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Involvement of chemical mediators in nasal allergic responses of HDC-KO mice

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Abstract

The present study was undertaken to investigate the involvement of chemical mediators in nasal allergic responses using histidine decarboxylase knockout (HDC-KO) mice. An allergic rhinitis model was developed in HDC-KO and wild-type mice by the intraperitoneal injection of ovalbumin, aluminum hydroxide gel and pertussis toxin. Five days later, they were boosted by a subcutaneous injection of ovalbumin into the back. From day 18 after the first immunization to day 39, intranasal sensitization with ovalbumin was performed every day and the severity of allergic rhinitis was observed by measuring nasal allergic responses and total IgE levels. It was found that the intranasal administration of antigen caused a significant increase of nasal sneezing and rubbing from day 25 to day 39 both in sensitized HDC-KO and wild-type mice. In addition, a significant elevation of total IgE levels in serum was also found both in sensitized HDC-KO and wild-type mice from day 18 to day 39 after the first immunization. L-733,060, a tachykinin NK_1 receptor antagonist at a dose of 10 mg/kg (s.c.), resulted in the dose-dependent inhibition of nasal allergic responses induced by antigen in both HDC-KO and wild-type mice. In addition, both chlorpheniramine at doses of 3 and 10 mg/kg (p.o.) and BW A868C at doses of 0.3 and 1 mg/kg (i.v.) also showed a dose-related reduction of the nasal allergic responses induced by antigen in sensitized wild-type mice. On the other hand, they had no effects on the nasal signs induced by antigen in HDC-KO mice. From these results, it was revealed that substance P induces nasal allergic responses in the mouse model of chronic allergic rhinitis through the activation of tachykinin NK_1 receptors. Therefore, it can be concluded that not only histamine, but also substance P and prostaglandin D_2, participated in the nasal allergic responses induced by antigen in mice.

Keywords: Nasal allergic response; Sneezing; Nasal rubbing; Histamine; Prostaglandin D_2; Chlorpheniramine; L-733,060; BW A868C; HDC (histidine decarboxylase) knockout mice; C57BL/6

1. Introduction

It has been reported that histamine-induced allergic reactions, such as sneezing, nasal itch, vasodilation, plasma exudation and mucus production, are mainly effected through histamine H_1 receptors (Raphael et al., 1989; White, 1990; Howarth et al., 2000). Moreover, histamine was found to exert its action in auto-, para- and endocrine ways through four types of histamine receptor (H_1, H_2, H_3 and H_4) signaling via different signal-transduction pathways (Hill et al., 1997; Leurs et al., 1995; Liu et al., 2001). There is some evidence that histamine H_2 receptor stimulation did not induce an allergic reaction in either humans or animals, but histamine H_3 receptor stimulation caused the release of mediators from mast cells, and also neurotransmitter release from sensory nerves (Kayasuga et al., 2002a; Ichinose and Barnes, 1989).

Kayasuga et al. (2002b) demonstrated that antigen caused a significant increase of nasal allergic responses in histamine H_1 receptor knockout mice and a selective histamine H_1 receptor antagonist failed to inhibit these responses completely, suggesting the involvement of other receptors in these responses. Thus, it is considered that histamine receptor blocking alone is not adequate for a complete understanding of the mechanisms underlying allergic reactions in animals.

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Recently, we reported that substance P also caused a significant increase of the nasal allergic responses in rats, and a selective tachykinin NK_1 receptor antagonist showed significant and dose-related inhibition of these responses (Rahman et al., 2006). On the other hand, Ohkubo et al. (1995) showed that the allergic reaction induced by substance P is partly mediated by histamine; therefore, it is very important to clarify the pathological cause of allergic rhinitis using histamine-deficient mice generated by disrupting the histidine decarboxylase gene.

Histamine is formed by L-histidine decarboxylase (HDC), stored in mast cells and basophils, and released from these cells in response to IgE and cytokines (Barnes et al., 1998). Recently, HDC gene knockout (HDC-KO) mice have been developed, and it was shown that the levels of histamine in various tissues of HDC-KO mice are much lower than in wild-type mice (Ohtsu et al., 2001). It is known that due to the overlapping and antagonistic role of receptors in the presence of endogenous histamine, receptor inhibition alone may not fully eliminate the histamine system. Moreover, it has also been reported that histamine receptors not only bind with histamine, but also with other substances (Ohtsu et al., 2001). Thus, mice lacking endogenous histamine can be considered an important tool to elucidate the precise role of chemical mediators other than histamine in allergic disease models in animals.

Therefore, the present study aimed to clarify the involvement of chemical mediators other than histamine in nasal allergic responses using HDC-KO and wild-type mice.

