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Activity-dependent plasticity in spinal cord injury

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Abstract—The adult mammalian central nervous system (CNS) is capable of considerable plasticity, both in health and disease. After spinal neurotrauma, the degrees and extent of neuroplasticity and recovery depend on multiple factors, including the level and extent of injury, postinjury medical and surgical care, and rehabilitative interventions. Rehabilitation strategies focus less on repairing lost connections and more on influencing CNS plasticity for regaining function. Current evidence indicates that strategies for rehabilitation, including passive exercise, active exercise with some voluntary control, and use of neuroprostheses, can enhance sensorimotor recovery after spinal cord injury (SCI) by promoting adaptive structural and functional plasticity while mitigating maladaptive changes at multiple levels of the neuraxis. In this review, we will discuss CNS plasticity that occurs both spontaneously after SCI and in response to rehabilitative therapies.

Key words: central nervous system, electrical stimulation, exercise, neuromuscular, neuroprostheses, neurotrophic factors, plasticity, recovery, rehabilitation, spinal cord injury, therapy.

INTRODUCTION

Spinal cord injuries (SCIs) disrupt both axonal pathways and segmental spinal cord circuitry, producing severe impairments of motor, sensory, and autonomic function at and below the level of the injury. However, significant recovery can and often does occur in the first year following SCIs classified as incomplete [1–4]. The amount and extent of recovery depend on multiple factors, including the level and extent of injury, postinjury medical and surgical care, and rehabilitative interventions. Rehabilitative therapies, such as intense repetitive training ("massed practice") [5] and locomotor training [6–7], have been shown to promote recovery after incomplete SCI in humans. Although the mechanisms mediating this recovery are not fully understood, activity-dependent plasticity likely plays a major role.

In this review, we discuss central nervous system (CNS) plasticity after SCI, occurring both spontaneously after injury and in response to rehabilitative therapies. Plasticity is a term widely used to describe a variety of biological phenomena. *Merriam-Webster's Medical Dictionary* defines plasticity as "the capacity for continuous alteration of the neural pathways and synapses of the living brain and nervous system in response to experience or injury" (http://medical.merriam-webster.com/). Furthermore, these plastic changes underlie learning, memory, and recovery from neural injury [8]. Several published reports support the view that the CNS is capable of

Abbreviations: BDNF = brain-derived neurotrophic factor, CNS = central nervous system, ESCS = epidural spinal cord stimulation, FES = functional electrical stimulation, FNS = functional neuromuscular stimulation, SCI = spinal cord injury, TrkB = tyrosine kinase B.

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significant plasticity after SCI and that rehabilitative interventions after neural injury affect this plasticity at several levels [8–10]:

- Behavioral (recovery of sensory, motor, or autonomic function).
- Physiological (normalization of reflexes, strengthening of motor-evoked potentials).
- Structural/neuroanatomical (axonal sprouting, dendritic sprouting, neurogenesis).
- Cellular (synaptogenesis, synaptic strengthening).
- Molecular (up-regulation of neurotransmitters and neurotrophic factors, alterations in gene expression).

SPONTANEOUS PLASTICITY AFTER SCI

Based mostly on the results of studies using animal models, reorganization of the CNS, including synaptic plasticity, axonal sprouting, and cellular proliferation, has long been known to spontaneously occur following spinal cord lesions [11–20]. This reorganization occurs in the spinal cord circuitry caudal to injury, in the spinal cord around the lesion, in the spinal cord rostral to injury, and in supraspinal structures.

In 1929, Pike and colleagues observed spontaneous hind limb recovery after spinal cord hemisection in cats and proposed that "the mechanism which takes over control of movements of the limb lying below the level of the lesion includes motor fibers coming down on the opposite side of the spinal cord, and commissural neurons lying in the spinal cord below the level of the lesion" [21]. A recent study reported that after midthoracic dorsal hemisection, the corticospinal tract collaterals of the hind limb sprout into the cervical gray matter where they contact descending propriospinal neurons and a new intraspinal circuit is formed [22]. Additionally, the affected propriospinal neurons arborize on lumbar motoneurons so that the detoured corticospinal signals reach their original targets [22]. Over time, these new connections self-prune to include only circuits that bridge the lesion site. At the level of the lesion, descending efferent corticospinal, raphespinal, reticulospinal, and coeruleospinal axons sprout and/or regenerate into the lesion cavity after incomplete contusive SCIs [18,23]. Additionally, cellular proliferation occurs around the lesion-producing oligodendrocytes and astrocytes, possibly replacing some of the cells lost during injury and remyelinating axons [17,20,24]. Thus the adult CNS can create novel pathways and substrates to reestablish lost supraspinal control to the spinal cord caudal to injury, possibly mediating some of the spontaneous recovery observed.

