Nitrite therapy reduces metabolic and cardiopulmonary dysfunction allied to obesity: Role of xanthine oxidase.

Nadiezhda Cantu-Medellin, Eric R. Weidert and Eric E. Kelley

University of Pittsburgh, School of Medicine, Pittsburgh, PA, 15213, USA

Being frequently present in insulin-sensitive tissues and the vasculature, oxidative stress is a common component of obesity. However, it remains unclear to what extent oxidative stress contributes to obesity-associated metabolic abnormalities such as insulin resistance, steatosis/dyslipidemia, and cardiovascular disease; while the identities of the sources of reactive species and the allied redox-sensitive pathways that mediate the effects of oxidative stress in obesity remain elusive. Data from our laboratory have identified a substantial source of reactive species in obesity to be xanthine oxidoreductase (XOR) which oxidizes hypoxanthine to xanthine and xanthine to uric acid (UA) while reducing O$_2$ to O$_2^*$ and H$_2$O$_2$. This is evidenced by a significant elevation of tissue and plasma XOR activity in both animal models of obesity and in the clinic. However, recent reports have identified XOR as a nitrite reductase and thus a source of salutary $^\bullet$NO under conditions where dietary nitrite supplementation results in elevated nitrite levels in plasma and tissues. As such, we compared the impact of XOR inhibition versus dietary nitrite supplementation on metabolic and cardiopulmonary dysfunction in a preclinical model of diet-induced obesity. Our results demonstrate salutary outcomes from XOR inhibition; yet, the greatest benefit being afforded by dietary nitrite. For example, treatment with nitrite reduced oxidative stress, improved impaired glucose tolerance and diminished hemodynamic indices (RVESP, PVR, mPAP, Tau and pulmonary arteriole remodeling) related to pulmonary arterial hypertension. We conclude that dietary nitrite supplementation may be a beneficial strategy to reduce both metabolic and cardiovascular dysfunction associated with obesity by altering XOR product formation from oxidants to $^\bullet$NO.