Role of the indoor environment in determining the severity of asthma

Ashley Woodcock, Adnan Custovic
North West Lung Centre, Wythenshawe Hospital, Southmoor Road, Manchester M23 9LT, UK

Introductory articles

Allergen exposure decreases glucocorticoid receptor binding affinity and steroid responsiveness in atopic asthmatics

SR Nimmagadda, SJ Szefler, JD Spahn, W Surs, DYM Leung

Allergen exposure can confound the management of asthma. To understand the potential mechanisms by which allergens increase the steroid requirements in atopic asthmatics, we examined the effects of allergens on glucocorticoid receptor (GCR) binding affinity and glucocorticoid (GC) responsiveness of peripheral blood mononuclear cells (PBMC) from atopic asthmatics. A significant reduction (p<0.001) in the GCR binding affinity (Kd) was observed in ragweed-allergic asthmatics during ragweed pollen season compared with PBMC obtained before and after ragweed season. In vitro effects of allergen on PBMC GCR Kd were also examined by incubating PBMC from atopic asthmatics with allergen (ragweed and cat) versus Candida albicans. GCR binding affinity was significantly reduced after incubation with ragweed (p<0.001) or cat allergen (p<0.001) compared with baseline or C. albicans stimulation. This effect was limited to atopic asthmatics in that in vitro cat allergen incubation for 48 h failed to significantly alter GCR binding affinity in nonasthmatic, atopic individuals. These allergen-induced reductions in GCR binding affinity also rendered the PBMC less sensitive to the inhibitory effects of hydrocortisone and dexamethasone on allergen-induced proliferation (p<0.01). To test the hypothesis that allergen-induced alterations in GCR binding affinity were cytokine-induced, we examined the effects of interleukin-2 (IL-2) and IL-4 neutralization using anticytokine antibodies. Addition of both anti-IL-2 and anti-IL-4 antibodies resulted in a significant (p<0.001) inhibition of allergen-induced alterations in GCR binding affinity. Furthermore incubation with cat allergen induced significantly higher concentrations of IL-2 (p=0.03) and IL-4 (p=0.02) by PBMC from atopic as compared with nonatopic subjects. Our current observations suggest that allergen exposure may contribute to poor asthma control by reducing GCR binding affinity in mononuclear cells. This appears to be mediated through IL-2 and IL-4. These findings may have important implications for novel approaches to the treatment of poorly controlled asthma. (Am J Respir Crit Care Med 1997;155:87±93)

Allergen reduction measures in houses of allergic asthmatic patients: effects of air-cleaners and allergen-impermeable mattress covers

S van der Heide, HF Kauffman, AEJ Dubois, JGR de Monchy

Recommendations for allergen avoidance or allergen reduction measures play an important part in the treatment of allergic asthmatic patients. The purpose of this study was to test recently developed air-cleaners with respect to their capacity to capture airborne allergen particles and to improve clinical parameters of asthmatic patients sensitized to aeroallergens. Forty five allergic asthmatic patients were studied in a double-blind procedure for 6 months. The patients were divided into three groups of 15 patients. In Group 1, the intervention consisted of the application of active air-cleaners in living-rooms and bedrooms. In Group 2, placebo air-cleaners were used in combination with allergen-impermeable mattress covers. In Group 3, the same intervention was performed as in Group 2 but with active air-cleaners. Allergen levels in mattress and floor dust were measured before, and 3 and 6 months after the interventions. After 6 months, the air-cleaners were dismantled and the filters were analysed for the amount of dust collected and allergen content. Immunological and lung function parameters were
measured before, and 3 and 6 months after the interventions. Considerable amounts of airborne dust and allergenic particles were captured in the filters of the air-cleaners. Up to the 18.9 g of dust, 4,513 ng of house dust mite allergen, Der p 1, and 50,000 mU of cat allergen, Fel d 1 (in houses with cats) were collected by air-cleaners in living-rooms. Only in Group 3 (in which both active air-cleaners and mattress covers were used) was a small (less than 1 doubling dose) but statistically significant improvement of provocative concentration of histamine causing a 20% fall in forced expiratory volume in one second (PC_{20}) observed (from 5.96 to 9.02 mg·ml⁻¹). The amount of dust and house dust mite allergen collected in the filters was significantly correlated with an improvement of peak flow variation. In combination with other allergen avoidance measures, the examined air-cleaners can contribute to diminished allergen exposure and improvement of airway hyperresponsiveness in asthmatic patients. (Eur Respir J 1997; 10:1217–1223)

