



Impaired olfactory function in mice with allergic rhinitis

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Abstract

Objective: It has been reported that olfactory function is impaired in patients with allergic rhinitis. However, the mechanism of olfactory dysfunction in allergic rhinitis remains poorly understood. Because of difficulties in obtaining and analyzing human olfactory mucosa due to both technical and ethical issues, an animal model needs to be established to clarify the mechanism of olfactory dysfunction in allergic rhinitis. The purpose of this study was to study olfactory function and changes in olfactory mucosa using allergic rhinitis mice.

Methods: A model of allergic rhinitis mice with olfactory dysfunction was developed by sensitizing with ovalbumin (OVA), and intranasally challenging with the same allergen. Olfactory function of mice with or without allergic rhinitis was assessed by odor detection ability test with cycloheximide and local field potential (LFP) with 1-octanal. We also evaluated histological changes in the olfactory mucosa of allergic rhinitis mice by both light and electron microscopy.

Results: Both of odor detection ability test and LFP showed that olfactory function was impaired in mice with allergic rhinitis, but not in mice without allergic rhinitis. Histopathological findings showed prominent infiltration of eosinophils, plasma cells, neutrophils, mast cells, and macrophages in lamina propria of olfactory mucosa of mice with allergic rhinitis, although infiltration of these cells was not seen in control mice. Allergic rhinitis also increased the number and size of glands in olfactory mucosa, suggesting an elevated amount of mucin in olfactory mucosa.

Conclusion: This study showed for the first time that mice with allergic rhinitis have impaired olfactory function, increased size and number of olfactory glands, and infiltration of eosinophils, neutrophils, mast cells, plasma cells, and macrophages in the olfactory mucosa. This suggests that allergic reactions are seen in olfactory mucosa of mice with allergic rhinitis, and that greater olfactory gland activity is associated with olfactory dysfunction. Also, this mouse model could provide an expedient system for analyzing mechanisms of olfactory dysfunction.

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1. Introduction

Many people worldwide suffer from allergic rhinitis. Allergic rhinitis causes sneezing, nasal discharge, and nasal obstruction. Clinical studies have also reported that allergic rhinitis impairs olfactory function [1–3]. Golding-Wood et al. [4] demonstrated that 60% of

patients with allergic rhinitis have olfactory abnormality even if they have no abnormal sinus X-ray, nasal polyp, or severe septal deformity. Quality of life is negatively correlated with olfactory dysfunction. Olfactory dysfunction is therefore a very important symptom in patients with allergic rhinitis. However, the mechanism of olfactory dysfunction in allergic rhinitis remains poorly understood.

It has been considered that olfactory dysfunction is caused by nasal obstruction. However, Cowart et al. [5]

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showed that nasal resistance was not related to olfactory function in two groups of patients with and without allergic rhinitis, although nasal resistance was significantly higher in patients with allergic rhinitis than in those without allergic rhinitis. This suggests that another mechanism is involved in olfactory dysfunction.

Because of difficulties in obtaining and analyzing human olfactory mucosa due to both technical and ethical issues, an animal model needs to be established to clarify the mechanism of olfactory dysfunction in allergic rhinitis. Many researchers have investigated allergic rhinitis using an animal model that they developed. For example, we previously showed that a model of allergic mice, made by ovalbumin (OVA) sensitization and challenge, had increased serum IgE and eosinophil infiltration in the respiratory region of the nasal mucosa [6]. However, olfactory function in allergic mice has not been reported. Therefore, it has been unclear whether these allergic mouse models have olfactory dysfunction or not.

In this study, we assessed olfactory function of an allergic rhinitis mouse model. We consequently developed an allergic mouse model with olfactory dysfunction, which enabled a histopathological investigation of changes in the olfactory mucosa with allergic rhinitis.

2. Materials and methods

2.1. Animals

Male C57/BL6 mice (Japan SLC, Shizuoka, Japan) at 11 weeks of age were maintained under specific-pathogen-free conditions. The protocols were approved by the Guidelines for Care and Use of Animals at Nagoya City University. Every effort was made to minimize any discomfort of the animals.

2.2. Immunization and challenge with ovalbumin (OVA)

Ten mice were injected intraperitoneally with 10 µg of OVA (Worthington Biochemical Corporation, Lakewood, NJ) containing 4 mg of alum as adjuvant two times at 1-week intervals on days 0 and 7. One week after the last sensitization, mice were challenged intranasally with 200 µg OVA. Liquid antigen of OVA was instilled intranasally twice a day for 2 weeks.

Immediately after the last nasal challenge, the number of sneezing and nasal rubbing movements was counted for 20 min according to the method previously described [6].

2.3. Odor detection ability

In order to assess olfactory function of allergic model mice, we performed odor detection ability tests with cycloheximide according to the method previously

described [7]. Cycloheximide has a peculiar and unpleasant odor. The odor detection ability test was performed on days 10, 13, 21, and 28 after the first intraperitoneal injection. For 48 h before each test the mice were not given access to water. The first and second tests were used to train the mice to avoid a 0.01% cycloheximide solution. Water bottles with and without cycloheximide were positioned randomly. The third test was performed 7 days after the first challenge. The fourth test was also performed 14 days after the first challenge. In each test the number of times the mice avoided the cycloheximide solution was counted. The third and fourth tests were conducted 12 h after nasal challenge in order to avoid blockage of the nasal cavity from the solution itself. Test was finished, when mice drank ten times or 10 min passed.

