

Full Paper

Nasal Blockage Induced by Oral Administration of Non-steroidal Anti-inflammatory Drugs in a Guinea-Pig Model of Allergic Rhinitis

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Abstract. To elucidate the mechanisms underlying nasal symptoms in patients with aspirin hypersensitivity, we evaluated the effects of orally administered non-steroidal anti-inflammatory drugs (NSAIDs) on the nasal patency of guinea pigs with cedar pollen-induced chronic allergic rhinitis. Indomethacin (10 mg/kg) administered 1 h before a pollen challenge amplified the antigen-induced nasal blockage. More interestingly, even in the absence of the pollen challenge, indomethacin induced nasal blockage at 30 min at 4 h after administration. However, indomethacin-induced nasal blockage was not provoked in non-sensitized animals. Another NSAID, diclofenac (30 mg/kg), also evoked nasal blockage, but unexpectedly, aspirin (500 mg/kg) did not affect nasal patency. Indomethacin-induced nasal blockage was unaffected by a cysteinyl leukotriene receptor (CysLT₁ receptor) antagonist, pranlukast (30 mg/kg, p.o.), or by prostaglandin E₂ (10⁻³ M, intranasal), suggesting that the nasal blockage may not be due to hyperproduction of cysteinyl leukotrienes or inhibition of prostaglandin E₂ production. These results indicate that the indomethacin-induced nasal blockage may not be an identical phenomena to airway symptoms in aspirin hypersensitivity patients. However, because chronic nasal inflammation is indispensable for the development of nasal blockage, indomethacin-induced nasal blockage may become a clue to elucidate new mechanisms underlying hypersensitivity to NSAIDs.

Keywords: nasal blockage, indomethacin, aspirin, cysteinyl leukotriene, prostaglandin E₂

Introduction

In 1922, Widal et al. (1) reported that when a certain population of asthmatic patients took aspirin, nasal blockage and hypersecretion were induced within 1 h after the medication, followed by the development of asthmatic airway obstruction. This drug-induced, harmful phenomena is termed aspirin-induced asthma/rhinitis (AIAR) or aspirin hypersensitivity, in which airway obstructive responses are caused in the lower and upper airways after oral dosing with non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and indomethacin (2). It was reported that 4%–11% of asthmatic patients are intolerant to NSAIDs (3).

The mechanisms that underlie AIAR have been

evaluated (2, 4–6). Because NSAIDs inhibit cyclooxygenase activity, the formation of prostaglandin E₂ (PGE₂), which suppresses bronchospasm and inflammatory cell activation, is reduced. In addition, inhibition of cyclooxygenase activity shunts arachidonic acid metabolism to the 5-lipoxygenase pathway, leading to increased generation of cysteinyl leukotrienes (CysLTs), which are potent bronchoconstrictive mediators. However, whether NSAIDs induce nasal symptoms has not been evaluated in experimental animal models, although AIAR patients develop nasal symptoms after NSAID medication. Thus, the mechanisms of NSAID-induced nasal responses in clinical settings have not been identified.

We have established a Japanese cedar pollen-induced allergic rhinitis model in which guinea pigs are sensitized by multiple intranasal instillations of pollen extracts and an adjuvant and then repeatedly challenged by weekly inhalation of the pollen (7). The sensitized

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guinea pigs exhibit biphasic nasal blockage with peaks at 1 and 4–6 h and sneezing at 0–1 h after the 4th–30th challenges (8). In this model, nasal hyperresponsiveness to histamine and LTD₄ is developed by the repeated pollen inhalation challenge (9, 10). Nasal hyperresponsiveness appears 2 days after a pollen challenge and disappears 7 days after the challenge (9, 10). Because the allergic nasal symptoms were reproducibly induced after a long period of repetitive challenges, chronic inflammation in the nasal tissue should underlie the pathophysiological mechanisms.

In the present study, to develop an AIAR model in which nasal symptoms develop after oral administration of NSAIDs, the effects of indomethacin on the pollen challenge-induced allergic nasal symptoms were evaluated in a preliminary experiment. Because NSAIDs evoke airway obstruction in AIAR patients even without an antigen challenge, we examined if oral administration of indomethacin, aspirin, or diclofenac causes nasal symptoms even in the absence of the pollen antigen challenge. Finally, we pharmacologically assessed the involvement of decreased PGE₂ and increased cysteinyl leukotrienes in indomethacin-induced nasal blockage.

