Significant Role of Peptide Leukotrienes (p-LTs) in the Antigen-Induced Contractions of Human and Guinea Pig Lung Parenchymas and Bronchi or Tracheas In Vitro

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ABSTRACT—Chemical mediators responsible for the antigen-induced contractions of isolated, passively sensitized human and guinea pig lung parenchymas and bronchi or tracheas were evaluated by several antagonists and enzyme inhibitors, with emphasis on the effects of the potent and selective peptide leukotriene (p-LT) antagonist MCI-826. All of these preparations showed long-lasting contractions in response to an antigen challenge which lasted for more than 60 min. In either the human lung parenchyma and bronchus or guinea pig lung parenchyma, pretreatment with 10^-6 g/ml (2.4 X 10^-9 M) MCI-826 significantly inhibited the late phase at 10 to 60 min after the challenge of the contraction following slight suppression of the early phase. The early phase contractions of these preparations were moderately antagonized by 10^-6 g/ml mepyramine, but the late phases were not influenced or even rather enhanced. The combination treatment of MCI-826 with mepyramine additionally and markedly inhibited both phases of these preparations. On the other hand, although mepyramine apparently inhibited the early phase of the guinea pig tracheal contraction but not the late phase, no synergistic inhibitions of the contraction were observed when it was combined with MCI-826. The p-LT antagonist FPL 55712, atropine and indomethacin at 10^-6 g/ml either slightly inhibited or enhanced the contractions of human lung parenchymas, guinea pig tracheas and lung parenchymas, but the effects were not significant. From these results, it should be emphasized that p-LTs largely contribute to induction of the anaphylactic contractions of human lung parenchymas as well as human bronchi and guinea pig lung parenchymas but not guinea pig tracheas.

Keywords: MCI-826, Anaphylaxis, Leukotriene (peptide), Bronchus, Lung parenchyma

Peptide leukotrienes (p-LTs), mainly consisting of LTC_4, LTD_4 and LTE_4, and one of the families formed from arachidonate by 5-lipoxygenase pathway, have been reported to be released from human and guinea pig lung fragments in large amounts during in vitro anaphylaxis (1–3).

Since the discovery of the slow reacting substance of anaphylaxis (SRS-A), which had been tentatively designated as p-LTs until identification of their structures, the p-LTs have been proven to be potent pulmonary tissue constrictors in some species, especially humans and guinea pigs (4–7). Because human or guinea pig lungs possess a great ability for p-LT formation and their airway smooth muscles markedly respond to p-LTs, p-LTs formed intrinsically may be largely responsible for the pulmonary tissue contractions during anaphylaxis.

In 1979, Adams and Lichtenstein (8) suggested that SRS-A contributes greatly to the in vitro antigen-induced contraction of both human bronchi and guinea pig tracheas from experiments using FPL 55712, one of the chromone derivatives (9) that has been frequently employed as a selective and standardized p-LT antagonist. Since their report, FPL 55712 has been used in several reports to study the role of p-LTs in the contraction induced by antigens of the guinea pig and human pulmonary tissue (10–12). However, there are some reasons for raising an objection to the conclusion that p-LTs play an important role in the reaction. The use of FPL 55712 has a number of potential problems.
that may invalidate this conclusion. First, FPL 55712 was reported to be a potent and noncompetitive inhibitor of cyclic adenosine 3',5'-monophosphate (cAMP) phosphodiesterase (13). The inhibitors of this enzyme are well-known to induce the relaxation of smooth muscles, particularly airway smooth muscles, by elevating intracellular cAMP levels. Second, although FPL 55712 specifically antagonizes the SRS-A-induced contractions of the isolated guinea pig ileum (9, 14), much higher concentrations of the compound are required for p-LT-induced airway smooth muscle contraction such as $10^{-5}$ to $10^{-4}$ g/ml, at which non-specific antagonism of other possible mediators for the anaphylactic contraction of the airway smooth muscle may occur (14, 15). From the above reasons, the use of FPL 55712 as a tool may lead to misunderstanding of the contribution of p-LTs to the antigen-induced contraction of airway tissues.

Our present investigation was performed to assess or reassess the antigen-induced contraction of human bronchi and especially lung parenchymas as well as guinea pig tracheas and lung parenchymas in vitro by using several antagonists and enzyme inhibitors, with emphasis on a newly synthesized, very selective p-LT antagonist, MCI-826 (15).

