PLATELET ACTIVATING FACTOR:

The Platelet Is Only The Beginning

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April 27, 1989

CONTENTS

I. INTRODUCTION

In 1970 Henson demonstrated that antigen-induced IgE-dependent release of a soluble factor from leukocytes resulted in platelet aggregation. This activity became known as "platelet activating factor" (PAF) (Benveniste et al., 1972). During the course of the next 7 years intensive studies by several groups resulted identification of the structure of this material - a subject described in more detail below. It is important to note that while PAF was initially described and assayed by its potent ability to initiate platelet activation, this compound has a broad range of biological effects on a variety of different tissues. Although a variety of other terms have been proposed by several authors (shown in Table 1), they have proven unwieldy and while the phonetic pronunciation of "PAF" is apparently unseemly in the french language, PAF has again returned to favor and will be used throughout this review.

PAF - Platelet Activating Factor

AGEPC - Acetyl-Glyceryl-Ether-Phosphorylcholine

PAF-acether - PAF-acetyl-ether

- TABLE 1 -

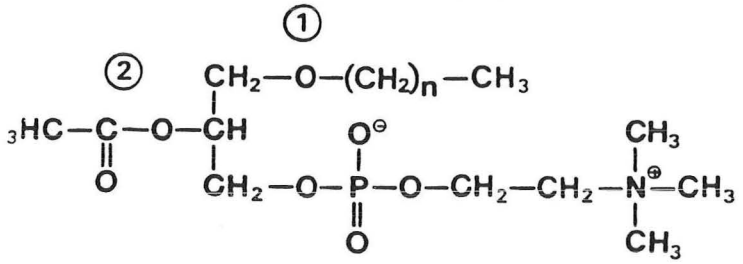
An important role for PAF has been suggested in a variety of homeostatic and disease states. A partial list is presented in Table 2. The diversity of cellular and tissue responses in which cells generate and/or respond to PAF are prominent justifies a serious consideration of this compound. This review will summarize: 1) knowledge of its structure including comments on structure/function relationships, 2) the mechanisms of PAF formation and cells that make PAF in response to physiologically relevant stimulation, 3) the mechanisms of PAF destruction and the role of some plasma constituents and cellular enzymes in reversing the effects of this compound, 4) the effect of PAF on a limited number of cells that have been most carefully studied and which participate in several disease processes 5) the role of PAF in asthma, vascular inflammatory responses and parturition as examples of three pathologic or homeostatic processes of particular interest.

- TABLE 2 -

Asthma	Renal allograft rejection
PMN chemotaxis	Ischemic bowel necrosis
Glomerulonephritis	Eosinophil chemotaxis
PMN adhesion	Regulation of LT synthesis
PMN activation	Inflammation / injury
Atherosclerosis	Regulation of RPF + GFR
Septic shock	Hypertension
Thrombosis	NK cell mediated killing
Parturition	T cell proliferation
Fetal Implantation	Negative cardiac inotropy
Pulmonary hypertension	Hepatic glycogenolysis
Pulmonary edema	Exocrine gland activation
Cytotoxic to neoplastic cells	

II. STRUCTURE OF PAF

The structure of PAF (Figure 1) evolved over approximately 7 years after the description of the activity. In a series of experiments by several groups, PAF was shown to be: 1) chloroform soluble, 2) acid stable, 3) sensitive to alkaline methanolysis and phospholipase A_2 resulting in a lipid soluble product, 4) migrate near lyso-phosphatidylcholine. In 1979 two groups (Benveniste et al.; Demopoulos et al) independently published the structure of PAF base in part on a synthetic proof that PAF activity was found to be associated with the 2-O-acetylated product of 1-O-alkyl,lysophosphatidylcholine. Independently Blank et al (1979) described the same structure associated with an agent causing hypotension. PAF is a structural



- FIGURE 1 -

variant of phosphatidylcholine (PC) - the most abundant membrane phospholipid

found in mammalian cells. Distinguishing PAF from other forms of PC are two critical structural features: 1) the long chain hydrocarbon moiety associated with glycerol's 1- position hydroxyl group is linked by an ether bond (as compared to the more common ester linkage) and 2) the presence of an acetate group esterified to the 2- position of glycerol [as compared to the more common long chain (16-22 carbons) fatty acids].

PAF actually represents a family of compounds with a variety of long chain fatty ethers in the 1-position of glycerol. Although the spectrum of the compounds with PAF activity and the general structure of PAF shown in Figure 1 have been described for some cells, most studies have not focused on the varying physiology of PAF's with 16:0 (terminology implies the number of carbon atoms and the number of double bonds) vs 17:0, 18:0, 18:1 and 22:2 fatty ethers in the 1-position (Weintraub et al, 1985; Pinkard, 1987). Although the concept of different molecular species of PAF introduces considerable complexity into its investigation (one that has considerable merit), the current discussion will only superficially address these issues despite their likely importance.

Structure function relationships have been examined and a summary of such studies in the rabbit platelet is illustrated in Table 3 (Pinkard, 1987). With respect to ability to cause platelet activation, the most active compound is that possessing a 16 carbon fatty group that has 0 double bonds (16:0), but 18:0 and 18:1 species are also fairly active. When the choline moiety is varied by substituting a tertiary amine (compared to PAF's quaternary amine) activity is only modestly altered, while very significant activity reduction is seen for the secondary and primary amines. Similarly, modifications of the 2 position acetate group have dramatic reductions in activity, even by simply adding a single methylene group (to form the proprionyl

	Molecular species	Relative PAF activity (%)[1]
1-0-alkyl:		
	C_{12}:0-AGEPC	8
	C_{14}:0-AGEPC	11
	C_{16}:0-AGEPC	100
	C_{18}:1-AGEPC	50
	C_{18}:0-AGEPC	27
	C_{16}:0/C18:0-AGEPDME[2]	35
	C_{16}:0/C18:0-AGEPMME[3]	4
	C_{16}:0-AGEPE[4]	0.04
1-0-acyl:		
	C_{12}:0-AGPC[5]	0.003
	C_{16}:0-AGPC	0.3
	C_{18}:0-AGPC	0.02

[1] PAF activify is expressed as a percentage relative to the platelet stimulating activity of C_{16}:0-AGEPC; C_{16}:0-AGEPC induced secretion of 50 per cent of the serotonin from washed rabbit platelets at 0.14 nM (final concentration) in 60 sec at 37 °C.
[2] 1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphodimethylethanolamine.
[3] 1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphomonomethylethanolamine.
[4] 1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphoethanolamine.
[5] 1-*O*-acyl-2-acetyl-*sn*-glycero-3-phosphocholine.

- TABLE 3 -

derivative) causes a 50 fold reduction in activity while the four carbon derivative (2-butyryl-PAF) demonstrates is 10,000 fold less active. More recently, a 2-N-methylcarbamyl substituted PAF has been shown to be quite active and is not subject to metabolism in the 2 position (Tessner et al, 1989). Also demonstrated in Table 3 is that the 1-ether linkage is critical to activity in that its substitution with an ester linkage causes a 300 fold reduction in activity.

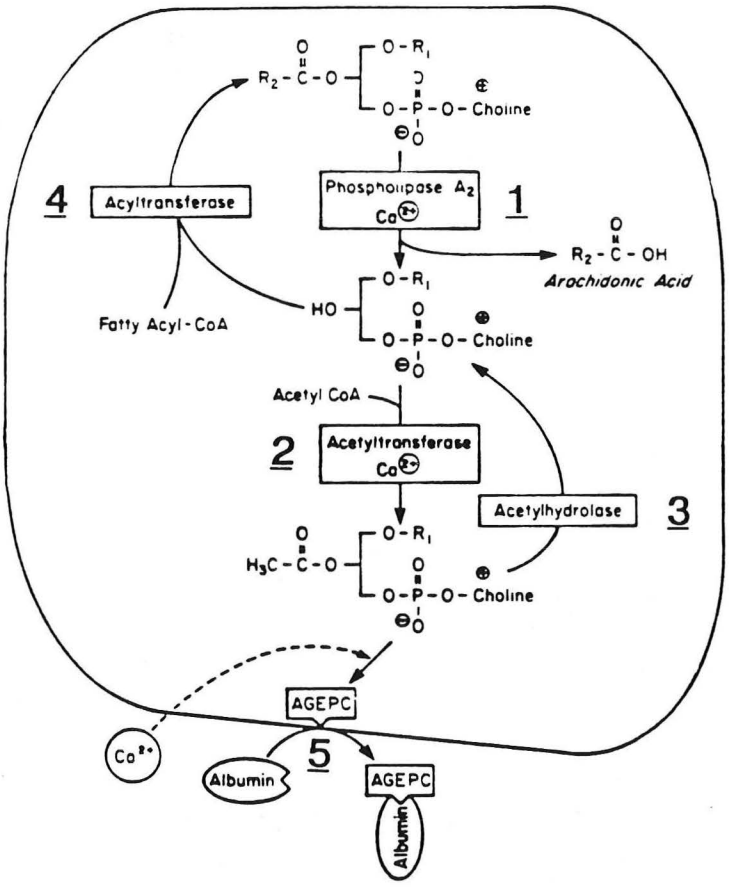
III. FORMATION OF PAF

Unlike several autocoids (potent biologically active compounds that act locally), PAF is not preformed, stored and released by exocytosis. Similar to the large family of eicosanoids (arachidonic acid-derived autocoids such as prostaglandins and leukotrienes), PAF is a newly synthesized mediator formed vigorously, but transiently, in response to appropriate cellular stimulation in cells able to synthesize it (reviewed by Wykle et al, 1986). It is formed in cellular membranes and because of its amphiphillic nature, tends to reside in membranes or in hydrophobic pockets of proteins (such as albumin) or in lipoproteins (such as LDL).

