Novel therapeutic concepts to improve motor function after spinal cord injury[1]

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Funding / potential competing interests: (CP-IP 258654), the European Research Council (ERC 261247), the International Paraplegic Foundation, the Christopher and Dana Reeve Foundation, the NCCR "neural plasticity and repair", and the Swiss National Science Foundation

Summary

The majority of spinal cord injuries (SCI) lead to severe motor impairments. However, there is overwhelming evidence that the neuronal circuitry, sufficient to coordinate locomotion, is embedded in lumbosacral segments of the spinal cord. Nevertheless, the interruption of descending input from the brain markedly depresses the physiological state of spinal circuitries, thus limiting their capacity to produce motor patterns. In this review, we summarise recent findings in rats and humans that demonstrate the remarkable ability of rehabilitative training enabled by epidural electrical stimulation of lumbosacral segments and monoamine agonists to restore coordinated standing and walking movements in subjects with paralysing SCI. We discuss the implication of these findings for the design of viable clinical interventions to return motor function in humans with severe spinal cord damage.

Key words: Spinal cord injury; electrical stimulation; pharmacological stimulation; motor function; neurorehabilitation

Abbreviations

EES	epidural electrical stimulation
SCI	spinal cord injury
TA	Tibialis Anterior
Sol	Soleus

Introduction

Severe spinal cord injury (SCI) significantly impacts the ability of affected individuals to generate functional standing and locomotor movements. A century of research on the organisation of the neural processes that control movements in mammals, however, has demonstrated that the neuronal circuitry, sufficient to coordinate basic movements, is embedded within the lumbosacral segments of the spinal cord [1–3], i.e., caudal to the level of most human SCI. Even when completely isolated from supraspinal structures, spinal neuronal networks are capable of generating efficient stepping patterns and independent standing. Indeed, current concepts on motor control suggest that the descending systems provide excitatory [4] and modulatory [5] drives to these spinal circuits, but the operations underlying the elaboration of motor patterns for walking and standing are essentially achieved by the 'smart' spinal brain [6]. However, the interruption of supraspinal input after a severe SCI leads to a markedly depressed state of spinal circuits, thus preventing the production of movement [7, 8]. In the recent years, this view sparked a surge of research projects that aimed at developing strategies to tune the physiological state of spinal circuitries to a level sufficient for stepping and standing to occur. The underlying objective is to promote a highly functional state during rehabilitation to steer use-dependent plastic changes in the trained sensorimotor pathways [9].

In this review, we briefly summarise the lessons that we have learned from this past decade of research. We describe innovative strategies combining electrical, pharmacological, and robotically-assisted step training paradigms which are capable of restoring full weight bearing locomotion of the paralysed hindlimbs in rats with complete SCI. We also document recent findings in a paraplegic man who regained voluntary leg movements using these therapeutic principles. Finally, we discuss the implications of these results for the design of viable interventions to return motor function in humans with severe spinal cord damage.

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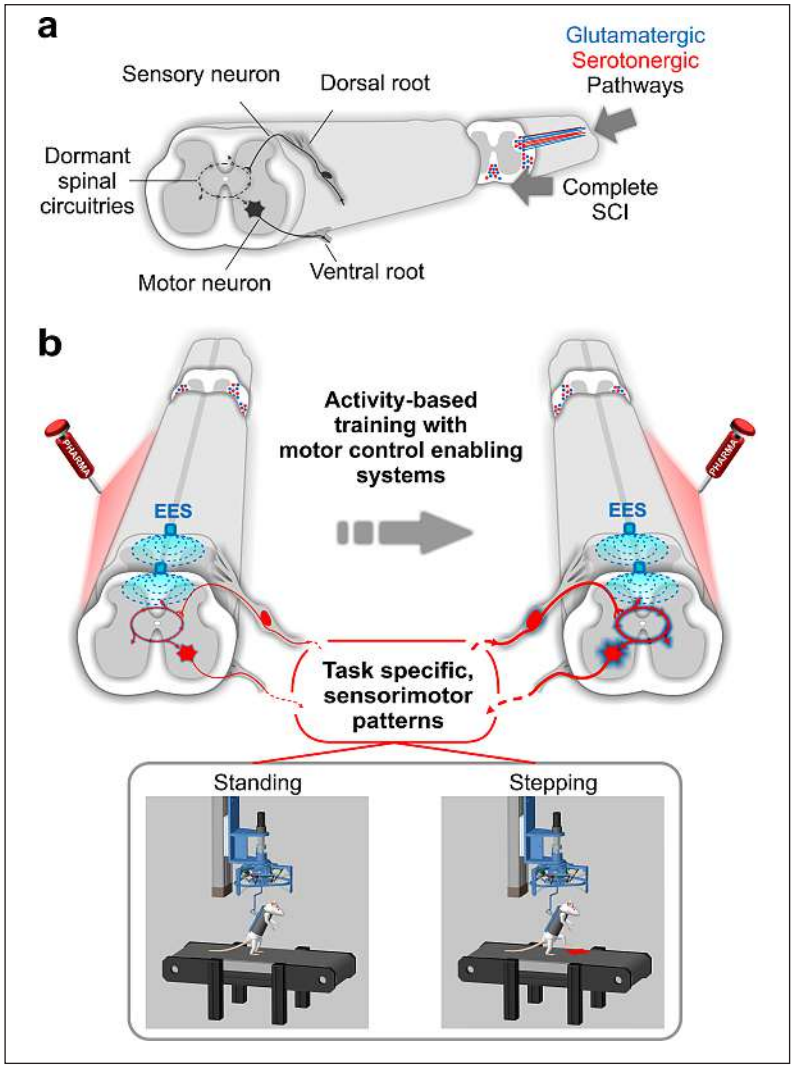
Motor control enabling systems after SCI

