REVIEW
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Therapeutic Stimulation for Restoration of Function After Spinal Cord Injury

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Paralysis due to spinal cord injury can severely limit motor function and independence. This review summarizes different approaches to electrical stimulation of the spinal cord designed to restore motor function, with a brief discussion of their origins and the current understanding of their mechanisms of action. Spinal stimulation leads to impressive improvements in motor function along with some benefits to autonomic functions such as bladder control. Nonetheless, the precise mechanisms underlying these improvements and the optimal spinal stimulation approaches for restoration of motor function are largely unknown. Finally, spinal stimulation may augment other therapies that address the molecular and cellular environment of the injured spinal cord. The fact that several stimulation approaches are now leading to substantial and durable improvements in function following spinal cord injury provides a new perspectives on the previously "incurable" condition of paralysis.

Paralysis due to spinal cord injury affects ~282,000 people in the U.S. (70). Spinal cord injury can lead to paralysis of both the upper and lower extremities, severely limiting activities of daily living. People with tetraplegia (paralysis of upper and lower limbs) cite restoration of hand and arm function as their highest priority for functional recovery (2, 22). People with paraplegia (paralysis of only the lower limbs) cite walking movement as a priority, although notably a lower priority than restoration of autonomic functions (2). Although many types of therapy may be prescribed for spinal cord injury rehabilitation, only a few of the most commonly applied methods have demonstrated reliable effects (37), and most do not completely restore motor function of the paralyzed limbs.

The application of electrical stimulation to treat spinal cord injury has garnered substantial interest from the research community, since it can enhance the electrical activity of neurons after spinal cord injury and may help to restore function. The spinal cord is an attractive target for stimulation-based rehabilitative therapies, since interventions at the spinal level can take advantage of preserved motor and sensory neural pathways below the injury. Stimulation of the spinal cord allows fatigue-resistant movements (42), which are typically difficult to achieve with more distal stimulation sites, such as peripheral nerves or muscles (53, 66). Spinal stimulation can also produce complex movements involving multiple muscles and joints, such as those required for walking (41, 63), reaching, and grasping (60, 90, 97).

Several groups have used electrical stimulation to improve limb function in awake, behaving, paralyzed animals. This includes the production of hindlimb stepping movements in paralyzed rats (8, 85), cats (5, 42, 63), and non-human primates (11), as well as forelimb reaching movements in rats (49) and non-human primates (60, 69, 97).

In addition to its somatic effects, spinal stimulation may also benefit the autonomic nervous system. Spinal stimulation during motor training can improve and trigger bladder voiding in animal models (26, 73), and a human case study cited improvements in bladder control, sexual function, and temperature regulation after motor training with spinal stimulation (36). Although this review is primarily focused on somatic motor improvements, these broad benefits illustrate that stimulation focused on motor rehabilitation may also confer important autonomic benefits to people with spinal cord injury (2).

Furthermore, targeted electrical stimulation may be useful in directing the rehabilitation of specific motor pathways (21). The spinal cord undergoes neural remodeling after injury, and this remodeling can lead to maladaptive changes in neural pathways that may increase detrimental effects such as pain and spasticity (6, 48). Targeted therapeutic electrical stimulation may guide these remodeling mechanisms toward the formation of functional, rather than maladaptive, neural pathways.

Types of Spinal Stimulation

Researchers have identified several methods of spinal cord stimulation for the restoration of movement after paralyzing spinal cord injury. Stimulation can be delivered *1*) epidurally, with electrodes on the dorsal surface of the cord above the dura; *2*), transcutaneously, with electrodes placed on the skin above the vertebral column; and *3*) intraspinally, with stimulating electrodes implanted within the spinal cord (FIGURE 1). The site of stimulation partly determines the neural pathways activated as well as the stimulation parameters required to elicit the desired result (86). The different approaches to spinal stimulation may also differ in their mechanisms of action; current opinion in the field is that intraspinal stimulation likely activates motor pools as well as intraspinal and propriospinal networks to enable coordinated whole-limb movements (91), whereas sub-threshold epidural and transcutaneous stimulation may increase the baseline excitability of the spinal cord, thereby enabling movements triggered by inputs that remain intact after spinal cord injury (20).

