Prostaglandins & other Lipid Mediators 120 (2015) 56–71

Contents lists available at ScienceDirect

Prostaglandins and Other Lipid Mediators

Review

The mechanistic basis of prostacyclin and its stable analogues in pulmonary arterial hypertension: Role of membrane versus nuclear receptors

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ARTICLE INFO

Article history:
Available online 23 April 2015

Keywords:
Cell proliferation
Pulmonary arterial hypertension
Vascular remodelling
Prostanoid receptors
Peroxisome proliferator-activator receptor
Prostacyclin analogues
Cyclic AMP
Treprostinil
Iloprost
Beraprost

ABSTRACT

Pulmonary arterial hypertension (PAH) is a progressive disease of distal pulmonary arteries in which patients suffer from elevated pulmonary arterial pressure, extensive vascular remodelling and right ventricular failure. To date prostacyclin (PGI_2) therapy remains the most efficacious treatment for PAH and is the only approved monotherapy to have a positive impact on long-term survival. A key thing to note is that improvement exceeds that predicted from vasodilator testing strongly suggesting that additional mechanisms contribute to the therapeutic benefit of prostacyclins in PAH. Given these agents have potent antiproliferative, anti-inflammatory and endothelial regenerating properties suggests therapeutic benefit might result from a slowing, stabilization or even some reversal of vascular remodelling in vivo. This review discusses evidence that the pharmacology of each prostacyclin (IP) receptor agonist so far developed is distinct, with non-IP receptor targets clearly contributing to the therapeutic and side effect profile of PGI_2 (EP_3), iloprost (EP_1), treprostinil (EP_2, DP_1) along with a family of nuclear receptors known as peroxisome proliferator-activated receptors (PPARs), to which PGI_2 and some analogues directly bind. These targets are functionally expressed to varying degrees in arteries, veins, platelets, fibroblasts and inflammatory cells and are likely to be involved in the biological actions of prostacylins. Recently, a highly selective IP agonist, selexipag has been developed for PAH. This agent should prove useful in distinguishing IP from other prostanoid receptors or PPAR binding effects in human tissue. It remains to be determined whether selectivity for the IP receptor gives rise to a superior or inferior clinical benefit in PAH.

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http://dx.doi.org/10.1016/j.prostaglandins.2015.04.007
1098-8823/

1. Introduction

Pulmonary arterial hypertension (PAH) is a debilitating and fatal disease, involving extensive remodelling and narrowing of the blood vessels within the pulmonary vasculature. This leads to increased pulmonary vascular resistance and right ventricular hypertrophy, with eventual heart failure and death [1]. Without appropriate treatment, adults with PAH have a median life expectancy of 2.8 years from diagnosis while children have less than 10 months [2,3]. The disease is probably initiated by endothelial damage, caused by a combination of sheer stress, hypoxia and genetic factors (including mutations in the transforming growth factor family of genes), leading to increased production of vasoconstrictors (endothelin and thromboxane) accompanying the loss of vasodilator and anti-platelet agents, prostacyclin (PGI_2) and nitric oxide (NO). This process is exacerbated by ion channel dysfunction, including loss of potassium channel activity/expression (voltage-gated and the two-pore domain K^+ channels) and upregulation of calcium entry through canonical transient receptor potential cation (TRPC) channels both of which will lead to smooth muscle membrane depolarisation and Ca^{2+} influx [4]. The earliest known pathology in PAH is medial thickening due to hypertrophy and hyperplasia. However, as the disease progresses, proliferation of adventitial and intimal layers take over and uncontrolled endothelial proliferation is thought to underlie plexiform lesions. High cell proliferation rates within all layers (adventitia, media and endothelium) coupled with decreased programmed cell death (apoptosis) is a widely accepted explanation for the structural changes seen in PAH [1,5–7]. Indeed proliferative rates of human pulmonary arterial smooth muscle cells (PASMCs) isolated from patients with idiopathic PAH (IPAH) and grown in culture are close to double that of normal cells, suggesting a switch from a less contractile to a more proliferative cellular phenotype [8,9]. Moreover proliferative rates are much higher in paediatric versus adult IPAH cells, consistent with the particularly aggressive nature of this disease in children [9]. In addition, PASMCs isolated from PAH patients lose responsiveness to bone morphogenetic protein (BMP) ligands and display excessive proliferation in response to transforming growth factor β1 (TGF-β1), when typically both these agents have antiproliferative and apoptotic effects in normal cells [10,11]. Thus, the disease appears to alter the intrinsic properties either of resident smooth muscle cells, or those cells which have become incorporated into the hyperplastic medial layer. One such event which may drive this is sustained hypoxia, which can cause the recruitment of cells with enhanced growth, migratory and pro-mitogenic features in the wall of distal pulmonary arteries [12]. Factors that appear to drive these phenotypic changes, include platelet-derived growth factor (PDGF), and other mitogens such as the chemokine stromal cell derived factor, SDF-1/CXCL12 as well as the calcium binding protein and a mediator of metastasis, S100A4 [12].

