Stretch-Activated Piezo1 Channel in Endothelial Cells Relaxes Mouse Intrapulmonary Arteries

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Résumé en anglais	In intrapulmonary artery (IPA), endothelial cells (EC) respond to mechanical stimuli by releasing vasoactive factors to set the vascular tone. Piezo1, a stretch-activated calcium permeable channel is a sensor of mechanical stress in EC. The present study was undertaken to investigate the implication of Piezo1 in the endothelium-dependent regulation of IPA tone and its potential involvement in pulmonary hypertension, the main disease of this circulation. IPA tone was quantified by means of a myograph in control Piezo1+/+ mouse and in mouse lacking endothelial Piezo1 (EC-Piezo1-/-). Endothelial intracellular calcium concentration ([Ca2+]i) and nitric oxide (NO) production were measured, in mouse or human EC, with fluo-4 and DAF-fm probes, respectively. Immunofluorescence labeling and patch-clamp experiments revealed the presence of Piezo1 channels in EC. Yoda1, a Piezo1 agonist, induced an endothelium-dependent relaxation that was significantly reduced in pulmonary arteries in EC-Piezo1-/- compared to Piezo1+/+ mouse. Yoda1 as well as mechanical stimulation (by osmotic stress) increased [Ca2+]i in mouse or human EC. Consequently, both stimuli increased the production of NO. NO and [Ca2+]i increases were reduced in EC from Piezo1-/- mouse or in the presence of Piezo1 inhibitors. Furthermore, deletion of Piezo1 increased alpha-adrenergic mediated contraction. Finally, in chronically hypoxic mice, a model of pulmonary hypertension, Piezo1 still mediated arterial relaxation and deletion of this channel did not impair the development of the disease. The present study thus demonstrates that endothelial Piezo1 contributes to intrapulmonary vascular relaxation by controlling endothelial [Ca2+]i and NO production and that this effect is still present in pulmonary hypertension.

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