

Occupational asthma: a valid model for adult asthma?

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Purpose of review

Developments in the understanding of causes and natural history of occupational asthma may allow improved primary, secondary and tertiary preventive strategies for occupational asthma. This may also lead to improved understanding of preventable contributing factors to the development and severity of nonoccupational asthma.

Recent findings

Animal studies have demonstrated the opportunity to identify chemical sensitizers relevant to asthma. Studies of genetic markers in occupational asthma pose logistic difficulties, but preliminary studies suggest that glutathione S-transferase genotypes may predispose to development of occupational asthma induced by diisocyanates and these have also been implicated in nonoccupational asthma. Some occupational sensitizers/irritants are also found outside the workplace and may be relevant in nonoccupational asthma, for example cleaning agents, epoxy glues, hairdressing products. Accidental exposures to high concentrations of respiratory irritants have the potential to induce new asthma as well as aggravate underlying asthma in both occupational and nonoccupational settings.

Summary

Better understanding of the pathogenesis of occupational asthma is important for affected workers, and also has potential relevance for nonoccupational asthma.

Keywords

occupational asthma, diisocyanates, asthma outcome

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Abbreviations

GST	glutathione-S-transferase
HDI	hexamethylene diisocyanate
RADS	reactive airways dysfunction syndrome
TDI	toluene diisocyanate

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Introduction

It has been suggested that occupational asthma is useful as a model for adult asthma acquired outside the workplace, for a number of reasons [1]. The presence of relatively well defined exposures in a specific workplace population, with exposure to allergens or chemical sensitizers not previously encountered before working, and the possibility of complete avoidance of the sensitizer among those who develop occupational asthma [1] allow study of the natural history of response to a respiratory sensitizer. Conversely, the model suffers from the disadvantages of including only adults, whereas nonoccupational asthma commonly begins in childhood and there may be age-dependent differences in immune response to allergens or chemical sensitizers. Specific workplace exposures to known respiratory sensitizers occur and are assessed in relatively small populations of individuals. Finally, although some workplace sensitizers are also encountered outside the workplace, most exposures in the workplace are likely to be higher than exposures to the same sensitizer outside an occupational setting [1].

Another consideration is that although high molecular weight allergens in the workplace produce IgE antibody mediated responses, a significant proportion of occupational asthma cases are caused by sensitization to low molecular weight workplace chemicals. The mechanism of this has only been shown to be IgE antibody mediated for a minority of chemical sensitizers and remains unknown for many agents. To date, a similar response has not been shown in the nonoccupational setting, causing sensitization to certain chemicals. Nevertheless, the development of asthma from low molecular weight sensitizers in the workplace may provide an impetus to demonstrate that similar responses might occur to the same or other low molecular weight chemicals outside the workplace, acting as haptens, or through non-IgE antibody mediated (presumed immunological) responses to cause asthma.

Some occupational sensitizers that are also encountered outside the workplace include animal and insect allergens, food allergens such as flour for baking, in addition to irritant exposures (which may aggravate underlying asthma and in high concentrations may induce new asthma) and possibly low molecular weight sensitizers, for example in household cleaning. Recent studies have suggested that the risk of occupational asthma among cleaners is significantly increased in several countries [2,3,4]. Thus studies in occupa-

tional asthma may further the understanding of non-occupational asthma.

The recognition that occupational asthma can also be caused by high-level accidental irritant exposure in the workplace (irritant-induced asthma, of which reactive airways dysfunction syndrome (RADS) is the most clearly diagnosed subtype) has parallels with adult asthma in nonoccupational settings with accidental chemical exposures in the home or outdoors. This can lead to new-onset asthma symptoms and airway hyper-responsiveness or prolonged worsening of underlying asthma. A recent report on the new onset of cough and airway hyperresponsiveness after exposures at the World Trade Centre site in firefighters [5•] illustrates these changes after irritant respirable dust exposures [6•], but similar responses can also occur in nonoccupationally exposed populations as has been described after a transportation accident [7] or a spill of glacial acetic acid in a hospital setting [8].

Recent publications from the past year which provide further understanding of the natural history of occupational asthma will be grouped under the following headings: mechanisms of sensitization as demonstrated in animal and human studies, development of sensitization and outcome of occupational asthma.

