Platelet Activating Factor: A Potent Constrictor of Cerebral Arterioles in Newborn Pigs

William M. Armstead, Massroor Pourcyrous, Robert Mirro, Charles W. Leffler, and David W. Busija

This study characterized the nature of the response to platelet activating factor (PAF) in the cerebral microcirculation of the newborn pig. Pial arterioles were observed directly using a closed cranial window in chloralose-anesthetized piglets. Topical application of 10–100 ng/ml PAF produced dose-dependent decreases in pial arteriolar diameter; diameters were 193 ± 27 μm for control, 167 ± 25 μm at 10 ng/ml, and 129 ± 21 μm at 100 ng/ml. Topical application of 30–300 ng/ml norepinephrine and 3–30 ng/ml U46619, a purported thromboxane A, receptor agonist, also produced dose-dependent decreases in pial arteriolar diameter. After topical administration of U66985 (1 μg/ml), a putative PAF antagonist, responses to PAF were attenuated significantly, but responses to norepinephrine and U46619 were unchanged. Moreover, intravenously administered U66985 (0.1 mg/kg) antagonized PAF responses as well. Responses to PAF were unchanged after cyclooxygenase and leukotriene receptor inhibition. Further, PAF did not increase cortical subarachnoidal cerebrospinal fluid prostaglandin or leukotriene levels. These data indicate that PAF is a potent constrictor of cerebral arterioles in newborn pigs and that its mechanism of action is independent of formation of cyclooxygenase and lipoxygenase products of arachidonic acid metabolism. These data also suggest that U66985 may be a selective PAF antagonist that crosses the blood-brain barrier. Since PAF is an endogenous lipid released from a variety of tissues and may be an important mediator of inflammation and allergic reaction, PAF could be involved in the pathophysiology of the cerebral circulation in the perinatal period. (Circulation Research 1988;62:1-7)

Platelet activating factor (PAF, PAF-acether, 1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholine) is an endogenous lipid released from various cells including basophils, neutrophils, macrophages, and endothelial cells, after immune or chemical challenges.1-3 In platelet-rich plasma, PAF produces platelet aggregation by a process that has been considered a third pathway of platelet aggregation.4 In addition to its effect on platelets, PAF induces systemic hypotension, bronchoconstriction, and coronary constriction, as well as increased systemic microvascular permeability.5-7 Moreover, PAF may play a role in various pathophysiologic states, including endotoxic shock.8 The mechanism of PAF’s action is controversial, but many authors have suggested that its effects may be mediated through the formation of cyclooxygenase and/or lipoxygenase products of arachidonic acid metabolism.9-11 Though the effects of PAF on several regional vascular beds have been investigated, the effects of PAF on cerebral vessels are unknown. Pial arterioles are important resistance vessels in the cerebral circulation.12 The risk of cerebral trauma during the perinatal period is considerable due to cerebral hemorrhage, ischemia, asphyxia, and infection, conditions which may predispose the infiltration of cells such as neutrophils and macrophages into the brain and the subsequent release of PAF. Therefore, the effects of PAF on pial arterioles of newborn pigs were examined and the following parameters were determined: 1) vasoactive effects of PAF; 2) whether responses to PAF are mediated by eicosanoids; and 3) effectiveness and specificity of blockade of the actions of PAF.

Materials and Methods

Sixteen piglets (3 animals were 2 days old, 4 were 4 days old, 3 were 5 days old, 3 were 6 days old, and 3 were 7 days old; 0.6–2.3 kg) of either sex were used in these experiments. Piglets were anesthetized with ketamine hydrochloride (33 mg/kg i.m.) and acepromazine (3.3 mg/kg i.m.) and maintained with chloralose (30–50 mg/kg initially, supplemented with 5 mg/kg/hr i.v.). A catheter was inserted into a femoral artery to record blood pressure and to sample for blood gases and pH. Blood pressure was determined using a Statham pressure transducer and a Gould recorder (Cleveland, Ohio). Another catheter was placed in a femoral vein for injection of drugs. The trachea was cannulated, and the animals ventilated with room air using a Harvard small animal respirator. Body temperature was maintained at 37–38° C with a water-circulating heating pad.

