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Platelet-activating factor-induced loss of vascular responsiveness to noradrenaline in pithed rats: involvement of nitric oxide

Tatsuya Shiga *, Daisuke Yoshikawa

Department of Anesthesiology and Reanimatology, Gunma University School of Medicine, 3-39-22 Showa-machi, Maebashi-shi, Gunma-ken 371, Japan

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Abstract

The role of nitric oxide and cyclo-oxygenase products in the platelet-activating factor (PAF)-induced hyporesponsiveness to noradrenaline was investigated in pithed rats. Infusion of PAF (30 ng/kg/min) for 60 min reduced the mean arterial blood pressure and impaired the pressor responses to noradrenaline (10 ng/kg, 100 ng/kg, 1 μg/kg). Administration of N^G-monomethyl-L-arginine (L-NMMA, 30 mg/kg) restored the reduced MABP and the impaired responses to their original levels. Indomethacin (5 mg/kg) had no significant effect on the PAF-induced hyporesponsiveness. Administration of 30 mg/kg L-NMMA caused hypertension in the PAF vehicle-treated animals and reduced the pressor response to 1 μg/kg noradrenaline. Administration of 3 mg/kg L-NMMA had no significant effect on the responsiveness to noradrenaline. These results suggest that nitric oxide contributes to the PAF-induced hyporesponsiveness to noradrenaline and that cyclo-oxygenase products do not play a major role in this hyporesponsiveness.

Keywords: PAF (platelet-activating factor); Nitric oxide (NO); Cyclo-oxygenase product; Vascular reactivity; L-NMMA (N^G-monomethyl-L-arginine); Indomethacin

1. Introduction

Platelet-activating factor (PAF) is a biologically potent phospholipid with a wide range of pharmacological activity (Braquet et al., 1987). It has been reported that there are analogies between endotoxin shock and the effects of systemic administration of PAF; these include hypotension, peripheral vasodilatation, cardiosuppression, plasma extravasation (Bessin et al., 1983; Otsuka et al., 1985; Siren and Feuerstein, 1989) and vascular hyporeactivity to vasoconstrictors (Sybertz et al., 1982; Gray et al., 1990; Bouvier et al., 1994). During endotoxemia, there is a marked impairment in the vascular responsiveness to noradrenaline and other vasoconstrictors (Parratt, 1973; Fink et al., 1985). The vascular hyporeactivity produced by endotoxin is reversed by inhibitors of nitric oxide synthase, suggesting that nitric oxide (NO) is a major mediator in this hyporeactivity (Julou-Schaeffer et al., 1990; Gray et al., 1991). The cyclo-oxygenase products of arachidonic acid metabolites have also been implicated in endotoxin-induced hyporeactivity because pretreatment with indomethacin completely inhibits this hyporeactivity (Fink et al., 1984; Gray et al., 1990). It is thought that these putative mediators are involved in a complex set of interactions.

PAF induces endothelium-dependent relaxation of arterial segments (Cervoni et al., 1983; Kasuya et al., 1984). The vasorelaxant effect of PAF is thought to be mediated by at least NO (Kamata et al., 1989; Chiba et al., 1990; Moritoki et al., 1992). It is now known that PAF is involved in the lipopolysaccharide induction of calcium-independent nitric oxide synthase, and that PAF itself induces this type of nitric oxide synthase (Szabó et al., 1993). Exogenous PAF increases plasma prostaglandin levels and may exert its effects, in part, by the generation of cyclo-oxygenase products (Bessin et al., 1983; Otsuka et al., 1985). Thus, there remains the possibility that PAF-induced vascular hyporeactivity is mediated by NO and/or cyclo-oxygenase products.

* Corresponding author. Tel. 81-272-20-8454, fax 81-272-20-8473.

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The purpose of this study was to investigate the effects of the nitric oxide synthase inhibitor N^G-monomethyl-L-arginine (L-NMMA) and the cyclo-oxygenase inhibitor indomethacin on the restoration of the PAF-induced vascular hyporesponsiveness to noradrenaline in pithed rats in order to evaluate the role of NO and cyclo-oxygenase products in PAF-induced vascular hyporeactivity.

