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Biological Basis of Exercise-based Treatments: Spinal Cord Injury

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Abstract

Despite intensive neurorehabilitation, extensive functional recovery after spinal cord injury is unattainable for most individuals. Optimal recovery will likely depend on activity-based, task-specific training that personalizes the timing of intervention with the severity of injury. Exercise paradigms elicit both beneficial and deleterious biophysical effects after spinal cord injury. Modulating the type, intensity, complexity, and timing of training may minimize risk and induce greater recovery. This review discusses the following: (a) the biological underpinning of training paradigms that promote motor relearning and recovery, and (b) how exercise interacts with cellular cascades after spinal cord injury. Clinical implications are discussed throughout.

INTRODUCTION

Advances in biomedical research hold great promise for treating functional deficits after spinal cord injury (SCI). Currently, activity-based neurorehabilitation is the foundation of clinical intervention, whereby residual neural circuitry is activated in the hope of forming or strengthening synapses that improve motor control. Despite intensive neurorehabilitation, deficits may persist, and locomotor recovery remains unattainable for most persons with SCI. To change functional outcomes, the interaction between exercise-related factors and SCI sequelae must be optimized.

Exercise paradigms elicit specific biophysical effects that alter central nervous system recovery after SCI. Therefore, it is important to determine the type of intervention and when to deliver it for different severities of SCI (Figure 1). Ultimately, task-specific training will likely be effective only when delivered to a permissive cellular environment. Animal models offer the greatest advantage to identify the cellular and behavioral determinants of recovery after SCI. This review contains 2 focus areas: (a) effective training components to promote

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motor relearning and recovery, and (b) exercise-induced cellular changes that accompany recovery.

Experimental SCI Models

Of the many experimental SCI models, contusion and complete transection (TX) provide important information about motor recovery and the cellular consequences of SCI [1,2]. The locomotor effects in these quadruped-based models appear to translate to bipedal human beings. The TX model severs all gray matter and axons typically in the mid-thoracic region, thereby isolating the lumbar cord from brain input. Behavioral and cellular changes in the isolated cord serve as “proof of principle” of the inherent capacity of the spinal cord to learn. Methods to promote spinal cord learning likely facilitate functional recovery after less-severe SCI. The contusion model offers a clinically realistic, complex injury that reproduces many of the molecular mechanisms in human SCI [3]. The injury has a central core lesion and a peripheral rim of spared white matter. Partially spared descending motor, ascending sensory, and autonomic systems replicate the behavioral dysfunction seen clinically, that is, paresis or paralysis, neuropathic pain, and autonomic dysreflexia [4-6]. Thus, contusion injury is more translationally relevant than TX for testing exercise and functional recovery.

Role of Spinal Learning and Plasticity in Recovery after SCI

Simple Learning and Reflex Modulation—The spinal cord has a remarkable capacity to adapt and learn, independent of supraspinal input. By using complete mid-thoracic TX, Grau et al [7] showed that the isolated lumbar cord learned to avoid hindpaw shock using an instrumental learning paradigm. In this paradigm, hindlimb extension closed a circuit that delivered a mild shock to that limb. The isolated lumbar spinal cord adapted the resting posture of the hindlimb by increasing flexion to minimize shock. This simple yet dramatic form of learning required protein synthesis, *N*-methyl-D-aspartate receptor activation and brain-derived neurotrophic factor (BDNF) expression, whereas γ -aminobutyric acid (GABA) A receptor activation inhibited learning [7]. Thus, sensory-driven spinal learning is capable of modulating reflex gain below the SCI and may be a fundamental component of activity-based rehabilitation.

Downregulating segmental reflexes holds promise for reducing hyperreflexia and spasticity after SCI. By using operant conditioning, Wolpaw and colleagues (as documented by Chen et al) [8] showed that animals learn to reduce reflex gain even after SCI (equivalent of the stretch reflex). On a cellular level, a positive shift in α motor neuron firing threshold was associated with more inhibitory F-type synapses and GABAergic terminals on motor neurons. In addition, reflex modulation improves motor function after SCI in rats. Translational work to reduce reflex gain in human SCI began recently with the expectation that leg spasticity would decrease and motor control would improve. Given that down-training in animal models requires spared descending supraspinal input to induce spinal plasticity and learning, such reflex modulation training in the clinic may be most effective after incomplete SCI [8].