For insertion of the cranial window, the scalp was cut and retracted over the cut bone edge. Using a
method similar to that described by Levasseur et al., a cranial window was placed into the hole and cemented into place with dental acrylic. The space under the window was filled with artificial cerebrospinal fluid (CSF) of the following composition (mg): KCl 220, MgCl₂ 132, CaCl₂ 221, NaCl 7,710, urea 402, dextrose 665, NaHCO₃ 2,066; pH was 7.33, Pco₂ was 46 mm Hg, and Po₂ was 43 mm Hg. We have previously shown that this artificial CSF does not affect resting pial arterial diameter in piglets.

Pial arterioles were observed with a Wild M75 trinocular stereomicroscope (Heerbruss, F.R.G.), television camera (model VC-6SSL, Dage-MIT, Michigan City, Ind.) mounted on the microscope, and video monitor (model CT 1930 V, Panasonic Corporation, Secaucus, N.J.). Vascular diameter was measured with a video microscaler (model VPA 1000, For-A-Corp., Los Angeles, Calif.).

Protocol

Pial arterial diameter was determined 1–4 minutes following infusion under the window of artificial CSF containing no drug and after infusion of CSF containing 10, 30, and 100 ng/ml of PAF (C16 analogue; Sigma Chemical Co., St. Louis, Mo.). Diameters were also measured 10–15 minutes after flushing the highest dose of PAF out with CSF containing no drug. Typically, 1–2 ml of CSF were flushed through the window over 30 seconds.

Needles inserted into the sides of the window allowed infusion of CSF under the window and runoff of excess CSF. The peak response was measured and was constant over 2–4 minutes after administration of CSF containing PAF. Infusion of CSF without PAF had no effect on diameter.

To determine whether constrictor responses to PAF could be prevented by PAF receptor blockade, effects of PAF were determined before and after topical and intravenous addition of U66985 (1 μg/ml topical, 0.1 mg/kg i.v.; The Upjohn Company, Kalamazoo, Mich.). To assess the specificity of the inhibitor, we also investigated the effects of 30–300 ng/ml (−)-norepinephrine hydrochloride (Sigma) and 3–30 ng/ml U46619 (Upjohn) on pial arterioles before and after topical application of U66985 (1 μg/ml). Small aliquots of the vehicles for PAF, U66985, norepinephrine, and U46619 (0.9% saline for norepinephrine; ethanol for all others) were added to CSF that was infused under the window. This CSF vehicle had no effect on arteriolar diameter. To investigate the possibility that PAF-induced constriction was mediated by eicosanoids, responses to topically applied PAF were obtained before and after indomethacin (5 mg/kg i.v.) and FPL55712 (10 mg/kg i.v.). All working drug solutions were made fresh on the day of use. Specifically, the PAF stock solution (1 mg/ml) in ethanol was stored at −70°C until the day of use when it was diluted to the working solution of 100 μg/ml in ethanol. Similarly, U46619 and U66985 in ethanol were also stored at −70°C until the day of use. Norepinephrine (100 μg/ml in saline) was made fresh on the day of use and stored in the dark.

Eicosanoid Analysis

CSF samples were analyzed for eicosanoids using radioimmunoassay by methods described previously. Antibodies to 6-keto prostaglandin F₁α (6-keto PGF₁α), thromboxane (TX) B₂, and prostaglandin E₂ (PGE₂) were produced in rabbits immunized with prostaglandins coupled to thyroglobulin using the mixed anhydride method. The leukotriene (LT) C₄ antibody was purchased from New England Nuclear, Boston, Mass. Cross-reactivities of the prostaglandin antibodies with other eicosanoids tested were all below 1%. The LTC₄ antibody cross-reacts extensively (about 50%) with LTD₄ and to a lesser extent (9%) with LTE₄. The assays were performed in gelatin-Tris buffer using the appropriate tritiated eicosanoid. After 24 hours of incubation at 4°C, the free fraction was separated from that bound to antibody by precipitating the rabbit antibodies with anti-rabbit γ-globulin and 60% saturated ammonium sulfate. Data were handled by computer, with determination of second order regression of free tracer over tracer bound to antibody against unlabelled eicosanoid by the method of least squares. All unknowns were assayed at three dilutions; the unknown dilution curves and the standard curve had to be parallel before the results were used.

