Response to Letter by Genc et al

Response:

We thank the authors1 for their thoughtful comments on our article in the May 2010 issue of Stroke regarding the role of erythropoietin (EPO) on oligodendrogenesis after neonatal hypoxic–ischemic (HI) brain injury. As mentioned, EPO is neuroprotective against ischemic or HI brain injury in both animal experiments2 and in humans, as evidenced by the recent clinical trial reported.3 Importantly, the cited clinical trial indicated that delayed EPO administration improved long-term outcomes in infants with moderate HI encephalopathy;4 an important consistency with our published treatment paradigm. However, the corresponding mechanism for the long-term functional improvement related to delayed EPO administration remains unknown. Our study2 indicated that delayed EPO administration was incapable of reducing brain volume loss, but significantly increased oligodendrogenesis, attenuated white matter injury, and improved behavioral neurological outcomes after HI injury. This study suggests that targeting oligodendrogenesis may enhance white matter remodeling, which may be closely related to the observed long-term neurological improvement after HI brain injury. In line with this, delayed EPO treatment was also shown to enhance reorganization of white matter and neurological improvement in adult rats.5 EPO thus may be a promising neurorecovery agent for the treatment of HI encephalopathy as well as poststroke patients.

White matter is typically more severely affected by ischemic insults compared with gray matter,6,7 and minor white matter strokes often cause extensive neurological deficits by interrupting the passage of large axonal bundles. Therefore, ischemic treatment strategies should target not only gray matter, but also white matter.8 Because rodents have a higher gray/white matter ratio than humans, the oligodendrogenesis profile after EPO treatment may be substantially different. It is a good suggestion to further explore the role of EPO on oligodendrogenesis in nonhuman primates or animals with a similar ratio of gray/white matter ratio as humans.

The signaling mechanism for EPO-induced oligodendrogenesis remains unknown. As Genc et al pointed out in their letter,1 oligodendrocyte progenitor cells and oligodendrocytes express EPO receptor, and thus EPO may activate downstream signaling such as STAT5, PI3K/Akt, and MAPK/Erk1/2 signaling pathways as has been demonstrated in neurons.9 These pathways may upregulate/activate the transcription factors, enhance the proliferation/differentiation of oligodendrocyte progenitor cells, or activate the antiapoptotic signaling pathway, therefore inhibiting the cell death of oligodendrocyte progenitor cells. EPO may also act on the surrounding neurons, endothelial cells, or astrocytes to stimulate the production of growth/neurotrophic factors, which in turn act on oligodendrocyte progenitor cells. Finally, it is possible that, as Genc et al proposed,1 EPO may regulate oligodendrogenesis through epigenetic mechanism such as histone modification, DNA methylation, and microRNAs. We agree completely that further elucidation of these mechanisms will bring new insight on the neurorecovery effect of EPO and fine-tune its potential as a therapeutic agent in brain ischemic settings.

Sources of Funding

Supported by National Institutes of Health grants NS053473 (to G.C.) and NS43802, NS45048, NS36736, NS56118 (to J.C.), VA Merit Review grants (to J.C. and G.C.), and American Heart Association grant 0630006N (to G.C.).

Disclosures

None.

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Stroke. 2010;41:e596; originally published online September 30, 2010;
doi: 10.1161/STROKEAHA.110.593574
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:
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