

Correspondence

Local mediator release in bee venom anaphylaxis

It is generally assumed that anaphylactic reactions to insect stings are caused by the widespread diffusion of venom, triggering mediator release from sensitized mast cells throughout the body. Clinical sensitivity to bee stings is less common in those with high levels of IgG antibody [1], and IgG antibodies can protect sensitized cells against bee venom-induced histamine release *in vitro* [2]. Furthermore, there is evidence that the passive infusion of IgG antibody can protect against bee venom-induced anaphylaxis [3,4], suggesting that this antibody can block the spread of free antigen.

This theory assumes that the local release of mediators at the site of a sting does not contribute to the cause of anaphylactic symptoms, but this remains an assumption. We have therefore attempted to analyse this aspect of the problem by studying local and systemic mediator release *in vivo*, in a 49-year-old beekeeper with a 3+ positive radio-allergosorbent test (RAST), whose anaphylactic sensitivity persisted in spite of a course of incremental injections of bee venom. After 12 months of treatment, his 50 µg venom injections were discontinued because of frequent asthmatic reactions which occurred within 15 min of the venom injections, but he agreed to have further injections of bee venom under test conditions. The left and right forearm veins were cannulated and 50 µg venom injected subcutaneously into the back of the right hand over the first web space. Blood samples were taken for immunoglobulin measurements, levels of histamine and prostaglandin D₂ (PGD₂), and levels of absorbed bee venom. Fifteen minutes after the venom injection the subject's peak flow reading had fallen from 630 l/min to 470 l/min. He became flushed and complained of itching of the eyes and mouth. Within 25 min his peak expiratory flow fell to 385 l/min and his peak nasal inspiratory flow, normally 170 l/min, fell to zero. After a salbutamol inhalation he recovered slowly, but after 2 hr his peak flow, at 530 l/min, still had not returned to the baseline reading.

Plasma histamine levels, assayed by a single isotopic radio-enzymatic assay [5], rose from <0.5 ng/ml in the injected arm to 15 ng/ml after 5 min and was still 12 ng/ml after 30 min, at which time the level in the venous blood of the contralateral arm was 0.8 ng/ml (Fig. 1). Prostaglandin D₂ as measured by gas chromatography-mass spectrometry [6], rose to 300 pg/ml at 5 min, 1300 pg/ml at 15 min and 1996 pg/ml at 30 min, by which time the level in the opposite arm was 897 pg/ml. To see if any bee venom proteins were absorbed into the blood, a two-site

enzyme-linked immunosorbent assay (ELISA) was developed. In the absence of serum this could detect 0.1 ng/ml of the major bee venom protein, phospholipase A₂ (PLA₂). However, when serum from the subject was added, the sensitivity fell to 1 ng/ml. Using this assay no PLA₂ could be detected in any sample, indicating that less than 1 ng/ml was passed into the blood. Specific anti-PLA IgE and IgG antibodies were also measured using RAST and ELISA respectively in the pre- and post-challenge samples. No change was detected in either.

The remarkably high levels of prostaglandin D₂ (1996 pg/ml) and histamine (13 ng/ml) which were found in the venous blood draining from the site of antigen injection were well above the circulating concentrations, 0.8 ng/ml histamine and approximately 1000 pg/ml PGD₂, at which flushing, headache and nasal congestion have been reported [7-9]. PGD₂ levels were also higher than we have previously encountered in cold urticaria [8], or after a PGD₂ infusion [9]. This raises the question of whether mediators which are released locally could have a systemic effect and might even explain those cases in which anaphylactic reactions can occur despite high levels of IgG 'blocking' antibody.

This argument cannot be sustained as far as PGD₂ is concerned. In previous studies an infusion rate of PGD₂ of 128 ng/kg/min was required to obtain a circulating concentration of the order of 1000 pg/ml—very similar to the level of 897 pg/ml achieved in the venous blood of our subject's left (non-challenged) arm. If his clearance of PGD₂ resembled that of normal volunteers, and assuming that all the venous blood leaving the challenged arm contained equally high PGD₂ concentrations, it would require a forearm blood flow of 4.5 l/min to deliver 128 ng/kg/minute, an impossibly high flow rate compared to the normal forearm blood flow of 20 ml/min [10].

Further studies of insect sting hypersensitivity will be needed to assess the relative importance of locally released inflammatory mediators and the mediators released by sensitized cells at distant sites. It may also be important to establish whether the rate of absorption of PLA₂, although less than our detection limit of 1 ng/ml, might be sufficient to trigger mediator release at distant sites. In either case it could be useful to study the effect of local adrenalin injection on the events which follow. Although adrenalin is not usually injected at the site of a sting, these pathophysiological studies support the suggestion that local administration [11] might have advantages in reducing local blood flow and mediator release.