2.4. Measurement of OVA-specific IgE

Twenty-four hours after the last challenge, blood samples were obtained from mice, and assayed for OVA-specific antibody subclasses. OVA-specific IgE was detected with Mouse OVA-IgE ELISA kit (AKRIE-030, Shibayagi Gunma, Japan). Briefly, 96-well plates were coated with OVA. Diluted serum samples were incubated, washed, and assayed. Finally, tetramethylbenzidine substrate was added to the plates and the reaction was stopped by 5% phosphoric acid. The absorbance at 450 nm was measured with a microplate reader (BioRad, USA).

2.5. Fixation and tissue preparation

Mice were perfused through the left ventricle of the heart with PBS (pH 7.4) followed by 4% paraformaldehyde in 0.1 M phosphate buffer (PB) for 10 min. The brains were removed from the skull, stored in the same fixative for 2 h at 4 °C, then cut into 50 µm thick serial sections with a Microslicer (Dosaka, Japan) for immunostaining of the olfactory bulb. The perinasal parts of the skull including total nasal cavity were also fixed with 4% paraformaldehyde in 0.1 M phosphate buffer overnight. We further decalcified nasal bone tissue with 45% formic acid overnight and partly decalcified nasal bone tissue with 15% 0.5 M EDTA solution (pH 8.0) (Wako Pure Chemical Industries, Japan) for 7 days. The serial cut paraffin sections were mounted on the glass slide for following staining.

2.6. Hematoxylin–eosin (HE) and periodic acid-Schiff stain (PAS) staining

Serial paraffin sections (4 µm in thickness) cut by microtome were rinsed in xylene and ethanol for removal of paraffin. Thereafter, sections were stained with conventional Mayer's hematoxylin–eosin (HE) and periodic acid-Schiff stain (PAS) stains.

2.7. Immunohistochemistry

Localization of macrophage in the nasal mucosa was analyzed by postembedding immunocytochemistry. After rinsing with xylene to remove paraffin, the sections were rinsed with PBS and pre-incubated for 1 h in 80% methanol containing 3% hydrogen peroxide to reduce endogenous peroxidase activity. They were then washed in PBS three times for 10–15 min, pre-incubated in 1% bovine serum albumin (BSA) containing 0.05% sodium azide and 0.3% Triton X-100 in PBS (pH 7.4) for 1 h, and incubated with a rat monoclonal anti-macrophage antibody (diluted 1:100; BM8) for 3 days to 1 week for 1 h each day at 20 °C. The sections were then washed three times for 10–15 min and incubated for 2 h at 20 °C in biotinylated donkey anti-rat IgG (diluted 1:200; Jackson, West Grove, PA) in PBS containing 1% BSA and 0.3% Triton X-100. They were then rinsed and incubated in avidin–biotin complex (ABC; diluted 1:200; Vector, Burlingame, CA) in PBS for 2 h at 20 °C. After rinsing in PBS followed by 50 mM Tris buffer (pH 7.6), the sections were incubated in 0.05% diaminobenzidine tetrahydrochloride (DAB) in 50 mM Tris buffer containing 0.01% hydrogen peroxide for 1–3 min at room temperature. After completing the immunocytochemical procedures, the sections were postfixed with 0.05% OsO₄ in 0.1 M PB for 15 min on ice. Finally, the sections were washed in distilled water, dehydrated in a graded series of ethanol, infiltrated with propylene oxide, and flat-embedded in Epon-Araldite. The embedded sections were examined with a microscope.

Multiple fluorescence-labeling immunocytochemistry was also performed for examination of neuronal immunorexpression in olfactory bulb, using neuronal markers. Microslicer sections were incubated in combinations of primary antibodies against olfactory marker protein (anti-OMP made from goat, diluted 1:10,000; gift from Dr. Margolis, University of Maryland) [8] and tyrosine hydroxylase (anti-TH; diluted 1:5000; Chemicon MAB318) [9] in PBS containing 1% BSA, 0.05% sodium azide, and 0.3% Triton X-100 for 1 week at 20 °C. After incubation in mixtures of primary antibodies, the sections were then incubated in mixtures of secondary antibodies, FITC-labeled donkey anti-goat IgG (diluted 1:200; Jackson, West Grove, PA) and indocarbocyanine (Cy3)-labeled donkey anti-mouse IgG (diluted 1:200; Jackson), for 2 h at 20 °C. After rinsing in PBS the sections were mounted in Vectashield and examined with confocal laser scanning microscope.