2. Materials and methods

This study was performed in accordance with the ethical principles set by the Experimental Animal Laboratory of Gunma University School of Medicine.

2.1. Surgical preparation

Male Wistar rats (250–300 g) were anesthetized with 4% isoflurane in oxygen. The animals were ventilated artificially (a Harvard rodent ventilator) via a tracheal cannula at a rate of 50–60 breaths/min with a stroke volume of 1 ml per 100 g body weight to maintain arterial PCO_2 at 30–35 mm Hg. Arterial blood pressure was monitored using a Gould pressure transducer connected to the left carotid artery via a cannula (PE-50) containing heparinized saline (100 IU/ml). The output from the pressure transducer was displayed on a chart recorder (Nihon Kohden). The vagal nerves were cut bilaterally. The rats were pithed by introduction of a blunt steel rod into the vertebral canal through the right orbit as described by Gillespie (Gillespie and Muir, 1967). Immediately after pithing, isoflurane anesthesia was discontinued. Twenty-four-gauge Teflon cannulas were placed in the tail vein and the right femoral vein for the administration of drugs. Body temperature was maintained at 36–37°C using a heated underblanket controlled by a rectal thermistor probe.

2.2. Experimental protocols

The animals were allowed to stabilize for 1 h prior to any experimental intervention. The vascular responsiveness was evaluated by the changes in the mean arterial blood pressure when noradrenaline (10 ng/kg, 100 ng/kg and 1 μg/kg i.v.) was injected into the rats. The pressor responses were determined by cumulative administration of noradrenaline. The effects of the various drugs were evaluated during the continuous infusion of PAF or its vehicle, according to the protocols described below.

Protocol 1: Control – The pressor responses to noradrenaline were determined after 60 min of continuous infusion of the PAF vehicle.

Protocol 2: PAF – The pressor responses to noradrenaline were determined after 60 min of continuous infusion of PAF (30 ng/kg/min).

Protocol 3: PAF + L-NMMA and PAF + L-NMMA + L-arginine – Fifty minutes after the start of PAF infusion, L-NMMA (30 mg/kg i.v.) was administered. The pressor responses were determined 10 min after the administration of L-NMMA. Then L-arginine (100 mg/kg i.v.) was administered. The pressor responses were determined 5 min after L-arginine administration. The volume of L-NMMA and L-arginine was 1 ml/kg.

Protocol 4: PAF + indomethacin (or 4% sodium bicarbonate) – Forty-five minutes after the start of PAF infusion, indomethacin (5 mg/kg i.v.) or its solvent (4% sodium bicarbonate) was administered in a volume of 1 ml/kg. The pressor responses were determined 15 min after the administration of indomethacin or its solvent.

Protocol 5: L-NMMA – Fifty minutes after the start of PAF vehicle infusion, L-NMMA (30 mg/kg or 3 mg/kg i.v.) was administered. The pressor responses were determined 10 min after L-NMMA administration.

Six experiments were carried out for each group.

2.3. Drugs used

Heparin sodium (Upjohn). Noradrenaline bitartrate, bovine serum albumin, platelet-activating factor (PAF), N^G-monomethyl-L-arginine (L-NMMA) and L-arginine hydrochloride (Sigma). Noradrenaline, PAF, L-NMMA and L-arginine were dissolved in 0.9% w/v saline. The PAF vehicles also contained 0.25% w/v bovine serum albumin. Indomethacin (Sigma) was dissolved in a 4% solution of sodium bicarbonate.

2.4. Statistical analysis

All data are expressed as the arithmetic means ± S.E.M. The mean arterial blood pressures and the pressor responses to noradrenaline were compared by analysis of variance (ANOVA). Further analysis was performed by using Scheffe's F-test for multiple comparison in cases where ANOVA showed significant differences. Statistical significance was defined as $P < 0.05$.

