

Hereditary angioedema: a bradykinin-mediated swelling disorder

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Summary

Edema is tissue swelling and is a common symptom in a variety of diseases. Edema form due to accumulation of fluids, either through reduced drainage or increased vascular permeability. There are multiple vascular signalling pathways that regulate vessel permeability. An important mediator that increases vascular leak is the peptide hormone bradykinin, which is the principal agent in the swelling disorder hereditary angioedema. The disease is autosomal dominant inherited and presents clinically with recurrent episodes of acute swelling that can

be life-threatening involving the skin, the oropharyngeal, laryngeal, and gastrointestinal mucosa. Three different types of hereditary angioedema exist in patients. The review summarises current knowledge on the pathophysiology of hereditary angioedema and focuses on recent experimental and pharmacological findings that have led to a better understanding and new treatments for the disease.

Keywords

Contact phase, inflammatory mediators, proteases, SERPINS

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Hereditary angioedema

Hereditary angioedema (HAE) is a rare inherited disease, which is clinically characterised by recurrent acute swelling episodes resulting from increased vascular permeability. There are about 5,000 affected individuals in Europe. The mechanisms that result in increased vessel leak in HAE are controversial; however, excessive bradykinin (BK) formation due to pathological activation of the factor XII (FXII)-driven plasma contact system is a consistent finding in acute episodes of HAE. BK belongs to the kinin family and initiates signalling cascades that increase vascular permeability and induce tissue swelling. Plasma levels of the peptide hormone are elevated during the swelling attacks (1-5). HAE patients either carry mutations in the C1 esterase inhibitor (C1INH) protein (which is the major inhibitor of the plasma contact system proteases, HAE types I and II) or have a mutation in the protease factor (FXII) (that is the principal initiator of the plasma contact system, HAE type III). Plasma level of C1INH is reduced in HAE type I whereas a dysfunctional protein circulates in type II patient plasma. Clinical symptoms and swellings are largely similar among the various HAE types. Additionally, there are inherited HAE forms that are not linked to known mutations in C1INH or FXII. The identification of the disease-associated defects in these families awaits future investigations. Urticaria (itching) is not a typical feature in HAE patients, indicating that histamine is not of critical importance for the pathology of the disease (6). It is often

challenging to diagnosis HAE due to variations in the clinical presentations. The swellings in HAE patients are highly variable regarding triggering factors, severity, frequency, and localisation.

Generation of kinins

Kinins are short-lived hormones that induce many characteristics of an inflammatory state, such as changes in blood pressure and vasodilation, pain sensations, leukocyte adhesion, and increased microvascular permeability (5). Kinins form a family of vasoactive peptides comprising BK, kallidin (Lys-BK) and their degradation products, respectively. Kinins are produced by two principal pathways: the nonapeptide BK is released by limited proteolysis from its precursor High-molecular-weight kininogen, (HK) by FXII-activated plasma kallikrein (PK) on cell surfaces (7-9). In contrast to inducible generation of BK, the decapeptide kallidin is constitutively produced by tissue kallikrein (TK) predominantly from its substrate low-molecular-weight kininogen (LK). HK and LK are splice products of the same gene (10) and accordingly kallidin and BK share the identical peptide-sequence with kallidin having one additional Lysine residue at its N-terminus. *In vitro*, kallidin can be rapidly converted to BK by kinin converting aminopeptidases, which cleave the N-terminal lysine residue (11) (► Figure 1).

