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Pharmacological interventions for spinal cord injury: Where do we stand? How might we step forward?

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ABSTRACT

Despite numerous studies reporting some measures of efficacy in the animal literature, there are currently no effective therapies for the treatment of traumatic spinal cord injuries (SCI) in humans. The purpose of this review is to delineate key pathophysiological processes that contribute to neurological deficits after SCI, as well as to describe examples of pharmacological approaches that are currently being tested in clinical trials, or nearing clinical translation, for the therapeutic management of SCI. In particular, we will describe the mechanistic rationale to promote neuroprotection and/or functional recovery based on theoretical, yet targeted pathological events. Finally, we will consider the clinical relevancy for emerging evidence that pharmacologically targeting mitochondrial dysfunction following injury may hold the greatest potential for increasing tissue sparing and, consequently, the extent of functional recovery following traumatic SCI.

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Contents

1. Introduction

1.1. Spinal cord injury: pathophysiology

The number of Americans in 2009 that are living with the typically devastating neurological deficits secondary to spinal cord injury (SCI) has been estimated to be approximately 262,000 persons (see https://www.nscisc.uab.edu/). After decades of research and clinical trials, however, there is currently no effective pharmacological treatment for acute or chronic SCI; notably targeting recovery of lost sensory–motor function. Traumatic SCI often fractures or dislocates vertebrae that can cause bone fragments or connective tissues to compress nerve fibers and damage the glial cells that insulate the spinal cord axons. Most cases of human SCI result from contusions (bruises) to the cord and not complete severing of the nerve fibers. Accordingly, optimism for promoting some functional recovery exists even in the chronic SCI population because compression or stretch injuries are incomplete due, primarily, to partially spared fiber tracts. Much of the spinal tissue degeneration that occurs following these types of SCI is due to secondary injury processes that are triggered by the primary mechanical trauma (Rabchevsky & Smith, 2001; Hall & Springer, 2004). During the past 25 years, many of the neurochemical and pathophysiological components of secondary injury have been elucidated resulting in the testing of several potential "neuroprotective"

Abbreviations: ALC, acetyl-L-carnitine; ALS, amyotrophic lateral sclerosis; CNS, central nervous system; CsA, cyclosporin A; Cyp-D, cyclophilin D; ETC, electron transport chain; MPSS, methylprednisolone sodium succinate; mPT, mitochondrial permeability transition; mPTP, mitochondrial permeability transition pore; MS, multiple sclerosis; NMDA, N-methyl-D-aspartate; PDHC, pyruvate dehydrogenase complex; ROS, reactive oxygen species; SCI, spinal cord injury; TBI, traumatic brain injury.

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pharmacological strategies that target different aspects of the acute neurodegenerative processes in animal models and clinical trials.

Clinically relevant experimental models of traumatic SCI result in both direct tissue damage and more delayed pathophysiological changes that lead to cell loss, demyelination, and related functional deficits (Stokes & Jakeman, 2002). A number of various factors are associated with the secondary pathology and subsequent delayed tissue loss that have been identified from experimental studies of SCI. These include blood–spinal cord barrier breakdown, disrupted ionic homeostasis, products of lipid peroxidation (oxidative stress), altered neurotransmitter release and receptor function, cellular dysfunction, and inflammatory and immune changes (Gris et al., 2008). Overall, these pathophysiological defects result in the progressive loss of neurons and oligodendroglial cells proximal to the injury site, with ensuing axonal demyelination, reactive astrogliosis and proliferation/activation of microglia. Such cellular alterations stem from excitotoxicity, calcium-mediated secondary injury, fluid–electrolyte imbalances, disturbances in mitochondrial function and apoptosis (Dumont et al., 2001). The dynamic temporal sequence of such pathophysiological processes is highly complex and continually overlapping in the hours, days and weeks following experimental SCI (for a comprehensive review see Donnelly & Popovich, 2008). Moreover, the time courses for many of these events are often biphasic in nature, adding to the complexity that has hindered the establishment of precise therapeutic windows of opportunity for acute and/or delayed treatments.

While early surgical spinal cord decompression/stabilization is often employed to reduce edema and minimize secondary damage, various emerging therapeutic strategies are designed to modulate immune system responses, enhance axonal regeneration or employ stem cell replacement strategies; all with the ultimate goal of preventing and/or restoring lost function following acute and/or chronic SCI (Fehlings & Baptiste, 2005). However, such approaches do not target specifically defined secondary injury processes and are, thus, beyond the scope of this review. For further information, the reader is referred to the following outstanding reviews on these topics for emerging SCI therapies (Fehlings & Louw, 1996; Blight, 2002; Schwab, 2002; Fehlings & Baptiste, 2005; Bradbury & McMahon, 2006; Thuret et al., 2006; Rossignol et al., 2007; Donnelly & Popovich, 2008; Popovich & Longbrake, 2008; Alexander & Popovich, 2009; Ankeny & Popovich, 2009).

