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PLATELET-ACTIVATING FACTOR ANTAGONISTS

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INTRODUCTION

History

In 1966 Barbaro & Zvaifler (1) noted the release of histamine from rabbit platelets in the presence of antigen and leukocytes. This activity was confirmed and described as complement independent (2, 3). Henson (4, 5) demonstrated that this labile factor was released from leukocytes by a calcium- and temperature-dependent process. The parameters surrounding the release of this factor and its potential role in immune complex deposition were described by Benveniste (6, 7) who first coined the term *platelet-activating factor* (PAF). Henson & Pinckard gave PAF a potential role in pathology when they described it as the mediator of IgE anaphylaxis in the rabbit (8, 9). After this early characterization, research interest with PAF focused on the structural determination of the molecule (10–12). In 1979 two laboratories (13, 14) chemically described PAF as acetyl glycerol ether phosphorylcholine (1-O-hexadecyl/octadecyl-2-acetyl-*sn*-glycerol-3-phosphorylcholine; Figure 1). A third laboratory determined that PAF was identical to a renal medullary hypotensive phospholipid (APRL) that was being investigated independently (15). Biosynthetic PAF was determined to be one of a family of active phospholipids of varying potency with structural modifications primarily in the length of the alkyl chain at position one (16). These observations, plus the determination that PAF activates many cells other than platelets, caused investigators to question the appropriateness of the term *platelet-activating factor*. Alternate terms used were *acetyl glycerol ether phosphorylcholine* (AGEPC) or *PAF-acether*. Investigators in the field and the authors of a recent review (17) agree that the term *PAF* should remain in use.

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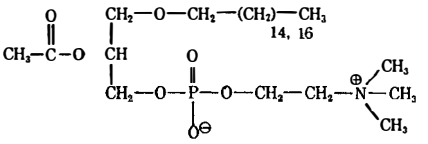

Figure 1 PAF structure.

The structural determination and synthetic preparation of PAF enhanced the interest in, and number of investigators using, this autocoid substance. The short biological half-life (18) and the concurrent release of other mediators in pathological models (19) have impeded the determination of PAF's importance in disease. The possession of specific PAF antagonists would aid the examination of the pathophysiological role of PAF. This review describes the evolution of such antagonists and, where possible, discusses the information on the potential role of PAF provided by their use. We also refer the reader to several recent reviews on this subject (17, 19–21).

Pharmacology of PAF

The association of PAF in serum sickness was postulated (6–8, 22) and substantiated (12), suggesting that this agent was indeed an autocoid mediator of inflammation. The most prominent and species-universal effect of PAF is increased vascular permeability (23–25). Plasma molecules as large as very low density lipoproteins extravasate from the vascular system when PAF is infused (25). This enhanced permeability is suggested to occur at postcapillary venules (24, 26). At low doses the effect of PAF is direct and does not require the participation of leukocytes (26, 27) or platelets (27). The concentration of PAF required to induce extravasation in the guinea pig is severalfold less than that needed for the extravasation of leukotrienes or histamine (28, 29).

Early quantitation of PAF was based on platelet-aggregation and -release reactions (5). The activation of platelets occurs by specific, saturable binding of PAF to a membrane receptor (30, 31). Platelet sensitivity to PAF varies greatly among the species evaluated; the rabbit and guinea pig (13, 32) are the most sensitive. The human, baboon, and canine platelets demonstrate intermediate sensitivity (32), and the rhesus and cebus apella primate platelets have minimal PAF sensitivity (33, 34). Rat (35, 36) and mouse (36) platelets are considered unresponsive to PAF and lack PAF receptors (37). The infusion of PAF into the sensitive species, guinea pig (38), rabbit (39), baboon (40), and man (J. Benveniste, personal communication), results in rapid and pronounced thrombocytopenia, which reverses within one hour. The relationship of this platelet aggregate formation with vascular thrombolic states has not been clearly defined. The topical superinfusion of PAF on the guinea pig

mesentery over an injured arterial segment produces a platelet thrombus (41). This observation suggests that local vascular PAF production could lead or contribute to occlusive thrombotic events.

