

Acute Spinal Cord Injury, Part II: Contemporary Pharmacotherapy

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Summary: Spinal cord injury (SCI) remains a common and devastating problem of modern society. Through an understanding of underlying pathophysiologic mechanisms involved in the evolution of SCI, treatments aimed at ameliorating neural damage may be developed. The possible pharmacologic treatments for acute spinal cord injury are herein reviewed. Myriad treatment modalities, including corticosteroids, 21-aminosteroids, opioid receptor antagonists, gangliosides, thyrotropin-releasing hormone (TRH) and TRH analogs, antioxidants and free radical scavengers, calcium channel blockers, magnesium replacement therapy, sodium channel blockers, *N*-methyl-D-aspartate receptor antagonists, α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid-kainate receptor antagonists, modulators of arachadonic acid metabolism, neurotrophic growth factors, serotonin antagonists, antibodies against inhibitors of axonal regeneration, potassium channel blockers (4-aminopyridine), paclitaxel, clenbuterol, progesterone, gabexate mesylate, activated protein C, caspase inhibitors, tacrolimus, antibodies against adhesion molecules, and other immunomodulatory therapy have been studied to date. Although most of these agents have shown promise, only one agent, methylprednisolone, has been shown to provide benefit in large clinical trials. Given these data, many individuals consider methylprednisolone to be the standard of care for the treatment of acute SCI. However, this has not been established definitively, and questions pertaining to methodology have emerged regarding the National Acute Spinal Cord Injury Study trials that provided these conclusions. Additionally, the clinical significance (in contrast to statistical significance) of recovery after methylprednisolone treatment is unclear and must be considered in light of the potential adverse effects of such treatment. This first decade of the new millennium, now touted as the Decade of the Spine, will hopefully witness the emergence of universal and efficacious pharmacologic therapy and ultimately a cure for SCI. **Key Words:** Spinal cord injury—Pharmacotherapy—Drug therapy—NASCIS clinical trials

Spinal cord injury (SCI), an injury resulting from an insult inflicted on the spinal cord that compromises, completely or incompletely, its major functions (motor, sensory, autonomic, and reflex), is both a common and formidable societal problem (1–10). The first decade of this millennium has been deemed the Decade of the Spine to promote awareness, advance our understanding of spinal disorders including SCI, and to improve

our treatment and ultimately mount burgeoning momentum toward realizing a definitive cure.

Contemporary treatment of acute SCI has focused largely on attenuating the damage of secondary pathophysiologic mechanisms of injury. Many of these pathophysiologic mechanisms share commonalities with those that underlie other injuries of the central nervous system (CNS) including head injury, cerebral ischemia and subarachnoid hemorrhage (8,11). Myriad pharmacologic strategies have been developed and subjected to the rigor of laboratory and/or clinical investigation, and substantial data have accrued that have

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influenced our contemporary management of SCI. Although considerable progress has been made in elucidating underlying pathophysiologic mechanisms and targeting them with appropriate pharmacotherapy, further delineation is necessary to optimize patient management. Consequently, novel treatments are being developed and studied that hold substantial promise for the treatment of SCI.

TREATMENT OF PRIMARY INJURY: STABILIZATION OF THE ACUTELY INJURED PATIENT

As in any medical emergency, stabilization of the patient's cardiopulmonary status is critical. Basic primary and secondary surveys are performed with the addition of appropriate resuscitation as indicated. The reader is referred to excellent reviews for comprehensive coverage of this topic (5,12–14).

Spinal cord injury may result in neurogenic shock. The severity of this shock is correlated with the anatomic level and magnitude of the injury (8). Although heart rate, blood pressure, and catecholamines may be transiently increased, prolonged bradycardia and hypotension subsequently ensue. This is particularly a complicating factor in complete cervical cord injuries and may be persistent for days to months after the cord insult (8). The pathophysiology of this state has been outlined in the preceding article. Treatment is focused on preventing the development of systemic hypotension and hypoperfusion, which may further exacerbate ischemic injury. Effective treatment may use fluid administration with vasopressor support (with agents such as ephedrine or phenylephrine). Invasive hemodynamic monitoring with central venous pressure and arterial pressure lines may be warranted. It is best to rely more heavily on volume support than pressure support in most patients, because excessive vasopressor administration can decrease organ perfusion, especially in the presence of inadequate volume resuscitation (15). Thus, neurogenic shock must be judiciously treated with volume and pressure support to prevent further ischemic insult and additional damage of critical spinal cord tissue.

TREATMENT OF SECONDARY INJURY: PHARMACOLOGIC MODULATION

Because primary mechanisms of injury are not amenable to pharmacologic treatment, secondary mechanisms have thus been targeted. Each therapeutic agent focuses on one or more mechanisms of secondary injury and endeavors to confer neuroprotection and/or restoration. Because useful voluntary control pursuant

to SCI can occur when 5%–10% of the cortical neurons retain physiologic connection through the lesioned segment to the caudal spinal cord, preservation and/or restoration of critical and functioning neural tissue is paramount (16). The ensuing discussion will review the major agents that have been subjected to human and/or animal investigation in the treatment of SCI (Table 1).