Reorganization of cortical maps has also been reported to occur spontaneously after both complete and incomplete SCIs in humans [25–27] and rodents [22]. The underlying mechanisms are hypothesized to be similar to those mediating reorganization after cortical injury, including disinhibition of latent cortical connections and axonal sprouting in multiple levels of the neuraxis [9,22,28]. Another mechanism may be injury-induced structural plasticity in the dendritic spines of cortical motoneurons. For example, changes in dendritic spine density and morphology in neurons of the motor cortex have been observed to occur over 3 days to 2 weeks after a fourth cervical spinal overhemisection in rodents [29]. Thus spontaneous plasticity after SCI does not appear to be limited to the spinal cord but can occur in supraspinal structures. However, how these cortical changes affect sensorimotor function, if at all, is not currently known.

As would also be expected, SCIs (both complete and incomplete) also produce considerable changes in the spinal cord circuitry caudal to injury. At the morphological level, SCIs can produce significant changes in dendritic morphology and marked loss of dendritic branching [30–32]. Structural plasticity at the dendritic level affects the integration of synaptic inputs to the neurons and can hence profoundly influence the electrophysiological responses of the neurons and therefore the neural circuitry [33–34]. After experimental SCI in rodents, one can observe increased group Ia afferent excitatory postsynaptic potentials, alterations in H reflexes, and changes in passive and active motoneuron resting membrane potentials, including development of persistent ionic current-based plateau-potentials [35–39]. In addition, spontaneous sprouting of afferent axons, including calcitonin gene-related protein positive C fibers, has also been well documented around and below the lesion site in rodents, which contributes to the development of hyperreflexia and autonomic dysreflexia [19,40–41]. These anatomical and electrophysiological changes indicate that spinal cord circuitry with impaired or absent descending supraspinal and spinal input is more excitable by peripheral stimulation and may partially explain the exaggerated reflex responsiveness, hypertonicity, and autonomic disturbances that occur after SCIs.

Thus, from days to weeks after experimental SCI in animal models, spontaneous cellular, structural, and

electrophysiological changes occur along the entire neuraxis. Evidence supports similar changes after SCI in humans [42]. Some of these spontaneous changes appear to be adaptive (promoting recovery and providing targets for therapy) and some appear to be maladaptive (inhibiting recovery and impairing function). Rehabilitative strategies could be used to enhance adaptive plasticity and/or mitigate maladaptive plasticity to enhance recovery after SCI.

ENHANCING CNS PLASTICITY AND RECOVERY USING REHABILITATION STRATEGIES AFTER SCI

The idea that neural activation may lead to anatomical and chemical changes in the CNS was first postulated in the 19th and early 20th centuries by influential figures such as Darwin, Ramón y Cajal, and Hebb. Further corroboration of this idea has occurred through numerous studies conducted over the last 50 or more years [8,43] and has led to strategies to elicit activity-dependent plasticity to promote recovery after spinal neurotrauma [1]. As summarized in the **Figure**, rehabilitative therapies can promote plasticity both rostral and caudal to injury in the spinal cord by activating the nervous system and influencing multiple substrates. One approach to activating the nervous system, particularly in the context of the sensorimotor system, is to use rehabilitative strategies that include stimulating somatic sensory afferents and activating functional movements. In this section, we review three such strategies for providing therapy to promote plasticity and recovery: (1) use of passive exercise, (2) use of active modes of exercise, and (3) use of neuroprostheses for electrical activation of motoneurons and sensory afferents.

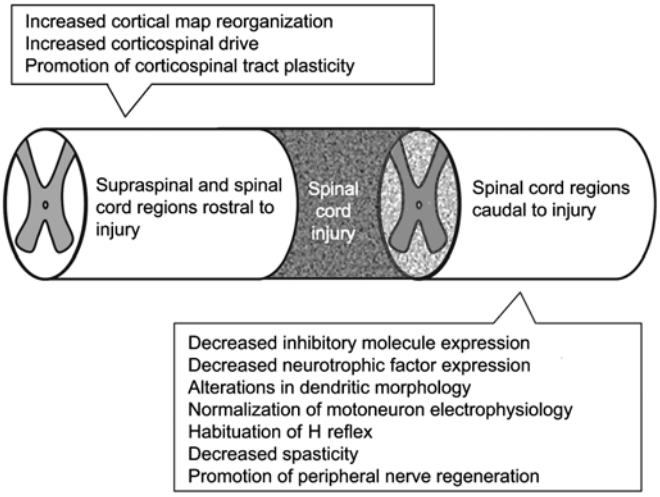

Figure.
Activity-dependent plasticity after spinal cord injury (SCI). Following SCI, rehabilitative therapies can promote significant structural and functional plasticity within central nervous system both rostral and caudal to injury.

