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The indoor air and asthma: the role of cat allergens

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Abstract

Purpose of review—The objective is to discuss recent progress in our understanding of the role of the indoor environment in asthma, focusing on the special role of cat allergens.

Recent findings—Sensitization to Fel d 1 is the dominant event in inhalant responses to cat; however, there are also IgE responses to the lipocalin (Fel d 4), to cat albumin (Fel d 2), and to the oligosaccharide galactose-alpha-1,3-galactose (alpha-gal) on cat IgA (Fel d 5w) and other molecules. The dose response and routes of sensitization for these allergens are now thought to be diverse. It is important to remember that exposure outside a house with a cat is sufficient to cause sensitization. Furthermore, the only solid evidence about a role in asthma relates to Fel d 1. Recently, it has been shown that tolerance associated with early exposure to cats can persist to age 18 and that IgE to alpha-gal (on cat IgA) is not related to asthma. In addition, a recent study of anti-IgE reinforces the evidence that IgE antibodies to indoor allergens make a major contribution to asthma severity.

Summary—Exposure to Fel d 1 in a home with a cat is far higher than the levels necessary to induce an allergic (IgE antibody) response. In keeping with that, children may develop tolerance, which can be long-lived. In addition, there is increasing evidence that IgE antibodies to an inhalant allergen, such as Fel d 1, dust mite, or cockroach, are causally related to lung inflammation and asthma.

Keywords

asthma; cats; inhalant allergens; Fel d 1; long-term tolerance

Introduction

Indoor air includes a wide range of particles including both those carrying foreign proteins and also inorganic particles, particularly those derived from smoking. That immediate hypersensitivity to one or more of the indoor allergens is a risk factor for asthma is well established. However, the steps to establishing a direct causal relationship between exposure to allergen laden particles in the indoor air and asthma are more complicated [1,2]. The

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major sources of allergens in the indoor air include dust mite, cockroach, and several fungi, as well as dander derived from domestic animals and rodents (see www.allergen.org for details of the proteins). A wide range of other proteins can occasionally contribute to allergens in the home; examples include moths, horse hair, birds kept as pets, and the Asian lady beetle [3]. Thus, it is always dangerous to simplify the situation by only analyzing a small number of indoor allergens when the true situation is more complex. On the other hand, it may be difficult to make a case for causality when more than one allergen source dominates the situation. For most sources of indoor allergens, we tend to assume that the allergen found in a home was produced there and that this is the major source of exposure for children living in the house. The situation is thought to be less simple for understanding exposure to cat allergen. This is because of two things: first, the allergen particles are sticky and are carried into other houses as well as public buildings, most importantly schools [4*, 5]; second, there appears to be either a true tolerance effect of high exposure to cat allergen or at least a plateau for exposure above which there is no increase in the prevalence of sensitization [6,7]. Many studies assume that there is or should be a direct quantitative relationship between exposure to an allergen and sensitization, as well as a direct quantitative relationship between exposure of sensitized individuals and inflammation of the lungs. The situation is made more complicated by the techniques used to define sensitization. If skin prick test results greater than 3 mm are regarded as positive and analyzed as a categorical variable, this ignores the very wide range of sensitivity that can occur, as serum tests for IgE antibodies can give results from 0.35 IU/ml to greater than 100 IU/ml (Table 1). Recently, evidence from several cohorts has demonstrated that the titer of IgE antibodies to indoor allergens is an important determinant of the risk of asthma.

