Effect of AA-861, a Selective 5-Lipoxygenase Inhibitor, on Models of Allergy in Several Species

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Abstract—The effects of 2,3,5-trimethyl-6-(12-hydroxy-5,10-dodecadiynyl)-1,4-benzoquinone (AA-861), a selective 5-lipoxygenase inhibitor, on immunological or non-immunological release of slow reacting substance of anaphylaxis (SRS-A) and histamine and its effects on experimental asthma were investigated. AA-861 showed a dose-dependent inhibition of SRS-A release, with no effect on histamine release from passively sensitized guinea pig, monkey (M. irus) and human lung fragments. An analysis of the anaphylactic diffusate from the human lung fragments, using the combined technique of high performance liquid chromatography and radioimmunoassay, revealed that AA-861 markedly suppresses biosynthesis of the leukotrienes. However, this drug inhibits the release of histamine as well as SRS-A from lung fragments of anaphylactic monkey (M. mulatta) and in the Ca ionophore-stimulated rat peritoneal cavity. AA-861 suppressed the anaphylactically-induced airway resistance in mepyramine and cimetidine-treated guinea pigs. These results suggest that AA-861 may be clinically effective for treating allergy-related asthma by modulating the 5-lipoxygenase pathway and that an inhibitory mechanism of histamine release by AA-861 may be present in some species.

Histamine, leukotrienes (LTs), prostaglandins, thromboxane A2, platelet activating factor, eosinophil chemotactic factor and other substances have been proposed as possible chemical mediators in anaphylaxis or in atopic diseases. However, the exact pathophysiological role of these chemical mediators in atopic diseases, even in allergic bronchial asthma, which is one of the representative diseases, is still not known. Histamine is one of the important chemical mediators in allergic rhinitis and recently has been reevaluated in allergic bronchial asthma. LTs are a family of arachidonate metabolites occurring through the 5-lipoxygenase pathway. The pathophysiological role of LTs in asthma has also been suggested (1). In particular, the sulfidopeptide LTs: LTC4, LTD4 and LTE4, designated as the slow reacting substance of anaphylaxis (SRS-A) elicit potent contractions of the human bronchi (2). In general, the formation and release of LTs or SRS-A from histamine-containing cells or tissues induced by stimuli is concomitant with the release of histamine. Kagey-Sobotka et al. (3) reported that the arachidonate 5-lipoxygenase metabolite(s) may trigger the histamine release from human basophils. On the other hand, the anaphylactic histamine release from the guinea pig lung (4, 5) and the Prausnitz-Küstner reaction in man (6) are not inhibited at all by disodium cromoglycate, an antiallergic drug, although the anaphylactic histamine release from rat peritoneal mast cells (7) and the human lung (8) is fairly prevented by this drug. Furthermore, the SRS-A release from rat peritoneal cells by stimuli (9) is inhibited by indomethacin, a cyclooxygenase inhibitor, but that from the guinea pig lung (10) is enhanced. From these
reports, it is suggested that at least a part of the mechanism of LT and histamine release and the physicochemical characteristics of 5-lipoxygenase may be different among species or tissues.

AA-861 is a newly synthesized compound that competitively inhibits 5-lipoxygenase and inhibits the formation of SRS-A (11).

In the present work, we examined whether AA-861 would consistently inhibit the SRS-A formation in various animal species and whether it would influence the release of histamine induced by immunological or non-immunological stimulation.

Materials and Methods

Reagents

Reagents and their sources were as follows: AA-861 and synthetic LTB₄, LTC₄, LTD₄ and LTE₄ (Takeda Chem. Ind., Osaka); histamine dihydrochloride (Wako Pure Chem., Osaka); atropine sulfate (Merck, Darmstadt); mepyramine maleate and cimetidine (Sigma Chem., St. Louis); disodium cromoglycate (DSCG, Fujisawa Pharm., Osaka); acetonitrile and methanol (HPLC grade, Wako Pure Chem., Osaka); acetic acid (HPLC grade, Nakarai Chem., Kyoto); ³H-LTB₄, -LTC₄, -LTD₄ and -LTE₄ (New England Nuclear, Boston); LTB₄[³H]radioimmunoassay (RIA) Kit (Amersham, Buckinghamshire); LTC₄[³H]RIA Kit (New England Nuclear, Boston); bovine gamma globulin (BGG, Cohn Fr. II, Sigma Chem., St. Louis); potassium benzylpenicillin (Meiji Confectionary, Tokyo); sodium 2,4-dinitrobenzene sulfonate (Eastman Kodak, Rochester); Ca ionophore A-23187 (A23187, Calbiochem-Behring, La Jolla). Other compounds used were of the highest grade available.