The platelet's sensitivity to PAF also appears related to the potential of this mediator to induce bronchoconstriction (38). Those species with reactive platelets, such as the guinea pig (38), rabbit (39), baboon (40), and man (42–45), also demonstrate bronchoconstriction with PAF infusion. Conversely, those species with minimal or reduced platelet sensitivity, such as the rat (35), rhesus primate, and cebus apella primate (33, 34), also demonstrate reduced or absent bronchoconstrictive responses (46). Platelet accumulation within the guinea pig lung after a one-hour infusion of low PAF concentrations has been suggested to induce airways hyperreactivity (47, 48). The presence of polymorphonuclear neutrophil leukocytes and eosinophils in the lungs (49, 50) after PAF infusion suggests that all of these cells contribute to the pulmonary response induced by PAF. The human eosinophil (51) and neutrophil (31, 52) demonstrate specific saturatable membrane binding of PAF. Pulmonary tissue has a direct contractile response (31, 53–55) to PAF. PAF binds specifically to the smooth muscle membrane (31), and PAF-induced intracellular calcium mobilization in smooth muscle cells can be blocked by a PAF receptor antagonist (56). This contractile effect of PAF on bronchial smooth muscle may be more apparent after aerosol administration (57) than after intravenous infusion (33).

PAF induces hypotension, as was noted early in its investigations (58). This activity is similar to the vascular permeability effect of PAF in that it occurs in all species tested (33, 40, 59) and is a non-platelet-mediated occurrence (60). Permeability and hypotension are independent events, since hypotension occurs at lower doses, and is immediate and reversible (61), whereas the extravasation response requires 4–10 min to peak and several hours to reverse (21, 29, 40). The vascular endothelium has been suggested to be required for the hypotensive activity of PAF in the rat (62, 63), but preliminary experiments in the rabbit do not support this hypothesis (64). The hypotensive response may be the result of arteriolar dilation, especially in the splanchnic vascular bed (65). Low doses of PAF administered by intracoronary injections produce coronary vasodilation in the dog (66), but systemic administration can produce coronary constriction in the same species (67). Investigations of the hypotensive mechanism have ruled out renin inhibition, central mechanism, and α-adrenergic antagonism as possible mechanisms (68). PAF release from isolated rat kidneys (69), and the presence of PAF in urine (70) and blood (71) of control, but not anephric, individuals (71), suggests that PAF may play a role in blood-pressure regulation, as hypothesized by early investigators (58).

TECHNIQUES FOR THE DISCOVERY OF PAF ANTAGONISTS

In Vitro Assays

The interaction of PAF with cells in vitro is accompanied by a variety of responses, which, depending upon the cell type, can include chemotaxis, aggregation, granule release, enzyme secretion, increased phagocytosis, and generation of toxic oxygen radicals. The simplicity of measuring platelet aggregation and the discovery of PAF receptors on platelets (30, 31, 72, 73) have led to the use of the aggregation assay in primary screening of anti-PAF compounds (32). PAF is thought to be the most potent low-molecular-weight platelet-activating agent reported to date (74, 75). Thus, the platelet aggregation assay is a sensitive, easy-to-use receptor-mediated response (32, 74, 76) that evaluates PAF antagonists. However, several antiplatelet agents (mepacrine, PGI_2, aspirin, indomethacin) partially inhibit PAF-induced aggregation and secretion (77).

In Vivo Models

The most prominent biological effects of PAF are observed following intravenous injection. In various species, PAF injections produce thrombocytopenia, neutropenia, hemoconcentration, bronchoconstriction, hypotension, cardiac dysfunction, pulmonary hypertension, and pulmonary edema. Many of the circulatory and pulmonary alterations are identical to those occurring during IgE-mediated anaphylaxis (78). However, not all of these PAF responses are sufficiently sensitive, reproducible, or governed by dose-response relationships to be useful parameters in animal pharmacology models. To date the physiological responses to PAF that are most reproducible and often cited are hypotension, hemoconcentration, and bronchoconstriction. Although the hypotensive response from PAF can be induced in mice (79), rats (58, 59, 61, 80), guinea pigs (59), rabbits (59, 81), and dogs (59, 82), the rat is most commonly used. The first reported PAF antagonist, CV-3988, was described as an inhibitor of PAF-induced hypotension in the rat (83, 84). Other PAF receptor antagonists, including SRI 63-072 (61), ONO-6240 (85), kadsurenone (86), and BN 52021 (87), as well as nonspecific agents such as glucocorticoids (88) and thyrotropin-releasing hormone (89), effectively inhibit PAF-induced anaphylactic lethality and hypotension. Models of endogenous PAF production are gram-negative sepsis (90), endotoxin challenge (84), infusion of immune aggregates (79), and renal artery ligation with contralateral nephrectomy (91). The endotoxin and immune challenges are dose dependent in terms of their hypotensive properties (61) and are effectively inhibited by several PAF antagonists (61, 84–87). The hypotensive re-

sponse of PAF may be assumed to be receptor mediated in the rat, since specific PAF receptor antagonists immediately raise the depressed blood pressure to pre-PAF values (61, 84, 87).

