REVIEWS

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The Role of Complement System, Kinin System, Coagulation System and Fibrinolysis System in the Pathogenesis of Urticaria and Angioedema

Rola układu dopełniacza, kininotwórczego, krzepnięcia oraz fibrynolitycznego w patogenezie pokrzywki i obrzęku naczynioruchowego

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Abstract

Pathogenesis of urticaria and angioedema is complex and depends on activity of many factors which are a part of complement, fibrinolysis, coagulation and kinin system. These systems interact through a complicated network of feedback loops and other mechanisms. Hageman factor (XII) which activates the coagulation also induces the activity of kinin and fibrinolysis system. It facilitates conversion of prekallikrein into kallikrein, which is responsible for degradation of HMWK (heigh molecular weight kininogen) resulting in formation of bradykinin. In turn, prekallikrein and HMWK cause the activation of factor XII. Moreover, kallikrein activates plasmin. Plasmin is necessary (besides complement proteins C1, C4 and C2) for generation of C2 kinin and facilitates formation of bradykinin from HMWK. C1-inhibitor, main regulator of complement cascade besides inactivating C1r and C1s subcomponent of complement, shows inhibitory properties of kallikein, Hageman factor and plasmin. Simultaneously, plasmin can activate the first component of complement. Effective trials of treatment of hereditary urticaria and angioedema with the use of C1-inhibitor purified concentrate (in HAE – hereditary angioedema – attacks) and antifibrynolytics – tranexamic acid and ε-aminocaproic acid (in long term prophylaxis of HAE and AAE – acquired angioedema) – indirectly (*ex iuvantibus*) prove the above mentioned relations, as well as efficacy of anti-coagulation agents in other types of urticaria (**Adv Clin Exp Med 2006, 15, 1, 107–112**).

Key words: angioedema, urticaria, complement system, kinin system, coagulation system, fibrinolysis system, Hageman factor, kininogen, kallikrein, plasmin, C1-inhibitor.

Streszczenie

Złożona patogeneza pokrzywki i obrzęku naczynioruchowego jest związana z aktywacją układu dopełniacza, fibrynolitycznego, krzepnięcia i kininotwórczego. Wymienione układy współdziałają ze sobą na zasadzie licznych sprzężeń zwrotnych i innych mechanizmów. Czynnik Hagemana (XII), którego zadaniem jest aktywacja układu krzepnięcia stymuluje również pobudzenie dopełniacza oraz układu kininotwórczego i fibrynolitycznego. Jego działanie przejawia się konwersją prekalikreiny do kalikreiny, która odpowiada za degradację HMWK z następowym formowaniem się bradykininy. Jednocześnie prekalikreina i HMWK powoduje aktywację czynnika XII. Kalikreina ponadto aktywuje plazminę. Plazmina jest niezbędna (oprócz białek komplementu C1, C4 i C2) do wygenerowania C2 kinin i umożliwienia formowania się bradykininy z HMWK. Inhibitor C1, główny regulator funkcjonowania układu dopełniacza, oprócz inaktywacji pierwszego aktywnego składnika (C1), wykazuje hamujące działanie na kalikreinę, czynnik Hagemana i plazminę, która zwrotnie może aktywować C1. Skuteczność leczenia wrodzonego obrzęku naczynioruchowego za pomocą oczyszczonego koncentratu inhibitora C1 (w napadach HAE) oraz antyfibrynolityków – kwasu tranksemowego i ε-aminokapronowego (w przewlekłej profilaktyce HAE i AAE) – świadczy pośrednio (*ex iuvantibus*) o wspomnianych powyżej zależnościach, podobnie jak zastosowanie antykoagulantów w terapii innych odmian pokrzywki i obrzęku naczynioruchowego (**Adv Clin Exp Med 2006, 15, 1, 107–112**).

Słowa kluczowe: obrzęk naczynioruchowy, pokrzywka, układ dopełniacza, układ kininotwórczy, układ krzepnięcia, układ fibrynolityczny, czynnik Hagemana, kalikreina, plazmina, inhibitor C1 esterazy.

