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Original article

A comprehensive model of allergic rhinitis in guinea pigs

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Abstract

Introduction: The economic and social impact of allergic rhinitis is substantial. The effectiveness of currently available medications is limited and therefore investigations for more effective drugs is essential. This study was intended to establish a model of allergic rhinitis in guinea pigs that can be utilized for further investigation of new drugs. **Methods:** Male Dunkin Hartley guinea pigs were sensitized intranasally to, and challenged with, ovalbumin. Sneezing (SN) and nose rubbing (NR) response to allergen challenge were observed on day 21 post-initiation of sensitization in conscious guinea pigs. Nasal blockade (NB), leukocyte infiltration, and lung inflation pressure (LIP) were assessed in the same guinea pigs 23–28 days post-initiation of sensitization. A ventilator/flow method was used to measure NB and LIP. Leukocyte infiltration into nasal lavage fluid 60 min after challenge in the same animals was recorded as total and differential cell counts. **Results:** Sensitized guinea pigs produced acute allergic responses after allergen challenge. This was characterized by increases in SN, NR, NB, and eosinophil infiltration. In addition, intranasal allergen challenge did not change lung inflation pressure. **Discussion:** Allergen-induced rhinitis in guinea pigs resembles that in humans. The model reported in this study can be used to reflect the effectiveness of drugs currently used to treat allergic rhinitis and to investigate new potential drugs for the treatment of allergic rhinitis.

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Keywords: Guinea pig; Cellular infiltration; Methods; Ovalbumin; Rhinitis; Sensitization

1. Introduction

Rhinitis, especially allergic rhinitis, continues to be a major health problem and although drugs are available for its treatment, none are ideal. The major signs and symptoms of allergic rhinitis include sneezing, itching, rhinorrhea and nasal congestion (Bousquet, Van Cauwenberge, & Khaltaev, 2001). These are accompanied by infiltration of the nasal mucosa with eosinophils. There are two temporal phases to the response to challenge in sensitized subjects. The first immediate response is mainly composed of sneezing, itching and rhinorrhea while nasal congestion and cellular infiltration take a little longer to develop (Naclerio et al., 1985; Skonner, Doyle, Boehm, & Fireman, 1988; Durham et al., 1992).

In order to study allergic rhinitis, it is necessary to have useful animal models in appropriate species. Ideally, all of the

above responses are produced in a single model in a single species. However, currently, there are no models that achieve this ideal, and neither has the definitive species been identified (Szelenyi, Marx, & Jahn, 2000).

With respect to species, mice (Saito et al., 2001; Murasugi et al., 2005), rats (Albert et al., 1998; Sugimoto et al., 2000), guinea pigs (Mizuno, Kawamura, Iwase, & Ohno, 1991; Zhao et al., 2005), dogs (Revington, Lacroix, & Potter, 1997; Tiniakov, Tiniakova, Mcleod, Hey, & Yeates, 2003) and pigs (Szelenyi et al., 2000) have all been used. With the advent of knockout animals mice have received much more attention since it is possible in this species to knockout what are perceived to be essential pathophysiological processes in a selective manner. In addition, techniques for recording functional responses to allergen challenge have been miniaturized so as to be usable in mice. However, mice appear to be poor analogues for humans in that allergic pathophysiological processes are often different between the two species. With respect to the latter point, it appears that the guinea pig is a better species in that it mimics humans in terms of rhinitic

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responses to allergic challenge, and in terms of the pathological mediators involved (Fukuda et al., 2003; Mizutani, Nabe, Sasaki, Takenaka, & Kohno, 1999; Nabe et al., 2001; Yamasaki et al., 2001; Zhao et al., 2005).

Many models are limited in the extent to which the changes induced by allergic challenge in sensitized animals are measured. Thus, some models concentrate on a single aspect of the allergic nasal response such as sneezing, or nasal congestion, or rhinorrhea, or nasal exudation, or cellular infiltration. Not many models concurrently measure more than one response. However, the concurrent measurement of the whole spectrum of responses is important for the following reasons. Many of the current treatments for allergic rhinitis are effective, but are limited in that they do not alleviate all symptoms simultaneously. In the experimental search for new treatments for allergic rhinitis, as opposed to mechanistic studies, it is important to use models that reflect all of the changes induced by the allergic response.

We have, therefore, attempted to develop a model that measures most of the changes induced by an allergen nasal challenge in guinea pigs.