Corticosteroids

The use of corticosteroids for the treatment of acute SCI has been extensively studied in both clinical and laboratory contexts. During the 1960s, when information pertaining to the pathophysiology of SCI was accumulating, corticosteroids were already known to have excellent antiinflammatory properties, and had been shown to be beneficial for treating certain neurologic disorders. The initial rationale for the use of corticosteroids in the treatment of acute SCI was based on the utility of its antiinflammatory action to reduce spinal cord edema (17). Early studies revealed only a modest benefit, but despite this, corticosteroids began to be widely used. Further studies have produced conflicting results (17–19). Despite publication of recent large clinical trials showing that methylprednisolone (MP) can improve neurologic recovery and reduce neurologic deficit to some extent, significant controversy remains regarding the use of corticosteroids in the treatment of acute SCI because of problems with study design and analysis/interpretation of data (17,20–22). It is also uncertain whether this statistically significant improvement actually results in clinically significant improvements in daily functioning. MP has become the corticosteroid of choice and has been extensively used in clinical trials. Compared to other corticosteroid agents such as dexamethasone and hydrocortisone, methylprednisolone appears to possess superior antioxidant properties (23), passes through cell membranes more rapidly, and appears to be more effective in inhibiting the neutropenic response to activated complement components (24). MP is thought to exhibit multiple mechanisms of action, the most significant of which is thought to be the inhibition of lipid peroxidation. Other proposed mechanisms have included prevention of progressive posttraumatic ischemia, support of energy metabolism, inhibition of neurofilament degradation, reversal of intracellular calcium accumulation, inhibition of vasoactive prostaglandin $F_{2\alpha}$ and thromboxane A_2 formation, and increases in spinal neuron excitability (18,19).

Three large clinical trials evaluating the use of MP and other agents in acute SCI have been performed to date. The National Acute Spinal Cord Injury Study (NASCIS 1) was the first large clinical trial to evaluate

TABLE 1. Pharmacotherapy of acute spinal cord injury

Agent	Mechanism(s) of action	Type of investigation
Corticosteroids (<i>e.g.</i> , methylprednisolone)	Inhibition of lipid peroxidation/antioxidative/antiinflammatory properties Decrease ischemia, support energy metabolism, inhibit neurofilament degradation, decrease intracellular Ca, decrease PG F/TxA, increase spinal neuron excitability, decrease cord edema	Human, animal
21-Aminosteroids (lazaroids) (<i>e.g.</i> , tirilizad mesylate)	Scavenge lipid peroxy radicals Facilitate endogenous vitamin E prevention of lipid peroxidation Scavenge hydroxyl radicals and membrane stabilization	Human, animal
Opioid receptor antagonists (<i>e.g.</i> , naloxone)	Antagonize the increase in endogenous opioid levels after SCI (opioid receptor activation can contribute to excitotoxicity)	Human, animal
Gangliosides (<i>e.g.</i> , GM-1)	Stimulate neurite regrowth/regeneration Decrease retrograde and anterograde degeneration Decrease excitatory amino acid release and regulate protein kinase C	Human, animal
TRH/TRH analogs	Antagonize endogenous opioids, platelet-activating factor, peptidoleukotrienes, and excitatory amino acids Augment spinal cord blood flow, restore ionic balances/cellular metabolism, and reduce lipid degradation	Human, animal
Antioxidants/free radical scavengers (<i>e.g.</i> , vitamin C, E)	Antagonize deleterious effects of free radicals (lipid peroxidation, reperfusion injury, etc.)	Animal
Calcium channel blockers (<i>e.g.</i> , nimodipine)	Decrease intracellular Ca ²⁺ accumulation Attenuate vasospasm	Animal
Magnesium	Replace Mg ²⁺ depletion that is common after SCI Diminish intracellular Ca ²⁺ accumulation, block NMDA receptor ion channel, modulate binding of endogenous opioids	Animal
Sodium channel blockers	Diminish intracellular Na ⁺ accumulation	Animal
NMDA/AMPA-kainate receptor antagonists	Decrease excitotoxicity	Animal
COX inhibitors/PGI ₂ and analogs	Prevents/antagonizes decreased blood flow/platelet aggregation from production of arachidonic acid metabolites	Animal
Neurotrophic growth factors	Prevent neuronal degeneration and promote regeneration	Animal
Serotonin antagonists	Antagonize deleterious effects of serotonin (vasoconstriction, platelet aggregation, endothelial permeability)	Animal
Antibodies against inhibitors of axonal regeneration	Promote regeneration	Animal
Potassium channel blocker, <i>e.g.</i> , 4-aminopyridine	Enhance nerve conduction/transmission	Human, animal
Paclitaxel	Cytoskeletal protection/preservation	Animal
Clenbuterol	β ₂ -Adrenoceptor agonist, preliminarily neuroprotective Not clearly delineated	Animal
Progesterone	Not clearly known	Animal
Gabexate mesylate	Protease inhibitor with anticoagulant and antiinflammatory activity Diminished leukocyte recruitment	Animal
Activated protein C	Serine protease with anticoagulant activity	Animal
Tacrolimus	Promote axonal regeneration synergy with methylprednisolone	Animal
Cyclosporin A	Inhibits Ca ²⁺ -induced mitochondrial permeability changes	Animal
Caspase inhibitors	Prevent cell death (apoptotic)	Animal
Antibodies against adhesion molecules and other immunomodulatory therapy	Prevent leukocyte recruitment/inflammatory response	Animal

COX, cyclooxygenase; AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; NMDA, *N*-methyl-D-aspartate; PGI₂, prostacyclin; TRH, thyrotropin-releasing hormone; TxA, thromboxane A₂.

MP in the treatment of acute SCI. The study enrolled 330 patients and compared the efficacy of high-dose (1,000-mg i.v. bolus, then 1,000 mg/d for 10 d) and low-dose (100-mg i.v. bolus, then 100 mg/d for 10 d) MP regimens, without a placebo control. No placebo control was included because the investigators believed that MP was efficacious and therefore, unethical to withhold. The disappointing results of this study called into question the efficacy of MP in the treatment of acute SCI (24,25).

