Hypertension, Nitrate-Nitrite, and Xanthine Oxidoreductase Catalyzed Nitric Oxide Generation: Pros and Cons

We read with great interest the article by Ghosh et al on the use of beetroot juice as a potential therapy for hypertension. This article proposes the intriguing concept that dietary nitrate in beetroot juice can be converted into therapeutically beneficial nitric oxide (NO) for use in treatment of essential hypertension. The proposed critical steps in NO generation seem to comprise conversion of nitrate into nitrite by bacteria present on the tongue, release of nitrite to the bloodstream, and conversion of nitrite into NO by erythrocyte-bound xanthine oxidoreductase (XOR).

The production of NO by XOR-catalyzed nitrite reduction requires the presence of the XOR reducing substrates, hypoxanthine or xanthine. Reduced XOR can then pass reducing equivalents to nitrite to generate NO. This reaction is significantly hypoxia- and pH-dependent, being optimal at acidic pHs that are well below both physiological pH and the pH optimum of XOR. Importantly, this reaction converts xanthine into uric acid, which is emerging as a possible contributing factor in both essential hypertension and pulmonary hypertension. Uric acid may have a role in driving intracellular oxidative stress, endothelial dysfunction, activation of the renin–angiotensin system, and restriction of NO bioavailability, which may contribute to hypertension particularly in adolescents and women. Furthermore, lowering serum uric acid with the XOR inhibitor allopurinol improves blood pressure in hypertensive adolescents.

Uric acid–induced reductions in endothelial NO involve scavenging by reactive oxygen species and nicotinamide adenine dinucleotide phosphate oxidase, as well as decreased L-arginine substrate because of increased arginase production and reduced L-arginine transport. Uric acid–induced reductions in endothelial NO synthase-3 activity and genome-wide association studies have identified the endothelial NO synthase downregulating single nucleotide polymorphism rs3918226 as a highly significant (P=2.58×10^{-13}) risk factor for the development of hypertension. Thus, any potential benefit of xanthine oxidase on generation of NO from nitrite must also take into account the potential deleterious effects of uric acid on vascular health.

Disclosures

Dr Johnson is an inventor on a patent for the clinical use of allopurinol to treat primary hypertension that has been licensed by XORT therapeutics, Inc. The other authors report no conflicts.
