National Heart and Lung Institute Workshop Series

Platelet-Activating Factor

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Platelet-activating factor: a potent mediator of inflammation

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Platelet-activating factor (PAF) was first shown to be released from rabbit basophils during an acute allergic IgE-mediated response with the capacity of activating platelets, hence its name.¹ Full chemical characterization of the PAF molecule as an ether-linked phospholipid, 1-O-alkyl-2-acetyl-sn-glycerol-3-phosphorylcholine was later obtained.^{2–4} There does not seem to be general agreement as to naming this molecule which is also referred to as Paf-acether, acetyl glyceryl ether phosphorylcholine (AGEPC), or anti-hypertensive polar renomedullary lipid (ARPL). However, the term platelet-activating factor or PAF seems to be generally accepted.

PAF is synthesized *de novo* from two distinct synthetic pathways.⁵ In many inflammatory cells, lyso-PAF, a biologically inactive intermediate, is released from ether-linked phospholipids by phospholipase A₂, in addition to arachidonic acid. Lyso-PAF is converted to PAF by acetyltransferase. Another synthetic pathway involves direct synthesis of PAF from ether-linked phospholipids by the action of cholinephosphotransferase and may be involved in generating physiological levels of PAF. PAF is degraded rapidly in biological fluids to lyso-PAF by the action of acetylhydrolase. Many inflammatory cells have been shown to possess the capacity to generate PAF *in vitro*, particularly neutrophils, eosinophils, macrophages, and endothelial cells. Eosinophils and macrophages can also release PAF through IgE-dependent mechanisms. In most cells, only a small fraction of the generated PAF is released and there is speculation as to the possible role of the PAF retained intracellularly.⁶

Apart from activating platelets, PAF also has potent effects on other inflammatory cells such as neutrophils, eosinophils and macrophages. In view of this, increasing interest is being centred on the possible

role of PAF in inflammation. Of particular interest is the capacity of PAF to interact with eosinophils to cause chemotaxis both *in vivo* and *in vitro* and to elicit release of eosinophil granule constituents. This interaction may be of important pathophysiological significance in certain allergic disorders, particularly in asthma and in other conditions in which eosinophils participate.⁷ The cellular mechanisms by which PAF activates eosinophils and neutrophils are, therefore, currently of considerable interest.

A lot of information has also been gathered over the past few years on the effects of PAF in circulatory haemodynamics, on myocardial function, on the pulmonary circulation and on the airways. One particular area of interest has been the potent effect of PAF in inducing airway microvascular leakage. In addition, it causes airway narrowing, an action that could be largely attributed to airway oedema; in many species including man, PAF induces an increase in airway responsiveness. For these reasons, PAF is being considered as an inflammatory mediator in asthma. In addition, PAF may play a role in shock states, particularly septic or anaphylactic, as it induces hypotension and a reduction in myocardial contractility. The interaction of PAF with other mediators of inflammation remains poorly studied, and the exact role of PAF in the inflammatory process needs to be evaluated.

Because of the difficulties in measuring the release of PAF into biological fluids, the availability of specific PAF receptor antagonist now provides us with a tool to dissect out the role of PAF in pathophysiological states.⁸ This area of research is rapidly expanding. The study of PAF receptors on inflammatory cells may become more feasible because some PAF antagonists can be tritiated with high specific activities. Already PAF antagonists have been shown to be effective in inhibiting anaphylactic shock, the late-phase airway and cutaneous responses to allergen, IgE-mediated release of granule proteins from eosinophils and

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eosinophil chemotaxis into the airways during allergic reactions. Although these observations obtained in animals *in vivo* or *in vitro*, suggest a role for PAF in several disease states, we must remain cautious until studies with PAF-antagonists are performed in man. It is possible that these antagonists may provide new forms of treatment in several diseases. Elucidating the role of PAF in normal physiological responses is also as important as assessing its contribution to disease.

In view of the recent rapid progress and increasing interest in PAF research,⁹ we organized a short

symposium at the Cardiothoracic Institute (now the National Heart & Lung Institute) in the summer of last year in order to review some of the new advances that have been made which are relevant to heart and lung disease. This symposium was the second in the Cardiothoracic Institute Workshop series we have recently initiated. Although the accompanying abstracts from the contributors are short, we hope they provide a framework on which the novice to 'PAF-ology' can build.

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