REVIEW

Episodic Hemorrhage During Honeybee Venom Anaphylaxis: Potential Mechanisms

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Abstract

Episodic hemorrhage is not a typical symptom of anaphylactic reaction to insect stings. Cases of reactions to honeybee (HB) sting or venom immunotherapy in which the uterus is the main target organ are very rare. Hemorrhage can be induced by HB venom components, especially melittin, which interfere with complement cleavage and bradykinin release. Both mechanisms are directly or indirectly associated with coagulation, thrombolysis, hemolysis, and smooth muscle tone. Induction of episodic hemorrhage through pathway destabilization in a defective bradykinin system or vulnerable organ may not be compensated by appropriate regulatory mechanisms. The pathological role of effectors is generally offset by the interaction of various regulatory systems, and the probability of hemorrhage is minimized thanks to this compensatory capability. In endometrial bleeding, the uterus becomes more vulnerable as a result of postmenstrual vascular fragility and additional induction of anaphylaxis-related uterine contractions.
Episodic hemorrhage, especially metrorrhagia, as a consequence of HB venom activity may be suspected by an allergologist, but not by a physician. Melittin-free or recombinant allergens of HB venom, as well as modulators of the biochemical systems involved, could help to reduce the likelihood of hemorrhage. However, further investigation is required before these strategies can be introduced in clinical practice.

Key words: Anaphylaxis. Bradykinin system. Hemorrhage. Honeybee venom. Melittin. Metrorrhagia.

Resumen

La hemorragia episódica no es un síntoma típico de las reacciones anafilácticas por picaduras de insectos. Los casos de reacciones por picaduras de abejas o tras inmunoterapia de veneno, en los que el útero es el órgano diana principal son muy raros. La hemorragia puede estar inducida por componentes del veneno de abeja, especialmente la melitina, que interfiere con el componente de anclaje y liberación de bradiquinina. Ambos mecanismos están directa e indirectamente asociados con la coagulación, trombolísis, hemólisis y tono del músculo liso. La inducción de hemorragia episódica de un órgano vulnerable producido por la presencia de un sistema defectuoso en la estabilización de la bradiquinina, puede producirse por la ausencia de compensación por los mecanismos reguladores apropiados. El papel patológico de los sistemas efectores se contrarresta generalmente por la interacción de varios sistemas reguladores, y la probabilidad de hemorragia se minimiza gracias a esta capacidad compensatoria. En el sangrado endometrial, el útero se vuelve más vulnerable como resultado de la fragilidad vascular postmenstrual y la inducción adicional de contracciones uterinas relacionadas con anafilaxia.
La hemorragia episódica y específicamente la metrorragia, se puede producir como consecuencia de la actividad del veneno de abejas y debe ser sospechada por el alergólogo. La inmunoterapia con extractos libres de melitina o con alérgenos recombinantes del veneno de abeja, así como con moduladores de los sistemas bioquímicos involucrados, podrían ayudar a reducir la propensión a hemorragia. Sin embargo, se requieren más investigaciones antes que estas estrategias puedan introducirse en la práctica clínica.

Palabras clave: Anafilaxia. Sistema de bradiquinina. Hemorragia. Veneno de abejas. Melitina. Metrorragia..

Introduction

Symptoms During Anaphylaxis

Allergic reactions to honeybee (HB) sting can involve the skin (erythema, pruritus, urticaria, and angioedema), the respiratory tract (laryngeal edema and bronchospasm), the cardiovascular system (myocardial depression, hypotension, and shock), and the gastrointestinal system (nausea, vomiting, and fecal incontinence) [1-3]. However, a temporal association has been observed between varieties of unusual or unexpected reactions and insect stings [4]. Consequently, severe anaphylactic shock could lead to cerebral or myocardial ischemia with permanent sequelae [3]. Other unusual conditions after HB sting include diffuse alveolar hemorrhage, rhabdomyolysis, thrombocytopenic purpura, and vasculitis [1,4]. The presence of specific serum immunoglobulin (Ig) E to HB venom does not account for the occurrence of these symptoms; however, venom immunotherapy (VIT) is only effective in the management of insect-related anaphylactic symptoms [5,6].

Design

After reading a case report of alveolar hemorrhage after HB sting and other case reports describing episodic metrorrhagia during HB venom immunotherapy (data not shown because of space restrictions), we conducted a literature search to find an explanation for this unusual symptom [1]. We found that hymenoptera venom, especially HB venom, was the most prevalent anaphylaxis-related inducer of hemorrhage, not only after natural exposure, but also during VIT, and that the uterus was the principal target [1,7-9]. Thus, metrorrhagia (also known as breakthrough bleeding or spotting), occurred from 1 to 12 hours (mean, 4.4 hours) after onset of anaphylaxis in women who denied a history of bleeding, complications of endocrine disorders, and menometrorrhagia [8,9].

We searched the PubMed database for relevant papers analyzing the biological role of HB venom allergens in the onset of episodic hemorrhage or metrorrhagia. For the purposes of the present study, we included the most relevant experimental papers on the mechanisms of hemorrhage induced by HB venom allergens. Our search terms included *hemorrhage* or *metrorrhagia* and terms associated with HB allergens such as *melittin* and *phospholipase* (PL) *A2*. We found no data on the association between minor HB allergens or toxins and hemorrhage or metrorrhagia [5]. We also combined HB allergen–related terms with terms referring to molecules implicated in the development of hemorrhage or metrorrhagia. Relevant terms such as *bradykinin* (BK) or *prostaglandins* (PG) were taken from the literature. However, most papers were excluded, as the expected association between the search terms was not found. Some of the papers excluded focused on specific hemorrhagic symptoms or syndromes, such as purpura and vasculitis, and the development of conditions not associated with hemorrhage, such as pancreatitis. Many authors focused on the biologic effect of hyaluronidase or PLA2 from other venomous species (eg, snakes). The exact number of papers excluded was impossible to calculate, because of the different combinations of search terms.

