Erythropoietin Depletes Iron Stores: Antioxidant Neuroprotection for Ischemic Stroke?

To the Editor:

Sullivan1 popularized the “iron hypothesis” of ischemic heart disease in 1981, highlighting a putative role for iron as a major player in the development of atherosclerosis and subsequent cardioprotective benefits of iron depletion. This is primarily attributable to iron’s ability to catalyze Fenton and Haber-Weiss chemistry to form the aggressively reactive hydroxyl radical, which, despite its fleetingly short half-life of less than a millionth of a second, can inflict significant cellular membrane destabilization and damage.2

Because the human brain is exquisitely susceptible to the ravages of redox chemistry,3 it is not surprising that in recent years, the iron hypothesis has been extended to cerebrovascular disease to help unravel the complexities of stroke. Recent publications in Stroke have focused on the pivotal relationship between raised serum ferritin stores, carotid atherosclerosis and risk of ischemic stroke3,4 with clear implications for the design of future neuroprotective agents.

One such intervention shown to exhibit remarkable and somewhat unexpected neuroprotective properties is the glycoprotein erythropoietin (EPO), better known in human circles for its abuse by elite athletes searching for an ergogenic boost in oxygen delivery. It is perhaps surprising to note that only 1 clinical trial has been conducted with acute ischemic stroke patients5 considering the wealth of in vitro evidence highlighting the multiple neuroprotective roles of this pleiotropic cytokine.6 What renders EPO so neuroprotective remains a mystery, and in this correspondence we would like to raise the possibility that altered iron metabolism may prove important.

As proof of concept in healthy volunteers, we tested the hypothesis that EPO’s neuroprotective properties may be related to its ability to deplete iron stores and reduce extracellular iron availability with catalytic potential. Venous injections (5000 IU) of recombinant human erythropoietin (rHuEpo; NeoRecormon, Roche; Manheim, Germany) were administered to 8 healthy males aged 27 ± 7 years in combination with 100 mg/d of ferrous sulfate according to the following dosing strategy: 1 injection every second day for the first 2 weeks; 3 injections on 3 consecutive days during the third week, and 1 injection every week between weeks 4 to 12 which aimed to increase hematocrit to 50%.

Hemoglobin and hematocrit increased rapidly during treatment from 14.3 ± 1.4 g/dL and 42 ± 5% at baseline to target values of 17.3 ± 0.9 g/dL (P < 0.05) and 49 ± 6% (P < 0.05) respectively by week 12. By week 6, plasma concentrations of ferritin, total iron and transferrin saturation reached a nadir having decreased markedly to 36 ± 11%, 47 ± 13% and 47 ± 12% of the pretreatment values (P < 0.05).

EPO’s ability to deplete iron stores and limit systemic availability may reduce oxidative catalysis and offer the “at-risk” patient some degree of neuroprotection against free radical-mediated vascular damage. This may prove especially important during the reperfusive phase after cerebral infarction when increased mitochondrial superoxide generation has the effect of mobilizing catalytic iron from ferritin. The notion that EPO is a potent antioxidant and that catalytic iron chelation lies at the heart (and brain!) of EPO’s antiexcitotoxic, antiapoptotic and neurogenic properties6 deserves future consideration. Whether EPO provides more effective prophylaxis than standard iron-chelation therapy also warrants investigation. Future studies may help extend Sullivan’s provocative hypothesis and establish more directly whether a “rusty” oxidative-stress prone brain is indeed a primary risk factor for stroke.

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Stroke. 2006;37:2453; originally published online August 17, 2006;
doi: 10.1161/01.STR.0000239787.92203.16
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/37/10/2453

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