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Scientific Review

Gait after spinal cord injury and the central pattern generator for locomotion

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Introduction

The clinical outcome of traumatic spinal cord injury (SCI) mainly depends upon the severity of the lesion, the recovery processes and neurorehabilitation programs. The percentage of SCI subjects who recover ambulation can range between 15–45% while the rest will remain wheelchair-bound.[1–3] However, even among those subjects who are clinically complete there are very few who can perform stepping movements,[4,5] and rhythmic myoclonic movements.[6] This clinical fact can be interpreted as: (1) evidence that humans do not possess a neuronal assembly system within the lumbar cord and, therefore, cannot produce the basic spatial-temporal patterns underlying stepping movements; (2) subclinical presence of brain influence below the level of SCI which can suppress or modify rather than facilitate central pattern generator (CPG) activity;[7] and (3) indication that our examination protocols do not provide the elements necessary for evoking rhythmic activity through the alternation of flexion and extension of the lower limbs stimulated by a moving treadmill surface.[8]

In this article we will review the locomotor capabilities of subjects with incomplete SCI and will discuss the role of the segmental and suprasegmental features of neurocontrol involved in the generation and maintenance of gait of ambulatory SCI subjects. Furthermore, we will address the topic of rhythmic locomotor EMG activity which becomes manifest when the lumbosacral spinal cord, isolated from suprasegmental control, is fed by segmental sensory input from the lower limbs.[8] We will then compare this activity with step-like EMG and locomotor synergies induced in paraplegic subjects through stimulation of the isolated lumbar cord by means of a train of electrical stimuli.[9]

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Neurocontrol of locomotion in SCI subjects

As a result of SCI, gait in humans is altered, and usually possible without or with assistive devices. Instead of developing a broad range of speeds, an ambulatory SCI subject is often only capable of very slow gait. Studies of gait performance after SCI show that the disturbing factors are spasticity and alteration in muscle activation patterns, including weakness and impaired control of weight bearing.[10,11]

We studied the locomotor patterns in humans with impaired spinal cord functions.[12] All the 16 subjects studied (five women and 11 men aged from 10–76 years), suffered from incomplete spinal cord lesions which were determined by the neurological and neurophysiological assessment of the long ascending and descending systems. The level of the spinal cord lesions in the subjects studied ranged from C2 to T10, and the post-injury period varied from 3–207 months. Spasticity in the lower limb muscles was mainly tonic and covered the range from mild to severe. Three subjects were functional ambulators without any supportive aid, while the other 13 subjects manifested various levels of functional ambulation with assistive devices, from a unilateral cane to a walker with bilateral braces. The peripheral neuromuscular system was not impaired in any of these 16 subjects. In addition, a control group of five healthy subjects (mean age 35 years) was studied. We used surface electromyography (EMG) to study segmental and suprasegmental motor control and concluded that in this group of subjects the EMG activity generated was diminished in amplitude, while motor unit activity became more prolonged and muscle strength

decreased. Furthermore, there was a close relationship between volitionally induced flexor/extensor patterns in the supine position and during gait performance. This finding, present in all the 16 subjects studied, led us to conclude that locomotor patterns in ambulatory SCI subjects was correlated with residual brain motor control. The more postural and volitional control were preserved, the better the subject walked.

This finding indicated that locomotor pattern generation was more dependent upon supraspinal motor control than spinal reflex activity. Although we did not test the gait of these 16 subjects on a treadmill to determine whether walking in suspension on a treadmill would improve gait performance, we concluded that gait performance depended upon the presence of suprasegmental control. This conclusion was substantiated by the findings of another study on neural control of gait in which we examined features of plantar withdrawal reflex, vibratory tonic reflex, reinforcement manœuvres and volitional motor tasks.[13] We recorded the responses by surface EMG in 38 SCI subjects, of which eight were ambulatory. We learned that in the clinically complete SCI there are two categories of smaller and larger reflex and reinforcement responses. Later studies of SCI subjects with smaller and larger reflex and reinforcement responses revealed that even those SCI subjects, in whom volitional movement was absent, could reveal subclinical evidence of the preservation of brain influence below SCI.[14]