Honeybee Venom and Mechanisms of Hemorrhage

Activation of Nonimmune Mechanisms by HB Venom Allergens During Anaphylaxis

Metrorrhagia is not usually considered a typical symptom of anaphylaxis [7-10], since onset cannot be explained by IgE-mediated mechanisms. The main causes of anaphylaxis-related metrorrhagia are currently considered to be "uterine contractions in postpuberal female patients" [9] and the effects of mediators on smooth muscle secondary to histamine and other agents [11]. However, as onset of hemorrhage after exposure to HB is uncommon, even in nonmuscular organs such as the brain and lungs, more in-depth investigation is necessary [1,12].

The biologic effects of the principal HB venom allergens play a key role in hemorrhage. The major HB venom allergens (and specific IgE inducers) are PLA2, melittin, and hyaluronidase, which have been synthesized in recombinant form [13-17]. Apart from IgE-mediated mechanisms, evidence suggests that allergens could also involve nonimmune (IgE-independent) inflammatory mechanisms during onset [18]. Thus, BK is a nonimmune mediator that promotes various anaphylactic symptoms and whose production could be induced by melittin [14]. Experiments in guinea pigs demonstrated that melittin also acts as a direct activator of PLA2 and mimics BK effects on tracheal tone [19]. Angioedema due to BK has the potential to cause airway obstruction, asphyxia, and severe gastrointestinal symptoms mimicking acute abdomen [18]. In this setting, the activation of a plasma kinin–forming cascade can lead to binding and autoactivation of factor XII, activation of prekallikrein to kallikrein by factor XIIa, and cleavage of high-molecular-weight kininogen by kallikrein to release the vasoactive peptide BK [20]. Moreover, in factor XII–deficient mice, approximately 50% of resting BK and all of the contact-stimulated plasma BK was provided by the factor XII–dependent pathway [21]. Therefore, melittin is a potent activator of the BK pathway and an inducer of various symptoms during HB sting reactions via nonimmune mechanisms [14,22].

Inhibition of Platelet Aggregation and Induction of Thrombolysis by Activation of the Melittin-Dependent BK Pathway

Recent evidence suggests that the BK pathway, especially factor XII, can activate and regulate clotting [23]. Thus, mice without the bradykinin B2 receptor and factor XII have a reduced risk for arterial thrombosis [23]. However, both BK and its metabolite BK 1-5 can inhibit thrombin-induced platelet aggregation in humans [24]. While Cleary et al [25] reported that BK inhibits the role of thrombin in clotting and platelet activation, BK level was shown to increase as a result of angiotensin II blockade, and subsequent nitric oxide production in endothelial cells inhibited adhesion of thrombocytes to the endothelia [26].

BK antagonism is also mediated through amplification of BK effects on tissue plasminogen activator during administration of angiotensin-converting enzyme (ACE)

inhibitors [27-29]. A similar thrombolytic effect due to this pathway was experimentally achieved in Wistar rats [30]. BK induced prolonged thrombolysis mediated by the B2 receptor and by PGI2 [27,28]. The role of BK in plasminogen activation was abolished by pretreatment with the BK B2 receptor blocker HOE 140 [29]. Meanwhile, boosting of BK-induced tissue plasminogen activator release by ACE inhibition could be blocked by plasminogen activator inhibitor-1 [31,32]. ACE inhibition seems to occupy a central position in modulating the fibrinolytic balance, in which an angiotensin II–mediated increase in plasminogen activation inhibitor-1 plays a major role [32]. In addition, coagulation disorders (decreased fibrinogen activity and moderate delay in prothrombin and partial thromboplastin times) were demonstrated after experimental subcutaneous application of HB venom in mice [33]. In summary, melittin induces release of BK in association with angiotensin-converting enzyme (ACE) dysfunction, thus leading to coagulation disorders and fibrinolysis.

Activation of the BK Pathway as an Inducer of Hemolysis and Barrier Hyperpermeability During Reaction to HB Venom

The BK pathway activator melittin has a hemolytic effect [17,34]. DeGrado et al [34] found that once melittin has bound to the outer surface of the erythrocyte membrane, surface-bound monomers produce transient openings through which approximately 40 hemoglobin molecules can escape. Induction of hemolysis by HB venom reduces the volume of erythrocyte ghosts to the extent that their volume is significantly lower than the initial cell volume [35]. An analogous phenomenon can be observed when melittin and PLA2 are mixed, but not when they act separately. Rudenko et al [35] showed that reduction in ghost volume is not due to osmotic effects or permeabilization/fragmentation of the membrane, but to membrane contraction, which may in turn be associated with the membrane cytoskeleton, thus indicating that HB-induced shrinkage mimics contractile events in nonmuscle cells.