Urticaria and angioedema is disease which has the same pathomechanism. The symptoms differ only by a place of secretion of allergic-inflammatory mediators. Urticaria is cutaneous eruption with presence of wheals, whereas edema is confined to swelling of cutis and mucosa with dynamic changes [1]. Pathomechanism of urticaria and edema is complex and not fully explained. Symptoms depend on many mediators of complement, kinin, coagulation and fibrynolysis systems. Dysfunction of some components of these systems potentiated by many feedback loop effects results in appearance of urticaria and oedema symptoms.

Role of Complement System, Importance of C1-Inhibitor

One of the most important systems involved in induction of urticaria and angioedema is the complement system. Its activity predominantly depends on the condition of the inhibitor of the first component of complement that acts by binding active C1r or C1s subcomponents of the molecule. C1-inhibitor plays an essential biological role since it prevents excessive vascular permeability due to decreasing development of vasoactive agents from complement cascade [2]. In some heterozygous patients, suffering from type 1 of hereditary angioedema, lowered synthesis of C1-inhibitor protein leads to recurrent episodes of edema of face tissues, extremities and/or respiratory system. Correct function of C1-inhibitor depends not only on its concentration, but also on proper structure of this compound. This abnormality was shown in another group of patients with type 2 hereditary angioedema (HAE), who had regular concentration of C1-INH (the inhibitor of the first component of complement), but synthesized C1-inhibitor was abnormal, not able to function effectively [3]. So far, over one hundred different mutations of C1-INH gene have been reported in HAE patients [4]. This is interesting enough that each dysfunctional C1-INH protein presents heterogeneous, unique inhibitory activity against purified C1s and active forms of Hageman factor (HFa, HFf), plasma kallikrein and plasmin [5]. Some of pathological states, especially acquired angioedema (AAE) and lymphoproliferative diseases, demonstrated the lower function of C1-INH, which depended on increased catabolism of the inhibitor [3, 6].

Regular C1-inhibitor inactivates factors C1r and C1s – initial proteases that commence activation complement via classical pathway. Moreover, low function of C1-INH may be incriminated in dysregulation of kallikrein activity in tissue fluid in HAE, where deficiency of kallikrein inhibitor was found. Indeed, experiments developing in this pattern demonstrated that the lacking plasma inhibitory molecule protein is C1-inhibitor, that belongs to main factor which inactivate kallikrein [7]. In addition to kallikrein, C1-INH can block activated Hageman factor, as well as belonging to coagulation system factor XIa and the key enzyme of fibrynolysis system – plasmin [8]. Thus, C1-INH discloses multifunctional activity and plays an important role as a regulatory protein in both activation of complement pathway and processes dependent on, belonging to contact coagulation system, factor XII and also fibrynolysis system. Relationships between complement and fibrinolysis systems are not confined only to possibility of plasmin to activate complement in classical pathway. It was shown that in AAE component C7 of the complement system bound plasminogen and was responsible for plasmin activation [9].

In blood obtained from patients with urticaria and angioedema changes in concentration of particular components of the complement system are observed. The ratio between C4 activation products (C4b, iC4b, C4c) and total C4 is higher in blood of AAE cases in comparison with control group. It is even more visible during edema attack, when additionally concentration of another component – C2 – drops significantly [10]. Type 1 HAE patients demonstrate decreased level of the first component of complement and reduced concentration of C2 and C4. Changes of components and regulators of the complement system do not take place in all types of edema. Patients with idiopathic non-histaminergic edema have correct concentrations of C3, C4 components and C1-INH [11]. Subjects suffering from type 3 hereditary angioedema, connected with chromosome X, estrogen dependent or with edema induced by drugs (ACE inhibitors – inhibitors of angiotensine converting enzyme) have normal amounts of complement components [8, 12, 13].

