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Interferon-α elevates pulmonary blood pressure in sheep—the role of thromboxane cascade

Masayuki Hanaoka, Keishi Kubo *, Toshihide Hayano, Tomonobu Koizumi, Toshio Kobayashi

First Department of Medicine, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan

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Abstract

We tested the effect of interferon-α on lung function to examine whether interferon-α causes some pathophysiological change in the lung. We prepared awake sheep with chronic lung lymph fistula, and measured the pulmonary hemodynamics, lung fluid balance and concentrations of prostanoid products. At 1 h after intravenous interferon-α administration (18×10^6 I.U.), pulmonary arterial pressure and pulmonary vascular resistance were significantly increased compared to the baseline values. The levels of thromboxane B_2 in both plasma and lung lymph were increased concomitant with early elevation on pulmonary arterial pressure. In addition, OKY-046 {sodium-3-[4-(1-imidazolylmethyl)phenyl]-2-propenoic acid} (10 mg kg^{-1}), a selective thromboxane synthase inhibitor, significantly prevented the interferon-α-induced pulmonary hypertension and thromboxane B_2 production. While no evidence of increased pulmonary vascular leakage was observed. These findings suggest that a single infusion of interferon-α stimulates a thromboxane cascade and causes transient pulmonary hypertension. However, interferon-α itself or increased thromboxane A_2 might not affect the pulmonary vascular permeability in sheep.

Keywords: Interferon-α; Permeability; Pulmonary hypertension; (Sheep); Thromboxane A_2

1. Introduction

Interferons were first detected in 1957 as virally induced host proteins involved in interference with viral replication (Isaacs and Lindemann, 1957). The interferon-α molecule, containing 165 to 172 amino acids, is produced by activated macrophages or lymphocytes in response to viral infection (Joklik, 1990). In addition to its antiviral activities, interferon-α has a wide range of actions on cells and is in clinical use (Vilcek and DeMaeyer, 1984; Friedman et al., 1986; Staeheli, 1990). Natural or recombinant interferon-α has been approved for treatment of human diseases, such as chronic hepatitis B or C viral infection (Greenberg et al., 1976; Shindo et al., 1991), chronic myelogenous leukemia (Talpaz et al., 1983) or multiple myeloma (Mellstedt et al., 1979). Its clinical efficacy has been demonstrated in the therapy of each of these diseases.

Interferon-α has multiple effects on macrophages and promotes those differentiation (Moore et al., 1984). Incubation of macrophages with interferon-α results in morphological changes such as cell enlargement, increased adherence, spreading, pseudopod formation, and vacuolization. Interferon-α increases the synthesis of lysosomal hydrolases, esterases, and neutral proteases by macrophages (Durum and Oppenheim, 1993). On the other hand, there are a large number of macrophages in alveolar space or intravascular of lung, which are thought to promote the development of acute lung injury (Kubo et al., 1994). These evidences led us to speculate that exogenous interferon-α could cooperate with pulmonary macrophages in the treatment using interferon-α. The present study was designed to examine whether interferon-α causes some pathophysiological change in the lung. We intravenously administered natural interferon-α to awake sheep with chronic lung lymph fistula and hemodynamic monitoring. Since a single infusion of interferon-α caused a small but

* Corresponding author. Tel.: +81-263-35-4600 (ext. 5252); Fax: +81-263-36-3722; E-mail: keishik@hsp.md.shinshu-u.ac.jp

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Table 1
The cross-reactivity of the antibodies between thromboxane B_2 and other prostanoids

Compound	% Cross-reactivity
Thromboxane B_2	100
Prostaglandin D_2	0.3
Prostaglandin E_2	0.04
Prostaglandin $F_{2\alpha}$	0.03
6-Keto-prostaglandin $F_{1\alpha}$	< 0.5
Prostaglandin A_2	< 0.05

significant increases in pulmonary arterial pressure, we focused on the role of thromboxane A_2, a powerful vasoconstrictor, and measured the levels of thromboxane B_2, the principle metabolite of thromboxane A_2, in plasma and lung lymph. Moreover, we noted an interaction of interferon-α and prostanoid cascade, and tested the effect of OKY-046, a selective thromboxane synthase inhibitor.