Nevertheless, melittin from HB venom is thought to adhere to the membrane surface, leading to pore formation and fluid extravasation, and has been shown to induce leakage in freshly added liposomes composed of pure DOPC (1,2-dioleoyl-sn-glycero-3-phosphatidylcholine) [36]. BK-induced vascular permeability has also been demonstrated in vivo in perfused rat lung [37], and melittin induces colonic mucosal hyperpermeability in rat tissue in vitro [38]. Maher et al [38] found that apical addition of melittin resulted in a reversible noncytotoxic concentration-dependent decrease in transepithelial electrical resistance across cell monolayers, and that this decrease was independent of the presence of mucus. When transepithelial electrical resistance was reduced, the addition of melittin increased the permeability of [(14)C]-mannitol across rat colonic mucosae [38]. Furthermore, the subepithelial layer (predominantly the lamina propria) is the major producer of eicosanoids in rabbit ileum and the major site of BK-stimulated eicosanoid synthesis and secretion. Therefore, eicosanoids released from subepithelial components may be important regulators of epithelial function, including cellular permeability [39].

Inhibition of Smooth Muscle Tone After Exposure to HB Venom: Development of Hemorrhage

The severity of episodic hemorrhage increases with inhibition of vascular smooth muscle contractility, which also occurs after HB sting reactions [33]. Thus, a myotoxic effect of HB venom and its allergenic compounds melittin and PLA2 was demonstrated in mice after subcutaneous injection [33,40]. Furthermore, increased levels of BK can reduce vascular tone through an effect on the epithelia [20,26,41]. These findings indicate that melittin and PLA2 can decrease muscular contractility and thus potentially induce hemorrhage.

Role of HB Venom Allergens in PG-Related Functions and Development of Uterine Bleeding

BK, melittin, and PLA2 also induce PGF2 in ileal and endometrial glandular cells [39,42]. Thus, melittin may even induce endogenous PLA2, leading to production of endometrial PGF2 late in the estrous cycle [42,43] and heavy menses [44]. Dysfunctional uterine bleeding can involve changes in the production of PGE2, PGF2-α, prostacyclin, and thromboxane, as well as increased endometrial fibrinolytic activity [45]. In addition, therapeutic use of PGF2 inhibits platelet aggregation mediated by adenosine diphosphate [46]. These data indicate that episodic endometrial hemorrhage is a possible symptom during HB venom allergy owing to the vulnerability of this target organ.

Endometrial Dysfunction as a Local Cause of Uterine Bleeding

Endometrial dysfunction can also cause blood loss [47]. The mechanisms involved in this process include local anatomical disorders and systemic mechanisms such as thromboplastic disorders (including coagulation disorders) [47-49]. Dysfunctional blood loss can even occur outside the endometrium, as in endometriosis [50]. Nevertheless, coagulation disorders with no recognizable cause can lead to increased uterine bleeding, particularly in girls and young women [51].

Activation of the BK Pathway as a Potential Cause of Compensatory Hemorrhage

Anaphylaxis-related hemorrhage after HB sting could result from BK-dependent hemodynamic processes, possibly as a compensatory reflex. Experimental intracerebroventricular infusion of melittin has been observed to increase blood pressure and heart rate, possibly as a result of mediation by brain kinins, since intracerebroventricular application of BK induces the same symptoms [52]. These effects can be inhibited by administration of BK antagonists. Yalcin and Savci [53] showed that centrally administered melittin (a PLA2 activator) increases blood pressure and reverses hypotension, even in hemorrhagic shock. Increases in the activity of plasma adrenaline, noradrenaline, vasopressin, and renin mediate pressor responses to melittin under normal and hypotensive conditions [53]. Similar results can be obtained after administration of human clotting factor XII in Brown

Norway rats [54]. Catecholamine, BK, and hemodynamic responses to ß-factor XIIa were absent in plasma kininogen–deficient Brown Norway Katholiek rats, whereas exogenous BK reproduced these responses in a dose-dependent fashion in both wild-type and kininogen-deficient Brown Norway rats [54]. In Wistar rats, the BK pressor effect was paradoxically boosted with the ACE inhibitor captopril and significantly attenuated with the BK B2 receptor antagonist HOE-140 [55]. Consequently, interaction between coagulation, kallikrein-kinin, and the sympathoadrenergic system can exert important pressor effects without counterregulatory autonomic reflexes [54]. In this context, HB venom extract can be administered relatively safely in routine practice [14,56]. Consequent activation of the melittin-induced BK pathway could be associated with hypertensive effects, especially in patients treated with ACE inhibitors [14,22,52-54]. This effect contrasts with the natural development of anaphylaxis-related hypotension, because the paradoxical hypertension observed during VIT could induce compensatory blood loss, maybe as a result of additional dysfunctions in the coagulation system. HB venom–related cerebral hemorrhage could be a consequence of this process [12].

Mast Cell Degranulation as an Additional Cause of Hemorrhage

Mast cell mediators can also induce hemorrhagic reactions. Cytoplasmic granules, for example, contain vasoactive substances (tumor necrosis factor α, histamine, heparin, and proteases). Once these mediators are released, mast cells act on the basal membrane and induce brain edema, prolonged extravasation, damage to the blood-brain barrier, and hemorrhage [57]. Systemic anaphylaxis in August rats was also accompanied by petechial hemorrhages in Peyer patches [58], although the petechiae observed were only associated with mast cell activity when mast cells were located outside the lymphoid follicles of the Peyer patches. Furthermore, injections of histamine, serotonin, or both did not cause hemorrhages in Peyer patches [58]. Additional investigations are necessary to clarify the role of mast cells in the development of hemorrhage.

