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Carbazochrome attenuates pulmonary dysfunction induced by a radiographic contrast medium in rats

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Abstract

The effects of carbazochrome sodium sulfonate (AC-17), a capillary stabilizer, on pulmonary edema and dysfunction induced by ioxaglate, an ionic radiographic contrast medium, were evaluated in rats. The pulmonary edema was evaluated by the extravasation of intravenously injected Evans blue into lung tissues, while pulmonary dysfunction was determined by monitoring blood gasses including pO_2. Ioxaglate (4 g I/kg, i.v.) caused a marked increase in vascular permeability and a decrease in arterial pO_2. AC-17 reversed the ioxaglate-induced vascular hyperpermeability in a dose-dependent manner. In addition, AC-17 (10 mg/kg) significantly inhibited the decrease in arterial pO_2. In isolated rat pulmonary mast cells, ioxaglate markedly enhanced the histamine release, which was not affected by AC-17. On the other hand, AC-17 did significantly blocked the hyperpermeability induced in cultured bovine endothelial cells by tryptase, thrombin and proteinase-activated receptor-2 agonist peptide (SLIGKV-NH_2). These findings suggest that AC-17 blocks radiographic contrast medium-induced pulmonary dysfunction by maintaining the endothelial barrier function. Thus, the compound is potentially useful for the prophylaxis of contrast media-induced acute pulmonary adverse events during angiography.

Keywords: Radiographic contrast media; Pulmonary edema; Vascular permeability; Evans blue; Carbazochrome; Endothelial barrier function

1. Introduction

Pulmonary edema is a rare but severe adverse reaction to the intravenous administration of radiographic contrast media (Lalli, 1980). The iodinated radiographic contrast media interact with vascular endothelial cells and cause neutrophil adhesion and thrombosis, which lead to the vascular hyperpermeability and ultimately pulmonary edema (Dawson, 1985; Beynon et al., 1994; Hayashi et al., 1994; Zhan et al., 1998). Such chemotoxic actions of intravascularly administered radiographic contrast media are most likely to cause serious clinical symptoms in patients who are debilitated or medically unstable. Although several administration regimens for the prevention of some acute adverse events associated with the intravascular injection of radiographic contrast media have been reviewed (Bush and Swanson, 1991), there is still no effective prophylaxis or treatment for the severe pulmonary symptoms such as respiratory insufficiency, pulmonary edema and bronchospastic reaction.

Carbazochrome sodium sulfonate (AC-17) is a capillary stabilizer and has widely been used for the treatment of hemorrhage due to the fragility of capillaries. In an experimental model of adult respiratory distress syndrome, a type of non-cardiogenic pulmonary edema, AC-17 has been reported to reduce the increase in pulmonary vascular permeability as well as the decrease in arterial pO_2 induced by oleic acid (Moriuchi et al., 1995). Both the clinical symptoms and roentgenographic finding associated with the adverse reaction of radiographic contrast media are quite similar to those of adult respiratory distress syndrome (Di Lauro et al., 1999). Taken together, it seems likely that AC-17 can attenuate the pulmonary dysfunction induced by intravenously administered radiographic contrast media. Therefore, the present study was designed to determine the effectiveness of AC-17 in attenuating the pulmonary dysfunction associated with radiographic contrast media. For this purpose, we studied the effects of AC-17 on the pulmonary vascular hyperpermeability and the decrease in

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arterial pO_2 induced in rats by an intravenous injection of ioxaglate, an ionic radiographic contrast medium.

2. Materials and methods

The present experiments were reviewed by the ethics committee for animal experiments at the Faculty of Medicine, Kyushu University, and the law (No. 105) and notification (No. 6) of the Japanese government.

2.1. Animals

Male Sprague–Dawley rats weighing 180–230 g were purchased from Kyudo (Saga, Japan). Animals were maintained on a 12-h light/dark schedule (lights on at 8:00 AM) at a temperature of 23 ± 2 °C with free access to food and water.

2.2. Drugs

Ioxaglate was obtained from a commercially available source (Hexabrix, 320 mg iodine/ml; Mallinckrodt Medical, St. Louis, MO, USA). Carbazochrome sodium sulfonate (AC-17) was obtained from Tanabe Seiyaku, Osaka, Japan. Evans blue, human tryptase and bovine serum thrombin were purchased from Wako (Osaka). Human proteinase-activated receptor-2 (PAR-2) agonist peptide (SLIGKV-NH_2) prepared by solid-phase synthesis was purchased from Cosmo Bio (Tokyo, Japan). The peptide composition and purity (>98%) were ascertained by high performance liquid chromatography (HPLC) analysis, mass analysis and amino acid analysis. AC-17 and Evans blue were dissolved in saline immediately before use in the in vivo experiments. In the in vitro experiments, drugs were all dissolved in Krebs–Ringer buffer (KRB) immediately before use.

