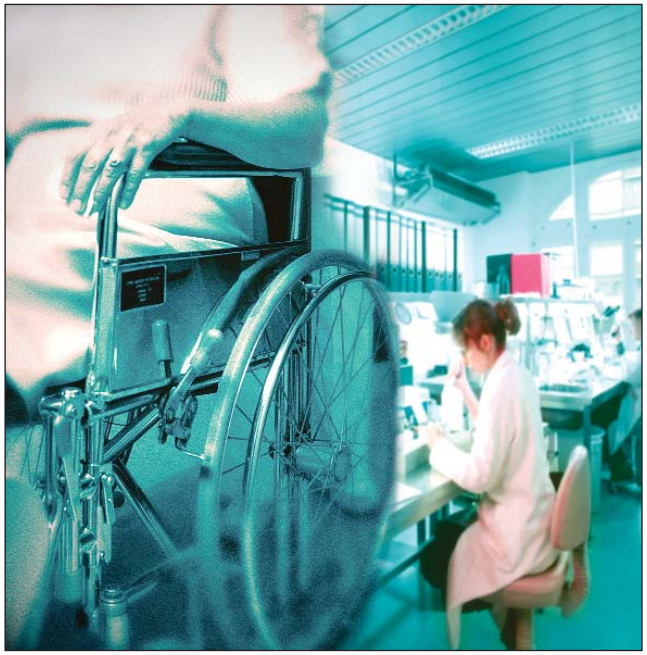
First publ. in: Science 305 (2004), 5681, pp. 184-185

A Boost for Translational Neuroscience

Hannelore Ehrenreich

Despite much progress in basic neuroscience research, the translation of these research findings into therapeutic advances for neurological and psychiatric diseases is frustratingly slow. Any step forward in treatments for stroke, acute brain or spinal cord injury, or for chronic neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, schizophrenia, or diabetic neuropathy, would be a major contribution to medicine. This is where the work of Leist and colleagues (*1*) published on page 239 of this issue comes into play. These authors take a big step forward in the treatment of neuropsychiatric diseases by engineering the hematopoietic growth factor erythropoietin (EPO) to have neuroprotective but not hematopoietic activity.

Pioneering studies on EPO revealed that this growth factor is synthesized by kidney cells and has its principal effects in the bone marrow, where it boosts the production of red blood cells. Building on this work, Leist and colleagues and other groups over the past decade showed that EPO is also a potent neuroprotective agent that is produced in the central nervous system (*2*–*9*). This discovery prompted Leist *et al*. to search for an EPO derivative that has the cytoprotective properties of EPO but not its hematopoietic activity. Such a compound would be a promising candidate for the long-term treatment of chronic neurological and psychiatric diseases. By carbamylating EPO to produce CEPO, Leist and co-workers engineered a tissue-protective "designer cytokine" that lacks hematopoietic activity (*1*). This new compound differs from EPO in two important respects: CEPO does not bind to the classical EPO receptor homodimer, nor does it have hematopoietic activity. Crucially, Leist *et al*. tested CEPO in a number of different animal models including rodent models of stroke, spinal cord contusion, multiple sclerosis, and diabetic neuropathy. In each case, CEPO conferred the same magnitude of neuroprotection as EPO.



Yet the mystery still remains as to how this separation of neuroprotective and hematopoietic activities can be explained. Is the central nervous system receptor bound by EPO different from the traditional homodimeric EPO receptor expressed by bone marrow cells? Is the neural EPO receptor a heterodimer composed of one EPO receptor monomer combined with a monomer from another cytokine receptor, as Leist *et al*. surmise? Association of different cytokine receptor monomers provides an assortment of receptors that can bind to many different ligands. The association of monomers, in turn, may depend not only on the ligand but also on the tissue-specific environment in which the receptor resides. For example, different populations of cell-surface integrins interacting with different extracellular matrix components have been reported to shape the activity of the neuregulin receptor during development of the nervous system (*10*).

Rather than modulating disease-specific pathogenic mechanisms, EPO seems to have more general tissue-protective effects. EPO accomplishes this by targeting components common to many different neurodegenerative pathways. This results in a plethora of different actions—anti-apoptotic, antioxidant, glutamate-inhibitory, anti-inflammatory, neurotrophic, stem cell–modulatory, and angiogenic. This combination of actions explains EPO's potent protective effects in various tissues, including the nervous system, eye, heart, and kidney. It also accounts for EPO's efficacy in a variety of different neurological and psychiatric diseases as demonstrated in animal models of cerebral ischemia, multiple sclerosis, spinal cord contusion, and diabetic neuropathy, and in human patients (*2*–*9*, *11*). As clinicians continue to optimize neuroprotective treatment regimens for human patients, short-term, high-dose application of recombinant human EPO for treating acute conditions like stroke may remain the strategy of choice. Indeed, EPO's ability to boost red blood cell production (*9*) may provide additional benefits to stroke patients. In contrast, CEPO may be the preferred drug for chronic neurological and psychiatric conditions that require long-term treatment. If EPO were to be used long-term, excessive stimulation of red blood cell production would necessitate frequent bloodletting to avoid thromboembolic complications, which are already common in bedridden patients or those with restricted mobility.

The safety of CEPO needs to be demonstrated in phase I clinical trials. However, the fact that its parent compound, EPO, is safe and has been well tolerated by millions of anemia patients holds promise that CEPO can be rapidly moved to the clinic. Moreover, carbamylation of EPO, as Leist and colleagues point out (*1*), appears to be a naturally occurring modification of this molecule. In a proof-of-principle trial, EPO was found to benefit stroke patients in both clinical outcome and recovery of infarcted brain tissue. Thus, EPO stands out from the numerous

The author is in the Division of Clinical Neuroscience, Max-Planck Institute for Experimental Medicine, 37075 Goettingen, Germany. E-mail: ehrenreich@em.mpg.de

neuroprotective treatments that have failed to be successfully transferred from rodent models to human patients (*9*). To consolidate the results of this small pilot study, a large multicenter trial to examine the efficacy of EPO for the treatment of stroke is under way in Germany. In addition, a small German multicenter trial to investigate whether long-term EPO treatment of patients with chronic schizophrenia could improve cognition (*11*) was initiated in April 2003. The initial results of this trial should be available by the end of this year, and, if promising, a large-scale trial using CEPO or similar compounds will follow. Clinicians eagerly await the clinical trial results of EPO, CEPO and other EPO derivatives.

Treatment of anemia has been a tremendously profitable market for the recombinant human EPO industry (although most licenses are set to expire in the near future). It is to be hoped that given this success, the pharmaceutical industry will contribute substantially to translating EPO and its derivatives into effective treatments for a variety of incurable neurological and psychiatric diseases.

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