Activity-Based Restorative Therapies: Concepts and Applications in Spinal Cord Injury-Related Neurorehabilitation

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Physical rehabilitation following spinal cord injury-related paralysis has traditionally focused on teaching compensatory techniques, thus enabling the individual to achieve day-to-day function despite significant neurological deficits. But the concept of an irreparable central nervous system (CNS) is slowly being replaced with evidence related to CNS plasticity, repair, and regeneration, all related to persistently maintaining appropriate levels of neurological activity both below and above the area where the damage occurred. It is now possible to envision functional repair of the nervous system by implementing rehabilitative interventions. Making the transition from "bench to bedside" requires careful analysis of existing basic science evidence, strategic focus of clinical research, and pragmatic implementation of new therapeutic tools. Activity, defined as both function specific motor task and exercise appears to be a necessity for optimization of functional, metabolic, and neurological status in chronic paralysis. Crafting a comprehensive rehabilitative intervention focused on functional improvement through neurological gains seems logical. The terms activity-based restorative therapies, activity-based therapies, and activity-based rehabilitation have been coined in the last 10 years to describe a new fundamental approach to deficits induced by neurological paralysis. The goal of this approach is to achieve activation of the neurological levels located both above and *below* the injury level using rehabilitation therapies. This article reviews basic and clinical science evidence pertaining to implementation of physical activity and exercise as a therapeutic tool in the management of chronic spinal cord-related neurological paralysis. © 2009 Wiley-Liss, Inc.
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INTRODUCTION

The field of neurorehabilitation is changing. After years of evidence from the basic science data, the old, deep rooted rehabilitative principles of compensation and adaptation are slowly starting to change. Strategies for stimulating the nervous system are being used to optimize functional recovery and eliciting abilities thought to be lost forever at the time of injury.

From basic science/animal model we have learned that the adult injured central nervous system (CNS) is capable of reorganization at multiple levels, thus allowing for significant improvement following injury. The reorganization occurs at all different levels: cortical, subcortical, spinal cord, and in the peripheral nervous system. The repair process can happen through various mechanisms: synaptic plasticity in preexisting connections (peripheral and central), sprouting, and formation of new connections. Remyelination and new cell birth also occurs, correcting, restoring, and replacing the damaged nervous system. Both reorganization and repair seem to be dependent on maintaining an optimal level of neurological activity.

Thus, the basic science evidence suggests that optimizing the activity of cellular processes, including synapse formation, remyelination, new cell birth, and reorganization and repair, can provide a rationale for fueling a clinical trend in neurorehabilitation based on attempting to achieve optimal activity following damage to the nervous system. The field of spinal cord injury allows for an easier exploration of activity–based concepts because the spinal cord is a "simpler" neurological structure, traditionally responsible for reflexogenic, preprogrammed–type activity.

Assuming most of basic science proven changes related to activity can be applied to the human spinal cord, activity–based restorative therapies (ABRT) is essentially an arsenal of previously extensively used evidence-based rehabilitative interventions utilized under the premise that impairment repair leads to improvement in disability and handicap.

ABRTs tools can simply be described as follows: (a) patterned motor activation (i.e., locomotor training, functional electrical stimulated (FES) ergometry), (b) nonpatterned motor activation (i.e., recruitment and strengthening, task specific training), and (c) sensory stimulation (i.e., sensorimotor therapy).

This article predominantly describes studies in animals and humans with neurologic injuries related to spinal cord injuries. Although the effect of different forms and amounts of physical activity on recovery has been evaluated in other adult and pediatric neurological conditions, like stroke and cerebral palsy (CP), this information will not be reviewed in this report due to the difficulty of assessing the results of intervention in the context of new onset neurologic damage superimposed on ongoing developmental changes. Thus this article emphasizes the importance of ABRT to advancing thinking and practice in the field of neurorehabilitation, specifically as it applies to the potential restoration of function in spinal cord injury related paralysis.

