

Impact of allergen exposure on bronchial hyperresponsiveness

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S. Dreborg
Oslo, Norway

S. Dreborg, Voksentoppen, Ullveien 14,
N-0394 Oslo, Norway

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The most prominent feature of clinical asthma is bronchial hyperresponsiveness (hyperreactivity, BHR). Another common observation by patients is that contact with animals or other objects may induce sudden worsening of asthma (1). Many papers have focused on the relation between allergen/allergy and asthma/BHR. Cockcroft et al (2) showed a correlation between the skin sensitivity to allergens and BHR. Although BHR is seen in many patients, especially adults, without allergy, the dominating opinion has been that exposure to allergens plays an important role for the development of the inflammation present in the bronchial wall of asthmatics.

The early bronchial response to allergen challenge starts within minutes after allergen exposure, whereas the late bronchial response to allergen appears 6 hours after allergen challenge and lasts for some days (3). In 1982, Cockcroft et al reported that BHR may remain for weeks after a single allergen contact. This may possibly explain why asthmatics are hyperresponsive for long periods of time, without any known allergen contact. The fact that many patients are hyperresponsive in their bronchi with no obvious exposure to allergen has been interpreted by some chest physicians as indicating that allergy does not play any role for the maintenance of asthma/BHR.

Early studies of the relation between asthma and allergen exposure were limited to high allergen dose exposure for only a short period of time, i.e. during bronchial challenges. More recent studies have pointed on the importance of continuous exposure to allergens for the maintenance of BHR, e.g. the study by Tom Platts Mills (5) showing that the BHR of mite allergic children gradually decreased, when staying in a mite-free environment for several months. This was later confirmed by Boner (6) and others.

Many different approaches have been used to investigate how much allergen is needed to induce allergic asthma. These studies will be reviewed in this paper.

Concentrations of mite allergen in dust inducing acute asthma

In a well designed study, Platts Mills et al (7) studied the allergen levels in dust from homes of asthmatic patients attending the emergency room because of an acute asthma attack and sensitized mainly to mites. They found that mite-allergic patients with acute asthma had $\geq 10 \mu\text{g}$ of the major mite allergen, *Der p 1*, per gram of dust in their housedust.

There are no data confirming these findings and no data on concentrations of allergen in dust inducing acute allergic asthma in children.

Doses of allergen inducing slight asthma – increased BHR

Only one study in adults has investigated the doses maintaining low-grade asthma-BHR, the study by Ihre & Zetterström (8). They performed allergen bronchial challenges in asthmatics with “ordinary” sensitivity to the allergen in question. The subjects were challenged once a day on 7 consecutive working days by bronchial provocation with an allergen to which they were sensitized. They were challenged with 1 Nordic BU per day using a nebulizer. No immediate symptoms were recorded. The BHR, as measured by histamine bronchial provocation tests, increased significantly from before to after the allergen challenge period. One Nordic BU is equal to 1 ng of major allergen (9). Thus, these authors showed that inhalation of 1 ng of major allergen during a few minutes/day can increase the BHR. Whether the same effect would be achieved by inhalation of 1 pg/minute (1 day = 1440 minutes) remains to be shown (see below).

Doses of allergen inducing acute asthma as measured by bronchial challenge tests

There is only one report (10) on how much inhaled allergen that induces acute asthma using standardized allergen extracts with known major allergen content. The mode of the distribution was between 1,000 and 10,000 BU, i.e. 1–10 µg of major allergen (9), for different allergens. The mode was used, since patients with low sensitivity were not included in this study. The most sensitive patients reacted to 1 BU, i.e. 1 ng of major allergen. The distribution of bronchial sensitivity was similar to that of skin prick tests and conjunctival provocation tests (11), both regarding concentrations and mode/median of the distribution. Thus, there is a million-fold variation in the bronchial reactivity among individuals sensitive to the same allergen.

The bronchial challenge can be compared to a sudden exposure to an allergen, e.g. a cat, i.e. the most sensitive patients may get asthma after inhalation of about 1 ng of major allergen within a short period, e.g. on direct contact with an animal. Compare these data to the data on airborne allergens in schools as related below.

Allergen levels in dust provoking slight to moderate asthma

Our group started to investigate allergen levels in the public environment of children, like schools (12, 13) and day care centres (14), trains, buses, etc. (15), when we observed that children with asthma sensitized to dog and cat got worse when they returned to school after the vacations most often spent in an animal-free environment. Most of these children were depending on inhaled steroids when attending school. Thus, the levels of major allergen found in school dust, i.e. about 1 µg of major allergen per gram of fine dust, has the ability to maintain moderate steroid-dependent asthma.

Allergen concentrations in the air

There are only a few published reports on the allergen concentrations in the air. Sachaguchi et al (16) reported on allergen levels in homes with cats and dogs and homes without any pets. They found about 100 ng/m³ in the air of homes with several animals and less than 16 pg/m³, i.e. below the detection limit, in homes without pets.

