CURRENT DEVELOPMENTS IN SPINAL CORD INJURY RESEARCH

by

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Review Article

Current developments in spinal cord injury research

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Abstract

Background context: Recent advances in neuroscience have opened the door for hope toward prevention and cure of the devastating effects of spinal cord injury (SCI).

Purpose: To highlight the current understanding of traumatic SCI mechanisms, provide information regarding state-of-the-art care for the acute spinal cord–injured patient, and explore future treatments aimed at neural preservation and reconstruction.

Study design/setting: A selective overview of the literature pertaining to the neuropathophysiology of traumatic SCI is provided with an emphasis on pharmacotherapies and posttraumatic experimental strategies aimed at improved neuropreservation and late neuroregenerative repair.

Methods: One hundred fifty-four peer-reviewed basic science and clinical articles pertaining to SCI were reviewed. Articles cited were chosen based on the relative merits and contribution to the current understanding of SCI neuropathophysiology, neuroregeneration, and clinical SCI treatment patterns.

Results: A better understanding of the pathophysiology and early treatment for the spinal cord–injured patient has led to a continued decrease in mortality, decreased acute hospitalization and complication rates, and more rapid rehabilitation and re-entry into society. Progressive neural injury results from a combination of secondary injury mechanisms, including ischemia, biochemical alterations, apoptosis, excitotoxicity, calpain proteases, neurotransmitter accumulation, lipid peroxidation/free radical injury, and inflammatory responses. Experimental studies suggest that the final posttraumatic neurologic deficit is not only a result of the initial impaction forces but rather a combination of these forces and secondary time-dependent events that follow shortly after the initial impact.

Conclusions: Experimental studies continue to provide a better understanding of the complex interaction of pathophysiologic events after traumatic SCI. Future approaches will involve strategies aimed at blocking the multiple mechanisms of progressive central nervous system injury and promoting neuroregeneration.

Keywords: Spinal cord injury; Somatosensory evoked potential recovery; Spinal cord decompression; Primary injury; Secondary injury

Introduction

Acute traumatic spinal cord injury (SCI) represents one the most devastating injuries to afflict the human body. The injury has a high rate of prevalence in the younger population, creating physical, emotional, and economic burdens on both the individual and society. Approximately 10,000 new cases of acute paralysis are documented per year in the United States. Societal costs are estimated at 10 billion dollars per year [137]. The epidemiology of spinal cord injury is in general a young male's disease, occurring most frequently in persons between 16 and 30 years of age. Recent injury demographics demonstrate a trend toward increasing average age at the time of injury and violence-related injuries [113]. Complete injuries are more common among younger individuals and men than older adults and women [113,17, 58,74] (Fig. 1).

Improvements in mortality and life expectancy have been achieved in the past two decades by instituting nationally funded Model Systems Spinal Cord Injury Care Centers [50]. A better understanding of early treatment of the spinal cord–injured patient has led to a continued decrease in the

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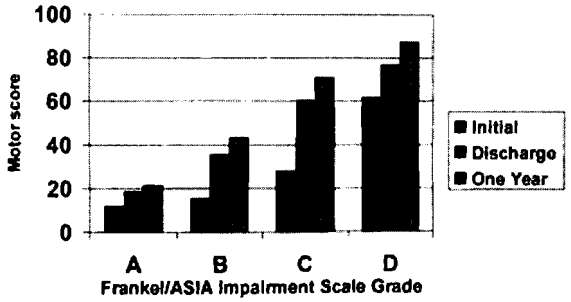

Fig. 1. Motor scores for tetraplegia. (Reprinted with permission from *Archives of Physical Medicine and Rehabilitation*, W.B. Saunders Company.)

risk of death after the first year after injury. Modern neuroscience techniques have led to a better understanding in the neuropathophysiology of permanent neural injuries. Investigators have recognized the importance of both primary (passive) and secondary (active) events causing progressive loss of neural tissue. With breakthroughs in the molecular understanding of neural injury and possible repair, new promising strategies for neural preservation and regeneration are on the horizon. Early surgical intervention once thought hazardous to central nervous tissue has been shown to decrease acute hospital length of stay and complication rates, facilitating more aggressive early rehabilitation and re-entry of the patient into society.

Recent neuroscience advances have opened the door for hope toward prevention and cure of the devastating effects of spinal cord injury. The objective of this article is to highlight the current understanding of spinal cord injury mechanisms and provide information regarding future treatments. The following will describe the interaction between primary and secondary injury mechanisms after blunt spinal cord trauma. The pathophysiology of cord injury will be related to the biomechanics of cord contusion and sustained compression. Clinical and experimental studies will be reviewed to provide a basis for initial injury evaluation and treatment. Current pharmacotherapeutic intervention will be reviewed with an eye toward future breakthroughs. Finally, promising experimental therapies for spinal neuroregeneration will be discussed in light of modern neuromolecular breakthroughs.

Pathophysiology

Primary and secondary injury

There is a growing body of evidence that the pathophysiology of acute spinal cord injury involves primary and secondary mechanisms of injury [150]. The primary injury usually involves blunt cord compression resulting from dislocation of spinal vertebral motion segments or displaced bone fragments. The vast majority of cord injuries do not involve complete cord transection [33]. The nature of the primary insult varies from initial dynamic cord contusion to longer-term sustained cord compression. Morphologic characteristics and clinical outcomes vary with the force of spinal cord compression, duration of compression, displacement of cord, acceleration of impacting forces, and kinetic energy absorbed at the time of spinal cord impact [130,131] (Fig. 2, left).The theory of secondary injury was first postulated in 1911 by Allen when he noted that myelotomy and removal of the posttraumatic hematomyelia resulted in improvement of neurologic function in dogs subjected to experimental acute spinal cord injury. Allen theorized that there was a "biochemical factor," a noxious agent, present in the hemorrhagic necrotic tissue that caused further damage to the spinal cord. Modern neuroscience has shed light on these complex interrelated processes of biochemical and molecular events within the neuronal cells and supporting tissue of the spinal cord that lead to progressive cellular death after blunt trauma (Fig. 2, right).

