Neurovascular Protection by Erythropoietin: From the Bedside Back to the Bench

To the Editor:
We read, with interest, the clinical trial study of erythropoietin (EPO) on patients with stroke by Ehrenreich et al and the comment paper by Dame.1–3 This clinical study has failed to show any effect of EPO on patients with acute ischemic stroke. Furthermore, the combination of EPO with thrombolytic therapy caused serious side effects such as intracerebral hemorrhage. Stroke Therapy Academic Industry Roundtable (STAIR) recommendations were only incompletely followed by preclinical EPO stroke studies, because the combination therapy and comorbidity studies are still missing.3,4 Beyond these concerns with preclinical studies, we agree with Dame that the effects of EPO on neurovascular biology need further clarification.2

Although the significance of recent basic findings is needed to be clarified in stroke conditions, data are beginning to associate cell-type specific effects of EPO with the interactions between EPO receptors (EPORs) and diverse receptors that lead to the activation of specific signaling pathways. A heterodimer composed of EPOR with common β chain receptor has been proposed as the specific receptor mediating EPO neuroprotection.5 However, this finding has not been confirmed by other studies.6,7 In contrast, common β chain receptor interacting with vascular endothelial growth factor receptor 2 mediates the nitric oxide induction by EPO in endothelial progenitor cells that are implicated in tissue repair after stroke.8 Although glial cells express EPOR, the functional significance of those findings are still unclear.9,10 EPO may use diverse receptors in different cells and tissues even in the same type of cell depending on the dose, time, and any other changes in the cellular microenvironment.

Gene regulation of EPOR in neuronal cells is under the control of epigenetic mechanisms such as DNA methylation.11 Furthermore, the discordance between the expression of EPOR mRNA and protein suggests the posttranscriptional regulation of EPOR transcript by noncoding RNAs, including microRNAs.12 Further cell culture and animal studies designed with the help of a nonreductionist systems biology approach are needed to clarify these mechanisms and their significance in pathological conditions such as stroke.

Disclosures
None.

2. Dame C. Back to the ground. Stroke. 2010;41:166.
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