Epidural Spinal Stimulation

Although electrical stimulation treatments for various disorders can be traced back as early as the first century, the utility of spinal cord stimulation for the restoration of motor function is a more recent development. Therapeutic electrical stimulation of the spinal cord first emerged as a treatment for pain described in clinical cases in the late 1960s and early 1970s (17, 87, 88). In a 1967 experiment, Shealy and colleagues stimulated the spinal cord through a single electrode placed on the dura of a man complaining of diffuse chest and abdominal pain. Stimulating at frequencies of 10–50 Hz caused a "buzzing" sensation for the patient but also eliminated his pain for 5–15 min, after which a change in stimulation frequency was required to continue control of the pain (88). This stimulation was believed to inhibit the conduction of pain signals via activating larger sensory fibers in the dorsal columns of the spinal cord and quieting the smaller pain fibers (87). Later experimental results demonstrated effective pain relief using bipolar electrode arrangements, which allowed for higher-frequency (100–200 Hz) stimulation while remaining well below the tissue damage threshold (7.75×10^{-3} W/cm^2) (87).

The clinical applications of spinal cord stimulation quickly expanded, as other groups observed its benefits for improved motor and sensory function in people with multiple sclerosis. Using similar epidural stimulation implants, Cook and Weinstein reported improvements in spasticity, motor function, and sensory function in people with multiple sclerosis treated with epidural spinal stimulation (12). Less than a decade later, Campos and colleagues reported improved motor function and bladder control, among other positive effects, following therapeutic spinal stimulation in people with spinal cord injury as well as in those with multiple sclerosis (10). Interestingly, Dimitrijevic and colleagues later observed variable effects of electrical stimulation on relief of spasticity in people with spinal cord injury, citing differences in body position (e.g., standing vs. sitting), differences in spasticity at a given time, and patient-controlled stimulation strength as likely contributors to this variability (18). The same group later outlined standards for epidural stimulation to relieve spasticity, observing that 50- to 100-Hz stimulation of 2- to 7-V strength and

