

Effect of YM158, a Dual Lipid Mediator Antagonist, on Immediate and Late Asthmatic Responses, and on Airway Hyper-responsiveness in Guinea Pigs

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ABSTRACT—The effects of lipid mediator antagonists: the LTD₄-receptor antagonist pranlukast, the TXA₂-receptor antagonist seratrodist, and the novel dual LTD₄- and TXA₂-receptor antagonist YM158 (3-[(4-*tert*-butylthiazol-2-yl)methoxy]-5'-[3-(4-chlorobenzenesulfonyl) propyl]-2'-(1*H*-tetrazol-5-ylmethoxy)benzanilide monosodium salt monohydrate) were investigated in animals exhibiting immediate asthmatic response (IAR), late asthmatic response (LAR) and airway hyper-responsiveness (AHR). Antigen-induced LAR and AHR are inhibited by orally administered pranlukast (30, 100 mg/kg) and seratrodist (3, 10 mg/kg). YM158 (30 mg/kg), orally administered before or after IAR induction, also inhibited both LAR and AHR. However, while the inhibitory effects of pranlukast and seratrodist on IAR were marginal, the effects of YM158 (3, 10, 30 mg/kg) were dose-dependent, probably due to its multiple sites of action. Additionally, orally administered YM158 (30 mg/kg) inhibited ozone-induced AHR in guinea pigs. Thus, an antagonist that inhibits several lipid mediators might exhibit greater efficacy in treating asthmatic responses than antagonists with a single site of action. Therefore, YM158 shows great promise as a drug that will be able to treat bronchial asthma and related disorders more potently than currently used single-pathway inhibitors.

Keywords: YM158, Leukotriene D₄, Thromboxane A₂, Receptor antagonist, Asthma

Traditionally, asthma has been regarded as an inflammatory disease. Its rapid progression is regulated by many mediators and cytokines, the actions of which result in bronchial constriction, accumulation of inflammatory cells into the airway, mucus secretion, mucosal edema and airway hyper-responsiveness (AHR) (1). The airways of patients with bronchial asthma usually respond to challenge by pathogenic antigens biphasically: first, an immediate asthmatic response (IAR) that peaks 15 to 30 min after challenge and disappears within 1–3 h, followed by a late asthmatic response (LAR) that begins 4 to 12 h after antigen challenge and lasts for several hours (2). Pharmacologic modulation of LAR and AHR by mediator antagonists, such as histamine, 5-hydroxytryptamine (5-HT), leukotriene (LT) D₄, thromboxane (TX) A₂ or platelet activating factor antagonists, have been reported by many investigators (3–6), but the exact mechanisms still remain not fully understood. Since β_2 -adrenoceptor agonists inhibit only IAR and steroids inhibit only LAR (7), the pathogenic mechanisms underlying IAR and LAR are thought to be

fundamentally different.

LAR is thought to be associated with the development of AHR (8), which is marked by increased bronchial responsiveness to non-specific stimuli and is considered an important characteristic of symptomatic asthma (9). Inhalation of a specific antigen or ozone or infection with one of many viruses may induce AHR in humans (9). In particular, ozone induces the release of physiologically active arachidonate metabolites such as prostaglandins E₂ and F_{2 α} , TXA₂ and cys-LTs, as measured in bronchoalveolar lavage samples from humans (10–12). Thus, simultaneous inhibition of both LAR and AHR progression is very important in treating an asthma attack, and a single inhibitor of AHR and LAR has been urgently sought.

In this report, the effects of three lipid mediator antagonists on models of bronchial asthma were examined. Two of these, pranlukast (13) and seratrodist (14), are used clinically to treat bronchial asthma (15). The third is a novel dual antagonist of LTD₄ and TXA₂ receptors, YM158 (16). Guinea pigs with antigen-induced IAR and

LAR and antigen- or ozone-induced AHR in guinea pigs were used to compare the efficacy of these compounds.

