Uric Acid: An Old Dog with New Tricks?

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Diseases traditionally associated with hyperuricemia include acute urate nephropathy, gouty arthropathy, and nephrolithiasis. In recent years, however, understanding of additional adverse effects of hyperuricemia has been advanced. Early scientific literature suggested an association between serum urate concentration and incidence of cardiovascular disease, but the field lay relatively dormant until a flurry of papers associated hyperuricemia with development of hypertension (1), microalbuminuria (2,3), the metabolic syndrome (4), endothelial dysfunction (5), and target organ damage from hypertension, including left ventricular hypertrophy (2,6). The Bogalusa Heart Study (1), an observational study that followed a cohort of 577 children into adulthood, found that serum urate levels in childhood correlated positively with childhood and adulthood systolic and diastolic BP; the correlations were particularly significant with women (1). While these findings are compelling, they can provide only associations with the human condition and it remains unclear whether elevation of the serum urate contributes to or merely reflects these underlying disorders.

Circulating urate concentration in humans is higher compared to other mammals because of efficient tubular reclamation of filtered urate (7), along with an evolutionary loss of hepatic uricase from inactivating mutations (8). Enomoto et al. (7) cloned the anion exchanger URAT1, which is responsible for urate reabsorption in the kidney. Immunohistochemistry demonstrated localization in the apical membrane of the proximal tubule epithelium. These investigators also showed that inactivating mutations in SLC22A12, the gene encoding URAT1, were responsible for the syndrome of idiopathic renal hypouricemia, thus confirming an important role for URAT1 in maintaining serum urate concentration in humans. Uricosuric agents, such as probenecid, inhibited urate reabsorption by altering the function of URAT1 (7). Interestingly, losartan and its metabolite were as effective as probenecid at inhibiting urate transport (7). A recent analysis of the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study suggested that attenuation of the serum urate concentration by losartan was responsible for perhaps 29% of the effect on the primary cardiovascular composite end point, particularly in women (9).

More recently, mechanistic studies have shown that experimental hyperuricemia in rats produces hypertension (10), along with diminished production of nitric oxide (11) and renal arteriolar damage with apparent proliferation of vascular smooth muscle cells (VSMC) and associated luminal narrowing (12,13). Incubating primary cultures of human VSMC or human umbilical vein endothelial cells in medium containing physiologic concentrations of urate (6 to 12 mg/dl) resulted in cell proliferation and apparent activation of the cells with elaboration of C-reactive protein (CRP) (14). Co-incubation with probenecid, an inhibitor of urate transport, prevented the cellular effects of urate. A significant association between CRP levels and serum urate concentration was observed in a cohort of 337 patients who had chronic kidney disease but were not yet on dialysis (15), and in a group of 217 patients with untreated, uncomplicated, essential hypertension (5).

In this issue of JASN, Price et al. (16) determined that human VSMC in culture expressed mRNA from SLC22A12. PCR analysis did not detect other anion exchangers known to function as urate transporters. In addition, Western blotting and immunohistochemistry confirmed expression of URAT1 on the cell membranes. The authors concluded that URAT1 was the major mechanism by which uric acid enters VSMC. Whether endothelial cells have the same urate transporter is not yet clear.

The potential mechanism by which urate exerts a deleterious effect might be related to oxidative stress. With a pH of 5.4, uric acid circulates as anionic urate. Ordinarily, the urate anion serves an antioxidant function thought to be related to the ability to reduce transition metals (17) and to react with potent oxidants such as peroxynitrite (18). However, depending upon ambient conditions, urate can switch from an antioxidant to a pro-oxidant. For example, while ordinarily serving an antioxidant effect with native LDL, urate becomes a prooxidant when the LDL is partially oxidized (17,19). Lipid peroxidation is enhanced by urate after reaction with peroxynitrite, perhaps by facilitating the formation of highly reactive aminocarbonyl radicals (18). Accelerating intracellular oxidant stress after uptake of urate might be responsible for hyperuricemia-associated endothelial cell dysfunction and activation of VSMC (20). That antioxidants, including N-acetyl-cysteine and diphenylethionium, inhibited urate-induced monocyte chemotactic protein-1 production by cultured VSMC (21) provides additional support for this view. These effects are likely different from those pro-

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Inflammatory mechanisms induced specifically by crystalline urate.

In summary, while the function of serum urate as a risk factor for cardiovascular and renal morbidity remains controversial, increasing evidence supports a causal role in hypertension and associated end organ damage in humans, especially in women. An interaction between the effects of estrogen and urate has not been examined. By providing data showing URAT1 expression on human VSMC, the recent findings by Price and associates (16) add another piece of information to the puzzle and permit continued rigorous testing of the role of urate in vascular pathobiology.

References


Please see related article, “Human Vascular Smooth Muscle Cells Express a Urate Transporter,” on pages 1791–1795.