PO Box 2345, Beijing 100023, China
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REVIEW

Role of platelet-activating factor in pathogenesis of acute pancreatitis

Li-Rong Liu, Shi-Hai Xia

Li-Rong Liu, Shi-Hai Xia, Department of Gastroenterology, Pancreas Center of Affiliated Hospital of Medical College of the Chinese People's Armed Police Forces, Tianjin 300162, China
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Correspondence to: Shi-Hai Xia, MD, Department of Gastroenterology, Pancreas Center of Affiliated Hospital of Medical College of the Chinese People's Armed Police Forces, Chenglinzhuang Road, Tianjin 300162, China. xshhcx@sina.com
Telephone: +86-22-60578765 Fax: +86-22-24370605
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Abstract

Platelet-activating factor (PAF) is a potent proinflammatory phospholipid mediator that belongs to a family of biologically active, structurally related alkyl phosphoglycerides with diverse pathological and physiological effects. This bioactive phospholipid mediates processes as diverse as wound healing, physiological inflammation, angiogenesis, apoptosis, reproduction and long-term potentiation. PAF acts by binding to a specific G protein-coupled receptor to activate multiple intracellular signaling pathways. Since most cells both synthesize and release PAF and express PAF receptors, PAF has potent biological actions in a broad range of cell types and tissues. Inappropriate activation of this signaling pathway is associated with many diseases in which inflammation is thought to be one of the underlying features. Acute pancreatitis (AP) is a common inflammatory disease. The onset of AP is pancreatic autodigestion mediated by abnormal activation of pancreatic enzyme caused by multiple agents, which subsequently induce pancreatic and systemic inflammatory reactions. A number of experimental pancreatitis and clinical trials indicate that PAF does play a critical role in the pathogenesis of AP. Administration of PAF receptor antagonist can significantly reduce local and systemic events that occur in AP. This review focuses on the aspects that are more relevant to the pathogenesis of AP.

Key words: Platelet-activating factor; Signal transduction; Pancreatitis; Pathogenesis

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INTRODUCTION

Inflammatory reaction is a common pathophysiological process. Appropriate inflammatory reaction has protective effects, but excessive reaction often induces injury. The underlying pathological changes of inflammation include exudation, alteration, and proliferation, which are the outcomes mediated by inflammatory mediators such as platelet-activating factor (PAF), leukotriene, tumor necrosis factor alpha (TNF-α), and interleukin-1 (IL-1). Numerous researches have shown that PAF is one of the most potent mediators in many inflammatory processes, and not only induces inflammatory reaction but also mediates synthesis and release of other mediators to aggravate the degree of inflammation.

Acute pancreatitis (AP) is a common clinical inflammatory disease. A single injection of PAF into the superior pancreaticoduodenal artery of rabbits induces dose-dependent morphologic alterations of pancreatic tissue and increases serum amylase levels[1]. Murine pancreatic acini synthesizes PAF[2] and pancreatic vascular endothelium expresses PAF receptor[3]. These findings suggest that this mediator may have a role in AP. AP is usually classified into mild and severe type. Severe acute pancreatitis (SAP) still has a high mortality rate, while the pathogenesis of AP is not well-defined. There is growing evidence that pathogenetic factors deciding the severity of AP are complicated. PAF has been strongly implicated in the development of AP.

Here we have reviewed the role of PAFs such as excessive leukocyte stimulation, microcirculatory disorder, gut endothelial barrier dysfunction, bacterial translocation, acinar cell necrosis and apoptosis in the pathogenesis of AP.

BIOLOGICAL CHARACTERISTICS OF PAF

Phospholipids are the major components of cellular membrane and are also known to be the source of arachidonic acid, which is metabolized into bioactive eicosanoids. Some phospholipids, including lysophosphatidic acid, sphingosine-1-phosphate, and PAF, exert bioactive effects. The term PAF is used because it

was first described as the substance responsible for the aggregation of platelets released from rabbit basophils after IgE stimulation[4]. Although PAF is still commonly used, it has diverse and potent physiological effects[5,6]. The chemical structure of PAF is 1-*O*-alkyl-2-acetyl-sn-glycero-3-phosphocholine determined in 1979 by three independent laboratories[7-9].