MATERIALS AND METHODS

The following experiments were conducted with the approval of the Animal Experimentation Ethics Committee of Yamanouchi Pharmaceutical company.

Animals

Male Hartley guinea pigs (SLC Japan Co., Hamamatsu) were used. Animals weighing 400 to 730 g were used in experiments on antigen-induced asthmatic responses, and animals weighing 380 to 540 g in ozone-induced hyper-responsiveness experiments. Animals were given food and water ad libitum until the day before antigen challenge, when they fasted overnight to eliminate the effect of food on absorption of the test compounds.

Chemicals

The following drugs and chemicals were used: YM158, 3-[[4-*tert*-butylthiazol-2-yl)methoxy]-5'-[3-(4-chlorobenzene-sulfonyl) propyl]-2'-(1*H*-tetrazol-5-ylmethoxy)benzanilide monosodium salt monohydrate (16), was synthesized by Yamanouchi Pharmaceutical Co., Ltd. (Tsukuba). Pranlukast, 4-oxo-8-[4-(4-phenylbutoxy) benzoylamino]-2-(tetrazol-5-yl)-4*H*-1-benzopyran hemihydrate (13), and seratro-dast, (\pm)-7-(3,5,6-trimethyl-1,4-benzoquinon-2-yl)-7-phenylheptanoic acid (14), were purified from the commercially available formulations ONON[®] (Ono Pharmaceutical Co., Osaka) and BRONICA[®] (Takeda Chemical Industries, Osaka), respectively. Ovalbumin (OA, Grade V), urethane, indomethacin and mepyramine were purchased from Sigma Chemical Co. (St. Louis, MO, USA) and acetylcholine (ACh), from Daiichi Pharmaceutical Co. (Tokyo). Mepyramine, OA and ACh were dissolved in 0.9% saline. YM158, pranlukast and seratro-dast for oral administration were dissolved or suspended in an aqueous 0.5% methylcellulose solution.

Sensitization and antigen challenge in guinea pigs

Male Hartley guinea pigs were sensitized by exposure to an aerosolized 1% OA solution in 0.9% saline 5 min daily for 10 days. By the ninth or tenth day, all animals exhibited asthmatic symptoms. The animals were given two 5-min duration booster exposures of 0.5% OA solution in 0.9% saline at weekly intervals. During the booster treatments, animals were pretreated with an intraperitoneal injection of 10 mg/kg mepyramine, an H₁-receptor antagonist, 30 min before antigen inhalation to eliminate the histamine-mediated reaction. One week after the second booster inhalation, the animals were pretreated with mepyramine (10 mg/kg, i.p.) 30 min before antigen challenge to prevent

death due to anaphylactic shock and then challenged by exposure to an aerosolized 2% OA solution in 0.9% saline for 10 min. Test compounds were orally administered before, after, or sometimes before and after antigen challenge.

Antigen-induced IAR and LAR

Airway function in conscious guinea pigs was measured with a two-chambered, restrained, whole-body plethysmograph (17). For each measurement, a conscious animal was positioned with its head extending through the partition of the two-chambered, rectangular plastic box, providing the restraint. Each chamber was fitted with identical wire screen pneumotachographs and identical differential pressure transducers. These transducers were connected to a pulmonary function analyzer (model P; Buxco Electronics, Inc., Sharon, CT, USA) to measure tidal volume, tidal air-flow, respiratory rate and specific airway resistance (sR_{aw}). Airway function was monitored for 5 min at each time point, and the animals were removed from the plethysmograph between these measurements. The following effects of test compounds on IAR and LAR were calculated: the percentage change in sR_{aw} within 30 min after antigen challenge and the area under the time- sR_{aw} response curve (AUC) between 4 and 11 h after antigen challenge.