2. Methods

2.1. Animals

The use of male Dunkin Hartley guinea pigs (Charles River Laboratories, Canada) for this study was approved by the University of British Columbia Animal Care Committee. The animals weighed 300–400 g during the sensitization period and 400–600 g at the time of experiments. Animals were housed in an air-conditioned room at 23 ± 2 °C, and $55 \pm 5\%$ humidity, with alternating 12 h light/dark cycles and with food and water ad libitum.

2.2. Sensitization

A sensitization procedure first described by Yamasaki et al. (1997) was used with some modifications. Guinea pigs were initially exposed to 1% ovalbumin (Grade V, Sigma, Germany) in saline given as a 1% aerosol twice for each of 10 min, 7 days apart. The aerosol was generated by an ultrasonic nebulizer (ULTRA-NEB 99, DeVILBISS Co., Canada) and a ventilation pump set at 4 ml/stroke, 70 strokes/min. On days 14, 15 and 16, a booster of 1% ovalbumin in saline was instilled intranasally at

a volume of 20 μ l/nostril/day into both nostrils. The instillation was performed using a micropipette (200 μ l capacity). On day 21 guinea pigs were challenged with 2% ovalbumin in saline instilled intranasally at a volume of 20 μ l/nostril in each nostril. The sensitization process is shown diagrammatically in Fig. 1. In this study, the same animal was used for the measurement of sneezing, nose rubbing, nasal airway pressure, lung inflation pressure and leukocyte infiltration.

2.3. Sneezing and nose rubbing

On day 21 post-first sensitization, conscious guinea pigs were challenged intranasally either with 2% ovalbumin in saline at 20 μ l/nostril, or control, 20 μ l saline/nostril. After challenge, guinea pigs were observed individually (one guinea pig at a time). Sneezing and nose rubbing were assessed by observation in a randomized blind fashion and were counted directly following nasal challenge, and for 30 min thereafter. A sneeze was characterized by an explosive expiration just after deep inspiration. A nose rub was characterized by an external perinatal scratch with the animal's forelimbs. It was used as an index of nasal itching. After determining sneezing and rubs, animals were left to recover for 2 days before being used in the next experiment.

2.4. Measurement of nasal airway pressure (nasal blockade) and lung inflation pressure

Nasal airway pressure and lung inflation pressure were measured in anaesthetized guinea pigs as previously described by Mizuno et al., 1991 with some modifications. Guinea pigs were anaesthetized with pentobarbital (35 mg/kg, or more as appropriate) given intraperitoneally. Subsequently, both carotid artery and jugular vein were isolated and cannulated with polyethylene tubing (PE50) for blood pressure monitoring, and drug delivery, respectively. The trachea was isolated and cannulated (14G catheters) in both directions: caudally for passive ventilation and lung inflation pressure measurements, and rostrally for nasal airway pressure.

For nasal airway pressure measurements, the catheter was passed from the trachea, through the laryngopharynx and the oropharynx, toward the nasopharynx ending around 1 mm before the posterior nares. Ventilation pumps (Harvard Apparatus Limited) was used to deliver pulsatile air at a rate of 8 ml/stroke, 72 times/min directed toward the nasal cavity,

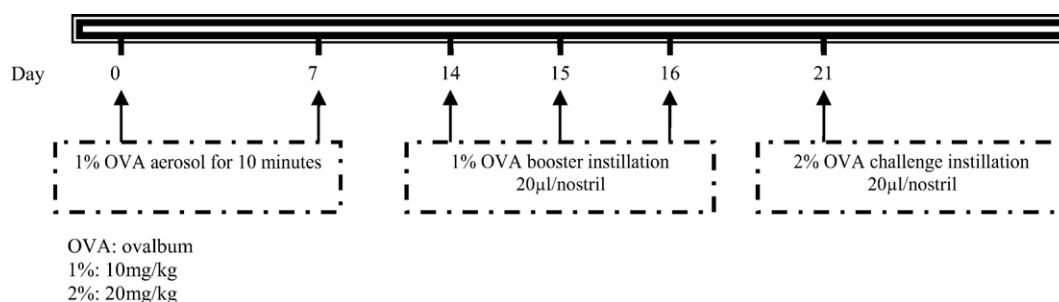


Fig. 1. The process of sensitization in guinea pigs.

