Pulmonary Edema Induced by Angiotensin I in Rats

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ABSTRACT—This study was performed to demonstrate an experimental procedure of pulmonary edema induced by angiotensin I (AT I) in rats and to elucidate the mechanism of hemodynamic pulmonary edema. In the previous pilot study, 20 $\mu\text{g}/\text{kg}$ of AT I was found to be an adequate dose for inducing pulmonary edema. To elucidate the mechanism of AT I pulmonary edema and protective measures against it, we observed the effects of captopril (CAP, 5 and 10 mg/kg), an angiotensin converting enzyme inhibitor; losartan (LOS, 10 mg/kg), an angiotensin II (AT II)-receptor antagonist; and phentolamine (PHE, 10 mg/kg), an α -adrenergic receptor blocker, on AT I-induced pulmonary edema in rats. Similarly, we also observed the effects of CAP (10 and 20 mg/kg) on pulmonary edema induced by 25 $\mu\text{g}/\text{kg}$ of adrenaline (ADR) in rats. The development of AT I-induced pulmonary edema was significantly suppressed by CAP and LOS, but was unaffected by PHE. In contrast, the development of ADR-induced pulmonary edema was not suppressed by CAP. These results suggest that AT I-induced pulmonary edema is developed via the AT II and a specific AT II-receptor, without the indirect action of adrenaline.

Keywords: Pulmonary edema, Angiotensin I, Angiotensin converting enzyme, Losartan, Phentolamine

The enhanced activities of the endogenous catecholamine and renin-angiotensin system largely contribute to the incidence of pulmonary edema in the end-stage of left ventricular failure. It was demonstrated that the angiotensin converting enzyme inhibitors (ACEI) could decrease the elevated pulmonary capillary wedge pressure in patients with heart failure (1, 2), and these agents are now employed with increasing frequency in the treatment of both hypertension and heart failure (3–5). They are also shown to exert beneficial effects in adult respiratory distress syndrome by reducing pulmonary capillary pressure and thereby pulmonary edema (6), and it has been reported that the addition of captopril, an ACEI, to the current standard regimen results in more rapid resolution of the clinical manifestations of acute pulmonary edema (7). It is well-known that by the angiotensin converting enzyme (ACE), angiotensin II (AT II) can be generated from the activation of angiotensin I (AT I) (8). Also, it is reported (9, 10) that AT I acts directly on the adrenal medulla to release catecholamines and is about as active as AT II. Although many experimental studies have shown that a high dose of adrenaline (ADR) and AT II induce pulmonary edema as a result of increased afterload in the systemic circulation which elevates the left atrial pressure (11, 12), it remains unclear whether the AT

I can induce the pulmonary edema and whether the endogenous catecholamines produced by AT I contribute to the AT I-induced pulmonary edema. To our knowledge, there are no reports on the experimental induction of pulmonary edema by AT I and the mechanism of AT I-induced pulmonary edema. Therefore, the aims of the present study are to propose an experimental procedure for inducing pulmonary edema by AT I in rats, to test if the α -adrenergic receptor blocker and ACEI have a protective effect on the AT I-induced pulmonary edema, and to determine the mechanism of AT I-induced pulmonary edema and the protective measures against it.

MATERIALS AND METHODS

General procedures

The experiments were carried out using albino rats of the Wistar strain (Saitama Animal Lab., Saitama) weighing 250–350 g, which had been housed under controlled conditions for at least two weeks before the experiments. Each rat was anesthetized with an intraperitoneal injection of 50 mg/kg of pentobarbital sodium and then fixed on its back. After the tracheal incubation with a polyethylene tube, the femoral vein and artery were catheterized to provide routes for administration of drugs and to

monitor the arterial blood pressure through a high pressure transducer (P10EZ; Nihon Kohden, Tokyo), respectively. After administering AT I or ADR, the peak values of arterial blood pressure were monitored as an index of the afterload in the systemic circulation. The respiratory movement was traced with a costabdominal pneumograph connected to a low pressure transducer (AR-650 H, Nihon Kohden). The respiratory rate and blood pressure were recorded with a polygraph (CP-602G, Nihon Kohden). A 0.2-ml sample of blood was withdrawn from artery at 1 min after AT I administration, and the PCO_2 and PO_2 were measured by a Blood Gas System (ABL 5; Radiometer Co., Copenhagen, Denmark). The body temperature of the rats was maintained at approximately 39°C during the experiment.

