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Experimental Asthma Developed by Room Air Contamination with Cockroach Allergen

Abstract

To study the asthmagenic effect of certain airborne elements of the home environment, we studied a group of guinea pigs exposed to aerosolized cockroach allergen (CRa) and side-stream cigarette (S-SC) smoke. Four groups of guinea pigs were exposed to aerosols, either saline or CRa, for 4 weeks, after a sham or S-SC smoke pretreatment. Anaphylactic antibodies were measured by passive cutaneous anaphylaxis (PCA) assay and by skin test. Animals were challenged with aerosol CRa on day 35, and lung function and leukotrienes (LTB₄ and LTC₄/D₄) were measured. Skin tests were positive on days 21 and 29. The antibodies were heat-stable, IgG1a-like antibodies (PCA titers 1:2–18). The CRa challenge caused an immediate reduction in both the maximal expiratory flow rate at 50% of the lung capacity and respiratory compliance. The decreased lung function continued for up to 6 h ($p < 0.0001$). LTB₄ and LTC₄/D₄ were elevated ($p < 0.0001$) in the sensitized animals at the corresponding times of reduced lung function. S-SC smoke did not affect the CRa sensitization; instead, a protective effect on the CRa-induced bronchospasms was noted. Thus, the study indicates that a simple airborne CRa exposure without an adjuvant sensitizes guinea pigs, and that the animals respond to antigen challenge with CRa-specific airway obstructions.

Key Words

Asthma
Side-stream cigarette smoke
PCA
Leukotrienes
Inhalation challenge

Introduction

The mortality and morbidity rates of inner-city asthmatics are rising despite substantial progress in understanding the immunopathogenesis of asthma as well as its pharmacomodulations [1–7]. Inner-city asthmatics generally have severe asthma and heavily utilize hospitals and emergency rooms. Moreover, they are frequently allergic to multiple inhalants, including indoor allergens such as dust mites and cockroaches [8–10]. A cockroach-allergic subgroup, which can be up to 40–60% of inner-city asthmatics, usually shows highly elevated IgE antibodies [11–13]. These high-risk asthmatics have often lifelong asthma starting in early

childhood and they are clustered in families of low socioeconomic status where smoking commonly takes place. These subjects often live in crowded urban dwellings infested with cockroaches, and the rate of cockroach sensitivity seems to correlate with the severity of the infestation of the pest [14].

The role of aeroallergens in the severity of asthma is well documented, particularly the role of indoor allergens [8–10]. Cockroach allergen (CRa), one of the indoor environmental allergens of the inner city, is well known for inducing dual asthmatic reactions in patients shown to have allergic sensitivities [11, 12]. However, the mechanism of the allergic sensitization process or asthmagenesis of the indoor allergen is not yet clearly understood. Moreover, de-

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spite considerable recent interest in inner-city, high-risk asthma, few attempts have been made to delineate whether a factor or factors in the indoor environment are responsible for the development of the allergic sensitization and asthma.

In order to study the risk factor(s) of inner-city asthma, the authors elected to study the asthmagenic effects of cockroach infestation and indirect cigarette smoking, both of which are often common denominators of the indoor environment in the clusters of high-risk asthmatics. The authors designed an experiment in which guinea pigs were exposed to the airborne CRa and/or indirect cigarette smoke. The sensitization to CRa was used to determine whether animals become allergic and asthmatic, while exposure to indirect cigarette smoke acts as an adjuvant in the allergic sensitization.

Animal models have been used to investigate allergic diseases [15–21]. Guinea pigs are frequently used, and sensitization is often achieved by intraperitoneal injection of an antigen boosted with an adjuvant, i.e., Al(OH)₃ or pertussis vaccine, to produce a human IgE equivalent of reaginic antibodies, IgG1a and IgE [18, 19]. However, the traditional model in which animals are sensitized by intraperitoneal injection of an antigen with or without an adjuvant is inappropriate for testing the hypothesis that chronic exposure to an airborne indoor allergen, with or without indirect cigarette smoke, sensitizes the animals to become asthmatic.

