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Histamine induces nasal obstruction via calcitonin gene-related peptide in sensitized guinea pigs*

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SUMMARY

The purpose of this study was to characterize the late phase nasal obstruction that is induced by a nasal histamine challenge in sensitized guinea pigs. The volume of the nasal cavity was measured using an acoustic rhinometer. A nasal histamine challenge to unsensitized animals induced nasal obstruction at 30 minutes after the challenge while a challenge to sensitized animals induced nasal obstruction not only at 30 minutes but also at 4-6 hours. Histamine (measured by high-performance liquid chromatography), cysteinyl leukotriene (enzyme-linked immunosorbent assay (ELISA)), prostaglandin D_2 (ELISA), eosinophils and basophilic cells of sensitized guinea pigs were not changed in the late phase after histamine challenge. Administration of pyrilamine, a histamine H_1 receptor antagonist, and calcitonin gene-related peptide (CGRP) (8-37), a CGRP-1 receptor antagonist, significantly improved histamine-induced nasal obstruction at 30 minutes and in the late phase, respectively. These results suggest that a nasal histamine challenge induces nasal obstruction not only immediately through the histamine H_1 receptors but also in a late phase via CGRP.

Key words: histamine, CGRP, nasal obstruction, acoustic rhinometer, guinea pig

INTRODUCTION

Allergic rhinitis is one of the most prevalent allergic disorders, with symptoms of sneezing, nasal discharge and nasal obstruction [(1)]. Histamine [(2)] plays a very important role in the nasal obstruction of nasal allergy patients. Histamine not only induces symptoms of rhinitis directly, but also enhances infiltration of eosinophils [(3)]. Histamine enhances the expression of intercellular adhesion molecule-1 (ICAM-1) on human vascular endothelial cells [(4)], and the production of superoxide anion from eosinophils [(5)]. Histamine also affects the T helper type 1/T helper type 2 (Th1/Th2) balance [(6)]. The effects by histamine vary according to the state of sensitization of the host [(7)]. Histamine-induced eosinophil infiltration appears to be more remarkable in the allergic than the non-allergic state [(8)]. The increased reactivity in the sensitized state is called "hypersensitivity", in which allergic responses are induced by lower doses of chemical mediators than those needed to evoke responses in non-allergic states [(9)].

In a guinea pig model of nasal allergy, although mediators including cysteinyl leukotrienes (CysLTs) [(10)], platelet activating factor (PAF) [(11)], nitric oxide [(12)], and neuropeptides [(13)] have been suggested to be associated with the nasal obstruction, histamine is the most important chemical mediator [(14)]. Histamine induces rhinitis symptoms directly [(15)]. Histamine stimulates vascular permeability, glandular secretion, production of superoxide anion from eosinophils [(5)], and sensory nerves, and release of both calcitonin gene-related peptide (CGRP) and substance P from the terminals of the trigeminal nerve [(15, 16)]. As in humans, the effects of histamine vary between sensitized and unsensitized animals [(17)]. The degree of infiltration of mast cells, which contain large amounts of histamine, in the nasal mucosa is also different between the allergic model and the normal state [(18)].

Thus, although histamine has an important place in early phase nasal obstruction in allergic rhinitis [(2)], there is a possibility that histamine plays an important role in late phase nasal

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obstruction also. However, no information about nasal obstruction by histamine in the late phase has been reported. Therefore, in this study, we compared the nasal obstruction induced by a nasal histamine challenge in both sensitized and unsensitized guinea pigs using an acoustic rhinometer (GJ Elektronic, Skanderborg, Denmark). The acoustic rhinometer can measure nasal obstruction noninvasively using acoustic reflections and has been widely used in clinical diagnosis [19]. The acoustic rhinometer modified for application to guinea pigs has been developed and found to be a precise and useful method for evaluating nasal obstruction in experimental allergy model animals [20]. Furthermore, we analyzed the infiltration of inflammatory cells into nasal mucosa, concentrations of chemical mediators in intranasal perfusate, and the effect of mediator receptor antagonists on histamine-induced nasal obstruction to elucidate the mechanism of pathogenesis.

