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Uric acid: A Danger Signal from the RNA World that may have a role in the Epidemic of Obesity, Metabolic Syndrome and CardioRenal Disease: Evolutionary Considerations

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Abstract

All humans are uricase knockouts; we lost the uricase gene due to a mutation that occurred in the mid Miocene approximately 15 million years ago. The consequence of being a uricase knockout is that we have higher serum uric acid levels that are less regulatable and can be readily influenced by diet. This increases our risk for gout and kidney stones, but there is also increasing evidence that uric acid increases our risk for hypertension, kidney disease, obesity and diabetes. This raises the question of why this mutation occurred. In this paper we review current hypotheses. We suggest that uric acid is a danger and survival signal carried over from the RNA world. The mutation of uricase that occurred during the food shortage and global cooling that occurred in the Miocene resulted in a survival advantage for early primates, particularly in Europe. Today, the loss of uricase functions as a thrifty gene, increasing our risk for obesity and cardiorenal disease.

Keywords

uricase; fructose; thrifty gene; anti-oxidant; oxidant; RNA world

Uric acid is a product of purine metabolism generated during the breakdown of nucleic acids (DNA and RNA) and ATP, and uric acid can also be generated from proteins. In most mammals uric acid is further metabolized by uricase (urate oxidase) to form 5-hydroxyisourate and later allantoin which is freely excreted in the urine.¹ However, the uricase gene became nonfunctional in two primate lineages during the middle Miocene at approximately 15 and 9 million years ago, and as a result humans, great apes, and lesser apes have higher serum uric acid that is also less regulatable than other mammals.²

Today serum uric acid levels vary greatly in humans, and can range from 2.5 to 12 mg/dl or more. Those subjects with higher levels are at increased risk for developing gout and uric acid kidney stones. More importantly, an elevated uric acid also predicts the development of obesity³, metabolic syndrome and diabetes⁴, fatty liver⁵, hypertension⁶ and cardiovascular

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Conflict of Interest

Dr Johnson and Dr Lanaspá are listed as inventors on patent applications to lower uric acid or block fructose metabolism as a means for treating obesity and metabolic syndrome or related conditions.

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and renal disease.⁷⁻⁸ Recent studies have suggested that the uric acid may have a participatory role in these latter conditions.⁹ This has led to the key question of what the biological benefits of uric acid are, and why the mutation was naturally selected for our species.

Parallel Mutations in the Uricase Gene

The Miocene epoch is famous for the introduction of the ape, which is distinct from monkeys by their larger head and body and absence of tail. The first apes, such as *Proconsul*, have been identified in the early Miocene (approximately 20–23 million years ago) and were limited to Africa. These early apes lived in tropical rain forests and subsisted almost entirely on fruits. Approximately 17–18 million years ago global cooling resulted in a lowering of the Tethys sea and the formation of a landbridge to Eurasia, and at this time the first apes entered Europe. As global cooling continued the apes living in Europe began to face food shortage due to the changing climate and flora, especially during the seasonal cooler periods. As such, these apes retreated to isolated sites (refugia) throughout Europe. In contrast, while global cooling also occurred in Africa, the major effect was a recession of the tropical forests, but they still remained such that changes in diet were not required.¹⁰

As global cooling continued, the apes in Europe began to show evidence of periodic starvation, as indicated by linear striations on the canines due to enamel hypoplasia that has been shown to reflect periods of starvation in young apes while the canines are still enlarging.¹¹ A binary asteroid impact also occurred in southern Germany 15 million years ago that showered detritus for up to 450 km from the site of impacts¹², although it is of uncertain significance as it is not thought to have significantly altered the flora or fauna in Europe. By 9–8 million years ago the progressive cooling in Europe led to an extinction of ape species in Europe.¹³

Studies based on the fossil record suggest that the European apes have skeletal and dental features that are more similar to modern great apes, and as such has led to the proposal that some of the European apes may have migrated back to Africa prior to their extinction in Europe (the ‘Back to Africa’ hypothesis).¹⁴ Both *Kenyapithecus* and *Dryopithecus* have been considered potential candidates for being this ancestral species.¹⁴⁻¹⁵

It was during this period of climatic upheaval that the silencing of uricase in the ancestral ape that led to humans and the great apes occurred. There is evidence that it occurred stepwise, first with progressive decrease in uricase activity due to mutations in the promoter region, followed by complete silencing of uricase due to a mutation in codon 33 of exon 2, the latter that has been dated to approximately 15.4 million years.² A separate mutation involving the ancestral ape for lesser apes (gibbons and siamangs) occurred in codon 18 of exon 2 and has been dated to approximately 9.8 million years ago.² Some new world monkeys may have also had independent mutations in uricase, and the old world monkeys also show less uricase activity than many other mammals.¹⁶ Therefore there appears to be a general selection pressure favoring a loss of uricase in this Order of mammals.

