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HIGHLIGHTED TOPIC | *Neural Control of Movement*

Locomotor activity in spinal cord-injured persons

V. Dietz[1] and Susan J. Harkema[2]

[1]*Spinal Cord Injury Center, University Hospital Balgrist, 8008 Zurich, Switzerland; and*

[2]*Department of Neurology and Brain Research Institute, University of California, Los Angeles, California 90095*

Dietz, V., and Susan J. Harkema. Locomotor activity in spinal cord-injured persons. *J Appl Physiol* 96: 1954–1960, 2004; 10.1152/japplphysiol.00942.2003.— After a spinal cord injury (SCI) of the cat or rat, neuronal centers 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 and modulated by locomotor training (facilitating stepping movements of the legs using body weight support on a treadmill to provide appropriate sensory cues). Individuals with incomplete SCI benefit from locomotor training such that they improve their ability to walk over ground. Load- or 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. However, it may be a critical combination of afferent signals that is needed to generate a locomotor pattern after severe SCI. Mobility of individuals after a SCI can be improved by taking advantage of the plasticity of the central nervous system and can be maintained with persistent locomotor activity. 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.

spinal neuronal circuits; locomotor training; neuronal plasticity; load receptors; hip joint afferents

SPINAL PATTERN GENERATION

Neuronal circuits (networks of interneurons) within the spinal cord that interact with specific sensory information are responsible for locomotion in nonprimate mammals (62). These spinal neuronal circuits are defined as central pattern generators (CPG) and were identified with experiments that demonstrated self-sustained patterns of locomotor-like neural activity generated independently of supraspinal and afferent input (65). The understanding of the basic principles of CPG function is based on research in invertebrates and primitive fish, such as the lamprey; this research has shown that a significant level of control of locomotion is mediated at the level of the spinal cord (62, 63, 82). In fact, spinally transected animals can relearn or reexpress hindlimb stepping in the absence of input from the brain (9, 33, 80).

PLASTICITY OF MAMMALIAN SPINAL NEURONAL CENTERS

There is convincing evidence in spinal animals that use-dependent plasticity of spinal neuronal circuits modifies the sensory-motor function of the adult mammalian lumbosacral spinal cord (9, 32–34). Regular training after complete spinal cord transection in adult cats improved the recovery of hindlimb function (9). The type of training was important; for example, the lumbosacral spinal cord of the cat could function to execute stepping (33) or standing (32) more successfully if that particular task was specifically practiced. Furthermore, when stand training alone was practiced, stepping ability was compromised (35). Observations in spinal cats also indicated that, if the training of a motor task was discontinued, the performance of that task deteriorated (34, 53). These results show that repetitive motor training provides sufficient stimulation of specific neural pathways to facilitate functional reorganization within the spinal cord and improve motor output. Furthermore, appropriate sensory input during training is of critical importance to achieve an optimal motor output of the spinal neuronal circuitry. Consequently, the loss of motor capacity after neural injury resulting in loss of supraspinal input could become greater when spinal networks are not activated by functionally relevant sensory input. In contrast, a much greater level of functional recovery might be possible if the concept of use dependence is applied.

Training paradigms of stepping and standing modify the glycinergic and GABAergic systems (53). For example, when strychnine, a glycine antagonist, is administered to a chronic spinal cat that has acquired the ability to step successfully, there is little change in its locomotor capability. However, when administered to a spinal cat that has a poor ability to step, the hindlimbs execute successful weight-bearing stepping (34, 53). This suggests that, by reducing inhibition of spinal networks, sensory input can be integrated to generate locomotor activity.

Whether these neuronal properties also exist in humans is a critical question 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

Address for reprint requests and other correspondence: V. Dietz, Balgrist Univ. Hospital, Spinal Cord Injury Center, Forchstr. 340, 8008 Zurich, Switzerland (E-mail: dietz@balgrist.unizh.ch); and S. J. Harkema, Dept. of Neurology and Brain Research Institute, Univ. of California, Los Angeles, A386 1000 Veteran Ave., Los Angeles, CA (E-mail: sharkema@mednet.ucla.edu).

exploited for rehabilitative purposes by the use of task-specific training approaches following a neural injury.