Two distinct pathways for the synthesis of PAF have been demonstrated: the remodeling pathway and *de novo* pathway[10]. The remodeling pathway is mainly involved in the synthesis of PAF by stimulated inflammatory cells. The activities of lyso-PAF acetyltransferase (lyso-PAF AcT) and PAF-synthesizing phosphocholine transferase (PAF-PCT) are directly responsible for PAF synthesis. Lyso-PAF AcT catalyzes the transfer of acetyl moiety from acetyl CoA to free hydroxyl at sn-2 position of 1-alkyl-sn-glycero-3-phosphorylcholine. PAF-PCT catalyzes the conversion of 1-alkyl-2-acetyl-sn-glycerols to PAF[11]. The synthesis and catabolism of PAF are highly regulated. The final molecular composition of PAF in tissues and the expression of its biological activities depend on the activation of catabolic pathways. The most important enzyme in limiting the PAF bioactivity is a PAF-specific acetylhydrolase (PAF-AH), which cleaves the short acyl chain at sn-2 position and forms biologically inactive lyso-PAF[12].

A diverse array of cells has been shown to synthesize PAF upon appropriate stimulation. In particular, PAF is produced by a variety of cells such as monocytes/macrophages, polymorphonuclear leukocytes (PMN), eosinophils, basophils, platelets, mast cells, vascular endothelial cells, and lymphocytes, which may participate in the inflammatory reaction[5,13]. Murine pancreatic acini can also synthesize PAF induced by cerulein[2].

PAF is a phospholipid mediator possessing a wide spectrum of potent proinflammatory action. *In vitro*, PAF promotes chemotaxis, aggregation, granule secretion, and oxygen radical generation of leukocytes and adherence of leukocytes to the endothelium. Moreover, PAF is involved in allergy, wound healing, atherosclerosis, angiogenesis, apoptosis, reproduction, and long-term potentiation[5,6,13]. Recent findings have revealed some novel effects of PAF. Through inflammatory cytokines, estrogen depletion enhances PAF production as a unique autocrine factor for osteoclast functions. Inhibition of PAF function might pave the way for a new strategy to prevent post-menopausal bone loss without disturbing osteoblast functions[14]. The study investigating the functional PAF receptor on cell and nuclear surfaces of leukemic B cells in chronic lymphocytic leukemic patients showed that the potent immunoregulatory role of PAF in B cell physiology and the presence or absence of PAF receptor on leukemic B cells may profoundly affect their *in vivo* behavior[15]. In jet fuel-induced immune suppression, PAF receptor binding can modulate immune function and is an early event in the induction of immune suppression by immunotoxic environmental agents targeting the skin[16]. PAF can amplify the heterogeneity between ischemic and normal cardiac myocytes during ischemia/reperfusion which might play a vital role in the pathogenesis of arrhythmia induced by ischemia/reperfusion[17], increase the expression of nerve growth factor mRNA and protein in human astrocytes under hypoxia which may protect the nervous tissue by promoting neuronal survival[18]. PAF is also involved in the etiopathogenesis of type 1 diabetes[19] and the pathogenesis of acute liver failure as well as in augmented compensatory liver tissue repair post-acetaminophen treatment[20].