Cell membranes of all mammalian cells are composed principally of phospholipid, cholesterol and protein. The phospholipid serves as an important structural element separating cells from one another and subcellular organelles from another in order to allow cellular or subcellular functional compartmentalization. In addition to providing a structural barrier function, phospholipids act as an important reservoir of substrate for the formation of lipids that serve as bioinformational molecules (R.M. Bell, Lecture, 4/89). Phospholipid derived second messengers or autocoids are produced primarily in response to some triggering event and serve to regulate cellular processes in either the cell of origin or alternatively those nearby or at a modest distance. Examples of the molecules possessing the ability to act in the transmission of information include 1,2-diacylglycerol (which acts to modulate protein phosphorylation by protein kinase C), arachidonic acid metabolites (prostaglandins, leukotrienes, lipoxins, HETE's, etc) and more recently recognized PAF and sphingoid bases.

Two pathways of PAF formation have been demonstrated in a variety of cells. While both pathways have considerable <u>in vitro</u> activity, one is felt to be involved in the tonic formation of PAF while the other is more actively regulated in that it can be stimulated by a variety of physiologically relevant agents in a number of different cell model systems. The latter is initiated by the action of phospholipase A_2 (PLA_2) and is discussed first.

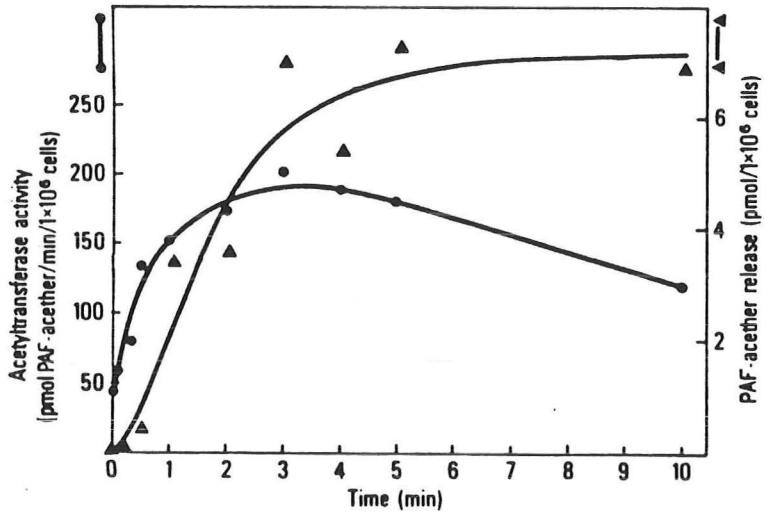
PHOSPHOLIPASE A_2-INITIATED PAF FORMATION - Reactions involved in activable PAF synthesis and degradation are illustrated in Figure 3. Discussion will be limited to the synthetic and degradative reactions involving the 1-O-alkyl,2-acetyl-PC. Because the principal biologically active PAF compounds have a 1-O-alkyl linkage (ie an ether, rather than an ester, at the 1 position), the principal substrate source for the formation of PAF is the subset of PC's that similarly possess an ether-linked moiety at their one position (1-O-alkyl-PC). The first step in synthesis is the activation of a phospholipase A_2 (PLA_2; reaction 1, Figure 3) which hydrolytically removes the long chain fatty acid from the 2- position leaving lyso-PAF (1-O-alkyl,2-lysoPC). Although beyond the scope of the current topic, this step is of considerable interest not only with regard to the formation of PAF, but as an important, if not principal, pathway for the release of arachidonic acid from alkyl-PC by PLA_2 (Chilton et al, 1984) - the fatty acid which can be acted upon by a number of pathways to form extremely potent and biologically active agents such as



- FIGURE 3 -

prostaglandins, leukotrienes, HETE's and lipoxins. The nature of the regulation of PLA_2-mediated formation of lyso-PAF is incompletely understood although it appears that Ca^{++} is likely important in this process and it may involve GTP-binding proteins (G proteins). Although the glucocorticoid-mediated formation of the protein lipomodulin (also known as macrocortin) was felt by many to be critical in the down regulation of PLA_2, more recent work by a number of investigators has cast serious doubts on the ability of this protein to exert physiologically meaningful regulation of PLA_2.

The second, and final, step in this pathway of PAF formation is the enzymatic acetylation of lyso-PAF using acetyl-CoA by lyso-PAF transacetylase (ATase; reaction 2, Figure 3). This reaction has received a great deal of attention inasmuch as it appears to be subject to regulation by protein kinase-mediated phosphorylation (Cambronen, 1985; Lenihan and Lee, 1984; Whatley et al, 1989). Thus, when appropriate cells are activated by any of a variety of means, the accumulation of second messengers can result in the activation of protein kinases that catalyze the phosphorylation of enzymes which can markedly increase or decrease their activity. While work in a variety of groups has suggested the involvement of cAMP-dependent, Ca^{++}/calmodulin-dependent protein kinases, recent work in endothelial cells (Whatley et al, 1989) indicates the important involvement of protein kinase C (PKC). Figure 4 illustrates the parallel increases in ATase activity and PAF accumulation in mast cells.



- FIGURE 4

1,2-diacylglycerol (DAG) is formed by one or more of three pathways (phospholipase C action on phosphoinositides, phospholipase C action on PC and an indirect pathway involving the conversion of PC to PA by phospholipase D and the subsequent formation of DAG by PA phosphohydrolase) can markedly enhance the activity of cellular PKC. DAG is important because, in concert with Ca^{++}, it regulates PKC-mediated phosphorylation of the transacetylase (and other PKC targets) resulting in markedly increased activity and thereby increased PAF synthesis. While the initial availability of lyso-PAF is rate limiting, significant regulation of PAF formation is accomplished by regulation of the ATase.

- FIGURE 5 -

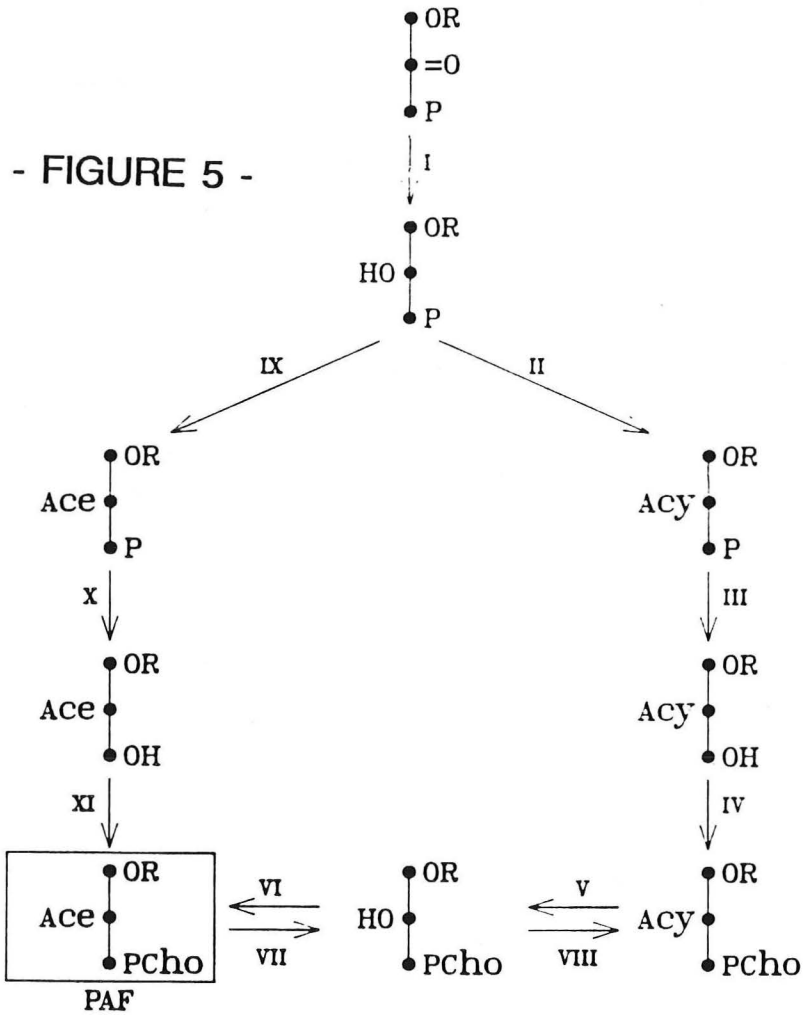
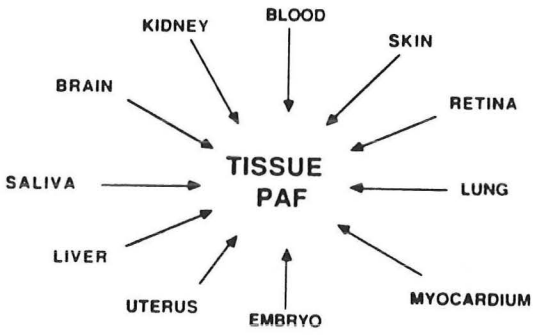


