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Spinal Cord Stimulation-Induced Locomotion in the Adult Cat

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IWAHARA, T., Y. ATSUTA, E. GARCIA-RILL AND R. D. SKINNER. *Spinal cord stimulation-induced locomotion in the adult cat.* BRAIN RES BULL **28**(1) 99–105, 1992.—Epidural and subdural stimulation of the dorsal surface of the spinal cord was found to elicit locomotion in the decerebrate cat in the active and fictive locomotion preparations. Stimulation of the cervical enlargement induced stepping in all four limbs, while stimulation of the lumbosacral enlargement induced hindlimb stepping. Lumbosacral enlargement stimulation induced hindlimb locomotion starting four hours following an acute midthoracic spinal cord transection. The preservation of the overall locomotor pattern and relationships between muscle groups, and of coordination between hindlimbs following transection, suggests that lumbar enlargement stimulation may be activating an intrinsically organized system. These findings suggest a method which may be applied clinically for the induction of limb alternation following epidural stimulation of the spinal cord.

Spinal cord Decerebrate Locomotion Spinal transection Epidural stimulation Cat

PREVIOUS studies have shown that spontaneous locomotion is evident in precollicular-premammillary transected cats (21, 22, 29), but locomotion must be induced by stimulation of certain brain stem structures in precollicular-postmammillary transected animals (18, 26, 30). These findings suggest that supraspinal structures are capable of inducing stepping by activating spinal elements in the decerebrate preparation. If the lower thoracic spinal cord is transected in the neonate cat, the hindlimbs appear able to generate well-coordinated stepping later in life without the need for electrical stimulation (13, 14, 19). However, in the case of an acute spinal transection, no locomotion is evident unless pharmacological stimulation (e.g., L-DOPA) is used (12,23). Stimulation of the dorsal columns or dorsal roots bilaterally also has been used to induce stepping in the L-DOPA treated, acute spinal cat preparation, either deafferented or paralyzed (6,23). These findings suggest that, even in the absence of supraspinal influence, spinal structures retain the capability of stepping under certain circumstances such as early spinalization, pharmacological activation or combined electrical and pharmacological stimulation.

The following series of studies was undertaken to determine if direct stimulation of the spinal cord by itself could be used to elicit locomotion in the a) decerebrate, b) midthoracic transected, c) active locomotion and, d) fictive (paralyzed) locomotion preparations. The underlying purpose of this approach was to determine the essential parameters of stimulation for inducing locomotion following both subdural and, especially, epidural stimulation of the spinal cord with a view toward designing a prosthetic device for eliciting stepping after spinal cord injury. Preliminary evidence has been reported (16). As a result of the findings described herein, a patent has been granted for a method and device for inducing locomotion by electrical stimulation of the spinal cord (17).

METHOD

Surgical Preparation

A total of 26 adult cats (3–4 kg) were anesthetized with halothane during surgical procedures. Following tracheal intubation, ligation of the carotid arteries and cannulation of one femoral vein, a precollecular-postmammillary brain stem transection was carried out using suction ablation. The head was fixed in a stereotaxic frame and partial laminectomies were performed between the C_4 and C_7 vertebrae as well as between the L_1 and L_6 vertebrae. Stimulation of the spinal cord was carried out using plate electrodes composed of a 100 μm insulated nichrome wire attached to a rectangular stainless steel plate (2 mm long by 1.2 mm wide, resistance 25 kohm) which was inserted along the midline between the remaining portion of each vertebra and the dorsal surface of the spinal cord. Stimulation was applied both epidurally and subdurally along spinal cord segments C_4 to C_8 and L_1 to L_6. In 14 animals actual locomotion was tested by suspending the body in a sling with the limbs touching a moving treadmill. In a few cases (3/14), only one enlargement was stimulated (see below).

