Restorative Neurological Approaches to the Rehabilitation of Individuals with Longstanding Spinal Cord Injury

Keith C. Hayes, Andrew L. Davies, and Patrick J. Potter

Recent advances in understanding the neurobiology of spinal cord injury (SCI) have led to the development of therapeutic approaches enabling restoration of neurological function in SCI patients. This review describes the status of restorative interventions that have already been introduced to clinical practice through clinical trials and other interventions that show promise for ameliorating neurological deficits and restoring functional independence. These approaches include management of central conduction deficits due to traumatic demyelination or channelopathy, strategies that capitalize on the intrinsic plasticity of the neuraxis following trauma, and pharmacotherapy to enhance target organ function, such as in the case of erectile dysfunction. **Key words**: *4-aminopyridine, channelopathy, cytokines, erectile dysfunction, fampridine, gait, phosphodiesterase inhibitors, plasticity, rehabilitation, sildenafil, spinal cord injury*

Over the past few decades, the rehabilitation of patients with spinal cord injury (SCI) has focused on enabling spontaneous recovery, maintaining life support in the case of ventilator-dependent patients, promoting functional independence through assistive devices, prevention and/or management of secondary medical or psychological complications, and removing barriers to social and vocational reintegration. There have been few, if any, therapeutic strategies with proven efficacy available for treating the underlying neurological deficits and restoring function per se. This situation developed in large part because of the long-recognized limited regenerative capacity of injured axons within the central nervous system (CNS) and the assumption that loss of sensory or motor function invariably stemmed from axonal degeneration.

Several new therapeutic strategies are now emerging with the potential to restore neurological function in paraplegic and tetraplegic patients. These strategies can be categorized as:

- therapies that unmask and maximize the functional properties of preserved parenchyma, i.e., spared long tract axons;
- techniques for augmenting plastic

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Top Spinal Cord Inj Rehabil 2004;10(1):51–62

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"compensatory" adaptations intrinsic to the cerebral cortex and spinal cord; and

- pharmacotherapies for enhancing the function of target organs with compromised innervation.

Each of these has the potential to introduce significant improvements in functional independence and enhanced quality of life.

These approaches have emerged coincident with the recognition, from studies of the neuropathology of SCI, that complete anatomical transection of the cord is relatively rare, even in the presence of majorly disruptive orthopedic trauma.[1] Sparing of long tract axons that traverse the lesion epicenter appears to a greater extent than would be expected from the functional (sensory, motor, and autonomic) losses evident on clinical examination.[2,3] In fact, in some cases of clinically complete functional loss, there may be as much as 28% sparing of long tract axons.[4] The preserved but oftentime dysfunctional innervation provides the anatomical substrate for restorative therapy.

Neuroanatomical Basis for Restorative Therapies

In many cases of compressive or contusive cord trauma, the emergent neuropathological picture is one of hemorrhagic necrosis in the central gray matter extending caudal and rostral to the site of primary insult, varying degrees of white matter pathology that spreads centrifugally, and preservation of a subpial rim of white matter.[1,3–5] The degree of white matter sparing is related to the degree of spared function, that is, the extent to which the injury is "incomplete." In some instances, however, the sensory and motor losses exceed that which is evident from the myelopathy. There are cases in which there is sparing of long tract axons with no evident preserved function on routine clinical or electrophysiological examination. These cases have been designated "discomplete" injuries.[4,6,7] Some of the preserved innervation is detectable only with sophisticated electrophysiological methods, such as transcranial magnetic stimulation of motor cortex[8] or somatosensory evoked potentials,[9] or when facilitation techniques are coupled with electromyographic recordings.[6,7]

Microscopic examination of preserved axons within compressed human spinal cords has revealed the presence of focal demyelination or incomplete remyelination.[10] Traumatic demyelination (myelinopathy) leads to exposure of fast voltage-gated potassium (K^+) channels in the paranodal region, an increase in membrane capacitance, and an impedance mismatch at the transition between myelinated and demyelinated areas.[11–13] This in turn leads to a decrease in action current density with associated conduction deficits and/or failure. Demyelination-based conduction block yields neurological deficits indistinguishable from axonopathy on clinical exam, but unlike axonopathy it may be reversible by pharmacotherapy.[13]