3. Results

3.1. Effects of the infusion of the various drugs on the mean arterial blood pressure

The mean arterial blood pressures just before the noradrenaline challenge are shown in Table 1. In the PAF group, the mean arterial blood pressure after 60 min of PAF was significantly lower than the control. In the PAF + L-NMMA group, the mean arterial blood

Table 1
The mean arterial blood pressures (MABPs) just before the administration of noradrenaline

Group	MABP (mm Hg)
Control (PAF vehicle)	64.0 ± 3.2
PAF	49.0 ± 2.6 *
PAF + L-NMMA (30)	61.7 ± 2.1
PAF + indomethacin	56.2 ± 1.4
PAF + sodium bicarbonate	51.8 ± 2.1 *
PAF vehicle + L-NMMA (3)	87.0 ± 8.4 *
PAF vehicle + L-NMMA (30)	148.3 ± 4.1 *

The mean arterial blood pressures just before noradrenaline challenge for various treatments. PAF (30 ng/kg/min) or its vehicle (0.9% saline containing 0.25% bovine serum albumin) was infused for 1 h. N^G-Monomethyl-L-arginine (L-NMMA, 3 mg/kg or 30 mg/kg) was administered at 50 min. Indomethacin (5 mg/kg) or its solvent (4% sodium bicarbonate) was administered at 45 min. Each value is the mean ± S.E.M. of 6 experiments. * $P < 0.05$ compared to control.

pressure was significantly higher than in the PAF group, but there was no significant difference when compared to the control. The subsequent administration of L-arginine reduced the mean arterial blood pressure to 48.0 ± 1.9 mm Hg, which was significantly lower than the control. In the PAF + indomethacin group, the difference in mean arterial blood pressure compared to the control and the PAF group was not statistically significant. The mean arterial blood pressure of the 4% sodium bicarbonate (the indomethacin solvent) group was significantly lower than the control.

In PAF vehicle-infused rats, L-NMMA produced a dose-dependent increase in mean arterial blood pressure. A dose of 30 mg/kg L-NMMA produced a marked increase in mean arterial blood pressure to 148.3 ± 4.1 mm Hg.

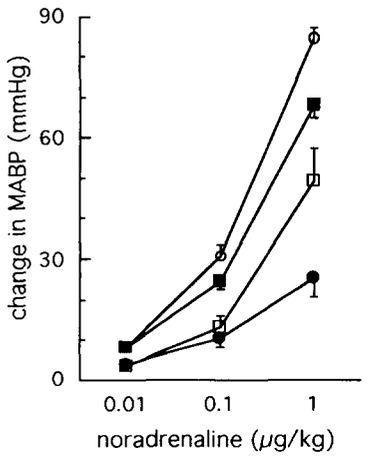

Fig. 1. The effects of L-NMMA and L-arginine on PAF-induced hyporeactivity to noradrenaline (NA, 10 ng–1 μg/kg) in pithed rats. Infusion of PAF (30 ng/kg/min, ●) for 60 min attenuated pressor responses to NA significantly compared to the control (○). Treatment with L-NMMA (30 mg/kg, ■) completely restored the PAF-induced hyporesponsiveness. Subsequent treatment with L-arginine (100 mg/kg, □) reduced the NA pressor responses again with the exception of a 1 μg/kg dose of NA. Each point is the mean ± S.E.M. of six experiments.

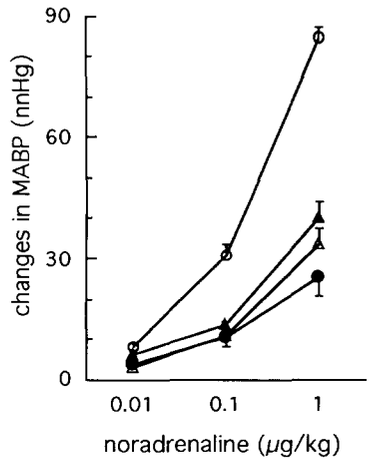

Fig. 2. The effects of indomethacin and its vehicle on PAF-induced hyporeactivity to NA (10 ng–1 μg/kg) in pithed rats. The administration of indomethacin (5 mg/kg, ▲) did not cause a significant restoration of PAF-induced hyporesponsiveness (●). The indomethacin solvent (4% sodium bicarbonate, △) produced no significant effect. Open circles show the control. Each point is the mean ± S.E.M. of six experiments.