We have hypothesized that the uricase mutation benefitted survival by augmenting the fat storing properties of fructose present in fruits.¹⁰ We have also proposed that this mutation occurred in Europe as it would have provided a selection advantage here and would have rapidly taken over the population of a geographically isolated refugia. We therefore have suggested that this mutation supports the Back to Africa hypothesis.¹⁰ Before we discuss this hypothesis, however, we will briefly review other theories for why this mutation occurred (Figure 1).

Uric acid and Water Conservation

The original interest in the evolutionary role of uricase related to studies of how nitrogenous waste products are excreted in different species.¹⁷ Some animals excrete their nitrogenous wastes as ammonia, others as urea, and yet others as uric acid. Reptiles and birds compose this latter group and facilitate this by having a mutation in uricase. Homer Smith and others have suggested that this mutation was critical for reptiles and birds so that they could excrete their nitrogenous wastes as uric acid.¹⁸ Since uric acid contains 4 nitrogens per molecule as compared to urea (2 nitrogens/molecule) and ammonia (1 nitrogen/molecule), the nitrogen waste can be concentrated more effectively in a small volume and thereby help preserve their total body water. Smith argued that this was critical for these species to maintain terrestrial life, especially under arid conditions. However, the animal must have a cloaca that allows the precipitation of the uric acid (present in guano) that can be excreted safely without concern for blocking the urinary tract.

While this certainly provides an evolutionary advantage for a uricase mutation in these species, it cannot explain why the uricase mutation occurred in humans. Humans continue to excrete almost all of their nitrogenous wastes as urea. Indeed, mammals in general conserve water via an elaborate loop of Henle concentration mechanism. Furthermore, whereas the mechanism for the uricase mutation with reptiles and birds suggest uric acid is simply a type of waste product, the activate mutation of uricase in primates suggests that uric acid must also have biological properties.

Uric acid, Intelligence, and Reaction Time

Havelock Ellis proposed in the early 1900s that uric acid might have a role in intelligence.¹⁹ He noted that gout was frequently a disease of the educated, and that many famous philosophers and scientists from the 1800s had gout. This concept was reintroduced in a letter to Science in the 1950s by Orowan, who noted that uric acid has chemical characteristics similar to caffeine.²⁰ Subsequently numerous studies were performed evaluating the uric acid levels of the general population and of special groups (university professors, students) to see if a general relationship between uric acid and I.Q. and other intelligence tests could be identified. Most studies showed either weak associations or none; but the strongest relationship was with reaction time.^{21–23}

The possibility that uric acid may have central nervous system effects has not been completely ruled out. Acute hyperuricemia in rats induced by uricase inhibition does increase locomotor activity.²⁴ At least one study suggests that uric acid may increase dopamine levels in the brain.²⁵ Indeed, hyperuricemic individuals appear to have a decreased risk for Parkinson's disease.^{26–27} Further studies are needed to assess the acute effects of hyperuricemia on the brain.

While hyperuricemia maybe associated with mild benefits on reaction time and intelligence, over time the reverse appears to be true. For example, an elevated uric acid is more common in subjects with vascular dementia^{28–29} and stroke.^{30–32} Whether this is causal has not been shown, but it is known that experimentally hyperuricemia can induce small vessel disease in the kidney that can alter autoregulation. If such events also occur in the brain, as suggested by increased white matter disease in hyperuricemic subjects, then this would suggest that uric acid may be a cause of vascular dementia.