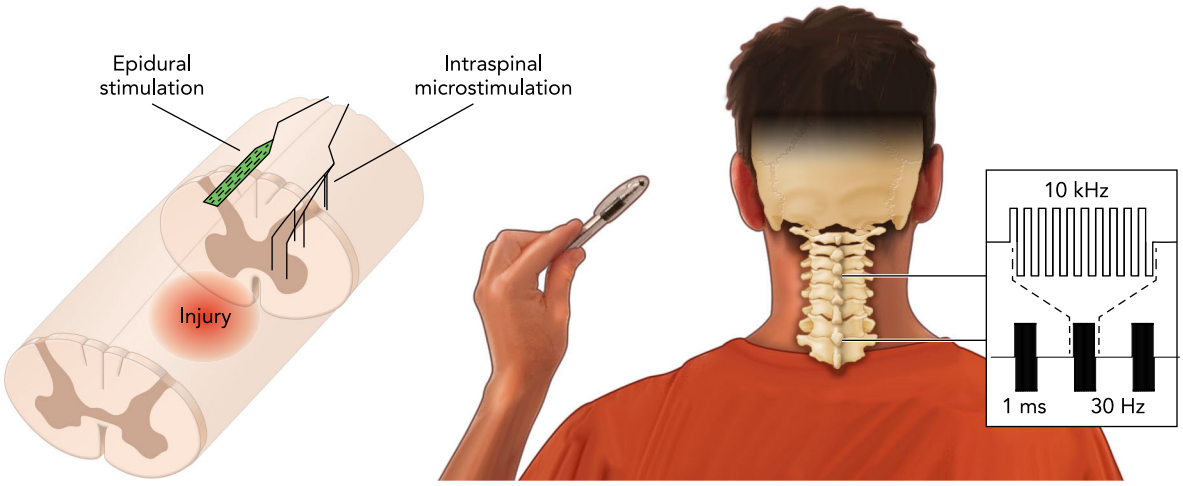

FIGURE 1. **Illustrations of the location of epidural, intraspinal, and transcutaneous spinal stimulation**
Left: illustrations of the location of epidural stimulation compared with intraspinal microstimulation, both applied distal to a contusion injury. *Right*: stimulation location and stimulation parameters for transcutaneous stimulation applied to the cervical spinal cord utilizing a 10-kHz carrier frequency to improve hand function after spinal cord injury.

210-ms pulse width worked best. They also noted, however, that the stimulation could be further optimized for each patient by testing different electrode combinations and adjusting stimulus amplitude based on body position (74), highlighting the anatomical variability of spinal pathways similar to those seen between the brains of different people.

Several groups proceeded to refine electrical stimulation of the spinal cord in animal models. They tested the threshold level of stimulation required to evoke movements, then experimented with stimulation that directly evoked movements (supra-threshold). The Skinner group demonstrated that supra-threshold stimulation of the dorsal surface of the spinal cord at a frequency of 3–5 Hz could reliably elicit stepping movements in decerebrated cats (44), and the Edgerton group induced bilateral stepping movements via similar methods in rats, observing that bilateral stepping movements occurred most often with 40- to 50-Hz stimulation delivered over the second lumbar spinal segment (43). More recently, the Courtine group observed improved locomotion with supra-threshold epidural stimulation in non-human primates with spinal cord injuries (11).

In contrast to supra-threshold stimulation, sub-threshold stimulation does not immediately evoke movements but may permit the animal to execute movements in contexts such as treadmill locomotion. For example, the Edgerton group demonstrated that sub-threshold stimulation could induce movement in the presence of proprioceptive inputs, likely by amplifying existing reflexive activity in the rat spinal cord (23).

Parallel findings were observed in human participants. Dimitrijevic's group demonstrated that supra-threshold epidural stimulation at 5–15 Hz could result in lower limb extension in people with complete spinal cord injury and paraplegia. They hypothesized that this effect relied on the activation of primary sensory afferents, which in turn activated a network of neurons within the spinal cord to elicit motor unit activity and muscle contraction (47). Human and animal studies indicate that epidural stimulation of the spinal cord may induce movements either by direct electrical activation of motor or sensory units (43, 44, 47) or by the facilitation, or increase, of baseline motor unit activity (23, 30). Increasing baseline motor unit activity could bring the motor units closer to threshold, the level of activity required to produce a movement. This sub-threshold stimulation technique has garnered substantial interest in the spinal stimulation research community in recent years.

In contrast to direct activation of motor units, epidural stimulation more recently enabled otherwise paralyzed people to make volitional movements in the presence of continuous, sub-threshold stimulation. Recent work has demonstrated the utility of this "enabling" epidural stimulation for promoting both lower (3, 36) and upper (52) limb movements. These studies show an impressive return of voluntary lower limb movement with epidural stimulation in people with complete and incomplete spinal cord injuries (3, 36), as well as improved volitional hand control with epidural stimulation in people with motor-limiting cervical spinal cord injuries (52).

For some participants, the benefits of sub-threshold epidural stimulation persist beyond the period of stimulation. The exciting therapeutic benefit was noted by both participants in the upper-extremity study, whose hand function remained improved after stimulation had ceased (52). This encouraging result further supports the need for an evaluation of the circuits activated by epidural stimulation. Just as customized stimulation parameters such as stimulation frequency and amplitude for individual patients and specific tasks typically lead to better functional improvements during the stimulation period (1, 76, 77, 85), customized parameters and pairing with other rehabilitation strategies geared toward enabling sustained function after stimulation may provide an additional benefit.