Animals

Seven week-old, male Wistar rats weighing 150–180 g, male Hartley guinea pigs weighing 350–600 g (Shizuoka Lab. Animal Ctr., Hamamatsu) and monkeys (M. irus and M. mulatta) of either sex (M. irus: 2.2–2.9 kg, M. mulatta: 6–8 kg) were used. Macroscopically normal human lung tissue was obtained at the time of surgical resection for carcinoma.

Antigens

1. BPO-BGG: Benzylpenicilloyl BGG (BPO-BGG) was prepared according to Levine and Redmond (12). Calculated with the methods of penamaldate (13) for BPO and microbiuret (14) for protein, the number of BPO groups conjugated to the BGG molecule was 29 [(BPO)₂₉-BGG].

2. Mite: Lyophilized aqueous extract of mite (D. farinae) following treatment with acetone was kindly provided by Dr. H. Nagai of Gifu Pharm. Univ.

Antisera

1. Anti BGG guinea pig serum: The anti BGG serum was obtained from guinea pigs sensitized with an emulsion of an equal volume of 2% BGG and Freund’s complete adjuvant, according to Levine et al. (15). The titer of 4 hr passive cutaneous anaphylaxis of antisera was 1:32,000.

2. Anti BPO-BGG guinea pig serum: According to Levine et al. (15), the anti BPO-BGG guinea pig serum was obtained by sensitizing once a month with 1 ml/animal of Tris-buffered saline (pH 8.2) containing 1 µg of (BPO)₂₉-BGG and 1 mg of Al(OH)₃ for 6 months. The 7 day passive cutaneous anaphylaxis titer of the antiserum was 1:810.

Standard SRS-A

SRS-A was obtained from the rat peritoneal cavity, according to Orange and Moore (16), with some reported modifications. In brief, 7.5 ml/animal of prewarmed mast cell medium containing 20 mM of L-cysteine and 15 µg of indomethacin (Merck, Darmstadt) followed by the same volume of mast cell medium containing 45 µg of A23187 were administered intraperitoneally. Ten min later, the animals were killed, and the fluid in the peritoneal cavity was collected.

Following centrifugation at 1,200 g for 15 min at 4°C, 80% ethanol extraction, centrifugation at 11,000 g for 20 min at 4°C and evaporation for removing ethanol under reduced pressure, the aqueous solution was adjusted to pH 7.4 with 1 N NaOH. After washing twice with ethyl acetate, the aqueous layer was evaporated under reduced pressure to remove the organic solvent, then diluted to 5 units (U) of SRS-A/ml with Tyrode’s solution. Finally, methanol at 0.1% final concentration was added for stabilization of SRS-A. The resultant solution served as the standard SRS-A for bioassay and was stored at −80°C until use. One U of SRS-A was
defined as the activity producing contraction equivalent to 5 ng of histamine or 1.6 ng of LTD₄ on the isolated guinea pig ileum in the presence of 5×10⁻⁸ g/ml of atropine and 10⁻⁷ g/ml of mepyramine in a 31°C organ bath containing 1 ml of Tyrode’s solution.

Preparation of sensitized lung fragments and chemical mediator release

1. Guinea pig: Guinea pigs were passively sensitized by giving an intravenous injection of 0.5 ml/animal of anti-BGG guinea pig serum. Four days later, the animals were killed by a blow on the head and bled from the femoral artery. The lungs were perfused with 20 ml/animal of Ca²⁺-free Tyrode’s solution via the pulmonary artery. The lung parenchyma was then cut into fragments of approximately 1.0×0.7×0.7 mm using a McIlwain tissue chopper. These fragments were then washed with 50 ml/g tissue of Ca²⁺-free Tyrode’s solution. Four hundred mg wet tissue/tube of the fragments were suspended in 3.952 ml/tube of Tyrode’s solution, preincubated at 37°C for 5 min, and then 8 μl/tube of drug solutions dissolved in dimethyl sulfoxide (Wako Pure Chem., Osaka) were added. Five min later, 40 μl/tube of the antigen solution at a final concentration of 5×10⁻⁵ g/ml was added to each tube, and the suspension was then incubated at 37°C for 15 min. After removal of the lung fragments on gauze, the anaphylactic medium was centrifuged at 1,200 g for 20 min at 4°C. The resultant supernatant was divided into two tubes for SRS-A and histamine assays.

