Letters to the Editor

Erythropoietin Depletes Iron Stores: Antioxidant Neuroprotection for Ischemic Stroke?

To the Editor:

Sullivan\(^1\) 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,\(^2\) 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 stroke\(^3,4\) with clear implications for the design of future neuroprotective agents.\(^1\)

One such intervention shown to exhibit remarkable and what 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 patients\(^5\) considering the impact 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 properties\(^6\) deserves future consideration. Whether 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 properties\(^6\) deserves future consideration. Whether EPO provides more effective prophylaxis than standard iron-chelation therapy also warrants investigation. Future studies may help extend Sullivan’s\(^1\) provocative hypothesis and establish more directly whether a “rusty” oxidative-stress prone brain is indeed a primary risk factor for stroke.

Damian Miles Bailey, PhD
Paul Robach, PhD
Jonas Juhl Thomsen
Carsten Lundby, PhD
Copenhagen Muscle Research Centre
Rigshospitalet
Copenhagen, Denmark

Erythropoietin Depletes Iron Stores: Antioxidant Neuroprotection for Ischemic Stroke?
Damian Miles Bailey, Paul Robach, Jonas Juhl Thomsen and Carsten Lundby

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
Copyright © 2006 American Heart Association, Inc. All rights reserved.
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

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/