Involvement of mitochondrial Na^+/Ca^{2+} exchanger in hypoxia-induced pulmonary arterial hypertension.

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Pulmonary arterial hypertension (PAH) is characterized by pulmonary artery remodeling and inappropriate vasoconstriction, which results in a marked increase in pulmonary arterial pressure and right ventricular hypertrophy. Because a multiple factor participates in the pathogenesis of PAH, elucidation of the further mechanism is needed. Mitochondrial dysfunctions have been reported in the pathogenesis of PAH. In this study, to investigate the involvement of mitochondrial Na^+/Ca^{2+} exchanger (NCLX) in the development and progression of PAH, we generated a mouse model of hypoxia-induced PAH using NCLX knockout (NCLX-KO) mice, vascular smooth muscle-specific NCLX transgenic (VSM-NCLX-Tg) mice and wild-type (WT) mice. Increase in right ventricle systolic pressure (RVSP) induced by chronic hypoxia was significantly reduced in NCLX-KO mice compared with WT mice, whereas it was markedly augmented in VSM-NCLX-Tg mice. Moreover, administration of CGP37157, a selective NCLX inhibitor, to WT mice with chronic hypoxia significantly attenuated the increase in RVSP. These results suggested that vascular smooth muscle NCLX is involved in the pathogenesis of chronic hypoxia-induced PAH.