# Prostaglandin E2 Signaling in Pulmonary Hypertension

Subjects: Cardiac & Cardiovascular Systems

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Mild-to-moderate pulmonary hypertension (PH) is a common complication of chronic obstructive pulmonary disease (COPD). As another well-known and extensively researched prostaglandins, prostaglandin E2 (PGE2) and its downstream signaling have been found to play an important role in various biological processes. Emerging evidence has revealed that PGE2 and its receptors (i.e., EP1–4) are involved in the regulation of pulmonary vascular homeostasis and remodeling.

chronic obstructive pulmonary disease | pulmonary hypertension | prostaglandin E2

## 1. Introduction

PGE2 is catalyzed by PGES and exerts its biological function by binding to EP receptors including EP1, EP2, EP3, and EP4. EP1 increases the intracellular Ca2+ level mainly by coupling with Gq protein. EP3 is usually coupled with Gi protein to inhibit intracellular cAMP level and PKA activity. Due to the existence of various isoforms, EP3 can be coupled with Gs to stimulate cAMP production and with Gq to stimulate the intracellular Ca2+ level. EP2 and EP4 increase intracellular cAMP levels by coupling Gs proteins and activating the PKA pathway. In general, PGE2 plays a critical role in blood pressure regulation. Its hypotensive effect is mainly achieved through EP2 and EP4, while activation of EP1 and EP3 raises systemic blood pressure [1]. Studies have shown that the COX/mPGES/PGE2/EPs system is essential for blood pressure regulation and vascular remodeling [2][3][4][5][6][7]. Studies have found that IP, EP3, and EP4 are highly expressed in normal pulmonary arteries, while EP2 is mainly located in the pulmonary veins [2]. Among the four EP receptors, EP3 and EP4 bind to PGE2 with the highest affinity (Kd < 1 nM), whereas EP1 and EP2 bind to PGE2 with low affinity (Kd > 10 nM) [3]. It has been found that PGI2 analogues both activate IP and act on EP receptors (**Table 1**). Many studies have revealed that different PGE2 receptors are involved in the occurrence and development of PH (**Figure 1**).