2. Materials and methods

2.1. Animals

Male HDC-KO and wild-type (C57BL/6) mice (body weight 25–30 g) were used. HDC-KO mice were prepared as reported by Ohtsu et al. (2001). In brief, an HDC targeting construct was designed to replace a 2.4 kb fragment extending from intron 5 to exon 9 with a PGK promoter-*neo* cassette. PCR-positive Es clones were confirmed for proper homologous recombination by Southern blot in two steps. First, it was checked whether there was a homologous recombination-based insertion at the 3′ homology arm in candidate cell lines by using *Pst*I-digested and *Eco*RI-digested DNA and a *Bam*HI-*Stu*I internal probe to get a 6.5 kb and 11 kb band. Loss of the wild-type *Stu*I band was shown in animals homozygous for the targeted allele. Two strains were bred in our laboratory and housed in aluminum cages with sawdust in an air-conditioned room maintained at 24±2 °C with relative humidity of 55±15%. Wild-type mice were given standard laboratory rodent chow (Oriental Yeast, Tokyo, Japan) and water ad libitum. HDC-KO mice were given a low histamine-containing diet (0.6 nmol/g diet) (Nihon Nosan Kogyo K.K., Yokohama, Japan) and water ad libitum from birth. All procedures involving the animals were conducted in accordance with the guidelines for Animal Experiments at Okayama University Advanced Science Research Centers.

2.2. Reagents and drugs

The following reagents and drugs were obtained from the sources shown in parentheses: ovalbumin (Grade VII; crystallized and lyophilized, essentially salt-free, Sigma, St. Louis, MO, USA), aluminum hydroxide hydrate gel (ALUM, LSL, Tokyo), pertussis toxin (Sigma), chlorpheniramine maleate (Sigma, St. Louis, MO, USA), L-733,060, (2S, 3S)-3-[(3,5-bis (trifluoromethyl) phenyl) methoxy]-2-phenyl piperidine hydrochloride (Sigma) and BW A868C, 3-[(2-cyclohexyl-2-hydroxyethyl) amino]-2,5-dioxo-1-(phenylmethyl)-4-imidazolidine-heptanoic acid (Cayman Chemical Co., Ann Arbor, MI, USA). L-733,060 was dissolved in saline and administered subcutaneously 30 min before antigen challenge. BW A868C was dissolved in saline and administered intravenously 10 min before antigen challenge. Other drugs were suspended in 5% gum arabic solution and administered orally 1 h before the topical application of antigen. Nasal allergic responses were measured for 30 min after the instillation of antigen into bilateral nasal cavities with a micropipette.

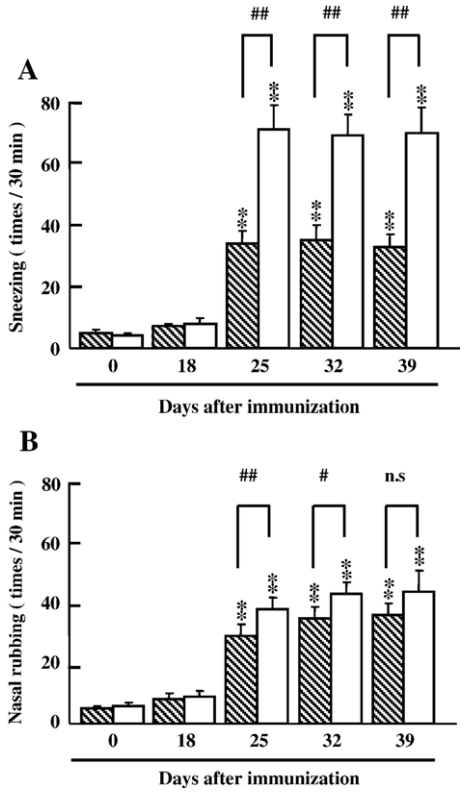

Fig. 1. Time course of development of nasal allergic responses induced by antigen in sensitized HDC-KO and wild-type mice. A: Sneezing, B: Nasal rubbing. Mice were immunized with an intraperitoneal injection of ovalbumin, aluminum hydroxide hydrate gel and pertussis toxin, and subjected to repeated intranasal application of antigen into the nasal cavities every day from 18 to 39 days after the first immunization. Nasal symptoms were observed immediately after nasal instillation of antigen for 30 min. HDC-KO mice (hatched columns); wild-type mice (open columns). Each column and vertical bar shows the means±S.E.M. ($n=10$). **: Significantly different from 0 day group at $P<0.01$ (Dunnett's test). #, ##: Significantly different in comparison with the value of HDC-KO mice at $P<0.05$ and $P<0.01$, respectively (Student's *t*-test).