Asthma doctors tend to fall within a spectrum of two extremes, either enthusiasts for allergy or for pharma-cotherapy. The former see asthma as an extrinsic problem which can be controlled by the strict avoidance of offending environmental insults or by immuno-therapy. In their support, there are differences in the prevalence of asthma between the same genetic stock in different environments, and also convincing evidence for increasing asthma prevalence with time. And the environment is changing; in addition to changes in ventilation, furnishings and house construction, in the UK there are now 15 million dogs and cats sharing our houses (more pets than children). On the other hand, the pharmacologically orientated physician sees asthma as an intrinsic airways disease involving whichever were sensitised or houses (more pets than children). On the other hand, investigated by incubating PBMCs from atopic asth-}

In the 1970s this was cyclic AMP, in the 1980s PAF, the pollen season and of cat allergic patients not exposed
cy
n
Cynics compare asthma to an inflammation goulash after incubation with ragweed and cat allergen, re-
namely, the environment. Whilst this is said tongue-in-}

asthmatic patients as no similar e

will not help patients. Perhaps we should try to work

soup and argue that ever more detailed pea splitting

Asthma doctors tend to fall within a spectrum of two extremes, either enthusiasts for allergy or for pharma-cotherapy. The former see asthma as an extrinsic problem which can be controlled by the strict avoidance of offending environmental insults or by immuno-therapy. In their support, there are differences in the prevalence of asthma between the same genetic stock in different environments, and also convincing evidence for increasing asthma prevalence with time. And the environment is changing; in addition to changes in ventilation, furnishings and house construction, in the UK there are now 15 million dogs and cats sharing our houses (more pets than children). On the other hand, the pharmacologically orientated physician sees asthma as an intrinsic airways disease involving whichever were sensitised or houses (more pets than children). On the other hand, investigated by incubating PBMCs from atopic asth-

In the 1970s this was cyclic AMP, in the 1980s PAF, the pollen season and of cat allergic patients not exposed
cy
n
Cynics compare asthma to an inflammation goulash after incubation with ragweed and cat allergen, re-
namely, the environment. Whilst this is said tongue-in-

asthmatic patients as no similar e

will not help patients. Perhaps we should try to work

soup and argue that ever more detailed pea splitting

Figure 1 Effect of exposure to ragweed pollen on GCR binding affinity in patients allergic to ragweed. Reproduced with permission from Nimmagadda et al.
of PBMCs from atopic asthmatics with cat allergen and either anti-IL-2 or anti-IL-4 antibodies inhibited the previously observed reduction in OCR binding affinity, suggesting that IL-2 and IL-4 may play an important role in altered steroid responsiveness, and that the effect of cat allergen is mediated via these cytokines. The finding that allergen exposure reduces OCR binding affinity in atopic asthmatics both in vitro and in vivo with the resulting functional alteration in cellular response to glucocorticoids supports the view that high allergen exposure in sensitised individuals may contribute to poor asthma control and maintenance of the inflammatory process in the airways, in spite of treatment with inhaled steroids.

Showing an effect of environment on inflammation or drug responsiveness is important, but what happens when patients try to reduce allergen exposure? In the past, many studies have looked at allergen exposure and allergen sensitisation separately as risk factors for the development and severity of asthma. Since house dust mites are the commonest source of allergens in temperate climates, we will look at the relationship between exposure to mites, atopic sensitisation, and asthma in more detail.

Allergens and asthma

The relationship between mites and asthma is complex and can be investigated with respect to: (1) exposure to mites and allergic sensitisation; (2) allergic sensitisation and asthma; (3) exposure to mites and asthma development; and (4) exposure to mites and asthma symptoms.

EXPOSURE TO MITE ALLEGEN AS A RISK FACTOR FOR SENSITISATION

In a German Multicentre Atopy Study 3141 newborn babies were selected for a prospective study of the influence of exposure to indoor allergens on atopic sensitisation (499 at high risk; remaining 815 chosen at random).1 Both dust samples (for determination of allergen exposure) and blood samples (for determination of sensitisation) were available for 764 children. Children sensitised to dust mite had a significantly higher level of mite allergen in their homes than those in the non-sensitised group (868 ng/g vs 210 ng/g). In a recent study in Linkoping (Sweden) Munir et al followed a group of 86 children at high risk from birth until five years of age.5 Eleven children developed sensitisation to indoor allergens, all 11 to cats, three to dogs, and one to dust mites. The finding that only one of 86 children in this study was sensitised to mites during the first five years of life, despite a strong family history of allergic disease, may relate to the very low exposure to mite allergens (the highest level recorded was only 3.5 µg/g). In a recent cross sectional study from Norway, sensitisation to mites correlated strongly with levels of mite allergen in mattresses (corresponding to odds ratio (OR) of 16).6 Warner et al reported that in three areas of Sweden the prevalence of sensitivity to dust mites and the level of mite specific IgE were both significantly associated with the concentration of mite allergen in homes.7