Statistical Analyses

Pial arteriolar diameter and systemic arterial pressure were analyzed using repeated measures analysis of variance. If the F value was significant, the Student-Newman-Keuls test was performed. An α level of p<0.05 was considered significant in all statistical tests. Values are represented as mean±SEM of raw values or as percent changes from control values.

Results

Topically applied PAF produced dose-dependent constrictor effects on pial arterioles, whereas systemic arterial pressure was unchanged (Table 1). Constriction was significant compared with control at all concentrations, the order being control<10 ng/ml<30 ng/ml=100 ng/ml. When expressed as a percent, these responses represent 14±3, 25±4, and 33±5% decreases in arterial diameter. The initial diameter, 193±27 μm, and the recovery diameter, 176±22 μm, were not significantly different. The artificial CSF had no effect on pial arteriolar diameter since the resting diameter was 194±27 μm and the diameter after CSF vehicle was 193±27 μm.

The purported PAF antagonist U66985 (1 μg/ml), applied topically with the agonist, was effective in blocking pial arteriolar constriction to PAF (Table 1, Figure 1). When compared with corresponding values before antagonist administration, the magnitude of the response was different only at 30 and 100 ng/ml (Table 1). When administered intravenously, U66985 (0.1 mg/kg) similarly antagonized responses to PAF. The diameters before blockade were 202±27, 178±23, 161±22, and 149±25 μm for control, 10, 30, and 100 ng/ml PAF, respectively, but after administration of U66985 (0.1 mg/kg i.v.), the diameters...
Table 1. Influence of PAF, U46619, and Norepinephrine on Pial Arteriolar Diameter in Newborn Pigs

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<th>Arteriolar diameter (μm)</th>
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<td>Before blockade</td>
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<td>Control</td>
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<tr>
<td>Arteriolar diameter</td>
<td>193 ± 27</td>
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<td>Before blockade</td>
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<tr>
<td>Arteriolar diameter</td>
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<td>138 ± 15†</td>
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U66985* (n = 5)

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<tr>
<th>Arteriolar diameter</th>
<th>Mean arterial pressure (mm Hg)</th>
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<tr>
<td></td>
<td>Before blockade</td>
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<tr>
<td>Arteriolar diameter</td>
<td>156 ± 24</td>
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<td></td>
<td>143 ± 21†</td>
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<td>130 ± 20†</td>
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<td>Mean arterial pressure</td>
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Norepinephrine (n = 5)

Values are mean ± SEM.

were 182 ± 38, 185 ± 39, 182 ± 38, and 186 ± 35 μm for control, 10, 30, and 100 ng/ml PAF, respectively. U66985 had no significant effect on pial arterial diameter or systemic arterial pressure when administered topically or intravenously. For these experiments, the diameter was 176 ± 22 μm (mean arterial pressure [MAP], 53 ± 2 mm Hg) under resting conditions and 176 ± 22 μm (MAP, 53 ± 2 mm Hg) after topical U66985. Similar results were obtained after U66985 given intravenously.

Levels of eicosanoids in the cortical subarachnoid fluid under the cranial window were measured under control conditions and at the end of 5 minutes following topical application of 100 ng/ml PAF. In two animals of this series, a higher concentration (10 μg/ml) was used. 6-keto-PGF1α, TXB2, and PGE2 levels were unchanged after administration of 100 ng/ml PAF, and levels of LTC4 were nondetectable (< 100 pg/ml) during control and during 100 ng/ml PAF application (Figure 2). All eicosanoid levels were unchanged after 10 μg/ml PAF as well. Moreover, responses to PAF were unchanged after indomethacin (5 mg/kg i.v.) and FPL55712 (10 mg/kg i.v.; Table 2). This dose of FPL55712 significantly blocked responses to topically applied LTC4, the diameters being 131 ± 17 μm for control and 112 ± 17 μm for 1,000 ng/ml LTC4 before and 119 ± 13 μm for control and 119 ± 13 μm for 1,000 ng/ml LTC4 after FPL55712. Indomethacin and FPL55712 had no significant effect on systemic arterial pressure 30 minutes after administration, when pial arteriolar diameter was measured (Table 2).