MATERIALS AND METHODS

Drugs

Histamine dihydrochloride, pyrilamine maleate salt, atropine sulfate salt hydrate, N-omega-nitro-L-arginine methylester (L-NAME), N-omega-nitro-D-arginine methylester (D-NAME), CGRP (8-37) and urethane were purchased from Sigma (St. Louis, MO, USA). Other reagents used were dinitrophenilated Ascaris suum (DNP-As; LSL, Tokyo, Japan, Lot: 747042) and aluminum hydroxide ($Al(OH)_3$; Wako Pure Chemicals, Osaka, Japan). Water was used to prepare the pyrilamine the others were prepared by saline.

Animals

Male Hartley guinea pigs were purchased from SLC Inc. (Shizuoka, Japan) and housed at constant temperature (23 ± 2˚C) and humidity (55 ± 10 %). All experiments were conducted according to the institution's guidelines for care and use of laboratory animals in research.

Sensitization and histamine challenge of guinea pigs

Sensitization of guinea pigs was performed according to the method of Ishida et al. with a slight modification [21]. Specifically, guinea pigs were actively sensitized with antigen using an intraperitoneal (i.p.) injection of 10 μg dinitrophenilated Ascaris suum (DNP-As) containing 1 mg $Al(OH)_3$ in 1 mL saline. A booster i.p. injection of the same concentration of a DNP-As / $Al(OH)_3$ mixture in 1 mL of saline was given per animal at 2, 4 and 6 weeks after the first sensitization. Two weeks after the last i.p. injection, 0.005 % DNP-As saline was intranasally administered by a spray twice a day, at a dose of 0.5 mL per day, for 10 days. The sensitized animals were used within 7 days after the end of the sensitization.

For histamine challenge, each nostril of both sensitized and unsensitized guinea pigs was instilled with either 20 μL of 0.1 mg/mL histamine. Saline was used as a control challenge.

Measurement of nasal cavity volume

Measurement of nasal cavity volume was performed by the method of Nakamoto et al. with a slight modification (14). Specifically, the nasal cavity volume in guinea pigs was measured using the acoustic rhinometer after anesthesia by urethane (1.0 mg/kg, i.p.). The "pre" time point represented acoustic rhinometry that was performed 15 minutes before either histamine or saline intranasal challenge. Acoustic rhinometry was performed 10, 30 and 60 minutes, and then every hour after the intranasal challenge for an 8-hour period.

In acoustic measurements, a generated sound impulse is passed into one nostril, and the reflection from the nose is captured by a microphone. Computerized analysis (Nadap v2.31c) of intensity and time delay from the nasal cavity was used to determine the nasal cavity volume. Nasal cavity volumes were estimated from the nostril to 2 cm into the nasal cavity. The sum of right and left values of nasal cavity volume were analyzed. Changes in volume after the intranasal challenge were expressed as the percentage change from the "pre" values. For each animal, the mean value of consecutive 3 measurements for each nostril was calculated. This measurement was repeated 3 times in each nostril and the median of the 3 mean values was used as the volume at that time point. In the experiments using animals, the cavity volume has been known to be a reliable parameter. An inverse correlation between individual percent change of nasal resistance and nasal cavity volume was statistically significant [14]. The intranasal instillation of histamine causes a dose-dependent reduction in percent change of nasal cavity volume in the challenged side [14].

Intranasal perfusion

After nasal instillation of either histamine or placebo, animals were anesthetized and placed in a supine position. The trachea was transected into two sections, one of which continued to have spontaneous respiration and the other had a cannulated polyethylene tube filled with saline attached to the nares. The tube was connected to a perfusion pump (Tubing Pump Rotor, Type 25N, Taitec, Saitama, Japan) for intranasal perfusion of saline at a rate of 0.2 mL/minute. Six hours after the histamine or saline challenge, 10-minute intranasal perfusates were done in each animal. The perfusates were collected in a container cooled by ice water and divided into 3 aliquots for measurement of histamine, CysLTs and prostaglandin (PG) D_2.

