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Uric acid: friend or foe? Uric acid and cognitive function "Gout kills more wise men than simple"

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Abstract. – OBJECTIVE: The association between hyperuricemia and cardiovascular risk is widely known, and hyperuricemia is associated with many pathological conditions due to its effect on the endothelial function and metabolic homeostasis. The aim of this study was to verify whether the available literature may support the hypothesis that uric acid has a protective and stimulating effect on the cerebral cortex.

MATERIALS AND METHODS: We reviewed the actual knowledge of the positive effects of uric acid in terms of antioxidant action, neuroprotection, cognitive function, and intellectual performance.

CONCLUSIONS: Uric acid has a stimulating effect on the cerebral cortex, and this could have allowed humans, compared with other animals, to develop higher brain mass volume, better intellectual performances, and maybe evolutionary supremacy. On the other, a growing body of evidence is accumulating on the independent association between uric acid and cardiovascular risk.

A careful interpretation of uric acid levels is appropriate and necessary in different kinds of patients, both at risk of cardiovascular or neurodegenerative diseases, due to its contrasting significance.

Key Words:
Uric acid, Hyperuricemia, Gout, Cognitive function, Neuroprotection.

Introduction

In 1683, the English physician Thomas Sydenham (Wynford Eagle 1624 – London 1689) first described the association between gout, hyperuricemia and high standard of living[1], supposing also that hyperuricemia was related to diet and good nutrition, and to greater intelligence and creativity ("gout kills more wise men than simple").

Egyptians first described disease due to gout, but Hippocrates defined gout as "arthritis of the rich" to distinguish it from "arthritis of the poor" (rheumatic fever) due to bacterial infection[2]. He also hypothesized that gout could depend on social differences, such as better nutrition and living conditions. In fact, due to the higher incidence in high social status people, gout was later defined as "the disease of kings and popes" (Table IA).

Uric Acid Metabolism, Hyperuricemia, and Gout

Gout is a joint disease characteristic of hominids, such as higher primates and certain New World monkeys. Its prevalence increased in the last years from 6.7 per 1000 inhabitants in 2005 to 9.1 per 1000 inhabitants in 2009, with a prevalence between 0.9% in Italy and 3.9% in the USA[3]. Gout is due to genetic mutations, responsible of the loss of uricase gene. Two nonsense mutations of this gene are present, located at codon 33 and 187, occurred between 24 million and 16 million years ago[4]; these genetic mutations had an important impact in the human evolutionary supremacy over other animal species. Uricase is an important enzyme in the metabolism of uric acid (UA), as it allows to degrade the UA in allantoin, a substance with high solubility in plasma. In animals with the uricase enzyme, plasma concentrations of UA is lower than in humans. UA is produced only in tissues that contain xanthine oxidase (liver and small intestine); in these tissues the production of UA is due to degradation of proteins or degradation of purines[5]. Plasma concentrations of UA change according to age and sex, they are lower in childhood (3-4 mg/dl), increasing thereafter in the male during puberty and in women after the menopause[6]; the pathological serum UA concentration is > 7.0 mg/dl in men and > 5.7 mg/dl in women[7]. Excretion of UA occurs through two pathways: intestinal bacteria degrade approximately 1/3 of UA, through intestinal uricolysis. Kidney is the main regulator of UA homeostasis,

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Table IA. Hypeuricemia and prominent and noble persons.

Popes	Onorius IV, Bonifacius VIII, Pius III, Julius II, Julius III, Clement VIII, Innocent XI, Clement XII, Pius VIII.
Prominent religious	Martin Luther, John Calvin, John Wesley, cardinal Giovanni de Medici, cardinal Leopoldo de Medici.
Kings or Emperors	Alexander the Great, Caesar Augustus, Charles the Great, Charles I, John II, Francis I of Bourbon, Charles V and Philip II of Habsburg, Charles II, Charles III of Lorraine, Catherine of Lancester, Louis XVIII, Stanislaus Leczinski, king of Poland, George IV, Napoleon Bonaparte, queen Anne of England.
Noble Houses	Duchy of Lorraine, Habsburg, Medici, Bourbon.

as more than 70% of urate excretion is renal. Furthermore, hyperuricemia in gout is frequently related to urate underexcretion, as the kidney has incredible ability for urate reabsorption[8].