Passive Exercise

Passive exercise can be used for inducing functional ranges of joint motion and sensory feedback to maintain or improve neuromuscular function after complete or incomplete SCIs, respectively. Motorized cycling is one such approach that both research laboratories and clinical settings now use to provide passive exercise. An advantage of this approach is that performing the exercise does not require any volitional control and can be initiated at early time points after injury.

Neural circuits within the spinal cord form reflex pathways that work together to help control the coordination of complex movements. These reflex pathways are not only triggered by sensory afferents but are also modulated by supraspinal inputs. After SCI, supraspinal control is impaired because of the tissue damage described earlier, thereby leaving the spinal neural circuitry to be driven primarily by the peripheral sensory input [44–45]. This shift toward peripheral control may contribute to the development of spasticity and abnormal muscle tone. An important sensory input to the spinal cord neural circuitry is from the group Ia muscle spindle afferents. Stretching of a limb muscle caused by joint movement activates the H reflex via the group Ia afferents. The reflex activation recruits synergistic muscles and inhibits antagonists [46]. Passive exercise activates the H reflex and, through repetition training, appears to be able to "condition" the caudal spinal circuitry to "normalize" specific spinal reflexes in the absence of supraspinal control [47]. Passive exercise has been provided with use of bicycles and robotic assistance [48]. Use of a motorized bicycle in rats [37,47,49] and in humans [50–51] causes some normalization of motoneuron electrophysiology, causes habituation of the H reflex and decreased spasticity, and can influence dendritic morphology [32]. However, at least for humans, continued cycling is required to maintain the effects. Most likely, exercise paradigms that promote activation of load receptors that trigger some of the reflex

pathways will be beneficial [4,45,52–53], as will approaches that include plantar cutaneous stimulation [4,54]. Thus continued research to increase our understanding of CNS plasticity mediated by passive exercise after SCI could help determine if passive exercise alone can lead to improved sensorimotor function.

Active Exercise

Another rehabilitation strategy following SCI is active exercise. This exercise approach requires subjects to perform assisted or unassisted active movements using varying degrees of supraspinal and/or segmental spinal control. Multiple approaches have been used to provide active exercise in people with incomplete SCIs. These approaches include locomotor training (manual-assisted and robot-assisted partial weight-supported treadmill training, as well as overground locomotion), repetitive upper-limb training, and general exercise/environmental enrichment. Using active voluntary exercise as a rehabilitation technique targets harnessing the neuroplasticity seen with passive exercise but with added benefits. Voluntary exercise elicits not only functional ranges of joint motion but also functional activation of muscles and multiple modes of afferent stimulation.

Increasing postinjury activity via locomotor training has been shown to improve motor recovery, although some questions remain about the role and degree of specificity of locomotor training needed to achieve significant recovery [55]. In rodents, exercise and treadmill training can support partial recovery of hind locomotion [10,56–59] and sensation [57] after incomplete SCIs. Studies conducted on spinal cord-transected cats suggest that recovery after locomotor training is task-specific and relies on sensory feedback mechanisms [60–61].

In rodent and feline models of thoracic SCI, the effects of locomotor training on neuroplasticity have been observed at the cellular level. The training decreases expression of inhibitory molecules [62], increases expression of neurotrophic factors [57], and alters electrophysiological properties in the lumbar enlargement [10,37]. These changes might mitigate some of the spontaneously occurring maladaptive plasticity that can cause spasticity and enable the isolated (partial or complete) spinal cord to produce locomotion with little or no descending control.

Locomotor training, both overground and on a treadmill using partial body weight support, has also been shown to promote recovery in humans with incomplete SCIs [4,6–7,9,44,63–69]. Evidently, the active exercise paradigm mediates plasticity at multiple levels of the neuraxis including the cortex, descending supraspinal motor pathways, and spinal cord circuitry caudal to injury.