There are other plausible neurophysiological bases for the failure of preserved axons to yield clinically or electrophysiologically detectable sensory or motor function. These include insufficient spatial or temporal summation of excitatory synaptic inputs to raise motoneurons to threshold, concurrent peripheral nerve injury, or preservation of axons with integrative functions, for example, with autonomic function or modulating interneuron activity. A newly

emerging concept is that some axons are dysfunctional because of immune-mediated alterations in axonal ion channel conductance or channelopathy.[14] Cytokine and antibody-mediated conduction deficits have been considered to be contributory to neurological deficits in other neuroinflammatory conditions.[15] An important element of this line of inquiry is that these types of deficits may be remediable by immunomodulatory therapies.

Caudal to the site of injury, the cytoarchitecture of the spinal cord remains essentially intact with the qualification that some or all descending motor tracts may have degenerated. This leaves the spinal circuitry subserving segmental reflex activity spared but poorly modulated by descending supraspinal inputs. This also means that the spinal centers and circuitry involved in step generation are putatively accessible for restorative therapies.

Restoration and Augmentation of Central Axonal Conduction

Fampridine (4-aminopyrdine, 4-AP) is a compound that blocks fast voltage-gated K^+ channels in excitable tissues.[11] It blocks the outward K^+ current that occurs following demyelination and allows an increase in the duration of the Na^+ current. By prolonging the duration of the action current (and thus the action potential), K^+ channel blockade increases the safety factor for conduction across demyelinated internodes.[11,16,17] The safety factor is the ratio of action current generated by an impulse to the minimum amount of action current needed to maintain conduction. Fampridine has been shown to reverse conduction failure in demyelinated axons.[11,16,17] K^+ channel blockade also increases calcium (Ca^{++}) influx at presynaptic terminals leading to increased neurotransmitter release and enhanced neurotransmission.[18] Because of these properties and the fact that it passes freely through the blood-brain barrier, fampridine has been proposed as a pharmacotherapy for overcoming demyelination-based central conduction deficits in patients with multiple sclerosis or SCI.[12,13,17,19,20]

Randomized, placebo-controlled, clinical trials of fampridine in individuals with chronic incomplete SCI have yielded evidence of improved sensory and motor function, enhanced control over bowel and bladder, reduced pain and spasticity, and increased penile tumescence.[19–23] Trials using an immediate release oral formulation are summarized in **Table 1**. The most consistent outcome has been reduction in spasticity. Approximately one third of all study participants have derived some therapeutic benefit sufficient to warrant continuation with the medication. Unwanted side effects include mild and usually transient paresthesias, gastric discomfort, or agitation.[20,24] Overdose or unregulated usage has been associated with confusion, cardiac and respiratory distress, and epileptiform seizure activity.[25–27] Functionally, the benefits of fampridine have been expressed as improvements in gait, activities of daily living, breathing, continence, and erectile dysfunction.[20,21] It is not surprising therefore that individuals with SCI who have received fampridine report significant improvements in quality of life.[20]

Not all of the clinical trials of fampridine have yielded evidence of therapeutic efficacy.[28] Many of the early trials utilized an immediate-release form of the drug with high peak serum concentrations and short

Table 1. Randomized clinical trials of fampridine in patients with incomplete spinal cord injury

Investigators	Form	Dose (mg)	Design	*n*	Positive outcomes
Hansebout et al.[19]	IV	18–33.5	Double-blind, placebo-controlled crossover	8	Sensory score Breathing Pain Spasticity
Segal et al.[21]	IR	6–30[a]	Randomized, open-label, active-treatment control, dose-blinded	21	Motor scores Sensory scores Ashworth Scale Breathing
Wolfe et al.[23]	IR	10	Double-blind, placebo-controlled crossover	25	Motor evoked potentials Central conduction
Van der Bruggen et al.[28]	IR	15–45[b]	Double-blind, placebo-controlled crossover	21	nil
Grijalva et al.[22]	IR	5–30	Randomized, double-blind, placebo-controlled	27	Motor function Sexual function Functional independence

