

Platelet activating factor in allergies

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Abstract

The platelet-activating factor (PAF) produced and released by mast cells, basophils, neutrophils, eosinophils, fibroblasts, platelets, endothelial cells, and even cardiac muscle cells plays an important role in inflammatory and thrombotic diseases. PAF has been shown to be an important mediator in anaphylaxis. Serum level of the factor correlates with the severity of systemic reactions. PAF is also involved in asthmatic patients' bronchoconstriction, mucus hypersecretion, and inflammation of bronchi. Furthermore, increased plasma levels of PAF have been reported in patients with urticarial. Studies have shown that PAF increases the permeability of skin's capillaries and induces the development of wheals, flare, and inflammatory reactions in the skin.

This review focuses on the actions of the PAF on the eosinophiles and mast cells. Following that pathophysiological mechanism of the PAF in anaphylaxis bronchial asthma and urticaria was discussed.

Keywords

anaphylaxis, bronchial asthma, platelet-activating factor, urticaria

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Introduction

Platelet-activating factor (1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholine) also known as PAF, was discovered by the French immunologist Jacques Benveniste (1935–2004). In 1972, Benveniste demonstrated that this factor was released from basophils.¹ Further reports have shown that PAF is produced and released by other cells such as neutrophils, eosinophils, fibroblasts, platelets, endothelial cells, and even cardiac muscle cells.² Phospholipase A₂ and acetyltransferase are required for the production of PAF in the most common pathway and an acetylhydrolase specific for PAF (PAF acetylhydrolase [PAF-AH]) is responsible for its degradation. The PAF elimination time is short, because its half-life is 3–13 min.³ It is interesting that most of the cells producing PAF also have receptors for it (PAFR). PAF is a phospholipid which is involved in the regulation of a variety of cells, principally in the immune and nervous systems. The importance of PAF is emphasized in inflammation and coagulation.^{4,5} This factor increases inflammation through chemotaxis,

stimulation of degranulation, and release of oxygen radicals from leukocytes. Furthermore, it promotes the adhesion of inflammatory cells to the vascular endothelium, which in turn also undergoes increased permeability under the influence of PAF. The group of agents stimulating the release of PAF from the vascular endothelium is particularly large. It has been demonstrated that thrombin, angiotensin II, vasopressin, leukotrienes (LTs), plasmin, interleukin-8 (IL-8), and tumor necrosis factor (TNF) can stimulate the release of this factor from endothelial cells. By contrast, PAF relaxes arterial smooth muscle, as opposed to the uterus

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Table 1. Biological properties of PAF.

	Characteristic	Reference
Source	Mast cells, basophils, eosinophils, monocytes, fixed tissue macrophages, neutrophils, endothelial cells, platelets	1, 2, 3
Inactivation	By platelet-activating factor acetylhydrolase (PAF-AH) to lyso-PAF	3, 4, 17
Mean plasma level	23.8 pg/mL	16,
Half-life of PAF	3–13 min	13, 14
Action	Via binding to a specific receptor (PAFR)	5
	Chemotaxin for neutrophils and eosinophils	10, 13
	Bronchoconstrictor	26, 27, 30
	Increases vascular permeability and edema	15
	Reduction of coronary blood flow	6, 15
	Depression of myocardial contractility	6, 15
	Direct arrhythmogenic effect	6, 15

Recent literature indicates that PAF is an important element of allergic reactions, especially anaphylaxis.

muscle in which it stimulates contractions. PAF has a pro-arrhythmic and negative inotropic effect on a heart muscle; moreover, it reduces blood flow through the coronary vessels (Table 1).⁶