Moreover, in our study of 38 SCI subjects we were able to illustrate how neurocontrol changes its features in supine or supported standing in subjects with clinically complete SCI. We showed that even in a clinically complete subject, who in the supine position revealed minimal subclinical findings of EMG activity, motor unit output would increase in supported standing and would be accompanied by traces of stepping movements.[13] Upon examination of the long ascending tracts in the eight ambulatory subjects who were independent walkers with the use of assistive devices (without support their gait was spastic with poor endurance) we found partial preservation of sensation to touch, position, vibration and pain as well as somatosensory cortical evoked responses, although altered in amplitude and morphology.[13] Thus, in order to establish neurocontrol of gait in SCI subjects, it is crucial that the functions of the long ascending and descending spinal pathways be partially preserved below the level of the SCI (Figure 1).

Apart from a few reports of 'spontaneous stepping' in clinically complete SCI, which were not supported by neurophysiological findings for complete SCI, studies of neurocontrol of gait in SCI subjects have shown that without volitional activity it is not possible to initiate and maintain stepping movement, even when SCI subjects were suspended over a running treadmill.[15]

Evidence for a spinal CPG in humans: locomotor training

Is there a CPG for locomotion in humans whose lumbosacral spinal cord has been isolated from brain influence by accidental injury?[16,17] Animal experimental studies provide evidence that the ability of the spinal kitten to walk on a treadmill is very similar to that of normal cats, and in the adult spinal cat it has been shown that the quality of hindlimb locomotion is improved by training and that the spinal locomotor pattern evolves with time.[18,19] On the basis of these 'rules of spinal locomotion', Wernig and Müller[20] concluded that activity-related learning was effective in improving hindlimb stepping in the adult spinal cat. Since locomotion improved with prolonged training and worsened with standing rather than walking,[21] they examined whether similar training would be beneficial to humans with incomplete and chronic SCI. Thus, Wernig and Müller were led to develop an exercise protocol which they named 'rules of spinal locomotion' to train wheelchair-bound SCI subjects to walk. They started with five incomplete but severely paralyzed SCI subjects and found that bipedal stepping could be elicited after a prolonged period of time from