A number of experimental models have been developed to simulate acute clinical spinal cord compression. The first technique, described by Allen in 1911, involved a weight decrease in dogs. This model has evolved through numerous modifications and is still the most widely used today [7]. Other injury models reflect either a dynamic contusion or a sustained compression, such as a small vascular clip or static application of weights to the surface of the spinal cord. More recent models have employed controlled contusion techniques that allow precise control over biomechanics and injury severity resulting in consistent populations of animals for comparison [7,30,91]. These studies have demonstrated that spinal cord tissue responds to load application in a predictable manner that can be mathematically modeled under precise loading conditions [7,38,130]. The probability of neurologic recovery after cord contusion can now be reliably computed based on displacement force and acceleration [7].

In order to better model the interaction between dynamic spinal cord compression and residual cord displacement, the authors have developed a consistent dynamic and sustained compression spinal cord injury model. Using micropressure transducers, it has been demonstrated that although spinal cord interface pressures decreased to only 13% of maximum loading pressures within the first 30 minutes after dynamic loading, no measurable recovery of electrophysiologic function or long-term motor recovery occurred without spinal cord decompression. This suggests that although pressure gradients relax to baseline levels after dynamic cord compression, residual spinal cord displacement is a significant factor in the propagation of secondary injury mechanisms [37,38] (Fig. 3).

Neuropathology

After acute contusion, the spinal cord undergoes a sequential progression of pathologic changes, including hemorrhage, edema, neuronal necrosis, axonal fragmentation, demyelination, and eventually cyst formation [9,10]. Studies using electron microscopy have demonstrated erythrocyte distension of the venules of the gray matter within the first 5 minutes after injury [53]. This is followed by small hemorrhages within the perivascular spaces and some axonal changes, 15 to 30 minutes after

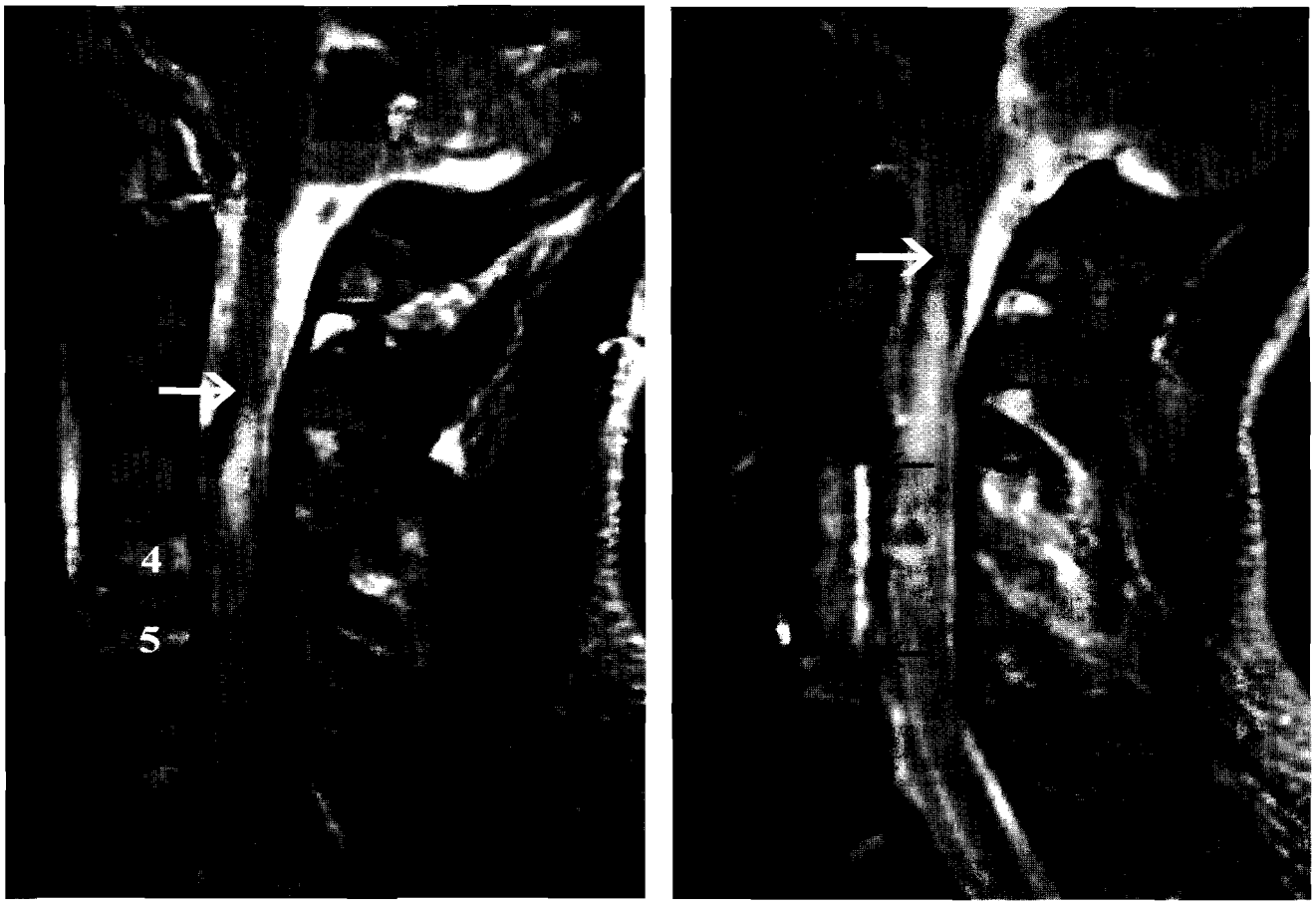

Fig. 2. Magnetic resonance images (MRIs) of a 21-year-old man with cervical trauma. The patient presented with mild diffuse tetraparesis below C4–5 dermatome and then rapidly progressed to severe tetraplegia within 6 hours of injury. Cervical corpectomy was performed 6 hours after injury. Patient recovered ambulatory function with crutches 3 months after injury. (Left) Initial MRI image obtained 4 hours after injury demonstrating high signal zone of injury within cord at level of C2 vertebrae (white arrow). (Right) MRI 2 days after injury. White arrows illustrate ascending necrosis. Black arrows show anterior decompression.

