

*Full Paper***Repeated Pre-treatment With Antihistamines Causes Transcriptional Up-regulations of Histamine H₁ Receptor and Interleukin-4 Genes in Toluene-2,4-diisocyanate-Sensitized Rats**

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Received August 26, 2008; Accepted October 22, 2008

Abstract. Antihistamines are effective for treatment of seasonal nasal allergy. Recently, prophylactic treatment with antihistamines in patients with pollinosis was reported to be more effective when started before the pollen season. The administration with antihistamines from 2 to 6 weeks before onset of the pollen season is recommended for management of allergic rhinitis in Japan. To determine the reason for the effectiveness of prophylactic treatment with antihistamines, the effects of repeated pre-treatment with antihistamines before provocation with toluene 2,4-diisocyanate (TDI) on their nasal allergy-like behavior and up-regulations of histamine H₁ receptors (H1R) and interleukin (IL)-4 mRNAs in their nasal mucosa were examined. Provocation with TDI induced sneezing and up-regulations of H1R and IL-4 mRNAs in the nasal mucosa of TDI-sensitized rats. Repeated pre-treatments with antihistamines including epinastine, olopatadine, or *d*-chlorpheniramine for 1 to 5 weeks before provocation with TDI suppressed TDI-induced sneezing and the up-regulations of H1R and IL-4 mRNAs in the nasal mucosa more than their administrations once or for 3 days before TDI provocation. Our data indicate that repeated pre-treatment with antihistamines before provocation with TDI is more effective than their single treatment in reducing nasal allergy-like behavior by causing additional suppression of up-regulations of H1R and IL-4 mRNAs in the nasal mucosa.

Keywords: antihistamines, histamine H₁ receptor, interleukin-4, nasal allergy, pre-seasonal prophylactic treatment

Introduction

Pollinosis is a seasonal allergic rhinitis (AR) caused by hypersensitivity to tree or grass pollens. More than 36 million people in the U.S. and about 16% of the Japanese population suffer from it (1, 2). Histamine is a major chemical mediator in the pathogenesis of AR. Activation of the histamine H₁ receptors (H1R) is responsible for the symptoms of AR including sneezing, watery rhinorrhea and nasal itching, which can be effectively blocked by antihistamines. Thus antihistamines are good for treatment of pollinosis.

Recently, pre-seasonal prophylactic treatment with antihistamines was reported to increase their effectiveness in patients with seasonal nasal allergy. Several studies involving astemizole (3), terfenadine (4), mizolastine (4), and cetirizine with montelukast (5) suggested that antihistamines have greater inhibitory effects on AR symptoms when applied before the pollen season. Accordingly, their administration from 2 to 6 weeks before the pollen season is recommended in their use against allergic rhinitis in Japan.

The objective of this study was to clarify the molecular mechanism of the effect of prophylactic pre-treatment of nasal allergy with antihistamines. As a model in this study, rats were sensitized with toluene-2,4-diisocyanate (TDI). TDI is an organic solvent that causes occupational asthma in 5%–15% of persons

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Published online in J-STAGE on December 10, 2008 (in advance)
doi: 10.1254/jphs.08222FP

exposed to it (6, 7). In previous studies, we found that intranasal application of TDI caused neuropeptide-mediated release of histamine from mast cells in the nasal mucosa and led to the development of nasal allergy-like symptoms such as sneezing and watery rhinorrhea in TDI-sensitized guinea pigs (8–11). We also developed the same nasal allergy model in rats and found in the rats that their expression of H1R was up-regulated at both the mRNA and protein level by provocation with intranasal TDI (12, 13). Furthermore, we found that activity of the histamine synthesizing enzyme histidine decarboxylase (HDC) and the histamine content of these sensitized rats were increased (14).

Other important mediators in the pathogenesis of AR are Th2 cytokines including interleukin (IL)-4 and IL-5 (15). Th1/Th2 imbalance in the immune system towards Th2 results in the clinical expression of nasal allergy and asthma (16). IL-4, which regulates the production of IgE by B cells and the expression of leukotriene C4 synthase by mast cells, enhances the Th2 responses (16, 17). Histamine is reported to modulate the releases of IL-4 and IFN- γ from T cells (18) and induce the releases of IL-5 (19) and IL-6 (20, 21). Thus, histamine-cytokine networks are suggested to be important in allergic inflammation.