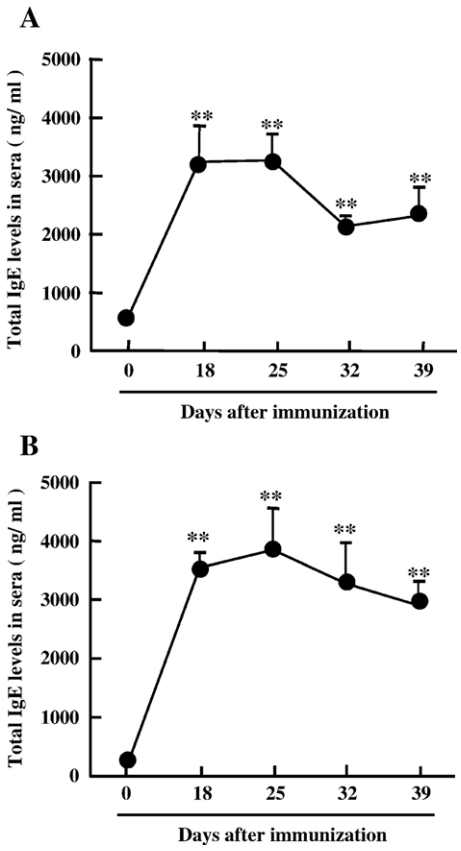

Fig. 2. Changes in total IgE levels in serum by repeated application of antigen in sensitized HDC-KO and wild-type mice. A: Total IgE levels in serum of HDC-KO mice, B: Total IgE levels in serum of wild-type mice. Each point represents the mean±S.E.M. (n=8). **: Significantly different from the control group at P<0.01 (Student's t-test).

2.3. Sensitization

The method reported by Kayasuga et al. (2002a) was used in this experiment. Mice were sensitized by an intraperitoneal injection of ovalbumin (100 μg), aluminum hydroxide hydrate gel (1 mg) and pertussis toxin (300 ng). Five days later, they were boosted by a subcutaneous injection of 50 μg of ovalbumin into the back. Local sensitization was performed every day from day 18 to day 39 by dripping ovalbumin (100 μg/2 μl) dissolved in physiological saline into the bilateral nasal cavities using a micropipette, and these mice were used as actively sensitized mice.

2.4. Evaluation of nasal allergic responses

Before the experiment, the animals were placed into a plastic cage (30×18×24 cm) for about 10 min for acclimatization. After the nasal instillation of ovalbumin (100 μg/2 μl) into the bilateral nasal cavities, the animals were placed into the plastic cage (one animal/cage) and the number of sneezes and nasal rubbing movements were counted for 30 min in accordance with the method of Ashequr and Kamei (2005).

2.5. Measurement of total IgE antibody

Blood was collected from the tail vein on day 0, 18, 25, 32 and 39. Serum was obtained by centrifugation of 500 ×g for 10 min at 4 °C and stored at −20 °C until use. Total IgE levels in the serum were measured by means of an enzyme immunoassay (Bethyl Laboratories Inc, Montgomery, TX, USA).

2.6. Effects of test drugs on nasal allergic responses

In this study, BW A868C was administered intravenously 10 min before the nasal instillation of ovalbumin (100 μg/2 μl). L-733,060 was administered subcutaneously 30 min before antigen challenge. Chlorpheniramine was administered orally 1 h before antigen challenge. Sneezing and nasal rubbing movements induced by antigen were counted for 30 min.

