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Biochimica et Biophysica Acta 1761 (2006) 1359–1372
BIOCHIMICA ET BIOPHYSICA ACTA
BBA
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Review

Clinical aspects of plasma platelet-activating factor-acetylhydrolase

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Received 13 May 2006; accepted 15 June 2006
Available online 1 September 2006

Abstract

Plasma platelet-activating factor (PAF)-acetylhydrolase (PAF-AH), which is characterized by tight association with plasma lipoproteins, degrades not only PAF but also phospholipids with oxidatively modified short fatty acyl chain esterified at the *sn*-2 position. Production and accumulation of these phospholipids are associated with the onset of inflammatory diseases and preventive role of this enzyme has been evidenced by many recent studies including prevalence of the genetic deficiency of the enzyme in the patients and therapeutic effects of treatment with recombinant protein or gene transfer. With respect to the atherosclerosis, however, it is not fully cleared whether this enzyme plays an anti-atherogenic role or pro-atherogenic role because plasma PAF-AH also might produce lysophosphatidylcholine (LysoPC) and oxidatively modified nonesterified fatty acids with potent pro-inflammatory and pro-atherogenic bioactivities. These dual roles of plasma PAF-AH might be regulated by the altered distribution of the enzyme between low density lipoprotein (LDL) and high density lipoprotein (HDL) particles because HDL-associated enzymes are considered to contribute to the protection of LDL from oxidative modification. This review focuses on the recent findings which address the role of this enzyme in the human diseases especially including asthma, septic shock and atherosclerosis.

Keywords: Platelet-activating factor; PAF; Platelet-activating factor-acetylhydrolase; PAF-AH; Atherosclerosis; Asthma; Shock; Inflammation; Lipoprotein; Atherogenesis; Oxidized phospholipid

1. Introduction

PAF (1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine) is a potent phospholipid mediator involved in inflammatory reactions [1]. Its actions are mediated via the specific receptor which belongs to the family of seven transmembrane-spanning G-protein-linked receptors [2]. PAF is hydrolyzed and converted to lysoPAF by the catalytic reaction of PAF-AH (3.1.1.47) which is a Ca^{2+} independent enzyme belonging to group 7 of the family of phospholipase A_2 [3]. At present, three isoforms of PAF-AH are identified: plasma PAF-AH, which is also known as lipoprotein-associated phospholipase A_2 (Lp-PLA_2) due to its characteristics of association with plasma lipoproteins, and intracellular Types I and II PAF-AHs [4]. Plasma PAF-AH shares 41% sequence identity with intracellular Type II PAF-AH, whereas both enzymes show less structural similarity to Type I PAF-AH [4]. Although plasma PAF-AH activity was first described in plasma [5], this enzyme has been observed in other extracellular fluids such as milk and the urine under the pathological conditions [6]. In the human plasma PAF-AH, Ser-273 residue located in the lipase and esterase motif (Gly–Xaa–Ser–Xaa–Gly) is the active-site nucleophile and forms a catalytic triad with His-351 and Asp-296 [7]. Another important feature of this enzyme is that this enzyme preferentially degrades oxidatively modified phospholipids which could be produced by oxidative stress. It has been reported that some of these oxidatively modified phospholipids show the potent bioactivities through the PAF-receptor. Many recent evidences suggest that plasma PAF-AH might play an anti-inflammatory role in human diseases by preventing the accumulation of PAF and PAF-like oxidized phospholipids. Based on this putative role of this enzyme, therapeutic effects of this enzyme have been assessed in the patients with asthma and septic shock in clinical studies. The role of this enzyme in atherosclerosis is, however, controversial, because this enzyme can also produce lysoPC and oxidatively modified nonesterified fatty acids which could promote the pathogenesis of atherosclerosis. This review focuses on the recent findings which address the role of this

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doi:10.1016/j.bbalip.2006.06.017

enzyme in the human diseases including especially asthma, septic shock and atherosclerosis.