2.3. Assessment of in vivo vascular permeability

The in vivo vascular permeability in the lung tissue was evaluated by using the Evans blue extravasation method, as described previously (Sendo et al., 2000). In brief, rats anesthetized with sodium pentobarbital (50 mg/kg, i.p.) were injected with saline or 4 g iodine/kg (g I/kg) ioxaglate in combination with Evans blue (20 mg/kg) through the femoral vein. The injection was performed by using a syringe pump whose injection rate was set at 1.5 ml/min, and the injection volume was adjusted to 16 ml/kg. Animals were killed by bleeding 10 min after a combined injection of ioxaglate and Evans blue, since in our previous report, the increases in Evans blue extravasation as well as the water content in the lung tissues induced by ioxaglate reach the maximum at 10 min after injection (Sendo et al., 1999). The thorax was opened and the lungs were perfused with physiological saline by means of a cannula inserted into the pulmonary artery to remove the intravascular pulmonary dye, then the lung parenchyma was dissected and weighed. Half of the dissected lung tissues was immersed into formamide (4 ml/g wet weight of tissue) for 24 h to extract Evans blue. The remainder was dried in an oven at 60 °C for 24 h. The concentration of Evans blue in the formamide was determined spectrophotometrically at 620 nm by using Immuno-mini, NJ-2300 (Intermed, Tokyo, Japan) and 96-well microplates. Values were calculated on a standard curve (0.5–40 μg/ml) and expressed as μg Evans blue per g dry tissue weight.

2.4. Measurement of blood gasses

Rats were anesthetized with sodium pentobarbital, and a cannula (Angiocath, 24G, 3/4 in, Deseret Medical, UT, USA) was inserted into the femoral artery for blood sampling. Rats were spontaneously breathing and no mechanical ventilation was performed during the experiments. AC-17 (10 mg/kg, i.v.) or saline (20 ml/kg, i.v.) was injected 30, 60, or 90 min before ioxaglate injection (4 g I/kg, i.v.). Aliquots (100 μl) of blood specimens were taken before and 5, 10, 20, 40 and 60 min after ioxaglate injection, and various arterial parameters including pO_2, pCO_2 and pH were immediately analyzed by using an automatic gas analyzer (i-STAT, East Windor, NJ, USA). The pO_2 values less than 70 mm Hg were regarded as respiratory dysfunction (hypoxemia).

2.5. Measurement of histamine release from rat pulmonary mast cells

Rat pulmonary mast cells were isolated, according to the method of Ali and Pearce (1985). Briefly, the lung tissues were isolated and immersed into ice-cold KRB, minced with scissors, then washed over gauze. The suspensions were incubated at 37 °C for 90 min with 0.05% collagenase (type-I, Sigma) under gentle agitation, then filtered through 70-μm Nylon mesh (Cell Strainer, Becton Dickinson Labware, NJ, USA). The filtrates were centrifuged ($100 \times g$ for 8 min at 25 °C) and washed four times with KRB containing 0.1% bovine serum albumin. The cell suspensions were finally filtered through 70-μm Nylon mesh. The number of mast cells was adjusted to 1.5×10^5 cells/ml. The reaction was started by mixing the cell suspension (0.5 ml) with 0.5 ml KRB containing 100 mg iodine/ml (mg I/ml) ioxaglate and various concentrations of AC-17, and the mixture was incubated at 37 °C for 10 min. The reaction mixture was then centrifuged at $800 \times g$ for 5 min at 4 °C, and the histamine contents in the supernatant and cells were separately determined by ion-pair HPLC coupled with post-column fluorescent derivatization, as described previously (Itoh et al., 1992). The histamine release was expressed as the percentage of histamine in the supernatant to the total.