PAF acts by binding to a specific receptor, subsequently activates multiple intracellular signaling pathways in various cell types. PAF receptor belongs to G protein-coupled receptor subfamily[21,22]. Most cells that produce PAF possess PAF receptors and are targets for PAF action. The pancreatic vascular endothelium also expresses PAF receptor[3]. It has been demonstrated that PAF binds to the receptor and activates the associated G protein. In turn, G protein activates a phosphatidylinositol-specific PLC which hydrolyzes a membrane phospholipid, phosphatidylinositol 4, 5-bisphosphate (PIP_2), to generate two second messengers: diacylglycerol and inositol 1,4,5-trisphosphate (IP_3). These compounds mediate the release of Ca^{2+} from intracellular store (ER) and activation of protein kinase C (PKC), respectively. Moreover, it has been shown that PAF can activate mitogen-activated protein kinases (MAPKs), including extracellular signal-regulated kinase (ERK)[23-27], p38 MAPK[25-27], and c-Jun N-terminal kinase (JNK)[28]. Using human umbilical vein endothelial cells (HUVECs) as a model system, Deo *et al*.[29] suggested for the first time that PAF activates pertussis toxin-insensitive $G\alpha_q$ protein upon binding to its seven transmembrane receptors and adenylate cyclase, as well as elevates cAMP levels, which activate protein kinase A (PKA). PAF exposure induces the expression of TIMP2 and MT1-MMP and binding of p^{130}Cas, Src, SHC, and paxillin to FAK. It was found that PAF is capable of stimulating nuclear factor kappa B (NF-$\varkappa$B) activation and transcription of c-fos and c-jun genes in inflammatory cells[30,31].

INVOLVEMENT OF PAF IN THE PATHOGENESIS OF AP

AP is a common clinical condition and is usually classified into mild and severe type. SAP is characterized by acute morbidity, rapid progression, multiple complications, and high mortality rate. While the pathogenesis of AP is not well-defined, considerable advances have been made in this research field. At present, it is considered that severity of pancreatitis is associated with excessive leukocyte stimulation, microcirculatory disorder, gut endothelial barrier dysfunction, bacterial translocation, and acinar cell necrosis and apoptosis. In the pathogenesis of AP, PAF has been strongly implicated (Table 1).

Role of PAF in excessive leukocyte stimulation

In the course of AP, abnormal intra-acinar cell activation of digestive enzymes induced by diverse stimuli triggers morphopathological changes in pancreatic and adjacent tissues, such as inflammation, edema, hemorrhage, necrosis, and even systemic manifestations. In 1988, Rinderknecht[32] proposed the hypothesis of excessive leukocyte stimulation. Consequently, a great number of studies have demonstrated that the initial injury results in the expression of inflammatory mediators such as PAF.

Table 1 Important roles of PAF in pathogenesis of AP

Main pathogenesis of AP	Important roles of PAF
Excessive leukocyte stimulation	To facilitate adhesion, chemotaxis and degranulation and to mediate the production of inflammatory mediators of leukocytes, and to delay PMN apoptosis
Microcirculatory disorder	To modulate indirectly/directly microvascular permeability
Gut endothelial barrier dysfunction	To upregulate adhesion molecules, intercellular signals and leukocyte–endothelial cell interactions
Bacterial translocation	To depend on its ability to induce gut endothelial barrier dysfunction
Acinar cell necrosis and apoptosis	To mediate neutrophil chemotaxis and delay neutrophil apoptosis in the pancreas, but neutrophils convert acinar cells undergoing apoptosis into necrotic cells

These mediators mediate activation and infiltration of leukocytes, a subsequent systemic inflammatory response, and multiple organ injury.

In vivo and *in vitro* studies suggest that proteolytic enzyme trypsin stimulates cytokine production from macrophages[33]. In an idealized *in vitro* experiment mimicking cerulein-induced AP, cerulein induces amylase release, increases $[Ca^{2+}]i$ and PAF synthesis of cultured pancreatic acini[2]. PAF plays a role in inflammatory reaction and induces expression of adhesion molecules that mediate neutrophil accumulation. However, PAF antagonists reduce expression of adhesion molecules and the severity of inflammation when given immediately after the induction of mild AP in mice[34]. Another research showed that PAF mediates macrophages to release thermolabile neutrophil chemotactic protein that induces neutrophil migration[35]. Moreover, activation of neutrophils with zymosan leads to the activation of PAF receptors followed by activation of CD11/CD18, phagocytosis of zymosan particles and subsequent IL-8 release. The production of IL-8 by neutrophils in response to particulate stimuli may play a role in the recruitment and activation of neutrophils in inflammatory reaction[36]. In addition, PAF is able to enhance superoxide production of PMN, expression of CD11b, and release of elastase, which are essential factors in the pathophysiology of multiple-organ failure[37]. PAF can delay apoptosis of PMN and amplify the inflammatory response by activating ERK signaling pathway[38,39]. Furthermore, PAF induces NF-κB activation and regulates gene expression through G protein-coupled transcription factor activation pathway[40]. NF-κB is a key element in inflammatory responses based on its ability to regulate the expression of inflammatory mediators. Activation of NF-κB within the pancreas is sufficient to initiate an inflammatory response[41].