Mechanisms: animal studies of sensitization to low molecular weight sensitizers

Experimental studies to specifically induce and characterize mechanisms of new sensitization in humans cannot be ethically performed, and animal models are not always reflective of human responses. Recent studies from Warbrick *et al.* [9•,10•], and Zhang *et al.* [11•] studying Brown Norway rats suggest that this may be a model to provide increased understanding of sensitization to low molecular weight chemicals. Using this model, increased IgE and IgG antibody responses to respiratory sensitizers such as trimellitic anhydride, have been shown, especially when the chemical sensitizer was applied topically to the rats rather than by inhalation [10•]. Immune sensitization occurred even with topical application of the powder form of trimellitic anhydride without other chemicals [11•], suggesting that an adjuvant was not necessary for this effect. In contrast, the application of a contact skin sensitizer, 2,4-dinitrochlorobenzene, which causes contact dermatitis but is not known to cause asthma, resulted in no significant antibody response despite a similar degree of lymph node cell proliferation [9•]. As indicated in a recent review article by a British group [12•], the use of cytokine fingerprinting in the same animal model showed a Th1 cytokine production pattern in rats induced by chemicals typically causing contact dermatitis in the occupational setting, such as 2,4-dinitrochlorobenzene, formaldehyde and hexyl cinnamic

aldehyde. In contrast a Th2 cytokine production pattern resulted from typical occupational respiratory sensitizers such as the acid anhydrides, diisocyanates, glutaraldehyde and complex platinum salts after the rats underwent skin exposure [12•].

If these animal studies truly reflect human changes, they would suggest that skin contact could be an important mechanism in immune sensitization preceding specific respiratory responses to inhaled chemical sensitizers. In addition, if the findings are valid as a mirror of human effects, the model could be used to screen for potential skin and respiratory chemical sensitizers to predict the likely effect in the occupational setting and in non-occupational uses of these chemicals.

Other studies of animal models within the past year [13,14,15•] have assessed immune responses to diisocyanates (the most common cause of occupational asthma in many industrial areas). Findings include a specific IgG and IgE antibody response, airway hyperresponsiveness, and airway inflammatory changes accompanied by increased expression of IL-4, tumour necrosis factor- α , RANTES, lymphotactin and lymphotoxin beta, similar to human changes [13]. In a different strain of mice [14], epicutaneously sensitized, an eosinophilic inflammatory response was seen with a mixed Th1 and Th2 cytokine pattern from lung cells (the eosinophilia mediated by the Th2 cytokines). Another rat model similarly showed Th2 cytokines [15•].

Mechanisms: human studies of genetic aspects

In an analogy to nonoccupational asthma, genetic factors are likely to be important in explaining why only a minority of exposed workers develop sensitization to low molecular weight occupational sensitizers as well as high molecular weight allergens, as reviewed by Park and Frew [16•]. The pi class glutathione-S-transferase (GST) genotypes, were shown to be associated with the development of allergic (nonoccupational) asthma, specifically GSTP1 Val/Val was associated with ninefold less asthma than GSTP1 Ile/Ile [17]. Enzymes of the GST supergene family, present in lung epithelium as cytosolic enzymes, are important in protecting the cells from oxidative stress (reviewed in Refs [18•,19•]). It has been suggested that these enzymes may be relevant in occupational asthma related to diisocyanates by this mechanism or possibly by acting to conjugate diisocyanates and their metabolites with glutathione, which may then form protein conjugates as reviewed by Piirila *et al.* [19•]. GST genotypes were assessed in 92 patients with toluene diisocyanate (TDI)-induced asthma by Mapp *et al.* [18•], and in a group of 109 patients with occupational asthma from various diisocyanates by Piirila *et al.* [19•]. Both studies compared the occupational asthma patients