Recording Procedures

Electromyographic (EMG) recordings were carried out using double hooked wire electrodes inserted into the triceps muscle

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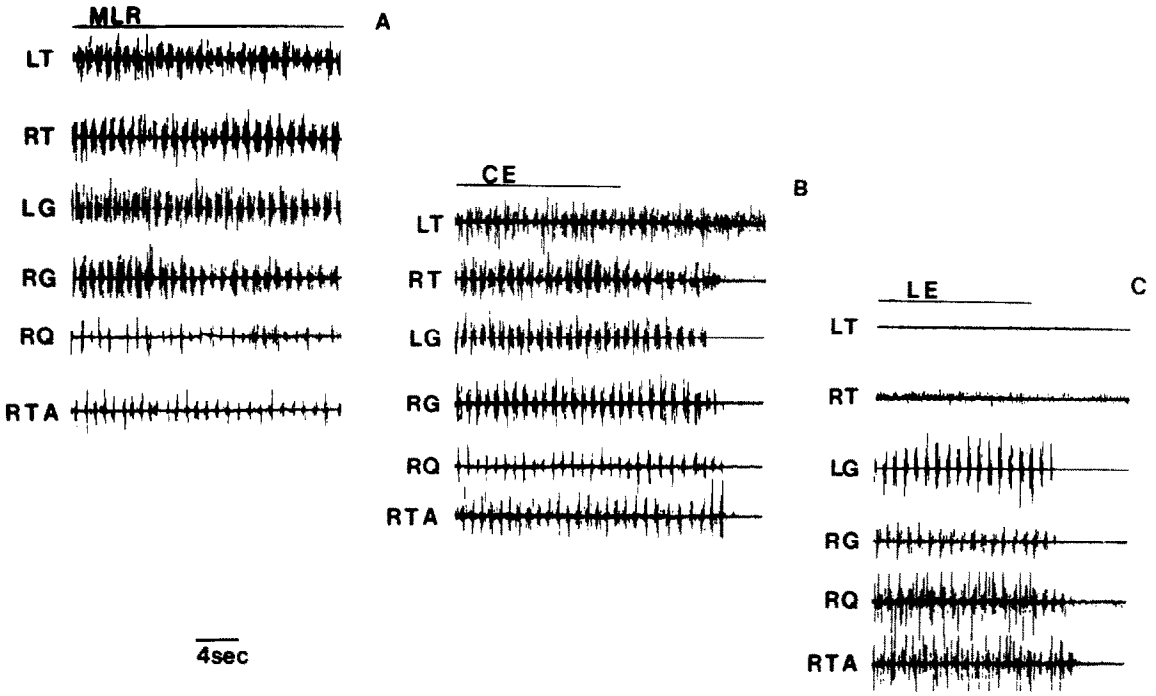

FIG. 1. Supraspinal and spinal stimulation-induced locomotion. (A) Stimulation of the MLR induced well controlled locomotion as evidenced by EMGs from the left and right triceps muscles (LT, RT) of the forelimbs, the left and right (ankle extensor) gastrocnemius muscles (LG, RG), the right (knee extensor) quadriceps (RQ) and the right (ankle flexor) tibialis anterior (RTA). (B) Stimulation of the CE induced a similar locomotor pattern in the same muscles. Note the continuation of stepping beyond the delivery of stimulation as denoted by the bar at the top of the records. (C) Stimulation of the LE induced no alternation in the forelimbs (LT, RT), but an organized pattern of stepping was evident in the hindlimbs, even after the end of stimulation. Calibration bar 4 s all records.

in each forelimb (extensor) and the lateral gastrocnemius (ankle extensor) and tibialis anterior (ankle flexor) muscles in each hindlimb. Recordings of the quadriceps muscle (knee extensor) also were carried out in each hindlimb. In 12 animals, fictive locomotion was tested after inducing paralysis with gallamine triethiodide (initial dose 16 mg/kg, maintenance dose 8 mg/kg/h) followed by artificial ventilation. In a few cases (3/12), only one enlargement was stimulated (see below). Neurographic (NG) activity was recorded with double hooked silver wire electrodes on small branches of the tibial nerve (containing branches innervating the medial or lateral gastrocnemius muscle) and of the peroneal nerve (innervating flexor muscles) in each hindlimb. Stimulation of the lumbar spinal cord was carried out in some active locomotion (n = 6) as well as fictive locomotion (n = 5) preparations after performing a midthoracic spinal cord transection using suction ablation. The completeness of the transection was assessed visually as a 5-mm gap between proximal and distal ends of the spinal cord.