2. Monkey: Monkeys were anesthetized with an intramuscular injection of 10 mg/kg of ketamine (Sankyo Co., Tokyo) and bled from the carotid artery. The lungs were perfused with 100 ml/animal of Ca²⁺-free Tyrode’s solution via the pulmonary artery. The tracheal cartilages and large blood vessels were removed from the isolated lung. The parenchymal tissue was cut into 1.0×1.0×0.8 mm-sized fragments using a tissue chopper, followed by washing with 50 ml/g tissue of Ca²⁺-free Tyrode’s solution. These fragments were incubated with serum obtained from an atopic patient (5-fold dilution, 5 ml/g tissue, RAST value against the mite antigen: >30%) at 37°C for 2–4 hr for passive sensitization. The sensitized fragments were washed with 50 ml/g tissue of Ca²⁺-free Tyrode’s solution to remove the serum, and 200–300 mg/tube of the fragments were then suspended in Tyrode’s solution (0.973 ml/100 mg wet tissue) and preincubated at 37°C for 5 min. Two μl/100 mg wet tissue of a drug solution was added, and the preparation incubated at 37°C for 5 min. The mite antigen solution (25 μl/100 mg wet tissue) at a 5×10⁻⁵ g/ml final concentration was added, and the incubation was continued at 37°C for 15 min. After completion of the incubation, the fragments were removed and after centrifugation at 1,700 g for 30 min at 4°C, the supernatant was divided into two tubes and stored at −80°C until the SRS-A and histamine assays.

3. Human: The large bronchi and visible blood vessels were removed from the lung and procedures employed were similar to those used for the monkey lung.

Measurements of SRS-A and histamine

SRS-A was bioassayed by the bracket technique described elsewhere (17). Histamine in the reaction medium or in the lung tissue was fluorometrically assayed according to May et al. (18).

Purification and RIA of LTs

LTs in the anaphylactic medium (4 ml/specimen) were purified and radioimmunoassayed as follows: LT specimens to which 0.05 ml/ml of 2.1% gelatin solution had been added were treated with 80% ethanol. After centrifugation at 11,000 g for 20 min at 4°C, the supernatant was evaporated to remove the ethanol, in vacuo below 25°C, followed by addition of distilled water to give a volume of 4 to 6 ml. The pH was adjusted to 5.6 using 0.1 M AcOH. The solution was then applied to a C-18-reversed-phase Sep-pak column (Waters Assoc., Milford) which had been washed with 5 ml of ethanol and 5 ml of 2.5 mM acetate buffer (AB, pH 5.6). After washing with 5 ml each (pH 5.6) of AB, ethanol/AB=2/8 and ethanol/AB=3/7, LTs were eluted with 5 ml (pH 5.6) of ethanol/AB=6/4. The eluate from the Sep-pak column was applied to high performance liquid chromatography (HPLC) following concentration to about 20 μl in vacuo below 20°C and then, addition of 200 μl of the mobile phase solvent (acetonitrile:methanol:water: acetic acid=40:15:44:1, pH 5.6) for HPLC.
HPLC was carried out using a C-18-reversed-phase column (4.6×250 mm, Rainin Inst., Oakland) at 35°C and a flow rate of 0.5 ml/min under continuous monitoring of UV absorbance at 280 nm. Each fraction corresponding to LTB₄, LTC₄, LTD₄ or LTE₄ from HPLC to which 40 μl of 2% gelatin solution had been added was evaporated to dryness, in vacuo, and used for RIA measurement.

RIA of LTB₄ and sulfidopeptide LTs (LTC₄, LTD₄ and LTE₄) was performed using antibodies against LTB₄ and LTC₄, respectively. In brief, a mixture of 100 μl of the LT sample or standard LT dissolved in 0.3 M HEPES (pH 7.5), 100 μl of ³H-LTB₄ (5,000 dpm) or ³H-LTC₄ (10,000 dpm) in 0.3 M HEPES (pH 7.5) and 100 μl of the antiserum was incubated for 18 hr at 4°C. After the completion of the reaction, 500 μl/tube of 0.5% dextran coated charcoal in 0.02 M HEPES were added. After allowing it to stand for 15 min in an ice-water bath, the mixture was centrifuged at 1,700 g for 15 min at 4°C. Five hundred μl of the supernatant were used for counting the radioactivity of bound ³H-LTB₄ or -LTC₄.

