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 mechanismically to amelioration of excitotoxicity.

This may partially explain the mismatch between animal and human trials with neuroprotectors. 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) anticytotoxic 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 acid3–6 and/or xanthine oxidase,2 while augmenting urates’ tissue-protective properties, eg, with superoxide dismutases (SODs).6 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 drug for the putative neuroprotectant NXY-059) and 2-methyl-2-nitrosopropane (MNPs), as well as the SOD-mimetic spin-labels TEMPO and TEMPOL. As we note1 SOD itself is neuroprotectant, as are TEMPO/TEMPOL. These agents have proven very nontoxic in human and animal trials. As “orgotein” or “ontosein,” SOD itself gained regulatory approval in Europe for radiation cystitis and Peyronies disease. Likewise, TEMPOL is currently in clinical trials for radiation alopecia and parotiditis and for hypertension. A TEMPOL ester is also in trials for age-related macular degeneration.

Similarly, Cutler and coworkers relate primate longevity to uric acid levels7 and separately demonstrate8 that the action of 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 work10) 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 nitrene and nitroxide spin traps and spin-labels.

Peter H. Proctor, PhD, MD

Drugscom, Inc

Houston, Tex

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Peter H. Proctor

Stroke. 2008;39:e126; originally published online June 19, 2008;
doi: 10.1161/STROKEAHA.108.524462
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/39/8/e126

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