In the present study, we examined whether repeated pre-treatments with the antihistamines, epinastine, *d*-chlorpheniramine, or olopatadine, for 1–5 weeks before provocation with TDI were more effective than their administration once in reducing TDI-induced nasal allergy-like behavior and up-regulations of H1R and IL-4 mRNAs in the nasal mucosa of TDI-sensitized rats.

Materials and Methods

TDI sensitization and provocation

Six-week-old male Brown Norway rats (SLC, Hamamatsu) were used. The rats were kept in a room maintained at $22 \pm 1^\circ\text{C}$ and 50% humidity under a 12-h light/dark cycle. Sensitization to TDI was achieved as described by Tanaka et al. (22) with slight modifications using the protocol shown in Fig. 1. Rats were painted bilaterally on the nasal vestibules once a day for 2 weeks with $10\ \mu\text{l}$ of 10% TDI (Wako Chemical Co., Tokyo) in ethyl acetate. One week later, 10% TDI solution was applied to the nasal vestibules to provoke nasal allergy-like symptoms. Control rats were treated with the vehicle (ethyl acetate) only by the same procedure. The numbers of sneezes during a 10-min period after TDI provocation were counted. All animal experiments were approved by the Ethical Committee for Animal Studies of the School of Medicine, the University of Tokushima.

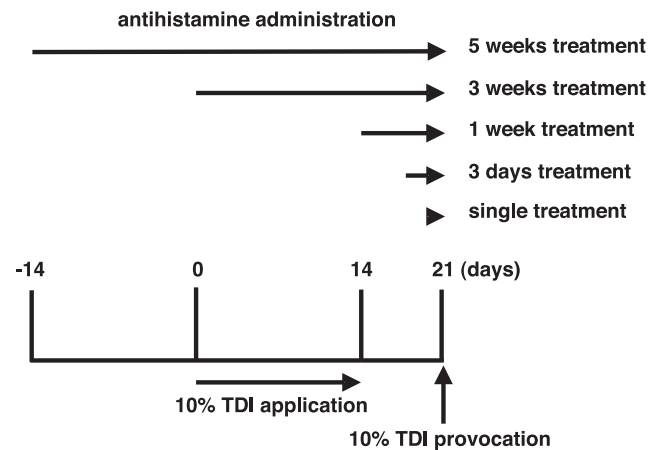


Fig. 1. Protocol for TDI sensitization and schedule for antihistamine pre-treatment. Rats were sensitized with $10\ \mu\text{l}$ of 10% TDI in ethyl acetate for 2 weeks. One week later, they were treated with 10% TDI in ethyl acetate. Control rats were treated similarly with ethyl acetate only. Antihistamines were administered orally as described under Materials and Methods.

Pre-treatment with antihistamines

Antihistamines were dissolved in distilled water and the drugs were administered using a gastric tube. Epinastine (30 mg/kg per day) was administered orally 1 h before provocation or once a day for 3 days, 1 week, 3 weeks, or 5 weeks before provocation with TDI (Fig. 1). *d*-Chlorpheniramine (30 mg/kg) and olopatadine (10 mg/kg) were also administered orally 1 h before provocation or once a day for 1 week before provocation (Fig. 1). We chose these doses because these doses of *d*-chlorpheniramine and olopatadine are expected to show similar antihistaminic effect to epinastine (30 mg/kg) according to the clinical dose of these antihistamines.

Dissection of nasal mucosa and isolation of total RNA

Nasal mucosa was removed from the nasal septum. Samples were frozen in RNeasy[®] (Applied Biosystems, Foster City, CA, USA) and stored in a tube at -80°C until use. Total RNA was isolated using TRIzol reagent (Invitrogen, Carlsbad, CA, USA) in accordance with the manufacturer's instructions. Samples were homogenized in a Polytron (Model PT-K; kinematica AG, Littau/Luzern, Switzerland) in 10 volumes of TRIzol reagent. The homogenates were mixed with chloroform and centrifuged at 15,000 rpm for 15 min at 4°C . RNA in the aqueous phase was precipitated with isopropanol. For this, samples were incubated at room temperature for 5 min and then centrifuged at 15,000 rpm for 15 min at 4°C . The precipitated RNA was washed with 70% ice-cold ethanol, air-dried, and dissolved in $20\ \mu\text{l}$ of diethylpyrocarbonate-treated water. The purity and yield

of total RNA were determined spectrophotometrically at 260 and 280 nm using a NanoDrop ND-1000 spectrophotometer (NanoDrop Technologies, Wilmington, DE, USA). The 260/280 nm ratios of absorption of all preparations were 1.8–2.0.