In some sensitized animals, repeated intranasal perfusates were performed for 10 minutes at 3 and 5 hours after the nasal histamine challenge.

Measurement of histamine

Histamine in the intranasal perfusate was quantified as described previously [22]. Briefly, 0.5 mL of each perfusate was mixed with 50μL of 30 % perchloric acid (Wako Pure Chemical) and kept at -30˚C overnight. The sample was centrifuged at 8,000 g for 15 minutes at 4˚C. The fluorescence method using a high-performance liquid chromatography system was used to quantify histamine in the supernatant

(Shimadzu, Kyoto, Japan). The results were expressed as ng/mL perfusate.

Measurement of CysLTs

CysLTs was quantified by the method of Nagai et al. [23]. A volume of 0.5 mL of perfusate was mixed with 2 mL of ethanol and centrifuged at 8,000 g for 10 minutes at 4°C. The sample supernatant was evaporated, the pH of the residue was adjusted to pH 5.1 using 0.1 N hydrochloric acid, applied to a C-18 column, then washed with 20 mL of distilled water. CysLTs were eluted with 10 ml of ethanol. The effluent was evaporated and CysLTs in the residual solution was measured by an enzyme-linked immunosorbent assay (ELISA) kit (Leukotriene $C_4/D_4/E_4$ EIA System, RPN224; Amersham, Biosciences, NJ, USA). The % cross-reactivity (50 % B/B_0 displacement) for the leukotriene C_4, leukotriene D_4, leukotriene E_4 and leukotriene B_4 antiserum are 100, 100, 70 and 0.3, respectively. The results were expressed as pg/mL perfusate.

Measurement of PGD_2

Perfusate was mixed with 2 mL of ethanol and centrifuged at 8,000 g for 10 minutes at 4°C and the supernatant was evaporated. Samples were adjusted to pH 3 with 0.1 N hydrochloric acid, applied to a C-2 column, washed with 5 mL distilled water, 5 mL 10 % ethanol and 5 mL hexane. PGD_2 was eluted with 5 ml of methyl formate. The effluent was then evaporated, and the amount of PGD_2 in the residual solution was measured by radioimmunoassay (ria) kit (PGD_2 [^{3}H] assay system, TRK 890; Amersham). The % cross-reactivity (50 % B/B_0 displacement) for the PGD_2, PGJ_2 and thromboxane B_2 antisera are 100, 7 and 0.3, respectively. The results were expressed pg/mL perfusate.

Nasal mucosa specimens

Procedures for obtaining nasal mucosa have been described [24]. In brief, 5 hours after the nasal challenge with either histamine or saline, all of the animals were anesthetized and bled. The animals were decapitated, the heads were fixed in 15 % formalin, and the nasal tissue was sectioned and stained with Giemsa to evaluate eosinophil infiltration and with Toluidine blue to evaluate basophilic cell infiltration, respectively. The number of eosinophils or basophilic cells was counted in the whole side of the intranasal epithelium that had the least mechanical injury. The result was expressed as the number of cells per whole side of an intranasal epithelial preparation.

Administration of mediator receptor antagonists

Pyrilamine (10 mg/5 mL/kg) was resuspended in water and administered orally 30 minutes before nasal histamine challenge of sensitized guinea pigs. Atropine (2 μg/100 μL/each nostril) was dissolved in saline and administered 3 hours after nasal histamine challenge of sensitized guinea pigs. Either L-NAME or D-NAME (10 mg/0.5 mL/kg) was administered intravenously 10 minutes before histamine challenge. CGRP (8-37) (0.2 μg/100 μL/kg), a CGRP-1 receptor antagonist, was administered intravenously 2 minutes before histamine challenge. The late phase nasal obstruction appeared 4-6 hours after histamine challenge, therefore, we evaluated the effect of each antagonist when the nasal cavity volume showed the minimum value in the late phase for each comparison.

