What Are the Key Arguments Against Uric Acid as a True Risk Factor for Hypertension?

Richard J. Johnson, Laura G. Sánchez-Lozada, Marilda Mazzali, Daniel I. Feig, Mehmet Kanbay, Yuri Y. Sautin

On March 24, 1882, at a dinner held by the Berlin Physiological Society, Robert Koch presented evidence to prove that galloping consumption, or tuberculosis, was attributable to a bacteria. His evidence was based on identifying the organism from the lungs of infected patients, growing it in a cell culture dish, and then injecting the bacteria in rabbits where it replicated the disease with similar lung lesions containing the bacteria. This approach, which included observations in humans as well as animal models, became adopted as Koch’s postulates for proving the cause of disease.

In recent years, uric acid has been proposed to have a causal role in some forms of hypertension. Nevertheless, there are observations that have challenged this hypothesis. Here we discuss some of the arguments that weaken the uric acid story, and how they might be addressed.

Uric Acid as a Cause of Hypertension

Uric acid is produced during purine metabolism with the generation of oxidants (Figure 1). In humans uric acid is the final end product, whereas in most mammals uric acid is further degraded into 5-hydroxyisourate by uricase, eventually producing allantoin. Serum uric acid levels vary in humans, with the normal range being between 3 and 7 mg/dL in the blood. Serum uric acid levels are increased by diets high in purine-rich foods or fructose, or by conditions associated with high cell turnover. Reduced urinary excretion of uric acid also results in higher serum uric acid levels, such as occurs with reduced renal function, reduced renal blood flow, and insulin resistance.

Serum uric acid was originally linked with hypertension in the 1870s. For years, this association was attributed to the effect of renal vasoconstriction to reduce urinary excretion of uric acid. More recently, uric acid has been proposed to have a causal role in hypertension. Hyperuricemia would seem to fulfill Koch’s postulates as a causal risk factor for hypertension (Table). Studies in animal models suggest that hyperuricemia may be particularly important in early hypertension, and similarly studies in humans show that the strongest association of hyperuricemia is with early hypertension such as observed in adolescents. Indeed, lowering uric acid with either allopurinol or probenecid reduces blood pressure markedly in adolescents with hypertension or prehypertension, whereas effects on adult primary hypertension is less marked. This may relate to the development of renal microvascular disease and interstitial inflammation that occurs in both animal models and humans with hypertension, and which has been shown experimentally to mediate salt-sensitive hypertension even if uric acid levels are reduced. Experimentally, the mechanism by which uric acid causes hypertension is via oxidative stress, endothelial dysfunction, and activation of the renin angiotensin system (Figure 2). So why do doubts remain?

Arguments Against the Uric Acid Hypothesis

Three observations challenge the hyperuricemic hypertension hypothesis. First, uric acid is recognized as an antioxidant, and in cell-free systems can inactivate superoxide, singlet oxygen, and peroxynitrite. Uric acid also chelates iron, blocks the inactivation of extracellular superoxide dismutase, and prevents the loss of NO in endothelial cells exposed to peroxynitrite. Consistent with these findings, the infusion of uric acid in humans acutely improves endothelial function. The antioxidant effects of uric acid have even been proposed to be a beneficial host response in subjects with cardiovascular disease and to explain the superior benefit of chlortalidone (which raises uric acid) in the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) study. The observation that uric acid is low in multiple sclerosis and Parkinson disease has been thought to reflect a loss in antioxidant activity that predisposes humans to these neurological conditions. Administration of uric acid protects animals with experimental allergic encephalomyelitis. As such, it has been suggested that raising uric acid should improve antioxidant function and protect against multiple sclerosis; this idea is in line with Ames’ hypothesis which states that the uricase mutation provided a survival benefit by raising uric acid and blocking oxidative stress, thereby combating cancer and aging.

The second observation follows from the first, and is based on the finding that the enzyme reactions producing uric acid...
also generate oxidants (Figure 1), and hence that the benefit of xanthine oxidase inhibitors such as allopurinol may be attributable to blocking xanthine oxidase-generated oxidants rather than lowering uric acid. Indeed, whereas lowering uric acid with allopurinol consistently improves endothelial function in clinical studies, one study reported that probenecid treatment was unable to improve endothelial function in subjects with congestive heart failure despite equivalent lowering of uric acid levels.18 Thus, these studies suggest that uric acid is an antioxidant, and the benefits of lowering uric acid with xanthine oxidase inhibitors are the result of the blockade of oxidants generated during the xanthine oxidase reaction.

The third observation relates to genome-wide association studies, which have identified genetic polymorphisms in various genes that can explain 5% to 7% of the variance of serum uric acid levels.19–21 In these studies, the presence of these polymorphisms has been consistently shown to increase the risk for gout, but not for hypertension or other features of the metabolic syndrome. Based on these findings, many authorities do not believe that hyperuricemia per se can be a cause of hypertension.