Real-time quantitative reverse transcription polymerase chain reaction

RNA samples were reverse-transcribed to cDNA in a reaction volume of 40 μ l in first-strand buffer [250 mM Tris-HCl, pH 8.3, at room temperature containing 375 mM KCl, 15 mM MgCl₂, 0.8 mM concentrations of each deoxyribonucleoside triphosphate (dNTP), 40 μ M oligo (dT) primers, 0.004 units of RNase inhibitor, and 8 units of reverse transcriptase (Superscript II, Invitrogen)]. Samples were incubated at 37°C for 60 min. Then, 2 μ l of 2 N NaOH was added and incubation was continued at 65°C for 30 min. The reaction mixture was then neutralized by adding 12.8 μ l of 1 M Tris-HCl, pH 8.0. The samples were then heated at 95°C for 10 min and chilled to 4°C for 5 min. TaqMan primers and probe were designed using Primer Express primer design software (Applied Biosystems). The sequences of the H1R primers were as follows: sense primer, 5'-TATGTGTCCGGGCTGCACT-3'; antisense primer, 5'-CGCCATGATAAAACCCAAGT-3'. The sequence of the probe was as follows: FAM-CCGAGAGCGGAA GGCAGCCA-TAMRA. The sequences of the IL-4 primers were as follows: sense primer, 5'-CAGGGT GCTTCGCAAATTTTA-3'; antisense primer, 5'-CAC CGAGAACCCAGACTTG-3'. The sequence of the probe was as follows: FAM-CCCACGTGATGTACC TCCGTGCTTG-TAMRA. Rodent glyceraldehyde-3-phosphate dehydrogenase (GAPDH) primer and probe (Applied Biosystems) were used as an internal standard. The transcripts were used for a 40-cycle, 3-step polymerase chain reaction (PCR) with the GeneAmp 7300 Sequence Detection System (Applied Biosystems) in 20 mM Tris-HCl, pH 8.4, 50 mM KCl, 3 mM MgCl₂, 200 μ M dNTPs, 900 nM of each primer, and 0.25 units of platinum Taq polymerase. The size and reaction specificity of amplicon were confirmed by agarose gel electrophoresis. Identification of the PCR products was carried out using a genetic analysis system (SEQ8000; Beckman Coulter Inc., Fullerton, CA, USA). For determination of whether the amplification products were derived exclusively from the RNA, a reverse transcriptase (RT)-negative reaction was run in which the enzyme was replaced by an RNase-free sample.

Statistical analysis

The results are presented as means \pm S.E.M. of at least three independent experiments, each carried out in

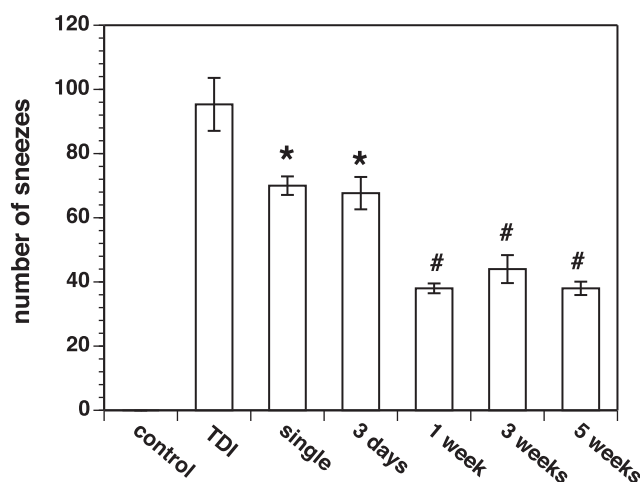


Fig. 2. Effect of repeated pre-treatment with epinastine before provocation on TDI-induced sneezing in TDI-sensitized rats. The numbers of sneezes were counted for 10 min just after TDI-provocation. Epinastine (30 mg/kg per day) was administered orally as described under Materials and Methods. Data are presented as means \pm S.E.M. * P <0.05 vs TDI and # P <0.05 vs single treatment (n =3).

triplicate. For statistical analysis, Fisher's paired least-significant difference test was used. P values of less than 0.05 were considered significant.