Determination of the edematogenic dose of AT I

AT I was dissolved in saline at various concentrations of 10, 20 and 40 $\mu\text{g}/\text{ml}$ (pH 6 to 7) before use. As shown in Table 1, 26 rats were divided into three different groups for administration of each different AT I solution (Group 1: eight rats, for 10 $\mu\text{g}/\text{ml}$ of AT I solution; Group 2: ten, for 20 $\mu\text{g}/\text{ml}$; Group 3: eight, for 40 $\mu\text{g}/\text{ml}$). A bolus dose of 1 mg/kg of AT I solution was administered through the venous cannula. The rats were sacrificed at once to examine the lung, when froth or pink fluid appeared in the tracheal tube, and otherwise immediately after observing the vital signs for 20 min. After exsanguination via the cut abdominal aorta, the lungs were rapidly removed and the attached tissues were trimmed away for gross observation. Then the net weight of the lung was measured to evaluate the degree of pulmonary edema. The development of pulmonary edema was judged by 1: macroscopic hemorrhaging, observed as hemorrhagic patches and spots in the lung, and 2: froth or liquid running out of the tracheal tube. The lung was considered not to have pulmonary edema only when no froth came out from the cut lower trachea, even by gently squeezing the lung (13). The lung body weight index (L.B.I. = lung weight / body weight) was calculated in every rat, to quantify the degree of excess fluid retention in the lung. We also calculated the incidence of pulmonary edema (the number of pulmonary edema induced $\times 100$ / the total number of pulmonary edema induced and non-induced). The edematogenic dose of AT I for our experiments was determined by evaluating the dose-incidence relationship.

Effects of pretreatments with captopril (CAP), losartan (LOS), phentolamine (PHE) and nitroglycerin (NTG) on AT I-induced pulmonary edema

Forty-four rats were subdivided into five groups for each specific pretreatment: Group CAP-S: eight rats, for

captopril, 5 mg/kg; Group CAP-L: ten, for captopril, 10 mg/kg; Group LOS: ten, for losartan, 10 mg/kg; Group PHE: nine, for phentolamine, 10 mg/kg; Group NTG: seven, for nitroglycerin, 1 mg/kg (Table 2). Fifteen minutes before injecting the edematogenic dose (20 $\mu\text{g}/\text{kg}$) of AT I, bolus doses of 5 mg/kg and 10 mg/kg of CAP, 10 mg/kg of LOS and 10 mg/kg of PHE were respectively administered to rats in the CAP-S, CAP-L, LOS and PHE groups. In the remaining rats of group NTG, a constant infusion of NTG was started just before administration of AT I at 0.1 mg/kg/min, which was a dose chosen from our previous study (12). In each rat, the development of pulmonary edema was assessed according to the same procedure described in the above section.

Effects of pretreatments with CAP on adrenaline (ADR)-induced pulmonary edema

A bolus dose of 25 $\mu\text{g}/\text{kg}$ of ADR was injected into 24 rats in order to produce pulmonary edema (12) (Table 3). Seven of them received no pre-treatment, as the control group; 15 min before the administration of ADR, another seven rats were given a bolus dose of 10 mg/kg, and ten were given 20 mg/kg of CAP. The lungs were investigated as previously described.

Test agents

The following agents were used: angiotensin I (Angiotensin I (human); Nacalai Tesque, Inc., Kyoto); angiotensin II (Angiotensin II (human); Nacalai Tesque Inc.); captopril (Captopril; Sigma Chemical Co., St. Louis, MO, USA); losartan (Losartan; Banyu Pharmaceutical Co., Ltd., Saitama); phentolamine mesylate (Regitin; Ciba-Geigy, Takarazuka); nitroglycerin (Milisrol; Nihonkayaku, Tokyo); adrenaline (Bosmin; Daiichiseiyaku, Tokyo). Losartan was kindly donated by Banyu Pharmaceutical Co., Ltd.; other drugs were purchased commercially.

Statistical analyses

All data are expressed as the mean $\pm$ S.D. The variances of the means were tested for homogeneity of distribution by the *F*-test; when the variances were found to be homogeneously distributed, the differences between two means were compared by the two-tailed Student's *t*-test for paired or unpaired observations. The differences of the incidence of pulmonary edema between pretreatments and control groups were examined by the χ^2 -test. A *P* value of less than 0.05 was considered to be statistically significant. The linear relationship between two variables was assessed by calculating the correlation coefficient (*r*).

