My Case Against Uricase: A critical examination of hypotheses

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Uric acid is a weak acid normally present in the blood, often viewed as a metabolic waste product, but with potent antioxidant properties (Ames et al. 1981). Humans, along with other apes, have evolved a series of mutations preventing the activity of uricase, an enzyme which breaks down serum uric acid in most other mammals (Kratzer et al. 2014). Additionally, we have further mutations increasing the renal retention of uric acid (Tan et al. 2016). As a result, apes, especially humans, have higher levels of uric acid than other mammals. There are many hypotheses about the selective advantage of these mutations, including benefits for the brain. However, higher uric acid levels make us more susceptible to fructose-induced metabolic syndrome, common in the modern food environment, which in turn can cause uric acid levels to rise pathologically (Johnson et al. 2009). This is associated with cognitive and psychiatric deficits (Verhaaren et al. 2013, Dos Santos Oliveira et al 2019). Some researchers have provided evidence that high uric acid itself induces metabolic syndrome, whereas other evidence seems to contradict this. Here I present an overview of evidence for and against the hypothesis that high uric acid is causally implicated in metabolic syndrome, and its relevance to brain health.

Several mutations reducing the production of uricase culminated in a “pseudogenization”, or complete functional loss, of the uricase gene in primates in the early Miocene (Kratzer et al. 2014). The pattern of occurrence of the mutations show a redundancy that strongly suggests selective advantage to increased uric acid levels. This is further supported by parallel mutations increasing reabsorption of uric acid in the kidneys (Tan et al. 2016). Several hypotheses have been put forth as to what that advantage may have been, including potential longevity benefits of antioxidation (Proctor 1970, Ames et al. 1981), improved intellectual performance and neuroprotection (reviewed by De Giorgi 2015), and maintenance of blood pressure under low salt conditions (Watanabe et al. 2002). For a review of these hypotheses and their criticisms, see Tovchiga and Shtrygol (2014).

A new explanation was recently offered by Johnson et al. (2010). They frame the loss of uricase as the missing “thrifty” (pseudo)gene from Neel’s Thrifty Gene Hypothesis (Neel 1962). The Thrifty Gene Hypothesis argues that the modern diabetes epidemic may be explained by a prevalent genetic propensity to fatten presumed to have been a survival advantage in times when famines were common, but which leads to obesity and associated chronic disease when no such famines regularly occur. Many criticisms have been levied against the hypothesis, most abundantly by Speakman (e.g. 2006, 2008, 2013) Criticisms include: questions about whether sufficient

famine pressure existed at appropriate times; lack of explanation for how such an advantageous gene could manage to penetrate only part of the population; lack of evidence for a reproductive advantage of fatness during famines (which tend to disproportionately affect children and the elderly, and lead to deaths via disease rather than actual starvation); observations that population booms follow famines and don't favor fatter survivors; and lack of evidence of fatness in populations experiencing long famine-free periods in recent historical record. Moreover, despite extensive search, no gene candidate has been found.

By proposing that the uricase pseudogene is the missing thrifty gene and making a few amendments, Johnson et al. solve some of these problems. A critical feature of this new hypothesis involves the role of fructose. In certain contexts, fructose can significantly raise serum uric acid (Le et al. 2012). This effect is robust enough that Kedar and Simkin argue that "the new epidemic of gout is likely secondary in significant part to the rise in fructose consumption" (2012). At the same time, fructose appears to have unique fattening properties. As Johnson and Andrews describe (2010), it can induce obesity, fatty liver, and hypertriglyceridemia independent of energy intake, and can interfere with satiety signaling. Additionally, they draw on evidence from Lanaspa et al. (2012) showing that uric acid itself can be a causal culprit in the fattening effect of fructose, by its effect on the fate of AMP (adenosine monophosphate).