Materials and Methods

Animals

Male, 3-week-old, Hartley guinea pigs weighing 250–300 g were purchased from Japan SLC (Hamamatsu). The animals were housed in a temperature-controlled room at 23 ± 1°C and 60 ± 10% humidity illuminated from 8:00–20:00. They were fed a standard laboratory diet and given water ad libitum. The first sensitization was started 2 weeks after the purchase.

This animal study was approved by the Experimental Animal Research Committee at Kyoto Pharmaceutical University.

Materials

The following reagents were used: indomethacin (Sigma-Aldrich Corp., St. Louis, MO, USA), diclofenac (Cayman Chem., Ann Arbor, MI, USA), aspirin (Wako Pure Chem., Osaka), pranlukast hemihydrate (donated from the laboratory of Ono Pharm. Co., Ltd., Osaka), and PGE₂ (Biomol Int., Plymouth Meeting, PA, USA).

Indomethacin, diclofenac, aspirin, and pranlukast were suspended in 0.5% methyl cellulose solution. PGE₂ was dissolved in 0.7% ethanol solution.

We harvested Japanese cedar (*Cryptomeria japonica*) pollens from the Shiga and Gifu prefectures of Japan. Cedar pollen extracts used for the sensitization were prepared as previously described (7, 8). Al(OH)₃ gels were prepared from 0.25 N NaOH and 0.25 N Al₂(SO₄)₃,

as previously described (11).

Sensitization and challenge

As previously described (8), guinea pigs were intranasally sensitized by instillation of 3 µL per nostril (6 µL per animal) of cedar pollen extracts adsorbed on Al(OH)₃ gel at a concentration of 1 µg protein/mg Al(OH)₃/10 µL twice daily for 7 days. Prior to each sensitization, the upper airway mucosal surface was topically anesthetized by a 5-min inhalation of 4% lidocaine hydrochloride mist, which was generated with an ultrasonic nebulizer (NE-U12; Omron, Osaka). Then, the sensitized animal was intranasally challenged by quantitative inhalation of cedar pollen at a dose of 1.8 mg per nostril (3.6 mg per animal) by using a hand-made inhalation apparatus (7).

Measurement of specific airway resistance (sRaw) and respiratory frequency

sRaw and respiratory frequency were measured by a two-chambered, double-flow plethysmograph system according to the method of Pennock et al. (12). In brief, an animal was placed with its neck extending through the partition of a two-chambered box, and sRaw and respiratory frequency were measured with the Data analyser Pulmos-I (M.I.P.S., Osaka) after detection of the airflow by sensors attached to both the front and rear chambers.

Elevations in sRaw after pollen inhalation in the sensitized guinea pig appeared to reflect total (upper and lower) airway resistance because the guinea pig functionally respire through the nose and not through the mouth. We previously demonstrated that our inhalation procedure deposits almost all of the pollen in the upper airway (7). It has been reported that the early bronchoconstrictor response is characterized by rapid and shallow breathing in a guinea-pig asthma model (13); however, the pollen inhalation challenge-induced elevation of sRaw correlates well with the decrease in respiratory frequency and is accompanied by deep breathing in our experimental allergic rhinitis model (8). Furthermore, after the pollen inhalation challenge, the accumulation of eosinophils in the lung, which is a characteristic feature of allergic bronchial asthma, was completely absent (S. Kohn et al., unpublished data). Therefore, it can be concluded that the changes in sRaw induced by antigen challenge in our guinea-pig model exclusively reflect the nasal response and not the lower airway response.

Counting of sneezing frequency

Sneezing frequency was determined during the time periods of 0–10 min and 10–60 min after the 22nd

pollen inhalation challenge.

Data analyses

Statistical analyses were performed by one-way analysis of variance using the StatView version 4.5 software (Concepts, Inc., Berkley, CA, USA). If a significant difference was detected, the individual group difference was determined by Bonferroni's multiple test. A probability value (*P*) less than 0.05 was considered statistically significant.