2. Materials and methods

2.1. Experimental preparations

Adult sheep weighing 20 to 30 kg ($n = 14$) were used. The lung lymph fistulas were prepared using a modification of the method of Staub et al. (1975) under general anesthesia. Briefly, the caudal mediastinal lymph node was isolated through a right thoracotomy in the sixth intercostal space, and the efferent duct of the node was cannulated with a thin silicon tube. Through a second right thoracotomy in the ninth intercostal space, the caudal portion of the caudal mediastinal lymph node was tied off to exclude systemic lymph contributions. Through a left thoracotomy, we placed catheters in the main pulmonary artery and in the left atrium. The catheters were placed in the superior vena cava and the thoracic aorta via the neck vessels. A Cordis introducer (Cordis, Miami, FL) was inserted into the jugular vein. A 7F thermodilution Swan-Ganz catheter was passed into the pulmonary artery via the Cordis introducer on the day prior to the start of the experiment. The sheep were allowed to recuperate for at least 7 days after the surgical procedure.

2.2. Measurements

All measurements were made with the sheep awake and standing. The aortic, pulmonary arterial pressure and left atrial pressure were continuously measured using calibrated pressure transducers (Statham P50; Statham Instruments, Oxnard, CA) attached to a point on the shoulder surmised to be at the level of the left atrium. These hemodynamic data were continuously recorded on an eight-channel recorder (WT-685G; Nihon Koden, Tokyo, Japan). We collected the lung lymph and measured the lung lymph flow every 30 min. The cardiac output and body temperature were measured by thermodilution technique using a cardiac output computer (Model 9520A; Edwards Laboratories, Santa Ana, CA). Pulmonary vascular resistance was calculated as (mean pulmonary arterial pressure − mean left atrial pressure)/cardiac output. Circulating blood leukocytes were counted with a microcell counter (CC-108; Toa, Kobe, Japan). Arterial blood gases were analyzed using a blood gas analyzer (ABL-2; Radiometer, Copenhagen, Denmark). The pooled lung lymph and blood samples were obtained every 30 min to determine the lung lymph-to-plasma total protein concentration ratio. The lymph protein clearance was calculated by mul-

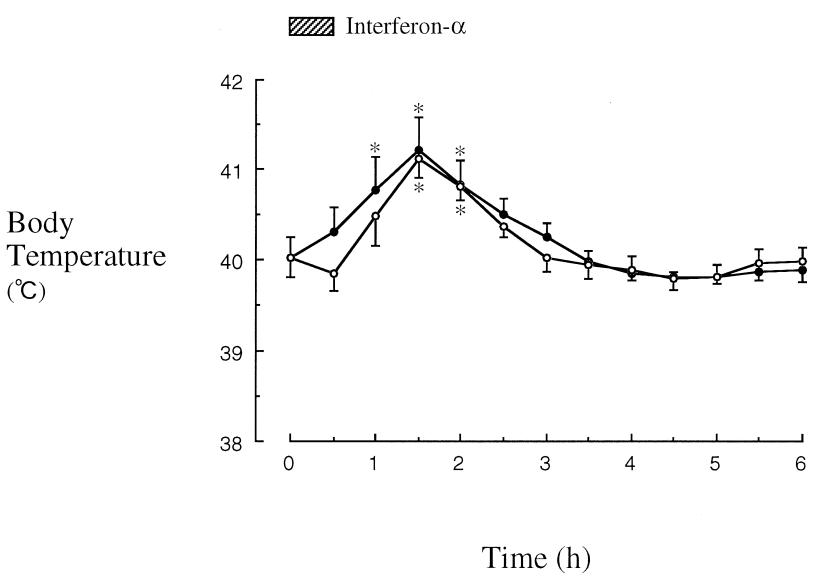

Fig. 1. Effects of interferon-α on body temperature in untreated sheep (closed circles) and OKY-046-pretreated sheep (open circles). Values are mean ± S.E.M. $^*P < 0.05$ compared to baseline.

tiplying the lung lymph-to-plasma total protein concentration ratio by lung lymph flow. The concentrations in plasma and lung lymph of thromboxane B_2 and 6-keto-prostaglandin $F_{1\alpha}$, as stable degradation products of the vasoconstrictor thromboxane A_2 and vasodilator prostaglandin I_2, respectively, were extracted according to the modified methods described by Tada et al. (1981) and by Jaffe et al. (1973), respectively. They were measured in duplicate by the radioimmunoassay using labeled (5,6,8,9,11,12,14,15-^{3}H) thromboxane B_2 and 6-keto-(5,6,8,9,11,12,14,15-^{3}H) prostaglandin $F_{1\alpha}$ purchased from New England Nuclear (Boston, MA). The antibodies had a little cross-reactivity between thromboxane B_2 and other prostanoids (Table 1).