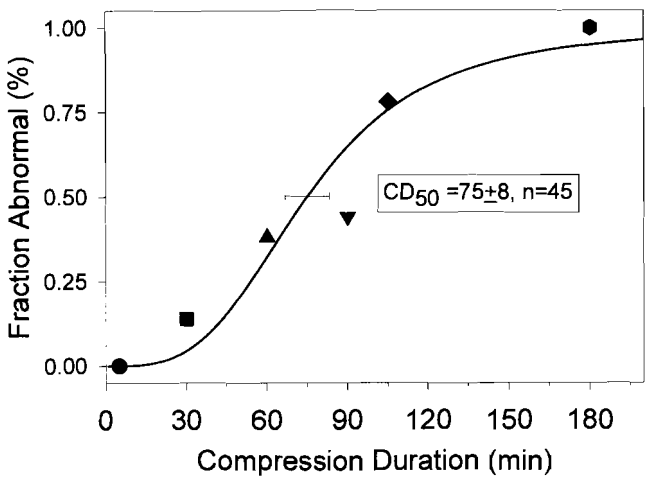

Fig. 3. Dose-response curve illustrating predicted somatosensory evoked potential recovery after sustained cord compression. CD_{50} is calculated as the compression duration 77 minutes, after which 50% of the subjects will not be expected to recover somatosensory evoked potential function under these loading conditions.

injury [53]. Within 1 hour after injury, damage characteristics of chromatolysis and ischemia begin to appear in the anterior ventral horn cells [140]. By 4 hours after injury, a central region of hemorrhagic necrosis forms and extends centrifugally and proximally in the shape of a spindle [56,57]. White matter breakdown begins at the gray matter junction with progressive edema noted as spongiform changes on light microscopy [54]. Axonal swelling attributed to axoplasmic stasis contains multiple organelles, mitochondria, neurofilaments, and smooth endoplasmic reticulum that undergo glandular dissolution [9,10,29,31]. Damage to the myelin sheath occurs through vesicular disruption [9]. Initially, polymorphonuclear cells infiltrate the injured region. These are replaced by macrophages within days after the injury [15,109]. Within 1 week the central necrotic region begins to show cystic changes. Within 4 weeks chronic changes have occurred, and a cystic cavity remains with astrocytic gliosis and demyelination of the remaining axons [140].

Systemic vascular changes

The early systemic effects of spinal cord injury may manifest as neurogenic shock, bradycardia, hypotension, and decreased cardiac output. These systemic changes are the result of a com-

bination of decreased sympathetic tone and parasympathetic myocardial effects. The exact cause of posttraumatic spinal cord ischemia remains unknown. The mechanisms of spinal cord blood flow autoregulation are damaged with acute spinal cord injury [126]. Under normal circumstances, the spinal cord autoregulates blood flow within the range of 50 to 130 mm of mercury, similar to the brain [93,104]. With loss of autoregulation, regional end-capillary blood flow becomes passively dependent on systemic arterial pressure. Vasospasm mediated through increased neurotransmitter accumulation, (i.e., noradrenalin, dopamine, and serotonin) may further restrict blood flow and the delivery of oxygen to an already ischemic environment [63,67].

The severity of cord injury correlates with the degree of posttraumatic ischemia and axonal dysfunction [68]. A consistent finding has been the occurrence of hypoperfusion in the gray matter. Using a consistent sustained cord compression model, the authors have demonstrated that the recovery of neurologic function after spinal cord decompression was dependent on return of regional spinal cord blood flow to baseline levels during and after sustained cord compression [35,36]. Posttraumatic spinal cord blood flow has been improved with a variety of methods, alone or in combination, including dextran and hemodilution [141], whole blood transfusion, adrenalin, calcium channel blockers [68,80], and steroids [46,151]. Clinical data from the Maryland Shock Trauma Center suggest that early hemodynamic stabilization of acute spinal cord shock may be neuroprotective. The recommended clinical treatment for spinal shock includes aggressive titration of the hemodynamic profile with judicious fluids, dopamine, and/or dobutamine to maintain adequate cardiac output and vascular resistance, targeting a mean blood pressure greater than 90 mm of mercury [99].

Biochemical alterations

Traumatic spinal cord injury causes cellular perturbation and an ionic membrane flux. The normaly tightly controlled intracellular concentration of sodium and calcium increases with a concomitant potassium. This results in neuronal depolarization and activation of membrane channels primarily associated with excitatory amino acids [111]. This loss of the normal sodium–potassium intracellular balance potentiates hypoxic-ischemic cell death by causing cytotoxic edema, intracellular acidosis, and increased calcium permeability through the cell membrane. Spinal cord injury initiates a cascade of calcium-mediated events that are deleterious to cellular survival [149]. An increase in intracellular calcium results in binding of the mitochondrial membranes halting ATP production and diverting mitochondrial electron transport to form oxygen free radicals [22]. These substances in turn may directly damage or destroy cell membranes, mediate platelet aggregation, vasospasm, and lead to lysosomal enzyme release [4,20,22–24,82,85].

Apoptosis

Apoptosis, a mechanism of cellular death determined by genetic program and dependent on active protein synthesis, is characterized by nuclear fragmentation and the histologic appearance of apoptotic bodies seen as small balls of basophilic material within the nucleus or as similar balls extruded from the cell within the blebs of cytoplasm [103]. In contrast to necrotic cell death, which is characterized by cellular swelling and nuclear shrinkage without apoptotic bodies, apoptotosis results in cellular shrinkage and eventual phagocytosis by macrophages. Cells undergoing necrosis release chemicals that injure the surrounding tissue and produce an inflammatory response typified by polymorphonuclear cells [123].