Results

Effects of indomethacin on allergen-induced sneezing and biphasic nasal blockage

In the first series of experiments, the effects of indomethacin on allergen-induced sneezing and nasal blockage were assessed at the 22nd challenge. Indomethacin (10 mg/kg) was orally administered 1 h before the challenge. The dose (10 mg/kg) of indomethacin has been used as a sub-maximum dose to show anti-inflammatory actions in experimental animals (14, 15).

As shown in Fig. 1A, sneezing that was induced within 1 h after the challenge was not significantly affected by the oral administration of indomethacin. However, allergic nasal blockage induced 1–3 h after the challenge was aggravated by indomethacin, and this effect was statistically significant 3 h after the challenge (Fig. 1B).

Effects of indomethacin on nasal patency in sensitized guinea pigs

NSAIDs cause aspirin-induced, asthma-like symptoms even without an antigen challenge (2). Therefore, we next evaluated whether indomethacin evokes nasal blockage even in the absence of the pollen allergen challenge in the sensitized guinea pigs. We previously reported that nasal hyperresponsiveness to histamine and LTD₄ is observed 2 days after a pollen challenge, but disappears by 7 days after the challenge (9, 10). Thus, the effects of indomethacin on nasal patency were assessed 2 or 7 days after the 9th or 7th pollen challenges, respectively. The sRaw was significantly increased at 0.5–3 h after the oral administration of indomethacin on both 2 and 7 days after challenge (Fig. 2: A and B).

Effects of indomethacin on respiratory frequency in sensitized guinea pigs

We have reported that antigen-induced nasal blockage coincided with decreased respiratory frequency in this guinea-pig model of allergic rhinitis (8). Thus, whether indomethacin also decreases respiratory frequency

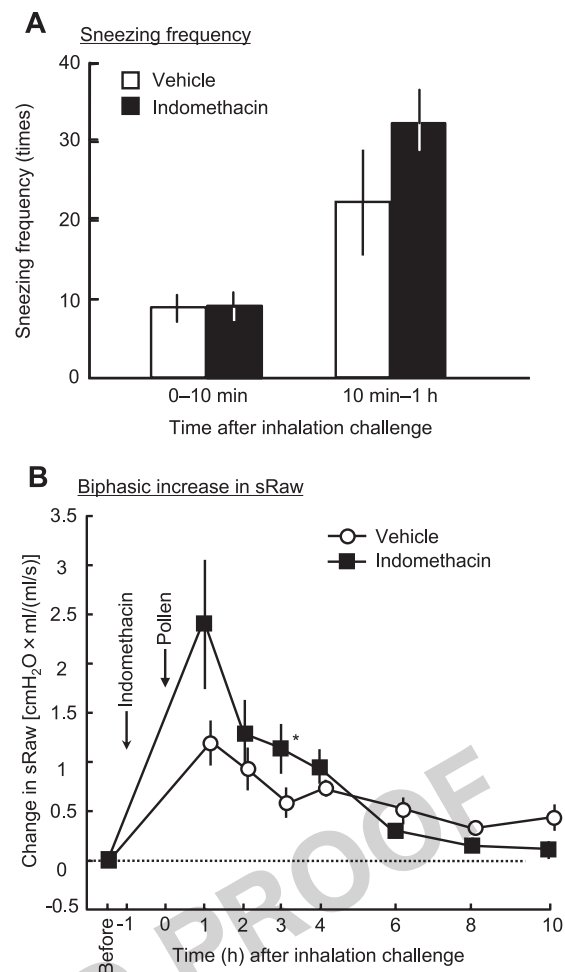


Fig. 1. Effect of indomethacin on sneezing frequency (A) and biphasic nasal blockage (B) induced by the inhalation challenge with Japanese cedar pollen in sensitized guinea pigs. Indomethacin (10 mg/kg) was orally administered once 1 h before the 22nd challenge. Each point represents the mean $\pm$ S.E.M. of 8–12 animals. sRaw, specific airway resistance. **P* < 0.05 vs vehicle-treated group.

during the induction of nasal blockage was assessed. As a result, oral administration of indomethacin significantly decreased the respiratory frequency 1–2 h after the treatment (Fig. 3).