Stimulation Procedures and Data Analysis

At least one hour elapsed after the cessation of anesthesia before stimulation was applied. Stimuli were delivered bipolarly between plate electrodes on adjacent segments or monopolarly with each plate electrode referred to the neck muscles. A monopolar electrode was inserted stereotaxically into the mesencephalic locomotor region (MLR) in order to compare MLR stimulation-induced locomotion (stereotaxic coordinates P 1.5, L 4.0, H −1). EMGs, NGs, and stimulus pulses were recorded on FM tape for off-line analysis. Statistical comparisons of thresholds and durations were carried out using a Student's *t*-test.

RESULTS

Stimulation of the Cervical Enlargement

Stimulation of the cervical enlargement (CE) was carried out in 11 active locomotion preparations. Stimulation applied at the preenlargement C_4 segment was as effective as that applied to the C_5–C_8 segments in inducing coordinated stepping. Stimulation of high thoracic (T_1 and T_2) segments was not effective in producing low threshold locomotion. In 10 of 11 cases, electrical stimulation of the CE induced locomotion at low current amplitudes (mean and S.D. 90.4 ± 72.9 μA, range 40–280 μA). The most effective current amplitudes (and frequencies) were not significantly different (*t*-test) for epidural and subdural stimulation (95.1 ± 75.8 μA and 48.0 ± 10.1 μA, respectively). The optimal location for the plate electrodes was along the midline, overlying the dorsal columns. In cases in which the plates were placed overlying the dorsal root entry zone, coordinated stepping was evident although with greater activation of the ipsilateral limbs. In one case, stimulation of the CE failed to elicit stepping, possibly due to inadvertent compression of the CE during surgery. Electrical stimulation typically induced stepping 2–10 s after its onset and locomotion could be maintained from 30 s to 5 min of continuous, low frequency, low amplitude stimulation. In a few cases (3/11), CE stimulation produced stepping for several (5–15 s) seconds beyond the end of current application. These observations suggest that a certain period of "recruiting" time is required upon stimulation and before stepping ensues, a

