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Epidural Stimulation : Comparison of the Spinal Circuits That Generate and Control Locomotion in Rats, Cats and Humans

Yury Gerasimenko^{a,d}, Roland R. Roy^c, and V. Reggie Edgerton^{a,b,c}

^aDepartment of Physiological Science, University of California, Los Angeles, Los Angeles, CA 90095

^bDepartment of Neurobiology, University of California, Los Angeles, Los Angeles, CA 90095

^cBrain Research Institute, University of California, Los Angeles, Los Angeles, CA 90095

^dPavlov Institute of Physiology, St. Petersburg, 199034, Russia

Abstract

Although epidural stimulation is a technique that has been used for a number of years to treat individuals with a spinal cord injury, the intended outcome has been to suppress plasticity and pain. Over the last decade considerable progress has been made in realizing the potential of epidural stimulation to facilitate posture and locomotion in subjects with severe spinal cord injury who lack the ability to stand or to step. This progress has resulted primarily from experiments with mice, rats and cats having a complete spinal cord transection at a mid-thoracic level and in humans with a complete spinal cord injury. This review describes some of these experiments performed after the complete elimination of supraspinal input that demonstrate that the circuitry necessary to control remarkably normal locomotion appears to reside within the lumbosacral region of the spinal cord. These experiments, however, also demonstrate the essential role of processing proprioceptive information associated with weight-bearing stepping or standing by the spinal circuitry. For example, relatively simple tonic signals provided to the dorsum of the spinal cord epidurally can result in complex and highly adaptive locomotor patterns. Experiments emphasizing a significant complementary effect of epidural stimulation when combined with pharmacological facilitation, e.g., serotonergic agonists, and/or chronic step training also are described. Finally, a major point emphasized in this review is the striking similarity of the lumbosacral circuitry controlling locomotion in the rat and in the human.

Keywords

rat; cat; human; epidural stimulation; locomotion; spinal cord injury; central pattern generation

Introduction

In mammals, networks of spinal neurons are able to generate a pattern of rhythmical, reciprocal activation of antagonistic muscles of the hindlimbs in the absence of supraspinal and/or afferent input. The networks that produce this rhythmical output are known as the spinal locomotor central pattern generators (CPG) (Grillner and Zangger, 1979). Recently it was shown that

Correspondence should be addressed to: V. Reggie Edgerton, PhD, Department of Physiological Science, University of California, Los Angeles, Los Angeles, CA 90095, Phone: 310 825-1910; Fax: 310 267-2071; E-mail: vre@ucla.edu.

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locomotor-like movements can be induced by epidural spinal cord stimulation (ES) in adult cats (Iwahara et al., 1991; Gerasimenko et al., 2002a, 2003) and rats (Ichiyama et al., 2005; Lavrov et al., 2006) after a complete thoracic spinal cord transection (ST) as well as in individuals with a complete spinal cord injury (SCI) (Dimitrijevic et al., 1998a; Gerasimenko et al., 2001; Shapkova, 2004; Minassian et al., 2007). In each of these preparations, those intraspinal neurons that generate locomotor-like patterns remain intact, but unlike in CPG all sensory information from the hindlimbs can functionally project to this intraspinal network after the complete loss of supraspinal input. It is the combination of the potential of the intraspinal networks to generate locomotor-like rhythms and their ability to utilize the sensory information associated with movement that can result in rather remarkable weight-bearing stepping in spinal animals. The studies mentioned above clearly demonstrate that ES can activate the intraspinal neural networks that, in turn, can coordinate and recruit the motoneuronal pools with enough precision to generate oscillating movements of the lower limbs in a step-like fashion. What has not been clear from the results of these studies is the degree to which these step-like patterns generate effective weight-bearing stepping as opposed to simply producing a range of oscillating behaviors. Intricately linked to this question is the degree to which these motor patterns can be attributed to the neurons associated with the CPG as opposed to the sensory information provided to this circuitry in the presence of lumbosacral ES.

We will examine this issue in this review. The primary emphasis will be to provide a comparative perspective on the properties of these neural networks among different mammals, including humans. Are there distinctive differences in the localization of the locomotor networks in the lumbosacral spinal cord among mammals? Is there specificity in the parameters of ES that can be taken advantage of while facilitating effective locomotor activity among the different mammals? What is the significance of peripheral sensory feedback in the modulation, or even control, of locomotor behavior in these mammals during ES? Are there significant differences among mammals in the ability to generate locomotor patterns in response to ES? From a clinical perspective an assessment of the similarities and dissimilarities of the locomotor networks among different mammals may provide clues as to the potential of ES as an effective clinical tool in enhancing the potential for ambulation following a SCI. Based on studies to date, it also appears that there is a high level of relevance of these same issues to a range of other neuromotor disorders in which the locomotor potential has been compromised. Each of these questions and issues are addressed in the present review.

