

Review

Uric acid and evolution

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Abstract

Uric acid (UA) is the end product of purine metabolism in humans due to the loss of uricase activity by various mutations of its gene during the Miocene epoch, which led to humans having higher UA levels than other mammals. Furthermore, 90% of UA filtered by the kidneys is reabsorbed, instead of being excreted. These facts suggest that evolution and physiology have not treated UA as a harmful waste product, but as something beneficial that has to be kept. This has led various researchers to think about the possible evolutionary advantages of the loss of uricase and the subsequent increase in UA levels. It has been argued that due to the powerful antioxidant activity of UA, the evolutionary benefit could be the increased life expectancy of hominids. For other authors, the loss of uricase and the increase in UA could be a mechanism to maintain blood pressure in times of very low salt ingestion. The oldest hypothesis associates the increase in UA with higher intelligence in humans. Finally, UA has protective effects against several neurodegenerative diseases, suggesting it could have interesting actions on neuronal development and function. These hypotheses are discussed from an evolutionary perspective and their clinical significance. UA has some obvious harmful effects, and some, not so well-known, beneficial effects as an antioxidant and neuroprotector.

Key words: Uric acid, Gout, Uricase, Hyperuricaemia, Oxidative stress, Neuroprotection, Evolution, Neurodegenerative diseases, Antioxidants, Salt ingestion.

Introduction

Unlike the majority of mammals, uric acid (UA) is the end product of purine metabolism in humans, due to the loss of uricase activity during the evolution of hominids [1, 2]. This loss, together with UA balance in the kidney, in which the majority of filtered UA is reabsorbed, and the lifestyle and eating habits of developed countries, has led to a high prevalence of hyperuricaemia and its consequences [1–4]. Hyperuricaemia is the primary risk factor for developing gout and this risk increases exponentially when the serum UA levels rise [2, 5, 6]. However, only a minority of those with high UA levels will develop gout [1, 3, 7]. Along with its association with gout, there is increasing evidence of a relationship between hyperuricaemia and hypertension, renal disease, metabolic syndrome, diabetes and cardiovascular disease [1–6].

Regulation of serum UA levels is complex, with diet and various genetic polymorphisms of renal urate transporters

being the main causal factors of hyperuricaemia and gout [1, 3, 8]. The importance of the interaction between genetic factors and lifestyle in the development of hyperuricaemia and gout has a clear example in the Maori of New Zealand [3, 9]. This population has a marked predisposition to develop hyperuricaemia and gout, because of a genetic defect in renal urate handling [10–12]. However, there is no mention of gout among them before the 18th century. The lean and strong ancient Maori ate a diet of sweet potato, taro, fern root, birds and fish. After the introduction of a diet low in dairy products and high in fatty meats and carbohydrates in the early 1900s, an epidemic of obesity and gout developed [9]. The drastic changes in their diet and the adoption of the lifestyle of developed countries, has led them to have the highest gout prevalence in the world. This demonstrates that genetically predisposed people will develop hyperuricaemia and gout if they are exposed to other risk factors, such as a high-purine content diet, obesity, increased alcohol consumption or diuretic use [3, 13, 14].

The loss of uricase in hominids

The importance of genetic and environmental factors, which have been mentioned before, is determined by the loss of the enzyme uricase, which took place during

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human evolution. The majority of mammals have very low serum urate levels because UA is converted by uricase to allantoin, a very soluble excretion product, which is freely eliminated by the urine [15]. The allantoin in most fish and amphibians is degraded via allantoic acid by allantoinase and allantoinase to urea and glyoxylate. In some marine invertebrates and crustaceans, the urea formed is hydrolysed to NH_3 and CO_2 by urease [15] (Fig. 1). The lack of uricase makes UA the end product of purine metabolism in humans and other higher primates [1, 2] and is the main reason why serum UA levels in adult males are ~ 6.0 mg/dl, compared with the majority of mammals who have UA levels <0.5 – 1 mg/dl [16–18]. This makes us particularly susceptible to changes induced by diet [6], and hence this is the main reason for humans to be the only mammals who develop gout spontaneously [3].

The origin of uricase is very old, being present in a great variety of organisms, from bacteria to mammals and it has different metabolic activities depending on the host organism. There is a cross-reaction between the uricases of different species, having the same tissue specificity and cell location, as well as similar molecular weight. Hence, it suggests that the uricases of diverse species have a common evolutionary origin [19, 20].

Humans, some higher primates and certain New World monkeys do not show any detectable level of uricase activity. This is due to the appearance of several mutations of its gene during the evolutionary process, which made it non-functional [21]. In other monkeys in the Old and New Worlds, uricase activity is moderate, between two and four times lower than that in mice and rabbits [20], and also less stable [21].