Complex Learning and Locomotion—Fundamental elements of stepping are controlled at the spinal cord level and represent an important target for activity-dependent

learning after SCI. When the lumbar cord is isolated from supraspinal control, it is capable of complex learning, which is dependent on task-specific afferent signals. Hodgson et al [9] established that the isolated spinal cord learned to stand on a stationary treadmill or step on a moving treadmill. However, stand- or step-training improvements did not transfer to the other task; hence, the cord has a limited capacity for relearning multiple tasks in the absence of supraspinal input. In contrast, robust adaptive learning occurs within a task. Spinal stepping accommodates variable environmental conditions, including obstacles and treadmill speed [2]. On the cellular level, GABAergic terminals are differentially expressed in a use-dependent manner. The GABAergic response decreased with step training but increased in flexor motor pools with stand training [10]. Remarkably, these cellular changes occurred after a few days of training and lasted 25 months. Perhaps the lasting cellular localization of GABA impedes transfer of training to other tasks.

Taken together, the lumbar cord performs simple and complex learning in the absence of supraspinal input. Although the breadth of skill learning appears limited when the SCI is complete, the intrinsic capabilities of the cord are sufficient to adapt to environmental demands within a given task. Inhibitory GABAergic input regulates spinal learning in a task-specific manner and may explain limitations in skill learning after SCI. Clinically, drugs that activate GABA receptors should be carefully considered because they may create a lasting barrier to activity-dependent relearning and recovery.

Training

Clearly, spinal learning and synaptic plasticity after SCI depend on intact sensory drive and task-specific training. Training changes functional outcome by pruning inhibitory synapses while strengthening synapses activated by the task. To be clinically relevant, activity-based training paradigms should induce skill learning that transfers to other tasks and environments. Interestingly, little is known about which exercise interventions and which dosing schedules will promote relearning and recovery for different SCI severities. Factors such as task specificity, training intensity, and complexity are beginning to receive attention in experimental SCI.

Intensity—For locomotion, intensity of training is modulated through body-weight support and stepping frequency, which varies with treadmill speed and performance duration. High body load impairs stepping kinematics so that optimal training requires some body-weight support to produce stepping of good quality and quantity [11]. Training sessions of 1000 steps produced better kinematics and stepping patterns than low-dose sessions of 100 steps. In fact, disuse of paralyzed limbs through wheelchair use prevents motor recovery after contusive SCI in rats [12]. Because multiple types of exercise promote different magnitudes of limb loading and stepping frequency, personalized training paradigms will depend greatly on task selection.

Unfortunately, intensity can be excessive and can induce detrimental effects. Perhaps best described after cortical injury, forced use of the impaired limb early after lesion worsens recovery and exacerbates lesion size [13]. In the spinal cord, we found that treadmill,

standing, or swimming training from 4 to 49 days after contusion did not exacerbate the lesion [14]; however, swimming at 3 days worsened a similar SCI [15].

Complexity—A fundamental tenet of skill acquisition is that the training task be sufficiently challenging to allow both success and failure. Movement errors promote refinement toward successful motor patterns; hence, training should encompass movement variability and trial and error to induce motor relearning and recovery after SCI. Clinically, 2 locomotor rehabilitation approaches, therapist-assisted stepping and robotic training, offer moderate or no variability, respectively. Recently, the necessity of variability for learning was shown in experimental SCI. Robotic training that provided no step-to-step variability in limb trajectory was compared with variable training in which self-initiated stepping was assisted as needed by a robot in rats with TX [16]. Fixed robotic training prevented distinct, alternating electromyography patterns and blocked skill learning. Thus, the opportunity for error correction is critical to locomotor recovery.