The present study is based on our earlier work [21, 22], and extends it to confirm that these sensitized guinea pigs develop the cockroach allergic asthma. Simultaneously, the authors compared the reliability and accuracy of skin test versus passive cutaneous anaphylaxis (PCA) assays in detecting the allergic state of the animals. This study has the full approval of the Institutional Review Board of the University of Kentucky.

Materials and Methods

Experimental Design

English short-hair guinea pigs were divided into four groups (8 in each group): control received sham smoke followed by diluent sensitization, Smoke + CRa received side-stream cigarette (S-SC) smoke followed by CRa sensitization, CRa received sham smoke followed by CRa sensitization, and Smoke received S-SC smoke followed by diluent sensitization. The order of the experimental groups was selected randomly. Four guinea pigs from each group were placed in a semiclosed chamber during smoke pretreatment and aerosol sensitization. During the period of sensitization, blood (1.0 ml) was drawn via cardiac puncture at day 0, 19, and 30, and the serum was stored at –20°C to be used later for PCA assay. An allergy skin test was performed on the shaved skin of the ventral side on days 21 and 29 of sensitization. After a full week of resting, all animals were challenged with CRa inhalation

on day 35. Arterial cannulation was done using a polyethylene tube, PE 50 (Clay Adams, Parsippany, N.J.), for measurement of leukotrienes, and an endotracheal tube was surgically inserted under pentobarbital sedation. Pulmonary responses and changes in anaphylactic mediators were measured at 0, 5, 45 and 360 min after completion of a 30-min challenge.

Animals

Male English short-hair guinea pigs weighing 200–250 g, used for sensitization, and male Hartley guinea pigs weighing 200–300 g, used for PCA, were obtained from Hilltop Laboratory (Scotsdale, Pa.). The animals were maintained at the animal quarters of the Tobacco and Health Research Institute and Division of Laboratory Animal Resources, University of Kentucky.

Cockroach Sensitization

Cockroach aerosol sensitization was done as previously described [22, 23]. Briefly, 4 guinea pigs were placed in a semiclosed chamber connected to an ultrasonic nebulizer (Ultra-Neb 100, DeVilbiss). CRa (0.5 mg in 10 ml of isotonic saline) or diluent was aerosolized for 45 min, and animals were kept in the chamber for an additional 60 min. This treatment was performed twice a day, 5 days a week. The CRa used was a lyophilized German cockroach extract obtained from Greer Laboratories (Lenoir, N.C.). The Smoke + CRa and the Smoke groups were exposed to S-SC smoke for a period of 10 min prior to antigen or diluent exposure. S-SC smoke was done as previously described by Griffith and Hancock [24]. Sham smoking was accomplished by keeping the animals in the chamber without a lit cigarette.

Measurement of Anaphylactic Antibodies

Guinea pig anaphylactic antibodies were measured by two independent methods, PCA assay and skin testing. First, PCA for both IgE and IgG1a-like antibodies was measured by the same method described in our earlier study [22, 23]. Briefly, thawed serum was divided into 2 aliquots, 1 nonheated for IgE, and the other heated (56°C for 4 h) for IgG1a antibodies. Each aliquot was serially diluted, 1:2, 1:6, 1:18, 1:54, 1:162 and 1:486, and inoculated to the shaved back skin of the Hartley guinea pigs. The nonheated serum was further divided into 2 aliquots, one of which was heat-treated at 56°C for 30 min. Both main aliquots for IgE antibody were assayed 7 days after inoculation. The heated serum for IgG1a was assayed for PCA 4 h after inoculation, by challenging with CRa intravenously (1 mg mixed with Evans blue in phosphate-buffered saline). Mean diameters of the bluing areas were measured 30 min after challenge. Second, a skin test was performed with 0.03-ml injections intracutaneously for three strengths of CRa, 0.5, 5 and 50 µg/ml, plus negative and positive (histamine base 0.1 mg/ml) controls. The resulting 'wheals' were measured lengthwise and vertically 30 min after antigen injection.