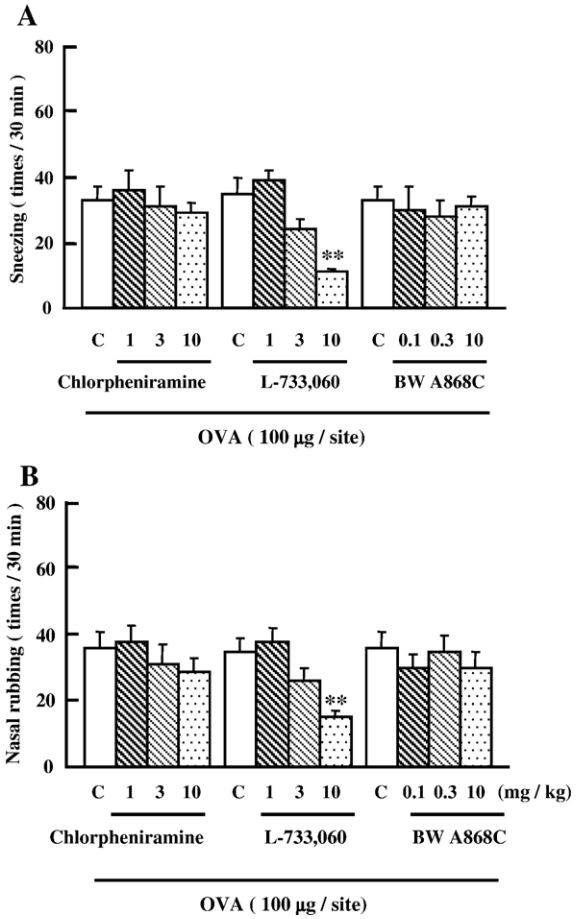

Fig. 3. Effects of H_1 receptor antagonists, tachykinin NK_1 receptor antagonist and prostaglandin D_2 receptor antagonist on nasal allergic symptoms induced by antigen in sensitized HDC-KO mice. A: Sneezing, B: Nasal rubbing, OVA: Ovalbumin. Nasal allergic symptoms were observed immediately after nasal instillation of antigen for 30 min. Chlorpheniramine was administered orally 1 h before antigen challenge. L-733,060 was administered subcutaneously 30 min before antigen challenge and BW A868C was administered intravenously 10 min before antigen challenge. Each column and vertical bar shows the means±S.E.M. (n=10). **: Significantly different from the control group at P<0.01 (Dunnett's test).

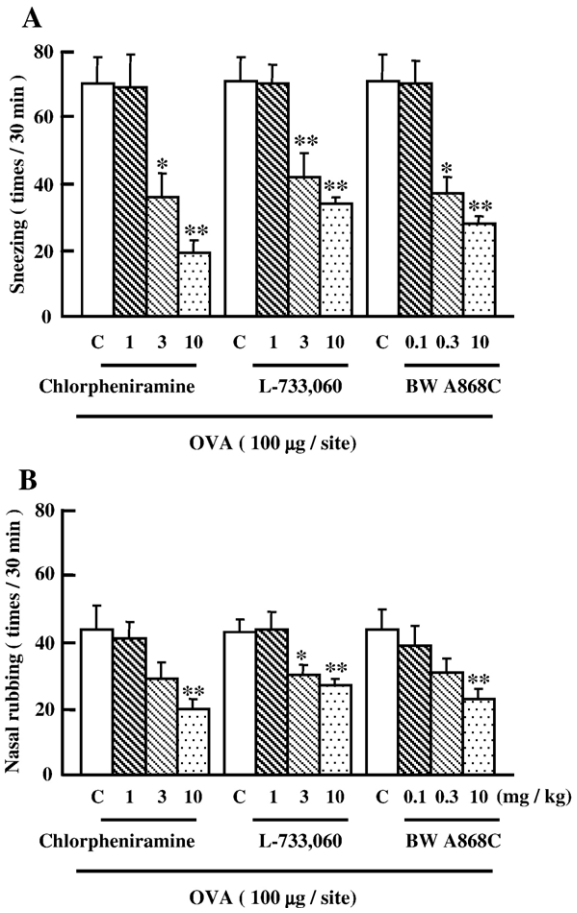

Fig. 4. Effects of H_1 receptor antagonists, tachykinin NK_1 receptor antagonist and prostaglandin D_2 receptor antagonist on nasal allergic symptoms induced by antigen in sensitized wild-type mice. A: Sneezing, B: Nasal rubbing, OVA: Ovalbumin. Each column and vertical bar shows the means ± S.E.M. ($n = 10$). *, **: Significantly different from the control group at $P < 0.05$ and $P < 0.01$, respectively (Dunnett's test).

2.7. Statistical analysis

Data are presented as the means ± S.E.M. Statistical analysis was performed by one-way analysis of variance with Dunnett's test or Student's *t*-test. A probability value of less than 0.05 was considered significant.

3. Results

3.1. Changes in nasal allergic responses after instillation of antigen in actively sensitized HDC-KO and wild-type mice

Fig. 1A and B show nasal allergic responses induced by antigen in HDC-KO and wild-type mice. Sneezing and nasal rubbing induced by antigen in both HDC-KO and wild-type mice are shown in Fig. 1A and B. In both HDC-KO and wild-type mice, 25 days after the first immunization, the topical application of antigen (ovalbumin) caused a significant increase of sneezing and nasal rubbing, and these responses were maintained during local sensitization up to day 39. It is worthy of special mention that the number of incidences of sneezing induced by antigen in wild-type mice was significantly higher than in HDC-KO mice. Moreover, the number of incidences of nasal rubbing induced by antigen in wild-type mice was also significantly higher than in HDC-KO mice from day 25 to 32.

3.2. Changes in total IgE levels by the repeated application of antigen in actively sensitized mice

Changes in total IgE levels in serum due to the repeated intranasal application of antigen in actively sensitized HDC-KO and wild-type mice are shown in Fig. 2A and B. After the repeated topical application of antigen, total IgE levels in both types of mice were significantly elevated from day 18 to day 39.

