Rehabilitation Strategies after Spinal Cord Injury: Inquiry into the Mechanisms of Success and Failure

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Abstract

Body-weight supported locomotor training (BWST) promotes recovery of load-bearing stepping in lower mammals, but its efficacy in individuals with a spinal cord injury (SCI) is limited and highly dependent on injury severity. While animal models with complete spinal transections recover stepping with step-training, motor complete SCI individuals do not, despite similarly intensive training. In this review, we examine the significant differences between humans and animal models that may explain this discrepancy in the results obtained with BWST. We also summarize the known effects of SCI and locomotor training on the muscular, motoneuronal, interneuronal, and supraspinal systems in human and non-human models of SCI and address the potential causes for failure to translate to the clinic. The evidence points to a deficiency in neuronal activation as the mechanism of failure, rather than muscular insufficiency. While motoneuronal and interneuronal systems cannot be directly probed in humans, the changes brought upon by step-training in SCI animal models suggest a beneficial re-organization of the systems' responsiveness to descending and afferent feedback that support locomotor recovery. The literature on partial lesions in humans and animal models clearly demonstrate a greater dependency on supraspinal input to the lumbar cord in humans than in non-human mammals for locomotion. Recent results with epidural stimulation that activates the lumbar interneuronal networks and/or increases the overall excitability of the locomotor centers suggest that these centers are much more dependent on the supraspinal tonic drive in humans. Sensory feedback shapes the locomotor output in animal models but does not appear to be sufficient to drive it in humans.

Keywords: locomotor function; neuroplasticity; rehabilitation; spinal cord injury

Introduction

CONSIDERABLE PROGRESS HAS BEEN MADE in the last few years in understanding the effects of spinal cord injury (SCI) on function and in developing treatments to ameliorate deficits. Although several promising therapies have reached the clinical trial stage, outcomes (e.g., early termination due to significant side effects and lower than anticipated recovery of motor function) often fall short of our expectations. Most of the tested strategies aimed at improving functional recovery in SCI individuals were pharmacological in nature (e.g., drugs or secreting cell transplants), which may have serious systemic effects that prevent meeting quality-of-life standards. Among the factors responsible for the failure to successfully translate therapies to the clinic, two are of main concern: 1) the lack of knowledge about human SCI to compare with animal data, and 2) the divergence between strictly standardized and reproducible animal models of SCI versus the heterogeneity of human injuries. Both play a significant role when comparing the locomotor recovery obtained with activity-based therapies in animals and individuals, and interfere with the interpretation of outcomes.

Locomotor recovery: successes from the bench to the bedside

Non-invasive interventions, including various types of motor training (e.g., ladder walking, reaching, bicycling, swimming, and locomotor training on a treadmill) decrease the inflammatory response, increase neurotrophin levels, and may strengthen spared functions and guide spinal reorganization. Locomotor training successfully improves the recovery of stepping movements in various animal models including mice,^{1,2} rats,^{3,4} and cats (Fig. 1).^{5–10} There is evidence that anatomical and physiological changes promoted by training in spinal animals occur both within^{11,12} and outside the locomotor circuitry,^{13–15} although the mechanisms are unclear.

Some success also has been achieved in SCI individuals (Fig. 1).^{16–18} Motor incomplete SCI individuals (i.e., C or D on the American Spinal Injury Association Impairment Scale [AIS])^{19–22} show some improvements in overground locomotion, as measured by a reduction in the requirement for body weight support and the return of some independent stepping. In motor complete SCI individuals (AIS A and AIS B), several aspects of the locomotor

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FIG. 1. Locomotor training induced plasticity in animals and humans. Summary of the effects of step-training on various aspects of the locomotor circuitry in animal models (all panels, left) and in humans (all panels, right). Electromyographic (EMG) data for complete and incomplete spinal cord injury (SCI) individuals provided courtesy of Dr. Maria Knikou. AIS, American Spinal Injury Association Impairment Scale; ES, electrical stimulation; NA, noradrenalin; VLF, ventrolateral funiculus; PICs, persistent inward currents.

electromyographic (EMG) pattern improve, including increased EMG amplitude, changes in EMG onset and offset, improved reciprocal activation between extensors and flexors, and better alternation between the left and right legs.^{23–25} Even if the improvement in EMG activity does not translate to better overground walking despite intensive treadmill training, this nonetheless indicates that the locomotor circuitry responsible for phase transition (stance to swing and vice versa) is functional and can be activated by afferent inputs provided by repetitive movements of the legs.

Conditioning the soleus H-reflex is another promising therapy that results in improvements in locomotion for rats, cats, non-human primates, and even humans.^{26,27} Although some changes occur within the spinal networks, evidence in rats suggests that up-conditioning requires an incomplete injury with an intact corticospinal tract (CST).²⁸ A combination of H-reflex operant conditioning and locomotor training demonstrated a possible transfer of plasticity acquired from non-locomotor training task to locomotion.^{29,30} This approach suggests that training a non-locomotor related task may actually translate into locomotor benefits when non-locomotor training targets the control of the spinal excitability state.

Limitations to successful translation

Body-weight supported locomotor training (BWST) is characterized by repetitive movements involving major muscle groups. An advantage of this therapy is the ability to tailor the program to the individual's specific needs and its integration into a complete rehabilitation program. However, little is known about the physiological adaptations to various "dosages" (intensity, volume, duration) and timing (e.g., onset time post-SCI). As we move forward, more studies will have to focus on this critical information given that an early training onset can be detrimental³¹ or beneficial³² and that locomotor ability depends on the amount of practice and the number of repetitions⁴ that can be achieved without reaching overtraining. This lack of information contributes to the limited success of BWST after SCI.

Treatments that improve function in animal models of SCI have shown little meaningful recovery in humans, especially in severely impaired individuals. The most effective approach in animal models is a combination of treatments directed at different aspects of the injury process, which include immune responses, neuroprotection, and activation of depressed systems. Outcome measures

for pre-clinical studies show a range of improvements, including cellular and molecular changes, while outcomes for clinical treatments are largely behavioral. Our understanding of just how the molecular and cellular plasticity affect the system's physiology, and subsequently the behavior, is limited in animals and even more so in humans. As long as this information remains unavailable, it will be challenging to evaluate the chance for a successful translation to SCI individuals.

It is difficult or, at present, impossible to assess and compare the effects of invasive treatments on the spinal cord structure and physiology in SCI patients with those shown in animal models. Invasive treatments are used only in adults with chronic severe (complete) injuries, who are the least likely to experience adverse effects but are also least likely to show recovery. Nevertheless, combination treatments, including locomotor training, identified from animal studies have been used in chronically injured motor complete individuals, although in small numbers. These have been shown to be safe and to provide some limited recovery. Similar treatments following incomplete injury have shown more functional recovery (Table 1).

Are Animal Models Still Valuable?