2.3. Experimental protocols

Group 1 ($n = 7$) sheep were administered only natural interferon-α (6×10^6 I.U. ml^{-1}; Sumitomo Pharmaceutical, Osaka, Japan), which was produced by human lymphoblasts and prepared without contamination. Before infusing interferon-α, we measured all variables during a baseline period of more than 2 h. Interferon-α (18×10^6 I.U.) diluted in sterile normal saline, was then infused over 30 min into the superior vena cava. After interferon-α infusion, observations were continued for 6 h. We selected this dosage because it is the maximum daily dose of interferon-α in humans in Japan.

Group 2 ($n = 7$) sheep were treated with OKY-046 {sodium-3-[4-(1-imidazolylmethyl)phenyl]-2-propenoic acid; Ono Pharmaceutical, Osaka, Japan}, a selective thromboxane synthase inhibitor, prior to interferon-α infusion. OKY-046 potently inhibits thromboxane A_2 synthetase without affecting other enzymes related to the arachidonic acid cascade (Hiraku et al., 1986). The OKY-046 (10 mg kg^{-1}) was injected intravenously as a single bolus, immediately before the infusion of interferon-α in the same manner as in Group 1, and observations were similarly made over 6 h. We have previously investigated the effects of OKY-046 alone on hemodynamics and lung fluid balance in awake sheep (Kubo and Kobayashi, 1985). There were no significant changes in the variables after infusion of OKY-046 alone.

2.4. Statistics

For each variable measured, the data are presented as the mean ± S.E.M. Repeated measures analysis of variance and Duncan's new multiple range test were used for comparisons between baseline and experimental periods and between experimental groups. We considered $P < 0.05$ as indicating statistical significance.

3. Results

3.1. Body temperature

After interferon-α infusion, all sheep developed trembling and shivering. The severity of this distress appeared to be similar in the two groups. The body temperature was increased significantly at 1.5 to 2 h after interferon-α infusion and then returned to baseline values by 3.5 h (Fig. 1). The difference between the two groups in the degree of increase in body temperature was not significant.

3.2. Pulmonary hemodynamics

The time courses of hemodynamic responses to interferon-α are presented in Fig. 2. In Group 1, pulmonary arterial pressure increased rapidly from 17.3 ± 1.2 cm H_2O at baseline to a peak of 31.5 ± 3.7 cm H_2O at 1 h after the start of interferon-α infusion. It then returned to the baseline level within 30 min. Left atrial pressure and cardiac output did not change significantly during the