Effects of indomethacin on nasal patency in non-sensitized guinea pigs

We evaluated whether indomethacin induces nasal blockage even in non-sensitized guinea pigs. In sharp contrast to the results in sensitized animals, the non-sensitized guinea pigs never showed any nasal blockage after the oral administration of indomethacin (Fig. 4).

Effects of diclofenac and aspirin on the nasal patency

Next, whether oral dosing with other NSAIDs,

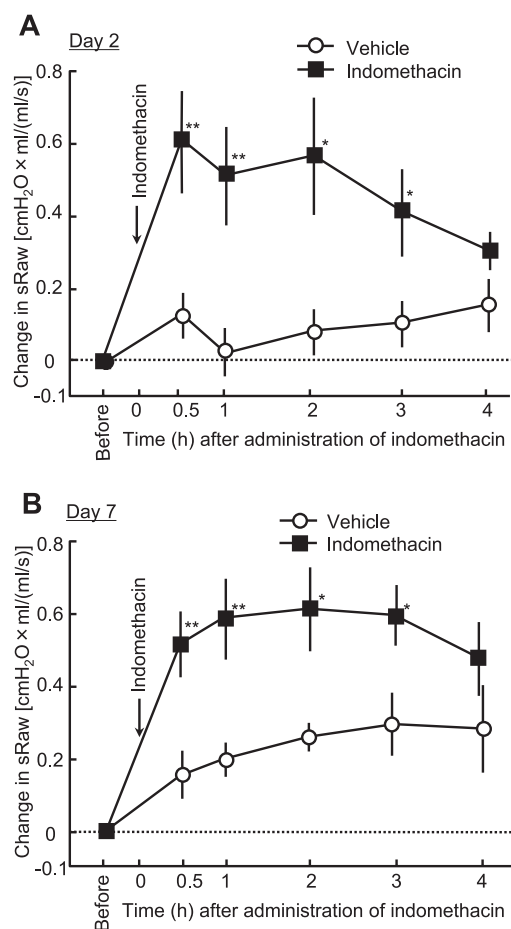


Fig. 2. Indomethacin-induced nasal blockage in sensitized guinea pigs. Indomethacin (10 mg/kg) was orally administered once 2 (A) or 7 (B) days after the 9th or 7th inhalation challenge, respectively, with Japanese cedar pollen. Each point represents the mean $\pm$ S.E.M. of 10 animals. sRaw, specific airway resistance. * $P < 0.05$, ** $P < 0.01$ vs vehicle-treated group.

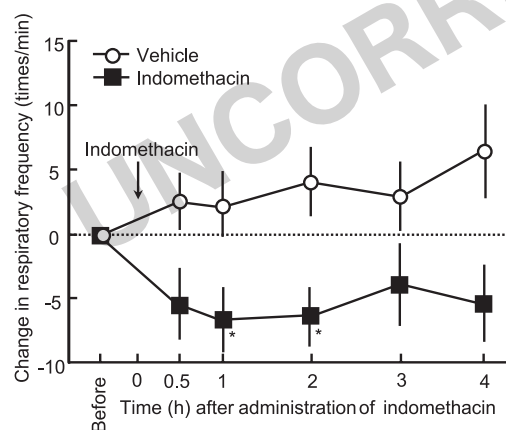


Fig. 3. Indomethacin-induced decrease in respiratory frequency in sensitized guinea pigs. Indomethacin (10 mg/kg) was orally administered once 2 days after the 9th inhalation challenge with Japanese cedar pollen. Each point represents the mean $\pm$ S.E.M. of 10 animals. * $P < 0.05$ vs vehicle-treated group.