Role of Coagulation System

Activation of the coagulation pathway by factor XII results in the local production of many substances that could induce allergic reactions [14] (Fig. 1). A remarkable similarity occurs between the mechanisms involved in the activation of complement cascade and those of the Hageman factor-dependent pathway, because both of them need initial contact with an activator. One of such agents is a suitable surface that initiates the coag-

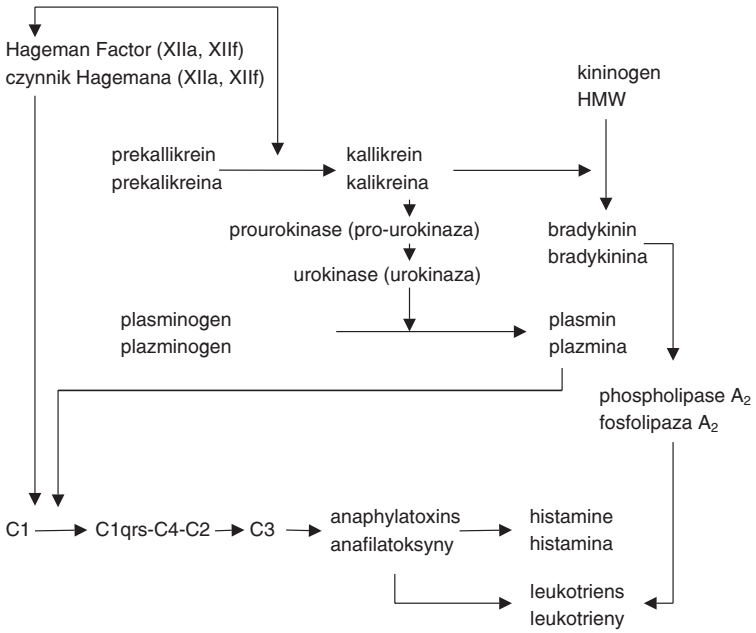

Fig. 1. Vicious circle in pathogenesis of urticaria and angioedema. The role of coagulation system, kinin system, complement and fibrinolysis system

Ryc. 1. Błędne koło w patogenezie pokrzywki i obrzęku naczynioruchowego. Rola układu krzepnięcia, kininotwórczego, dopełniacza i fibrynolitycznego

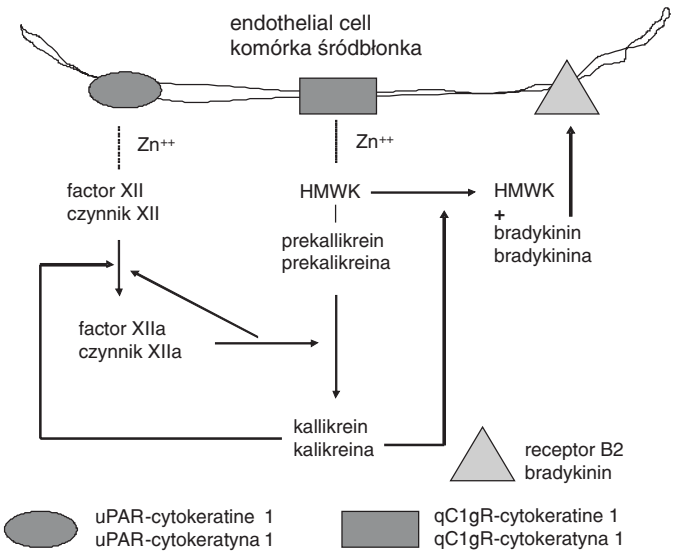

Fig. 2. Contact activation mechanisms embrace common for coagulation, fibrinolysis, kinin and complement system elements. Complement and HMWK receptor on surface of epithelial cell is qC1gR connected with cytokeratine 1. Factor XII binds to epithelial cell surface by urokinase plasminogen activator receptor (uPAR) connected with cytokeratine 1. Zinc-dependent binding of factor XII and HMWK-prekallikrein complex to cell begins bradykinin production over epithelial surface (modified from Kaplan AP, 2004)