Statistical analysis

Data are shown as the mean ± standard error (S.E.). Statistical evaluation was performed using Student's t-test corrected by the Bonferroni method for multiple comparisons or the Dunnett test for ANOVA (both Stat View, ver.5.0). A p-value of less than 0.05 was significant.

RESULTS

Effect of histamine challenge on nasal obstruction in sensitized and unsensitized guinea pigs

Both sensitized and unsensitized guinea pigs were given intranasal histamine (4 μg/40 μL/animal). Thirty minutes after nasal challenge of unsensitized guinea pigs (n=11), histamine caused a nasal obstruction resulting in a reduction in nasal cavity volume by 23.4 ± 5.9% of "pre" nasal volume (hereafter designated as -23.4 ± 5.9%). The nasal obstruction improved gradually. In sensitized guinea pigs (n=11), the nasal volume at 30 minutes after histamine challenge was -15.3 ± 5.9% and at 5 hours was -28.1 ± 6.4%. Differences in nasal obstruction between sensitized and unsensitized guinea pigs were significant at 5 hours after histamine challenge, but not after 30 minutes (Figure 1). The repeated experiments revealed that the range of time for the appearance of the late phase nasal obstruction was between 4-6 hours after nasal histamine challenge (data not shown). The peak of the late phase obstruction also fluctuated slightly depending the lots of the experimental animal used. Therefore, in the subsequent experiments, the effects of histamine and drugs were evaluated at the times of the peak of the obstruction, which were 30 min in the early phase and 5 or 6 hours in the late phase, respectively.

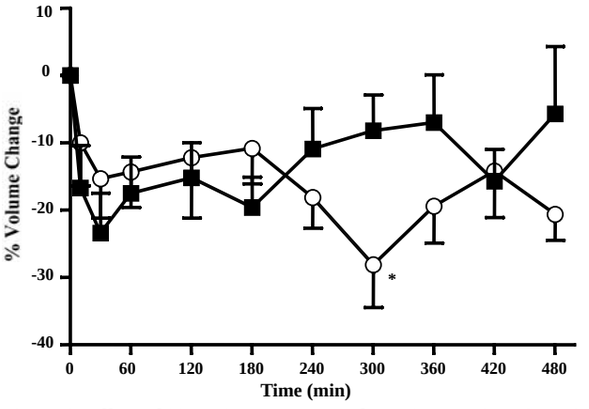

Figure 1. Effect of histamine on volume from the nostril to 2 cm into the nasal cavity in sensitized and unsensitized guinea pigs. The mean baseline values were 0.105 ± 0.006 mL and 0.105 ± 0.005 mL in sensitized and unsensitized animals, respectively. Each point and vertical bar represents the mean ± S.E. of 11 animals. *Significant differences from unsensitized animals at $p < 0.05$. , ○: Sensitized guinea pigs; ■: unsensitized guinea pigs.

