBP)); MPGN = membranoproliferative glomerulonephropathy; SLE = systemic lupus erythematosus.

Table 2. Clinical significance of complement deficiencies [20–24].

7. Classification of angioedema due to functionally active C1 esterase inhibitor protein (C1 inhibitor) deficiency

Functionally active C1-INH deficiency can be hereditary or acquired. The hereditary form is a primary immunodeficiency [25] and is the most common genetic defect of the complement system [26]. The absence or malfunction of C1-INH results in the presence of attacks of AE (subcutaneous or mucosal swelling) due to uncontrolled activation of the contact system, with the generation of bradykinin, a vasoactive peptide released from HMWK [9].

7.1. Hereditary angioedema

C1-INH-HAE is a genetic autosomal dominant disease characterized by a deficiency of the functionally active C1 esterase inhibitor (C1 inhibitor) protein. Initially, it was believed that it affected one individual per 10,000–150,000 people, but being a rare disease it makes an estimate of prevalence difficult to pinpoint [27]. It could affect around 2000–3000 people in the USA [28]. There is a register of patients in Spain where the minimum prevalence is 1.09 per 100,000 inhabitants [29], while another register in Denmark describes a prevalence rate of 1.41 per 100,000 inhabitants [30]. The highest published prevalence is in Norway with 1.75 per 100,000 inhabitants [31]. Delays in diagnosis (an average of 13.1 years in the Spanish study) [29] along with the possibility of misdiagnosis and lack of recognition of the disease may mean that the true prevalence may be higher than estimates suggest. To date, no studies have shown differences in prevalence between ethnic groups.

Two phenotypic variants were described [32, 33]. *Type I* (HAE-I) is the most common (85%), characterized by a quantitative decrease of C1-INH, which results in a decrease in functional activity; *type II* (HAE-II) (15%) is characterized by normal or elevated levels of dysfunctional C1-INH. In both cases, the defect is transmitted as an autosomal dominant form, although with different genetic alterations. There is another estrogen-dependent hereditary AE variant in which both levels and function of C1-INH are normal and which has been called HAE *type III* [34, 35].

7.2. Acquired angioedema

C1-INH-AAE is biochemically characterized by low C1-INH concentrations and/or functions and no evidence of heredity. It is mainly associated with B cell lymphoproliferative disorders and occasionally with autoimmune, neoplastic, or infectious diseases [14]. Initially, it was classified into two types: type I, with most patients having an associated B cell line malignancy; type II, there were anti-C1-INH autoantibodies that interfered with C1-INH functional activity [36]. C1-INH production is normal or slightly increased. In many patients with type I, the paraproteinemia or M component actually behaves as an anti-C1-INH autoantibody, so some authors such as Cicardi suggest that the distinction between types I and II may be artificial [37].

Acquired C1-INH deficiency is characterized by the activation of the classical complement pathway and accelerated catabolism of C1-INH and the activation of the contact system [9]. This results in low C4 and C2 levels and normal C3 levels in plasma. C1q levels are frequently

very low in C1-INH-AAE and this feature is frequently used to differentiate the acquired from the hereditary form of C1-INH deficiency [14].

8. Bradykinin as common final mediator of “bradykininergic” angioedema

8.1. Formation of bradykinin

BK is a linear nonapeptide (with sequence Arg1-Pro2-Pro3-Gly4-Phe5-Ser6-Pro7-Phe8-Arg9) produced endogenously in humans and other mammals as a result of the proteolytic activity of kallikrein on kininogens [38, 39].

Kallikreins belong to serine proteases and fall into two groups: tissue and plasma kallikreins. Within the tissue kallikreins, a family of 15 proteins is true kallikrein (hk1) and prostate-specific antigen (PSA or hk3) [39–41]. Plasma kallikrein is involved in processes that initiate coagulation especially during the activation phase due to contact with negatively charged surfaces. The plasma and tissue kallikreins release vasoactive peptides known as kinins implicated in biological processes such as the relaxation of vascular smooth muscle (hypotension), increased vascular permeability, smooth muscle contraction of the bronchial tree, and pain [39–41]. This peptide family produces BK release due to plasma kallikrein action on the HMWK, while it also releases Lys-bradykinin (Lys-BK) by the action of tissue kallikrein hk1 on low-molecular-weight kininogen (LMWK) [39–41] (**Figure 8**).