ROLE OF ACTIVITY IN NEURORESTORATION: THE BASIC SCIENCE ARGUMENT

Effect of Activity on Synaptogenesis

Synapses are specialized junctions between multiple neurons or between neurons and other cells they interact with. Synapse formation, strength, and modulation are all dependent on membrane electrical activity generated by release of chemical neurotransmitters. For example, N-methyl D-aspartate (NMDA) receptor activation induces synaptogenesis by driving the formation of dendritic spines through intracellular calcium elevation [Ciani and Salinas, 2008]. Brief presynaptic activity rapidly converts early nonfunctional contacts between cultured hippocampal neurons into functional synapses by enhancing presynaptic glutamate release [Shen et al., 2006].

Uncontested, activity plays a critical role in development and plasticity within the nervous system, including activity-dependent gene expression [Mingo et al., 1997; Ono et al., 1997; Sgambato et al., 1997; Karlsson and Hallbook, 1998; Muslimov et al., 1998]. Activity is also essential for normal synaptic function [Howe, 2003], modification of synaptic strength [Daoudal and Debanne, 2003; Zhou and Poo, 2004], homo and heterosynaptic plasticity [Riegle and Meyer, 2007], and synapse elimination [Zhou and Poo, 2004].

Effect of Activity on Myelination/ Remyelination

Myelination and remyelination are achieved by wrapping a myelin sheath around an axon. In the peripheral nervous system, myelination and remyelination is achieved by Schwann cells while in the CNS the process is done by oligodendrocytes. One Schwann cell wraps one myelin sheath around a single axonal segment. One oligodendrocyte can myelinate up to 40 axons. Axonal loss, disruption of astro-glial interactions, oligodendroglial default, and dysregulation of cellular environment all play important roles in remyelination failure.

Both myelination and remyelination are dependent on neuronal impulse activity. A significant amount of the basic science data that supports the role of activity in myelin formation comes from the visual system. Mice reared in the dark develop fewer myelinated axons in the optic nerve compared with normally reared mice [Gyllensten and Malmfors, 1963]. Myelination is highly decreased in the optic nerve of blind cape mole rats [Omlin, 1997], whereas premature opening of eyelids accelerated the process of myelination in the optic nerve of rabbit [Tauber et al., 1980].

Other cellular processes involved in myelination and axonal growth are also activity dependent. For example, myelination of the peripheral sciatic nerve in newborn rats is regulated by activity controlled potassium exchanges [Wilson and Chiu, 1990]. NMDA dependent axonal growth [Cantallops and Routtenberg, 1999] and adequate dendritic neuronal network development [van Ooyen and van Pelt, 1994] are all highly regulated by neural activity.

Effect of Activity on New Cell Birth

Under normal conditions, neurogenesis only occurs in two "privileged" regions of the human adult brain: hippocampus and olfactory system. In the hippocampus, physical activity stimulates neurogenesis by acting on the proliferation of neuronal stem cells [Kempermann et al., 2000]. In addition to stimulating neurogenesis, exercise and activity also reverses the decline in neurogenesis commonly associated with aging [van Praag et al., 2005]. Activation of neighboring axons plays a major role in the proliferation of oligodendrocyte precursor cells in the developing rat optic nerve [Barres and Raff, 1993].

Effect of Activity on Reorganization and Repair

The widespread dependence of development and plasticity in the CNS on neural activity suggests that optimized neural activity might also be important for neural repair.

Activity modulated release of brain-derived neurotrophic factor (BDNF) seems to occur in both the CNS [Neeper et al., 1996] and the peripheral nervous system [Al-Majed et al., 2000]. Beaumont et al. [2008] compared sedentary T10 spinal cord injured rats with rats gait trained through stepping in voluntary wheel cages, then measured lumbar spinal cord BDNF levels and recorded electromyographic (EMG) tracings from the tibial motor neuron pool. Trained rats had significantly decreased stance/swing duration and decreased number of limbs simultaneously activated in the stance phase. Their lumbar BDNF level was elevated, and there was significant increase in the amplitude of EMG extracellular recordings from the tibial motor neuron pool in response to descending neuronal drive.