U46619 and norepinephrine also produced dose-dependent constrictor effects on pial arterioles (Table 1). Constriction was significant compared with control at all concentrations, the order for U46619 being control<3 ng/ml<10 ng/ml<30 ng/ml, and the order for norepinephrine being control<30 ng/ml<100 ng/ml = 300 ng/ml. When expressed as a percent, these responses represent 19 ± 5, 31 ± 3, and 46 ± 5% decreases in arterial diameter. On a molar weight basis, the order of constrictor potency was

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**Figure 1.** Effect of PAF (30 ng/ml), U46619 (10 ng/ml), and norepinephrine (100 ng/ml) in the control period and each agent plus U66985 (1 μg/ml) on pial arteriolar diameter. Values are mean ± SEM. *p<0.05 compared with control.

**Figure 2.** Effect of PAF (100 ng/ml) on concentration of eicosanoids in cortical subarachnoid CSF of piglets (n = 7 for 6-keto-PGF1α, n = 7 for TXB2, n = 7 for PGE2, n = 5 for LTC4). Values are mean ± SEM. ND, nondetectable (less than 100 pg/ml).
Table 2. Influence of Indomethacin and FPL55712 on Pial Arteriolar Responses to PAF in Newborn Pigs

<table>
<thead>
<tr>
<th>Arteriolar diameter (μm)</th>
<th>Before blockade</th>
<th>Control 10 ng/ml</th>
<th>30 ng/ml</th>
<th>100 ng/ml</th>
<th>After indomethacin*</th>
<th>Control 10 ng/ml</th>
<th>30 ng/ml</th>
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<td></td>
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<td>167 ± 29</td>
<td>146 ± 28†</td>
<td>122 ± 24†</td>
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<td>161 ± 29</td>
<td>141 ± 26†</td>
<td>126 ± 25†</td>
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<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>53 ± 5</td>
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<tr>
<th>Arteriolar diameter (μm)</th>
<th>Before blockade</th>
<th>Control 10 ng/ml</th>
<th>30 ng/ml</th>
<th>100 ng/ml</th>
<th>After FPL55712†</th>
<th>Control 10 ng/ml</th>
<th>30 ng/ml</th>
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<td></td>
<td>129 ± 14</td>
<td>107 ± 14†</td>
<td>90 ± 13†</td>
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<td>119 ± 13†</td>
<td>99 ± 13</td>
<td>87 ± 11†</td>
<td>74 ± 10†</td>
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<td>Mean arterial pressure (mm Hg)</td>
<td>50 ± 6</td>
<td>50 ± 6</td>
<td>50 ± 6</td>
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<td>47 ± 2</td>
<td>46 ± 2</td>
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*Indomethacin, 5 mg/kg i.v.; †p<0.05 compared to corresponding control. ††FPL55712, 10 mg/kg i.v. Values are mean ± SEM.

U46619 >> norepinephrine (Figure 3). The initial diameters (171 ± 12 and 156 ± 24 μm) and recovery diameters (166 ± 15 and 144 ± 19 μm) for U46619 and norepinephrine, respectively, were not significantly different.

In contrast to PAF, responses to U46619 and norepinephrine were unchanged after administration of U66985 (1 μg/ml; Table 1 and Figure 1). When compared with corresponding values before antagonist administration, the magnitudes of responses for norepinephrine were different at 100 and 300 ng/ml due to the small, nonsignificant difference in initial diameters.

Blood gases were measured at the beginning and at the end of the experiment. The values for pH, PCO₂, and PO₂, obtained initially were 7.49 ± 0.02, 28 ± 2, and 92 ± 4, while those obtained at the end of the experiment were 7.49 ± 0.02, 27 ± 2, and 83 ± 5, respectively (n = 13).