Apoptosis has been observed after human SCI. Emery et al. [60] evaluated the spinal cords of 15 patients who had died after traumatic SCI and described evidence of apoptotic cells at the edges of the lesion epicenter and in the adjacent white matter. Oligodendrocytes, microglia, and neurons are susceptible to apoptosis. Apoptotic mechanisms of cell death have been implicated in delayed Wallerian degeneration of white matter after spinal cord injury [47]. The process of apoptosis associated with central nervous system (CNS) injury is complex with numerous key molecules upregulated after injury [124]. Therapeutic benefits may be achieved with the development of protease inhibitors to prevent programmed cell death [60,121,124,129].

Excitotoxicity

The excitatory pathway mediated by excitatory neurotransmitters glutamate and aspartate have been described as the most important mediators of neuronal cell death [45]. Glutamate has been implicated in the death of neurons and oligodendrocytes associated with hypoxia and ischemia. Intraspinal injection of glutamate results in a significant loss of neurons around the injection site demonstrating that the concentrations of excitatory amino acids released upon spinal cord injury are neurotoxic [102]. Glutamate has harmful effects through several receptors, including the N-methyl-D-aspartate (NMDA) receptor and "non-NMDA receptors," the most common of these being alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate type glutamate receptor [106]. NMDA-receptor activation promotes delayed neuronal and glial cell death resulting from apoptosis both 24 hours and 7 days after injury [139]. Administration of NMDA receptor antagonist (MK-801) decreases excitatory amino acid release mediated by N-methyl-D-aspartate (NMDA) receptors delaying neuronal and glial cell death resulting from apoptosis [139]. MK-801, administered after cord contusion, significantly improved motor recovery after injury and reduced edema formation at the injured site without altering spinal cord blood flow or vascular permeability [146]. NBQX (2,3-dihydro-6-nitro-7-sulfamoyl-benzo(f)quinoxaline) a highly selective and potent antagonist of non-N-methyl-D-aspartate ionotropic EAA receptors administered intravenously (1 mg/kg per minute for 30 minutes) after rat spinal cord injury resulted in a reduced lesion volumes and improved distal neurologic function [144].

Calpain

Calcium-activated neutral proteases (calpains) degrade cytoskeletal proteins and mediate necrotic and apoptotic cell death [41]. The activation of calpain can be triggered by calcium influx and oxidative stress with resultant neurodegeneration. Banik et al. [11] demonstrated that calpeptin (a calpain inhibitor) and methylprednisolone administered after SCI resulted in diminished protein breakdown. Calpeptin was associated with a reduction in the internucleosomal DNA fragmentation indicative of apoptotic cell death [11]. The inhibition of cytoskeletal protein degradation suggests that calpeptin may be neuroprotective by decreasing cellular death and inhibition of cytoskeletal breakdown.

Neurotransmitter accumulation

Large elevations in endogenous endorphins have been found in the plasma after experimental spinal cord injury with the endogenous opioid dynorphin A (1-17) implicated as the most likely to be involved in spinal cord injury [61]. This is supported by findings of selectively increased dynorphin immunoreactivity immediately after injury in direct proportion to the severity of injury [65,67]. Naloxone and thyrotropine-releasing hormone (TRH) are opioid receptor antagonists that have proven beneficial in the treatment of experimental spinal cord injury [63,64,67]. These antagonists have been shown to improve posttraumatic spinal cord blood flow independent of the systemic vascular effects [152]. Although there is considerable evidence for an opioid-mediated component to spinal cord injury, a clinical trial comparing Naloxone and methylprednisolone with a placebo did not demonstrate a significant improvement in neurologic function in the Naloxone treatment group [19].

TRH, initially hypothesized to act as a physiologic opioid antagonist, has demonstrated neuroprotective benefits in models of spinal cord injury [64,132]. A small clinical trial with TRH did not appear to have significant neuroprotective effects in patients with complete neurologic injuries. However, the patient sample size was too small to make conclusive determinations of efficacy [116]. Because the effective half-life of TRH is short, experimental studies have focused on synthetic analogs with longer effective durations of action [62,13].

Lipid peroxidation/free radical injury

Oxygen free radical formation and lipid peroxidation enhance adverse mechanisms of neuronal injury, such as spinal cord hypoperfusion, development of edema, axonal conduction failure, and breakdown of energy metabolism [82]. Experimental studies suggest that oxygen free radicals, molecules that possess unpaired electrons in their outer orbit and are predisposed to increased reactivity, play a key role in posttraumatic damage of brain and spinal cord tissue [20,49]. Free radical mediation occurs through disruption of cell and myocardial membranes, denaturation of proteins, and DNA breakdown. The importance of free radicals and lipid peroxidation in spinal cord injuries is supported by the large number of experimental and clinical studies demonstrating potential neural protective efficacy of pharmacologic agents with antioxidant properties [5,6,18,19,24,42,46,69,70,83,86,133,151].

Immune response

The inflammatory response involves activation of resident and recruited immune cells. One of the first inflammatory events occurring shortly after spinal cord trauma is the activation of the complement cascade. This is followed by the cellular response, first by the local resident microglia, then by infiltration of T lymphocytes and macrophages, and finally by reactive astrocytes [142]. Neutrophils and macrophages, when activated, produce reactive oxygen species and lipid peroxidation. The presence of neutrophil migration into the injury zone peaks within 24 hours of injury. The amount of phagocytic cells at the injury site correlates with quantitative damage [39]. Popovich et al. [117] demonstrated peak microglial activation within the lesion epicenter between 3 and 7 days after injury preceding the bulk of monocyte influx and macrophage activation that occurred 7 days after injury [117]. In response to local trauma, expression of cytokine transforming growth factor-beta 1 (TGF-beta 1) can enhance immune cell infiltration and intensify the impairment resulting from immune response [145].