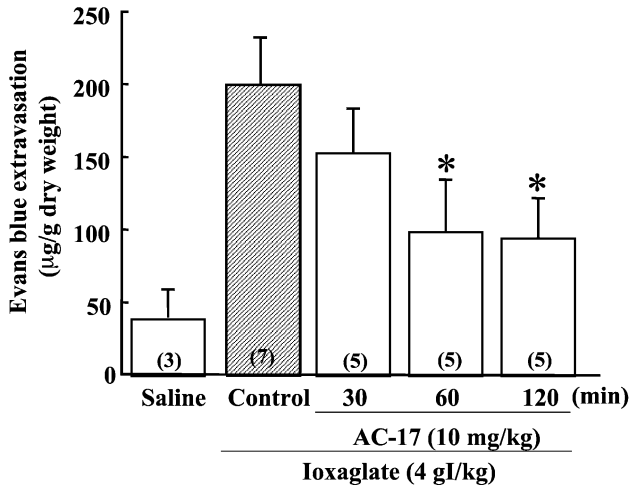

Fig. 1. Effect of pretreatment with AC-17 on ioxaglate-increased vascular permeability in rats. AC-17 (10 mg/kg, i.v.) was injected 30, 60 or 120 min prior to ioxaglate (4 g I/kg). Control rats were injected with saline 60 min before ioxaglate treatment. The vascular permeability was evaluated by Evans blue extravasation in lung, and determined at 10 min after intravenous injection (1.5 ml/min) of ioxaglate in combination with Evans blue (20 mg/kg). The injection volume of ioxaglate or saline was 16 ml/kg. Each column and vertical bar indicates the mean ± S.E.M. The number of rats is shown in each parenthesis at the top of each column. * $P<0.05$ versus control.

2.6. Measurement of the permeability in cultured bovine endothelial cells

Bovine aortic endothelial cells (BAECs) were cultured in DMEM (GIBCO Life Technologies, Rockville, MD) supplemented with 10% fetal bovine serum, as previously described (Oike and Ito, 1997). The second to fourth subculture was used for experiments, and cells were seeded at 4.0×10^4 cells/cm^2 onto fibronectin-coated polycarbonate membrane (1.1 cm^2, 3.0-μm pore size) of the Transwell insert (12-well type, Corning Costar). The permeability of bovine serum albumin-conjugated Evans blue was determined, as described previously (Furuta et al., 2002). In brief, Evans blue was mixed with 4% bovine serum albumin and diluted with KRB. After washing the cells three times with KRB, the insert was immersed in a well containing 1.5 ml KRB, AC-17 was then added to the insert for 30 min. The incubation medium was replaced with 0.5 ml of Evans blue-labeled BSA diluted in KRB (0.67 mg Evans blue/ml KRB). Agonist peptides and AC-17 or its diluent were added to the incubation medium. Samples (0.5 ml aliquot) were taken from the outer chamber at 10, 20 and 30 min. The concentration of Evans blue in the outer chamber was measured from the absorbance at 620 nm using a microplate reader (Immuno-mini NJ-2300, Intermed). The clearance was calculated, according to the method described previously (Dehouck et al., 1992), and expressed as the amount (μl) of the tracer diffused to the outer chamber, according to the following equation: Clearance (μl)=$[C]_A \times V_A/[C]_L$, where $[C]_A$ and $[C]_L$ are the tracer concentrations in the outer chamber and the initial concentration in the inner chamber, respectively, and V_A is the volume of the outer chamber. The average clearance volume was plotted versus time, and the slope was estimated by the linear regression analysis.

2.7. Statistics

Data are shown as the mean ± S.E.M. Data were statistically analyzed by one-way analysis of variance followed by the Dunnett's test for multiple comparisons, or by Student's *t*-test for comparison between two groups (StatView; Abacus Concepts, CA, USA). Statistical significance was defined as $P<0.05$.

3. Results

3.1. Effect of AC-17 on ioxaglate-increased vascular permeability

Evans blue extravasation in the ioxaglate-treated group was approximately five-fold higher than in the saline-treated group (Fig. 1). AC-17 injected 60 or 120 min prior to ioxaglate injection significantly attenuated the ioxaglate-increased vascular permeability, while the benefit of AC-17 injected 30 min prior to ioxaglate injection was not statistically significant (Fig. 1). Therefore, in the subsequent experiments where the dose–response relationship for AC-17 in suppressing vascular hyperpermeability and the effect of the compound on ioxaglate-induced changes in pulmonary function were examined, AC-17 was administered 60 min before ioxaglate injection.