The mechanisms responsible for the effect of epidural stimulation on paralyzed limbs have intrigued many researchers. A 1975 review of early work in neural stimulation described the multitude of factors at play, explaining that an understanding of the precise cells and tissues activated by stimulation will require detailed knowledge of the cell and tissue properties, electrode configurations, and stimulus parameters, such as waveform shape, duration, and magnitude (75). Although the field may yet lack a complete understanding of the complex interactions of these elements, some generalized mechanistic explanations have emerged, as described below.

Although epidural stimulation activates both afferent and efferent pathways (57, 79), supraspinal and sensory inputs driven by the patient's intent and position may dictate the specific motor units recruited for a given task. For example, it is likely that the sensory signals produced by weight-bearing standing can selectively enhance the activity of relevant motor units during stimulation periods (34, 79), effectively increasing activity in the units required to maintain an upright position. Supraspinal input in the form of volitional, conscious motor commands can control lower limb movement in a supine position in the presence of epidural stimulation, even for people with clinically motor and sensory complete injuries (3, 34,

36). These results are aligned with the current general view of epidural stimulation as an "enabling" technology capable of enhancing baseline activity or physiological state of the spinal cord such that additional inputs such as proprioceptive inputs in the case of locomotion may activate the appropriate motor pathways for a given task (20). In one study, all 12 participants with motor complete spinal cord injuries could voluntarily produce electromyographic activity in two independent muscles of the paralyzed limbs, although not sufficient to result in movement (61). This provides evidence of spared pathways passing the spinal cord injury in nearly all persons with clinically complete injuries. These spared pathways may carry signals that could be useful in triggering movements in the presence of spinal stimulation. In most cases, epidural stimulation must be applied to observe benefits (3, 34, 76), and carryover of lower extremity motor benefits after the period of stimulation is limited (76). Nonetheless, benefits to autonomic functions such as bladder, bowel, and sexual function persist beyond the period of stimulation in both human (36) and animal subjects (26), suggesting a persistent and beneficial reorganization of spinal neural pathways is possible due to stimulation therapy.

Transcutaneous Stimulation

Both electrical and magnetic stimulation applied to the skin surface can improve motor function after injury. Magnetic stimulation applied over the lumbar spinal cord improves spasticity for up to 24 h following stimulation (50). Similarly, transcutaneous electrical stimulation applied over the thoracic spinal processes leads to improvement in spasticity and augmented stepping ability during stimulation periods for people with spinal cord injuries (39, 40, 55). The adoption of high-frequency electrical stimulation permits the application of higher current transcutaneous stimulation to the skin above the spinal cord with minimal discomfort (93, 94). The 10-kHz carrier frequency (FIGURE 1, RIGHT) permits over 100 mA of current to pass through the skin without painful sensations (27). Such stimulation is capable of activating the lumbar spinal cord both in spinally intact (28, 31, 80, 81) and injured participants (24, 25, 27, 29). As with epidural stimulation, the effects of transcutaneous stimulation depend on body position. For example, the current required to elicit a movement is greater in prone compared with standing positions, and the magnitude of the response is highest in supine compared with standing and prone positions (16). These findings reinforce the context-dependent nature of spinal neural pathways that may be leveraged for therapy.

Several groups are also exploring transcutaneous spinal stimulation applied to the cervical region for improving hand and arm function with promising results. Early results suggest that transcutaneous stimulation may confer similar benefits to those of epidural stimulation (29).

Although the electrodes are positioned further from the spinal cord, the basic mechanisms responsible for the effects of transcutaneous stimulation likely also rely on increasing baseline electrical activity to enable movements induced by remaining volitional motor commands or sensory inputs. The Gerasimenko group recently demonstrated that specific electrode configurations can also contribute to enhanced effects of transcutaneous spinal stimulation (81). By stimulating at two sites in rostro-caudal order, first at the site closer to the head and then at the site further down the spinal cord, they were able to elicit stronger responses than by stimulating at individual locations. They suggest that this may be explained by recruitment of motoneurons via both direct and indirect (e.g., sensory, interneuron) pathways in the rostro-caudal stimulation paradigm (81).