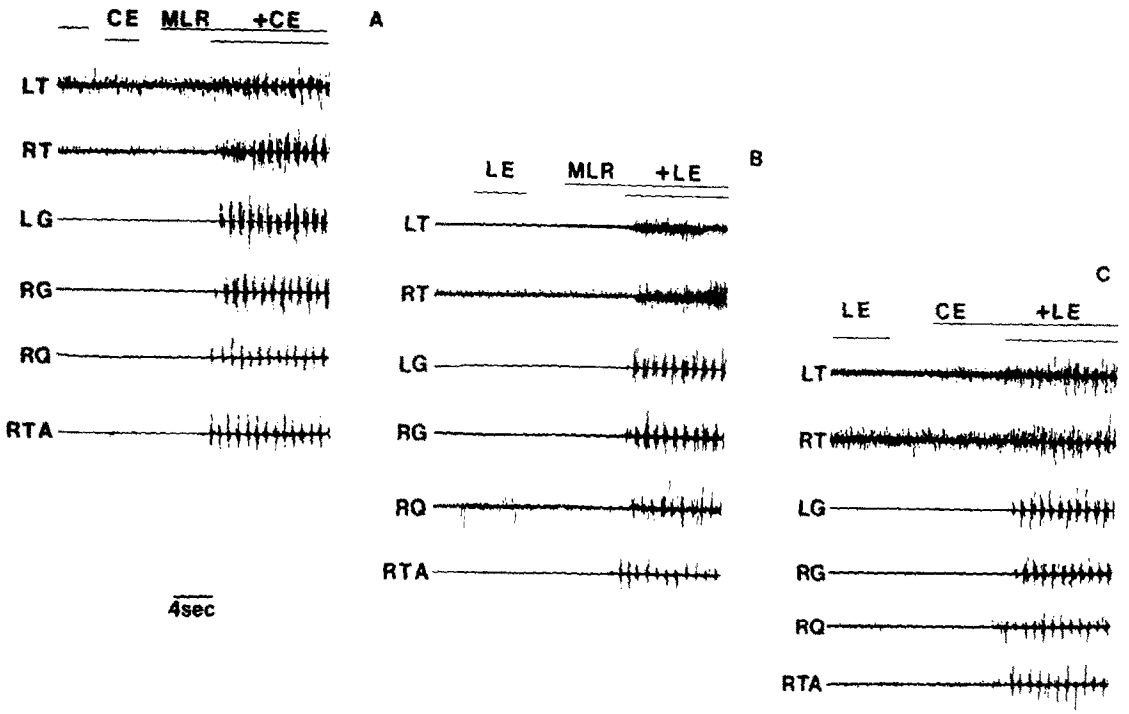

FIG. 2. Combined supraspinal and spinal stimulation-induced locomotion. (A) Subthreshold stimulation of the MLR and the CE independently and simultaneously. Combined subthreshold stimulation induced stepping in all four limbs (EMGs as in Fig. 1). (B) Subthreshold stimulation of the MLR and the LE independently and simultaneously. Combined subthreshold stimulation induced stepping in the hindlimbs but not the forelimbs. (C) Subthreshold stimulation of the CE and the LE independently and simultaneously. Combined subthreshold stimulation induced stepping in all four limbs. Calibration bar 4 s all records.

process which may continue to "cycle" beyond the time of stimulus application.

The locomotion induced by CE stimulation was indistinguishable from that produced by brain stem stimulation. Figure 1A shows EMGs of fore- and hindlimb muscles during stimulation (45 μA, 60 Hz) of the MLR. Alternation between agonists in different limbs, between agonists and antagonists in the same limbs, and proximodistal delay in the activity of agonists acting on different joints in the same limb were evident. These are all characteristics of a well-organized locomotor pattern. Figure 1B shows a similar pattern induced in the same animal following CE stimulation (40 μA, 4 Hz). Of interest in this case is the continuation of locomotion for approximately 10 s beyond the end of stimulation, indicative of a prolonged activation of the spinal cord and possibly the brain stem.

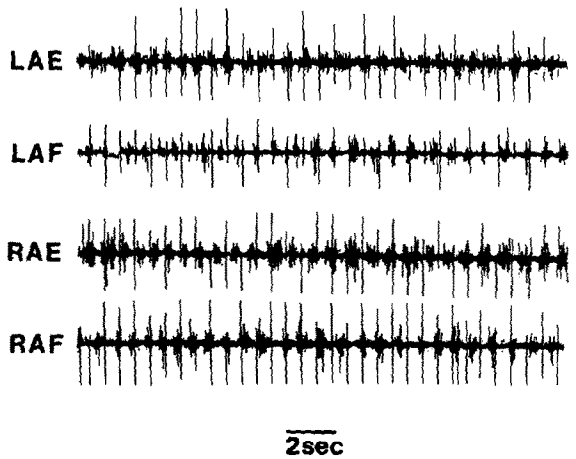

FIG. 3. LE stimulation-induced fictive locomotion at 40 μA. Alternation of the left ankle extensor (LAE) and flexor (LAF) and the right ankle extensor (RAE) and flexor (RAF) nerves during LE stimulation. Stimulus artifacts at 2 Hz are superimposed on the NG recordings. Calibration bar 2 s.

Stimulation at frequencies lower than 0.5 Hz failed to elicit reliable stepping, while stimulation at frequencies higher than 10 Hz occasionally (2/11) led to coactivation of antagonists with concomitant rigidity. Therefore, the optimal range of frequencies for activation of the CE was 0.5–10 Hz. The optimal pulse duration was in the 0.5–1.0 ms range, with shorter duration pulses being ineffective or requiring higher current amplitudes and longer duration pulses leading to shorter duration of stepping or to rigidity. At the higher current amplitudes (100 μA and above), electrical stimulation induced twitch contractions of forelimb muscles with each pulse. These twitches were superimposed on appropriately timed bursts of EMG activity and did not affect the manifestation of forelimb stepping except to give it a jerky appearance.