Pial arteriolar response to PAF and U46619 did not depend upon the initial size of the vessel. Specifically, the equation for the line relating initial diameter with percent change in diameter for PAF was y = -0.044X + 43.79; r = -0.33; n = 16; the line for U46619 was y = 0.048X + 54.16; r = -0.22; n = 5. The slopes of these lines were not significantly different from zero. We have previously shown that responses to norepinephrine are not dependent on the initial diameter.¹⁴

**Discussion**

Results of the present study show that PAF has potent constrictor effects on pial arterioles of newborn pigs in vivo. Since the CSF levels of 6-keto-PGF₁α, TXB₂, PGE₂, and LTC₄ were unchanged after the administration of PAF, these data suggest that responses to PAF are independent of formation of cyclooxygenase and lipoxygenase products of arachidonic acid metabolism. Moreover, since these decreases in diameter were unchanged after indomethacin and FPL55712, these data further suggest that responses to PAF are not mediated via the formation of eicosanoids. Thus, PAF appears to potently directly constrict pial arteries of newborn pigs. The intravenous dose of indomethacin used in this study has been previously shown to cross the blood–brain barrier and inhibit the formation of cyclooxygenase metabolites.¹⁶ Similarly, topically applied FPL55712, 5,000 ng/ml, previously has been shown to inhibit responses to LTC₄.¹⁷ The intravenous dose of FPL55712 used in this study (10 mg/kg) also decreased responses to LTC₄, suggesting that it, too, crosses the blood-brain barrier.

Responses to PAF were blocked by the topical or intravenous administration of U66985, suggesting that this antagonist crosses the blood-brain barrier. Inasmuch as norepinephrine and U46619, an agent thought to mimic the actions of TXA₂,¹⁸ also produced dose-dependent decreases in pial arterial diameter that were unchanged after the administration of U66985, these data further suggest that U66985 may be a selective PAF antagonist. These results, indicating that the responses resulted from activation of PAF receptors, provide direct evidence that pial arteries are very responsive to PAF in the immediate neonatal period.

Since the discovery of the chemical structure of PAF as 1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholine,¹⁹ this phospholipid has been suggested to play a role in various pathophysiologic states. PAF is released by various cells, including basophils, neutrophils, macrophages, and endothelial cells after immune or chemical challenge.¹,¹³ In platelet-rich plasma, PAF produces platelet aggregation by a process that has been considered to be a third pathway of platelet aggregation.⁴ PAF reduces coronary flow and contractile force when administered to isolated perfused guinea pig hearts.²¹ When administered intravenously, PAF elicits
an anaphylactic reaction characterized by hypotension, leukopenia, thrombocytopenia, bronchoconstriction, and increased microvascular permeability. Moreover, PAF can produce sudden death at high doses. The analogies between endotoxic shock and the effects of systemically administered PAF have been noted. Although there have been many studies on the in vitro and in vivo effects of PAF, the mechanism of its action remains elusive. PAF exerts both platelet-dependent and platelet-independent actions in the cardiovascular system. It has been suggested that cyclooxygenase- and lipooxygenase-derived metabolites contribute to alterations in pulmonary hemodynamics and development of pulmonary edema seen subsequent to the administration of PAF. In rat isolated perfused lungs, PAF induces vasoconstriction accompanied by release of leukotrienes and antagonized by diethylcarbamazine, but in the awake sheep, PAF elicits pulmonary vasoconstriction accompanied by an increase in TXB, formation and antagonized by meclofenamate. Similarly, it has been suggested that the coronary vasoconstriction induced by PAF may be mediated primarily via the release of leukotrienes on the basis of the inhibitory actions of BW755C and FPL55712. Others, however, ascribe a more important role for TXA, in the mediation of coronary constriction and ischemia seen with PAF. In contrast, our results indicate that constrictor effects of PAF on the cerebral vasculature do not involve eicosanoids. Thus, the mechanisms by which PAF produces vasoconstriction appear to be different in different vascular beds.