Table 1. Determination of the edematogenic dose of angiotensin I

Material groups	Dose of AT I ($\mu\text{g/kg}$)	MAP (mmHg)		L.B.I.	Incidence of PE (%)
		before AT I	after AT I		
Group 1 (n=8)	10	109.7 $\pm$ 17.5	173.9 $\pm$ 10.5 ^{##}	0.55 $\pm$ 0.08*	37.5
Group 2 (n=10)	20	99.1 $\pm$ 13.3	173.8 $\pm$ 10.7 ^{##}	0.64 $\pm$ 0.08	90
Group 3 (n=8)	40	112.0 $\pm$ 15.8	167.3 $\pm$ 10.8 ^{##}	0.75 $\pm$ 0.10*	100

angiotensin I (AT I); mean arterial pressure (MAP); lung body weight index (L.B.I.); pulmonary edema (PE). Data: mean $\pm$ S.D. Significant difference (^{##} $P<0.01$) compared to the values before AT I and significant difference (* $P<0.05$) from Group 2 by the paired *t*-test.

RESULTS

Determination of the edematogenic dose

The incidences of AT I-induced pulmonary edema are summarized in Table 1. The incidence was more likely correlated with the logarithmic value of the dose of AT I ($r=0.931$) than with the value of the dose itself ($r=0.845$), although both correlations did not reach a significant level because of the small number of sample points ($n=3$). As Fig. 1 shows, the relationship between the dose and the incidence was curvilinear rather than linear, and the dose-incidence curve flattens out in the dose range of 20 $\mu\text{g/kg}$ and more. This finding indicated that doses of 40 $\mu\text{g/kg}$ or more had an excessively strong effect to induce pulmonary edema. We thereby selected 20 $\mu\text{g/kg}$ of AT I as the edematogenic dose. The administration of AT I produced a sustained rise in systolic and diastolic blood pressure, and it usually depressed the respiratory amplitude throughout the period of observation. The elevated blood pressure after AT I injection in-

dicated an increased afterload in the systemic circulation due to the vasoconstrictive effect of AT I. However, despite no signs of developing pulmonary edema (no froth and no elevation in blood pressure) during the 20-min observation, the lungs in several cases obviously exhibited an edematous appearance, and froth came out upon transection of the lower trachea. These results suggested that the elevation in blood pressure was not necessarily related to the development of pulmonary edema. The larger the dose given, the larger the value of L.B.I. was, indicating the dose-dependent severity of AT I-induced pulmonary edema (Table 1).

Effects of pretreatments

Table 2 shows the preventive effects of pretreatments against pulmonary edema induced by the edematogenic dose (20 $\mu\text{g/kg}$) of AT I. Although every pretreatment somewhat decreased the blood pressure, AT I administrations significantly increased the blood pressure in all five groups, and the elevations of the blood pressure were particularly remarkable in rats that received either of PHE or NTG. With the administration of 10 mg/kg of CAP, the pressor response and the increase of L.B.I. induced by AT I were significantly reduced, and similar effects were seen with 5 mg/kg of CAP or 10 mg/kg of LOS, compared with the control animals. And the larger the given dose of CAP was, the smaller both the L.B.I. value and the incidence of pulmonary edema were. Furthermore, the pneumogram did not show any remarkable irregularities in rats that received CAP. Namely, the pretreatment with CAP completely prevented the lung from AT I-induced pulmonary edema. Respiratory irregularity and elevated blood pressure were still observed in rats that received NTG. Nonetheless, NTG was also judged as protective because of the lower incidence of pulmonary edema and the significantly smaller value of L.B.I. compared with the control animals. Conversely, the pretreatment with PHE failed to prevent AT I-induced pulmonary edema, and the L.B.I. value was almost the same as that of control animals.

Fig. 1. The curvilinear relationship between the incidence of pulmonary edema and the dose of angiotensin I. The solid line indicates the curvilinear regression line between the incidence and the dose ($y = 45.08\text{Log}_e x - 59.23$).