It seems likely that the original observation by Ellis was not due to uric acid being associated with higher intelligence, but rather because those subjects prone to developing gout in the 1700s and 1800s tended to be wealthy and sedentary, often with the ability to afford sugar, the latter which is known to raise uric acid. Indeed, today gout is increasing in all populations, and if anything is more common among the poor and less educated.^{33–34}

Uric acid as an Antioxidant

Ames, Hochstein, and colleagues proposed in the early 1980s that the uricase mutation provided a survival advantage because uric acid can function as an antioxidant.³⁵ These authors and others showed that uric acid could react with a wide variety of oxidants, especially peroxynitrite, superoxide, and hydroxyl radical.^{35–36} Uric acid could be shown to protect cells from oxidant injury.³⁷ Infusing uric acid into humans was also shown to acutely increase antioxidant capacity and to improve endothelial cell function.^{38–40}

Ames et al suggested that the mutation in Vitamin C synthesis that had occurred 40 million years ago left early primates at increased risk for oxidative stress.³⁵ Since oxidative stress could drive cancers, cardiovascular disease and aging, the uricase mutation thus provided a survival advantage. In this scenario, the rise in uric acid observed in patients with cardiovascular disease likely was due to a compensatory response by the host to combat oxidative stress.^{41–42} Finally, the observation that species with higher uric acid levels tended to live longer was consistent with this hypothesis.³⁵

For sure, uric acid is an antioxidant, at least in the extracellular environment. We and others have shown that uric acid potently reacts with superoxide to generate allantoin. Allantoin levels rise in humans in response to oxidative stress.^{43–45} Since humans do not have uricase, this is evidence for a direct uric acid-superoxide reaction. Furthermore, uric acid can react with peroxynitrite to form triuret.⁴⁶ Triuret levels are increased in preeclampsia and likely reflect this pathway.⁴⁷ Uric acid can also react with nitric oxide to generate different products, particularly 5-aminouracil.⁴⁸

Thus, it remains possible that the extracellular antioxidant effects of uric acid could explain why the uricase mutation resulted in a natural selection advantage. However, we and others have found that uric acid is a prooxidant inside the cell. This has been shown in a variety of cell types.^{49–51} The mechanism may be due to the selective stimulation of NADPH oxidase.⁵¹ However, uric acid also generates radicals when it reacts with peroxynitrite, including the triuret carbonyl radical and the aminocarbonyl radical.⁵² The intracellular prooxidative effects of uric acid have been shown to mediate a host of proinflammatory effects, both in cell culture^{53–54} and in animal models.⁵⁵ Furthermore, recent studies have challenged whether uric acid really functions as an important antioxidant in vivo.⁵⁶ In addition, an elevated uric acid in humans is not associated with longevity, but rather correlates with increased cardiovascular mortality.⁵⁷ These findings, coupled with increasing experimental and clinical evidence for a role for uric acid in driving hypertension and metabolic syndrome, raises questions as to whether the antioxidant hypothesis can provide a viable mechanism for why humans have the uricase mutation.

Uric acid as a Mechanism for Amplifying Fructose Effects on Fat Formation

As mentioned the primary food staple of apes during the mid Miocene was fruits, which is rich in fructose.¹⁰ Fructose is distinct from glucose in its superior ability to increase fat stores, including in the liver, visceral fat, and plasma triglycerides.^{58–59} As such, fruits were not simply a food source, but also have effects that can be helpful for an animal that may have intermittent bouts of food shortage.

The specific reason why fructose is superior than glucose in increasing fat stores likely relates to the unique first steps in fructose metabolism. When fructose enters the hepatocyte, it is metabolized by a specific enzyme, fructokinase C. Unlike glucokinase, which has a negative feedback system to prevent excessive phosphorylation, the phosphorylation of fructose by fructokinase will proceed uninterrupted, and as a consequence intracellular phosphate depletion and ATP depletion frequently occur.⁶⁰ The fall in intracellular phosphate results in the stimulation of AMP deaminase that helps accelerate the degradation

of AMP to IMP and later to uric acid.^{60–61} In turn, the intracellular generation of uric acid results in oxidative stress.⁶¹ These processes likely have a role in fatty liver formation and triglyceride generation. Evidence supportive of this is the condition of hereditary fructose intolerance, in which the subsequent enzyme in fructose metabolism, aldolase B, is mutated. In this circumstance the fructose metabolism is blocked, but the subjects still develop fatty liver disease.^{62–63}