PAF and eosinophils

Eosinophils play an important role in allergic diseases. They are activated by numerous cytokines. The factors that significantly regulate the differentiation and maturation of eosinophils include IL-3, IL-5, IL-33, and granulocyte macrophage-colony stimulating factor (GM-CSF). Eotaxin is a chemotactic factor for eosinophils.⁷ In addition to these factors, it has been shown that PAF is not only produced by eosinophils, and at the same time it also multidirectionally modulates their function. *In vitro* studies have shown that PAF is a chemoattractant for eosinophils, and via β_2 integrin it increases their adhesion to vascular endothelium. PAF increases the production of leukotriene C₄ (LTC₄), oxygen-derived radicals, and degranulation of eosinophils.⁸

Very interesting observations by Kato et al.⁹ have shown that PAF can activate eosinophils in two stages. Phase one – fast activation of eosinophils is carried out by G proteins that, with the participation of phospholipase C β (PLC β), lead to the rapid but short release of oxygen-derived free radicals, and the second phase, which also occurs with the participation of PAF, but eosinophils must be additionally stimulated by cell adhesion involving β_2 integrin. This phase is characterized by a slower but longer release of oxygen-derived radicals.¹⁰

Dyer et al.⁸ demonstrated in an animal model that PAF causes the release of factors such as IL-13, eotaxin-1, a protein blocking receptor for IL-1, basic fibroblast growth factor (bFGF), RANTES, IL-9 and platelet-derived growth factor (PDGF) from eosinophils.

PAF and mast cells

Mast cells, also known as mastocytes, play a key role in type I allergic reactions according to the Gell and Coombs classification. Anaphylactic reactions begin with the activation of these cells. Classic mast cell activation occurs via the Fc ϵ RI receptor to which a complex of IgE-allergen is attached. An alternative pathway of mast cell activation is IgE-independent, and may occur under the influence of complement components, chemokines, immune complexes, or factors released during the decomposition of various types of microorganisms.¹¹ Activated mast cells release a variety of factors involved in allergic inflammation, e.g. cytokines, and factors influencing blood vessels including histamine and enzymes. Mast cells not only produce PAF, but they can also be activated by it. In the case of mast cells located in the skin, exposure to PAF leads to degranulation of their granules via neuropeptides.¹² Kajiwar et al.¹³ has demonstrated *in vitro* that PAF can directly activate mast cells derived from lung tissue through surface PAFRs. An interesting aspect of mast cells that have been highlighted by these studies is that the release of histamine from lung mast cells mastocytes is dependent on the concentration of PAF.

The greater the concentration of this factor in the mast cell environment, the more enhanced is the release of histamine.

Mastocytes located between muscle fibers, in the area of blood vessels and myocardial artery intima have been a subject of interest for approximately 20 years. It appears that PAF-activated myocardial mast cells locally release factors responsible for cardiac dysfunction and hypotension that occurs in severe anaphylactic reactions.¹⁴

Anaphylactic reactions and PAF

Anaphylaxis is a severe, immediate, life-threatening reaction that occurs in hypersensitive individuals, caused by exposure to a stimulus that is well tolerated by healthy individuals. Anaphylactic reactions are divided into allergic, non-allergic, and idiopathic. The allergic anaphylaxis is mediated by an immunologic mechanism and usually is IgE, IgG, and immunocomplex-component dependent. The non-allergic anaphylaxis is non-immunologic and IgE-independent caused by drugs, physical factors, exercise, and other factors. The cause of idiopathic anaphylaxis is unknown.¹⁵ The main cells involved in the allergic anaphylaxis are mast cells and basophils, which release histamine, serotonin, proteolytic enzymes, cytokines, and lipid mediators such as prostaglandin D₂ (PGD₂), LTB₄, cysteinyl LTs, LTC₄, LTD₄, LTE₄, and PAF. PAF has recently attracted a large amount of attention and interest, as it is a very important element of pathogenic severe anaphylactic reactions.¹⁶ Examining the concentration of serum PAF in individuals with anaphylaxis, Vadas et al.¹⁷ has found that compared to the control group, it is significantly higher and positively correlated with the severity of anaphylactic reaction. It has been found that in healthy individuals, a serum concentration of PAF is approximately 23.8 pg/mL and in persons with severe anaphylaxis can reach 805 ± 595 pg/mL. Vadas et al.¹⁷ has observed that serum PAF levels in patients with grade 1, 2, and 3 anaphylaxis were 2.5-, 5-, and 10-fold higher than in the control group, respectively. Observations of the activity of PAF-AH, an enzyme neutralizing PAF, are particularly interesting. Acetylhydrolase activity studies have revealed significantly lower activity of this enzyme in people with very severe anaphylaxis caused by eating peanuts.¹⁸ Generally, it has been