EXISTENCE OF LOCOMOTOR-RELATED PATTERN GENERATION IN HUMANS

The role of CPG in the generation of walking in humans is controversial (72). The existence of CPG in humans is difficult to definitively demonstrate because this requires observations of oscillating neural networks after anatomically complete spinal lesions and deafferentiation. Nevertheless, many human studies have provided evidence of oscillatory neural networks that interact with afferent input with limited or no detectable functional supraspinal input. Alternating extension and flexion movements of the legs were reported over 50 years ago in individuals classified with surgically verified complete spinal lesions (78). More recently, electrical stimulation of flexor reflex afferents showed characteristics of neuronal networks in humans (93, 94) that were similar to those that were critical in identifying central pattern generation in animals (73, 74). Furthermore, rhythmic contractions of the trunk and lower limb extensor muscles were described in an individual with clinically complete SCI, demonstrating oscillatory properties of spinal networks in the absence of detectable functional supraspinal input (20, 21). This rhythmic activity could be stopped, induced, and modulated by peripheral stimulation of flexor reflex afferents (22). Also, involuntary steplike movements that were modulated by sensory input were observed in an individual with chronic incomplete cervical SCI several years after injury (23). Furthermore, in individuals with clinically complete SCI, nonpatterned electrical stimulation can produce extensor patterns similar to those expected for standing (75) as well as alternating flexor and extensor patterns similar to those expected for stepping (50).

Studies have also shown that locomotor-like EMG patterns in individuals with clinically complete SCI could be induced when leg movements were assisted externally to provide stepping-related sensory cues to the spinal cord (40, 41, 51, 67). These patterns could not be solely attributed to rhythmic segmental reflexes, such as stretch reflexes, but were consistent with the interaction of peripheral events with central mechanisms (16, 67). The pattern of leg muscle activation during such locomotion resembled in many aspects the pattern observed in an intact cat (8, 9, 80) or a healthy individual (2, 84, 96). However, the amplitude of leg muscle EMG activity in the individuals with clinically complete SCI was lower than that of healthy subjects, and no independent leg movements resulted from this leg muscle activation (40, 41). More recently, higher levels of muscle activation did result in independence of stepping of one leg with minimal assistance on the other leg in three clinically complete SCI subjects after several months of locomotor training, although complete independent stepping with full weight bearing was not achieved (15, 81).

Several neurotransmitter systems within the spinal cord are suggested to be involved in the generation of locomotor patterns and the adaptation to repetitive use. In spinal cats, serotonin agonists modulated established locomotor patterns, whereas antagonists worsened the locomotor pattern (10, 11). In contrast, one study in humans after SCI reported a minimal increase in stepping speed ($\sim$0.06 m/s increase), a reduction in clonus, and a reduced need for assistance with a serotonin antagonist (85). In animals with a spinal cord transection, stepping can be induced by the administration of the noradrenergic agonist clonidine, which enhances the activity in the locomotor spinal circuits (7, 25, 26). In clinically incomplete spinal-injured and intact cats, clonidine had either no effect or negatively affected the stepping pattern (59). The response to clonidine in humans was varied; for example, in clinically complete SCI subjects, motor activity was abolished over hours after intrathecal application of clonidine (41), whereas in some incomplete spastic SCI subjects stepping was reported to be improved after these subjects received oral administration of clonidine (100).

The difference in results with the use of pharmacological interventions between animal and human studies may be due to several factors. In animal studies, the time elapsed from injury to study is most often days or weeks and can be strictly controlled; in human studies, however, time elapsed from injury to study can be weeks to months and is highly varied across subjects. Also, the actual "state" of the nervous system may affect the response to a particular agonist or antagonist, and this condition may be affected by type of injury, time since injury, history of antispasticity medication use and level, and type of exercise or rehabilitation. Further studies exploring the use of pharmacological agents in conjunction with locomotor training for the recovery of walking are warranted.

Nevertheless, according to earlier observations, bipedal locomotion and quadrupedal locomotion share some common spinal neuronal control mechanisms. As in quadruped individuals, long-projecting propriospinal neurons couple the cervical and lumbar enlargements in humans (83). Furthermore, the coordination of limb movements that have been attributed to brain stem and spinal pathways during walking in human infants (86, 114) are reported to be similar to that in quadruped individuals (61, 62). However, there are also distinct differences because the upper limbs in primates have become specialized to perform skilled hand movements. The evolution of upright stance, gait, and balance, in association with a differentiation of hand movements, represents a basic requirement for human cultural development. This phylogenetic development does, however, not exclude that human bipeds still use quadrupedal coordination for their locomotor activities (38, 42).

