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Abstract Title

Superoxide Driven S-Nitrosylation of Adenylate Cyclase 6 Mediates Hypoxic Pulmonary Vasoconstriction

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Background

Persistent pulmonary hypertension of the newborn (PPHN) is a multifactorial, lethal failure of pulmonary vascular relaxation, affecting 0.6% of births. ~40% of PPHN results from hypoxia. The adenylyl cyclase (AC) - cAMP signaling pathway is a central mediator of pulmonary vasodilation. AC6 is the predominant AC isoform in neonatal pulmonary arteries. Hypoxia induced oxidative and nitrosative stress promotes the formation of reactive nitroso species, leading to S-nitrosylation of AC6 at cysteine 1004, a residue essential

for Gαs interaction and catalytic activity. This modification inhibits AC6 activation, decreasing cAMP production.

Objective

We hypothesized that reactive nitroso species (sNO) generated from nitric oxide and superoxide drive AC6 S-nitrosylation during hypoxia and disrupt catalytic subunit (C1 - C2) interaction.

Methods

First-passage PASMCs from newborn piglets (<24h), and primary PASMCs cultured from newborn piglets exposed to 10% O₂ for 72h (PPHN) or room air (controls), were studied under normoxia (21% O₂) or hypoxia (10% O₂) for 72h, +/- nitroso/superoxide donors and scavengers. ROS/RNS; protein S-nitrosylation; AC activity; cAMP generation were measured.

Results

Hypoxia in vivo or in vitro increased intracellular superoxide and protein S-nitrosylation of AC6, eNOS, and Gαi (but not Gαs). Hypoxia-induced S-nitrosylation was attenuated by SOD or FeTTPs, implying a superoxide-dependent pathway. Hypoxia or sNO donors diminished AC activity and cAMP generation; reversed by scavenging superoxide or peroxynitrite.

Conclusion

We conclude hypoxia promotes pulmonary arterial superoxide production, which scavenges nitric oxide to form peroxynitrite, leading to AC6 S-nitrosylation; this disrupts catalytic subunit interactions and suppresses cAMP synthesis. AC6 S-nitrosylation represents a novel therapeutic target in PPHN.