Hemoconcentration results from a complete loss of selective endothelial permeability (25), leading to extravasation of plasma and elevation of hematocrit levels. Active at the picomolar range, PAF is one of the most potent inducers of increased vascular permeability identified to date (92). PAF can increase systemic (25, 93), microvascular (26, 94), and pulmonary (95–97) permeabilities. The species most sensitive to PAF-induced hemoconcentration are the guinea pig (93, 98, 99) and rabbit (23, 39), although the rat (24, 27), dog (80, 95), and primate (40, 46) exhibit this response at somewhat higher PAF challenges. The hyperpermeability effects of PAF are reproducible when PAF is given by intradermal (12, 27, 100, 101) or intravenous (39, 40, 46, 80, 93) routes. PAF antagonists SRI 63-072 (21, 46, 102), CV-3988 (29, 98, 103), BN 52021 (87, 104), kadsurenone (28, 105), and SRI 63-441 (80) are reported effective against exogenous or endogenous PAF-induced hyperpermeability and hemoconcentration effects.

Similarly, various species develop a platelet-dependent bronchoconstriction following PAF administration, of which the guinea pig (38, 106, 107) and the rabbit (54, 108) are most sensitive. Bronchoconstriction induced by intravenous PAF injection is platelet dependent and develops rapidly, whereas the aerosol PAF administration appears to be independent of platelet involvement (46, 107), develops slowly, and is markedly tachyphylactic (17). The aerosol route brings PAF to an area of the lung where alveolar macrophages would normally generate PAF in response to airborne antigens (57, 109). Several PAF antagonists inhibit PAF-related pulmonary responses, including SRI 63-072 (102), BN 52021 (53, 110), L-652-731 (111), and ONO-6240 (112).

IDENTIFIED PAF ANTAGONISTS

PAF Analogues

The structures of many PAF antagonists discussed in this review are illustrated in Figure 2. The first PAF receptor antagonist to appear in the literature was CV-3988 (83), which contains an octadecyl carbamate in position 1, a methoxy group in position 2, and a thiazolium ethyl phosphate group in position 3. In rats CV-3988 inhibits hypotension induced by PAF (83) and endotoxin (84). CV-3988 also inhibits PAF-induced hemoconcentration in the rat (84), guinea pig (29, 98), and cebus primate (113), and in the hypertensive rat it counteracts the hypotension that occurs after unclipping the renal artery

