Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

**Published:** May 31, 2022

**Citation:** Ibe BO, Hanouni M, et al., 2022. Persistent Pulmonary Hypertension of the Newborn: Role of Platelet Activating Factor, Medical Research Archives, [online] 10(5). https://doi.org/10.18103/mra.v10i5.2802



**DOI:** https://doi.org/10.18103/mra.v10i5.2802

**ISSN:** 2375-1924

RESEARCH ARTICLE

# Persistent Pulmonary Hypertension of the Newborn: Role of Platelet Activating Factor

**Basil O. Ibe[1], Mona Hanouni[2] J Usha Raj[3], James Popoli[1], and Steven Popoli[1]**

[1]Division of Neonatology, Department of Pediatrics, The Lundquist Institute at Harbor-UCLA Medical Center, Torrance, CA 90502
[2]Attending Neonatologist, Children's Hospital of Los Angeles, Los Angeles, CA 90027
[3]University of Illinois, Chicago, IL 60607

* ibe@lundquist.org

ABSTRACT

The fetus is exposed to chronic low oxygen environment, which is a desirable physiological condition for fetal pulmonary development and hemodynamics. On the other hand, if the newborn is exposed to low oxygen levels, the blood vessels of the lung thicken and narrow due to overgrowth of the smooth muscle cells in the vessel walls, the baby remains blue, resulting in the condition known as persistent pulmonary hypertension of the newborn (PPHN). In the United States, PPHN occurs in 0.43-6.8 newborns per 1000 live births and is most common in term and near-term newborns. Despite the significant advances in management of newborn respiratory diseases, PPHN is still associated with a high morbidity and mortality, accounting for about 10-20% of neonatal mortality. The current mainstay of therapy for PPHN is mechanical ventilation, fluid therapy and use of anti-inflammatory agents for cardiovascular support. Correction of hemodynamic acid/base balance and oxygen supplementation are also commendable therapeutic interventions. New ideas in PPHN therapy should include incorporation of in vivo, ex vivo and in vitro studies on intracellular signaling pathways of pulmonary vascular development in the state of PPHN. These new ideas will entail studies of the cross talk between vasodilators and vasoconstrictors in perinatal pulmonary hemodynamics.

**Keywords:** Hypoxia, Hyperoxia, PAF-acetyl hydrolase, PAF receptor, PAF receptor binding, pulmonary smooth muscle.

## Introduction

In utero, the fetus is exposed to chronic low oxygen environment, which is a desirable physiological condition for fetal pulmonary development and hemodynamics[1-5]. On the other hand, if the newborn is exposed to low oxygen levels (hypoxia), the blood vessels of the lung thicken and narrow due to overgrowth of the smooth muscle cells in the vessel walls, the baby remains blue, with elevated pulmonary vascular resistance,resulting in the condition known as persistent pulmonary hypertension of the newborn (PPHN). The incidence of PPHN in the United States ranges from 0.4 to 6.8 per 1000 live births[6-9]. Although PPHN was considered a disease of the term newborn, it is now being recognized as a pathologic condition in preterm infants[10-16]. Interestingly, the long-term effects of oxygen therapy in the newborn with PPHN are not yet clear. In severe cases, a common intervention is inhaled nitric oxide (iNO) therapy, which activates guanylyl-cyclase in smooth muscle cells and platelets, thereby increasing levels of the intracellular second messenger cyclic guanylyl monophosphate (cGMP)[17-22], and cyclic adenylyl monophosphate (cAMP) in the pulmonary vasculature[23-28]. Nitric oxide also acts by reducing intracellular free Ca2+ concentration[29-33]. Additionally, phosphodiesterase enzyme inhibitors are used as treatment options, although studies are ongoing to assess the safety and efficacy of these agents[34-38]. Extracorporeal membrane oxygenation (ECMO) is also a common therapeutic regimen available besides use of iNO agonists and analogs in clinical setting to manage severe PPHN[35, 39-41]. At its worst disposition, PPHN can leave a clinician at a non-ECMO center with the desperate hope for the quick arrival of the transport team. In the hopes of uncovering new ideas in PPHN therapy, the aim of this review is to advance the involvement of the endogenous and potent inflammatory lipid mediator platelet activating factor (PAF) and PAF receptor (PAFR) mediated responses in the pathogenesis of PPHN. In the lung,

