Sodium nitrite attenuates hypobaric hypoxia-induced oxidative stress and provides cardioprotection in rodent heart

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Introduction: Hypobaric hypoxia induces severe oxidative stress to cardio-vascular and cardio-pulmonary system characterized by increased reactive oxygen species (ROS) formation, compromised antioxidant system and decrease in nitric oxide levels. This leads to pathological cardiopulmonary conditions like pulmonary arterial hypertension (PAH), high altitude pulmonary edema (HAPE) and high altitude cerebral edema (HACE).

Hypothesis: We hypothesized that dietary equivalent dose of sodium nitrite could help in ameliorating hypobaric hypoxia induced oxidative stress and confer cardioprotection in rats.

Materials and Methods: Rats (n = 6-10) were supplemented with sodium nitrite (50mg/L) in drinking water for 24 hrs and subsequently exposed to short term (3 h) hypobaric hypoxia (25,000 ft). Hypobaric hypoxia-induced oxidative stress was measured by estimation of free radical, glutathione reduced/oxidized (GSH/GSSG) ratio, HNE-adduct, protein and lipid oxidation in heart tissues of normoxic (control), nitrite supplemented normoxic, hypoxic and nitrite supplemented hypoxia exposed rats. NOx species bioavailability was assessed by measuring plasma and cardiac NOx and cGMP levels. Peroxynitrite formation was estimation by immunohistochemical staining of cardiac tissue with 3-Nitrotyrosine. To elucidate pathways and nitrite modulated genes in heart during hypoxia, we performed a microarray analysis on Illumina Rat Ref-12 BeadChip. The microarray results were further validated by qRT-PCR and western blotting.

Results and discussion: Sodium nitrite supplementation significantly attenuated hypoxia-induced oxidative stress and promotes NO-cGMP signaling in hypoxic heart. Sodium nitrite also decreased nitrotyrosine formation in hypobaric hypoxia exposed heart thus inhibiting peroxynitrite mediated tissue damage. Transcriptome analysis revealed a profound upregulation of cardioprotective and antioxidant genes while downregulating necrotic and apoptotic genes in nitrite supplemented rat hearts.

Conclusion: Sodium nitrite supplementation attenuates hypobaric hypoxia-induced oxidative damage, restores NOx and antioxidant homeostasis, provides cardioprotection and cytoprotection by activating antioxidant, anti- and pro-inflammatory pathways.

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