Quality of locomotion facilitated by ES in different mammals

In decerebrated cats, ES at the cervical enlargement induces quadrupedal step-like movements on a moving treadmill belt whereas ES at the lumbosacral enlargement induces locomotor activity only in the hindlimbs (Iwahara et al., 1991). In decerebrated cats consistent weight bearing and plantar foot placement on a moving treadmill belt is induced by ES of the lumbar cord (Gerasimenko et al., 2002a). In acute ST (T9) cats, in contrast to decerebrated cats, ES induces only weak rhythmic hindlimb movements without any weight bearing (Musienko et al., 2007). In ST rats ES applied at T9 one week following a complete spinal cord transection did not induce locomotor activity (Lavrov et al., 2006). ES applied to the lumbar spinal cord six weeks post-injury, however, generates coordinated step-like movements in non-trained cats and rats, although the stepping movements are not weight bearing and there is little ability for plantar placement of the paws.

ES at approximately L2 also can induce step-like alternating flexion and extension movements in individuals with a complete SCI cervical or thoracic injury (Dimitrijevic et al., 1998a). More specifically, while the patients are in a supine position, large, alternating excursions of the hip and knee joints are observed with ES at L2.

In summary, there is now strong evidence that ES can activate at least some components of the lumbosacral locomotor networks and initiate step-like movements in spinal animals as well as in individuals with a SCI. However in the absence of supraspinal control, there has not been convincing evidence that ES alone can generate full or even modestly, effective weight-bearing stepping in humans with a complete SCI. As will be discussed in subsequent sections of this review, however, it appears that effective locomotor performance can be generated in response to ES when combined with pharmacological or afferent modulation.

Methodology of ES in facilitating locomotor-like activity

What are the specific parameters of ES that can facilitate locomotor-like activity in spinal animals? An important concept to emphasize at this point is that ES has the potential to facilitate, as well as induce, locomotor-like activity. The difference between facilitating and inducing locomotion has major clinical implications. For example, it will be inordinately more desirable clinically to modulate the properties of the spinal cord circuitry into a physiological state in which the individual can manipulate afferent information on a voluntary basis to enable standing or stepping, rather than directly inducing locomotor-like movements. On the other hand ES can actually induce step-like movements when it is applied with sufficient stimulation intensity. In a number of publications on this topic it is not always clear to what extent the motor pattern that is being recorded is a function of direct induction by the stimulation as opposed to the motor pattern being defined primarily by the nature of the sensory information provided, i.e., when the limbs are placed on moving treadmill belt and in a weight-bearing position. In the present review we emphasize the potential of ES as a facilitator rather than an inducer. Our interpretation of the experiments examining the facilitating potential of ES has been the basis for the concept that the true potential of ES lies in its “enabling” effects on standing and stepping.

Site of stimulation

Iwahara et al. (1991) reported that ES at the L1 and L4 spinal segments was more effective than at the L5-S1 segments for inducing hindlimb stepping in the decerebrated cat. Subsequent studies have shown that ES at the L4-L5 segments elicits hindlimb stepping more effectively than stimulation at other spinal levels (Gerasimenko et al., 2002a, 2003). In chronic spinal rats, ES at the lumbosacral level elicits some hindlimb rhythmic movements, with coordinated bilateral stepping being evoked more often when ES is applied at L2 (Ichiyama et al., 2005) or S1 (Lavrov et al., 2006). An example of the EMG pattern during stepping facilitated by ES at L2 (40 Hz) is shown in Figure 1A.

Dimitrijevic et al. (1998a) demonstrated that ES applied at L2 (30 Hz) can induce rhythmic step-like EMG bursting activity and flexion/extension movements in the lower limbs of individuals with a complete SCI while in a supine position (Fig. 1B). Stimulation above or below the L2 segment elicited either tonic or rhythmic, synchronous EMG activity in the leg muscles (Dimitrijevic et al., 1998a). Subsequent studies have confirmed the importance of ES at L2 in producing stepping patterns in individuals with a SCI (Gerasimenko et al., 2001, Gerasimenko, 2002b).