MATERIALS AND METHODS

Reagents

Reagents and their sources were: (E)-2,2-diethyl-3'-(2-[2-(4-isopropyl)thiazolyl]ethenyl)succinanilic acid sodium salt (MCI-826, supplied from Dr. K. Takahashi of Mitsubishi Kasei, Tokyo), (E)-3-[4-(1-imidazolylmethyl)phenyl]-2-propenoic acid hydrochloride (OKY-046, supplied from Kissei Pharm., Matsumoto), mepyramine maleate (Sigma Chem., St. Louis), atropine sulfate and acetylcholine chloride (ACh) (Nacalai Tesque, Kyoto), indomethacin (Merck, Darmstadt), and sodium 7-[3-(4-acetyl-3-hydroxy-2-propylphenoxy)-2-hydroxypropoxy]-4-oxo-8-propyl-4H-1-benzopyran-2-carboxylate (FPL 55712, supplied from Mr. P. Sheard of Fisons, Loughborough). MCI-826 and FPL 55712 were dissolved in distilled water; OKY-046, mepyramine and atropine, in Tyrode's solution; and indomethacin, in ethanol.

Animals

Hartley female and male guinea pigs weighing 250–300 g for immunization and antigen-induced contraction experiments, respectively, were purchased from Japan SLC, Hamamatsu. They were used for the experiments after breeding for 3 to 6 weeks under the following conditions: temperature, $22 \pm 1.5^\circ C$ and humidity, $55 \pm 15\%$.

The macroscopically normal portions of the human lung, obtained from the resection for carcinoma, were used as soon as possible.

Antigens

Benzylpenicilloyl bovine gamma globulin (BPO-BGG): BPO-BGG was prepared according to the method of Levine and Redmond (16). The antigen, which was 29 BPO groups bound to a BGG molecule as described elsewhere (3), was used for immunization and provocation experiments. The lyophilized antigen was dissolved in physiologic saline before use.

Mite extracts: Mite extracts (from Dermatophagoides farinae, supplied from Dr. H. Nagai of Gifu Pharmaceutical University) were dissolved in physiologic saline at the concentration of $2 \times 10^{-3}$ g/ml and stored at $-80^\circ C$ until use.

Antisera

Anti-BPO-BGG guinea pig serum: According to the method of Levine et al. (17), the guinea pig was sensitized monthly with $1 \mu g$ (BPO)$_{29}$BGG/mg Al(OH)$_3$/ml/time for 8 months. Two weeks after the last sensitization, the blood was drawn from the carotid artery. The antiserum with a titer of 1:2000 when evaluated by 7 day passive cutaneous anaphylaxis, was kept at $-80^\circ C$ until use.

Human atopic serum, which possessed a radioallergosorbent test (RAST) score of 4 against mite extracts, was used after a tenfold dilution with Ca$^{2+}$-free Tyrode's solution.

Passive sensitization and preparation of isolated pulmonary tissues

Guinea pigs: Guinea pigs were passively sensitized by i.v.-injection with anti-BPO-BGG guinea pig serum (0.25 ml/animal). Two days later, the animal was killed by a blow on the head and the lung was perfused through the pulmonary artery with Ca$^{2+}$-free Tyrode's solution (20 ml/animal). The lung and trachea were removed, and the preparation of their strips was made as follows: Trachea: The tracheal chain strip was prepared as reported previously (15). Lung: Eight lung parenchymal strips, each of which consisted of a piece of the lung surface cut into a cylindrical strip (2 mm in diameter and 2 cm in length) were made from one animal.

Humans: Bronchial and lung parenchymal strips were prepared as follows: Bronchus: Bronchial spiral strips were prepared as described elsewhere (15). At least 4 spiral strips, each of which was 2 cm in length, were prepared from one bronchus of the sample. Lung: Lung strips were prepared in Ca$^{2+}$-free Tyrode's solution. Following the removal of the pleura, at least 16 strips from the peripheral lung, each of which was cylindrical
and 3 mm in diameter and 2 cm in length, were prepared from one sample.

Both the bronchi and lung parenchymal preparations were passively sensitized with a tenfold dilution of human atopic serum (1 and 2 ml/preparation for bronchi and lung parenchymas, respectively) for 1.5 hr at 37°C. After completion of the sensitization, the preparation was washed with Ca²⁺-free Tyrode’s solution (10 and 30 ml/preparation for bronchi and lung parenchymas, respectively) before suspension in a Magnus bath.