There are similarities in the organization of the spinal cord among mammals. The central pattern generator (CPG) for locomotion is present in all vertebrates, including humans. The general features of its output are similar in rats, cats, and humans as evidenced by the flexion-extension rhythm evoked by non-patterned brainstem/spinal stimulation in all these species.^{33–35} The potential for greater complexity of the CPG in humans may, however, lead to an increased difficulty in identifying the effects of SCI and treatments. There also are similarities in the responses to interventions. Locomotor responses to epidural stimulation of the spinal circuits share similarities in rats, cats, and humans.^{36,37} Operant conditioning of the H-reflex^{26,27} or pharmacologic stimulation also can improve locomotion and diminish spasticity in rats,^{38–41} cats,^{42,43} and humans.^{44,45} Sprouting patterns after dorsal column lesion also are generally similar among animal models, and may contribute to recovery of sensory function in rats, primates, and humans.^{46,47} While dorsal root injury elicits sprouting of central pathways in rodents and cats, it surprisingly appears to be far more robust in non-human primates.^{48–51}

However, there are significant differences across species that likely contribute to failure of translation. Rodents have smaller bodies, smaller brains, smaller descending tracts, and presumably fewer spinal interneurons and less sophisticated circuitry than large mammals. Despite the smaller size of the central nervous system (CNS) in rodents, their spinal cord accounts for 30% of the CNS net weight, while it only accounts for 3% in humans.⁵² Overall, the spinal cord in rodents may actually have proportionally more computing power than in humans. Mice show spontaneous recovery after transection,⁵³ whereas rats require training and other treatments, although locomotion can be elicited by non-invasive strategies (i.e., training and perineal stimulation).^{54,55}

Cats have provided important understanding of the CPG. Unlike humans, they show recovery of weight-support and locomotion after a complete spinal cord transection with single treatments such as step-training on the treadmill or delivery of neurotrophins.^{5,6,56} Cats are no longer used widely but perhaps they should be, considering the wealth of information about their spinal circuit organization, and could give clearer insight into the failure of translation in primates. Mini-pigs have also recently emerged as a promising

new large animal model that may represent a useful intermediary between rodents and humans, especially for testing cell transplantation and regenerative strategies.⁵⁷ Unfortunately, rehabilitation strategies involving BWST have not been tested so far in this model.

Monkeys and humans show greater recovery of locomotion and hand function than rats after a hemisection injury, and the extent of recovery is correlated with the formation of corticospinal detours that develop in monkeys but not in rats.⁵⁸ The rat CST is located in the dorsal columns, with some CST axons descending in the ventral and lateral funiculi, whereas it is mostly found in the lateral funiculus in large animals, with some axons descending in the lateral and ventral funiculi. In addition to this differential location, the greater CST complexity in primates and humans versus rodents is evidenced by the increased abundance of bilateral projections, the joint participation of the motor and sensory cortices to the CST, a larger target spinal interneuronal pool,⁵⁸ and the presence of direct monosynaptic projections to motoneurons. In addition, the CST innervating the spinal cord has at least nine different cortical origins in primates and humans, with a unique spinal termination pattern for each cortical region, whereas it mostly originates from the primary and somatosensory cortices in rodents. Given that the response to injury depends on the cortical origin, the potential for complexity is far greater.⁵⁹ Together, these factors likely contribute to the failure of translation.

Relatively few studies directly compare species differences, and this limits interpreting translatable data from animal models. For example, an intervention that improves locomotor performance in rats by increasing appropriate sensory feedback may not be as successful in SCI individuals who appear to be much more dependent on supraspinal input to the cord (see sections below). Conversely, targeting an increase in supraspinal control of the locomotor centers may improve stepping more significantly in SCI individuals and show only minimal improvements in rats. Inconsistencies in results obtained in different animal models and primates/humans suggest that it might actually be more beneficial to conduct studies directly in humans for non-invasive interventions. Nevertheless, animal models remain valuable in understanding the mechanisms for recovery and failure and testing the safety of invasive treatments.

Injury Severity: Are Animal Models Comparable to Humans?

Complete injury results in the loss of supraspinal input, sprouting by interneurons, dorsal roots, and propriospinal neurons, with substantial changes in spinal circuits. A true complete transection of the spinal cord is uncommon in SCI individuals (14.3%),⁶⁰ and the majority of AIS A cases (clinically classified as motor and sensory complete) have a discomplete injury with some fibers surviving as illustrated by the rudimentary control of EMG responses below the lesion site.⁶¹ Treatments that increase excitability of spinal circuits in transected animals elicit robust recovery of locomotor function. These treatments usually include combinations of neurotrophins, grafts, pharmacotherapy, brain-machine interface, epidural stimulation, and intensive activity-based therapy, all of which may contribute to improved function. Both spinal cats and rats can achieve locomotion with either step-training or administration of neurotrophins.^{56,62} Such a successful recovery is not observed in motor complete SCI individuals with single treatments (Fig. 1).

Incomplete lesions include individuals with AIS B, C, and D. Asymmetric injury (i.e., hemisection) produces asymmetric impairment and spared contralateral projections can partially compensate for the ipsilateral loss. The greater spontaneous recovery in

TABLE 1. FUNCTIONAL RECOVERY WITH LOCOMOTOR TRAINING IN SCI INDIVIDUALS

<i>Publication</i>	<i>Treatment</i>	<i>Rehabilitation program</i>	<i>Injury</i>	<i>Number of patients</i>	<i>Outcomes</i>
Tabakow et al., 2013 ¹	OEC transplant	Post OEC transplant: intense rehab (range of motion, stretch, locomotor and sensory training) pre- and post-transplant 4-5 h/day, 3-5 days/week	AIS A	Clinical trial phase 1 Transplant + Rehab N=3 Rehab only N=3	Safe Slightly improved sensory and motor function below injury in patients receiving the transplant only
Tabakow et al., 2014 ²			AIS A	Transplant + Rehab N=1	
Harkema et al., 2011 ³	Epidural stimulation	Pre- and post-epidural implant: stand-training and BWST with manual assistance	AIS B	N=1	Standing with minimal assistance
Rejc et al., 2015 ⁴		Pre-implant: stand-training and BWST with manual assistance Post-implant: stand-training 1 h/day, 5 days/week post-implant	AIS A AIS B	N=4	Safe Slight recovery Standing with minimal (n=2) or no assistance (n=2)
Hofstoetter et al., 2014 ⁵	Transcutaneous stimulation	None	AIS D	N=3	Improved gait speed values Decreased spasticity Improved stepping responses mediated by sensory feedback on treadmill
Minassian et al., 2016 ⁶		None	AIS A	N=4	
Possover, 2014 ⁷	FES	Assisted standing and walking	AIS B AIS C AIS B	N=3 N=3	All recovered some motor/sensory Achieved independent standing Improved walking (6-min walk test)
Forrest et al., 2012 ⁸		Transition sit to stand Standing			
Johnston et al., 2005 ⁹		Overground walking			
Jones et al., 2014 ¹⁰		Varied activity-based therapy including locomotor training 9 h/week	AIS C AIS D	N=48	Improved walking
Field-Fote, 2001 ¹¹		BWST and common peroneal stimulation	AIS C	N=19	Improved walking
Zewditie et al., 2015 ¹²		Precision (obstacle course) and endurance training (step-training on a treadmill)	incomplete	N=16	Improved walking
Harkema et al. 2012 ¹³		1 h/day, 5 days/week BWST with manual assistance 20-250 sessions	AIS C AIS D	N=196	Improved balance Improved walking measures