Overall recovery throughout the purification was 85–91% for LTB₄, 72–77% for LTC₄, 75–81% for LTD₄ and 62–70% for LTE₄, when ³H-LTs added to the specimen were used as the marker.

Addition of gelatin solution to the specimen prior to the purification and to the LT fraction from HPLC resulted in better recovery and prevented the decomposition of each LT which may be caused by AcOH. The minimum detectable amounts of LTB₄, LTC₄, LTD₄ and LTE₄ in RIA were approximately 3, 10, 10 and 100 pg, respectively.

Experimental asthma in guinea pigs

Guinea pigs were passively sensitized by an intravenous injection of 0.2 ml/animal of antiBPO₂₉-BGG guinea pig serum. Four days later, the animals were anesthetized with sodium pentobarbital (50 mg/kg, i.p.), and the jugular vein was cannulated. The trachea was cannulated and connected to a respirator (Harvard model 680, Harvard Apparatus, So. Natick) to deliver 4 ml/stroke, 40 strokes/min in a partially closed circuit. A side arm from this system was connected to a bronchospasm transducer (Ugo Basile, Camerio-Varese) which measured the airway resistance. In order to suppress pulmonary response which was induced by histamine released, the animals were given 25 mg/kg of cimetidine, i.v., and 5 mg/kg of mepyramine via the cannula 5 min before antigen (80 μg/animal) provocation. Changes in airway resistance were expressed as % of the response seen in the case of complete obstruction of the trachea. AA-861 was administered intravenously through the cannula 2 min before giving the antigen.

SRS-A and histamine release in the rat peritoneal cavity

Rats were given intraperitoneally 10 ml/animal of drug solution and 5 min later, administered with 5 ml/animal of A23187 at a final concentration of 0.3 μg/ml, given by the same route. After 10 min, the rats were killed, and the fluid in the cavity was collected into a tube chilled in an ice-water bath and then centrifuged at 1,700 g for 30 min at 4°C. The supernatant was divided into two tubes for SRS-A and histamine assays.

Results

SRS-A and histamine release from the passively sensitized lung fragments

1. Guinea pigs: The effect of AA-861 on SRS-A and histamine release from lung fragments of passively sensitized guinea pig is shown in Fig. 1. The antigen-induced SRS-A release from these fragments was dose-dependently inhibited by 25–93%, with doses of 10⁻⁸–10⁻⁵ M, whereas the release of histamine was little influenced by the drug given in the same doses.

2. Monkeys (M. irus): The effect of AA-861 on anaphylactic SRS-A and histamine release from lung fragments from the passively sensitized monkey (M. irus) is shown in Fig. 2. AA-861 suppressed the release of SRS-A by 55–97%, dose-dependently in doses of 10⁻⁸–10⁻⁵ M. Here also, the histamine release was little affected.

3. Monkeys (M. mulatta): The effect of AA-861 on SRS-A and histamine release from lung fragments of the passively sensitized monkey (M. mulatta) is shown in Fig. 3. AA-861 at 10⁻⁸–10⁻⁶ M, reduced the release of SRS-A to almost the spontaneous level, while the inhibitory potency at 10⁻⁶ M decreased.
The release of histamine, which markedly differed from the results in guinea pigs and the monkey M. irus, was suppressed in a dose-dependent manner at concentrations of $10^{-7}$–$10^{-6}$ M, but the inhibitory effect at $10^{-5}$ M was less in magnitude.

4. Humans: The effect of AA-861 on anaphylactic SRS-A and histamine release in the case of human lung fragments is shown in Fig. 4. AA-861 produced a dose-dependent inhibition of the SRS-A release at $10^{-8}$–$10^{-5}$ M with no effect on the release of histamine, similar to the events seen in guinea pigs and monkeys (M. irus).

HPLC and RIA for LTs from human lung fragments

HPLC for LTs was carried out on the anaphylactic diffusates from non-treated (control) or AA-861-treated human lung fragments, and the results are shown in Fig.
In the controls, the peaks of UV absorption at 280 nm corresponding to LTD₄ and LTE₄ were evident, but the peaks at the position LTE₄ and LTC₄ were not clear. In the AA-861-treated sample, the LTD₄ or LTE₄ peaks were not clearly detected. Each LT fraction of the pooled diffusates from H PLC was assayed by RIA, and the results are shown in Table 1. In the controls, the amounts of LTB₄, LTC₄ and LTD₄ were 1.27, 1.30 and 18.60 ng/g tissue, respectively. In the AA-861-treated sample, the values were 0.14, less than 0.21, and 0.88 ng/g tissue, respectively. Thus, the anaphylactically stimulated release of LTs from human lung fragments was suppressed by more than 80% at 10⁻⁷ M of AA-861.

