Beta3-adrenergic stimulation restores endothelial mitochondrial dynamics and prevents pulmonary arterial hypertension

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Background: Endothelial dysfunction is one of the most important hallmarks of pulmonary arterial hypertension (PAH). This leads to anomalous production of vasoactive mediators that are responsible for a higher vascular tone and a subsequent increase in pulmonary artery pressure (PAP), and to an increased vascular permeability that favors perivascular inflammation and remodeling, thus worsening the disease. Therefore, preservation of the endothelial barrier could become a relevant therapeutic strategy.
Purpose: In previous studies, others and we have suggested the pharmacological activation of the β3-adrenergic receptor (AR) as a potential therapeutic strategy for pulmonary hypertension (PH) due to left heart disease. However, its potential use in other forms of PH remain unclear. The aim of the present study was to elucidate whether the β3-AR agonist mirabegron could preserve pulmonary endothelium function and be a potential new therapy in PAH.
Methods: For this purpose, we have evaluated the effect of mirabegron (2 and 10 mg/kg·day) in different animal models, including the monocrotaline and the hypoxia-induced PAH models in rats and mice, respectively. Additionally, we have used a transgenic mouse model with endothelial overexpression of human β3-AR in a knockout background, and performed in vitro experiments with human pulmonary artery endothelial cells (HPAECs) for mechanistic experiments.
Results: Our results show a dose dependent effect of mirabegron in reducing mean PAP and Right Ventricular Systolic Pressure in both mice and rats. In addition, the use of transgenic mice has allowed us to determine that pulmonary endothelial cells are key mediators of the beneficial role of β3-AR pathway in ameliorating PAH. Mechanistically, we have shown in vitro that activation of β3-AR with mirabegron protects HPAECs from hypoxia-induced ROS production and mitochondrial fragmentation by restoring mitochondrial fission/fusion dynamics.
Conclusions: This protective effect of mirabegron would lead to endothelium integrity and preserved pulmonary endothelial function, which are necessary for a correct vasodilation, avoiding increased permeability and remodeling. Altogether, the current study demonstrates a beneficial effect of the β3-AR agonist mirabegron that could open new therapeutic avenues in PAH.