1. Tabakow et al. 2013, Cell Transplant. 22, 1591-1612; 2. Tabakow et al. 2014, Cell Transplant. 23, 1631-1655; 3. Harkema et al. 2011, Lancet 377, 1938-1947; 4. Rejc et al. 2015, PLoS One 10, e0133998; 5. Hofstoetter et al. 2015, Artif. Organs 39, E176-E186; 6. Minassian et al. 2016, Neurorehabil. Neural Repair 30, 233-243; 7. Possover 2014, Arch. Phys. Med. Rehabil. 95, 610-614; 8. Forrest et al. 2012, Disabil. Rehabil. Assist. Technol. 7, 340-344; 9. Johnston et al. 2005, Spinal Cord 43, 713-723; 10. Jones et al. 2014, Arch. Phys. Med. Rehabil. 95, 2239-2246 e2232; 11. Field-Fote 2001, Arch. Phys. Med. Rehabil. 82, 818-824; 12. Zewditie et al. 2015, Prog. Brain Res. 218, 127-155; 13. Harkema et al. 2012, Arch. Phys. Med. Rehabil. 93, 1508-1517.
SCI, spinal cord injury; OEC, olfactory ensheathing cells; AIS, American Spinal Injury Association Impairment Scale; rehab, rehabilitation; BWST, body-weight supported locomotor training; FES, functional electrical stimulation.

humans and primates⁵⁸ is related to supraspinal pathways that project bilaterally and rely on spared pathways to support recovery. Consequently, the extent of laterality predicts the extent of recovery after incomplete SCI.⁶³ Recovery of walking after incomplete lesions is critically dependent on descending input from the motor cortex and the ability to strengthen corticospinal connections.⁶⁴ Spared descending axons rescue propriospinal plasticity,⁶⁵ but propriospinal interneurons in primates appear to be more dependent on descending input than in rodents.⁶⁶ It is difficult to assess whether there is a relative difference in the number or type of propriospinal interneurons in small versus large animals⁶⁷ and how it may contribute to this effect. Another confounding factor may be the homogeneity of lesions in animal studies. Treatments successful in a given model of SCI in animals may poorly translate in clinical trials that include individuals with widely different injuries (cause and severity). Testing in various models of injury is critical to circumvent this problem.

Changes in Skeletal Muscles Triggered by SCI Do Not Account for Failure

Spinal cord injury and the ensuing muscular disuse lead to muscle atrophy for the muscles innervated by the motor pools below the lesion and conversion of these muscles' fiber type to fast-fatigable glycolytic Type IIb. Atrophy occurs quickly with a 33–45% decline in muscle cross-sectional area 6 weeks following the injury.^{68,69} This rapid atrophy is accompanied by a slower conversion of type I muscle fibers to type IIb in both humans and animal models of SCI.^{70–75} The two phenomena combined produce a loss in muscle output for hind limb muscles in SCI individuals. Electrical stimulation can reverse the muscle mass loss and to some extent reverse the conversion of muscle fibers to a different type (Fig. 1), although the amount of conversion and gain in muscle force output varies depending on the stimulation protocol and the loading presented to the muscles being stimulated.^{72,73,76,77} The increased muscle activation brought on by spasticity may have effects similar to electrical stimulation. Spasticity can protect against muscle atrophy in SCI individuals⁷⁸ but its effects on fiber types appear to be mixed.⁷⁹

Potential contribution of reduced force output to the failure of locomotor training program

Studies in spinal cats show that the force-generating capacity of hind limb muscles is similar whether they received stand-training or not; all the trained animals could stand but stand-trained animals stand for longer periods.^{80,81} Stand-trained animals, however, show limited locomotor capabilities, compared with the step-trained animals. This suggests that difference in activation rather than muscular capacity is responsible for the stepping performance. Further support for this idea comes from studies in rats transected as neonates. There is less than a 10% difference in muscle mass (normalized to body mass) between animals able to weight-support versus non-weight-supporting animals as adults.⁸² The gain in muscle cross-sectional area following BWST also appears to be minimal in chronic incomplete SCI individuals (on the order of 5–10%),^{83,84} although trained individuals show greater recovery with BWST. Overall, both animal and human experiments suggest that muscular atrophy and loss of joint torque following SCI are not major contributors to the failure of BWST training at restoring locomotor activity in complete SCI.

The muscular system output after SCI should therefore be sufficient to produce a locomotor pattern if fed an appropriate muscle

activation sequence. The failure of BWST in humans seems to be more related to a failure in the spinal locomotor centers being either more depressed and/or more dependent on descending systems.

Evidence in favor of the locomotor centers being depressed

Recent successes in producing a locomotor pattern in motor complete SCI individuals, using a combination of BWST and epidural stimulation to increase the excitability of the spinal cord circuits, suggest that the inability to activate the locomotor centers may contribute to the failure of the use of BWST alone in humans (Fig. 1). Activation failure may be occurring in a number of locations within the locomotor circuitry chain including motoneurons, interneurons, and reflex pathways from the limbs' sensory feedback. Time since injury also influences the excitability state of the locomotor circuitry, with sustainable locomotor output driven by sensory feedback being diminished in chronic complete SCI.⁸⁵

Motoneurons as a Target for Locomotor Training: A Balancing Act between Increased and Decreased Activity

Persistent inward currents (PICs) contribute to increased excitability after SCI

The intrinsic properties of motoneurons are significantly influenced by neuromodulatory inputs that alter the resting potential, reduce the spike voltage threshold, and transform the input–output processing through the activation of voltage-gated PICs.^{86–90} PICs are strongly facilitated by monoamines (5-HT and noradrenalin) that are released by brainstem–spinal pathways^{91,92} and even more so after a chronic SCI.^{93,94} SCI leads to an immediate and dramatic reduction of motoneuronal excitability.⁹⁵ The lack of neuromodulation prevents motoneurons from producing a firing frequency sufficient to generate muscle activation and production of enough force to sustain locomotion. After the spinal shock period during which no amount of synaptic activity can bring motoneurons to firing threshold, motoneuronal excitability gradually increases.

