Naunyn-Schmiedeberg's Arch Pharmacol (1987) 336:459–463

Naunyn-Schmiedeberg's
Archives of
Pharmacology

PAF-acether induced cardiac dysfunction in the isolated perfused guinea pig heart*

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Summary. PAF-acether (1-O-alkyl-2-acetyl-sn-glyceryl-3-phosphorylcholine) has been implicated in a variety of inflammatory and ischaemic disorders (e.g., myocardial ischemia, anaphylactic shock). Recently, the peptide leukotrienes (i.e., LTC_4, LTD_4) have been shown to mediate the increase in coronary vascular resistance induced by PAF-acether in the isolated perfused rat heart. In isolated perfused guinea pig hearts, PAF-acether produced a dose-dependent increase in coronary perfusion pressure (CPP) and a decrease in contractile force (CF). At 50 pmol/l, PAF increased CPP by 13 ± 3 mm Hg and decreased CF by $47 \pm 12\%$ in 8 hearts. Radioimmunoassay of the coronary effluent did not detect peptide leukotrienes or thromboxane B_2 (TxB_2) in response to PAF. Addition of a specific PAF-acether receptor antagonist, CV-6209 (25 nmol/l), blocked the increase in coronary perfusion pressure and decrease in contractile force. OKY-1581 (400 nmol/l), a thromboxane synthetase inhibitor or LY-171,883 (7.3 μmol/l) a leukotriene D_4 receptor antagonist, failed to prevent the increase in CPP or the decrease in CF. These data indicate that the PAF-acether induced increase in CPP is not mediated by the peptide leukotrienes or thromboxane A_2 (TxA_2). Possible mechanisms for the increase in CPP induced by PAF-acether in the isolated perfused guinea pig heart include a direct receptor mediated constriction of coronary resistance vessels, release of a non-eicosanoid coronary constrictor as a mediator of the response, or via enhancement of coronary microvascular permeability.

Key words: Cardiac contractile force – PAF-acether antagonists – Thromboxane A_2 – Coronary vasoconstriction – Peptide leukotrienes

Introduction

PAF-acether (1-O-alkyl-2-acetyl-sn-glyceryl-3-phosphorylcholine, PAF, AGEPC) has been shown to be synthesized by a variety of cells, including polymorphonuclear leukocytes, platelets, and endothelial cells and to be released by a variety of immunologic and pathophysiologic stimuli (Benveniste et al. 1972; Benveniste et al. 1982; Camussi et al. 1983; Zimmerman et al. 1985; Braquet and Vargaftig 1986). Nanomolar concentrations of this phospholipid are capable of aggregating blood platelets and neutrophils in a variety of mammalian species (Pinckard et al. 1982; Benveniste and Vargaftig 1983). Furthermore, PAF-acether does not appear to directly constrict vascular smooth muscle (Cerrina et al. 1983; Stahl and Lefer 1987), although it does contract other types of smooth muscle including the guinea pig ileum and lung parenchyma (Pinckard et al. 1982).

Recently, it has been shown that the PAF-induced coronary constriction in the isolated perfused rat heart is mediated by the peptide leukotrienes (i.e., LTC_4 and LTD_4) (Piper and Stewart 1986; Stahl and Lefer 1986). Furthermore, PAF-acether induced vasoconstrictor effects in the isolated perfused rat intestine are mediated by peptide leukotrienes and norepinephrine (Hsueh et al. 1986). In the isolated perfused rat liver, PAF-acether induced vasoconstriction that was blocked by β-adrenergic agonists (Olson et al. 1986). Thus, in the rat, PAF-acether appears to release other mediators which then contract vascular smooth muscle.

Several groups have previously reported that PAF-acether increases coronary vascular resistance and decreases cardiac contractility in the isolated perfused guinea pig heart (Benveniste et al. 1983; Levi et al. 1984; Saeki et al. 1985). The objectives of this study were (a) to examine the response of PAF-acether in the isolated perfused guinea pig heart in order to determine its direct effects on coronary vascular resistance and cardiac contractility and (b) to ascertain the effects of PAF-acether via release of other mediators. In this connection, we examined the mechanisms of PAF-acether induced cardiac effects with particular reference to mediation by the eicosanoids (e.g., lipoxygenase and cyclooxygenase products).