Ryc. 2. Mechanizmy pobudzenia kontaktowego, obejmujące wspólne dla układu krzepnięcia, fibrynolitycznego, kininotwórczego i dopełniacza, elementy. Receptorem dla dopełniacza i HMWK na powierzchni komórki śródbłonka jest qC1gR związany z cytokeratyną 1. Czynnik XII łączy się z powierzchnią komórki śródbłonka za pomocą receptora aktywującego urokinazę plazminogową (uPAR), związanego z cytokeratyną 1. Zależne od cynku przyłączenie czynnika XII i kompleksu HMWK-prekalikreina do komórki rozpoczyna wytwarzanie bradykininy na powierzchni śródbłonka (według Kaplan AP, 2004)

ulation process triggering series of reactions leading also to fibrin formation [15] (Fig. 2). Fibrin formation may aggregate fluids locally at the site of inflammation and thus contributes to the prolonged reaction (LPR – late phase response) observed after antigen injection into the skin and may cause proteolytic conversion of plasminogen to plasmin protein. Augmented fibrin formation during allergic reaction was found in Atkins [14] study in which this phenomenon assessed by fibrinopeptide A (FPA) levels at antigen sites were compared with those at sites challenged with buffer diluent alone or with codeine for the first 3 hours, followed by antigen challenge during the subsequent 2 hours. Those findings showed that fibrinopeptide A levels were higher at antigen challenge sites than at codeine challenge sites, but antigen challenge of the previous codeine sites led to a further increase in fibrinopeptide A levels. Another study developed by the same author revealed that skin blister fluids after allergen challenge showed increased Hageman factor activity in atopic persons in comparison with subjects without antigen hypersensitivity [16]. Mentioned above relationships firmly point to involvement of this system in pathogenesis of allergic urticaria and angioedema of atopic persons.

In vitro experiments have shown very close relation between coagulation and kinin system and provided data, that contact activation of plasma results in the formation of two different types of activated factor XII. One of them factor XIIa remains surface-bound and activates prekallikrein and factor XI, while second type of Hageman factor – XIIf leaves the surface and reveals ability to be a potent activator of prekallikrein in solution

but exhibits minimal clot-promoting activity. In addition, factor XIIf can initiate the classical pathway of the complement system by activating the C1 macromolecule [17]. It seems important to emphasize that activation of factor XII induces also fibriolysis and kinin pathway leading to production of vasoactive mediators like bradykinin, which play pivotal role in urticaria and angioedema [10, 14, 17]

Angioedema and Fibrinolysis System

Fibrin formation activates proteolytic reaction that cause conversion of plasminogen to plasmin in order to prevent excessive blood coagulation. The fibrinolysis system is involved in the pathogenesis of angioedema and urticaria because plasmin itself is recognized and bound by C1 [18]. This phenomenon reveals in complement cascade activation with subsequent release of anaphylatoxins, which are very potent compounds that enhance vascular permeability and wheal or edema formation. Moreover, activation of the fibrinolysis system with the subsequent generation of plasmin during attack of angioedema may augment formation of bradykinin from heigh molecular weight kininogen (HMWK) [8]. It is well known that during swelling attacks of hereditary angioedema abundance of plasmin appears, as well as plasmin–antiplasmin complexes [10, 19]. However, this reaction does not seem to depend on the level of plasmin activators, tissue plasminogen activator and urokinase plasminogen activator (t-PA and u-PA) which were at normal physiological ranges, as reported in study by Cugno et al. [19]. Latest results of Nielsen et al. [10] also indicate an increase of the amount of plasmin-α_2-antiplasmin complexes in patients with HAE during attacks. Plasmin presence was proved to be necessary (together with C1s, C4 and C2) for synthesis of C2 kininlike peptide *in vitro*. Activity of this kinin resulting from C2 cleavage, is considered to be one of HAE mediators isolated from patients' plasma [17].