Results

Pre-treatment with epinastine

Intranasal application of 10% TDI induced 95 ± 8.3 (mean \pm S.E.M., n =3) sneezes in TDI-sensitized rats (Fig. 2). The administration with epinastine at a dose of 30 mg/kg once 1 h before provocation partially, but significantly suppressed the numbers of sneezes induced by TDI in TDI-sensitized rats. Administration with epinastine for 3 days before provocation also suppressed sneezes to the same extent. Repeated pre-treatment with epinastine at a dose of 30 mg/kg for 1 to 5 weeks before provocation suppressed TDI-induced sneezing further; the numbers of sneezes induced by TDI in rats after repeated pre-treatment with epinastine for 1 to 5 weeks were significantly less than those after its administration once (Fig. 2).

Intranasal application of 10% TDI significantly increased the levels of H1R and IL-4 mRNAs in the nasal mucosa of TDI-sensitized rats (Fig. 3: A and B). The increases of H1R (12) and IL-4 [this study (data not shown)] mRNAs reached a maximum 4 h after TDI provocation. The H1R mRNA level in the nasal mucosa was 10 times higher in TDI-sensitized rats 4 h after TDI provocation than control rats (Fig. 3A). The single administration with epinastine at a dose of 30 mg/kg once at 1 h before provocation or its pre-administration

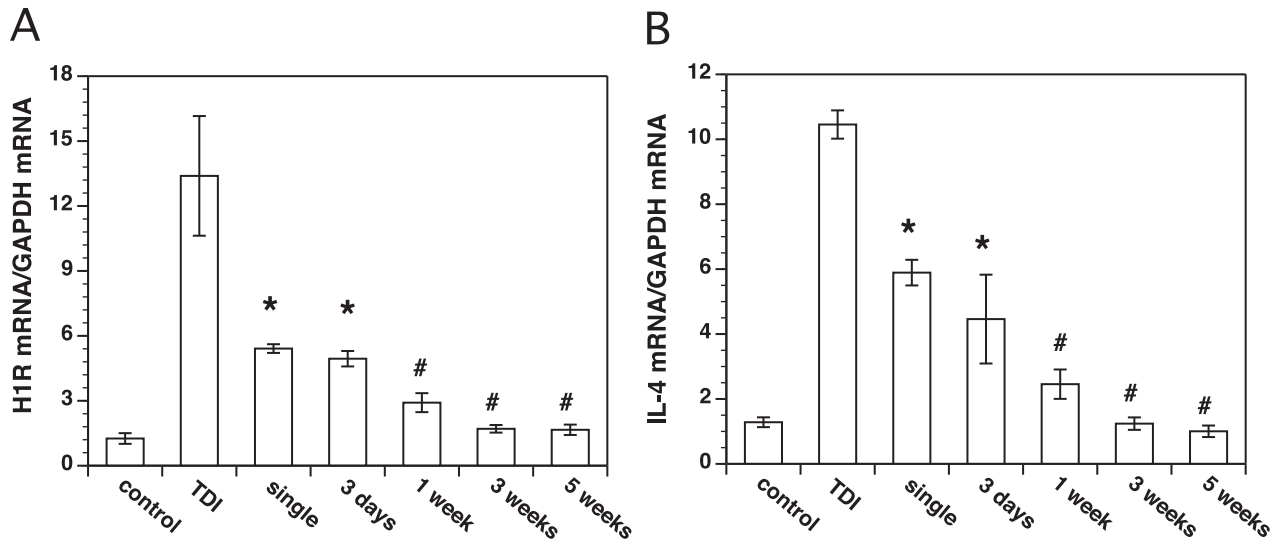


Fig. 3. Effects of repeated pre-treatment with epinastine on TDI-induced up-regulations of histamine H_1 receptor (H1R) mRNA (A) and interleukin (IL)-4 mRNA (B) in TDI-sensitized rats. Nasal mucosa was collected 4 h after provocation. Total RNA was extracted and the mRNA levels of H1R (A) and IL-4 (B) were determined by real-time quantitative RT-PCR. Epinastine (30 mg/kg per day) was administered orally as described under Materials and Methods. Data are presented as means \pm S.E.M. * $P < 0.05$ vs TDI and # $P < 0.05$ vs single treatment ($n = 4$).

for 3 days partially, but significantly suppressed TDI-induced up-regulation of H1R mRNA in the nasal mucosa of TDI-sensitized rats (Fig. 3A). Moreover, repeated pre-treatment with epinastine for 1–5 weeks before provocation suppressed TDI-induced up-regulation of H1R mRNA in the nasal mucosa significantly more than its administration once (Fig. 3A). Repeated pre-treatment with epinastine at 1–30 mg/kg before provocation suppressed TDI-induced H1R gene expression in a dose-dependent manner (Fig. 4).

