Uric Acid and Neuroprotection

To the Editor:

Having arguably originated both sides and after long-equivocation over whether urate is physiologically primarily pro- or antioxidant, we finally declared in favor of a neuroprotective role in acute ischemic stroke.¹ But, as Dawson et al² note, this leaves unanswered the role of xanthine oxidase and the putative pro-oxidant role of urate in atherosclerosis, metabolic syndrome, and so forth.³–⁶ Perhaps treatment will ultimately involve both allopurinol and urate.

Besides the work of Chamorro and others, our support for an acute neuroprotective role is based on new evidence for specific regulation of urate levels, combined with a wider tissue-protective role. This includes activation of redox-sensitive glutamate transport elements such as glial EAAT-1 (review, ref 3), tying urate mechanistically to amelioration of excitotoxicity.

This may partially explain the mismatch between animal and human trials with neuroprotectants. Essentially absent in animal models, arguably responsible for 60% to 70% of human plasma antioxidant activity, and with no treatment time lag, uric acid likely leaves much less therapeutic room for similar extracellular reducing antioxidants or (say) antiexcitotoxic agents in humans. Thus, the effectiveness of such agents in animals led to therapeutic dead ends.

A more-directed approach to neuroprotection blocks the pro-oxidant effects of uric acid⁴–⁶ and/or xanthine oxidase,² while augmenting urates’ tissue-protective properties, eg, with superoxide dismutases (SODs).⁷ Similar examples include agents acting mitochondrially and/or across the blood-brain barrier. This first drew us to the spin-traps phenylbutylnitrone (PBN—the parent of both group’s PBN work in proposing that the positive results in SAINT-I were due to production of such products from MNP).⁸

PBN might be related to its hydrolysis products, especially the nitric oxide–releasing spin-trap tert-nitrosobutane, aka MNP. This was taken up by Ames and his coworkers,⁹ especially with MNPs reduced form, NtBHA. Previously, their rediscovery (a decade after our similar work)¹⁰ of both the antioxidant properties of urate and its putative role as an evolutionary substitute for ascorbate made this scientifically respectable. In turn, we cite¹¹ both group’s PBN work in proposing that the positive results in SAINT-I were due to production of such products from NXY-059, a matter we shall shortly revisit.

Disclosures

P.H.P. has certain patent claims to nitro and nitrooxide spin traps and spin-labels.

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