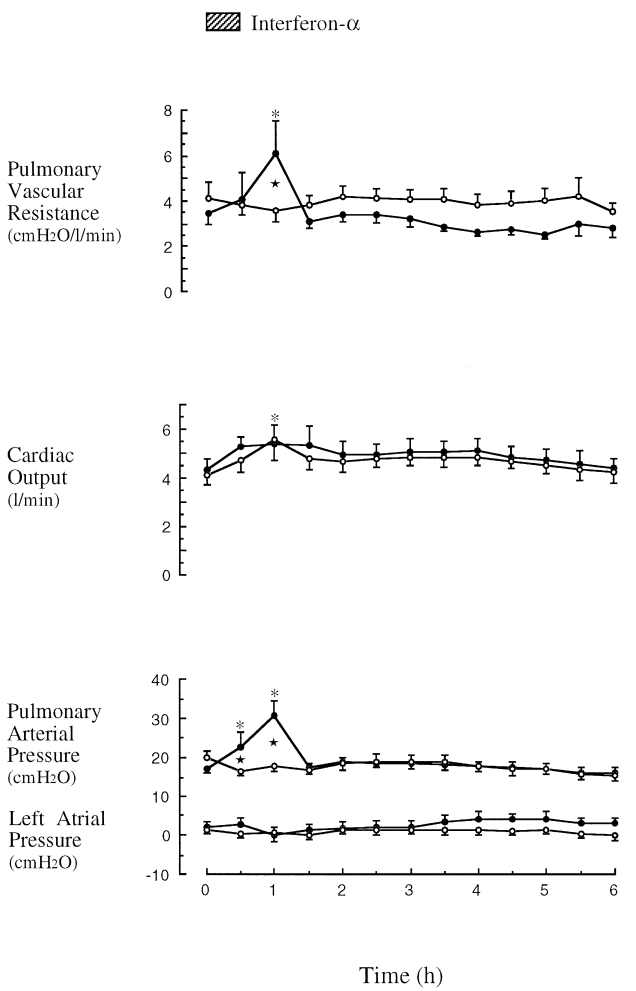

Fig. 2. Effects of interferon-α on pulmonary hemodynamics in untreated sheep (closed circles) and OKY-046-pretreated sheep (open circles). Values are mean ± S.E.M. *$P < 0.05$ compared to baseline. *$P < 0.05$ compared to pretreated group.

experiments. Pulmonary vascular resistance increased from 3.4 ± 0.4 cm H_2O l^{-1} min^{-1} at baseline to 6.1 ± 1.5 cm H_2O l^{-1} min^{-1} at 1 h after the start of interferon-α infusion, and returned to the baseline value within 30 min, similarly to pulmonary arterial pressure. In Group 2, pulmonary arterial pressure, left atrial pressure and pulmonary vascular resistance did not change after interferon-α infusion. The cardiac output in this group was increased significantly at 1 h after the start of interferon-α infusion; however, the time course of the response was almost the same as that in Group 1.

3.3. Lung lymph balance

The time course of lymphatic parameters is shown in Fig. 3. In Group 1, lung lymph flow was significantly increased at 1 h after the start of interferon-α infusion, and its values during the experiments were higher than those at baseline. However, the increase in lung lymph flow was significantly suppressed in Group 2. Lung lymph-to-plasma total protein concentration ratio and lung lymph protein clearance did not change significantly in either group after the start of interferon-α infusion.

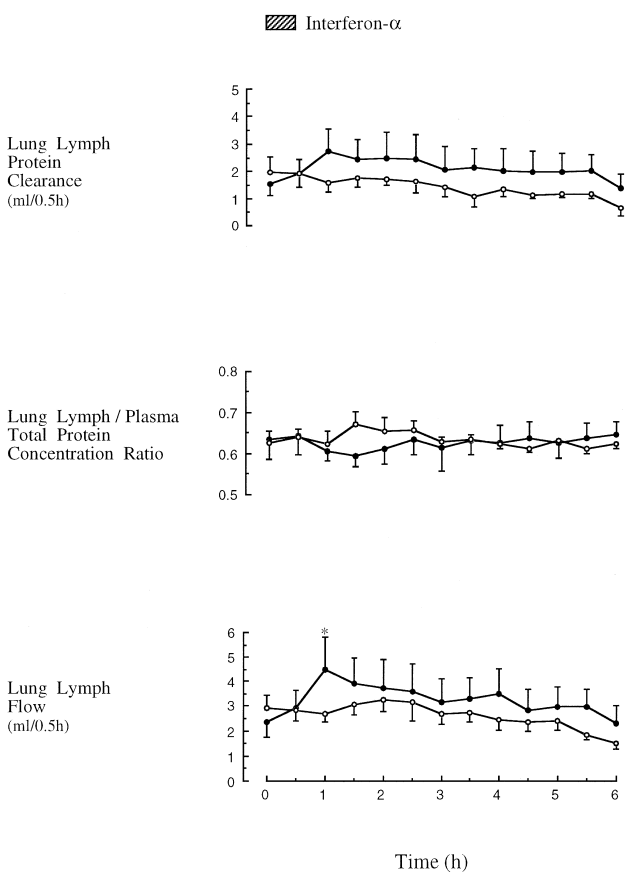

Fig. 3. Effects of interferon-α on lung lymph balance in untreated sheep (closed circles) and OKY-046-pretreated sheep (open circles). Values are mean ± S.E.M. $^*P < 0.05$ compared to baseline.