2.8. Ultrastructural analysis by electron microscopy

After fixation and tissue preparation by 3% glutaraldehyde in 0.1 M phosphate buffer, the nasal regions of allergic rhinitis and control mice were stored in the same fixative for 2 h at 4 °C, and bone was demineralized by formic acid for

overnight as described above. After rinsing with PBS, coronary sliced tissues were stored in 2.5% glutaraldehyde and 2% paraformaldehyde in 0.1 M phosphate buffer at 4 °C overnight. After rinsing with 0.1 M PBS twice, the tissue slices were immersed in 1% osmium tetroxide (OsO₄) 0.1 M PB for 1 h on ice. After rinsing and dehydrating in a graded series of ethanol, they were washed with propylene oxide for 10 min and infiltrated with a mixture of propylene oxide and epoxy resin for 2 h. Samples embedded in epoxy resin were polymerized at 60 °C for 2 days. They were then cut into serial sections of 80 nm in thickness, mounted on meshes made of copper, and stained with lead citrate solution. Sections were observed by transmission electron microscopy.

2.9. Local field potential recording of the olfactory bulb (LFP)

In another experiment, LFP was recorded in mice that were sensitized and challenged with OVA using the methods described above in Section 2.2. Ten mice were implanted with bipolar stainless steel electrodes (200 µm diameter) to record LFP. The position of the electrode was determined using a stereotaxic atlas (external plexiform layer of the olfactory bulb; 2 mm deep, 0.5 mm to the left and 4 mm ventral from bregma). In pairs, mice were connected by flexible cables to a polygraph and a computer-assisted data acquisition system CED 1401 data processor (Cambridge Electronic Design (CED), UK). Polygraphic recordings for LFP (200 Hz) were collected 10 days after surgery. During recording, mice were exposed to a specific odor (1-octanal, Wako Pure Chemical, Japan) [10] using a cotton swab. Recordings were made ten times for 2 s each at 10-s intervals. LFP during odor exposure and at the mid-point during the interval period (2 s × 10) was analyzed. The averaged LFP power spectrum in each animal was calculated by 512-point fast Fourier transform (FFT) using the Spike 2 analyzing program (CED, UK) for each group. LFP power was divided into 5 frequency bands: delta (0.5–4.0 Hz); theta (4.0–8.5 Hz); sigma (8.5–14.0 Hz); beta (14.0–30.0 Hz); and gamma (30.0–50.0 Hz). The percentage of change due to odor exposure was calculated by the LFP power during exposure to the odor compared with background findings. One hundred percent indicates that odor exposure did not affect the LFP power.

2.10. The number of mice used in each experiment

Schematic protocols of experiments were shown in Fig. 1. Odor detection ability test was performed in 10 allergic rhinitis mice and 10 control mice. We examined OVA-specific IgE, nasal symptoms, and eosinophilia in respiratory and olfactory mucosa using these 10 mice in the both groups. LFP was also performed using other 10 allergic rhinitis mice and 10 control mice. Also, HE staining, PAS staining, and

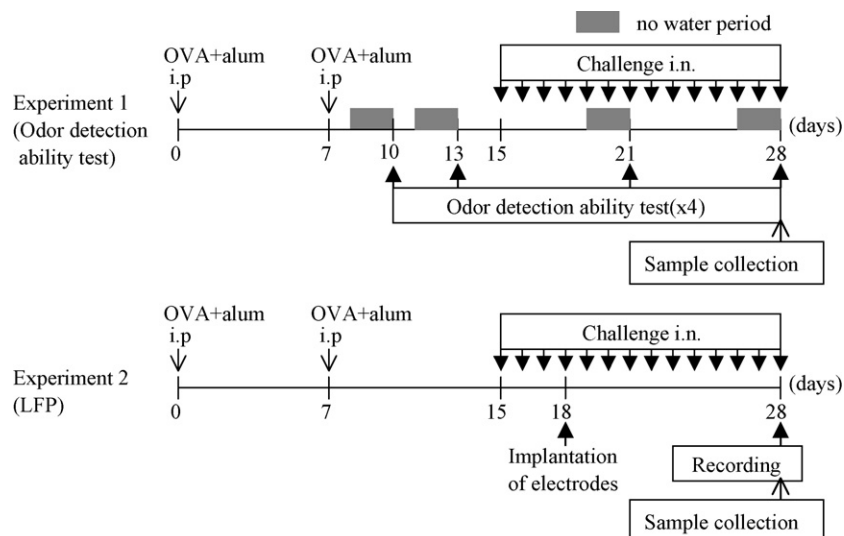


Fig. 1. Schematic protocols of experiments. i.p. and i.n. stand for intraperitoneal injection and intranasal administration.

immunohistochemistry were performed using 10 mice, which consist of 5 mice for odor detection ability test and 5 mice for LFP, in the both groups. Furthermore, analysis with electron microscopy was performed using the other mice (10 mice) in the both groups.

2.11. Statistical analysis

Data are shown as means $\pm$ S.D. Statistical comparisons were performed with Student's test. Differences with P -value less than 0.05 were considered significant.