Antigen-induced AHR

Twenty-four hours after exposure to aerosolized OA, animals were exposed to aerosolized ACh. Under urethane anesthesia (1.2 g/kg, i.p.), a PE-50 tube was inserted into a carotid artery and a catheter was placed in the trachea. The animals were ventilated using a constant-volume respirator (model 683; Harvard Bioscience, South Natick, MA, USA). The tracheal catheter was connected to a low-pressure transducer (TP-101T; Nihon Kohden, Tokyo). Intra-airway pressure was measured using a carrier-amplitude amplifiers (AP620G or AP621G, Nihon Kohden) and recorded on a polygraph (RM-6100, Nihon Kohden) on a Macintosh computer by MacLab 8 software system (AD Instruments, Castle Hill, Australia). Gallamine triethiodide (1 mg/kg, i.v.) was administered to eliminate spontaneous respiration and stabilize ventilation. Five minutes after respiration stabilized, an escalating exposure series consisting of 0.9% saline, and 1, 3, 10, 30, 100, 300 mg/ml of ACh in 0.9% saline solution was nebulized (NE-U12; Omron, Kyoto) and administered as an aerosol. Each dose was delivered over 6 strokes of the respirator, with 3-min intervals between different dose strengths. Changes in intra-airway pressure were recorded as the difference between pressure after inhalation of 0.9% saline and pressure after ACh inhalation at each concentration. The concentration of ACh which elicited 200% of the intra-airway pressure (PC_{200}) was determined by plotting the differential pressure along

the ordinate on a standard scale and the ACh concentration along the abscissa on a common-logarithmic scale. Consequently, the common logarithm of the PC_{200} value was used as the index of airway response.

Ozone-induced AHR

Male Hartley guinea pigs were restrained in a closed-type nasal exposure apparatus (Shibata Science Institute, Tokyo) and then exposed to 2.5 ppm ozone (Ozone generator: MOT-001A; Nippon Ozone Co., Tokyo; Monitor: model 1200; Dylec Inc., Tokyo) for 2 h. Three hours after the end of ozone exposure, AHR was measured by the procedure described above for the measurement of antigen-induced AHR. Anesthetized animals were treated with gallamine triethiodide (1 mg/kg, i.v.), and then an endotracheal tube was inserted and connected to a respirator. Aerosols were produced using a nebulizer and six puffs were delivered for 0.9% saline, followed by increasing ACh concentrations (0.1, 0.3, 1, 3, 10, 30, 100 mg/ml 0.9% saline). Intra-airway pressure was measured by a low-pressure transducer and the peak response was determined for each concentration.

Statistical analyses

The data are presented as the mean \pm S.E.M. Statistical significance was assessed by SAS (statistical analysis system), using Student's *t*-test for comparison of the values from the normal group with the values from the control group. Multiple comparisons between the control group and test compound-treated groups were evaluated by Dunnett's multiple range test. P-Values of less than 0.05 were defined as significant.

RESULTS

Antigen-induced IAR and LAR

The basal levels of sR_{aw} measured in actively sensitized guinea pigs did not differ significantly from those measured in non-sensitized animals. Inhalation of the aerosolized 2% OA solution induced an increase in sR_{aw} within 30 min of exposure only in sensitized, conscious guinea pigs (Fig. 1A). Additionally, increases in sR_{aw} from basal levels were observed in all animals between 4 and 11 h after antigen inhalation (Fig. 1B). The peak increase in sR_{aw} within 30 min of antigen challenge and the AUC from 4 to 11 h were determined to be indicators of IAR and LAR, respectively, since these values differed significantly between sensitized and non-sensitized guinea pigs (Table 1).

Effects of YM158, pranlukast and seratrodist on antigen-induced IAR and LAR

Both IAR and LAR were inhibited dose-dependently when YM158 was administered orally 30 min before antigen inhalation (Fig. 1A). The effects of the 10 and 30 mg/kg doses were statistically significant on both IAR and LAR (Table 1). Even when administered orally 3.5 h after antigen exposure, YM158 significantly inhibited LAR (Table 1). In contrast, when either selective LTD₄- or TXA₂-receptor antagonist was orally administered 1 h before antigen inhalation (10, 30 and 100 mg/kg pranlukast or 1, 3 and 10 mg/kg seratrodist), dose-dependent inhibitory effects were exhibited only on LAR (Table 1).

