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Letter to the Editor

Pegloticase and lowering blood pressure in refractory gout; is it uric acid or hydrogen peroxide?

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Dear Editors,

Epidemiologic and experimental studies have demonstrated that high levels of serum uric acid ((SUA) Hyperuricemia) are strongly associated with poorly controlled hypertension, arterial stiffness, metabolic syndrome, chronic kidney disease and cardiovascular disease [1–3]. Likewise, high SUA in patients with gout was predictive of and associated with hypertension, atherosclerosis, high urinary albumin levels and systemic vascular injury [4]. Despite these associations, the causal role of uric acid (UA) in cardiovascular diseases has been the center of debate in part due to some inconclusive data from human treatment studies of hyperuricemia with XOR inhibitors. SUA is largely derived from degradation of purines by the enzyme xanthine oxidoreductase (XOR), which is the major source of both reactive oxygen species (ROS) and UA. Uricase converts UA to 5-hydroxy isourate and hydrogen peroxide (H_2O_2), leading to the formation of inert and highly soluble allantoin which is readily eliminated. Hyperuricemia occurs mainly in higher primates, including humans, primarily due to evolutionary inactivation of the uricase (Urate oxidase; UOX) gene [5]. The mechanisms that link elevated SUA level and gout with cardiovascular comorbidities seem to be multifactorial and include low grade systemic inflammation and xanthine oxidase (XO) activity, as well as the deleterious effects of hyperuricemia itself. A recent report used a novel approach to target SUA in a cohort of refractory gout patients with hypertension using recombinant uricase, pegloticase as opposed to pharmacological inhibitors of XOR which decrease both SUA and XOR activity [6]. In this letter we propose the potential mechanisms that could answer some of the outstanding questions regarding the differential role of UA and XOR derived ROS in modulation of the outcome in these trials.

Pegloticase is a pegylated form of uricase which offers an extended half-life of 10–12 days compared to rasburicase's eight hours. An 8 mg dose every 2–4 weeks, is expected to provide sufficient control of hyperuricemia in patients with treatment-refractory gout or chronic tophaceous gout. Significant increase in H_2O_2 production occurs in the first 24h after pegloticase therapy and a major portion of it is metabolized by heme peroxidases and catalase [5]. Although PEGylation restricts pegloticase to plasma, FDA prescription labeling states toxicological and animal evidence suggesting phagocytic removal of pegloticase from the circulation by macrophages in the liver and spleen and the cytoplasm of endothelial cells in the intimal lining of the aorta.

ROS can have deleterious effects on biological processes and contributes to many pathological conditions such as inflammation, vascular injury, diabetes and hypertension. However, some ROS such as H_2O_2 may act as signaling molecules in many physiological processes. H_2O_2 is generated by mitochondria, some oxidases and the metabolism of superoxide by superoxide dismutase (SOD). H_2O_2 freely crosses cell membranes. At low levels it can contribute to many signaling pathways by oxidizing thiols such as glutathione (GSH) and thioredoxins and at higher levels to production of toxic and highly reactive oxygen species including hydroxyl radicals. Although the exact role of H2O2 signaling in the cardiovascular system remains to be determined, there is evidence suggesting that H2O2 plays a major role in vasoregulation under both physiological and pathological conditions [7]. H2O2 is recognized as an endothelium derived hyperpolarizing factor (EDHF) with opposing vasoactive effects depending on its concentration, the vascular bed and redox status. The exact mechanisms and cellular targets through which H_2O_2 induces vasodilatation remain to be determined. At low concentrations ($\leq$10 uM), endothelial cells are the primary cells involved in H_2O_2 induced arteriolar dilatation. The major signaling pathway involved in this response is the COX1 – PGE2 axis and subsequent activation of smooth muscle cells (SMC). At higher concentrations of H_2O_2 ($\geq$30 uM), the role of endothelial cells is diminished and replaced by direct effects of peroxide on SMCs through increase in K+ conductance. A recent report confirmed the aforementioned pathway and further showed that these dilatory effects were influenced by redox status of the SMCs and diminished by condition of high ROS level in these cells [8]. Another example of endothelium independent effects of H_2O_2 induced arteriolar dilatation shows transient and catalase inhibitable relaxation of blood vessels by the superoxide dismutase mimetic, tempol, in part via production of H_2O_2.

The role of alternative redox sensitive peroxide induced arterial dilatation is critical in physiological conditions including organ specific differential responses to hypoxia and oxygen sensing [9] or in pathophysiological conditions where nitrite-NO pathway is inefficient in maintaining the blood pressure (BP) [10]. An example of the latter clinical condition is chronic hyperuricemia-induced disruption of NO-cGMP-PKG1α and endothelial dysfunction. In these scenarios, any

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factors affecting endothelial COX-1-PGE2 and/or changes in SMC K^+ conductance may dampen compensatory H_2O_2 effects and exacerbate vascular dysfunction. In their study of patients with refractory gout, Johnson et al., showed that pegloticase significantly reduced the mean BP in the subgroup of 29 responders with repeated pegloticase administration every 2 weeks (q2w) [6]. This effect was not seen in those 27 responders that were given pegloticase every 4 weeks (q4w). The vasodilatory effects of pegloticase catalyzed peroxide generation might explain the differential response among q2w and q4w responders as well as the lack of any effects on kidney function (eGFR) among q2w responders possibly due to differential catalase expression/activity in kidney vs other target cells [7]. Also H_2O_2 and not lowering UA per se could explain the reason behind the greater magnitude of BP reduction in responders in this report which was independent of age, gender and BMI compared to those reported in previous studies of hyperuricemic patients receiving oral urate-lowering therapy. Additionally, it can be proposed that the 10–12 days half-life of pegloticase is critical for maintaining effective low level of peroxide while not as critical for maintaining low SUA.

Although, these reports open a new avenue in therapeutic approaches to redox modulation using peroxide as a signaling molecule, one should not forget its narrow safety range. Thus, any potential benefit of pegloticase on generation of peroxide from UA oxidation must also take into account the potential deleterious effects of peroxide on vascular health. Also analysis of SUA over a broad concentration range has revealed a complex (U-shaped) dose response in cardiovascular and all-cause mortality with pathologic effect when its levels reach extremes at both high and low levels. This may be of particular significance for those individuals who undergo chronic long-term uricolytic treatment with pegloticase.

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