Kininogens and kallikreins are proteins of the plasma contact system that encompasses FXII, and C1-esterase inhibitor (C1INH)

the major inhibitor of activated PK and FXII (12-14). The plasma contact system is a protease cascade that assembles on cell surface heparan- and chondroitin-sulfate type proteoglycans (15, 16). Other proteins such as the p33/gC1qR that lacks a transmembrane domain but bears a mitochondrial targeting sequence and is involved in mitochondrial energy metabolism have been reported to bind HK. Overexpression of heparan sulfates largely increases HK cell binding. In contrast, overexpression of p33/gC1qR does not increase HK binding to transfected cells, challenging the *in vivo* relevance of p33/gC1qR as receptor for HK (15). BK production is started by FXII coming in contact to surfaces. FXII zymogen binding to negatively charged surfaces induces a conformational change in the molecule resulting in FXII activation (autoactivation). Activated FXII (FXIIa) cleaves surface associated plasma prekallikrein to generate PK, which in turn reciprocally activates further FXII molecules, thereby amplifying the initial signal (17). Plasma prekallikrein and PK are surface-bound via HK. In a complex with its substrate HK, PK cleaves the HK peptide bond Arg371-Ser372 at the C-terminus of the BK sequence (17). The proteolytic step generates a two-chain HK form and BK remains attached to the C-terminal end of the HK heavy chain (18). A subsequent second PK-mediated cleavage at Lys362-Arg363 liberates BK from the heavy chain (19). Under physiological conditions, C1INH controls proteolytic activity of the contact system cascade by inactivating FXIIa and PK-mediated BK generation (14). C1INH is a member of the serpin protein family, which inhibits contact system proteases by irreversible binding to their enzymatic pockets (14). In addition to the BK-producing kallikrein-kinin system (7, 17) the FXIIa-driven contact system triggers other plasma protease cascade such as the intrinsic pathway of coagulation, the fibrinolytic and the complement systems (17, 20).

Despite having a similar name, TK is nor structurally neither evolutionary related to PK (21). TK activations occur intracellularly by evolutionary proteolysis of the serine protease precursor, tissue prekallikrein. However, the enzyme responsible for the conversion *in vivo* has not been identified yet (22). Two candidate enzyme classes that have the capacity for activating tissue prekallikrein *in vitro* are serine proteases (trypsin, plasmin, PK or tissue kallikreins), and metalloproteinases (thermolysin) (23). Tissue-type kallikreins form a large multigen family of structurally and functionally related serine proteases that are differentially expressed in an organ-specific pattern (24).

LK is the principal substrate of TK. The entire LK heavy chain that is composed of domains D1-D4 and a short stretch of domain 5 are identical to sequences in HK. Compared to HK the light chain of LK is significantly shorter (626 vs. 409 residues) (25) and lacks the binding site for PK and FXI (12, 15, 26) that has been mapped to the extreme C-terminus of HK D6_H domain (12, 27). TK-driven kallidin production contributes to maintain arterial pressure homeostasis (28). TK-deficient mice have reduced basal kinin levels and consistently arterial systolic blood pressure is elevated (29). Intraventricular injection of TK triggers kinin-mediated arterial hypertension in rodent brains, suggesting a function of TK for maintaining pressure homeostasis in the central nervous circulatory system (30).

Receptors, signalling pathways and degradation of kinins

Kinins are ligands of two distinct receptor types: kinin B2-receptor (B2R) and B1-receptor (B1R), respectively, are characterised by seven transmembrane-spanning helices and are coupled to G proteins in most cells of the G_{α_q} and G_{α_i} families (31, 32). B1R expression is inducible and is largely up-regulated by cytokines such as interleukin-1β (7, 11). Thus, B1R is exposed on cell surface in response to injury or inflammation. In contrast, B2R is constitutively expressed by various cell types, such as endothelial cells, vascular smooth muscle cells and cardiomyocytes (11). Ligand binding to B1R and B2R initiates signalling cascades that increase vascular permeability and fluid efflux in humans (4, 5, 33), rats (34), and mice (3). Kinins also activate various other pro-inflammatory signalling pathways such as vessel dilatation, prostaglandin E2 biosynthesis, and induction of chemotaxis of neutrophils (5, 11, 35).

