Platelet-Activating Factor (PAF): An Introduction[1]

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Acidic lipid mediators, such as prostaglandins and leukotrienes, play important physiological roles and are generally regarded as autacoids or local hormones. One of the most potent autacoids, platelet-activating factor (PAF), belongs to a more recently discovered class of mediators with a broad range of biological activities. Research by three independent groups led to the discovery of PAF as the first example of a complex phospholipid, a minute amount of which exhibits potent bioactions. Earlier studies on ether-linked glycerophospholipids provided the basis for establishing the chemical structure of PAF as a 1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine. Two significant biological activities, platelet activation and hypotensive activity, of this unique lipid factor were independently discovered and further defined by the groups of prominent scientists who opened up this interesting research field.

In 1922, the first structural determination of an ether-linked lipid was made by Tsujimoto and Toyama (1), who isolated three types of alkyl glycerol ethers from the unsaponifiable lipids of liver oil of ray, shark and rat fish. The first ether-linked glycerophospholipids were isolated in 1958 by Carter and his associates (2), who identified 1-*O*-octadecylglycerophosphoethanolamine derived from egg yolk phosphatides.

It is now known that significant amounts of alkylacylglycerophosphocholine, a precursor of PAF, occur in a variety of animal tissues, cells and microorganisms, including various blood cells such as macrophages, platelets and neutrophils. In 1972, Benveniste, Henson and Cochrane (3) reported the leukocyte-dependent aggregation of rabbit platelets. When leukocytes were prepared from IgE-sensitized rabbits and treated with the specific antigen, platelets were strongly aggregated. The investigators reasoned that, upon stimulation, IgE-sensitized basophils degranulated and released a soluble factor that caused the platelet aggregation. Benveniste *et al.* (3) called this soluble factor platelet-activating factor and suggested a possible role of PAF in acute allergic reactions.

In 1979, Demopoulos, Pinckard and Hanahan (14) found that a synthetic glycerophospholipid, 1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine (AAGPC) had the same physicochemical and biological properties as native PAF. AAGPC elicited the secretion of serotonin from rabbit platelets. They also showed that both AAGPC and PAF were converted to inactive forms through base-catalyzed methanolysis and restored to functional forms by reacetylation. In 1980, Hanahan and his group (5) purified native PAF from activated basophils and characterized it extensively. The authors concluded that naturally occurring PAF is indeed AAGPC.

Long before the discovery of "PAF" through the cultivation of activated basophils, Muirhead, Jones and Stirman (6) found in 1960 that two lipid fractions of renomedullary tissue with different polarity exerted a hypotensive effect. Since these fractions protected animals from the development of experimental hypertension, they were called antihypertensive polar renomedullary lipid (APRL) and antihypertensive neutral renomedullary lipid (ANRL). In 1979, Blank, Snyder, Byers, Brooks and Muirhead (7) reported that the structure of APRL is 1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine. They showed that semisynthetic PAF exhibited potent antihypertensive action in experimentally hypertensive rats with the same effectiveness as did natural APRL.

PAF is a very potent autacoid; the ED_{50} value for guinea pig platelet activation is about 3×10^{-10} M. An intravenous injection into rat of about 60 ng/body PAF causes severe hypotension. In addition to activation of platelets and induction of hypotension, PAF has a wide spectrum of biological activities. PAF induces contraction of smooth muscle cells, cardiac effects and increase of vascular permeability. It also activates neutrophils, and induces monocyte aggregation, eosinophil chemotaxis, macrophage activation, an increase in liver glycogenolysis, and many other effects. It is now widely accepted that PAF-sensitive cells and tissues are activated upon binding of PAF to a specific binding site, which is probably a PAF receptor present on the cell surface.

PAF is generated, upon appropriate stimulation, by basophils, monocytes-macrophages, neutrophils, platelets and endothelial cells. Several organs, including lung and kidney, have been shown to produce PAF. So far, the assay of the amount of PAF present in biological materials has been done by bioassay or gas chromatography-mass spectrometry. A new radioimmunoassay method recently has been developed, enabling us to quantify the amount of PAF in a more reliable and sensitive manner than before.

The precursor of PAF, alkylacylglycerophosphocholine, is stored in the cell membrane and, upon stimulation of the cell, is immediately utilized to generate PAF. So far two routes of PAF biosynthesis have been demonstrated. In the "remodelling pathway", lysoPAF is formed by deacylation of alkylacylglycerophosphocholine. Subsequent acetylation of lysoPAF is catalyzed by a PAF acetyltransferase, which is assumed to be activated by stimulus-coupled phosphorylation. In the "*de novo* pathway", alkylacetylglycerol serves as a substrate for a cholinephosphotransferase. Degradation and inactivation of PAF is mainly catalyzed by PAF acetylhydrolase (known to be present in both plasma and various tissues) to yield lysoPAF. In target cells, lysoPAF is often converted further to alkylacylglycerophosphocholine by an arachidonoyl-specific transferase. It has therefore been argued that the synthesis and degradation of PAF is coupled with arachidonic acid metabolism.

Although the precise role of PAF *in vivo* is still not fully understood, PAF has been implicated in a number of pathological reactions, such as gram-negative septic shock and asthma. Several anti-PAF drugs (receptor antagonists) which are expected to be utilized as either

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Abbreviations: AAGPC, 1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine; ANRL, antihypertensive neutral renomedullary lipid; APRL, antihypertensive polar renomedullary lipid; PAF, platelet-activating factor.

therapeutic or prophylactic medications against these PAF-related disorders have been developed.

Recent research on PAF bioaction has led to a better understanding of the roles of PAF in many physiological and pathological reactions. Further studies are obviously required to determine the precise *in vivo* involvement of PAF in inflammation, allergy-asthma, nephritis, reproductive processes, hypotension, neuropathology and other biological processes in which PAF is though to be involved.

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