Chapter 11

AN ENDOGENOUS PATHWAY PREVENTING AXONAL DEGENERATION MEDIATED BY SCHWANN CELL– DERIVED ERYTHROPOIETIN

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Abstract: Most common peripheral neuropathies are characterized by distal axonal degeneration, rather than neuronal death. The pathways that mediate axonal degeneration and neuronal death are likely to be diverse. In this chapter, we describe a novel, endogenous pathway that prevents axonal degeneration. We show that in response to axonal injury, peri-axonal Schwann cells release erythropoietin (EPO), which via binding to EPO receptors on neurons prevents axonal degeneration. We demonstrate that the relevant axonal injury signal that stimulates EPO production from surrounding glial cells is nitric oxide. In addition, we show that this endogenous pathway can be therapeutically exploited by administering exogenous EPO in vivo and in vitro. Our data suggest that EPO prevents axonal degeneration, and may therefore be therapeutically useful in a wide variety of human neurological diseases characterized by axonopathy.

Key words: axonal degeneration, Schwann cells, neuroprotection, neuropathy, axonopathy

1. INTRODUCTION

Peripheral neuropathies are common and cause significant morbidity. The vast majority of peripheral neuropathies, including diabetic and HIV-associated neuropathy, are ‘dying back’ axonopathies, characterized by degeneration of the most distal portions of axons, with centripetal progression (Sidenius, 1982; Pardo et al., 2001). Although most published in vitro studies of neurotoxicity and neuroprotection in the peripheral nervous system have focused on neuronal apoptosis as the sole outcome measure,
neuronal death, in contrast to distal axonal loss, is not a prominent pathological feature of most human peripheral neuropathies. Furthermore, the signaling pathways mediating axonal degeneration are distinguishable from those mediating neuronal apoptosis (Glass et al., 2002; Raff et al., 2002; Zhai et al., 2003; Ehlers, 2004). Thus, in considering whether a particular ‘neuroprotective’ agent may have therapeutic relevance to human peripheral neuropathies (and to other neurological diseases where axonopathy is prominent), it is important to discover if it robustly prevents axonal degeneration, independent of neuronal death (Coleman and Perry, 2002).

2. EPO NEUROPROTECTION IN THE PNS

The glycoprotein, erythropoietin (EPO), is a very promising neuroprotective agent, whose anti-apoptotic properties have been thoroughly evaluated by several investigators. The administration of EPO prevents central nervous system neurons from death caused by a variety of insults, including hypoxia, hypoglycemia, glutamate toxicity, growth factor deprivation and free radical injury (Digicaylioglu and Lipton, 2001; Siren et al., 2001; Chong et al., 2002; Gorio et al., 2002; Ruscher et al., 2002). Recently, Campana et al also demonstrated that EPO administration prevented apoptosis of DRG sensory neurons (Campana and Myers, 2003). In this chapter, we discuss the ability of EPO to prevent axonal degeneration in the PNS. Furthermore, we demonstrate the evidence for an endogenous ‘axonoprotective’ pathway mediated by EPO production from Schwann cells, the major glial cells of the PNS (Keswani et al., 2004).

2.1 EPO and EPOR expression in DRG neurons and Schwann cells

Immunostaining of dissociated DRG neuron-Schwann cell co-cultures reveal that both neurons and Schwann cells express EPO (Fig. 11-1A), whereas neurons predominantly express EPO-R (Fig. 11-1B). Of interest, as can be seen in Figure 1b, neuronal EPO-R is localized on axons as well as perikarya. A similar pattern of EPO and EPO-R immunostaining is observed in DRG sections harvested from adult rats (Figs. 11-1C and D), EPOR immunostaining again being particularly intense in DRG neurons as compared to Schwann cells.