The IL-4 mRNA level in the nasal mucosa 4 h after TDI provocation in TDI-sensitized rats was 8 times that in control rats (Fig. 3B). The administration with epinastine at a dose of 30 mg/kg once at 1 h before provocation or its pre-administration for 3 days partially, but significantly suppressed TDI-induced up-regulation of IL-4 mRNA in the nasal mucosa of TDI-sensitized rats. Furthermore, repeated pre-treatment with epinastine for 1–5 weeks before provocation decreased IL-4 mRNA up-regulation in the nasal mucosa induced by TDI significantly more than its administration once (Fig. 3B). Repeated pre-treatment of epinastine for 3 or 5 weeks significantly suppressed up-regulations of H1R and IL-4 mRNA versus 1 week treatment ($P < 0.05$). However, there was no significant difference between 3 weeks and 5 weeks.

Pre-treatments with *d*-chlorpheniramine and olopatadine

The effects of repeated pre-treatment with *d*-

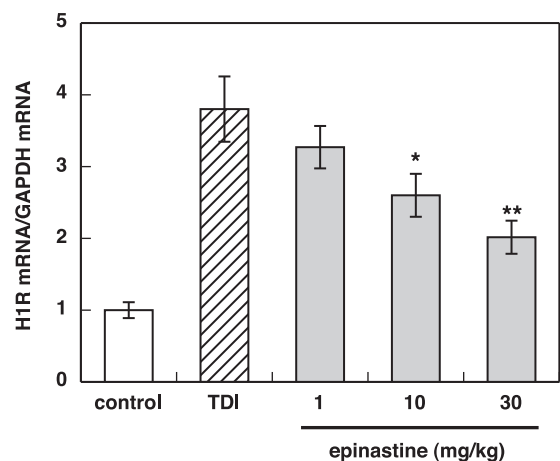


Fig. 4. Effect of repeated pre-treatment with epinastine before provocation on TDI-induced H1R mRNA up-regulation in TDI-sensitized rats. Epinastine at a dose of 1, 10, or 30 mg/kg was administered orally once a day for 1 week before provocation. Nasal mucosa was collected 4 h after TDI-provocation. Total RNA was extracted and the mRNA level of H1R was determined by real-time quantitative RT-PCR. * $P < 0.05$ vs TDI and ** $P < 0.01$ vs TDI ($n = 4$).

chlorpheniramine or olopatadine for 1 week before provocation with TDI on sneezing and the nasal gene-expressions of H1R and IL-4 were examined in TDI-sensitized rats. The numbers of sneezes induced by TDI after repeated pre-treatment with *d*-chlorpheniramine or olopatadine for 1 week were significantly fewer than those after their single administration, which were slightly, but significantly suppressed sneezing (Fig. 5A).