Further studies are now being carried out, both in

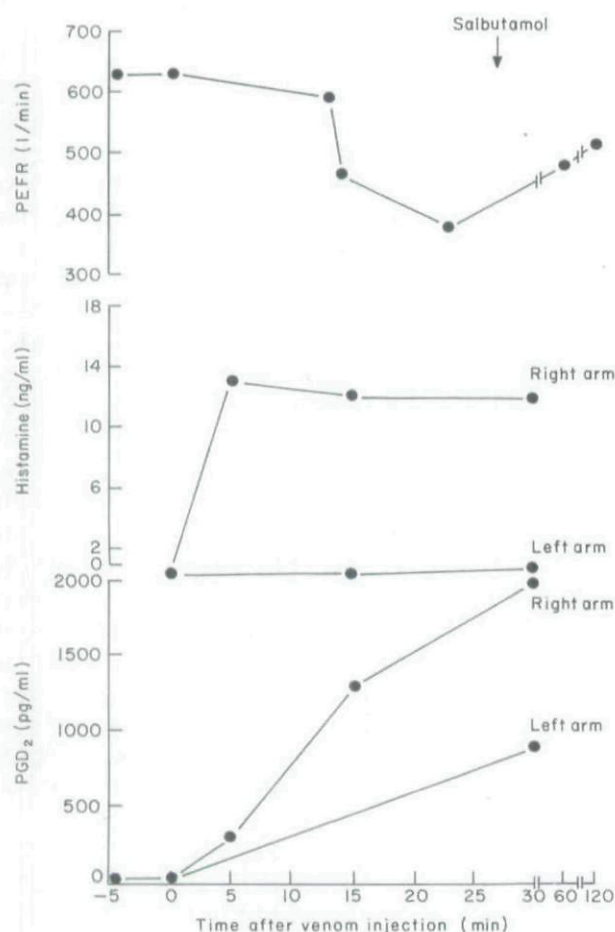


Fig. 1. Response to bee venom challenge into the right hand of a bee venom-allergic subject. PEFR=peak expiratory flow rate (l/min). PGD₂=prostaglandin D₂.

sensitive subjects who appear to be responding satisfactorily to treatment and also in those who are not. It may be anticipated that further measurements of the local release of inflammatory mediators may add to our understanding of this form of anaphylaxis.

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References

- 1 Lichtenstein LM, Valentine MD, Sobotka AK. Insect allergy: the state of the art. *J Allergy Clin Immunol* 1979; 64:5-12.
- 2 Clinton PM, Kemeny DM, Youten LJF, Lessof MH. The effect of blocking antibody on histamine release from peripheral blood leukocytes. *Int Arch Allergy Appl Immunol* 1989; in press.
- 3 Lessof MH, Sobotka AK, Lichtenstein LM. Effects of passive antibody in bee anaphylaxis. *Johns Hopkins Med J* 1978; 142:1-6.
- 4 Bousquet J, Fontez A, Aznar R, Robinet-Levy M, Michel F-B. Combination of passive and active immunization in honeybee venom immunotherapy. *J Allergy Clin Immunol* 1987; 79:947-54.
- 5 Church MK, Pao GJK, Holgate ST. Characterization of histamine secretion from mechanically dispersed human lung mast cells: effects of anti-IgE, calcium ionophore A23187, compound 48/80, and basic polypeptides. *J Immunol* 1982; 129:2116.
- 6 Barrow SE, Heavey DJ, Ennis M, Chappell CG, Blair IA, Dollery CT. Measurement of prostaglandin D and identification of metabolites in human plasma during intravenous infusion. *Prostaglandins* 1984; 28:743.
- 7 Ind PW, Brown MJ, Lhoste FJ, Macquin I, Dollery CT. Concentration effect relationships of infused histamine in normal volunteers. *Agents and Actions* 1982; 12:12.
- 8 Heavey DJ, Kobza-Black A, Barrow SE, Chappell CG, Greaves MW, Dollery CT. Prostaglandin D and histamine release in cold urticaria. *J Allergy Clin Immunol* 1986; 78:458-61.
- 9 Heavey DJ, Lumley P, Barrow SE, Murphy MB, Humphrey PPA, Dollery CT. Effects of intravenous infusions of prostaglandin D in man. *Prostaglandins* 1984; 28:755-67.
- 10 Collier JG, Cleary J, Webster J, Lewis PJ. In: Lewis PJ, O'Grady J, eds. *Clinical Pharmacology of Prostacyclin*. Raven Press, New York, 1981: 153.
- 11 Wasserman SI, Marquardt DL. Anaphylaxis. In: Middleton E, Reed CE, Ellis EF, et al., eds. *Allergy principles and practice*, 3rd Edn. St. Louis: C V Mosby Co., 1988:1365-76.

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