Uric Acid: Neuroprotective or Neurotoxic?

To the Editor:
A decades-old scientific dispute pits “as a pro-oxidant, uric acid causes disease”1–3 against “uric acid is an important antioxidant.”2–6 The antioxidant properties of urate are long-known.6 However, arguably, this issue per se originated in our complimentary reports of urate as both a primate evolutionary substitute for ascorbate4 (a putative antioxidant neuroprotectant7) and as a pro-oxidant.2,3 Simply stated, in addition to being an important human antioxidant, urate mediates radical oxidations2 and likely, oxidative-stress–related disease2,3 in a manner similar to homocysteine,2,3 transition-series metals,2,3 etc. Examples include Lesch-Nyhan syndrome with its inflammatory symptoms and choreoathetosis.2,3 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 pigmenatory abnormalities (here, “bronzing”), inflammatory disease, and deafness3—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”8, the veterinary formulation of the antioxidant enzyme superoxide dismutase (SOD), implying a direct role for superoxide in this disease. Significantly, both orgotein7 and SOD mimetics such as TEMPOL9 are also neuroprotective in animal models for acute ischemic stroke. Like urate, SOD presumably acts outside the blood-brain barrier, say, at the endothelium.7

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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