Wu *et al.* [21] identified three mutations in the uricase gene in humans, chimpanzees and gorillas, including two nonsense mutations, one of codon 33 and another of codon 187, and a mutation in the splice acceptor signal of exon 3. The codon 33 mutation is also present in the orangutan. Based on the phylogeny of human evolution,

Wu *et al.* [21] established that the codon 33 mutation happened 24 million years ago; the mutation of codon 187 took place 16 million years ago, when the orangutan had already followed another line; and the exon 3 mutation occurred 13 million years ago, affecting the human/gorilla/chimpanzee line [21].

Later on, Oda *et al.* [20] did not find any uricase activity in humans, chimpanzees, gorillas, orangutans or gibbons, but they find functional uricase in other monkeys, such as baboons and rhesus monkey. They found up to eight independent nonsense mutations in hominids without uricase activity. They mainly attribute the loss of uricase activity to the nonsense mutation of codon 33 of exon 2, dating it to 15 million years ago. The promoter region of the gene had probably already been degraded in the evolutionary process by previous mutations, being more likely a gradual loss of uricase activity rather than a single step loss [20, 22]. This is reasonable because the inactivation of the uricase gene in the mouse causes a pronounced hyperuricaemia nephropathy due to urate, resulting in more than half the mutant mice dying before 4 weeks of age [23]. A gradual loss of activity would allow adaptation measures to the new situation to be developed [22].

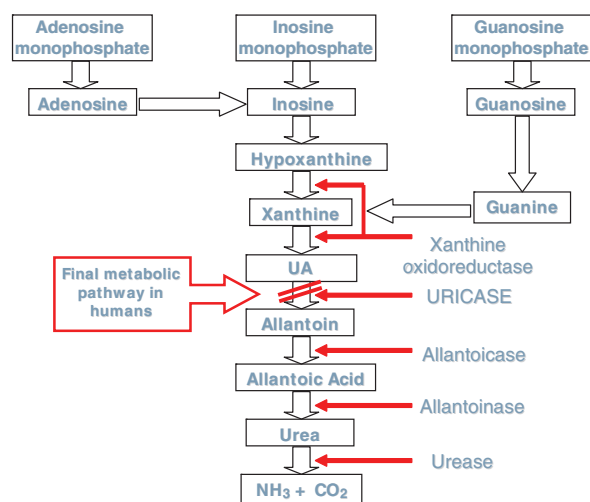
Hypotheses on evolutionary advantages of the loss of uricase

Several independent mutations in the uricase gene occurred during the evolution of hominids as well as in monkeys of the Old and the New Worlds. These mutations have been interpreted as clear evidence of an important evolutionary advantage for the early primates that had increased UA [21, 24]. In the same way, as purine degradation is much less complete in higher animals than in others that we consider lower, it is obvious that certain enzymes had been lost during animal evolution and it is assumed that it provided some evolutionary advantage [15]. On the other hand, if UA was a harmful waste product, it would not explain how the kidneys recover 90% of filtered UA [25], instead of eliminating it. The evolution of hominids and the physiology of renal urate balance have associated UA as something beneficial that we must keep instead of something harmful that has to be removed. These facts have led various authors to propose some hypotheses, which are mentioned below, on the evolutionary advantages of the loss of uricase and the subsequent increase in UA.

Higher antioxidant capacity and greater longevity

One paradox of metabolism is that, while a large majority of complex life forms require oxygen to live, it is a highly reactive molecule that damages living organisms by producing reactive oxygen species (ROS). ROS are present in cells under physiological conditions, producing toxic effects when their production rate increases and exceeds the antioxidant defence capacity of the cells [26]. Thus, oxidative stress generally means a disturbance in the pro-oxidant–antioxidant balance in favour of the former.

Fig. 1 Schematic diagram of purine metabolism.



The protection system to prevent and repair the oxidative damage includes enzymes such as superoxide dismutase and glutathione peroxidase, and antioxidants and radical scavengers such as vitamin E and the β -carotenes in the lipid portion of the cells, and glutathione, ascorbic acid and UA in the aqueous phase [17]. UA, being a powerful radical scavenger as well as being able to act as chelator of metal ions, such as iron and copper, by converting them to poorly reactive forms unable to catalyse free-radical reactions, is one of the most important antioxidants in human biological fluids [26]. It is thought that UA contributes to >50% of the antioxidant capacity of blood [26, 27]. For this reason, Ames *et al.* [16] proposed that the loss of uricase expression and the subsequent increase in UA levels had the evolutionary benefit of increasing antioxidant capacity, increasing the life expectancy of hominids and decreasing age-specific cancer rates. The loss of uricase could be associated with the previous loss of capacity to synthesize vitamin C [28], which occurred 40–50 million years ago due to a mutation in L-gulonolactone oxidase, in a period in which the primates of the epoch ate large quantities of vitamin C in their diet, so it was an inoffensive mutation [22]. In later epochs changes occurred in their diet, with a lower ingestion of vitamin C and the subsequent loss of antioxidant capacity, which could be corrected with the loss of uricase and the increase in UA [22].