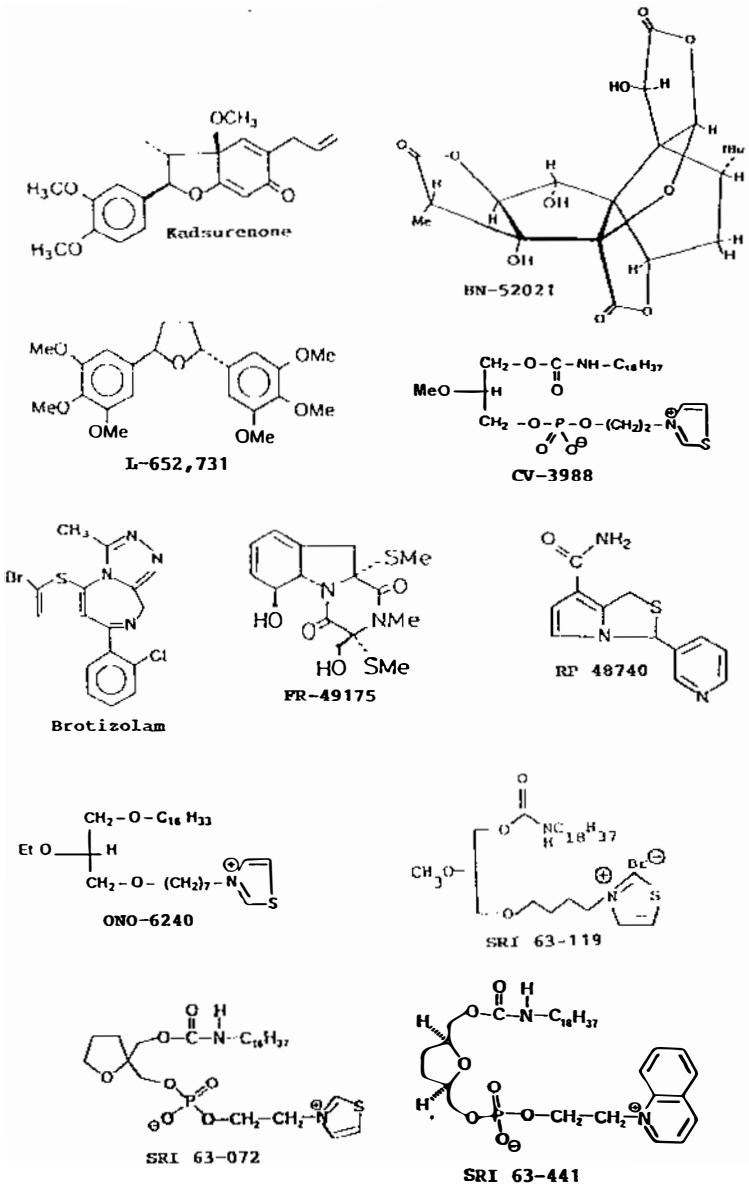

Figure 2 PAF antagonists structures.

in the one-kidney clip model (91). It also inhibits a variety of dermal inflammatory reactions (103) and endotoxin-induced gastrointestinal damage (114).

Substitution of the phosphoryl choline moiety of CV-3988 with a heptamethylene thiazolium results in a group of quaternary salt PAF antagonists, including ONO-6240. This compound inhibits several endotoxin-induced circulatory and pulmonary manifestations in unanesthetized sheep (112), PAF-induced hypotension in the rat (85), and dermal vascular permeability in the guinea pig (85).

Several PAF antagonists related to CV-3988 and ONO-6240 have recently been developed by Sandoz, including SRI 63-072, SRI 63-073, SRI 63-119, and SRI 63-441. These compounds inhibit PAF-, endotoxin-, and immune aggregate–induced hypotension in the rat (61, 80), PAF-induced hemoconcentration and bronchoconstriction in the guinea pig (21, 80, 99, 115), and PAF-induced hypotension and hemoconcentration in the dog (80). They also inhibit PAF-induced hemoconcentration and airway responses in the primate (80, 100, 102) and the reverse-passive arthus reaction in the guinea pig (116). However, unlike PAF, which loses a significant amount of activity when the chirality at carbon 2 changes from R to S (117), both enantiomeric forms of SRI 63-072 demonstrate similar PAF receptor binding inhibition (32) and similar inhibition of PAF-induced hemoconcentration in the guinea pig (D. A. Handley, unpublished observations). SRI 63-072 and SRI 63-119 inhibit PAF-induced ischemic bowel necrosis in the rat (118). The most potent of the series, SRI 63-441, inhibits all major physiological responses in rats, guinea pigs, dogs, and primates, indicating a broad intraspecies potency (80).

When the C-2 ester function of the PAF molecule is replaced with an amide and the phosphate ester, with a phosphonate ester, an amido phosphono analogue of PAF results (119) that moderately inhibits PAF-induced platelet aggregation (120). A series of PAF antagonists, having a heterocyclic group linked by an ester, have been developed. In this series RO 19-3704 is the most potent and inhibits PAF-induced platelet aggregation and in vivo platelet thrombi (121, 122).

RP-48740, a (3-pyridyl)-^{1}H,^{3}H-pyrrolo[1,2-C]-thiazole derivative, is a specific PAF antagonist that inhibits PAF-induced dermal extravasation (123, 124), hemoconcentration (123), bronchoconstriction (123), and hypotension (123, 124).

A number of substances exhibit PAF antagonistic properties, including triazolobenzodiazepines (125), calcium channel blockers (126), prostaglandins (17, 127), glucocorticoids (88), and thyrotropin-releasing hormones (89). Within the triazolobenzodiazepines, brotizolam inhibits PAF-

induced platelet aggregation (128). When given orally, brotizolam inhibits PAF-induced bronchoconstriction and systemic hypotension. One of the calcium channel blockers, diltiazem, inhibits PAF receptor binding (126).