Antigen-induced AHR

Although aerosolized ACh induced concentration-dependent increases of intra-airway pressure in both sensitized and non-sensitized guinea pigs, the increases in sensi-

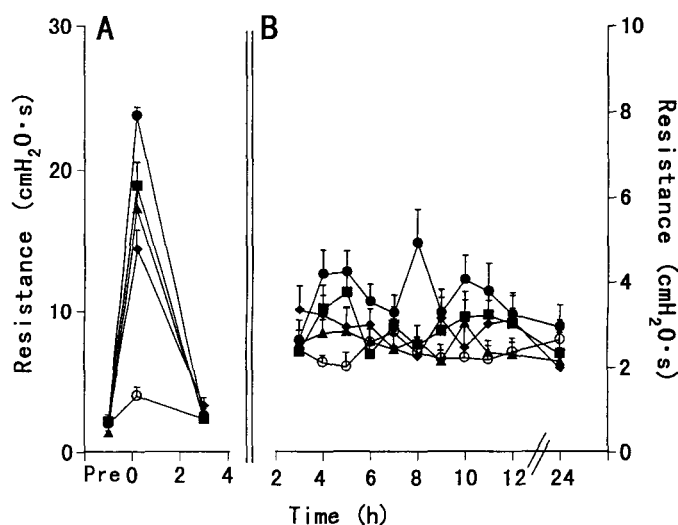


Fig. 1. Effect of YM158 on the increase in sR_{aw} induced by ovalbumin challenge in actively sensitized guinea pigs. The increases in sR_{aw} were observed as IAR (A) and LAR (B). YM158 was orally administered to guinea pigs 30 min before antigen challenge. Results represent the mean \pm S.E.M. \circ : non-sensitized control ($n=10$), \bullet : sensitized control (10), \blacksquare : 3 mg/kg YM158 (9), \blacktriangle : 10 mg/kg YM158 (10), \blacklozenge : 30 mg/kg YM158 (9).

Table 1. Effects of YM158, pranlukast and seratrodist on antigen-induced IAR and LAR in actively sensitized guinea pigs

Compound	Time of dosing h	Dose mg/kg, p.o.	Number of animals	IAR	LAR
				sR _{aw} (cmH ₂ O-s) peak within 30 min	AUC (cmH ₂ O-s-h) 4–11 h
None	–0.5		10	4.04 ± 0.35	16.40 ± 1.43
Sensitized control	–0.5		10	23.75 ± 0.63 ^{##}	27.35 ± 2.64 ^{##}
YM158	–0.5	3	9	18.89 ± 1.67	20.90 ± 2.22
	–0.5	10	10	17.28 ± 1.93 ^{**}	18.35 ± 1.94 [*]
	–0.5	30	9	14.45 ± 1.35 ^{***}	19.39 ± 2.20 [*]
None			8	3.78 ± 0.62	12.18 ± 0.63
Sensitized control			8	20.98 ± 1.57 ^{##}	23.34 ± 1.96 ^{##}
YM158	–0.5	30	9	13.26 ± 1.49 ^{**}	13.21 ± 0.84 ^{***}
	+3.5	30	8	20.17 ± 1.84	17.58 ± 2.04 [*]
None	–1		10	5.42 ± 0.47	25.40 ± 1.59
Sensitized control	–1		11	23.98 ± 0.60 ^{##}	33.29 ± 1.47 ^{##}
Pranlukast	–1	10	10	20.37 ± 1.97	32.22 ± 2.56
	–1	30	10	20.99 ± 1.43	26.88 ± 1.48 [*]
	–1	100	11	20.40 ± 1.57	25.31 ± 1.74 ^{**}
None	–1		9	4.70 ± 0.44	19.29 ± 2.33
Sensitized control	–1		9	22.93 ± 1.26 ^{##}	30.80 ± 3.66 ^{##}
Seratrodist	–1	1	9	19.44 ± 2.01	29.61 ± 1.96
	–1	3	10	20.03 ± 1.94	21.21 ± 2.53 [*]
	–1	10	10	19.74 ± 1.29	19.52 ± 2.33 [*]

