Mechanisms of platelet-activating factor (PAF)-mediated responses in the lung

Stefan Uhlig, Rolf Göggel, Stephanie Engel

Division Pulmonary Pharmacology, Research Center Borstel, Leibniz-Center for Medicine and Biosciences, Parkallee 22, 23845 Borstel, Germany

Correspondence: Stefan Uhlig, e-mail: suhlig@fz-borstel.de

Abstract: Platelet-activating factor (PAF) is a potent lipid mediator that has been implicated in asthma, sepsis, acute lung injury and ischemia/reperfusion injury. Its actions in the lungs include vasoconstriction, bronchoconstriction, and edema formation. Despite the fact that PAF exerts these actions within minutes, they are mediated by other lipid mediators, in particular eicosanoids generated by cyclooxygenase and lipoxygenase enzymes and sphingolipids generated by acid sphingomyelinase. We will discuss the mechanisms of the PAF-induced pressor responses that are triggered by thromboxane $A_2$ and leukotrienes, as well the PAF-induced increase in vascular permeability that is mediated by prostaglandin $E_2$ (PGE$_2$) and ceramide.

Key words: pulmonary edema, acute lung injury, ARDS, asthma


Introduction

Platelet-activating factor (PAF) is one of the most potent and versatile pro-inflammatory mediators. In contrast to cytokines, PAF exerts many of its actions within minutes, rather than hours, although it does have long term effects as well. The pro-inflammatory actions of PAF include the activation of many leukocytes such as monocytes, macrophages, eosinophils, neutrophils and of course platelets, and in the lungs the induction of vascular permeability, vasoconstriction, bronchoconstriction, and airway hyperreactivity [30, 132, 193]. In healthy humans inhalation of PAF causes leukopenia, bronchoconstriction, ventilation-perfusion mismatch and decreased systemic arterial pressure [37, 138].

A plethora of experimental studies implicate PAF in respiratory disease. Increased PAF levels are found in patients with asthma, acute respiratory distress syndrome (ARDS), hydrostatic pulmonary edema, trauma, sepsis and intestinal ischemia reperfusion [5, 20, 51, 52, 63, 74, 113, 142]. As an example Table 1 lists animal models of sepsis and systemic inflammatory response syndrome (SIRS) in which PAF contributes to the development of acute lung injury. Chronically, PAF induces vascular remodelling, a decrease in pulmonary vascular compliance, and loss of hydroxyproline and vascular matrix [119], as well as goblet cell hyperplasia and mucin gene expression in the air-