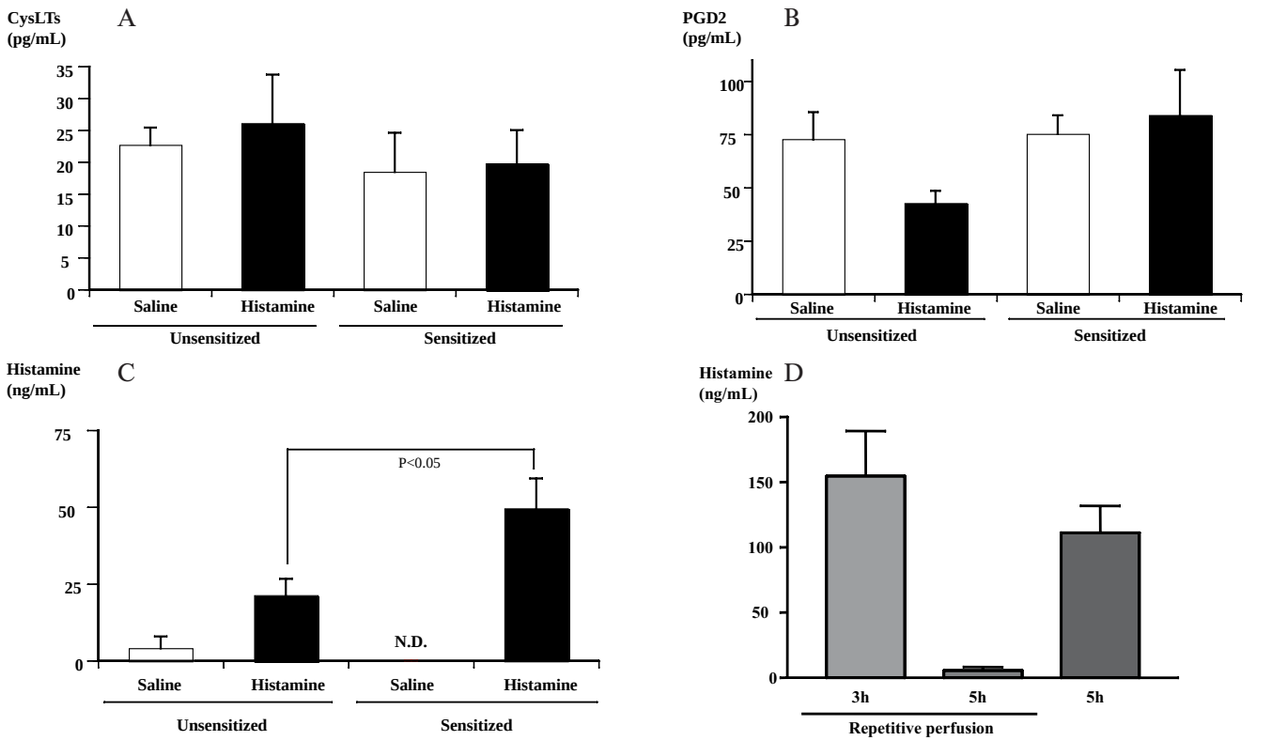

Figure 2. Amount of CysLTs, PGD_2 and histamine in nasal fluids in the late phase induced by histamine or saline nasal challenge of either sensitized or unsensitized guinea pigs. A) CysLTs in nasal fluid. B) PGD_2 in nasal fluid. C) Histamine in nasal fluid. D) Histamine in nasal fluid with and without repeated perfusion. White columns are nasal saline challenge groups, and black columns are nasal histamine challenge groups. Each column and vertical bar represents the mean ± S.E. of 9-10 animals. In A, B and C, guinea pigs nasal perfusion was performed once at 6 hours after either histamine or saline intranasal challenge. N.D.: not detected (under the detection limit).
Repeated nasal perfusions were performed twice at both 3 and 5 hours after histamine challenge in sensitized guinea pigs (D).

Analyses of chemical mediators in intranasal perfusates

The CysLTs, PGD_2, and histamine were quantified in nasal fluids at the late phase following intranasal challenge with either histamine or saline. Neither CysLTs (Figure 2A) nor PGD2 (Figure 2B) levels were significantly different between sensitized and unsensitized guinea pigs. Histamine levels after challenge in sensitized guinea pigs (49.5 ± 9.9 ng/mL) were significantly different from levels in either unsensitized animals (21.2 ± 5.5 ng/mL) or levels induced by saline challenge in sensitized animals (not detected) (Figure 2C). To clarify the origin of the increased histamine in the nasal fluid, the intranasal perfusates were collected repeatedly at 3 and 5 hours after histamine challenge. The nasal fluid collected at 5 hours contained only trace amounts of histamine (2.7 ± 1.4 ng/mL) (Figure 2D).

Histology of nasal mucosa

The eosinophils and basophilic cells that had infiltrated the nasal septum and the nasal turbinate in the late phase were counted (Table 1). The eosinophil and basophilic cell counts in sensitized guinea pigs after either saline or histamine challenge were significantly increased as compared to unsensitized guinea pigs challenged in the same way. However in sensitized guinea pigs, neither the mean eosinophil nor basophilic cell infiltration into the nasal mucosa induced by histamine challenge were significantly different from that induced by saline challenge.