In humans, intense repetitive training (massed practice) after a cervical spinal injury and robotic locomotor training after a thoracic spinal injury appear to promote cortical plasticity as cortical map reorganization [5,70–71]. As with spontaneously occurring cortical plasticity, the substrates and implications of this activity-dependent cortical reorganization after SCI are unclear. However, recent data from neurologically intact nonhuman primates indicate that activity can reorganize the motor cortex, such that cortical motoneurons "learn" to control additional muscles and produce novel movements when stimulated [72]. Rehabilitative therapies may possibly promote a "rewiring" of the cortex to bypass pathways interrupted by an incomplete SCI, thereby reestablishing supraspinal control of caudal circuitry using novel supraspinal-spinal circuits. In fact, locomotor training on a treadmill after incomplete SCI in humans promotes improved corticospinal drive to muscles of the lower limb that correlates with improved locomotor function [73–74]. This increased corticospinal drive could come from plasticity occurring in the cortex (see aforementioned data) or in the descending pathways themselves. In rodents after incomplete SCI, increased activity via enriched environment promotes plasticity in spared corticospinal but not raphespinal or rubrospinal axons [75].*

Based on studies in animal models, a possible molecular mechanism has been proposed for the neuroplasticity events known to occur because of voluntary exercise after SCI. Brain-derived neurotrophic factor (BDNF) and its associated receptor, tyrosine kinase B (TrkB), may be the primary modulators of a biochemical cascade resulting in neuroplasticity. BDNF is known to synthesize and phosphorylate synapsin 1 [16,76], a phosphoprotein responsible for neurotransmitter release and axonal growth [77–78]. In rodent models of SCI, increased expression of BDNF, TrkB, and synapsin 1

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occurred in the spinal cord starting in the secondary phase and persisting in the chronic phase following injury after voluntary exercise [79].

In rats with SCI following voluntary exercise, further elevation of BDNF levels was found in skeletal muscles and in the innervating level of the spinal cord [80]. Other research has also found that BDNF can be retrogradely transported through motoneurons from the skeletal muscles to the spinal cord [81–82]. These data suggest that up-regulation of BDNF expression may have a causal relationship with neuroplasticity, neuronal growth, and functional recovery and that increased recovery results from voluntary exercise. BDNF and other neurotrophic factors have been hypothesized to facilitate neuronal plasticity in an autocrine or paracrine fashion [83]. This neurotrophic up-regulation is not only activity-dependent but also activity-specific, which reinforces the notion that differential recovery results from differential voluntary exercise regimes [57]. All the nuances of BDNF up-regulation appear to coincide with the recovery observed following rehabilitation after incomplete SCI. This finding suggests that neuroplasticity can occur through a BDNF-mediated pathway [80,84–88].

Voluntary exercise, as just described, shows promise as an effective promoter of recovery and activity-dependent plasticity throughout the neuraxis after incomplete SCI. In future multifaceted treatment, strategies could be used to maximize the effectiveness of rehabilitative therapies. Passive exercise, such as motorized cycling, could be administered early postinjury (to promote plasticity caudal to injury and possibly mitigate spasticity) followed by more active exercise (to promote plasticity both rostral and caudal to injury). However, voluntary exercise can only be performed by individuals who have some preexisting level of motor function, which limits rehabilitative interventions to those with incomplete SCIs.

Neuroprostheses for Rehabilitation

Use of neuroprostheses is another rehabilitative strategy that combats the limitations of both passive and active voluntary exercise. Neuroprostheses use electrical stimulation to activate neural structures [89]. In applications in people with SCI, functional electrical stimulation (FES) is one neuroprosthetic approach to improve locomotor function that stimulates the peroneal nerves to elicit a flexion withdrawal reflex and thereby cause limb movement [90]. A second approach is functional neuromuscular stimulation (FNS). It stimulates multiple leg muscles at their motor points in an appropriate sequence to produce coordinated functional movements, such as grasping, standing, or rhythmic leg movement [91–95]. A third approach called epidural spinal cord stimulation (ESCS) stimulates the dorsal aspect of the spinal cord at a particular spinal level using implanted electrodes [96–98].

When used in a paradigm for motor therapy, neuroprostheses seek to enhance standard therapist-provided rehabilitation by generating active muscle contractions, generating improved movement patterns, and reducing the physical demands on the therapists. FES therapy, which elicits the flexion withdrawal reflex to assist persons with an incomplete SCI bring their leg into the swing phase of gait, has resulted in a carryover of increased functional mobility and speed, decreased effort, and improved intralimb coordination during unstimulated overground locomotion [90,99–104]. Electrical stimulation of sensory afferents alone may also contribute to recovery after incomplete SCI [105].