After NASCIS 1 concluded, data from experimental models provided more insight into the proper use of MP in acute SCI (19). The first important finding was that large intravenous doses were required. It was also found that MP has a biphasic dose–response curve for its beneficial effects, including prevention of lipid peroxidation. For example, an intravenous dose of 30 mg/kg is required to inhibit lipid peroxidation, but an intravenous dose of 60 mg/kg has no effect on lipid peroxidation. Another observation was that MP therapy should be initiated as early as possible after injury because the distribution of MP into spinal tissue decreases rapidly after insult, whereas lipid peroxidation occurs rapidly after injury and is irreversible. The final observation was that the time course of MP's beneficial effects parallels the tissue distribution and elimination of MP. Thus, more frequent doses of MP were proposed to be necessary.

Some of these data were taken into consideration in the design of the next phase of NASCIS (NASCIS 2). NASCIS 2 was a multicenter, randomized, double-blinded, placebo-controlled study designed to overcome the limitations of NASCIS 1 and to evaluate the efficacy of MP (30 mg/kg bolus over 15 minutes, 45 minute pause, 5.4 mg/kg/h continuous infusion for 23 h) and the opioid receptor antagonist naloxone (5.4 mg/kg bolus, 45 minute pause, 4 mg/kg/h continuous infusion for 23 h) in the treatment of acute SCI (26,27). There was some controversy with the results of this study, because preplanned comparisons were abandoned and arbitrary data stratification was necessary to obtain significant differences in sensory or motor recovery. An interesting result was that there was a trend toward less motor recovery compared to placebo if MP was initiated more than 8 hours after the initial injury.

Because patients with penetrating SCI (*e.g.*, resulting from gunshot wounds) were excluded from the study, the results of NASCIS 2 do not apply to patients in this subcategory (26). A retrospective study conducted by Levy et al. (28) demonstrated that the administration of MP to patients with penetrating SCIs did not significantly improve functional outcome.

The evaluation criteria used in NASCIS 2 did not allow the investigators to determine whether MP im-

proved neurologic function via recovery of segmental function at the level of the injury (which may be because of recovery in one or more nerve roots at the level of the injury site) or via recovery of neurologic function below the level of the spinal cord lesion because of the recovery of long spinal tract function. Two of the investigators involved in the NASCIS 2 attempted to elucidate this information (29). They used data from the trial and performed a *post hoc* statistical analysis using statistical methods that were developed after NASCIS 2 was concluded. The results confirmed the benefit obtained by initiating MP treatment within 8 hours after injury. Also, the neurologic recovery observed was determined to result from recovery of neurologic function in one or more nerve roots below the site of the injury, with only a modest contribution from recovery at the level of the injury (29). Therefore, more distal motor and sensory function was recovered compared to function at the level of injury.

The first results of NASCIS 3 were published in 1997 (30). The objectives of this double-blinded, randomized, non–placebo-controlled study were threefold. First, the investigators endeavored to determine whether a 48-hour treatment regimen of MP (30 mg/kg i.v. bolus, then 5.4 mg/kg/h continuous infusion \times 48 h) would lead to greater neurologic recovery than a 24-hour treatment regimen (30 mg/kg i.v. bolus, then 5.4 mg/kg/h continuous infusion \times 24 h). Second, the efficacy of tirilazad mesylate (TM), a potent nonglucocorticoid inhibitor of lipid peroxidation, in the treatment of acute SCI would be evaluated. Third, subgroup analyses of early versus late administration of MP within the first 8 hours after injury and the effect of treatment in patients with initial complete versus initial incomplete injuries would be performed. Notable exclusions to the study included patients who weighed more than 109 kg and patients who had gunshot wounds. All patients were given an initial 20 to 40 mg/kg intravenous bolus of open-label MP, and an additional intravenous bolus if the original dose was less than 20 mg/kg. No placebo control was implemented because it was believed that the efficacy of MP had been established and that withholding MP would probably constitute unethical medical practice. NASCIS 3 included additional Functional Independence Measure criteria to determine improvements in everyday function (30,31). Functional Independence Measure assessed self-care, sphincter control, mobility, locomotion, communication, and social cognition.

Patients who were randomized to the TM group had significantly worse initial motor function than patients randomized to either MP group. There was no significant initial difference in motor function between the two MP groups. In addition, there were only small dif-

ferences in the other outcome measures used in this study (30).

Mortality was similar between treatment groups at each of the scheduled follow-ups (31). The investigators concluded that the results of NASCIS 3 provided additional support to the continued use of high-dose MP in the treatment of acute SCI (31). Also, it was suggested that patients who receive MP within 3 hours of injury should receive the 24-hour regimen, whereas patients who receive MP treatment 3 to 8 hours after injury should receive the 48-hour regimen. Forty-eight-hour treatment with TM was as efficacious as 24-hour treatment with MP, but not as efficacious as 48-hour MP treatment. Finally, it was concluded that there was no rationale to use TM in the treatment of acute SCI at this point in time until further study with alternative dosing regimens is performed (30).

21-Aminosteroids (Lazaroids)

Inhibition of lipid peroxidation by high-dose MP does not appear to be glucocorticoid receptor-mediated (11). Thus, it has been postulated that a glucocorticoid analog that inhibited lipid peroxidation without activating the glucocorticoid receptor could be synthesized. Such a compound could protect against the secondary damage of SCI and remain devoid of the classic side effects of glucocorticoids in addition to remaining free of mineralocorticoid activity. This led to the discovery of the 21-aminosteroids. U-74600F (tirilazad mesylate, TM) was selected for clinical development as a parenteral agent indicated for the acute treatment of brain and SCI, subarachnoid hemorrhage, and stroke (32).

TM appears to have three major mechanisms of action. The first is a scavenging mechanism of lipid peroxyl radicals analogous to that of vitamin E. Facilitation of endogenous vitamin E prevention of lipid peroxidation is the second mechanism. The third mechanism entails hydroxyl radical scavenging and membrane stabilization, which results from a decrease in membrane fluidity (19,32,33).