Effects of mediator receptor antagonists

The effects of mediator receptor antagonists on nasal obstruction induced by histamine nasal challenge were tested in sensitized guinea pigs (Table 2). Pyrilamine (10 mg/kg; orally) caused a significant improvement in the nasal obstruction at 30 minutes after the histamine challenge as compared to the water pretreated group. However, pyrilamine had no significant effect on the late phase nasal obstruction. Atropine also had no significant effect on the late phase nasal obstruction. L-NAME (10 mg/kg; intravenously) had no significant effects on the histamine induced nasal obstruction at either 30 minutes or the late phase compared to D-NAME pretreatment group. Intravenous CGRP (8-37) had no effect on the nasal obstruction at 30 minutes after histamine challenge, but did give a significant inhibition in late phase when compared to the saline pretreated group.

DISCUSSION

It is well known that the symptoms of allergic rhinitis occur as a biphasic response, with both early and late phases [25], our

Table 1. Eosinophil and basophilic cell counts in nasal mucosa in the late phase induced by intranasal histamine or saline challenge of sensitized or unsensitized guinea pigs.

		Eosinophils		Basophilic cells	
	Nasal challenge	Nasal septum	Nasal turbinate	Nasal septum	Nasal turbinate
Unsensitized	Saline	162 ± 69	195 ± 36	8 ± 1	9 ± 3
	Histamine	122 ± 58	174 ± 42	12 ± 2	13 ± 2
Sensitized	Saline	1014 ± 260##	1655 ± 373##	26 ± 5##	66 ± 12##
	Histamine	786 ± 189**	1335 ± 254**	25 ± 2**	55 ± 8**

Each value represents the mean±S.E. of the cell number per side of intranasal epithelial preparations (n = 8~10). Guinea pigs were sacrificed at 5 hours after either histamine or saline intranasal challenge. ## Significant differences from saline challenge in unsensitized group at $p < 0.01$. ** Significant differences from histamine challenge in unsensitized group at $p < 0.01$.

data show that a single histamine challenge can produce late phase nasal obstruction in sensitized guinea pigs in the absence of an antigen. It is well known that nasal challenge with histamine cannot evoke a late-phase reaction, but this fact was established using unsensitized animals. No information about nasal obstruction by histamine in sensitized animals in the late phase has been available. In this paper we show that histamine challenge can induce late-phase nasal obstruction in sensitized guinea pigs. Therefore, we investigated this phenomenon to clarify the factors participating in the late phase nasal obstruction induced by histamine.

Table 2. Effects of drugs on nasal obstruction induced by nasal histamine challenge in sensitized guinea pigs.

Drug	Dose	% Volume Change	
		early phase (30 minutes)	late phase (5 or 6 hours)
Water	5 mL/kg	-15.0 ± 3.6	-16.2 ± 3.6
Pyrilamine	10 mg/kg	-6.0 ± 2.1*	-11.1 ± 3.3
Saline	100 μL	-13.3 ± 7.4	-30.1 ± 8.0
Atropine	20 μg/mL	-11.6 ± 5.7	-15.2 ± 7.4
D-NAME	10 mg/kg	-15.6 ± 4.0	-16.2 ± 2.5
L-NAME	10 mg/kg	-12.3 ± 3.7	-9.4 ± 4.0
Saline	100 μL/kg	-22.3 ± 6.2	-22.3 ± 5.7
CGRP(8-37)	0.2 μg/kg	-12.9 ± 6.5	-3.1 ± 4.4*

Each value represents the mean ± S.E. of 6~12 animals. Water and pyrilamine were administered p.o. 30 minutes before nasal histamine challenge. Saline and atropine were administered intranasally 3 hours after nasal histamine challenge. D-NAME and L-NAME were administered intravenously 10 minutes before nasal histamine challenge. Saline and CGRP (8-37) were administered intravenously 2 minutes before nasal histamine challenge. *Statistical differences from contrast group at $p < 0.05$.

