URIC ACID AND COGNITION: WHAT IS THE CONNECTION?

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*Cognitive decline is one of the most frequent and disabling non motor features in ageing. The relationship between uric acid (UA) levels and cognitive impairment varies with dementia subtype. In this context, dysmetabolism, oxidative stress and neuroinflammation play a role in cognitive impairment and are all affected by UA. The mechanisms of neuroprotection against oxidative stresses include both the antioxidant activity against reactive oxygen species (ROS) and the induction of the gene expression of the antioxidant enzymes. On the other hand, hyperuricemia induces the production of ROS and inflammatory cytokines, leading to neuroinflammation and neurodegeneration. The increased brain gliosis could link neuroinflammation and dysmetabolism. Also the gender-related differences in the clinical features of cognitive impairment could be partly related to UA and should be taken into account for the “normal” range set for UA concentration. In conclusion, UA affects cognitive function, by interacting with neural, immune, cardiometabolic and, probably, adipose pathways and could be a target of the neuro-immune-adipose interactions. **Biomed Rev 2016; 27: 51-57***

Key words: antioxidant, dementia, gliosis, neurodegeneration, neuroprotection, obesity-related diseases, Alzheimer’s disease, adipose tissue

INTRODUCTION

Uric acid (UA), the end product of purine metabolism in humans produced by hypoxanthine and xanthine under the catalysis of xanthine oxidase (XO), is a potent endogenous antioxidant in the extracellular environment (1). In Lesch-Nyhan Disease, an inborn error of purine metabolism, the hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency results in hyperuricaemia, urate nephrolithiasis, gout and cognitive impairment (2-4). On the other hand, gout

is inversely associated with the risk of developing Alzheimer’s disease (AD) (5). Therefore, there is still a considerable debate concerning whether UA is neuroprotective or neurotoxic.

URIC ACID AND COGNITIVE DECLINE

Cognitive decline is one of the most frequent and disabling non motor features in ageing and includes different subtypes, such as AD, mild cognitive impairment (MCI), Parkinson’s disease (PD), vascular dementia (VaD) and mixed dementia

Received 21 November 2016, revised 7 December 2016, accepted 18 December 2016.

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(MD) (6-12). Although higher levels of UA were generally associated with slower cognitive decline (7-12) and UA has been suggested as an inverse biomarker for dementia (9, 10), results of a recent meta-analysis suggest that the relationship between UA and cognitive impairment varies with dementia subtype (12). Subgroup analyses for patients with AD, PD, MCI, VaD and MD revealed that, compared to controls, UA was lower in AD (SDM -0.33), PD (SDM -0.67), but not in MCI (SMD -0.24), VaD (SDM -0.05) or MD (SDM 0.19) (12) (Fig. 1). In particular, authors pointed out that the relationship between UA and cognitive impairment may differ in patients with VaD compared to other dementia subtypes (12). In this context, it is well known that hyperuricemia is positively associated with hypertension, arterial intima-media thickness, impaired brachial artery flow-mediated dilation and aortic dilatation in patients with ascending aortic aneurysms (13-16) (Fig. 1). Uric acid is directly correlated with age and increased after hypoxia-reoxygenation, leading to endothelial cell death and endothelium-dependent relaxation impairment (17, 18). High UA is associated with increased cerebral ischemia (CI) (Fig. 1) and it has been suggested that severity of CI might mediate the association between UA and cognitive dysfunction (19). However, although diastolic blood pressure was consistently correlated with plasma amyloid beta ($A\beta$)

levels ($r=-0.19$, $p=0.032$) and $A\beta_{40}$ was associated with UA ($r=0.285$, $p=0.001$) (20) low UA levels in patients with preexisting cardiovascular disease were associated with poorer cognitive function a decade later (21).

DYSMETABOLISM AND COGNITIVE DECLINE

The relationship between obesity, dysmetabolism and cognitive decline in elderly is unclear.

Although high level of UA are associated with obesity, metabolic syndrome, type 2 diabetes (T2D), kidney and cardiometabolic diseases (22-25), weight loss occurs frequently in patients with AD (26) and lower UA levels are linked to cognitive dysfunction in elderly (27).

Higher diastolic blood pressure, body mass index and abdominal obesity index, as well as higher serum glycated hemoglobin, triglycerides, cholesterol and UA are associated with MCI (28) and/or diabetes related cognitive dysfunction (29) (Fig. 1). However, it has also been reported that MCI patients had lower plasma total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol than control subjects (30) (Fig. 1). In this context, it must be taken into account that genetic susceptibility plays a role. For example, the genetic risk factor Apolipoprotein E (ApoE) $\epsilon 4$ allele (OR = 5.90) was associated with an increased risk of AD (31) and there is an interaction between oxidative stress and ApoE genotype in the development of the neurodegeneration (32, 33).

URIC ACID AND OXIDATIVE STRESS

Oxidative stress is the result of the imbalance between reactive oxygen species (ROS) and antioxidant defense (34). Systemic oxidative stress is common in patients with cognitive impairment and markers of lipid peroxidation are elevated and total antioxidant capacity is decreased in AD and MCI (35).