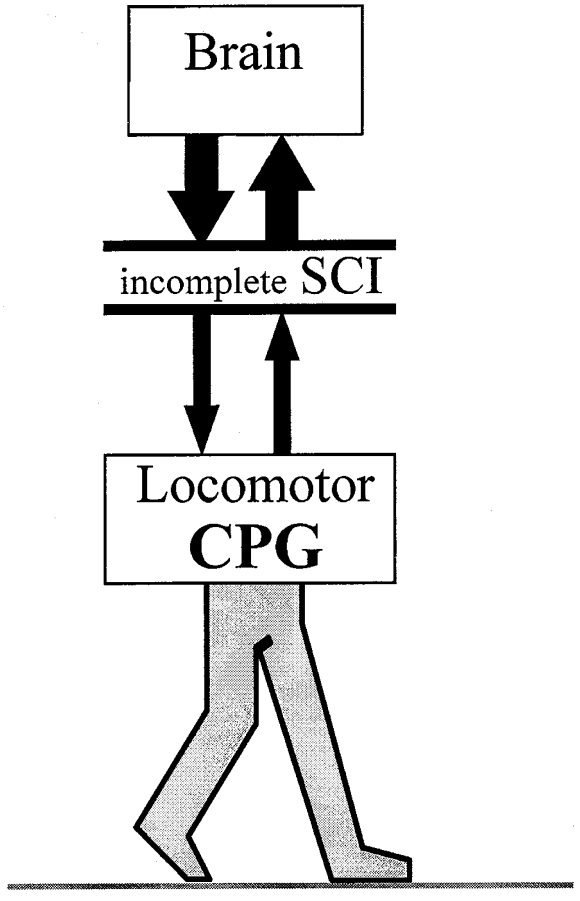

Figure 1 Locomotion after 'spontaneous' recovery of the SCI

the onset of injury.[22] In parallel, Barbeau also reported improvement in the locomotion of incomplete SCI subjects with locomotor training.[23] Furthermore, in 1995, Wernig *et al*[22] included seven paraplegic subjects functionally paralyzed below T5–8 in their report on effective treadmill therapy for locomotion in 44 chronic and 45 acute incomplete SCI subjects. They reported that despite daily exercise, during which the limbs were set and controlled by two therapists, no significant improvement in stepping on the treadmill was observed and no full step cycles were accomplished in these paraplegic, clinically complete patients.[20] Dobkin *et al*[24] in their study of clinically complete and incomplete SCI confirmed that only subjects with incomplete lesion could benefit from the training with respect to performance of unsupported stepping movements. In the case of severe incomplete lesion, this category of subjects could regain minimal motor control but not the ability to walk. However, the timing and structure of the EMG pattern of leg muscle activity in paraplegic patients were similar to those seen in healthy subjects during treadmill locomotion.[24] Moreover, Dietz *et al*[25] in their study on the locomotor capability of the spinal cord found a significant increase in leg extensor EMG activity, in addition to locomotor EMG responses, in complete paraplegics subjected to partial unloading on the moving treadmill and manually assisted movements of the feet.

Thus, the spinalized cat can respond to prolonged locomotor training with rhythmic, locomotor-like EMG activity and stepping movements, a human in whom the spinal cord has been transected by accidental injury can also be trained to respond with locomotor-like EMG activity, but only if the isolated spinal cord responds to the afferent volleys from manually and externally induced stepping movements. This finding can be considered as evidence for the presence of CPG circuitry responsible for the generation of rhythmic activity within the lumbar cord isolated from brain influence. However, in the absence of descending brain control involved in the initiation of locomotion, CPG activity is then induced by activating afferents from muscles, tendons and joints by means of peripheral afferent feedback. Studies of the role of proprioceptive regulation of gait in the walking systems of cats, insects and crustaceans have identified the reflex pathways that regulate the timing and magnitude of motor unit activity of the transition from stance to swing.[26,27] According to Pearson *et al*[27] two characteristics of the motor pattern are particularly dependent upon proprioceptive regulation: (1) activity in knee and ankle extensor muscles, and (2) duration of extensor bursts during stance. Therefore, the increased amplitude of leg extensor EMG in paraplegic patients during locomotor training can be explained as a response to the influence of load receptors affected by the magnitude of the activity of leg extensors during stance of locomotor training along with other related proprioceptive regulatory mechanisms of locomotion which reveal that transmission in afferent pathways is modifiable.[27] Thus, the human lumbar cord isolated from brain influence can be trained to respond with rhythmic, locomotor-like EMG activity to peripheral afferents activated by externally induced stepping movements in a subject suspended over a running treadmill (Figure 2). The next question we asked ourselves was what would happen if we directly stimulated the spinal cord instead of activating peripheral afferents with externally induced stepping movements. Could we provide evidence for a spinal cord network which would respond with rhythmic activity?

Evidence for a spinal CPG in humans: spinal cord stimulation

There is another approach to elicit stepping movements from the isolated lumbosacral cord which differs from the activation of patterned, sensory, phasic input from the lower limbs associated with load-bearing stepping and elicited locomotor-like EMG activity and stepping