Involvement of the Venom Enzyme Hyaluronidase in the Development of Hemorrhage

In addition to PLA2 and melittin, HB venom contains hyaluronidase, histamines, and hemolysins that cause toxic and hemolytic effects [59,60]. Hyaluronidase catalyses hyaluronic acid degradation [61,62]. Although enzymatic homology exists between HB and mammalian protein, evidence shows differences in their biologic activities [62]. According to Tan and Ponnudurai [63], HB hyaluronidase exhibits strong anticoagulant activity. A recent clinical survey showed that serum hyaluronidase level increased a few days after subarachnoid hemorrhage, although no difference was found between serum hyaluronidase levels and the severity of subarachnoid hemorrhage [64]. Local injection of purified ovine hyaluronidase was used for the management of vitreous hemorrhage [65]. Hyaluronidase iontophoresis has proven useful for the prevention and treatment of the damage produced by hemorrhages in hemophilic patients [66]. Consequently, hyaluronidase seems to be implicated in the coagulative properties of biological fluids, and HB venom hyaluronidase promotes anticoagulant and hemolytic effects [60,63].

Role of Estrogens as a Potential Factor in the Development of Hemorrhage

Development of coagulation disorders during anaphylactic reactions could depend on gender differences, and interest in the role of sex hormones in the homeostasis of immunity is growing [67]. Findings on the prevalence of immediate hypersensitivity to hymenoptera venom remain open to debate; however, experiments performed by Chen et al [66] in rodents confirm an estrogen effect on mast cell activation and allergic sensitization and show that progesterone boosts induction of IgE [66]. Data from human studies are lacking.

As for estrogen-associated dysfunction of the BK pathway, recent studies reported a gain-of-function mutation in the gene encoding clotting factor XII in 5 German and French families with a common ancestor [68]. Moreover, a missense mutation of clotting factor XII was present in 3 affected females with estrogen-dependent inherited angioedema in a family of Italian

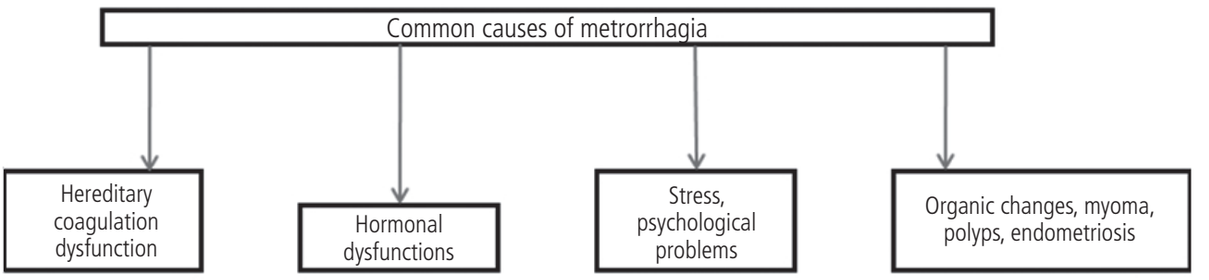

Figure 1. Common causes of metrorrhagia.