Recruitment of leukocytes from the blood compartment to the site of inflammation in the injured spinal cord has been attributed to locally generated chemotactic agents (i.e., cytokines and chemokines). Using a chemokine antagonist, vMIPII after experimental SCI, Ghirnikar et al. [75] demonstrated a decrease in infiltrating hematogenous cells at the site of injury and increased expression of Bcl-2 gene, an endogenous inhibitor of apoptosis. This supports the contention that disrupting chemokine–receptor interaction may be an effective approach in reducing the secondary damage after spinal cord injury.

Energy metabolism

Injury to the CNS tissue creates significant energy demands on cells attempting to regulate normal ionic balance [88]. Acute energy demands are met with hyperglycolysis, which leads to accumulation of lactate and the development of acidosis [2,3]. ATP stores are depleted in the hypoxic environment, which leads to inactivation of calcium-dependent ATP and sodium/potassium ATP-activated channels. This may precipitate cellular membrane depolarization and an uncontrolled influx of calcium ions [153].

Pharmacotherapies

There are three stages of spinal cord injury where pharmacotherapy may have a therapeutic role [77,78]. In the acute stage treatments aimed towards diminishing the immune or inflammatory response, excitotoxicity and lipid

peroxidation may limit secondary mechanisms of injury [19]. In the subacute stage, initiation of neuroregenerative or neurotrophic therapies may help to reconstitute the damaged tissue [73,74]. Interventions in the chronic stage of spinal cord injury will more than likely involve neurotrophic substances in combination with tissue or mesenchymal stem cell transplantation [25,26,28,43,51,52].

Methylprednisolone is the first pharmacotherapy proven to alter the neurologic outcome after SCI. In randomized human trials, National Acute Spinal Cord Injury Study 2 (NACIS-2) comparing naloxone, placebo, and methylprednisolone (30 mg/kg IV bolus and 5.4 mg/kg per hour for 23 hours), patients receiving methylprednisolone showed neurologic improvement only if treatment was instituted within 8 hours of injury. Unfortunately, functional motor improvement was minimal. Corticosteroids have been shown to improve neural recovery through a combination of mechanisms [12,14,16–21,23,24,42,46,49,66,69,70,82–86,95,112,127,143,147,151]. Serum cortisol decreases in the first 24 hours after a spinal cord injury [48]. Corticosteroids aid in normal homeostasis of plasma glucose and electrolytes [101]. Membrane stabilization and prevention of lipid peroxidation may be one of the most important mechanisms of corticosteroid neuroprotection [82,85]. Steroids exhibit strong anti-inflammatory properties and may decrease spinal cord edema [101]. Methylprednisolone administered in animals has been associated with a reduction in the zone of injury and improved axonal conduction [112]. Neuroprotective effects include preservation of vascular and cellular membranes through potentiation of free oxygen radical scavengers, and stabilization of white matter in hemorrhagic lesions [4].

Tirilazad mesylate, a synthetic 21-aminosteroid with strong lipid peroxidation inhibition, has been advocated as an alternative to glucocorticoid treatment. Experimental studies using Trilazad have demonstrated cell membrane stabilization and improved posttraumatic spinal cord blood flow by inhibiting oxygen radical microvascular lipid peroxidation [21,24, 70,83,84,86]. Experimental studies with Tirilazad have demonstrated improved neurological recovery after injury [5,6,69]. The NASCIS-3 clinical trials comparing efficacy of methylprednisolone administered for 24 hours with methylprednisolone administered for 48 hours or Tirilazad mesylate administered for 48 hours in patients with acute spinal cord injury showed that patients treated with methylprednisolone for 48 hours had improved motor recovery at 6 weeks ($P=.09$) and 6 months ($P=.07$) after injury. Although the Tiralazad group tended to have fewer complications, these differences were small and the neurologic motor recovery did not match that of patients who received 48 hours of methylprednisolone [17]. The NASCIS 3 study underscores the benefits of earlier treatment regimens after acute injury. Improved neurologic recovery was demonstrated when methylprednisolone maintenance dosing was extended to 48 hours in patients treated 3 to 8 hours after injury [17].

Gangliosides are complex acidic glycolipids that form a major component of the cell membrane. They are present in high concentrations in the cells of the central nervous system, located primarily in the outer leaflet of bilayer cell membranes [97]. They are thought to induce neuronal regeneration of neurons and restore function after injury [148]. In vitro studies have demonstrated that GM-1 ganglioside protects against excitatory amino acid–related neurotoxicity. In animal models, GM-1 ganglioside appears to reduce acute nerve cell damage and aids in functional recovery after trauma [128]. A prospective randomized, double-blind trial of GM-1 ganglioside demonstrated neurological improvement of patients up to 1 year after the initial injury. Thirty-four patients were given either 100 mg of GM-1 ganglioside intravenously per day for 18 to 32 days, or a placebo with treatment initiated within 72 hours of initial injury [74]. A larger randomized multicenter trial is currently being concluded in the United States [72]. The concurrent use of methylprednisolone with GM-1 ganglioside is controversial. GM-1 ganglioside may counteract some of the desirable anti-inflammatory properties of methylprednisolone [46]. GM-1 modulates protein kinase activity, which inhibits lipocortins. These lipocortins are partly responsible for the anti-inflammatory effects of glucocorticoids [154].

Acute management of spinal cord injury

Timing of surgical decompression and stabilization

The immediate goals of acute spinal cord injury management are to realign the spine and maintain stability of the damaged segments. In many circumstances re-alignment of the spinal canal is the most efficacious means of spinal cord decompression. The ultimate objective is to support neurologic recovery and hasten the patient's return into a functional recovery. Although the efficacy of early surgical decompression to enable neurologic recovery after spinal cord injury remains hotly debated, clinical studies have demonstrated no increase in morbidity or complications associated with early intervention.