Materials and methods

Male Hartley guinea pigs weighing 550–650 g were given 1000 IU/kg of heparin intraperitoneally 15 min prior to induction of anaesthesia with pentobarbital sodium (40 mg/kg, i.p.). Following a midsternal thoracotomy, the hearts were rapidly excised and placed in ice cold oxygenated (95% O_2 + 5% CO_2) Krebs-Henseleit (K-H) solution. The K-H solution contained the following (in mmol/l: NaCl, 118; KCl 4.7, KH_2PO_4 1.2, $MgSO_4 \cdot 7\,H_2O$ 1.2, $CaCl_2 \cdot 2\,H_2O$ 2.5, $NaHCO_3$ 12.5, and glucose 11 at pH 7.3. Within 30 s, the hearts were transferred to a perfusion apparatus and

* Supported by Research Grant No. HL-25575 from the National Heart, Lung and Blood Institute of the NIH
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perfused retrogradely via the aorta with oxygenated K-H solution at pH 7.3 and 37° C according to the Langendorff technique. The hearts were adjusted to perfusion conditions at a constant pressure of 55 mm Hg for 10 min and then switched to constant perfusion flow at a perfusion pressure of 50 mm Hg according to previously described procedures (Roth et al. 1985). Coronary perfusion pressure (CPP) was measured in a side branch of the inflow line using a Statham P23AC pressure transducer and was continuously recorded on a Grass Model 7 oscillographic recorder. Contractile force (CF) was measured continuously via a silk suture attached to the apex of the heart which was connected to a Grass Model FT03C force-displacement transducer. A preload of 9.8 mN was applied to each heart. The hearts were stable for at least 60 min, and untreated hearts did not show any significant variation in perfusion pressure or contractile force over this time.

Each experiment consisted of a 15 min control period during which constant flow perfusion was maintained at 15 ± 1 ml/min yielding a perfusion pressure of 50 mm Hg. The exact flow rate (i.e., 14–16 ml/min) was maintained throughout the remainder of the experiment for each heart. At the end of this period, PAF-acether was infused by a Rainin low flow peristaltic pump at 1 ml/min for 1 min via a small polyethylene cannula placed in the aortic inflow tract. The dose was adjusted for the actual coronary flow so that the actual dose delivered to the coronary circulation was the amount specified. The corresponding changes in CF and CPP were observed for the following 10 min. Each heart was subjected only once to a given concentration of PAF-acether in the presence or absence of a pharmacologic agent.

To investigate the mechanisms of the induced changes in CF and CPP, a PAF-acether receptor antagonist, a TxA_2 synthetase inhibitor, or a LTD_4 receptor antagonist were employed. All drugs or their vehicles were infused via a second polyethylene cannula placed in the aortic inflow tract. Infusion of drug or vehicle started 1 min before and continued for 1 min following the infusion of PAF-acether, except for CV-6209 which continued for 30 s following the infusion of PAF-acether. Each drug or its vehicle was infused at a rate of 68 µl/min via a Harvard infusion pump (Model 901) corrected for the actual coronary flow rate. This infusion rate did not alter CPP or CF in these experiments.

Radioimmunoassay (RIA) of coronary effluent. Samples of the coronary effluent were collected at 30 s intervals between 1.0 and 3.5 min and at 12 min for analysis of peptide leukotrienes (i.e., LTC_4, LTD_4, and LTE_4) and TxB_2 concentration.

Samples of heart perfusates (i.e., K-H solution) and TxB_2 standards (100 µl) were added to centrifuge tubes. The samples were then subjected to RIA for TxB_2 using the method of Lewy et al. (1980). The TxB_2 standard curve was constructed with a lower detection limit of 0.250 pmol/ml TxB_2.

The radioimmunoassay for the peptide leukotrienes was carried out according to the methods of Aharony et al. (1983). This group has previously described the formation of the antibody which cross-reacts equally with LTC_4, LTD_4, and LTE_4, but not with prostaglandins, hydroperoxides, endoperoxides or thromboxanes. The lower limit of detection of this assay in these studies was 0.025 pmol/ml LTD_4. All values are expressed as pmol/ml sample.