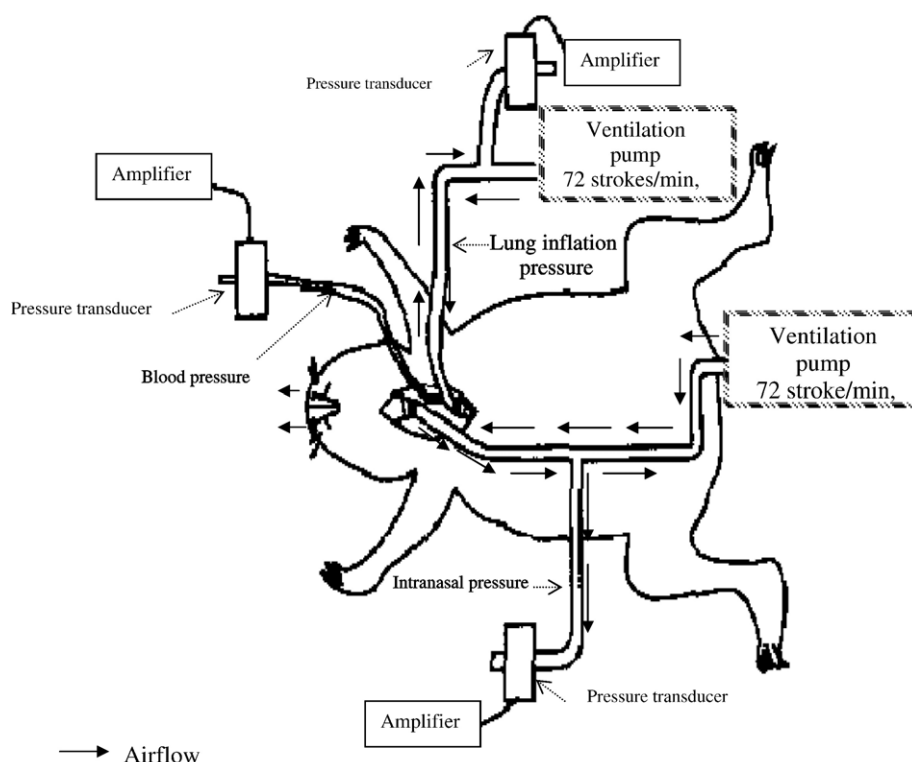


Fig. 2. Schematic representation of surgical and technical connections for nasal airway pressure, lung inflation pressure and blood pressure measurements.

and at a 10 ml/kg, 72 times/min toward the lungs. To prevent air leakage during nasal airway pressure recording, the buccal (oral) cavity was filled with epoxy-soaked cotton wool and the oesophagus was ligated with surgical thread. Intranasal pressure and lower tracheal pressure were used as indices of nasal airway pressure and lung inflation pressure, respectively, and were recorded via a port on the cannula using a pressure transducer (Astromed, Canada) and a GrassPolygraph (model 79D, Grass instrument Co. Quincy, MA, USA) (Fig. 2).

Following surgical preparation, guinea pigs were kept for 15 min to obtain stable baseline blood pressure, nasal airway pressure and lung inflation pressure. Thereafter, the nasal

ventilation pump was disconnected and 0.5 ml of 2% ovalbumin challenge infused from the tracheal side toward the nasal cavity for 5 min. At the end of the infusion, the nasal ventilation pump was reconnected and the animal was observed for 1 h (Fig. 3) as previously described by Sakairi et al. (2005) with modifications. At the end of the 60 min observation period, a nasal lavage technique was used to assess leukocyte infiltration.

2.5. Assessment of leukocyte infiltration

Nasal cellular infiltration (extravasation of leukocytes) is a characteristic hallmark of allergic rhinitis. Total and differential

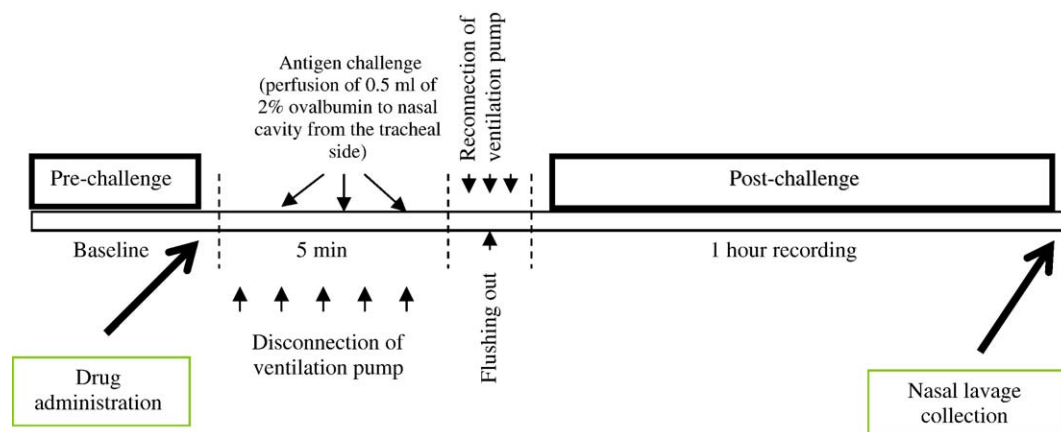


Fig. 3. General protocol for experiments in which for blood pressure, heart rate, nasal airway pressure, lung inflation pressure and cellular infiltration were measured.