AMP comes from ATP, adenosine *tri*phosphate, our cellular energy "currency", when its other two phosphate bonds are broken to release energy. At this point, AMP can be used to regenerate ATP from fat oxidation, via the AMP kinase (AMPK) pathway, or it can be further broken down by AMP deaminase (AMPD), which eventually results in the formation of uric acid and in fat storage. In Lanaspa et al.'s (2012) model, fructose consumption initiates a feedforward cycle of fattening that reinforces itself through the formation of uric acid, which they show upregulates AMPD and inhibits AMPK.

By focusing on fructose, they replace the problematic theoretical role of famines for this adaptation with periods of low-to-no fructose, a more plausible environmental circumstance, given that year-round fruit availability in many parts of the world is recent. By focusing on the lack of uricase–which is a species-wide mutation, not merely a polymorphism–they explain the differences in obesity prevalence by dietary differences, not inheritance. In other words, their thrifty pseudogene is ubiquitous in humans, and only differentially activated. However, some of the other criticisms remain unresolved. Additionally, there is an apparent paradox in the claim that hyperuricemia itself causes obesity.

Lanaspa et al.'s (2012) experimental evidence shows that the addition of uric acid abolishes metabolic effects of starvation on cells in vitro, namely, the drop in triglyceride synthesis and the increase in AMPK and beta-hydroxybutyrate. This would seem to imply that even the AMPK-induced switch from fat synthesis to fatty acid oxidation and ketosis in the context of fasting would be prevented in the presence of hyperuricemia. But this is not the case. In fact, it is well established that fasting and carbohydrate restriction is routinely accompanied by a large rise in serum uric acid that can take weeks to subside (See e.g. Lecocq and McPhaul 1965

and Lu et al. 2014). This is due to competition for renal excretion between ketone bodies and uric acid. Clearly, this spike in uric acid does not prevent these fatty acid oxidation mechanisms from becoming dominant and allowing a state of ketosis that is critical to survival during fasting and carbohydrate restriction.

Therefore, I suggest that uric acid is guilty in metabolic syndrome only by association, as a by-product and an amplifier, but not a root cause of dominant AMPD pathways. Because metabolic syndrome is extremely prevalent, hyperuricemia in association with it would be expected to overwhelm data showing any advantage that may exist from higher uric acid in its absence. It may be for this reason that previous hypotheses such as increased longevity or intellectual performance have not been supported in data analyses. This would be further corroborated if, when metabolic syndrome is adjusted for, we see no disadvantage, or perhaps even an advantage in all-cause mortality or in brain health with higher uric acid levels. This latter link has been found in at least one study (Euser et al. 2009), where adjusting for cardiovascular risk factors (e.g., markers of metabolic syndrome) revealed a small positive association between uric acid and cognitive function.

Note that a refutation of a necessary causal relationship between high uric acid and fat accumulation would not refute the Thrifty (Pseudo)Gene Hypothesis, because the fattening effect of fructose does not depend on it, and it could even remain a causal factor in the specific context of high fructose intake. That is, the loss of uricase could still be the thrifty pseudogene by amplifying the fattening effect of fructose, even if uric acid does not cause metabolic syndrome when carbohydrate intake, and fructose intake in particular, are low. A decoupling of these contexts would, however, have implications for the appropriateness of treatment of hyperuricemia when metabolic syndrome is not present, and on the evaluation of the safety of therapies that increase uric acid without inducing metabolic syndrome.

Finally, given that uric acid competes with ketone bodies for excretion in the kidneys, another hypothesis is suggested. That is that higher baseline uric acid levels may be advantageous in raising levels of beta-hydroxybutyrate higher and more quickly during keto-adaptation. Interestingly, migrating birds make extensive use of ketogenesis on their long, fasted flights (Guglielmo 2010), and also have no uricase (Johnson et al. 2010). Quick adaptation to ketosis under low glucose conditions may have been of particular advantage to early hominins given their relatively large brains. Higher uric acid may also explain why humans are able to attain higher ketosis levels, and faster than most other species we've studied (O'Hearn 2018).

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