Table 2
Effects of interferon-α on arterial oxygen gas tension and circulating leukocyte count in untreated sheep and OKY-046-pretreated sheep

	PaO_2 (Torr)	Leukocytes (mm^{-3})
Baseline		
IFN-α	77.6 ± 0.7	7400 ± 910
IFN-α + OKY-046	83.3 ± 2.1	7330 ± 840
0.5 h		
IFN-α	78.3 ± 2.9	7490 ± 740
IFN-α + OKY-046	82.6 ± 2.7	7510 ± 900
1 h		
IFN-α	74.2 ± 2.6	7310 ± 880
IFN-α + OKY-046	75.8 ± 2.6	6660 ± 620
2 h		
IFN-α	75.3 ± 3.9	6300 ± 920
IFN-α + OKY-046	81.9 ± 2.7	5910 ± 560
3 h		
IFN-α	80.2 ± 4.2	6190 ± 1010
IFN-α + OKY-046	80.8 ± 2.0	5840 ± 750
4 h		
IFN-α	76.9 ± 3.5	6840 ± 1030
IFN-α + OKY-046	85.4 ± 2.6	5990 ± 660
5 h		
IFN-α	80.8 ± 3.9	6970 ± 1040
IFN-α + OKY-046	81.6 ± 2.0	5540 ± 870
6 h		
IFN-α	80.0 ± 3.1	6860 ± 950
IFN-α + OKY-046	81.8 ± 3.0	6080 ± 1090

Values are mean ± S.E.M.
PaO_2: arterial oxygen gas tension. IFN-α: interferon-α.

3.4. Circulating leukocytes

The circulating leukocyte counts, as shown in Table 2, did not change significantly during the experiments in either group.

3.5. Arterial blood gas tensions

In both groups, PaO_2 declined somewhat at 1 h after interferon-α infusion, but there was no significant change (Table 2). The time courses of PaO_2 were not significantly different in the two groups, nor were there any significant differences between them in $PaCO_2$ and pH.

3.6. Concentrations of thromboxane B_2 and 6-keto-prostaglandin $F_{1\alpha}$

The changes in plasma and lung lymph concentrations of thromboxane B_2 and 6-keto-prostaglandin $F_{1\alpha}$ are shown in the Table 3. In Group 1, the plasma thromboxane B_2 concentration increased significantly from the baseline level

Table 3
Effects of interferon-α without and with OKY-046 on plasma and lung lymph concentrations of thromboxane B_2 and 6-keto-prostaglandin $F_{1\alpha}$ in awake sheep

	Thromboxane B_2 (pg ml^{-1})		6-keto-$PGF_{1\alpha}$ (pg ml^{-1})	
	Plasma	Lung lymph	Plasma	Lung lymph
Baseline				
IFN-α	122.6 ± 15.8	162.3 ± 21.8	13.1 ± 2.6	11.1 ± 2.6
IFN-α + OKY-046	95.8 ± 13.2	162.4 ± 27.7	10.8 ± 3.0	11.6 ± 2.2
0.5 h				
IFN-α	220.1 ± 31.9[a,b]	264.6 ± 41.7[a]	27.8 ± 4.7	13.3 ± 3.1
IFN-α + OKY-046	126.4 ± 26.7	166.7 ± 17.4	19.9 ± 3.8	17.8 ± 3.2
1 h				
IFN-α	275.4 ± 35.8[a,b]	270.7 ± 30.8[a,b]	17.3 ± 3.7	16.2 ± 5.3
IFN-α + OKY-046	99.0 ± 14.6	147.0 ± 28.4	15.4 ± 4.1	21.0 ± 4.0
3 h				
IFN-α	133.4 ± 26.1	188.4 ± 28.2	18.1 ± 5.6	14.1 ± 4.1
IFN-α + OKY-046	108.9 ± 12.3	176.5 ± 33.0	17.6 ± 6.3	18.9 ± 2.3
5 h				
IFN-α	129.8 ± 14.0	174.2 ± 25.4	20.0 ± 9.4	11.9 ± 3.1
IFN-α + OKY-046	94.9 ± 8.6	167.6 ± 34.9	21.0 ± 6.2	16.0 ± 1.1