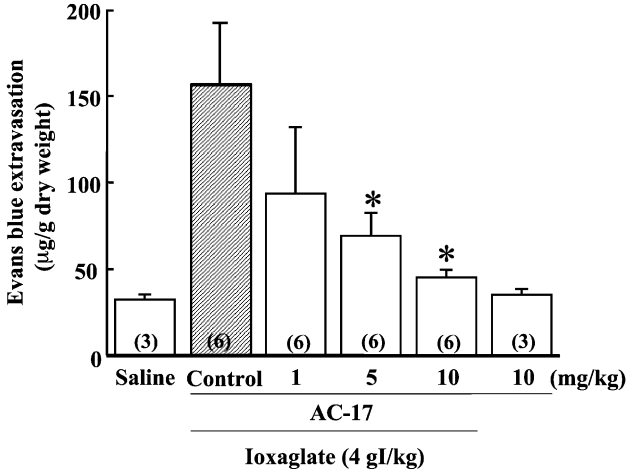

Fig. 2. Dose–response study for the inhibitory effect of AC-17 on ioxaglate-increased vascular permeability in rats. AC-17 (1–10 mg/kg, i.v.) was injected 60 min prior to ioxaglate (4 g I/kg, i.v.) treatment. Control rats were treated with saline 60 min prior to ioxaglate injection. Evans blue extravasation in lung tissues was determined at 10 min following combined treatment with ioxaglate and Evans blue (20 mg/kg). The injection volume of ioxaglate and saline was 16 ml/kg. Each column and vertical bar indicates the mean ± S.E.M. The number of rats is shown in each parenthesis at the top of each column. * $P<0.05$ versus control.

As shown in Fig. 2, AC-17 at the dose of 1, 5 and 10 mg/kg attenuated the ioxaglate-increased vascular permeability in a dose-dependent manner, achieving statistical significance at 5 and 10 mg/kg. AC-17 (10 mg/kg) had no significant effect on Evans blue extravasation in animals not treated with ioxaglate (104.3 ± 5.7% of control, mean ± S.E.M.).

3.2. Effect of AC-17 on ioxaglate-induced hypoxemia

As shown in Fig. 3, a marked decrease in pO_2 (< 70 mm Hg) was observed 5 min after the injection of ioxaglate (4 g I/kg). The arterial pO_2 value decreased maximally at 5–10 min after ioxaglate injection, then recovered gradually over a period of 60 min. Pretreatment with AC-17 significantly reversed the decrease in arterial pO_2. The significant protective effect of AC-17 was observed at 5, 10 and 20 min. On the other hand, there were no significant changes in pCO_2 or pH after injection of ioxaglate at any time points, except for a slight but significant decrease in pH value at 10 min in ioxaglate-treated control group.