Figure 1. Dual pathways for the biosynthesis of PAF. The individual reaction steps are catalyzed by the following enzymes: I—NADPH:alkyldihydroxyacetone-P oxidoreductase (EC 1.1.1.1000); II—acyl-CoA:1-alkyl-2-lyso-*sn*-Gro-3-P acyltransferase (EC 2.3.1.63); III—1-alkyl-2-acyl-*sn*-glycero-P phosphohydrolase; IV—1-alkyl-2-acyl-*sn*-Gro:CDP-choline cholinephosphotransferase (EC 2.7.8.2); V—phospholipase A_2; VI—acetyl-CoA:alkyl-2-lyso-*sn*-Gro-3-PCho acetyltransferase (EC 2.3.1.67); VII—1-alkyl-2-acetyl-*sn*-Gro-3-PCho acetylhydrolase (EC 3.1.1.48); VIII—donor phospholipid (20:4):1-alkyl-2-lyso-*sn*-Gro-3-PCho transacylase; IX—acetyl-CoA:1-alkyl-2-lyso-*sn*-Gro-3-P acetyltransferase; X—1-alkyl-2-acetyl-*sn*-Gro-3-P phosphohydrolase; and XI—CDP-choline:1-alkyl-2-acetyl-*sn*-Gro cholinephosphotransferase (EC 2.7.8.16). Symbols used in this illustration represent Alk for alkyl, Acy for acyl, and Ace for acetyl.

PAF FORMATION INVOLVING ALKYL-lyso PA - The left hand portion of Figure 5 illustrates an alternative pathway of PAF formation (reviewed in Snyder, 1987). This pathway has been described in detail by Snyder's group and although it appears not to be subject to regulation by agents activating cells, it possesses considerable in vitro activity. Thus, its role has been proposed to be involved with tonic production of PAF - a role potentially important in regulation of vascular tone. As illustrated, the pivotal substrate is 1-alkyl,2-lyso-PA which can be esterified either by long chain fatty acids (for the formation of alkyl-PC) or by acetate to form 1-alkyl,2-acetyl-PA (reaction IX, Figure 5). The latter is then converted to 1-alkyl,2-acetyl-DAG by a unique PA phospholydrolase (reaction X, Figure 5). Although of uncertain physiologic significance Blank et al (1984) demonstrated that 1-alkyl,2-acetyl-DAG causes hypotension in an animal model system. PAF is finally formed by the transfer of phosphorylcholine to the 1-alkyl,2-acetyl-DAG backbone by a DAG,CDP-choline phosphotransferase that is distinct from that involved in the usual synthesis of long chain PC's for structural lipid formation (reaction XI, Figure 5).

IV. CELLULAR AND TISSUE SOURCES OF PAF

Illustrated in Table 4 are a selected group of purified cells that synthesize PAF in response to physiologically relevant agonists. PAF has also been shown to be synthesized by a variety of tissues as is illustrated in Figure 6. Together with the cells that can respond to PAF (discussed below), the richness of the cellular and tissue sources of PAF indicates that it is likely of considerable importance in a variety of homeostatic and pathologic processes.



- FIGURE 6 -

- TABLE 4 -

Cellular Sources of PAF

PMN	FMLP, C5a, LTB_4, aggregated IgG
Monocyte	Bacteria, Immune Complexes, Ag / IgE
Mast cell	Ag / IgE
Endothelium	Histamine, Bradykinin, Thrombin, Vasopressin, LTC_4
Platelet	Thrombin, ADP
Fetal Lung	Maturation

V. RELEASE OF PAF

Although the biosynthetic and degradative reactions for PAF are relatively straight forward, the balance of these reactions in a given cell and the ability of a cell to release PAF and PAF precursors into the surrounding the cell are complex. For example, in the endothelial cell (EC), treatment bradykinin, histamine, thrombin or LTC_4 causes a dramatic increase in the formation of PAF (McIntyre et al, 1985 & 1986), but after separating the cells from the medium, only a small fraction of the newly synthesized PAF can be detected in the medium and the majority found associated with the cell. The potential physiologic importance of EC-associated PAF is discussed later. In contrast to endothelial cells, the PAF formed in neutrophils as a result of stimulation by bacterial chemotactic peptides (FMLP), for example, is roughly equally divided into that retained in the cell and that released into the extracellular environment. It is important at this juncture to reiterate that, unlike highly water soluble mediators such as peptides and histamine, PAF is not preformed and secreted and is not stored in organelles for release. Thus, the PAF formed in cells that is not released is almost certainly membrane associated (due to the

hydrophobicity of PAF), but its exact location in most cells is uncertain although it has been shown to be present on the EC plasma membrane. Release of PAF into the medium in vitro requires the presence of extracellular Ca^{++} and albumin as an acceptor (Ludwig et al, 1984 & 1985). Much experimental controversy regarding whether cells are able to release PAF into the medium (vs accumulating cell associated PAF) as a result of stimulation has been resolved as a result of this observation. In cells able to release PAF, the absence of albumin result in termination of PAF synthesis which is restored by its addition. This suggests that either the accumulation of PAF results in feedback inhibition of its subsequent synthesis (not supported by the observations of Whatley et al, 1989) or the increased degradation by cellular PAF AHase (described below, reaction 3, Figure 3) as a result of increasing PAF levels in appropriate subcellular sites. Some investigators have proposed the existence of a protein that specifically removes PAF from the plasma membrane and releases it into the extracellular milieu, but this area remains both controversial and exciting.

VI. PAF DESTRUCTION

As illustrated in Figure 3, PAF activity is principally destroyed by the action of a unique PLA_2 which has specificity for the presence of a very short chain fatty acid (such as acetate) in 2- position of PAF (reaction 3, Figure 3). This enzyme is termed PAF acetylhydrolase (PAF AHase). This enzyme [originally known as "acid labile factor"(Farr et al, 1980)] has been isolated and characterized primarily from human plasma (Wardlow et al, 1986; Stafforini et al, 1987). Some of its characteristics are described in Table 5. Distinguishing PAF AHase from other PLA_2's is its dramatic preference for short chain fatty acids in the 2-position of PC and its resistance to inhibition by some classic inhibitors of snake venom PLA_2's. While all of the plasma PAF AHase is associated with lipoproteins (Stafforini et al, 1987a), most cells have varying levels of intracellular PAF AHase that is distinct from the plasma enzyme. The PAF AHase from platelets and macrophages has been shown to be liberated as a result of cellular activation (Suzuki et al, 1988) suggesting that some of the intracellular enzymes may also contribute to the catabolism of PAF in inflammatory sites - particularly those into which plasma lipoproteins are denied access.

Plasma PAF AHase has been studied by a number of investigators in a variety of disease states. Although correlative studies examining AHase activity in the plasma in patients with a variety of disease processes such as atherosclerosis, cerebrovascular disease, renovascular hypertension, ischemic heart disease and

- TABLE 5 -

Properties of PAF AHase
(acetylhydrolase)

Associated with lipoproteins

Most active in LDL

Specific for 1-o-alkyl PCs

Specific for 2-acetyl or 2-(oxidized)fatty acyl forms

MW = 43 kD

Ca^{++} independent

Trypsin & pronase sensitive / papain insensitive

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cirrhosis (Sato et al, 1988; Blank et al, 1983; Caramelo et al, 1987; Crook et al, 1986; Masugi et al, 1988) have become increasingly common, most have shown modest differences and the role of plasma AHase in the evolution of the disease (as opposed to an unrelated or peripherally related observation) is uncertain at best. However, other studies examining PAF AHase and its role in certain disease processes are very exciting and one will be discussed in detail below.