TM has been shown to be efficacious in experimental cat models of SCI. Anderson and colleagues (34) demonstrated that cats, which received 48-hour doses of TM ranging from 1.6 to 160 mg/kg, had significantly better recovery at 4 weeks after injury when compared to cats given placebo. In addition, cats treated with TM recovered 75% of normal neurologic function. Hall (32) compared the effects of placebo, TM 3 mg/kg and TM 10 mg/kg on spinal cord blood flow (SCBF). SCBF fell below baseline values in cats given placebo or the 3 mg/kg dose at 4 hours after injury. However, cats given 10 mg/kg of TM had significantly higher SCBF when compared to the other groups. Another interesting find-

ing was discovered when cats originally given placebo were given a 3 mg/kg bolus of TM at the end of the study. SCBF was significantly higher within 30 minutes, and there also was a partial reversal of ischemia. Another study (33) attempted to elucidate a mechanism of action of TM and examined SCBF. In cats given placebo, SCBF had decreased by 42% at 4 hours after injury. In contrast, the treatment groups that received the three highest doses of TM had significantly higher SCBF at 4 hours after injury. Anderson and colleagues (35) demonstrated that TM retains its beneficial effects if treatment is delayed until 4 hours after injury.

As mentioned previously, TM was evaluated in NASCIS 3 (30,31). TM treatment did not result in higher complications than the other treatment groups (in fact, lower rates of pneumonia and urinary tract infection were observed at 6 weeks and 6 months/1 year, respectively). Survival rates at the 1-year assessment point were also similar among the three groups.

The TM treatment regimen used in NASCIS 3 appeared to be as efficacious as the 24-hour MP regimen. This inference relies on the assumption that MP was conclusively proven to be more effective than placebo in NASCIS 2. Because no placebo treatment arm was included in the study, the efficacy of the treatments implemented are better than placebo only if one relies on the conclusions, albeit controversial, drawn from the NASCIS 2 data. Therefore, it is difficult to discern the efficacy of TM in the treatment of acute SCI, and further carefully planned study is necessary.

Opioid Receptor Antagonists

The increase in endogenous opioid levels after acute SCI and subsequent activation of opioid receptors can contribute to secondary damage. Pharmacologic strategies targeted at this secondary mechanism of injury, including opioid antagonism, have been studied.

Naloxone, a nonspecific opioid receptor antagonist, has been the most widely examined agent. It has proven beneficial in several experimental models of SCI, however, not all studies have confirmed this (for a comprehensive review, see Olsson et al. [36]). Naloxone, given as an intravenous bolus of 5.4 mg/kg followed by an infusion of 4 mg/kg for 23 hours, failed to show benefit in NASCIS 2. The authors concluded that naloxone had no role in the clinical management of SCI (27). Further statistical analysis by two of the authors found that for patients with incomplete SCI who were given naloxone within 8 hours of injury, recovery below the lesion was significantly greater than placebo (29). They concluded that naloxone may still be useful for treatment of SCI, but drug dosing regimens and timing of administration may need further refinement in animal studies (29).

It is possible that more specific opioid receptor antagonists may be beneficial in acute SCI (37). It has been shown that κ -receptor binding increases after SCI (38) and that intrathecal administration of dynorphin, the endogenous opioid that binds to κ -receptors, causes paralysis (39). Nalbuphine, a κ -receptor antagonist, improved outcome after SCI in rats (40). Other studies using κ -receptor-specific antagonists in experimental CNS injury models have shown benefit as well (41,42). It is possible that opioid receptor antagonists may have several other mechanisms of action in addition to opioid receptor antagonism. These may include improvement of SCBF, reduction of calcium influx, enhancement of free magnesium concentration and cellular bioenergetic state, and/or modulation of excitatory amino acid release (36,42).

Gangliosides

Gangliosides are complex acidic glycolipids present in high concentrations within central nervous system (CNS) cells. They form a major component of the cell membrane and are located mainly in the outer leaflet of the cell membrane bilayer (43–48). Monosialotetrahexosylganglioside (GM-1 ganglioside) is found in the CNS, particularly in the axons of neurons, myelin sheaths, and glial cells within the white matter (49). GM-1 ganglioside has been shown to accelerate neurite growth and stimulate nerve regeneration. In addition, GM-1 can stimulate regrowth and protect against both retrograde and anterograde degeneration in experimental models of CNS injury (43–49). Gangliosides may also attenuate excitatory amino acid release and regulate protein kinase C, which functions to influence neuronal conductance. Inhibition of protein kinase C may prevent postischemic neuronal damage (11).

A clinical trial published in 1991 evaluated GM-1 ganglioside in the treatment of acute SCI (43). Therapy was initiated within 72 hours after injury, and was administered as an intravenous dose of 100 mg/d for 18 to 32 doses. After 1 year, neurologic function was significantly enhanced when compared to placebo. The authors concluded that GM-1 ganglioside was safe and efficacious in treating SCI. A larger placebo-controlled study using GM-1 ganglioside, in which 797 patients were enrolled, will have results published in the near future (46). To date, a citation has not yet appeared on MEDLINE.

Thyrotropin-Releasing Hormone (TRH) and TRH Analogs

TRH is a tripeptide that has several other physiologic actions in addition to its hypophysiotropic role (50). It

has pronounced autonomic and analeptic effects, and may assume a homeostatic role in regulating body temperature (50). TRH and its analogs may antagonize proposed autodestructive factors such as endogenous opioids, platelet activating factor, peptidoleukotrienes, and excitatory amino acids and thereby impart benefit in the treatment of SCI (39). In addition, they may also augment spinal cord blood flow, restore ionic balances and the cellular bioenergetic state, and reduce lipid degradation (39).