Values are mean ± S.E.M.
6-Keto-$PGF_{1\alpha}$: 6-keto-prostaglandin $F_{1\alpha}$. IFN-α: interferon-α.
[a] $P < 0.05$ compared to baseline; [b] $P < 0.05$ compared to IFN-α + OKY-046 group.

of 122.6 ± 15.8 pg ml^{-1} to 275.4 ± 35.8 pg ml^{-1} at 1 h after interferon-α infusion, and then declined to the baseline value by 3 h. The thromboxane B_2 concentration of lung lymph also increased significantly from 162.3 ± 21.8 pg ml^{-1} at baseline to 270.7 ± 30.8 pg ml^{-1} at 1 h. In Group 2, the interferon-α did not cause any increases in the thromboxane B_2 concentration of the plasma or lung lymph. The 6-keto-prostaglandin $F_{1\alpha}$ concentrations of plasma and lung lymph increased slightly after interferon-α infusion, but there were no significant changes from the baseline values. These patterns of 6-keto-prostaglandin $F_{1\alpha}$ response to interferon-α were almost the same in the two groups.

4. Discussion

The major findings of the present study are the elevation of pulmonary arterial pressure and pulmonary vascular resistance in an early period after the start of interferon-α infusion, and the coincidence of this pulmonary vascular response to interferon-α with an increase in thromboxane production. To our knowledge there are no previous reports about interferon-α-induced pulmonary hypertension. We also examined the effect of OKY-046, a selective thromboxane synthase inhibitor, on the pulmonary hemodynamics of sheep infused with interferon-α. Pretreatment with OKY-046 significantly suppressed the increases of pulmonary arterial pressure and pulmonary vascular resistance, and significantly attenuated the production of thromboxane B_2 after interferon-α infusion. Our results indicate that thromboxane A_2 plays an important role in the transient pulmonary hypertension induced by interferon-α in sheep.

There are some reports about the relation between interferon-α and arachidonic acid metabolism. Pretreatment of human monocytes with recombinant human interferon-α resulted in enhanced release of arachidonic acid and increased conversion to autacoids after phorbol ester (12-*O*-tetradecanoylphorbol-13-acetate) or calcium ionophore (A23187) stimulation (Hoffman et al., 1987). Bovine alveolar macrophages incubated with recombinant bovine interferon-α produced increased amounts of leukotriene B_4 when stimulated with A23187 or opsonized zymosan (O'Sullivan et al., 1990). Moreover, preincubation of uterine tissue isolated from ovariectomized rats with high dose of interferon-α augmented the formation of thromboxane B_2 (Motta et al., 1995). These findings demonstrate that interferon-α may modulate the arachidonic acid metabolism. Similarly, the results of our study reveal that interferon-α may stimulate the prostanoid cascade, i.e., increased thromboxane A_2 production in sheep. interferon-α has been suggested to be no species specificity, although there is no previous study about cross-reactivity from human interferon-α with sheep. The body temperature was actually increased at early phase after interferon-α infusion in this study, such as in humans (Balkwill, 1989; Vial and Descotes, 1994).

At 1 h after the start of interferon-α infusion, the thromboxane B_2 concentrations of plasma and lung lymph reached those maximum levels consistent with the increases in pulmonary arterial pressure, pulmonary vascular resistance and lung lymph flow. Similarly, the thromboxane B_2 concentration showed the highest value at 0.5–1 h after endotoxin infusion into sheep (Kubo and Kobayashi, 1985). After endotoxin, thromboxane synthesis could occur in platelets, leukocytes, and possibly cells in the lungs and other organs (Kubo and Kobayashi, 1985). On the other hand, the interferon-α concentration reached its maximum level in plasma, kidney, lung, spleen, liver and thoracic duct lymph at 1 h after intramuscular administration in Sprague–Dawley rat (Yoshikawa et al., 1987). It is expected that the similar mechanism with prostanoid production after endotoxin may exist on interferon-α-induced thromboxane A_2 synthesis. Further studies are needed to identify the source of thromboxane synthesis after interferon-α.