8.2. Other forms of angioedema with activation of the contact system

HAE *type III*, described in 2000 by two independent research groups [35, 42], has been also named as hereditary angioedema with normal C1-INH (nC1-INH-HAE) [7]. A subgroup of patients with nC1-INH-HAE (approximately 30%) has a mutation in exon 9 of *F12* gene [7] and this type of AE is known as FXII-HAE [7]. The rest have not known mutation and are known as unknown-HAE (U-HAE) [7].

FXII is a protease involved in the activation of the coagulation and contact systems and these mutations found in *F12* gene in patients with FXII-HAE have been shown to produce hyperactivity of coagulation factor FXII, with the consequent activation of the contact system [43].

8.3. Inhibition of bradykinin-metabolizing enzymes

Once produced, kinins are rapidly metabolized by metallopeptidases: neutral endopeptidase (NEP), angiotensin-converting enzyme (ACE), dipeptidyl peptidase-IV (DPP-IV), aminopeptidase P (APP), carboxypeptidases (CPN, CPM), and endothelin-converting enzyme-1 (ECE-1). Dendorfer et al. [44] described the metabolic pathways of BK degradation in murine models. In human plasma, BK is cleaved on the Pro7-Phe8 and Phe8-Arg9 bonds by the action of the two largest kininases: ACE and CPN [45]. Besides, in the 1960s it was reported that carboxypeptidase A cleaved the Pro7-Phe8 bond [46], while carboxypeptidase B cleaved the

Phe⁸-Arg⁹ bond [46]. Generally, carboxypeptidases remove Arg⁹ (carboxyl terminus) from the kinin molecule. Although NEP plays an important role in the kidney and epithelium, unlike ACE it barely exerts its action in plasma. APP cleaves BK in the Arg¹-Pro² bond [47]. NEP and ACE cleave BK at the Pro⁷-Phe⁸ bond (releasing the dipeptide Phe⁸-Arg⁹) [48]; NEP further cleaves the Gly⁴-Phe⁵ bond and ACE in the Phe⁵-Ser⁶ bond [48].

The following drug classes can cause acute AE by inhibition of the BK-metabolizing pathway (Figure 8):

- ACE (EC 3.4.15.1) inhibitors: lisinopril, captopril, enalapril, and ramipril.
- DPP-IV (EC 3.4.14.5) inhibitors: sitagliptin, vildagliptin, saxagliptin, alogliptin, and linagliptin.
- APP (EC 3.4.11.9) inhibitors: apstatin [49].
- CPN and CPM inhibitors.
- NEP, also known as neprilysin (EC 3.4.24.11) inhibitor: SQ29072 [50], SCH39370 [51], candoxatrilat [52], phosphoramidon [53], BP102 [54], and ecadotril [55].
- ECE-1 (EC 3.4.24.71) inhibitor: CGS35066 [56].
- Dual inhibitor of NEP and ACE: omapatrilat [57], fasidotril [58], sampatrilat [59], and mixanpril [60].
- Dual inhibitor of NEP and ECE-1: SLV-306 [61], S-17162 [62], CGS 26303 [63, 64], CGS 26393 [65], CGS 31447 [66], WS 75624B [67], B-90063 [68], CGS 34226 [69], and CGS 34043 [70].
- Triple inhibitor of ECE-1, NEP, and ACE: CGS 35601 [71–73] and CGS 37808 [74].