shown that people with low PAF-AH activity have been characterized by a higher concentration of serum PAF compared to people with normal acetylhydrolase activity. Studies on the biology of this enzyme are interesting. It has been demonstrated that 70% of serum PAF-AH is bound to low-density lipoprotein (LDL), while the remainder is bound to high-density lipoprotein (HDL), moreover it has been found that lowering LDL levels prolongs PAF half-life. Therapy with lovastatin or fenofibrates, in addition to lowering LDL, leads to a proportional reduction in the activity of PAF-AH and can increase the risk of anaphylaxis.^{19,20}

The significance of PAF in the development of anaphylactic reactions has been confirmed by animal experiments. Anaphylaxis could not be induced in rabbits, mice, and rats in which cellular receptors for PAF were blocked.²¹

A comparison of the significance of diagnostic measurements of the concentrations of histamine, tryptase and PAF in anaphylactic reactions, has shown that the levels of serum PAF is the most useful as it correlates most accurately with the severity of the anaphylactic reaction. In the case of histamine, an increase in serum levels has been observed in 35% of patients with a moderate reaction and 61% with a severe reaction. Tryptase levels have correlated slightly better, the serum concentration of which has increased in 55% of patients with a grade 2 anaphylactic reaction and in 75% of patients with severe anaphylaxis. The serum concentration of PAF has been shown to be higher in 100% of patients with severe anaphylaxis.²²

According to the experts' guidelines, epinephrine administered intramuscularly is the first-line treatment for anaphylaxis. It is recommended that administration of this drug should occur as soon as possible during the development of anaphylaxis with cardiovascular symptoms.²³ Epinephrine directly affects blood vessels by preventing their dilatation, and it has positive ino- and chronotropic activity on cardiac muscle. Moreover, it causes bronchial smooth muscle relaxation and reduces edema of the respiratory tract epithelium. Epinephrine also blocks the release of histamine and other mediators from mast cells and basophils. In the case of food allergy, it has been demonstrated that delayed administration of epinephrine results in an increased risk of severe anaphylaxis.²⁴ A hypothesis to explain the role of epinephrine administration timing on the course of anaphylactic shock

development has been published by Vadas and Perelman.²⁵ They have shown *in vitro* that human vascular smooth muscle cells (HVSMCs) stimulated with PAF release prostaglandin E₂ (PGE₂), which is a strong smooth muscles relaxing factor. However, pre-incubation of HVSMCs with epinephrine completely abolishes the stimulatory effect of PAF. Furthermore, the authors have noted that the block of PGE₂ release is more effective the quicker epinephrine is added to the HVSMC culture following PAF stimulation.

PAF and bronchial asthma

PAF produced by several types of inflammatory cells participates in the pathogenesis of bronchial asthma. It has been demonstrated that PAF can directly cause bronchial obstruction in animals under experimental conditions, while in humans it belongs to a group of factors that increase bronchial tree hyper-reactivity.^{26,27} The use of PAF receptor blockers has been shown to abolish the bronchoconstriction effect of this factor. Moreover, it has also been demonstrated that PAF increases bronchial epithelial structure mucus production, and increases the permeability of pulmonary blood vessels. Howard²⁸ suggests that PAF is an important driver of inflammation in the bronchial epithelium. The production of PAF increases in inflammatory cells both during exposure to inhaled allergens, as well as during infection. As mentioned above, PAF is a chemotactic factor for neutrophils and it increases the release of oxygen-derived radicals from both neutrophils and eosinophils. Pro-inflammatory PAF activity is also manifested by the stimulation of LTB₄ production. It is additionally suspected that PAF may be involved in the stimulation of bronchial tree remodeling. Studies on salbutamol, (short-acting β_2 -adrenergic receptor agonist [SABA]), have revealed that inhalation of the drug results in the release of PAF, which in turn stimulates smooth muscle proliferation.^{29,30}