The special example of cat allergens

The cat allergen Fel d 1 is a well-defined protein which is produced in the skin and also in the salivary glands of cats. This is the major cat-derived protein that becomes airborne in homes with a cat [8]. It, or a very similar molecule, is found in all members of the cat family. There is evidence for a homology between Fel d 4 and the dog protein Can f 2 [9**]. Although an allergen cross-reactive with Fel d 1 has been reported in dog dander, there is little evidence that this is important clinically and there does not appear to be a homolog of Fel d 1 in humans [10]. This means that Fel d 1 is seen as a fully foreign protein despite the limited evolutionary distance (i.e., approximately 60 million years). Recent evidence, based on the structure of Fel d 1, suggests that the allergenicity of this molecule depends, at least in part, upon its ability to bind to the mannose receptor [11*]. Shortly after it became possible to measure Fel d 1 using a monoclonal antibody based ELISA, it was shown that this allergen, unlike mite allergen, was continuously airborne in homes with a cat and could be detected in homes without a cat [8,12]. The resulting estimates of daily exposure to Fel d 1 (i.e., 200–1000 ng) were much higher than comparable estimates for the dust mite allergen Der p 1 (i.e., 5–50 ng) [2]. Given the high exposure levels in homes with a cat, it would be reasonable to expect that countries with a high prevalence of cat ownership would have a high prevalence of cat allergy and that children raised in a home with a cat would have a much higher prevalence of cat allergy. In fact, the prevalence of cat allergy is never very high compared with the values seen with dust mite or grass pollen [13]. Even in New Zealand, where at least 50% of the homes have one or more pet cats, the prevalence of IgE antibodies to cat is much lower than the prevalence of IgE antibodies to dust mite or grass pollen [14,15].

In 1999, Bjorksten and his colleagues reported results on a Swedish cohort showing that children raised in a house with a cat were less likely to become allergic to cats [16]. Since then, this phenomenon has been confirmed in a large number of studies [6,7,17]. There are some birth cohorts in Europe where living in a house with a cat does not decrease the risk of

sensitization. However, the striking thing is that in virtually none of those studies does living in a house with a cat *increase* the risk of sensitization. The problem is complicated because the exposure of children without a cat at home is dependent upon passive transfer of cat allergen to other homes and schools. The accumulation of allergens in schools and homes (without an animal), which occurs by passive transfer is a reflection of the overall prevalence of cat ownership in the community [18]. If only a small proportion of the local community has cats, then exposure in the schools and other public places may not be adequate to sensitize the children who do not have a cat at home.

An important question about the effects of cat ownership is what age the effect occurs. In most cohorts, it is not possible to assess whether the critical exposure occurs in the first year or simply at some time during the first five years. Thus, the 18-year follow-up of a birth cohort in Detroit provides important results [19**]. They found that children who had a cat in the home during the *first* year of life were significantly less likely to be sensitized to cat allergens at age 18 years [19**,20*]. This result is interestingly in keeping with the results of Von Mutius and her colleagues, in that exposure to farm animals has to occur in the first year of life [21]. However, by contrast with the effects of exposure to farm animals the effects of cat ownership in most studies appears to be cat-specific [6,19**]. The results of Wegienka et al. clearly imply that the “tolerance” to cat allergen exposure achieved in early childhood can be maintained for a long period of time and presumably does not change easily when subjects undergo a change in exposure. The obvious example of a change in exposure occurs when children who previously lived in a home with a cat leave home to live in a college dorm. Preliminary results show that allergic children experience a fall in IgG antibodies with no concurrent fall in IgE antibodies. A partial objective of that study was to see whether “tolerant” subjects would develop skin test positivity or detectable serum IgE antibodies; however, that did not happen within one year (Erwin EA et al, unpublished data). The results support the view that once true tolerance to cat exposure has developed, it is not easily changed.

Understanding the relevance of IgE antibodies in tropical countries

In most tropical countries, children are routinely exposed to a variety of parasites. They have elevated total serum IgE, but despite this, asthma and other forms of allergy are rare [22–24*]. In most of these countries, dust mite allergens are present in homes (because of the humidity) and positive prick tests to mite are not uncommon. In addition, there have been reports of serum IgE antibodies to cat allergens, which were equally not related to asthma or any allergic symptoms [22]. In the last year, two developments have helped to explain this confusion. In a detailed study of school children in a large city in Ghana, it was found that asthma was more common and more severe among the children attending a relatively affluent school [25**]. Moreimportant, it was clear that a major feature of the children in the affluent school was the presence of high titer IgE antibodies to dust mite that correlated highly significantly with asthma [25**]. By contrast, in the poor schools, although low titer IgE antibodies to mite were common, they were not associated with wheezing or exercise-induced bronchospasm. In a completely new development, it was recently discovered that IgE antibodies to the oligosaccharide galactose-alpha-1,3-galactose (alpha-gal) are common in the southeastern United States [26]. Two aspects of this discovery are relevant here; first, that these IgE antibodies bind to some proteins derived from cats and dogs as well as other mammals and second, that they can be induced by bites of the lone star tick, *Amblyomma americanum* [27**], which is increasingly common in the southeastern United States. Completely unexpectedly, we have found that the IgE antibodies to cat found in sera from Africa can be fully explained by IgE antibodies to alpha-gal, both in our study in Kenya and also in a recent report from Zimbabwe [28*]. Thus, IgE antibodies to alpha-gal provide a