with relatively small numbers of asymptomatic exposed control workers (39 and 73, respectively). This illustrates the paradigm of studies in occupational asthma: exposure is relatively well characterized but populations are relatively small, in contrast to nonoccupational asthma, for which larger groups can be studied but the causative exposure agent(s) are less well defined. The other difficulty in this type of study is that although occupational sensitization commonly occurs within the first 2 years of exposure, it can develop even after many years, so that the control exposed workers could subsequently become sensitized. The study by Piirila and colleagues [19•] showed that the null genotype for GSTM1 was associated with an increased risk of occupational asthma, with lack of specific IgE antibodies to the relevant diisocyanate and a late asthmatic response on bronchial challenge with the diisocyanate, especially when combined with the presence of the GSTM3 AA genotype. These authors found that the GSTP1 Val/Val genotype was associated with high total IgE levels, but it did not show associations with the relative risk of occupational asthma. Similarly, Mapp and colleagues [18•] did not find a significant association of GSTP1 Val/Val with the relative risk of occupational asthma from TDI in their total population. In contrast, however, they did find a protective effect from the presence of GSTP1 Val/Val genotype in patients exposed to TDI for over 10 years. These differences with the time of onset of sensitization were hypothesized to reflect different mechanisms for TDI-induced asthma [18•]. If these associations are confirmed by further studies on well characterized groups, they may lead to a better understanding of the pathway(s) of diisocyanate-induced asthma, which might have parallels with nonoccupational asthma.

Development of occupational asthma and outcome

The development of IgE antibody mediated immune sensitization and allergic upper and lower respiratory symptoms has been well described previously in studies of students undertaking training programs in dental hygiene, laboratory animal care and pastry-making [20•,21]. Less prospective data have been available to study the development of occupational asthma related to low molecular weight sensitizers, and information has mainly relied on cross-sectional studies. A recent study by Redlich and colleagues [22•] has looked at immunologic sensitization to hexamethylene diisocyanate (HDI) in autobody shop workers exposed to spray paint. In a study of 75 workers, no overt occupational asthma was identified, but immunologic responses to HDI were common: almost one-third demonstrated HDI-specific lymphocyte proliferation and a third had HDI-specific IgG antibodies, while two workers had HDI-specific IgE antibodies. These findings demonstrate the potent

immunogenicity of HDI but raise further questions about the pathogenic role of these immunologic responses in diisocyanate-induced occupational asthma. In particular, the role of antibodies in the pathogenesis of occupational asthma related to diisocyanates is unclear: Bernstein *et al.* [23••] have recently shown that diisocyanate antigen-stimulated monocyte chemoattractant protein-1 synthesis is a better diagnostic test for occupational asthma than assay of specific antibodies.

In contrast, for complex platinum salts, skin test responses are highly predictive for the development of occupational asthma in exposed workers, enabling an effective medical surveillance program to be introduced with periodic skin testing and removal of sensitized workers from further exposure [24•]. Of interest, rapid removal from further exposure to platinum salts within months of skin test conversion in this study was associated with a decrease or disappearance of the skin test response within 6 months, and also clearing of work-attributed respiratory symptoms. This suggests that when there is an effective screening test for relevant immunologic sensitization, occupational asthma can be prevented with a surveillance program.

Although there is no equivalent current immunologic screening test for diisocyanate-induced asthma, medical surveillance using questionnaires and spirometry combined with improved worker education have been used as provincially legislated in Ontario, Canada since 1983, in combination with workplace monitoring of diisocyanate exposure concentrations. A temporal association has been found between these measures and earlier diagnosis of diisocyanate-induced occupational asthma, at a younger age, and with milder occupational asthma at the time of diagnosis [25•], features previously associated with a better prognosis [26], possibly due to removal from the sensitizer prior to development of airway remodeling [27]. Such findings emphasize the need in all patients with asthma to try to identify causative environmental factors early after the onset of symptoms, at a time when relevant environmental control measures (e.g. removal of an animal from the home) may be most effective in improving prognosis.

Conclusion

Published studies over the past year have improved our understanding of the factors contributing to the natural history of occupational asthma: development of sensitization, clinical asthma, and the outcome of asthma. It is unclear at present whether low molecular weight sensitizers may be relevant to nonoccupational asthma but, potentially, better early identification of any avoidable relevant sensitizers in nonoccupational asthma might be expected to improve prognosis as has been shown in occupational asthma.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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A study demonstrating that adjuvants are not necessary in the above animal model to induce IgE-antibody mediated sensitization to a chemical by transdermal exposure.
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