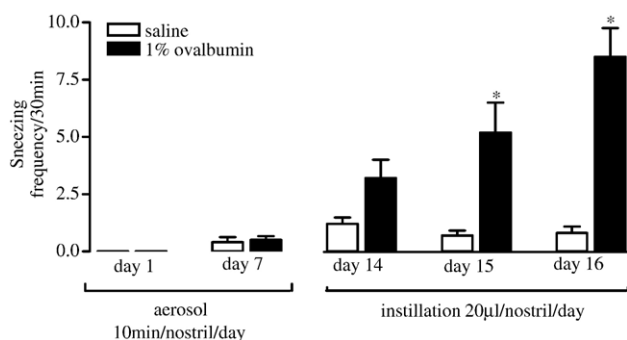


Fig. 4. Time-dependent effect of ovalbumin administration on sneezing frequency in guinea pigs measured during the sensitization period. On days 1 and 7 guinea pigs received 2% aerosolized ovalbumin or saline for 10 min in both nostrils. On days 14–16 guinea pigs were boosted with intranasal instillation of 1% ovalbumin, or saline, 20 µl/nostril in both nostrils. Sneezes were counted for 30 min immediately after aerosol/liquid exposure. *Significant increase in number of sneezes as compared to saline group ($p < 0.001$, Bonferroni multiple comparison test). Data are means from 10 guinea pigs and vertical bars are standard error of mean.

cell counts in nasal washings can be used as indices of cellular infiltration, and therefore, the allergic response. The animals described previously were monitored for 60 min before nasal lavage was performed. Nasal lavage fluid was collected from guinea pigs 1 h post-challenge as follows: nasal cavities were washed with 2 ml of pre-warmed saline infused from the tracheal side. The recovered saline was collected from the anterior nares. Total and differential leukocyte counts were made of the lavage fluid immediately after sample collection.

Total cell count was assessed using a standard hemocytometer. Methylene blue was used for cell staining and clarity of counting. Leukocytes were counted under light microscope at power 40×. The mean of two chambers cells was considered as total cell count. To determine the number of cells per milliliter, the following formula was used:

number of cells/ml

$$= \text{total number of cell counted} \times \text{dilution factor} \times 1000$$

(there are 1000 mm³/ml)/total volume counted(0.1 mm³)

To perform differential counts, 100 µl of nasal lavage was centrifuged using a cytopsin (Shandon Cytospin 1) at a speed of 1500 rpm for 5 min. The sample was then stained with a solution of Wright's stain (Fluka, D89555, Steinheim, Germany) for 5 min. White blood cell types (eosinophil, neutrophil, basophil, monocyte and lymphocyte) were determined based on their morphological characteristics. The number of each type of cell was counted under 40× power. Total number of cells, per three consistent fields observed, was used to reflect the total number of cells.

2.6. Experimental design and statistical analysis

The experiments were performed in a randomized double blind fashion to minimize observational bias. Guinea pigs were divided into sensitized ovalbumin challenged groups, and non-

sensitized ovalbumin/saline challenged groups (controls). The data from all the studies were analyzed using parametric statistical tests to determine the probability of rejecting the null hypothesis. In all the studies, the null hypothesis was that there was no effect of allergen in sensitized and non-sensitized groups (i.e., all the means were equal). In studies where more than two groups were involved, one way multi-way analysis of variance (ANOVA) was used, and in studies where two groups were involved and studied over a period of time, a repeated measure two-way ANOVA was used to determine whether variances were different. If they were different ($p < 0.05$), a post hoc test was used to compare groups. The post hoc test used was Bonferroni multiple comparison test. A probability (p) of less than 0.05 was taken as being statistically significant. In the following “bar” figures, the error bars shown are one standard error of mean.