Kinin-binding to B1R and B2R increases intracellular calcium ([Ca²⁺]_i) in smooth muscle and endothelial cells. [Ca²⁺]_i levels are raised through the phospholipase C pathway by inositol 3-phosphate (IP3) formation and consecutive InsP3R-mediated Ca²⁺ release from intracellular stores. [Ca²⁺]_i in turn can activate multiple signalling cascades, including the phospholipase A2 pathway that releases arachidonic acid that is converted to prostacyclins (e.g. PGI₂) in a cyclooxygenase-dependent manner. BK also triggers kinase C (PKC) activity (36) resulting in VASP-mediated disassembly of cortical cytoskeletons (37) and VE-cadherin junctions (38). Similar BK/VASP-dependent pathways may also contribute to angiogenesis (39, 40). Increase in [Ca²⁺]_i is a potent stimulator of endothelial nitric-oxide synthase (eNOS) resulting in NO-driven protein kinase G activity and VASP phosphorylation (41, 42). BK signalling increases Rac1-driven leakage (43). All these pathways have a role in BK-driven vasodilation and increased permeability (44).

Kininsases degrade kinins, and one of the major kininsases is kininase I (carboxypeptidase N) that removes the C-terminal arginine residue both from BK and kallidin. The resulting peptides des-Arg⁹-BK and des-Arg¹⁰-kallidin, respectively, do not longer bind to B2R. However, des-Arg⁹-BK and des-Arg¹⁰-kallidin are the principal agonists of B1R (33) (► Figure 1). Stimulation of B1R by des-Arg⁹-BK and des-Arg¹⁰-kallidin increases vascular leakage similarly as BK and kallidin binding to B2R (33).

Non-receptor bound kinins have short half-lives of <1 minute in plasma (11, 45) and are rapidly metabolised by multiple endo- and exopeptidases (46). The major kinin-degrading enzyme is kininase II, also known as angiotensin converting-enzyme (ACE). ACE cleaves BK at two sites to produce breakdown products such as the pentapeptide Arg1-Pro2-Pro3-Gly4-Phe5 and dipeptides Ser6-Pro7 and Phe8-Arg9. Kallidin is similarly processed to these dipeptides and the hexapeptide Lys-Arg-Pro-Pro-Gly-Phe (47). ACE generates biologically inactive kinin fragments (48) and eliminating kinin's activity for activating B2R or B1R (11, 48) (► Figure 1). Other kinin-degrading enzymes are aminopeptidase P, dipeptidyl peptidase IV and neutral endopeptidase (11).

Bradykinin formation in HAE

The detailed pathophysiology underlying increased vascular leak in HAE patients is not completely understood. In addition to FXIIa-driven BK generation other pathways such as the intrinsic pathway of coagulation, the complement, or fibrinolytic systems may contribute (49). Genetic ablation of C1INH expression results in excessive BK production, which increases vascular permeability in humans (50) and mice (51). Mouse models with combined deficiency in C1INH and kinin B2 receptors or treated with kinin receptor antagonists make the case that elevated vascular leakage in C1INH-dependent HAE forms is predominantly mediated by BK and due to aberrant B2R signalling (3). BK plasma levels are elevated in acute swelling attacks, whereas BK levels in HAE patients are similar to healthy control individuals in the interval (remission phase) (52). Further evidence that BK signalling mediates edema formation in HAE originates from ACE inhibitor therapy. ACE inhibitors block ACE activity and thus interfere with degradation of BK. ACE inhibitor treatment is an established trigger for edema in HAE patients (53), individuals with impaired BK-metabolism (54) and HAE mouse models (3). Furthermore, acute swelling attacks in HAE patients respond to infusion of plasma purified or recom-

binant C1INH, B2R antagonists and PK inhibitors suggesting that the contact system mediates pathological BK production (55). Together, these clinical, pharmacological and experimental findings make a strong case for BK being the principal if not exclusive mediator for acute swelling episodes in HAE (14).