Because transcutaneous approaches do not require surgery, they may be more attractive to some people. This experimental approach, however, is quite new, and optimal application schedules and activities to be performed during stimulation are still being discovered. Although precise parameters used in epidural stimulation are unlikely to translate given the more distant application of current through the skin, a common theme appears to be the need for intensive therapy and exercise to be performed during the application of spinal cord stimulation to realize the full benefits to motor function (3, 24).

Intraspinal Stimulation

Intraspinal stimulation differs from epidural and transcutaneous stimulation in that it delivers electrical current through electrodes implanted within the spinal cord. Thus far, intraspinal stimulation studies in humans are rare, but animal work provides insights into the potential benefits of this approach. Intraspinal stimulation can elicit a wide variety of functionally relevant movements in animal models, including movements required for stepping (33, 42, 51, 63–67, 78). It can also elicit a variety of movements related to reaching and grasping (60, 90, 97). When intraspinal stimulation is applied to the ventral spinal cord, direct activation of motoneurons or ventral root axons can occur, leading to single joint movement. When it is applied to the intermediate lamina of the spinal cord, consensus is that stimulation most likely activates axons and subsequently interneurons, cells

within the spinal cord that can in turn activate complex neural pathways and result in coordinated motor patterns. This is because electrical stimulation generally activates fibers of passage rather than cell bodies (75), and interneuron fibers are abundant within the spinal cord. The activated interneurons can then activate the reflex and movement coordination pathways in which they participate, which may lead to coordinated multijoint movements.

Intraspinal stimulation may be especially useful when paired with physical rehabilitation in experiments geared toward activating specific motor pathways or strengthening synapses—the connections between neurons. Rodent studies have demonstrated lasting forelimb motor improvements after intraspinal stimulation of a specific movement (49, 54), even weeks after stimulation had ceased (54, 56). These results allude to the potential long-term therapeutic effect of intraspinal stimulation. Pairing intraspinal stimulation with rehabilitative physical training may have added benefits, and specific studies that directly address a combined approach would be useful.

Intraspinal stimulation may also confer more benefits if the user can easily control the stimulation. One way to enable such control would be to use signals that are already present during a particular task, such as a brain signal that occurs when an animal attempts to move. Stimulation controlled by activity-related signals is called activity-dependent stimulation. Activity-dependent stimulation may confer long-term benefits when the time between recording of the activity signal and delivery of stimulation falls within a specific time window (54). Activity-dependent stimulation that takes advantage of this time window can strengthen cortico-cortical (45) and cortico-spinal (68) connections in uninjured animals, and further investigation of the utility of this approach in spinal cord injury rehabilitation is warranted. It would be extremely useful to understand the maximum duration of these changes and whether they can be extended from days (68) and weeks (54) to months or years.

Challenges

Although the stimulation of the spinal cord at epidural, transcutaneous, and intraspinal locations as described above has led to substantial advancements in the field, all of these approaches currently fall short of fully restoring natural movements and achieving long-term rehabilitation. Our understanding of the underlying mechanisms responsible for the effect of exogenous stimulation on biological tissue is incomplete, leading to challenges in translation from animal models to humans (13) and difficulty facilitating motor improvements that persist beyond the period of stimulation. Additionally, although epidural stimulation benefits from widespread clinical acceptance due to its long history as a pain treatment, translation of intraspinal stimulation methods will likely take more time, since development of hardware and novel surgical and application techniques is still underway.

Nonetheless, electrical stimulation shows therapeutic potential in the treatment of spinal cord injury motor deficits, and investigations of the underlying mechanisms and optimal stimulation parameters should continue to drive progress toward restoring natural movements to paralyzed limbs.

Future Directions

Although promising early results of electrical spinal stimulation indicate a prominent role in enhancing motor recovery, the potential of this technology to elicit long-term, sustained improvements will most likely require further refinement and perhaps a combination of multiple treatment approaches. Such approaches are referred to as combinatorial treatments, since they include a combination of interventions.

