

Effect of oral antigen administration on nasal blockage in experimental allergic rhinitis in guinea pigs

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Abstract. *Objective and design:* We evaluated the effectiveness of oral treatment with Japanese cedar pollen on experimental allergic rhinitis in guinea pigs.

Subjects: Male Hartley guinea pigs.

Treatment: From 16 days before the first sensitisation, 1 and 100 mg/time/animal pollen suspension was orally administered twice weekly. Animals were then sensitised and repeatedly challenged with the pollen.

Method: Guinea pigs were sensitised by intranasal instillation of cedar pollen extracts adsorbed onto Al(OH)₃ at a dose of 0.3 µg pollen protein/0.3 mg Al(OH)₃/3 µl/nostril twice a day for 7 days. Then the animal was challenged by inhalation with cedar pollen (1.8 mg/nostril) once every week. We evaluated the effects of the oral treatment with antigen on: 1) sneezing frequency, 2) nasal blockage after antigen challenge, 3) nasal hyperresponsiveness to histamine and leukotriene D₄, and 4) titres of anaphylactic antibodies.

Results: During the course of the high dose administration, several animals died from a possible cytotoxicity, whereas the low dose caused no discernible change. The oral administration of the pollen at both the doses significantly inhibited nasal blockage, and the hyperresponsiveness to the stimuli was also strongly suppressed by the oral treatment. Inhibitory effectiveness did not differ substantially between the 1 and 100 mg/animal-treated groups. In contrast, neither sneezing frequency nor the increasing level of anaphylactic antibodies was influenced by the oral administration.

Conclusions: In this study, we found that the pollen-induced nasal blockage and hyperresponsiveness were suppressed by the oral administration of the pollen in the sensitised guinea pig.

Key words: Allergic rhinitis – Hyperresponsiveness – IgE – Nasal blockage – Oral antigen

Introduction

Although sneezing and watery rhinorrhea in allergic rhinitis are suppressed by anti-histaminics, nasal blockage is resistant to these [1–4] and relieved only by decongestants [5] and glucocorticoids [6]. However, such treatment is not sufficiently effective in a subset of patients with allergic rhinitis. Many investigators have reported that specific immunotherapy using antigen, usually administered subcutaneously, is effective for the treatment of allergic rhinitis [7], even though the exact mechanism of subcutaneous immunotherapy in the disease remains to be elucidated. It has been pointed out that subcutaneous immunotherapy might induce life-threatening anaphylactic reactions [8, 9]. However, because few such incidences in the oral immunotherapy have been reported, clinical trials of oral immunotherapy for patients with allergic rhinitis have been conducted [10–14], but the results are conflicting and efficaciousness of this method remains controversial.

In an attempt to explore the issue of efficaciousness further, we recently reported an experimental allergic rhinitis model, which is developed by repetitive inhalation challenge of Japanese cedar pollen as an antigen in sensitised guinea pigs [15–17]. Nasal symptoms of the model are fairly similar to those of allergic rhinitis patients: 1) antigen-specific anaphylactic antibodies are produced in the serum [15, 16], 2) frequent sneezing is induced immediately after antigen provocation [16], 3) biphasic nasal blockage is induced in a reproducible manner after respective pollen challenges [16], and 4) nasal hyperresponsiveness to histamine [17] and leukotriene (LT) D₄ [18] is acquired by the repeated challenge. Features of the nasal hyperresponsiveness to LTD₄ are particularly characteristic in the model because the degree is considerably marked (more than 4 orders higher than non-sensitised–non-challenged animals) [18]. The hyperresponsiveness to histamine and LTD₄ is reproducibly observed 2 days after, but disappears 7 days after inhalation challenge [18].

These similarities to clinical allergic rhinitis symptoms prompted us to investigate in this study whether successive oral administration of the cedar pollen could modify the

symptoms induced in this model. The results of evaluations of sneezing, nasal blockage, nasal hyperresponsiveness to histamine and LTD₄, and serum anaphylactic antibody production revealed that nasal blockage and hyperresponsiveness were inhibited by oral administration of the cedar pollen.

Materials and methods

Animals

Male, 3-week-old, Hartley guinea-pigs weighing 280–340 g were purchased from Japan SLC, Hamamatsu, Japan. The animals were housed in an air-conditioned room at a temperature of $23 \pm 1^\circ\text{C}$ and $60 \pm 10\%$ humidity with lights on from 8:00 a.m.–8:00 p.m., and were fed a standard laboratory diet and given water ad libitum. The first sensitisation was started 4 weeks after their purchase.