3.3. Effects of histamine H1 receptor antagonist, tachykinin NK1 receptor antagonist and prostaglandin D_2 receptor antagonist on antigen-induced nasal allergic responses in HDC-KO mice

L-733,060 caused the dose-related inhibition of sneezing induced by antigen and showed a significant effect at a dose of 10 mg/kg (Fig. 3A). Nasal rubbing induced by antigen was also inhibited by L-733,060 in a dose-dependent fashion and showed a significant effect at a dose of 10 mg/kg (Fig. 3B). On the other hand, both chlorpheniramine and BW A868C showed no inhibitory effects on these responses even at doses of 10 and 1 mg/kg, respectively.

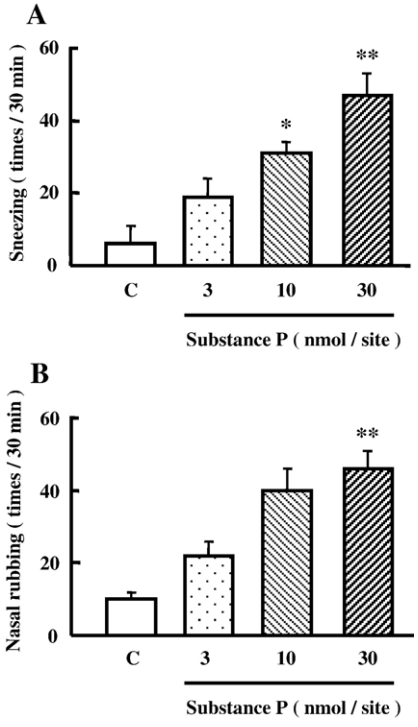

Fig. 5. Nasal allergic symptoms induced by substance P in HDC-KO mice. A: Sneezing, B: Nasal rubbing. Nasal allergic symptoms were observed immediately after the nasal instillation of substance P for 30 min. Each column and vertical bar shows the means ± S.E.M. ($n = 10$). *, **: Significantly different from the control group at $P < 0.05$ and $P < 0.01$ (Student's *t*-test).

3.4. Effects of histamine H1 receptor antagonist, tachykinin NK1 receptor antagonist and prostaglandin D_2 receptor antagonist on antigen-induced nasal allergic responses in wild-type mice

In wild-type mice, chlorpheniramine, L-733,060 and BW A868C dose-dependently inhibited sneezing induced by antigen, and significant effects were observed with doses of 3 and 10 mg/kg (chlorpheniramine), 3 and 10 mg/kg (L-733,060) and 0.3 and 1 mg/kg (BW A868C), respectively (Fig. 4A). In addition, antigen-induced nasal rubbing was also inhibited by chlorpheniramine, L-733,060 and BW A868C, and significant effects were observed with doses of 10 mg/kg (chlorpheniramine), 3 and 10 mg/kg (L-733,060) and 1 mg/kg (BW A868C), respectively (Fig. 4B).

3.5. Changes in nasal allergic responses induced by exogenous substance P in HDC-deficient mice

Fig. 5 shows the nasal allergic responses induced by exogenous substance P in HDC-deficient mice. The intranasal application of substance P resulted in a dose-related increase of sneezing and nasal rubbing, and significant effects were observed at doses of 10 and 30 nmol (sneezing) and at a dose of 30 nmol (nasal rubbing).

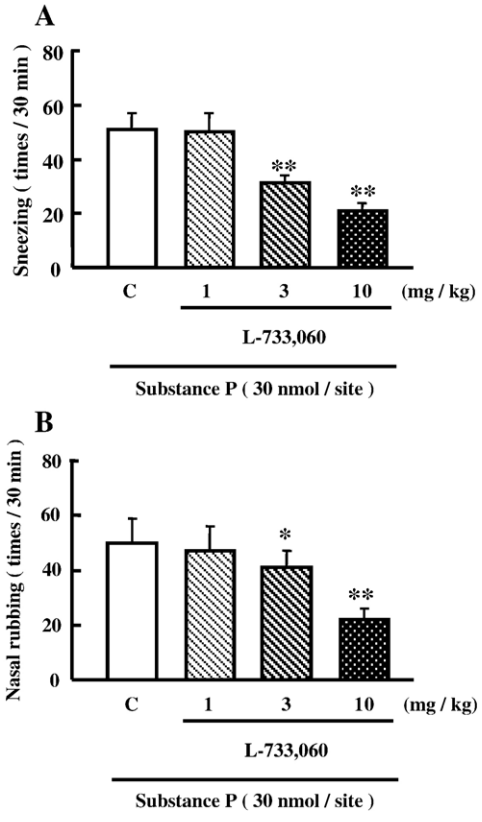

Fig. 6. Effect of tachykinin NK_1 receptor antagonist on nasal allergic symptoms induced by substance P in HDC-KO mice. A: Sneezing, B: Nasal rubbing. Nasal allergic symptoms were observed immediately after nasal instillation of substance P for 30 min. L-733,060 was administered subcutaneously 30 min before substance P challenge. Each column and vertical bar shows the means ± S.E.M. ($n=10$). *, **: Significantly different from the control group at $P<0.05$ and $P<0.01$, respectively (Dunnett's test).