**A23187-induced SRS-A and histamine release in the rat peritoneal cavity**

The effects of AA-861 and DSCG on A23187-induced SRS-A and histamine

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**Fig. 3.** Effect of AA-861 on SRS-A release and histamine release from lung fragments of passively sensitized monkey (M. mulatta). AA-861 was added 5 min before antigen challenge. In control samples, anaphylactic SRS-A release and histamine release were 1.1–24.6 U and 2.2–3.5 μg/g tissue, respectively. Total histamine contents were 19.1–36.1 μg/g tissue. Each column represents mean±S.E. of 3 experiments.  ■: SRS-A,  ▪▪▪▪: Histamine.

**Fig. 4.** Effect of AA-861 on SRS-A release and histamine release from lung fragments of passively sensitized humans. AA-861 was added 5 min before antigen challenge. In control samples, anaphylactic SRS-A release and histamine release were 9.0–24.6 U and 1.6–13.4 μg/g tissue, respectively. Total histamine contents were 5.6–25.2 μg/g tissue. Each column represents the mean±S.E. of 4 experiments.  ■: SRS-A,  ▪▪▪▪: Histamine.
release from the rat peritoneal cavity are shown in Fig. 6. The release of SRS-A and histamine by the ionophore in the controls was 19.7±1.1 U/ml and 1.8±0.2 μg/ml, respectively. Intraperitoneal injection of 10⁻⁷ or 10⁻⁶ M AA-861 5 min before the A23187 challenge dose-dependently inhibited the release of not only SRS-A by 36 and 66% but also histamine by 14 and 49%, respectively. On the other hand, 5 mg/ml of DSCG induced a weak suppression of both release. 

Asthma induced in guinea pigs

The effect of AA-861 on antigen-induced airway resistance in mepyramine- and cime-
network-treated guinea pigs is shown in Fig. 7. In the controls, the airway resistance increased with time during 10 min after the antigen provocation, and a plateau was reached within 30 min. AA-861 (5 mg/kg, i.v.), given 2 min before this antigen challenge, produced inhibition of the increased airway resistance with a statistical significance at 10–30 min after the antigen challenge.

Fig. 6. Effect of AA-861 and disodium cromoglycate (DSCG) on A23187-induced SRS-A and histamine release from rat peritoneal cavity. Drugs were intraperitoneally administered 5 min before the A23187 challenge (0.3 μg/ml). Each column represents the mean±S.E. of the No. of animals indicated in parentheses. ***represents a statistically significant difference from the control at P<0.001.

Fig. 7. Effect of AA-861 on antigen-induced airway resistance in mepyramine- and cimetidine-treated guinea pigs. AA-861 was intravenously administered 2 min before antigen challenge. Each point represents the mean±S.E. of 16 animals. *represents a statistically significant difference from the control at P<0.05.

Discussion

Nordihydroguaiaretic acid, originally reported to be a 15-lipoxygenase inhibitor, produced a relatively selective inhibition of 5-lipoxygenase activity in mice (19), rats (20) and guinea pigs (21). BW-755c has been regarded as a non-specific inhibitor of both lipoxygenase and cyclooxygenase (22). As
for 5,8,11,14-eicosatetraynoic acid (ETYA), a cyclooxygenase inhibitor (23), there have been some controversy concerning the effect on 5-lipoxygenase; i.e., ETYA produced an inhibition of the enzyme activity in rat basophilic leukemia cells (24, 25), guinea pig peritoneal leukocytes and human neutrophils (26, 27), but not in porcine leukocytes, rabbit peritoneal leukocytes and human lymphocytes (28). Further, it was reported that ETYA produced an inhibition of the enzyme activity in rat basophilic leukemia cells (24, 25), guinea pig peritoneal leukocytes and human neutrophils (26, 27), but not in porcine leukocytes, rabbit peritoneal leukocytes and human lymphocytes (28). Further, it was reported that ETYA produced the production of LTB4 and 5-hydroxy-6,8,11,14-eicosatetraenoic acid (5-HETE) in guinea pig peritoneal polymorphonuclear leukocytes stimulated by A23187 (29). ETYA suppressed the histamine release from rat peritoneal mast cells, but did not suppress that from guinea pig lung fragments (21, 30). These observations suggest that there are differences among the 5-lipoxygenase(s) from different species or regulating mechanisms of these chemical mediators in various species or cell types.