3. Results

3.1. Olfactory function of mice with allergic rhinitis

To develop model mice with allergic rhinitis, mice were sensitized with ovalbumin (OVA) and challenged by the same allergen. This allergic mouse model showed significantly greater elevation of OVA-specific IgE in sera (data not shown, $P < 0.01$), compared to the control mice. The number of sneezing and nasal rubbing after nasal challenge in allergic rhinitis mice was also more than that in the control

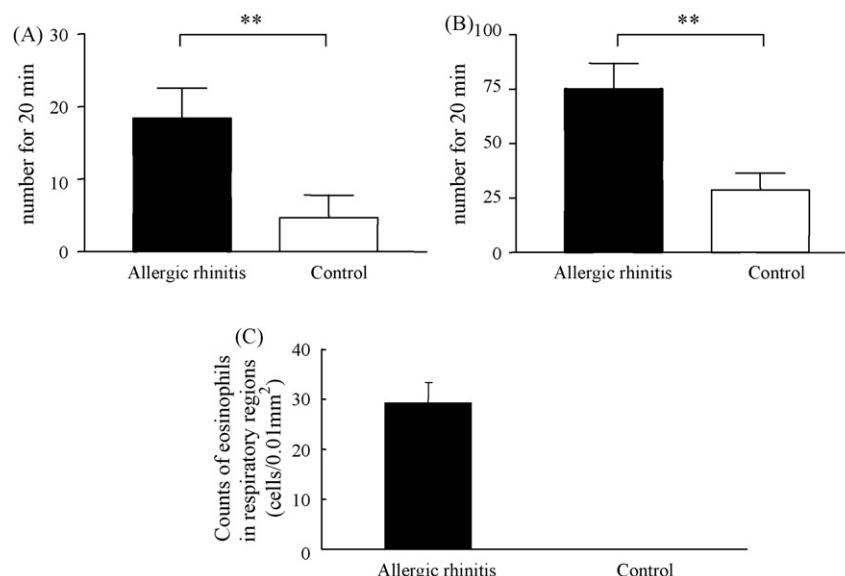


Fig. 2. Nasal allergic symptoms and eosinophilia in mice with allergic rhinitis. Mice were sensitized and challenged with OVA. (A) The number of sneezing after the last nasal challenge. $**P < 0.01$ compared with control mice. (B) The number of nasal rubbing after the last nasal challenge. $**P < 0.01$ compared with control mice. (C) Eosinophils in respiratory mucosa of mice with allergic rhinitis. The number of eosinophils in respiratory mucosa was counted in mice with allergic rhinitis and in control mice.

mice (Fig. 2A and B, $P < 0.01$). Also, a prominent eosinophilia in the respiratory region of nasal mucosa was shown in allergic mice (Fig. 2C), although no eosinophils were seen in control mice. This suggested that allergic rhinitis was established in these mice.

Next, odor detection ability test was performed with cycloheximide in the mice with allergic rhinitis and control mice to assess change in olfactory function caused by allergic rhinitis. Odor detection ability was determined by the percentage of times the mice avoided drinking the cycloheximide solution. Both allergic rhinitis and control mice avoided the cycloheximide solution about 80% of the time in the first test before intranasal challenge, and there was no significant difference between the two groups. In the second test before intranasal challenge, mice in both groups had learned to avoid the cycloheximide almost 100% of the time. After intranasal challenge for 7 days, the rate of avoidance in mice with allergic rhinitis fell to 65%, while the results for the control mice was 100%. After challenge for 14 days, the rate of avoidance was 55% in mice with allergic rhinitis, compared with almost 100% in control mice. There were significant differences between the two groups 7 and 14 days after initial challenge (Fig. 3A, $P < 0.01$). We also showed raw data in each one of mouse in the both groups (Table 1).

Local field potential (LFP) of the olfactory bulb was also recorded to study olfactory function of mice with allergic rhinitis. Under LFP recording, we investigated behavior and olfactory function in response to a specific odor, 1-octanol. At first we recorded normal LFP pattern of both non-allergic and allergic mice at resting condition. Afterwards, 1-octanol was given to both types of mice, which were recorded to compare the difference in their response to the given odor between non-allergic and allergic mice. The control mice showed large escape reaction during exposure of the given odor. In contrast, the allergic rhinitis mice did not show such escape reaction. We showed typical example of LFP raw signal in both mice with or without allergic rhinitis (Fig. 3B). There was no remarkable change of response by odor stimulation in mice with allergic rhinitis, although we found increase of response by odor stimulation in control mice. Also, responses were weak during spontaneous activity in mice with allergic rhinitis compared with control mice, suggesting no or low responses by airborne odor. LFP power was divided into 5 frequency,