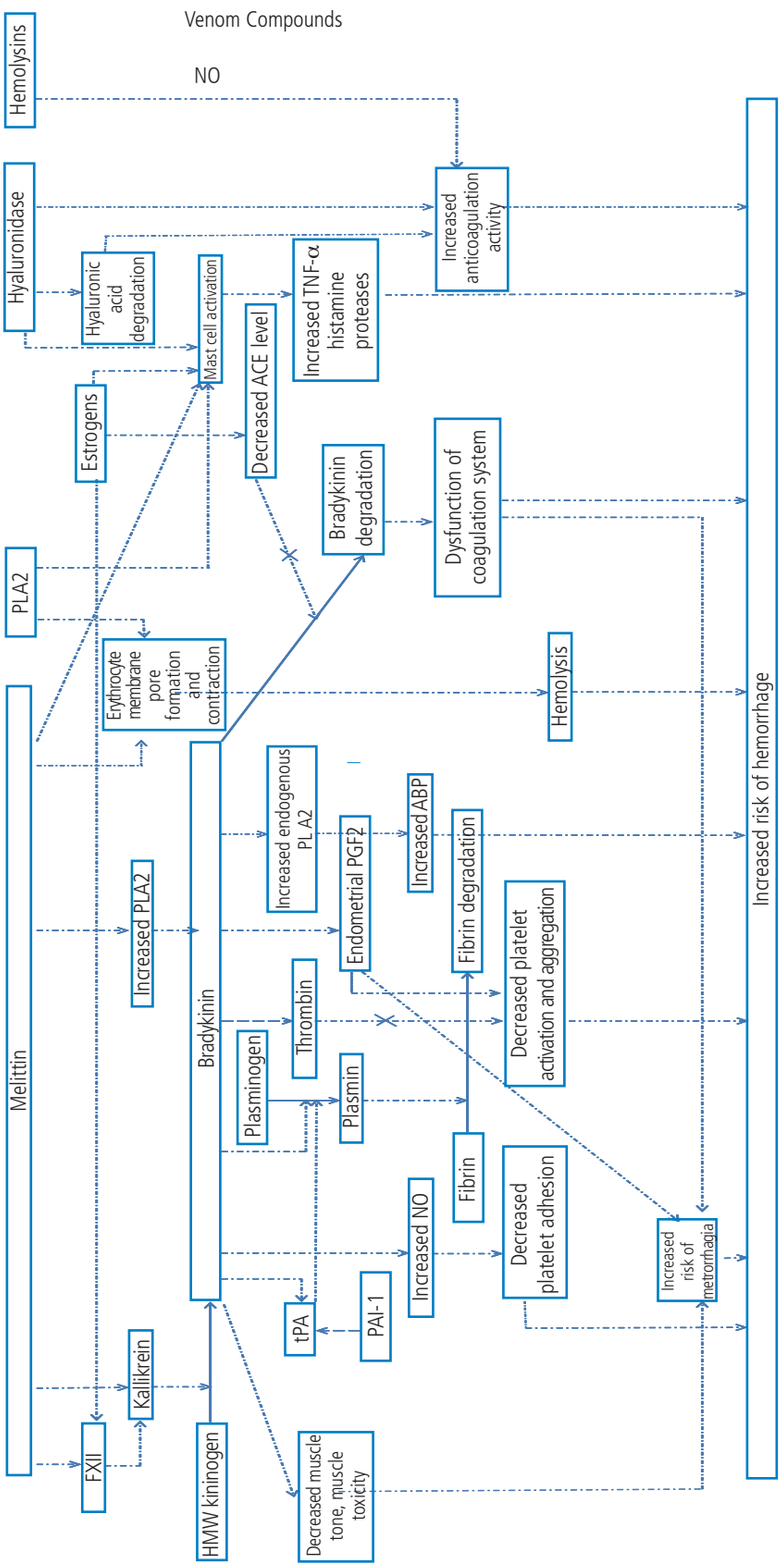

Figure 2. Mechanisms of hemorrhage induction during exposure to honeybee venom. Allergens can interfere with the complement system and enhance hemorrhage or fibrinolysis. Solid line, transformation; broken line, activation; line-line arrow, inhibition; X-crossed broken line, missed effect. PL indicates phospholipase; PG, prostaglandin; FXII, clotting factor XII; tPA, tissue plasminogen activator; PAI-1, a plasminogen activator inhibitor; ACE, angiotensin-converting enzyme; NO, nitric oxide; ABP, arterial blood pressure; TNF, tumor necrosis factor; HMW, high molecular weight.

origin. In addition, these individuals had polymorphisms associated with lower levels of aminopeptidase P and ACE, the enzymes responsible for degradation of BK [37,68]. These reports indicate that several genes could contribute to estrogen-dependent or estrogen-associated inherited angioedema, although the additional role of these genes in coagulation disorders during allergic reactions cannot be ruled out.

Conclusions

Common Causes of Uterine Bleeding

The causes and frequency of bleeding disorders in women vary with age, although hormones are the main cause before and during the menopause (up to 90% of cases) [51]. Uterine disorders (eg, myoma, adenomyosis uteri, and endometrial polyps) can cause bleeding in up to 70% of cases. Coagulation disorders not associated with other recognizable causes can lead to increased bleeding, particularly in girls and young women. Stress and psychological problems also play a role in uterine bleeding (Figure 1) [69].

Role of HB Venom Allergens in the Development of Episodic Hemorrhage

Uterine bleeding and other types of episodic hemorrhage are also an unusual symptom during HB venom reactions [1,2,4,12,51,57,60,69], as some HB venom allergens (especially melittin) can interfere with coagulation, thrombolysis, and smooth muscle tone [17,22,24,28-30,32,34,41]. An overview of these processes is presented in Figure 2. These reactions can also target the lungs and central nervous system [1,12,58]. In women, coagulation disorders may be associated with hormonal and psychological factors affecting pathological uterine and extrauterine bleeding [48-50,69]. Hemorrhage may also act as a compensatory mechanism, even during VIT with natural HB extracts, since melittin-induced release of BK can increase systemic arterial pressure. In vespid venoms, phospholipase and hyaluronidase are similar to HB as potential inducers of hemorrhage [14,63]. The absence of melittin in vespid venoms may explain the lower frequency of metrorrhagia in patients allergic to vespid venom [7]. In contrast to hymenoptera allergy, especially HB venom allergy, the association between vespid venom allergy and episodic hemorrhage seems to be even less prevalent [7]. To our knowledge, metrorrhagia is an uncommon reaction to drug-induced or aeroallergen-induced IgE-mediated pathologies [7-10], although it could be induced in IgE-mediated conditions caused by nonimmune BK pathway mechanisms, even in the absence of hymenoptera-related BK activators [14,18,70].

Frequency of Hemorrhage During Reactions to Insect Venom

The onset of episodic hemorrhage during HB venom anaphylaxis is unusual, as it depends on the regulatory mechanisms of the biochemical systems involved. Identification of nonimmune inflammatory mediators within the coagulation system seems to provide a link between activation of coagulation and hemorrhage. Activation of these mediators by coagulation factors triggers a broad range of signaling pathways that are relevant for inflammatory and allergic disorders. In this context, the association between defects in the BK system and allergic symptoms after HB sting has been suggested since as early as 1983 [14,71]. In the presence of severely defective target systems/organs, additional induction of episodic hemorrhage by nonimmune mediators such as BK was not suppressed by the responsible regulatory mechanisms. However, the interference of regulatory pathways generally balances the pathological role of certain effector mechanisms, thus minimizing the possibility of unusual hemorrhage. This observation could explain the exceptional nature of hemorrhage during HB venom anaphylaxis. In endometrial bleeding, an additional promoting factor is anaphylaxis-related uterine contraction, which, together with its postmenstrual vascular features, could explain why the uterus is the most vulnerable target [9,11,47]. In summary, these findings demonstrate that episodic hemorrhage (especially metrorrhagia) as a consequence of HB venom activity may go unnoticed by a physician but not by an allergologist [70].