None of the pharmacologic blockers used in this study interfered with the radioimmunoassay of TxB_2 or with the peptide leukotriene radioimmunoassay.

Materials. The following compounds were used during this study: 1-O-hexadecyl-2-acetyl-sn-glycero-3-phosphorylcholine, from Avanti Polar Lipids, Inc. (Birmingham, AL, USA), lyso-PAF (1-O-hexadecyl-sn-glycero-3-phosphocholine) from Sigma (St. Louis, MO, USA); the PAF-acether receptor antagonist CV-6209, 2-[N-acetyl-N-(2-methoxy-3-octadecyl-carbamoyloxypropoxycarbonyl) aminomethyl]-1-ethylpyridinium chloride from Takeda Chemical Co., Osaka, Japan; the LTD_4 receptor antagonist LY-171,883 [4-[2-(chlorobenzene-sulphonylamine)-ethyl]benzene acetic acid from Eli Lilly and Co., Indianapolis, IN, USA; the thromboxane synthetase inhibitor OKY-1581 (sodium (E)-3-[4-(3-pyridylmethyl) phenyl]-2-methylacrylate) from Ono Research Institute, Osaka, Japan; the TxA_2 receptor antagonist BM-13,505 (4-(2-(4-chlorobenzene sulphonylamino)-ethyl) benzene acetic acid) from Boehringer, Mannheim, FRG. All drug solutions were prepared fresh daily. The solvents for the various inhibitors and receptor antagonists were as follows: K-H solution for LY-171,883 and BM-13,505; 0.025% BSA in K-H solution for CV-6209; 1% BSA in Krebs-Henseleit for PAF-acether and Lyso-PAF, and 0.9% NaCl for OKY-1581.

Statistical analysis. Significance of the results of these experiments was determined using the Student's "*t*"-test for unpaired data and multigroup comparisons were compared by analysis of variance (ANOVA). All values given in the text, figures, and tables are means ± SEM of *N* experiments. *P* values of less than 0.05 were considered statistically significant.

Results

Figure 1 illustrates the time course and changes in CPP and CF with varying concentrations of PAF. With increasing concentrations of PAF from 1.0 pmol/l to 1.0 nmol/l, we observed a dose-dependent rise in CPP and a decrease in CF. At 50 pmol/l, CPP peaked at 13 ± 3 mm Hg above control value, as CF decreased to $53\% \pm 12\%$ of control. The CPP remained elevated and cardiac contractile force remained depressed with time. Lyso-PAF (1 nmol/l), an inactive analogue of PAF-acether, did not significantly alter the coronary vascular resistance or contractility in 3 hearts, thus showing the need of the acetyl group in the sn-2 position for biological activity.

The effects of a novel PAF-acether receptor antagonist (Terashita et al. 1986), CV-6209, are summarized in Fig. 2. CV-6209, at a concentration of 25 nmol/l, significantly reduced the elevated CPP and decreased CF induced by PAF-acether (50 pmol/l). This protection remained throughout the course of the experimental period. Thus, the PAF-acether receptor antagonist totally protected the guinea pig heart against the cardiac effects of PAF-acether.

A LTD_4 receptor antagonist, LY-171,883 was used to further evaluate the role of peptide leukotrienes in this model of cardiac dysfunction. LY-171,883, at a concentration of 7.3 µmol/l (Fig. 3), failed to block the increase in CPP or the decrease in CF induced by 50 pmol/l PAF-acether. This concentration of LY-171,883 significantly protects the