Experimental studies support a time-dependent course of events that starts with the initial spinal cord impact [55,81, 94,134,135]. Tarlov demonstrated that duration of compression was an important factor in determining final neurologic outcome. Using a balloon compression model, Tarlov demonstrated recovery after 1 hour of sustained compression with a medium-sized balloon. Sustained compression with larger balloons resulted in recovery only if decompression was performed [134,135]. Kobrine et al. [94] observed somatosensory evoked potential recovery only in those animals decompressed within 1 minute after acute balloon compression of the thoracic spinal cord. Guha et al. [81] determined that duration of compression was a significant determinant of neurologic recovery only if the spinal cord was subject to relatively lower forces. From this experimental data, the authors theorized that greater neurologic recovery may be realized by early decompression in patients with incomplete injuries, whereas there may be little to be gained by early decompression in situations of more severe primary trauma.

Carlson et al. [38] demonstrated a time-dependent window of opportunity for evoked potential recovery with early spinal cord decompression using a consistent spinal cord injury model that characterized both the dynamic and sustained compression phases of injury. Increasing duration of spinal cord compression resulted in greater histopathologic lesional volume and diminished motor recovery 4 weeks after injury. Although mechanical factors differ between models, these studies suggest that final neurologic function is not only a result of the initial impaction forces of injury but rather a combination of these forces with secondary time-dependent events that follow shortly after initial impact (Fig. 4).

The surgical treatment of spinal cord injury continues to evolve as a result of better understanding of the pathophysiology of spinal cord injury, modern surgical techniques, and advancements in neuroroimaging. The results of early postinjury surgery in 1975 were such that Heiden [87] wrote, "surgery during the first seven days following cervical cord injury is associated with a significant increase in morbidity and should be avoided." In the 1970s, he thought that the only indication for early surgery was progressive neurologic deterioration, which occurred in less than 5% of patients after arrival to the hospital. In a prospective randomized study of 283 spinal cord–injured patients, Marshall et al. [105] identified 14 patients who deteriorated neurologically after hospitalization. A specific management event was associated with neurologic decline in 12 of the 14 patients. Cervical spine surgery performed within 5 days after injury was associated with neurologic deterioration in three patients with cervical injuries. In comparison, no deterioration in neurologic function was noted in patients who underwent surgery 6 or more days after injury. This led the authors to recommend avoidance of early surgery in the patient with cervical cord injury except in the incomplete patient incompletely injured with progressive neurologic deterioration.

Conversely, Levi et al. [100] reported on 103 consecutive patients with cervical spinal cord trauma who underwent anterior decompression and stabilization at Maryland Shock Trauma Center. Comparisons were made between early surgery (less than 24 hours after injury), and delayed surgery (more than 24 hours after injury). Although no statistical differences in the level of functional motor recovery between

