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Title: Resveratrol attenuates hypoxic pulmonary vascular remodeling in simulated high altitude-exposed rats: potential role of Hif-1α/NOX4/ROS inhibition

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Body: Objectives: Chronic high altitude hypoxia induces pulmonary vascular remodeling with medial hypertrophy and luminal narrowing leading to the development PAH. Pulmonary oxidative stress has been implicated in hypoxic PAH. This study aimed to investigate the effects of resveratrol, an anti-oxidant polyphenol, on hypoxic pulmonary vascular remodeling in rats. Methods: Rats were exposed to simulated high altitude of 6000 m in a hyperbaric chamber for 8 h/d, for up to 28 days. Resveratrol (10 mg/kg, ip) was daily administered 0.5 h before hypoxia exposure. Rat primary pulmonary arterial smooth muscle cells (PASMCs) were incubated under hypoxia (2% O_2) in the presence of 10, 25, or 50 μM resveratrol. Pathophysiological changes and signal transduction were examined using histochemistry, fluorescence probing, Western blotting and RT-PCR. Results: Resveratrol administration significantly reduced hypoxia-induced elevation in mPAP (23.6±2.4 mmHg vs. 30.3±1.9 mmHg; $P<0.05$) and medial wall thickness of pulmonary arterioles (16.5±1.8 % vs. 22.7±2.4 %; $P<0.05$) in rats. Resveratrol also decreased pulmonary MDA and H_2O_2 levels as indicators of oxidative stress in hypoxic PAH rats. In vitro studies show that resveratrol dose-dependently inhibited hypoxia-induced rat PASMC proliferation and cellular ROS accumulation. Moreover, resveratrol reduced hypoxia-increased Hif-1α and NOX4 (a ROS contributor) expression both in vitro and in vivo. Conclusions: Resveratrol attenuates hypoxic pulmonary vascular remodeling in rats exposed to intermittent simulated high altitude, possibly through its inhibition on Hif-1α/NOX4/ROS-generated oxidative stress under hypoxia.