Communications to the Editor

[Chem. Pharm. Bull. 34(11)4896—4898(1986)]

SUPPRESSION OF PHORBOL MYRISTATE ACETATE-INDUCED PLEURISY BY CV-3988, AN ANTAGONIST OF PLATELET-ACTIVATING FACTOR

Sachiko Oh-ishi,*[,a] Kohji Yamaki,[a] Masahiko Hayashi,[a] Susumu Tsushima[b] and Hiroaki Nomura[b]

Department of Pharmacology, School of Pharmaceutical Sciences, Kitasato University,[a] Shirokane, Minatoku, Tokyo 108 and Central Research Division, Takeda Chemical Industries, Ltd.,[b] Osaka 532, Japan

Pleurisy was induced in rats by intrapleural injection of 10 uM phorbol myristate acetate (PMA) or 2 % carrageenin. Thirty minutes after PMA was administered following pretreatment with CV-3988, a specific antagonist of platelet activating factor (PAF), pleural fluid accumulation and its exudation rate were significantly suppressed. However the pleurisy induced by carrageenin was not affected by CV-3988. These results indicate that PAF may contribute to the exudation of PMA-induced pleurisy but not in carrageenin-induced pleurisy.

KEYWORDS ——— platelet-activating factor (PAF); rat pleurisy; phorbol myristate acetate; carrageenin; PAF-antagonist

Platelet-activating factor (PAF) appears to be a potential mediator of inflammation and anaphylaxis.[1] The involvement of PAF in endotoxin shock was demonstrated by use of a specific PAF-antagonist to attenuate the shock,[2] and endotoxin-induced gastro-intestinal damage was also attenuated by the antagonist.[3] We recently demonstrated that PAF is the most potent autacoid to increase vascular permeability in rat skin and to enhance the activities of other autacoids, such as bradykinin, PGI_2, and PGE_2.[4] Furthermore, as we previously reported, indomethacin and mepyramine only partially suppressed the pleural exudate in rats in which pleurisy was induced by phorbol myristate acetate (PMA), and in whose exudate we detected histamine and 6-keto $PGF_{1\alpha}$.[5,6] Therefore we set up experiments to determine if there is PAF involvement in PMA or carrageenin-induced pleurisy.

The experimental method was as previously reported.[6] Briefly, 8-week-old male Sprague-Dawley rats under light ether anesthesia were injected intrapleurally with 0.1 ml of 10 uM PMA (Sigma) or 0.1 ml of 2% carrageenin (Sigma). Pontamine sky blue 6B, a marker for plasma exudation was injected intravenously (50 mg/kg) 20 min prior to the sacrifice. The exudation rate was assessed by the amount of

dye that leaked into the pleural cavity during these last 20 min. The rats injected with PMA were exsanguinated 30 min after the injection; and those injected with carrageenin, 3 h after. The pleural fluid was collected, the dye concentration was measured, and white cells were counted as previously reported.[4] CV-3988 (rac-3-(N-n-octadecylcarbamoyloxy)-2-methoxypropyl-2-thiazolioethyl phosphate),[7] a specific PAF-antagonist, was dissolved in saline (10 mg/ml) and injected into the tail vein (10 mg/kg) 2 min prior to irritant injection. The control groups received the same volume of saline solution.

TABLE 1. Effects of CV-3988 (10 mg/kg) on Rat Pleurisy Induced by Phorbol Myristate Acetate (PMA, 0.5 h) or Carrageenin (3h)

	Exudate (ml)	Exudation rate (ml/20 min)	Leukocytes ($\times 10^6$)
PMA			
Control (n=6)	0.49 ± 0.05	0.27 ± 0.05	6.6 ± 1.7
CV-3988 (n=7)	0.25 ± 0.03*	0.10 ± 0.02*	7.0 ± 1.0
Carrageenin			
Control (n=6)	0.79 ± 0.08	0.18 ± 0.01	69.5 ± 11.7
CV-3988 (n=5)	0.80 ± 0.08	0.17 ± 0.02	69.2 ± 9.7

*$p<0.05$.

As shown in Table 1, CV-3988 significantly suppressed the pleural fluid accumulation and exudation rate in the pleurisy induced by PMA, but not those induced by carrageenin at 3 h. However, CV-3988 did not attenuate the leukocyte number in the pleural fluid of either pleurisy. These results agree with the direct effect of PAF previously reported,[4] in which PAF-induced pleural fluid accumulation was significantly suppressed by CV-3988. Hwang et al. reported the involvement of PAF in the initial phase of rat paw edema induced by carrageenin.[8] We found no evidence of PAF involvement even in the earlier phase of rat pleurisy induced by carrageenin (data not shown). The discrepancy may only be considered as the different characteristics of cell types in rat paw and pleural cavity.

As mentioned above, we previously reported the involvement of histamine and PGI_2 in the pleurisy induced by PMA.[5,6] In that study, the portion of the PMA-induced exudate not affected by indomethacin or mepyramine might well have been due to PAF action. Thus our results clearly demonstrate that PAF can contribute to the accumulation of exudate in PMA-induced pleurisy, but that it does not have any significant role in carrageenin-induced pleurisy, where bradykinin and PGE_2 are considered to be the main agonists to induce pleural exudation.[9,10]

ACKNOWLEDGEMENT This work was partly supported by a Grant-in-aid for Scientific Research (598041) from the Ministry of Education, Science and Culture, Japan.

REFERENCES

1) J. Benveniste, Nature, 249, 581 (1974).

2) Z. Terashita, Y. Imura, K. Nishikawa and S. Sumida, Eur. J. Pharmacol., 109, 257 (1985).

3) J. L. Wallace and B.Jr. Whittle, Eur. J. Pharmacol., 124, 209 (1986).

4) S. Oh-ishi, M. Hayashi and K. Yamaki, Prostaglandins Leukotrienes Med., 22, 21 (1986).

5) K. Kiyomiya, and S. Oh-ishi, Jpn. J. Pharmacol., 39, 201 (1985).

6) K. Kikuchi and S. Oh-ishi, Jpn. J. Pharmacol., 39, 467 (1985).

7) Z. Terashita, S. Tsushima, Y. Yoshioka, H. Nomura, Y. Inada and K. Nishikawa, Life Sci., 32, 1975 (1983).

8) S. Hwang, M. Lam, C. Li and T. Shen, Eur. J. Pharmacol., 120, 33 (1986).

9) Y. Harada, K. Tanaka, Y. Uchida, A. Ueno, S. Oh-ishi, K. Yamashita, M. Ishibashi, H. Miyazaki and M. Katori, Prostaglandins, 23, 881 (1982).

10) S. Oh-ishi, I. Hayashi, M. Hayashi, K. Yamaki, A. Yamasu, T. Nakano, I. Utsunomiya and Y. Nagashima, Agents and Actions, 18, 450 (1986).

(Received October 1, 1986)