RELEVANT AFFERENT INPUT FOR THE GENERATION OF A LOCOMOTOR PATTERN

The interaction of specific sensory information with CPG is essential for successful locomotion in spinally transected mammals. Understanding the critical sensory patterns recognized by the mammalian spinal cord and exploring their importance in human locomotion will provide insight to the neural control of walking and can help guide more effective rehabilitation strategies after SCI. The actual requirements during a particular locomotor task and the availability of afferent input guide the selection and level of influence of multisensory proprioceptive feedback in modulating efferent output. Recent observations made in healthy subjects, as well as in small children and individuals with SCI, showed that afferent input from load receptors and hip joints essentially contribute to the activation pattern of leg muscles during human locomotion.

Significance of load receptor input. The significance of loading for the regulation of stance and gait has previously been established in the cat (52, 92) as well as in healthy human subjects (43). Proprioceptive inputs from extensor muscles, and probably also from mechanoreceptors in the foot of the sole, provide load-related afferent information. The signals arising from the afferent input are likely to be integrated into the polysynaptic spinal reflex pathway, which adapts the programmed locomotor pattern to the actual ground conditions. Simple stretch and cutaneous reflexes may be involved in this modulation (1, 3, 14, 24, 97, 99, 112, 113, 115). The role of this afferent activity for rhythmic locomotor pattern is to shape the pattern, control phase-transitions, and reinforce ongoing activity (52, 57, 70, 102, 108–110).

In individuals with SCI, an essential contribution of load-related input to the generation of a locomotor pattern has also been recognized. Several studies have shown that physiological locomotor-like leg movements alone (100% body unloading) generated by the application of a driven gait orthosis (45) or by manually assistance (54, 67) are not sufficient to generate leg muscle activation in either healthy subjects or in subjects with complete para-tetraplegia. However, leg movements in combination with loading of the legs lead to appropriate leg muscle activation. Furthermore, the absence of leg muscle EMG activity in the individuals with SCI when physiological stepping movements were imposed during full body unloading indicates that stretch reflexes without loading contribute little to the leg muscle activation in the normal walking conditions.

The amplitude of muscle activation in the legs was directly related to the level of loading on the legs during stepping of healthy and SCI subjects (67). Therefore, it is not surprising that body unloading and reloading plays an essential role for the success of a locomotor training in paraplegic (41) and hemiplegic (68) patients. However, an appropriate rhythmic loading of one extended leg alone while stepping movements are performed by the contralateral leg was not always sufficient for the activation of the static leg (45, 54). This indicates that a combination of different afferent inputs is required to achieve locomotor-like leg muscle activation.

The differential strength of upper and lower leg muscle activation in individuals after SCI compared with healthy subjects with greater EMG amplitude in proximal leg muscles (45) might reflect the phylogenetically earlier locomotor pattern observed in infants (86) and cats (69). Alternatively, this difference might be compensatory to the reduced lower leg muscle activation. It still remains unclear whether Ib afferents are responsible for the effects of actual body load during locomotion in human subjects, as suggested for the cat (88, 89).

Significance of hip joint afferents. Afferent input from hip joints is important for muscle activation during locomotion in mammals mainly because it initiates the transition from stance to swing (64, 90). Preventing the hip from obtaining an extended position in chronic spinal cats inhibited the generation of the flexor burst and the onset of the swing phase. Furthermore, entrainment of a locomotor rhythm was obtained by using rhythmic hip movements in immobilized spinal (4, 5) and decerebrate cats (77). Proprioceptive input from hip flexor muscles has also been shown to enhance hip flexor activity (79).

Hip kinematics have been shown to modulate muscle activation during locomotion in humans. The effects of controlled hip and knee movements on the leg muscle activation during stepping were studied in clinically motor-complete paraplegic patients with the use of a driven gait orthosis applied to proximal leg joints (45). The pattern of leg muscle activation was similar when the knee joint movements were blocked while the hip underwent the usual flexion and extension patterns. Furthermore, isolated foot joint movements (simulated stepping with or without loading the sole of the foot) evoked only local responses, which is in line with earlier reports (43, 60, 97). These results suggest that hip joint afferents play a role in the leg muscle activation in the functionally isolated human spinal cord. Initiation of swing has also been shown to be dependent on hip position for human infancy stepping (86, 87).

Interlimb coordination. Studies in healthy subjects demonstrated a coordination of bilateral leg muscle activation during stance and locomotion (Refs. 17, 44, 47; for review, see Ref. 36). An interlimb neuronal mechanism that coordinates the activity between muscles of both legs was also described for pedaling movements (101). In these experiments, an influence of contralateral extensor phase afferent input on the ipsilateral flexion movements indicated a bilateral coupling of amplitude modulation. In addition, in healthy subjects during unilateral stepping (stepping of one leg while the other leg was static but rhythmically loaded when the contralateral leg was in the swing phase) with 70% body weight support showed a preserved activation of leg flexor but minimal EMG activity in the leg extensor muscles of the nonmoving leg (45). This also supports a differential neuronal control of these muscles with a central dominance in the control of leg flexor activity (36). During normal locomotion, the leg extensor activity is continuously modulated by proprioceptive feedback during the stance phase; the static position that prevented roll off the body over the standing leg could explain the reduced extensor EMG activity even with partial weight bearing of the leg.

