Vascular remodeling in pulmonary arterial hypertension: roles of CaSR and PDGF

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Pulmonary arterial hypertension (PAH) is a progressive and fatal disease associated with remodeling of the pulmonary artery. The major pathogenesis of PAH is sustained pulmonary vasoconstriction and pulmonary vascular remodeling. Excitable and structural abnormality in the pulmonary artery, such as vasoconstriction and vascular remodeling in PAH patients, are mostly mediated by an elevated cytosolic Ca^{2+} concentration in pulmonary arterial smooth muscle cells (PASMCs). We previous found that the Ca^{2+}-sensing receptor (CaSR) is upregulated in PASMCs from idiopathic pulmonary arterial hypertension (IPAH) patients, and contributes to enhanced Ca^{2+} responses and excessive cell proliferation (vascular remodeling). In this study, the molecular mechanisms underlying the upregulation of CaSR were examined in PASMCs from normal subjects and IPAH patients. In normal-PASMCs, expression of CaSR was increased by platelet-derived growth factor (PDGF), which is known as an endogenous signal associated with IPAH. The expression of PDGF receptors was higher in IPAH-PASMCs than in normal-PASMCs. PDGF-induced activation of PDGF receptors and its downstream molecules (ERK1/2, p38, Akt, and STAT1/3) sustained longer in IPAH-PASMCs. In addition, PDGF stimulation facilitated both proliferation and migration of normal-PASMCs. On the other hand, siRNA knockdown of PDGF receptors attenuated the CaSR upregulation in IPAH-PASMCs. Imatinib (an tyrosine kinase inhibitor of PDGF receptors) and NPS2143 (an antagonist of CaSR) inhibited the PDGF-induced CaSR upregulation in IPAH-PASMCs. These results suggest that PDGF signal activates the upregulation mechanism of CaSR in IPAH-PASMCs. In conclusion, the linkage between CaSR and PDGF signals is a novel pathophysiological mechanism contributing to the development of PAH including excessive cell proliferation (vascular remodeling). The combination of tyrosine kinase inhibitors of PDGF receptors and CaSR antagonists may be useful for the treatment for PAH.