3. Results

3.1. Assessment of model

3.1.1. Effectiveness of sensitization procedures

During the process of sensitization, a time effect of ovalbumin administration on the frequency of sneezing and nose rubbing in guinea pigs was observed. There was a frequency-dependent effect of ovalbumin administration on number of sneezes and nose rubbings ($p < 0.0001$ two-way ANOVA). The number of sneezes increased from day 1 to day 16 in the ovalbumin group. No significant effect of saline aerosol/instillation on sneezing frequency was observed (Fig. 4). The effect of ovalbumin on sneezing frequency achieved significance ($p < 0.001$) compared to the saline group on days 15 and 16.

In comparison to saline, ovalbumin sensitization increased nose rubbing ($p = 0.002$ two-way ANOVA). Significant levels

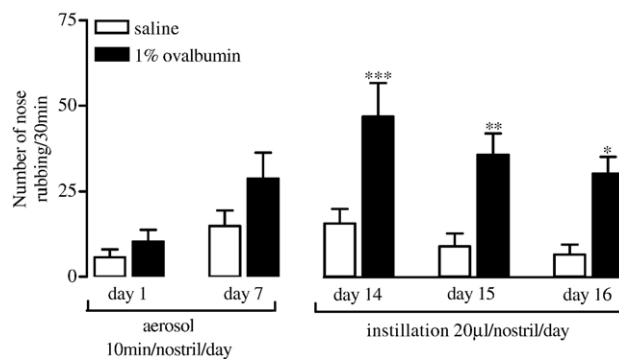


Fig. 5. Time-dependent effect of ovalbumin administration on nose rubbing frequency in guinea pigs measured during the sensitization period. On days 1 and 7 guinea pigs received 2% aerosolized ovalbumin, or saline, for 10 min in both nostrils. On days 14–16 guinea pigs received booster doses as intranasal instillation of 1% ovalbumin, or saline, 20 µl/nostril in both nostrils. Nose rubs were counted for 30 min immediately after aerosol/liquid exposure. *Significant increase in number of nose rubbing as compared to saline group (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, Bonferroni multiple comparison test). Data are means from 10 guinea pigs and vertical bars represent standard error of mean.

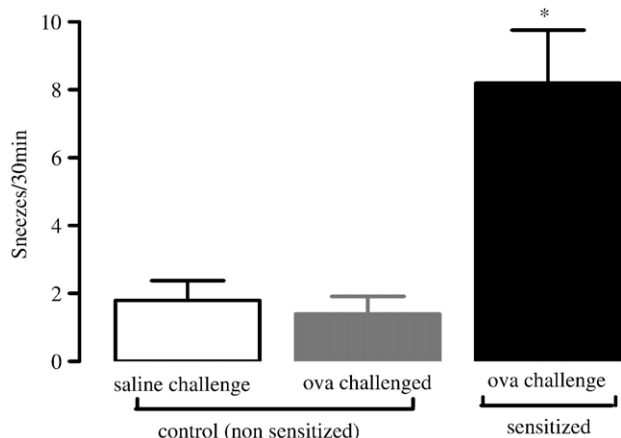


Fig. 6. Effect of ovalbumin (ova) challenge on sneezing frequency in sensitized and non-sensitized guinea pigs 21 days post-first sensitization. Guinea pigs received a challenge dose of 2% ovalbumin, or saline, 20 μ l/nostril in both nostrils and sneezes were counted for 30 min after challenge. *Significant increase in sneeze frequency as compared to non-sensitized ovalbumin challenged guinea pigs (* $p < 0.01$, Bonferroni multiple comparison test). Data are means from 5 guinea pigs and vertical bars represent standard error of mean.

of increased nose rubbing were observed on days 14 ($p < 0.05$), 15 ($p < 0.01$) and 16 ($p < 0.001$) (Fig. 5).

3.1.2. Sneezing and nose rubbing responses to allergen challenge

Ovalbumin challenge in sensitized group significantly increased sneezing frequency ($p < 0.01$) and number of nasal rubs ($p < 0.001$) as compared to a non-sensitized group (Figs. 6 and 7). Also there were no differences in responses between in non-sensitized animals challenged with ovalabumin versus saline.