In a preliminary study (17), we largely confirmed the data of Sachaguchi et al (16) and added data on allergen levels in the air in schools, where we found about 1 ng/m³, and in the air of homes without animals, where we found about 1 pg/m³ of air.

Since then, we have performed several studies in homes and schools confirming these levels. Egmar et

al (18) found nanogram-levels per m³ in the air of ordinary day-care centres and lower, down to pg/m³, in special day-care centres adopted to the needs of allergic children, albeit there was a wide variation.

Allergen concentrations in the air provoking allergy/asthma

In 1976, David Marsh (19) calculated that about 1 µg of major allergen was inhaled by humans during the ragweed season, i.e. during about one and a half months. This means that about 25 ng is inhaled per day, $\approx$ 1 ng/h and provided a child is playing outdoors for 4 h a day he will inhale 5 ng/h, i.e. 20 and 100 pg/min in the two cases, respectively.

Since then, Tom van Maetre et al (20) have studied the doses inhaled in a "cat room", i.e. a room housing a cat. The patient is observed until symptoms develop and the amounts of allergen in the air is measured. They found the median dose of *Fel d 1*, the major allergen of cat dander, provoking asthma in their patients was 60 ng. Recently, Ohman et al (21) reported on allergen levels in cat rooms in a larger number of exposures. Patients got symptoms within one hour and many had to leave the room before one hour of exposure. The allergen levels in the cat room varied considerably, i.e. at the start of the experiments between 1 and 4 µg/m³ (median), i.e. much higher than found by us in catteries (17).

From our data it can be calculated that asthmatic school-children inhale about 60 ng/h in a home with several cats or dogs, i.e. about 600 pg/h or 10 pg/min, assuming a minute ventilation of 10 l, in schools, day-care centres and other public places and about 0.6 pg/h at home. At least levels < 600 ng/h or 10 pg/min, i.e. the amounts inhaled in schools, are able to maintain slight to moderate asthma in allergic children.

In a recent preliminary study, we used a personal high volume sampler (4 m³/h) for collection of dust close to the face of an individual. When sampling by a person in ordinary office work for 6–24 h, we found less than 0.1 pg of the major cat allergen (*Fel d 1*) was inhaled/m³, i.e. during about 3 h (unpublished data). Thus, these tiny amounts are able to maintain slight to moderate asthma in cat or dog allergic children.

Time course of allergic inflammation and BHR after long-term allergen exposure

Boner et al (22) found that both the BHR and eosinophil mediators in serum (ECP, EPX) normalize when children are brought from their homes with high mite allergen content in the dust to a boarding school in the Alps with low mite allergen exposure and that both BHR and eosinophil mediators increase again when returning home for vacations.

In children with pollinosis we found (23) that both the BHR as measured by methacholine bronchial provocation tests and the peak expiratory flow rate variability were maintained for several months after the pollen season, whereas eosinophil mediators, i.e. eosinophil cationic protein (s-ECP) and eosinophil protein X (s-EPX) in serum, disappeared after the pollen season. This finding suggests that eosinophil mediators are present during the late phase reaction/period of allergic inflammation but then disappear from the circulation (and the bronchial secretions?), whereas the BHR persists. This would explain why there is no correlation between asthmatic symptoms and the presence of eosinophil mediators in serum.

Time course of allergic inflammation and BHR after single allergen exposure

There are a few studies on the time course of BHR in relation to allergen challenge. Durham et al (24) found that the BHR increased already 3 h after allergen provocation, whereas the late asthmatic response did not start to develop before 6 h after challenge, i.e. the BHR was present before the late asthmatic response and the allergic inflammation.

There are two studies (25–26) reporting on the presence of eosinophil mediators in serum after allergen challenge. Both were short-term studies and showed presence of eosinophil mediators in serum for up until 72 h after challenge.

Based on our results from the PAT study (27), we have suggested that eosinophil mediators and allergic inflammation disappear after some days after direct allergen exposure in parallel with the decline of the late asthmatic reaction, whereas BHR persists for weeks (4), i.e. BHR and allergic inflammation are varying independently of each other.

Conclusion

Bronchial hyperresponsiveness is associated with allergen exposure, but the mechanism and time course is different from that of the allergic inflammation.

Bronchial hyperresponsiveness is provoked by direct allergen contact, starts earlier than the late reaction and lasts for weeks after the late reaction, closely related to the allergic inflammation, has disappeared.

Allergen levels ≥ 10 $\mu\text{g/g}$ of fine dust are favouring acute asthma in mite-allergic subjects and levels of < 1 μg of cat or dog allergen/g of dust maintain slight to moderate asthma.

Allergen levels in the air of about 1 ng/m^3 , maintain slight to moderate asthma, whereas 100 times more is found in environments where acute asthma is induced in many patients.

Concentrations of allergen in dust and air protecting most individuals allergic to mite, cat or dog, from symptoms have not been established. This must be further investigated by studies of allergen levels in environments where allergic children get acceptable levels of symptoms. Furthermore, ongoing studies investigate the association between BHR, allergic inflammation and clinical asthma.

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