Evidence for a Spinal Central Pattern Generator in Humans[a]

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ABSTRACT: Non-patterned electrical stimulation of the posterior structures of the lumbar spinal cord in subjects with complete, long-standing spinal cord injury, can induce patterned, locomotor-like activity. We show that epidural spinal cord stimulation can elicit step-like EMG activity and locomotor synergies in paraplegic subjects. An electrical train of stimuli applied over the second lumbar segment with a frequency of 25 to 60 Hz and an amplitude of 5–9 V was effective in inducing rhythmic, alternating stance and swing phases of the lower limbs. This finding suggests that spinal circuitry in humans has the capability of generating locomotor-like activity even when isolated from brain control, and that externally controlled sustained electrical stimulation of the spinal cord can replace the tonic drive generated by the brain.

Is there a central pattern generator (CPG) for locomotion in humans within the lumbosacral spinal cord?[1,2] Definite evidence exists for a CPG for locomotion in lower mammals (cat, rat, rabbit, dog),[3] yet there is only inconclusive evidence for stepping movement in spinal primates.[4] Eidelberg provided evidence that in acute and chronic spinal macaque monkeys it was not possible to evoke locomotor movement.[5] However, Hultborn reported that it was possible to evoke fictive locomotion movement in spinal marmoset.[6]

Bussel discussed indirect evidence for a central mechanism for stepping movements by demonstrating that flexor reflexes in paraplegic subjects have long-latency, late-flexion reflex responses.[7] Rhythmic spinal activity in a patient with clinically complete spinal cord transection was also observed. [8]

Furthermore, it became possible to induce locomotor-like EMG activity, as well as complex bilateral muscle activation of the leg by means of external and manual control of stepping movements in patients with complete paraplegia.[9,10] These findings indicate that the lumbosacral spinal cord in humans, although completely deprived of brain motor control, can respond with a motor pattern underlying locomotion if it is activated by patterned sensory, phasic input from the lower limbs associated with load-bearing stepping.

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An obvious question, then, is whether the human lumbosacral spinal cord isolated from brain control can respond with patterned, stepping movements to an externally generated, sustained, non-patterned electrical train of stimuli delivered via intact segmental input. Such external input might partially replace the missing suprasegmental tonic activity. Under normal conditions, the tonic input necessary for driving lumbosacral CPG for locomotion is generated by brain-stem neurons and mediated by long-descending axons to the interneuronal surface of the lumbosacral spinal cord where it converges with phasic peripheral input.[11]

To address this question, we studied the effect of a train of electrical stimuli applied to the posterior structures of the lumbosacral spinal cord isolated from the brain by accidental injury. 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 spinal cord injury (SCI) and, therefore, it became possible to use the same method in studies of lumbosacral cord mechanisms for locomotion in humans.[12] In this report, we will describe under what conditions spinal cord stimulation of the lumbosacral cord can induce locomotor-like EMG activity and movement of the lower limbs in subjects with chronic, complete paraplegia. The preliminary results of this study were reported at the annual meetings of the Society for Neuroscience.[13,14]

MATERIAL AND METHODS

We examined the locomotor capability of the lumbosacral cord in six individuals with complete SCI by inducing epidural spinal cord stimulation. The inclusion criteria were (1) healthy adults with closed, post-traumatic SCI; (2) more than one year post onset; (3) no antispastic medication; (4) preserved stretch and cutaneomuscular reflexes; and (5) complete absence of volitional or other suprasegmental activation of motor units below the spinal cord lesion confirmed by brain motor control assessment,[15] and presence of surface recorded lumbosacral evoked potentials.[16] According to neurological criteria and the ASIA classification, they were classified as complete SCI or ASIA A category with no motor or sensory functions below the lesion (TABLE 1). Informed consent was obtained from all subjects with the approval of the local Institutional Review Board for Human Research.

In addition, we carried out a neurophysiological evaluation of motor and sensory spinal cord functions. We assessed motor functions by recording motor unit potentials below the level of the lesion with surface EMG electrodes. One pair of recessed, silver-silver chloride surface electrodes was placed 3 cm apart over the midline of the muscle bellies of the quadriceps, adductors, hamstrings, tibialis anterior, and triceps surae muscles of each leg. EMG channels were amplified, processed, and displayed while conducting a standardized protocol for the evaluation of volitional and reflex motor tasks.[15]

We used lumbosacral evoked potentials (LSEP) to assess the functions of the posterior structures and gray matter of the spinal cord. LSEPs were recorded with silver-silver chloride surface electrodes placed at the T12, L2, L4, and S1 spinous processes referenced to an electrode at T6. The characteristic LSEP responses were recorded after tibial nerve stimulation.[16,17] To assess posterior column functions, we used cortical evoked potentials elicited by tibial and peroneal nerve stimulation.[18]

Epidural stimulation was carried out with quadripolar electrodes (Medtronics) placed in the posterior epidural space at vertebral levels T11 through L1 (TABLE 1), and the positioning of the electrode was verified by fluoroscopy. In addition, we elicited muscle twitches by means of an epidural electrode connected to an external stimulator.[19] We increased the amplitude of the stimulus until muscle contractions appeared within the corresponding segmental innervations. We found that these additional neurophysiological criteria were useful in monitoring the relation between the active electrode and the corresponding segmental input-output of the tested spinal cord.[19]

TABLE 1. Clinical Data and Placement of the Epidural Electrode

Subjects Initials	Sex	Date of Birth	Date of SCI	Cause of SCI	Level of SCI	Year of Study	Electrode-Spinal Level
S.W.	M	10/06/53	5/01/90	Plane crash	T4/T5	1995–1996	T11
A.L.	F	5/14/62	11/18/94	Car accident	T4	1996	T11
G.B.	F	2/25/66	1/17/90	Car accident	C5	1995–1996	T10
M.N.	F	2/21/78	12/25/94	Car accident	T3/T4	1996–1997	T12
P.E.	M	3/24/73	8/01/96	Car accident	T3/T4	1997	T11
W.H.	M	5/10/39	7/17/94	Fall from tree	T7/T8	1997	T11

Summary of patient history with information about the placement of the stimulating electrode. All the patients were injured in car accidents, with the exceptions of S.W. (plane crash) and W.T. (fall from tree).

On the day following the placement of the quadripolar electrode, we connected the externally secured 4-electrode leads to the extension lead under sterile conditions. This extension lead was then connected to the external stimulator to generate stimuli of different frequencies and amplitudes.