Early infancy has been identified as a critical period for primary sensitisation. Evidence to support this view comes from studies relating atopy to month of birth. Exposure to pets in early infancy is associated with specific IgE sensitisation and allergic disease later in childhood. Exposure to Der p 1 at a level of >2 µg/dust during infancy is associated with increased prevalence of positive skin tests and increased concentrations of IgE specific to dust mite by the age of five in children of atopic parents.8

SENSITISATION TO MITE ALLEGEN AS A RISK FACTOR FOR ASTHMA

On the east coast of the USA sensitisation to mite allergens is the single strongest risk factor for asthma among middle school children.9 Wickman et al reported that even in an area with low mite allergen exposure (Sweden) there was a close association between mite sensitisation and asthma (OR 4.9).10 Leung et al have recently reported that sensitisation to allergens was a significant risk factor for asthma in Chinese populations living in three different areas of south-east Asia, with adjusted ORs for mite sensitisation being between 1.9 and 3.8.11 In a group of 68 children of atopic parents prospectively followed from birth in Poole, Dorset, sensitisation to mites at the age of 10 years was associated with an OR of 19.7 for having asthma.12

EXPOSURE TO MITE ALLEGEN AS A RISK FACTOR FOR ASTHMA

A recent study of children from six regions of New South Wales, Australia with a range of levels of mite allergens has provided further strong evidence on the role of exposure to mite allergens in childhood asthma.13 Children who were skin test positive to mites in each of the areas were at significant risk for having asthma, with the risk of mite sensitised children having asthma doubling for every doubling of the current level of exposure to mite allergens. In a previously mentioned study from Poole, exposure to Der p 1 at a level of >10 µg/g measured in infancy was associated with a 4.8 fold relative risk of developing atopic asthma at the age of 11.14

EXPOSURE TO MITE ALLEGEN AND ASTHMA SYMPTOMS

It is difficult to demonstrate the dose-response relationship between exposure to indoor allergen and asthma severity. Many asthmatic patients are sensitised and exposed to more than one allergen, and the relative contribution of each to the airway inflammation may be difficult to elucidate. ‘Trigger factors’ such as viruses, air pollution, exercise, and emotion, may make asthma severity worse. In addition, some sensitised patients react to a very low dose of allergen, whilst in others the level required to cause symptoms is considerably higher. Nevertheless, when Peat et al compared children living in areas with different levels of exposure to mites, they found a similar prevalence of mite sensitisation and asthma in both regions, but more severe bronchial hyper-reactivity in sensitised children in the area with the highest mite levels.15 We have found a modest but significant correlation between the concentration of Der p 1 in the bed and objective indices of asthma severity (non-specific bronchial hyperreactivity, FEV1, and PEF Variability) in mite sensitised adult asthmatics, but not for patients with negative skin prick tests to mites.16 We have recently shown that exhaled nitric oxide (NO), a marker of bronchial inflammation, is increased in asthmatics who are both sensitised and exposed to the relevant allergen compared with those who are sensitised but not exposed.17 In addition, patients with more severe asthma, and especially those with brittle asthma, are both sensitised and exposed to high levels of pet allergens.18
Allergen avoidance

Effective control of allergen levels in the treatment of asthma was first suggested in studies in which patients were removed from their homes containing high levels of mite allergen into environments where allergen levels were low. In Europe the mite population density is very low at high altitudes (>1500 m) where humidity is insufficient to support mite survival. A number of studies conducted at high altitude sanatoria (e.g. Davos, Misurina) have demonstrated an improvement in non-specific bronchial hyperresponsiveness and symptoms with re-exposure resulting in a rapid relapse. The high altitude studies were not controlled and it is possible that other domestic factors such as pets, environmental tobacco smoke, or indoor pollution contributed to the observed improvement in asthma control. The lesson from high altitude studies is that it is essential to achieve and maintain a major reduction in allergen levels, and that even with such a reduction in exposure it may take many months for the improvement in asthma control to become fully apparent.

The importance of allergen levels in homes is that they can be reduced sufficiently to improve asthma control in sensitised patients. We have recently reviewed the practical measures for allergen avoidance. There are conflicting data on the effectiveness of allergen avoidance carried out in houses, primarily because the majority of studies have been small, poorly controlled, and have often used measures that do not reduce mite allergen exposure. Consequently, many fail to show clinical benefits and, as a result of low power, it is not clear which subgroups of patients will benefit most from the reduction in allergen exposure. Double blind, placebo controlled trials of allergen avoidance are difficult to conduct. Almost every controlled study has observed a significant reduction in mite allergen levels and sometimes improved clinical symptoms in both the control group as well as the active group.