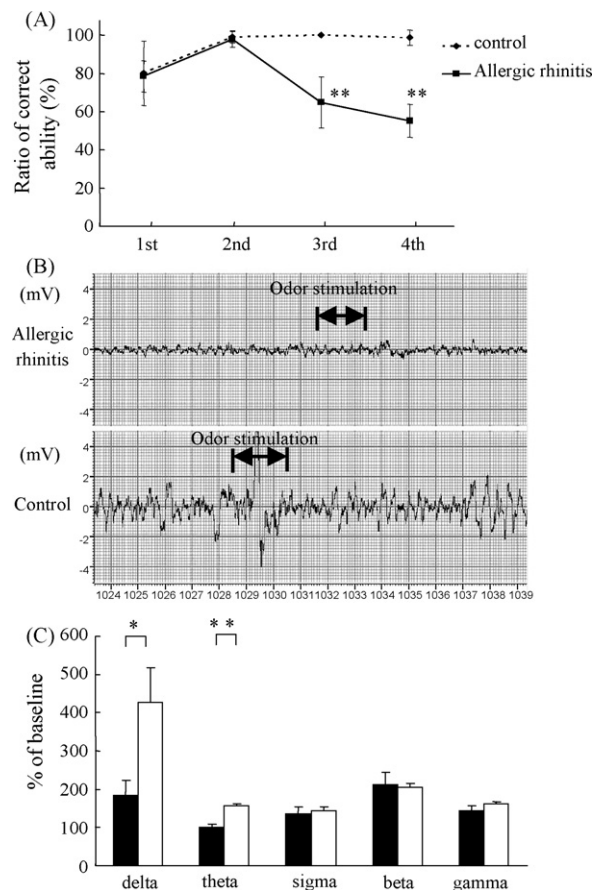


Fig. 3. Odor detection ability in mice with allergic rhinitis. Mice were sensitized and challenged with OVA. (A) Result of odor detection ability test. An odor detection ability test was performed in mice with and without allergic rhinitis four times, on days 10, 13, 21, and 28. $**P < 0.01$ compared with control mice. (B) Local field potential raw signal in both mice with or without allergic rhinitis. (C) Changes in integrated power spectral densities of local field potential of the olfactory bulb by odor (1-octanol) stimulation in allergic rhinitis mice (black column) and control mice (white column). Data are expressed as percentages of baseline (resting with no odor). Delta: 0–4.0 Hz, theta: 4.0–8.5 Hz, sigma: 8.5–14.0 Hz, beta: 14.0–30.0 Hz, gamma: 30.0–50.0 Hz. $**P < 0.01$, $*P < 0.05$ compared with control mice.

delta, theta, sigma, beta, and gamma. There were significant differences in the delta and theta bands between the two groups, allergic rhinitis mice and control mice (Fig. 3C). These results from the odor detection ability test and LFP suggest that allergic rhinitis induced olfactory dysfunction.

Table 1

Typical result of odor detection ability test in each one of mouse with or without allergic rhinitis.

	1st test	2nd test	3rd test	4th test
Allergic rhinitis				
The rate of avoidance	87.5%	100%	62.5%	62.5%
The number of drinking water without cycloheximide	7	9	5	5
The number of drinking	8	9	8	8
Control				
The rate of avoidance	87.5%	100%	100%	100%
The number of drinking water without cycloheximide	7	9	8	10
The number of drinking	8	9	8	10