In the chronic state, the emergence of constitutive activity of the 5-HT_{2C} receptors leads to Ca²⁺ PICs recovery with the presence of plateau potentials that prolong and amplify inputs to motoneurons leading to excessive activity associated with muscle spasms in rodents.^{96–98} These studies were conducted in rats with a sacral SCI that have been used as a model that reproduces the clinical development of spasticity in humans.⁹⁹ Although this model does not allow the investigation of the spinal control of limb movement but rather the activity of sacral motoneurons and tail musculature, studies in SCI individuals support the presence of a similar phenomenon in limb motoneurons.^{100,101} In addition, although PICs are recovered following SCI in cats, the movement-related receptive fields (MRRF) are no longer joint-specific: ankle extensor motoneurons are not only activated by passive ankle rotations but also by rotations of the hip.^{102,103} The injury-related widening of the MRRF is most likely due to the loss of monoaminergic modulation causing a disinhibition of polysynaptic excitatory pathways on target motoneurons, which has the potential to activate muscles through the entire limb and possibly contribute to spasms.¹⁰² It also is important to note that although a complete spinal cord transection typically is not considered the most clinically relevant model, these animals display more spasticity than contused animals,¹⁰⁴ unlike SCI individuals who show more spasticity with moderate injuries. Therefore,

successful translation may not always rely on matching the type/extent of injury but rather on mimicking the clinical profile.

Na^+ PICs (I_{NaP}) also are a key conductance for the locomotor networks as they can drive plateau potentials in motoneurons¹⁰⁵ and contribute to repetitive firing and motoneuron hyperexcitability after chronic SCI.⁹³ A recent study suggests that the upregulation of I_{NaP} after SCI contributes to the development of spasticity through a cleavage of the Nav1.6 channel.¹⁰⁶ SCI increases the expression of Nav1.6 channels in the lumbar spinal cord¹⁰⁷ and preliminary results suggest that exercise could decrease the expression of β_1 and β_4 subunits.¹⁰⁸ This pathway has recently been proposed to interact in synergy with the disruption in chloride homeostasis and lead to spasticity after chronic SCI.¹⁰⁶

Passive motoneuronal properties contribute to reduced excitability after SCI

Beyond the development of PICs, little is known about the effect of SCI on electrical properties of motoneurons and even less after a rehabilitation program. Muscle disuse and reduced neuromuscular activity decrease motoneuronal excitability with an elevated rheobase, lower afterhyperpolarization (AHP) depth, depolarized spike threshold, and a positive shift in the frequency-current (f - I) relationship.^{109,110} However, changes in motoneuronal properties based on AHP depth, rheobase, input resistance, and f - I relationship after chronic SCI remain controversial. Most reports suggest no change and if anything, a general decrease in motoneuronal excitability,^{111–116} while increased excitability also has been reported.^{117,118} The heterogeneity of results obtained after chronic SCI may arise from various factors, including the model utilized (rat vs. cat), the type of muscle innervated by a motoneuronal pool (fast vs. slow muscle), time post-injury, and inter-animal variability (spastic vs. non spastic). Such a high degree of variability impedes interpretations of data about the changes in motoneuronal properties following SCI, and their potential effects on locomotor capability.

Step-training modifies motoneuron excitability in response to limb loading and cutaneous stimulation in an afferent-motor pool specific manner (see the section “Afferent feedback and spinal reflexes contribute to locomotor recovery”).^{13,14} Studies conducted in rats that sustained a complete transection as neonates showed that step-training does not change the rheobase but rather decreases the AHP amplitude and increases monosynaptic excitatory postsynaptic potentials (EPSPs).¹¹⁹ The efficacy of step-training is also correlated with the amplitude of synaptic inputs to motoneurons in particular from axons descending in the ipsilateral ventrolateral funiculus (VLF).^{119,120} Further, locomotor activity in spinal cats can be initiated by the activation of reticulospinal pathways that reside largely in the VLF.¹²¹ Further studies in rodents showed that the VLF also contains ascending and descending long propriospinal neurons (ipsilateral and commissural) that interconnect the cervical and lumbar enlargements.^{122–124} Increased motoneuronal responses to VLF stimulation in step-trained animals after a complete SCI suggest an increased inter-enlargement connectivity that could participate in recovery. This interpretation is supported by clinical evidence in incomplete SCI individuals that show an improvement in the leg muscle activation upon engaging arm swing during gait.^{125,126}

Overall, it remains unclear if direct modulation of motoneuronal properties contributes to motor recovery and/or failure for improvement (Fig. 1). Our current knowledge suggests a complex balance between decreased excitability (e.g., reduced response to specific afferent activation) and consequent decrease in hyperreflexia coupled to a facilitation in their response to descending pathways.

Whether these changes rely on plasticity in motoneuronal properties, increase/decrease in the number of synapses, or change in the strength of synapses to motoneurons needs further investigation.

Changes in Interneuron Systems Involved in Locomotion

Recent years have seen a breakthrough in interneuron identification supported by new genetic mouse models that provide increased specificity and the possibility to assess their roles and the identification of circuits. A number of ventral interneurons have been identified using transcription factors and shown to be either critical elements of the CPG or involved in locomotor pattern formation/shaping.^{127–129}

Interneurons controlling locomotion

Interneurons play a significant role in the control of locomotion and are the main termination control and distribution sites for descending tracts and propriospinal systems.^{130,131} The expression of the locomotor pattern is facilitated by the intrinsic electrophysiological properties of interneurons. For example, PICs in interneurons can be triggered to amplify synaptic inputs and the consequent sustained firing is thought to be involved in rhythmogenesis by setting the timing and shaping the motor output during locomotion.¹³² Although the concept of a CPG for locomotion is generally accepted in both animals and humans,^{33,133} its interneuronal composition is only partly described and little is known about the effects of SCI and step-training on spinal interneurons, particularly in primates.¹³⁴

Recent electrophysiological data support the concept that training-dependent plasticity does indeed occur within the CPG,^{135–137} as well as in reflex pathways^{13,14} and muscle spindles.¹⁵ The specific nature of the changes in CPG interneurons is unknown and warrants further investigation in both animals and humans (Fig. 1). Few studies have focused on direct changes in intrinsic properties of spinal interneurons with step-training after SCI. To our knowledge, the only available reports are in a mouse hemisection model that suggest that step-training selectively increases the efficacy of synaptic connections from residual descending pathways to interneurons located in the vicinity of the lesion.^{138,139} There was relatively little change in the intrinsic properties of spinal interneurons (input resistance, rheobase current, threshold, action potential amplitude, afterhyperpolarization peak, etc.) between control and SCI mice whether they were step-trained or not.^{138–140} The data suggests that step-training favors plasticity of synaptic strength rather than intrinsic changes in properties of interneurons. However, it must be noted that this set of studies did not examine interneurons directly involved in locomotor output. The synaptic efficacy of descending systems, notably the CST, onto other interneurons caudal to the injury was enhanced with step-training as evidenced by the increased EPSP responses to deep dorsal column stimulation for deep dorsal horn interneurons caudal to the injury.¹³⁹ It is again unclear if those interneurons are actually part of the locomotor circuitry.