3.2. Effects of L-NMMA and indomethacin on the PAF-induced hyporesponsiveness to noradrenaline

Infusion of PAF significantly impaired the pressor response to noradrenaline compared to the control (Fig. 1). Treatment with L-NMMA (30 mg/kg) re-

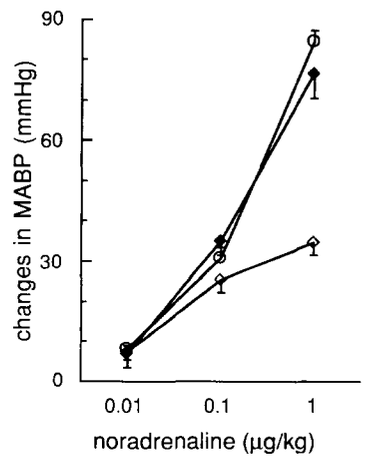

Fig. 3. The effects of L-NMMA on responsiveness to NA (10 ng–1 μg/kg) in pithed rats infused with the PAF vehicle. L-NMMA (3 mg/kg, ◆) produced no significant effect on the pressor responses to NA compared to the control (○). L-NMMA (30 mg/kg, ◇) significantly reduced the pressor responses to 1 μg/kg NA. Each point is the mean ± S.E.M. of six experiments.

stored the PAF-induced hyporesponsiveness for all doses of noradrenaline. Subsequent administration of L-arginine (100 mg/kg) induced a significant reduction in pressor responsiveness in all cases except when a dosage of 1 μg/kg noradrenaline was used (Fig. 1). Indomethacin had little effect on the PAF-induced hyporesponsiveness (Fig. 2). The indomethacin vehicle (4% sodium bicarbonate) had no effect on the PAF-induced hyporesponsiveness.

In PAF vehicle-infused rats, 3 mg/kg L-NMMA showed no significant effect on the pressor responses compared to the control. A 30 mg/kg dose of L-NMMA produced a significant attenuation of the pressor response to 1 μg/kg noradrenaline, although it did not affect reactivity to 10 and 100 ng/kg noradrenaline (Fig. 3).

4. Discussion

The principal findings of this study are: (1) that continuous infusion of PAF caused hypotension and an impaired pressor response to noradrenaline within 1 h of administration, (2) that L-NMMA restored the PAF-induced hypotension and vascular hyporesponsiveness to their original levels, (3) that indomethacin did not restore the PAF-induced hyporeactivity to noradrenaline.

4.1. Experimental model

We chose the pithed rat as the experimental model because: (1) there is no intrinsic sympathetic nerve activity and compensatory reflex in the pithed rat (Gray et al., 1990), and (2) there is no anesthetic effect on pressor responsiveness. In addition, anesthetics are thought to affect the pressor response of nitric oxide synthase inhibitors (Wang et al., 1991). To avoid any anesthetic effect, we used the inhaled anesthetic isoflurane, because isoflurane is eliminated from the body more rapidly than ether or halothane (Eger, 1994). Furthermore, we waited for 1 h after the termination of isoflurane administration to enable the animal's condition to stabilize.

4.2. Nitric oxide and PAF-induced vascular hyporesponsivenss

This study suggests that an enhanced release of NO contributes to the PAF-induced hyporeactivity to noradrenaline which occurs within 1 h of treatment because: (1) administration of L-NMMA restored the hyporeactivity, (2) administration of L-arginine after L-NMMA treatment reproduced the hyporeactivity, (3) administration of L-NMMA did not increase the pressor response to noradrenaline in vehicle-treated animals.

PAF is known to cause endothelium-dependent relaxation of isolated rat blood vessels (mesenteric artery and thoracic aorta) by stimulating the production of NO (Chiba et al., 1990; Moritoki et al., 1992). It is also known that there are two different classes of nitric oxide synthase, constitutive, calcium-dependent nitric oxide synthase and inducible, calcium-independent nitric oxide synthase (Moncada, 1992). PAF-induced acute hypotension is thought to be mediated in part by the generation of NO from the constitutive isoform of nitric oxide synthase (Szabó et al., 1993). These authors have also reported that administration of PAF causes the induction of calcium-independent nitric oxide synthase activity in the lung within 3 h in anesthetized rats (Szabó et al., 1993). As the infusion time of PAF was relatively short (1 h) in our experiment, PAF seemed to activate the constitutive nitric oxide synthase and not the inducible nitric oxide synthase, resulting in the excessive formation of NO.