The quadripolar epidural electrode had four independent stimulating leads, 10 mm apart, which were arbitrarily labeled 0, 1, 2, 3; the lead labeled 0 was on the top of the electrode and the lead labeled 3 on the bottom. We used bipolar stimulation by connecting the cathode and anode to each of the pair of leads. The epidural stimulation protocol was based on testing muscle twitches using each of the available 0–3 leads as a cathode. We then tested the elicited motor output for frequencies from 1–120 Hz, and amplitude from 1–10 V.

Spinal cord motor output was recorded with a pair of surface electrodes as previously described for the electromyographic assessment of motor control of the spinal cord.[15] A pair of electrodes was placed over the thigh and leg muscle groups (quadriceps, adductor, hamstrings, tibial anterior, and triceps surae). Amplified and processed EMG signals were later displayed on a strip chart recorder for further analysis. In order to illustrate our findings, we chose recordings that lasted over 30 s, with findings that remained constant at least on three different occasions throughout the same recording session. Moreover, we also sought to confirm the presence of the same findings in other subjects in the following sessions. We measured the latency time between two bursts of EMG activity. In addition to the EMG recordings, we used a position sensor to record knee movement (Penny & Giles XM-180). During the recording sessions, the subjects were placed in a supine position on a comfortable examination table covered with soft sheepskin to allow smooth flexion/extension movement and minimize friction between the heel and the supportive surface. The typical study session lasted approximately one to two hours, during which time the effect of different sites, strength of stimulus, and frequencies were tested from 1 to 5 min followed by resting periods from 2 to 4 min.

FIGURE 1 illustrates the patient setup with the stimulating electrode placed in the epidural space and recording sites of surface EMG from the thigh and leg muscles of the lower limbs.

RESULTS

In order to study the locomotor capability of the isolated lumbosacral cord, we stimulated the posterior structures of the spinal cord between T10 and S1. We will present our results regarding the optimal site of stimulation, and strength and frequency of stimulation for the elicitation of step-like EMG activity and locomotor-like synergies.

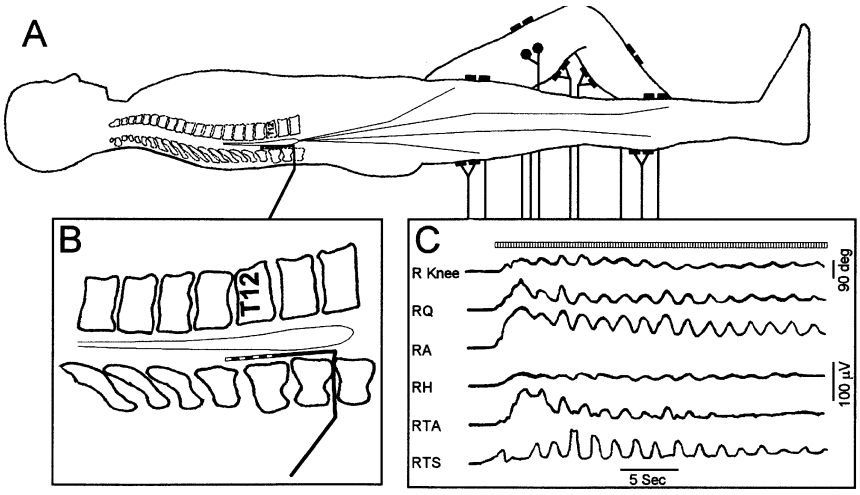

FIGURE 1. Diagrammatic sketch of the experimental design of this study. In (**A**), the subject under examination is in the supine position with the stimulating epidural electrode above the lumbar cord. Pairs of surface electrodes for EMG recording are placed over both quadriceps, adductors, hamstrings, tibial anterior, and triceps surae muscle groups. Diagram of the quadripolar epidural electrode placed within the spinal canal above the posterior lumbar cord structures (**B**); EMG recording of rhythmic activity from the right lower limb during stimulation of the upper segments of the lumbar cord, with position sensor trace recording movement of the knee during flexion and extension of the lower limb (**C**). **C**, upper vertical marker 90 degrees, lower 100 μV.

Site of Stimulation

While seeking the optimal site of stimulation for eliciting rhythmic, step-like EMG activity, we found that by applying a stimulus of 5–9 V, width .2–.5 ms, and frequency between 25 and 50 Hz to the posterior structures of the L2 segment, we could elicit rhythmic, step-like EMG discharges with flexion/extension movements in the lower limbs. However, when we stimulated the site above or below the L2 segment, we elicited either a tonic or rhythmic EMG response, but no locomotor-like activity. In most of our recordings, we stimulated with the epidural electrode the left or right posterior structures of the spinal cord. Only in two recordings, in two subjects, were we able to stimulate the posterior structures symmetrically from the middle portion of the spinal cord. Thus, in the majority of our recordings, we obtained ipsilateral, locomotor-like EMG activity in the lower limbs (FIG. 2A and B).

In FIGURE 2A, a stimulus of 5.5 V, applied with a train of 25 Hz over the left side of the posterior L2 structure, elicited characteristic locomotor-like EMG activity in all the recorded muscle groups of the left lower limb. When the stimulating electrode was applied over the right L2 posterior structures of another subject with a stimulus strength of 9 V and a train of 30 Hz, rhythmic locomotor-like EMG activity and movement were induced in the right lower limb. Instead of the previous contralateral tonic activity seen in FIGURE 2A, FIGURE 2B shows EMG responses of lower amplitude and synchronous bursts of activity in all muscle groups with a frequency of approximately .4 Hz.

To demonstrate the importance of selecting the appropriate site of stimulation of the L2 segment to elicit locomotor-like activity, we have shown and compared in FIGURE 3 the results achieved by stimulating the T10 and L2 segments in the same subject during the