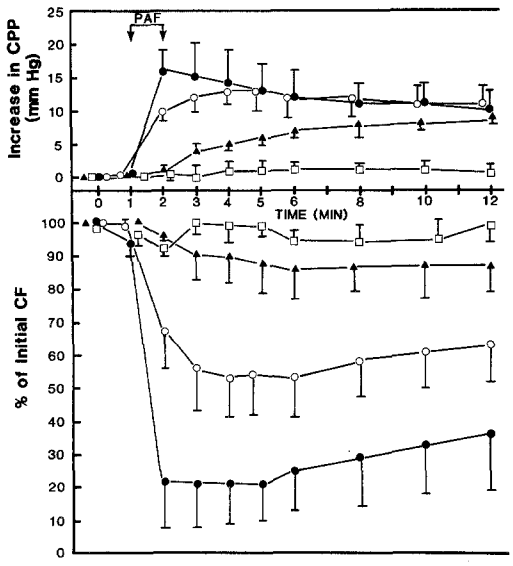

Fig. 1. Dose-response relationships for PAF-acether in the isolated perfused guinea pig heart. The *upper panel* represents the increase in coronary perfusion pressure (*CPP*) in mm Hg. Control CPP was maintained at 50 ± 1 mm Hg. The *bottom panel* represents the percent change from initial contractile force (*CF*). Control CF was 9.8 ± 0.7 mN for 20 hearts. Each line represents a mean of at least 6 hearts except for the lyso-PAF line which represents 3 hearts. ▲, PAF (1 pmol/l); ○, PAF (50 pmol/l); ●, PAF (1 nmol/l); □, lyso-PAF (1 nmol/l)

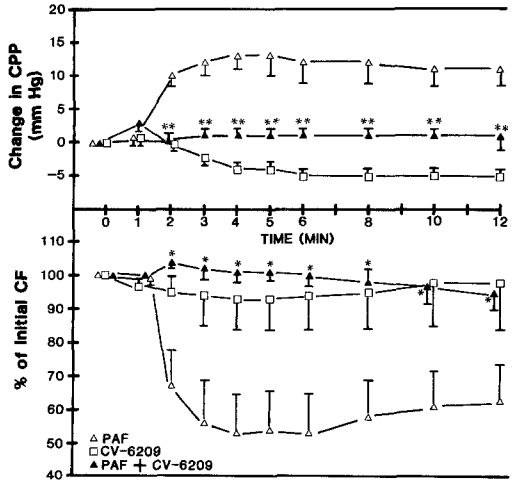

Fig. 2. Effect of a PAF-acether receptor antagonist, CV-6209 (25 nmol/l) and PAF-acether (50 pmol/l) in the isolated perfused guinea pig heart. ($n = 8$ for the PAF-acether hearts. $n = 4$ for the CV-6209 alone experiments, and $n = 6$ for the PAF-acether + CV-6209 hearts.) Control CPP was maintained at 50 ± 1 mm Hg. Control CF was 9.5 ± 0.5 mN for 16 hearts. * $p < 0.01$; ** $p < 0.001$ from the PAF-acether group

isolated perfused rat heart against PAF-acether induced increase in coronary vascular resistance (Stahl and Lefer 1986) and totally blocks the increase in CPP induced by 25 ng/ml LTD_4. Higher concentrations (i.e., 14 μmol/l) of LY-171,883 produced adverse cardiac effects. Furthermore, RIA of the coronary effluent revealed no significant increase in leukotriene concentrations (i.e., LTC_4, LTD_4, LTE_4). Therefore, the peptide leukotrienes do not appear to mediate

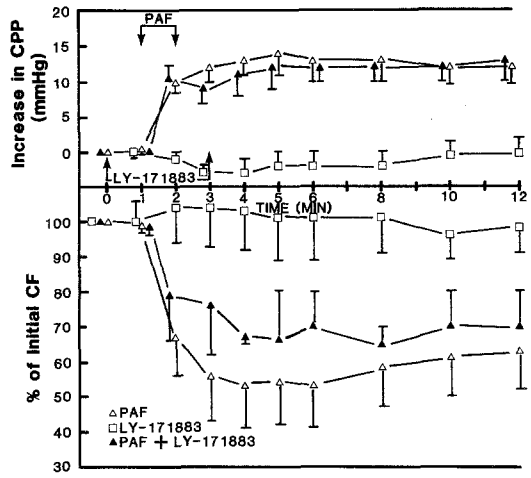

Fig. 3. Effect of a LTD_4 receptor antagonist, LY-171,883 (7.3 μmol/l) and PAF-acether (50 pmol/l) in the isolated perfused guinea pig heart. Control CPP was maintained at 50 ± 1 mm Hg. Control CF was 10.9 ± 0.9 mN for these hearts. ($n = 8$ for the PAF-acether hearts, $n = 5$ for the LY-171,883 alone experiments and $n = 6$ for the PAF-acether + LY-171,883 hearts)