There is further evidence of activity dependent neural reorganization and repair supported by modulation of multiple components of spontaneous regeneration by increasing and decreasing neural activity. Spinalized rats (T10 level) underwent motor-driven bicycling of the hind legs starting 2 and 5 days after the injury and continuing for 2 weeks. Gene expression of BDNF and glial cell line-derived neurotrophic factor (GDNF) was elevated 11- and 14-fold, respectively, in soleus muscle after one bout of exercise performed 5 days after spinal cord transection. When exercise was started 2 days after the injury, the changes in gene expression were not observed. Long-term exercise for 4 weeks attenuated muscle atrophy equally well in rats started at 2 days or 5 days after injury [Dupont-Versteegden et al., 2004]. Mice that underwent 3 weeks of preinjury activity (wheel running) recovered locomotor function significantly better following T9 contusion injury than mice that were sedentary preinjury [Engesser-Cesar et al., 2005].

The ability of the adult rat spinal cord to reorganize through regeneration of lesioned fibers has also been demonstrated. After incomplete spinal cord injury in rats, transected hindlimb corticospinal tract (CST) axons sprouted into the cervical gray matter to contact long propriospinal neurons, which in turn arborized on lumbar motor neurons, creating a new intraspinal circuit relaying cortical input to its original spinal targets [Bareyre et al., 2004]. In another experiment in rats, the rubrospinal tract reorganized, invading the ventral horn and

connecting to motor neurons normally innervated by the CST following bilateral CST transection at its entry into the pyramidal decussation [Raineteau and Schwab, 2001; Raineteau et al., 2002].

ROLE OF ACTIVITY IN NEURORESTORATION: THE CLINICAL SCIENCE ARGUMENT

Effect of Activity on Function Optimization

There is no doubt that spinal cord injuries induce a dramatic decrease in the amount of physical activity that an individual exerts [van den Berg-Emons et al., 2008].

Maintaining an adequate level of physical activity is undoubtedly helpful with numerous anatomic, physiological, and functional characteristics related to the normal human body, such as cardiovascular function, muscle and bone mass, longevity [Paffenbarger et al., 2001], cognition [Angevaren et al., 2008] quality of life [Kell et al., 2001]. Regular physical activity can significantly reduce the risk of coronary heart disease [Thompson et al., 2003], colon cancer, diabetes, and high blood pressure. Regular physical activity also helps to: (1) control weight, (2) contribute to healthy bones, muscles, and joints, (3) reduce falls among the elderly, (4) reduce the pain of arthritis, (5) reduce symptoms of anxiety and depression, (6) reduce the need for medication, and (7) reduce hospitalizations and physician visits [Fernhall et al., 2008].

Although there is an abundance of literature pertaining to the effects of physical activity in general population, the literature pertaining to the SCI population is, understandably, more limited. However, data related to cardiovascular function is plentiful. Individuals with paralysis related to SCI have an added degree of cardiovascular challenge on top of deconditioning; their autonomic nervous system is markedly affected by the spinal injury, especially if the injury is above T6-T9 level, where the major splanchnic autonomic outflow emerges.

It is well recognized that cardiovascular conditioning can be achieved and maintained in individuals with SCI-related paralysis utilizing FES ergometry. This intervention utilizes a robotic device that delivers a quantified amount of workload. Bhambhani and Maikala [2000] reported that acute FES exercise produced a 2-fold increase in the oxygen uptake, a 3-fold increase in ventilation rate and a five beats/min increase in heart rate from the resting value in seven volunteers with C5 to T12 spinal cord injury. Kakebeeke et al. [2008] reported 103% increase in peak oxygen uptake and 113% increase in maximum power output after 1 year of home-based FES ergometry training in an individual with C6 motor complete SCI. This case study also demonstrated a significant level of compliance with the home-based exercise regimen (22.9–82.9%) and the feasibility of undergoing a sustained, home-based program, with interventional guidance from a trained physical therapist. Faghri et al. [1992] showed significant decrease in heart rate and blood pressure during submaximal exercise and significant increase in stroke volume and cardiac output after completion of a 3 months (three sessions/week) FES training program in 13 individuals with SCI. Raymond et al. [2002] compared low power output FES training in six individuals with SCI-related paralysis with

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Cardiovascular conditioning can be achieved and maintained in individuals with SCI related paralysis utilizing FES ergometry.