## Platelet Activating Factor and PKA/PKG PPHN

PAF acts through its membrane-bound receptors to evoke vasoconstriction[55, 61-65], and PAF-induced smooth muscle contraction is mediated by Rho-kinase[66-68], demonstrating that significant cross activation and functional inhibition exits between PAF-PAFR and RhoA-Rho kinase pathways in perinatal pulmonary hemodynamics. Such endogenous receptor cross activation and/or inhibition have been reported in a variety of perinatal pulmonary function[69-71]. RhoA, a member of Rho family of low molecular weight G proteins regulates a variety of cell functions including cell growth, gene expression, $Ca^{2+}$ sensitization, and cytoskeletal rearrangement. RhoA activities are regulated by extra cellular stimuli, which activate some cell surface receptors[72-75]. Studies investigating the involvement of RhoA in various cellular responses have been facilitated by the generation of RhoA cDNA and MiRNA constructs and specific Rho kinase inhibitors[76,77], suggesting that, in part, an interaction between PAF and RhoA pathways exists to modulate pulmonary hemodynamics. Rho kinase (ROCK) is a down-stream target of small GTP-binding protein Rho, which regulates cell motility and Ca2+ sensitization. Inhibition of Rho-kinase activity with Y-27632 or fasudil in vivo or in vitro, attenuates PAF-induced pressor responses in isolated perfused lungs and also modulate pulmonary vascular smooth muscle growth[67, 78, 79].

## Platelet Activating Factor and Perinatal Pulmonary hemodynamics

In the hopes of uncovering new additional PPHN therapy, the aim of this mini review is to delineate the intracellular signaling pathways downstream of platelet activating factor receptor (PAFR), in particular, those that interact with the intracellular messenger cyclic adenylyl monophosphate (cAMP) via activation of its receptor Protein kinase A (PKA). By understanding the crosstalk between PAFR-mediated effects and cAMP, we may place ourselves a step closer to a multi-pronged therapy approach in treating some of the most refractory cases of PPHN. Thus with not only iNO in our repertoire but also a concurrent intervention by way of cAMP intracellular signaling, a more comprehensive management approach toward improved pulmonary vasodilation and oxygenation may ultimately lead to decreased mortality and morbidity outcomes for infants with severe PPHN. PAF acts through its specific G protein-coupled receptor (GPCR) to stimulate Ca2+ release and induce smooth muscle constriction.