PAF AHase and LDL clearance: a potential role in atherogenesis - Recent work suggests that plasma AHase may be critical to pathologic LDL uptake by macrophages in developing plaques. Macrophages can only ingest modified LDL (studied in the past by using acetylated LDL) utilizing a receptor distinct from the normal LDL receptor and take up native LDL poorly. The foam cells in atherosclerotic plaques are lipid laden macrophages. Modifications of the LDL that might take place in vivo that might result in enhanced uptake by macrophages may be important to the development of atherosclerotic lesions. Recent studies (Stremler et al, 1989; Parthasarathy et al, 1985 and Tokumura et al, 1988) have led to an interesting hypothesis (Figure 7). If the LDL-associated phospholipid PC is oxidized

MODIFICATION OF LDL
- Role of PAF AHase -

PC —Toxic oxygen—> 1,acyl-2,oxyacyl-PC

PC —LDL-assoc. AHase—> no hydrolysis

PC —LDL-assoc. AHase—> lyso-PC + oxy-fatty acid

oxy-fatty acid ——> loss of apo-B and MO uptake

- FIGURE 7 -

(as a result of the formation of toxic oxygen species by leukocytes in inflammatory sites) at its 2 position fatty acid and if that fatty acid is liberated from the PC backbone by a PLA_2 activity, then apo B is rapidly degraded by means that are as yet uncertain. This loss of apo B (and/or the presence of the oxidized lipid) dramatically enhances the ability of macrophages to ingest this modified LDL. Of interest with regard to the metabolism of PAF is the finding by (Stremler et al, 1989) that the LDL-associated PAF AHase is the enzyme responsible for the critical liberation of these oxidized fatty acids. Also supporting this view are the results of Quinn et al (1988) demonstrating that alkyl-lyso-PC (the PAF-derived AHase-catalyzed hydrolytic product) is chemotactic to monocytes. Thus, appropriate targets for intervention would not only include the use of antoxidants to reduce oxidative damage to LDL, but also the potential pharmacologic inhibition of LDL-associated PAF AHase-mediated cleavage of oxidized fatty acids.

PAF AHase and hypertension - It is well known that PAF causes hypotension in experiments of acute intravenous administration. Further, it is implicated as an important mediator in the development of septic shock as a result of endotoxin-mediated increases in cytokines that can cause dramatic increases in PAF synthesis

in endothelial cells (discussed later). However, interest in the ability of PAF to act in some forms of chronic hypertension have also been investigated. Blank et al (1983) demonstrated that spontaneously hypertensive rats had 25% more plasma AHase activity than matched controls (125 vs 102 pmol/min/ul plasma). The authors suggested that the vasodepressor effects of PAF and its more rapid inactivation by plasma in the spontaneously hypertensive rats might represent a cause and effect relationship. No carefully controlled studies were found that examined humans with essential HTN, but a single abstract (Crook et al, 1986) suggested that in white males, plasma AHase levels were 47% greater in hypertensives than normal controls ($p<0.02$) - a finding not supported by their observation in black males. Strongly arguing against a central causative role for plasma PAF AHase for hypertensive states is the recent finding described below (Miwa et al, 1988) that individuals totally lacking this enzyme have been discovered and found to be "healthy".

VII. THE PAF "CYCLE" AND ARACHIDONIC ACID RELEASE

Also illustrated in Figure 3 is the mechanism by which the precursor for PAF biosynthesis (1-O-alkyl,2-acyl-PC) is reformed (reaction 4). In this process any of a variety of long chain fatty acids can be esterified to the 2-position of lyso-PAF to form 1-O-alkyl,2-acyl-PC. While this 1-alkyl,2-acyl-PC can then be used as a substrate in the formation of PAF by the two step actions of PLA_2 and lyso-PAF acetyltransferase (reactions 1 and 2, Figure 3), most of PAF is formed from 1-O-alkyl,2-arachidonoyl-PC. Enrichment of 1-O-alkyl,2-acyl-PCs with arachidonate in the 2- position is accomplished by a non CoA-dependent transacylation involving 1-acyl,2-arachidonoyl-PC as the arachidonate donor and 1-O-alkyl,2-acyl-PC as the arachidonate recipient resulting in the formation of 1-alkyl,2-arachidonoyl-PC and diacyl-PC (Kramer et al, 1984). The importance of enriching the alkyl-PC with arachidonic acid at the 2 position is that phospholipase A_2 action on 1-O-alkyl,2-arachidonoyl-PC results in the coordinate formation of products that are both able to be converted to different potent autocoids (1-O-alkyl,2-lyso-PC is a PAF precursor and free arachidonic acid can be converted to a variety of physiologically potent eicosanoids) (Chilton et al, 1984). This concept may be important in the interpretation of data involving the dietary consumption of fish oils (rich in 20:5 and 22:6) inasmuch as the transacylation reaction is less effective and less of the 1-O-alkyl,2-arachidonyl-PC is formed when 20:4 tends to be replaced by 20:5 and 22:6 in the diacyl-PC's.

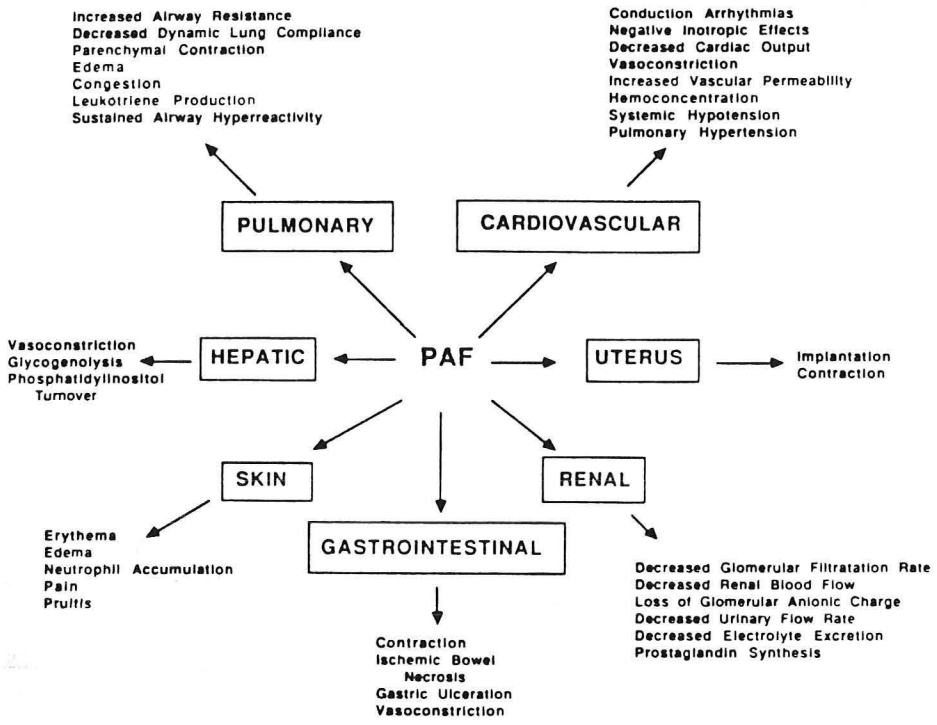
The ability of a cell to accumulate and potentially release PAF compared to

one that does not probably rests with the balance of the endogenous ATase and AHase pathways. To the extent that PAF destruction is more efficient than synthesis (AHase >> ATase), then the cell will likely not accumulate or release PAF.

VIII. SELECTED CELLS/TISSUES RESPONSIVE TO PAF

Although initially described as a potent agent initiating platelet aggregation and exocytosis, PAF has been shown to cause a very broad spectrum of responses in a variety of cells and tissues. With the ultimate goal of establishing the role of PAF in homeostasis and pathologic processes, one must first describe tissue responses to realistic concentrations of PAF. Table 1 and Figure 8 give a panorama of some of the effects PAF has on tissues and cells. Described subsequently are some of PAF's best described effects on isolated cells involved in inflammation. Although outside of the scope of the current discussion, it is important to keep in mind that PAF has many synergistic relationships with other autocoids in the activation of a variety of cells. Thus, while the concentrations of PAF necessary to cause a given reaction may seem high, the ability of 100 fold lower concentrations is often found to be sufficient to turn on a cell in the presence of even modest concentrations of other inflammatory mediators (example: Baggiolini and Dewald, 1986).