In cats, TRH significantly improved long-term motor recovery after SCI (51,52). Beneficial effects were dose related (52), and treatment was still efficacious if delayed until 24 hours (52,53) or even 1 week (53) after injury. In a small clinical trial, Pitts et al. (50) demonstrated that TRH, when given as an intravenous bolus of 0.2 mg/kg followed by a 0.2 mg/kg/h infusion for 6 hours, resulted in significant improvement in sensory and motor function at 4 months after injury. TRH was administered within 12 hours of injury. TRH analogs, which are more resistant to enzymatic degradation than TRH and therefore have a longer half-life *in vivo*, have also shown benefit in experimental models of SCI (54–58).

Not all analogs of TRH that possess TRH-like activity are effective in SCI. In one study, treatment with the TRH analogs CG3509 and YM14673 resulted in significant improvement in function, whereas the analogs MK-771 and RX77368 were ineffective (57). MK-771 and RX77368 were synthesized by modifying the N-terminus of TRH. Thus, it would appear that an unmodified N-terminus together with modification at the C-terminus is necessary for the beneficial effect of TRH analogs in the treatment of SCI (56,59).

Overall, TRH and appropriate TRH analogs appear to be promising for the treatment of SCI. In studies that have directly compared TRH or TRH analogs to other types of drug treatment including MP, dexamethasone, opioid receptor antagonists, calcium channel blockers, and 5-HT receptor antagonists, TRH or TRH analogs were found to be superior (50). All comparisons involved optimal doses of each compound.

Antioxidants and Free Radical Scavengers

Lipid peroxidation after acute SCI can be attenuated to some degree by endogenous antioxidants (60). However, it has been shown that levels of endogenous antioxidants such as α -tocopherol (vitamin E), retinoic acid (vitamin A), ascorbic acid (vitamin C), selenium, and certain ubiquinones, such as coenzyme Q, are decreased after trauma (11). Thus, replacement of endogenous antioxidants may be effective in preventing damage caused by lipid peroxidation.

Vitamin A and vitamin C pretreatment has shown benefit in experimental models of SCI (23,61). However, adequate levels must be available before injury as uptake into the CNS may be slow (particularly with vitamin E) (62) and therefore, clinical applicability may be limited. Other compounds that act as antioxidants or as free radical scavengers have shown benefit in experimental models of CNS injury. These compounds include desferroxamine, polyethylene glycol conjugated superoxide dismutase, and α -phenyl-*n*-tert-butyl-nitron (38,63–65).

Calcium Channel Blockers

Intracellular calcium accumulation has been labeled the final common pathway in toxic neuronal cell death and may, indeed, assume an integral role in the pathophysiology of SCI. In addition to producing direct neurotoxic effects, intracellular calcium influx into vascular smooth muscle may result in vasospasm (8). Sodium channel blockers, N-methyl-D-aspartate (NMDA), and α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)-kainate receptor antagonists can help prevent intracellular calcium accumulation. Calcium-channel blockers, such as nimodipine, have also been studied to target this derangement in calcium physiology.

Benzamil and bepridil, which are antagonists of the Na^+ - Ca^{2+} exchanger, have been shown to be effective *in vitro* (66). Nimodipine, a member of the dihydropyridine class of calcium channel blockers, has been the most widely studied agent, presumably because of its preferential effects on CNS circulatory function. Nimodipine has been used to reduce the intracellular accumulation of calcium in vascular smooth muscle because this accumulation has been postulated to result in vasospasm and posttraumatic ischemia. Nimodipine has been demonstrated to augment SCBF (67) and reverse posttraumatic ischemia in an experimental model of SCI (68). However, studies examining the effects of calcium channel antagonists on reducing neurotoxic damage and improving outcome after injury have not demonstrated substantial benefit. Calcium overload and associated neurotoxic damage was only minimally reduced by calcium channel blockers such as nimodipine in one experimental study (8). This may result because the voltage-sensitive calcium channels targeted by drugs such as nimodipine are not as important as other mechanisms contributing to intracellular calcium accumulation. For instance, glutamatergic mechanisms involving the NMDA channel appear to be important in the development of neurotoxicity. Several other animal studies have not demonstrated efficacy of calcium channel antagonists in the treatment of SCI

(69–71). When administered after SCI has occurred, nimodipine does not appear to have a significant beneficial effect. Nimodipine does appear to have a benefit when therapy is initiated before injury (8,41), but the clinical significance and practicality of this treatment remains limited. Several reasons underlying the failure of calcium channel antagonists to have beneficial effects on SCI have been proposed. Calcium influx and its consequences may manifest immediately after injury, thereby limiting the window of opportunity for intervention (11). This may underscore the benefit substantiated from pretreatment with nimodipine. Additionally, dosages used in the aforementioned studies may have been inadequate to impart benefit on damaged spinal cord tissue (11). Increasing dosages of calcium channel antagonists may, however, exacerbate hypotension, although augmentation of SCBF has been demonstrated after administration of nimodipine despite concomitant decrease in mean arterial pressure in rats (67,72). The present data examining calcium channel antagonists for the treatment of SCI are therefore equivocal, but methodologic problems have been noted in completed studies, and data from quality human trials are lacking.

Magnesium

Aberrations in magnesium homeostasis leading to depletion appear to be contributing factors to secondary mechanisms of injury. Magnesium replacement therapy has been studied as a means of impacting secondary injury.

Experimental rat models of brain injury have shown some promise. Pretreatment with 0.1 mEq of magnesium sulfate prevented the decrease in free magnesium concentration and significantly improved cellular bioenergetic state and neurologic outcome (73). A later study showed that treatment with magnesium chloride 30 minutes after injury resulted in a significant, dose-dependent improvement in neurologic function when compared to placebo (74). A more recent study (75) demonstrated that treatment with high-dose magnesium (600 mg/kg of MgSO_4) resulted in significant improvements in axonal function (as evaluated by spinal somatosensory evoked potentials) and significant decreases in lipid peroxidation after acute SCI in rats.