Experimentally, robust training variability occurs with environmental enrichment. The environment consists of interactive toys and structures (ie, ramps, rope ladders, tunnels) that require a variety of motor control patterns. Continuous enrichment improves motor coordination through insulin-like growth factor (IGF)–dependent synaptic plasticity in the lumbar cord after contusion [16a]. Delivering enrichment at doses effective in animals will be difficult clinically, because exposure 24 hours a day, 7 days a week to a complex environment may not be unfeasible. Recent work in animal models of traumatic brain injury demonstrate effective enrichment doses at 6 hours rather than 24 hours [17]. The minimal effective dose for environmental enrichment in SCI must be determined before clinical feasibility is established.

Task Specificity—Motor relearning depends on the quality of afferent input delivered to the cord during training. Training must be task specific to engage neural circuits, to produce motor patterns, and to regulate afferent input that closely mimics the real-world task. Supportive evidence is 2-fold: simple general activity does not promote skill learning, and demanding task-specific training improves recovery after central nervous system injury. In stroke and cervical SCI models, locomotion was used as general exercise training and compared with task-specific reach and grasp training in rats [18,19]. The stroke study used reaching and retrieving multiple pellets on a tray from various trajectories. The SCI study combined drug treatment with reaching through a grid to retrieve and shell sunflower seeds. Simple limb use failed to promote motor relearning after cortical ischemia or cervical SCI with drug treatment. Alternatively, robust recovery occurred with task-specific training. Thus, nonspecific activity may not promote relearning, especially for forelimb function. More research is needed to identify the critical components of task-specific training for other tasks.

Task-specific training also benefits sensory function after SCI. We compared mechanical sensation after swimming, standing, and treadmill training in rats with contusive SCI [14]. Each exercise paradigm differentially regulated mechanotransduction through the paw. After SCI, profound, lasting hypersensitivity occurred below the injury. Importantly, only treadmill training that provided high mechanosensory input ameliorated the allodynia-like

sensory dysfunction. This task-specific effect was associated with normalization of peripheral and central BDNF.

When to Deliver Training—Timing of exercise interventions may determine beneficial or detrimental outcomes after SCI. Intervening early after SCI may impose a greater neurotoxic risk than no intervention [15,20]. Increasing physical activity, heart rate, and blood flow when the blood–spinal cord barrier is compromised may exacerbate the existing inflammatory state. Benton and Magnuson (as documented by Smith et al) showed that 8 minutes of swimming 3 days after SCI worsened intraparenchymal inflammation at the epicenter [15]. Behaviorally, swimming kinematics also were impaired compared with a 2-week intervention. Detriments associated with early robotic step training also have been observed [20]. Aberrant stepping kinematics and high variability in movement trajectories occurred with early training, whereas delayed training improved motor control.

Cellular Factors That Influence Training Effects

Mechanical injury initiates multiple intracellular processes that create short- and long-term challenges for activity-based rehabilitation. Direct damage to neuropil and blood vessels initiate inflammatory and excitotoxic cascades that produce primary and secondary cell death along the neuroaxis [21]. Within hours, the blood–spinal cord barrier opens and robust inflammation begins. A toxic milieu comprising high levels of pro-inflammatory cytokines tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and IL-6 combines with a massive release of glutamate from damaged astrocytes and peripheral afferents. The resulting excitotoxicity induces mitochondrial dysfunction within 12 hours of injury and initiates apoptotic cascades within injured and bystander neurons and glia. Progressive mitochondrial dysfunction and phagocytosis produce oxygen free radicals (ROS), which further threaten neurons and glia, especially oligodendrocytes [22]. The injury is compounded by decreased trophic support for neurons and glia from BDNF, IGF, and neurotrophin 3/4. A lack of trophic support, combined with inflammation, produces apoptosis at progressively greater distances from the epicenter. Reactive astrocytes move to the lesion border and secrete inhibitory molecules such as chondroitin sulfate proteoglycans, which create both a physical and chemical barrier to axon regeneration. The early inflammatory and excitotoxic events spread to spinal cord regions remote to the injury epicenter over several weeks. High levels of pro-inflammatory cytokines, activated microglia, glutamate, and apoptosis of oligodendrocytes occur in remote cervical or lumbar enlargements after contusive SCI. Chronically, low levels of BDNF, neurotrophin 3/4, and IGF occur in the lumbar enlargement. Thus, inflammatory cascades, excitotoxicity, apoptotic cell death, and glial scarring create a nonpermissive environment for synaptic plasticity within primary sites of motor relearning (enlargements) [21].

