Chapter 9

ERYTHROPOIETIN IN SPINAL CORD INJURY
Challenges for a novel neuroprotective strategy

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Abstract: Spinal cord injury (SCI) is a devastating condition lacking a clearly effective pharmacological treatment. The cytokine erythropoietin (EPO), which mediates cytoprotection in a variety of tissues through activation of multiple signaling pathways, is markedly effective in preclinical models of ischemic, traumatic and inflammatory SCI. The recent development of non-erythropoietic derivatives of EPO with outstanding preclinical characteristics encourages evaluation of tissue-protective cytokines in clinical trials of spinal cord injury.

Key words: spinal cord injury, erythropoietin, tissue protection, methylprednisolone, ischemia, inflammation, apoptosis, regeneration, animal models, neuroprotection, clinical trials

1. INTRODUCTION

Each year 11,000 new cases of spinal cord injury (SCI) are reported in the United States, over half of which occur among individuals under 30 years of age (National Spinal Cord Injury Statistical Center 2003). Aside from the incalculable human suffering, the medical surgical and rehabilitative care for patients with SCI is estimated at over four billion dollars per year (Kwon et al. 2002). Currently, there is no clearly effective therapy for spinal cord injury. Evidence supporting improved neurological recovery following treatment with the synthetic glucocorticosteroid methylprednisolone sodium succinate (MPSS), the standard therapeutic intervention for SCI, has been called into question in recent years. More importantly, this treatment may have potentially deleterious effects on early mortality and morbidity (Short et al. 2000; American Association of Neurological Surgeons 2002).
A number of other pharmacological means of reducing the extent of the injury are in various stages of animal and human evaluation (Blight et al. 2001). One of the most promising candidates is erythropoietin (EPO), a hematopoietic growth factor produced mainly by kidney and fetal liver, which stimulates proliferation and differentiation of erythroid precursor cell (Fisher 2003). However, EPO is also produced in the central nervous system (Sasaki 2003) and mediates neuroprotection against experimental brain injury and ischemia (Sakanaka et al. 1998; Brines et al. 2000; Digicaylioglu et al. 2001; Siren et al. 2001; Sasaki 2003). Notably, a recent clinical trial demonstrated significant improvement in outcome of stroke patients with documented non-hemorrhagic infarcts within the distribution of the middle cerebral artery who were given recombinant human EPO (rhEPO) intravenously within 8 hours of the onset of symptoms (Ehrenreich et al. 2002).

Spinal cord injury shares many pathophysiological features with brain injury and recent studies in animal models indicate that EPO is very effective in attenuating the severity of spinal cord damage (Celik et al. 2002; Gorio et al. 2002; Sekiguchi et al. 2003; Kaptanoglu et al. 2004). This review discusses the results of these studies and the prospects for developing non-hematopoietic EPO-based drugs with an enhanced pharmacological profile for use in the clinic.

2. SPINAL CORD INJURY

Spinal cord injury is the result of damage to the nerves within the spinal canal, disrupting the spinal cord's ability to integrate afferent and efferent information for control of sensory, motor and autonomic functions. Injury commonly occurs during blunt, non-penetrating trauma (for example, as a result of vehicular accidents) whereby the bony and ligamentous components of the spinal column are laterally displaced and impart sudden compression to the spinal cord.

The trauma that occurs at one site within the spinal cord may kill many resident neurons, glia and capillary endothelial cells outright, but the clinical severity of the injury is dictated primarily by the fibers passing through the vicinity of the lesion that become non-functional because of edema and other factors. A cascade of more extensive cell death, thought to be caused by a combination of inflammation, ischemia and apoptosis (Dumont et al. 2001; Carlson et al. 2002; Norenberg et al. 2004), spreads out along the spinal cord away from the lesion epicenter as a function of time (hours to days), similar to a fire spreading outward from its ignition point. The extent of this secondary damage is what largely determines clinical outcome.