3.6. Effect of tachykinin NK1 receptor antagonist on nasal allergic responses induced by substance P in HDC-deficient mice

The effect of the NK_1 receptor antagonist on nasal responses induced by substance P is shown in Fig. 6. L-733,060 caused a dose-related significant decrease in the incidence of sneezing induced by substance P in HDC-deficient mice, and significant effects were observed at doses of 3 and 10 mg/kg. In addition, nasal rubbing induced by substance P was also inhibited by L-733,060 in a dose-dependent fashion, and showed significant effects at doses of 3 and 10 mg/kg.

4. Discussion

In the present study, we demonstrated that the repeated topical application of antigen resulted in a significant increase of sneezing and nasal rubbing both in sensitized HDC-KO and wild-type mice. These results suggested that chemical mediators other than histamine contributed to the responses induced by antigen in HDC-KO mice; however, it was also observed that the number of incidences of sneezing induced by antigen in wild-type mice was relatively more than in HDC-KO mice, indicating the greater involvement of endogenous histamine in this response. Similar findings were also shown by Kayasuga et al. (2002a) in histamine H_1 receptor-deficient mice, in which the involvement of histamine in the sneezing response was greater than that of nasal rubbing. On the other hand, the incidences of nasal rubbing induced by antigen in HDC-KO and wild-type mice were almost the same, which suggested that in addition to histamine, other chemical mediators participated in this response in a similar fashion.

Recently, we demonstrated in an allergic rhinitis model of rats that substance P played a significant role in nasal allergic responses (Rahman et al., 2006). Thus, it may be assumed that substance P might be a favorable candidate in nasal allergic responses induced by antigen in HDC-KO mice. As speculated, this study also showed that antigen-induced nasal allergic responses in HDC-KO and wild-type mice were significantly inhibited by a selective tachykinin NK_1 receptor antagonist, L-733,060. These results further confirmed our earlier observation that substance P significantly contributed to nasal allergic signs through the activation of tachykinin NK_1 receptors in animals. In addition, very recently, Ueda et al. (2006) demonstrated that L-733,060 at a dose of 10 mg/kg caused a significant decrease of the scratching behavior induced by 2,4,6-trinitrochlorobenzene (TNCB) in hairless mice, which is also analogous to the present study. Furthermore, substance P-induced normal vascular changes were found in mast cell-deficient mice, and L-733,060 resulted in a significant inhibition of skin vascular permeability in mast cell-deficient mice, indicating that substance P induced its effect through the tachykinin NK_1 receptor (Kowalski et al., 1990; Hossen et al., 2003) and that mast cells had no involvement. Although there are some reports claiming that the nasal allergic responses

induced by substance P are partly mediated by histamine (Hanf et al., 2000), the present study showed clearly in HDC-KO and wild-type mice that antigen-induced nasal allergic responses were significantly blocked by a tachykinin NK_1 receptor antagonist.

On the other hand, chlorpheniramine failed to block nasal allergic responses in HDC-KO mice, which indicates that histamine might not be associated in these responses. It is known that histidine decarboxylase synthesizes histamine in mammals, and due to the disruption of the gene of histidine decarboxylase, these HDC-KO mice lack endogenous histamine release from mast cells after antigen challenge to induce nasal allergic signs (Ohtsu et al., 2001). Moreover, Kozma et al. (2003) reported that HDC-KO mice showed altered cytokine and chemokine gene expression profiles compared with wild-type mice after antigen challenge. Based on these findings, it is very conceivable that histamine has no involvement in the nasal allergic responses induced by antigen in HDC-KO mice, and thereby, chlorpheniramine shows no inhibition of nasal allergic responses induced by antigen in these mice.

It was also found that a prostaglandin D_2 receptor antagonist, BW A868C, caused no inhibition of nasal allergic responses induced by antigen in HDC-KO mice. In line with this, Ohtsu et al. (2001) and Wiener et al. (2002) stated in their studies that mice lacking histidine decarboxylase exhibit a decrease in the number of mast cells, and the remaining mast cells had reduced granular content and defective degranulation characteristics, which might be the cause of the non-inhibition of nasal allergic responses induced by antigen by BW A868C in HDC-KO mice.

