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Recent Advances in the Pharmacologic Treatment of Spinal Cord Injury

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Introduction

The first known documented case of SCI has been dated to 2500 years BCE. During that era, SCI was considered “an ailment not to be treated” (Donovan 2007). Tremendous advances have been made in the field since this ancient beginning; however, a panacea for spinal cord injury remains elusive. Extensive bench research has led to a better understanding of the pathophysiology of SCI, thereby uncovering potential therapeutic targets. Novel therapeutics showing promise in preclinical models of SCI have been translated into clinical trials. In addition to advancements in the pharmacological treatment of spinal cord injury there is now a growing field of non-pharmacological interventions such as: stem cell transplantation, gene therapy, RNAi, electrical stimulation, etc. However, these topics will not be reviewed herein. This review will provide a brief historical overview, followed by a summary of the mechanisms and pharmacological therapeutics studied over the past decade; therein a particular emphasis is placed on mechanistic studies highlighting neuroprotection and regeneration of the spinal cord.

Historical Overview

The concept that SCI was an “ailment not to be treated” reflects the long-lasting belief that the catastrophic nature of the injury and lack of regenerative capacity of the spinal cord made the injury medically futile to treat. Over the course of the last 4,000+ years, treatment for spinal cord injury was centered on surgical interventions to stabilize and decompress the spine (Donovan 2007). Only in the second half of the 20th century did scientists begin using pharmacologic interventions.

The first randomized clinical trial investigating a pharmaceutical agent in SCI was initiated in 1979 when the National Acute Spinal Cord Injury Study I (NASCIS) investigated the efficacy of the synthetic glucocorticoid steroid methylprednisolone (a derivative of prednisone, FDA approved 1955) in SCI (Bracken 1992). Glucocorticoid steroids are potent anti-inflammatory and immunosuppressant drugs, and in the first known publication investigating steroids in spinal cord injury, researchers found that treatment with a high dose of glucocorticoid steroid (dexamethasone) significantly improved the functional recovery in a dog model of SCI (Ducker and Hamit 1969). These preclinical findings, along with findings from many additional studies, were translated into this seminal clinical trial in 1979. NASCIS I was followed by two subsequent studies, NASCIS II and NASCIS III, both investigating doses and timing of methylprednisolone treatment after SCI (Bracken et al. 1984; Bracken et al. 1990; Bracken et al. 1997). The reported findings of these trials have led to wide off-label use of methylprednisolone in acute SCI. However, these studies have fallen under intense scrutiny and have not resulted in FDA approval of methylprednisolone treatment in acute SCI.

The largest randomized clinical trial ever conducted in SCI investigated the efficacy of monosialotetrahexosylganglioside sodium (GM-1), proprietary name Sygen. GM-1 is a ganglioside (complex glycolipid predominant in plasma membrane) that through unknown mechanisms can elicit neuroprotective effects in SCI by promoting neural outgrowth, repair and regeneration (Geisler et al. 1991). As with the NASCIS trials, there is controversy over the potential effectiveness of this therapeutic. The GM-1 study failed to report statistically significant efficacy in a clinical setting (Geisler et al. 2001). Due to lack of efficacy, the current guidelines published by the American Association of Neurological Surgeons (2013), do not recommend treatment with either corticosteroids or GM-1 ganglioside.

While progress certainly has been made through clinical trials over the last 30 years, the need for effective pharmacological intervention in acute SCI remains. The drug that has been most extensively clinically evaluated, methylprednisolone, functions primarily as an immunosuppressant and anti-inflammatory in the setting of acute ACI. Since these early days of SCI research and clinical testing, it is now accepted that inflammation is only one of many pathophysiological mechanisms in SCI. Through the use of animal models, it has been demonstrated that SCI is marked by a primary injury, that results from the mechanical trauma, followed by a more insidious phase referred to as secondary injury (Tator and Fehlings 1991). The secondary injury cascade begins within seconds of the primary injury and results in further tissue damage, cell death, inflammation, Wallerian degeneration and glial scarring. Considerable progress has been made to unravel the complex molecular signals that drive secondary injury. These mechanisms, along with their cognate therapeutic approaches, will be discussed in the following three broad categories: acute, intermediate, and chronic mechanisms of secondary injury.