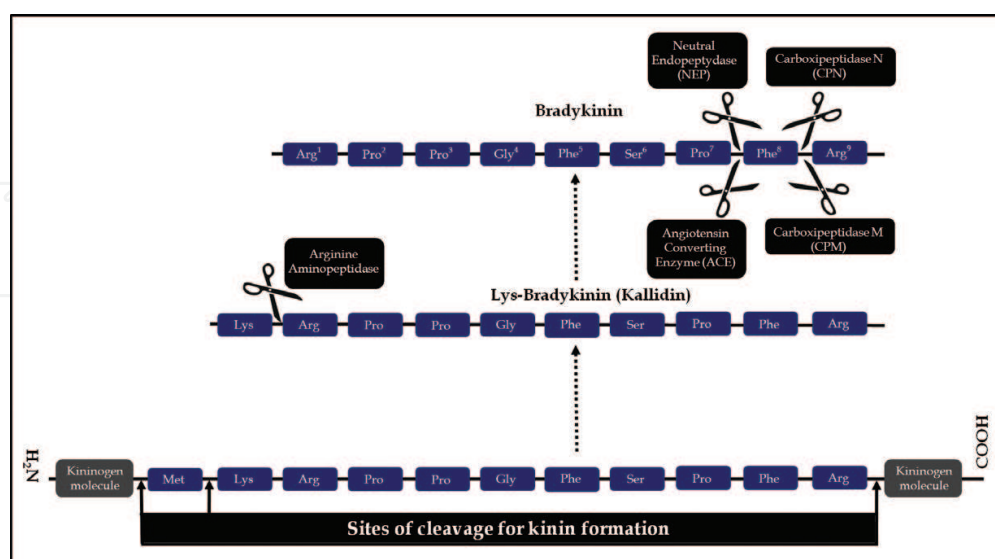


Figure 8. Formation of kinins in plasma and tissues. Each kinin is formed from kininogen by the action of a different enzyme.

8.4. Bradykinin receptor ligands

The biological effects of kinins involve the activation of specific receptors on the surface of the target cell. At least two different kinin receptors are known [75, 76]: BK receptor B1 (bradykinin receptor B1, also known as BDKRB1, B1R, BKR1, B1BKR, BKB1R, and BRADYB1) [77], which is coded in region 14q32.1-q32.2, and BK receptor B2 (bradykinin receptor B2, also known as BDKRB2, B2R, BK2, BK-2, BKR2, and BRB2) [78], which is coded in region 14q32.1-q32.2.

BKR1 binds and is activated by des-[Arg⁹]-bradykinin (DBK) and des-[Arg⁹]-Lys-bradykinin (Lys-BK), formed by the action of carboxypeptidases on Lys-BK and BK, respectively [79].

BKR1 is expressed in low amounts on normal physiological conditions in smooth muscle of blood vessels being regulated additively by inflammation [75, 79]. During stressful situations (trauma, tissue pressure, or inflammation with increase of IL1 β or TNF α) [80, 81], the effects on BKR1 can predominate.

On the contrary, BKR2 binds selectively with BK and kallidin, mediating most of the effects of the contact system activation in the absence of inflammation.

Antagonists have been developed for both types of receptors, such as des-[Arg⁹]-bradykinin-Leu⁸ for BKR1 and HOE140 (icatibant acetate) for BKR2 [82]. Icatibant acetate has been shown to be effective for the treatment of acute AE attacks in C1-INH-HAE [7, 8, 83].

In summary, most of the biological effects of kinins are mediated by BKR2 and under conditions of inflammation or tissue damage there is induction of BKR1 [84] (**Figure 9**).