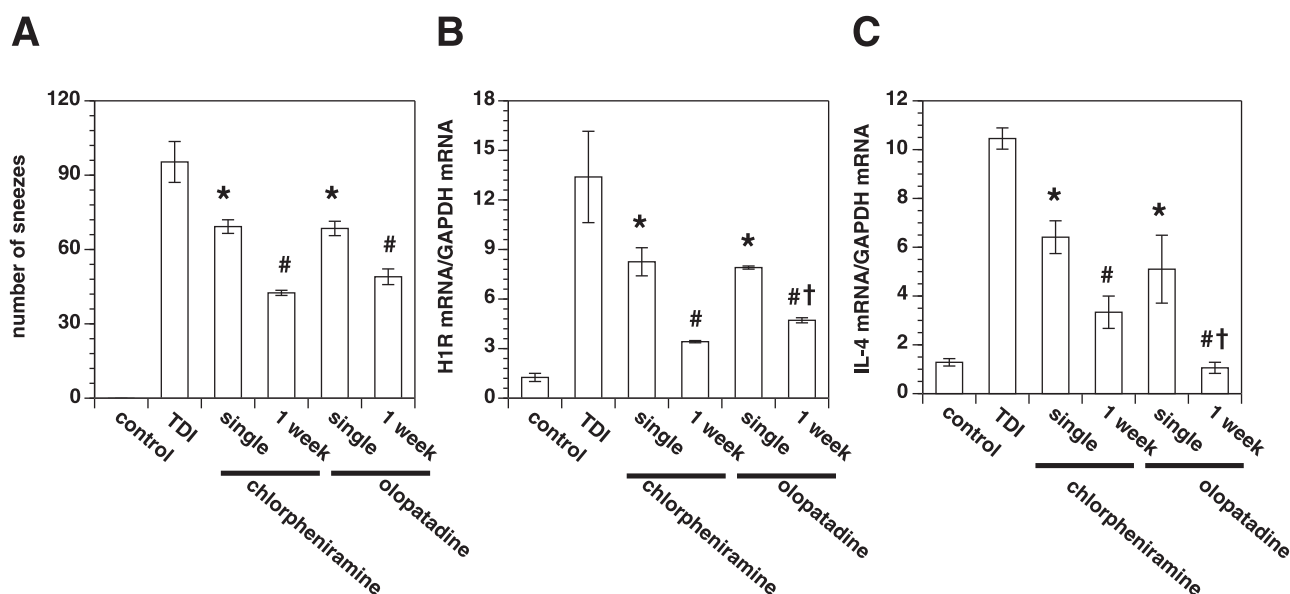


Fig. 5. Effects of pre-treatment with *d*-chlorpheniramine and olopatadine on TDI-induced sneezing (A) and up-regulations of H1R mRNA (B) and IL-4 mRNA (C) in TDI-sensitized rats. *d*-Chlorpheniramine (30 mg/kg per day) and olopatadine (10 mg/kg per day) were administered orally 1 h before provocation or once a day for 1 week before the provocation. A: The numbers of sneezes were counted for 10 min just after TDI provocation. Data are presented as means \pm S.E.M. * $P < 0.05$ vs TDI and # $P < 0.05$ vs single treatment ($n = 3$). B and C: Nasal mucosa was collected from the TDI-sensitized rats 4 h after TDI-provocation. Total RNA was extracted and the mRNA levels of H1R (B) and IL-4 (C) were determined by real-time quantitative RT-PCR. Data are presented as means \pm S.E.M. * $P < 0.05$ vs TDI, # $P < 0.05$ vs single treatment, and † $P < 0.05$ vs 1 week treatment with *d*-chlorpheniramine ($n = 4$).

TDI-induced up-regulations of H1R and IL-4 mRNAs in the nasal mucosa were also significantly decreased in TDI-sensitized rats after repeated pre-treatment with *d*-chlorpheniramine or olopatadine for 1 week before compared with those after their administration once, which also slightly, but significantly suppressed the up-regulations (Fig. 5: B and C).

Discussion

The present study showed that the single administration with epinastine, an antihistamine, significantly suppressed sneezes and up-regulations of H1R and IL-4 mRNAs in TDI-sensitized rats after provocation with TDI. Repeated pre-treatment with epinastine for 1–5 weeks before provocation further suppressed TDI-induced sneezing (Fig. 2). Moreover, the up-regulations of H1R and IL-4 mRNAs in the nasal mucosa induced by TDI were suppressed more by repeated pre-treatment with epinastine for 1–5 weeks before provocation than after its single administration (Fig. 3). These findings suggest that the prophylactic effect of repeated pre-treatment with epinastine for more than one week before provocation on nasal allergy-like behavior is due to its additional effect in suppressing the up-regulations of H1R and IL-4 mRNAs in the nasal mucosa. Repeated

pre-treatment with epinastine for 1 week before provocation dose-dependently suppressed TDI-induced up-regulation of H1R mRNA in the nasal mucosa of TDI-sensitized rats (Fig. 4).

The present study also demonstrated the similar prophylactic effects in TDI-sensitized rats of repeated pre-treatments with the other antihistamines, the first generation antihistamine *d*-chlorpheniramine and the second generation antihistamine olopatadine, for 1 week before provocation with TDI (Fig. 5). These effects were significantly more after their repeated administrations than after their administration once. Statistical analysis showed that pre-treatment with *d*-chlorpheniramine, the first generation antihistamine for 1 week significantly suppressed TDI-induced up-regulation of H1R mRNA versus olopatadine treatment. On the other hand, pre-treatment with olopatadine, the second generation antihistamine for 1 week showed significant suppression of TDI-induced IL-4 mRNA up-regulation compared with *d*-chlorpheniramine. In the number of sneezing, we could not see any significant difference between the two antihistamines, although the effect of *d*-chlorpheniramine seems somewhat strong. We think the reason why we could not see the difference in the suppressive effect on sneezing is that histamine plays a major role in sneezing and nasal rubbing and its action

is through H1R on the sensory nerve endings (23, 24). The strong suppressive effect of olopatadine in IL-4 mRNA up-regulation may be due to its anti-allergic effect such as inhibition of releases of prostaglandins and leukotrienes.