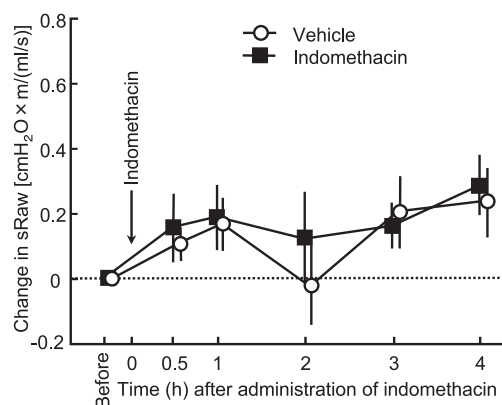


Fig. 4. Lack of indomethacin (10 mg/kg, p.o.)-induced nasal blockage in non-sensitized guinea pigs. sRaw, specific airway resistance.

diclofenac or aspirin, also induces nasal blockage was evaluated 2 days after the 20th challenge. Because it has been reported that diclofenac is almost equipotent to indomethacin in cyclooxygenase-1 inhibitory activity (14, 15), doses of 10 and 30 mg/kg of diclofenac were selected. On the other hand, because it has been reported that the potency of aspirin to inhibit PG synthesis and show anti-inflammatory actions is more than 10-times less than indomethacin (16, 17), we evaluated aspirin at doses of 200 and 500 mg/kg.

Figure 5 shows the effects of diclofenac and aspirin on the nasal patency of sensitized guinea pigs. Almost identical to the effect of indomethacin (10 mg/kg), 30 mg/kg diclofenac significantly induced nasal blockage at 0.5–4 h after the oral dosing. Diclofenac at 10 mg/kg also significantly caused nasal blockage, whereas the degree was weaker than those of 10 mg/kg indomethacin and 30 mg/kg diclofenac (data not shown). On the other hand, aspirin did not cause any increase in sRaw at 200 mg/kg (data not shown) and 500 mg/kg (Fig. 5).

Effects of pranlukast and PGE₂ on indomethacin-induced nasal blockage

It has been suggested that mechanisms underlying aspirin-induced asthma are closely associated with the inhibition of cyclooxygenase (2, 4–6). Therefore, we examined if the indomethacin-induced nasal blockage is reversed by antagonism against CysLT₁ receptors or supplementation with PGE₂. Effects of pranlukast and PGE₂ on the indomethacin-induced nasal blockage were tested 2 days after the 15th and 23rd challenges, respectively. Oral administration of pranlukast (30 mg/kg) 1 h before the dosing with indomethacin produced no significant effect on the nasal blockage (Fig. 6). In addition, intranasal application of PGE₂ (10⁻³ M, 20 μ l

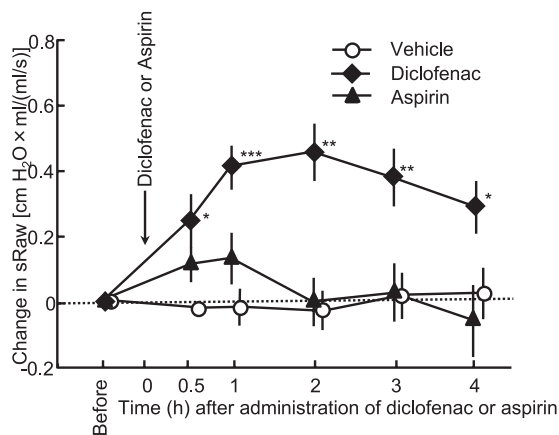


Fig. 5. Induction of nasal blockage by diclofenac, but not by aspirin, in sensitized guinea pigs. Diclofenac (30 mg/kg) or aspirin (500 mg/kg) was orally administered once 2 days after the 15th inhalation challenge with Japanese cedar pollen. Each point represents the mean $\pm$ S.E.M. of 10 animals. sRaw, specific airway resistance. * P <0.05, ** P <0.01, *** P <0.001 vs vehicle-treated group.

/animal) 15 min before the oral treatment with indomethacin did not affect the nasal blockage (Fig. 6).