The present review indicates that melittin-free or recombinant allergens of HB venom could be used as diagnostic and immunotherapeutic tools to minimize the possibility of severe immune and nonimmune reactions [14,72,73]. This strategy can only prove effective when the culprit allergen is not also the inducer of hemorrhage. In order to reduce side effects, a useful alternative could be preventive or therapeutic administration of modulators associated with the biochemical systems affected, for example, bradykinin B2 receptor blockers [14,73]. Nevertheless, further studies are necessary before more robust conclusions can be drawn.

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References

1. Lam SM. Acute pulmonary hemorrhage following a honeybee sting: a case report. J Microbiol Immunol Infect. 1998;31:133-6.
2. Bilo MB, Bonifazi F. The natural history and epidemiology of insect venom allergy: clinical implications. Clin Exp Allergy. 2009;39:1467-76.
3. Müller UR. [Insect venom allergy]. Ther Umsch 1994;51:38-44. German.
4. Reisman RE. Unusual reactions to insect stings. Curr Opin Allergy Clin Immunol. 2005;5:355-8.
5. Biló BM, Rueff F, Mosbech H, Bonifazi F, Oude-Elberink JN; EAACI Interest Group on Insect Venom Hypersensitivity. Diagnosis of Hymenoptera venom allergy. Allergy. 2005;60:1339-49.
6. Demain JG, Minaei AA, Tracy JM. Anaphylaxis and insect allergy. Curr Opin Allergy Clin Immunol. 2010;10:318-22.
7. Alcoceba E, Marquès L, Lara S. Metrorrhagia in anaphylactic reactions. Allergy. 2009;64(Suppl 90):214.