Measurements of Airway Responses to Antigen Challenge

A sensitized guinea pig was anesthetized with an intraperitoneal injection of sodium pentobarbital (30–35 mg/kg), cannulated for blood drawing, intubated with an endotracheal tube, paralyzed with gallamine triethiodide administered intravenously (10 mg/kg), and artificially ventilated. The animal was placed supine inside a 2.8-liter whole-body plethysmograph. The maximal expiratory flow volume maneuver was carried out as described previously [25, 26]. Briefly, the flow rate was monitored with a Statham PM 15 differential pressure transducer as the pressure dropped across three layers of 325-mesh wire screen in the wall of the plethysmograph. The lung volume

Table 1. Results of allergy skin test

Group	Diluent	CRa 0.5 µg	CRa 5 µg	CRa 50 µg	Histamine
Control (n = 8)	0±0	0±0	0.1±0.1	0.6±0.3	8.7±0.2
Smoke + CRa (n = 8)	0.5±0.3	3.6±0.4 ^{a,b}	6.8±0.3 ^{a,b}	8.9±0.3 ^{a,b}	9.1±0.2
CRa (n = 8)	0.6±0.3	3.5±0.2 ^b	6.3±0.3 ^b	8.6±0.4 ^{a,b}	9.2±0.2
Smoke (n = 8)	0.3±0.2	0.3±0.2	0.6±0.3	1.4±0.3	8.6±0.2

Values are means ± SEM. Size of wheals in diameters (mm) is given in the four groups of guinea pigs on day 21.

^a p<0.05 vs. control;

^b p<0.05 vs. Smoke.

change was measured via integration of flow. Airway opening pressure (Pao) was measured and the lung was inflated 3 times to total capacity (lung volume at Pao = 30 cm H₂O). At peak volume during the third inflation, the inflation valve was shut off, and immediately another solenoid valve for deflation was automatically turned on. The deflation valve was connected to a 20-liter container with a negative pressure of 40 cm H₂O. This negative pressure produced the maximal expiratory flow (Vmax). The maximal expiratory flow volume plot was recorded and stored on a cathode ray storage oscilloscope (Hitachi, V-134). Respiratory compliance (Crs) was obtained by dividing the tidal volume by its accompanying Pao difference during artificial ventilation. The Pao difference was measured between end inspiration and end expiration (i.e., instrument zero flow). The maximal expiratory flow rate at 50% total lung capacity (Vmax50) was obtained.

After baseline measurements of lung function were made and blood was drawn, the animal was challenged with CRa. 1 mg/10 ml of buffered saline. The aerosolized CRa was delivered by an ultrasonic nebulizer, connected to the respirator for a duration of 30 min. The Harvard respirator used was set at a rate of 60 breaths per minute with a tidal volume of 8–10 ml/kg.

Measurement of Leukotrienes B₄ and C₄ D₄ in Arterial Blood

Leukotrienes B₄ (LTB₄) and C₄ D₄ (LTC₄ D₄) were measured by ELISA Technologies kit (product B₄: No. 406110 and C₄ D₄: No. 406210) according to the manufacturer's instructions. Reagents for leukotrienes, LTB₄ and LTC₄ D₄, were bought from ELISA Technologies (Lexington, Ky.). Heparinized blood was drawn from a carotid artery at 0, 5, 45, and 360 min after completion of the CRa challenge and stored at -20°C for later use. The minimal detectable level was 0.02 ng/ml with a constant variance of ≤10%.

Statistical Methods

Values are reported as means ± SEM. Variances in deviation from the mean were analyzed to establish the statistical significance of the four groups for each variable collected. A repeated-measure ANOVA was performed on the raw values. Post hoc comparisons were based on Fisher's least significant difference procedure. p values less than 0.05 were deemed statistically significant. A mainframe SAS application was used.