The efficacy of other descending systems also appears to increase following SCI since a 100- to 1000-fold increase in serotonin sensitivity is observed in V2a interneurons responsible for left-right hind limb coordination in spinal animals.¹⁴⁰ However, the specific effects of step-training on this hypersensitivity, which is not accompanied by changes in intrinsic properties, have not been explored. Although spinal interneurons become more responsive to descending inputs after SCI, the actual output of interneuronal systems may in fact be depressed. The cholinergic output of propriospinal neurons in lamina X, those interneurons located around

the central canal, onto motoneurons is significantly decreased after injury.¹⁴¹ These interneurons are believed to participate in locomotion^{142,143} and receive extensive descending inputs from the mesencephalic locomotor region.¹⁴²

An emerging hypothesis is that interneuronal systems in primates and humans may be more highly dependent on supraspinal tracts and that the loss of descending inputs may lead to a more severe impairment of the interneuronal systems that support the locomotor circuitry. Differences in the contributions of the interneuronal systems to locomotion and changes in those systems after injury and training have not been explored extensively, even in animal models of SCI, but may contribute to the differences in the recovery observed with training between humans and animal models of SCI.

Propriospinal neurons contribute to novel relays after SCI

The extent of recovery is often associated with the amount of spared descending tracts. With that in mind, several strategies aim at increasing the efficacy (through training-dependent plasticity) or the number of connections (sprouting) from supraspinal centers to interneuronal and/or motoneuronal pools located below the lesion site. However, locomotor improvements also can occur without direct projections from the brain beyond the lesion site, through the reorganization of indirect descending pathways and propriospinal connections. Both short and long propriospinal interneurons have been shown to form new intraspinal circuits following SCI.^{144,145} Propriospinal relay connections can bypass the injury site^{144,146} and mediate modest functional recovery^{147,148} even with a total disruption of long descending supraspinal pathways.¹⁴⁵ Short propriospinal interneurons are more likely to die after SCI, but survivors show transient upregulation of regeneration-associated genes, as well as pro-apoptotic genes.^{149,150} The potential of harnessing the plasticity of propriospinal neurons to improve functional recovery is twofold. Not only do they contribute to the formation of novel relays by receiving input from damaged descending axons and transmitting this information to the caudal cord (see the section "Can step-training guide sprouting and regeneration toward the right target?"), but they can also regenerate into growth-promoting grafts.^{144,146,151,152} Cycling exercise, for example, has been shown to increase propriospinal regeneration into peripheral nerve grafts and modulates the expression of genes associated with regeneration.¹⁵² Together, these studies suggest that propriospinal interneurons have a remarkable plastic potential and could be utilized to enhance functional recovery with activity-based therapies.

Afferent Feedback and Spinal Reflexes Contribute to Locomotor Recovery

In addition to changes in the motoneuronal and interneuronal CPG constituents, SCI and step-training also cause profound neuroplastic changes in proprioceptive feedback pathways triggered by the repetitive activation of muscle groups (Fig. 1). Locomotor control is highly dependent on, and driven by, information originating from muscle and cutaneous afferents.¹⁵³ In the absence (or disruption) of supraspinal pathways, the dependence on sensory feedback is dramatically increased after SCI.^{9,154} In a model of complete spinal cord transection, step-training is shown to modulate transmission in reflex pathways originating from group Ia/b muscle afferents,¹³ as well as cutaneous afferents¹⁴ in a complex manner that is contingent on both the origin of the stimulated af-

ferents and the specific motor pool activated. It is well known that cutaneous afferents play a critical role in controlling and shaping locomotor movements¹⁵⁵ and enhanced cutaneous feedback improves locomotor recovery.^{156–158} At least one source of cutaneous feedback originating from the leg/paw is necessary for recovery in spinal cats.¹⁵⁹ Of all cutaneous feedback, the information originating from the sole of the foot appears to be the most critical¹⁴ and this has later been shown to be of critical importance in normalizing spinal reflex circuits in SCI individuals.¹⁶⁰ Changes in the feedback system are critical to locomotor recovery, yet most of this information has yet to find its way into clinical rehabilitation programs.

Most of what we know suggests that treadmill training produces similar re-organization of the reflex circuitry in humans and animal models. While it is not possible to explore direct changes in the activity of motoneurons and interneurons in SCI individuals after BWST, comparisons of reflex responses with spinal animal models can shed light about the similarities in the reflex re-organization. In SCI individuals, BWST contributes to the restoration of the phase-dependent modulation of the soleus H-reflex with a clear depression occurring during the swing phase.^{161–163} The modulation persisted after the BWST training sessions ended and was associated with a decrease in the body weight support required and increase in walking speed, although reflex re-organization did not correlate with improvements in overground walking ability evaluated through clinical assessments.¹⁶³ Locomotor training also normalizes flexor reflexes in SCI individuals: TA flexor reflex is decreased during the stance phase and increased during swing.^{160,164}

In addition, locomotor training normalized reciprocal and non-reciprocal inhibition of the soleus H-reflex. Notably, the Ib facilitation of the soleus H-reflex obtained with medial gastrocnemius nerve stimulation in spinal cord-injured individuals returned to the normal Ib inhibition after training when evaluated in the sitting position. During stepping, the Ib inhibition was decreased at early swing and increased at late swing in AIS C, and decreased in early stance in AIS D.¹⁶⁵ This was similar to the reduction in Ib inhibition seen in able-bodied subjects during the stance phase,¹⁶⁶ but the reversal from inhibition to excitation seen in the intact cat^{167,168} was absent. It is also interesting that the reflex modulation produced by locomotor training varied based on the amount of spared functions. Although the reflexes could not be evaluated during stepping in the two motor complete subjects (one AIS A and one AIS B), reciprocal inhibition of the soleus H-reflex returned after training, as well as Ib-inhibition, with both reflexes being evaluated in the sitting position in those two subjects. In fact, relatively impressive re-organization of the spinal reflex circuitry can be obtained with sensory locomotor feedback alone. Assisted locomotion alone (using Lokomat robot to move the legs, no BWST) was sufficient to normalize the late and early components of the tibialis anterior response to tibial nerve stimulation in chronic complete SCI individuals.¹⁶⁹

In SCI animal models, reflex re-organization after SCI and step-training has been studied via intracellular recording and transmission in muscle and cutaneous pathways to extensor and flexor motoneurons was tested. Monosynaptic excitation evoked by group Ia afferents was decreased by step-training. Its phase-dependent modulation also was restored by step-training during locomotor episodes with peak activity occurring during extension, the depolarized phase of the motoneurons.¹³ Cutaneous transmission also was modulated by step-training, but only in a few specific pathways.¹⁴ Signal transmission in most pathways was depressed, suggesting that post-SCI hyperexcitable reflexes^{170,171} can be normalized by step-training. Interestingly, one of the pathways that was not depressed but facilitated originated from the sole of the foot

(medial plantar nerve) and facilitated the response of MG motoneurons, possibly contributing to weight-bearing upon signaling of ground contact.¹⁴ This type of experiment cannot be repeated in humans but can be indirectly estimated through the EMG responses evoked by nerve stimulation in humans as presented above; however, the difference in methodologies must be considered.

