Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

Research Report

Neurotrophic factors for spinal cord repair: Which, where, how and when to apply, and for what period of time?

Alan R. Harvey, Sarah J. Lovett, Bernadette T. Majda, Jun H. Yoon, Lachlan P.G. Wheeler, Stuart I. Hodgetts*

School of Anatomy, Physiology and Human Biology, The University of Western Australia, 35 Stirling Highway, Crawley, WA 6009, Australia

ARTICLE INFO

Article history:
Accepted 23 October 2014
Available online 1 November 2014

Keywords:
Spinal cord injury
Neurotrophic factors
Brain-derived neurotrophic factor
Neurotrophin-3
Nerve growth factor
Glial cell-derived neurotrophic factor
Fibroblast growth factor
Ciliary neurotrophic factor
Platelet-derived neurotrophic factor
Regeneration
Plasticity
Cell death

ABSTRACT

A variety of neurotrophic factors have been used in attempts to improve morphological and behavioural outcomes after experimental spinal cord injury (SCI). Here we review many of these factors, their cellular targets, and their therapeutic impact on spinal cord repair in different, primarily rodent, models of SCI. A majority of studies report favourable outcomes but results are by no means consistent, thus a major aim of this review is to consider how best to apply neurotrophic factors after SCI to optimize their therapeutic potential. In addition to which factors are chosen, many variables need be considered when delivering trophic support, including where and when to apply a given factor or factors, how such factors are administered, at what dose, and for how long. Overall, the majority of studies have applied neurotrophic support in or close to the spinal cord lesion site, in the acute or sub-acute phase (0–14 days post-injury). Far fewer chronic SCI studies have been undertaken. In addition, comparatively fewer studies have administered neurotrophic factors directly to the cell bodies of injured neurons; yet in other instructive rodent models of CNS injury, for example optic nerve crush or transection, therapies are targeted directly at the injured neurons themselves, the retinal ganglion cells. The mode of delivery of neurotrophic factors is also an important variable, whether delivered by acute injection of recombinant proteins, sub-acute or chronic delivery using osmotic minipumps, cell-mediated delivery, delivery using polymer release vehicles or supporting bridges of some sort, or the use of gene therapy to modify neurons, glial cells or precursor/stem cells. Neurotrophic factors are often used in combination with cell or tissue grafts and/or other pharmacotherapeutic agents. Finally, the dose and time-course of delivery of trophic support should ideally be tailored to suit specific biological requirements, whether they relate to neuronal survival, axonal sparing/sprouting, or the long-distance regeneration of

*Corresponding author.
E-mail address: alan.harvey@uwa.edu.au (A.R. Harvey).

http://dx.doi.org/10.1016/j.brainres.2014.10.049

axons ending in a different mode of growth associated with terminal arborization and renewed synaptogenesis.

This article is part of a Special Issue entitled SI: Spinal cord injury.

1. Introduction

Our intention in this brief update is not to provide an exhaustive list of the neurotrophic factors that have been, or are being, tested in experimental models of spinal cord injury (SCI), nor to detail all of the associated changes in cell viability, tissue repair and behaviour. Much of this information is provided in other detailed reviews and the reader is directed to these for further information (e.g. Arvanian, 2013; Awad et al., 2013; Blesch et al., 2012; Boyce and Mendell, 2014; Bregman et al., 2002; Gerin et al., 2011; Hollis et al., 2009; Lu and Tuszynski, 2008; McCall et al., 2012; Oudega et al., 2012; Smith et al., 2012; Tetzlaff et al., 2011; Weishaupt et al., 2012). Rather, the primary aim of the present review is to consider in a more general sense where, how and when such factors might optimally be delivered in studies aimed at promoting morphological and functional sparing/recovery after SCI. The type of therapeutic intervention and overall mode and timing of neurotrophic delivery may also vary depending on the level and type of SCI, which may involve transection or different intensities of contusion/compression. We will not consider here avulsion injuries of spinal roots.