Sheep with lung lymph fistula is useful to see the lung fluid exchange. The increases in lung lymph flow with protein rich fluid indicate increased pulmonary vascular permeability after endotoxin or tumor necrosis factor ad-

ministration into sheep (Kubo and Kobayashi, 1985; Koizumi et al., 1992; Koyama et al., 1992). In the present study, however, interferon-α infusion did not induce significant increase in lung lymph flow or in lung lymph-to-plasma total protein concentration ratio in the late period, which could mean that pulmonary vascular permeability was unchanged. These findings suggest that interferon-α may not produce acute lung injury in the maximum daily dose of interferon-α in humans.

The circulating leukocyte count did not change significantly during interferon-α infusion. In studies of endotoxin-induced lung injury or tumor necrosis factor-induced lung injury in sheep, the leukocyte count showed an immediate decrease and reached a nadir within 1 h after infusion (Koizumi et al., 1992, 1993; Hanaoka et al., 1998). Activated neutrophils accumulate in the lung and cause oxygen free radical production and/or protease damage to the endothelium, resulting in increased pulmonary vascular permeability in the late period (Koyama et al., 1992; Kubo et al., 1994). Thus neutrophil-mediated pulmonary microvascular injury is thought to contribute to the pathogenesis of acute lung injury or acute respiratory distress syndrome (Koizumi et al., 1993; Hanaoka et al., 1998). Since interferon-α did not cause any leukopenia during our experiments, pulmonary microvascular injury through neutrophils mediated pathway may not be induced by interferon-α.

Several investigators described the potential mechanism of thromboxane A_2 in the alternation of lung fluid balance. Yoshimura et al. (1989) showed that a thromboxane A_2 analogue increased pulmonary leakage in isolated newborn lambs. Moreover, thromboxane A_2 has been shown to increase pulmonary microvascular permeability after ischemia–reperfusion in intestine and limb, respectively (Klausner et al., 1989; Turnage et al., 1997). However, we have shown in sheep that thromboxane A_2 mainly mediates pulmonary hypertension and has little effect on protein-rich lung lymph flow after endotoxin (Kubo and Kobayashi, 1985) and tumor necrosis factor (Koizumi et al., 1992) infusion, respectively. Likewise, we found that interferon-α caused thromboxane A_2 release and transient pulmonary hypertension. But there was no evidence of increased pulmonary permeability by increased thromboxane A_2 in the present study.

There are increasing evidences that interferon-α causes some noxious effects in its therapy, which include leukopenia, hepatic dysfunction, gastrointestinal and neurological toxicity, and myocardial dysfunction (Balkwill, 1989; Vial and Descotes, 1994). Recently, it has been clarified that severe interstitial pneumonia is developed in patients treated with daily interferon-α administrations, and sometimes results in fatal respiratory failure (Kamisako et al., 1993; Hizawa et al., 1994; Moriya et al., 1994; Yufu et al., 1994). These reports speculated that interferon-α caused some pathophysiological change in the lung. Interferon-α has a complicated network and/or interaction with other cytokines or cells (Staeheli, 1990). For example, interferon-α stimulates interleukin-1 release from macrophages (Gerrard et al., 1987). Interferon-α also could stimulate lymphocyte, neutrophil or fibroblast. It has been postulated that these activated cells in interstice or alveolar space lead to pulmonary fibrosis (Kelley, 1990). On the other hand, thromboxane A_2 could alter the endothelial cell cytoskeleton with microfilament disassembly and widening of interendothelial tight junctions (Welles et al., 1985; Zamora et al., 1993), which might lead to increased pulmonary microvascular permeability. Since there are many related cells and mediators during interferon-α therapy, the mechanism of developing interstitial pneumonia may be complicated. In the present study, we found no evidence of lung injury after a single infusion of interferon-α. To examine the mechanism how interstitial pneumonia is developed, it should be tested the effect of repeated and prolonged treatment with interferon-α on lung function.

In summary, infusion of interferon-α into awake sheep resulted in early transient pulmonary hypertension that was attenuated by OKY-046, a selective thromboxane synthase inhibitor. OKY-046 also prevented the increases in lung lymph flow and prostanoid production. However, no evidence was observed of increased pulmonary vascular permeability after interferon-α infusion. We conclude that a single administration of interferon-α causes transient pulmonary hypertension and that thromboxane A_2 plays an important role in this lung dysfunction.

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