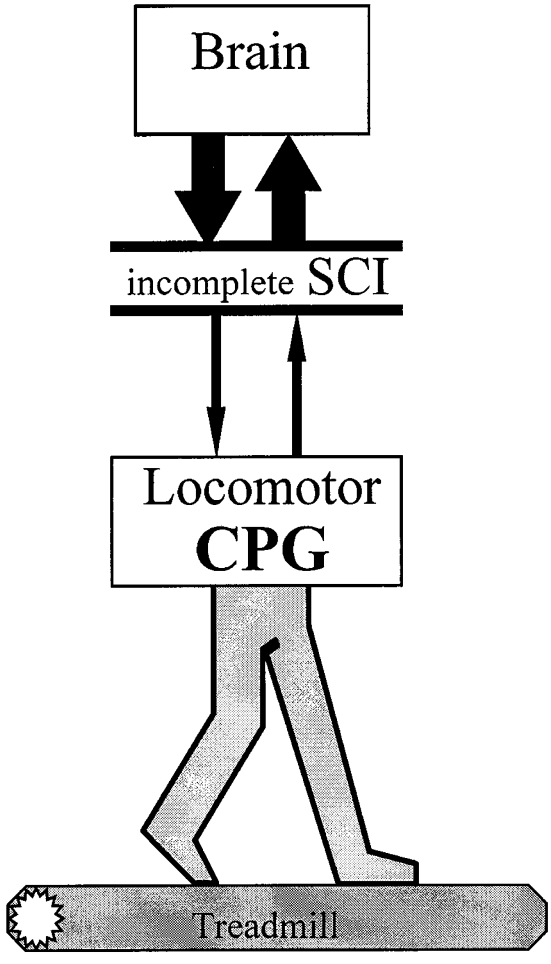

Figure 2 'Peripheral' phasic input from lower limbs during manually controlled stepping

movement. This is electrical stimulation of the spinal cord with sustained, non-patterned electrical stimuli of variable frequency, amplitude and duration. Focal electrical stimulation was applied to the sites within the dorsolatereal funiculus of the spinal cord with a constant frequency between 10–100 Hz to activate swimming movements of the limbs of spinal turtle, which, when spinalized, does not produce swimming spontaneously.[28,29] Locomotion was induced in acute and chronic spinal cats with a train of 30–50 Hz that stimulated the posterior roots and columns of the spinal cord.[30,31] This procedure of electrical spinal cord stimulation of the posterior lumbar structures from the epidural space became a clinically accepted method for the control of spasticity in subjects with SCI.[32] It also became feasible to use the same method in studies of lumbosacral cord mechanisms for locomotion in humans. The possibility of eliciting segmental input to the lumbar cord by means of electrical stimulation of the spinal cord's posterior structures led us to explore whether the human lumbosacral cord isolated from brain control could respond with patterned, stepping movement to an externally generated, sustained, non-patterned electrical train of stimuli. The actual question was whether this external tonic input could replace the missing suprasegmental tonic activity. Under normal conditions, the tonic input needed to drive lumbosacral CPG activity to locomotion is generated by brainstem neurons and mediated by long-descending axons to the interneuronal synapses of the lumbosacral network where it converges with phasic peripheral input.[33]

Thus we conducted a study on the locomotor capabilities of the lumbosacral cord induced by epidural spinal cord stimulation in six subjects with complete, long-standing SCI and found that non-patterned electrical stimulation of the posterior structures of the lumbar cord induced patterned, locomotor-like activity.[9] Thus, an electrical train of stimuli applied over the second lumbar segment with a frequency between 20–60 Hz and an amplitude of 5–9 Volts, induced rhythmic, alternating stance and swing phases of the lower limbs. This rhythmic, locomotor-like activity lasted as long as the stimulus was on. An increase in the frequency of the stimulating train corresponded to an increase in the frequency of rhythmic activity, whereas an increase in the strength of the stimulus resulted in a decrease in rhythmic activity. This observation led us to the conclusion that when the integrity of segmental input–output was preserved, the mechanism within the lumbosacral cord network which determined the temporal pattern of rhythm generation and shaped motor output could initiate and maintain locomotor-like activity in response to non-patterned, segmental stimulation of a particular site of the lumbosacral cord.[9] In other words, it was possible to induce in humans with chronic and complete SCI locomotor-like EMG activity induced by stepping movements generated by 'peripheral', patterned, sensory, phasic input, or 'central' tonic input. Such tonic input was generated by a quadripolar stimulating electrode placed in the epidural space and by applying an electrical train of stimuli to the posterior structures of the second lumbar segment[9] (Figure 3).