PAF Receptors - Considerable effort has been expended on the characterization of PAF receptor antagonists, but studies of the receptor itself have been slow to evolve and considerably different results have been obtained from different groups. For example, in the rabbit platelet K_D values for PAF binding range from 1.1 nM to 37 nM with a total of 150-1400 receptors/platelet (Hwang et al, 1983 & 1985; Kloprogge, 1984; Stewart and Dusting, 1988). There exists low affinity unsaturable binding which likely represents PAF association with membranes although more recently a low affinity binding protein has been described in platelets. The neutrophil has a very high affinity receptor (K_D = 0.11 nM) with 5 x 10^6 receptors/cell (Hwang, 1988; Valone and Goetzl, 1983) - a similar density to platelets given the difference in cell surface area. Valone (1984) described partial purification of a PAF binding protein of 180 kD - a finding confirmed by Nishihira et al (1985). Several problems associated with the study of the PAF receptor is the rapid metabolism of PAF, its 'stickiness', its very high affinity, and the limited number of receptors per cell. The rapid desensitization to PAF seen in vivo has not been fully characterized at a molecular levels, but it appears that the receptors are both internalized and modified to result in markedly reduced affinity for PAF.


Increased Airway Resistance
Decreased Dynamic Lung Compliance
Parenchymal Contraction
Edema
Congestion
Leukotriene Production
Sustained Airway Hyperreactivity
Conduction Arrhythmias
Negative Inotropic Effects
Decreased Cardiac Output
Vasoconstriction
Increased Vascular Permeability
Hemoconcentration
Systemic Hypotension
Pulmonary Hypertension
PULMONARY
CARDIOVASCULAR
Vasoconstriction
Glycogenolysis
Phosphatidylinositol
Turnover
HEPATIC
PAF
UTERUS
Implantation
Contraction
SKIN
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GASTROINTESTINAL
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Neutrophil Accumulation
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Loss of Glomerular Anionic Charge
Decreased Urinary Flow Rate
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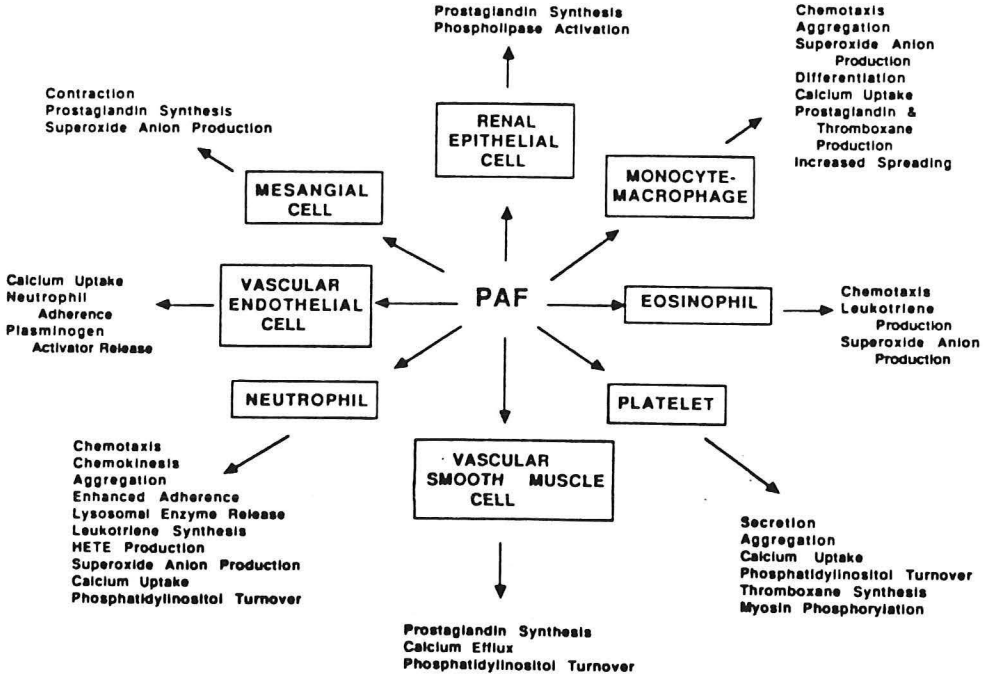
Ischemic Bowel
Necrosis
Gastric Ulceration
Vasoconstriction

- FIGURE 8 -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Production
Differentiation
Calcium Uptake
Prostaglandin &
Thromboxane
Production
Increased Spreading
Contraction
Prostaglandin Synthesis
Superoxide Anion Production
RENAL
EPITHELIAL
CELL
MONOCYTE-
MACROPHAGE
MESANGIAL
CELL
Calcium Uptake
Neutrophil
Adherence
Plasminogen
Activator Release
VASCULAR
ENDOTHELIAL
CELL
PAF
EOSINOPHIL
Chemotaxis
Leukotriene
Production
Superoxide Anion
Production
NEUTROPHIL
PLATELET
Chemotaxis
Chemokinesis
Aggregation
Enhanced Adherence
Lysosomal Enzyme Release
Leukotriene Synthesis
HETE Production
Superoxide Anion Production
Calcium Uptake
Phosphatidylinositol Turnover
VASCULAR
SMOOTH MUSCLE
CELL
Secretion
Aggregation
Calcium Uptake
Phosphatidylinositol Turnover
Thromboxane Synthesis
Myosin Phosphorylation
Prostaglandin Synthesis
Calcium Efflux
Phosphatidylinositol Turnover

Although not the major focus of the clinical discussion at hand, PAF receptor-mediated platelet activation appears to involve enhanced PI hydrolysis (Billah et al, 1983). Preliminary data in permeabilized platelets indicate the likely, but not unexpected, involvement of G proteins in PAF-associated signal transduction.

Platelets - Although the first model system of PAF effects (its namesake) is the platelet, it also represents one of the more complex cells responding to PAF. In the absence of plasma (containing PAF-AHase capable of rapid destruction of PAF), PAF over increasing concentrations in the nanomolar range produces 1° aggregation, 2° aggregation and exocytosis and arachidonic acid release resulting in thromboxane A_2 synthesis. With high nanomolar concentrations, increasingly rapid aggregation and exocytosis occur in human platelets. PAF-induced platelet activation is synergistic with other agents causing platelet activation, but its inhibition in cells desensitized to PAF does not affect the ability of agents such as thrombin or ADP to cause platelet activation.

Neutrophils - In the presence of extracellular Ca^{++}, PAF induces a dose-dependent increase a variety of neutrophil parameters such as lysosomal enzyme release, aggregation, LTB_4 formation and superoxide anion generation. Some of these reactions, but not all, appear to be partially the result of PAF-mediated synthesis of the lipoxygenase products HETE and LTB_4 since specific inhibitors of this pathway can attenuate certain of these physiologic responses. Of particular interest in the finding that a nonmetabolizable PAF analogue that causes PMN activation also causes a dramatic increase in PAF synthesis (Tessner et al, 1989) suggesting that amplification modest signals and positive feedback may be important consequences of PAF formation and which may commit the cell to an "fully committed" state.

Monocytes/macrophages - PAF induces Ca^{++}-dependent monocyte aggregation, but fails to induce increased superoxide generation or exocytosis of lysosomal components. Chemotaxis to PAF is weak, but may be augmented by the presence of other autocoids. A number of studies seem to indicate that PAF is increasingly effective in eliciting the expected physiologic responses (lysosomal enzyme release, superoxide generation, arachidonic acid release and eicosanoid production) in macrophages that have been obtained by treatment that results in greater states of activation (Hartung et al, 1983). Of note are recent studies demonstrating that during the differentiation of monocytes to macrophages, PAF AHase activity increases dramatically within the cells and appears to be released (Elstad et al, 1989). This suggests that macrophages might not only be responsive to PAF, but

may also importantly contribute to the destruction of PAF during wound healing responses.

Eosinophils - PAF is the most potent chemotactic agent for eosinophils thusfar described. In addition to chemotaxis, it effectively activates the cell resulting in the release of a number of toxic granule proteins (major basic protein, eosinophil cationic protein, eosinophil peroxidase and eosinophil-derived neurotoxin). Further, it causes arachidonate liberation and the vigorous formation of LTC_4. Of note is that like PMN's, eosinophils not only respond to PAF, they vigorously synthesize it in response to physiologically relevant agonists (Lee et al, 1984) including PAF. Thus, perhaps the common theme with these two cells and their common pattern of synthesis and responsiveness to PAF lies with the fact that they are "kamikaze" cells - cells that, by and large, enter an inflammatory focus and with the intent to do damage and do not expect to survive.

IX. ROLE OF PAF IN HOMEOSTASIS AND DISEASE

With the knowledge of both the cells that synthesize PAF in response to known physiologic triggers as well as the spectrum of physiologic responses that PAF causes in a variety of tissues, this section will begin to integrate this knowledge by examining the role of PAF in two homeostatic processes (neutrophil adherence to endothelial cells and fetal lung maturation and its association with parturition) and one disease (asthma) that have been the subjects of considerable investigative effort. Because PAF effects on tissues not previously examined are evolving rapidly in the literature, it is expected that there will be large expansion of understanding in this area during the next few years.