We will first provide several examples of the types of neurotrophic support that have been used to date. These include some of the neurotrophins and neuropoetic cytokines as well as other growth factors such as glial cell-derived neurotrophic factor (GDNF), the fibroblast growth factors (FGF), and insulin-like growth factors (IGF). A summary of some of these studies is provided in tabular form (see Tables 1–4). We then consider the important issue of where to apply such factors: (i) delivery to the spinal cord lesion site itself, whether rostral, within the lesion or caudal to the injury, (ii) delivery to the location(s) containing the cell bodies of neurons whose axons are affected by the SCI, and/or (iii) application external to the nervous system, usually intrathecally but perhaps also systemically, although the latter may be problematic due to detrimental off-target effects.

In addition, irrespective of placement, the mode of delivery of neurotrophic factors is also an important variable, whether delivered by acute injection of recombinant proteins, sub-acute or chronic delivery using osmotic minipumps, cell-mediated delivery, delivery using polymer release vehicles of some sort, or the use of gene therapy to modify neurons, glial cells or precursor/stem cells. Finally, the "when" relates to the timing of delivery of neurotrophic support in the hours and days after SCI, and in particular how long such support could be given. Can the type of support be altered over time, depending on whether the aim is to promote neuronal survival, axonal sprouting, or the long-distance regeneration of axons which at some point will need to be curtailed in order to allow a different mode of growth involving terminal arborization and the reformation of synaptic connections?

What are the targets for neurotrophic factors after SCI? These vary. To achieve functional improvement these factors would ideally target long-distance descending and ascending projections, involving parent supraspinal or sensory neurons and their respective axons in spinal cord white matter tracts. It may also be important to target spinal neurons involved in segmental or short-range inter-segmental circuits (Boyce and Mendell, 2014). Finally, targeting of glial cells with different types or combinations of neurotrophic factors may reduce the negative effects of inflammation and scarring, and promote other beneficial actions such as reduced demyelination or enhanced remyelination (Plemel et al., 2014) as well as alter the phenotype of glia and other non-neuronal cells that reside within, or outside, the spinal cord. Spatial and temporal changes in the endogenous expression of neurotrophic factors, cytokines, chemokines and their various receptors (e.g. Blesch et al., 1999; Cizkova et al., 2014; Gerin et al., 2011; Hougland et al., 2012; King et al., 2000; Lee et al., 1998; Liebl et al., 2001; Nakamura and Bregman, 2001; Qin et al., 2006; Tripathi and McTigue, 2008; Wong et al., 2010; Zai et al., 2005) in the injured spinal cord, meninges and vasculature should also be taken into consideration when applying extrinsic factors, either alone or in combination with grafted cells or tissues. The experimental procedure may itself alter these expression patterns (e.g. Hawryluk et al., 2012). Most importantly, morphological and behavioural outcomes may reflect the actions of such endogenously released factors, their release potentially triggered by the presence of externally introduced neurotrophic factors, indirectly adding to or perhaps detracting from any primary effect of the exogenous agent.

2. Neurotrophic factors used to treat SCI

A wide-range of growth factors that enhance neuronal survival, alter glia phenotype and/or promote plasticity and axonal regrowth has been tested in animal models of SCI. Different factors can be used for different ascending or descending fibre systems, the choice dependent upon knowledge of receptors expressed by specific cell populations, and known sensitivity to a particular factor. For example, primary sensory neurons that project axons into the spinal cord to terminate in the dorsal horn or ascend in the dorsal white matter columns are comprised of different populations that express different receptors and are thus sensitive to different neurotrophic factors (reviewed in Boyce and Mendell, 2014; Hollis and Tuszynski, 2011). On the other hand some spinal axon populations appear to be responsive to multiple factors (Blesch et al., 2012). Knowledge of how receptor expression in projection neurons and in local neurons and glia within the cord is altered at different times after SCI (Hougland et al., 2012; King et al., 2000; Liebl et al., 2001; Nakamura and