The purpose of this review is to provide the reader with 1) a historical perspective of the standard of care in terms of drug intervention, 2) translational issues related to experimental models of SCI, and 3) the rationale and current status of several drugs that are in different stages of clinical development.

2. Retrospective on clinical trials for spinal cord injury

2.1. Historical standard of care for spinal cord injury

Despite various experimental approaches to promote neuroprotection following SCI (Onose et al., 2009), the only compound reported to show modest beneficial effects following acute SCI in human clinical trials is methylprednisolone (Bracken et al., 1997), and until the past decade, the standard therapeutic clinical intervention following acute SCI was the systemic (i.v.) administration of the synthetic glucocorticoid methylprednisolone sodium succinate (MPSS) within the first hours after injury and continuing for 24 h. This therapy is based on reported improvements in behavioral recovery in humans and laboratory animals (Young et al., 1988; Bracken et al., 1992; Geisler, 1993; Young, 1993; Behrmann et al., 1994; Farooque et al., 1994; Bracken et al., 1997). The mechanisms by which MPSS exerts its reported actions are not fully understood (Taoka et al., 2001), but reductions in lipid peroxidation (Hall & Braughler, 1982; Braughler & Hall, 1992; Hall, 1992;1993; Diaz-Ruiz et al., 2000) and inflammatory cytokine production (Xu et al., 1998) are thought to play major roles (Hall & Springer, 2004). In addition, macrophage infiltration is significantly attenuated by MPSS in the acute phases of injury (Bartholdi & Schwab, 1995; Oudega et al., 1999; Mabon et al., 2000).

However, reducing these early pathophysiological events with MPSS in rat models of SCI has not translated into significant functional recovery or tissue sparing (Chikawa et al., 2001; Rabchevsky et al., 2002). Other reports on the effects of MPSS, both clinical and experimental, range from no noticeable change to moderate improvements compared to controls. Such experimental disparity likely depends on either the species or SCI models employed, the dosage regimen, the outcome parameters investigated or the time of intervention post injury (Fernandez et al., 1991; Amar & Levy, 1999). Nevertheless, the lack of retrospective evidence for improved neurological recovery in clinical cases, along with its deleterious effects on early mortality and morbidity, has led to scrutiny and reevaluation of high dose MPSS as the standard therapy for acute SCI by which other potential clinical remedies are measured (Hurlbert, 2000; Short et al., 2000). Currently, the clinical usage of MPSS across the United Sates is not mandated and, because it is FDA approved but not indicated in acute SCI, its routine use is at the discretion of the medical provider.

2.2. Clinically meaningful models of spinal cord injury

Such a broad recant of a therapeutic drug that was reported to be beneficial for both motor and sensory dysfunction after acute SCI, in what was deemed as a successful clinical trial (Bracken, 1990; Bracken et al., 1990; Bracken et al., 1992; Bracken et al., 1997), leaves both the medical research and SCI communities questioning why anti-oxidant therapies have such a solid foundation experimentally, yet do not translate into clinical efficacy. One of the major confounding factors may be that many of the various experimental models of SCI are not clinically meaningful in the context of method of trauma and/or behavioral outcome measures (Grill, 2005; Onifer et al., 2007; Choo et al., 2009). Germane to this point is that while the vast majority of experimental SCI studies have focused on restoring lost locomotion and/or sensory functions, it is reported that alleviating autonomic dysfunction (bowel, bladder, autonomic dysreflexia) is of higher priority than even restoration of walking when both quadriplegics and paraplegics were surveyed (Anderson, 2004). This has manifested into a recent documentation of the under-appreciated impact of SCI on clinical autonomic function, with delineation of the effects on cardiovascular, pulmonary, pseudomotor, bladder, bowel and sexual functions (Alexander et al., 2009). In retrospect, therefore, many of the past clinical trials for SCI may have, indeed, preserved and/or modulated critical autonomic functions that were not monitored systematically and, therefore, not considered to be efficacious therapies.

2.3. Guidelines for spinal cord injury clinical trials

Based on the paucity of clinical translation or replication studies among SCI laboratories, NIH–NINDS contracts were recently established to fund selected Facilities of Research Excellence in Spinal Cord Injury (FORE-SCI) to address key factors that have hampered the translation of potential novel therapeutic strategies from the laboratory to clinical trials (see http://www.ninds.nih.gov/funding/areas/repair_and_plasticity/fore_sci.htm). This has led to published studies designed to re-assess the reported benefits of experimental SCI therapeutics; none of which supported efficacy of certain neuroprotective and/or pro-regenerative approaches (Steward et al., 2006; Pinzon et al., 2008a; 2008b; Steward et al., 2008). In addition, important steps have been taken throughout Europe and the western hemisphere to implement stronger study designs in all SCI clinical trials. Notably, through support of the ICCP (International Campaign for Cures for spinal cord injury

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