There is a report indicating that histamine increases IgE production via the histamine H_2 receptor and reduces its production through the histamine H_1 receptor, which leads to the speculation that endogenous histamine might play a significant role in IgE production in allergic reaction (Jutel et al., 2001). In contrast, it was found in this study that repeated nasal instillation of antigen caused a significant elevation of total IgE levels in the serum of both sensitized HDC-KO and the wild-type mice. Therefore, the present results suggest that endogenous histamine does not affect IgE production in this allergic rhinitis model of mice. In association with these findings, Koarai et al. (2003) also demonstrated in an asthma model using HDC-KO mice that endogenous histamine did not affect total IgE production in the allergic reaction. On the other hand, Kozma et al. (2003) reported that OVA-specific IgE was found to fall in HDC-KO mice in comparison with wild-type littermates, different from our present study. However, in the present study, we used the background of C57BL/6 for HDC-KO mice, whereas Kozma et al. (2003) used the background of BALB/c for their HDC-KO mice; moreover, their sensitization and challenging protocol were quite different from our methods. This might be the cause of the differences between these studies.

In contrast to HDC-KO mice, it was observed that chlorpheniramine and BW A868C showed a dose-related and significant inhibition of nasal allergic behavior induced by antigen in wild-type mice. Similar results were also reported, in which antigen-induced nasal allergic signs in rats and mice were also significantly inhibited by chlorpheniramine (Sugimoto et al., 2000; Kayasuga et al., 2002b). There are ample studies indicating that prostaglandins have been implicated in the genesis of allergic rhinitis, and Raphael et al. (1991) reported that prostaglandin D_2 might be a more sensitive marker of mast cell degranulation than histamine. In addition, a close correlation between nasal allergic responses and prostaglandin D_2 other than histamine was found in patients with allergic rhinitis (Lebel et al., 1988). Furthermore, a significant increase of prostaglandin D_2 concentration was observed in nasal lavage fluid from patients with allergic rhinitis compared with those of volunteers (Sugimoto et al., 1994). In an allergic rhinitis model of guinea pigs, BW A868C caused a significant inhibition of sneezing induced by antigen, consistent with our findings (Arimura et al., 2001). Therefore, from the findings above, it seems that not only substance P, but also prostaglandin D_2 might be involved in the genesis of allergic rhinitis in mice.

In conclusion, although the allergic reaction seems to involve a complex interaction between antigen and multiple effector cells, our findings suggest that substance P and prostaglandin D_2 participate in the pathology of allergic rhinitis, and that these might be favourable candidates for anti-allergic therapy.

References

Arimura, A., Yasui, K., Kishino, J., Asanuma, F., Hasegawa, H., Kakudo, S., Ohtani, M., Arita, H., 2001. Prevention of allergic inflammation by a novel prostaglandin receptor antagonist, S-5751. J. Pharmacol. Exp. Ther. 298, 411–419.

Ashequr, R.M., Kamei, C., 2005. Electroencephalogram and behavioral changes induced by histamine application into the nasal cavity and the effects of some H_1-receptor antagonists. Int. Immunopharmacol. 5, 1741–1748.

Barnes, P.J., Chung, K.F., Page, C.P., 1998. Inflammatory mediators of asthma: an update. Pharmacol. Rev. 50, 515–596.

Hanf, G., Schierhorn, K., Brunnee, T., Noga, O., Verges, D., Kunkel, G., 2000. Substance P induced histamine release from nasal mucosa of subjects with and without allergic rhinitis. Inflamm. Res. 49, 520–523.

Hill, S.J., Ganellin, C.R., Timmerman, H., Schwartz, J.C., Shankley, N.P., Young, J.M., Schunack, W., Levi, R., Haas, H.L., 1997. International union of pharmacology: XIII: classification of histamine receptors. Pharmacol. Rev. 49, 253–278.

Hossen, M.A., Fujii, Y., Sugimoto, Y., Kayasuga, R., Kamei, C., 2003. Histamine H_3 receptor regulate vascular permeability changes in the skin of mast cell deficient mice. Int. Immunopharmacol. 3, 1563–1568.

Howarth, P.H., Salagean, M., Dokic, D., 2000. Allergic rhinitis: not purely a histamine-related disease. Allergy 55, 7–16.

Ichinose, M., Barnes, P.J., 1989. Inhibitory histamine H_3-receptors on cholinergic nerves in human airways. Eur. J. Pharmacol. 163, 383–386.

Jutel, M., Watanabe, T., Klunker, S., Akdis, M., Thomet, O.A., Malolepszy, J., Zak-Nejmark, T., Koga, R., Kobayashi, T., Blaser, K., Akdis, C.A., 2001. Histamine regulates T-cell and antibody responses by differential expression of H_1 and H_2 receptors. Nature 413, 420–425.

Kayasuga, R., Sugimoto, Y., Watanabe, T., Kamei, C., 2002a. Histamine H_1 receptors are involved in mouse nasal allergic responses: a demonstration with H_1 receptors deficient mice. Int. Immunopharmacol. 2, 745–750.

Kayasuga, R., Sugimoto, Y., Watanabe, T., Kamei, C., 2002b. Participation of chemical mediators other than histamine in nasal allergy signs: a study using mice lacking histamine H_1 receptors. Eur. J. Pharmacol. 449, 287–291.