Rossignol and colleagues have shown that the L4 segment is critical for the initiation of stepping movements in cats (Langlet et al., 2005; Barthelemy et al., 2007). Selective injection of clonidine, a norepinephrine β -receptor agonist, into the L3-L4 spinal segments facilitated locomotion (Langlet et al., 2005), whereas inactivation of these receptors by the pharmacological antagonist yohimbine abolished locomotion in the cats (Marcoux and Rossignol, 2000). Furthermore, spinal cord transection at L4 abolished locomotion evoked by intraspinal stimulation of the caudal segments (Barthelemy et al., 2007). The experiments

involving localized application of pharmacological agents, selective lesions and selective sites for stimulation as well as molecular signals of neuronal activation are generally consistent with the conclusion that these segments play a major role in the genesis of locomotor behavior. In interpreting the different results it is important to recognize that the L4 spinal level in cats corresponds to the L2 spinal level in humans and rats, i.e., the spinal level most responsive to ES for inducing locomotor-like activity. A plausible explanation for inducing stepping movements in response to ES of the caudal lumbosacral segments may be due to the activation of rostral segments through the projection of propriospinal neurons (Shik, 1997; Guevremont et al., 2006).

Frequency of ES

In decerebrated cats the optimal frequency range of ES for inducing hindlimb stepping was 3-5 Hz (Iwahara et al., 1991, Gerasimenko et al., 2002). In decerebrated cats spinalized 5-7 days before an acute experiment the optimal frequencies for intraspinal microstimulation eliciting long-lasting locomotion was 2-6 Hz, although a few cycles of bilateral locomotion could be triggered during high-frequency (30-70 Hz) stimulation (Barthelemy et al., 2007).

In chronic ST rats ES in the range between 20 to 110 Hz induced step-like movements (unpublished observations). In contrast, ES at less than 10 Hz produced tonic activity in hindlimb muscles, but did not evoke locomotor-like activity. Figure 2A shows step-like EMG activity in spinal rats induced by ES at S1 at a frequency of 30 Hz (A) or 110 Hz (C). Note that the frequency of the step-like EMG activity is similar during ES at 30 and 110 Hz, suggesting a general activation of the same neural networks can facilitate the rhythmic activity. However, the relative changes in the EMG amplitudes and patterns in the flexors and extensors change disproportionately with changes in frequency of ES, i.e., the effects of the stimulus are dependent upon the stimulation patterns as well as the accessibility to sensory information associated with a weight-bearing stepping.

ES at frequencies < 10 Hz produces a constant EMG amplitude response to each stimulus in the leg muscles of individuals with a complete SCI injury, but does not evoke locomotor-like activity (Dimitrijevic et al., 1998a; Minassian et al., 2007). Frequencies of ES between 30-40 Hz were optimal for inducing locomotor-like EMG activity in these patients (Fig. 2B). Increasing the frequency of stimulation from 30 to 70 Hz resulted in a slower stepping rhythm, i.e., the stepping rhythm was twice as fast at 30 than at 70 Hz (Dimitrijevic et al., 1998a). Higher frequencies, e.g., 120 Hz, did not induce locomotor-like activity (Fig. 2D).

The different responses to varying frequencies of ES between animals and humans may be related to the different conditions under which the stepping patterns are induced. In most studies ES has been administered during stepping on a forward-moving treadmill for the animals, whereas locomotor-like activity has been induced usually in the supine position for individuals with a complete SCI.

Strength of ES

The threshold intensity of ES for activation of the locomotor networks differs in animals and humans. In the decerebrated cat ES applied at L1-L4 with a current of ~100 μ A is most effective for inducing locomotion (Iwahara et al., 1991). In chronic ST rats the threshold to induce locomotor activity in response to ES at L2 is ~7.5 V. Interestingly, the threshold for a hindlimb muscle response to a single epidural pulse was reported to be 3.4 V in rats (Ichiyama et al., 2005). To initiate hindlimb locomotor activity by ES it is necessary to increase the strength of the stimulation by approximately two-fold above the muscle twitch threshold. The threshold for evoking locomotor activity at S1 in ST rats was ~4 V. In the absence of pharmacological agents, ES at a frequency of 40 Hz and an intensity of 4 V initially elicits tonic activity in the

proximal muscles (e.g., the semitendinosus) which eventually becomes bursting activity (Fig. 3A). The rhythm of the evoked locomotor activity is rather fast. Administration of quipazine (a non-selective 5-HT_{2A} agonist, 0.3 mg/kg, i.p.) facilitates the initiation of the stepping pattern (Fig. 3B). The locomotor rhythm induced by ES plus quipazine is significantly slower than with ES alone, whereas the intensity and frequency of ES are similar under the two conditions. Increasing the strength of ES, however, results in more rapid stepping, attributable primarily to a shortening of the stance phase of the step cycle. A similar effect on locomotor behavior was observed by Shik et al. (1966) in cats during stimulation of the mesencephalic locomotor region at different intensities.