The effect of UA on oxidative stress depends on its concentration. UA at concentrations below the saturation level for urate precipitation (6.0 mg/dl) inhibits significantly oxidations caused by the Fenton reaction (36) and by the peroxy radicals (37) (Fig. 2). On the other hand, UA induces the nuclear translocation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) protein in primary astrocytic cultures (38), leading to the transcription of antioxidant genes through the antioxidant responsive elements (ARE) (Fig. 2). Antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX) and glutathione reductase (GR), and glutathione (GSH) are major antioxidants at the cellular level (39). Superoxide dismutase

Figure 1. Uric acid, dysmetabolism and cognitive decline. AD: Alzheimer's disease; CI: cerebral ischemia; CVD: cardiovascular diseases; DrCD: Diabetes related cognitive dysfunction; MCI: mild cognitive impairment; MD: mixed dementia; PD: Parkinson's disease; T2D: type 2 diabetes; UA: uric acid; VaD: vascular dementia.

Figure 2. Uric acid and neuroprotection against oxidative stress. ARE: antioxidant responsive elements; Nrf2: nuclear translocation of the nuclear factor (erythroid-derived 2)-like 2; ROS: reactive oxygen species; UA: uric acid.

catalyzes the one-electron dismutation of superoxide into hydrogen peroxide and oxygen, catalase then operates the two electron-dismutation into oxygen and water (39). Glutathione peroxidase is involved in hydrogen peroxide removal and in the conversion of lipid hydroperoxides to their corresponding alcohols, through the oxidation of GSH to glutathione disulphide (GSSG), which is reduced back to GSH by the GR (39). The reduction of the Nrf2 ubiquitination and degradation has been suggested as the mechanisms of neuroprotection on dopaminergic cells against oxidative stresses (40).

URIC ACID AND NEUROINFLAMMATION

Although, low levels of UA are detrimental to the neurons, UA has been identified as an endogenous danger signal for immune system (41, 42). In particular, hyperuricemia may lead to the formation of monosodium urate crystals (MSU), the latter activating monocytes via the inflammasome (43, 44), in part through Toll-like receptor 4 (TLR4)/CD14 pathway (44) (Fig. 3). Besides, in response to MSU, the neutrophils recruited to sites of inflammation undergo oxidative burst (45). The main enzymes, operating during oxidative burst, are NADPH oxidase (NOX), myeloperoxidase (MPO) and nitric oxide synthase (NOS) (46), producing superoxide, hypochlorous acid (HClO) and nitric oxide (NO), respectively (Fig. 3). NADPH oxidase (47, 48), MPO (49-51) and NOS (52) have been involved in neurodegenerative disorders (Fig. 3). In this context, the activation of microglia, the resident macrophages of the central nervous system, has a central role

Figure 3. Uric acid, neuroinflammation, neurodegeneration and dysmetabolism. MPO: myeloperoxidase; MSU: monosodium urate crystals; NOS: nitric oxide synthase; NOX: NADPH oxidase; TLR4: Toll-like receptor 4; UA: uric acid.

in neuroinflammation and ROS-mediated neurodegeneration (53). Microglia induce neurodegeneration also by secreting inflammatory cytokines, such as tumor necrosis factor- α (TNF- α), in response to the synergistic induction by chromogranin A (CGA), beta-amyloid (β A) and interferon- γ (IFN- γ) (54). Recent results in animal models suggest that a high-UA diet increases gliosis by inducing the expression of proinflammatory cytokines, through the Toll-like TLR4/nuclear factor (NF)- κ B pathway (55) (Fig. 3). Besides, the high-UA diet-induced NF- κ B activation triggered the expression of proinflammatory cytokines and increased gliosis in the hypothalamus, linking neuroinflammation and dysmetabolism (56) (Fig. 3). In fact, the rats treated with UA showed dyslipidemia, increased blood pressure, higher glucose and insulin concentrations than control rats (56).

URIC ACID, GENDER DIFFERENCES AND COGNITIVE DECLINE

The existence of substantial gender-related differences in the clinical features of cognitive impairment could be partly related to UA. Serum UA showed an inverse association with cognitive function among aged women, but not among men, and the association was amplified by the presence of cardiovascular disease, suggesting that women may be particularly vulnerable to the elevated UA (57-59). In fact, the association of serum UA with cardiovascular risk factor (60), metabolic syndrome (60, 61) and T2D (62) is gender-specific and more pronounced in women. From that, although the “normal” range set for UA concentration is still disputed,

gender specific normal values are always applied (60-64). However, it has been reported that in nonagenarian and centenarian men, the higher level of UA is related to a lower risk of cognitive impairment compared to women (65, 66).

Intriguingly, it was reported that adipose tissue may secrete UC related to obesity (67), the latter being associated with Alzheimer's disease (68). In such an adipocentric approach, UA could play a role in the neuro-immune-adipose interactions referred to as triactome (69).

Taken together, UA may affect cognitive function by interacting with neural, immune, cardiometabolic and, probably, adipose pathways.

Conflict of interest statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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