Note: IV = intravenous; IR = immediate release capsule.
[a]Total dose per day: 6 mg active treatment control. [b]Total dose per day: range based on 0.5 mg/kg body weight.

half-life.[29] Low dosages and outcome assessment without due consideration of the pharmacokinetic profile, coupled with limited duration of bioactivity, may have contributed to the failure to detect any therapeutic benefit. More recent trials with a sustained release (SR) matrix tablet formulation that has a longer half-life[24,30] have demonstrated consistent therapeutic benefits, tolerable side effects, and a good safety profile.[31,32] These trials are summarized in **Table 2**. The prolonged half-life also enables a dosing regimen likely to meet with greater patient compliance. Phase 3, multicenter clinical trials of fampridine-SR are close to completion, and it is anticipated that the drug will satisfy Federal regulations and be marketed in the near future.

The importance of the fampridine-SR development is that this compound is the first pharmacotherapy to directly restore neurological function. It likely represents the leading edge of a new generation of pharmaceuticals designed to overcome trauma-induced axonal conduction deficits and thereby increase functional independence. Other candidate drugs are in early stages of investigation.

Although the primary mechanism of action for the therapeutic efficacy of fampridine has been considered to be the reversal of demyelination-induced axonal conduction failure, there are other possibilities. Smith et al.[18] have suggested the primary benefit derives from enhanced neurotransmission in spared axons, and Köller et al.[15] have speculated that fampridine reverses immune-mediated (cytokine?) axonal ion channel dysfunction.

Proinflammatory cytokine or antibody-mediated axonal dysfunction is thought to contribute to the neurological deficits associated with various neuroinflammatory diseases.[15] Consideration is now being given to the suggestion that a similar process may be occurring in chronic SCI.[14] Appreciable numbers of chronic SCI patients exhibit abnormally high serum titers of the proinflammatory cytokines interleukin 2 (IL-2), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF-α).[14] High serum liters of antibodies against GM_1, ganglioside (anti GM_1), and myelin-associated glycoprotein (anti MAG) have been reported.[14] Serum concentrations of these cytokines and antibodies are greatest in SCI patients with medical complications of pressure sores or infection, although they can also be abnormally elevated in chronic SCI patients who are asymptomatic for infection or inflammation. It has now been established that peripherally circulating proinflammatory cytokines pass through the blood-brain barrier and into the cerebrospinal fluid and CNS. They also influence CNS induction of cytokines through other means.

The proposition that cytokine or antibody-mediated alterations in axonal or glial ion channel conductance contribute to neurological dysfunction in SCI is particularly intriguing as it raises the possibility of another reversible (therapeutically remediable) form of deficit. It is conceivable that immunomodulatory therapies such as plasmapharesis, high dose IgG, anticytokine therapies, or simply effective management of depression, infections, and pressure sores could lead to restoration of neurological function. The late onset neurological recovery of a C2 quadriplegic patient reported by McDonald et al.[33] has a time course that corresponds to resolution of his immunological challenge and thus is compatible with the channelopathy hypothesis.

Table 2. Randomized clinical trials of fampridine–SR in patients with incomplete spinal cord injury

Investigators	Form	Dose (mg)	Design	*n*	Positive outcomes
Potter et al.[20]	SR	12.5–17.5 bid	Multicenter (2) double-blind, placebo-controlled crossover	26	Motor score Sensory score Ashworth Scale Quality of life Patient satisfaction
Ditunno et al.[31]	SR	10–25 bid	Multicenter (6) randomized, double-blind, placebo-controlled crossover dose escalation	60	Erectile dysfunction Ashworth Scale
Lammertse et al.[32]	SR	25–40 bid	Multicenter (11) double-blind, placebo-controlled, parallel group	91	Subject global impression Bowel function Ashworth Scale

Note: SR = sustained release tablet; bid = twice a day.