Various strategies including electrical stimulation of the muscles [10] or dorsal roots [11], epidural [12, 13] or intraspinal [10, 11] electrical spinal cord stimulation, administration of a variety of pharmacological agents [8, 14, 15], and smart robotic systems [16, 17] have shown the capacity to facilitate standing and stepping after a severe SCI. Since these interventions are not used to induce, but rather to allow the production of movements, we termed these paradigms *motor control enabling systems*.

In this review, we specifically focus on the ability of epidural electrical stimulation (EES) and monoamine agonists to enable locomotion in rats with complete SCI (fig. 1A). The use of EES to facilitate locomotion dates back to the early 1990's. Garcia-Rill and colleagues [18] first reported that EES applied both at the cervical or lumbar enlargements with plate electrodes induces locomotion in decerebrated cats. Since then, tonic EES applied over the dorsal surface of virtually any lumbar or sacral segment [19] has shown the ability to facilitate stepping on a treadmill as well as standing in rats [14, 20], rabbits [21], cats [21], and humans with a severe SCI [22, 23]. The mechanisms underlying the facilitation of motor activities with EES are not yet

1 Laureate of the Schellenberg award 2010.

Figure 1 Schematic diagram illustrating the mechanisms through which activity-based training with motor control enabling systems enhances standing and stepping capacities after a complete SCI. (a) The complete SCI interrupts all descending monoaminergic and glutamatergic input from the brain. However, the essential neuronal circuitry to coordinate movements remain intact, but dormant, caudal to the lesion. (b) These dormant spinal circuitries can be engaged by motor control enabling systems combining EES and monoaminergic agonists. In turn, spinal circuitries can recognise task-specific sensorimotor patterns and use this information to coordinate movement without the brain. Training with motor control enabling systems leads to the selection and reinforcement of the repetitively activated neuronal networks in a way that improves the performance of the trained tasks.



fully understood [24]. Electrophysiological recordings [25] and computer simulations [26, 27] suggest that EES directly engages spinal circuits by recruiting posterior root fibers at their entry into the spinal cord as well as along the longitudinal portions of the fiber trajectories (fig. 1B).

Current evidence thus suggests that EES activates motor pools through the recruitment of afferent pathways, which follow a strict muscle-specific architecture along the rostrocaudal extent of the spinal cord [28]. Consequently, can EES delivered at specific locations elicit distinct patterns of motor responses in lower limb muscles? To test this hypothesis we applied EES over lumbar (L2) versus sacral (S1) segments during both standing and stepping in spinal rats [8]. Consistent with the rostrocaudal anatomical gradient of flexor and extensor motor pools, we observed a facilitation of flexion with lumbar EES, whereas stimulation applied at the sacral level primarily encouraged extension, both during standing and stepping. Moreover, the combination of two [8], and even more efficiently three [20], sites of EES promoted clear synergistic facilitation of locomotion.