Although 30 mg/kg L-NMMA raised the blood pressure in PAF-treated rats, this increase was less than that observed in PAF vehicle-infused rats. Similar results are reported for endotoxin-treated pithed rats (Guc et al., 1992). These findings contrast with the results of a study in which L-NMMA-induced hypertension was significantly enhanced in anesthetized dogs treated with tumor necrosis factor (Kilbourn et al., 1990), and of a study in which hypertension was observed to be of the same magnitude in both endotoxin-treated and control rats (Gray et al., 1991). The discrepancies mentioned above may reflect differences in the degree of nitric oxide synthase activation. Alternatively, there is also the possibility that the dose of L-NMMA (30 mg/kg) used in this study may have inhibited nitric oxide synthase submaximally. Rees et al. (1989) have found that 30 mg/kg L-NMMA is submaximal in increasing the blood pressure of anesthetized rabbits.

4.3. Nitric oxide synthase inhibitors and vascular responsiveness

It has been reported that L-NMMA (30 mg/kg) and another nitric oxide synthase inhibitor, N^G-nitro-L-arginine methyl ester (L-NAME, 1 mg/kg), elevate the mean arterial blood pressure in anesthetized rats but have no effect on the pressor responses to noradrenaline (Gray et al., 1991). Guc et al. (1992) have reported that 4 mg/kg L-NAME increases the mean arterial blood pressure with augmented pressor responses to noradrenaline in pithed rats. They suggest that the pressor effect of L-NAME is important in preventing endotoxin-induced hyporesponsiveness.

As shown in Fig. 3 and Table 1, in this study the responsiveness to noradrenaline was not augmented by L-NMMA, regardless of the mean arterial blood pressure just before the noradrenaline challenge. Our results are consistent with Gray's study (Gray et al., 1991) in which an anesthetized rat model was used. The downward shift of the dose-response curve in the 30 mg/kg L-NMMA group must be derived from the blood pressure ceiling phenomenon. In other words, the blood pressure in the 30 mg/kg L-NMMA group is considered to have almost reached the maximum point of elevation at a dose of 100 ng/kg noradrenaline. Furthermore, the reduced cardiac output due to increased systemic vascular resistance and/or the direct negative inotropic effect of the nitric oxide synthase inhibitor (Gardiner et al., 1990) may also contribute to the hyporeactivity induced by 30 mg/kg L-NMMA.

4.4. Cyclo-oxygenase products and vascular hyporesponsiveness

Prostaglandins have been extensively studied in models of endotoxemia and septic shock. Treatment with cyclo-oxygenase enzyme inhibitors before induction of sepsis or infusion of lipopolysaccharide prevents the development of vascular hyporesponsiveness (Fink et al., 1984; Gray et al., 1990). PAF antagonists have been shown to diminish endotoxin-induced increases in the plasma concentrations of prostaglandin E_2 and tumor necrosis factor (Ravinovici et al., 1990). Prostaglandin E_2 has been implicated in the impairment of the vascular responsiveness observed in the early stage of endotoxemia (Gray et al., 1990). It has also become increasingly apparent that the catabolism and biosynthesis of PAF and arachidonic acid are closely interrelated in several types of cell (Chilton et al., 1991). These observations suggest a possible role for cyclo-oxygenase products in the PAF-induced vascular hyporeactivity.

However, in this study, the administration of indomethacin during PAF infusion at a dose which inhibits prostaglandin synthesis did not restore the pressor responses to noradrenaline. These data suggest that cyclo-oxygenase products do not play a major role in PAF-induced hyporesponsiveness to noradrenaline in pithed rats.

In summary, this study shows that nitric oxide contributes to the PAF-induced hyporeactivity to noradrenaline, whereas cyclo-oxygenase products do not play a major role in the hyporesponsiveness.

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