A. PAF, PLATELETS AND ASTHMA

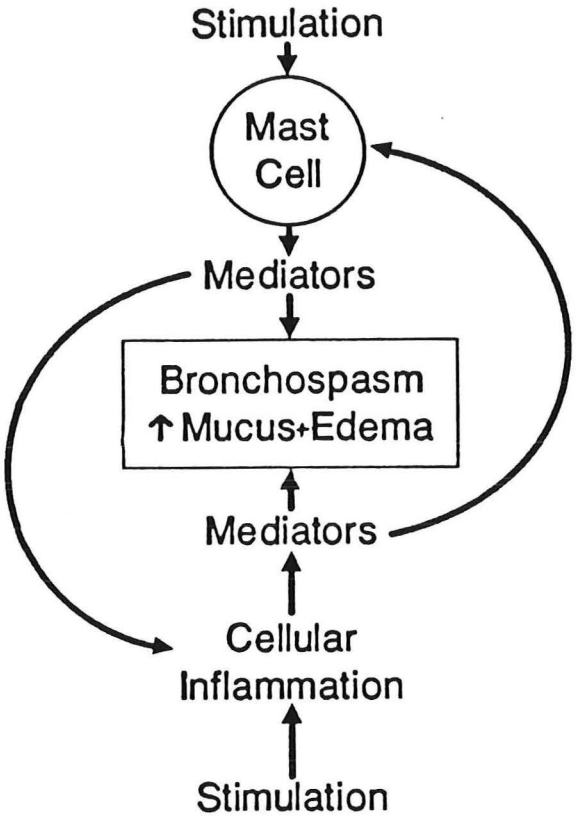
(Reviewed in Page et al, 1985 & 1988; Braquet, 1988a & 1988b; Barnes, 1988; Barnes et al, 1988; Patterson et al, 1984) On a molar basis, PAF is an extremely potent bronchoconstrictive agent in both experimental animals and, more recently, in human studies (Chung et al, 1987; Cuss et al, 1987) causing rapid evolution of airway obstruction (peaking 15-30 minutes after administration) that resolves slowly over several hours. It is approximately 1000 fold more potent than histamine on molar basis. In addition to bronchoconstriction, subjects inhaling PAF also develop flushing. Although not extensively studied in man for ethical reasons, the acute bronchoconstrictive effect of PAF in animal models appears to be dependent upon the presence of circulating platelets. In isolated bronchial smooth muscle, PAF is

unable to cause contraction in both human and animal studies suggesting that PAF-induced bronchocontriction is due to PAF-mediated release of a secondary mediator. Controversy exists over the importance of a variety of secondary autocoids, but LTC_4, PGD_2, neuropeptides, and TxA_2 represent likely candidates (Chung et al, 1986). In addition to bronchial smooth muscle contraction as a mechanism of airway obstruction, the lung parenchyma has been shown to contract in response to a number of agents. In this model, PAF has been shown to cause a largely platelet-dependent parenchymal contraction in tissue obtained from humans - a reaction that may be partially mediated through parasympathetic mechanisms (Stimler-Gerard, 1986).

In models of acute asthma, PAF may also importantly contribute to airway obstruction by facilitating the development of mucosal edema. Indeed, bronchoscopic segmental allergen challenge of allergic asthmatics demonstrates that, although slower to develop than bronchoconstriction, edema is a prominent feature observed. PAF is able to induce increased vascular permeability in human skin (not platelet dependent) (Archer et al, 1984 & 1985) probably by its effect on venular endothelial cells (discussed in more detail subsequently) which result in leakage of plasma proteins into the airway mucosa in animal models utilizing PAF inhalation challenge (Gillespie and Bowdy, 1986).

Chronic asthma is increasingly being viewed as a disorder causes, in large part, by the evolution of a chronic inflammatory reaction. As illustrated in Figure 9 and discussed in greater detail in my previous Parkland Grand Rounds on Asthma (August 13, 1987), the development of the signs of asthma (bronchospasm, increased mucus production and edema) is likely the result of a complex self-perpetuating cycle of inflammation. This process involves mast cells, eosinophils, neutrophils, macrophages, lymphocytes, and platelets and a panoply of inflammatory autocoids. Thus, in the search for important agents causing and/or perpetuating asthma, the ability of a compound to act as a potent bronchoconstrictive agent would appear to be less important than the ability to sustain this complex cellular inflammatory reaction.

Strongly supporting the importance of PAF in chronic asthma lies with its ability to both cause nonspecific bronchial hyperreactivity in normal individuals (Figure 10) and recruit and activate neutrophils, eosinophils, and monocytes. Further, the sine qua non of asthma is the presence of nonspecific bronchial hyperreactivity (susceptibility to vigorous bronchospasm by histamine or cholinergic agents at very low concentrations which cause modest or no bronchoconstriction in individuals without asthma). Supporting experiments were discussed in greater detail



- FIGURE 9 -

in the previous Parkland Grand Rounds. The duration of single dose PAF-inducedincreases in nonspecific bronchial hyperreactivity were noted to last as long as 4 weeks. Of interest is the finding that patients with asthma are not more sensitive to PAF than are nonasthmatic patients, in contradistinction to other bronchoconstrictive agents. Further, the finding that tachyphylaxis to the acute bronchoconstrictive effects of PAF develops rapidly in both human and animal models may explain why asthmatic patients have equal or less intense bronchoconstriction than nonasthmatic individuals in response to PAF.

Other findings effects of PAF consistent with a role in the development of asthma include the development of basement membrane thickening which might be the result of the release of platelet-derived growth factor (PDGF) from PAF activated platelets. Further, the excessive mucus secretion characterizing chronic asthma may in part be due to PAF inasmuch PAF causes an increase in this

parameter in isolated human airway preparations (Goswami et al, 1987).

A recent and provocative study (Miwa et al, 1988) demonstrated that roughly 4% of apparently healthy adults had deficiencies of plasma PAF AHase activity, but normal levels of platelet cytosolic PAF AHase. Reduction in activity was due to deficiency of the AHase (not the presence of an AHase inhibitor) and was shown by kindred studies to be inherited in an autosomal recessive fashion. Further, plasma

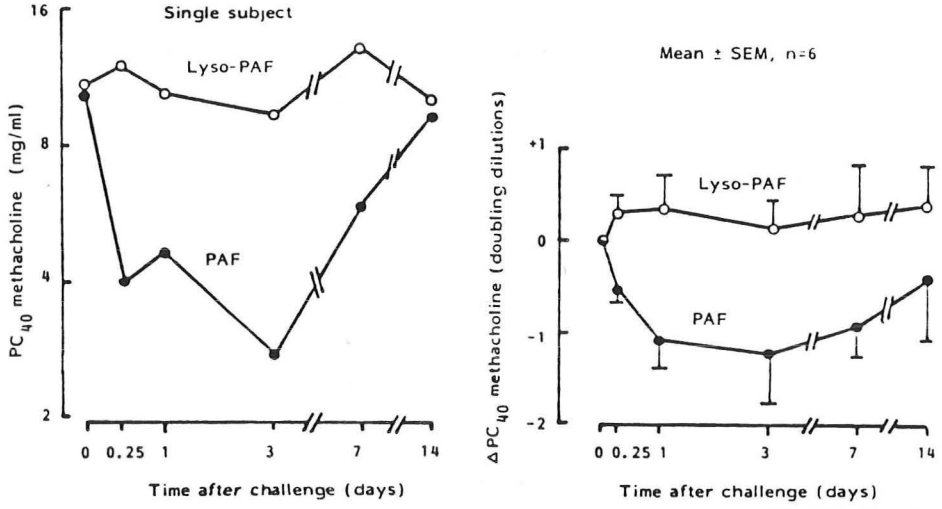


FIG. 5. Increased bronchial responsiveness to methacholine after PAF inhalation in a single subject *(left panel)* and mean values (±SEM) of six normal subjects. The concentration of methacholine causing a 40% fall in V_{p30} (PO_{40}) was determined.[81]

- FIGURE 10 -

AHase activity in children with asthma was modestly, but significantly lower than that of children without respiratory disease. Of children with severe asthma, 30% had very low levels of AHase activity. This raises the possibility that in the near future, asthma may be subdivided into different classes according to mechanisms of causation and that the inability to rapidly inactivate PAF as a result of plasma AHase deficiency may be an important constitutional factor predisposing individuals to the development of asthma. Similarly, the abilty of individuals to develop IgE antibody responses to inhaled allergens would constitute a different group of individuals at risk for developing allergic respiratory disease. I suspect that, as this field unfolds, abnormalities at a variety of enzymatic and/or cellular levels will be found to be important in the pathogenesis of asthma and that those unfortunate individuals with severe asthma might bear multiple defects.

