Rehabilitation of Locomotor Function After a Central Motor Lesion

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Abstract
After spinal cord injury (SCI) of the cat or rat neuronal circuits below the level of lesion exhibit plasticity that can be exploited by specific training paradigms. In individuals with complete or incomplete SCI, human spinal locomotor centers can be activated by providing an appropriate afferent input. This includes to facilitate and assist stepping movements of the legs and to provide body weight support (BWS) of SCI subjects standing on a moving treadmill. Individuals with incomplete SCI benefit from such locomotor training such that they improve the ability to walk over ground. Load- and hip-joint-related afferent input seems to be of crucial importance for both the generation of a locomotor pattern and the effectiveness of the training. It appears to be a critical combination of afferent signals that is needed to generate and improve a locomotor pattern after a SCI. Several years of driven gait orthoses can provide a standardized locomotor training. In the future, if regeneration approaches can successfully be applied in human SCI, even individuals with complete SCI may recover walking ability with locomotor training. However, recent studies also indicate that in individuals with a severe SCI, spinal neuronal circuits undergo a degradation of their function 1 year after injury.

Generation of locomotor activity
Neuronal circuits (networks of interneurons) within the spinal cord that interact with specific sensory information under supraspinal control are responsible for locomotion in non-primate mammals (Barbeau and Rossignol 1987). These spinal neuronal circuits are defined as central pattern generators (CPGs) and were identified with experiments that demonstrated self-sustained patterns of locomotor-like neuronal activity generated independently of supraspinal and afferent input (Barbeau and Rossignol 1994, Pearson 2000). The understanding of the basis principles of CPG function is based on research in vertebrates and invertebrates. This research has shown that a significant level of control of locomotion is mediated at the level of the spinal cord. In fact, spinally transected animals can relearn or reexpress hindlimb stepping in the absence of input from the brain (Barbeau and Rossignol 1987, Barbeau and Rossignol 1994, Pearson 2000).

There is convincing evidence in spinal animals that use-dependent plasticity of spinal neuronal circuits modifies the sensory-motor function of lumbosacral spinal cord. Regular locomotor training after complete spinal cord transection in adult cats improved the recovery of hindlimb function. Whether these neuronal properties such as the CPG also exist in humans is of crucial importance for the recovery of standing and walking
after severe spinal cord injury (SCI). The control of locomotion by spinal centers and activity-dependent plasticity could then be exploited for rehabilitative purposes by the use of task-specific training approaches following a neural injury (Dietz 2002b, Dietz and Harkema 2004).

**Physiological basis of locomotion in humans**

Leg muscle activation during locomotion is produced by spinal neuronal circuits within the spinal cord, i.e. the spinal pattern generator (CPG, for review see Dietz 1992). For the control of human locomotion, afferent information from a variety of sources within the visual, vestibular and proprioceptive systems is utilised by the CPG. The convergence of spinal reflex pathways and descending path-ways on common spinal interneurons seem to play an integrative role (for review see Dietz 2002b), similar as in the cat (Schomburg 1990). The generation of an appropriate locomotor pattern depends on a combination of central programming and afferent inputs as well as the instruction for a respective motor condition by supraspinal commands. This information determines the mode of organization of muscle synergies which are designed to meet multiple conditions of stance and gait (Dietz 2002b, Dietz 1992, Dietz et al. 1989a, Dietz et al. 1989b, for review see Mac Kay-Lyons 2002).

Central mechanisms and afferent inputs interact in such a way that the gain of a reflex in a muscle or a synergistic group of muscles follows a program that is dependent on the actual task. The actual weighting of proprioceptive, vestibular and visual inputs to the equilibrium control is task- and context-dependent. These inputs can profoundly modify the central program. Through this weighting, inappropriate responses are largely eliminated (for review see Mac Kay-Lyons 2002). Any evaluation of reflex function has to be assessed in connection with the actual motor program, the biomechanical events, including their needs and their restraints.

