Letters to the Editor

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White Matter Protection by Erythropoietin: An Emerging Matter in the Treatment of Neonatal Hypoxic–Ischemic Brain Injury

To the Editor:

We read with great interest the study by Iwai et al,[1] which reports increased oligodendrogenesis and recovery of neurological function by delayed and repeated administration of erythropoietin (EPO) after neonatal hypoxic–ischemic brain injury in rats. Since the first in vivo evidence of EPO-mediated neuroprotection against neonatal hypoxic–ischemic brain injury in 2003,[2,3] many experimental studies have confirmed the efficacy of EPO in neonatal hypoxic–ischemic encephalopathy in rodents.[4] Then, it was shown that EPO administration immediately after neonatal hypoxic–ischemic brain injury significantly improves long-term neurobehavioral outcomes and brain injury in rats when analyzed during the subsequent phase of brain maturation and even in adulthood.[5] Finally, a recent clinical trial has shown that repeated administration of EPO reduces the risk of disability in newborns with moderate hypoxic–ischemic encephalopathy without apparent side effects.[6] However, the mechanisms of the beneficial effect of EPO in hypoxic–ischemic encephalopathy are not fully elucidated.

Iwai et al,[1] for the first time, report enhanced oligodendrogenesis and recovery of injured white matter (WM) as a novel mechanism by which EPO exerts its beneficial effect in hypoxic–ischemic encephalopathy. Although delayed administration of EPO does not decrease infarct volume, EPO-stimulated oligodendrogenesis and WM recovery are also correlated with the improvement of neurological functional outcomes. As the authors discuss, further studies are needed to clarify the exact mechanisms of oligodendrogenesis stimulated by EPO. Although oligodendrocytes and their progenitors and oligodendrocytes express EPO receptor,[7,8] data are beginning to associate cell type-specific effects of EPO with the interactions between diverse receptors that lead to the activation of specific signaling pathways.[9] Besides the classical EPO receptor, other receptors such as a heterodimer composed of EPO receptor with a common β chain receptor may mediate oligodendroglial cell responses stimulated by EPO or its modified derivatives. How the selection of the specific pathways is determined by a specific cell type is not known, although cell type, changes in cellular microenvironment, receptor availability, and the nature and severity of the insult are implicated in this process. The interplay of transcription factors and epigenetic modifiers, including histone modifications, DNA methylation, and microRNAs, during development is also essential for oligodendrogenesis.[10] The possible interaction between EPO and these mechanisms during this process is almost unknown.

Although rodents have been used extensively to model neonatal WM injury, and have provided essential information, there are significant limitations to these models.[4] Experimental studies with species that have gray/WM ratios similar to humans, including nonhuman primates, piglets, and sheep, may provide further information in preclinical testing of WM protection by EPO, especially in preterm neonates.[4] Emerging neuroimaging techniques[11] for the longitudinal evaluation of the WM will also be useful to confirm the restorative effect of EPO on WM and translate the results of the study by Iwai et al[1] to the neonatology clinics.

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Disclosures

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1. Iwai M, Stetler RA, Xing J, Hu X, Gao Y, Zhang W, Chen J, Cao G. Enhanced oligodendrogenesis and recovery of neurological function by erythropoietin after neonatal hypoxic/ischemic brain injury. *Stroke.* 2010; 41:1032–1037.
2. Matsushita H, Johnston MV, Lange MS, Wilson MA. Protective effect of erythropoietin in neonatal hypoxic ischemia in mice. *Neuroreport*. 2003; 14:1757–1761.
3. Kumral A, Ozer E, Yilmaz O, Akhisaroglu M, Gokmen N, Duman N, Ulukus C, Genc S, Ozkan H. Neuroprotective effect of erythropoietin on hypoxic–ischemic brain injury in neonatal rats. *Biol Neonate*. 2003;83:224–228.
4. McPherson RJ, Juul SE. Recent trends in erythropoietin-mediated neuroprotection. *Int J Dev Neurosci*. 2008;26:103–111.
5. Kumral A, Uysal N, Tugyan K, Sonmez A, Yilmaz O, Gokmen N, Kiray M, Genc S, Duman N, Koroglu TF, Ozkan H, Genc K. Erythropoietin improves long-term spatial memory deficits and brain injury following neonatal hypoxia–ischemia in rats. *Behav Brain Res*. 2004;153:77–86.
6. Zhu C, Kang W, Xu F, Cheng X, Zhang Z, Jia L, Ji L, Guo X, Xiong H, Simbruner G, Blomgren K, Wang X. Erythropoietin improved neurologic outcomes in newborns with hypoxic–ischemic encephalopathy. *Pediatrics*. 2009;124:218–226.
7. Sugawa M, Sakurai Y, Ishikawa-Ieda Y, Suzuki H, Asou H. Effects of erythropoietin on glial cell development; oligodendrocyte maturation and astrocyte proliferation. *Neurosci Res*. 2002;44:391–403.
8. Castillo-Meléndez M, Yan E, Walker DW. Expression of erythropoietin and its receptor in the brain of late-gestation fetal sheep, and responses to asphyxia caused by umbilical cord occlusion. *Dev Neurosci.* 2005;27:220–227.
9. McPherson RJ, Juul SE. Erythropoietin for infants with hypoxic–ischemic encephalopathy. *Curr Opin Pediatr*. 2010;22:139–145.
10. Liu J, Casaccia P. Epigenetic regulation of oligodendrocyte identity. *Trends Neurosci*. 2010;33:192–201.
11. Ment LR, Hirtz D, Hüppi PS. Imaging biomarkers of outcome in the developing preterm brain. *Lancet Neurol*. 2009;8:1042–1055.

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