Selective antagonists are useful tools for defining the biologic role of a purportedly active mediator. The substantial inhibition of a pathologic situation by a specific PAF antagonist would indicate the importance of PAF as a mediator of that pathology. Such antagonists could have the added potential of becoming efficacious therapeutic agents. Previously described PAF antagonists have demonstrated the role of PAF in animal models of disease. CV3988, a structural analogue of PAF, decreased the hypotension and improved the survival rate for endotoxin-treated rats. Similarly, the PAF antagonist kadsurenone reversed the hypotension induced by endotoxin infusion in rats. Moreover, the natural product antagonist BN52021 prevented the antigen-induced changes in coronary pressure and contractile force seen in isolated hearts from passively sensitized guinea pigs, suggesting that this agent may be of therapeutic value in cardiac anaphylaxis. Recently, U66985, another structural analogue of PAF, has been shown to be a PAF antagonist. In our experiments, we investigated the influence of PAF on pial arterial diameter and further characterized the selectivity of the purported PAF antagonist U66985. The dose range of PAF used in this study is similar to values of PAF previously reported to be present in rat blood after the administration of endotoxin. The concentration of PAF in the CSF is not known. The present study shows that PAF can constrict cerebral arterioles in vivo via receptors sensitive to blockade by U66985. Whether PAF can reach sufficient levels at these receptors during physiologic or pathophysiologic conditions cannot be stated. On a molar basis, U46619 was a slightly more potent constrictor than PAF, but both agents were much more potent than norepinephrine. On the basis of Poiseuille's law, constriction of the magnitude induced by PAF would have substantial effects on resistance. Moreover, pial arterioles are important resistance vessels in the cerebral circulation. The present report is the first to document that PAF is a potent constrictor in the cerebral circulation. Furthermore, pharmacologic and biochemical results of this study are in agreement and suggest that PAF-induced cerebral vasoconstriction does not require the production of cerebral vasoconstrictor metabolites of arachidonic acid via the cyclooxygenase or lipooxygenase pathways. In previous studies, we have found that other stimuli such as asphyxia, hemorrhagic hypotension, and topical application of norepinephrine increase cerebral prostanoij production, indicating that the prostanoij concentration in cortical subarachnoid fluid can change rapidly in response to stimuli that increase synthesis. Thus, such an increased synthesis could be detected using these techniques if it occurred. Although it should be noted that in experiments in which CSF was assayed for prostanoij levels, the PAF concentration level chosen for investigation was in general 100 ng/ml; a higher concentration (10 µg/ml) was investigated in two animals of this series. Even at this very high concentration, no significant changes were noted in prostanoij levels. However, a small, nonsignificant increase was seen in 6-keto-PGF, and PGE, levels. This increase in vasodilator prostanoij levels may reflect either a primary stimulation induced by PAF or may be the expression of increased dilator prostanoij synthesis in response to PAF's potentiating action. PAF has been shown to increase the production of vasodilator prostaglandins in several tissues. Furthermore, if a PAF receptor antagonist is to be used to determine the role of PAF in different physiologic and pathologic states, then it is of great importance that this agent be very selective. Data from the present study suggest that U66985 is a potent and very selective PAF antagonist. Since it crosses the blood-brain barrier and has no adverse hemodynamic effects itself, this antagonist may be beneficial as a therapeutic agent and very valuable in future PAF studies.

It is possible that PAF could produce vasoconstriction by a receptor-mediated decrease in local metabolism as well as by a direct receptor-mediated vasoconstriction. Which mechanism is involved cannot be determined from the design employed. Since PAF would be released over a wide area of the brain and would have access to neurons as well as to blood vessels under pathologic conditions, it seems logical to apply it broadly, rather than by microapplication.

The risk of cerebral trauma during the perinatal period is considerable, due to cerebral hemorrhage, ischemia, asphyxia, and infection, conditions that may predispose the infiltration of cells such as neutrophils...
and macrophages into the brain and the subsequent release of PAF. Infants can become hypoxic-ischemic at birth, and a large percent of low birth weight (≤1,000 g) infants suffer from intraventricular hemorrhage. Under conditions of cerebrovascular stress in neonates, PAF may be released, which would have detrimental effects on the cerebral circulation.

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