The second introductory paper by van der Heide et al highlights the difficulties faced by investigators when conducting studies of allergen avoidance. In this trial a relatively small number (45) of house dust mite sensitive adults with mild asthma were randomised into one of the three groups: group 1, active air cleaners in living rooms and bedrooms; group 2, placebo air cleaners and mattress and pillow covers; group 3, active air cleaners and mattress and pillow covers. Unfortunately, in addition to house dust mite, most of the patients were also sensitised to other inhalant allergens (22 to pollens and cats; four of the cat allergic patients lived in a home with a cat). Mattress covers were once again shown to be very effective in reducing the amount of mite allergen Der p 1. Unexpectedly, the placebo air cleaners (essential to prevent unblinding of patients and investigators) also captured dust and allergens on the coarse filter. Using changes in the airway hyperresponsiveness as a primary outcome measure, in the multiple regression analysis the authors have shown that the greatest improvement in PC20 histamine was found in patients who had textile floor covering in the living room, possessed domestic animals, and experienced the largest decrease in the concentration of mite allergen Der p 1 in mattress dust.

This study raises two important questions, unfortunately without providing the answer to them: (1) what are the most appropriate avoidance measures for individual patients with asthma and (2) who are the patients who will benefit most from allergen avoidance?

**What are the most appropriate avoidance measures for individual patients with asthma?**

Mite allergens can be detected in the air in significant amounts only after vigorous disturbance and are predominantly contained within relatively large particles (>10 μm diameter). We deduce that most mite allergen exposure is from bedding, and this raises the question of whether allergen avoidance carried out in houses, primarily because the majority of studies have been small, poorly controlled, and have often used measures that do not reduce mite allergen exposure. Consequently, many fail to show clinical benefits and, as a result of low power, it is not clear which subgroups of patients will benefit most from the reduction in allergen exposure. Double blind, placebo controlled trials of allergen avoidance are difficult to conduct. Almost every controlled study has observed a significant reduction in mite allergen levels and sometimes improved clinical symptoms in both the control group as well as the active group.

The second introductory paper by van der Heide et al highlights the difficulties faced by investigators when conducting studies of allergen avoidance. In this trial a relatively small number (45) of house dust mite sensitive adults with mild asthma were randomised into one of the three groups: group 1, active air cleaners in living rooms and bedrooms; group 2, placebo air cleaners and mattress and pillow covers; group 3, active air cleaners and mattress and pillow covers. Unfortunately, in addition to house dust mite, most of the patients were also sensitised to other inhalant allergens (22 to pollens and cats; four of the cat allergic patients lived in a home with a cat). Mattress covers were once again shown to be very effective in reducing the amount of mite allergen Der p 1. Unexpectedly, the placebo air cleaners (essential to prevent unblinding of patients and investigators) also captured dust and allergens on the coarse filter. Using changes in the airway hyperresponsiveness as a primary outcome measure, in the multiple regression analysis the authors have shown that the greatest improvement in PC20 histamine was found in patients who had textile floor covering in the living room, possessed domestic animals, and experienced the largest decrease in the concentration of mite allergen Der p 1 in mattress dust.

Conclusions: allergen avoidance in tertiary prevention of asthma

The cost of asthma care is increasing. It seems likely...
that an integrated approach which combines anti-inflammatorv treatment (usually with an adequate dose of inhaled steroid) with environmental control of the relevant allergens (those to which the patient is sensitised) will be the most successful. Since mite sensitisation and exposure are most relevant in temperate climates, an effective, simple and widely applicable environmental intervention could have major benefits.

While the overall effect of an intervention may be small at an individual level, in population terms this could still translate into clinically important and worthwhile health benefits. A randomised, blinded and controlled trial of house dust mite avoidance for one year is about to commence in the UK with 2000 enrolled asthmatic patients. Only studies such as this with adequate power will show which patients (and in which domestic environments) will benefit from the intervention. The results of such trials, along with long term studies of primary allergen avoidance, are awaited with interest.

LEARNING POINTS
- Allergen exposure has been shown to reduce glucocorticoid receptor binding affinity and glucocorticoid responsiveness of peripheral blood mononuclear cells in atopic asthmatic subjects.
- This link may be important in explaining reduced efficacy of steroid anti-inflammatory therapy in some asthmatic subjects.
- This study is important as it demonstrates a potential link between environmental allergen exposure and pharmacotherapy in asthma.
- The relation between allergen exposure and asthma is complex and multi-faceted.
- Studies of house dust mite avoidance on incidence and severity of asthma are methodologically difficult and have produced conflicting data.
- Mite avoidance may become an important component in the management strategy of asthma following further well designed studies.

Role of the indoor environment in determining the severity of asthma

A Woodcock and A Custovic

Thorax 1998 53: S47-S51
doi: 10.1136/thx.53.2008.S47

Updated information and services can be found at:
http://thorax.bmj.com/content/53/suppl_2/S47

These include:

References
This article cites 5 articles, 2 of which you can access for free at:
http://thorax.bmj.com/content/53/suppl_2/547#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/