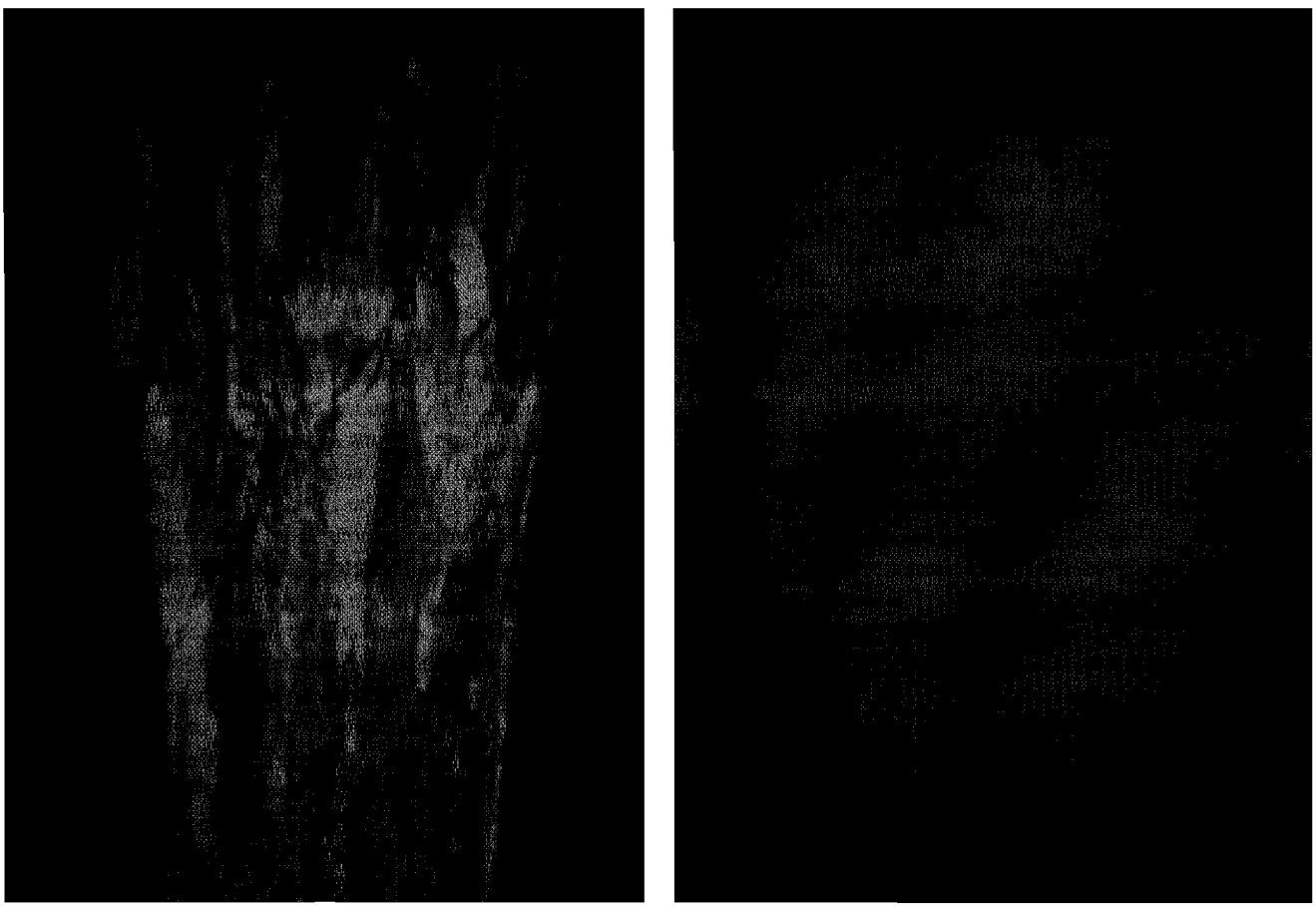

Fig. 4. Progressive neurologic damage caused by sustained spinal cord displacement in a dog spinal cord model. (Left) Longitudinal spinal cord sections with luxol fast blue stain for myelin (30 minutes of sustained cord compression). Notable cavitary changes in gray matter with preservation of white matter (black arrows). Early decompression was associated with recovery to almost completely normal gait pattern 4 weeks after injury. (Right) Section through T13 after 3-hour sustained compression. There is greater lesional volume and damage to surrounding myelinated tracts (black arrows). This animal failed to regain ambulatory function 4 weeks after experimental injury.

early and delayed surgery were identified in the 53 patients who presented with complete injury, early surgery allowed quick mobilization and less intensive respiratory physiotherapy, thus shorter hospitalizations and rehabilitation time.

Early spinal column reduction is also supported by Aebi et al. [1] in a study of 100 cervical spinal cord injuries. In total, only 31 of patients showed neurologic improvement after manual or surgical reduction in long-term follow-up of greater than 1 year. Of those, 75% were reduced within the first 6 hours after the accident, whereas 85% of the remaining 69 patients without neurologic recovery were reduced later than 6 hours after injury.

In an effort to determine the effect of timing on length of stay and medical complications, Campagnolo et al. [34] reviewed 38 cervical spine-injured patients equally split between complete and incomplete injury. They noted significantly lower hospital duration without increased numbers of complications in the early stabilized groups (i.e., less than 24 hours). This led the authors to conclude that active rehabilitation within the first 2 weeks after SCI is critical in reducing complications of long-term immobilization.

In a review of 38 patients with acute cervical spinal cord injuries treated with surgical stabilization, Krengel et al. [96] reported greater improvement in Frankel grade in patients treated within 72 hours of injury. Although the study was limited in patient numbers, they also noted fewer pulmonary complications and a trend toward shorter hospital duration and mechanical ventilation in those patients treated early. Similar findings were noted by Schlegel et al. [125] after review of 138 patients surgically treated for cervical spine injury. In those patients with neurologic injury, operative treatment within 72 hours of injury greatly reduced medical complications and morbidity. However, timing of surgery did not affect the functional neurologic recovery.

The answer to the seminal question of whether earlier spinal decompression and stabilization can improve long-term function remains to be answered. An unsuccessful attempt by the North American Spine Society to orchestrate a multicenter prospective trial testing early surgical intervention highlights the logistical difficulty of activating ancillary support, including emergency room personnel, radiology, and operating room availability, for surgical decompression within an 8-hour window after trauma. Thus, closed reduction and spinal realignment in a controlled trauma management setting may pose the best opportunity for early spinal cord decompression [1]. In centers with a high volume of spinal trauma that routinely employ closed reduction techniques, these risks appear quite low, although closed reduction may precipitate disk or bone fragment migration, resulting in compression of an already traumatized spinal cord [59,122]. Although substantial information can be obtained through neural imaging of the injured spine, this usually comes at the cost of lost opportunity for early reduction. In order to provide potential benefit to those patients with the least favorable outcomes, the risks of early closed reduction are justified in patients with complete spinal cord injury. In those patients with stable incomplete neurologic deficits, the benefits of prereduction neural imaging may outweigh the risks of potential neurologic loss associated with either closed reduction or surgical intervention.

Promising therapies for spinal cord injuries

IN-1

After spinal cord injury, there is little axonal regrowth across the injury zone. Affected neurons undergo a process of dieback or involution of the axon proximal to the injury. Discoveries of myelin-associated proteins in the CNS that block axonal regeneration [40] and neutralization of these proteins by monoclonal antibody IN-1 has led to pronounced axonal regeneration in the lesioned spinal cords of adult rats [136]. Myelin-associated proteins are expressed by oligodendrocytes and located in the CNS white matter. The administration of IN-1 leads to long-distance regrowth of a proportion of CNS axons after injury that is associated with a recovery of specific reflex and locomotor functions in adult rats [27]. Treatments with IN-1 have not prevented the dieback phenomena. Newer strategies have focused on a combination of IN-1 and growth factors, such as acidic fibroblast growth factor, to support the regeneration of injured corticospinal tract fibers and prevent dieback [79].

Activated macrophages

Regeneration of nerve damage in the peripheral nervous system is partly the result of the early arrival of macrophages. Macrophages contribute to the phagocytosis of myelin debris, which inhibit axonal regrowth, and stimulate the proliferation of Schwann cells. Activated macrophages promote a permissive extracellular matrix notably containing laminin, a substance favorable to sprouting, and may indirectly stimulate neurotrophic factors from resident glial cells through macrophage-released cytokines [71]. Transplantion of macrophages into the spinal cord injury site may be a novel means of providing an environment beneficial to the promotion of regeneration of axons, possibly by the release of cytokines and interaction with other nonneuronal cells in the immediate vicinity [118].