Values are the mean ± S.E.M. of the indicated number of animals. ^{##}P<0.01, compared to non-sensitized control animals (Student's *t*-test). ^{*}P<0.05, ^{**}P<0.01, ^{***}P<0.001, compared to sensitized control animals (Dunnett's multiple range test).

tized animals were observed at lower ACh concentrations than those in non-sensitized animals (Fig. 2). Additionally, the PC_{200} values were significantly lower in sensitized animals than untreated controls, indicating that sensitized guinea pigs remained in a constant state of hyper-responsiveness (Table 2).

Effects of YM158, pranlukast and seratrodist on antigen-induced AHR

A 30 mg/kg dose of YM158 induced a rightward shift of the ACh concentration-response curves (Fig. 2) and inhibited the PC_{200} decrease in sensitized animals, regardless of whether administration was performed before (–30 min) or after (+3.5 h) antigen exposure (Table 2). These inhibitory effects were dose-dependent, and PC_{200} values improved to non-treated control levels after administration of 10 or 30 mg/kg YM158 (Table 2). Pranlukast or seratrodist given alone also dose-dependently inhibited the antigen-induced decrease of PC_{200} values.

Effects of YM158 on ozone-induced AHR

After ozone exposure, baseline measurement averages of intra-airway pressures taken before beginning the ACh escalation series were 14.1 ± 0.7 cmH₂O ($n=7$) in the

non-treated control group, while that of the ozone-exposed control group was 17.8 ± 0.7 cmH₂O ($n=7$). There was a concentration-dependent increase in the intra-airway pressure with increasing ACh concentrations in all groups. These increases began at a lower ACh concentration in the ozone-exposed control group compared with the non-treated control group and were statistically significant at ACh doses from 1 to 30 mg/ml (Fig. 3A). As a result, the ACh concentration-response curve for the ozone-exposed control group shifted to the left of the non-treated control group with a concomitant decrease in the PC_{200} of the ozone-exposed control group (Fig. 3B). These results confirmed ozone exposure enhanced airway response and that guinea pigs were in a hyper-responsiveness state. Orally administered YM158 dose-dependently shifted the concentration-response curve for ACh response in ozone-exposed animals back to the right at doses of 10 mg/kg or more, resulting in intra-airway pressures similar to the non-treated control group at a dose of 30 mg/kg. Additionally, 30 mg/kg YM158 significantly increased PC_{200} values, and suppressed airway hyper-responsiveness (Fig. 3). Additionally, basal intra-airway pressure, before the inhalation of 0.9% saline, was not affected by oral YM158 (data not shown).