Additional research is necessary to further evaluate the potential benefits of magnesium therapy in the management of acute SCI.

Sodium Channel Blockers

After initial injury, there is a deleterious accumulation of intracellular sodium. Thus, drugs that can block

sodium channels and ameliorate this response may be beneficial. Local anesthetics (66,76), antiarrhythmics (77,78), and certain anticonvulsants (79) all targeting sodium channels have been shown to be neuroprotective in *in vitro* models.

Sodium channel blockers have also demonstrated beneficial *in vivo* effects. A study in rats evaluated the use of tetrodotoxin, a potent sodium channel blocker, in acute SCI (80). Although tetrodotoxin appears to be excessively toxic for clinical use, the authors found that local administration of tetrodotoxin after injury resulted in significant long-term tissue sparing and reduced functional deficits (80). Another study involving rats evaluated the potent sodium channel blocker QX-314 (77). Although there was some tissue sparing, there was no significant improvement in neurologic function after injury. Schwartz and Fehlings (81) demonstrated that systemic administration of the sodium channel blocker riluzole provided significant neuroprotection resulting in sparing of both gray and white matter and improvements in behavioral recovery in a rodent model of SCI. Others have found sodium channel blockers to be effective in experimental models of trauma (20,39) and ischemia (82,83). Although the use of sodium channel blockers remains an intuitive therapeutic strategy, there is a paucity of convincing data supporting its efficacy in acute SCI.

NMDA and AMPA-Kainate Receptor Antagonists

Agents that can counter the effects of increased levels of excitatory amino acids (i.e., excitotoxicity), through antagonism of excitatory amino acid receptors, have potential therapeutic uses. Competitive NMDA receptor antagonists can cause inhibition of the receptor by binding at the glutamate recognition site. Non-competitive antagonists bind to the NMDA-associated ion channel and produce inhibition of the receptor. Finally, antagonism of the glycine-binding site can cause NMDA receptor inhibition (84–86).

A study involving the NMDA receptor antagonist memantine, which is used as an antiparkinsonian drug in some countries, was evaluated in two different rat models of SCI (87). The authors found no evidence of a neuroprotective effect in either their ischemic or traumatic SCI model. Other investigators have examined the efficacy of both competitive and noncompetitive NMDA receptor antagonists in experimental CNS injury and have demonstrated beneficial effects (20,88–92). The agents tend to be toxic at therapeutic doses, whereas agents of lesser toxicity appear to lack sufficient receptor affinity. NMDA receptor antagonism may prove to be a future beneficial intervention.

Wrathall et al. (93) evaluated the use of NBQX, a highly selective antagonist of AMPA-kainate receptors in the treatment of SCI in rats. They found that local administration of NBQX at 4 hours after injury spared gray matter adjacent to the injury site, and may have resulted in some neuronal sparing caudal to the injury site (93). However, there was no significant difference in functional recovery between the treatment and control groups until two weeks or more after injury (93). An earlier study by Wrathall et al. (94) in which NBQX was locally administered 15 minutes after injury found that there was significant white matter sparing in addition to gray matter sparing, as well as a more rapid functional recovery. A further study (95) looked at the effects of NBQX after spinal contusion in rats. Focal microinjection of NBQX resulted in a significant improvement in the axonal injury index, which is a quantitative representation of axoplasmic and myelinic pathologies. In addition, glial loss (primarily of oligodendrocytes) was reduced by 50%.

Modulation of Arachidonic Acid Metabolism

Conversion of arachidonic acid to thromboxanes, prostaglandins, and leukotrienes after acute SCI is harmful because of the propensity for subsequent compromised blood flow and platelet aggregation, resulting in ischemia. Drug therapy aimed at inhibiting the enzymes responsible for the conversion of arachidonic acid may be useful. Administration of prostacyclin (PGI₂) or related analogs has also been studied. Prostacyclin is a natural metabolite of arachidonic acid, predominantly produced from vascular endothelium, that exerts powerful vasodilatory effects and inhibits platelet aggregation (96).

Hallenbeck et al. (97) evaluated naloxone and combined indomethacin, heparin, and prostacyclin therapy in cats. In the combined treatment group, therapy was initiated 1 hour after injury. Indomethacin (4 mg/kg) and heparin (300 U/kg) were given by intravenous bolus at 1 hour and 2 hours after injury. Prostacyclin (200 ng/kg/min) was administered by continuous intravenous infusion. Combined treatment resulted in significantly improved neurologic function compared to placebo. Efficacy of the combined treatment regimen was comparable to naloxone treatment.

The efficacy of pretreatment with ibuprofen and meclofenamate (both nonsteroidal antiinflammatory drugs and inhibitors of cyclooxygenase), a selective thromboxane A₂ synthetase inhibitor, or a prostacyclin analog in maintaining SCBF has been evaluated in cats (41). SCBF was maintained within normal limits when pretreatment with ibuprofen or meclofenamate was used. Pretreatment with the thromboxane A₂

synthetase inhibitor or the prostaglandin I₂ analog was not effective, but pretreatment with both agents together limited the decline in SCBF (41). Derivatives of prostacyclin and mixed cyclooxygenase-lipoxygenase inhibitors have also shown benefit in rat models of SCI (98,99). The stable prostacyclin analog, iloprost, has been effective in experimental models of SCI (100,101).