Measurement of movement of the isolated pulmonary tissue preparation

The isolated, passively sensitized guinea pig or human tracheal, bronchial or lung parenchymal strip was suspended in the Magnus bath. Conditions of the experiments other than the antigen challenge were similar to those of the previous report (15). In brief, the movement of the smooth muscle was isotonically recorded under the following conditions: 37 ± 0.1°C, loading weight: 300 mg and volume of the Magnus bath: 5 ml of Tyrode’s solution aerated with 95% O₂ and 5% CO₂. Prior to beginning the experiments, to the respective preparations, 10⁻⁶ g/ml ACh was repeatedly applied until almost equal contractions (time of observation: 10 min/time) were observed as an indication that the sensitivity has become stable.

Antigen-induced contractions of passively sensitized pulmonary preparations

Following repeated exposures to 10⁻⁶ g/ml histamine (10 min/time) until almost equal contractions were seen, the reactions induced by 10⁻⁵ g/ml (BPO)₃BGG or 5 × 10⁻⁶ g/ml mite extract antigen were observed for over 60 min in the presence or absence of drugs which had been added 5 min before the antigen challenge.

Statistical analysis

Statistical analysis was conducted by the paired t-test. P values under 0.05 were taken as significant.

RESULTS

Contraction of isolated guinea pig tracheas

Figure 1 (a and b) shows the time course contraction induced by antigen of the isolated guinea pig trachea and how this is affected by drugs at 10⁻⁶ g/ml. The contractile response was observed already at 1 min and reached maximum between 3 and 5 min after antigen challenge. Then, the reaction time-dependently reduced to the extent of 55% of the maximum at 60 min.

By the treatment with MCI-826, the contraction was slightly inhibited with or without significance, namely, by less than 30%. On the other hand, an antihistaminic, mepyramine, significantly inhibited the phase of the contraction at 1 to 5 min after antigen challenge, although the later phase at 5 or 10 to 60 min was not influenced by the drug. The combination treatment of mepyramine with MCI-826 showed no synergistic inhibition. In contrast with mepyramine, FPL 55712 manifested no effect on the contraction at 1 to 3 min, but showed substantial inhibition of the following contraction.

The cyclooxygenase inhibitor indomethacin slightly
enhanced the contraction with or without significance through the time observed, but a thromboxane (TX) A₂ synthetase inhibitor OKY-046 and an anticholinergic atropine did not affect the contraction at all.

Contraction of isolated guinea pig lung parenchymas

Figure 2 (a and b) shows the time course contraction induced by antigen of the isolated guinea pig lung parenchyma and the effect of the drug at 10⁻⁶ g/ml on it. The contraction swiftly and gradually increased at 1 to 3 min and 5 to 30 min, respectively, after antigen challenge. At 60 min, the contraction slightly declined.

MCI-826 had a modest inhibitory effect on the contraction at 1 to 3 min. The drug produced, however, potent and time-dependent inhibition of the following contraction, which became as strong as 70% of the contraction at 60 min. Like the results of the guinea pig trachea, mepyramine significantly inhibited the contraction at 1 to 10 min and did not show any ability to inhibit the later contraction. The combination of MCI-826 and mepyramine scarcely produced any synergistic inhibition. FPL 55712, indomethacin and atropine minimally affected the contraction. The late contraction at 10 to 60 min was, however, fairly inhibited by OKY-046.

Contraction of isolated human bronchi

Antigen-induced contraction of the isolated human bronchus and the effect of MCI-826 and mepyramine at 10⁻⁶ g/ml on it are illustrated in Fig. 3.

Mepyramine appeared to delay slightly the onset of the contraction without significance and hardly influenced the maximum and subsequent contraction. MCI-826 not only completely suppressed the late phase of the contraction but also tended to lower the early phase. Combination treatment with MCI-826 and mepyramine completely inhibited the whole reaction.

Fig. 2. Effects of various drugs on antigen-induced contraction of isolated guinea pig lung parenchymas. Drugs were added 5 min before antigen challenge at 10⁻⁶ g/ml, final concentration. Each point represents the mean ± S.E. of 7 experiments. *, ** and ***: statistically significant difference from the control at P = 0.05, 0.01 and 0.001, respectively.