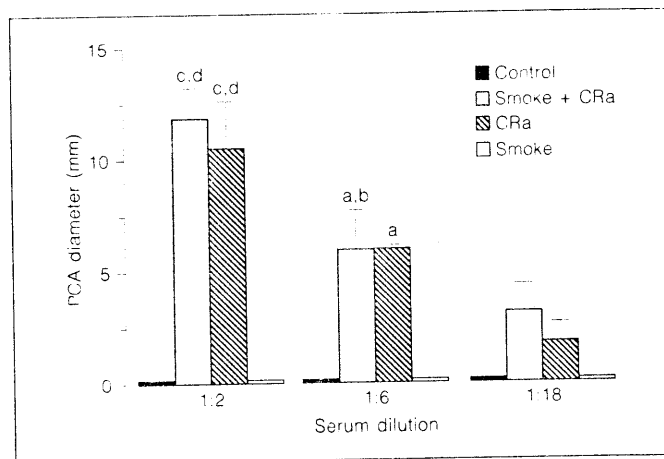


Fig. 1. Result of PCA for IgG1a antibody. Guinea pig serum was collected on day 30. Results shown are means ± SEM (n = 8, each group). ^ap<0.05 vs. control; ^bp<0.05 vs. Smoke; ^cp<0.01 vs. control; ^dp<0.01 vs. Smoke.

Results

Development of Anaphylactic Antibodies upon Allergen Sensitization

A skin-sensitizing anaphylactic antibody was detected on days 21 and 29 by means of allergy skin testing in the Smoke + CRa and the CRa groups (see table 1). Potencies and dose responsiveness were similar on both days of sensitization in both antigen-sensitized groups. 'Flare' reactions (erythema) were mild, the flares only slightly larger than the 'wheals' themselves. However, PCA assays did not pick up positive reactions on days 0 and 19 in these animals (the Smoke + CRa and the CRa groups) and failed to do so until day 30 when low titers (1:2–1:8) of IgG1a-like antibodies appeared (see fig. 1). No IgE-like heat-labile antibodies were detected on day 19 and 30. The noted IgG1a-like antibodies were similar in potency in both groups of animals, the Smoke + CRa and CRa.

Table 2. Comparative changes in Vmax50 following CRa challenge in the four groups

Group	Vmax50, ml s				p values	
	baseline	5 min	45 min	6 h		
Control (n = 8)	77.9±6.6	77.4±6.8 (99±2)	74.8±6.6 (96±1)	76.9±7.4 (98±3)	>	p<0.0001
Smoke + CRa (n = 8)	73.3±3.0	57.0±3.0 (78±4)	56.3±3.8 (77±4)	58.7±2.8 (80±3)		
CRa (n = 7)	72.0±1.5	51.2±4.3 (71±4)	51.5±3.5 (69±5)	50.1±3.8 (69±5)		
Smoke (n = 7)	76.0±2.4	70.6±2.6 (93±4)	70.1±2.1 (93±3)	71.3±3.4 (94±2)		

Values are means ± SE. Numbers in parentheses represent % baseline values.

Pulmonary Function Changes upon Inhalation of Cockroach Extract

The CRa challenge did not induce any changes in the animals of the control group. A decrease in Vmax50 of more than 20% of baseline values was noted in 14 of 15 CRa-sensitized guinea pigs, regardless of S-SC smoking status, as compared to 1 of 14 of the non-antigen-sensitized animals ($p<0.0001$). The decreased Vmax50 was apparent at 5 min and was sustained steadily up to 6 h postchallenge in both of the antigen-sensitized groups, Smoke + CRa and CRa, as compared to the groups without antigen, control and Smoke ($p<0.0001$). Table 2 shows the comparative changes in Vmax50 induced by CRa challenge for each group of animals. Of the two groups of CRa-sensitized animals, the CRa group showed the greater reduction in Vmax50, compared with the Smoke + CRa group ($p<0.0001$).

Crs was also significantly reduced in the antigen-sensitized guinea pigs, the Smoke + CRa and CRa groups, compared to that in the control and Smoke groups. The reduction started at 5 min postchallenge, persisted, or slowly worsened during the measured duration, up to 6 h, in a similar pattern (see fig. 2).