Koarai, A., Ichinose, M., Ishigaki-Suzuki, S., Yamagata, S., Sugiura, H., Sakurai, E., Makabe-Kobayashi, Y., Kuramasu, A., Watanabe, T., Shirato, K., Hattori, T., Ohtsu, H., 2003. Disruption of L-histidine decarboxylase reduces airway eosinophilia but not hyperresponsiveness. Am. J. Respir. Crit. Care Med. 167, 758–763.

Kowalski, M.L., Sliwinska-Kowalska, M., Kaliner, M.A., 1990. Neurogenic inflammation, vascular permeability, and mast cells. II. Additional

evidence indicating that mast cells are not involved in neurogenic inflammation. J. Immunol. 145, 1214–1221.

Kozma, G.T., Losonczy, G., Keszei, M., Komlosi, Z., Buzas, E., Pallinger, E., Appel, J., Szabo, T., Magyar, P., Falus, A., Szalai, C., 2003. Histamine deficiency in gene-targeted mice strongly reduces antigen-induced airway hyper-responsiveness, eosinophilia and allergen-specific IgE. Int. Immunol. 15, 963–973.

Lebel, B., Bousquet, J., Morel, A., Chanal, I., Godard, P., Michel, F.B., 1988. Correlation between symptoms and the threshold for release of mediators in nasal secretions during nasal challenge with grass-pollen grains. J. Allergy Clin. Immunol. 82, 869–877.

Leurs, R., Smit, M.J., Timmerman, H., 1995. Molecular pharmacological aspects of histamine receptors. Pharmacol. Ther. 66, 413–463.

Liu, C., Ma, X., Jiang, X., Wilson, S.J., Hofstra, C.L., Blevitt, J., Pyati, J., Li, X., Chai, W., Carruthers, N., Lovenberg, T.W., 2001. Cloning and pharmacological characterization of a fourth histamine receptor (H_4) expressed in bone marrow. Mol. Pharmacol. 59, 420–426.

Ohkubo, T., Shibata, M., Inoue, M., Kaya, H., Takahashi, H., 1995. Regulation of substance P release mediated via prejunctional histamine H_3 receptors. Eur. J. Pharmacol. 273, 83–88.

Ohtsu, H., Tanaka, S., Terui, T., Hori, Y., Makabe-Kobayashi, Y., Pejler, G., Tchougounova, E., Hellman, L., Gertsenstein, M., Hirasawa, N., Sakurai, E., Buzas, E., Kovacs, P., Csaba, G., Kittel, A., Okada, M., Hara, M., Mar, L., Numayama-Tsuruta, K., Ishigaki-Suzuki, S., Ohuchi, K., Ichikawa, A., Falus, A., Watanabe, T., Nagy, A., 2001. Mice lacking histidine decarboxylase exhibit abnormal mast cells. FEBS Lett. 502, 53–56.

Rahman, M.A., Inoue, T., Kamei, C., 2006. Role of substance P in allergic nasal symptoms in rats. Eur. J. Pharmacol. 532, 155–161.

Raphael, G.D., Meredith, S.D., Baraniuk, J.N., Druce, H.M., Banks, S.M., Kaliner, M.A., 1989. The pathophysiology of rhinitis. I. Assessment of the sources of protein in histamine-induced nasal secretions. Am. Rev. Respir. Dis. 139, 791–800.

Raphael, G.D., Igarashi, Y., White, M.V., Kaliner, M.A., 1991. The pathophysiology of rhinitis. V. Sources of protein in allergen-induced nasal secretions. J. Allergy Clin. Immunol. 88, 33–42.

Sugimoto, M., Sugiyama, S., Yanagita, N., Ozawa, T., 1994. Laser high performance liquid chromatography determination of prostaglandins in nasal lavage fluid in allergic rhinitis. Clin. Exp. Allergy 24, 324–329.

Sugimoto, Y., Kawamoto, E., Chen, Z., Kamei, C., 2000. A new model of allergic rhinitis in rats by topical sensitization and evaluation of H_1-receptor antagonists. Immunopharmacology 48, 1–7.

Ueda, Y., Inoue, T., Rahman, M.A., Yatsuzuka, R., Jihang, S., Kamei, C., 2006. A new chronic itch model accompanied by skin lesions in hairless mice. Int. Immunopharmacol. 6, 1609–1615.

White, M.V., 1990. The role of histamine in allergic diseases. J. Allergy Clin. Immunol. 86, 599–605.

Wiener, Z., Andrasfalvy, M., Pallinger, E., Kovacs, P., Szalai, C., Erdei, A., Toth, S., Nagy, A., Falus, A., 2002. Bone marrow-derived mast cell differentiation is strongly reduced in histidine decarboxylase knockout, histamine-free mice. Int. Immunol. 14, 381–387.