I. Acute Mechanisms

Hypoxia & Ischemia—One of the first pathophysiological changes to occur immediately following a traumatic SCI is disruption of blood flow with resultant hypoxia to the injured tissue. The mechanical trauma results in disruption of cell membrane, vasospasm,

hemorrhage, and loss of microvasculature necessary to supply spinal cord tissue with oxygen and other vital nutrients. The loss of both oxygen and nutrients to the spinal cord immediately following injury triggers the subsequent secondary injury with influx of Ca⁺, calpain and caspase activation, glutamate excitotoxicity, and inflammation. Hypoxia, therefore, contributes to the expansion of the primary lesion (Tator and Fehlings 1991; Tator and Koyanagi 1997). Pharmacological agents that have the capacity to restore oxygen and nutrients to the damaged region of the spinal cord have been an area of research interest. One such compound that has been studied is Oxycyte (a new generation perfluorocarbon), an oxygen carrier that can be intravenously injected to increase oxygen availability in damaged tissue. Oxycyte treatment in a rat model of moderate-severe contusion spinal cord injury significantly increased oxygen saturation and reduced apoptotic cell death with better tissue and myelin preservation, respectively (Yacoub et al. 2013; Schroeder et al. 2008). Additionally, it has been shown in a swine model of decompression sickness Oxycyte treatment reduced spinal cord lesion size (Mahon et al. 2013). Oxycyte may be suitable as an adjunctive therapy in the treatment of SCI; Oxycyte treatment ideally should begin at the earliest possible time point following an acute injury to lessen the detrimental cascade triggered by hypoxia.

The mechanical trauma from the initial injury will cause massive disruption in both macro and micro vasculature that will disrupt blood flow to the spinal cord and result in ischemia. Numerous studies have reported that Ischemia contributes to the subsequent neuronal degeneration and loss of motor function in SCI (Anthes et al. 1995; Muradov and Hagg 2013; Tator and Koyanagi 1997). Ischemia, unlike SCI, can be studied as a single entity to provide some enlightenment about the contribution it plays in the complex network of mechanisms driving secondary injury. Researchers have attempted to determine what role ischemia plays in SCI using a model of focal ischemia in the spinal cord to investigate effects on axonal degeneration. Focal ischemia alone has been reported to cause both loss of sensory axons and death of oligodendrocytes (Muradov et al. 2013); these findings suggest that restoration of blood flow should be of utmost importance in the treatment of SCI.

In addition to triggering cell death, Ischemic injury also activates microglia, the resident macrophages of the CNS. Inhibition of microglial activation has been shown to elicit neuroprotective effects (Cho et al. 2011). Activation of the toll-like receptor 4 on microglia may be a potential mechanism for microglial activation in the setting of ischemic injury (rodent aortic occlusion model) (Bell et al. 2013). As research continues to further elucidate the exact signaling mechanisms of ischemia that trigger the activation of microglia, additional pharmacological targets may be identified. Activated microglia are primary drivers of both innate and adaptive immune response through the release of proinflammatory cytokines and chemokines (Schomberg and Olson 2012) and will be discussed in more detail in the inflammation section of this review.

Excitotoxicity—Excitotoxicity is a pathological state in which high levels of the excitatory neurotransmitter glutamate results in toxicity or death to neurons (Doble 1999). Immediately following spinal cord injury, the levels of glutamate can rise to excitotoxic threshold levels (Liu et al. 1991). Glutamate binds one of three receptors, N-Methyl D-Aspartate (NMDA), Alpha-amino-3-hydroxy-5-methylisoxazolepropionate (AMPA) or Kainate; the binding of

