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Chemical respiratory allergy: role of IgE antibody and relevance of route of exposure

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Abstract

Chemicals are able to cause various forms of allergic disease in susceptible individuals. Among those of greatest importance in the context of occupational disease is chemical respiratory allergy, where allergic sensitization of the respiratory tract is associated with elicitation of rhinitis, asthma and/or other pulmonary symptoms following inhalation exposure to the inducing chemical allergen. Although for some chemical respiratory allergens (including the acid anhydrides) there exists a strong correlation between symptoms and the presence of specific IgE antibody, for other respiratory sensitizers (and notably the diisocyanates) such an association is variable or absent. These data have resulted in speculation about a universal mandatory role for specific IgE antibody in the induction and elicitation of respiratory allergy to chemicals and of the nature of alternative or complementary mechanisms of sensitization. There is debate also regarding the routes through which exposure to relevant chemical allergens may result in the acquisition of respiratory sensitization. Although inhalation exposure is probably the most common and most important route through which allergic sensitization of the respiratory tract is achieved, there is evidence also that respiratory sensitization to chemicals may be acquired also by dermal contact; observations that have important implications for occupational health management. The significance of IgE antibody and dermal exposure in the context of occupational respiratory allergy to chemicals is discussed.

Keywords: Chemical respiratory allergy; IgE antibody; Dermal exposure

1. Chemical respiratory allergy

It is now well established that a variety of chemicals (including certain diisocyanates, acid anhydrides, platinum salts and reactive dyes) is able to cause allergic sensitization of the respiratory tract associated with occupational asthma and other symptoms (Kimber and Dearman, 1997a). This remains an important occupational health issue and poses practicing toxicologists with a number of challenges (Ross et al., 1995; Kimber and Wilks, 1995; Venables and Newman Taylor, 1997; Hendrick, 2001). The latter arise largely from some uncertainty about the mechanisms through which chemicals induce and elicit respiratory allergic disease. In this article we explore two aspects of this; the requirement for IgE antibody and the relevance of the route of exposure.

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2. Role of IgE antibody in chemical respiratory sensitization

There is no doubt that specific IgE antibody plays a pivotal pathogenetic role in respiratory allergy to inhaled proteins. Regarding a similar requirement for IgE antibody in the acquisition of allergic sensitization of the respiratory tract to chemicals there is uncertainty and controversy. By definition, allergic sensitization requires the stimulation of a specific immune response; the question in the context of chemical respiratory allergy is whether the induced response must necessarily include IgE antibody.

Studies in mice have demonstrated that known human chemical respiratory allergens provoke selective type 2 immune responses associated with specific IgE antibody production, increases in the total serum concentration of IgE and the induced or elevated expression of cytokines that favour the elicitation of immediate type allergic reactions (Dearman and Kimber, 1991, 1992; Dearman et al., 1998, 1999, 2000; Kimber and Dearman, 1997b). In addition, it has been reported that the pathophysiology of airway reactions in occupational asthma is equivalent to that associated with atopic asthma (Bentley et al., 1992). The difficulty is that it has not always been possible in clinical investigations to demonstrate a correlation between symptoms of occupational asthma and specific IgE antibody (Kimber et al., 1998).

With some chemical allergens there exists a strong association between IgE antibody and clinical symptoms, this being the case for several of the allergenic acid anhydrides, reactive dyes and platinum salts (Health and Safety Executive, 1997). An illustrative example is provided by an analysis of workers exposed to the known respiratory allergen methyltetrahydrophthalic anhydride (MTHPA). It was found that work-related rhinitis was significantly more common among subjects with IgE antibody specific for MTHPA. On this basis it was concluded that specific IgE antibody is an important cause and predictor of symptoms (Yokota et al., 1998; Cullinan, 1998). However, with other chemical respiratory allergens, and notably with the diisocyanates, it has been reported that symptomatic individuals may lack detectable IgE antibody. In fact, in the case of diisocyanate occupational allergy it has been estimated that in less than half of clinically confirmed cases can IgE antibody be found (Cartier et al., 1989; Vandenplas et al., 1993; Cullinan, 1998; Tee et al., 1998; Tarlo, 1999).