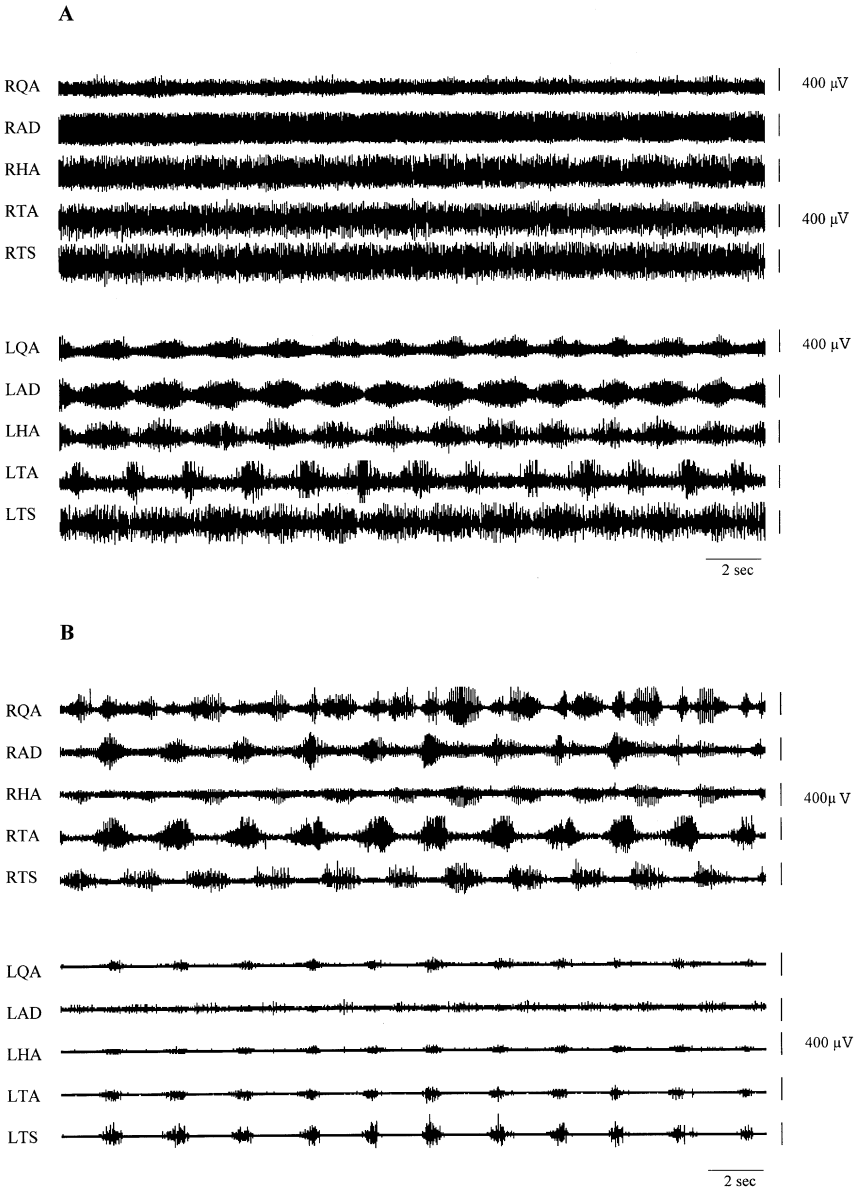
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FIGURE 2. Illustration of rhythmic and tonic activity during spinal cord stimulation above the L2 segment and EMG recording from five muscle groups of the lower limbs (Q, quadriceps; A, adductor; H, hamstring; TA, tibial anterior, and TS, triceps surae). FIGURE 2A illustrates locomotor-like EMG activity in the left lower limb with bursts of EMG activity of approximately .4 Hz in response to epidural stimulation with a train of stimuli of 25 Hz and 5.5 V. The contralateral right lower limb responded to the stimulus over the left side of the posterior cord with tonic EMG activity (subject W.H.). FIGURE 2B illustrates locomotor-like EMG activity in the right lower limb with a frequency of approximately .3 Hz in response to epidural stimulation with a train of stimuli of 30 Hz and 9 V above the L2 segment on the right side. Simultaneous contralateral recording of EMG responses with lower amplitude and synchronous bursts of activity in all muscle groups with a frequency of approximately .4 Hz (subject P.E.). The time marker is 2 s, the vertical marker for amplification is 800 μV, with the exception of RQA, RTA, LQA (FIG. 2A) and RHA, LHA (FIG. 2B), for which the vertical marker for amplification is 400μV.

same recording session. The epidural electrode was situated so that the stimulating lead 0 was placed over the right side of the T10 posterior structure and the stimulating lead 3 over the L2 posterior structure. It can be seen that when the thoracic segment was stimulated, we elicited rhythmic but irregular flexor withdrawal movements in the right limb (FIG. 3A). Only four segments lower, the same stimulus induced well organized locomotor-like EMG activity of approximately .5 Hz, and flexion and extension movement of the lower right limb (FIG. 3B).

Strength of Stimulation

When the stimulating electrode was placed over the optimal site of stimulation of the L2 segment, we applied a constant train of stimuli of 30 Hz and progressively increased the strength of stimulation from 0 to 9 V. As can be seen in FIGURE 4, at the level of 3.5 V we obtained low amplitude EMG activity within the quadriceps and adductor muscles. With a further increase in stimulus strength to 4 V, tonic EMG activity increased in amplitude and also appeared in the hamstring muscles. An additional increase of stimulus strength to 4.5 V activated EMG activity in the tibial anterior and triceps surae muscles of smaller amplitude than the ongoing tonic EMG activity in the quadriceps, adductor, and hamstring muscles. Another increase in stimulus strength to 5 V replaced tonic activity with rhythmic and locomotor-like EMG activity, as well as flexion/extension movement in the lower limbs. Finally, a slight increase to 5.5 V generated well-organized patterns of rhythmic, locomotor-like activity and flexion/extension movement. After locomotor activity was established in the limbs, a decrease in stimulus strength resulted in a reverse sequence of EMG events from rhythmic, locomotor-like activity to progressively decreasing amplitude of tonic activity in a reduced number of muscle groups. This stimulus-dependent EMG as well as movement responses are shown in FIGURE 4. This finding could be repeated in the same subject in the same study session, during different sessions, as well as in different subjects.

We have already seen in FIGURE 4 that after the threshold for locomotor-like activity was reached, a slight increase in the strength of stimulation contributed to the organization of rhythmic activity. In order to study the effect of a marked change in stimulus strength, we elicited locomotor-like activity and tested the effect that was induced by changing stimulus strength from 6 to 9 V while maintaining the same frequency of 30 Hz (FIG. 5). We also observed during continuous stimulation from 30 to 60 s, with stimulus strength of 5–6 V effective in inducing rhythmic activity, that the amplitude of EMG responses would progressively decrease. This declining amplitude of EMG responses could be enhanced by a further increase in stimulus strength but, again, this effect would only last for a limited period from 30 to 60 s. So far, we have not examined systematically the relationship