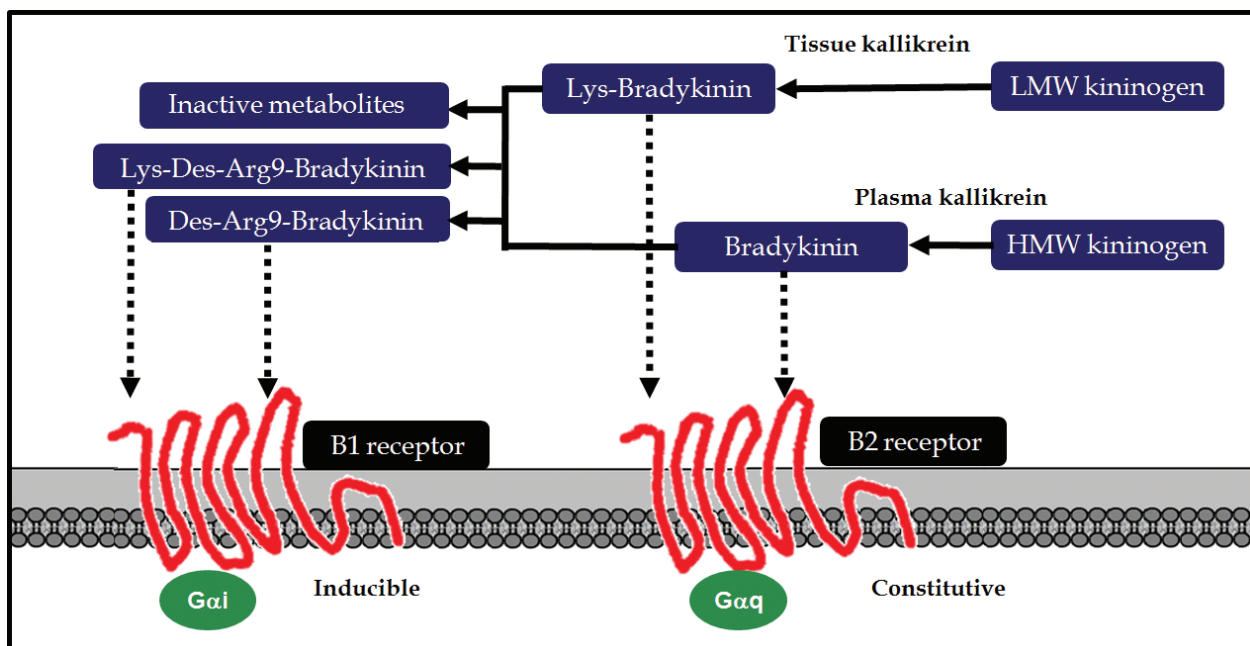


Figure 9. Bradykinin receptor ligands.

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 BKR1 interacts with Gq and Gi proteins, using the same signaling pathways as BKR2 (Figure 10).

BKR2 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 Ca^{++} ions it translocates to the cell membrane to exert its function of protein kinase in serine and threonine

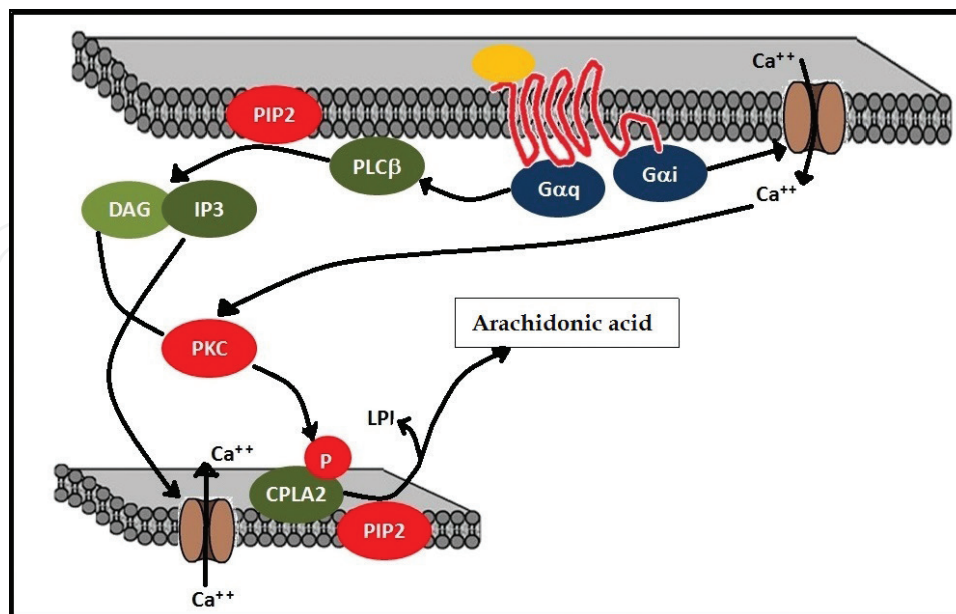


Figure 10. Bradykinin receptors and G-protein-coupled receptor-signaling pathway.

amino acids. BK has been shown to activate a Ca^{++} -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 transiently 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 hyper-activability.

BK (common final mediator of BK-AE) is a linear nonapeptide (with sequence Arg1-Pro2-Pro3-Gly4-Phe5-Ser6-Pro7-Phe8-Arg9) produced endogenously in humans and other mammals as a result of the proteolytic activity of kallikrein on kininogens.

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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