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Treprostinil signals via the IP or EP₂ receptor to inhibit dynamin-related protein (DRP1) and promote mitochondrial elongation in pulmonary arterial smooth muscle cells (PASMCs) from patients with pulmonary arterial hypertension (PAH).

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Abstract:

Introduction. Prostacyclin analogues, such as treprostinil, are used clinically in the treatment of pulmonary arterial hypertension (PAH), a rare, progressive, life-threatening cardiopulmonary disorder (1). Central to the pathogenesis of PAH is the proliferation of pulmonary arterial smooth muscle cells (PASMCs) within the medial layers of small pulmonary arteries (1). Increased PASMC proliferation is associated with excessive mitochondrial fragmentation due to increased expression and activity of DRP1, a key effector of mitochondrial fragmentation (2). We sought to elucidate whether treprostinil acting on the IP or EP₂ prostanoid receptors inhibits DRP1 to promote mitochondrial fusion and elongation in PASMCs derived from patients with PAH.

Method. PASMCs were cultured with treprostinil (100 nM) for 3 hours alone or with either the IP receptor antagonist RO1138452 (1 μM), the EP₂ receptor antagonist PF04418948 (1 μM) receptor antagonist, a combination of both antagonists or the PKA inhibitor H-89. PASMCs were also treated with either the IP receptor agonist MRE-269 (100 nM) or the EP₂ receptor agonist butaprost (100 nM). Inhibitory DRP1 phosphorylation on serine 637 (pDRP1^{S637}) was determined by western blotting. Live-cell imaging with MitoTracker Red CM-H2Xros was used to assess mitochondrial morphology.

Results. Low levels of pDRP1^{S637} were observed in untreated PASMCs, while treprostinil markedly increased the levels of pDRP1^{S637} (n = 3; p < 0.05) and promoted mitochondrial fusion and elongation. Although, individually, RO1138452 and PF04418948 had no effect on treprostinil-induced DRP1 phosphorylation, together they significantly blocked treprostinil-induced phosphorylation of DRP1 (n = 3; p < 0.01). Treprostinil-induced DRP1 phosphorylation was also abolished by H-89. (n = 3; p < 0.0001). Moreover, butaprost and MRE-269 were also able to stimulate DRP1 phosphorylation in PASMCs.

Conclusions. IP or EP₂ receptor agonism leads to inhibitory DRP1 phosphorylation on serine 637 by

PKA to promote mitochondrial fusion and elongation in PSMCs. **References** 1. Clapp, LH and Gurung, R (2015) Prostaglandins Other Lipid Mediat **120**: 56-71. 2. Marsboom, G, Toth, PT, Ryan, JJ, Hong, Z, Wu, X, Fang, YH, Thenappan, T, Piao, L, Zhang, HJ, Pogoriler, J, Chen, Y, Moorow, E, Weir, EK, Rehman, J and Archer SL (2012) Circ Res **110(11)**: 1484-1497.

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