The presence of hyperuricemia in hominids has allowed an evolutionary advantage in several aspects such as high blood pressure (BP), even in conditions of low salt intake[9], a greater stimulation of the cerebral cortex[10] and a longer life of hominids due to the antioxidant effects of the UA. These conditions represent essential mechanisms in the maintenance of upright position and intellectual supremacy on other primates, two crucial steps in the evolutionary development and human dominance.

Uric Acid and Cardiovascular Risk

The association between hyperuricemia and cardiovascular risk is widely known, and hyperuricemia is associated with many pathological conditions due to its effect on the endothelial function and metabolic homeostasis[11]. Although this is not the topic of the present review, many trials showed a direct association between hyperuricemia and diseases such as hypertension[12], diabetes mellitus[13], atherogenic dyslipidemia[14], and abdominal obesity[15]. Moreover, metabolic syndrome is frequently found in hyperuricemic patients[16]. Hyperuricemia is frequently associated with chronic kidney disease (CKD) and appears to be implicated with microvascular damage due to parenchimal deposit of UA[17], cerebrovascular events, such as ischaemic or hemorragic stroke, coronary heart disease and acute myocardial infarction[18], and congestive heart failure[19]. A recent review showed that UA increase the cardiovascular risk in healthy adults[20], and in elderly, in which was a important predictor of all-cause mortality, in particular in women[21]. Interestingly, although a diet poor in acid uric minimally affect plasmatic levels, recent data on elderly subjects at high cardiovascular risk showed that Mediterranean diet, rich in antioxidant and anti-inflammatory agents, was associated with a reduced risk of hyperuricemia[22].

Uric Acid, Antioxidant Action, and Neuroprotection

An important protective role of UA is due to the scavenger action on free radicals, and UA is considered one of the most important natural antioxidants in humans[23]. In a recent experimental study on diethylnitrosamine (DEN) toxicity in rats, UA levels were lower in DEN group than in control, but increased after supplementation with n-3 fatty acids; this toxic substance induce damage in many enzymes involved in DNA repair, that UA allows to reduce[24].

The oxidant damage in the central nervous system (CNS) is due to oxidation and nitration of proteins, DNA, and lipids, with evolution towards necrosis and apoptosis. Cellular oxidation is the molecular cause of the major neurodegenerative diseases and antioxidant action of UA could reduce the burden of damage. Reduced glutathione (GSH), a reducing natural agent, plays an important role in the regulation of acid-base balance, and its synthesis is regulated by cysteine, whose neuronal reuptake is mediated by excitatory amino acid transporter (EAAT-1)[25]. UA utilizes this action of GSH to reduce brain free radicals, increasing cysteine uptake via an activation of transporter EAAT-1 in hippocampal neurons[26]. Neuroprotective effects do not occur at non-physiological UA concentrations, that instead attenuate the increase in cysteine.

Glutamate, a toxic metabolite for the brain, reaches very high extracellular concentrations when UA concentrations are low[27]. UA has been identified as an important metabolite for preventing cell damage induced by glutamate. Damage is governed by astroglia, which present the glutamate transporters (EAAT-1 and EAAT-2), which it is the important mediators UA detoxifying ef-

fect against glutamate[28]. The anti-glutamate effect of UA is particularly important, since glutamate is produced in response to neuronal cellular damage as in stroke events as well, and elevated circulating levels of UA, in fact, have been shown to be useful in reducing brain damage from ischemic stroke in humans[29]. Again, administration of glutamic acid appears to improve cognitive function in patients with intellectual disability[30].

Therefore, UA represents neuroprotective metabolite acting through suppression of oxyradical accumulation, stabilization of calcium homeostasis, and preservation of mitochondrial function. The presence of high circulating levels of UA is related with lower severity of neurological damage and lower volume of cerebral infarction[31], and UA administration in the course of acute ischemic stroke is associated with smaller cerebral ischemia, with an effect that appears to be additional to fibrinolysis in experimental animal[32,33].