Restoration of Gait

Restoration of the capability of SCI patients to walk has been the focus of extensive investigation.[34–38] Several well-established phenomena provide impetus to the research effort: the capability of the isolated mammalian spinal cord to generate rhythmic stepping movements, adaptive plasticity and "learning" properties of the isolated cord, and the responsiveness of incomplete SCI patients to intense locomotor training with or without adjunctive pharmacotherapy.

Although the most convincing evidence of the rhythmic step-generating capability of the isolated cord undoubtedly comes from animal models, there are accumulating reports of similar properties in human SCI patients with complete or incomplete functional loss. Calancie et al.[39] induced rhythmic involuntary leg movements in a patient with chronic, incomplete SCI and hip pain by positioning the patient supine with hips in extension. The leg movements disappeared if hip pain was temporarily abolished by xylocaine infiltration. Similarly, Dimitrijevic et al.[35] used epidural electrical stimulation of patients with longstanding complete SCI and elicited patterned locomotor-like leg muscle activity. Nonpatterned trains of stimuli applied (25–60 Hz; 5–9 V) over the second lumbar segment were effective in inducing rhythmic alternating stance and swing phase muscle activity in the lower limbs. Although the movements were neither functional nor involved weight bearing in these studies, they do appear to support the notion that a "central pattern generator" or step-generating mechanism is intrinsic to the human cord and can be activated by appropriate stimulation.

Cats with complete spinal cord transaction at low thoracic levels that have been trained to induce hind limb stepping on a treadmill are able to execute appreciably more weight-bearing steps than nontrained cats.[40] Similar observations of a training effect have been reported for postural control.[41] Cats with transected cords that received 12 weeks of postural training stood with full weight bearing on the hind limbs for a greater length of time than did untrained cats. These and other studies illustrate that the cord isolated from descending supraspinal modulatory influence can "learn" to produce appropriate adaptive locomotor responses. Emerging from this work has been the motivation and the guiding concepts for human SCI locomotor training programs.[38]

Gait retraining programs for SCI patients have developed along several lines. Harness-supported locomotion, with treadmill training, assistance from exoskeletal robotic drive, functional electrical stimulation, or pharmaceuticals have all been used in varying combinations. The concept of "forced reuse" has also been introduced. While many reports claim successful outcomes from these novel therapies, few to date have been subjected to rigorous methodological control. In one of the largest trials, Wernig et al.[38] investigated the effects of treadmill training (with harness support and therapist assistance) on 89 individuals with incomplete SCI. Forty-four of these individuals had chronic disability, the remaining 45 patients were in the acute stage after trauma. A control group of 64 SCI patients undergoing conventional therapy served as controls. On completion of the treadmill training, appreciably more of the treadmill-trained individuals were able to walk independently. In most instances, these gains were sustained for many years. Since many of the treadmill-trained patients improved their gait without

commensurate gains in voluntary muscle activity, it would appear that the beneficial outcomes stem from enhanced reflex or central pattern generator activity.

Collectively the locomotor training programs provide optimism that some degree of functional restoration of gait is possible. Building on this neurological base with pharmaceutical and/or assistive devices (functional electrical stimulation or orthoses for example) should eventually enable more functional gait, at least in patients with incomplete injuries.[36]

Restoration of Sexual Function

Erectile dysfunction (ED) is a frequent consequence of traumatic SCI, with the incidence and nature of dysfunction dependent on the neurological level of injury and whether the injury is "complete" or "incomplete." Restoration of ED has been the focus of considerable investigation with respect to SCI in recent years.[42–45] There has been notable success to date utilizing phosphodiesterase-5 (PDE-5) inhibitors, and several other novel approaches are in development. ED is just one of several factors contributing to compromised sexual function.