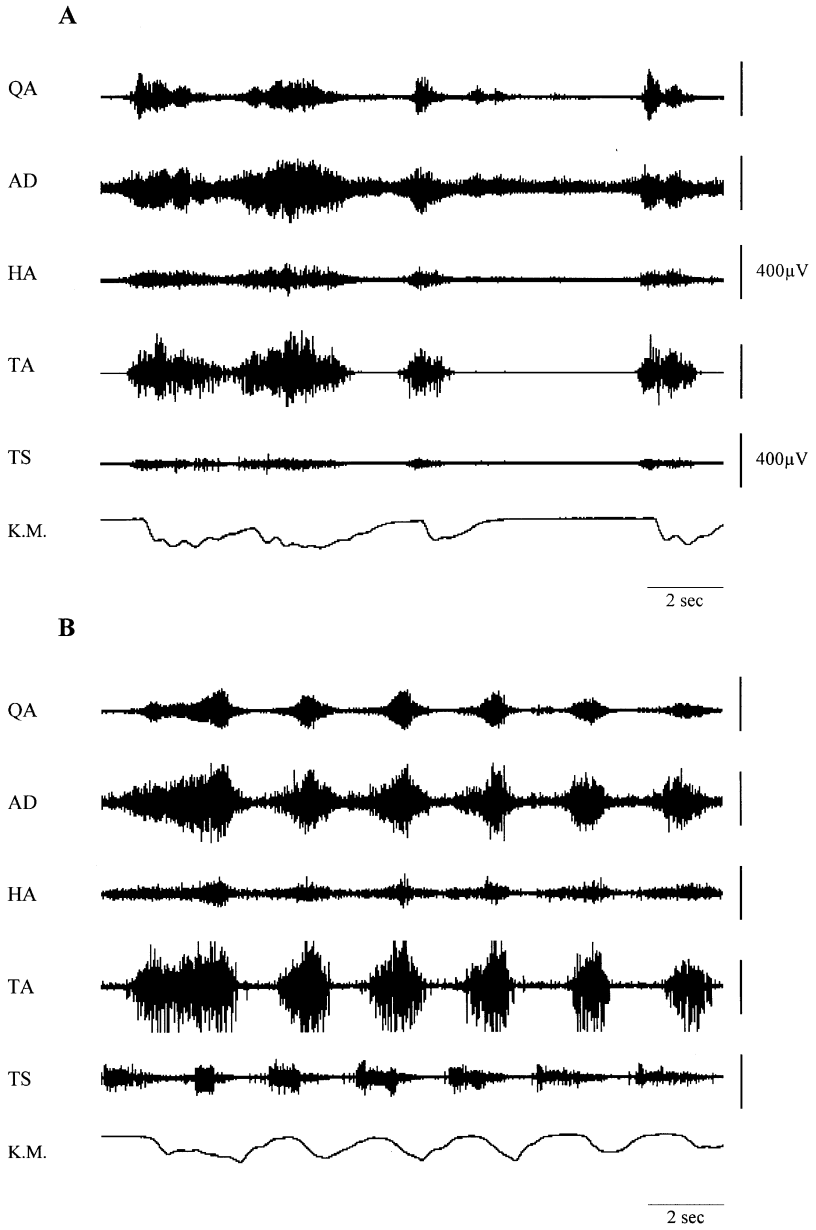


FIGURE 3. Surface EMG recording from the right quadriceps, adductor, hamstrings, tibial anterior, and triceps surae as well as recording of knee movements (subject P.E.). Illustration of irregular, rhythmic, synchronized EMG activity in all muscle groups of the right limb in response to stimulation of T10 with a train of stimuli of 80 Hz and 9 V. In FIGURE 3B, the stimulus site shifted from T10 to the L2 segment with unchanged frequency and stimulus strength, which induced locomotor-like activity of approximately .3 Hz. The time marker is 2 s, the vertical marker for amplification is 800 μV, with the exception of HA, TS (FIG. 3A), for which the vertical marker for amplification is 400 μV.

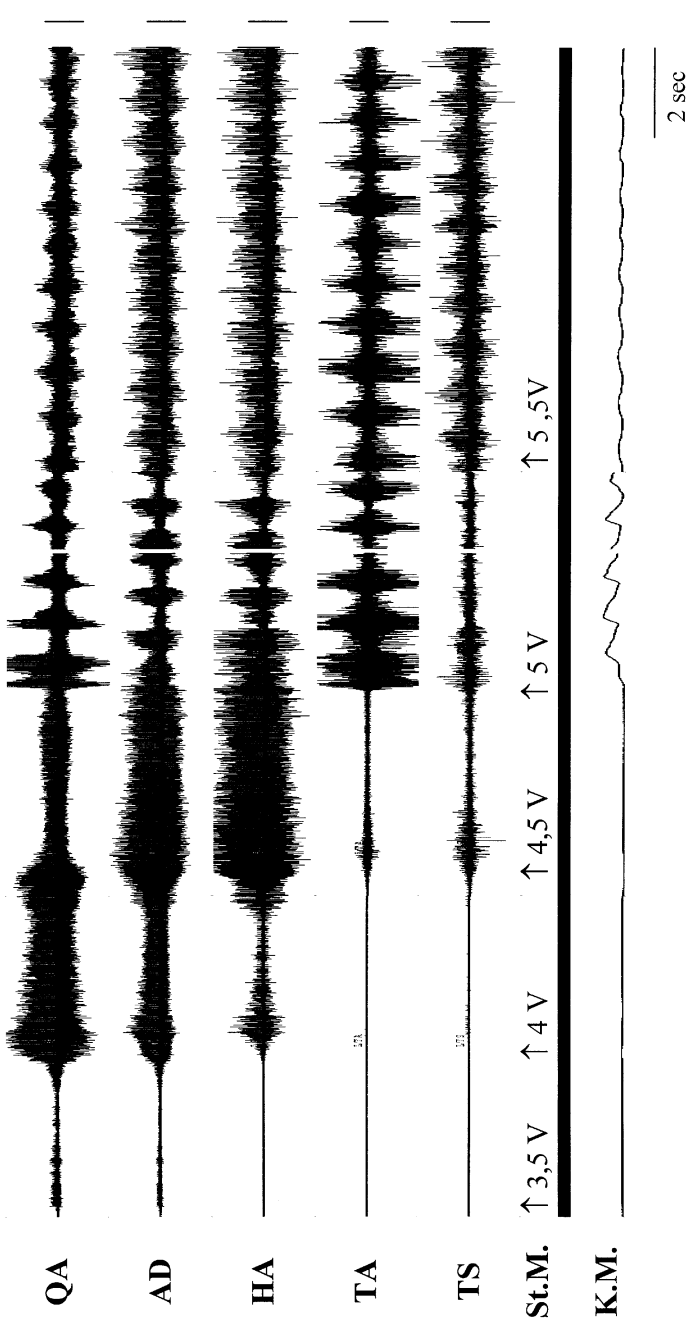


FIGURE 4. Surface EMG recording from the right quadriceps, hamstrings, tibial anterior, triceps surae, and flexion/extension movement recorded with a position sensor from the right lower limb in a complete SCI subject (W.H.). Records illustrate the effect of a progressive increase in stimulus strength from 3.5 to 5.5 V and a train of 30 Hz over the right L2 posterior structures. EMG tonic output was replaced by locomotor-like activity of approximately .7 Hz after stimulus strength reached 5 and 5.5 V. The time marker is 2 s, and the vertical marker is 400 μv.

between stimulus strength, duration of continuous stimulation, and behavior of elicited rhythmic responses.

