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Functional Expression of Two-Pore Domain K^+ Channels in Pulmonary Hypertension

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Summary

Pulmonary arterial hypertension (PAH) is a progressive and fatal disease of the pulmonary artery. The major pathogenesis is sustained vasoconstriction and vascular remodeling of the pulmonary artery. These cause progressive elevations in pulmonary vascular resistance and pulmonary arterial pressure. Elevated pulmonary arterial pressure leads to right heart failure and finally death. The vascular remodeling is caused by the enhanced proliferation and reduced apoptosis of pulmonary arterial smooth muscle cells (PASMCs). The excessive PASMC proliferation is triggered by increase in cytosolic Ca^{2+} concentration ($[Ca^{2+}]_{cyt}$). $[Ca^{2+}]_{cyt}$ is predominantly determined by the balance of the activity of ion channels. In the present study, the functional expression of two-pore domain K^+ (K_{2P}) channels (KCNK family; KCNK1-18 except for KCNK8, 11, and 14) was examined in PASMCs from normal subjects and patients with idiopathic pulmonary arterial hypertension (IPAH). Expression analyses revealed that, in PASMCs from IPAH patients, the expressions of KCNK1 (TWIK1) and KCNK2 (TREK1) channels were upregulated, whereas those of KCNK3 (TASK1) and KCNK6 (TWIK2) channels were downregulated. K_{2P} channel currents with inward and outward rectifications were detected in PASMCs from IPAH patients. The excessive proliferation of PASMCs from IPAH patients was inhibited by a K_{2P} channel blocker, quinine. In conclusion, these results suggest that upregulated KCNK1 (TWIK1) and KCNK2 (TREK1) channels facilitate the proliferation of PASMCs, leading to the development of PAH. Therefore, KCNK1 (TWIK1) and KCNK2 (TREK1) channels may be novel therapeutic targets for PAH.