Natural Substances

Several naturally occurring PAF antagonists have been isolated. Kadsurenone, a terpene from the Chinese herbal plant *Piper futokadsurae*, is a competitive receptor antagonist to PAF (105). This neolignan is a specific and potent inhibitor of PAF-induced platelet aggregation and neutrophil degranulation (105). Kadsurenone also inhibits PAF-induced cutaneous permeability in the guinea pig (28, 105) and rat (28), as well as hematocrit changes (105), foot edema (129), and hypotension (86) in the rat. Other related structures isolated from the same plant demonstrated only weak PAF antagonist activity, however a synthetic derivative of kadsurenone is a potent PAF antagonist (130). This compound, L-652-731, inhibits ^{3}H-PAF receptor binding to rabbit platelets, PAF-induced platelet and PMN aggregation, and PAF-induced cutaneous vascular permeability (130) and hypotensive effects in the rat (131). It also inhibits immune complex–induced hypotension (131) and PAF-induced foot edema in the rat (129).

Several terpenoids isolated from the Chinese tree *Ginko biloba* L. were chemically characterized in the late 1960s (132, 133). Much later, these structures were determined to be PAF receptor antagonists (134). Three of these unique molecules (termed *Ginkgolides A, B,* and *C* or *BN 52020, BN 52021,* and *BN 52022*) are PAF receptor antagonists. BN 52021 is the most potent of the three. This compound is the most-evaluated PAF antagonist to date. BN 52021 inhibits PAF-induced responses including platelet aggregation (135), hypotension and extravasation in rats (87, 104), in vivo thrombus formation in injured arterial segments (41), and lung parenchymal strip contraction (53). BN 52021 is also effective in models involving endogenous PAF release such as immune aggregate–induced hypotension (87), endotoxin-induced lethality (104), antigen-induced pulmonary anaphylaxis (110), and cardiac allograft survival (136).

A fermentation broth product from *Streptomyces phaeofaciens*, FR-900452, has recently been described as a PAF antagonist (137). This cyclopentenopiperazinylindolinone blocks PAF-induced aggregation of rabbit platelets (138) and endotoxin-induced thrombocytopenia and leukopenia in rabbits (137). A second PAF antagonist isolated from the fermentation products of *Penicillium terlikowski* has been structurally characterized (139). This compound, FR-49175, inhibits PAF-induced platelet aggregation, bronchoconstriction, hypotension, and dermal vascular permeability (139). FR-49175, however, does not prevent systemic anaphylaxis in guinea pigs (139).

In a comparison of the leading PAF antagonists (SRI 63-441, BN 52021,

Table 1 Summary of PAF antagonist activity

Clinical condition	Animal model	Compound reference
Asthma/Pulmonary dysfunction	PAF-induced bronchoconstriction	BN 52021 (124), FR-49175 (139), L-652-731 (111), RP-48740 (123, 124), ONO-6240 (85), SRI 63-072 (102), SRI 63-119 (99), SRI 63-441 (80), brotizolam (128)
	Antigen-induced bronchoconstriction	BN 52021 (110)
	Endotoxin-induced pulmonary dysfunction	ONO-6240 (112)
Septic shock	PAF-induced hypotension	Kadsurenone (86), BN 52021 (87, 124), L-652-731 (131), RP-48740 (123, 124), CV-3988 (83, 84), ONO-6240 (85), SRI 63-072 (61), SRI 63-441 (80)
	Endotoxin-induced hypotension	Kadsurenone (86), CV-3988 (84), BN 52021 (104), SRI 63-072 (61)
	Immune complex–induced hypotension	BN 52021 (87), L-652-731 (131), SRI 63-072 (61)
Inflammation	PAF-induced vascular permeability	Kadsurenone (28, 105, 129), BN 52021 (87, 104), L-652,731 (100, 129, 130), CV-3988 (29, 98, 103), RP-48740 (123), ONO-6240 (85), SRI 63-072 (21, 46), SRI 63-119 (46, 99), SRI 63-441 (80)
	Carrageenin-induced edema	Kadsurenone (129), L-652-731 (129)
	Immune complex–induced vascular permeability	BN 52021 (87), L-652-731 (100, 131), SRI 63-072 (116), CV-3988 (103)
Ulcerogenic/ Enterocolitis	Endotoxin-induced	CV-3988 (114), ONO-6240 (118, 160), SRI 63-072 (118, 160), SRI 63-119 (118, 160)
Transplanted organ rejection	Cardiac allograft	BN 52021 (136)

RP-48740, L-652-731, SRI 63-072, CV-3988), L-652-731 exhibited the best oral activity against PAF-induced hypotension in the rat, followed by BN 52021, RP-48740, and SRI 63-072 (140). A similar order of oral potency was observed for inhibition of PAF-induced hemoconcentration and

bronchoconstriction in the guinea pig (140). Recently, BN 52021 was found to be more potent in vitro than CV-3988 or kadsurenone (74).

