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Is uric acid causative or just correlative in the Metabolic and cardiovascular consequences of obesity/diabetes?

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Abstract

Systemic hyperuricemia (HyUA) in obesity/diabetes is facilitated by the elevated activity of xanthine oxidoreductase (XOR) and has been associated with as well as proposed to contribute to the pathogenesis of obesity/diabetes-mediated metabolic and cardiovascular dysfunction. Unfortunately, the mechanistic details distinguishing correlative versus causative roles for UA are not defined. As such, we examined the metabolic and cardiovascular consequences of systemically diminishing UA (XOR inhibitor) or specifically reducing XOR and UA in the liver (genetic ablation) in diet-induced obese mice (male C57Blk/J6). Mice with hepatocyte-specific ablation of Xdh (HXO) and genetic controls were subjected to diet-induced obesity (41%) for 26 weeks and characterized metabolically. Likewise, wildtype mice were subjected to high-fat feeding (60%) for 13 weeks and then maintained on this diet while being treated with the XOR inhibitor febuxostat for 7 additional weeks. Lean HXO mice demonstrated substantially lower liver and plasma UA levels compared to genetic or wildtype controls; yet, in the context of obesity, systemic HyUA was absent in HXO mice. Despite this, obese HXO mice became as insulin resistant and dyslipidemic as obese controls. Similarly, febuxostat dramatically lowered plasma and tissue UA in obese wildtype mice without altering obesity-associated dyslipidemia or insulin resistance (euglycemic clamps). On the other hand, both HXO and febuxostat-treated mice displayed diminished obesity-mediated vascular dysfunction. Combined, these data demonstrate that: 1) hepatocyte Xdh is a critical determinant of systemic UA homeostasis and deletion of hepatocyte Xdh is sufficient to prevent systemic HyUA allied to diet-induced obesity, 2) neither prevention nor correction of HyUA, in this/these models, improves insulin resistance/dyslipidemia and 3) both genetic ablation and pharmacologic inhibition of XOR resulted in improved vascular and cardiac function. These results indicate, in this/these models of obesity, UA is not causative of metabolic dysfunction whereas elevated XOR activity does alter cardiovascular function.

Publications

Cerebrovasculature Remodeling Accompanies Functional Impairment in Chronically Stressed Mice.

Hydrogen sulfide stimulates xanthine oxidoreductase conversion to nitrite reductase and formation of NO

Heme Overload Triggers Xanthine Oxidase Release and Mediates the Inflammatory Response

Diminishing Inflammation by Reducing Oxidant Generation: Nitrated Fatty Acid-Mediated Inactivation of Xanthine Oxidoreductase

The impact of xanthine oxidase (XO) on hemolytic diseases

Biography

Eric E Kelley received his Ph.D. in Free Radical Biology from the University of Iowa in 2002, conducted his postdoctoral studies at the Center for Free Radical Biology at the University of Alabama at Birmingham from 2002-2006. He was an Assistant Professor at the University of Pittsburgh until 2016 and then joined the department of Physiology and Pharmacology at West Virginia University as Associate Professor in 2016. The overarching theme of his research is the convergence of inflammation and enhanced rates of oxidant generation; both of which are hallmarks of metabolic syndrome and diabetes; yet, are allied to many disease processes including cancer. A current focus of his efforts involves manipulating the enzymatic activity/product identity of xanthine oxidase (XO), a critical source of oxidants and uric acid in obesity/diabetes and cardiovascular dysfunction. A component of these endeavors is distinguishing contributions of oxidants from uric acid in driving the inflammatory phenotype.

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