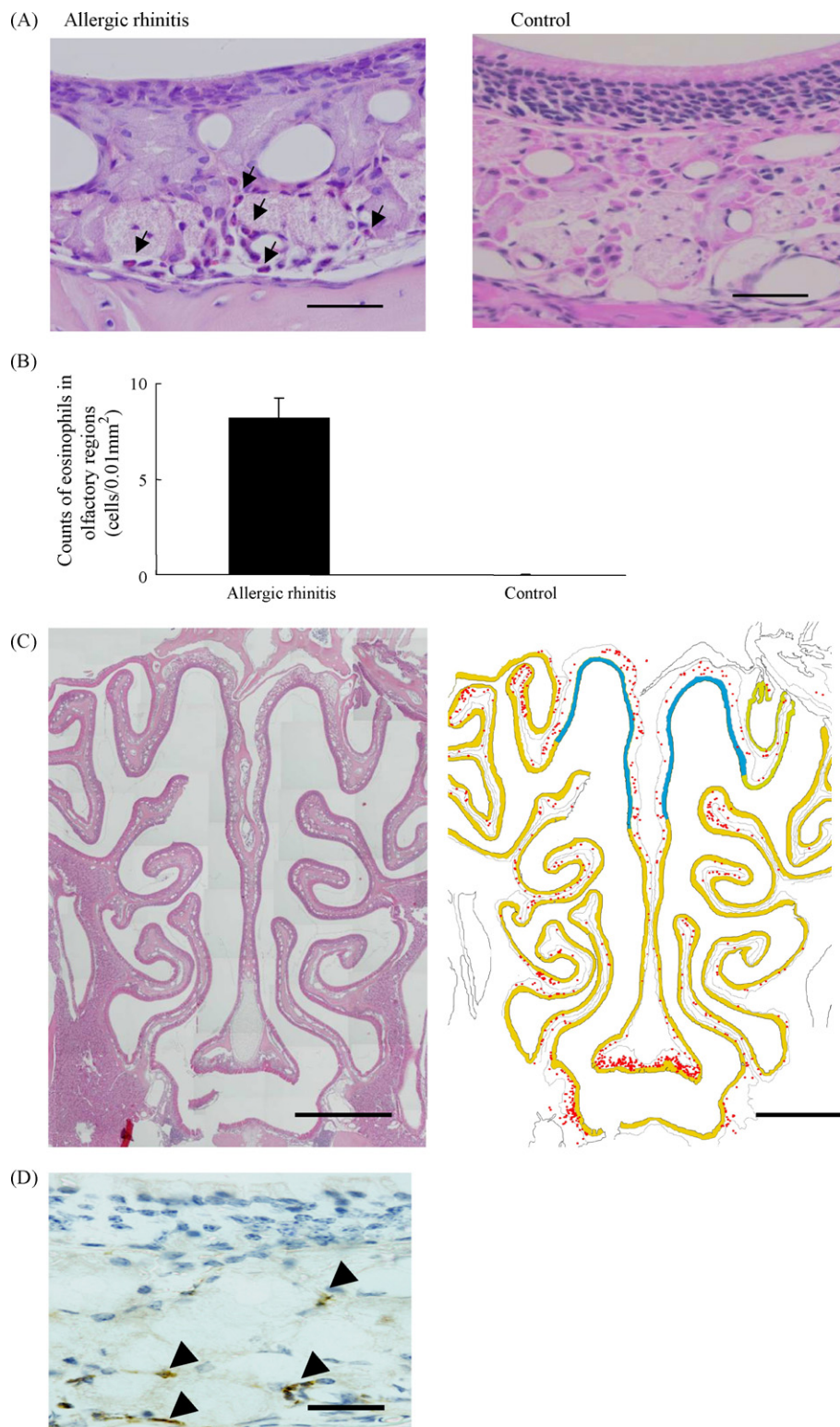


Fig. 4. Staining with hematoxylin and eosin (HE), immunohistochemistry, and periodic acid-Schiff stain (PAS). Mice were sensitized and challenged with OVA. Nasal mucosa was stained with HE or PAS staining. (A) Eosinophilia of olfactory mucosa. Eosinophils are seen in olfactory mucosa in mice with allergic rhinitis, but not in control mice. Arrows show eosinophils. Bar = 100 μ m. (B) The number of eosinophils in olfactory mucosa was counted. (C) Distribution of eosinophils shown with low magnification HE image (left) and its traced image (right). The entire nasal cavity and localization of eosinophils are shown. Bars = 1 mm. (D) Olfactory mucosa by means of immunohistochemistry with anti-macrophage antibody. Immunoreactive cells by DAB reaction (brown in A) were seen in allergic rhinitis. Bar = 20 μ m. (E) PAS staining. Olfactory glands were detected by PAS staining. Bars = 20 μ m. (F) The number of olfactory glands was counted in olfactory mucosa. $**P < 0.01$ compared with control mice. (G) Immunohistochemistry for olfactory marker protein (OMP in green) and tyrosine hydroxylase (TH in red) in glomeruli of the olfactory bulb of allergic rhinitis and control mice. Bar = 50 μ m. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

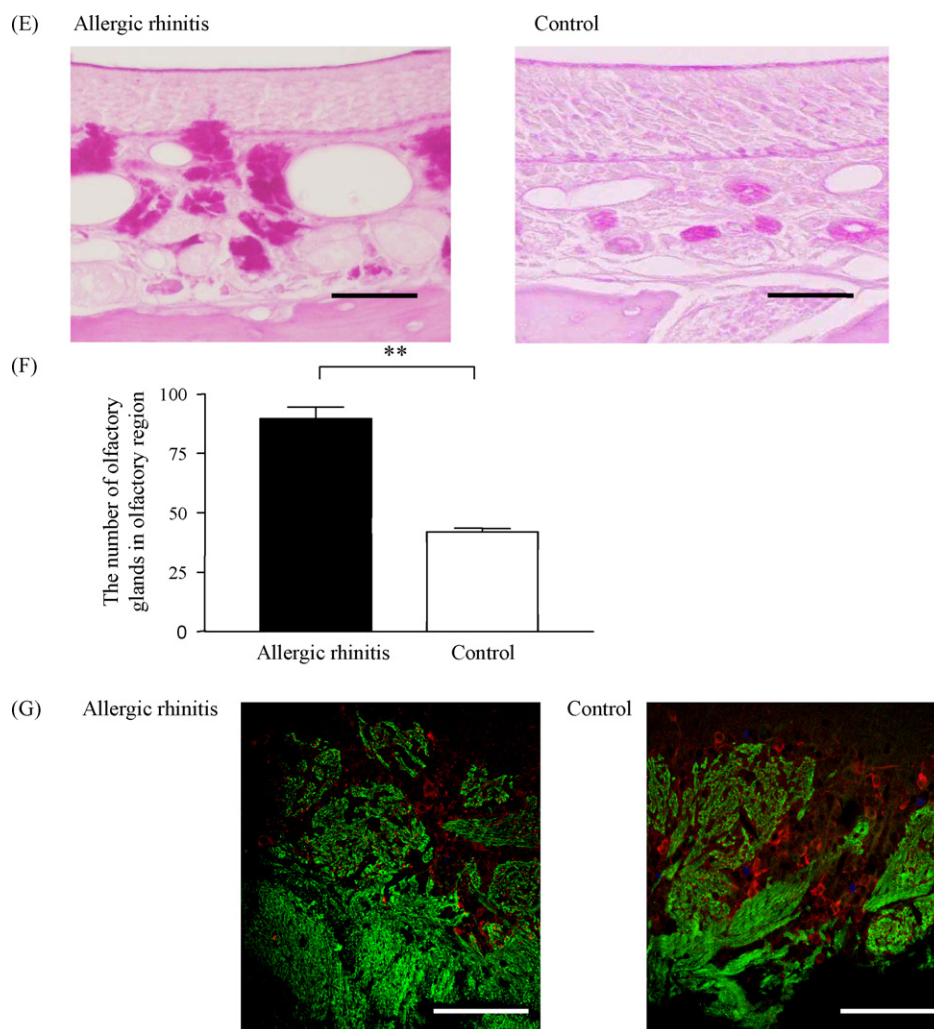


Fig. 4. (Continued).