Careful studies examining the efficacy of PAF receptor antagonists on acute pulmonary responses to antigen or in the control of chronic asthma are in progress in humans. Data obtained in animal models (Coyle et al, 1988) demonstrate that PAF receptor antagonists are able to reduce allergen-induced eosinophil accumulation and bronchial hyperreactivity, but the effects were modest. In general, the "first wave" of these agents have been somewhat disappointing with regard to their potency (Guinot et al, 1987). Further, testing efficacy of these agents in acute antigen challenge (rather than with long term administration in the attempt to suppress **chronic** asthma) may represent a poor choice of model system. Thus, the ability to both better test the hypothesis that PAF and platelets are important in human asthma and treat patients with chronic asthma will likely await the development of increasingly potent agents that can block the effects of PAF and long term antagonist administration.

B. REPRODUCTIVE PATHOPHYSIOLOGY

The role of bioactive lipids and, most recently, PAF in normal pregnancy has been pioneered by the work of Johnston at this institution. What follows will be a brief summary of findings with regard to the role of PAF metabolism in implantation, parturition and fetal lung maturation.

The role of prostaglandins (particularly PGE_2) in labor is supported by an extensive literature and a detailed discussion will not be presented here (Bygdeman, 1968; Dray and Frydman, 1976; Karim and Filshie, 1972). PGE_2 causes uterine contraction and its levels increase 4-10 fold during labor. Fetal amnion tissue displays greater PLA_2 activity in when obtained at the time of labor vs. amnion obtained at term, but not in labor - a finding that suggests that activation of PLA_2 prior to parturition may be important in generating prostanoids that have been documented to cause uterine smooth muscle contraction which may contribute to parturition. Although the mechanism in not certain, PAF causes a rise in the synthesis of PGE_2 in the amnion. Coincident with the appearance of eicosanoids is the modest, but significant, disappearance of arachidonate-containing phospholipid precursors from the amnion.

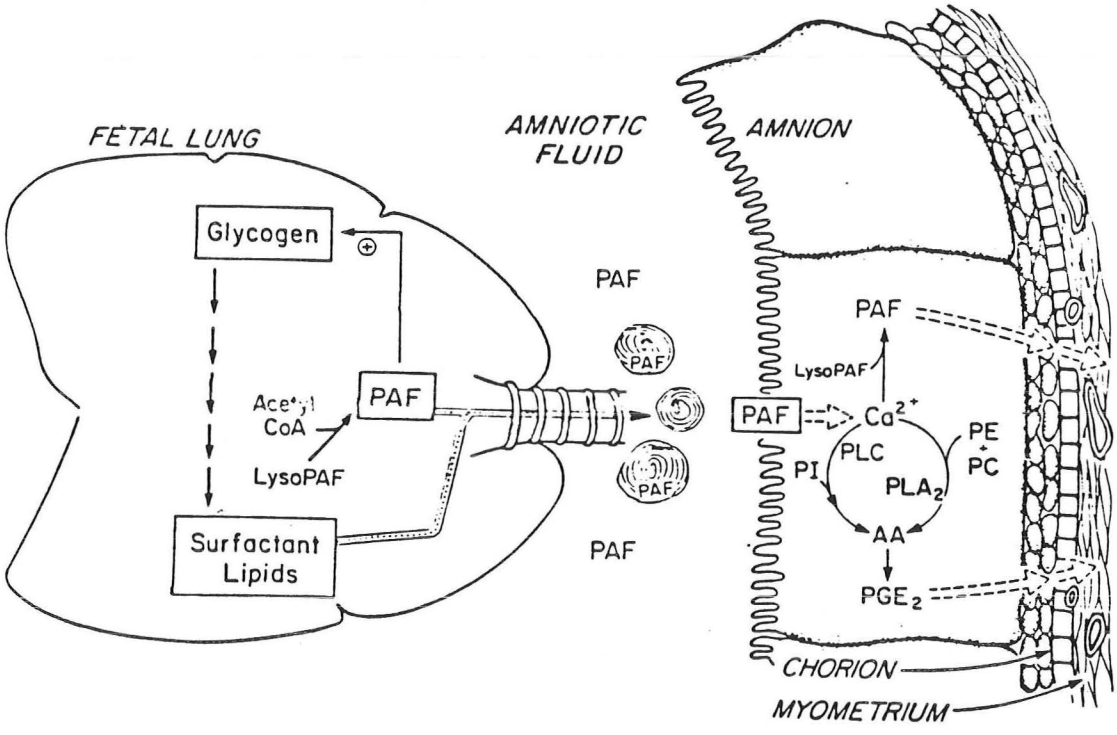
Early studies demonstrated that PAF levels in amniotic fluid increased nearly 10 fold when obtained during labor compared to fluid obtained from term pregnancies not in labor (Billah and Johnston, 1983). Although isolated amnion in culture could produce PAF in response to treatment with a Ca^{++} ionophore (A23187), it did not release it into the medium. This motivated a search for other

tissues that might produce it. Nishihira et al (1984) demonstrated that the 1-O-alkyl chain length of PAF isolated from amniotic fluid was 18 carbons while that produced by the fetal kidney was 16 carbons suggesting that perhaps the fetal lung might be a better candidate for a fetal tissue responsible for the production of PAF. Nearly half of the PAF in the amniotic fluid was found to be associated with surfactant (lipoprotein lamellar bodies formed by the type II pneumocyte) also supporting the fetal lung as a possible source of PAF. It is attractive to consider that the tissue which matures most proximal to parturition is that might be responsible for PAF synthesis which can could initiate the cascade of events that results in uterine contraction. This possibility is illustrated in Figures 11 and 12.

Immature Fetal Lung —> Inadequate Surfactant + Little PAF

Mature Fetal Lung —> Adequate Surfactant + Increased PAF —> Parturition (PAF and PGE_2)

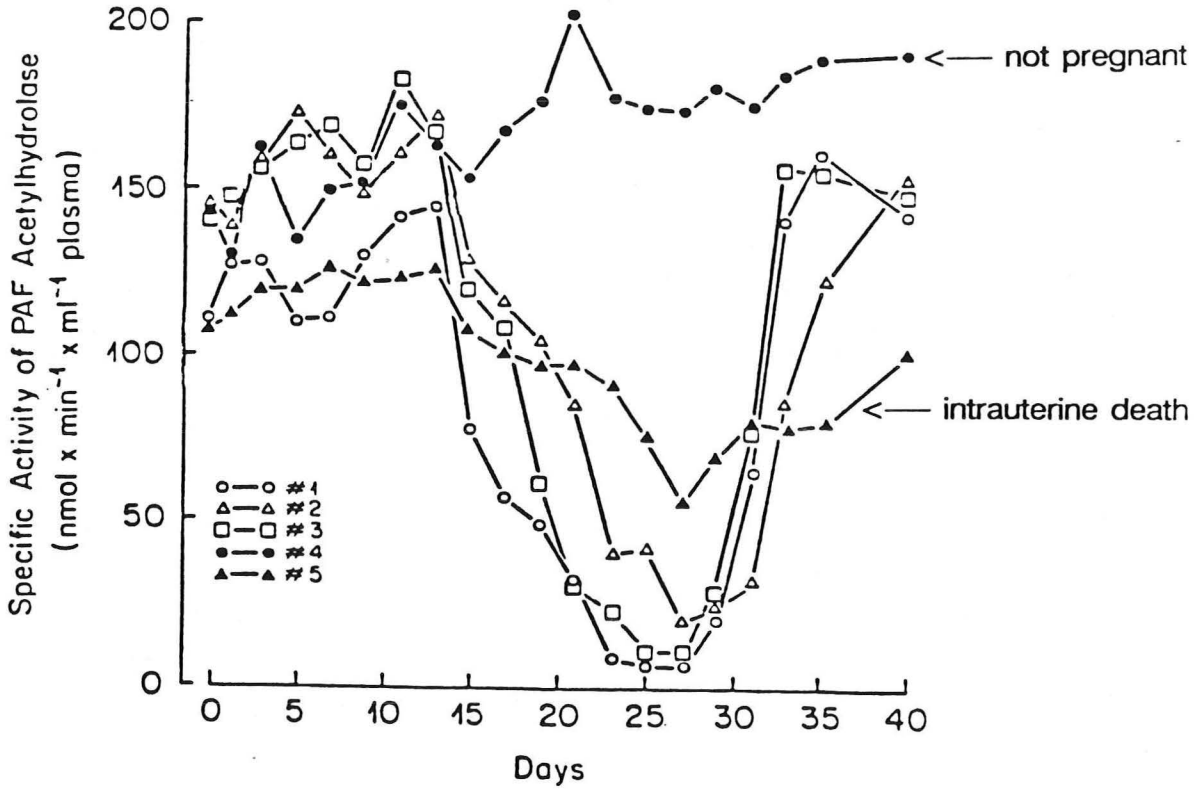
- FIGURE 11 -



- FIGURE 12 -

Fetal lung PAF increased 3 fold in rabbit during the last 10 days of gestation, while no changes were seen in hepatic and renal PAF during the same period. The PAF precursor (1-alkyl,2-acyl PC) declined 60% during this same period, lending support for the hypothesis that as fetal lung matures, it produces PAF which may contribute to the triggering of parturition. Supporting these observations are biochemical studies examining the activities of PAF synthetic enzymes in fetal lung tissue from rabbit. The activity of a Ca^{++} independent PLA_2 activity specific for the alkyl-acyl-PC precursor for PAF was demonstrated in fetal lung and shown to increase approximately 1 week prior to labor. The second enzyme in the remodeling pathway of PAF synthesis (the acetyltransferase, ATase; reaction 2, Figure 3) was also shown to increase during this same time course and to be principally present in the type II pneumocyte (the cell responsible for the production of surfactant) (Hoffman et al, 1986a & 1986b; Johnston et al, 1987).

