Antihypertensive Inorganic Nitrate and Nitrite: What Is the Underlying Mechanism?

To the Editor:
L-Arginine, organic nitrates such as nitroglycerin, inorganic nitrate (NO\textsubscript{3}\textsuperscript{−}), and inorganic nitrite (NO\textsubscript{2}\textsuperscript{−}) are precursors of nitric oxide (NO), a potent vasodilator and blood pressure–lowering molecule. How NO is released from nitroglycerin,\textsuperscript{1} NO\textsubscript{3}\textsuperscript{−}, and NO\textsubscript{2}\textsuperscript{−} is incompletely understood. Ghosh et al\textsuperscript{2} reported that erythrocytic xanthine oxidoreductase (XOR) plays a crucial role in lowering blood pressure in hypertensives as it releases NO\textsubscript{3} from nitroglycerin,\textsuperscript{1} NO\textsubscript{3}\textsuperscript{−}, and NO\textsubscript{2}\textsuperscript{−} is a potent vasodilator and blood pressure–lowering molecule. How NO\textsubscript{3}− is released from nitroglycerin,\textsuperscript{1} NO\textsubscript{3}\textsuperscript{−}, and NO\textsubscript{2}\textsuperscript{−} is incompletely understood. XOR is unlikely to generate NO from NO\textsubscript{2}− in erythrocytes.

Allopurinol is frequently used to support XOR involvement in various processes. Yet, the action of allopurinol is not restricted to XOR. Allopurinol decreases significantly the concentration of circulating asymmetric dimethylarginine (ADMA),\textsuperscript{3} an endogenous inhibitor of NO synthase.\textsuperscript{4} Thus, allopurinol may normalize endothelial dysfunction\textsuperscript{5} by abolishing the inhibitory action of ADMA on NO synthase activity. Reduction of oxidative stress by allopurinol has been proposed as a mechanism explaining the decrease of circulating ADMA seen on allopurinol administration.\textsuperscript{6} Yet, allantoin is not a reliable oxidative stress biomarker, because allopurinol inhibits XOR-induced formation of uric acid,\textsuperscript{7} the precursor of allantoin. In plasma and urine of patients with peripheral arterial occlusive disease, we did not find any correlation between ADMA and the oxidative stress biomarkers malondialdehyde and 15(S)-8-iso-prostaglandin F\textsubscript{2α} (Figure). This suggests that allopurinol is unlikely to reduce circulating ADMA concentration by decreasing oxidative stress.

NO\textsubscript{3}− and NO\textsubscript{2}− are emerging experimental drugs for the treatment of NO-related dysfunctions. The mechanisms by which NO\textsubscript{3}−, NO\textsubscript{2}−, and nitroglycerin are reduced to NO are unresolved, and their resolution provides a challenging task.

Disclosures

None.

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2. Ghosh SM, Kapil V, Fuentes-Calvo I, Bubb KJ, Pearl V, Millsom AB, Khanhata R, Maleki-Toyserkani S, Youssif M, Benjamin N, Webb AJ, Caulfield MJ, Hobbs AJ, Ahluwalia A. Enhanced vasodilator activity of NO\textsubscript{3}−, NO\textsubscript{2}− and ADMA was measured by GC-MS/MS (gas chromatography-mass spectrometry-mass spectrometry).
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