FIGURE 5A illustrates a recording of rhythmic locomotor-like activity with stimulus strength of 6 V, whereas FIGURE 5B shows rhythmic locomotor-like activity with stimulus strength of 9 V. It is apparent that an increase in stimulus strength altered the amplitude, duration of the EMG bursts of activity, as well as the rhythmicity of locomotor flexion and extension movement. Thus, a large increase in stimulus strength from 6 to 9 V can modify the components of locomotor-like activity, but basic and rhythmic activity are preserved.

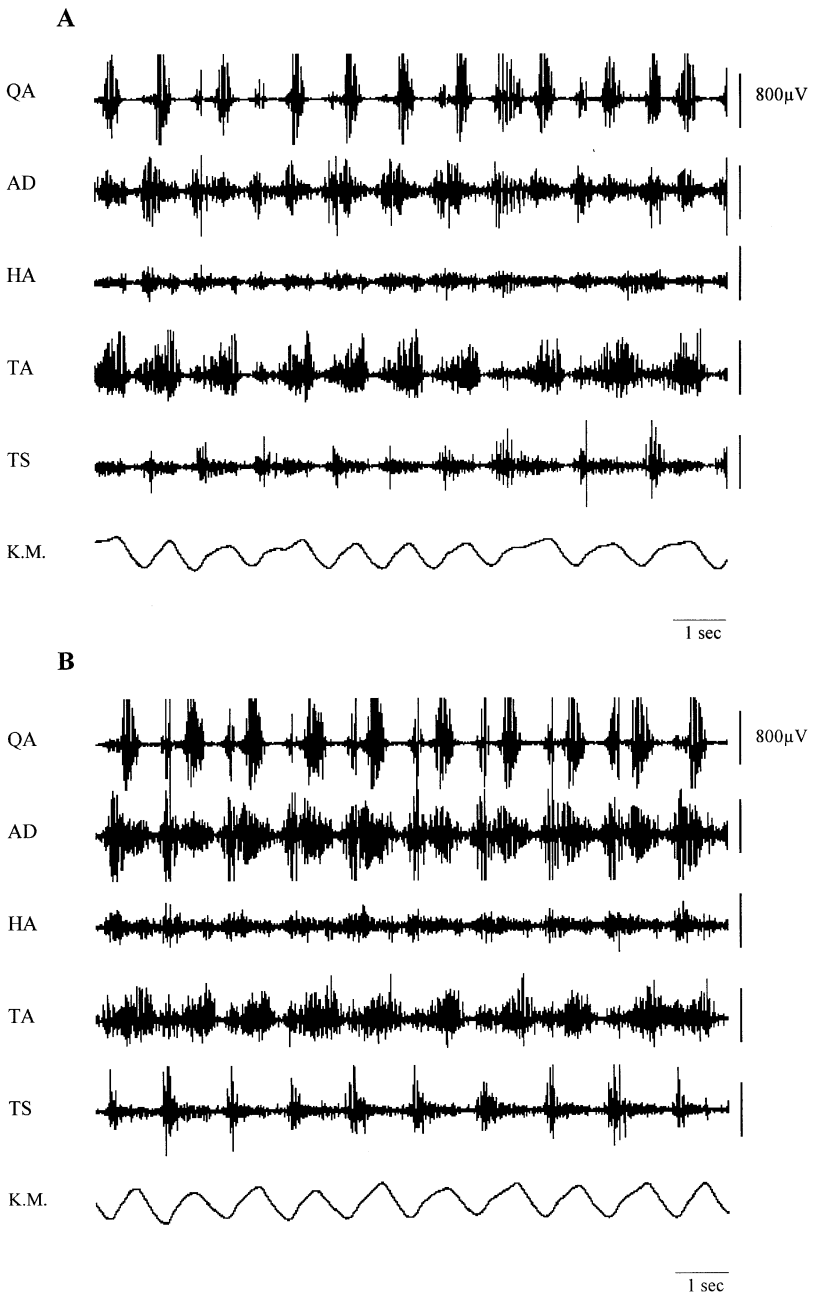
In FIGURE 6, we illustrated the mean values of interburst latency time between the onset of two EMG bursts of activity, interburst latency, for the tibialis anterior and the triceps surae during the same recording session, as shown in FIGURE 5. We can see in FIGURE 6 that interburst latencies for the tibial anterior and triceps surae progressively decreased while stimulus strength increased and the train of stimuli remained constant at 30 Hz. In the same subject, but in another session, when the stimulus strength was 5 V, the interburst latency for the tibial anterior was 1.8 ± 0.58 during 34 s; when the stimulus strength was 6 V, the interburst latency was 1.48 ± 0.30 during 30 s; with stimulus strength of 7 V, the interburst latency was 1.34 ± 0.24 during 34 s; with stimulus strength of 8 V, the interburst latency was 1.29 ± 0.16 during 33 s. Thus, a stronger stimulus can increase the frequency of rhythmic responses.

We observed that when we stimulated the posterior L2 structure, the threshold for tonic EMG activity was lower than the threshold for rhythmic activity. Once rhythmic activity was developed, there was a relatively wide range in which the stimulus strength could modify the components of rhythmic activity.

Frequency of Stimulation

We found that by applying a train of stimuli of 25–50 Hz within the L2 segment, with stimulus strength of 5–9 V, it was possible to elicit rhythmic locomotor-like EMG activity and movement in the lower limbs (FIG. 7A). A characteristic recording of locomotor-like activity in the quadriceps, adductor, hamstring, tibial anterior, and triceps surae of the left lower limb is shown in FIGURE 7A. This response was induced by a stimulus of 7 V with frequency of 30 Hz. When we altered the frequency from 30 to 120 Hz without changing the stimulus strength or stimulus site, the previous locomotor like activity was replaced by tonic EMG activity. (FIG. 7B). The effect of altered frequency from 30, 50, 70 and 90 Hz on interburst latency time for the tibial anterior and triceps surae is shown in FIGURE 8. We can see that by increasing the frequency of the train of stimuli and maintaining constant the site and strength of stimulation, the interburst latency of the tibial anterior and triceps surae muscles increased. Thus, the change of frequency within the range of 30–70 Hz induced locomotor-like activity by steadily decreasing the frequency of bursts of EMG activity.