A growing body of evidence suggests that COX-2 is important in the evolution of secondary SCI as previously outlined. Resnick et al. (102) demonstrated that COX-2 mRNA and protein expression were increased after SCI and that treatment with a selective COX-2 inhibitor (SC58125) improved functional outcome after experimental SCI. Additionally, in an experimental model of reversible spinal cord ischemia, treatment with the selective COX-2 inhibitor SC-236 resulted in neuroprotection and improvements in behavioral deficits in rabbits (103).

The preliminary data examining the effects of modulation of arachidonic acid metabolism are encouraging. Hence, further study delineating the role for modulation of arachidonic acid metabolism in the treatment of SCI seems appropriate.

Other Possible Treatment Strategies

Neurotrophic growth factors can prevent neuronal degeneration after injury and may also stimulate reactive sprouting of spared neurons (104). Neurotrophic growth factors have been of some benefit in experimental models of SCI (105–114). Serotonin antagonists may also be beneficial in the treatment of SCI. Agents with antagonist activity at 5-HT₁ and 5-HT₂ receptor subclasses have shown benefit in experimental SCI (58,115). Because it has been shown that nerve grafts are capable of regenerating and elongating under experimental conditions (108,116,117), it is possible that agents that aid in axonal elongation may be beneficial in the treatment of SCI. It has been shown in experimental models that antibodies against inhibitors of axonal regeneration (*e.g.*, MAG) (118) have potential in the treatment of SCI through the neutralization of the antiregenerative effects (119–125).

The potassium channel blocker 4-aminopyridine has been evaluated in several small clinical trials. It is beneficial in the treatment of patients with “chronic” SCI. That is, some patients who have been living with a SCI for some time show benefit in terms of recovery of neurologic function (126–132). This recovery is thought to be caused by the potassium channel blocking action of 4-aminopyridine, which enhances conduction across demyelinated internodes and enhances neuroneuronal and neuromuscular transmission in preserved axons

(129,130). A recent qualitative study (133) evaluated the antineoplastic paclitaxel, MP, and 4-aminopyridine in the treatment of acute SCI in rats. Paclitaxel was administered at a dose of 18.75 mg/m² 6 days a week for 2 weeks. Behavioral tests, recording of cortical somatosensory evoked potentials, and histologic tests were performed to evaluate improvement. Both the paclitaxel- and MP-treated groups showed benefit in terms of the evaluation criteria, whereas the 4-aminopyridine group did not. The rationale for the use of paclitaxel in the study was that a low dose administered after acute SCI would protect the cytoskeleton of spinal axons. This would maintain neuronal shape and still allow the intracellular transport of vesicles and cellular organelles (133).

A number of other less widely known therapeutic agents have also been studied. Clenbuterol, a β_2 -adrenoceptor agonist, was shown to enhance recovery of locomotor function and result in significant neuroprotection in the injured spinal cord in rats (134). Progesterone also appears to improve outcome after SCI in rats. In one study, progesterone resulted in significantly better functional outcomes (as evaluated by the Basso-Beattie-Bresnehan locomotor rating scale) and significantly greater sparing of white matter tissue at the epicenter of the injury (135). Gabexate mesylate, a protease inhibitor with both anticoagulant and antiinflammatory activity, has also shown benefit in experimental SCI. Both pre- and posttreatment with gabexate mesylate resulted in significant reductions in motor disturbances as evaluated by Tarlov’s score, as well as significant reductions in leukocyte accumulation in the injured tissue, as measured by tissue myeloperoxidase activity (136). Finally, activated protein C, a serine protease with anticoagulant activity, has been beneficial in the treatment of experimental SCI. Pre- or postinjury treatment reduced the number of intramedullary hemorrhages as well as the severity of motor disturbances (137).

Targeting the apoptotic cascade of cell death after SCI is emerging as a potential avenue for therapeutic intervention (16,138), although investigation in this area is still in its infancy. Caspase activation is important in the apoptotic pathway and secondary SCI (139–142). Recently, caspase-3 inhibition (with intraperitoneal zDEVD fmk) has been found to be neuroprotective in experimental SCI (139). Administration of Bcl-2 (an antiapoptotic protein) was also found to be neuroprotective in experimental SCI (143). The putative protective effects of Bcl-2 have also been confirmed by the demonstration that transgenic mice overexpressing this protein are resistant to ischemic injury (144). Additionally, based on the premise that apoptosis involves protein synthesis, investigators have examined the effects

of protein synthesis inhibitors in experimental models of SCI. Indeed, administration of protein synthesis inhibitors such as cycloheximide improves behavioral outcome after SCI in rats (145). Inhibitors of the calcium-activated protease calpain (146) and of the c-Jun N-terminal kinase signaling pathway (147) can also attenuate the development of apoptosis in motor neurons. In addition, because apoptosis can be triggered by a plethora of other mechanisms of secondary injury including cytokines, inflammatory injury, free radical damage, and excitotoxicity (16), treatment aimed at these mechanisms of injury can further prevent programmed cell death. For example, treatment with low doses of a nitric oxide synthase inhibitor (*N*-nitro-L-arginine) significantly reduced motor disturbances in experimental SCI (148). Inducible nitric oxide synthase is important in inflammation and the generation of free radicals, but also activates the apoptotic cascade.

Tacrolimus (FK-506), a widely used immunosuppressant in transplantation medicine, was shown to be neuroprotective as demonstrated by significant increases in axonal sparing after SCI in rats (149). It also helped to promote axonal regeneration in severed sensory axons in one study (149) and accelerated the elongation of spinal cord axons and promoted regeneration of rubrospinal neurons in another (150). Tacrolimus has also proven to increase neuronal expression of GAP-43 (a neuronal growth-associated protein) and improve functional recovery after SCI in rats (151). In addition, tacrolimus appears to have a synergistic effect with MP (149). Cyclosporine A has similarly demonstrated some efficacy in the treatment of traumatic CNS injury. Cyclosporine A has antiinflammatory/immunosuppressive properties and appears to target Ca^{2+} -induced permeability changes of the inner mitochondrial membrane (which reduce the membrane potential and may contribute to osmotic swelling and mitochondrial lysis) by inhibiting this process and thereby preventing cell death (152,153). Furthermore, cyclosporine A inhibits lipid peroxidation to the same extent as MP and produces clinical improvement after SCI in experimental models (154,155). Recent investigation has helped to discern the optimal dosing strategy to impart neuroprotection in experimental SCI (156). Although perhaps better studied in traumatic brain injury, these agents hold promise in the treatment of SCI, and further investigation may prove fruitful.