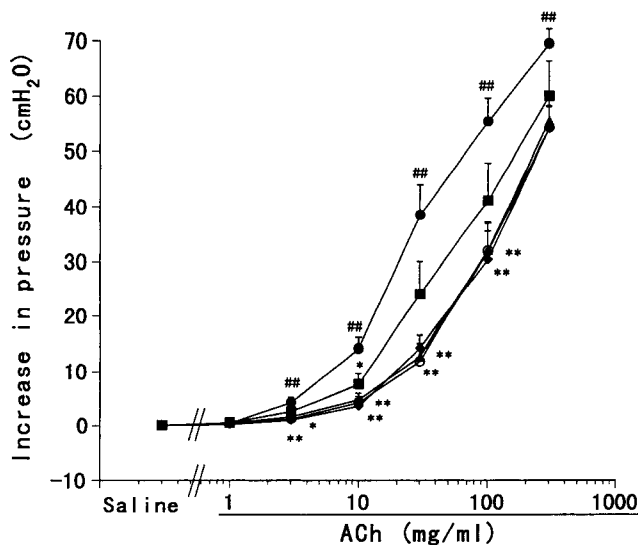


Fig. 2. Effect of YM158 on ACh response in actively sensitized guinea pigs with AHR 24 h after ovalbumin challenge. YM158 was orally administered to guinea pigs 30 min before antigen challenge. Results are expressed as a change in intra-airway pressure and are the mean \pm S.E.M. \circ : non-sensitized control ($n=10$), \bullet : sensitized control (9), \blacksquare : 3 mg/kg YM158 (9), \blacktriangle : 10 mg/kg YM158 (9), \blacklozenge : 30 mg/kg YM158 (9). $^{##}P<0.01$: significant difference compared to the non-sensitized control using Student's *t*-test. $^{*}P<0.05$, $^{**}P<0.01$: significant difference compared to the sensitized control using Dunnett's multiple range test.

DISCUSSION

Pranlukast and seratrodist are specific lipid mediator antagonists; pranlukast inhibits LTD₄ (13) and seratrodist inhibits TXA₂ (18). Currently, these compounds are used to treat asthma. YM158 is an orally active, well-balanced dual antagonist for both LTD₄ and TXA₂ receptors (19). Indeed, although pranlukast or seratrodist given alone failed to inhibit IAR significantly in guinea pigs with antigen-induced asthma, these compounds had been reported previously to suppress IAR (5, 6). The difference in the effects of lipid mediator antagonists on IAR may be explained by differences in the experimental conditions used. Therefore, the effect of each LTD₄- or TXA₂-receptor antagonist on the predominantly lipid mediator-controlled IAR were confirmed (19). These and our previously reported results are similar to those of Nakagawa and co-workers (5) who observed that an LTD₄-receptor antagonist exerted its effect in cyclooxygenase inhibitor-treated guinea pigs, while a TXA₂-receptor antagonist exerted its inhibition in guinea pigs not treated with a cyclooxygenase inhibitor (6). Thus, the predominant mediator of antigen-induced IAR in guinea pigs is TXA₂, while LTD₄ contributes partially. However, since clinical results showing the efficacy of pranlukast and seratrodist were not significantly different, the

Table 2. Effects of YM158, pranlukast and seratrodist on antigen-induced AHR in actively sensitized guinea pigs

Compound	Time of dosing h	Dose mg/kg, p.o.	Number of animals	log PC ₂₀₀ for [ACh (mg/ml)]
None	-0.5		10	1.64 \pm 0.11
Sensitized control	-0.5		9	1.02 \pm 0.10 ^{##}
YM158	-0.5	3	9	1.42 \pm 0.17
	-0.5	10	9	1.60 \pm 0.10 ^{**}
	-0.5	30	9	1.57 \pm 0.14 [*]
None			8	1.62 \pm 0.08
Sensitized control			8	1.33 \pm 0.08 [#]
YM158	-0.5	30	8	1.83 \pm 0.13 [*]
	+3.5	30	8	1.73 \pm 0.13 [*]
None	-1		9	1.23 \pm 0.06
Sensitized control	-1		11	0.93 \pm 0.05 ^{##}
Pranlukast	-1	10	9	1.14 \pm 0.04 [*]
	-1	30	9	1.30 \pm 0.07 ^{***}
	-1	100	11	1.30 \pm 0.07 ^{***}
None	-1		8	1.43 \pm 0.08
Sensitized control	-1		9	0.95 \pm 0.06 ^{##}
Seratrodist	-1	1	9	1.12 \pm 0.08
	-1	3	10	1.39 \pm 0.12 ^{**}
	-1	10	10	1.44 \pm 0.10 ^{**}

Values are the mean \pm S.E.M. of the indicated number of animals. [#] $P<0.05$, ^{##} $P<0.01$, compared to non-sensitized control animals (Student's *t*-test). ^{*} $P<0.05$, ^{**} $P<0.01$, ^{***} $P<0.001$, compared to sensitized control animals (Dunnett's multiple range test).