Production of Leukotrienes, LTB_4 and LTC_4/D_4 , upon CRa Challenge

To investigate the nature of the reduced lung function in response to the allergen challenge, we measured LTB_4 and LTC_4/D_4 in arterial blood (postpulmonary). Neither leukotriene changed from the baseline values in the control group. But both leukotrienes (LTB_4 and LTC_4/D_4) were markedly elevated in the CRa and the Smoke + CRa animals

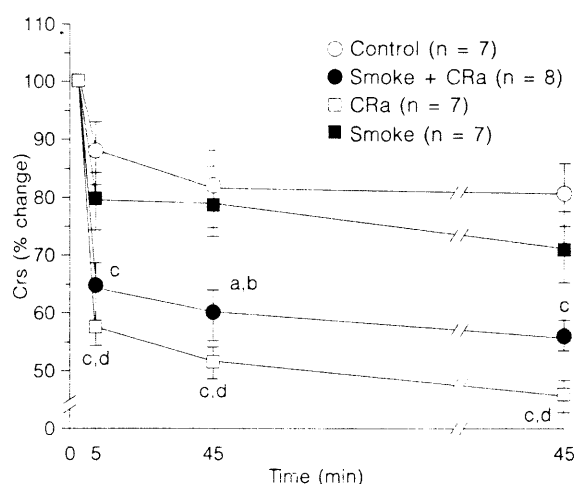


Fig. 2. Effect of acute CRa challenge on Crs. Crs was compared in 4 groups. Bar means ± SEM. ^a $p<0.05$ vs. control; ^b $p<0.05$ vs. Smoke; ^c $p<0.01$ vs. control; ^d $p<0.01$ vs. Smoke.

(see table 3) as a result of CRa challenge (both $p<0.0001$). The high leukotriene levels noted at 5 min were also sustained during the rest of the observed duration and did not fluctuate significantly from the values at 5 min postchallenge, at 45 min, and 6 h postchallenge. The elevation was more pronounced in the Smoke + CRa group than in the CRa group ($p<0.0001$).

Table 3. Comparative changes in LTB₄ following CRa challenge in the four groups of guinea pigs

Group	LTB ₄ , ng/ml				p values
	baseline	5 min	45 min	6 h	
Control (n = 8)	0.23±0.005	0.19±0.04 (91±12)	0.24±0.05 (127±31)	0.18±0.04 (95±19)	> p<0.0001 > p<0.0045 > p<0.0006 p<0.035
Smoke + CRa (n = 8)	0.22±0.06	0.87±0.23 (522±216)	0.65±0.20 (449±235)	0.79±0.18 (504±208)	
CRa (n = 7)	0.42±0.06	1.10±0.28 (261±43)	0.92±0.09 (236±27)	0.94±0.25 (220±40)	
Smoke (n = 7)	0.45±0.05	0.45±0.04 (105±13)	0.34±0.06 (82±13)	0.24±0.04 (57±13)	

Values are means ± SE. Numbers in parentheses represent % baseline values.

Effects of S-SC Smoke on CRa Sensitization

The effects of the S-SC smoke pretreatment in the production of anaphylactic antibodies are negligible (table 1, fig. 1). CRa-specific reagins in the guinea pigs of the Smoke + CRa group did not differ from those of animals in the CRa group as detected by either allergy skin test or PCA assay. The effects of the pretreatment, however, were shown in the bronchoconstrictive responses of the sensitized animals to the CRa challenge (table 2, fig. 2) and in the levels of leukotrienes (table 3). The CRa challenge induced more significant reductions in Vmax50 and in Crs in CRa animals than in that of Smoke + CRa animals (both $p < 0.0001$). The bronchoconstrictive responses began at 5 min postchallenge and continued throughout the duration. The S-SC pretreatment effects were again reflected in the Crs, i.e., less severe reductions in the Smoke + CRa group than in the CRa animals ($p < 0.0001$).

The changes in the leukotriene LTB₄ level of the Smoke + CRa group were more exaggerated than those of the CRa group in response to the CRa challenge (table 3). Changes in the levels of LTC₄/D₄ followed a pattern similar to those of LTB₄.