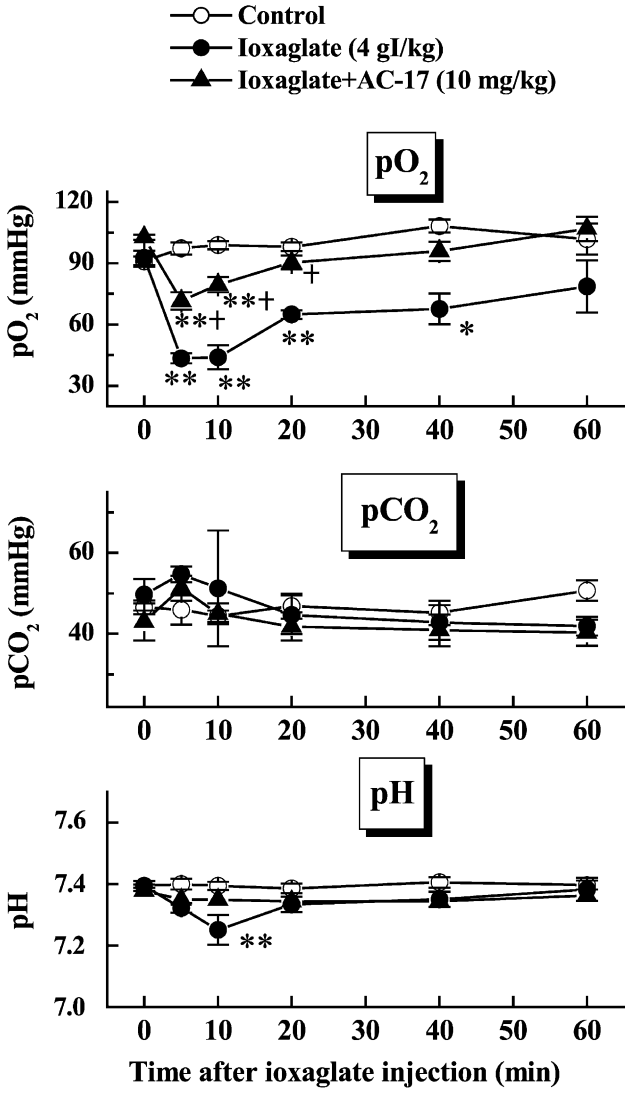

Fig. 3. Effect of AC-17 on changes in the partial pressure of blood gasses (pO_2 and pCO_2) and pH after intravenous injection of ioxaglate. AC-17 (10 mg/kg, i.v.) or saline was injected 60 min prior to injection of ioxaglate (4 g I/kg). Control rats were injected with saline instead of ioxaglate. Aliquots (100 μl) of blood specimens were taken immediately before, and 5, 10, 20, 40 and 60 min after ioxaglate injection, and pO_2, pCO_2 and pH were immediately analyzed by an automatic gas analyzer (i-STAT). The injection volume of ioxaglate or saline was 16 ml/kg. Each point and vertical bar indicates the mean ± S.E.M. of six animals. * $P < 0.05$, * * $P < 0.01$ versus control; † $P < 0.05$ versus ioxaglate + saline.

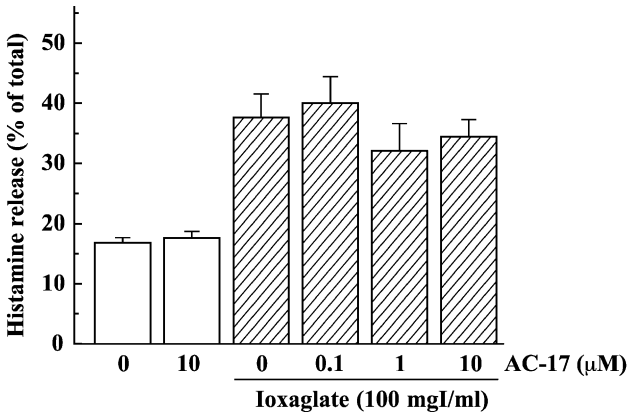

Fig. 4. Effect of AC-17 on histamine release from rat pulmonary mast cells. Rat pulmonary mast cells were incubated at 37 °C for 10 min with 100 mg I/ml ioxaglate or saline in the absence or presence of AC-17. Each column and vertical bar indicates the mean ± S.E.M. of four experiments.

3.3. Effect of AC-17 on ioxaglate-induced histamine release from rat pulmonary mast cells

As shown in Fig. 4, ioxaglate (100 mg I/ml) significantly increased the histamine release from rat pulmonary mast

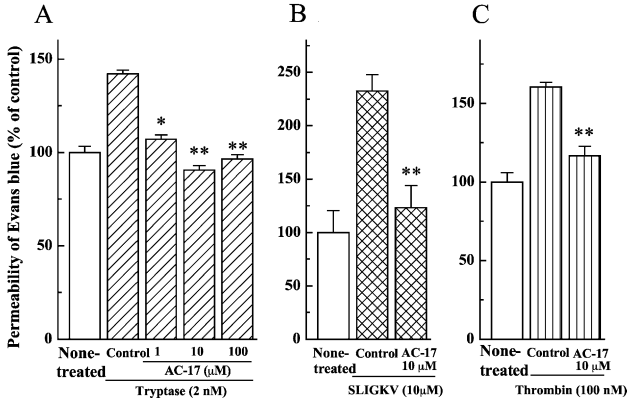

Fig. 5. Effect of AC-17 on the increase in the permeability of albumin-conjugated Evans blue induced by (A) tryptase, (B) PAR agonist peptide SLIGKV, and (C) thrombin in cultured BAECs. Cells were pretreated with AC-17 for 30 min, followed by stimulation of various PAR agonist peptides. Data are mean ± S.E.M. of four to six experiments. * $P < 0.05$, * * $P < 0.01$ versus control.

cells. AC-17 at concentrations of 0.1–10 μM did not block the ioxaglate-induced histamine release.