HAE types

HAE (HAE [MIM #106100]) patients suffer from recurrent painful swelling episodes indicating that under some pathologic conditions the contact system gets activated. The underlying mechanisms for the BK-driven swelling episodes are not entirely understood but excessive BK-formation may be facilitated due to three distinct mechanisms: (i) hereditary deficiency in C1INH that is coded by the *SERPING1* gene, (ii) a dysfunctional C1INH or (iii) a gain of function mutation in FXII. All these defects increase the susceptibility for contact system-driven BK formation in HAE patients. The prevalence of HAE type I and II is 1 in 10,000 and 1 in 50,000 inhabitants, respectively, with no differences in prevalence in relation to gender and race, however there are no prevalence and incidence studies on HAE type III [pic](56). There are also multiple patients with inherited swelling symptoms that closely resemble HAE. So far no defined genetic or biochemical defect has been identified in these families suggesting that more HAE types than the currently known types exist.

Patients who are deficient in C1INH are diagnosed with HAE type I. Individuals who have a dysfunctional C1INH protein and "normal" C1INH antigen plasma level are classified as HAE type II (6, 57). HAE type I and II are transmitted in an autosomal dominant manner, and patients are heterozygous, except in few cases having consanguineous parents. The structural abnormalities of the *SERPING1* gene in HAE patients are heterogeneous, with more than 200 mutations registered, <http://hae.enzim.hu/>. A high prevalence of *de novo* mutations has been described. The mutations are different in the two HAE types. In type I, they are randomly distributed throughout the *SERPING1* gene and consist of point mutations, large rearrangements, including partial deletions and duplications (58-60). In contrast, most mutations involved in HAE type II are clustered in exon 8 of the *SERPING1* gene, which encodes the active center or hinge region of C1INH protein (61). In addition to these two classical types a third variant of HAE was recently described and termed HAE type III (62). HAE type III affects almost exclusively women and was originally epidemiologically associated with estrogen intake. Meanwhile few male patients with HAE type III have been identified questioning elevated estrogen levels to be causative for the disease (63). HAE type III patients have normal C1INH functions and plasma concentration (62) but present similar swelling symptoms as other HAE types. Using genome wide linkage analysis Cichon and coworkers showed that HAE type III is associated with a single point mutation in FXII, (Thr328Lys) which leads to increased FXII activity by unknown mechanisms (64). Others have identified another SNP affecting the same amino acid (Thr328Arg) that is found in some HAE type III families (63). In addition a *FXII* gene deletion

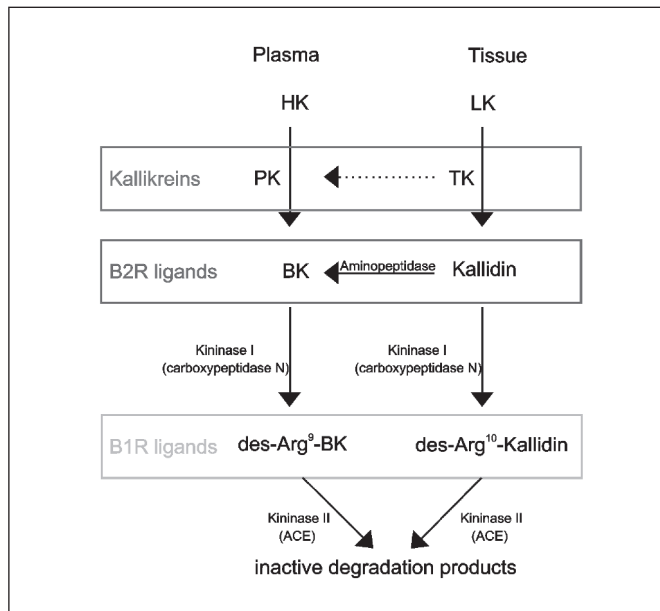


Figure 1: Schematic overview on kinin formation, signalling and degradation. High-molecular-weight kininogen (HK) and its splice product low-molecular-weight kininogen (LK) are substrates for plasma kallikrein (PK) and tissue kallikrein (TK) in plasma and tissues or other fluids, respectively. The kininogenases liberate the peptide hormones bradykinin (BK) and Lys-bradykinin (kallidin) by limited proteolysis of the precursor molecules. BK and kallidin activate kinin B2 receptors (B2R) and induce intracellular signalling cascades. Aminopeptidase activities convert kallidin to BK. Both BK and kallidin are further processed by kininase I to desArg⁹-BK and desArg¹⁰-kallidin, respectively, that are agonists for kinin B1 receptors (B1R). Further degradation of kinin hormones by kininase II results in inactive peptide fragments.

