The Potential Pathophysiological Role of Platelet-Activating Factor in Human Diseases

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Summary. Platelet-activating factor (PAF) is a new phospholipid mediator released from various cell types and tissues by the catalytic action of phospholipase A2 and acetyl transferase upon immunological and non-immunological stimuli. It activates the cells by binding to specific binding sites. PAF exhibits a broad range of biological and pharmacological activities including platelet and neutrophil aggregation, eosinophil chemotaxis, bronchoconstriction, hypotension, and acute renal failure. In addition, PAF is involved in acute graft rejection, endotoxin shock, and gastrointestinal ulceration. Furthermore, it closely mimics the pathology of bronchial asthma and is capable of producing most of the phenomena seen in inflammation. So far several PAF antagonists have been described and shown to afford protection. In future, pharmacological studies using such antagonists will help to elucidate the pathophysiological role of PAF in human diseases.

Key words: PAF – Pathophysiological roles – Human diseases

The term platelet-activating factor (PAF) was introduced in 1972 by Benveniste et al. [6]. He noted that during immunoglobulin E-induced anaphylaxis, basophils generated and released a platelet-activating activity. Since then this substance has been characterized as a phospholipase A2-sensitive phospholipid [7]. Further biochemical studies identified the PAF as a 1-0-alkyl-2-acetyl-sn-glyceryl-3-phosphorylcholine [17]. The detection of this ubiquitous compound in a wide variety of cell types or organs has led to its acceptance as a pivotal molecule in different pathophysiological conditions.

Biochemical Structure and Metabolism

The chemical structure of PAF is shown in Fig. 1. A series of enzymic steps are involved in the formation of PAF. It is derived from alkyl-acyl-glyceryl-phosphorylcholine (alkyl-acyl-GPC) by phospholipase A2, resulting in "lyso-PAF," which is then acetylated by an acetyl transferase to give PAF. In plasma, PAF is rapidly hydrolyzed by an acetyl hydrolase, leading to the formation of lyso-PAF as the end-product [31]. In various cells, PAF is converted into alkyl-acyl-GPC by a sequential deacylation-reaacylation reaction. Stored in cellular membranes, alkyl-acyl-GPC is not only the end-product of the cellular catabolism of PAF, but also its potential precursor in stimulated cells. Figure 2 summarizes the metabolic pathway of PAF.
**Mode of Action**

PAF acts via specific binding sites present on various tissue and cell types. Therefore, very low concentrations of the ether lipid are needed to trigger its biological effects. In addition, specific desensitization occurs after cell or tissue is exposed to PAF. The specific binding of PAF to plasma membranes is regulated by monovalent and divalent cations and by guanosine triphosphate (GTP). Furthermore, the high-affinity binding site appears to be linked to the adenyl cyclase system [8]. There are now several PAF antagonists available which displace the mediator from its receptors.

**Pathophysiological Roles**

PAF is generated by various cell types including platelets, leukocytes, mast cells, and endothelial cells (Table 1). Although the direct demonstration of its involvement is not always available, its role in several pathophysiological processes is suspected. These include acute inflammation, acute allergic diseases, arterial thrombosis, or endotoxic shock. The potential biological effects of PAF in various pathophysiological conditions are shown in Table 2.

**I. Acute Inflammation**

PAF is capable of producing most of the phenomena seen in inflammation [2]. Injected intradermally in humans PAF is claimed to induce a biphasic inflammatory response. The acute onset component is characterized by endothelial swelling...