A similar relationship between the threshold for tonic activity and the threshold for bursting activity has been reported in individuals with a complete SCI (Dimitrijevic et al., 1998a). There is a transformation from tonic EMG activity into bursting EMG activity when ES strength is progressively increased from 3.5 to 5.5 V (Fig. 4). Subsequent increases in stimulus strength up to 10 V altered the amplitude, duration, and rhythmicity of the EMG bursts (Dimitrijevic et al., 1998a).

Role of afferent input to the spinal cord in controlling stepping facilitated by ES

Chronic spinal rats can generate some weight-bearing stepping in response to ES (Lavrov et al., 2006), but a key factor in defining the details of the stepping is the pattern of the afferent information being projected to the spinal cord. For example, if the speed of the treadmill belt is changed, then the details of the stepping pattern will adapt proportionately. If the level of weight bearing during stepping is increased, then the spinal cord will accommodate accordingly, i.e., increase the activation levels of both the extensor and flexor motor pools to enable stepping. The same responses to changes in speed and loading level have been observed in human subjects having a clinically complete SCI (Harkema et al., 1997).

In response to ES the specific motor response is highly dependent on the degree of load bearing, the direction of the treadmill belt on which the spinal animals is placed (spinal animals have the ability to step forward or backward), and the speed at which the treadmill belt is moving. These responses have been demonstrated in complete spinal rats (Gerasimenko et al., 2006b), cats (Musienko et al., 2007), and, to a large degree, humans with a complete SCI (Harkema et al., 1997). However, little is known about the relative importance of the different sensory receptors in modulating these motor patterns. Many experiments have been performed demonstrating the importance of virtually all peripheral receptors, but none of these studies provide information related to the relative importance of specific receptor types under *in vivo* conditions.

Even less is known about the relative importance of these afferents in chronic spinal animals. Cutaneous information associated with the ankle can have a dramatic impact on the locomotor capability of chronic spinal cats (Rossignol, 2006). The induction of ischemia, which has a primary effect on blocking Ia input from the muscle spindles in cats (unpublished observations) and humans with a complete SCI (Dimitrijevic et al., 1998b), suggests that stepping is only moderately affected by eliminating Ia input. An example of step-like patterns that can be generated in response to ES in an individual with a SCI categorized as ASIA A both before and after ischemia is shown in Figure 4. These results, however, seem contradictory to the observation that when uninjured humans are suspended in a horizontal position (facing perpendicular to the gravitational forces) application of a vibratory stimulus to the quadriceps induces non-voluntary locomotor movements of the lower limbs (Gurfinkel et al., 1998). Although vibration of sufficient amplitude and frequency can activate Group Ib and II sensory receptors, it is generally assumed that vibration selectively activates Ia afferents. A note of

caution in interpreting many of the lesion type of experiments is that demonstration of the apparent absence of an effect on locomotion by eliminating the function of a specific receptor, e.g., Ia afferents by ischemia, cannot be interpreted as evidence that it plays no important role in locomotor activity. An alternative interpretation is that the remaining afferents provide sufficient network information to compensate for the disruption of that specific receptor.

Which axons and neurons are being activated by ES?

In animals and in humans with a chronic but incomplete SCI, ES will activate descending and ascending dorsal column axons as well as projections from the dorsal root, particularly as they project vertically and enter the spinal cord at the dorsal surface (Minassian et al., 2007). In humans and laboratory animals with a complete SCI above the lumbosacral segments, there will be no descending axons activated by ES, but the dorsal root afferents will be readily activated and, theoretically, the larger axons will be preferentially activated. Even less is known about which specific interneuronal circuits that project to the motor pools will be activated by ES. Some progress, however, has been made by examining the amplitudes and latencies of potentials simultaneously evoked in multiple muscles by single pulses of ES in both laboratory animals and human subjects. Both monosynaptic and polysynaptic responses are modulated in a phase-dependent manner during treadmill locomotion in normal rats (Gerasimenko et al., 2006a). A similar phenomenon has been observed in uninjured humans subjects when stimulating the spinal cord transcutaneously (Courtine et al., 2007).