Oxidative stress has been associated with 100 physiological and pathological conditions, including ageing and cancer [26]. There is a gradual accumulation of macromolecular oxidative damage products with age as well as a higher production of ROS by the mitochondria, and these facts are inversely related to the maximum life expectancy of the species [29]. However, there is not much evidence to support the increase in life expectancy in hominids due to the antioxidant effect of UA. Although there are data to support the role of oxidative stress in ageing in invertebrate organisms [28, 30], the evidence in mammals is less clear [31, 32]. In fact, in mice with a combined deficiency in the antioxidant enzymes superoxidase dismutase and glutathione peroxidase, increased levels of oxidative stress parameters were observed, as well as an increase in neoplasia in older mice but not a decrease in life expectancy [32]. Likewise, the increase to double the superoxide dismutase activity in mice did not increase the life expectancy [30]. Neither is there any evidence that patients with a high UA live longer. In fact, patients with gout have a high risk of death, mainly due to cardiovascular causes [33–35]. Furthermore, other mammals, such as elephants, have achieved similar survival rates to humans, and higher than the majority of other higher primates, despite having uricase and UA levels as low as 0.2 mg/dl [36].

To maintain blood pressure during low salt ingestion

Fossil evidence suggests that hominids of the Miocene epoch (a period between 24 and 6 million years ago) inhabited sub-tropical forests and were woodland quadrupeds that had a diet based mainly on fruit [37, 38]. The salt

content of the diet at the beginning of the Palaeolithic period, in the mid-Pleistocene (1–2 million years ago), was very low, ~690 mg/day (1.9 g NaCl) compared with a mean of 4000 mg/day (10 g NaCl) in the current American diet. Salt ingestion in hominids in the Miocene was probably even less, because they only ate fruit and leaves, estimating that with such a strict vegetarian diet salt ingestion could only be 225 mg (0.6 g NaCl) [17, 22]. Watanabe *et al.* [17] demonstrated that the increase in UA can maintain blood pressure in conditions of low salt ingestion, both acutely (by stimulation of the renin–angiotensin system) as well as chronically (inducing sensitivity to salt by the development of microvascular and interstitial renal disease). The increase in blood UA could enable the hominids to maintain blood pressure in times of low salt ingestion and it has been suggested that this increase in blood pressure from the increase in UA could be essential for hominids to maintain their vertical position [27].

Various studies have shown that hyperuricaemia leads to an increased risk of hypertension in the following 5 years, regardless of other risk factors [39–41]. Furthermore, hyperuricaemia is also common among adults with pre-hypertension, particularly when there is microalbuminuria. The observation that hyperuricaemia precedes the development of hypertension shows that hyperuricaemia is not just a result of hypertension *per se* [4]. On the other hand, increased levels of UA have been observed in 40–60% of patients with untreated hypertension and in almost 90% of adolescents with recent-onset essential hypertension [4]. The strength of the relationship between UA levels and hypertension decreases with the age of the patient and the duration of the hypertension, suggesting that UA could be more important in younger patients with recent-onset hypertension [42]. However, accepting the association between UA and hypertension gives the impression that this increase in blood pressure caused by the loss of uricase is more a result of, than a cause, of this loss. In fact, other herbivorous mammals of the epoch, with diets presumably as low in salt as that of the hominids, and still around now, were able to adapt to the situation while maintaining uricase activity. In any case, if the gain has been to maintain blood pressure in times of low salt ingestion, evolution would have already thought of how to get us out of this problem, in times such as now, with a very high ingestion of salt in the diet [38].

UA and intelligence

The oldest hypothesis was expressed by Orowan [43], due to the similarity of the structure of UA and some brain stimulants, such as caffeine and theobromine. According to this idea, the loss of uricase activity and the subsequent increase in UA levels could have given rise to a quantitative and qualitative leap in the intellectual capacity of hominids in the evolutionary process. It has been suggested that UA, like other purines, is able to stimulate the cerebral cortex and that the superior intellectual power of higher primates may partly be due to these higher levels of UA [44]. Consistent with this idea

is the finding that glutamic acid, which is involved in the endogenous production of UA, seemed to improve cognitive functions when given therapeutically in cases of mental retardation [45].

Several authors have found a significant correlation between UA levels and higher intelligence in children and young adults [46–48] and an association of gout with higher intelligence. Sofaer and Emery [44] studied the presence of gout in highly gifted people, with an intelligence quotient >148, and their families, observing that the prevalence of gout in males with an average age of 36 years was 1.8%, higher than that in the general population aged 58 years (1.5%), and that the prevalence of gout among families of both sexes at a mean age of 34 years was double (0.6%) that of the general population aged 44 years (0.3%). That is to say, the highly gifted people and their families have a higher prevalence of gout at earlier ages than the general population. However, other authors have not seen this association between UA and higher intelligence [49], and the findings observed are difficult to separate from the eating and social habits associated with economic, cultural and intellectual situations.