The protocol of this study was approved by the Experimental Animal Research Committee at Kyoto Pharmaceutical University.

Materials

Japanese cedar (*Cryptomeria japonica*) pollen was harvested in Gifu and Shiga Prefectures (Japan). Evans' blue was purchased from Merck (Darmstadt, Germany). Ovalbumin (OA), histamine dihydrochloride, and leukotriene D₄ (LTD₄) were from Wako Pure Chem (Osaka, Japan). The other reagents used were the highest grade of commercial products available.

Al(OH)₃ gels were prepared with 0.5 N NaOH and 0.5 N Al₂(SO₄)₃ as previously described [19].

Anti-OA guinea pig serum was obtained by the modified method of Levine et al. [20]. In brief, guinea pigs were sensitised by i.p. injection of 10 µg OA/mg Al(OH)₃/animal/time, once every 2 weeks, for a total of 10 times. Both the 4-h and 7-day homologous passive cutaneous anaphylaxis (PCA) titres of the serum were 1:500. This serum served as the standard for quantification of γ 1 and IgE antibody levels in sensitised guinea pig sera by PCA and was stored at -80°C until use.

Sensitisation and challenge (Fig. 1)

As previously described [16], 30 guinea pigs were sensitised by bilateral intranasal instillation of cedar pollen extracts adsorbed onto Al(OH)₃ gel at a concentration of 0.3 µg protein/0.3 mg Al(OH)₃/3 µl/each nostril twice a day for 7 days. Prior to each sensitisation, the upper airway mucosal surface was anaesthetised by 2-min inhalation of 4% lidocaine hydrochloride solution (Fujisawa Pharm. Co., Osaka, Japan) mists, gen-

erated by an ultrasonic nebulizer (NE-U12, Omron, Osaka, Japan), to prevent the rapid elimination of antigen by ciliary movement. Each sensitised animal was then intranasally challenged once every week until the 20th challenge by inhalation of cedar pollen using a hand-made inhalation apparatus [15], which allowed quantitative inhalation of pollen. The apparatus, into which 3 mg of the pollen was poured, was positioned in one nostril of the conscious guinea pig for 1 min so that it could inhale the pollen by spontaneous breathing. During the inhalation, the other nostril was plugged with a finger. The same manner was performed reversibly.

As a negative control, a non-sensitised–non-challenged group (n = 6) was prepared.

Oral administration of Japanese cedar pollen suspension (Fig. 1)

The pollen suspension was successively administered twice a week from 16 days before the first sensitisation at doses of 1 and 100 mg/2 ml/animal.

Counting of sneezing frequency

The frequency of sneezing at 0–10 min, 10 min–1 h and 1–3 h after the 1st, 2nd, 5th, 7th, 11th, 13th and 20th pollen inhalation challenges was counted.

Measurement of specific airway resistance (sRaw)

sRaw as an indication of nasal blockage was measured by a two-chambered, double-flow plethysmograph system according to the method of Pennock et al. [21]. In brief, the animal was placed with its neck extending through the partition of a two-chambered box. Airflow was detected by sensors equipped to both the front and rear chambers. sRaw was measured using the Data analyser Pulmos-I (MIPS, Osaka, Japan) and a PC 9801 FA computer (NEC, Tokyo, Japan).

sRaw was measured before, and 1, 2, 3, 4, 6 and 10 h after the 1st, 2nd, 5th, 7th, 11th, 13th and 20th challenge.

Nasal responsiveness to histamine and LTD₄

Two days after the 10th or 12th inhalation challenge, nasal responsiveness to the intranasally-instilled histamine or LTD₄ was measured as previously described [17, 18]. Ten microlitres per nostril of two increasing doses of 0.1 and 10 mmol/l histamine or 0.01 and 1 µmol/l LTD₄ solution was bilaterally applied at an interval of 20 min. sRaw was measured 10 min after respective dosing of the agonist.