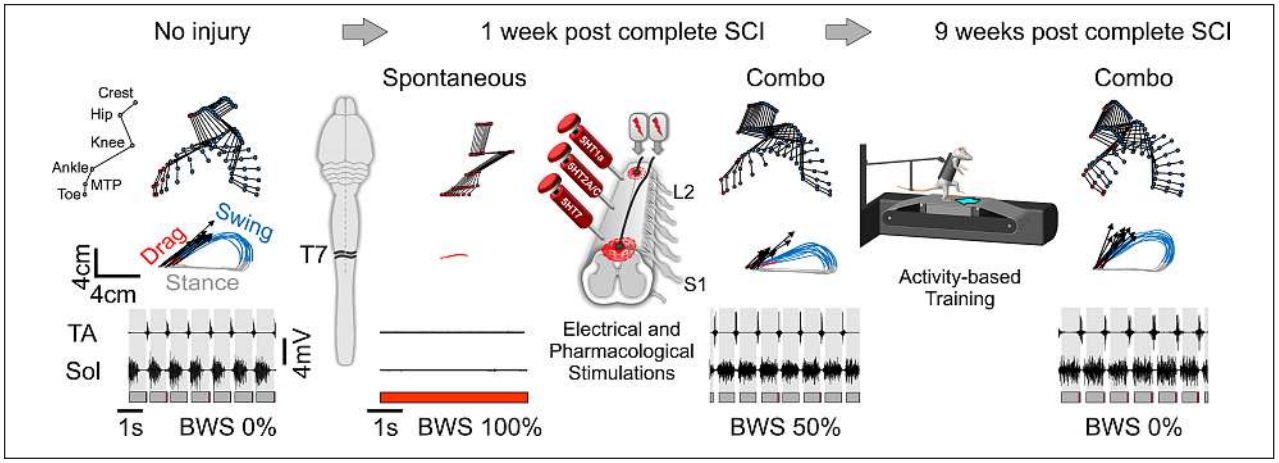
Under normal conditions glutamatergic reticulospinal neurons provide the tonic excitatory drive to engage spinal locomotor networks [4]. Here, we summarise results that collectively demonstrate the powerful ability of basic spinal cord electrical stimulation to replace the descending source of tonic excitation, enabling standing and stepping in paralysed rats with a severe SCI. In the complete absence of a descending source of monoaminergic modulation, however, EES alone fails to promote substantial levels of weight bearing with plantar placement of the feet on the treadmill belt [8]. Similarly, in the absence of monoamines, descending glutamatergic inputs alone fail to elicit long-lasting step-like patterns [4].

Indeed, spontaneous locomotor activity is associated with a substantial release of monoamines within most laminae of the lumbosacral segments [29]. These monoaminergic inputs are not restricted to the classical, hardwired synaptic communication, but also and primarily operate peri-synaptically through three-dimensional signal diffusion, i.e., volume transmission [30]. Monoaminergic neurotransmitters easily escape the synaptic cleft, enter the extracellular space, and reach extrasynaptic, G-protein-coupled receptors located on the surface membrane of neighboring cells. This signaling transduction pathway profoundly alters cell properties over timescales that span from minutes to hours [30]. Volume transmission communication suggests that pharmacological agents mimicking the action of monoamines could act in concert with epidural electrical stimulation to orchestrate the functional tuning of spinal circuitries [31].

We directly tested this hypothesis in adult rats with a complete SCI [8]. We investigated the ability of a broad range of monoaminergic receptor agonists to promote specific tuning patterns of gait features. Using advanced neurobiomechanical analyses, we demonstrated the intriguing ability of serotonergic, dopaminergic, and noradrenergic receptor subtypes to modulate stepping patterns in qualitatively unique ways [32] (see online video: http://www.neuroreha.uzh.ch/expneuroreha/research/Musienko2011.html). We thus elaborated a catalogue of monoaminergic tuning functions that allowed us to anticipate the modulation patterns mediated by specific pharmacological agents as well as their interactions. Capitalising on these predictive interactions, we elaborated a multidimensional monoaminergic intervention that, combined with dual site EES, restored coordinated hindlimb locomotion with normal levels of weight bearing and partial equilibrium maintenance in spinal rats (fig. 1B, left side).

Taken together, these results show that stimulation of spinal monoaminergic receptors pharmacologically, and recruitment of spinal circuits electrically can modulate recognisable qualitative features of locomotion indepen-

Figure 2 Accessing spinal locomotor circuits in combination with activity-based step training on a treadmill restores full weight-bearing locomotion in paralysed rats. Representative illustration of EMG and kinematic characteristics underlying bipedal locomotion in a non-injured rat, and in a rat with a complete SCI at 1 week post injury, spontaneously and with electrical and pharmacological stimulations (Combo), and after eight weeks of activity-based step training on a treadmill. In each panel from top to bottom a representative stick diagram decomposition of hindlimb locomotion during swing is shown together with successive limb endpoint trajectories. Traces are colour-coded for stance, swing and drag by grey, blue and red, respectively. The vectors represent the direction and intensity of the limb endpoint velocity at swing onset. Below, a sequence of raw EMG activity from the tibialis anterior (TA) and the soleus (Sol) muscle is shown. Grey and red bars represent the stance and drag phases, respectively. The percentage of body weight support (%BWS) for the trial is reported below each panel. MTP, metatarsophalangeal joint.



dently, as well as collectively, in rats deprived of any supraspinal influences (fig. 2).