Since the flexion withdrawal reflex habituates, its use in a repetitive therapy paradigm has some inherent limitations. Use of FNS to stimulate the muscles via the motor points attempts to overcome this limitation. As therapy, FNS can decrease the fatigability of muscles after SCI [106–107], reverse muscle atrophy, and increase bone density [108]. FNS, along with cycling exercise, may also promote recovery in individuals with chronic incomplete SCIs [109–110]. Since muscles fatigue with ongoing stimulation and have nonlinear properties, using an adaptive control approach would help tailor the stimulation to the individual muscle properties and automatically adjust stimulus strength for repeatable movements [111–113].

ESCS, which has traditionally been used as a modality for pain control [114], has been shown to reduce spasticity after SCI [97–98,115]. Appropriate levels of ESCS can promote stepping movements and even locomotion in humans [96,116–118] and animals (rodents and cats) [119–120] with SCIs.

How electrical stimulation likely promotes recovery remains unclear, but the mechanisms may include plastic changes at the cellular/molecular and circuitry levels. The sensory afferent input provided by peripheral electrical stimulation likely provides drive to the spared CNS. In decerebrate cats, electrical stimulation of hind limb muscles can cause reflex withdrawal of the contralateral hind limbs [121] and direct electrical stimulation of sensory afferents

in the dorsal root entry zone can activate the lumbar spinal pattern generator [122]. ESCS appears to produce significant plastic changes. These changes include altering the electrophysiological properties of spinal motor pattern-generating circuitry [115,123–124], altering amino acid neurotransmitter levels in the spinal cord (glycine and taurine) [125], and altering blood flow (both centrally and peripherally) [126–128].

Electrical stimulation may also trigger the BDNF-mediated mechanism of recovery described earlier. Direct electrical stimulation to both motor [129–131] and sensory [132] peripheral neuron cell bodies increases BDNF and TrkB expression in those cells and leads to axonal regeneration. Additionally, electrical stimulation can partially restore segmental spinal reflex responses in the lumbar spinal cord, in particular the H reflex [133], that are altered by thoracic SCI [134]. For continued examination of the circuit level and cellular mechanisms, a rodent-model for FNS therapy has recently been developed [135–136]. Short-term FNS therapy in a rodent model of contusion injury also results in a carryover into improved symmetry of treadmill walking [137].

Thus electrical stimulation, used alone or combined with active exercise, promotes recovery and plasticity after neural injury. Multiple characteristics of therapeutic electrical stimulation (including being noninvasive, not requiring volitional muscle control, producing graded muscle contractions, and producing functional ranges of motion) allow for its use as both an early intervention (possibly along with passive exercise) and a chronic intervention (along with locomotor training).

ENHANCING CNS PLASTICITY AND RECOVERY USING MULTIFACETED TREATMENT APPROACHES AFTER SCI

Scientists and clinicians have widely theorized that given the myriad of issues preventing recovery of function after SCI, multifaceted treatment approaches will be most successful [1]. In fact, the goals of most rehabilitative strategies are to complement and optimize the more invasive transplantation and pharmacological treatment strategies required to “cure” SCI. These goals are reasonable considering that the data from initial treatment approaches of combined locomotor training and pharmacological interventions after complete SCI in cats produced favorable results [44]. However, recent studies using similar approaches after incomplete SCIs in rodents have not produced the anticipated additive results. In rodents, combined treatment involving passive motorized cycling and stromal cell transplants did not improve plasticity or sensorimotor behavioral recovery after incomplete contusive injury [138]. In addition, electrical stimulation combined with peripheral nerve grafts does not improve rubrospinal tract regeneration after partial transection [139]. Furthermore, treatment combining robotic-assisted locomotor training on a treadmill and quipazine administration does not enhance recovery of locomotion [140]. Thus despite multiple studies in animal models of SCI and tremendous advances in our understanding of the postinjury response process, significant gaps remain in the mechanisms and substrates underlying treatment-mediated recovery (rehabilitation, transplantation, and pharmacology). Development of successful multifaceted treatment paradigms applicable to people with SCI will require enhancing our knowledge of the mechanisms targeted by both the individual and combined therapeutic regimens. The windows of opportunity for application of one or more of these interventional strategies will also need to be assessed.

CONCLUSIONS

The adult mammalian CNS is capable of considerable spontaneous structural and functional plasticity, both in health and disease. Significant evidence from both human and animal studies indicates that rehabilitation strategies exploit this plasticity to promote recovery. Furthermore, rehabilitative strategies are not limited to targeting activity-dependent plasticity of the spinal cord below an injury but appear to promote plasticity in both cortical and descending pathways. While our understanding of rehabilitation-mediated activity-dependent plasticity after SCI has greatly increased, significant gaps remain and continued diligent research is required to optimize the effectiveness of rehabilitative interventions, given alone and as part of a multifaceted treatment approach.

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