Table 2. Effects of various pretreatments on angiotensin I-induced pulmonary edema

Pretreatment groups	Mean arterial pressure (mmHg)			L.B.I.	Incidence of PE (%)
	before pretreatment	before AT I	after AT I		
Control (n=10)		99.1±13.3	173.8±10.7 ^{##}	0.64±0.08	90
CAP-S (n=8)	105.8±16.6	98.3±14.0	126.5±17.4 ^{##}	0.56±0.08*	37.5
CAP-L (n=10)	112.0±6.5	92.1±7.8	118.7±8.6 ^{##}	0.53±0.05**	0 ^{††}
LOS (n=10)	104.0±14.4	96.6±14.4	129.0±12.4 ^{##}	0.54±0.03**	0 ^{††}
PHE (n=9)	103.9±12.2	90.7±11.9	153.7±6.8 ^{##}	0.64±0.14	55.6
NTG (n=7)	108.7±4.6	62.0±14.3	147.8±11.7 ^{##}	0.55±0.06*	28.6 [†]

angiotensin I (AT I); captopril, 5 mg/kg (CAP-S); captopril, 10 mg/kg (CAP-L); losartan, 10 mg/kg (LOS); phenolamine, 10 mg/kg (PHE); nitroglycerin, 1 µg/kg (NTG); lung body weight index (L.B.I.); pulmonary edema (PE). Data: mean±S.D. Significant difference (^{##}P<0.01) compared to the values before AT I and significant difference (*P<0.05, **P<0.01) from the control group by the paired *t*-test; significant difference ([†]P<0.05, ^{††}P<0.01) from the control group by the χ^2 -test.

Effects of CAP on ADR-induced pulmonary edema

The indirect effect of AT I on ADR-induced pulmonary edema was studied using CAP. As shown in Table 3, the blood pressure, after administration of ADR, significantly rose regardless of the pretreatment with either the large or small dose of CAP. As to the blood pressure and L.B.I. values after administrations of ADR, there were no significant differences between rats that received pretreatments and those that did not. Namely, CAP did not suppress the development of ADR-induced pulmonary edema.

Effects of CAP on the respiratory rate, PCO₂ and PO₂ in AT I-induced pulmonary edema

As shown in Table 4, after AT I administration, even though the respiratory rate was not significantly different, the breathing was rather rapid and shallow, and some cases exhibited transient apnea. In addition, there were remarkable changes of PCO₂ and PO₂ after administration of AT I, which were inhibited by the pretreatment of CAP.

Table 3. Effects of captopril on adrenaline-induced pulmonary edema

Pretreatment groups	Mean arterial pressure (mmHg)			L.B.I.	Incidence of PE (%)
	before pretreatment	before ADR	after ADR		
Control (n=7)		105.1±18.7	166.7±19.1 ^{##}	1.08±0.16	100
CAP-S (n=7)	106.8±17.0	92.0±15.7	165.0±15.2 ^{##}	1.15±0.16	100
CAP-L (n=10)	89.4±15.7	76.8±15.7	163.9±18.3 ^{##}	1.14±0.20	100

adrenaline (ADR); captopril, 10 µg/kg (CAP-S); captopril, 20 µg/kg (CAP-L); lung body weight index (L.B.I.); pulmonary edema (PE). Data: mean±S.D. Significant difference (^{##}P<0.01) compared to the values before ADR by the paired *t*-test.

Table 4. Effects of CAP on the RR, PCO₂ and PO₂ in the angiotensin I-induced pulmonary edema

Groups	RR		PCO ₂		PO ₂	
	before AT I	after AT I	before AT I	after AT I	before AT I	after AT I
AT I (n=7)	84.7±7.3	87.6±6.8	26.1±5.3	35.6±5.2*	86.4±10.4	58.3±15.3**
CAP+AT I (n=7)	72.0±15.3	73.2±13.0	31.4±6.9	35.6±5.1	89.4±16.7	79.4±18.5

angiotensin I, 20 µg/kg (AT I); captopril, 10 µg/kg (CAP); respiratory rate (RR). Data: means±S.D. Significant difference (*P<0.05, **P<0.01) compared to the values before AT I by the paired *t*-test.