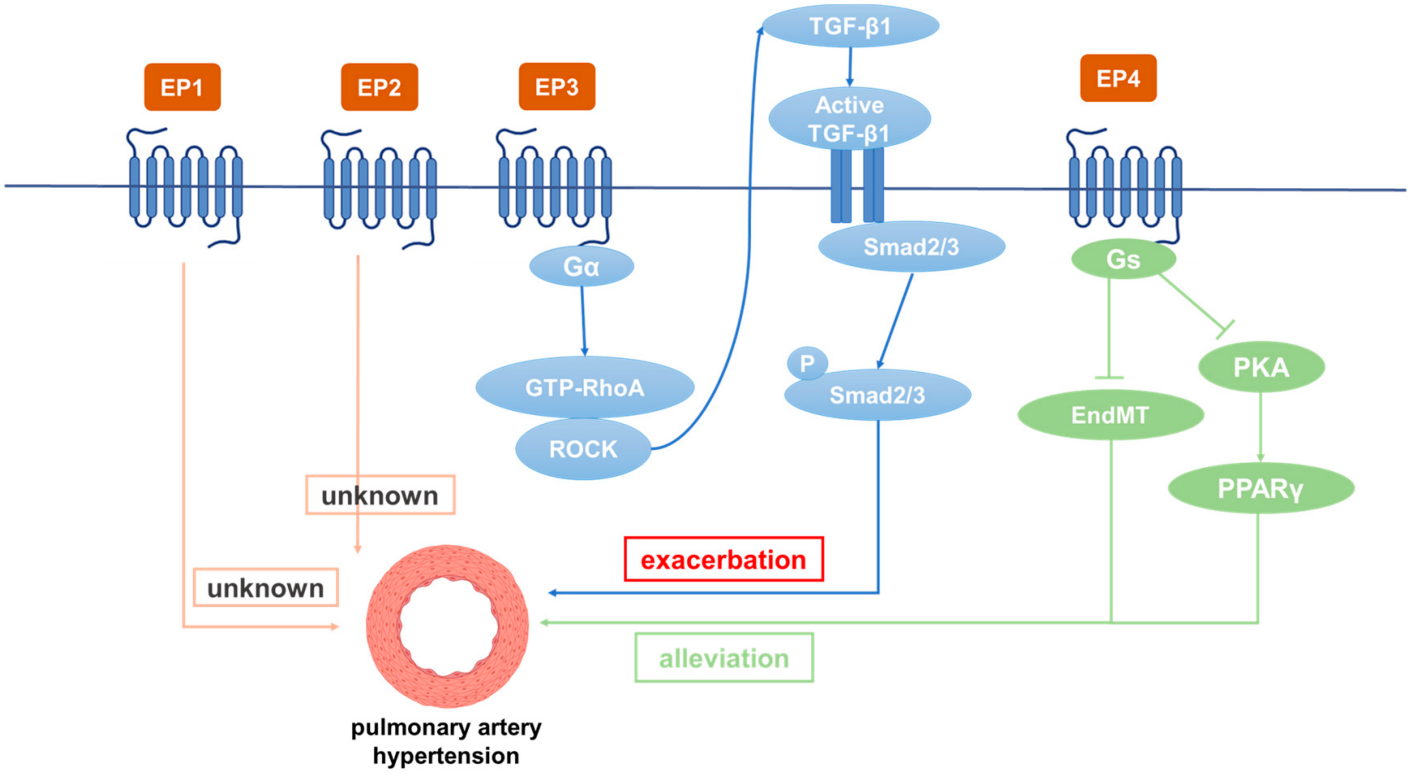


**Figure 1**. The role of different PGE2 receptors in the occurrence and development of PAH.

**Table 1**. IP and EP1–4 binding affinities (Ki) for PGI2 analogues in human and mouse. Radioligand binding data (Ki in nM) are from original study references for PGI2 analogues [3][4][5][6]. Blank means Ki value > 3 μM, ND means not done, and YES indicates evidence for functional activity.

| PGI2 analogues | | IP | EP1 | EP2 | EP3 | EP4 |
|---|---|---|---|---|---|---|
| Iloprost | Human | 4 | 1 | 1172 | 203 | 212 |
| | Mouse | 11 | 21 | 1600 | 27 | 2300 |
| Treprostinil | Human | 32 | 212 | 3.6 | 2505 | 826 |
| | Mouse | YES | ND | YES | ND | ND |
| Beraprost | Human | 39 | | | 680 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Mouse | 16 | | | 110 | |
| Cicaprost | Human | 17 | > 1340 | > 1340 | 255 | 44 |
| | Mouse | 10 | 1300 | | 170 | |

## 2. Role of EP1 in PH

It has been reported that oral administration of EP1 antagonist SC51322 reduces the blood pressure of spontaneously hypertensive rats. In addition, the systolic blood pressure of EP1 gene knockout mice was significantly lower than that of wild type mice, indicating that EP1 has the effects of constricting blood vessels and increasing blood pressure [7]. In a severe hypertension model, EP1 knockout was able to reduce blood pressure and alleviate organ damage [8]. In the pulmonary vein, EP1 counteracts the relaxation induced by PGs [9]. The selectivity of iloprost to different receptors is poor, and its effect of activating IP and EP1 is basically the same [10]. Iloprost has poor clinical efficacy, as it targets EP1 as well [11]. The EP1 antagonist SC-19220 inhibits the endocannabinoid arachidonyl ethanolamide (anandamide)-induced increase in pulmonary artery pressure [12]. Studies have shown that PDGF and VEGF promote abnormal proliferation and migration of ECs and SMCs to promote vascular remodeling, which can be reversed by the tyrosine kinase inhibitor imatinib in a dose-dependent manner [13]. Blockade of EP1/3 and TP or inhibition of the MAP2K, p38MAPK, PI3K-α/γ, and AKT/PKB signaling pathways prevented PDGFinduced contraction [14]. Due to the high contribution of the pulmonary venous bed to pulmonary vascular resistance, PDGF-BB-induced contraction is enhanced in the varicose veins of the pulmonary venous system [15]. Immunohistochemistry has shown that EP1 is mainly expressed in human pulmonary veins [16] [86]. However, in PH patients and hypoxiainduced PH mice, EP1 expression did not change significantly [17]. Currently, the effect of EP1 on PH has not been reported.

