Exposure–response in occupational allergy

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Purpose of review

This review examines the relationship between exposure to workplace allergens and the risk of developing occupational allergy.

Recent findings

Evidence suggests that the risk of developing occupational allergy increases with allergen exposure; however, with some occupational allergens, this exposure–response relationship is more complex. In laboratory animal workers, the risk of developing occupational allergy increases with exposure, except at high allergen exposure when there is a reduction in sensitization. This attenuation of specific immunoglobulin E antibody is associated with increased specific immunoglobulin G_4 antibodies, which are likely to play a protective role, leading to a form of natural tolerance. Exposure–response relationships are also very dependent on the genetic susceptibility of the individual. The interaction between genes, occupational allergens and other cofactors in the environment, such as endotoxin, are also important risk factors in the development of sensitization and asthma.

Summary

Occupational allergy provides a good opportunity to understand the complex relationships between exposure to allergens in the workplace, interaction with genes and the coexposures with other factors in the working environment and the increased risk of developing occupational allergy.

Keywords

exposure, gene–environment interaction, occupational allergy, specific immunologublin E, specific immunologublin G_4

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Introduction

There is considerable evidence to indicate that the risk of developing occupational allergy and asthma increases with increasing allergen exposures to both high and low molecular weight allergens in the workplace (including isocyanates, platinum salts, acid anhydrides, laboratory animal allergens, flour and enzymes amongst many others). Similarly, a positive exposure–response relationship has also been observed with immunoglobulin (Ig)-E antibody to acid anhydrides, bakery enzymes, laboratory animal allergens and platinum salts (http://www.bohrf.org.uk/downloads/asthevre.pdf).

Exposure to occupational allergens was recently reported [1] to account for 10–25% of the population attributable risk for adult asthma, which is equivalent to an incidence of new-onset occupational asthma of 250–300 cases per million per year. Thus exposures to occupational allergens cause a considerable proportion of adults to develop new onset asthma. There is, therefore, a particular need to understand the exposure–response relationship between occupational allergy and exposures to workplace allergens in order to reduce the incidence of the disease.

Recent studies which will be discussed in this review suggest that the relationship between allergen exposure and occupational allergy is complex, and involves several factors including allergen dose and gene–environment interactions.

Occupational allergy as a model of hypersensitivity to determine exposure–response relationship

Occupational allergy lends itself particularly well to determine exposure–response relationships for the following reasons:

(1) The major workplace allergens are well characterized [2] and it is relatively straightforward to estimate allergen exposure, either through direct immunoassay [3] or careful recording of stereotyped job tasks [4].
(2) Large workplace populations are easily enumerated and readily accessible and assembled, allowing for efficient study of representative populations.

(3) Prior sensitization to workplace allergens among new employees is rare [5] and early immunogenetic processes can be examined following initial exposure.
(4) The incidence of IgE sensitization, allergy and asthma can be high [6,7], developing in most instances within just 2 years of initial exposure [7].
(5) Highly specific phenotypes are readily established.
(6) The majority of workers remain healthy, allowing for the examination of early responses that lead to immunotolerance.

Occupational allergy provides us with the opportunity to understand exposure–response relationships with occupational allergens but, perhaps as importantly, it can also act as a well defined model of human allergic adult asthma.

The complex exposure–response relationship

Increasing exposures to occupational allergen has been associated with an increased risk of developing allergy and asthma. A strong and positive association between flour allergen exposure and wheat flour sensitization was demonstrated in a cross-sectional study of 393 workers exposed to wheat allergen [8]. In a cross-sectional study of 342 detergent enzyme workers [9], there was a positive correlation between enzyme exposure and sensitization and work-related respiratory symptoms.

Although a positive exposure–response relationship has been reported for several high and low molecular weight allergens, there are some interesting exceptions with mammalian allergens, which have identified a more complex relationship between certain occupational allergen exposures and the induction of allergy and asthma. In a recent study with laboratory animal workers [10,11], the relative risks for sensitization do not show a linear association with increasing exposures. In a prospective cohort of laboratory animal workers [6], an attenuation of specific IgE antibodies was observed at high exposure, which was confirmed in a more recent study of laboratory animal workers [12]. These studies observed increasing risk of sensitization and work-related symptoms with increasing exposures to rats, except at the highest exposure levels when the risks of both outcomes were lower.

Immunology

The attenuation of sensitization, observed at high allergen exposure in laboratory animal workers, was associated with an increased prevalence of individuals producing high levels of rat-specific IgG_4 antibodies [12]. Ratios of specific IgG_4 : IgE antibodies were found to be significantly increased in those handling the highest number of rats. Laboratory animal workers who produced both specific IgG_4 and IgE antibodies compared with those producing specific IgE only had an almost two-fold reduction in work-related symptoms, suggesting a protective role for IgG_4 antibodies. The reduction of sensitization and work-related symptoms at high exposures and the increased ratio of IgG_4 : IgE in laboratory animal workers is suggestive of a 'modified T helper type 2 (Th2) response'.