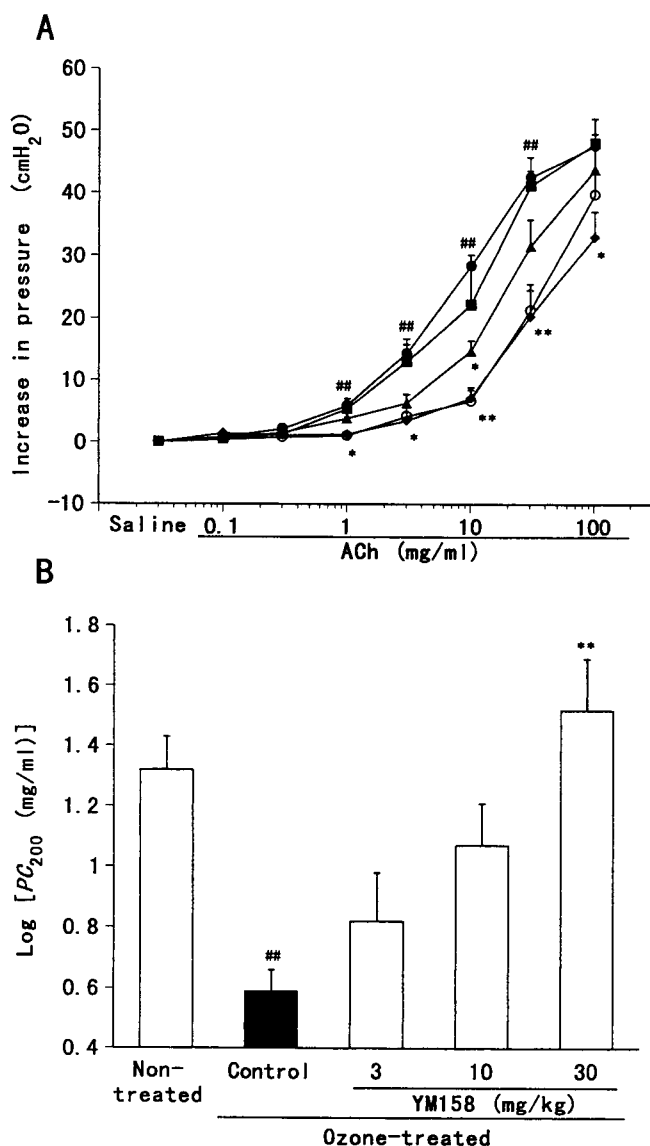


Fig. 3. Effect of YM158 on ACh response in guinea pigs with AHR 3 h after ozone exposure. YM158 was orally administered 30 min before the start of ozone exposure. Results are expressed as a change in intra-airway pressure (A) and as a PC_{200} values (B). Data represent the mean \pm S.E.M. ○: normal control ($n=7$), ●: ozone exposed-control (7), ■: 3 mg/kg YM158 (7), ▲: 10 mg/kg YM158 (6), ◆: 30 mg/kg YM158 (6). $^{##}P<0.01$: significant difference compared to the normal control using Student's t -test. $^{*}P<0.05$, $^{**}P<0.01$: significant difference compared to the ozone exposed control using Dunnett's multiple range test.

participant lipid mediators in human IAR were not only TXA_2 but also LTD_4 . However, in the asthmatic model used in the present study, pranlukast or seratrodist given alone did not significantly inhibit IAR, indicating that selective antagonism of either the LTD_4 or the TXA_2 receptor was not enough to suppress IAR. It is well known that IgE-related histamine and 5-HT have roles in IAR develop-

ment, and bronchodilators, such as β -agonists, alleviate IAR. However, YM158 has been confirmed not to have affinity to those other receptors (20). Thus, the inhibitory effects of YM158 on IAR indicate that both LTD_4 and TXA_2 exert their effects on IAR in this asthma model, and inhibition of both receptors are needed for significant suppressive effects.