model for a parasite-induced IgE antibody response that can increase total IgE and has no effect on asthma.

Challenge studies and intervention studies to evaluate the response of the lungs to allergens

Bronchial and nasal provocation of the nose and the lungs was introduced by Charles Blackley over 100 years ago. Freddy Hargreave and his colleagues in Hamilton took provocation a major step further with their demonstration that allergen provocation could not only induce a late response lasting many hours, but could also produce an increase in non-specific bronchial hyperreactivity to histamine [29]. In a recent study designed to investigate the cellular events that are associated with increased bronchial reactivity, Imaoka et al. demonstrated an increase in endothelial progenitor cells in the lungs at 24 hours [30*]. Interestingly, although they used several other allergens for the provocation, for ten out of the 13 cases they used mite (n = 6) or cat (n = 4) allergen. The form of allergen exposure used for these challenges is fine droplets (generally approximately 2 μm in diameter). Comparing this allergen exposure to the normal exposure in the home, the provocation represents a much larger number of particles with a much lower quantity of allergen on each particle [31]. However, cat exposure in a home is much closer to the conditions of a provocation study.

Several other forms of intervention have been used, including allergen avoidance, immunotherapy, and specific antifungal therapy [31]. Most recently a major study using monoclonal anti-IgE (omalizumab) demonstrated that this treatment could dramatically decrease exacerbations of asthma in children whose predominant sensitization was to cockroach [32**]. Although this evidence clearly supports the view that cockroach allergens contribute to the exacerbations, the seasonality of the exacerbations in children is generally attributed to the seasonal peaks in rhinovirus (RV) infections. There are certainly good reasons for thinking that the combination of RV infection and preceding allergen-related inflammation are both important in the genesis of acute exacerbations of asthma in childhood [33]. Interestingly, several recent studies have suggested that it is the combination of *high titer* IgE antibodies and RV infection that creates the risk of asthma exacerbation. The really interesting question now is whether omalizumab acts directly by decreasing IgE antibodies and FcεRI on basophils and mast cells or secondarily by decreasing the inflammation associated with allergen exposure of allergic subjects.

The efficacy of anti-IgE can clearly be taken as evidence that the IgE antibodies that it removes from the circulation are relevant to exacerbations of asthma. By contrast, other monoclonals that are designed to interfere with some aspect of inflammation cannot be taken to provide evidence for a role of inhaled allergens. Thus successful trials of anti-IL-5 [34] and most recently anti-IL-13 [35*] provide evidence that a Th2 mechanism is relevant, but cannot provide evidence about what foreign antigen caused the inflammation.

Understanding the relevance of indoor air to the increase of allergic disease and asthma

During the latter half of the 20th century, the rise in asthma from 1960–2000 coincided with truly remarkable changes in lifestyle. However, the changes in hygiene that appear to be sufficient to induce a Western model of asthma in Africa or Costa Rica had occurred in London, Berlin and New York almost 40 years earlier (i.e., by 1920). The question then is what changes between 1960 and 2000 were critical to the increase in prevalence and severity of asthma [36]? What is clear is that there was no decrease in the strength of the relationship between sensitization and asthma. We would argue further that there is also a relationship

between the titer of IgE antibodies and both the prevalence and severity of asthma. A recent analysis of a birth cohort in Boston at age 12 years showed that these children had a strong correlation between IgE antibodies to cat, dog, or dust mite and exhaled nitric oxide. Furthermore, this relationship was strengthened by allergen exposure in the home and also if the child reported greater than 10 hours of weekday television watching [37**]. There are many studies that have documented the relationship between obesity and a diagnosis of asthma [38*,39]. However, it is important to realize that obesity is strongly associated with decreased fitness as judged by cardiopulmonary exercise test [40], and that this often presents as breathlessness, which in normal practice may be interpreted as asthma.