Obesity is an important factor that negatively affects the control of asthma in patients with bronchial asthma. A study by Grotta et al.³¹ of obese children and young adults suffering from bronchial asthma has shown that they have an increased serum concentration of PAF in addition to leptin, eotaxin, RANTES, and TNF- α . These factors are responsible for chemotaxis and activation of inflammatory cells, particularly eosinophils. According to

the authors, PAF is one of the factors responsible for poor control of bronchial asthma.

PAF and urticaria

Urticaria is characterized by formation of wheals and erythema on the skin. From an etiological point of view, urticaria is divided into three types: allergic, non-allergic, and idiopathic. Based on the duration of the lesions the urticaria is described as either acute or chronic.³² Activation of mast cells either directly (e.g. chemical, physical factors) or indirectly (e.g. anaphylatoxins, eicosanoids, plasmin, Hageman factor) can result in degranulation of mast cells and formation of the skin lesions.³³ Mastocytes play a central role in both acute and chronic urticaria. Mediators released from these cells, such as histamine, serotonin, proteolytic enzymes, proteoglycans, TNF- α , IL-6, and LTs directly or indirectly affect the development of wheals and erythema. Histamine plays a key role in the development of wheals. It has been also noted that vascular endothelial growth factor (VEGF) and PAF play an important role in patients with urticaria. These factors complement pathogenetic changes by increasing the permeability of capillaries in the skin and enhancing the development of wheals.³⁴ Moreover, PAF can also intensify the inflammation process by chemotactic action on other cells involved in inflammation such as eosinophils, neutrophils, and macrophages. This effect is especially noticeable in chronic urticaria. Studies on volunteers have shown that PAF injected subcutaneously induces typical urticarial wheals.³⁵

Urticaria etiology is very diverse and therefore treatment of this type of lesions is troublesome and often ineffective. Drugs that act mainly on mast cells by blocking the H₁-receptor are recommended including first and second generation antihistamines and H₂ receptor blockers as adjunctive therapy. Drugs not registered for the treatment of urticarial diseases (e.g. sulfasalazine, montelukast, methotrexate, cyclosporine) have been used in attempt to find a therapy without success. A large therapeutic efficacy in urticaria has been shown by rupatadine, a second generation antihistamine having blocking activity on both H₁ and PAF receptors on the surface of mast cells.³⁶ Recent investigations have confirmed the efficacy of this drug in the therapy of both acute and chronic urticarial.^{37,38} In turn, promising results have been shown in a

study of omalizumab at doses of 150 or 300 mg delivered subcutaneously. Interestingly, omalizumab is a monoclonal antibody against the C3 fragment of the IgE heavy chain and the main indication for this drug is severe asthma that is poorly controlled with the use of classical treatment.³⁹

Conclusion

In summary, we conclude that an important role is emerging for PAF in allergic reactions, particularly of the first type. Studies on anaphylaxis have shown that PAF contributes to the development of anaphylactic shock. In bronchial asthma PAF can directly and indirectly enhances obstructive changes of bronchi, by stimulation of allergic inflammation of the respiratory tract epithelium. Studies that have looked into the role of PAF in urticaria pathogenesis have shown that this factor is capable of causing wheals and erythema, and it can increase skin lesions by acting on inflammatory cells.

Declaration of conflicting interests

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