Platts-Mills *et al.* [13] were the first to describe a 'modified Th2 response' in children exposed to high current exposures to cat allergens and who produced specific IgG and IgG_4 antibodies in the absence of specific sensitisation or risk of asthma. This response is described as a modified Th2 response as both IgE and IgG_4 antibody classes require Th2 cytokine interleukin-4 for their production, and is suggestive of a natural form of immunotolerance, since similar immunological changes are present during specific immunotherapy [14]. It has been shown that specific serum levels of both IgE and IgG_4 increase during the early phase of immunotherapy, but the increase in specific IgG_4 is more pronounced, causing in the ratio of specific IgG_4 : IgE to increase by 10 to 100-fold, suggesting a protective role for IgG_4 [14].

A similar exposure–response relationship has been reported for mouse-exposed laboratory animal workers [15–17]. In a study of 260 workers in a mouse facility [17], mouse-specific IgG_4 levels were significantly associated with an increased risk of mouse skin test sensitivity and mouse allergen exposure, but at the highest levels of mouse-specific IgG_4 there was a reduction in skin test sensitivity. Another study of 529 rat-exposed workers [18] examined the longitudinal relationship of specific IgG_4 antibodies with exposure over a 2-year follow-up period. High exposure to rats was associated with a strong allergen-specific IgG_4 antibody response. High numbers of rat-specific IgG_4 antibodies were associated with atopy, positive skin prick test to rat, and allergic respiratory symptoms to rats independent of cumulative exposure to rats. When workers were analysed according to their duration of exposure, those atopic workers who had worked for more than 4 years showed an inverse relationship between increasing exposure and sensitization. Interestingly those with highest cumulative exposures had the lowest prevalence of skin prick test positivity to rats and were less likely to report allergic symptoms to rats. Ratios of specific IgG_4 : IgE were not reported, so the findings from this study cannot be directly compared with the rat and mouse studies already described, although they again suggest that high exposure to rats drives a specific IgG_4 antibody response.

The studies described above provide evidence to suggest that specific IgG_4 production is driven by increasing allergen exposures which is associated with a reduction in sensitization in laboratory animal workers exposed to rats [12] and mice [17] and also in children exposed to cats [13].

To add a further complexity to the topic of exposure–response, high-dose tolerance is not observed with every group of workers at risk of developing occupational asthma. The reduction of sensitization at high-dose exposure has not been observed with either bakers [8] or detergent manufacturers [9]. Similarly, in contrast to cat exposure, children exposed to house dust mites demonstrate a linear exposure–response relationship with sensitization [13]. These differences are intriguing and the mechanisms by which certain allergens induce tolerance at high exposures, compared with those which drive a linear exposure–response relationship, remain unclear. Currently there are no data available to determine whether the linear exposure–response relationship observed in bakers and detergent manufacturers is due to a lack of a modified Th2 response.

Cat and house dust mite allergens have been compared to ascertain their ability to develop a modified Th2 response [19]. Cat allergens are readily airborne due to their presence on small particles (<5 μm diameter), and can persist in the air even in undisturbed conditions. Combining the aerodynamic properties of cat allergen coupled with levels that may be 10 times higher than house dust mites may facilitate efficient delivery of high-dose allergen to the respiratory tract and the induction of tolerance.

We have hypothesized that the route of allergen delivery may also be important in the development of natural tolerance. The decreased risk of sensitization and symptoms demonstrated with laboratory animal allergens is similar to both natural tolerance observed with beekeepers who have been frequently stung by bees and the tolerance induced by subcutaneous injection of natural allergen in immunotherapy [20]. One common theme with beekeepers, laboratory animal workers and cat owners, who develop tolerance at high exposures, is that they are at high risk of being bitten or scratched. We suggest that the intradermal route may result in high-dose tolerance. In support of our hypothesis is the observation that repeated inhalation of cat peptides as an experimental method of immunotherapy was not – in contrast to an intradermal method – associated with the induction of hyporesponsiveness ('tolerance') in the skin or the lung [21]. If this hypothesis is correct, it would imply that bakers and detergent workers do not develop tolerance at high exposure levels because they are primarily exposed by inhalation alone. Further studies are now required to test our hypothesis on the role of route of allergen exposure and its association with natural tolerance.

Is there a protective role for IgG_4 at high allergen exposure?