8. Toubi E, Kessel A, Golan TD. Vaginal bleeding – a rare complication of immunotherapy. Allergy. 1997;52:782-3.
9. Gonzalo-Garijo MA, Pérez-Rangel I, Alvarado-Izquierdo MI, Pérez-Calderón R, Sánchez-Vega S, Zambonino MA. Metrorrhagia as an uncommon symptom of anaphylaxis. J Invest Allergol Clin Immunol. 2010;20:540-1.
10. Frank DE. Metrorrhagia due to allergy to cold. Ann Allergy. 1947;5:574.
11. Simons FE. Anaphylaxis. J Allergy Clin Immunol. 2010;152:S161-81.
12. Remes-Troche JM, Téllez-Zenteno JF, Rojas-Serrano J, Senties-Madrid H, Vega-Boada F, García-Ramos G. Thalamic and mesencephalic hemorrhages after multiple honeybee stings: a life-threatening apitherapy complication. Eur Neurol. 2003;49:188-9.
13. Müller UR. Insect venoms. Chem Immunol Allergy. 2010;95:141-56.
14. Mingomataj EÇ, Bakiri A. The inhibition of kallikrein-bradykinin pathway may be useful in the reduction of allergic reactions during honeybee venom immunotherapy. Irn J Med Hypotheses Ideas. 2009;3:10.
15. Mingomataj EÇ, Ohri D, Dhimitri V, Priftanji A, Qirko E, Pani L, Fischer TC, Dinh QT, Peiser C, Fischer A, Groneberg DA. Hymenoptera sting anaphylactic reactions in the Mediterranean population of Albania. J Invest Allergol Clin Immunol. 2003;13:272-7.
16. Binder M, Fierlbeck G, King T, Valent P, Bühring HJ. Individual hymenoptera venom compounds induce upregulation of the basophil activation marker ectonucleotide pyrophosphatase/phosphodiesterase 3 (CD203c) in sensitized patients. Int Arch Allergy Immunol. 2002;129:160-8.
17. Gauldie J, Hanson JM, Rumjanek FD, Shipolini RA, Vernon CA. The peptide components of bee venom. Eur J Biochem. 1976;61:369-76.
18. Kaplan AP. Kinins, airway obstruction, and anaphylaxis. Chem Immunol Allergy. 2010;95:67-84.
19. Da Silva A, Amrani Y, Trifilieff A, Landry Y. Involvement of B2 receptors in the bradykinin-induced relaxation of guinea-pig isolated trachea. Br J Pharmacol. 1995;114:103-8.
20. Joseph K, Kaplan AP. Formation of bradykinin: a major contributor to the innate inflammatory response. Adv Immunol. 2005;86:159-208.
21. Iwaki T, Castellino FJ. Plasma levels of bradykinin are suppressed in factor XII-deficient mice. Thromb Haemost. 2006;95:1003-10.
22. Nishimura K, Alhenc-Gelas F, White A, Erdös EG. Activation of membrane-bound kallikrein and renin in the kidney. Proc Natl Acad Sci U S A. 1980;77:4975-8.
23. Schmaier AH. Assembly, activation, and physiologic influence of the plasma kallikrein/kinin system. Int Immunopharmacol. 2008;8:161-5.
24. Murphey LJ, Malave HA, Petro J, Biaggioni I, Byrne DW, Vaughan DE, Luther JM, Pretorius M, Brown NJ. Bradykinin and its metabolite bradykinin 1-5 inhibit thrombin-induced platelet aggregation in humans. J Pharmacol Exp Ther. 2006;318:1287-92.
25. Cleary DB, Ehringer WD, Maurer MC. Establishing the inhibitory effects of bradykinin on thrombin. Arch Biochem Biophys. 2003;410:96-106.
26. Landmesser U, Drexler H. Effect of angiotensin II type 1 receptor antagonism on endothelial function: role of bradykinin and nitric oxide. J Hypertens Suppl. 2006;24:S39-43.
27. Gryglewski RJ, Uracz W, Chłopicki S, Marcinkiewicz E. Bradykinin as a major endogenous regulator of endothelial function. Pediatr Pathol Mol Med. 2002;21:279-90.
28. Wojewódzka-Zelezniakowicz M, Stankiewicz A, Malinowska-Zaprzałka M, Chabielska E. [The influence of tissue and plasma angiotensin converting enzyme inhibitors on haemostasis with respect to experimental and clinical investigations]. Kardiol Pol. 2005;63(4 Suppl 2):S420-7. Polish.
29. Pretorius M, Rosenbaum D, Vaughan DE, Brown NJ. Angiotensin-converting enzyme inhibition increases human vascular tissue-type plasminogen activator release through endogenous bradykinin. Circulation. 2003;107:579-85.
30. Gryglewski RJ, Swies J, Uracz W, Chłopicki S, Marcinkiewicz E. Mechanisms of angiotensin-converting enzyme inhibitor induced thrombolysis in Wistar rats. Thromb Res. 2003;110:323-9.
31. Labinjoh C, Newby DE, Pellegrini MP, Johnston NR, Boon NA, Webb DJ. Potentiation of bradykinin-induced tissue plasminogen activator release by angiotensin-converting enzyme inhibition. J Am Coll Cardiol. 2001;38:1402-8.
32. Felmeden DC, Lip GY. The renin-angiotensin-aldosterone system and fibrinolysis. J Renin Angiotensin Aldosterone Syst. 2000;1:240-4.
33. Prado M, Solano-Trejos G, Lomonte B. Acute physiopathological effects of honeybee (Apis mellifera) envenoming by subcutaneous route in a mouse model. Toxicon. 2010;56:1007-17.
34. DeGrado WF, Musso GF, Lieber M, Kaiser ET, Kézdy FJ. Kinetics and mechanism of hemolysis induced by melittin and by a synthetic melittin analogue. Biophys J. 1982;37:329-38.
35. Rudenko SV, Bojok GA, Nipot EE. Bee venom-induced shrinkage of erythrocyte ghosts. Biochemistry (Mosc). 1997;62:104-9.
36. van den Bogaart G, Guzmán JV, Mika JT, Poolman B. On the mechanism of pore formation by melittin. J Biol Chem. 2008;283:33854-7.
37. Dragović T, Igić R, Erdös EG, Rabito SF. Metabolism of bradykinin by peptidases in the lung. Am Rev Respir Dis. 1993;147:1491-6.
38. Maher S, Feighery L, Brayden DJ, McClean S. Melittin as a permeability enhancer II: in vitro investigations in human mucus secreting intestinal monolayers and rat colonic mucosae. Pharm Res. 2007;24:1346-56.
39. Lawson LD, Powell DW. Bradykinin-stimulated eicosanoid synthesis and secretion by rabbit ileal components. Am J Physiol. 1987;252:G783-90.
40. Sciani JM, Marques-Porto R, Lourenço Junior A, Orsi Rde O, Ferreira Junior RS, Barraviera B, Pimenta DC. Identification of a novel melittin isoform from Africanized Apis mellifera venom. Peptides. 2010;31:1473-9.
41. Vapaatalo H, Mervaala E. Clinically important factors influencing endothelial function. Med Sci Monit. 2001;7:1075-85.
42. Naderali EK, Poyser NL. Factors controlling prostaglandin production by guinea-pig endometrial cells. J Reprod Fertil. 1996;108:321-8.
43. Graf GA, Burns PD, Silvia WJ. Expression of a cytosolic phospholipase A2 by ovine endometrium on days 11-14 of a simulated oestrous cycle. J Reprod Fertil. 1999;115:357-63.
44. Cameron IT, Leask R, Kelly RW, Baird DT. Endometrial prostaglandins in women with abnormal menstrual bleeding. Prostaglandins Leukot Med. 1987;29:249-57.
45. Sheppard BL. The pathology of dysfunctional uterine bleeding. Clin Obstet Gynaecol. 1984;11:227-36.