Several studies have addressed the role of spinal mechanisms in interlimb coordination during human locomotion. The EMG short latencies of interlimb responses in healthy subjects during perturbation of stepping supported a spinally mediated mechanism (47). Also, interlimb coordination was demonstrated in early infancy, i.e., well before the onset of independent walking and full development of supraspinal input (87). In contrast, in a group of clinically complete SCI subjects, no significant EMG activity was observed in any leg muscles of the nonmoving leg during unilateral stepping as described above (45). Therefore, it was assumed that the coordination of bilateral leg muscle activation depends on facilitation by supraspinal centers. Indeed, a cerebellar contribution via reticulospinal neurons has been suggested in both cats (6) and humans (18). Furthermore, the supplementary motor area was recently shown to be involved in the interlimb coordination (31).

However, one recent study demonstrated, in humans with clinically complete SCI, that ipsilateral limb loading without limb movement could result in rhythmic EMG activity if the other leg was stepping (54). Rhythmic EMG bursts also occurred in a stationary unloaded leg when the contralateral leg was stepping, indicating that coordination between two limbs can occur even in the absence of detectable supraspinal input. However, all SCI subjects studied did not show this response.

Two important differences between the studies were the speed of stepping and the amount of loading. Dietz and colleagues' (45) subjects stepped at a fairly slow speed and high body weight support, whereas, in the other study (54), the subjects stepped at speeds closer to normal walking speeds with greater loading on the legs. In some cases, the resting excitability of the spinal cord may have been lower in the nonmoving leg than in the moving leg, and thus the level of segmental excitation from the moving leg was not sufficient to excite the contralateral motoneuron pools. Other factors that could have played a role in the differences include the amount of previous training, the level of injury, and/or the time since injury. For example, improved intralimb coordination was described in incomplete SCI subjects after training with body weight support on a treadmill with electrical stimulation (56).

These results support that this combination of hip with other afferent input, especially from loading, contributes to the pattern of leg muscle activation during human locomotion (Fig. 1). There is significant evidence that the human spinal cord, even in the absence of supraspinal input, can process complex sensory information. However, a critical combination of afferent signals is needed to generate a locomotor pattern in the functionally isolated human spinal cord.

In complete paraplegic patients, a locomotor pattern can be induced after spinal shock disappears, and this pattern reaches a plateau usually ~4 wk after injury (48, 71). However, after locomotor training, gastrocnemius EMG activity further increases during the stance phase. This effect is connected with progressive loading (i.e., reduced unloading) during locomotion. In these patients, it appears that the locomotor pattern depends on the level of lesion, i.e., the higher the lesion the more "normal" the pattern (46). This would imply that neuronal circuits up to cervical levels contribute to the locomotor activity, as it was suggested for the mudpuppy (27).

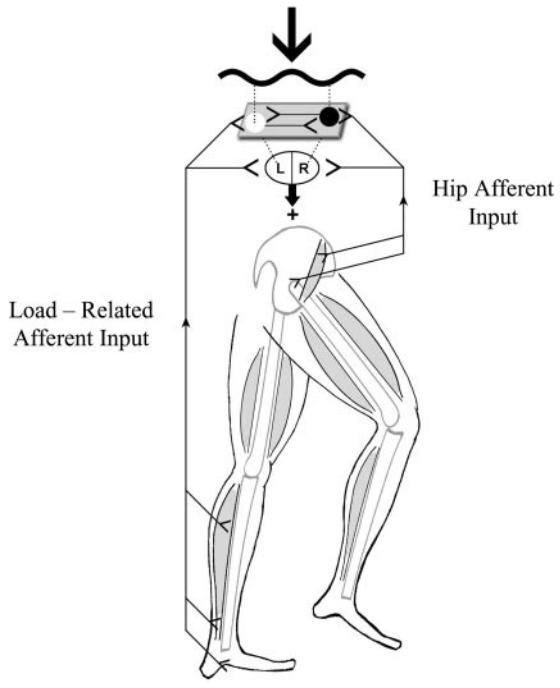

Fig. 1. Schematic illustration of the afferent input (load related and hip afferent) that has been shown to modulate locomotor output after human spinal cord injury and has been considered important for the generation and training of the locomotor patterns in patients with SCI. Large arrow, supraspinal input that is disrupted (wavy line) after injury. Load and hip afferent inputs influence interneuronal systems and motoneurons (L, left; R, right), including interlimb coordination, resulting in the final efferent output (small arrow, +).