Stimulation of the Lumbosacral Enlargement

Stimulation of the lumbosacral enlargement (LE) was carried out in 9 active locomotion preparations. Stimulation of the preenlargement L_1 and L_4 segments was as effective in inducing stepping as the L_5–S_1 segments, whereas activation of lower sacral segments was not effective in producing low threshold locomotion. In 8 of 9 cases, electrical stimulation of the LE induced locomotion at low current amplitude (mean and S.D. 108.8 ± 108.4

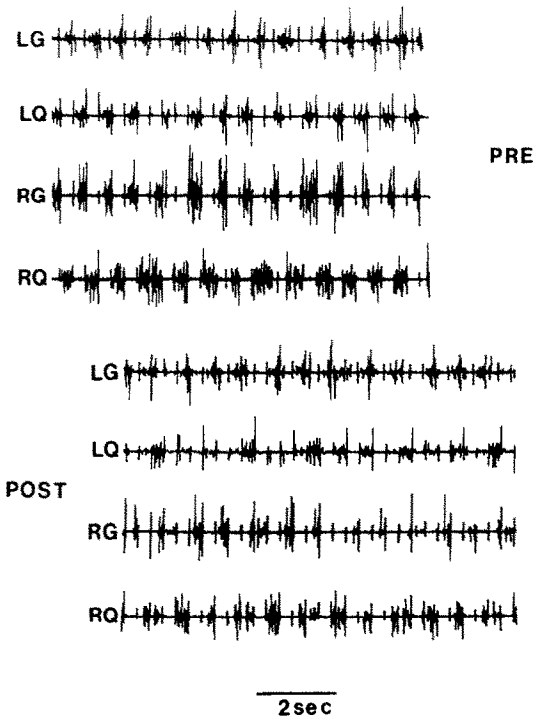

FIG. 4. LE stimulation-induced active locomotion before and after midthoracic spinal cord transection. Alternation of left hip flexor (LG) and extensor (LQ) muscles, and of right hip flexor (RG) and extensor (RQ) muscles induced by LE stimulation before (PRE) transection. Alternation of the same muscles 4 hours following (POST) a midthoracic spinal cord transection.

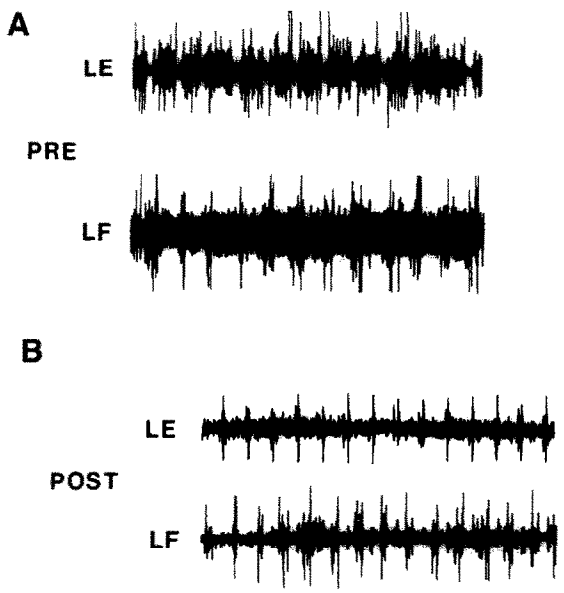

FIG. 5. LE stimulation-induced fictive locomotion before and after midthoracic spinal cord transection. (A) Alternation of left peroneal (extensor) and tibial (flexor) nerve branches before transection. (B) Alternation of the same NGs 4 hours following transection. Note the reduced background activity and burst duration and amplitude but with retention of the same pattern of alternation.

μA, range 40–360 μA). The most effective current amplitudes (and frequencies) were not different (*t*-test) for epidural (103.0 ± 107.3 μA) and subdural (132.0 ± 152.4 μA) stimulation. The optimal location for the plate electrodes was the same as that for CE stimulation, i.e., along the midline, overlying the dorsal columns, although activation of the dorsal root entry zone also was effective. In some cases (4/9), such unilateral stimulation induced stepping only of the ipsilateral hindlimb. No obvious cause was evident for the failure of LE stimulation to induce stepping in one case. As in the case of CE stimulation, LE stimulation required several seconds (2–10 s) before it would induce stepping. LE activation maintained stepping for 30 s to 3 min as long as low frequency, low amplitude stimulation was applied, and occasionally (3/9) elicited locomotion for several seconds beyond the end of stimulation.

