Abstract: P6012

Active selexipag metabolite MRE-269 increases endothelin receptors in pulmonary artery smooth muscle cells

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Topic(s):
Pulmonary Circulation, Pulmonary Embolism, Right Heart Failure: Pharmacotherapy

Citation:
Background: The pathology of pulmonary arterial hypertension (PAH) indicates the abnormal outgrowth of pulmonary artery smooth muscle cells (PASMCs) of the media. Abundant expression of endothelin 1 (ET-1) is observed in vessels of PAH, and has been considered to play a pathogenic role. There are several endothelin receptors including ETA, ETB. Compared to ETA, ETB mRNA is less expressed in PASMCs from control individuals, and is reported to be increased in those from PAH patients. However, how ETB is involved in PAH remains unclear. Selexipag, a non-prostanoid IP receptor agonist, was recently authorized for treating PAH. Compared to selexipag, the active metabolite MRE-269 has a higher affinity for the IP receptor. Initial combination therapy come to be accepted as a standard strategy for this disease, although the interaction of each drug has not been discussed enough.

Purpose: To assess the effect of selexipag on ET-1 receptors in PASMCs.

Methods: We stimulated purchased human PASMCs and endothelial cells by MRE-269 (300 nM), ET-1 (100 nM) or combination of them in vitro. Quantitative PCR was performed to quantify mRNA expressions. Cell proliferation was assessed by CCK8 cell proliferation assay kit. BQ123, A192621, bosentan was used as blocker against ETA, ETB, or both, respectively.

Results: In PASMCs, MRE-269 increased ETA and ETB expressions 2- and 7-fold, respectively. On the other hand, it increased ETB 1.2-fold in pulmonary artery endothelial cells; ETA was not detected in those cells. After pretreatment by MRE-269, ET-1 accelerated the proliferation of PASMCs. A192621 and bosentan abrogated this proliferation. In contrast, BQ123 did not abrogate it.

Conclusions: In PASMCs, active selexipag metabolite MRE-269 increases ETB more strongly than ETA, resulting in accelerated cell proliferation by ET-1 predominantly via ETB. These data call for further study focused on the choice of ET-1 receptor antagonists in the case of combination therapy with selexipag.