LOCOMOTOR TRAINING IN PATIENTS WITH CLINICALLY INCOMPLETE SCI

Locomotor training is a new rehabilitative approach that takes advantage of critical sensory cues, including those reported above that are recognized by the human spinal cord as essential for locomotion (67, 91, 103, 104). Plasticity of the nervous system occurs by specific retraining of stepping, resulting in a significant level of recovery of walking after incomplete SCI. The intervention provides repeated practice of stepping with assistance from therapists or driven gait orthoses during stepping on a treadmill with body weight support. The beneficial effect of locomotor training in incomplete SCI patients is well established (Refs. 49, 58, 105; for review, see Ref. 12). Even chronic SCI patients who underwent locomotor training had greater mobility compared with a control group with conventional rehabilitation (55, 106).

The main effect of locomotor training seen in incomplete SCI patients can be attributed to an enhancement of leg muscle EMG activity connected with an improvement of locomotor function (40, 41). Even in complete SCI patients during locomotor training, the gastrocnemius EMG activity increased during the stance phase. This improvement of locomotor activity could have been attributed to spontaneous recovery of spinal cord function because recovery can occur over several months following SCI (28–30, 76). However, observations made in both incomplete and complete SCI after locomotor training demonstrate that the increase of leg extensor EMG activity with a decrease of body unloading occurs independently of the spontaneous recovery of spinal cord function (48, 49).

Nevertheless, it remains unclear to what extent these training effects are only due to a training of spinal locomotor centers. Only by systematic EMG recordings of leg muscles, reflecting the activity of spinal neuronal circuits, can the effect on this presumed, spinal locomotor pattern generator be separated from rather nonspecific effects on muscles and tendons. In patients with SCI due to a lesion of the cauda, i.e., of peripheral nerves, locomotor training indeed resulted in improved locomotor function that did not correspond to changes in leg muscle EMG activity (48, 49). Therefore, the improved locomotor function described earlier for cats and humans can also be partially attributed to nonspecific effects on the locomotor apparatus, i.e., muscular tendon systems (Refs. 9, 12, 105; for review, see Ref. 37).

A considerable degree of locomotor recovery in mammals including humans with SCI can be attributed to a reorganization of spared neural pathways (28–30). It has been estimated that, if as little as 10% of the descending spinal tracts are spared, some locomotor function can recover (13). Furthermore, the neuronal networks that exist below the level of the lesion adapt to generate locomotor activity, even in the absence of supraspinal input (32, 33, 111). Also, hindlimb exercise was shown to normalize the excitability of spinal reflexes in adult rats following spinal cord transection (98).

Long-term effects of locomotor training have been shown in individuals after SCI. Functional recovery was maintained in individuals several years after initial locomotor training; some individuals also improved their ability to walk over ground (107). In addition, individuals with complete or incomplete SCI that received locomotor training for several months were able to generate coordinated stepping movements and increased leg extensor EMG activity (111). The leg extensor EMG activity remained elevated more than 3 yr after training in those with incomplete SCI who regularly maintained locomotor activity. In contrast, the EMG activity fell significantly in those with complete SCI who remained wheelchair bound. These results suggest that a training-induced plasticity of neuronal centers in the isolated spinal cord can be maintained only by continued locomotor activity. This is in line with observations made in the cat (34, 53) and might be of significance for future interventional therapies.

FUTURE DIRECTIONS

Locomotor training is presently an effective method for improving the recovery of walking in many individuals with incomplete SCI. However, at this point, complete recovery of walking is not routinely attained with severe injury. Looking ahead, it may be important to discover combination strategies to further enhance the locomotor output, such as the application of pharmacological interventions, spinal electrical stimulation, and functional electrical stimulation. Furthermore, rehabilitation approaches should be refined and directed to take advantage of the plasticity of the central nervous system and the intrinsic neuronal properties of the human spinal cord (for reviews, see Refs. 39 and 66). However, the most promising approach may be to induce some regeneration of corticospinal axons within the spinal cord (Ref. 19; for review, see Ref. 95). In the future, individuals with complete or almost complete SCI may profit from a combination of regeneration approaches and exploitation of neuronal plasticity driven by appropriate retraining of the nervous system, taking advantage of spinal neural networks and critical sensory cues.

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