3.4. Effect of AC-17 on the increase in the permeability of albumin-conjugated Evans blue induced by tryptase, PAR-2 agonist peptide and thrombin in cultured bovine endothelial cells

During the 30-min incubation period in cultured BAECs, the clearance volume increased linearly with time. Tryptase, a PAR-2 agonist peptide SLIGKV-NH_2 and thrombin all produced a significant increase in the permeability to bovine serum albumin-conjugated Evans blue (Fig. 5). AC-17 at 1–100 μM significantly attenuated the tryptase-induced increase in permeability. Moreover, AC-17 at 10 M significantly inhibited the increase in the endothelial permeability induced by PAR-2 agonist peptide and thrombin, a PAR-1 agonist.

4. Discussion

The present study demonstrated for the first time that AC-17, a capillary stabilizer, markedly attenuated the vascular hyperpermeability induced by ionic radiographic contrast medium such as ioxaglate. Vascular permeability was determined by Evans blue extravasation. Evans blue binds to the circulating albumin soon after intravascular injection. The dye has been most commonly used as a marker of protein extravasation into tissues. This technique is more sensitive than the measurement of lung hypertrophy in detecting microvascular dysfunction (Patterson et al., 1992). Moreover, it was noteworthy that AC-17 significantly reversed the pulmonary dysfunction estimated from the decrease in arterial pO_2.

In the present study, the decrease in pO_2 was maximum at 5–10 min after ioxaglate injection. We have already reported that ioxaglate causes an extravasation of Evans blue into lung tissues and an increase in tissue water content, both of which reach the maximum at 10 min after its intravenous injection (Sendo et al., 1999). Thus, the time course of pulmonary dysfunction was quite parallel with that of changes in vascular permeability after ioxaglate injection. Our present findings were generally consistent with those of Saldeen (1979), who demonstrated that the diffusive pulmonary edema subsequent to the increase in pulmonary vascular permeability is the predominant cause of acute respiratory failure associated with the decrease in pO_2. Therefore, it is likely that the inhibition of the pulmonary vascular hyperpermeability is an effective strategy against radiographic contrast media-induced pulmonary edema and respiratory insufficiency.

In the present study, we examined the possible mechanisms underlying the inhibitory action of AC-17 on ioxaglate-induced vascular hyperpermeability. It has been reported that the concentrations of histamine and tryptase, both of which are highly condensed in mast cell granules, increase in human plasma in relation to the severity of the adverse reactions to radiographic contrast media (Laroche et al., 1998). Indeed, iodinated radiographic contrast media cause a histamine release from human (Ennis, 1982) as well as rat pulmonary mast cells (Amon et al., 1990). We previously observed in rats that the pulmonary vascular hyperpermeability induced by radiographic contrast media injection was inhibited by the depletion of mast cells with repeated administration of compound 48/80, a mast cell degranulator (unpublished observations). Taken together, it is suggested that mast cells play a crucial role in the pulmonary vascular hyperpermeability induced by radiographic contrast media injection adverse reactions to radiographic contrast media. In the present study, the effect of AC-17 on the ioxaglate-induced histamine release from rat pulmonary mast cells was investigated. However, AC-17 did not affect the histamine release induced by 100 mg I/ml ioxaglate. Thus, it is unlikely that the protective effect of AC-17 is due to the inhibition of radiographic contrast media-mediated mast cell degranulation.

On the other hand, AC-17 has been reported to play an important role in the maintenance of cellular junction by preventing the degradation of hyaluronic acid, an important constituent in connective tissues (Kiyonaga, 1960). Moreover, AC-17 attenuates the increase in vascular permeability induced by kallikrein (Kodera et al., 1966) or histamine (Shimizu et al., 1965). Therefore, it is likely that AC-17 inhibits the leakage of serum protein by maintaining the endothelial barrier function. This idea was supported by the present findings that AC-17 reduced the protein leakage induced by tryptase or PAR-2 agonist peptide in cultured BAECs. The inhibitory effect of AC-17 was not specific for PAR-2, since the compound also inhibited the hyperpermeability caused by thrombin, a PAR-1 agonist (Henriksen et al., 1997).

Although the precise mechanisms underlying the protective effect of AC-17 on endothelial barrier function remains unclear, it is probable that AC-17 inhibit the radiographic contrast media-induced pulmonary dysfunction by blocking the actions of various inflammatory chemical mediators.

In conclusion, AC-17 was found to be a potent agent that inhibits the severe pulmonary dysfunction induced by the intravenous injection of radiographic contrast media. The stabilization of endothelial barrier function may be associated with such a protective action of AC-17. Therefore, the compound may be potentially useful for the prophylaxis of pulmonary adverse reactions of radiographic contrast media during angiography.

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