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voluntary leg cycling in able bodied individuals and found similar changes in several cardiovascular parameters (oxygen uptake, heart rate, and stroke volume).

The role of physical activity and exercise in maintenance of muscle and bone mass in SCI is also well documented. Mohr et al. [1997] reported on the effect of 1 year FES training in 10 individuals with chronic C6 to T4 SCI. Their proximal tibia bone mineral density increased by 10% and the bone mass gain was reversed after 6 months of subsequent inactivity. Belanger et al. [2000] reported recovery of 30% lost bone mass at the proximal tibia level and significant muscle strength gains following a 24 weeks resisted quadriceps strengthening utilizing electrical stimulation. The fact that the bone and muscle gains disappear after discontinuation of activity [Chen et al., 2005] point to the need for sustained, preferably home-based intervention to maintain physiological gains.

Effect of Activity in Neurorestoration

Exercise becomes an important tool when used in individuals with neurological paralysis. It is *a treatment* that enhances neurological function by affecting musculoskeletal and neural plasticity.

McDonald et al. [2002] reports in a prospective single case study significant improvement of neurological function in an individual with severe chronic spinal cord injury after instituting 3 years of patterned neural activity utilizing FES ergometry. Harness et al. [2008] reports a prospective study involving 21 individuals with motor complete (American Spinal Injury Association (ASIA) impairment A and B) SCI individuals performing a 6 months intense exercise program that significantly improved their motor scores (total ASIA motor score, ASIA lower extremity motor score LEMS) when compared with a matched group ($n = 9$) that performed a self regulated exercise program. Shields and Dudley-Javoroski [2006] report on significant muscle properties changes following a 2-year training program utilizing electrically stimulated strengthening of one sided ankle plantarflexors muscle group when compared with the untrained, internal control opposite leg. Significant gains in torque (24%), torque-time integral (27%), fatigue index (50%), torque rise time (45%), and between–twitch fusion (15%) were recorded in the group that underwent the 2 year training (with a 83% compliance rate). Other studies showed preservation of muscle fiber type when electrical stimulation was applied shortly (less than 4 weeks) after acute injury [Crameri et al., 2000]. Long-term FES training reverses muscle atrophy even in cases of lower motor neuron injury, universally accepted as "unresponsive" to electrical stimulation and FES [Kern et al., 2005].

THE ROLE OF TASK SPECIFIC TRAINING (QUALITY) AND SPINAL CENTRAL PATTERN GENERATORS ACTIVATION (QUANTITY)

The role of task specific training is an essential concept in the field of rehabilitation ("practice makes perfect"). But it might not be the only factor accounting for the success of a therapeutic intervention when rehabilitating individuals with neural paralysis. In one cross over design study, eight subjects with chronic (more than 3 years) ischemic stroke and severe hand dysfunction underwent two different types of neuro-

muscular electrical stimulation (NMES). One was "active" (resulting in grasping and release of a tennis ball) and one "passive," consisting of sequential wrist flexion and extension. Both groups had significant improvements in sensori-motor score and spasticity, with the "active" group having also significant functional gains [Santos et al., 2006]. Beekhuizen and Field-Fote [2008] studied the effect of different patterns of interventions (specific task training and somatosensory peripheral nerve stimulation, specific task training, peripheral nerve stimulation and no intervention) on the hands of 24 subjects with incomplete tetraplegia. All three intervention groups had functional improvements, but only the group undergoing specific task training and somatosensory peripheral nerve stimulation had significant changes in sensory score as well.