FIGURE 5. Surface EMG recording from the right quadriceps, adductor, hamstrings, tibial anterior and triceps surae and knee flexion/extension in a complete paraplegic (subject P.E.). FIGURE 5A shows locomotor-like bursts of EMG activity of approximately .9 Hz, and FIGURE 5B similar activity with a frequency of .8 Hz. Epidural stimulation was applied over the right posterior structure of L2 with a train of 30 Hz and stimulus strength of 6 V (**A**) and 9 V (**B**). The bottom trace in **A** and **B** is the position sensor indicating that deflexion up is flexion, and deflection down extension of the lower limb. The time marker is 1 s, and the vertical marker is 400 μV, with the exception of QA (FIG. 5A) and QA (FIG. 5B) for which the vertical marker for amplification is 800 μV.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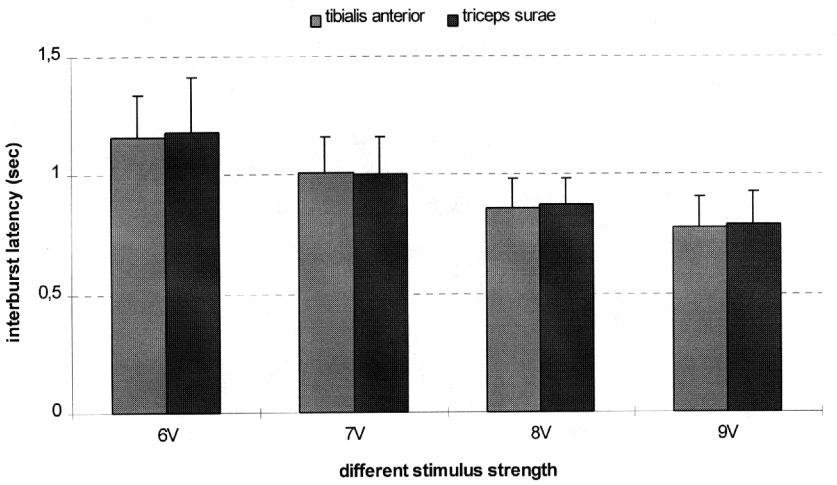


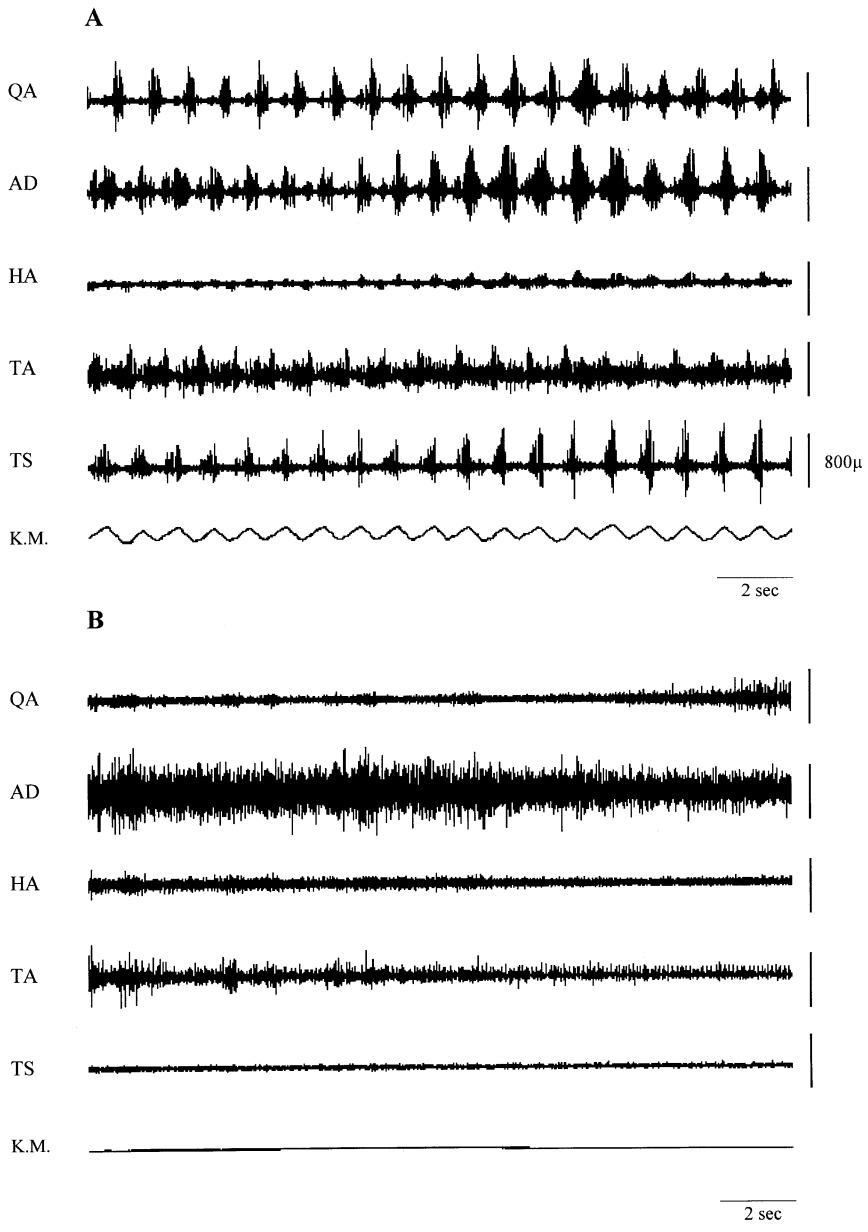
FIGURE 6. Graphic representation of latency time between the onset of two bursts of activity for the tibial anterior and the triceps surae during locomotor-like activity shown in FIGURE 5. Every bar shows the mean value of interbust latencies in seconds with standard deviation of 10 readings and stimulus strength of 6, 7, 8, and 9 V.

In summary, we found that in all the complete SCI subjects studied, it was possible to induce locomotor like EMG activity and movement in the lower limbs when a train of electrical stimuli was applied to the second lumbar segment with a stimulus strength between 5 and 9 V and a frequency from 25 to 50 Hz.