## 3. Role of EP2 in PH

The expression of EP2 in PASMCs is upregulated in patients with PH [18]. Treprostinil, a drug currently used to treat PH, has high affinity for EP2 and IP [4] and increases cAMP content by activating EP2 in macrophages [19]. It is the only PGI2 analogue that can effectively bind to EP2, and the EP2 antagonist PF-04418948 (1 μM) significantly reduced the anti-proliferative effect of treprostinil [18]. In addition, studies have found that EP2 is associated with increased proliferation and migration of SMCs, all of which suggests that EP2 receptors have a protective role in vascular remodeling [20][21]. Treprostinil can significantly reduce the recruitment of fibroblasts at the site of vascular remodeling in hypoxic PH, and fibroblasts play a role in the inflammatory and proliferative phase of blood vessels [22]. Interestingly, EP2 expression in PASMCs was not affected in an MCT-induced rat PH model [23]. At present, the effect of EP2 on PH needs to be further explored.

## 4. Role of EP3 in PH

EP3 is widely expressed in the whole-body tissues of mice [24]. EP3 agonists have a strong contractile effect on isolated human pulmonary arteries [25]. The mean arterial pressure of EP3 knockout mice was found to be lower than that of wild type mice, suggesting that EP3 has the functions of constricting blood vessels and increasing blood pressure [26]. As the first stable oral PGI2 analogue, beraprost is mainly used in the clinical treatment of PH, arterial occlusive diseases, peripheral vascular diseases, renal failure, etc. [27]. Beraprost has been shown to improve exercise capacity and hemodynamics, thereby alleviating PH symptoms [28]. Other results have demonstrated that in addition to binding to IP, beraprost has a strong binding affinity with EP3 (Ki 110 Nm) in rats [19]. Many studies have provided evidence that the contractile effects of PGI2 analogues are mediated through EP3 receptors [5][29][30]. In patients with PH who were treated with beraprost but not selexipag (a prostaglandin receptor selective agonist), the vasodilator efficacy was reduced by the constriction caused by activation of EP3 in the pulmonary artery. In addition, a common side effect of beraprost is paradoxical constriction of the femoral artery due to activation of EP3 receptor. Therefore, patients with PH treated with PGI2 analogues experience leg pain, whereas selexipag is less likely to cause this side effect [31]. Esuberaprost, an isoform of beraprost, is five times more potent than beraprost in vasodilation of rat pulmonary arteries. Esuberaprost promotes cAMP production and inhibits proliferation of human PASMCs with inhibitory effects 40 times more potent than beraprost (EC50 3 nM and EC50 120 nM). The EP3 antagonist L-798106 can significantly reduce the pulmonary artery constriction effect of high concentrations of Esuberaprost. It is important to understand the role of EP3 in the contractile response, as this could limit the dose of PGI2 analogues provided therapeutically and potentially give rise to unwanted side effects [32]. In addition, EP3 plays a role in pulmonary vascular remodeling. Overexpression of EP3, especially its α and β isoforms, promotes the proliferation and migration of vascular SMCs, and EP3 knockout significantly improves vascular remodeling caused by a femoral artery guidewire strain [33]. Furthermore, EP3 expression has been found to be upregulated in hypoxia-treated PASMCs. The EP3 antagonist L-798106 ameliorated MCT- and hypoxia-induced PH and inhibited ECM deposition in pulmonary arteries. EP3 (mainly EP3α and EP3β) knockout in SMCs alleviated PH by inhibiting Rho/TGF-β1 signaling [17]. However, EP3-deficient mice have increased bleeding tendency [34]. Distal human PASMCs isolated from the pulmonary arteries (outer diameter: 1 mm) were found to be more susceptible to PGI2 analogue-induced proliferation inhibition than PASMCs isolated from the proximal pulmonary arteries (outer diameter: 0.8 mm) [35]. The expression of IP, EP3, FP, and TP in MCT-treated rats were all decreased compared with control rats ($p < 0.05$ or $p < 0.01$) [35]. Thus, EP3 is involved in the occurrence of PH, and its antagonists have therapeutic potential.