of 72 base pairs (starting at Lys324 on the protein level) was identified in a single HAE type III family. The FXII deletion was found in three family members two women and one man; however, it was only the women, who developed swellings (65). The mechanisms how FXII mutations that are not in the enzymatic domain of the protease result in a gain of FXII enzymatic function and edema formation warrant further analyses.

Endogenous contact system activators

HAE patients experience recurrent swelling attacks. One component of the disease mechanism is either a deficiency in functional C1INH (57) or a gain of function mutation in FXII (64). However these inherited defects do not fully explain the pathology of the disease. HAE patients suffer from swelling episodes indicating that under some specific pathological conditions the BK-forming contact system gets activated. Inherited mutations in the BK-forming cascades lower the threshold for triggering the protease reactions and thus edema. However, to initiate swelling episodes a second component is necessary: a triggering agent that starts the more susceptible FXII-driven contact system (► Figure 2). In contrast to C1INH and FXII mutations, the FXIIa-initiating stimuli are poorly defined (51, 66). A common feature of all known FXII activators is that they are negatively charged macromolecules. What is the endogenous trigger that initiates contact system-driven BK generation *in vivo*? Recently, several biologic substances have been shown to support FXII auto-activation *in vivo*, these include heparin released from mast cells (MC), misfolded protein aggregates and platelet polyphosphates (51, 66, 67). Extra cellular nucleotides activate FXII and drive the intrinsic coagulation pathway (68), whether RNA has the capacity for triggering BK formation *in vivo* is awaiting further analyses.

Heparin

Heparin is a linear, unbranched, and highly sulfated polysaccharide consisting of repeating disaccharide units that is exclusively stored in secretory MC granules. Heparin initiates formation of BK in an FXII-dependent manner (51). Minute amounts of heparin (<4 µg/ml) are sufficient to trigger FXII activation and to protect FXIIa from inhibition by C1INH. Heparin specifically activates the BK-forming kallikrein kinin-system. In contrast, the FXIIa-driven intrinsic pathway of coagulation is not activated by the polysaccharide (51). It is well established that MC and their mediators contribute to capillary leakage. Edema models in mice showed that MC-heparin, initiates BK formation by FXIIa/PK-mediated cleavage of HK in plasma. Intravital laser scanning microscopy and tracer based experiments revealed heparin-driven leakage and fluid extravasation in the skin of microvessels of wild-type mice in response to IgE-mediated MC activation. Deficiency in FXII (which blocks FXII-mediated BK formation) (69, 70) and B2R (which blocks BK signalling) largely protected mice from heparin and allergen-activated MC-induced edema formation. In mice lacking C1INH, MC activation or direct heparin application generated excessive BK-driven edema (51) suggesting that sub-clinical allergic relations could initiate swelling attacks in HAE.

Contaminated heparin

Heparin has been widely used as an anticoagulant drug to prevent the formation and extension of blood clots in the circulatory system via increasing antithrombin activity. During 2007-2008, there was a dramatic increase in lethal acute hypersensitivity reactions in patients receiving commercial heparin of certain batches from a single manufacturer (71). A contaminant was identified in preparations of heparin that was characterised as a non-natural occurring over-sulfated chondroitin sulfate (OSCS) (72). OSCS-contaminated heparin has a greatly increased potency for activating