One of the limitations in comparing reflex re-organization due to step-training is that the reflexes in spinal animals are typically measured after the animals have recovered a locomotor pattern so that the modulation of the reflexes during stepping can be evaluated.^{172–174} Although the cutaneous reflexes are modulated in a phase-dependent manner in trained spinal animals, some differences exist, compared with in intact animals. Soleus responses to tibial nerve stimulation in intact cats show a short-term depression and longer latency excitation, while the responses show a short-term excitation in the trained spinal cats.¹⁷² In untrained chronic spinal cats, triceps surae stretch reflexes are depressed,¹⁷⁵ although a number of knee and hip muscles not normally activated by the stretch are recruited in the spinal state. Unfortunately, there are few studies in SCI animal models that have examined the afferent reflex re-organization due to locomotor training. A possible comparison with the clinical work would be to evaluate the reflex at rest (mimicking sitting in human subjects) in SCI animals before training is initiated, and then re-examining the same reflex at rest after training.

Greater Dependence of the Locomotor Centers on Descending Systems in Humans

Amelioration in the locomotor patterns of incomplete SCI individuals following BWST includes an increase in EMG activity and a decrease in burst duration and cocontractions.^{176,177} Gorassini and colleagues point out that the improvement in EMG activity is greater in muscles that receive more cortical projections (i.e., tibialis anterior [TA] and hamstrings), compared with muscles mainly under the influence of local spinal circuits (i.e., soleus).¹⁷⁶ It is argued that there may be a reinforcement of the remaining cortical and/or brainstem projections, a point that also is supported by the fact that the individuals more responsive to BWST were the ones with the highest remaining motor score for lower limb muscles.¹⁷⁸ These observations complement results in contused rats for which the recovery of locomotor function with step-training was largely dependent on spared supraspinal pathways.¹⁷⁹

While firing of primary motor cortex neurons remains largely unmodulated during unobstructed walking in cats,¹⁸⁰ the synchrony between cortical electroencephalography signals and EMG activity of the TA during walking in humans show coherence between the two signals, indicating that primary motor cortex (directly or through the corticobulbar/bulbosplinal pathways) is involved in the control of level unobstructed walking in humans.¹⁸¹ This supplies additional support for a greater dependence on cortical command for locomotion in the human spinal cord. It has been shown, for example, that stimulating the CST in chronic incomplete but ambulatory SCI individuals can improve gait¹⁸² and diminish spasticity.^{183,184} In addition, a training regimen that targets improving voluntary ankle dorsiflexion in incomplete SCI (as compared with training the soleus H-reflex) increases the walking distance on a 2-min walk test and the dorsiflexor muscle test score,¹⁸⁵ supporting the notion that improvements in the control of descending commands may contribute more to recovery than afferent feedback training in humans.¹⁸⁶ However, improvements in voluntary motor control do not always translate to improvements in walking ability

in larger cohorts. In a prospective study, larger gains in lower extremity scores with locomotor training were only weakly correlated to gait speed and distance.¹⁸⁷ Other factors, such as time since injury, spasticity, and walking ability before training onset, have been shown to be better predictors of improvements in walking speed following locomotor training in a small prospective study in motor incomplete SCI individuals.¹⁸⁸

Most of the clinical work in testing the influence of supraspinal tracts has been conducted using transcranial magnetic stimulation (TMS) over the motor cortex, which leads to preferential activation of the CST. However, the potential contribution of spared extrapyramidal pathways to the state of excitability of the spinal circuitry has not been explored thoroughly. It is known from galvanic stimulation of the vestibular system in incomplete SCI subjects that transmission in this pathway, as measured by the soleus muscle response to the galvanic stimulation, is relatively well correlated with balance test and moderately well to some gait function.¹⁸⁹ Studies showing greater activity in the cerebellar regions over the sensorimotor cortical regions following BWST in incomplete SCI humans¹⁸⁸ provide further evidence that sub-cortical systems and projections from the brainstem nuclei to the spinal cord may play a greater role in recovery than traditionally recognized. In those individuals, measures of locomotor recovery correlated better with cerebellar activation than with cortical activation. The cerebellar plasticity associated with sensorimotor training also serves as a reminder that ascending tracts, whether spinothalamic or spino-cerebellar, are likely participants in the recovery observed with BWST in incomplete SCI individuals. Variations in the damage to sensory tracts may be as important as variations in the motor tracts in determining the outcome, although spared sensory pathways have been relatively unexplored.

Most of our knowledge about the contribution of varying tracts to locomotion comes from lesion studies that show a number of similarities between species but also some important differences. Differences in the role and compensatory ability of spinal tracts are revealed between human and non-human mammals following partial injury.¹⁹⁰ Injuries to the CST or even the entire dorsal columns and dorsolateral columns have little effect on locomotion in cats and non-human primates. Bilateral lesions to the dorsolateral funiculi and dorsal column cause little more than a paw drag during swing in cats¹⁹¹ and lesions to the pyramidal/CST tract at the brainstem or spinal level have limited effects on locomotion in monkeys.^{192–194} Humans, on the other hand, are much more susceptible to injuries to the lateral CST. Cordotomies performed for pain relief in cancer patients show that bilateral damage to the posterior lateral quadrant at the thoracic level essentially renders the patient paraplegic.¹⁹⁵

It seems that in non-human mammals, the ventral tracts (most notably the vestibulospinal and reticulospinal) can compensate for damage to the lateral CST and rubrospinal tracts, but this compensation does not occur in humans. In cats, spared ventrolateral pathways will allow recovery of locomotion after injury to the dorsolateral CST/rubrospinal tracts, albeit with an increased paw drag during swing and a change in the timing of activation for certain muscles.¹⁹¹ Spared dorsolateral pathways will also lead to recovery of locomotion after injury to the ventrolateral reticulospinal and vestibulospinal pathways, although interlimb coordination will be affected.^{196–199} Evidence in non-human primates is limited but suggests a greater role for the reticulospinal and vestibulospinal pathways in locomotion. “Medial system” lesions,²⁰⁰ which damage most of the reticulospinal and vestibulospinal pathways, produces deficits in posture and walking with only one of four monkeys able to walk across the floor after a long

recovery period. Surprisingly, Nathan reports little to no motor deficits in humans following a ventrolateral cordotomy, indicating that the dorsolateral funiculus tracts can compensate for damage in the ventrolateral tracts in humans.¹⁹⁵

In summary, although vestibulo- and reticulospinal tracts are important for the initiation of locomotion, it appears that the lateral CST can compensate for damage to the ventrolateral funiculi tracts in humans and non-human mammals, but that humans are particularly dependent on the CST for locomotion, compared with non-human primates and other mammals.