3.2. HE staining, immunohistochemical staining, and PAS staining

We succeeded in developing a murine model of allergic rhinitis and olfactory dysfunction. Using this model, we were able to histochemically investigate the change in nasal mucosa caused by allergic rhinitis.

Nasal mucosa is divided into two regions, the respiratory mucosa and olfactory mucosa. Eosinophilia in respiratory mucosa is a typical allergic phenomenon and is associated with allergic reaction [11]. However, infiltration of eosinophils into olfactory mucosa has not been documented. To study the change in olfactory mucosa from allergic rhinitis, we compared HE-stained sections between allergic rhinitis mice and controls. There was remarkable infiltration of eosinophils into olfactory mucosa in allergy rhinitis mice, but not in control mice (Fig. 4A and B). We traced eosinophils in the entire nasal cavity, including respiratory mucosa (Fig. 4C, yellow area) and olfactory mucosa (Fig. 4C, blue area). Eosinophils existed over a wide area of respiratory mucosa and olfactory mucosa and extended

deep into the lamina propria near skull base. This suggests that eosinophils invade not only respiratory mucosa but also olfactory mucosa.

In addition to eosinophil infiltration, macrophages immunolabeled with a pan-macrophage marker were identified in the lamina propria of allergic rhinitis mice, but not in control mice (Fig. 4D).

As almost all allergic rhinitis patients have nasal discharge and obstruction, we investigated the change in mucin productivity with the use of PAS staining, which specifically labels glycogen. The findings showed that allergic rhinitis increased the intensity and area of PAS stain (Fig. 4E). We also counted the number of olfactory glands in olfactory mucosa. The number of olfactory glands was significantly higher in mice with allergic rhinitis than in control mice (Fig. 4F, $P < 0.01$). This indicates that allergic rhinitis leads to an increase in the size and number of olfactory gland in olfactory mucosa, suggesting that mucin production was elevated.

Furthermore, we examined whether any neuropathological change in olfactory bulb was seen or not. Immunostaining of

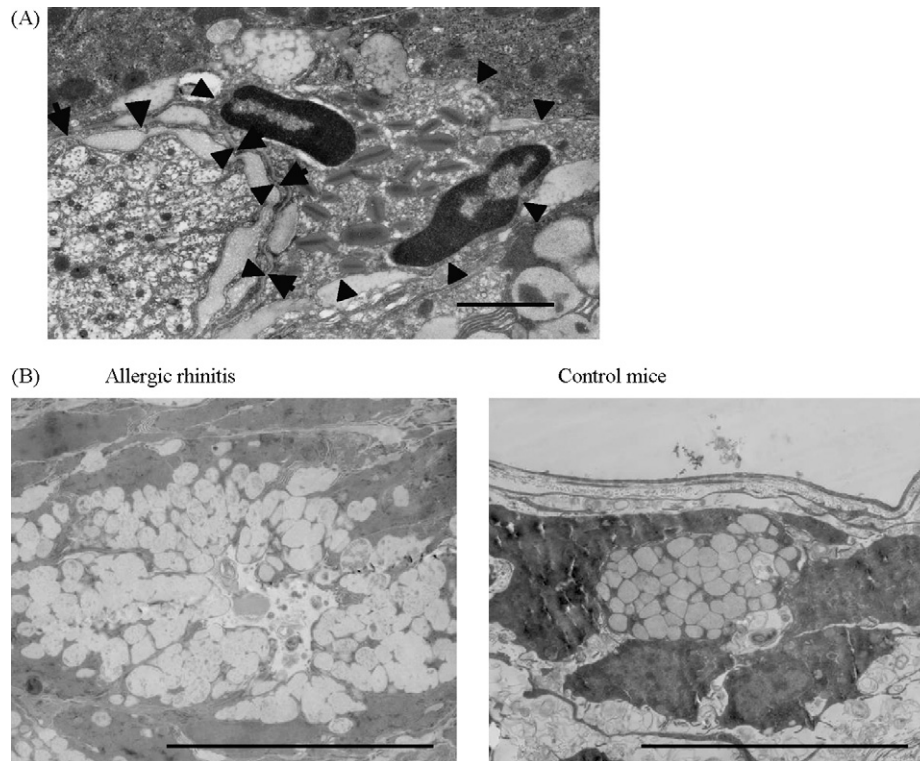


Fig. 5. Transmission electron microscopic analysis. Mice were sensitized and challenged with OVA. Nasal mucosa was analyzed by electron microscopy. (A) Eosinophil infiltration near olfactory nerve. Arrow (→) shows olfactory nerve and arrowhead (►) shows eosinophil. Bar = 1 μ m. (B) Olfactory glands of allergic rhinitis and control mice, showing well developed olfactory glands by allergic rhinitis. Bars = 10 μ m.

olfactory bulb in allergic rhinitis mice did not show remarkable change of immunoexpression for olfactory nerve (labeled by OMP) (Fig. 4G). However, there was weaker immunoexpression of afferent-regulated interneuron (labeled by TH) in allergic rhinitis mice compared with the control mice (Fig. 4G), although we could not have a quantitative analysis exactly.