As mentioned in other reports (6, 21), LTD_4 - or TXA_2 -receptor-selective antagonists given alone significantly suppressed LAR. YM158 also significantly inhibited LAR in our study, exerting this inhibition even when administered 3.5 h after antigen exposure. Thus, the inhibitory effect of YM158 on LAR may be induced by direct effects on LAR, but not by effects on IAR. Although the effects of either an LTD_4 - or a TXA_2 -receptor-selective antagonist given alone after IAR induction were not examined in this study, LTD_4 and TXA_2 probably contribute to the narrowing of the airway during both IAR and LAR. Evidence for this comes from observations on lipid mediator antagonists, which were indicated to have abilities to suppress contraction of airway smooth muscle caused by LTD_4 and TXA_2 (22, 23), plasma extravasation induced by LTD_4 and TXA_2 (24, 25), and enhanced mucus secretion induced by LTD_4 (26).

AHR is also an important characteristic of bronchial asthma and is considered to be closely related to both the severity of asthmatic reactions (9) and LAR (8). The effects of lipid mediator antagonists on non-specific enhancement of responsiveness were investigated in this report. Significant decreases in PC_{200} and development of AHR was observed in animals with antigen-induced asthma. YM158, pranlukast and seratrodist inhibited the antigen-induced PC_{200} decrease in ACh response, and the effective doses of each compound on LAR and AHR were almost the same. Since these effective doses were enough to completely antagonize each related receptor, the antagonism of LTD_4 receptors, TXA_2 receptors or both is the therapeutic target for both LAR and AHR. From the results obtained from 30 mg/kg YM158 administered 3.5 h after antigen exposure, YM158 is thought to act directly on AHR mechanisms. Since the direct role of TXA_2 in AHR (27) and the significant inhibition of LAR by a seratrodist administered after IAR (6) were reported, the inhibitory effects of YM158 on LAR and AHR in our study were thought to be partially caused by its antagonism for the TXA_2 receptor.

Ozone, a major pollutant in photochemical smog, has been reported to cause AHR in human and animal lung tissue (28–30), which induced by inflammation and tissue damage (30, 31). Many kinds of arachidonic acid metabolites, including LTD_4 and TXA_2 , have been reported to be released upon exposure to ozone (10–12). In this study, ozone exposure increased the intra-airway pressure and induced AHR; a significant increase in intra-airway pressure was observed at ACh concentrations of 1 mg/ml and great-

er, which was lower than that needed to induce the same response in antigen-induced AHR. This result indicates that AHR induced by ozone was more severe than that caused by an antigen and that ozone-exposed animals were in a state of AHR. Stenosis of the lung and trachea was thought to have steadily progressed in all animals exposed to ozone, although this was not confirmed. In contrast, YM158 inhibited increases in the intra-airway pressure at doses of 10 mg/kg and greater, which is equivalent to the dose needed to show inhibitory effects in antigen-induced AHR and in lipid mediator-induced increase of airway resistance (19). The PC_{200} significantly increased at a YM158 dose of 30 mg/kg, with accompanying suppression of AHR.

In conclusion, antigen-induced asthma in guinea pigs exhibited IAR, LAR and AHR. The inhibitory effects of the lipid mediator receptor antagonists, pranlukast, seratroast and YM158, indicate that LTD_4 and TXA_2 have important roles in the development of these responses, and a broad spectral receptor antagonist for these mediators, such as YM158, promises to be a beneficial therapeutic agent in treating bronchial asthma.

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