The functional role of IgG_4 antibodies in the protection of sensitization at high allergen exposures has not been demonstrated with rat, mouse or cat-exposed individuals; however, there is evidence to suggest a functional role for IgG_4 in grass pollen immunotherapy studies [22]. Inhibition of allergen–IgE complex binding to B cells was demonstrated with sera from individuals expressing a modified Th2 response following grass pollen immunotherapy, and this activity was observed to coelute with IgG4 antibodies. This finding suggests that IgG_4 antibodies disrupt the IgE network by inhibiting allergen–IgE complexes binding with low-affinity IgE receptor CD23 which is expressed on B cells, thus inhibiting the facilitated antigen presentation process. In grass pollen immunotherapy studies, the blocking activity exhibited in the facilitated antigen binding assay correlated with patients' perceived improvement of allergic symptoms. Preliminary studies from our laboratory suggest that these inhibiting antibodies are also present in rat-exposed individuals, especially those who experience high allergen exposures (M. Jones, personal communication).

Gene–environment interaction

There is a clear, although often complex, relationship between allergen exposure and development of allergy and asthma. Recent studies have also demonstrated a significant effect of genotype on the development of allergy and asthma with exposure to allergen.

A gene–environment interaction was demonstrated in a group of workers ($n = 136$) from a beryllium ceramics plant [23]. HLADPB1Glu69 was found to be present in 30% of the nonsensitized workers and in 83% of the berylliosis-affected individuals. The authors analysed the association of HLADPB1Glu69 in workers at low and high beryllium exposure. At low exposure none of the HLADPB1Glu-negative and only 4% of the HLADPB1-Glu69-positive workers developed berylliosis. Strikingly, among those exposed to high exposure levels of beryllium, 3% of the HLADPB1Glu69-negative and 25% of the HLADPB1Glu69-positive workers developed berylliosis. HLADPB1Glu69 genetic marker predicted berylliosis independent of exposure, suggesting that genetic and exposure factors had at least an additive effect in this particular workforce.

A similar gene–environment interaction was demonstrated in workers exposed to ammonium hexachloroplatinate (ACP) in a large platinum refinery [24]. Cases that were sensitized to ACP ($n = 44$) were matched with nonsensitized referents ($n = 57$) matched on age, race, duration of employment and category of ACP exposure. HLA-DR3 phenotype was more common among cases [odds ratio (OR) 2.3], but this was more apparent at low exposures (OR infinite) than at high exposures (OR 1.6). HLA-DR6 was found to be less common among the cases

(OR 0.4); again the association was found to be stronger in the low exposure group (OR 0.1) than at high exposures (OR 0.5). There was evidence of an HLA association with sensitization to platinum, but interestingly this association varied with the intensity of the exposure. Thus genotype seemed to have the greatest influence at low exposure levels. This implies that with increasing control of allergen exposure, disease will increasingly be a consequence of individual susceptibility.

In occupational asthma due to isocyanates, particular genotypes of glutathione-S transferase confer protection against toluene diisocyanate (TDI)-induced asthma [25], particularly in those patients exposed to TDI for 10 or more years. Thus the protective effect of certain genotypes of glutathione-S transferase increases in proportion to the duration of exposure, and these genes are likely to play a critical role in protecting cells from reactive oxygen species, key components of inflammation.

Interesting, studies on gene–environment interaction have emerged examining the association of CD14 genotype with endotoxin exposure levels. In the Barbados Asthma Genetics study [26], there was evidence to suggest a dose-dependent response to endotoxin exposure for specific genotypes of CD14 at position –260. The CD14 TT genotype appeared protective for asthma at low endotoxin levels. Individuals with CD14 TT genotype at high endotoxin levels, however, were more than 11 times more likely to have asthma than those with the CD14 CC genotype.

In another study [27], higher house dust endotoxin exposure was associated with a marked and significant reduction in the risk of sensitization and eczema. Thus increasing endotoxin exposures is associated with reduced risk of allergic sensitization and eczema in children with CC genotype, suggesting the impact of environmental endotoxin may be enhanced in individuals with this genotype. Similarly, Williams *et al.* [28] reported that allergic sensitization was inversely related to house dust endotoxin, but only among the CD14 CC genotype. The association between CD14 at position –159 (later determined to be at position –260) and allergic sensitization depended on level of exposure to endotoxin, with TT homozygotes being protected at low levels of exposure and at risk at high levels.

Exposure to endotoxin is also encountered in occupational settings such as farming. In adult farmers, the TT homozygotes at position –159 of CD14 had significantly lower lung function and increased wheezing compared with other genotypes, possibly due to increased soluble CD14 levels interacting with inhaled endotoxin from the agricultural environment [29].

Conclusion

Exposure–response relationships are linear for some but not all occupational allergens. The mechanisms leading to attenuation of sensitization and symptoms at high allergen exposure with some occupational allergens but not others have not been elucidated, but may relate to properties of the allergen or route of exposure.

The genotype of the individual exposed to occupational allergens and environmental agents such as endotoxin can significantly influence the exposure–response relationship. Genetic susceptibility may become a major factor in this relationship as engineering and hygiene measures are taken to reduce occupational allergen exposures.

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