The question these data raise is whether there exist pathogenetic mechanisms through which allergic respiratory sensitization can be achieved in the absence of IgE antibody. Although possible IgE-independent mechanisms have been proposed, there is little direct evidence that they are able alone to effect clinical sensitization (Fabbri et al., 1994). The other possibility is of course that in many or most instances IgE antibody does play a mandatory role in inducing sensitization, but that for one or more of a number of reasons such antibody is not always detected successfully. For instance, it is clear that the kinetics and persistence of antibody responses and the time of analysis relative the last exposure will impact on the sensitivity of serological evaluations. In radioallergosorbent tests (RAST) of serum drawn from patients with confirmed diisocyanate asthma it was shown that measurements of specific IgE antibody were more likely to be positive if the blood samples had been taken within 30 days of the last exposure to the chemical allergen (Tee et al., 1998). Another confounder of IgE measurements may be the lack of availability of suitable serological detection methods. In RAST (or related assays) for measurement of IgE antibodies specific for chemical allergens the antigen substrate used is in the form of a hapten–protein conjugate. There are clear indications that the characteristics of this conjugate are of critical importance (Wass and Belin, 1989; Son et al., 1998; Aul et al., 1999). Traditionally human serum albumin has been the protein of choice for preparation of conjugates, but there is no reason to suppose that this is necessarily the most suitable. Isocyanates are very reactive chemicals and are able to combine rapidly and extensively with OH, SH and NH_2 groups on proteins and this may result in intra-protein cross-linking. The argument is that the antigenic determinant recognized by IgE antibody is dependent on the extent of conjugation and the characteristics of cross-

linking and that these requirements may not be modelled accurately by the conjugates prepared for serological investigations (Kimber et al., 1998).

The conclusion we draw is that, for the reasons summarized above, associations between clinical symptoms of chemical respiratory allergy and occupational asthma and IgE antibody may be considerably stronger than has been appreciated previously. The corollary is that IgE antibody is an important, and possibly essential, requirement for the acquisition of respiratory sensitization to chemical allergens.

3. Influence of route of exposure

It is of course self-evident that in previously sensitized subjects the elicitation of respiratory allergic reactions and occupational asthma will require inhalation exposure to the relevant chemical sensitizer. The question we explore here is whether the induction of sensitization, rather than the elicitation of reactions, is similarly dependent upon exposure via inhalation. It is frequently assumed that respiratory sensitization is necessarily associated with local exposure, but in fact there is no a priori reason to believe that this is the case. It must be appreciated that by definition allergic sensitization is achieved through the stimulation of a specific immune response and that immune responses are designed, in general terms, to provide systemic host resistance. Certainly as the molecular vectors of humoral immune responses antibodies will distribute systemically. In the case of IgE antibody this distribution will result in the systemic sensitization of mast cells, and it is for this reason that the diagnosis of food allergy and hay fever may be made on the basis of skin prick tests (where injected allergen provokes the degranulation of IgE-sensitized cutaneous mast cells and a local inflammatory reaction).

It should come as no real surprise, therefore, that cutaneous (intradermal or topical) exposure of experimental animals to chemical respiratory allergens may result in effective sensitization of the respiratory tract (Botham et al., 1989; Rattray et al., 1994). In fact in one series of comparative investigations it was found that either topical or intradermal exposure of guinea pigs to diphenylmethane diisocyanate (MDI) was far more effective at inducing sensitization of the respiratory tract (as judged by the elicitation of pulmonary reactions following subsequent challenge with atmospheres of MDI) than was inhalation exposure (Rattray et al., 1994). This result was not necessarily unexpected, however as there are many instances where in experimental systems inhalation exposure to proteins or to chemical allergens has been found to cause suppression of immune function, including IgE antibody responses (Holt et al., 1981; Dearman and Botham, 1990; Kimber, 1996a).

Despite the evidence deriving from the experimental studies summarized above there is every reason to suppose that inhalation exposure to the inducing chemical allergen represents the most important and most common route through which sensitization of the respiratory tract is induced in workplace settings. Nevertheless, there are indications that occupational respiratory sensitization is not a function exclusively of inhalation exposure. Thus, there is some largely anecdotal evidence that dermal contact may effectively cause respiratory sensitization to some chemicals, particularly when there is acute exposure to high concentrations resulting possibly from accidental spillages or splashes (Karol, 1986; Nemery and Lenaerts, 1993; Kimber, 1996b).

The implication is that in the workplace appropriate risk management measures for the prevention of chemical respiratory sensitization should consider not only control of inhalation, but also control of opportunities for skin contact and dermal exposure.

4. Concluding comments

Chemical respiratory allergy is an area of occupational health that continues to provide toxicologists and physicians with important and difficult challenges. We have considered here two aspects of sensitization and conclude that: (a) IgE antibody is an important and, in many instances, an essential requirement for the genesis of allergic

sensitization of the respiratory tract to chemicals, and (b) that respiratory sensitization can in some instances result from skin contact with relevant chemical allergens.

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