The locomotion induced by LE stimulation was similar to that produced by MLR or CE activation. However, in most cases (6/9), LE stimulation failed to induce forelimb locomotion unless current amplitude was increased. With increasing current amplitudes, however, the hindlimbs became rigid as the forelimbs began to alternate. Figure 1C shows EMGs of limb muscles following LE stimulation-induced stepping. The pattern of muscular contractions was the same as described above for CE stimulation and was evident beyond the application of stimulation. The optimal frequency range for LE-induced stepping was 3–5 Hz although frequencies between 0.5 and 10 Hz or higher were effective.

Figure 2 shows EMGs of fore- and hindlimb muscles following combined stimulation of spinal and supraspinal sites. In Fig. 2A, stimulation of the MLR at subthreshold levels for inducing stepping (30 μA) or stimulation of the CE at subthreshold levels (25 μA) did not produce locomotion. When stimulation of the MLR was combined with that of the CE at these subthreshold current levels, four limb stepping was induced. When stimulation of the MLR or of the LE was applied at subthreshold levels, no locomotion resulted. When subthreshold stimulation of the MLR and LE was applied simultaneously, stepping was induced (Fig. 2B). In Fig. 2C, individual stimulation of the CE (25 μA) or of the LE (25 μA) failed to induce stepping. However, when combined CE and LE stimulation was carried out at these subthreshold levels, locomotion was evident in all four limbs.

Fictive Locomotion

Fictive locomotion, as evidenced by alternation of neurographic (NG) activity of limb nerves, was evoked in 8 of 9 animals which had been decerebrated and paralyzed. Stimulation of the CE induced alternation of antagonist nerves in the same hindlimb and alternation of agonists in different hindlimbs. The mean current amplitude for eliciting fictive locomotion following CE stimulation was 64.8 ± 38.6 μA (range 20–120 μA), which was numerically, but not statistically, lower than the threshold for eliciting actual locomotion following LE stimulation. Figure 3 is a representative example of alternating NG activity in hindlimb nerves to ankle extensors and ankle flexors. The optimal frequencies of stimulation for both CE- and LE-induced fictive stepping ranged from 1–10 Hz. There was no statistical difference in the thresholds observed following epidural (84.0 ± 41.0 μA) and subdural (37.7 ± 15.3 μA) stimulation.

Spinal Cord Transection

A spinal cord transection was carried out using suction ablation of the midthoracic (T_6–T_7) cord and confirmed visually by