While it is evident that spared descending systems are important determinants in locomotor recovery and likely contribute to the beneficial effect of step-training, assessing the residual transmission in spared pathways remains technically challenging in humans.¹⁸⁹ The effect of locomotor training on transmission through these pathways is still largely unexplored. The limited clinical evidence suggests that training enhances the excitatory influence of descending pathways recruited by motor cortex TMS and the excitability of inhibitory spinal networks: the inhibition of the common peroneal nerve on TA TMS response is increased after locomotor training in incomplete SCI individuals, as is the inhibitory components of the tibial nerve reflex on the TA.²⁰¹ Recent results with epidural or transcutaneous spinal cord stimulation^{37,183,202,203} in complete and incomplete SCI individuals demonstrate an enhancement of locomotor activity with stimulation of the dorsal aspect of the lumbar cord. These studies have uncovered a latent volitional control of muscles paralyzed with no evidence of twitch or EMG activity prior to the stimulation being applied.²⁰⁴ The elements activated by the stimulation would involve low threshold dorsal root afferents (proprioceptive and cutaneous) that could in turn activate spinal interneurons to reduce the activation threshold of the locomotor circuitry, allow the few remaining descending fibers to control the activation of the circuitry, and improve the appropriate phase-dependent modulation of the locomotor circuitry by afferent feedback.^{202,203,205}

Potential Role of Locomotor Training in Promoting Axonal Sprouting and Growth

Anatomical plasticity studies in response to injury have mainly focused on axonal growth after SCI, regeneration/sprouting/synaptogenesis, formation of novel relays, and strengthening of existing pathways. Providing a more permissive environment (e.g., cellular transplants or peripheral nerve graft) can promote some regeneration and sprouting, leading to reorganization of the spinal cord circuitry that may improve recovery. Injury-induced sprouting has been shown to be enhanced by activity such as the stimulation of descending pathways and by activity including treadmill training.²⁰⁶

The CST has received the most attention, presumably because of its importance in hand function and also because of its recalcitrance to regeneration. Other pathways that respond more robustly to injury might provide more interesting information.^{146,207,208} Electrical stimulation of the motor cortex promotes CST sprouting and recovery of function, and also elicits sprouting from motor cortex to other targets (e.g., red nucleus) that in turn can stimulate sprouting of rubrospinal axons.^{209,210} Sprouting into the spinal cord from supraspinal areas—including the motor cortex,²¹¹ red nucleus,²⁰⁷ reticular formation,¹⁴⁶ and raphe²¹²—can be evoked by incomplete SCI. Sprouting in primates is surprisingly more extensive than in smaller animals after hemisection but recovery of function is better in smaller animals.^{50,51,59} To date, there is no convincing data supporting a role for locomotor training in increasing the regenerative potential and improving function in SCI models of regenera-

tion.^{213–216} The understanding of how axonal growth is regulated in adult animal models remains largely unknown²¹⁷ and needs to be evaluated in terms of maladaptive, as well as beneficial effects.

From Step-Training Dependent Plasticity to Functional Recovery: The Ultimate Challenge of Molecular Correlates

The training-dependent increase in neuronal activity is ultimately transduced at the cellular and molecular level into functional recovery. However, specific cellular mechanisms responsible for spinal cord activity-dependent learning remain largely unknown (Fig. 1). Multiple descending tracts have a significant role both in the initiation and the control of locomotion, including glutamatergic, noradrenergic, dopaminergic, and serotonergic pathways. Early studies have focused on the loss of monoaminergic spinal projections (5-HT, NA) following SCI and the activity-dependent plasticity in these systems following step-training, essentially due to their involvement in the control (initiation and maintenance) of locomotion.²¹⁸ Step-training triggers a reorganization of synaptic inputs to spinal motoneurons below the injury, with a net decrease in the inhibitory influence associated with successful locomotor recovery.²¹⁹ A general increase in synaptic input to motoneurons,²²⁰ a selective increase in cholinergic input, and a decrease in the expression of GABA_A receptor gamma 2 subunit to extensor motoneurons^{221,222} also are reported. This suggests a high degree of specificity in the changes triggered by locomotor training but fails to clearly identify how locomotor training translates into functional recovery.

Spinal motoneurons express a wide variety of 5-HT receptors²²³ and 5-HT release increases in the ventral horn during locomotion.²²⁴ The majority of locomotor-activated interneurons also co-localize with 5-HT₇, 5-HT_{2A}, and 5-HT_{1A} receptors.²²⁵ Locomotor recovery after a chronic SCI is facilitated by exogenous application of 5-HT or 5-HT₂ and 5-HT₇ receptor agonists and embryonic 5-HT grafts after chronic SCI in adult rats^{226–232} and cats,^{233,234} and the complex modulation of motoneuronal intrinsic properties by 5-HT has been extensively described.²²³ The activation of 5-HT_{2A} receptors in the spinal cord enhances spinal excitability and facilitates locomotor networks activity.^{235,236} Wheel running following an incomplete SCI stimulates serotonergic fibers regrowth and improves locomotor recovery.²³⁷

In the human spinal cord, serotonergic processes have been identified within the ventral horn surrounding motoneurons, as well as in the intermediolateral region,²³⁸ similar to what is reported for rodents and non-human primates. The lack of monoamines after SCI is clearly detrimental for locomotor performance and providing exogenous monoamines to improve recovery definitely has potential for success, at least in animal models. However, its systemic administration to SCI individuals leads to significant unwanted side effects and also can be associated with psychiatric disorders²³⁹ depending on the type of receptor targeted. In addition, serotonin selective re-uptake inhibitors were shown to augment strength, but also spasticity and spasms, and did little, if anything, to improve locomotor function in incomplete SCI individuals.^{240,241} While this pathway was first identified as being promising, its critical involvement in spasticity and serious side effects raises the question as to whether it really is an appropriate target.