3.1.3. Nasal and lung inflation pressure responses to allergen challenge

Ovalbumin challenge in sensitized animals 23–28 days post-initiation of sensitization significantly increased nasal

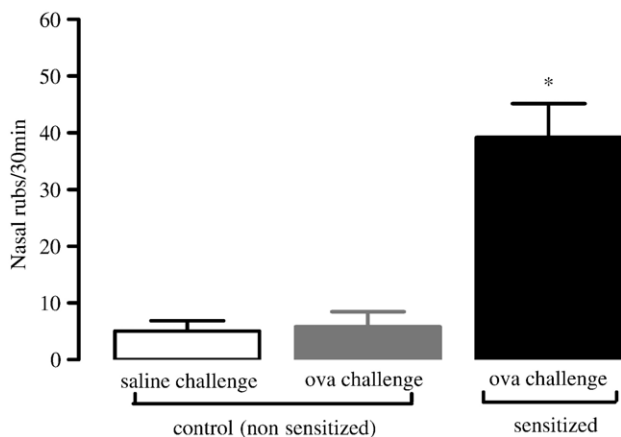


Fig. 7. Effect of ovalbumin (ova) challenge on nose rubbing frequency in sensitized and non-sensitized guinea pigs day 21 post-first sensitization. Guinea pigs received a challenge dose of 2% ovalbumin, or saline, 20 μ l/nostril to both nostrils and nose rubs were counted for 30 min after challenge. *Significant increase in nose rubbing frequency as compared to non-sensitized ovalbumin challenged guinea pigs (* $p < 0.001$, Bonferroni multiple comparison test). Data are means from 5 guinea pigs and vertical bars represent standard error of mean.

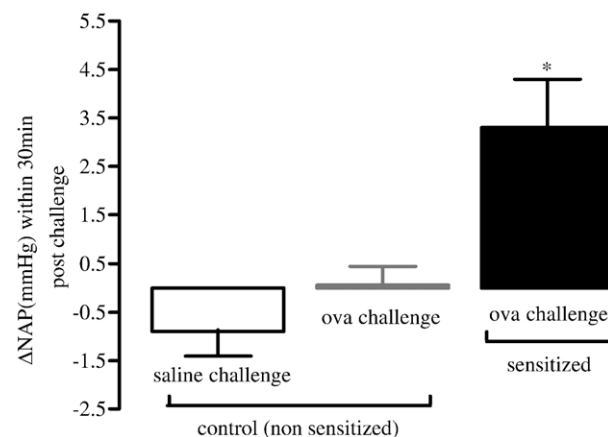


Fig. 8. Effect of ovalbumin (ova) challenge on nasal airway pressure (NAP) in pentobarbital anaesthetized (sensitized and non-sensitized) guinea pigs 23–28 days following initiation of sensitization. Guinea pigs were challenged with 2% ovalbumin or saline at a volume of 0.5 ml infused to the nasal cavities for 5 min. Nasal airway pressure was measured 30–35 min after challenge. The difference between pre-challenge and 30–35 min post-challenge values was considered as a change in nasal airway pressure. *Significant increase in nasal airway pressure as compared to non-sensitized ovalbumin challenged guinea pigs ($p < 0.05$, Bonferroni multiple comparison test). Data are means from 5 guinea pigs and vertical bars represent standard error of mean.

airway pressure ($p < 0.05$) as compared with non-sensitized groups. No significant change in nasal airway pressure was observed in ovalbumin or saline challenged non-sensitized groups (Fig. 8). Simultaneous recording of lung inflation pressure and blood pressure at the time of nasal airway pressure recordings showed no significant changes in these variables when compared between sensitized and non-sensitized groups. Thus, intranasal ovalbumin did not cause significant changes in lung inflation pressure (Fig. 9 and Table 1). However, the intravenous injection of ovalbumin caused significant increases in lung inflation pressure as discussed in Section 3.1.5.

Nasal airway pressure, lung inflation pressure, blood pressure and heart rate were also measured pre-ovalbumin

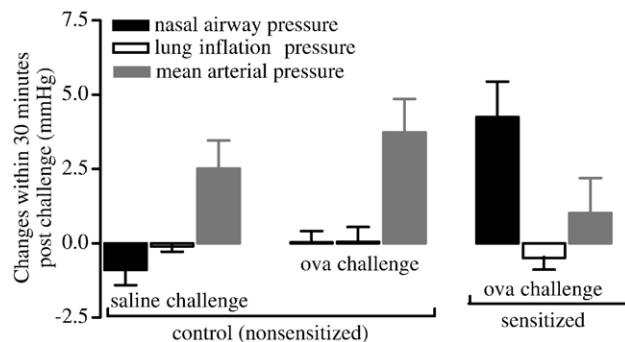


Fig. 9. Effect of ovalbumin (ova) challenge on nasal airway pressure, lung inflation pressure, and blood pressure measured simultaneously 30 min after 2% ovalbumin or saline challenge at a volume of 0.5 ml infused to the nasal cavities for 5 min in pentobarbital anaesthetized sensitized and non-sensitized guinea pigs. The experiments were conducted 23–28 days following initiation of sensitization. Data are means from 5 guinea pigs and vertical bars are standard error of mean.