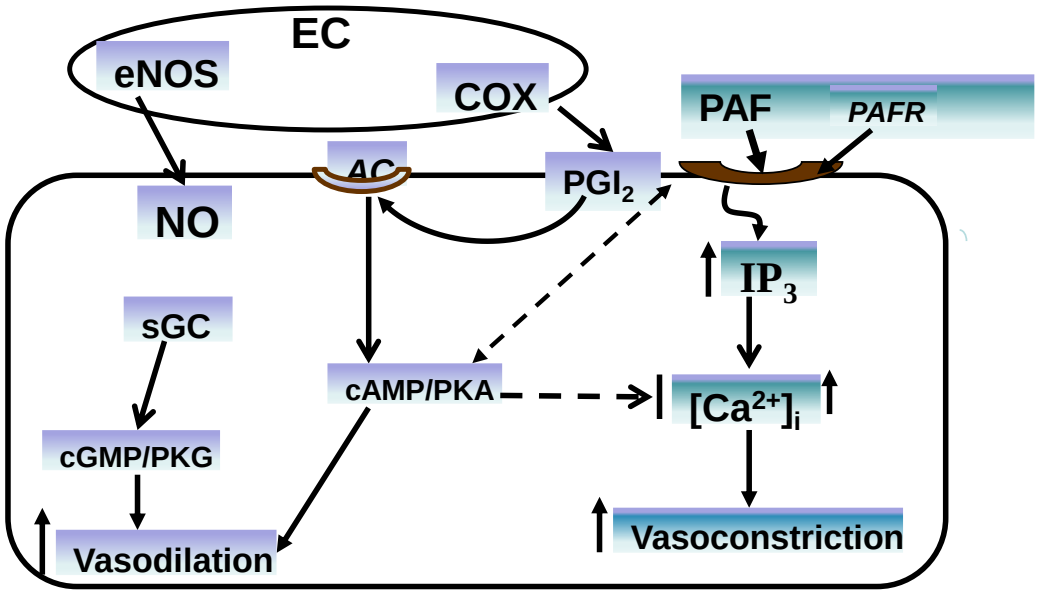



***Figure 1.*** *Scheme of PAF/PAFR crosstalk in cAMP/PKA, cGMP/PKG mediation of vasodilation and vasoconstriction of perinatal pulmonary vessels. Conceptually, eNOS generated in endothelial cells (EC) releases NO, which eventually activates cGMP/PKG leading to vasodilation of pulmonary vascular smooth muscle. In corollary, cyclooxygenases (COX), also emanating from EC anabolizes prostacyclin ($PGI_2$), subsequently resulting in activation of cAMP/PKA in smooth muscle cells with consequent dilation of pulmonary vascular smooth muscle. In the similar manner, platelet activating factor (PAF) released from membrane lipids of pulmonary vascular smooth muscle cells, binds to its receptor (PAFR) activating a signal transduction pathway that increases phosphorylation of inositol phosphate ($IP_3$) and release of intracellular $Ca^{2+}$, which ultimately leads to pulmonary vasoconstriction. The information in the scheme was summarized from published reports including those from our laboratories, for instance references* [23, 53, 55, 59, 73, 74].

The conceptual scheme presented in Figure 1 shows that cAMP/PKA production in the affected system is able to inhibit $Ca^{2+}$ release thereby preventing vasoconstriction. Similarly, PAF binding to its receptor can induce down regulation of cAMP/PKA production. The PAF/PAFR and cAMP/PKA crosstalk operate in the pulmonary system under the appropriate oxygen tension, i.e., hypoxia or hyperoxia as has been reported[23, 73, 74].

**Fetal hypoxia, platelet activating factor and pathogenesis of PPHN**

Current therapies of PPHN are directed at the management of symptoms of PPHN disease by targeting the affected end organ, mostly the lung [34, 35, 39, 42-50]. In utero, fetal lung environment is hypoxic and characterized by a high pulmonary vascular resistance and low systemic vascular resistance[51, 52]. The low oxygen environment of fetal lung generates potent pulmonary vasoconstrictors such as platelet activating factor (PAF), thromboxane $A_2$ ($TxA_2$), and endothelin-1 (ET-1) with an imbalance of vasodilator [23, 51-59]. Thus, PPHN arising from perinatal hypoxia have high levels of PAF, $TxA_2$ and other pulmonary vasoconstrictors after birth[23]. In human newborns with PPHN, the condition improved with decrease in PAF level, and increase in the level of PAF acetylhydrolase activity, the PAF degrading enzyme[80, 81]. In animal models of PPHN, hypoxia and PAF increase growth of pulmonary vascular arterial and venous smooth muscle cells in culture[23, 72]. In previous reports of perinatal lung studies, whether in vivo or in vitro, PAF acetylhydrolase activity decreases with oxygenation with a concomitant increase in PAF level due to increased PAF synthesis and decreased PAF enzymatic degradation[83-89]. PAF receptor protein and PAFR mRNA expression in lungs of newborn lambs were downregulated from fetal to newborn state and

then PAFR binding and receptivity were also downregulated in the newborn period[90]. In fetal sheep models where the fetus was subjected to chronic in utero hypoxia by rearing the pregnant ewe in high altitude (Long Term Altitude Hypoxia: LTHAH) at early pregnancy stage, and compared with control pregnant ewe reared at sea level. Newborns from the LTHAH group exaggerated expression of PAFR protein in vessels compared to vessels from the control newborn lambs. PAFR expression was studied by specific immunohistochemistry of PAFR protein. The increased PAFR expression was associated with increased %Vessel wall.