glutamate will modulate Ca^{+} influx into the cell thereby regulating Ca^{+} homeostasis and downstream signaling cascades (Mehta et al. 2013). Given the potential critical role the NMDA receptor plays in mediating Ca^{+} influx, it has been an attractive pharmacological target for many years now. The NMDA receptor antagonist, MK-801, was reported to attenuate numerous inflammatory markers in a mouse model of SCI (Esposito et al. 2011). Although MK-801 cannot be used in SCI patients due to toxicity, an opportunity exists for the development of a safe NMDA receptor antagonist. Riluzole (a sodium channel blocker / glutamate receptor modulator), a drug approved for the treatment of amyotrophic lateral sclerosis, has been shown in a preclinical rodent study to act as a neuroprotectant through modulation of excitotoxicity (Wu et al. 2013; Schwartz and Fehlings 2001; Springer et al. 1997). A phase I safety trial of Riluzole in acute cervical spinal cord injury patients reported a rate of complication with drug use similar to that of matched patients, as well as an enhanced improvement in motor score with drug-treated patients compared to matched patients (Grossman et al. 2013). Follow-up placebo controlled trials evaluating Riluzole in SCI patients are anticipated.

Downstream effectors of excitotoxicity, such as the activation of intracellular proteases, provide additional targets for therapeutic intervention. Calpain, a Ca^{+} activated cysteine protease, has emerged as a potential target in SCI. The role of calpain in spinal cord tissue degeneration has been discussed in the scientific literature for over 30 years (Banik et al. 1980; Banik et al. 1982). Mechanistically, the role of calpain in spinal cord tissue degeneration has been further elucidated over the past 10 years. Studies have shown that apoptosis following SCI requires *de novo* protein synthesis and can be blocked with a pharmacological inhibitor of calpain (Ray et al. 2001; Ray et al. 2003). Rodent studies have shown an improvement in both tissue and motor function recovery after treatment with various synthetic calpain inhibitors (Akdemir et al. 2008; Yu et al. 2008; Sribnick et al. 2007; Arataki et al. 2005). Calpain inhibition by the endogenous inhibitor, calpastatin, has also been shown to be involved in Wallerian degeneration in an optic nerve transection model (Ma et al. 2013). These findings suggest that both early and prolonged inhibition of calpain may provide protection against both apoptosis and Wallerian degeneration. Over the years, a number of calpain inhibitors have been reported (leupeptin, calpeptin, E64D) (Momeni and Kanje 2006; Ray et al. 1999; Tsubokawa et al. 2006); however, difficulties with drug safety and solubility have precluded advancement of these compounds into the clinic. Currently, researchers have an intense interest in the development of a targeted safe therapeutic to inhibit pathological calpain activation.

Melatonin, a naturally occurring hormone, has also been reported to show beneficial effects in SCI potentially through mechanisms modulating calpain activation (Samantaray et al. 2008). Numerous rodent models of SCI have shown increased neuroprotection with melatonin treatment (Schiaveto-de-Souza et al. 2013; Park et al. 2012; Park et al. 2010; Esposito et al. 2009; Fujimoto et al. 2000). Melatonin is a pleiotropic agent, and thus may exert neuroprotective effects through its anti-oxidant, anti-nitrosative, and immunomodulatory mechanisms (Samantaray et al. 2009). The abundance of preclinical studies reporting neuroprotection with melatonin treatment as well as melatonin's high

safety profile make melatonin a potential candidate for clinical trial investigation as either a stand-alone agent or as an adjunctive therapeutic in acute SCI treatment.

II. Intermediate Mechanisms

Inflammation—The acute mechanisms of hypoxia, ischemia and excitotoxicity give rise to an inflammatory response that contributes to the expansion of the secondary injury. In rodent models, activation of resident astrocytes and microglia can be seen as early as 2 hours following injury and persist up to 6 months (Gwak et al. 2012). Human studies have shown that the first peripheral immune cell to enter the spinal cord lesion site is the neutrophil, which arrives as early as 4 hours post injury; activated microglia were found at 1 day post injury, and macrophages were seen by day 5 (Fleming et al. 2006). In animal models, blockade of neutrophils has been found to decrease markers of inflammation following SCI (Gris et al. 2004; Chatzipanteli et al. 2000). These findings suggest that, mechanistically, neutrophils may contribute to the inflammation seen post SCI.

Significant advances in the understanding of the complex role of macrophages in SCI have revealed macrophages play dual roles as both pro-and anti-inflammatory mediators. Results of rodent studies indicate that altering the ratio of M1/M2 macrophages in favor of the anti-inflammatory M2 may promote regenerative growth (Kigerl et al. 2009; Busch et al. 2011). The complexity of macrophage signaling and therapeutic potential are beyond the scope of the current review; however, signaling is detailed in two recent review articles (David and Kroner 2011; Ren and Young 2013). While modulating the types of cells present in the setting of acute neurotrauma may represent an avenue for therapeutic intervention, another important approach is regulation of cell signaling.