To simplify the distinction between 'manually' and 'electrically' induced locomotion in the complete paraplegic, we can see in locomotion induced by manual control of the subject suspended over a continuously running treadmill, an example of 'mechanically' induced locomotor activity through mechanical simulation, and in the case of a subject with epidural spinal cord stimulation, an example of 'electrically' induced locomotor activity. At first glance, we can see that these two different stimulating paradigms are initially based on tonic features induced by the running treadmill as well as continuous electrical stimulation of the posterior structures of the upper lumbar segments. However, the manually controlled steps on the treadmill generate phasic input, so that after a while it becomes possible to record EMG locomotor-like activity similar to the EMG activity generated by a person with intact nervous system functions walking on the treadmill under identical conditions. During tonic electrical stimulation of the posterior structures of the lumbosacral cord, one of the functions of the neuronal network is to generate rhythmic, locomotor-like EMG activity and stepping movement.

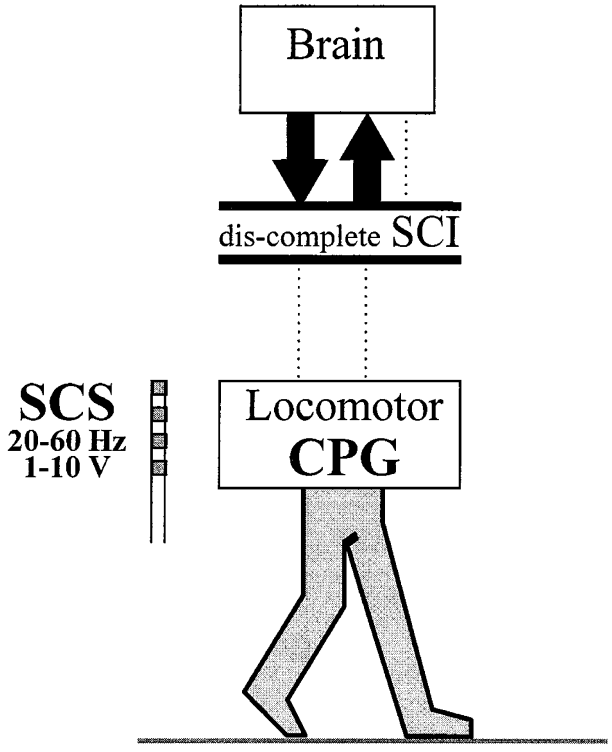

Figure 3 'Central' tonic input, external train of electrical stimulation, delivered by SCS can induce stepping movements

Experimental researchers have endeavoured to learn to what extent the isolated spinal cord can generate locomotor rhythm by eliminating all supraspinal influence in the cord of the cat through spinalization, and destroying phasic peripheral input by dorsal root transection and curarization. They were successful in demonstrating that even though the cord may be fully deprived of any afferent input, it can generate patterned, locomotor-like activity which can be recorded by electroneurograms from the anterior roots. Such activity is known as fictive locomotion and these experiments have been conducted in the acute spinal cat which was given an injection of DOPA and Nilamid, or in the chronic spinalized cat stimulated by a continuous train of stimuli of 6 Hz.[34] The capability of the isolated lumbar spinal cord to generate rhythm has also been shown in *in vitro* preparations from newborn rats,[18] and an *in vitro* preparation isolated from a mature aquatic amphibian mudpuppy (Necturus maculatus).[35]

The model of fictive locomotion in humans with SCI has not yet been established, yet we have observed the effect of reduced peripheral afferent input on lumbar CPG in SCI.[36] After inducing stepping movement with spinal cord stimulation, we reduced afferent input by inducing ischemia with a temporary cuff applied over the thigh muscles to diminish input from large afferents. While maintaining constant the parameters of epidural stimulation of the posterior structures of the second lumbar segment, we observed that reduced afferent input resulted in diminished amplitude and increased frequency of step-like EMG activity and movement. Thus, CPG activity in the isolated human lumbosacral cord was dependent upon stimulating parameters, the sites of epidural and 'central' stimulation, as well as from 'peripherally' induced afferent input by manual movement of the paralyzed lower limbs.