DISCUSSION

A variety of motor responses have been recorded electromyographically in humans, whose spinal cord was isolated either partially or completely from brain control, after muscle stretching, electrical stimulation of peripheral nerve afferents, and other kinds of cutaneous stimulation.[20] Peripheral and central mechanisms of spinal reflex activity were extensively studied in humans which led to a better understanding of the features of motor control in humans with complete, discomplete, and incomplete spinal cord lesions.[21,22] However, it was not possible to demonstrate the locomotor capability of the human lumbosacral spinal cord isolated from brain control until the paralyzed SCI underwent treadmill training with partial weight support.[23] During manually assisted stepping on the treadmill, clinical researchers recorded in subjects with thoracic spinal transection EMG bursts which were temporarily synchronized to the swing and stance phase of the step

FIGURE 7. Characteristic recording of locomotor-like activity during low frequency stimulation and tonic activity during higher frequency stimulation. In (**A**), locomotor-like EMG activity in the quadriceps, adductor, hamstring, tibial anterior, and triceps surae of the left lower limb (subject P.E.) induced by a stimulus of 7 V and 30 Hz. (**B**) Shows the effect of increased frequency of stimulation from 30 to 120 Hz with stimulus strength maintained at 7 V. Previous locomotor-like EMG activity was replaced by tonic EMG activity. The last bottom trace is the position sensor recording knee movement with deflexion up indicating extension of the lower limb, and the opposite with deflexion down. The time marker is 2 s, and the vertical amplification is 200 μV, with the exception of TS (FIG. 7A), for which the vertical marker for amplification is 800 μV.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cycle, and modulated by varying treadmill speeds and level of loading.[10] This finding suggested that when patterned afferent input was induced by external movement of the lower limbs, the central network of the lumbosacral spinal cord was able to respond with patterned, basic locomotor synergy in which each muscle displayed its own characteristics during the stepping cycle and generated rhythmic, locomotor-like EMG activity. In addition to peripheral input, central input to the lumbosacral cord was present under normal conditions and absent in the subjects with complete SCI.

Is it possible to initiate locomotor-like activity in paraplegic patients by means of non-patterned, direct electrical stimulation of the posterior structures of the spinal cord? The answer to this question has been sought in the acute and chronic low-spinal kitten and the acute spinal cord–transected adult cat. In both studies it has been shown that non-patterned electrical stimulation of the lumbosacral enlargement can induce hindlimb stepping.[24,25] Therefore, when electrical stimulation applied to the human spinal cord became a clinical method for the control of spasticity, we introduced this method of direct electrical stimulation of the posterior structures of the spinal cord in order to examine the locomotor capability of the spinal cord in paraplegics.[26]

The subjects we examined had no supraspinal control, which we interpreted as meaning that brainstem-originated, phasic and tonic activity from the peduncolopontine nucleus and mesencephalic locomotor regions had been abolished by accidental SCI.[27] One of the missing components of this putative phasic and tonic supraspinal input was replaced with tonic input generated by an electrical stimulus of 25–50 Hz. Thus, under the influence of this externally generated tonic segmental afferent input, we showed that in subjects with complete SCI, the lumbar cord was capable of initiating locomotor-like EMG activity and stepping movements, whereas when the spinal cord was connected to the brain, this function was controlled by the brain stem.[28]

This finding led us to consider our observations as further evidence for the existence of a CPG in the human spinal cord, as was shown in the cat and other experimental animal mod-

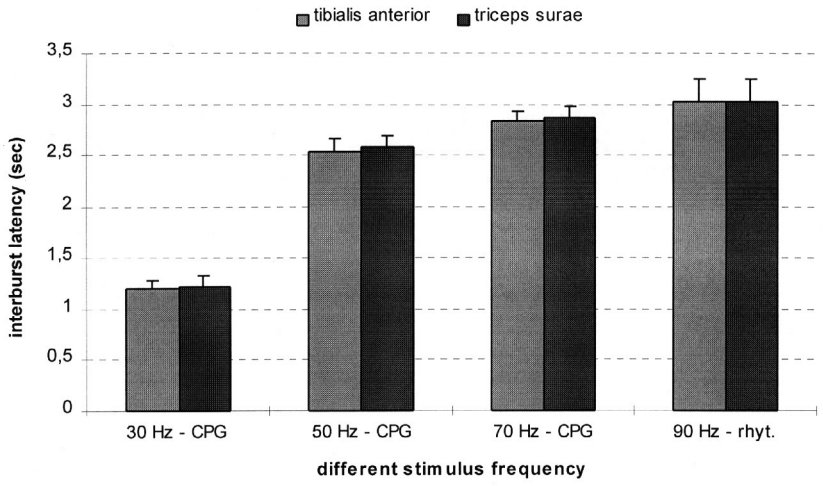

FIGURE 8. Graphic representation of the effect of different stimuli frequencies on the latency time between the onset of two EMG bursts (interburst latency) of the tibial anterior and triceps surae while changing stimulus frequency from 30 to 50 and 70 Hz. Individual graphs show the mean value of 10 measured interburst latency times.

els on the basis of so-called fictive locomotion.[24] During fictive locomotion in the animal experimental model, patterned, locomotor-like activity was recorded by electroneurograms from the anterior roots under pharmacological or electrical stimulation of central nervous system structures of the decerebrate and/or spinalized lumbar spinal cord, while peripheral segmental input was removed by posterior rhizotomy or by curare-induced muscle paralysis. The model for fictive locomotion in humans with SCI has not yet been established, yet we have observed in our study that the isolated lumbosacral cord can respond to non-patterned segmental input with locomotor capacity. We concluded that when the integrity of segmental input-output is preserved, the lumbosacral cord network mechanism determining the temporal pattern of rhythm generation and motor output shaping can initiate and maintain locomotor-like activity in response to non-patterned, segmental stimulation of a particular site, with specific strength and frequency. Consequently, the initiation of movement might be due to the activation of neurons of the locomotor CPG by a train of stimuli and later, additional peripheral input. However, this locomotor activity decreases in amplitude and is limited in duration to a few minutes, probably as a result of the lack of modulatory capabilities of the serotonergic and adrenergic descending pathways originating in the brain-stem nuclei which normally serve as "global" transmitter systems in gain, setting sensory and motor output.[29] Supportive evidence for this proposed explanation of the human SCI injury model can be found in reported recordings of low amplitude, rhythmic EMG activity in subjects with complete SCI, as opposed to higher amplitude EMG activity in incomplete SCI subjects during treadmill training with partial body weight support.[10] Furthermore, in subjetcs with complete SCI, EMG amplitude clearly increased during the stance phase in the antigravity leg muscles after the intrathecal injection of ephedrine, an adrenergic substance.[9]