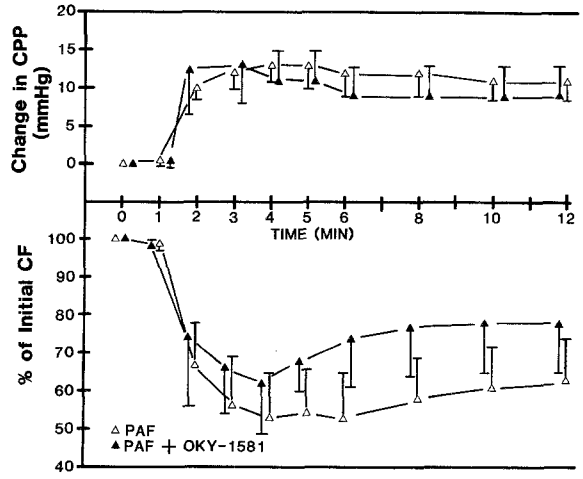

Fig. Effect of a thromboxane A_2 synthetase inhibitor, OKY-1581 (400 nmol/l) and PAF-acether (50 pmol/l) in the isolated perfused guinea pig heart. Control CPP and CF was maintained at 50 ± 1 mm Hg and 9.8 ± 0.6 mN, respectively. ($n = 8$ for the PAF-acether hearts, and $n = 4$ for the PAF-acether + OKY-1581 hearts)

the increase in coronary vascular resistance induced by PAF-acether in the isolated perfused guinea pig heart.

A thromboxane synthetase inhibitor, OKY-1581, was used to evaluate the role of TxA_2 in the PAF-acether induced increase in CPP. OKY-1581, at a concentration of 400 nmol/l failed to alter the increase in CPP induced by 50 pmol/l PAF-acether (Fig. 4). This concentration has been shown previously to inhibit the production of TxA_2 by > 80% in isolated rat peritoneal macrophages (Feuerstein and Ramwell 1981). Furthermore, a TxA_2 receptor antagonist, BM-13,505 (300 nmol/l) failed to block the cardiac effects induced by PAF-acether in 6 perfused hearts. This concentration of BM-13,505 (300 nmol/l) totally blocked the increase in CPP caused by exogenous U-46,619 (20 ng/ml), a TxA_2 mimetic. Moreover, RIA of the coronary effluent revealed no significant increase in TxB_2 concentration.

Thus, TxA_2 does not appear to mediate the increase in coronary vascular resistance induced by PAF-acether in the isolated perfused guinea pig heart.

Discussion

Several possibilities exist which might explain the increase in coronary vascular resistance induced by PAF-acether in the isolated guinea pig heart. Firstly, PAF-acether could directly constrict the coronary arteries. However, both isolated perfused and helical strips of the renal, superior mesenteric, and coronary arteries of the cat failed to demonstrate any vasoconstrictor activity to PAF-acether (Stahl and Lefer 1987). Similar results were obtained in isolated rabbit pulmonary artery strips (Lefer et al. 1984). Moreover, these lack of effects are not endothelially mediated and are not due to an absence of endothelially derived relaxing factor (Lefer and Lefer 1986). Therefore, PAF-acether does not appear to possess any direct vasoconstrictor activity on vascular smooth muscle of large arteries. However, PAF-acether may constrict the smaller resistance vessels of the coronary vasculature. Thus, PAF-acether may exert a direct vascular constriction on small coronary vessels, although it is unlikely to be the only mechanism explaining the cardiac effects of PAF-acether.