Inflammation in the central nervous system is thought to be regulated by the nuclear transcription factor, nuclear factor kappa β (NF- κ B). Blockade of NF- κ B, thereby, may be a therapeutic approach for decreasing inflammation. A transgenic mouse model of SCI, where NF- κ B is selectively inhibited in astrocytes, has been reported to show decreased inflammation as well as increased axonal sprouting (Brambilla et al. 2005; Brambilla et al. 2009). Regulation of inflammation via modulation of gene transcription has also been tested with Thiazolidinediones (TZDs), synthetic agonists of the ligandactivated transcription factor peroxisome proliferator-activated receptor-gamma (PPAR γ). One such TZD, pioglitazone, has been tested in a rat model of SCI as a potential neuroprotectant. Authors reported a significant decrease in inflammatory gene expression with enhanced motor function recovery in a rat SCI model were only seen when drug treatment began within 2 hours of injury induction (Park et al. 2007). These findings highlight the critical role early inflammation may play in SCI.

Apoptosis—Loss of cells in the spinal cord following injury may be attributable to both apoptosis and necrosis. Necrosis, caused by mechanical tissue damage, is considered irreversible. In contrast, apoptosis is regulated through cell signaling and may be triggered by a variety of external or internal stimuli, thereby becoming an attractive candidate for pharmacological modulation. Cellular stressors triggering release of pro-apoptotic signaling molecules from the mitochondria and activation of death receptors are the two broad

independent pathways through which apoptosis is triggered (Green 1998). The last 10 years of research into mechanisms of apoptosis specific to SCI have yielded many promising therapeutic targets. One potential modulator of apoptosis in SCI is cell cycle activation. The cell cycle inhibitor, flavopiridol, was shown to reduce both neuronal and oligodendrocyte apoptosis in a rat model of severe SCI (Byrnes et al. 2007). Another potential modulator is Phospholipase A2 (PLA2); a lipolytic enzyme thought to contribute to neurodegeneration in secondary injury, which has recently been implicated in the pathogenesis of SCI through its ability to induce neuronal death when injected into normal spinal cord tissue (Liu et al. 2006). An animal study has shown that PLA2 is upregulated following injury *in vivo* and blockade of PLA2 *in vitro* protects against oligodendrocyte cell death (Titsworth et al. 2009).

An additional promising anti-apoptotic therapeutic is the antibiotic Minocycline, which has been shown in numerous animal models to decrease apoptosis (Sonmez et al. 2013; Watanabe et al. 2012; Takeda et al. 2011; Stirling et al. 2004). Treatment with Minocycline has also shown functional improvement in a number of preclinical models (Wells et al. 2003; Teng et al. 2004). Based on these preclinical studies, Minocycline was evaluated for safety in a placebo controlled phase II clinical trial in acute SCI patients. Authors report that the drug regimen was safe and well tolerated and suggested improved motor function in patients with cervical injuries (Casha et al. 2012). The positive results of the minocycline phase II clinical trial warrant further investigation of drug efficacy in a phase III multi-center placebo controlled trial.