Inflammation and Learning

Given the predominance of inflammation after SCI, surprisingly little is known about its impact on motor relearning. In the brain, inflammation impairs spatial learning and activity-dependent plasticity in the cortex and hippocampus. Generally, elevated levels of pro-inflammatory cytokines (IL-1, TNF- α) act as impediments, but their absence may also be deleterious [23]. Within the spinal cord, inflammation appears to impede learning and

plasticity by creating central sensitization, a common mechanism of neuropathic pain [24,25]. Moreover, elevated cytokines and glial activation below the SCI induces profound hypersensitivity, which may be similar to neuropathic pain [6]. These robust sensory alterations provide aberrant input and likely further disrupt motor relearning.

Exercise may effectively modulate hypersensitivity and cellular inflammation. We showed that treadmill training over 7 weeks ameliorates hypersensitivity after contusive SCI [14]. Moreover, this training normalized TNF- α within 14 days of injury (unpublished data). Whether exercise-induced normalization of sensation and inflammation can be used to improve motor control remains unknown.

Influence of Exercise on Mitochondrial Dysfunction and ROS Production

Exercise, if performed too intensely or under declining health, promotes oxidative stress. Given the widespread induction of ROS after SCI, the additional demands placed on mitochondria by exercise must be carefully examined. Activity-based interventions may induce greater mitochondrial dysfunction, jeopardizing neurons, glia, and oligodendrocytes that survive the initial mechanical damage [22]. By precisely grading exercise treatment type, intensity, and/or intervention timing, it may be possible to reduce the risk of cell death and lesion exacerbation. An optimal exercise intervention should consider the time course of mitochondrial dysfunction and whether mitochondria are capable of responding to task-specific demands of different training paradigms.

Influence of Exercise on Trophic and Growth Factors

Exercise elevates trophic and growth factors throughout the central nervous system, which serve neurogenerative and neuroprotective functions. After SCI, widespread declines compound a destructive cellular milieu, which leave surviving neurons and glia susceptible to a host of degenerative processes. Re-establishing trophic support is critical, and weight-supported motor activity represents a natural in vivo drug delivery system [14]. Exercise-regulated trophic factors BDNF and IGF promote learning, synaptic plasticity, and sensory function after SCI [14,16]. However, excessive nerve growth factor (NGF) produces autonomic dysreflexia, a clinically life-threatening condition [5]. Exercise paradigms must be screened for their effects on growth factors to minimize the risk of inducing deleterious effects.

Combinatorial Interventions—Given that pharmaceutical interventions for SCI can be combined with rehabilitation, it is critical that we know how and when to deliver different exercise interventions. Surprisingly, drug treatments combined with activity-based training may compete with each other and may actually worsen motor outcome [19,26]. For example, combining robotic treadmill training with an antibody to neutralize the myelin growth inhibitor Nogo-A impaired stepping kinematics to a greater extent than if no exercise training had been administered [26]. Combining chondroitinase, which degrades chondroitin sulfate proteoglycan, with environmental enrichment after cervical SCI produced greater motor deficits than no rehabilitation [19]. Whether task specificity, intensity, and timing can improve combinatorial treatments is unknown. Given that a Nogo inhibitor is in clinical trials in Europe, it is especially important that effective exercise paradigms be identified.

CONCLUSION

Delivering optimal task-specific training at the best time for the appropriate injury will facilitate motor relearning and recovery. Viewing exercise paradigms as a biologics intervention seems fitting, given that activity-based treatments can be potentially toxic or beneficial. Modulating the type, intensity, complexity, and timing of training may minimize risk and induce greater recovery.

The interaction between type of training, timing of the intervention, and severity of injury within a permissive cellular environment has not been widely studied. It is at this intersection of factors that innovative personalized medical treatment emerges. Using exercise as a biological therapy to enhance the cellular environment offers a new perspective in creating state-of-the-art neurorehabilitation for SCI.

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Figure 1.
Optimal activity-based rehabilitation emerges at the intersection of task specificity, and appropriately timed delivery of training according to the severity of the spinal cord injury.