Ca^{2+}-sensing Receptor and Receptor-operated Ca^{2+} Entry in Pulmonary Hypertension

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Pulmonary vasoconstriction and pulmonary vascular remodeling are two major causes for the elevated pulmonary vascular resistance and pulmonary arterial pressure in patients with idiopathic pulmonary artery hypertension (IPAH). An increase in cytosolic Ca^{2+} concentration ($[Ca^{2+}]_{cyt}$) due to Ca^{2+} influx and/or release in pulmonary artery smooth muscle cells (PASMC) is a major trigger for pulmonary vasoconstriction and an important stimulus for PASMC proliferation/migration which ultimately cause pulmonary vascular remodeling. In IPAH-PASMC, we previously reported that the resting $[Ca^{2+}]_{cyt}$ was higher and the amplitude of receptor-operated Ca^{2+} entry (ROCE) was greater than that in normal PASMC. The aim of this study was to examine the potential mechanisms involved in the elevated resting $[Ca^{2+}]_{cyt}$ and enhanced ROCE in IPAH-PASMC. In normal PASMC superfused with Ca^{2+}-free solution, restoration of extracellular Ca^{2+} (to 1.8-2.2 mM) had little effect on $[Ca^{2+}]_{cyt}$. In IPAH-PASMC superfused with Ca^{2+}-free solution, addition of Ca^{2+} caused a concentration-dependent increase in $[Ca^{2+}]_{cyt}$.

The extracellular Ca^{2+}-mediated rise in $[Ca^{2+}]_{cyt}$ was significantly inhibited by La^{3+}, but not by SKF96365 (a blocker of nonselective cation channels), KB-R7943 (an inhibitor of Na^+/Ca^{2+} exchanger) or nifedipine (a blocker of voltage-dependent Ca^{2+} channels). Protein expression of Ca^{2+}-sensing receptors (CaSR) was significantly higher in IPAH-PASMC than in normal PASMC. Under the resting conditions, we also observed spontaneous and periodic increases in $[Ca^{2+}]_{cyt}$, or Ca^{2+} oscillations, in very few (<5%) normal PASMC. However, more than 50% of IPAH-PASMC showed spontaneous Ca^{2+} oscillations. The amplitude and frequency of spontaneous Ca^{2+} oscillations in IPAH-PASMC were significantly greater than in normal PASMC. Removal of extracellular Ca^{2+} abolished the Ca^{2+} oscillations in IPAH-PASMC, while 10 μM La^{3+} significantly decreased the amplitude and frequency of the Ca^{2+} oscillations. Furthermore, OAG (100 μM), a membrane-permeable diacylglycerol analogue, only slightly increased $[Ca^{2+}]_{cyt}$ in 30% of normal PASMC, but elicited a large increase in $[Ca^{2+}]_{cyt}$ followed by Ca^{2+} oscillations in IPAH-PASMC. Overexpression of Orai2 and STIM2 significantly enhanced Ca^{2+} oscillations in normal PASMC. These data indicate that upregulated CaSR, Orai2 and STIM2 may contribute to the enhanced spontaneous Ca^{2+} oscillations and augmented ROCE in PASMC from patients with IPAH. Functional interaction of CaSR, Orai2/STIM2 and TRPC3/6 localized in the caveolae in PASMC may be an important mechanism for sustained pulmonary vasoconstriction and excessive pulmonary vascular remodeling in patients with IPAH.