The above findings indicate that PAF is involved in adhesion, chemotaxis, degranulation and, the whole procedure of activation of leukocytes. Besides, it can amplify inflammatory response via delaying apoptosis of PMN. PAF receptor is almost ubiquitous in diverse type cells and acts not only on local pancreas but also on distant organs to induce systemic inflammatory response and multiple organ injury.

Role of PAF in microcirculatory disorders

A number of experimental studies suggest that pathogenesis of AP correlates with microcirculatory disorders. Many complications of SAP are due to the amplifying effects of microcirculatory disruption. Constriction of interlobular pancreatic arteries 2 min after intraductal infusion of sodium taurocholate has been observed, indicating that microcirculatory changes may occur in early AP[42]. There is evidence that pancreatic microcirculatory changes are closely related to the process of AP. Ligating duodenum over half its circumference at 2 cm on either side of the duodenal entry of the biliopancreatic duct induces histopathologic alterations of the pancreas such as edema, parenchymal necrosis, thrombosis and hemorrhage, indicating that tissue ischemia plays a role in increasing the severity of pancreatitis[43].

Many vasoactive mediators activated during the inflammatory response to pancreatic injury can cause microcirculatory disorders in AP. PAF is one of the most important mediator. Increased microvessel permeability caused by PAF may be related to direct endothelial cell activation, adhesion molecule expression, and leukocyte activation. Synthesis of PAF by endothelial cells at the site of plasmin generation may render the endothelial cell surface pro-adhesive for neutrophils and favor a local increase in vascular permeability[44]. Recent data suggest that PAF is able to directly modulate microvascular permeability and increase venular permeability[45]. Increased capillary permeability permits sequestration of macromolecules and fluid, which causes a deficiency of circulating blood volume and microcirculatory disorders. Predominant microcirculatory disorders are nutritive capillary perfusion failure, with the consequence of prolonged focal hypoxia or anoxia, and inflammation-associated microvascular leukocyte recruitment, CD11b and intercellular adhesion molecule (ICAM)-1-mediated leukocyte-endothelial cell interaction and loss of endothelial integrity, which may result in both edema formation and necrosis. Moreover, vasospasm and microthrombi formation due to hypercoagulability can also lead to the deterioration of pancreatic microcirculation and pancreatic necrosis.

It has been shown that the treatment of AP with PAF antagonists can significantly improve capillary blood flow in the pancreas and colon, renal, and respiratory function as well as survival rate, stabilize capillary permeability, decrease fluid loss into the third space[46,47]. The partial protective effect of PAF antagonists further supports the role of PAF in microcirculatory disorders.

Role of PAF in gut endothelial barrier dysfunction

Gut endothelial barrier dysfunction is a critical factor for the development of tissue injury and organ dysfunction in AP. The study on dogs colonized with a strain of *Escherichia coli* (*E coli* 6938K) bearing plasmid pUC4K showed that most dogs with severe pancreatitis have ischemic changes in the small bowel mucosa and *E coli* translocation to the pancreas and mesenteric lymph nodes (MLNs), suggesting that the gut is a primary source of infection in pancreatitis[48].