1.1. Behavior of plasma PAF-AH in the blood

The human plasma PAF-AH is produced as a protein composed of 441 amino acid residues and is secreted into the circulation after cleavage of a hydrophobic signal peptide at the cleavage position, Ala-17/Val-18 [7,8]. The liver is the main source of this enzyme appeared in the blood and hematopoietic stem cell-derived cells (primarily macrophages) are responsible for production and secretion of the circulating plasma PAF-AH activity [9,10]. In human plasma, PAF-AH activity is associated mainly with the apolipoprotein B (apoB)-containing lipoproteins and primarily with LDL (d=1.019–1.063). A small portion of circulating enzyme activity (less than 20%) is also associated with HDL. Carboxyl terminus of apoB plays a key role in the association of this enzyme with LDL [11]. The cellular secretion of plasma PAF-AH is likely to occur independently of the secretion of LDL or other lipoprotein particles. After secretion, the enzyme is subsequently bound to these particles in plasma. Within these lipoprotein pools, the enzyme is preferentially associated with small dense LDL (LDL-5; d=1.050–1.063 g/mL) and very high density lipoprotein-1 (VHDL-1), alternatively denoted as HDL3c [12]. It is of special interest that plasma PAF-AH is preferentially associated with small dense LDL because small dense LDL is closely related to the process of atherogenesis [13]. Small dense LDL is susceptible to oxidative stress due to a large surface area and has higher affinity to proteoglycans on the vascular arterial walls [14]. The presence of lipoprotein (a) [Lp(a)], which contains apolipoprotein (a) with apoB, affects the distribution of plasma PAF-AH in the lipoprotein particles. The association of PAF-AH with small dense LDL is increased, when plasma levels of Lp(a) exceed 30 mg/dL [15]. In a more recent study, it has been reported that most plasma PAF-AH activity is associated with electronegative subfraction of LDL [LDL(−)] which contains 8% and 15.6% of plasma LDL in normolipidemic and familial hypercholesterolemic subjects, respectively [16]. This observation coincides with the preferential association of the enzyme with small dense LDL, because LDL(−) is abundant in small dense LDL [17]. It has been shown that LDL(−) induces the release of chemokines such as interleukin-8 and monocyte chemotactic protein-1 [18,19], and is cytotoxic to human cultured endothelial cells [20,21]. Chemokine release induced by LDL(−) in part be a result of the bioactivities of lysoPC and/or oxidized nonesterified fatty acids, which could be produced from LDL(−) by the reaction of associated plasma PAF-AH activity. Although association of plasma PAF-AH with lipoprotein particles is not essential for enzyme activity, the difference in distribution of this enzyme among these lipoprotein particles could affect the regulatory function of this enzyme.

1.2. Substrate of lipoproteins-associated plasma PAF-AH

In order to maintain the homeostatic function, PAF level is maintained at the constant level as low as 54±40 pg/mL in normal human plasma [22]. The purified human plasma PAF-AH shows a greater Km value [13.7 μM [23] or 12 μM [24]] than the PAF level detected in human plasma under physiological and even pathological conditions. The half-life of PAF is only a few minutes in normal plasma, because this enzyme, which is constitutively expressed in human plasma at concentrations ranging between 0.5 and 1.0 μg/mL [25], has a high Vmax value (170 μmol/min/mg). Although HDL-associated lecithin-cholesterol acyltransferase also shows hydrolytic activity towards PAF, its contribution to removal of PAF *in vivo* is very low [26]. Another HDL-associated enzyme, paraoxonase-1 (PON-1) has been reported to show hydrolytic activity towards PAF [27], but this hydrolytic activity is probably a result of contamination of PON-1 preparations with plasma PAF-AH [28,29]. Plasma from the subjects with a point mutation of plasma PAF-AH (Val279Phe) shows no hydrolysis of PAF and exogenously added PAF remains unchanged [30] in this plasma. Thus, plasma PAF-AH accounts for almost all the hydrolytic activity towards PAF in the human plasma.

Although plasma PAF-AH was discovered as an enzyme which degraded an acetyl ester of PAF, subsequent studies showed that this enzyme had relatively broad substrate specificity. Plasma PAF-AH also shows the hydrolytic activity towards phosphatidylcholine (PC) with a short fatty acyl chain at the *sn*-2 position. Although plasma PAF-AH hardly degrades PC with a C_9 acyl chain at the *sn*-2 position, the enzyme activity is remarkably increased in the presence of an aldehyde group at the ω-end of the fatty acyl chain [31]. The increased activity is probably due to increased water solubility of the substrates [32]. Additionally ω-carboxyl and ω-aldehydic PAF analogs with a C_5 acyl chain at the *sn*-2 position are also preferentially hydrolyzed by plasma PAF-AH. In addition, their *sn*-1 acyl analogs are also preferential substrates for this enzyme. These phospholipids may originate from non-enzymatic radical-mediated oxidation of polyunsaturated fatty acids esterified at the *sn*-2 position. Indeed, oxidatively fragmented PAF-analogs [1-*O*-hexadecyl-2-(butanoyl or butenoyl)-*sn*-glycero-3-phosphocholines] [33] or oxidatively modified PAF-analogs [(1-palmitoyl-2-(5-oxovaleryl)-*sn*-glycero-3-phosphocholine and 1-palmitoyl-2-glutaroyl-*sn*-glycero-3-phosphocholine)] [34] have been identified in oxidize LDL particles. Among these oxidized phospholipids, some, but not all, show the pro-inflammatory bioactivities. For example, 1-palmitoyl-2-(5-oxovaleryl)-*sn*-glycero-3-phosphocholine and 1-palmitoyl-2-glutaroyl-*sn*-glycero-3-phosphocholine induce monocytes binding to endothelial cells [35,36]. In addition to these PAF analogs, PAF may be possibly formed in LDL by the free radical oxidation and decomposition of polyunsaturated fatty acids esterified at the *sn*-2 position of alkyl acyl PC [37]. These observations led to the hypothesis that LDL-associated plasma PAF-AH plays a protective role in removal of pro-inflammatory phospholipids generated by oxidation of LDL particles. Very recently, Stafforini et al. reported that plasma PAF-AH catalyzes the release of F_2-isoprostanes from esterified phospholipids [38]. Given that free F_2-isoprostanes show potent bioactivities relevant to atherosclerosis including vasoconstriction, platelet aggregation and proliferation of smooth muscle cells [39],