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Keivan Zandinejad, MD

Case Western Reserve University
Cleveland, OH

S-Nitrosylation Therapy to Treat Hypoxia-Induced Pulmonary Arterial Hypertension

Pulmonary hypertension (PH) frequently complicates and worsens the course of patients with advanced lung diseases. And despite many years of research, the interventions for PH remain more palliative than curative.

Chronic alveolar hypoxia associated with these diseases is a major factor in the characteristic alterations in the pulmonary and systemic circulations. Although the exact molecular mechanisms responsible for initiating and propagating these processes are not well understood, PH is recognized as having impairments in nitric oxide (NO) signaling. However, current NO-based therapies (inhaled NO and sildenafil) act exclusively via cGMP pathways, even as it is now well-accepted that the vast majority of NO's cellular activities are mediated through protein S-nitrosylation; the covalent modification of cysteine thiols to form S-nitrosothiols (SNOs).

Disruption of S-nitrosylation is an important component in a number of pathologic conditions, particularly in disease states characterized by disruptions in oxygenation. This includes PH, where we have previously documented reduced SNO/NO bioactivity; notably, levels of S-nitrosylated hemoglobin (SNO-Hb; the main regulator of oxygen delivery) were inversely correlated with disease severity. At the same time, because of the wide spectrum of activities regulated by SNOs, resolution of aberrant S-nitrosylation provides an attractive therapeutic target for disease amelioration. Indeed, acute administration of an S-nitrosylating agent to PH patients rapidly restored SNO-Hb levels, reduced pulmonary arterial pressure (PAP), and improved systemic oxygenation.

The current study builds on the earlier work to determine the long-term benefits of S-nitrosylation therapy. We hypothesize that: 1. Disruption of SNO homeostasis in the body caused by exposure to chronic hypoxia results in elevated PAP and other organ dysfunctions seen in hypoxia-induced PH; and 2. Restoration of SNO homeostasis by administration of an S-nitrosylating agent can prevent or reverse these changes. We will test these hypotheses in a rodent model of hypoxia-induced PH. Positive findings may well lead to clinical assessment of the therapeutic efficacy of S-nitrosylating agents to treat human PH patients.