In ventral mesencephalon cultures of mice with Parkinson's disease, UA reduced intracellular concentrations of 1-methyl-4-phenylpyridinium[34], a toxic metabolite that is involved in the degeneration of dopaminergic neurons and in the development of frameworks of Parkinson's disease in humans, with reduced ATP synthesis and neuronal death[35]. The same authors demonstrated such protective effect on astrocyte also in an experimental model of exposure to H_2O_2[36]. In both studies, the expression of uricase in transgenic cell was associated with an intracellular reduction of UA concentrations leading to a reduction in the number of astrocytes, due to inhibition of antioxidant action. These data were recently confirmed by Chen et al[37] in a group of transgenic mice with uricase gene overexpression.

The protective action of UA on intracellular oxidative stress of dopaminergic neurons is indipendent of its intracellular accumulation and could be mediated by factors acting similarly to iron chelating agent desferrioxamine, H_2O_2 scavenger catalase enzyme and inhibitor of lipid peroxidation[38]. Squadrito et al[39] have also demonstrated an effect of UA on the reduction of neuronal damage induced by peroxynitrite. This toxic is a derivative of the *in vivo* reaction of nitric oxide with superoxide radicals, and is considered to be responsible for the processes of cell damage in stroke, Alzheimer's disease (AD), Parkinson's disease and amyotrophic lateral sclerosis. UA acts as scavenger for radical CO_{3-} and NO_2, that are the reaction products of peroxynitrite with CO_2.

A recent study[40] conducted on mice with intraperitoneal administration of UA, twice daily at a dose of 200 mg/kg, showed slowing down effect on deterioration of motor performance, loss of dopaminergic neurons in the substantia nigra, reduction of dopamine and its metabolites in the striatum, accumulation of products of lipid oxidation, as well as depletion of GSH and oxide reductive activity in the striatum caused by 6-hydroxydopamine (6-OHDA), a hydroxylated analog of dopamine. These results demonstrated the protective effects of UA on dopaminergic neurons in the substantia nigra against 6-OHDA induced degeneration. Furthermore, toxic effect in the brain of 6-OHDA was greatly alleviated in parkinsonian rats treated with UA via protein kinase B activation and inactivation of glycogen synthase kinase 3 beta (GSK3b).

Neuroferritinopathy is another mechanism of cell damage dependent redox processes, secondary to damage of ferritin leading to alteration of iron homeostasis in the brain. The formation of iron-ferritin aggregates may promote cell death and reduction in the activity of the proteasome, resulting in impairment of motor and cognitive functions. In these cases, the addition of iron chelators and antioxidants, restores cell function, reducing reduction formation of aggregates of iron[41].

Uric Acid and Dementia

Oxidative stress has been related to a direct neuronal injury, mechanism involved in the development of several neurodegenerative diseases, such as AD[42], Parkinson's disease[43], and multiple sclerosis[44]. Inflammation and demyelination of neuronal cell have been described in all these conditions. Therefore, the inverse relation between UA and CNS injury suggests a decreased incidence of neurodegenerative diseases with increasing UA concentrations. On the one hand, oxidation of proteins, DNA damage, lipid peroxidation and formation of advanced glycosylation end (AGE) products, production of beta-amyloid substance, presence of abnormalities of the mitochondrial cytochrome c-oxidase, are related to the production of free radicals and local inflammatory reactions[45]. Rinaldi et al[46] showed that patients with mild cognitive impairment (MCI) and AD, had reduced antioxidant activity. On the other, however, data from the InCHIANTI study[47] reported that in elderly subjects with

Table IB. Hypeurircemia and prominent personalities of culture and arts.

Politicians	Francis Bacon, Oliver Cronwell, William Pitt, Horatio Nelson, Ferdinando I de 'Medici, Lorenzo the Magnificent, Cosimo II de' Medici, Prince Mattias de 'Medici, Kublai Khan, Winfield Scott.
Writers	Quintus Horatius Flaccus (Horace), Publius Ovidius Naso (Ovid), Marcus Valerius Martialis (Martial), Johann Wolfgang Goethe, John Milton, Michel de Montaigne, Edward Gibbon, Marie-Henri Beyle (Stendhal), Samuel Johnson, Alfred Tennyson.
Artists & Composers	Michelangelo, Leonardo da Vinci, Peter Paul Rubens. Ludwig van Beethoven.
Philosophers	Francois-Marie Arouet (Voltaire), Immanuel Kant, Gottfried Leibnitz, Karl Marx, Johann Fichte.
Scientists and Physicians	Isaac Newton, Galileo Galilei, Charles Darwin, Benjamin Franklin, Jons Jacob Berzelius, Jean-François Champollion, William Harvey, Carl Linnaeus, Giovanni Battista Morgagni, Walter Harry Pitts Jr, Thomas Sydenham.