The orchestrated inflammatory response after SCI is important both as a pathophysiologic mechanism and potential therapeutic target. Leukocyte migration has received attention as a therapeutic target. Monoclonal antibodies specifically directed against adhesion molecules including P-selectin (157,158) and

ICAM-1 (159) impart neuroprotection in experimental models of SCI. In a complementary line of investigation, Mabon et al. (160) demonstrated that monoclonal antibodies directed against integrin α D (a protein on monocytes/macrophages and neutrophils that binds to vascular adhesion molecule-1) inhibited monocyte/macrophage migration (and neutrophil migration to a lesser extent) to the site of SCI (160). Because chemokines and chemokine receptors are up-regulated and implicated in secondary SCI, infusion of the chemokine antagonist vMIPII blocking the interaction of chemokine receptors with their ligands reduced cellular infiltration in experimental SCI and provided neuroprotection (161). Additionally, other treatments including iloprost, gabexate mesylate, and activated protein C inhibit leukocyte activation and diminish the motor disturbances resulting from traumatic spinal cord compression (101,136,137). Clearly, the inflammatory cascade as a potential focus for intervention merits further investigation as a means for attenuating the secondary damage apparent after SCI.

CONCLUSION

SCI results from both primary and secondary mechanisms of injury (6–8,162–164). Secondary mechanisms of injury encompass an array of pathophysiologic processes including neurogenic shock, vascular insult including hemorrhage and ischemia–reperfusion, excitotoxicity, calcium-mediated secondary injury and fluid-electrolyte disturbances, immunologic injury, apoptosis, mitochondrial injury, and various other mechanisms. It is these secondary mechanisms of injury that appear amenable to pharmacologic therapeutic strategies. Pharmacotherapy targeted at specific secondary mechanisms of injury has been extensively studied. In particular, the efficacy of MP has been examined in large clinical trials. Many individuals consider MP administered within 8 hours of injury (with a 24-hour course if instituted within 3 hours of injury and a 48-hour course if instituted within 3 to 8 hours of injury) to be the standard of care for the treatment of acute SCI. However, this has not been established definitively, and questions pertaining to methodology have emerged regarding the NASCIS trials that provided these conclusions (17,20–22). Additionally, the clinical significance (in contrast to statistical significance) of recovery after MP appears equivocal and must be interpreted with the realization that MP treatment is not innocuous. High-dose MP treatment is associated with immune suppression and increased morbidity from infection in addition to prolonged hospitalization (22,165). GM-1 ganglioside treatment appears to be a potentially beneficial strategy for SCI based on preliminary clinical

and experimental data. Results from a multicenter trial evaluating the efficacy of GM-1 ganglioside treatment may be available soon.

The current standard of care in the management of patients with acute SCI is evolving. The principal goals of initial management of the patient with SCI are to prevent secondary injury and obtain a clinical assessment and radiologic evaluation. Patients are immobilized in the field and transferred to the appropriate medical facility with spinal precautions including a rigid collar and backboard. On arrival, a primary survey is performed and resuscitation is of course initiated according to American Trauma Life Support guidelines (166), and oxygen saturation is maintained at 100%. Patients with high cervical injuries may require intubation and mechanical ventilation. Neurogenic shock is treated with volume and pressor administration. Associated injuries are evaluated and treated accordingly. Neurologic and radiographic evaluation is undertaken during the secondary trauma survey. Patients presenting with neurologic deficit and evidence of cervical spine injury should generally be placed in cervical traction (with the exception of atlantooccipital injuries and type IIA hangman's fractures where its use is contraindicated). A more detailed neurologic assessment, using evaluation tools such as the American Spinal Injury Association's standardized form, can then be performed and repeated at regular intervals. Pharmacologic therapy in acute SCI remains a matter of present controversy. As mentioned, there are data (albeit controversial) to support the use of MP and GM-1 in acute SCI. However, the present authors contend that these agents do not necessarily represent the current standard of care. Indeed, in the Province of Alberta, Canada, neither of these treatments is used in the treatment of acute SCI as decided by a Consensus Committee comprising all neurosurgeons and other practitioners in the Province. Although beyond the scope of this discussion, surgical therapy, incorporating early decompression and stabilization, may be applied in certain situations. Patients with SCI are then cared for to maximize function through extensive and intensive rehabilitation and minimize medical complications including pulmonary complications, deep venous thrombosis, contractures, and inadequate nutrition.

A variety of other agents have shown benefit in experimental models of SCI but must be subjected to rigorous evaluation in clinical trials before being readily adopted in the management of patients with SCI. Additionally, delineation of optimal dosages must be undertaken to ensure maximal efficacy of currently available agents. Future research must also examine polypharmacotherapy to elucidate potential additive, synergistic, or antagonistic effects with combinations

of various agents. Finally, subsequent research must also evaluate the use of staged pharmacotherapy, with different agents being used during their respective therapeutic windows. Although substantial progress has been made thus far in SCI research, SCI still remains a significant cause of morbidity and mortality. The 21st century, and in particular the Decade of the Spine, will prove to be an exciting and fruitful period for SCI research, hopefully culminating in a cure for this devastating neurologic disorder.

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