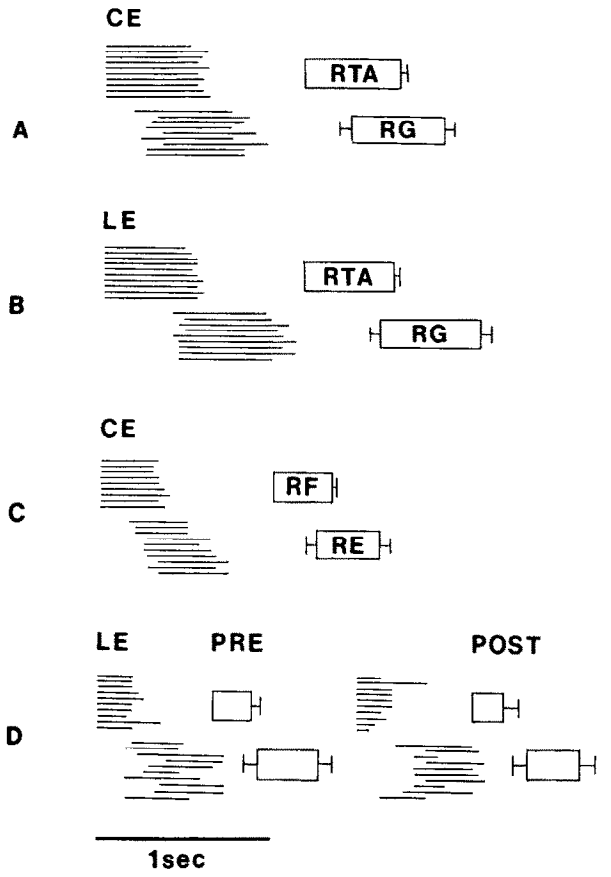

FIG. 6. Muscle burst durations during stimulation-induced locomotion. (A) Active locomotion induced by CE stimulation showing the right ankle flexor (RTA) and right ankle extensor (RG) muscle burst durations of 10 consecutive steps normalized to the beginning of the RTA burst. (B) Active locomotion induced by LE stimulation showing alternation of the same muscles as in A. (C) Fictive locomotion induced by CE stimulation showing alternation of right ankle flexor (RF) and right ankle extensor (RE) NGs. (D) Active locomotion induced by LE stimulation before (PRE) and after (POST) midthoracic transection showing muscle burst durations of the right andle flexor (RF) and right ankle extensor (RE) nerves. Note the shortened duration of muscle bursts (decreased cycle time) induced by suprathreshold (120 μA) stimulation in this case.

a 5-mm gap between proximal and distal ends. LE stimulation was carried out before and after transection in both actual and fictive locomotion preparations. Figure 4 shows EMG activity induced by LE stimulation before and after transection using the same current amplitude (80 μA). EMG activity decreased following transection, but the overall pattern of the step cycle was unchanged, as there was no major shift in the timing of each of the muscles during the cycle. Actual locomotion was evident in 4 of 6 animals tested, but locomotion could not be elicited until 4 hours posttransection, with testing taking place up to 10 hours posttransection with positive results.

Figure 5 shows NG activity in hindlimb nerves induced by LE stimulation before and after spinal cord transection. While NG activity decreased after transection, LE stimulation was still capable of eliciting alternating NG activity in hindlimb nerves. As in the case of active locomotion, LE stimulation-induced fictive locomotion became manifest 4 hours posttransection in 4 of 5 animals tested. The optimal stimulation frequencies and pulse durations were similar for acutely transected and decerebrate animals.

In the present experiments, while acute transection did not prevent LE stimulation from inducing stepping, the locomotion elicited was not weight-bearing. On the other hand, it was evident that the hindlimb (ankle) actively pushed against the treadmill during the stance phase rather than the limb being dragged backwards. This was supported by preliminary analysis of joint angles showing a gradual increase in ankle joint angle at the end of the stance phase. A more detailed kinematic analysis and development of weight support in the chronic spinal preparation is under way.

Analysis of muscle burst durations under each of the conditions described above revealed that the durations of flexor and extensor bursts were similar following CE stimulation compared to LE stimulation (Fig. 6A and B) (CE stimulation, flexor EMG 560 ± 35 ms duration, extensor EMG 550 ± 28 ms duration, LE stimulation, flexor EMG 527 ± 31 ms duration, extensor EMG 590 ± 21 ms duration). Similarly, the nerve burst durations were shorter but not significantly different after CE stimulation during active locomotion compared to fictive locomotion (Fig. 6A and C) (CE stimulation, flexor NG 343 ± 27 ms duration, extensor NG 363 ± 43 ms duration). Moreover, the duration of muscle bursts elicited by LE stimulation-induced active locomotion was similar before and after midthoracic spinal transection (Fig. 6D) (LE stimulation pretransection, flexor EMG 220 ± 51 ms duration, extensor EMG 356 ± 81 ms duration; posttransection, flexor EMG 180 ± 91 ms duration, extensor EMG 310 ± 93 ms duration). The preservation of the overall locomotor pattern and relationships between muscle groups, and of the coordination between hindlimbs following transection, suggests that LE stimulation may be activating an intrinsically organized system.

DISCUSSION

The main findings reported herein suggest that: a) subdural and, especially, epidural stimulation of the dorsal surface of the spinal cord can elicit locomotion at low amplitude currents as long as low frequency, long duration pulses are applied, b) stimulation of preenlargement and enlargement segments can induce stepping, c) such stimulation is independent of afferent input since fictive locomotion can be induced, d) stimulation of the CE can induce stepping in all four limbs, and e) stimulation of the LE can result in hindlimb stepping, even after acute midthoracic spinal cord transection.