### Table. Koch's Postulates and Hyperuricemic Hypertension

- An elevated serum uric acid predicts the development of hypertension
- Serum uric acid levels increase linearly with blood pressure in most population studies
- Raising uric acid in rats with a uricase inhibitor increases blood pressure with renal hemodynamic and pathological features similar to that observed in human hypertension
- Lowering uric acid in animal models results in a decrease in blood pressure
- Pilot studies in humans also suggest that lowering uric acid can lower blood pressure in subjects with primary hypertension, especially adolescents

### Serum Uric Acid Versus Intracellular Uric Acid: Could This Be the Answer?

An important distinction between the mechanisms by which uric acid causes gout and vascular dysfunction relates to the site of action. Gout is a result of the extracellular precipitation of urate crystals into the synovial fluid of the joint, whereas several studies have shown that the mechanism by which uric acid induces vascular dysfunction requires entry of uric acid into cells with the induction of intracellular oxidative stress resulting from activation of nicotinamide adenine dinucleotide phosphate oxidase (NADPH) and the development of mitochondrial dysfunction.22–24 This could explain why the infusion of uric acid induces an initial antioxidant effect, as its initial effects would be primarily extracellular. It could also explain why xanthine oxidase inhibitors are more effective at improving vascular effects of hyperuricemia than uricosuric agents, as the former also blocks uric acid synthesis within the cell. It could also explain the genome-wide association studies, as most of the variance in serum uric acid is driven by polymorphisms in SLC2A9 and ABCG2,19–21 and polymorphisms associated with hyperuricemia in these genes would be predicted not to increase intracellular uric acid levels. Hence, increased SLC2A9 function is expected to increase transport of uric acid out of the cell into the circulation,25,26 and this might be expected to block uric acid effects on vascular cells as SLC2A9 is highly expressed in these cells (unpublished observations). In contrast, decreased ABCG2 function also leads to hyperuricemia, but at the expense of reducing uptake of uric acid from the urine.27 Although the mechanism for the latter finding remains unknown, it likely involves a reduction in URAT1 expression, and as URAT1 is also expressed on vascular cells it would also result in a dissociation of serum from...
intracellular uric acid levels. Hence, although serum uric acid would normally predict intracellular levels, this would be dissociated with the genome-wide association studies analyses that have been reported.

The antioxidant hypothesis of uric acid is also being reassessed. For example, studies in humans show that the lowering of uric acid with uricase does not result in increased oxidative stress, but if anything tends to reduce oxidative stress.28 Furthermore, the reaction of uric acid with peroxynitrite is not benign, but generates alkyllating species and radicals (aminocarbonyl and triuretcarbonyl).29,30 Indeed, the administration of inosine to raise uric acid levels was ineffective in subjects with multiple sclerosis in one study,31 with minimal benefit in another.32 The concept that low uric acid is contributing to multiple sclerosis has also been challenged by the finding that uric acid levels in the cerebral spinal fluid are high in this disorder.33 Indeed, the original hypothesis that uric acid may provide protection against aging and cancer can be seriously questioned, as hyperuricemia predicts mortality and not longevity,34 and is also more likely to predict the development of cancer rather than the opposite.35

Summary
Koch’s postulates have been satisfied for the uric acid–hypertension relation, but there are still important questions to be addressed before completely accepting hyperuricemic hypertension as a clinical entity. In addition to resolving the key arguments against the uric acid hypothesis (see above), we need more studies to address the ends of the spectrum in the uric acid–hypertension pathway, by both identifying the intracellular mechanisms of action of how uric acid might induce intracellular oxidative stress, as well as definitive clinical trials in larger populations to assess the benefit of lowering uric acid in high blood pressure. We need to determine whether the benefits of lowering uric acid are primarily mediated by the inhibition of the renin angiotensin system, as suggested by some experimental32,36,37 and clinical studies,38 or whether it involves effects beyond the renin angiotensin system.39 The role of xanthine oxidase-induced oxidants needs further study. Some studies suggest that both uric acid and oxidants induced by xanthine oxidase may drive inflammation,40 whereas under other conditions the suppressive effects of xanthine oxidase inhibition on cell metabolism can be reversed by adding back uric acid.41

Integrating the uric acid story with current theories of the cause of hypertension is also important. An elevated uric acid is now recognized as a feature in low birth weight infants and is associated with endothelial dysfunction and the future development of hypertension.1 The uric acid pathway may also be important in obesity-associated hypertension, as uric acid has profound effects on adipocytes and adipokines, including adiponectin and leptin,42–44 as leptin is emerging as a key mediator in this condition.45 The observation that mitochondrial oxidants have a role in hypertension46 is also consistent with recent studies in the hyperuricemia model.24 Finally, the emerging role of intrarenal T cells in driving salt-sensitive hypertension47–50 is supported by the finding that chronic hyperuricemia in animals leads to salt-sensitive hypertension in association with tubulointerstitial inflammation and microvascular disease.2 In conclusion, multiple questions about the role of uric acid in blood pressure remain. Nevertheless, we predict that hyperuricemic hypertension will one day be recognized as a clinical entity.

Disclosures
Dr Johnson and Dr Mazzaliti are listed as inventors on a patent on use of allopurinol to treat hypertension associated with hyperuricemia (University of Washington and Merck). Dr Johnson is also listed as an inventor on patent applications related to lowering uric acid in metabolic syndrome and in diabetic nephropathy (University of Florida). A company, Revascor, has recently licensed these patents and has provided Dr Johnson with some Founder shares. Dr Johnson also has 2 lay books that discuss the role of uric acid in hypertension, that being the Sugar Fix (Rodale, 2008) and the Fat Switch (Mercola.com, 2012). The other authors have no conflicts to report.

References
17. Hooper DC, Spitsin S, Kean RB, Champion JM, Dickson GM, Chaudhry I, Koprowski H. Uric acid, a natural scavenger of peroxynitrite, in


What Are the Key Arguments Against Uric Acid as a True Risk Factor for Hypertension?
Richard J. Johnson, Laura G. Sánchez-Lozada, Marilda Mazzali, Daniel I. Feig, Mehmet Kanbay and Yuri Y. Sautin

_Hypertension_. 2013;61:948-951; originally published online March 4, 2013;
doi: 10.1161/HYPERTENSIONAHA.111.00650
_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/61/5/948

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Hypertension_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Hypertension_ is online at:
http://hyper.ahajournals.org//subscriptions/