higher UA concentrations the risk for dementia was approximately 3-fold greater than in those with lower UA levels, although this association was weaker after correction for the presence of CKD and previous cardiovascular and cerebrovascular events.

Afsar et al[48] evaluated CKD patients and found an inverse relationship between UA and MCI, due to the fact that UA was related independently to Standardized Mini-Mental State Examination (SMMSE) score. A prospective population-based cohort study[49] among 4,618 participants aged 55 years and over, and the subsample of 1724 participants who remained free of dementia during follow-up found that only after correcting for several cardiovascular risk factors, higher UA levels were associated with a decreased risk of dementia, and in subjects who remained free of dementia, higher UA concentrations at baseline were associated with better cognitive function later in life. Thus, it seems plausible that the antioxidant effects of UA may play an important role in reducing the risk of dementia, probably due to a direct actions in the brain.

Uric Acid and Intellectual Performance

The cerebral cortex of hyperuricemic hominids has developed more than other animals, with an intellectual supremacy of hominids on other primates[10]. The beneficial effect of high serum concentrations of UA has been known so far[50], and it has been hypothesized that hyperuricemia was correlated with the intellectual performance (Table IB, Table II; 10, 50-53, 55-66). Park et al[53] investigated plasma and urine UA levels in twins, and UA was related to intelligence quotient (IQ) of the subjects. Genetic evaluation of serum UA levels in different families suggested that polymorphisms in purine metabolism pathway could be the link with the inheritance of IQ. This association has been evaluated in several clinical trials performed on healthy adults. Patil et al[54] investigated a cohort of medical students, and showed that mean serum UA in subjects with high IQ (> 160) was higher than in subjects with normal IQ (81-120). Several investigations were performed in children (aged 0 to 16 years)[55] and in British superintelligent members of Mensa (the high IQ society)[10] showed this relationship between UA concentration and intelligence. A study performed in high school children in Michigan[56] showed that high serum levels of UA were not related to high IQ, but to a high

Table II. Hyperuricemia and intellectual effects.

Investigated item	Year	Author (ref. n°)
Intelligence quotient	1959	Stetten et al[50]
	1963	Erlenmeyer-Kimling et al[51]
	1965	Mikkelson et al[52]
	1980	Park et al.[53]
	1981	Sofaer et al[10]
	1982	Cervini et al[55]
	1984	Inouye et al[56]
Achievement	1966	Brooks et al[59]
	1966	Kasl et al[60]
	1970	Kasl et al[61]
	1973	Montoye et al[57]
	1973	Fowler[58]
Leadership	1966	Brooks and Mueller[59]
	1973	Fowler[58]
Activity	1953	Inouye[62]
Learning	1975	Stevens et al[63]
Motivation	1970	Kasl et al[61]
	1972	Rahe et al[64]
	1973	Fowler[58]
Business executives	1967	Montoye HJ et al[65]
	1969	Anumonye et al[66]

performance that could predict IQ. This conclusion reinforced the idea that the main effect of UA is a brain stimulation, responsible of best intellectual performance. Serum UA was also related to behaviour scales measuring personal motivation, leadership skills, personal responsibility and efficiency[58,59].

Conclusions

UA has a stimulating effect on the cerebral cortex, and this could have allowed humans, compared with other animals, to develop higher brain mass (in terms of volume), better intellectual performances, and maybe evolutionary supremacy. On the other, a growing body of evidence is accumulating on the independent association between UA and cardiovascular risk.

Thus, a careful interpretation of UA levels seems to be appropriate and necessary in different kinds of patients, both at risk of cardiovascular or neurodegenerative diseases, due to its contrasting significance. The maintenance of optimal UA serum concentrations may represent important balance in the view of disease prevention.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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