**Target for rehabilitation: plasticity of the central nervous system**

There is increasing evidence that a defective utilization of afferent input by spinal neuronal circuits, in combination with secondary compensatory processes is involved in typical central movement disorders, such as spasticity following stroke or SCI and Parkinson's disease. Furthermore, cat (for review see Pearson 2000) and human (for review see Dietz 2002b, Dietz 2003) experiments show that spinal and supraspinal neuronal networks underlying the generation and control of motor patterns are quite flexible after central or peripheral neural lesions. Therefore, the aim of rehabilitation should concentrate on the improvement of function by taking advantage of the plasticity of neuronal centers, and should less be directed to the correction of isolated clinical signs, such as the reflex excitability.

There is convincing evidence in spinal animals that a use-dependent plasticity of the spinal cord exists (Pearson 2000, Edgerton et al. 1997). When stepping is practiced in spinal cat, this task can be performed more successfully than when it is not practiced (Lovely et al. 1986, Lovely et al. 1990). The training of functional motor tasks provides
sufficient stimulation to initiate a reorganization of neural networks within the spinal cord after injury with the goal to allow the generation of a locomotor pattern. Consequently, the loss of motor capacity following neural injury can become enhanced when locomotor networks are no longer used, for example, following a stroke (Edgerton et al. 1997). A greater level of functional recovery becomes possible if the concept of use-dependence is applied in both the clinical and rehabilitative settings (Edgerton et al. 1997).

A considerable degree of locomotor recovery in mammals with a spinal cord injury can be attributed to a reorganization of spared neural pathways (Curt and Dietz 1997, Curt et al 1998, for review see Curt and Dietz 1999). It has been estimated that if as little as 10-15% of the descending spinal tracts are spared, some locomotor function can recover (Basso 2000, Metz et al. 2000). If the loss of supraspinal input to the spinal cord is complete, these neuronal networks that exist below the level of the lesion adapt to generate locomotor activity even in the absence of supraspinal input (De Leon et al. 1998a, De Leon et al. 1998b, Wirz et al. 2001).

**Locomotor function after spinal cord injury**

**Neuronal capacity of spinal cord from cat to humans**

In the cat, recovery of locomotor function following spinal cord transection can be improved using regular training even in adult animals (Barbeau and Rossignol 1987). When stepping was not trained, the cat lost the ability to step spontaneously. During such a locomotor training the animal was supported and thus only beared a part of its body weight. Locomotor movements of the hindlimbs were induced by a treadmill while the forelimbs stood on a platform. With ongoing training the body support was decreased associated with improving locomotor function. Later on the cat was able to completely take over body weight and perform well-coordinated stepping movements (Barbeau and Rossignol 1994). The locomotor pattern at this stage closely resembles the pattern of the normal adult cat. Furthermore, hindlimb exercise in adult rats after spinal cord transection can normalise the excitability of spinal reflexes (Skinner et al. 1996). Thus, it can be concluded that the training represents an important factor for the recovery of locomotor function. Recently, stepping movements could also be demonstrated in a monkey after transection of the spinal cord, suggesting that also the isolated primate spinal cord is capable of generating hindlimb stepping movements (Vilensky and O'Connor 1988).

Human locomotion differs in several aspects from that described for the cat but it is also based on a quadrupedal neuronal co-ordination (for review see Dietz 2002a). Step-like movements are present at birth and can be initiated spontaneously or by peripheral stimuli. The EMG activity underlying this newborn stepping is centrally programmed and, as it has also been observed in anencephalic children, it is likely that spinal mechanisms generate the EMG activity (Forsberg 1992). The apparent loss of locomotor movements in humans suffering a severe SCI has been suggested to be due to a greater predominance of supraspinal over spinal neuronal mechanisms (Kuhn 1950). Nevertheless, there are indications that in humans spinal interneuronal circuits exist which are involved in the generation of locomotor EMG activity (Galaode et al. 1994) similar to those described for the cat (Barbeau and Rossignol 1994). Involuntary step-like
leg movements described in patients with an incomplete or complete injury to the spinal cord (Harkema et al. 1997, Nicol et al. 1995), as well as the appearance of complex movements that can be released after cervical trauma (Pepin et al. 2003), are indicative for a spinal pattern generator in humans.