Important regulation of fetal/maternal PAF metabolism may rest with PAF destruction by the maternal PAF AHase. Figure 13 illustrates that during pregnancy in rabbits, there is a striking decline in PAF AHase activity in the maternal plasma



- FIGURE 13 -

during late gestation (days 24-30) which returns to baseline levels after parturition (Maki et al, 1988). Thus, it is attractive to speculate that the increased levels of PAF and/or increased functional activity of PAF may relate both to an increase in the formation of PAF by the fetal lung in response to the normal maturation process in combination with the reduction in its destruction by maternal PAF AHase.

The increased levels of PAF in amniotic fluid may have several effects. First, it may enhance the formation of prostanoids (particularly PGE_2) by fetal membranes. Coincident with the decline in the ability of the mother to degrade PAF (due to reduced PAF AHase levels late in gestation), PAF together with PGE_2 may initiate myometrial contraction. Glycogen in fetal lung is thought to be important as a substrate source for the synthesis of surfactant inasmuch as fetal lung blood flow is modest. PAF administration to fetal rabbits causes pulmonary glycogenolysis and in vivo may serve as a signal to liberate substrates necessary in the formation of the disaturated PC (surfactant) necessary for fetal lung maturation in anticipation of delivery. As PAF levels continue to rise (perhaps as a result of declining maternal PAF AHase levels), parturition would then ensue as a result of increased uterine contractility in conjunction with other agents such as PGE_2 which themselves may be formed as a result of increasing levels of PAF. Of note is that PAF has, in some model systems, been shown to enhance its own synthesis suggesting that after a critical level is reached, perhaps the processes accelerates and becomes precipitous - a situation that would be of value in parturition.

In addition to roles in fetal lung development and parturition, PAF has been proposed to be important in the process of implantation. Early data in rodents and humans demonstrates that mild thrombocytopenia occurs with the establishment of pregnancy (O'Neil, 1985). More recently, a role for PAF has been supported by the predictive value of PAF production of human embryos (O'Neill et al, 1987) with respect to the success of achieving pregnancy during in vitro fertilization and embryo transfer in humans. Experiments involving culture of rabbit embryos demonstrate that PAF synthesis occurs in the zygote until blastula stage is reached (when it would already normally be implanted) [Johnston (personal communication), 1989]. Also, the synthetic rate of PAF in endometrium is >10 fold greater just prior to implantation and drops to normal levels shortly thereafter. Taken together, these findings suggest that PAF is probably of central importance in the process of embryo implantation.

C. ROLE OF PAF IN VASCULAR RESPONSES

Overview - PAF is formed by endothelial cells in response to a variety of physiologically relevant stimuli including thrombin, histamine, bradykinin, LTC_4, IL-1, and TNF (McIntyre et al, 1985 & 1986; Bussolino et al, 1988). As described in a previous section, PAF is also formed by many of nonerythrocytic elements of the blood and perivascular tissues. Similarly, these same cells vigorously respond to the presence of PAF. The goal of this section is to present arguments supporting the concept of an important role for PAF in a variety of homeostatic and pathologic vascular processes. While some PAF-induced processes are obvious (injury-induced thrombosis), others are have evolved only recently and still require thorough studies to confirm their importance. The role of endothelial cell associated PAF is both exciting and rapidly evolving. Work from Prescott's group indicates that PAF may importantly function in neutrophil adhesion to vascular endothelium at inflammatory sites - a role that may be pivotal in developing neutrophillic infiltration into appropriate sites of infection and/or injury. Further, animal models support a significant role of PAF in septic shock and other forms of hypotension. More recent studies support that PAF metabolism may be important in the atherogenesis as was touched on earlier in the discussion of PAF AHase.

Neutrophil adhesion to endothelial cells (EC) - At least two different mechanisms are known to be involved in the adhesion of PMN's to EC (Zimmerman and McIntyre, 1988; Zimmerman et al, 1985). Not the focus of the current discussion is the activation of PMN's by a variety of soluble inflammatory mediators (the complement-derived anaphylatoxin C5a, the bacterially derived family of formyl-methionyl peptides and LTB_4). This activation results in the increased expression of molecules on the surface of these cells that termed "cell adhesion proteins" which interact with specific targets present on the surface of EC and other cells. (Anderson et al, 1986). In work presented locally by Prescott, an important role for PAF produced by the EC in adhesion of PMN's to vascular endothelium has been shown. PAF synthesis and accumulation is observed in cultured EC by after exposure to thrombin. The increased presence of EC-associated PAF after thrombin treatment or after exogenous addition of PAF to EC monolayers causes dramatically increased binding of PMN's. Further, pretreatment of PMN's with PAF receptor antagonists blocks EC-associated PAF's ability to cause PMN adhesion. That PAF is the active component in the EC stimulated with thrombin is supported by the loss of PMN adherence to stimulated and subsequently fixed EC (which are still able to bind PMNs) by methanol extraction, PLA_2 treatment, or PAF AHase treatment, but not by protease treatment of EC. The documented ability of a variety of autocoids

to rapidly cause PAF accumulation in EC (histamine, bradykinin, LTC_4 and H_2O_2) suggests that their genesis during injury/inflammation may result in neutrophil accumulation in large part due to their ability to facilitate PAF-dependent PMN-EC binding at the vessel wall and perhaps to lesser extents due to their ability to cause chemotaxis.

In addition to rapid changes in PMN adherence to EC induced by agents such as thrombin, a more slowly evolving PAF accumulation is induced by cytokines (such as TNF-alpha and IL-1) (Bussolino et al, 1988). Increased PAF synthetic capacity (PAF ATase) and PAF accumulation is seen over 2-8 hours and is blocked by cycloheximide (a protein synthesis inhibitor). In contrast to the studies by Prescott's group, Bussolino demonstrated that in addition to PAF accumulation, PAF is also **released** by cytokine-stimulated EC.

Acute vascular reactions not principally involving PMN adherence - In human skin, injection of PAF results in initial blanching presumably as a result of arteriolar vasoconstriction. This is rapidly followed by the appearance of a histamine-independent wheal and flare that evolves as a result of venular dilation and endothelial contraction and increased vascular permeability (Archer et al, 1984 & 1985). PAF is 1,000-10,000 fold more effective than histamine (on a molar basis) in this regard. Although intravenous injection of PAF causes profound activation of a number of cells with the resultant production of a multitude of mediators, studies utilizing PAF receptor antagonists support the ability of PAF to cause hypotension directly (Feuerstein and Hallenbeck, 1987). Although direct vascular effects are one element in PAF-induced hypotension, negative cardiac inotropy is also seen (Kenzora et al, 1984). A role for PAF in septic shock is supported not only by the role of TNF in endotoxin-induced hypotension and the ability of TNF to cause PAF accumulation in EC, but more direct studies in animal models demonstrate that PAF receptor antagonists significantly attenuate endotoxin-induced hypotension and death (summarized in Figure 14).

In addition to endotoxic shock, an important role for PAF in IgE-mediated anaphylactic reactions has been suggested (Halonen et al, 1976; Sybertz et al, 1986). Further the ability of PAF to reverse hypertensive states has been shown (Vandogen, 1987).

Table I. Effect of PAF antagonists on endotoxin shock

	GI damage	Survival	Hypotension	Cardiac depression	Leukopenia	Thrombocytopenia	Hypoxia	Plasma extravasation
FR-900452	ND	ND	ND	ND	+	+	ND	ND
BN 52021	+	+	+	+	ND	+	ND	+
SRI 63-072	+	ND	+		+	ND	ND	+
ONO 6240	+	ND	+	+	+	–	–	–
Kadsurenone	ND	ND	+	ND	ND	ND	ND	ND
L-652731	ND	ND	+	ND	ND	ND	ND	ND
CV-3988	+	+	+	ND	ND	ND	ND	ND

ND = Not determined; GI = gastrointestinal; + = blockade of effect; – = no effect.

- FIGURE 14 -

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