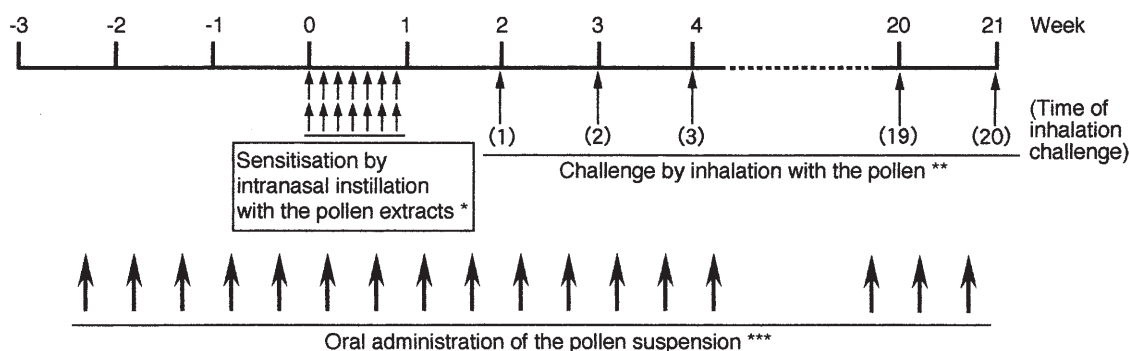


Fig. 1. An experimental design for sensitisation with Japanese cedar pollen extracts, subsequent nasal challenge by inhalation of the pollen, and oral administration of the pollen in guinea pigs. *: 0.6 µg pollen protein/0.6 mg Al(OH)₃/animal/time, **: approximately 3.6 mg/animal/time, ***: 1 and 100 mg/animal/time.

Passive cutaneous anaphylaxis (PCA)

To estimate antigen-specific $\gamma 1$ and IgE antibody titres in the serum of the sensitised-challenged guinea pig, 4-h and 7-day PCAs were performed according to the method of Ovary [22] and Levine et al. [20], respectively. The serum for the PCAs was obtained 1 day before the 5th, 10th and 20th inhalation challenges. The cedar pollen extracts were used as a challenging antigen at a dose of 90 μ g protein/ml/animal.

Statistical analysis

Statistical analysis was performed by one-way analysis of variance (ANOVA). If a significant difference was detected, the individual group difference was determined by Bonferroni's multiple test. A probability value (P) of less than 0.05 was considered to be statistically significant.

Results

Changes in general condition

Successive oral administration of the pollen at 1 mg/animal/time induced no change in the general condition of the sensitised-challenged guinea pig during the entire experimental course. However, 4 out of 10 animals in the high dose (100 mg/animal/time) group died at some point between the 18th–20th oral administrations of the pollen.

Influence on sneezing frequency

Sneezing frequencies of individual animals did not vary significantly from the 1st to the 20th inhalation challenges. In addition, time course-sneezing frequencies were consistent at each challenge: the highest number of sneezes was observed within 10 min, and then successively decreased in frequency at 10 min–1 h and 1–3 h after challenge. Successive oral administration of the pollen suspension at both the low (1 mg/animal/time) and high (100 mg/animal/time) doses did not significantly influence the intensity of the sneezing symptom through the inhalation challenges (Fig. 2).

Influence on nasal blockage (sRaw elevation)

Only very slight nasal blockage at the 1st challenge and slight blockage at the 2nd challenge was observed in the time course changes of sRaw. However, at, during and after the 5th inhalation challenge, biphasic nasal blockage with peaks at 1 and 4 h was obviously and consistently demonstrated. The effect of oral administration of 1 and 100 mg/animal/time of the pollen suspension on the nasal blockage at the 1st and 2nd challenges could not be evaluated, because very mild nasal blockage occurred even in the control group. However, nasal blockage at, during and after the 5th inhalation challenge was always suppressed by the oral administration of the pollen