Secondly, PAF-acether could release another mediator which in turn could constrict coronary vascular smooth muscle. In the isolated perfused rat heart, PAF-acether induces the production of endogenous peptide leukotrienes (i.e., LTC_4 and LTD_4) which mediates the increase in coronary vascular resistance (Piper and Stewart 1986; Stahl and Lefer 1986). Furthermore, in the anaesthetized pig, indometacin attenuates the decrease in coronary blood flow induced by PAF-acether suggesting TxA_2 mediates the vasoconstrictor effects (Ezra et al. 1985). With the use of selective inhibitors, specific receptor antagonists, and radioimmunoassay we have shown that the PAF-acether induced increase in coronary vascular resistance in the isolated guinea pig heart is not mediated by the peptide leukotrienes or thromboxane A_2. Thus, if PAF-acether constricts the coronary vasculature in the guinea pig effects via release of another mediator, this substance remains to be identified and is probably not an eicosanoid.

Thirdly, PAF-acether may increase coronary vascular permeability which in turn may lead to an increase in CPP. PAF-acether is known to increase vascular permeability in a variety of species in vivo. Extravasation of protein-rich plasma results in hemoconcentration (McManus et al. 1981) in vivo and may involve alterations in endothelial permeability of postcapillary venules (Humphrey et al. 1984). Microvascular (Bjork et al. 1983), pulmonary (Mojarad et al. 1983; Bessin et al. 1983; Heffner et al. 1983), and systemic (Humphrey et al. 1982) increases in permeability also occur as a result of PAF-acether. Thus, an increase in CPP as a result of increased coronary permeability may occur although we have no data to either include or exclude this possibility.

Several groups have previously suggested that PAF-acether is a direct negative inotropic agent (Levi et al. 1984; Alloatti et al. 1986). PAF-acether (96 nmol/l) decreased the force of contraction by 16% $\pm$ 8% in six electrically driven right papillary muscles of the guinea pig (unpublished observations), which is in agreement with Levi et al. (1984). However, this concentration is about 1000 times higher than that needed to induce vascular and subsequent inotropic effects in the guinea pig heart. PAF-acether (1.0 nmol/l) decreases developed tension in the isolated right ventricular guinea pig papillary muscle by approximately 10% (Levi et al. 1984). However, this concentration of PAF given to the perfused guinea pig heart markedly depressed the contractile state of the myocardium (Fig. 1), presumably via the PAF-acether induced increase in coronary vascular resistance. Thus, it appears that the indirect cardiodepressant effect resulting from coronary constriction far outweighs any direct inotropic effect of PAF-acether in the guinea pig heart.

In summary, we have shown that PAF-acether induces a dose-dependent increase in CPP as well as a decrease in CF in the isolated perfused guinea pig heart. The increase in coronary vascular resistance is not mediated by peptide leukotrienes (i.e., LTC_4, LTD_4, and LTE_4) or TxA_2. The decrease in CF may have two components. Firstly, PAF-acether may have small direct negative inotropic effect. Secondly, the increase in coronary perfusion pressure appears to induce a major depression of cardiac contractile force indirectly via an increase in coronary vascular resistance. The primary effect of PAF-acether in the isolated guinea pig heart appears to be either a receptor mediated vasoconstriction of small resistance vessels, the release of a non-eicosanoid vasoconstrictor, enhancement of vascular permeability or a combination of these effects. These effects are significantly different from those obtained in the rat (Stahl and Lefer 1986; Piper and Stewart 1986). Thus, the mechanism of the PAF-acether induced increase in coronary vascular resistance differs among mammalian species. These considerations may be of significance in circulatory shock where PAF is thought to be a mediator of the pathophysiological sequelae of the ischemia occurring in shock states (Braquet and Vargaftig 1986; Etienne et al. 1985).

Acknowledgements. We gratefully acknowledge the expert technical assistance of Judith Komlosh during the course of these studies. We also thank Dr. Jerry Fleisch of Eli Lilly Laboratories, Indianapolis, IN, USA, for the LY-171,883, Dr. Masao Nishikawa of Takeda Chemical Ltd., Osaka, Japan, for the CV-6209, and Dr. Tadao Okegawa of Ono Research Institute, Osaka, Japan, for the OKY-1581, and Dr. Karlheinz Stegmeier of Boehringer Mannheim GmbH, Mannheim, FRG, for the BM-13,505.

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Received December 10, 1986/Accepted May 25, 1987