**Effect of locomotor training in paraplegic patients**

In patients with incomplete or complete paraplegic a bilateral leg muscle activation combined with coordinated stepping movements can be induced in partially unloaded patients standing on a moving treadmill (Dietz et al. 1994, Dietz et al. 1995, for review see Barbeau and Rossignol 1994). The leg movements have to be assisted during the first phase of the training (dependent upon the severity of paresis) in incomplete and during the whole training period in complete paraplegic patients. Walking in incomplete SCI patients is usually achieved only at a low speed (Pepin et al. 2003). While the pattern of leg muscle electromyographic (EMG) activity is similar to that seen in healthy subjects, the EMG amplitude is considerably smaller in complete compared to incomplete paraplegics. Both patient groups have smaller EMG levels compared to the healthy subjects. Despite the reduced EMG activity, spastic symptoms (e.g. increased muscle tone, exaggerated reflexes) are present in both patient groups. This supports earlier suggestions claiming that alterations of mechanical muscle fibre properties are mainly responsible for the clinical signs of spasticity and of spastic movement disorder (for review see Dietz and Sinkjaer 2007).

When the EMG of tibialis anterior and gastrocnemius muscles is analysed over the step cycle, it becomes evident that leg muscle EMG activity is about equally distributed during muscle lengthening and shortening in both healthy subjects and patients during locomotion (Dietz et al. 1995). Furthermore, imposing locomotor movements in complete paraplegic patients with full body unloading does not lead to a significant leg muscle activation (Dietz et al. 2002). This indicates that stretch reflexes are unlikely to play a major role in the generation of the leg muscle EMG pattern in these patients, but that it is rather programmed at a spinal level.

During the course of a daily locomotor training program, the amplitude of gastrocnemius EMG activity increases significantly during the stance phase, while an inappropriate tibialis anterior activation decreases (Dietz et al. 1994, Dietz et al. 1995). This is associated with a greater weight bearing function of the extensors, i.e. body unloading during treadmill locomotion can be reduced. These training effects are seen in both incomplete and complete paraplegic patients. Only patients with incomplete paraplegia benefit from the training program in so far as they learn to perform unsupported stepping movements on solid ground. Patients with complete paraplegia experience positive effects upon, the cardiovascular and musculoskeletal systems, i.e. they suffer less from the spastic symptoms.

Successive reloading of the body during the training may serve as a stimulus for extensor load receptors which have been shown to be essential for leg extensor activation during locomotion in both cat (Pearson and Collins 1993) and man (Dietz and Colombo 1996, Dietz et al. 1992). The generally smaller EMG amplitude in patients with complete
paraplegia may be due to a loss of input from descending noradrenergic pathways to spinal locomotor centres (Barbeau and Rossignol 1994).

In order to standardize locomotor training and to allow longer training sessions special devices were developed during the last years. A driven gait orthosis (DGO) was designed primarily for the training of patients with a spinal cord injury (Colombo et al. 2000, Colombo et al. 2001), and an electromechanical gait trainer for the restoration of gait in stroke patients (Werner et al. 2002).

**Relevant afferent input**

For a successful training of patients with a spinal or cerebral lesion, the appropriate afferent input has to be provided to activate spinal neuronal circuits. In healthy subjects during locomotion multi-sensory proprioceptive feedback is continuously weighted and selected. According to recent observations made in healthy subjects (Dietz et al. 1989b, Dietz et al. 1992), small children (Pang and Yang 2000) and patients with paraplegia (Harkema et al. 1997, Dietz et al. 2002) afferent input from load receptors and hip joints essentially contribute to the activation pattern of leg muscles during locomotion.