Conclusions

Although domestic animals have been in our homes for thousands of years, the last one hundred years have seen two major developments: firstly, the combination of clean water, shoes, separation from animals, and helminth eradication that we refer to as hygiene, and secondly, the lifestyle changes associated with overheated, airtight homes and indoor sedentary entertainment [36,41]. The result has been a dramatic increase in immediate hypersensitivity to indoor allergens, an immune response that is very strongly associated with asthma. For cat allergens, understanding the relationship between indoor exposure and disease has been complicated not only because high exposure does not progressively increase either the prevalence of sensitization or the titer of IgE antibodies, but also because the major cat allergen Fel d 1 becomes distributed throughout a community, including schools and homes that do not have a cat. When it is possible to sort out the separate effects of exposure on both sensitization and inflammation of the lungs in allergic individuals, it appears that the latter relationship is similar for cat, dust mite, and cockroach [13]. It is sensitization that may be inhibited by very high exposure. However, the cat may have more to teach us about allergic disease. It appears that there are a significant number of children and young adults living in homes with a cat, who despite having positive skin tests, are not aware of significant symptoms. It is this population that is at risk of increased symptoms after a month or two away from home. Furthermore, this may reflect a more rapid fall in IgG than IgE with a major decrease in exposure. This in turn reflects the fact that IgE plasma cells are long lived and become established in protected sites in the bone marrow [42] and may not be influenced in the short term by major changes in exposure. These results present a challenge to simplistic views about allergen avoidance and remind us that we still have much to learn about the ways in which the immune system adapts to high exposure.

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Key points

- Allergens that contribute to allergic diseases including asthma are diverse and sometimes unsuspected.
- While the amount of allergen to which a sensitized individual is exposed may correlate with degree of lung inflammation, the same does not hold true for amount of exposure to cat and the risk for sensitization.
- The reasons for increasing prevalence of asthma are not clear but may be related to lifestyle changes including sedentary habits amongst children as well as sensitization to indoor allergen.
- Cat is a particularly complex allergy that has served as the platform for discovering: 1) how an indoor allergen can be important even in children not living with the allergen source (i.e., cat); 2) that tolerance may be lost when young adults lose constant exposure by moving from a home with a cat to a dorm room; and 3) the existence of an ectoparasite induced IgE response that cross-reacts with cat but does not create risk for asthma.

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Table 1

Partial list of proteins and other molecules that we are exposed to in a house with a cat

Molecule	Allergen Name	Nature of Epitope	Inhalant Allergen	Prevalence of Sensitization	Cross-reactivity
Uteroglobin[‡]	Fel d 1	Protein	+++	≥ 90%	Other cats
Cat albumin	Fel d 2	Protein[*]	±	5%	Pork and other albumins
Cat IgA	Fel d 5w	Oligosaccharide[#]	No	0–15%[#]	Selected proteins in all mammals
Lipocalin	Fel d 4	Protein	Unknown	?	Can f 2
Cat DNA[¶]	-	NR	-	-	-
Endotoxin[†]	-	NR	-	-	-

[‡]The function of the protein in the cat is not well understood.

[*]Primary sensitization to cat (or dog) albumin with cross-reactivity to pork (and sometimes beef) albumin (i.e., pork-cat syndrome).

[#]The epitope is galactose-α-1,3-galactose and the prevalence of sensitization is highly dependent upon the prevalence of tick bites [27].

[¶]Cat DNA, as with other mammalian DNA, is fully methylated.

[†]Although cats produce endotoxin, it is not clear that airborne endotoxin is increased in homes with a cat.