Fig. 3. Effects of mepyramine and MCI-826 on antigen-induced contraction of isolated human bronchi. Drugs were added 5 min before antigen challenge at 10⁻⁶ g/ml, final concentration. Each point represents the mean ± S.E. of 5 experiments. *: statistically significant difference from the control at P = 0.05.
Contraction of isolated human lung parenchyma

The time course of the contraction induced by antigen of the isolated human lung parenchyma showed a similar pattern but exhibited more potent contractions than the isolated guinea pig lung parenchyma, when compared on the basis of the intermediation of 10^{-6} g/ml histamine-induced contraction of the preparations from both species, as shown in Fig. 4 (a and b).

MCI-826 at 10^{-6} g/ml fairly inhibited the contraction with or without significance throughout the observation period. Mepyramine at 10^{-6} g/ml also significantly or insignificantly inhibited the phase of contraction up to 10 min, but not those at 30 and 60 min. Its combination with MCI-826, however, potently inhibited the contraction. Enhancement by indomethacin and moderate inhibition by OKY-046 were seen with or without significance. Atropine did not affect the reaction, similar to the results in the other preparations.

DISCUSSION

We have reported that MCI-826 is a more selective and much more potent p-LT antagonist than FPL 55712; antagonistic activities of MCI-826 against either LTD_4- or LTE_4-induced contraction of the isolated guinea pig trachea are over 100 times stronger than those of FPL 55712, and the former compound has less effect on other agonist-induced contractions than the latter (15).

From the present experiments using MCI-826 and other antagonists or enzyme inhibitors, the conclusion can be reached that p-LTs largely contribute to the contraction, particularly the late phase (5 to 60 min after the challenge) of the contraction, induced by antigen of not only isolated bronchi but also lung parenchymas in humans. A high probability of a significant role of p-LTs in the immunological response of human pulmonary tissue was further backed by the facts that the tissue has an ability to release a substantial amount of p-LTs immunologically (2, 18) and the airway smooth muscle is highly responsive to p-LTs (4, 5).

Employing p-LT antagonists including FPL 55712, previous studies have shown similar results that p-LTs play a considerable role in antigen-induced contractions of isolated human bronchi (8, 12, 19, 20). However, according to our present results, p-LTs must play a more significant role than indicated in the previous studies, which may be due to the inherently weak potency of the antagonists used in those studies or short time observation during anaphylaxis in their experiments.

Treatment with the combination of MCI-826 and mepyramine thoroughly and greatly inhibited the whole phase contraction throughout the observation time of the human bronchi and lung parenchymas, respectively. It should be emphasized that, in the bronchi, treatment with this combination not only achieved complete abolishment of the contraction but also tended to induce a lowered resting tonus, which did not appear in the previous reports (16, 17) even though the experiments were performed under similar conditions. The reason for the different results is not clear, but we have now obtained results that MCI-826 as well as a selective 5-lipoxygenase inhibitor, AA-861, potently lowers the resting tonus of the isolated human bronchus (data not shown). Thus, the anaphylactic contraction of the isolated human bronchus can be almost entirely accounted

![Fig. 4. Effects of various drugs on antigen-induced contraction of isolated human lung parenchymas. Drugs were added 5 min before antigen challenge at 10^{-6} g/ml, final concentration. Each point represents the mean ± S.E. of 5 experiments. * , ** and *** : statistically significant difference from the control at P = 0.05, 0.01 and 0.001, respectively.](image-url)
for by the sum of p-LTs and histamine released.

Although mepyramine alone minimally affected the reaction in both the isolated human bronchi and lung parenchymas, its combination with MCI-826 reduced the contraction of the human lung parenchymas as greatly as that of the human bronchi. Generally, synergistic inhibition of the late phase reaction by the combination treatment of mepyramine with MCI-826 should be due to the responsiveness of the airway smooth muscle to the agonists; approximately tenfold higher concentrations of the agonists than the prior case were required to make the contraction double in the range between 20% and 80% of the maximum contraction. In actuality, the immunologically induced remaining contraction in the preparation that had been treated with MCI-826, was largely and swiftly reduced by the further addition of mepyramine in both human preparations, although mepyramine did not affect the antigen-induced sustained contraction without treatment of MCI-826, suggesting again much greater contribution of p-LTs to resultantly the human anaphylactic airway tissue contraction than histamine. Yet, histamine can more obviously participate in the anaphylactic pulmonary tissue contractions of humans than those of guinea pigs in vitro because treatment with the combination of MCI-826 and mepyramine synergistically inhibits the contraction of neither isolated trachea nor lung parenchyma in the guinea pig.