PAF plays a key role in the development of pancreatitis-associated gut endothelial barrier dysfunction and acts via the upregulation of adhesion molecules, intercellular signals and leukocyte-endothelial cell interactions. Leukocyte β2-integrins play an important role in PAF-induced intestinal necrosis, and CD11b/CD18 are the main adhesion molecules involved in the pathogenesis of injury[49]. Moreover, PAF can activate rapidly intestinal xanthine oxidase (XO) by converting proteolytic xanthine dehydrogenase (XD) to XO in the ileal epithelium. This effect is mediated by neutrophils. XO is an important source of reactive oxygen species in the small intestine and its activation promotes PAF-induced PMN sequestration in the intestine, thus causing gut endothelial injury[50]. PAF can alter the cytoskeletal structure of intestinal epithelium and cause the influx of FD-4 (an index of intestinal permeability) from intestinal lumen to systemic circulation, and induce tyrosine phosphorylation of E-cadherin and cadherin-associated proteins. These findings reveal the possible mechanism of PAF in modulating intestinal mucosal permeability, PAF modulates macromolecular movement across the intestinal mucosal barrier probably via tyrosine phosphorylation of E-cadherin and cytoskeletal alteration of enterocytes[51]. In addition, gut microcirculatory disorder plays a pivotal role in endothelial barrier dysfunction.

Further support for the role of PAF in gut endothelial barrier dysfunction is provided by the fact that the administration of PAF antagonists improves pancreatitis-associated gut barrier dysfunction characterized by increased endothelial permeability, albumin leakage from blood to the mucosal interstitium and intestinal lumen, and bacterial translocation[52-54].

Role of PAF in bacterial translocation

Bacterial translocation is an important source of pancreas infection in AP and is responsible for the high incidence of pancreas and distant infections occurring after AP. Support for the role of PAF in bacterial translocation is provided by the fact that PAF antagonists reduce bacterial translocation. Pretreatment with PAF antagonists, WEB-2170, lexipafant and BN52021, reduces bacterial translocation to distant organs other than the pancreas[55]. Similar findings showed that AP induced by supramaximal cerulein stimulation significantly increases bacterial translocation in MLNs, pancreas, liver, spleen and blood[56]. Both recombinant PAF-acetylhydrolase (rPAF-AH) and PAF receptor antagonist, BN52021, can decrease bacterial translocation in the pancreas and blood. In addition, rPAF-AH decreases bacterial translocation in MLNs. The action of PAF involved in bacterial translocation may be due to its ability to induce gut endothelial barrier dysfunction in AP.

Role of PAF in acinar cell necrosis and apoptosis

Pancreatitis is characterized by inflammation and death of acinar cells. Death can occur due to either necrosis or apoptosis. Kaiser *et al*.[57] have observed marked necrosis but very little apoptosis in severe pancreatitis models. In contrast to the findings in severe pancreatitis, mild pancreatitis is characterized by very little necrosis but a high degree of apoptosis, suggesting that apoptosis may be a teleologically beneficial response to acinar cell injury in general, especially in AP. Deficiency of pancreatic connexin converts reversible AP into severe disease and decreases the sensitivity of acinar cells to apoptotic stimuli, demonstrating that apoptosis determines the severity of AP[58].

It has been reported that PAF is involved in acinar cell damage[59]. Treatment with antineutrophil serum (ANS) and BN52021 can prevent inflammatory responses caused by cerulein and decreases cell damage. Treatment with ANS increases apoptosis in cerulein-infused animals, indicating that cerulein stimulates pancreatic production of PAF. PAF mediates both apoptosis and neutrophil chemotaxis in the pancreas. Neutrophils in turn may convert acinar cells undergoing apoptosis to necrotic cells.

THERAPEUTIC EFFECTS OF PAF ANTAGONISTS ON AP

Recent studies have established the critical role of inflammatory mediators such as TNF-α, IL-1β, IL-6, IL-8, IL-10, PAF, C5a, ICAM-1 and substance P, in the progression of AP from local pancreatic inflammation to a systemic inflammatory disease. Elucidation of the key mediators in AP coupled with the discovery of specific inhibitors makes it possible to develop clinically effective anti-inflammatory therapy. At present, a number of inflammatory mediator antagonists are tested. PAF antagonists, including ginkgolide B (BN52021), lexipafant (BB-882), CV-6209, TCV309, and WEB-2170, *etc*., have shown beneficial effects on the manifestations of AP. In experimental pancreatitis and clinical trials, administration of several PAF antagonists significantly reduces the level of serum amylase, leukocyte infiltration, and improves capillary blood flow in the pancreas and distant organs, renal and respiratory function, and survival rate.