We have shown in this study that the isolated lumbosacral spinal cord has the capability of responding with a variety of patterns of motor activity which depend upon the site and stimulating parameters. When the upper segments of the lumbosacral spinal cord (L2) were stimulated with a train of stimuli below 25 Hz and stimulus strength below 5–6 V, we were successful in inducing tonic motor output more pronounced on the right or left side depending on the site of stimulation of the posterior spinal cord structures. When we increased the frequency of the stimulus above 25 Hz and the strength of the stimulus above 5 V, tonic motor output was replaced by rhythmic activity. This rhythmic EMG activity revealed a feature of locomotor-like EMG activity and stepping movement or some other feature of alternating and synchronized EMG activity. With an increase above 100 Hz, the previous locomotor-like activity was replaced with tonic motor output. Therefore, the efficacy of stimuli for eliciting locomotor-like activity depended upon repetition of stimulation and the strength of the stimulus. When the same stimulating parameters were applied above or below the upper lumbar segments, we were able to record tonic or rhythmic activity, but no locomotor-like stepping movements. These findings suggest that within the upper lumbar segments there are neuronal structures that respond with step-like activity and movement to non-patterned electrical stimulation with a frequency of .2–.5 Hz and stimulus strength between 5 and 9 V. It is possible that external input to the L2 segment might activate command neurons which can then recruit interneurons involved in rhythm generation. However, further studies will be necessary to describe the neuronal organization of the CPG for locomotion in the human lumbosacral cord.

The importance of peripheral input to the upper segments for the initiation of locomotor movement can be found in the demonstration that input from the hip afferents can elicit cyclic movement in humans. It has been reported that hip extension at the end of the stance phase during treadmill training can induce involuntary hip flexion and initiate the swing phase.[10] Moreover, in a case study of a subject with incomplete chronic SCI with hip pain, the subject developed alternating flexion and extension of the lower extremities during

locomotor training as long as the hip was placed in extension. This movement pattern disappeared if hip pain was temporarily abolished by xylocaine infiltration.[30] In another study on how the human spinal cord interprets peripheral input, the authors found that hip-joint position could have an important effect on EMG amplitude.[31] Therefore, it is not surprising that we were successful in eliciting locomotor activity also by means of non-patterned stimulation of the upper lumbar segments of the spinal cord.

Thus far, our study does not allow us to determine with accuracy which posterior structure of the spinal cord we are stimulating. There is evidence that epidural spinal cord stimulation is likely to stimulate dorsal root fibers as well as dorsal column fibers, and that threshold stimuli of dorsal root fibers are lower than the threshold of dorsal column fibers.[32] Our finding that effective stimulus strength for rhythmic activity was much higher than for tonic activity suggests that we need to stimulate both low and high threshold nerve fibers in order to induce patterned motor activity. We also learned in this study that asymmetrical epidural stimulation of one side of the posterior structure of the spinal cord will only elicit ipsilateral locomotor-like rhythmic activity. Only in two of our subjects were we able to place the stimulating electrode at an approximately equal distance from both sides of the posterior structures of the spinal cord and elicit bilateral and coordinated alternating stepping movement of both legs. Thus, further studies are necessary to define the unilateral and bilateral capabilities of neuronal control for locomotion in the human isolated spinal cord.

Locomotor training, pharmacology, and functional electrical stimulation can gradually improve locomotor capability in subjects with incomplete, subacute, and chronic SCI.[33] Thus, spinal plasticity after incomplete spinal cord lesion with preserved residual brain control can contribute to the improvement of the functional outcome in wheelchair and ambulatory people with SCI.[34] The next question to be addressed is whether long-term changes in plasticity can be induced and retained after "interactive locomotor training" with additional externally generated tonic afferent input to the human lumbar cord completely isolated from brain influence. Experimental evidence exists for use-dependent plasticity in spinal stepping and standing in the cat spinal cord after complete spinal cord transection at a low thoracic level which can be further enhanced by pharmacological manipulation.[35] We have provided evidence that in complete paraplegics it is possible to induce and modify ongoing locomotor-like activity with non-patterned stimulation of the upper segments of the lumbosacral cord. This finding opened an opportunity to further examine neurocontrol mechanisms for locomotion.

The findings we report in this study can offer new strategies for the restoration of locomotion in paralyzed SCI people. The method we have described for the substitution of missing brain control to the spinal cord to support locomotion or activity would be of practical value as a neuroaugmentive procedure for CPG activity in subjects with incomplete lesions. In our ongoing study with ambulatory SCI subjects we showed that spinal cord stimulation of the lumbosacral spinal cord can increase locomotor capacity. Finally, this is a procedure that can be developed for clinical use within programs based on the repertoire of interactive locomotor training, pharmacological and functional electrical stimulation.[36] Thus, activity-dependent and injury-induced plasticity can lead to the further improvement of locomotor activity in people with SCI.[37]

SUMMARY

Spinal cord stimulation of the upper segments of the lumbosacral cord in complete paraplegics elicited locomotor-like EMG activity and stepping movement. We induced rhythmic locomotor activity by placing a quadripolar stimulating electrode in the epidural space and applying an electrical train of stimuli of 25–50 Hz, with stimulus strength from

5 to 9 V, to the posterior structures of the second lumbar segment. While stimulating the other segments with an effective train of stimuli that elicited locomotor activity, we were able to generate rhythmic activity with synchronized EMG discharges and repetitive withdrawal, flexor movement in the lower limbs. Tonic EMG activity was elicited by stimulating the same spinal cord structure using different stimulating parameters. We discussed that when the integrity of segmental input-output was preserved, the lumbosacral network mechanism determining the temporal pattern of rhythm generation and motor output shaping was able to initiate and maintain locomotor-like activity in response to non-patterned stimulation of a particular site according to specific strength and amplitude of frequency. Our findings indicate that initiation of movement is probably due to the activation of the neurons of the locomotor CPG by a train of stimuli, followed by additional peripheral input. We concluded, therefore, that both patterned and non-patterned input to the neuronal network generated locomotor-like activity. This led us to propose that a difference exists between peripheral and central input to the CPG, but once the generator for locomotion is activated, then the system of spinal neurons coordinates movement in the lower limbs while developing locomotor synergies.

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