The neurological level of SCI is particularly significant in consideration of ED because the capability to develop and sustain an erection depends on penile innervation from three systems: the sacral parasympathetic (pelvic nerve), thoracolumbar sympathetic (hypogastric nerve and lumbar sympathetic chain), and somatic (pudendal nerve). Men with functionally complete lesions above the thoracolumbar outflow (T6) are unable to transmit descending "psychogenic" input to the sacral levels but do have reflex (peripheral sensory stimulation) erections preserved as a result of diminished cortical inhibition. Male patients with sacral damage but intact thoracolumbar pathways lose the reflexogenic erectile response but retain psychogenic erections. Patients with lesions between T6 and S1 frequently have some preservation of both psychogenic and reflexogenic erections, but the diminished coordination among erectogenic sources may lead to unreliable erections.

The primary restorative approach to management of ED in SCI patients has been through the PDE-5 inhibitor sildenafil. Sildenafil has been shown to effectively treat ED in SCI, with only mild and tolerable side effects in a series of case control studies and controlled clinical trials.[42–45] Sildenafil-induced inhibition of PDE-5 results in prolongation of the biologic activity of cyclic guanosine monophosphate, allowing smooth muscle relaxation and facilitation of erections. Side effects of sildenafil are mild and transient.

Investigational new oral pharmacotherapies for ED with potential application in SCI include (a) modulators of activity within the hypothalamic and brainstem nuclei and descending central pathways mediating psychogenic inputs[46,47]; (b) new, more sensitive, and potent PDE-5 inhibitors, for example, vardenafil, which is currently being studied in SCI patients, and tadalafil, which has a very long half-life; and (c) smooth muscle K_{ATP} channel openers such as cromakalim, pinacidil, and minoxidil.[48] In addition, it has been noted that the K^+ channel-blocking agent fampridine has erectogenic properties, an effect most probably mediated by enhancing the descending erectogenic inputs rather than producing a direct effect on smooth

muscle K^+ channels. Modulators of descending inputs would likely be more effective for patients with incomplete or discomplete injury than patients with complete cord transection. The more selective PDE-5 inhibitors would be expected to benefit patients with either incomplete or complete injuries.

Other Restorative Therapeutic Opportunities

Cortical reorganization after SCI is now being described and elaborated by various neurostimulation and neuroimaging techniques.[49] Studies using transcranial magnetic stimulation (TMS), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI) have revealed changes in the sensory and motor cortical representation, that is, in the sensory and motor homunculi.[50–54] This is thought to reflect adaptation to deafferentation and the modifications in motor cortical output. In addition, TMS has provided evidence of reduced intracortical inhibition,[55,56] a phenomenon also indicated by PET evidence of reduced cortical gamma aminobutyric acid (GABA).[57] Reduced cortical inhibition is thought to reflect a compensatory process offsetting compromised motor output. Additional compensatory changes are indicated by EEG recordings that show that the dipole source of motor potentials moves posteriorly, reflecting an increased role of somatosensory cortex in movement production of SCI patients.[58] This observation has been independently verified by fMRI.[54]

The documented changes in cortical organization beg the question: Are there beneficial compensatory adaptations that can be manipulated by physical means, such as forced use, or by pharmacotherapy? Much remains to be elucidated about how current and novel pharmaceuticals such as GABA agonists or K^+ channel blockers influence the demonstrated cortical plasticity. Opportunities may exist to pharmacologically enhance intrinsic compensatory adaptations within the cerebral cortex.

Summary

Whereas it has long been held that little functional restoration could be expected after approximately 18 months post injury, there is now emerging an optimism that at least some neurologic deficits can be reversed or ameliorated, even in individuals with longstanding disability. Prominent among the restorative strategies are pharmacotherapies for overcoming central conduction deficits due to demyelination and for overcoming erectile dysfunction. These therapies are the first wave of designer drugs to be developed to address these issues. More are currently in phase 1 and 2 clinical trials. Also emerging are therapeutic strategies designed to capitalize on the intrinsic plasticity of the spinal cord to aid recovery of walking. Exploration of ways to maximize beneficial adaptations in cortical plasticity remains an untapped opportunity to achieve functional restoration. Combining these restorative approaches with existing rehabilitation strategies is likely to yield even greater benefit than when either are applied alone, and collectively they hold promise for increasing functional independence with associated enhancement of quality of life.

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