The literature supporting specificity in locomotor training following SCI, using mostly supported gait training on treadmills, is abundant [Barbeau et al., 2006; Behrman et al., 2006; Hicks and Ginis, 2008]. As for pediatric literature, Behrman et al. [2008] reports the case of a 4 1/2 year old wheelchair dependent child with cervical spinal cord injury and a lower extremities motor score of 4/50, 16 months postinjury, who was able to ambulate in the community following 76 sessions of locomotor training utilizing body weight support (BWS) and treadmill training. The improved ambulatory ability was achieved despite no change in lower extremities muscle strength.

Recent clinical work suggests that passive or FES-assisted lower extremities ergometry in pediatric population improves bone mineral density, muscle volume, stimulated quadriceps strength, and lowers the resting heart rate [Johnston, 2008]

The combination of task specific locomotor training with FES ergometry may deliver high quality motor activation in sufficient quantity to stimulate functional restoration in spinal cord injury. FES ergometry and gait training both activate the central pattern generators (CPG) located in the lumbar region of the spinal cord (approximately L2-5) [Kiehn and Kjaerulff, 1998; Nishimaru and Kudo, 2000]. Very limited input can cause activation of the CPG as well as produce interlimb CPG activation [Kiehn and Kjaerulff, 1998; Frigon and Rossignol, 2006]. For example, focal sensory activation or stimulation as well as nonfocal activation (e.g., epidural stimulation or intrathecal delivery of NT-3 or BDNF) can produce complex lower limb cycling like movements.

There are pragmatic advantages and disadvantages for both specific gait training and FES ergometry. Gait training is center-based and can only be done under direct supervision of rehabilitation specialists. FES ergometry can be done in a home-based setting, with remote monitoring of compliance (via internet) (RT 300 ES cycling for adults and pediatric population; Restorative Therapies, Baltimore, MD). Gait training is limited by endurance (patient and therapist alike), while FES ergometry is only limited by patient's endurance. Gait training is operator dependent and requires highly trained therapists utilizing a standardized technique that suffers from significant inter-practitioner variance; FES is delivered by a robotic device, ensuring repetitive accuracy. Robotic gait training devices have been

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Passive or FES assisted lower extremities ergometry in pediatric population improves bone mineral density, muscle volume, stimulated quadriceps strength, and lowers the resting heart rate.

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built: the Lokomat and Pediatric Lokomat (Hocoma AG, Switzerland), the Autoambulator (HealthSouth, Birmingham, AL), REOAmbulator (Motorika Ltd.) but in clinical practice they do not yet deliver the same results like therapist guided gait training [Edgerton and Roy, 2009; Hidler et al., 2008].

FUTURE DIRECTIONS AND THOUGHTS

This article is intended to support the idea of utilizing physical activity and exercise as a therapeutic intervention in spinal cord injury, and eventually other disorders of the CNS like stroke and CP. Much like other chronic diseases (i.e., diabetes mellitus, hypertension), paralysis is associated with a multitude of complications that ultimately increase morbidity and mortality. Paralysis does not have a cure per se just as diabetes or hypertension are not yet "curable." We manage these conditions, utilizing drugs and life style modifications. In the case of paralysis, exercise and physical activity is not a luxury, but needed therapy to manage the condition. The paralysis "cure," much like the cure for diabetes or hypertension, is still to come. It could even come from those stem cell trials that we so fondly and ardently talk about. Activity-based interventions are not "the cure" for paralysis and might indeed appear expensive at societal level, but they are needed. The challenge presented here is to view paralysis like any other devastating disease, where results of standard treatment are poor (e.g., nonsmall cell lung cancer), but patients are still encouraged to become candidates for studies evaluating new forms of treatment. ABRTs are evidence-based rehabilitative interventions that are applied according to a new conceptual paradigm that uses activity as a tool for neurological recovery, and not only as a means to achieve compensatory function. ∎

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