Neurotrophins, in particular brain-derived neurotrophic factor (BDNF), play a critical role in adaptive plasticity in the nervous system and contribute to restoring function following SCI. BDNF has a widespread and complex effect ranging from cell survival to

increased nociception. It is also a potent neuromodulator that significantly impacts synaptic strength in the spinal cord.²⁴² It can be produced in an activity-dependent manner by a variety of non-neuronal cells in the nervous system including Schwann cells in the periphery and microglia in the dorsal horn of the spinal cord, which contribute to robust nerve regeneration²⁴³ and nociception, respectively.²⁴⁴ An important pathway for transducing the effect of locomotor training is *de novo* BDNF synthesis. The expression of BDNF in the spinal cord of rodents is significantly increased in response to locomotor training with protein and messenger RNA levels correlated with the intensity and volume of training and also to the extent of functional recovery.^{4,54,245,246} BDNF serum levels also correlate with the intensity and volume of exercise in humans,^{247,248} but it remains unclear if this is also the case for SCI individuals.

Exogenous BDNF increases the activity of neurons in the locomotor circuitry. After a complete thoracic SCI, delivery of neurotrophins promotes locomotor recovery in rats and cats, even in the absence of step-training.^{56,62,249–251} Interneurons of the L2 intermediate zone of the BDNF-treated animals displayed an increased expression of the transcription factor c-Fos, a marker of neuronal activity, indicating an augmented activation of interneurons in the vicinity of the locomotor CPG.⁶² It remains unknown if the enhanced activation of interneurons is generalized or restricted to a specific subgroup of interneurons. BDNF delivery also causes an increased excitability of motoneurons after SCI as evidenced by a reduced rheobase.⁶² However, step-training does not similarly modulate rheobase but rather decreases the AHP and increases monosynaptic EPSPs.^{242,252} Although some specific details differ, the similarity between the functional recovery triggered by step-training and by BDNF delivery further supports the idea that the step-training-dependent increase in BDNF levels is a critical player in locomotor recovery. It is noteworthy that the relationship between BDNF, stepping, nociception, and spasticity is complex after SCI²⁵³ and that great care will be required so as not to improve motor recovery at the cost of increasing pain and spasticity. The complexity of spinal cord physiology after SCI is not sufficiently addressed in the field. BDNF is certainly not the only one molecule impacting different systems in a conflicting fashion, and it should be recognized that manipulating a single molecule to treat all SCIs is unlikely to have significant and predictable effects. This needs to be better addressed for a more successful translation of treatments to the clinic.

Several inhibitory pathways driven by GABA/glycine are impaired in SCI individuals, including reciprocal inhibition,^{254,255} Ib inhibition,²⁵⁶ and presynaptic inhibition.^{257–259} These reflexes influence and shape the locomotor pattern.²⁶⁰ Reduced spinal inhibition also has detrimental consequences on locomotor activity.^{261–263} Despite the apparent hyperexcitability in spinal pathways, the “inhibitory potential” of the spinal cord was reported to be increased after SCI.^{263–266} How can we reconcile a clear lack of inhibition as displayed by spasms, clonus, and exaggerated reflexes and an increased presence of biological markers of inhibition (GAD67, gephyrin, GABA_AR)^{9,222,265,266} Normal GABA_AR function is critically dependent on [Cl]_i, which is largely determined by the relative expression of two cation chloride cotransporters in neurons, the inwardly directed Na⁺-K⁺-Cl⁻ cotransporter isoform 1 (NKCC1) and the chloride-extruding K⁺-Cl⁻ cotransporter isoform 2 (KCC2).^{267,268} An elegant study established that the loss of spinal inhibition resulted not only from the lack of descending inhibition due to the disruption of supraspinal tracts, but also from the collapse in GABAergic activity mediated by a downregulation of KCC2 in spinal motoneurons.²⁶⁹ The disruption in chloride homeostasis after SCI is associated with chronic

pain and spasticity. The strength of postsynaptic inhibition is reduced and excitability increased due to a downregulation of KCC2 in neurons of the superficial layers of the dorsal horn^{270,271} and in the motoneuronal membrane of the ventral horn,^{269,272,273} causing a depolarizing shift in the chloride equilibrium potential.

Given the beneficial effect of BDNF and 5-HT on functional recovery after SCI, it is not surprising that they both have the potential to modulate KCC2 expression and contribute to the restoration of chloride homeostasis after SCI. KCC2 expression is tightly controlled by neuronal activity.²⁷⁴ This regulation involves BDNF, neuronal intrinsic activity, or activity of excitatory synapses.^{275–278} A single dose of BDNF after SCI increases the expression of KCC2 in motoneurons.²⁶⁹ Similarly, exercise increases KCC2 levels in the spinal cord after SCI in a BDNF-dependent manner and contributes to the suppression of spasticity and allodynia.^{273,279,280} Recent studies also show that activation of 5-HT_{2A} receptors can shift the chloride equilibrium potential in the hyperpolarizing direction²⁷² through an upregulation of KCC2 function.

The pharmacological treatments currently available for spasticity have serious side effects since they act upstream of *N*-methyl-D-aspartate and Ca²⁺-dependent mechanisms. Baclofen, for example, is routinely used to treat spasticity, but it produces a deep and long-lasting depression of spinal excitability^{281,282} and weakens the muscle force generated by the more fatigable motor units.²⁸³ Although it is certainly beneficial to decrease the recruitment of inappropriately active muscles, it also interferes with motor recovery. Direct therapeutic treatment to counteract disruption of chloride homeostasis would restore endogenous inhibition rather than actively depress excitability. Current data suggest that beyond pharmacological avenues, step-training also has the potential to target this pathway.

Conclusion

SCI creates a complex set of multilayered complications and disruptions that create the need for rehabilitation programs that involve many targets and processes (motoneurons, interneurons, sprouting, etc.; Fig. 1). Some of the treatments developed in animal models have shown positive but limited results in SCI individuals with better results obtained when a combination of strategies were utilized. An interesting conclusion made by Eidelberg and colleagues after failing to initiate stepping in spinal monkeys using methods that were effective in spinal cats was that “step generators do exist in primates, but their access to skeleton-motor neurons may depend, more heavily than in cats, upon the presence of tonic descending facilitatory influences.”¹⁹⁴ The limited locomotor recovery seen with BWST in SCI individuals may be an indication that the spinal locomotor centers are more depressed in humans than they are in animals, and/or more dependent on a tonic excitatory supraspinal drive. This would explain the high correlation between the degree of meaningful recovery and amount and type of spared descending input. New analyses indicate remarkably greater sprouting and probably a larger interneuron pool in primates than in rodents. It is difficult to assess the extent to which relative differences in the number or type of propriospinal neurons and networks in small versus large animals are not simply related to scale.⁶⁷ This large untapped interneuron pool and increased sprouting capability suggest that focusing on interneuronal populations as potential targets for spared descending tracts sprouting, as well as task-appropriate proprioceptive feedback to increase recovery of function, is probably key.

Strategies for achieving functional motor improvement for severe SCI individuals will probably require task specific training

with enhanced proprioceptive feedback and some form of next-generation spinal cord stimulation and pharmacological treatments. Our ability to project translatable data from animal models using new techniques will continue to be impaired by the relatively few studies directly comparing species differences.

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