46. Ailamazyan EK, Petrishchev NN, Vivulanets EV, Maryutina LV, Mindukshev IV, Khachaturyan AR. Effects of oxytocin and prostaglandin F(2alpha) (enzaprost) on platelet aggregation. Bull Exp Biol Med. 2002;134:439-41.
47. Milovanov AP, Kirsanov IaN. [The pathogenesis of uterine hemorrhages in the so-called placental polyps]. Arkh Patol. 2008;70:34-7. Russian.
48. Vijapurkar M, Mota L, Shetty S, Ghosh K. Menorrhagia and reproductive health in rare bleeding disorders: a study from the Indian subcontinent. Haemophilia. 2009;15:199-202.
49. Ferenczy A. Pathophysiology of endometrial bleeding. Maturitas. 2003;45:1-14.
50. Gilabert-Estelles J, Ramon LA, España F, Gilabert J, Castello R, Estelles A. Expression of the fibrinolytic components in endometriosis. Pathophysiol Haemost Thromb. 2006;35:136-40.
51. Gaetje R, Scharl A, Kaufmann M, Ahr A. [Management of abnormal uterine bleeding]. Zentralbl Gynakol. 2006;128:196-201. German.
52. Yang XP, Carretero OA, Jacobsen G, Scicli AG. Role of endogenous brain kinins in the cardiovascular response to intracerebroventricular melittin. Hypertension. 1989;14:629-35.
53. Yalcin M, Savci V. Cardiovascular effects of centrally injected melittin in hemorrhaged hypotensive rats: the investigation of peripheral mechanisms. Neuropeptides. 2007;41:465-75.
54. Amfilochiadis AA, Backx PH, Floras JS. Adrenomedullary catecholamine, pressor and chronotropic responses to human coagulation beta-FXIIa mediated by endogenous kinins. J Hypertens. 2008;26:61-9.
55. Amfilochiadis AA, Papageorgiou PC, Kogan N, Boomsma F, Osmond DH. Role of bradykinin B2-receptor in the sympathoadrenal effects of 'new pressor protein' related to human blood coagulation factor XII fragment. J Hypertens. 2004;22:1173-81.
56. Mingomataj E, Priftanji A, Qirko E, Dinh QT, Fischer A, Peiser C, Groneberg DA. Specific immunotherapy in Albanian patients with anaphylaxis to hymenoptera venom. BMC Dermatology. 2002;2:11.
57. Lindsberg PJ, Strbian D, Karjalainen-Lindsberg ML. Mast cells as early responders in the regulation of acute blood-brain barrier changes after cerebral ischemia and hemorrhage. J Cereb Blood Flow Metab. 2010;30:689-702.
58. Levine S, Saltzman A. Petechial hemorrhages in the small intestinal Peyer's patches: a new manifestation of systemic anaphylaxis. Immunol Invest. 1998;27:135-44.
59. Binder M, Fierlbeck G, King T, Valent P, Bühring HJ. Individual hymenoptera venom compounds induce upregulation of the basophil activation marker ectonucleotide pyrophosphatase/phosphodiesterase 3 (CD203c) in sensitized patients. Int Arch Allergy Immunol. 2002;129:160-8.
60. Noble SJ, Armstrong PJ. Bee sting envenomation resulting in secondary immune-mediated hemolytic anemia in two dogs. J Am Vet Med Assoc. 1999;214:1026-7.
61. Soldatova LN, Crameri R, Gmachl M, Kemeny DM, Schmidt M, Weber M, Mueller UR. Superior biologic activity of the recombinant bee venom allergen hyaluronidase expressed in baculovirus-infected insect cells as compared with Escherichia coli. J Allergy Clin Immunol. 1998;101:691-8.
62. Kreil G. Hyaluronidases--a group of neglected enzymes. Protein Sci. 1995;4:1666-9.
63. Tan NH, Ponnudurai G. Comparative study of the enzymatic, hemorrhagic, procoagulant and anticoagulant activities of some animal venoms. Comp Biochem Physiol C. 1992;103:299-302.
64. Isman F, Kucur M, Tanriverdi T, Kacira T, Sanus GZ, Kemerdere R, Hanimoglu H, Kaynar MY. Serum hyaluronidase levels in patients with aneurysmal subarachnoid haemorrhage. Singapore Med J. 2008;49:405-9.
65. Kuppermann BD, Thomas EL, de Smet MD, Grillone LR; Vitrase for Vitreous Hemorrhage Study Groups. Safety results of two phase III trials of an intravitreous injection of highly purified ovine hyaluronidase (Vitrase) for the management of vitreous hemorrhage. Am J Ophthalmol. 2005;140:585-97.
66. Gandini S, Panicucci F. [Cutaneous iontophoresis of hyaluronidase in the treatment of hemorrhages in hemophilic patients]. Electrodiagn Ther. 1977;14:99-105. French.
67. Chen W, Mempel M, Schober W, Behrendt H, Ring J. Gender difference, sex hormones, and immediate type hypersensitivity reactions. Allergy. 2008;63:1418-27.
68. Duan QL, Binkley K, Rouleau GA. Genetic analysis of Factor XII and bradykinin catabolic enzymes in a family with estrogen-dependent inherited angioedema. J Allergy Clin Immunol. 2009;123:906-10.
69. Heinman M. The role of stress situations and psychological factors in functional uterine bleeding. J Mt Sinai Hosp N Y. 1956;23:775-81.
70. Ben-Shoshan M, Clarke AE. Anaphylaxis: past, present and future. Allergy. 2011;66:1-14.
71. Neuman I, Ishay JS, Creter D. Hyperreactivity to bee stings: reevaluation. Ann Allergy. 1983;50:410-2.
72. Müller U, Akdis CA, Fricker M, Akdis M, Blesken T, Bettens F, Blaser K. Successful immunotherapy with T-cell epitope peptides of bee venom phospholipase A2 induces specific T-cell anergy in patients allergic to bee venom. J Allergy Clin Immunol. 1998;101:747-54.
73. Mingomataj EÇ, Bakiri A. Insights on perspectives of hymenoptera venom immunotherapy. In: Gjersoe J, Hundstad S, editors. Venoms: sources, toxicity and therapeutic uses. Nova Science Publishers Inc.; 2010. p. 1-28;

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