That the spinal cord retains the capability of generating stepping movements after an acute spinal transection is supported by a host of studies showing that pharmacological manipulations (L-DOPA with and without monoamine oxidase inhibitors and/or potentiated by 4-aminopyridine) can elicit locomotor-like movements soon after cordotomy (9, 21, 23, 34, 35). Animals pretreated with L-DOPA and nialamide also exhibited locomotion when combined with electrical stimulation of the dorsal columns and dorsal roots (23). Dorsal-root stimulation also was used to elicit stepping in the decerebrate cat, but the effect disappeared after cordotomy, although it is not clear how long after transection testing took place (6). The present results show that electrical stimulation of the dorsal surface of the cord without pharmacological manipulation is sufficient to elicit stepping. After a spinal transection, it is necessary to wait at least four hours before locomotor movements can once again be induced. The frequencies of stimulation used in the present investigation were similar to those employed in dorsal root stimulation studies (6) and lower than those employed in pharmacologically treated animals (23).

The locomotor pattern produced by epidural (and subdural) stimulation of the spinal cord was well organized and indistinguishable from that generated following brain stem stimulation. Such a pattern appears also to be elicited following combined pharmacological and electrical activation (23) or electrical activation alone. It is not clear if the pattern observed immediately following spinalization has the same properties as that induced by L-DOPA alone. On the other hand, a great deal of success appears to have been experienced in generating a well-organized locomotor pattern in adult chronic spinal animals, including weight support (8, 27, 28). Further studies have shown that treadmill training following cordotomy as adults can enhance the organization of the locomotor pattern and capability for weight support (24,27). Of course, as mentioned previously, animals spinalized as neonates can perform walking movements similar to those observed in the adult cat (11, 15, 19, 20, 21, 31). The present observations, then, should not be unexpected, and have the potential for serving as a valuable adjunct to postspinalization treadmill training and other therapeutic interventions.

An interesting observation in the present studies was the ability of preenlargement stimulation to elicit well-organized stepping movements. The preenlargement spinal cord segments are considered to integrate descending information from motor pathways controlling forelimb and hindlimb movements (1, 2, 25, 32, 33). Propriospinal fibers arising from forelimb preenlargement regions project to the nearby enlargement where the final motor program is carried out. These probably interact there with descending motor pathway fibers in regulating movements. However, some motor programs can be elicited in the absence of organization from descending pathways, as evident here for locomotion following spinal cord stimulation. This observation needs to be confirmed by further experimentation since it would be ideal to be able to recruit stepping without directly stimulating areas containing the majority of limb nerve motoneurons. This would minimize the direct effects of stimulation (i.e., twitch responses to each shock) which are superimposed on the locomotor pattern in cases in which the threshold for eliciting stepping is higher than 100 μA.

Several other observations require additional study. For example, the inability to electrically induce stepping within four hours of transection may suggest the presence of a period of inactivation immediately following trauma which is followed by a stabilization of intrinsic mechanisms. Recent studies using anti-inflammatory agents have shown beneficial effects following spinal cord injury in animals and humans (3–5, 7, 10). Of interest in view of the effects observed in the present studies is that patients and animals needed to be treated within eight hours after injury in order for beneficial effects to be observed in the long run. These observations suggest that corticosteroid treatment can alleviate a deleterious, late-onset set of events of undetermined nature. It, thus, appears that a host of timed changes occur following transection which may be amendable to manipulation. Current studies are aimed at determining how long after transection epidural stimulation still can induce stepping.

In general, the present findings are promising, if preliminary, and indicate that it may be possible at some point to use conventional electrodes such as those implanted epidurally in humans for intractable pain (i.e., multiple electrode contacts on the dorsal surface of the spinal cord). The results of this study suggest the appropriate frequencies and durations optimal for eliciting stepping movements following low current amplitude stimulation (17). The resulting movements, although not weight bearing, may represent a degree of "exercise" and perhaps provide sufficient force to propel the subject as long as postural support is provided by a "walker." Preliminary results using such a preparation in the cat and rat are encouraging.

ACKNOWLEDGEMENT

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