Table 1

Summary of changes in nasal airway pressure (NAP), lung inflation pressure (LIP) and main arterial blood pressure (MAP) in sensitized and un-sensitized guinea pigs measured 30 min post-nasal allergen challenge

Group	Δ NAP (mm Hg)	Δ LIP (mm Hg)	Δ MAP (mm Hg)
NSC	-0.9 ± 0.5	-0.1 ± 0.2	2.5 ± 0.9
NOC	0.1 ± 0.3	0.5 ± 1.0	6.2 ± 3.5
SOC	3.3 ± 0.9^a	-0.7 ± 0.6	4.7 ± 3.7

NSC: non-sensitized saline challenged, NOC: non-sensitized ovalbumin challenged, SOC: sensitized ovalbumin challenged. The values represent mean $\pm$ S.E.M. of $n=5$.

^a Indicates $p < 0.05$ for SOC versus NSC or NOC.

challenge in both sensitized and non-sensitized guinea pigs. There was no difference in these four variables between non-sensitized and sensitized guinea pigs as is shown in Table 2 for two groups, each of 9 guinea pigs.

3.1.4. Leukocyte infiltration responses to allergen challenge

Following nasal allergen challenge in sensitized guinea pigs, there was a significant increase in total cell count ($p < 0.01$) as compared with non-sensitized groups. No significant effects of ovalbumin/saline challenge in non-sensitized groups was observed (Fig. 10). Furthermore, ovalbumin significantly induced both eosinophil ($p < 0.01$) and neutrophil ($p < 0.05$) infiltration in sensitized guinea pigs compared with non-sensitized guinea pigs. No significant effect of ovalbumin challenge was observed on other cell types (Fig. 11). As shown, ovalbumin given to non-sensitized guinea pigs did not increase leukocytes in nasal lavage. There was no indication that saline given to sensitized guinea pigs provoked leukocyte infiltration.

3.1.5. Sensitization test

To test whether the guinea pigs were systemically sensitized, at the end of the experiment (after nasal lavage sampling), 1 mg/kg of ovalbumin was administered intravenously. In sensitized guinea pigs anaphylactic shock and cardiovascular collapse

Table 2

A summary of main arterial pressure (MAP), nasal airway pressure (NAP), lung inflation pressure (LIP) and heart rate (HR) measured before ovalbumin challenge in anaesthetized sensitized and non-sensitized guinea pigs

Non-sensitized					Sensitized			
Animal number	MAP	NAP	LIP	HR	MAP	NAP	LIP	HR
1	32	14	14	235	32	16	8	220
2	37	15	7	240	33	10	12	220
3	26	11	5	250	63	10	11	300
4	15	11	11	205	37	12	13	230
5	32	14	7	240	37	18	9	280
6	40	11	10	250	30	11	10	230
7	38	17	8	300	33	30	6	245
8	32	12	5	225	48	20	13	215
9	39	12	5	250	28	10	5	220
Mean	32	13	8	245	38	15	10	240
S.D.	8	2	3	26	11	7	3	30

In each group, there were 9 guinea pigs. The pressures are in mm Hg and heart rate is in beat/min.

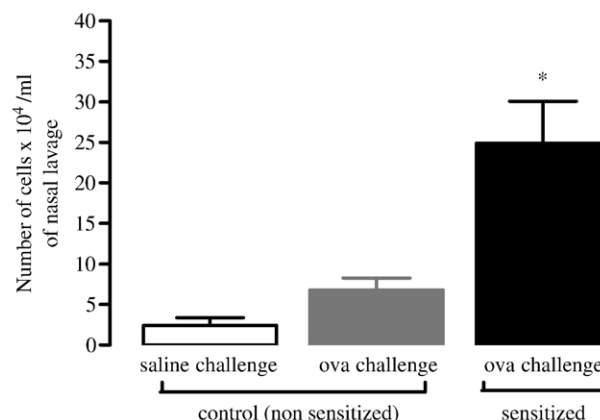


Fig. 10. Effect of ovalbumin (ova) challenge on leukocyte infiltration (total cell count) in anaesthetized (sensitized and non-sensitized) guinea pigs in nasal lavage collected 60 min following 2% ovalbumin or saline challenge at a volume of 0.5 ml infused to the nasal cavities for 5 min 23–28 days post-initiation of sensitization. Cells were counted using hemocytometer under light microscope and the values were expressed as number of cells per milliliter of nasal lavage. *Significant increase in total cell count as compared to non-sensitized ovalbumin challenged guinea pigs ($p < 0.01$, Bonferroni multiple comparison test). $n=5$ per group. Vertical bars represent standard error of mean.