Discussion

In the present study, indomethacin amplified the antigen-induced nasal blockage in the sensitized guinea pigs. This phenomenon may be associated with nasal responses to NSAIDs in AIAR patients. However, NSAIDs can cause airway responses even without antigen challenge in clinical settings. Thus, effects of NSAIDs on nasal patency were evaluated in the absence of the pollen challenge. As results, both indomethacin and diclofenac induced nasal blockage in sensitized guinea pigs after oral administration without the antigen challenge, and the indomethacin-induced nasal blockage was accompanied with the decrease in respiratory frequency. It was unexpected, however, that aspirin did not affect the nasal patency. In contrast to these results, various NSAIDs including aspirin and indomethacin cause upper and lower airway obstructive responses in a certain population of AIAR patients (2, 4–6). Although a CysLT₁-receptor antagonist effectively improved nasal responses to aspirin in such patients (18, 19), the indomethacin-induced nasal blockage in the present study was not affected by a high dose of pranlukast. Therefore, the nasal blockage induced by indomethacin and diclofenac in the present study may not be an identical phenomenon to airway symptoms in clinical settings. However, it was quite interesting that although naïve animals did not show any nasal signs after oral administration of indomethacin, the NSAID caused

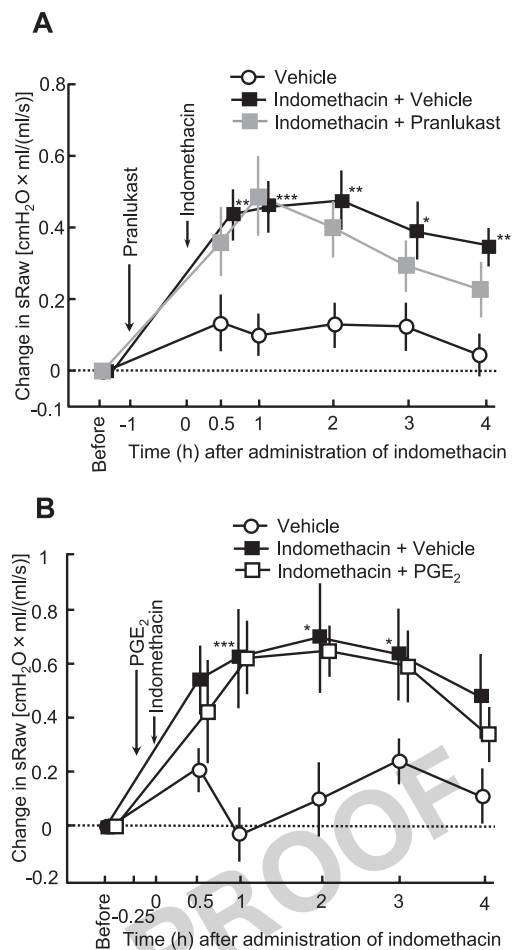


Fig. 6. Neither pranlukast (A) nor prostaglandin (PG) E₂ (B) influences the indomethacin-induced nasal blockage in sensitized guinea pigs. Pranlukast (30 mg/kg, p.o.) or PGE₂ (10⁻³ M, 20 μ l/animal, intranasally) was administered 1 h or 15 min before the indomethacin treatment (10 mg/kg, p.o.) 2 days after the 23rd inhalation challenge with Japanese cedar pollen. Each point represents the mean $\pm$ S.E.M. of 9–16 animals. sRaw, specific airway resistance. * P <0.05, ** P <0.01, *** P <0.001 vs vehicle-treated group.

nasal blockage, even in the absence of allergen challenge, in the sensitized guinea pigs. Thus, we are considering the possibility that the indomethacin-induced nasal blockage may provide a clue for understanding new mechanisms underlying AIAR.

In guinea-pig models of asthma, indomethacin has been usually used to change an asthmatic response to a state where CysLTs are largely involved (20). On the other hand, regarding the allergic rhinitis model of guinea pigs, there is only one study evaluating effects of indomethacin on nasal allergy (21). Fujita et al. (21) showed that indomethacin enhanced antigen-induced increase in nasal airway resistance, and the amplified response was inhibited by a treatment with pranlukast (10 mg/kg). However, there is no report that showed

systemic administration of indomethacin provoked nasal blockage in the absence of antigen challenge in experimental animals. Therefore, the indomethacin-induced nasal blockage response in the present study may be a useful experimental model to elucidate harmful effects of NSAIDs in the upper airway.