Fast-tracking a drug (with prior FDA approval for an alternate indication) is a potentially promising strategy for rapid translation into the treatment of acute SCI. This approach is currently being applied to the development of estrogen as a potential therapeutic in SCI. The naturally occurring steroid hormone estrogen has emerged as a potential therapeutic in the treatment of SCI. Clinically estrogen is delivered via the drug Premarin (cocktail of equine conjugated estrogens) and has been used in hormone replacement therapy since 1942. Estrogen is highly pleiotropic, and may serve as a neuroprotectant in part due to its action as an anti-apoptotic along with its actions as an anti-inflammatory, antioxidant, and as a promoter of angiogenesis. Numerous studies conducted in a rat SCI model have shown a reduction in apoptosis and/or improved locomotor function recovery with estrogen (or Premarin) treatment (Siriphorn et al. 2012; Samantaray et al. 2011; Sribnick et al. 2010; Chen et al. 2010). A recent study reported that estrogen treatment protected against oligodendrocyte cell death mediated via the RhoA-JNK3 pathway in a rat model of SCI (Lee et al. 2012). Preservation of oligodendrocytes is key to preventing the Wallerian degeneration seen in the secondary injury phase of SCI. Estrogen may also be exerting neuroprotective effects by modulating excitotoxicity. More specifically, estrogen was reported to upregulate expression of the glutamate transporter 1 (glial specific glutamate transporter) along with the Kir4.1 channel (inwardly rectifying potassium channel) expression in a rat SCI model (Olsen et al. 2010). Since estrogen binds to its cognate receptor and, thus, can regulate expression of 137 genes, estrogen may be simultaneously driving neuroprotection through numerous mechanisms (Lin et al. 2004). Given the highly pleiotropic nature of estrogen and the robust preclinical findings, estrogen is a promising

candidate for continued development as a therapeutic in SCI. Estrogen therapy, in the form of Premarin, has been clinically evaluated in a small safety trial of 5 patients with ASIA A or B grade injuries (Varma, et al. Medical University of South Carolina, results pending publication). However, estrogen treatment poses significant safety concerns, as it is known to be a prothrombotic agent. Recently, a study using a low dose of estrogen, 1 µg/kg, reported neuroprotective effects (Samantaray et al. 2011), suggesting potential for clinical translation at a safer dose. Another potential answer to this problem is the use of estrogen receptor modulators such as Genistein. Genistein, an estrogen receptor beta agonist, has been shown in *in vitro* models of neurotoxicity to elicit protective effects (McDowell et al. 2011). *In vivo* studies with estrogen receptor agonists are needed, as this approach may alleviate safety concerns while maintaining the multiple neuroprotective effects seen with estrogen treatment. Pharmacological approaches, such as Minocycline and estrogen treatment, are not the only area of research into preservation of spinal cord tissue. Additional work is being conducted to evaluate a centuries old approach to injury recovery, ice.

Hypothermia (both epidural and systemic) has been found to decrease apoptosis in a rat model of SCI (Ok et al. 2012). Two clinical trials investigating the safety and potential benefit of modest hypothermia in acute cervical spinal cord injury reported promising results for both safety and potential neuroprotection (Levi et al. 2010; Dididze et al. 2013). As hypothermia treatment is posited to potentially provide an early adjunctive therapeutic in the treatment of SCI, additional clinical studies investigating hypothermia are warranted.

III. Chronic Mechanisms

Epigenetic Alterations—Over the last 10 years, the field of epigenetics has expanded to include research into the mechanisms that may limit the central nervous system's ability to regenerate. More specifically, researchers have speculated that the mature chromatin status of the cells comprising the spinal cord may be blocking these cells from reactivating the developmental programs necessary to successfully rebuild the damaged tissue (York et al. 2013). DNA methylation, chromatin structure, and histone acetylation status are the broad categories of epigenetic modifications that drive changes in gene expression. Histones, the spool like proteins that DNA winds around to achieve the highly condensed state in chromatin, can be modified through acetylation. The acetylation status of a histone will then drive gene silencing or transcription. Valproic acid (VPA), a histone deacetylase (HDAC) inhibitor, has been found to reduce gliosis and increase production of both brain and glial-derived neurotrophic factors in a rodent model of SCI (Abdanipour et al. 2012). Another study in rodent SCI has reported that treatment with VPA can decrease gliosis and improve functional outcomes in open-field behavioral assays (Lu et al. 2013). The field of epigenetic regulation in both spinal cord injury and, more broadly, in neuroregeneration is arguably still in its infancy. A tremendous promise exists in the approach of selectively regulating gene expression to simultaneously decrease degenerative processes and increase regenerative processes that will ultimately drive restoration of damaged nervous tissue. Hopefully, as this field matures an emergence of new therapeutics will provide the tools necessary to achieve these goals.