occurred after a period of minutes. The response to the intravenous challenge was initially characterized (within the first minute of injection) by an initial increase in mean arterial blood pressure (34 ± 11 mm Hg, $n=5$) and heart rate (27 ± 16 beat/min, $n=5$), a sustained increase in lung inflation pressure (25 ± 4 mm Hg, $n=5$), but a paradoxical decrease in nasal airway pressure (-4.2 ± 1.1 mm Hg, $n=5$). The values shown above were the difference between pre-ovalbumin and post-ovalbumin intravenous administration. In non-sensitized guinea pigs, no effects of 1 mg/kg ovalbumin were seen following intravenous administration.

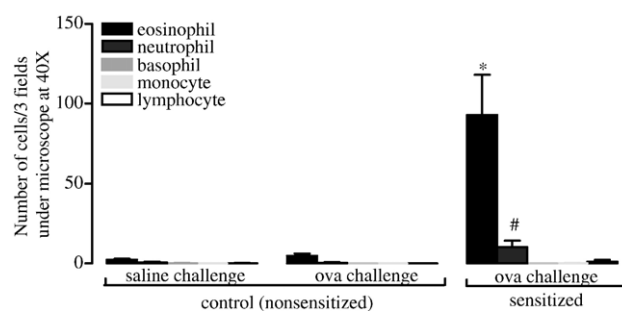


Fig. 11. Effect of ovalbumin (ova) challenge on cellular infiltration (differential cell count) in anaesthetized (sensitized and non-sensitized) guinea pigs evaluated from nasal lavage collected 60 min following 2% ovalbumin or saline challenge at a volume of 0.5 ml infused to the nasal cavities for 5 min. Cells were counted under light microscope at 40 $\times$ power and total cells counted in three consistent fields were used to express the changes. *Significant increase in eosinophil number as compared to non-sensitized ovalbumin challenged guinea pigs ($p < 0.01$, Bonferroni multiple comparison test). #Significant increase in neutrophils as compared to non-sensitized ovalbumin challenged guinea pigs ($p < 0.05$, Bonferroni multiple comparison test). Values are means $\pm$ S.E.M. of $n=5$.

4. Discussion

This study evaluated a guinea pig model of acute allergic rhinitis induced by intranasal sensitization and challenge with ovalbumin. The method of sensitization was effective. Nasal allergen stimulation (aerosol/solution forms) induced sneezing and nose rubbing in an administration-dependent manner. Furthermore, guinea pigs with allergic rhinitis (sensitized) developed acute (within 1 h) allergic responses characterized by sneezing, nose rubbing “itching”, nasal blockade and mainly eosinophil infiltration as a response to allergen challenge. In clinical situations, people with allergic rhinitis experience symptoms of sneezing, itching, nasal secretion and nasal blockade (Bousquet et al., 2001) which are accompanied by eosinophil infiltration (Bradding et al., 1993).

For the first time in the literature, we have simultaneously measured nasal, lung and blood pressure in sensitized guinea pigs subjected to allergen challenge during an acute phase response. Intranasal allergen challenge did not affect lung inflation pressure. This indicates that intranasal allergen challenge specifically triggered nasal inflammatory responses without affecting those of the lower respiratory tract. However, sensitized guinea pigs had anaphylactic shock when the allergen was administered intravenously. The response was characterized by rapid increase in blood pressure, heart rate and lung inflation pressure. These observations were not seen in non-sensitization animals reflecting systemic sensitization following topical nasal sensitization.

We also attempted in this study to measure nasal secretions (glandular secretions+vascular leakage) as an index of rhinorrhea. However, the volumes of secretions produced following allergen challenge were not sufficient to be properly quantified.

This study supports previous findings (Fujita et al., 1999; Narita, Asakura, Shirasaki, & Kataura, 1997; Mcleod, Young, Erickson, Parra, & Hey, 2002; Sakairi et al., 2005) that allergic rhinitis can be induced in guinea pigs and that the pathophysiological changes of the disease in this animal species resemble those of humans.

In conclusion, the currently established model can be used to compare the effectiveness of drugs used clinically for allergic rhinitis. Furthermore, this model can be potentially used for investigation of new drugs.

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