Effects of S-SC Smoke in Nonsensitized Guinea Pig

The effects of repeated S-SC smoke alone in the development of anaphylactic antibody are shown in the Smoke group by skin test (table 1) and by PCA assay (fig. 1). Baseline Vmax50 and Crs of the Smoke animals were 76.0 ± 2.4 ml/s and 0.44 ± 0.02 ml/cm H₂O, respectively. In comparison, those of control animals were 77.9 ± 6.6 ml/s and 0.42 ± 0.02 ml/cm H₂O, respectively. The pulmonary re-

sponse of the Smoke animals to the CRa challenge was slightly exaggerated from the baseline values in Vmax50 compared to that of the control animals ($p < 0.0001$). Yet there was no difference in the changes in the Crs (fig. 2). Levels of LTB₄ in Smoke animals were higher than those in the control animals; still, the changes from the baseline value after the CRa challenge were negligible (table 3). LTC₄/D₄ levels in Smoke animals were not different from those of control animals at baseline or of the control group in the postchallenge period.

Discussion

Our findings indicate that repeated exposure of animals to air contaminated with CRa makes animals allergic. Moreover, the sensitized animals appear to develop 'asthma-like' responses to CRa inhalation challenges. The CRa-sensitized animals develop IgG1a-like, but not IgE-like antibodies in contrast to other guinea pig asthma models reported [15–18]. In our earlier work animals sensitized by CRa aerosol produced IgG1a antibody, while animals sensitized by the intraperitoneal route produce both IgE and IgG1a antibodies [22, 23]. The reasons for the absence of IgE, one of two guinea pig reagins, in aerosol-sensitized animals are not clear. The absence could be related to either the entry of allergens or the lack of adjuvant during the sensitization process. In our animal model, unlike in other asthma models, no adjuvant or intraperitoneal injections were used. Importantly, however, the present study shows clearly that the CRa-sensitized guinea pigs with IgG1a show 'asth-

ma-like' bronchoconstrictions lasting at least 6 h after CRa challenge.

In addition, this study indicates that the sensitized state of the animal is easily determined by a simple skin test for immediate hypersensitivity *in vivo*. The dose-responsiveness and the minute doses of allergen eliciting a positive reaction serve to document the specificity and the sensitivity of the skin test method (0.0125 µg of allergen elicited positive reactions). The skin test appears to detect the anaphylactic antibody as accurately as a PCA assay, if not more so. The test was positive by day 21, while the PCA assay was still negative on day 19 in the sensitized groups. This result suggests that the skin test may be more sensitive than a PCA assay in detecting anaphylactic antibodies. This finding is of significance in that it simplifies the detection of the allergic status of animals. While the PCA assay has been considered the 'gold standard' in determining the atopic status in experimental asthma [15–20], it is both expensive and time-consuming, and it requires that many animals be sacrificed. Skin testing on the other hand, is simple, reproducible, and cost-effective.

The significant allergen-specific decreases in both of the lung function parameters, Vmax50, which detects large airway dynamics [27], and Crs, which represents peripheral airway changes [28, 29], indicate that the narrowings occur in both large and small airways. Moreover, the data reveal that the airway obstructions begin immediately upon CRa challenge and persist for up to at least 6 h, the point at which we ceased taking measurements. Such persistent airway narrowings appear to differ from common ovalbumin-induced, short-term, immediate bronchoconstriction, which lasts about 30 min [30]. It is known, however, that allergic animals, if observed for more than 6 h, show bronchoconstrictions of varying durations in various patterns, including dual bronchoconstrictions – early bronchospasms and late-phase inflammation [31–33]. Dual persistent obstructive airway responses have been reported in ovalbumin-sensitized guinea pigs [31], in *Alternaria tenuis*-sensitized rabbits [32] and in *Ascaris suum*-extract-sensitized guinea pigs [33]. Such persistent airway obstruction has been observed in the cockroach-sensitive human asthmatics [11]. The similarity of human and guinea pig responses to the cockroach allergen underscores the usability of the present animal model to investigate cockroach-allergic asthma.

