

Human Immune Response to Hymenoptera Venoms

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Venoms from the five most common groups of stinging insects are potent antigens and allergens in man. Approximately 91 % of beekeepers have IgE antibodies reacting with honeybee venom and about 76 % have significant levels of IgG antibodies reacting with bee phospholipase [1]. Similarly, a large fraction of laboratory workers who handle venom and venom products develop IgE and IgG antibodies against venoms. The most common stinging insects in the United States are honeybees (*Apis mellifera*), yellow jackets (*Vespula* spp.), yellow hornets (*Dolichovespula arenaria*), white-faced hornets (*Dolichovespula maculata*) and paper wasps (*Polistes* spp.). Each of these insects is found in much of the country, but the relative distributions are variable [2]. A significant fraction of those individuals who have IgE antibodies against hymenoptera venoms experience clinical reactions of varying severity. Systemic reactions include anaphylactic shock, hypotension, respiratory distress, urticaria, laryngeal edema as well as a variety of other symptoms. Another group of individuals experience large local reactions which consist of angioedema contiguous with the sting site extending at least 5 cm.

During the last years several investigators have been involved in studies leading to improved diagnosis and therapy of allergic reactions to hymenoptera venoms culminating in the introduction of venom preparations for clinical diagnosis and therapy and in attempts to predict successful treatment from serologic studies [3-5]. A few investigators have studied the composition of venoms and the antigenic and allergenic properties of some venom proteins [6-9]. The known allergens in each of the venoms are listed in table I. Honeybee venom is readily obtainable by electrical stimulation in a relatively uncontaminated form and in multigram quantities. The other venoms can be obtained in small quantities by electrical stimulation, but are usually obtained from venom sacs. The vespid venoms are also less stable than bee venom leading to more difficulty in isolation and characterization of their protein components.

There are five known allergens in honeybee venom: hyaluronidase, acid phosphatase and allergen C are potent allergens and immunogens, while phospholipase A is slightly weaker and only about half of bee-reactive individuals respond to the peptide melittin

without intensive immunization. Of the three allergens known to be in vespid venoms, antigen 5 appears to be the strongest and hyaluronidase seems to be a relatively weak allergen. Phospholipase A and B appear to be the same molecule by gel filtration and ion-exchange chromatography. However, the data on vespid allergens are very limited. Almost all individuals who produce IgE antibody to one antigen in a venom produce it to several antigens.

Many people have IgE that reacts with multiple venoms. Venoms from *Vespula* and *Dolichovespula* are closely related and true antigenic cross-reactivity is common, although there are species-specific antigenic determinants [10, 11]. Many people react only to venom from yellow jackets. Species-specific reactivity is uncommon among the yellow jackets, but there are occasional individuals whose IgE reacts with venoms of the *Vespula maculifrons* group but not with the southern yellow jacket, *Vespula squamosa*.

Vespula and *Dolichovespula* venoms are related to *Polistes* venoms, but there is much less cross-reactivity. *Polistes* venoms also show some species specificity [12]. A weak cross-reactivity is observed in some individuals between honeybee venom and vespid venoms. Recently cross-reactivity due to a carbohydrate determinant found on venom, food and pollen allergens has been reported in a few patients.

IgE antibodies against venoms are found by radioallergosorbent test or skin test in a large percentage of individuals clinically allergic to venom. In a study of death from venom anaphylaxis IgE antibodies against venom were found in portmortem blood from each victim. As was mentioned earlier, most beekeepers have anti-bee venom IgE whether they are clinically allergic or not. A preliminary study of tobacco field hands also showed a high incidence of IgE anti-*Vespula* and *Polistes*. The incidence of IgE antibodies against venoms in the non-sting-allergic

Table I. Allergens in hymenoptera venoms

Insect	Allergen	Molecular weights
Honeybee	phospholipase A ₂	15,800
	hyaluronidase	50,000
	acid phosphatase (B)	98,000 (dimer)
	allergen C	102,000
	melittin	2,840
	3 or 4 minor allergens	
<i>Vespula</i> , <i>Dolichovespula</i>	antigen 5	25,000
	phospholipase A and B	35,000
	hyaluronidase	45,000
	probably others	
<i>Polistes</i>	antigen 5	
	phospholipase A and B	
	hyaluronidase	

Table II. Prevalence of IgE antibodies against hymenoptera venoms in various populations

Group	Venoms tested	% positive
Nonallergic beekeepers (1)	BV	95
Sting-allergic beekeepers (1)	BV	92
Recent systemic allergy to bee sting	BV	96
Recent large local allergy to bee sting	BV	80
Fatal anaphylaxis to sting, North Carolina	BV, YJ, YH, WFH, PW	100
Recent bee sting, normal reaction	BV	6
Random adult, Nebraska	BV, YJ	3
Pollen allergy, adult, California	BV, YJ, YH, WFH, PW	10
Severe atopic, not sting-allergic	BV	16
Sudden death (includes field workers), North Carolina	BV, YJ, YH, WFH, PW	50
Non-sting-allergic (literature)	BV, YJ	1-12

BV = Bee venom; YJ = yellow jacket; YH = yellow hornet; WFH = white-faced hornet; PW = paper wasp.

population is not definitively known, but may be as high as 10-12% in adult males. Some of the prevalence studies are summarized in table II.

IgE antibodies reacting with venom are found in almost all persons who experience systemic allergic reactions, in all cases of anaphylactic death and only in about 10% of the nonclinically allergic population [4] strongly suggesting the involvement of IgE antibodies in allergic reactions to venom, while on the other hand IgG antibodies against venom are thought to be protective against IgE-mediated allergic reactions. Almost all venom-allergic patients treated with adequate dose venom immunotherapy and who can tolerate a challenge sting have significantly increased titers of IgG anti-venom [3, 4, 13]. Studies of sting-allergic and nonallergic beekeepers showed that the allergic beekeepers had much lower levels of IgG antibodies than those who tolerated stings; IgE antibody levels were comparable in both groups [1]. In a direct experiment *Lessoif* et al. [14] sting-challenged bee venom-allergic individuals,

then passively infused serum with a high titer of anti-bee venom IgG into those individuals who reacted and then rechallenged them. In each case the reaction was substantially less serious and 1.5-5 times the original venom dose was required to elicit symptoms.

At present it is not clear how one can serologically determine if a particular allergic individual is protected from a sting by IgG antibodies. Two theories have been proposed. The first is that a minimal level of IgG anti-venom is required [4, 15] and the second that the ratios of IgG to IgE for each allergen determines protection [13]. Since obtaining an answer to this question requires sting-challenging a substantial number of treatment failures, it is difficult to obtain enough suitable volunteer subjects.

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