## 5. Role of EP4 in PH

EP4 plays a critical role in the closure of the ductus arteriosus at birth [36]. EP2 and EP4 have been reported to be the major mediators causing pulmonary vasodilation in rabbits [12]. The expression of IP, EP3, and EP4 in normal pulmonary arteries is much higher than EP1 and EP2. Patients treated with beraprost exhibited less disease progression at 6 months [37]. Additionally, it binds to EP4 and results in AC activation at lower affinity [38]. Levels of both PGI2 and PGE2 in plasma were dramatically depressed in experimental PH rats compared with controls. However, these depressed levels were elevated by beraprost treatment. Furthermore, both the dilatation response of vascular rings and the magnitude of the $K_V$ channel response to beraprost were shown to be attenuated by the

EP4 selective antagonist GW 627368X, suggesting involvement of EP4 in mediating the effects of PGI2 on $O_2$-sensitive $K_V$ channels and vasomotion [2]. While further studies are required to directly prove the interaction of beraprost and EP4, studies have reported that IP expression is significantly decreased in PH patients and rats, while the expression of EP4 is decreased slightly. The EP4 antagonist AH23848 can inhibit intracellular cAMP accumulation induced by iloprost in a dose-dependent manner, indicating that iloprost may mediate the diastolic function caused by EP4 instead of IP in PASMCs [23]. Cicaprost elevated cAMP in PASMCs four-fold compared with control, while iloprost only caused a one-fold increase [39]. This is probably because cicaprost has strong binding affinity to EP4 [19]. The PGE2-EP4 signal transduction pathway aggravates chronic inflammation and various autoimmune diseases. Therefore, specific antagonists for EP4 are expected to be effective therapeutic drugs for acute and chronic inflammation as well as for autoimmune diseases in non-pregnant adults [40]. Results have shown that reduced EP4 expression in macrophages can alleviate bleomycin-induced pulmonary fibrosis [41]. An increase in perivascular macrophages is essential in the development of hypoxia-induced PH in experimental animals [42]. Another study showed that EP4 knockout in mice increased airway inflammation induced by lipopolysaccharide (LPS) and cigarette smoke, while PGE2 inhibited the production of TNF-α and IL-6 in human lung macrophages by binding with EP4 [43][44]. SMC-specific EP4 knockout exacerbated angiotensin II-induced aortic dissection by increasing vascular inflammation [45]. PGE2 exerted anti-inflammatory effects by binding to EP4 to regulate macrophage and T lymphocyte functions, which are essential in innate and adaptive immunity as well as in tissue remodeling and repair. Evaluation of respiratory function is essential for patients with PH. For PH caused by COPD, inducing bronchial relaxation and reducing hypoxia may bring benefits to patients [46]. It has been found that EP4 agonists have a 10-fold to 50-fold greater bronchorelaxing effect than IP receptor agonists, and that PGE2-induced bronchiectasis is attenuated due to decreased expression of EP4 in PH associated with lung disease and/or hypoxia. Restoration of EP4 expression may be an effective way to improve the respiratory function of patients [47]. PGE2 inhibited PDGF-BB-induced proliferation and migration of human airway SMCs through EP4 to improve airway remodeling and improve COPD [48]. EP4 may be a new effective target for the treatment of PH. In addition, EP4 plays an important role in physiological and pathological vascular remodeling [45]. It was subsequently demonstrated that the expression of PPARγ in PAECs is decreased in PH patients [48] and that the loss of PPARγ in PASMCs or PAECs can cause pulmonary vascular remodeling, leading to PH and distal pulmonary artery muscularization [49]. L-902688, a selective EP4 agonist, has been reported to inhibit MCT-induced PASMC proliferation and migration as well as pulmonary vascular remodeling through PKA/PPARγ activation, which can ameliorate right ventricular fibrosis and TGF-β-induced endothelial–mesenchymal transition (EndMT) in PAH models [50][51]. Therefore, EP4 can inhibit the proliferation of PASMCs, improve pulmonary vascular remodeling, and suppress human lung macrophage inflammation, which is an important target for the treatment of PH [52].

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