The elevated levels of selected leukotrienes, both LTB₄ and LTC₄/D₄, in this study support the supposition that the bronchoconstriction is most likely secondary to an allergen-induced inflammation. Apparently, the CRa-allergic guinea pigs that develop IgG1a antibody are producing the leukotrienes in response to the CRa challenge. Bioactive leuko-

trienes, known to be reflective mediators of allergic asthmatic responses, are generated *de novo* by a large number of inflammatory cells: LTB₄ is the predominant eicosanoid product of mast cells, neutrophils, monocytes, and macrophages, whereas LTC₄ is one of the predominant lipoxygenase products of many inflammatory cells, including eosinophils and basophils [34–37]. Recent studies, however, convincingly argue that mast cells account for virtually all of the reagin-dependent release of leukotrienes in humans [38]. The noted LTB₄ and sulfidopeptide leukotrienes in this study are likely derived from mast cells in the earlier phase and from macrophages and other influxed inflammatory cells in the latter part of the observed period, as noted in our earlier report [23]. Consequently, the appearance of leukotrienes in the carotid arterial blood is not unexpected. Other mast cell mediators might well have been detected had measurements been made. The seemingly early appearance (within 5 min) of both LTB₄ and LTC₄/LTD₄ may be somewhat puzzling, as both are considered to be newly generated secondary mediators of anaphylactic inflammation. However, the early appearance can be accounted for by the fact that the animals underwent antigen challenge for a duration of 30 min before measurements were initially recorded. The levels of the leukotrienes in the antigen-sensitized and challenged groups did not change at 6 h postchallenge. Leukotrienes are found to be increased in bronchoalveolar lavage fluid in allergic dogs [36]. Also, elevated LTC₄/LTD₄ and LTE₄ have been noted in sheep during acute systemic anaphylaxis [39]. However, there have been no reports, to the authors' knowledge, of elevated leukotrienes in arterial circulation after bronchial challenge, particularly, in conjunction with pulmonary function changes. Further study is in progress to clarify the kinetics of mediators in this animal model.

Finally, the present study shows an unexpected and interesting fact, namely that S-SC smoke exposure failed to exert any additive harmful influence on the allergen sensitization. There was no difference in the levels of anaphylactic antibodies detected by either skin test or PCA assay in the two groups of sensitized animals (the Smoke + CRa and the CRa groups, see table 1 and fig. 1). Furthermore, the pretreatment with S-SC smoke actually resulted in a protective effect on the allergic bronchospasms induced by the CRa challenge. This is contrary to the anticipated harmful effect: the pulmonary responses in the animals of the Smoke + CRa group were weaker than those of the CRa group. The S-SC smoke pretreatment tended to lessen the antigen-induced airway constrictions (see table 2). The explanation for this effect is speculative at present. The effect could be due to the reduced CRa penetration to lungs during antigen sensi-

zation. It is well known, for example, that acute inhalation of cigarette smoke causes transient airway constriction in humans as well as in animals [29, 40, 41]. The transient airway constriction and/or bradypnea in guinea pigs caused a reduction in the amount of allergen entering the lungs. On the other hand, the cigarette smoke might also have directly caused suppressed inflammation in the lungs by the effect of repeated exposure to cigarette smoke during the sensitization, as described by Bjerner et al. [42]. Our study reveals clearly that indirect cigarette smoke does not exert an adjuvant effect in the allergic sensitization in this animal model of asthma.

Our demonstration that cockroach allergic guinea pigs show 'asthma-like' airway obstruction may have practical implications, since the model may provide a tool for studying high-risk inner-city asthma. Although one cannot extrapolate an animal experiment to the human disease directly, the study offers a possible explanation as to why and how humans living in cockroach-infested dwellings develop a cockroach-allergic state. Particularly the sustained airway obstructions in the sensitized animals show a striking resemblance to the pulmonary responses of humans to CRA

[11]. To fully clarify the mechanisms involved, further studies are needed, and several are in progress. To our knowledge, ours is the first study in which a cockroach-allergic animal model has shown 'asthma-like' sustained bronchoconstrictions accompanied by elevated LTB₄ and LTC₄ D₄ in postpulmonary circulation. Because the animal model used in our study was developed without unnatural immunological manipulation, it may be uniquely qualified to serve as a model for the further study of naturally occurring 'indoor-allergen-induced allergic airway disease'.

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