2. Vascular wall remodeling in PAH

The aggressive pulmonary vascular obliterative disease characteristic of PAH, as already mentioned, involves all cell types within the vessel wall. Smooth muscle cells are initially hyperplastic and hypertrophied, and then become atrophied as fibrotic intimal proliferation develops. Adventitial fibroblasts proliferate and migrate. Endothelial damage is marked and plexiform lesions are thought to consist of proliferating abnormal endothelial cells which may sometimes consist of monoclonal endothelial cell expansion [6,13]. Thus, it comes as no surprise that patients with PAH have elevated levels of several growth factors, including PDGF, vascular endothelial growth factor (VEGF), TGF-β, epidermal growth factor (EGF), fibroblast growth factor (FGF) and angiopoietin [6,7,14,15]. A number of proproliferative signalling pathways involving growth factors, cytokines, metabolic signalling, and elastases and proteases have been identified in the pathophysiology of PAH. These combine to induce proliferation and migration of smooth muscle, endothelial cells and fibroblasts, while VEGF and angiopoietin (1 and 2) are also key markers of angiogenic remodelling. Metalloproteinases (MMPs) which are also elevated in PAH [15] and other inflammatory lung diseases [16] contribute to structural remodeling by growth factor activation, degradation of extracellular matrix proteins (collagens, gelatins and proteoglycans) and disruption of the internal elastic lamina [6]. Inflammation is also a key component of PAH, with thrombotic lesions and infiltration of T-cells, monocytes, macrophages, dendritic and mast cells into other types of lesions, commonly observed [7,14]. While traditionally inflammation is thought to center around the recruitment of inflammatory cells to the intima of blood vessels, driven by the expression of adhesion molecules on the endothelium (see later), increasing evidence suggest that inflammation may be initiated and/or driven from within the perivascular and adventitial layers – the so called “inside out hypothesis”. Here adventitial fibroblasts play a key role in providing the environment in which leukocytes can rapidly infiltrate and recruit monocytes and progenitor cells to the site of vascular injury, where they produce many factors driving the expression of adhesion molecules, growth factors, cytokines and chemokines [7]. Of note, the adventitial layer was reported to undergo the highest expansion in arteries between 50 and 100 μm in IPAH patients, with increased collagen deposition being the major cause of this increase in thickness [17]. The extent to which venous remodelling contributes to the pathology in IPAH is currently a subject of much debate [7], and is thwarted by the difficulty in identifying veins that might masquerade as a remodelled artery, and for which there is no consistent cellular biomarker. That said, in a systematic study of veins identified as vessels having a single elastic lamina, a doubling of intimal and adventitial layers was documented, but reported to result from collagen deposition rather than cell proliferation [17]. Evidence of chronic inflammation with resident monocytes and intra alveolar macrophages was also seen in 65% of patients. Thus, structural changes in the venous circulation probably contribute to disease pathology in PAH.

2.1. Rationale for PAH therapy: beyond just pulmonary vasodilatation

The rationale behind the treatment of PAH is to lower pulmonary arterial pressure (PAP) and hence bring about a reduction in pulmonary vascular resistance (PVR) and right heart afterload [1]. Thus, it is not surprising that therapies based around promoting vasodilatation have been developed, and include PGI_2 (epoprostenol) or stable analogues, endothelin-1 (ET-1) receptor antagonists (ERAs) as well as cyclic GMP (cGMP) elevating agents that combine to increase NO bioavailability by either inhibiting phosphodiesterase type five (PDE5) (siledenafil, tadalafil) and preventing the breakdown of cGMP or by stimulating guanylyl cyclase (riociguat) [18,19]. Randomized controlled trials have described improvements in pulmonary hemodynamics, exercise tolerance and clinical symptoms with each class of agents, though to date the only monotherapy demonstrating a significant impact on long-term survival (3–5 years) in controlled clinical trials is PGI_2, where survival at 3 and 5 years was 63% and 55%, respectively in PAH patients [1]. In open labeled or retrospective long-term analysis of subcutaneous (SC) treprostinil, patterns of observed survival versus predicted appear to be similar or possibly slightly better (69% at 3 years) than those seen with IV epoprostenol involving patients with similar baseline characteristics [20–24]. In the latter study, this occurred despite a high proportion (44%) of