3.3. Transmission electron microscope of olfactory mucosa

Transmission electron microscopy was used to examine the ultrastructural features of nasal mucosa in allergic rhinitis. A remarkable difference appeared in the lamina propria of olfactory mucosa in allergic rhinitis and control mice. Various cells, including eosinophils, neutrophils, mast cells, plasma cells, and macrophages were observed in the lamina propria in allergic rhinitis mice (data not shown), although no eosinophils, neutrophils, macrophages, mast cells, or plasma cells were seen in control mice. The most prominently appeared cells were plasma cells. The second most frequent cells were eosinophils. Eosinophils were found to be present especially near nerve fascicles of olfactory neurons in the lamina propria (Fig. 5A). Olfactory glands in lamina propria were increased in number and size compared with the control mice (Fig. 5B).

4. Discussion

Studies using allergic mice with olfactory dysfunction have been not documented. However, it is necessary to develop a murine model mice of allergic rhinitis with olfactory dysfunction for the future, for several reasons: (1) it is not easy to obtain and investigate olfactory mucosa and bulbs for technical and ethical reasons; (2) patients with olfactory dysfunction may have several background conditions that are associated with olfactory dysfunction; and (3) new medicines cannot be developed using humans. Therefore, we assessed olfactory function in mice with allergic rhinitis to establish a murine model using an odor detection ability test and LFP. The results of both tests showed that sense of smell was impaired in mice with allergic rhinitis.

This study demonstrated that allergic rhinitis increases the number and size of olfactory glands, suggesting that mucin levels are elevated. Odor-bearing particles go to olfactory cilia through the olfactory cleft. Increased mucin may close the olfactory cleft and therefore obstruct transportation of odor-bearing particles to olfactory cilia. Transportation of odor-bearing particles may be also obstructed by mucin covering the olfactory cilia. This may be one possible mechanism of olfactory dysfunction caused by allergic rhinitis.

In this study, we showed that eosinophils infiltrated not only the respiratory mucosa but also olfactory mucosa as a result of allergic rhinitis. We also found that eosinophils

exist near the olfactory nerve in olfactory mucosa. Eosinophils can induce cytotoxicity and neurotoxicity [11–13]. Kumar et al. [14] reported a case of childhood hemiplegia due to idiopathic hypereosinophilic syndrome. In Churg-Strauss syndrome characterized by a necrotizing vasculitis with eosinophil infiltration, peripheral neuropathy is also common [15]. Therefore, olfactory function may be deteriorated by allergic rhinitis through cytotoxicity and neurotoxicity of infiltrated eosinophils in olfactory mucosa. Plasma cells and mast cells were also seen in olfactory mucosa. These findings suggest that allergic reaction is seen not only in respiratory mucosa but also in olfactory mucosa from allergic rhinitis.

Mast cells are important sources of IL-4 and IL-13 [16], which induce mucous cell differentiation in allergic diseases [17,18]. Macrophages secrete IL-6 [19], which induces mucin production [20]. The above suggests that mast cells and macrophages are associated with increased size and number of olfactory glands in olfactory mucosa. Furthermore, macrophages promote cytotoxicity and damage of the peripheral nervous system, such as demyelination [21]. Considering this, mast cells and macrophages may play important roles in olfactory dysfunction from allergic rhinitis.

In this study, we showed that olfactory function deteriorated in mice with allergic rhinitis. We also demonstrated the presence of eosinophils, plasma cells, neutrophils, mast cells, and macrophage in olfactory mucosa, and increases in olfactory glands and mucin using this murine model. These findings provide insight into the mechanisms of olfactory dysfunction caused by allergic rhinitis, and may contribute to the development of new therapies for olfactory dysfunction caused by allergic rhinitis.

5. Conclusion

In this study, we investigated olfactory function and changes in olfactory mucosa in allergic rhinitis mice. Consequently, it was demonstrated that allergic rhinitis induced olfactory dysfunction, increased size and number of olfactory glands, and infiltration of eosinophils, neutrophils, mast cells, plasma cells, and macrophages in the olfactory mucosa. This suggests that allergic responses are observed in olfactory mucosa of mice with allergic rhinitis, and that greater olfactory gland activity is associated with olfactory dysfunction. Blockade of greater olfactory gland activity may inhibit olfactory dysfunction caused by allergic rhinitis. Also, this developed mouse model will provide an expedient system for analyzing mechanisms of olfactory dysfunction.

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