On the other hand, if we associate the higher intelligence of the *Homo* genus with the significant increase that occurred in its brain volume in a relatively short space of time, it is unlikely that the loss of uricase could be involved in these changes if we agree with the dating of the mutations. As we mentioned earlier, it is thought that the loss of uricase in hominids occurred in the Miocene epoch, dating the fundamental mutations to >13–15 million years ago [20, 21]; however, the large increase in cerebral volume occurred much later. *Australopithecus afarensis* was already a biped 3.5–4 million years ago, and had a brain capacity of 375–500 cc, similar to the large apes today, which tripled in a short period of time, 2.5 million years, in the *Homo* genus [50].

UA and neuroprotection

Other authors have pointed out that the evolutionary advantage of an increase in UA could be its antioxidant activity in the brain [51]. Scott and Hooper [51] argued that the brain is very vulnerable to oxidative damage as it has a high metabolic rate, using one-fifth of the oxygen that we breathe every day, and because it contains abundant lipid material with a high content of unsaturated fatty acids. Therefore, the antioxidant defence mechanisms against lipid peroxidation in the brain could be of great importance in the prevention of oxidative damage in an increasingly complex brain [51].

There is increasing evidence that UA has protective effects against various diseases such as multiple sclerosis and neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease or amyotrophic lateral sclerosis [25]. Lower levels of UA than in controls have been reported in all these conditions that have been associated with a higher prevalence and a worse evolution of these diseases, which have led to a proposal to increase UA as a treatment to improve their prognosis [25, 52–55]. For

example, gout and multiple sclerosis are mutually exclusive, in that there are no reported cases of multiple sclerosis with gout [25]. However, the appropriate level of UA to achieve these neuroprotective effects and whether the improvements obtained by increasing UA levels are clinically relevant are unknown.

The link between these different diseases could be the role played by oxidative stress in their aetiology and, in particular, the negative effects of peroxynitrite, a powerful oxidant formed by the reaction of the superoxide with nitric oxide, on the neurons [51, 56]. UA prevents peroxynitrite formation by neutralizing cellular superoxide and preventing its reaction with nitric oxide [56]. UA does not seem to be a direct scavenger of peroxynitrite *in vivo*, since the peroxynitrite binds to CO₂ almost 1000 times faster than to UA [57]. However, UA is a scavenger of free radicals, such as CO₃ and NO₂, which are formed from the breakdown of peroxynitrite [25, 26]. Thus, a reduced concentration of UA could decrease the body's capacity to prevent the actions of peroxynitrite and other free radicals on the various neuronal components [26]. Besides its antioxidant effects, UA may also have neuroprotective effects through mechanisms mediated by astroglia, preventing the toxicity induced by glutamate [25, 58]. It does not seem likely that protection against these types of disease, with a higher prevalence at advanced ages, was the cause of the loss of uricase. However, it shows us that UA has an important role in neuronal activity, with increasing levels of UA favouring the development of more complex neuronal functions.

Conclusions

The reason is still not clear why the evolutionary process of hominids strived to lose uricase activity and increase UA levels. UA is mainly known for its harmful effects such as gout and uric lithiasis, as well as its association with hypertension, metabolic syndrome, renal disease and cardiovascular disease [4, 25]. Less well known are its beneficial effects as a powerful antioxidant [16, 26], its neuroprotective activity [52–55] and, from the data on the evolution of hominids, it is likely that it has other not very well-known important physiological effects. The initial signs and symptoms of hyperuricaemia are not life threatening, have an excellent treatment and few patients with hyperuricaemia end up developing gout. On the other hand, treatment with allopurinol is not free of serious adverse effects [59, 60]. These observations, plus the lack of a well-established causal role of hyperuricaemia in other associated diseases, have restricted the enthusiasm to routinely treat the majority of patients having asymptomatic hyperuricaemia with UA-lowering drugs. Asymptomatic hyperuricaemia is currently not considered as an indication for treatment [2–4, 59]. Due to the increasing evidence of the association of UA with hypertension and cardiovascular diseases, it is likely that the indications for treating hyperuricaemia will be extended in patients with other risk factors. When making these decisions, the positive effects of a reduction in UA

should be weighed up against the possible negative effects in neurodegenerative diseases.

Rheumatology key messages

- The biological reason for the loss of uricase activity and increased levels of UA in humans and certain primates is unknown.
- UA is one of the most important antioxidants in human biological fluids.
- UA probably has neuroprotective activity.

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