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NEUROPROTECTIVE ROLE OF ERYTHROPOIETIN IN SPINAL CORD ISCHEMIC INJURY: WHERE HAVE WE BEEN AND WHERE ARE WE GOING?

To the Editor:

I read with great interest the study recently published by Yamanaka and colleagues,¹ reporting the results of the study aimed to pharmacologically induce β common receptor (β cR) subunit upregulation before ischemia to optimize the neuroprotective effect of erythropoietin (EPO). The authors hypothesized that β cR subunit upregulation by diazoxide (DZ) before ischemia amplifies the neuroprotective effects of EPO in mice after spinal cord injury (SCI). They reported that that optimal β cR upregulation occurred at 36 hours after DZ administration, and the optimal DZ dosage for β cR induction was 20 mg/kg. Motor function at 48 hours after treatment was significantly better preserved in the DZ with EPO group compared with all other groups, and was significantly better preserved in the DZ-only and EPO-only groups compared with the control group.

The authors should be complimented for highlighting the neuroprotective role of EPO in SCI. It has been less than 20 years since the discovery that EPO and its receptor are expressed by the nervous system. In that brief time, a remarkable acceleration in understanding the biology of this paracrine-autocrine system has occurred, radically changing our concept of the biological functions of EPO. The observation that systemically administered recombinant human EPO can reach local sites within the brain has suggested many potential clinical indications. Additional evidence also shows widespread efficacy of recombinant human EPO in injury models of the spinal cord,² subarachnoid hemorrhage,³ retina, and the heart. Available evidence suggests that EPO acts in a coordinated fashion at multiple levels to limit the production of tissue-injuring molecules such as glutamate, reverse vasospasm, attenuate apoptosis,

modulate inflammation, and recruit stem cells. Multiple studies have shown that EPO plays a major role in ischemic preconditioning. Our research team was one of the pioneering groups to suggest the beneficial effect exerted by EPO after experimental SCI and that pretreatment with EPO and its derivatives increases tolerance of the spinal cord against compressive injury.⁴ Recent evidence suggests that the hematopoietic and tissue-protective activities could be separated and that the hormonal and neuroprotective actions of EPO can occur via different signaling systems.⁵ Specifically, the receptor complex mediating the neuroprotective effects of EPO has been reported to be associated with the common β receptor (β cR) subunit, also known as CD131. It is reasonable to assume that the endogenous EPO, by interacting with the EPO receptor or other cytokine receptors, acts in a protective manner that becomes rapidly activated after injury, serving to promote neuronal survival. This could well explain the increased expression of EPO receptor observed in neurons and endothelial cells of the spinal cord beginning in the first hours after injury.⁶ Conversely, the limited recovery and permanent disability that most neuronal-injured patients show suggest that the endogenous system is not fully preventive of neuronal damage, which is likely in part because of the presence of proinflammatory cytokines. The results by Yamanaka and collaborators¹ stimulate for further investigation and suggest an intriguing chance to increase the efficacy of EPO in SCI by pharmacologic upregulation of β cR.

Giovanni Grasso, MD, PhD

Section of Neurosurgery

Department of Experimental Biomedicine and Clinical

Neurosciences (BIONEC)

University of Palermo

Palermo, Italy

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