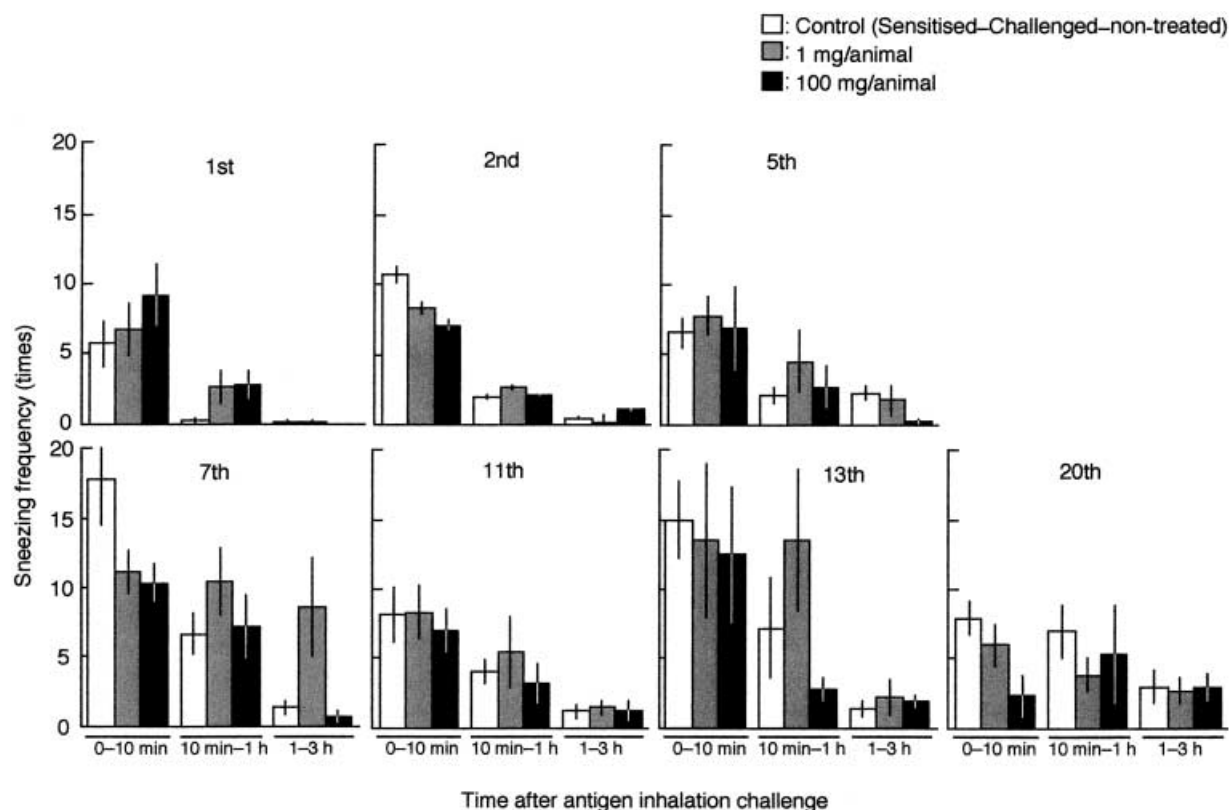


Fig. 2. Effect of oral administration of Japanese cedar pollen on sneezing frequency at the 1st–20th inhalation challenges of the pollen in the sensitised guinea pig. The pollen as a suspension was orally administered twice a week from 16 days before the first sensitisation at doses of 1 and 100 mg/animal/time. Each column represents the mean $\pm$ SEM of 6–10 animals.