Role of Kinins

The kinin system comprises prekallikrein, HMWK, bradykinin and together with Hageman factor and suitable surface constitutes components of contact activation. In this contact activation components prekallikrein is transformed into kallikrein by factor XII (Fig. 2). Important role of this system in the pathogenesis of angioedema and urticaria results from ability of kalllikrein to enzymatic cleavage of HMWK to form bradykinin [20]. In healthy individuals and patients with HAE in remission predominantly exists 130 000 MW kininogen and a small amount of 107 000 MW (native form). Presence of edema results in decrease of 130 000 MW kininogen, increase of 107 000 MW kininogen and appearance of 98 000 MW form of kininogen [19]. Additionally, during enzymatic cleavage of HMWK bradykinin, that is the most important vasoactive mediator of urticaria and angioedema responsible for vascular permeability, is generated. In the previously cited study of Cugno et al. [19] it was shown that HAE attacks lead to degradation of HMWK. This process does not occur in patients with HAE during remission or in healthy individuals. Further research of the same group revealed very high level of degraded kininogen during swelling attacks both in patients with HAE and AAE. The same patients with HAE and AAE during remission have normal or slightly increased levels of kininogen respectively [20]. Another research group found almost whole degradation of HMWK with subsequent bradykinin formation during HAE attacks [10].

Angioedema is also characterized by a change in the plasma concentration of kallikrein. In the liquid obtained by a technique where chambers were placed on the skin of atopic patients at the site exposed to antigen challenge, an increased activation of the kinin system was observed in comparison to liquid obtained from unchallenged control skin areas treated with diluted buffer solution. Further experiments revealed that the level of kallikrein in the vesicles liquid obtained after subcutenous injection increased only after injection with grass pollen antigens contrary to buffer solution [16]. It is important to emphasize herein that activation of the kinin system occurs together with activation of the contact system. However, C1-IHN-kallikrein complexes in angioedema cases occur in higher ratio then the C1-INH-XIIa complexes. This data suggested that activation of Hageman factor may trigger activation of more prekallikrein particles, comparing to C1-INH molecules. Above mentioned results show that C1-INH-kallikrein complexes are more sensitive markers of the activation pro angioedema sequences, than C1-INH-XIIa complexes.

Study of Curd et al. [7] in which concentration of kallikrein was elucidated by measurement of two different types of complexes – C1-INH-kallikrein and antibody-prekallikrein complexes also indicated increased amount of kallikrein detected in the skin blister fluid of patients suffering from HAE in comparison to the control group. The crucial role of bradykinin in the pathogenesis of angioedema and

urticaria is emphasized by the fact that bradykinin may be synthesized *in vitro* in patients' plasma with HAE arised from C1-INH deficiency [8]. Moreover, experiments carried out on mice with C1 inhibitor deficiency showed that the increased vascular permeability was reversible after administration of bradykinin receptor antagonists [2, 8]. In addition, both mice showing C1-inhibitor deficiency as well as bradykinin receptor (Bk2R) absent mice did not express increased vascular permeability [2]. The next important problem, which may have an impact on the clinical state of patients with HAE is bradykinin receptor polymorphism [21].

During studies on the role of bradykinin in the idiopatic angioedema it was found that the level of bradykinin increases only at the angioedematous site for example in one arm with developed angioedema. At the same time at the site without swelling, the level of bradykinin was unchanged. Similar data obtained in cases of edematous arms of patients with C1-INH deficiency points to an universal role of bradykinin in angioedema [8].

In patients with angioedema resulting from the treatment with ACE inhibitors elevated level of bradykinin is a consequence of its attenuated degradation by convertase. Predisposition towards angioedema caused by treatment with ACE inhibitors is also important. Among predisposition factors in ACE inhibitors related angioedema are also low levels of the other bradykinin converting enzymes e.g. carboxypeptidase N i aminopeptidase P. In this type of angioedema the level of bradykinin rises up during ACE-inhibitor treatment and returns to the physiological level after these medicines are excluded from the treatment.

The kinin system influences other components of contact system involved in the pathomechanism of urticaria and angioedema due to feedback loop effects especially with C1-INH [22]. Decreasing of bradykinin concentration after infusion of C1-INH may be a proof of these relationships [15, 21, 23].

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