It is suggested that proprioceptive input from extensor muscles and probably also from mechano-receptors in the foot sole provide load information (Dietz and Duysens 2000). The signals arising from load receptors are likely to be integrated into the polysynaptic spinal reflex pathway, which adapts the programmed locomotor pattern to the actual ground condition. The afferents that signal hip-joint position are suggested to come from muscles around the hip. The role of this afferent activity is to shape the locomotor pattern, to control phase-transitions and to reinforce ongoing leg muscle activity. Short-latency stretch and cutaneous reflexes may be involved in the compensation of irregularities and in the adaptation to the actual ground conditions.

**Assessment of function during rehabilitation**

According to the task-dependent regulation of nervous system function clinical tests must be functional and specific. At present it is a common, well-accepted approach to score isolated clinical measures, such as reflex excitability, muscle tone, or voluntary force of single muscles. For example, muscle tone and spasm frequency can be assessed by the Ashworth scale and Penn spasm frequency scale, respectively (Priebe et al. 1996). For patients with spinal cord injury, the American Spinal Injury Association (ASIA) has developed a standardized neurological assessment, i.e. the ASIA classification of motor and sensory deficits (Maynard et al. 1997). The question is first, whether such scoring systems can serve as a sensitive outcome measure for new interventional therapies and second, whether they can reflect the functional impairment, which is the most important aspect in terms of the patients' quality of life.

Only recently has a score been developed which relates to function. Locomotor ability has been classified into 19 items (Ditunno et al. 2000). A current study indicates that a close relationship between motor scores and locomotor ability exists only in patients with moderately impaired motor function. Patients with a low motor score undergoing a locomotor training can achieve an improved locomotor function without much change in
motor score (Dietz 2002b, Maegle et al. 2002). In these cases, relatively little voluntary force in the leg muscles (reflected in the ASIA score) is required to achieve the ability to walk.

For the future, the effectiveness of any new interventional therapy should be assessed by functional scores in combination with motor scores of selected limb muscles. Motor and sensory scores are most likely to reflect the spontaneous recovery of function, as they depend on the integrity of cortico-spinal connections. In contrast, improvement of locomotor function after SCI also reflects the plasticity of neuronal circuits below the level of lesion. With the combined assessment of voluntary force and automatically performed locomotor function, the superiority of any new interventional therapy on functional movements might reliably become assessed.

**Outlook**

The advantage of gait analysis represents the quantitative assessment of a functional movement with its underlying neuronal mechanisms and biomechanical consequences. In the future, this approach may further be developed to assess the factors responsible for a movement disorder. For future application in the rehabilitation field, gait analysis may help to select the most effective pharmacological and physiotherapeutical approaches. This may not only be of benefit for the patient but also could lead to reduced health care costs as most physiotherapeutic approaches are not based on controlled studies and their effectiveness was never convincingly demonstrated. For future application in the clinical diagnosis, gait analysis may help to achieve an early diagnosis and detection of subtypes of a movement disorder with the consequence of an early onset of an appropriate training (for review see Dietz 2002b).

With the gait analysis of patients with a central motor lesion, the best therapeutical approach and the effect of any treatment on the locomotor function can be determined. Such an analysis has revealed, for example, that the development of spastic muscle tone can be advantageous, in that it provides body support during stepping movements (for review see Dietz and Sinkjaer 2007). This knowledge has, of course, consequences for physiotherapy and drug application.

In severely affected paretic patients the strength of leg muscle activation is not sufficient to build up enough muscle tone or to control limb movements for locomotion. One approach to enhance spinal locomotor activity in the patients with incomplete and complete paraplegia represents the search for substances which influence the gain of locomotor EMG activity. The most promising approach for the future may be to induce partial regeneration of the lesioned spinal cord tract fibres. Recent experiments in the rat have indicated that after inhibition of neurite growth inhibitors, a partial regeneration can occur (for review see Schwab 1991, Schwab and Bartholdi 1996). Connected with an inappropriate locomotor training this approach may improve functional mobility even that of severely affected paraplegic patients. Electrophysiological and biomechanical recordings of locomotion in rats with spinal cord lesions has provided Information that this model can be applied in humans with spinal cord injury (Metz et al. 2000).
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References