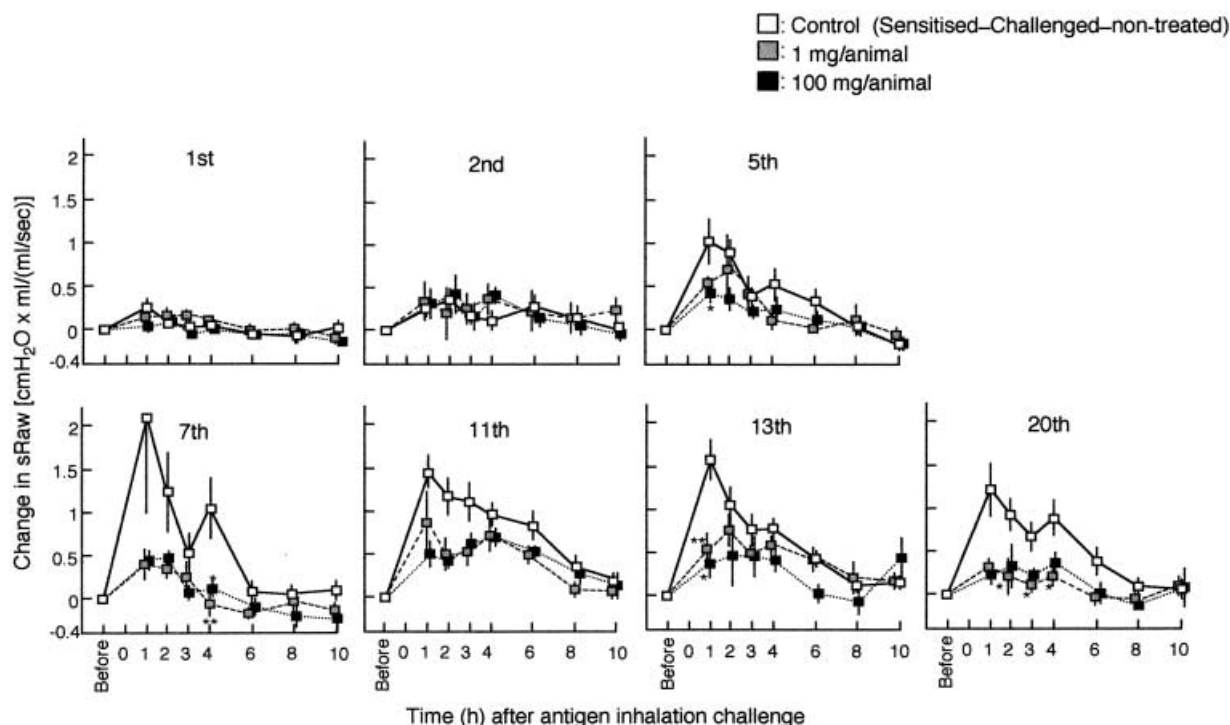


Fig. 3. Effect of oral administration of Japanese cedar pollen on the increase in specific airway resistance (sRaw) at the 1st–20th inhalation challenges of the pollen in the sensitised guinea pig. The pollen as a suspension was orally administered twice a week from 16 days before the first sensitisation at doses of 1 and 100 mg/animal/time. Significantly different from the control (* $p < 0.05$, ** $p < 0.01$). Each point represents the mean $\pm$ SEM of 6 or 10 animals.

suspension at the low as well as the high dose. Early as well as late nasal blockage was consistently alleviated with or without statistical significance. There were no differences in the inhibitory effects of the oral treatment at the low and high doses of the pollen (Fig. 3).

Influence on nasal hyperresponsiveness to histamine and leukotriene (LT) D_4

In the non-sensitised – non-challenged guinea pig, intranasal instillation of 0.1 and 10 mmol/l histamine induced a concentration-dependent increase in sRaw, but the degree was very modest. Meanwhile, the sensitised–challenged animal (control) acquired nasal hyperresponsiveness, indicated by a strong increase in sRaw in a dose-dependent fashion following exposure to the agonist. The oral treatment with 1 mg/animal/time of the pollen suspension completely abolished this nasal hyperresponsiveness. The high dose of the pollen suspension also inhibited the hyperresponsiveness, but not to a significant degree when compared with the control (Fig. 4, left panel).

The sensitised–challenged group showed nasal hyperresponsiveness to LTD₄ at as low as 0.01 and 1 μ mol/l, while the non-sensitised–non-challenged group responded only very slightly to the agonist at these concentrations. The oral administration of the pollen suspension at either 1 mg/animal/time or 100 mg/animal/time completely suppressed the hyperresponsiveness (Fig. 4).

Influence on production of γ 1 and IgE antibodies

The levels of γ 1 and IgE antibodies in the sera obtained one day before the respective 5th, 10th and 13th challenges were quantitated by measuring titres of 4-h and 7-day PCA, respectively. In the control group, only 2 of the 6 animals were positive for both PCAs at the 5th challenge, yet all animals were positive for either PCA at the 10th challenge. At the 20th challenge, their PCA titres tended to increase further. Although the oral administration of 1 mg/animal/time increased both γ 1 and IgE antibody levels slightly at the 20th challenge and that of 100 mg/animal/time lowered both antibody levels somewhat, none of these levels differed significantly from those of the control (Fig. 5).

Discussion

In this study, we demonstrated that when the sensitised–challenged guinea pig was successively treated with oral administration of the pollen suspension, irrespective of low (1 mg/animal/time/day) and high (100 mg/animal/time/day) dosage during the course of sensitisation/challenge, both the antigen-induced biphasic nasal blockage and the nasal hyperresponsiveness to histamine and LTD₄ were potently suppressed. In contrast, anaphylactic antibody production in the serum and the induction of sneezing were unaffected by the oral treatment.