Yoshimoto et al. (11) reported that AA-861 competitively inhibited the 5-lipoxygenase of guinea pig peritoneal polymorphonuclear leukocytes (ID50, 0.8 μM) but did not inhibit porcine leukocyte 12-lipoxygenase and bovine vesicular gland cyclooxygenase, even in a dose of 10 μM.

In our study, we investigated the effect of AA-861 on the release of SRS-A and histamine in various species, in vitro and in vivo. In guinea pigs, cynomolgus monkeys (M. irus) and humans, AA-861 inhibited the release of SRS-A from passively sensitized lung fragments with no effect on the release of histamine. In these species, the formation of SRS-A is considered to be inhibited by AA-861 through suppression of the 5-lipoxygenase activity in lung tissue. In experiments on lung fragments from the anaphylactically stimulated human lung, the combined technique of HPLC and RIA revealed that LTD4 represented the major part of SRS-A activity and that the stimulated biosynthesis of LTB4, LTC4, LTD4 and LTE4 in the tissue fragments was suppressed by more than 80% with a 10⁻⁷ M dose of AA-861.

Kagey-Sobotka et al. (3) suggested that the release of histamine might be triggered by 5-lipoxygenase products, as deduced from their observation that the antigen-induced histamine release from human basophils was significantly enhanced by both 5-hydroperoxy-6,8,11,14-eicosatetraenoic acid and 5-HETE, metabolites of arachidonic acid via the 5-lipoxygenase pathway, while Morita et al. (31) reported that the histamine release from human basophils was little influenced by AA-861.

From our results in guinea pigs, monkeys (M. irus) and humans, AA-861 seemed to have little effect on the release of histamine. Engineer et al. (32) found that SRS-A injected into isolated perfused guinea pig lungs induced formation of thromboxane A2 (TXA2). Folco et al. (33) and Zijlstra et al. (34) reported that LTC4 stimulated the release of TXA2 from the guinea pig lung parenchyma. Piper and Samhoun (35) showed that LTB4-, LTC4- and LTD4-induced contractions of the isolated guinea pig lung parenchyma were inhibited by carboxyheptylimidazole, a specific inhibitor of TXA2 synthetase. The partial inhibition of increased pulmonary resistance induced by LTE4 as well as LTC4 and LTD4 in guinea pigs in vivo by indomethacin also has been reported (36). From these observations, the antigen-induced bronchospasm in sensitized guinea pigs was probably due to histamine, SRS-A and TXA2.

AA-861 was found to reduce significantly the antigen-induced airway resistance in mepyramine- and cimetidine-treated guinea pigs. This coincided with the findings of Ashida et al. (37) who reported that the compound significantly reduced IgE-mediated bronchoconstriction. This inhibitory effect would be due to both the inhibition of LT through the suppression of 5-lipoxygenase and the resultant suppression of TXA2 formation.

On the other hand, AA-861 inhibited the release of SRS-A and histamine from the antigen-induced rhesus monkey (M. mulatta) lung fragments and rat peritoneal cavity stimulated by A23187. Two possibilities are proposed for inhibition of the histamine release by AA-861 in these species. The first is that the mechanism of histamine release is at least partially dependent on the stimulation of 5-lipoxygenase metabolite(s). The second is that AA-861 inhibits the release of
histamine by other mechanism(s).

Yoshimoto et al. (11) reported that AA-861 failed to suppress 12-lipoxygenase of bovine platelets and inhibited little that of both the porcine leukocytes and rat lung at 10 μM; however, Nakadate et al. (38) stated that 12-lipoxygenase in the mice epidermis was strongly inhibited by AA-861 (ID50, 1.9 μM).

We conclude that AA-861 may be clinically useful for the treatment of allergic bronchial asthma and should aid in explaining the role of 5-lipoxygenase products in asthma. However, AA-861 does not always act as a selective 5-lipoxygenase inhibitor. The selectivity and potency as a lipoxygenase inhibitor depends on the species and strains, cell types and experimental conditions. In addition, the histamine releasing mechanism(s) in rhesus monkeys and rats may differ from the mechanism in the other species studied.

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