In animal pancreatitis model, ginkgolide B could significantly reduce vascular permeability, pancreatic edema, hyperamylasemia, diminute superoxide dismutase (SOD) activity, and inhibit lipid peroxidation in pancreatic tissue. These changes are accompanied with significant reduction of acinar cell vacuolization and remarkable inhibition of inflammatory cell infiltration in the interacinar space[60,61]. In addition, treatment with ginkgolide B has shown protective effects on slow mesenterio-angial small arteriolar and venular blood flow velocity and dilated mesenterio-angial small venular diameter at the early phase of AP[62]. Moreover, ginkgolide B reduces bacterial translocation to distant sites, has a significant effect on serum pancreatic enzymes and histologic score of pancreatitis, and suppresses elevation in IL-6 levels. Preventing bacterial dissemination in early AP may have beneficial effects on the evolution of this disease[55,56]. Furthermore, ginkgolide B reduces malondialdehyde accumulation in pancreatic tissue, prevents sulfhydryl depletion in lung tissue, necrotic and inflammatory changes in the pancreatic tissue, and improves survival rate[63]. Activation of pulmonary alveolar macrophages (PAMs) might play an important role in

severe complications of AP. Ginkgolide B reduces total and free activity of lysosomal hydrolases of PAMs and partly prevents labilization of their lysosomal membranes. Therefore, an important mechanism of ginkgolide B underlying pulmonary complications of AP is to stabilize PAM lysosomes[64]. Moreover, BN50739 can reduce intestinal injury, levels of endotoxin and bacterial counts in the portal blood, MLNs and pancreas and increase intestinal mucosal blood flow[54]. In pigs with SAP, pre- and post-treatment with BN50739 can effectively reduce PAF levels in lung and tracheal mucosa and the severity of acute lung injury following SAP by reducing PMN sequestration and the amount of elastase, or by inhibiting PLA_2 activities in lung and tracheal mucosa[65].

In rats with AP induced by intraductal infusion of 5 g/L sodium taurodeoxycholate, pretreatment with lexipafant could reduce pancreatic endothelial barrier dysfunction and severity of pancreatitis-associated intestinal dysfunction as well as systemic concentrations of IL-1 and local leukocyte recruitment[53,66,67]. AP lexipafant reduces the activity of serum cytokines (TNF-α, IL-1β), lung myeloperoxidase (MPO) and serum amylase[68]. Lexipafant treatment can decrease bacterial spread to distant sites in AP induced by pressure injection of 3% taurocholate and trypsin into the common biliopancreatic duct[69].

In rats, TCV-309 administered prior to cerulein and/or PAF reduces cerulein-induced pancreatitis and prevents PAF-induced pancreatitis[70]. It was reported that treatment with TCV-309 before septic challenge effectively prevents hyperactivity of bronchoalveolar macrophages and pancreatitis-associated lung injury by reducing serum concentrations of cytokine-induced neutrophil chemoattractant (CINC) and CINC messenger RNA (mRNA) in the lung, as well as pulmonary infiltrates immunoreactive for CINC or Mac-1 (CD11b/CD18)[71].

CONCLUSION

In the pathogenesis of AP, PAF exhibits pleiotropic function and is involved in both local pancreatic injury and systemic multiple organ damage. The effectiveness of PAF antagonists depends not only on their ability to block the effects of inflammatory mediators but also on their administration early enough in the course of pancreatitis before pancreatic necrosis or organ dysfunction occur. PAF antagonist therapy for systemic inflammatory response syndrome and multi-organ dysfunction syndrome in the management of patients with SAP has been considered as an important advance in the treatment of these patients.

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