The inhibitory action of the high dosage of the pollen on nasal blockage and nasal hyperresponsiveness did not exceed

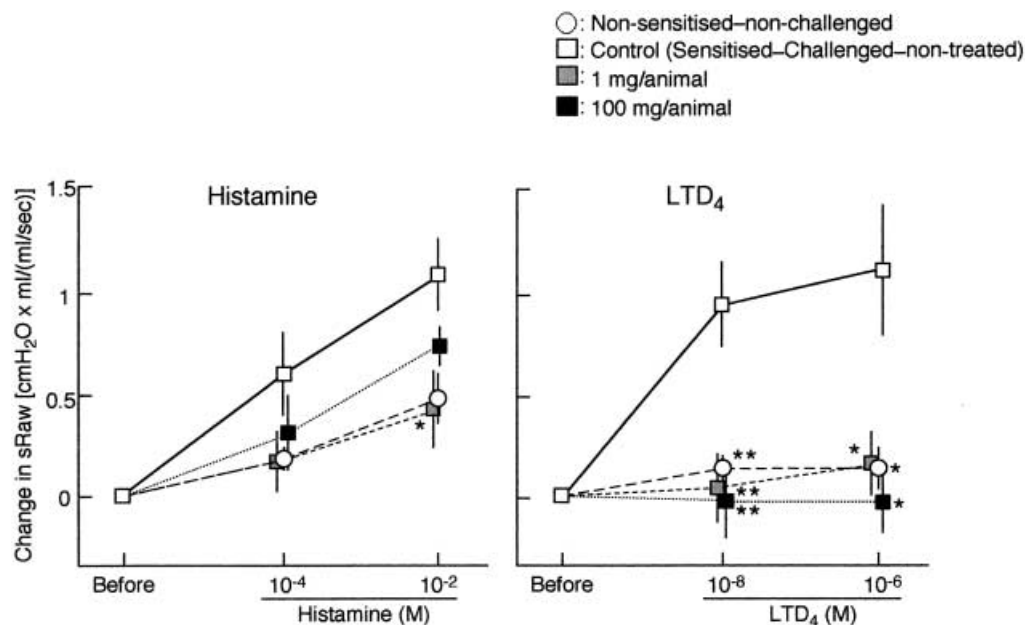


Fig. 4. Influence of oral administration of Japanese cedar pollen on nasal hyperresponsiveness to histamine and leukotriene (LT)₄ in the sensitised guinea pig. The pollen as a suspension was orally administered twice a week from 16 days before the first sensitisation at doses of 1 and 100 mg/animal/time. Nasal responsiveness to histamine and LTD₄ was assessed 2 days after the respective 10th and 12th inhalation challenges. Each point represents the mean $\pm$ SEM of 4–6 animals. Significantly different from the control (* $p < 0.05$, ** $p < 0.01$).

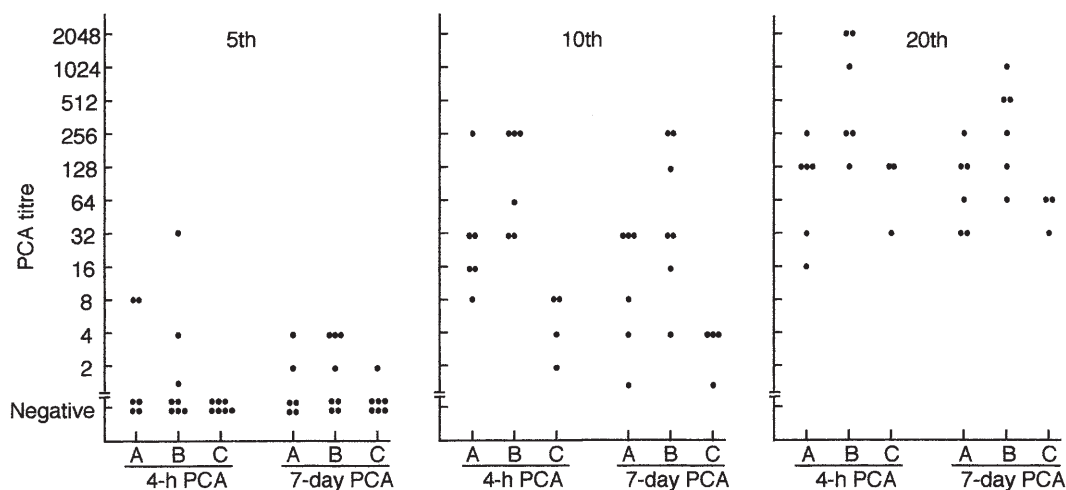


Fig. 5. Effect of oral administration of Japanese cedar pollen on the elevations of 4-h and 7-day homologous passive cutaneous anaphylaxis (PCA) titres in the sera of sensitised guinea pigs. The pollen as a suspension was orally administered twice a week from 16 days before the first sensitisation at doses of 1 and 100 mg/animal/time. Sera were obtained 1 day before the 5th (left panel), 10th (middle panel) and 20th (right panel) inhalation challenges. A: Control (Sensitised–Challenged–non-treated), B: 1 mg/animal, C: 100 mg/animal.

that of the low dosage. As for the toxicity of the oral pollen, 4 out of 10 animals died from complications of diarrhoea during the course of the high dose administration possibly due to a cytotoxic effect of the resin or essential oil contained in the pollen on the digestive tract, whereas the low dose of pollen caused no discernible changes in general condition.