Blockade of Myelin Inhibitors—Regeneration of axons following injury is inhibited by a number of molecules, such as NoGo, myelin associated glycoprotein (MAG), and oligodendrocyte myelin glycoprotein (OMgP) (Hunt et al. 2002). The existence of these inhibitors and their ability to block regeneration have been known since the late 1980s (Schwab et al. 1993). Early publications in the field of axon regeneration have shown that blockade of NoGo with the IN-1 antibody promoted regrowth after injury in animal models (Brosamle et al. 2000; Schnell and Schwab 1990). The exact contribution of these molecules to successful axon regeneration *in vivo*, however, is not yet clearly defined, as a recent publication investigating the role of these three inhibitors demonstrates. The authors of this publication demonstrate using mutant transgenic mouse models that blockade of all three myelin inhibitors (NoGo, MAG and OMgP) compared to blockade of any single inhibitor failed to show additive effects (Lee et al. 2010). These authors state that while “MAG, Nogo, and OMgp may modulate axon sprouting, they do not play a central role in CNS axon regeneration failure” (Lee et al. 2010). Regardless of the exact role each of these inhibitors may play in spinal cord regeneration, the wealth of positive preclinical findings with pharmacological blockade has resulted in two agents moving into clinical evaluation. The two agents, ATI-355 (humanized anti-Nogo antibody, Novartis) and Cethrin (recombinant protein RHO GTPase antagonist, BioAxone BioSciences) are being clinically evaluated for their potential to modulate axon regeneration in SCI. Results from the ATI-355 trials have not yet been released, although the trial was registered as complete in November, 2013. Results from the phase I/IIa clinical trial reported Cethrin to be safe and tolerable in acute SCI patients, and also suggested that Cethrin enhanced motor function recovery (Fehlings et al. 2011). Cethrin works by inhibiting the RHO pathway, the final common signaling pathway of the myelin inhibitors. To date, Cethrin is the only drug to attain orphan drug status from the FDA (2005) in the treatment of acute cervical and thoracic spinal injuries. The next step in the development path of Cethrin will be a placebo-controlled efficacy trial.

Myelin Regeneration & Scar Remodeling—Progesterone, a naturally occurring steroid hormone, has emerged as a potential therapeutic in SCI through findings that suggest it may serve as both a neuroprotectant and promyelinating agent. Results of a study conducted in a rat SCI model indicated that treatment with progesterone resulted in sparing of white matter tissue with concomitant improvement in motor function (Thomas et al. 1999). A mechanistic study examining the effects of progesterone in a rat model of SCI reported that progesterone treatment restored myelin levels and increased the density of oligodendrocyte progenitor cells, potentially responsible for remyelination (De Nicola et al. 2006). An additional study reported that progesterone may be working by suppressing gliosis at the early stage of SCI while promoting oligodendrocyte differentiation and remyelination at the later stages (Labombarda et al. 2011).

Glial scarring and wound cavitation are thought to be major inhibitors of spinal cord regeneration. Recently, a pan Tgfb 1/2 antagonist, Decorin, was shown to decrease wound cavitation and scar tissue mass through suppression of inflammatory fibrosis (Ahmed et al. 2013). The authors of this study also reported that Decorin treatment has potential for dissolution of mature scars through induction of matrix metalloproteinases with subsequent axonal regeneration. The concept that existing scar tissue may be remodeled to drive

regeneration is an exciting one, as it would potentially offer a treatment option to patients chronically living with paralysis due to SCI.

Conclusions

The complex pathophysiological mechanisms driving secondary injury and regenerative capacity of the spinal cord are beginning to be unraveled. For a field that has suffered from a dearth of clinical trials, SCI research has greatly expanded over the last 10 years, evaluating a number of potential treatments: hypothermia, Riluzole, Cethrin, Premarin, ATI-355, and Minocycline to name some. As this review highlights, SCI involves a sequence of pathophysiological changes that can be manipulated to minimize secondary injury and promote regeneration. In addition to the review presented here there are many other earlier reviews that pay particular attention to both translation and clinical studies advancing the field of SCI (Tsai and Tator 2005; Kwon et al. 2010; Hawryluk et al. 2008). As the field advances, combination therapeutic strategies utilizing agents aimed at multiple pathological processes occurring in acute, intermediate and chronic stages of SCI may be developed. A rational, timed, combination drug treatment approach may thus prove successful in treating SCI patients and, with that hope, SCI will no longer be an “ailment not to be treated.”

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