Neurorehabilitation with motor control enabling systems

Intensive rehabilitative training has shown the capacity to prevent deterioration of function and improve stepping and standing capacities in cats with a complete SCI [33]. Comparable activity-based approaches alone, however, failed to promote similar improvements in rats [34] and humans [7] with a severe SCI. We surmised that the absence of robust motor activity during locomotor training is largely responsible for the poor effects of rehabilitation. We directly tested this hypothesis by training spinal rats on a treadmill under the presence of EES and monoamine agonists to enable locomotion of the paralysed hindlimbs. Specifically, we tested the therapeutic potential of locomotor training enabled by lumbar (L2) plus sacral (S1) EES and agonists to 5-HT_{1A}, 5-$HT_{2A/C}$, and 5-HT_7 receptors (quipazine and 8-OH-DPAT) [8]. This combination enables coordinated stepping patterns with some weight bearing as early as one week post-injury (fig. 2). After 8 weeks of neurorehabilitation, the spinal rats recovered the impressive capacity to perform full weight-bearing locomotion with features that were nearly indistinguishable from those underlying walking patterns of the same rats recorded before the injury (fig. 2). Rats trained with electrical stimulation alone or serotonin agonists alone developed specific patterns of locomotion, but these interventions failed to prevent the deterioration of functional capacities in the chronic state of the injury. Collectively, these results suggest that the repetitive activation of unique combinations of sensorimotor circuits under the influence of distinct electrical and pharmacological stimulations and through task-specific sensory patterns leads to the selection and reinforcement of those neuronal networks in an activity-dependent manner [35] (fig. 1B). As exemplified in cats [36–39], the rodent spinal motor circuitries deprived of any supraspinal influences can learn the task that is trained and practiced.

Perspective for the recovery of function in humans with SCI

We are approaching a new and exciting era for the capability to recover significant levels of motor control after a severe SCI [23] and a variety of degenerative motor diseases [40]. This optimism is based on years of evolving perspectives and concepts related to how the CNS controls movement, as well as on recent breakthroughs obtained in a paraplegic patient.

Reggie Edgerton and colleagues reported the first attempt to translate these promising findings in animal models of SCI to a viable application for human beings with motor complete SCI. They surgically implanted an epidural electrode array over the lumbosacral segments of a 23-year-old man who became paraplegic after a motor-vehicle accident 3–4 years earlier. Before implantation, the patient showed no residual supraspinal control of leg movements despite a year of intense locomotor training. In the first weeks after surgery, EES enabled full weight-bearing standing when sensory information related to bilateral leg extension and loading was present. In turn, EES adjusted for stepping elicited locomotor-like patterns during manually assisted leg movements on a treadmill. More strikingly, after several months of basic stand training enabled by EES, the patient regained the capacity to consciously control joint-specific movements of the leg, but only when enabled by EES. This unexpected recovery of supraspinally-mediated movement in a severely injured man suggests that activity-dependent mechanisms promoted plasticity of axonal projections that

presumably were spared by the injury. A proposed mechanism by which such level of recovery could have occurred involves the interaction of these spared fibers with EES. Our current experiments reinforce this view. We observed that, in rats with severe SCI, activity-based interventions can promote extensive functional recovery that coincides with ubiquitous plasticity of spared neuronal circuitries when boosted with robotic, electrical, and pharmacological enabling factors [41]. Further research is necessary to investigate the mechanisms underlying the facilitation of motor activities with EES, as well as its interaction with residual descending fibers and local circuitries.

These combined results in animals and humans open the possibility of a paradigm shift in the future design of strategies to restore function in motor-impaired individuals. Thus far, recovery of function after SCI has widely been interpreted as the need to regenerate severed fibers across the injury. Instead we suggest that a more immediate intervention might be feasible by capitalising on the impressive capacity of spared neuronal systems to reorganise through activity-dependent mechanisms. Additionally, therapies that promote nerve growth might substantially increase this plastic remodeling of neuronal circuitries. Furthermore, our challenge in the near future is to exploit current progress in neuroelectronics and neurorobotics to develop neuroprosthetic interfaces and adaptive control algorithms that will take full advantage of the remarkable potential for plasticity and functional recovery that remains after even some of the most severe injuries to the neuromotor system.

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