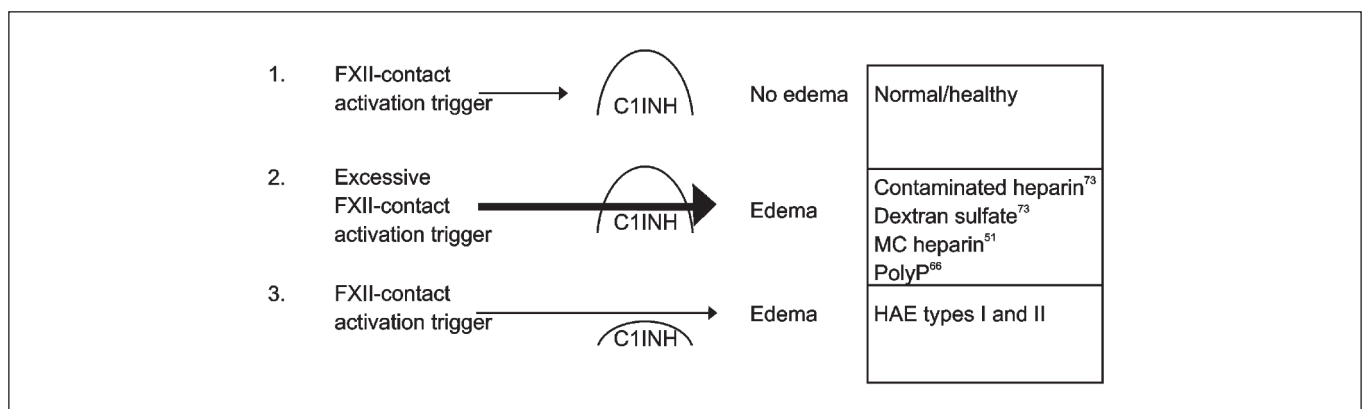


Figure 2: Control of contact-driven edema in HAE patients. In normal healthy individuals C1 esterase-inhibitor (C1INH) controls the trigger-driven contact activation cascade. Bradykinin is not generated and no edema is formed (1). Excessive trigger-activity such as seen in OSCS (see above), dextran sulfate, MC heparin or polyP may overcome the endogenous inhibitory

capacity of C1INH and initiates the contact system cascade resulting in edema (2). Deficiency in a functional C1INH in hereditary angioedema patients facilitates edema formation initiated by trigger factors that under "normal" conditions as in (1) are not sufficient for activating the contact system (3).

FXII and triggering PK-mediated BK formation in human plasma and in a swine model of experimental hypotonic shock *in vivo* (73). OSCS BK-forming activity is dependent on negative charge density of the polysaccharide rather than on a defined structure. Both OSCS and heparin initiate contact system-driven BK formation; however, potency for FXII activation decreases from OSCS (with an average of four sulfate residues per disaccharide) (51), to MC heparin (average of 2.7 sulfate residues per disaccharide) (51). OSCS is an example for contact system mediated BK formation in “normal” individuals that do not have a hyper-susceptible contact system due to C1INH or FXII mutations. To prevent lethal side effects due to pathological contact system activation elaborated analytical methods including capillary electrophoresis and NMR spectrometry, have been established to control quality of heparin that is clinically used for anticoagulation (93).

Polyphosphate

MC heparin is not the sole FXII activator. Platelet-derived polyphosphate (polyP) initiate the contact system *in vivo*. PolyP is an inorganic, linear polymer of 60-100 orthophosphate units linked by phosphoanhydride bonds (74). Platelet polyP can trigger fibrin and BK formation via activation of the FXII-driven contact system in plasma. PolyP activates contact system-mediated capillary leakage in a BK-dependent manner in microvessels of normal mice. In contrast B2R- and FXII-deficient mice were protected from polyP-induced edema. PolyP initiated edema in C1INH deficient mice is largely increased and BK formation is excessive (66). PolyP has recently been discovered as a component of MC granules (75) suggesting that polyP could contribute to MC stimulated BK formation. The relative importance of heparin versus polyP for aberrant MC-mediated leakage remains to be characterised (66, 75). Infections are a known trigger for swelling attacks in HAE (14, 76). Bacteria contain huge amounts of polyP and bacterial polyP potentially trigger contact system-driven BK formation in plasma (66) offering a rationale for onset of vascular leak being associated with infectious states.