CLINICAL INDICATIONS FOR PAF ANTAGONISTS

Animal Models

The variety of in vivo responses to PAF are consonant with involvement in respiratory diseases, inflammation, and anaphylactic shock (141). Although the role of PAF in human disease has yet to be determined, specific areas of suspected involvement include septic shock, hyperacute organ rejection, cardiac anaphylaxis, necrotizing enterocolitis, and asthma. Animal models developed to mimic these diseases generally involve endogenous PAF production through immunological and nonimmunological stimuli. Endotoxin is the biological provoker of endogenous PAF release that has most often been used to simulate disease states related to man. Endotoxin (84), and the related condition of gram-negative sepsis (90), stimulates PAF production resulting in hypotension and increased vascular permeability leading to extravasation. Endotoxin challenge is used in animal models of septic shock (97), necrotizing enterocolitis (142), adult respiratory distress syndrome (112, 143), intravascular thrombocytopenia and leukopenia (138), and lethality (104).

Immunologically, IgE-mediated responses are accompanied by endogenous PAF production, leading to lethal systemic anaphylaxis (144), severe alterations in pulmonary and cardiac function (78, 145), and immune complex deposition in acute serum sickness that leads to glomerulonephritis (146). These IgE-mediated models of PAF release suggest its potential involvement in pulmonary, cardiac, and renal failure during systemic anaphylaxis and serum sickness. The role of PAF in renal failure is further supported by observations that PAF can induce a loss of glomerular anionic charges (147), can cause fibrinogen accumulation in the perfused kidney (148), and is released from sensitized animals to participate in hyperacute renal allograph rejection (149).

IgG-mediated models of PAF release are not as severe as the IgE or endotoxin models in terms of the resulting pathology. IgG responses can be induced with soluble aggregates of IgG (79, 87), and by passive sensitization to nonspecific (110, 150) or pulmonary-specific (151) antigens. These models simulate affected pulmonary function and induced vascular leakage (79, 87, 103), and are related to the development of inflammatory lung disease and asthma (110, 150).

PAF in Humans

PAF has been identified in human blood (71), urine (70), amniotic fluid (152), and saliva (153). Release of PAF has been suggested to occur in

systemic lupus erythematosus (154), cold urticaria (155), parturition (152), and psoriasis (156). The intradermal injection of PAF produces an immediate weal-and-flare response (157). A later (3–6 hr) response at the same site is characterized by erythema and algesia. Topical application of PAF to the nasal mucosa induced a dose-dependent vasoconstriction of the capacitance vessels and a reduction in mucosal blood flow (158). Two groups characterized the airway response to aerosolized PAF in man (44, 45). In these studies PAF induced bronchoconstriction in 11 of 12 subjects tested. Nonspecific bronchial reactivity, as measured by methacholine aerosol administration, was enhanced for as long as two weeks after a single PAF inhalation.

SUMMARY

Over the past decade platelet-activating factor has achieved the status of an important inflammatory mediator. The scientific enthusiasm and number of research investigators, publications, and meetings recently devoted to PAF suggest that this mediator will be the subject of continued study in the foreseeable future. The potential for the presence and involvement of PAF in human disease is easily concluded from the reports described in this review.

Both the need for low concentrations for cellular response and the rapid biological clearance mechanisms have made the proof of the involvement of PAF in human disease difficult. The discovery of PAF receptor antagonists and structure-activity relationships of such antagonists (159) will make this determination possible in the near future. The current PAF antagonists may be considered as first generation agents, since the most potent antagonist is still less than 1/100th as potent as PAF is as an agonist. The wide diversity of clinical applications from asthma to septic shock may also require antagonists with selective attributes such as delivery route (oral vs intravenous vs topical) or biological half-life (prolonged vs short). PAF may prove to be the key mediator of several poorly understood disease syndromes such as hyperacute organ transplant rejection, ischemic bowel necrosis (160), and adult respiratory distress syndrome. We must wait for clinical results to draw further conclusions.

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