The incidence of aspirin hypersensitivity in the general population ranges from 0.6%–2.5%, while the incidence in adult asthmatics ranges from 4.3%–11% (3), suggesting that chronic airway inflammation should underlie the mechanism of AIAR. In agreement with these epidemiological results (3), the nasal blockage response induced by indomethacin occurred in the sensitized guinea pigs, but not in naïve animals. In relation to the chronicity of nasal allergy, we have reported that nasal hyperresponsiveness to histamine and LTD₄ is developed by repeated pollen inhalation challenge in this guinea-pig model of allergic rhinitis (9, 10). The nasal hyperresponsiveness appears 2 days after a pollen challenge and disappears 7 days after the challenge, implying that nasal mucosal inflammation responsible for the development of nasal hyperresponsiveness should be caused at 2 but not 7 days after antigen challenge (9, 10). Thus, we assessed the relationship between the nasal hyperresponsiveness and the indomethacin-induced nasal blockage in the sensitized guinea pigs, and we found that indomethacin caused nasal blockage at both 2 and 7 days after challenge. These results suggest that nasal hyperresponsiveness is not required for indomethacin-induced nasal blockage. Because non-sensitized animals did not show any nasal response, inflammatory changes that are not directly related to the development of nasal hyperresponsiveness are required to induce nasal blockage after the indomethacin treatment.

We were surprised that the CysLT antagonist did not affect the indomethacin-induced nasal blockage at a dose of 30 mg/kg. It has been reported by researchers in the laboratories of the manufacturer of pranlukast that 10–30 mg/kg pranlukast caused potent inhibition in *in vivo* experiments of CysLT-mediated allergic reactions (21, 22). The present result is different from clinical findings, in which not only the CysLT antagonist montelukast (18, 19), but also the 5-lipoxygenase inhibitor zileuton (23) improved nasal function after aspirin administration in aspirin-sensitive asthmatics. However, from the present findings, we have to consider that CysLTs are not substantially involved in the indomethacin-induced nasal blockage.

Regarding the supplementing effect of E-series PGs on nasal response in AIAR, a clinical study found that aspirin-induced rhinorrhea was reduced by the daily administration of misoprostol, a stable analog of PGE₁

(24). However, whether intranasal application of PGE prevents NSAID-induced nasal blockage has not been addressed by clinical studies. In the present study, intranasal application of 20 μ l/animal of 10⁻³ M PGE₂ did not relieve the indomethacin-induced nasal blockage. Because Martin et al. (25) reported that intratracheal administration of 100 μ l/animal of 30 μ g/ml (approximately 10⁻⁴ M) PGE₂ suppressed an antigen-induced late asthmatic response and eosinophilia in sensitized rats, the dose of PGE₂ used in our study may be enough to represent biological functions in the airway. Therefore, the ineffectiveness of the supplementation of PGE₂ in this study suggests that a decrease in PGE₂ is not a main cause of the indomethacin-induced nasal blockage.

It was also surprising that a high dose of aspirin (500 mg/kg) did not induce nasal blockage in sensitized guinea pigs. The lack of nasal blockage after aspirin administration may further imply that the indomethacin-induced nasal blockage is not related to the inhibition of arachidonic acid metabolism. However, the cyclooxygenase inhibitory mechanism of aspirin is substantially different from those of indomethacin and diclofenac. Although aspirin irreversibly inhibits cyclooxygenases by acetylation of serine in structures, indomethacin and diclofenac inhibit the enzyme in a reversible and competitive fashion (26). In addition, it has been reported that aspirin is involved in synthesis of 15(R)-hydroxyeicosatetraenoic acid, which can lead to a production of an anti-inflammatory metabolite, 15-epi-lipoxin A₄ (27, 28). The different effects of aspirin and indomethacin may lead us to elucidate the mechanisms underlying indomethacin-induced nasal blockage.

In conclusion, both indomethacin and diclofenac induced nasal blockage in the sensitized, repeatedly challenged guinea pigs after oral administration, whereas aspirin did not affect the nasal patency. Because the indomethacin-induced nasal blockage was not induced in non-sensitized guinea pigs, chronic inflammation of the nasal mucosa may be required for the nasal blockage. In addition, the indomethacin-induced nasal blockage was not mediated by CysLTs. Studies of NSAID-induced nasal blockage may help to elucidate the mechanisms responsible for AIAR.

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