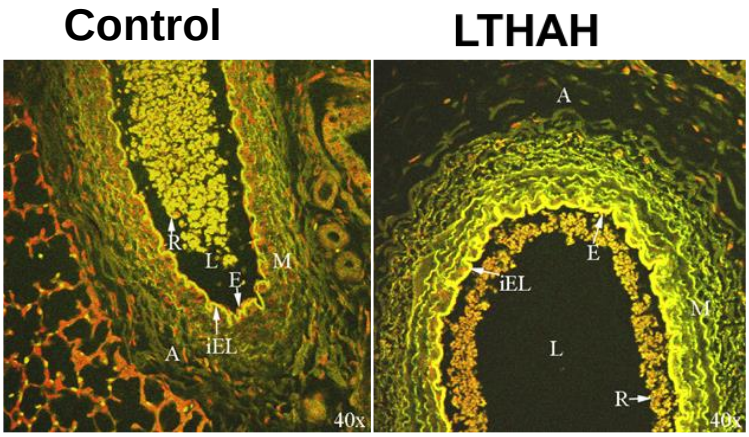



***Figure 2.*** *Effect of chronic in utero LTHAH exposure on utero PAFR protein expression by ovine fetal pulmonary vasculature. We obtained two groups of term pregnant ewes. One group was raised under low oxygen saturation (high altitude hypoxia,LT HAH). The other group was raised at sea level (Control). Fetuses were exteriorized from anesthetized ewes. Fetal lungs were harvested and sectioned for immunohistochemical staining and analytical confocal microscopy of PAFR protein expression. Fetal lung tissue sections from control lambs (akin to normoxia) and lamb lungs from the LTHAH ewes (akin to hypoxia) were fixed in formaldehyde and then thin sectioned for confocal microscopy. Slides were stained with monoclonal anti-PAF Receptor antibody and FITC-linked secondary antibody. Finally, Propidium Iodide was applied to identify the nuclei of the cells. The slides were subjected to confocal microscopy. There was greater expression of PAFR protein by lung slices of the LTHAH lambs compared to expression by the control lambs. The legends are as follows: A, adventitia; M, media (with smooth muscle cells); E, endothelium; iEL, internal elastin; R, red blood cells; L, lumen.*

**Newborn oxygenation in PPHN**

I has been shown that in ovine fetal lung in utero, increased PAFR protein expression and PAFR binding contribute to pulmonary vascular remodeling in these animals and may predispose them to persistent pulmonary hypertension after birth[55]. In the lung, PAF acts through its specific G protein-coupled receptor to evoke pathological and physiological effects [23, 53, 64, 73, 74, 82, 83, 90, 91, 92]. Indeed, PAF is a potent phospholipid mediator that plays an integral role in a variety of biological processes[93]. It is an important mediator of the pulmonary circulation[94-99]. In utero, endogenous PAF maintains high pulmonary vasomotor tone and vascular resistance in fetal lambs[73, 74]. In ovine model, the switch from fetal high $TxA_2$-low $PGI_2$ to postnatal low $TxA_2$-high $PGI_2$ in the pulmonary circulation facilitates salient pulmonary circulation to an air breathing newborn[23]. Failure of this smooth high/low coupling of these important mediators of pulmonary vascular response disposes the newborn to pulmonary circulatory abnormalities. Additionally, failure of the down-regulation of PAFR-mediated effects in the newborn pulmonary circulation leads to untoward neonatal pulmonary circulatory abnormalities, including PPHN[23, 72-74]. G protein-coupled receptors (GPCRs) comprise a large family of specific genome regulated proteins, which are widely expressed in the cardiovascular system. They regulate such critical functions such as vasoconstriction, vasodilation, and control of remodeling mechanism. All these in dysregulation are attributes of PPHN. PAF receptor as GPCR has been described and functionally characterized for over 20 years with regards to its mediation of normal and abnormal lung functions[99-103]. However, little has been done to anchor pulmonary PAF/PAFR-mediated effects in the therapeutic

management of PPHN. Therefore, in this PAF related PPHN review, our intention is to highlight the necessary pieces of information concerning regulation of PAFR-mediated pathophysiological pulmonary abnormalities. It has been reported, in an *in vitro* study with smooth muscle cells from pulmonary artery, that both hypoxia and hyperoxia produced pathologic effects on PAFR-mediated pulmonary function[23].The site of PAF binding to its GPCR has been characterized[64, 91,100]. The exigencies of therapeutic application of PAFR antagonist demand an understanding of the binding of PAF to its receptor. Here we present our computer modelling of the binding of PAF receptor antagonists CV-3988 and WEB 2086 to PAFR protein.