DISCUSSION

ATI is a decapeptide that has limited intrinsic pharmacological activity, but it is then cleaved by ACE to yield the highly active octapeptide AT II that has strong pressor activity; it regulates systemic vascular resistance and fluid balance; and it physiologically stimulates the secretion of ADR, which can induce pulmonary edema almost exclusively by α -adrenergic action (13–18). It was reported (11, 12) that an α -adrenergic blocker completely suppressed the development of ADR-induced pulmonary edema and that an AT II-receptor antagonist completely suppressed the development of AT II-induced pulmonary edema. Additionally, it was also reported (9, 10) that AT I could stimulate the release of adrenal catecholamines. As such, in the present experiment, we studied the indirect effect of ADR on AT I-induced pulmonary edema using the α -adrenergic blocker PHE, and we also studied the effects of CAP, an ACE inhibitor, and LOS, an AT II-receptor antagonist, on AT I-induced pulmonary edema. Our results revealed that PHE could not sufficiently suppress AT I-induced pulmonary edema, whereas CAP and LOS could. This suggests that AT I-induced pulmonary edema develops as the result of increased afterload via AT II and a specific AT II receptor, without indirect action of ADR, and CAP could prevent the AT I-induced pulmonary edema through blocking endogenous AT II formation. On the contrary, the indirect effect of AT I on ADR-induced pulmonary edema was also investigated using CAP, which could not decrease the incidence of ADR-induced pulmonary edema. These results indicate that AT I and ADR caused pulmonary edema by different respective processes. Since NTG reduces the venous return and directly decreases the vascular resistance of arteries, it is theoretically possible that NTG has a preventive effect on the development of AT I-induced pulmonary edema (19, 20).

The development of pulmonary edema is probably due not only to elevated afterload in the systemic circulation but also to hyperpermeability in pulmonary vascular beds (21). In our study, CAP and LOS could suppress the elevation of blood pressure after administration of AT I. This implies that CAP prevents AT I-induced pulmonary edema by suppressing the elevation of afterload mediated by AT II and specific AT II receptor in large part. On the other hand, this study showed that the AT I could induce the pulmonary edema dose-responsibly, while the increase of blood pressure was not dose dependent. It suggests that other agents may exist which may contribute to AT I-induced pulmonary edema. With regards to pulmonary vascular hyperpermeability, an experiment by Leeman et al. showed that dogs pretreated with an ACEI developed less pulmonary edema than control

dogs after administration of oleic acid, which caused hyperpermeability, and the beneficial effect of the ACEI on canine oleic acid pulmonary edema did not result from a reduction in pulmonary filtration pressure (22). This report suggests an additional suppressive effect of ACEI on pulmonary vascular permeability. Kanazawa et al. also reported that AT II can stimulate peptide leukotriene production (23). These observations suggest that the hyperpermeability in pulmonary vascular beds may be related to the development of AT II-induced pulmonary edema, but how the AT II is related to the pulmonary vascular hyperpermeability remains to be elucidated.

Although many common causes of pulmonary edema are due to combinations of both the increasing hydrostatic pressure and the hyperpermeability in the pulmonary capillary bed, cardiogenic pulmonary edema is mainly attributable to hydrostatic etiology. The heart failure can result in pulmonary edema due to increasing hydrostatic pressure. The data of this study show that the incidence of pulmonary edema increases with a higher dose of AT I, and this form of pulmonary edema is attributable to increasing afterload and following heart failure. Additionally, CAP and LOS can prevent the induction of pulmonary edema by a suppressive effect on the BP elevation in large part that is induced by AT I.

Although it is suggested that an ACEI's effect of blocking endogenous AT II formation is the major factor responsible for the anti-pressor response, this does not exclude the possibility that potentiation of bradykinin (BK) might also contribute (24), because an ACEI leads to BK accumulation by reducing BK breakdown (24, 25). However, according to the report of Chauvin et al. (24), endogenous BK after the administration of an ACEI was not involved in the sympathoinhibitory effects of the ACEI. This suggests that the potentiation of endogenous BK after administration of an ACEI could not contribute to the preventive effect of the ACEI on AT I-induced pulmonary edema.

In this study, we also observed that after AT I administrations, even though the respiratory rate was not significantly changed, the breathing tended to become rapid and shallow, and in some cases even exhibited transient apnea. There were also remarkable changes of PCO_2 and PO_2 after administration of AT I, which was inhibited by the pre-treatment with CAP. This may be an indirect effect due to the primarily induced increase in blood pressure (26). In order to clarify the mechanism, we need further studies.

In conclusion, AT I induces pulmonary edema via AT II and a specific AT II receptor without the indirect action of ADR, and CAP prevents edema by blocking the endogenous AT II formation.

The enhanced activities of the endogenous catechol-

amine and reninangiotensin system largely contribute to the incidence of pulmonary edema in the end-stage of left ventricular failure, and as such, further studies are needed to investigate the effects of ADR, AT I and AT II on pulmonary edema. For this purpose, we consider that our experimental models may contribute to elucidating the mechanism of pulmonary edema and establish preventive measures against it.

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