Different from the previous report (21), FPL 55712 only minimally inhibited the reaction of the guinea pig lung parenchyma; the reason for this is presently unclear. On the other hand, MCI-826 rather than FPL 55712 significantly inhibited the late phase of the contraction, strongly suggesting that p-LTs consequently assume an important role in the reaction of this tissue. Furthermore, FPL 55712 fairly inhibited the tracheal contraction of the isolated guinea pig trachea as reported (8). However, the more selective p-LT antagonist MCI-826 showed significant, but weak inhibitory effect on the reaction, which indicates that p-LTs do not contribute so much to the reaction in this tissue unlike those in human pulmonary tissue or guinea pig lung parenchyma. MCI-826, but not FPL 55712 in the guinea pig trachea and human lung parenchyma, still consistently, although slightly, inhibited the early phase of the contractions in all guinea pig and human pulmonary tissues with or without significance, indicating that p-LTs can be responsible for the contraction to some extent. The different behaviors of MCI-826 and FPL 55712 on the contraction of either guinea pig or human pulmonary tissue may take place because the latter compound has a weak p-LT antagonistic activity in addition to non-specific antagonism by antagonists other than p-LTs and other characteristics as represented by inhibition of other agonist-induced contractions (15) and cAMP elevation (13).

The effects of the drug on the anaphylactic reactions of the pulmonary tissues of both species share some common characteristics: The developing contraction seen within 5 min after antigen challenge is most likely due to the released histamine, and no cholinergic substance(s) is involved significantly because atropine shows no inhibitory effects.

The contraction, which was not antagonized by the combination treatment with the antihistaminic and p-LT antagonist, was still seen to some extent in preparations of the human lung parenchyma and guinea pig trachea and lung parenchyma. In the remaining contraction, which was conspicuously seen in the both trachea and lung parenchyma of the guinea pig, p-LTs in addition to histamine appeared not to participate. However, in general, LTC₄ bound to the cell membrane of lung homogenates is not readily displaced by p-LT antagonists in the specific binding assay (22). Furthermore, the airway smooth muscle contraction induced by not only LTC₄ but also LTD₄ through the low affinity receptors has been reported to be resistant to the p-LT antagonist (23, 24). Therefore, the possible contribution of these p-LTs to the residual constriction of these preparations can not be denied, although it is partly contradicted as explained above.

Indomethacin enhanced the reaction of the isolated human lung parenchyma as well as the human bronchus and guinea pig trachea. One of the possible explanations for this is that the arachidonic acid formed by immunological stimulation leads to additional formation of arachidonate metabolites, particularly p-LTs in this case, of the lipoxygenase pathway (25). In fact, we have found that spontaneous p-LT release from human pulmonary tissue was enhanced by indomethacin and that the drug-induced contraction of the human bronchus was completely antagonized by low concentrations of MCI-826 (data not shown). Therefore, p-LTs are likely to participate in the enhanced contraction. However, this does not deny the postulation that the drug abolishes the preferentially formed relaxative arachidonate metabolite(s) stimulated by the contraction as is generally accepted.

The anaphylactic contraction of the guinea pig and human lung parenchyma was blocked to some extent by the TXA₂ synthase inhibitor OKY-046. Unlike human bronchi and lung parenchymas, the guinea pig lung parenchyma preferentially forms TXA₂ by stimulation of p-LTs (26, 27). Thus, the inhibitory mechanism of the drug-induced contraction of the tissue can be explained as follows: p-LTs released during immunologi-
cal reaction indirectly induce the additional contraction of airway smooth muscle through the action of TXA2 formed by their stimulation. However, the mechanism in the guinea pig lung parenchyma is not likely to be applicable to that of the inhibitory effect of the drug on the human lung parenchymal contraction because the latter contraction was not reduced by certain, selective TXA2 antagonists at all (data not shown). The reason for the inhibitory effect is yet unknown.

The fact that indomethacin did not inhibit significantly the contraction of the lung parenchyma may be explained as the summed results from reduced and increased contraction by inhibition of TXA2 and relaxative arachidonate cyclooxygenase metabolite(s) and stimulation of additional p-LT formation, respectively, by the drug.

Taken these results together, it is most probable that p-LTs play an important role in the anaphylactic contraction of isolated human lung parenchymas and bronchi as well as guinea pig lung parenchymas, but not guinea pig tracheas. From this, it can be deduced that p-LTs largely participate in allergic asthma.

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