The next step we undertook was to determine the effect of the motor task induced by epidural lumbar spinal cord stimulation on stepping movement in SCI subjects. We chose subjects who were ambulatory, with incomplete spinal cord lesion. They were recruited from clinical programs for studies of supraspinal innervation on externally and centrally induced CPG since such programs used epidural lumbar stimulation in ambulatory SCI subjects to control spasticity and enhance walking endurance (MM Pinter, not published observation). In this category of post-traumatic, incomplete, ambulatory, and closed SCI subjects, we were able to examine the effect of the motor tasks of volitional dorsal and plantar ankle contraction, and volitional flexion and extension of the whole lower limb, as well as stepping movement and EMG activity induced by epidural stimulation. Both motor tasks cancelled ongoing rhythmic activity and were replaced by volitional motor task performance.[37] However, in the same subjects, postural motor tasks, sitting and walking had a facilitatory effect on rhythmic stepping induced by epidural stimulation.

Moreover, it was possible to show that in the sitting position, with feet above the floor, and stepping movements induced by spinal cord stimulation, if the subject was asked to 'think about enhancing' ongoing rhythmic activity of the lower limbs, this 'mental task' had a marked effect on augmenting the amplitude of ongoing rhythmic activity.[37]

Thus, in all postural conditions in which the lower limbs carry-out swing and pro-gravity movements, or shortening of extremity, rhythmic activity induced by epidural stimulation of the partially isolated lumbar cord can be either facilitated or suppressed.[37] This finding supports the hypothesis that control of postural antigravity and pro-gravity swing movements plays an important role in the interaction with ongoing stepping movements, whereas isolated volitional motor tasks are powerful in cancelling established locomotor-like stepping movements. This hypothesis is supported by independent evidence in studies which show that the outcome of locomotor treadmill training in wheelchair-bound SCI subjects is not determined by the degree of preservation of volitional, isolated movements of muscle groups, but by functional gait if postural control is present, even though control of volitional single motor tasks can be severely diminished.[20]

Conclusion

Can we increase the number of SCI people who will be trained to become ambulatory? The first step will be to further advance acute treatment of SCI and the pharmacological prevention of secondary lesions. We can also introduce into clinical practice a number of treatment procedures based on the neurobiological principle that a part of the recovery process depends upon neuroplasticity and upon specific and nonspecific activities of the uninjured neuronal system. As a whole, we are witnessing the improved outcome of subacute and even chronic SCI thanks to new interactive locomotor training (locomotor training, electrical stimulation and pharmacological substances).[38] Hopefully, in the coming years we shall further enhance in our practice the control of neuronal networks, such as the CPG, when the conducting spinal systems are non- or only partially operational. In addition to approaches based on electrophysiology and neuropharmacology, we should also use emerging neurobiological interventions for rebuilding and reconstructing lost cells and their axons. Contemporary neurorehabilitation programs are continuously making progress and there are more opportunities for clinical researcher to advance knowledge of motor control in SCI subjects. For instance, we have learned from clinical neurophysiological studies of motor control in so-called transected or clinically complete SCI that the tonic features of spinal reflex activity, spasticity and spasms are due to subclinical brain influence mediated through the SCI

zone.[14] These manifestations of unrecognized brain influence on the segmental network have opened new research avenues for the development of methods designed to enhance residual brain influence and restore mobility.[39,40]

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