Several kinds of antihistamines were reported to have better effects on AR patients' symptoms when given before the pollen season (2). Thus, suppression of the expressions of H1R and IL-4 seems to be a common reason for the therapeutic value of antihistamine prophylactic treatment of patients.

Previously, we showed up-regulation of H1R at both the mRNA and protein levels after provocation with TDI in TDI-sensitized rats as a model of AR (12, 13). In humans, H1R binding activity in the nasal mucosa was also found to increase after provocation of antigen-induced nasal allergy (25). Increased expression of H1R mRNA was also observed in the nasal mucosa of patients with allergic rhinitis (26) and in cultured epithelial, mucus, and inflammatory cells in the nasal mucosa of patients with perennial allergic rhinitis (27). The up-regulation of H1R in the nasal mucosa could lead to nasal hypersensitivity to histamine, as shown in TDI-sensitized rats (12, 13). Diesel exhaust particles commonly present in diesel engine-powered car exhaust may also cause up-regulation of H1R mRNA in the human airway (28).

We have shown that the IL-4 mRNA level was elevated after TDI provocation of TDI-sensitized rats (Fig. 3B). In allergic diseases, Th2 cytokines skew the Th1/Th2 balance toward Th2. IL-4 regulates the differentiation of stem Th cells into Th2 cells, which produce Th2 cytokines such as IL-4 and IL-5 (16). In addition to its direct effect on cells, IL-4 primes cells for subsequent responses to other stimuli. Pre-treatment with IL-4 primes the FcεRI to induce release of histamine, prostaglandins, leukotrienes, and cytokines (29, 30). Thus, IL-4 is important in the pathogenesis of allergic diseases and IL-4 gene expression could be a target for anti-allergic drugs.

Repeated pre-treatment of epinastine for 3 or 5 weeks significantly suppressed up-regulations of both H1R and IL-4 mRNAs versus 1 week treatment (Fig. 3). As shown in Fig. 5B, suppression of up-regulation of H1R by the single treatment of *d*-chlorpheniramine (30 mg/kg) 1 h before TDI provocation was only partial (about 40%). This suggests the existence of other factors that suppress TDI-induced up-regulation of H1R mRNA. We think IL-4 may be one of the candidates. Increasing experimental evidence suggests the involvement of histamine-cytokine networks in allergic inflammation, in which histamine influences the expression and actions of several cytokines and some cytokines modulate the

production and release of histamine (20, 31–33). It was reported that IL-4 stimulates the expression of H1R mRNA in human rheumatoid synovial fibroblasts (34), and direct application of histamine into the nasal cavity for more than 1 week caused the increase in IL-4 mRNA elevation in TDI-sensitized rats (unpublished observation). During the sensitization with TDI, histamine would be released continuously and up-regulate the IL-4 gene expression. Accordingly, the level of IL-4 is already high by the time of provocation, and IL-4 increases H1R gene expression that was not affected by antihistamines. As the result, the effect of antihistamines is only partial when they were administered just before provocation. On the other hand, pre-treatment with antihistamines suppressed up-regulations of both H1R and IL-4 mRNAs (Fig. 3). Consequently, antihistamines suppress both H1R-induced and IL-4-induced H1R up-regulation and shut down the histamine-IL-4 "vicious" circuit. According to the kinetics of histamine's effect on IL-4 mRNA elevation, more than 1 week of pre-treatment with antihistamines seems to be necessary to obtain the maximum effect.

In conclusion, repeated pre-treatment with antihistamines before provocation with TDI further suppressed TDI-induced sneezing and up-regulations of H1R and IL-4 mRNAs in the nasal mucosa of TDI-sensitized rats. These findings suggested that pre-seasonal prophylactic treatment with antihistamines is more effective than their single administration to patients with AR in reducing nasal allergy symptoms by causing the additional suppression of the expressions of H1R and IL-4 in the nasal mucosa.

Acknowledgments

This work was supported by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (18390167 to H.F.) and by a grant from the Osaka Medical Research Foundation for Incurable Diseases. The authors have no competing financial interests.

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