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Prostaglandin E-mediated Vascular Remodeling of the Ductus Arteriosus and Ductus-Dependent Congenital Heart Diseases

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Description

Prostaglandin E_2 (PGE_2) is known to be a potent endogenous vasodilator of the ductus arteriosus (DA) [1], which is an essential bypass artery between the aorta and the main pulmonary artery. In some types of congenital heart diseases (CHDs) such as hypoplastic left heart syndrome or pulmonary atresia, blood flow through the DA is required for systemic or pulmonary circulation. Life-threatening conditions such as shock and severe acidosis would progress when the DA constricts a few hours to days after birth. Therefore, PGE_1, a synthetic analog of PGE_2, is widely used to maintain DA patency in neonates with ductus-dependent CHDs [2]. Although there is considered to be no serious side effect of PGE_1 for short-term use, fever and apnea are known to be common side effects [2]. Administration of PGE_1 is thought to be a palliative treatment before surgical intervention. However, in some cases, PGE_1 might be continuously required for a longer duration. Therefore, long-term side effects of PGE_1 should be taken into account.

The vessel characteristics of the DA are morphologically different from the adjacent arteries, which are the aorta and the main pulmonary artery [3]. Physiological intimal thickness is well developed in the DA during a perinatal period. Elastic fibers in the medial walls are sparse and the internal elastic lamina is fragmented in the DA. Elastic fiber formation is attenuated more in the area where intimal thickening occurs. In addition to the vasodilatory effect of PGE, we have demonstrated that PGE stimulation and its downstream signals via EP4, the DA-dominant PGE receptor, play a critical role in these morphological changes [4-6] (Figure 1). Chronic PGE_2-EP4-cyclic AMP (cAMP)-protein kinase A (PKA) signaling during gestation promotes hyaluronan-mediated intimal cushion formation [4]. Epac, an alternate downstream target of cAMP, has an acute promoting effect on smooth muscle cell migration without hyaluronan production, which also contributes to intimal thickening in the DA [5]. Therefore, PKA and Epac, both EP4-cAMP downstream targets, regulate vascular remodeling in the DA. PGE-EP4 signals also significantly inhibit elastogenesis because of the decrease in lysyl oxidase (LOX) protein, which catalyzes elastin cross-links in the DA, but not in the aorta [6]. We found that c-Src-phospholipase C (PLC) gamma activation but not cAMP is the downstream signaling pathway of PGE-EP4-mediated poor elastogenesis. Therefore, our data indicate that long-term use of PGE_1 could cause a structural change in the DA such as intimal cushion and elastic fiber formations.

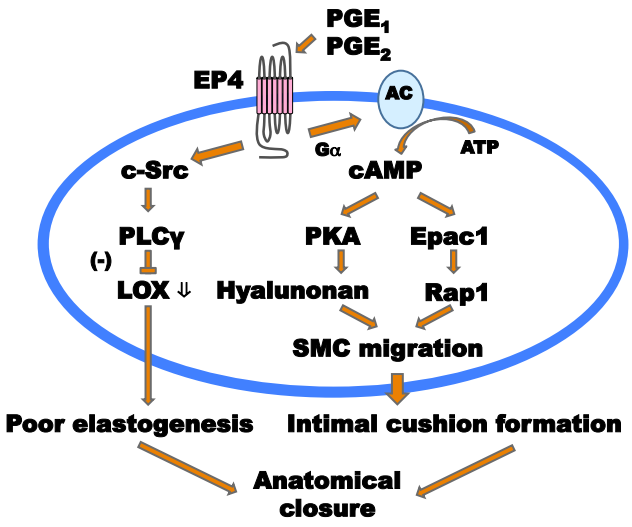

Figure 1: Prostaglandin E (PGE)-EP4 mediated DA remodeling has diverse signal pathways for intimal cushion formation and poor elastogenesis. (Abbreviations PGE: Prostaglandin E; EP4: Prostaglandin E-specific receptor subtype 4; AC: adenylyl cyclase; Gα: Small GTP protein α; PLCγ: phospholipase C gamma; LOX: lysyl oxidase; PKA: cAMP-dependent protein kinase A; Epac1: exchange factor directly activated by cAMP 1; SMC: smooth muscle cell).

Previous studies have demonstrated that PGE_1 administration has a profound weakening effect on the structure of the DA wall in some cases [7,8], although other investigators did not find PGE_1-induced specific changes over a short time [9,10]. Gittenberger-de Groot et al. first reported pronounced pathological changes in four infants with ductus-dependent CHDs [8]. The changes consisted of edema of the media, pathological interruptions of the internal elastic lamina, and intimal lacerations. Calder et al. reported intimal tears in two and hemorrhage into the media in five out of 12 infants who were treated with PGE [7]. These changes were not found in 12 control infants. Although we expected that long-term PGE_1 administration could produce prominent intimal cushion formation, we did not observe intimal thickening in our six patients (unpublished data). Immunohistochemical analysis revealed that the EP4 protein expression was markedly decreased in the DA that was treated with PGE_1 (unpublished data). This down-regulation of EP4 might be the reason why we did not observe intimal thickening in our cases.

Physicians must consider both local and systemic side effects of long-term PGE_1 administration. In addition to fever and apnea, possible adverse effects of PGE_1 administration are fluid and electrolyte imbalance, metabolic alkalosis, gastric outlet obstruction, and feeding difficulties [11-13]. A significant and unusual side effect of PGE_1 treatment is the symmetrical development of periostitis of the long bones [14]. Moreover, it is important to be aware of a possible adverse effect of PGE_1 on hematopoietic progenitor or stem cells, because recent studies have demonstrated that PGE_2 regulates hematopoietic stem and progenitor cell function [15-17]. Further investigation is required to safely use PGE_1 for patients with ductus-dependent CHDs for a long-term period.

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