Previous clinical studies of oral immunotherapy have yielded conflicting results. One-year oral administration of a

high dose of grass pollen to patients with hay fever failed to produce any beneficial change in either clinical symptoms or the serum antigen-specific IgE level [12]. On the other hand, when patients with allergic rhinitis to short ragweed were treated orally with encapsulated short ragweed extract for 6 weeks followed by nasal antigen challenge, nasal congestion was significantly suppressed, although sneezing, nasal secretion and the serum antigen-specific IgE antibody level were

not substantially attenuated [14]. Since nasal blockage is apparently induced mainly by nasal congestion, our present findings correspond well with those of the latter report [14].

As previously described, the oral administration of the cedar pollen did not suppress the anaphylactic antibody formation. This indicates that the oral administration of antigen has no effect on the anaphylactic antibody formation of the induction phase.

Antigen-induced sneezing was almost entirely suppressed by the treatment with antihistaminics [23, 24]. This indicates that histamine from the mast cell plays a major role in the occurrence of the symptom. Nevertheless, the oral administration of the cedar pollen did not affect the anaphylactic sneezing at all. Therefore, it can be concluded that the oral administration of the cedar pollen has no effect on the mast cell activation in effector phase and may protect the target organ. But the detailed mechanism is not clear.

Our results appear to correspond well with the report that the oral administration of antigens inhibited allergen-induced bronchoconstriction and hyperresponsiveness in guinea pigs without diminishing IgE antibodies [25].

The nasal hyperresponsiveness was potentially inhibited by the oral administration of the pollen. The inhibitory mechanism is also unknown. Recently, Turner et al. [26] found that kinins are involved in induction of nasal hyperresponsiveness to histamine through the activation of bradykinin B₂ receptors in subjects with seasonal allergic rhinitis. In preliminary experiment using the present model, the treatment with not only bradykinin B₂ but also B₁ antagonists prior to inhalation challenge significantly inhibited the development of the nasal hyperresponsiveness (Sugawara et al., unpublished data). Thus, the present effectiveness of the oral immunotherapy might be due to suppression of formation and/or actions of kinins, although the mechanism how kinins are affected is not known. Interestingly, nasal hyperresponsiveness to histamine had already been acquired at 4 h after the challenge (Mizutani et al., unpublished data), the time at which the late phase response occurred. Thus, it might be postulated that late phase nasal blockage may be caused by the acquisition of nasal hyperresponsiveness. If this can be indeed the case, the oral administration of pollen may suppress some pathways that lead to hyperresponsiveness, which may, in turn, result in the inhibition of the antigen-induced late phase nasal blockage. However, the treatment with bradykinin B₂ and B₁ antagonists prior to inhalation challenge did not inhibit the late phase nasal blockage as well as the early one (Sugawara et al., unpublished data). Accordingly, this possibility can be excluded.

In the present study, successive oral administration of the pollen was started before the first sensitisation. However, it is easily supposed that the schedule for the administration is not applicable to patients suffering from allergic rhinitis, in which immunotherapy may be performed after achievement of sensitisation to the pollen. Based on this consideration, in preliminary experiment, the successive pollen administration was started at the time when circulating anaphylactic antibody titres had significantly elevated and the biphasic nasal blockage had been constantly induced. Resultantly, similar to the present findings, the post-treatment of the pollen potentially suppressed induction of both the biphasic nasal blockage and hyperresponsiveness, although neither

the antibody elevation nor occurrence of sneezing was substantially affected.

In conclusion, the oral cedar pollen administered to the sensitised guinea pig during the course of the sensitisation/challenge not only effectively suppressed antigen-induced nasal blockage but also nasal hyperresponsiveness to histamine and LTD₄. This suppressive effect was not due to inhibition of anaphylactic antibody production.

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