Uric Acid: Neuroprotective or Neurotoxic?

To the Editor:

A decades-old scientific dispute pits “as a pro-oxidant, uric acid causes disease” against “uric acid is an important antioxidant.” The antioxidant properties of urate are well-known. However, arguably, this issue per se originated in our complimentary reports of urate as both a primate evolutionary substitute for ascorbate and as a pro-oxidant. Simply stated, in addition to being an important human antioxidant, urate mediates radical oxidations and likely, oxidative-stress-related disease in a manner similar to homocysteine, transition-series metals, etc. Examples include Lesch-Nyhan syndrome and other neurological disorders, gout, Dalmatian hyperuricemic syndrome, and atherosclerosis. We also noted, “the well-established association between high urate levels and atherosclerosis could be a protective reaction (antioxidant) or a primary cause (pro-oxidant)”. Thus, I feel able to comment on a current manifestation of this issue—lowering urate levels versus urate infusion as treatment for acute ischemic stroke.

Basically, “It depends”. As with other powerful reducing agents like ascorbate, the exact mix of pro-oxidant versus antioxidant properties for uric acid depends on a complex mix of concentration, oxygen availability, electronically-active species, transition-series metals, and so forth. However, besides gout, chronic extreme hyperuricemia likely causes clinically significant oxidative stress in at least 2 defined conditions. The first is the Lesch-Nyhan syndrome with its inflammatory symptoms and choreoathetosis. Similarly, oxidative stress is an important component of hyperuricemic syndrome in Dalmatian dogs. This disease presents with the classic oxidative stress-related symptomology of skin pigmenary abnormalities (here, “bronzing”), inflammatory disease, and deafness—the latter may be related to inner-ear melanin. Because the gene lesion involves liver uptake of uric acid and not purine hyper-production, oxidative stress is likely due to uric acid per se and not xanthine oxidase.

Likewise, Dalmatian hyperuricemic syndrome responds to treatment with “orgotein”, the veterinary formulation of the antioxidant enzyme superoxide dismutase (SOD), implying a direct role for superoxide in this disease. Significantly, both orgotein and SOD mimetics such as TEMPOL are also neuroprotective in animal models for acute ischemic stroke. Like urate, SOD presumably acts outside the blood-brain barrier, say, at the endothelium.

However, in conditions of extraordinary oxidative stress, the balance between the pro- and antioxidant properties of uric acid may shift in favor of tissue protection. This is particularly so since urate scavenges oxidants such as peroxinitrite, whose normal background levels are low, except in pathogenic processes such as ischemia. Thus, a low level of chronic, sometimes pathogenic, oxidative stress may be the price paid for the protective presence of urate when things go bad acutely. Similarly, the uniquely high levels of urate and other antioxidants in primates might partially account for the mismatch between human and animal studies on antioxidant neuroprotectants.

Disclosures

P.H.P. has patent claims to TEMPOL.

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