Histamine is important in early phase responses [1,2]. Other factors, such as PGD_2 and CysLTs participate in the nasal obstruction accompanying antigen-induced late phase responses [10,26,27]. However, the amount of these mediators in nasal fluid did not increase in our guinea pig models of histamine-induced late phase responses. Histamine caused the release of CGRP and substance P in the peripheral endings of the trigeminal nerve in the nasal mucosa [15,16]. In turn, the released CGRP and substance P induced the release of histamine from mast cells in the nasal mucosa [28]. Our results showed that the amount of histamine in nasal fluid increased in the late phase, but little histamine was detected in sequential repeated perfusates after 3-5 hours. Therefore, the increase of histamine in the late phase in histamine-challenged sensitized guinea pigs is likely to represent the residue of the histamine challenge rather than de novo production by basophilic cells. The clearance of the challenged histamine may decrease in sensitized guinea pigs due to either disturbances in nasal mucociliary transport or enhancement of damage to the nasal epithelium by an antigen-containing spray [29,30].

It is well known that the antigen challenge can induce infiltration of eosinophils and basophils in the late phase response in allergic rhinitis [31-34]. Histamine has chemotactic activity for eosinophils [3,8]. However, in our experimental setting, the effect of histamine challenge on the infiltration of eosinophils or basophilic cells was not observed. Although Giemsa stains not only eosinophils but also neutrophils in guinea pigs [35], we interpreted the staining signal as mainly eosinophils because this nasal allergy model is well known by the characteristic infiltration of eosinophils and basophilic cells rather than neutrophils, in the late phase [36].

In the present study, the nasal obstruction in the late phase was strongly inhibited by the CGRP-1 receptor antagonist. CGRP is known as the most potent endogenous vasodilator. CGRP may also play a role in the regulation of vasomotor responses [37]. Recent studies have suggested that CGRP has protective effects against tissue damage and inflammatory responses [38-42], and Gawin et al. reported that the peptide may enhance plasma extravasation, albumin exudation, and glandular secretion in guinea pigs, and that these mechanisms possibly contribute to nasal responses to injury in this species [42]. Histamine stimulates the trigeminal nerve, including CGRP, via histamine H_1 receptors [43], resulting in the antidromic release of CGRP from terminals of the nerve at 1-3 hours after the stimulation in naive guinea pigs [18]. Furthermore, repeated toluene diisocyanate nasal challenges result in enhancement of the biosynthesis of CGRP in the trigeminal nerve [44]. Therefore, the repeated nasal antigen challenge may enhance the biosynthesis of CGRP in the trigeminal nerve. Nasal hista-

mine challenge to the sensitized guinea pigs could cause release of CGRP from terminals of the trigeminal nerve for a longer time and/or in larger quantities than unsensitized animals. In this scenario, CGRP-induced vasodilatation in nasal mucosa would play an important role in late phase nasal obstruction. Histamine plays an important and direct role in the early phase nasal obstruction, but in the late phase, it would be acting as a trigger for CGRP release rather than a direct effector. However, further studies are necessary to clarify the mechanisms that the release of CGRP induced by histamine in sensitized guinea pigs.

Stimulation of trigeminal nerves is transmitted to the parasympathetic nervous system [45]. Nitric oxide, a transmitter in the parasympathetic nervous system, causes the nasal obstruction [46]. However, L-NAME (an inhibitor of nitric oxide synthetase) and atropine (an anticholinergic drug) did not inhibit the nasal obstruction in the late phase. Therefore, in this model, the parasympathetic nervous system may not play an important role in the late phase nasal obstruction.

Nasal obstruction is a distressing symptom for patients with allergic rhinitis. Our findings point to the importance of CGRP induced by histamine in the late phase nasal obstruction in the animals with hypersensitivity. Histamine-induced CGRP may be clinically important because nasal antigen challenge to patients with allergic rhinitis evokes a 1.5- to 4-fold increase in CGRP for 15 minutes-24 hours, when compared to normal controls [47]. Regulation of either the release or function of CGRP may be a useful therapeutic approach for the suppression of nasal obstruction in allergic patients with hypersensitivity.

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