***Figure 3A***. *Extracellular binding of CV 3988 to PAFR protein*

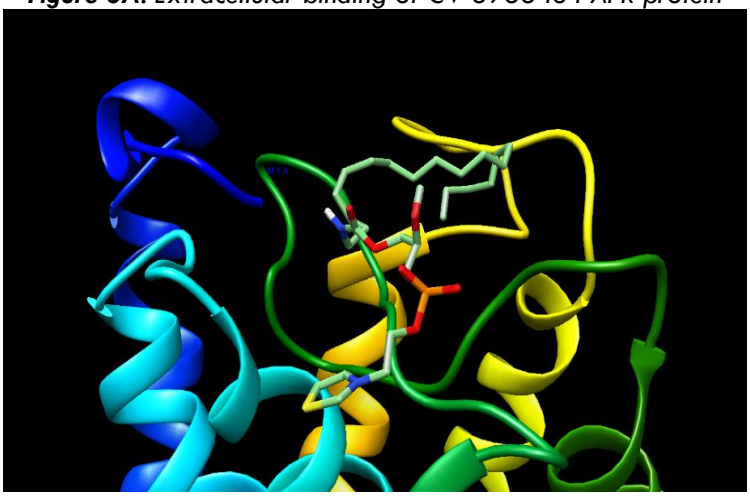


***Figure 3B***. *Intracellular binding of CV 3988 to PAFR protein.*

***Figure 3C.*** *Extracellular binding of WEB 2086 to PAFR protein.*

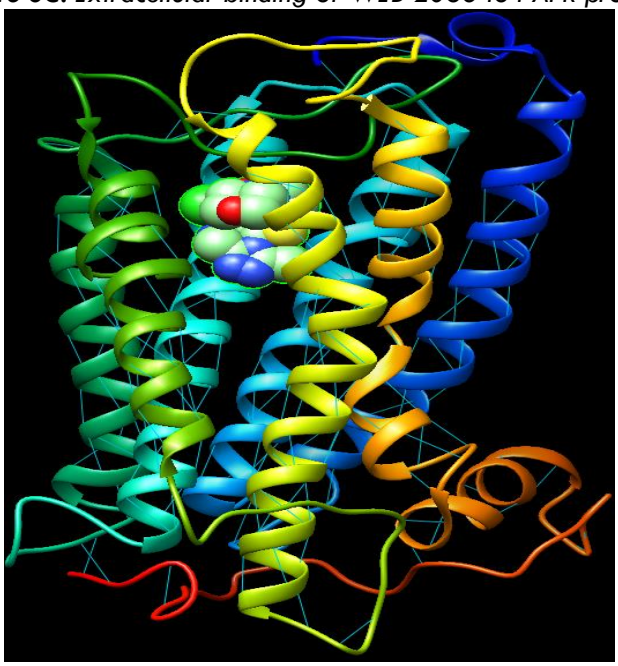
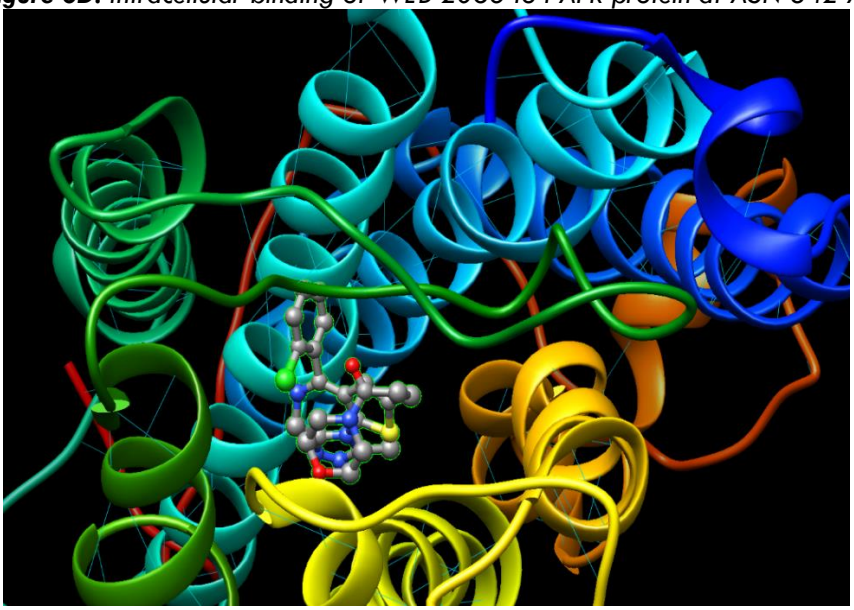


***Figure 3D.*** *Intracellular binding of WEB 2086 to PAFR protein at ASN 342 A.*



Our laboratories and others have used these two PAFR antagonists, as well as other PAFR antagonists, to elaborate PAF functional studies in lung physiology and pharmacology. Earlier studies demonstrated the inhibition of PAF binding to its receptors by WEB 2086, for instance[104-110], and by the lipid structurally similar PAFR antagonist CV 3988[23, 82, 111-115]. The role of PAF in neonatal lung physiology and pathology has been long described[53-55, 68, 69, 73, 74, 80-83, 90, 95], but application of PAF receptor antagonist in the management or therapy of PPHN had not been established. As an autocoid, the adverse effects of PAF on lung physiology and pathology should be controllable by preventing the binding of this molecule to its receptor in the local environment. It is hoped that this subject-targeted mini review would spur accelerated interest in clinical trials to develop novel therapies of PPHN with PAF receptor antagonists.

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