Such combinatorial interventions might target the molecular environment of the injured spinal cord to further increase its excitability and enhance the effects of therapeutic electrical stimulation. For example, pharmacological agents that increase excitability, such as serotonergic agonists or inhibitory neurotransmitter antagonists, appear to enhance the effects of epidural stimulation (8, 32). These pharmacological treatments can in some cases enhance the effects of locomotor training (21) and epidural stimulation (14). When administered orally during a period of transcutaneous stimulation treatment in humans, the serotonergic agonist buspirone enhanced motor function during and beyond acute stimulation treatments (29). This is consistent with prior results in animals, in which quipazine, another serotonergic agonist, appeared to regulate the stepping rhythm induced by epidural stimulation (30). Combinatorial approaches that employ multiple tools may prove to be the most useful. For example, combinations of low-dose pharmacological agents, electrical stimulation, and motor training have demonstrated functional improvements in animal models of spinal cord injury (8, 19, 21). The combinations of stimulation and pharmacological approaches are reviewed in greater detail elsewhere (21, 30).

In addition to pharmacological agents that directly affect spinal cord excitability, agents that enhance the plasticity of the spinal cord may also improve motor outcomes. These agents typically interfere

with molecular pathways that inhibit plasticity. For example, approaches that interfere with Nogo-A, a component of myelin that inhibits neurite outgrowth, can enhance cerebrospinal tract sprouting and improve hindlimb locomotion after spinal cord injury (84). Similarly, dissolution of chondroitin sulfate proteoglycans (CSPGs), extracellular matrix components that limit synapse formation (7), has resulted in sprouting of ascending and descending neural projections and improved motor function (7, 46, 89). Interestingly, a combination of anti-Nogo and enzymatic treatment to dissolve CSPGs yielded greater improvements in motor function than either treatment alone (96). Ongoing and future work testing the combination of electrical spinal stimulation and these plasticity-promoting interventions is a promising avenue to improve function after spinal cord injury.

Although pharmacological interventions may promote excitability and plasticity in the cells that remain viable after spinal cord injury, replacing damaged cells may further enhance electrical stimulation treatments. Spinal cord injury often results in cellular damage and demyelination or dysmyelination, whereby the insulating material that enables efficient electrical conduction through axons is lost or damaged. Stem cells might promote the repair of this damage; for example, neural and glial cells derived from transplanted neural stem and progenitor cells (62, 71, 92) promote remyelination of axons near the injury site and promote motor improvement after spinal cord injury (15, 38). However, because stem cells may mature into many different cell types, it is important to carefully direct the cell toward a specific type, or fate, before transplant to achieve optimal results (38). Stem cell and neural progenitor treatments also improve reaching performance and hand function (72, 83).

Intriguingly, stem cells might also respond to therapeutic electrical stimulation, potentially by migrating toward the site of injury and providing support to damaged neurons or by forming new neural networks to bridge the gaps caused by spinal cord injury. Early results from studies investigating this combination are promising. Electrical stimulation appears to promote transplanted cell survival after peripheral nerve axotomy in vivo (35), indicating the potential for a positive interaction of the two approaches. Additionally, the application of electrical current can affect neural stem cell migration in vitro (4, 58, 95). Based on these findings, perhaps electrical stimulation could be used to guide stem cells toward sites of cellular damage in vivo.

Taken together, these currently disparate approaches suggest many potential avenues for combined therapeutic electrical stimulation, cell-based, and pharmacological therapies in future work. The early successes of electrical stimulation therapies are encouraging, but restoring complete function may require the combination of many approaches that address the multi-faceted effects of spinal cord injury. It is an exciting time in the field of spinalcord injury, since future studies have a multitude of potentially viable treatment options to explore. Going forward, careful and systematic evaluation of therapeutic stimulation approaches and their combinations with molecular and cellular interventions may be necessary to deliver effective new treatments to benefit people with spinal cord injuries. ■

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