Misfolded protein-aggregates

Misfolded protein-aggregates activate FXII and specifically trigger the kallikrein kinin-system without activation of the intrinsic pathway of coagulation. BK formation was activated in blood from patients with systemic amyloidosis, a disease characterised by the accumulation and deposition of misfolded plasma proteins. Misfolded protein-aggregates are hallmark of Alzheimer's disease (67), suggesting that the contact system might have implications for Alzheimer's pathology. A rationale for selective FXIIa-mediated PK activation is still speculative but could be nature of the negatively charged surfaces that are exposed by the misfolded proteins. Additionally, different FXIIa forms that occur in the activation reactions may also contribute for selective BK-formation (77). The artificial FXII activator high-molecular-weight dextran sulfate also specifically triggers BK formation (78).

Therapy of hereditary angioedema

Although substantial progress has been made in understanding the molecular mechanisms underlying swelling attacks in HAE, treatment options using replacement therapy with intravenous C1INH has been limited to a few countries only. Prophylactic therapy had been relied on attenuated androgens or antifibrinolytic agents such as danazol and stanazolol or tranexamic acid, respectively, for decades. Although rather effective, these drugs have been fraught with side effects. Recently, new rational treatment strategies have emerged from understanding the mechanisms of HAE and were approved by the European Commission and Food and Drug Administration with proven efficacy for the treatment of HAE attacks. The novel drugs are recombinant or plasma derived C1INH (79), plasma kallikrein inhibition (Ecallantide) (55) and B2R antagonists (Icatibant) (80). A detailed overview of HAE treatment is not in the scope of our review, and we would like to refer interested readers to another recent review (81). Intravenous infusions of C1INH concentrate shortened the length of and frequency of swelling attacks in HAE I and II patients (82). In contrast to C1INH infusions, the peptidic drug Icatibant and Ecallantide can be injected subcutaneously in an acute attack in HAE I and II patients, result in a relief the symptoms (55, 80). In comparison to established therapies in HAE I and II types not much is known how to treat edema in patients with type III disease.

Future perspective

Currently available drugs for HAE patients do not completely protect against edema attacks. Nanofiltered C1INH concentrate shortens the duration of acute attacks and when used for prophylaxis, the drug reduces the frequency of acute attacks (82). The swelling attacks in untreated HAE patients typically last 2-5 days and there is a delay before symptom relief in HAE patients using C1INH, Icatibant or Ecallantide. This suggests that additional mechanisms contribute in maintaining swellings in HAE. B1R antagonists reduce vessel leakage in HAE (34), indicating B1R signalling to be involved in longer lasting edema formation. The relative contribution of B1R and B2R seems to be tissue dependent (83). Combined B1R and B2R inhibition may block edema formation, and provide a future therapeutic option. Another option could be to combine the currently established drugs and to increase the dose, this might be sufficient to block edema during the attacks. For HAE type III there are no larger clinical studies and rational treatments, with the exception to avoid estrogens (84). In some small patient cohorts tranexamic acid (85), Icatibant (86) or C1INH (87) concentrate have been off-label used for treatment of acute swelling attacks. For prophylaxis regimen various drugs have been orally applied including tranexamic acid (88) or progesterone (89). Novel strategies are required to treat and prevent edema in HAE type III. AS FXII deficiency or inhibition is not associated with any increase in bleeding (90), pharmacological inhibition of FXII offers the unique chance to develop drugs for efficient, specific and safely interference with edema. A new and excit-

ing method to inhibit FXII and PK activity is based on antisense technology (91). Another method to block FXII activity is based on monoclonal anti-FXIIa antibodies that block activation of the contact system (92). Anti-FXIIa antibodies have a long half-life in the circulation and an inhibitory function for up to a few weeks and thus could be used prophylactic.

In summary, HAE is a rare swelling disorder that is driven by excessive BK formation. Understanding the mechanisms of HAE offers the rationale to treat the disease and potentially other disorders associated with aberrant vascular leak.

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Conflicts of interest

None declared.

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