Neurotrophins

Growth factors or neurotrophins enhance neuronal survival and promote the growth of axons. Members of the neurotrophin family, including nerve growth factor (NGF), brain-derived neurotrophic factors (BDNF), and neurotrophin 3 (NT-3), are capable of supporting survival of injured CNS neurons both in vitro and in vivo. Neurotrophins are responsible for stimulating neurite outgrowth needed for reorganization of the injured CNS and expression of key enzymes for neurotransmitter synthesis that may need to be upregulated to compensate for reduced innervation. Grafts containing a combination of NT-3 and BDNF have demonstrated the formation of new oligodendrocytes and myelination of regenerating axons after SCI in adult rats [108]. Kim et al. [92] demonstrated functional locomotive improvements in rats with

contusion injuries that received an injection of fibroblasts with either NGF or BDNF compared with controls.

Research has focused on the optimal combination of neurotrophins and temporal pattern of delivery. Novikova [114] demonstrated that both BDNF and NT-3 can prevent cell death in the axotomized adult rat rubrospinal neurons but that the efficacy of neuroprotection depends on the temporal pattern of treatment. When administration of either BDNF or NT-3 was delayed and performed during postoperative weeks 5 to 8, the number of surviving neurons was increased compared with early treatment. Delayed treatment with a combination of BDNF and NT-3 resulted in complete survival and a reduction in neuronal atrophy.

Another class of neurotrophic polypeptides, fibroblast growth factor (FGF), not only sustains survival of injured neurons but also stimulates revascularization and certain glial responses to injury. Both the neurotrophins and the FGFs, as well as their respective receptors, have been shown to be upregulated after experimental CNS injury [110]. Neurotrophins and FGFs administered after injury have been associated with decreased lesional volumes, increased capillary counts, and improved behavioral function [8,98]. Rabchevsky et al. [119] demonstrated that rats injected with basic FGF after injury regained coordinated movement earlier than the control group and were able to sustain the recovery. An acute focal injection of FGF2 has been shown to protect ventral horn neurons from death after experimental contusive spinal cord injury in the thoracic spine, thereby ameliorating respiratory deficits [138].

Transplantation

Transplantation strategies are focused on the implantation of tissue into cystic cavities that can serve as scaffolding for axonal regeneration and the implantation of cellular support tissue. The first part of this approach focuses on laying a scaffolding that allows new growth and directs injured axons toward their proper destination. This method tries to bridge the gap through axonal regeneration across the cystic cavity and stimulate the release of proteins helpful in axonal regeneration. Schwann cells transplanted from the peripheral nervous system secrete proteins that promote axonal extension and remyelination [90].

Techniques aimed at providing support for axonal regeneration include transplantation of Schwann cells, olfactory-ensheathing glial cells (OEG) and fibroblasts. Current research focuses on a combination of transplant techniques. Guest et al. [79] showed that the addition of acidic FGF fibrin glue to Schwann cells transplants through the use of guidance channels was effective in regenerating fibers into the grafts. OEG are unique in that the olfactory nerve is the only nerve in the CNS that regularly regenerates in adults, thus providing autologous transplant opportunities. Ramaon-Cueto et al. [120] demonstrated that OEG injected into Schwann cell guidance channels in transected rat cords demonstrated serotonergic axonal crossing through the lesion using connective tissue bridges formed on the exterior of the channels, avoiding the channel interior. Transplanted OEG migrate longitudinally and laterally from the injection sites. Tracer-labeled axons showed elongation up to 1.5 cm.

Techniques aimed at replacing neuronal tissue include transplanting stem cells, fetal tissue, and peripheral nerves. Cheng and Olson [43,44,115] developed a new technique to bridge spinal cord gaps in adult rats with multiple intercostal nerve grafts that redirect pathways from white matter proximal to gray matter distal, resulting in improved hind limb function. This technique lead to corticospinal tract regeneration through the grafted region to the distal lumbar enlargement. These data suggest a novel repair strategy for spinal cord injury. Giovanini et al. [76] transplanted human fetal spinal cord tissue into lesioned rat cords, demonstrating extensive neurite outgrowth and a survival of host–graft integration rate between 85% and 92% in both acute and chronic lesions. Fetal tissue transplants, when combined with neurotrophic factors, have been shown to reverse neuronal atrophy completely [25]. Gait analysis demonstrated hindlimb weight bearing and partial hindlimb coordination in rats receiving fetal tissue transplants. Application of fetal tissue transplants has proven efficacious in animal models of SCI, yet because of the ethical dilemmas associated and lack of donor tissue, researchers have recently focused an alternatives, such as stem cell transplants. Self-renewing, totipotent embryonic stem cells offer an unlimited donor source for transplantation. Progenitor cells are implanted with the hope of differentiating into the needed lineages, thereby establishing channels for synaptic transmission. Transplantation in a rat model of a human myelin disease shows that these embryonic stem cell–derived precursors interact with host neurons and efficiently myelinate axons in the spinal cord [32]. McDonald et al. [107] reported that neural differentiated embryonic stem cells implanted into a traumatically injured rat cord survived and migrated up to 8 mm away from the lesion, resulting in weight bearing with partial hindlimb coordination. Transplantation of glial cell progenitors into demyelinating lesions demonstrated normal locomotor function in rats using a beam-walking test [89].

Future directions

Experimental studies continue to provide a better understanding of the complex interaction of pathophysiologic events immediately after traumatic spinal cord injury. These studies suggest that early intervention in the form of new pharmacotherapeutic strategies will diminish neurologic damage from secondary injury. Future approaches will involve strategies aimed at blocking the multiple mechanisms of progressive CNS injury. This will include specific proteases aimed at blocking protein synthesis and interrupting apoptosis and calpain injury. Treatments aimed at excitotoxic receptor blockade could mediate secondary injury damage. A better understanding of the immune response to CNS injury will allow modulation of inflammation and injury-specific neurotrophic support of regeneration. As the

mechanisms of action of the neurotrophic compounds is better understood, treatment strategies will be developed to encourage regeneration of the injured central nervous system. Unlocking the molecular secrets of the central nervous system has for the first time provided the basis for hope and optimism for patients of this generation to experience enhanced neurologic function after spinal cord injury.

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