In this regard, there is increasing evidence that the intracellular generation of uric acid may have a role in the fat accumulation. First, we have reported that uric acid can induce proinflammatory changes in the adipocyte that are similar to that observed in the prediabetic subject.⁵¹ Lowering uric acid can also reduce hypertriglyceridemia and weight gain in rats exposed to fructose.⁶⁴ Moreover, we have unpublished data that uric acid regulates both the intestinal transporter for fructose, Glut 5, as well as the level of fructokinase C in the liver. These effects would accelerate fructose absorption and in the presence of both increased substrate and metabolizing enzyme (fructokinase), would be expected to result in greater ATP depletion and a greater effect on fat production. Indeed, in collaboration with Dr Abdelmalak and Dr Anna Mae Diehl at Duke, we have found that subjects with higher uric acid levels show greater ATP depletion in their liver in response to intravenous fructose (manuscript submitted).

Given these circumstances, a loss of uricase would potentiate the ability of fructose to increase fat stores. Indeed, the inhibition of uricase increases the sensitivity of the rat to raise its serum uric acid⁶⁵ and develop insulin resistance to fructose.⁶⁶ Therefore a mutation in uricase could have provided a survival advantage for Miocene apes during the progressive food shortage that occurred in Europe with global cooling.¹⁰

Uric acid: A Danger Signal from the RNA World?

There is increasing evidence that the earliest life forms consisted solely of RNA.⁶⁷ Vestigial products from the RNA world that have key functions have carried over to current life, such as ATP (energy) and cAMP (intracellular messenger). It is tempting to consider the breakdown of RNA to uric acid as a potential danger signal for the host, and that in turn the uric acid may act to increase survival by increasing fat stores and other functions.

Certainly conditions in which ATP depletion and energy crisis occurs are associated with a rise in uric acid.⁶⁸ Uric acid is released from dying cells where it has been shown to activate inflammation via both the innate and adaptive immune system.^{69–71} Uric acid is an adjuvant for activation of dendritic cells⁶⁹ and T cells.⁷² Uric acid also increases in the setting of starvation or in the late stages of hibernation when fat stores are depleted and protein degradation occurs.^{73–75} In this setting it generates a danger signal and results in a foraging response to get more food. Preeclampsia, a condition in which there is fetal compromise, is also associated with a rise in uric acid.⁷⁶ One wonders if the hypertension and fatty liver that occurs in the mother in this condition may in part be due to the rise in uric acid. Indeed, there is some evidence that uric acid may have a contributory role to the pathogenesis of preeclampsia.⁷⁶

Thrifty Gene Hypothesis and the Current Obesity Epidemic

An increase in uric acid may have some protective effects on survival in the setting of severe energy depletion, such as may occur with starvation, or with tissue injury and ischemia. We hypothesize in early primates faced with intermittent starvation, the loss of uricase may have therefore provided a survival advantage.^{10, 77} A rise in uric acid may have potentiated fructose effects to gain fat, and may have led to a greater activation of the immune system. A rise in blood pressure and increased salt sensitivity, stimulation of the renin angiotensin

system, and the development of insulin resistance (which by maintaining increased blood glucose might preferentially provide fuel for the brain) would have all been beneficial.⁷⁸ The ability of uric acid to increase dopamine responses in the brain and to acutely stimulate increase locomotor activity would also have been helpful.

However, what was advantageous during starvation may not be beneficial in the setting of excessive food availability. With higher and less regulatable uric acid levels we are at marked increased risk for obesity, insulin resistance, and cardiovascular and renal disease. We have therefore proposed that the loss of uricase represents the “thrifty gene” originally proposed by Neel⁷⁹ whose loss results in a marked propensity for obesity.⁸⁰

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Figure 1. Hypotheses for Evolutionary Benefit of Uricase Mutation

The parallel mutations that occurred in early hominoid evolution in both ancestral humans and great apes, and in lesser apes, suggests a natural selection advantage with the mutation. The primary hypotheses proposed for this mutation are shown. These include the possible role of uric acid as an extracellular antioxidant that would combat oxidative stress associated with aging, cancer and cardiovascular disease, a role for uric acid in increasing intelligence and reaction time, and finally a potential role as a danger and survival signal to protect against starvation, but which in today's society translates into increased risk for obesity, diabetes, and cardiorenal disease.