Additional and unexpected information about the neural circuitries that are being activated by ES has been derived from comparisons of the evoked potentials in flexor vs. extensor muscles in rats and humans. There is a very consistent difference between the evoked potentials in flexor and extensor motor pools in both rats and humans (Gerasimenko et al., 2001; Minassian et al., 2004). For example, monosynaptic responses are prominent in extensor motor pools, whereas the flexor motor pools are activated predominantly polysynaptically in response to ES. An example of this phenomenon in a rat with a complete mid-thoracic transection (Fig. 5A) and in a human with a complete SCI (Fig. 5B) shows a clear spectral frequency difference in the EMG patterns during stepping movements in the presence of stimulation at 25 Hz in the human subject and at 40 Hz in the rat. Note the absence any clear dominant frequencies evoked in the tibialis anterior muscle (a primary ankle flexor) in both the human and rat because of the varying latencies within the flexor circuitry, whereas the predominant response in the medial gastrocnemius (a primary ankle extensor) was monosynaptic, i.e., a consistent monosynaptic latency in response to each evoked potential was observed in the extensor circuitry. This interesting flexor-extensor difference in evoked potentials was examined further by comparing the frequency spectrum of the bursting EMG patterns in the biarticular semitendinosus muscle during stepping in a rat (Fig. 4C). This muscle occasionally generates both a flexor and an extensor EMG burst associated with knee flexion and hip extension, respectively. Comparing the spectral frequency during the flexor bursts (marked as 1 and 3) and extensor bursts (marked as 2 and 4) during continuous ES of S1 at 40 Hz, a predominant periodic and harmonic of the stimulation frequency is observed only in the burst associated with hip extension. This observation is particularly revealing in that it suggests that there is an interneuronal pool that is linked to a flexor function and a separate interneuronal pool that is linked to an extensor function, both of which project to the same motor pool. These data represent some of the first observations suggesting a fundamental difference in the *in vivo* functional behavior of the neural circuitry interconnecting the peripheral input to flexor vs. extensor motor pools.

What is the true potential of the spinal circuitry that remains in the lumbosacral spinal cord following a complete SCI at a thoracic or higher level?

Two experimental preparations provide strong evidence that the circuitry within the lumbosacral spinal cord, in the absence of any supraspinal input, is capable of generating remarkably normal locomotion, assuming the circuitry has access to the sensory input that is normally provided to the spinal circuitry during weight-bearing stepping. One preparation is the acute decerebrated cat when the dorsum of the spinal cord is stimulated at a frequency of 5 Hz at L4-L5 with a monopolar electrode. This preparation has the capability of generating weight-bearing stepping with forward propulsion and without any supplemental pharmacological intervention. The second preparation that has demonstrated remarkably normal full weight-bearing stepping is the chronic spinal rat when stimulated by ES at S1 and L2 simultaneously, receiving multiple serotonergic agonists, and after several weeks of step training (unpublished observations). The importance of these observations is the clear demonstration that the circuitry needed to generate very effective locomotion persists in the lumbosacral spinal cord in the absence of any supraspinal input. Therefore, one of the primary opportunities for enhancing the ambulatory potential of humans with a severe SCI is to identify strategies to gain access to this highly functional circuitry.

How do we gain access to the lumbosacral circuits?

We must first reiterate the importance of the fact that the spinal circuitry has the capability to generate coordinated stepping and standing as well as to respond effectively to variations in the environment. To utilize this potential, it appears that the spinal circuitry remains in a dynamic state, but that it is possible to stabilize this circuitry at different physiological states. Given the appropriate sensory information, the circuitry may have a propensity for performing a given type of locomotor task at any specific physiological state. There are three interventions that have proven successful in modulating the physiological state of the spinal circuits associated with successful postural and locomotor activity. The first intervention involves the modulation of the locomotor circuits through activity-dependent mechanisms. Several studies have shown that the spinal cord learns to perform the task that it practices (Edgerton et al., 2004). For example, the spinal cord can be trained to a physiological state that results in improved locomotion (Edgerton et al., 2001) or to a state where it can generate improved standing capability (de Leon et al., 1998). Evidence also indicates that the training is quite specific, e.g., spinal cats trained to stand do not step very well (Edgerton et al., 1997). A second intervention involves modulation of the locomotor circuits pharmacologically. It is quite evident that the spinal circuitry can be modulated quite rapidly by titrating different combinations of pharmacological agonists and antagonists to neurotransmitter systems known to persist in the lumbosacral spinal cord and known to be important in the generation of locomotion. One of the more successful pharmacological interventions has been the disinhibition of inhibitory neurotransmitter systems within the spinal cord, i.e., the glycinergic and GABAergic systems (Edgerton et al., 2001; Tillakaratne et al., 2002). Similarly successful pharmacological interventions under *in vivo* conditions have been demonstrated by administering serotonergic and noradrenergic agonists (Barbeau and Rossignol, 1991).

A third intervention, the primary topic of the present review, is the modulation of the physiological state of the spinal circuitry via ES. We are only beginning to understand the extent of the potential of this minimally invasive technique. It seems highly probable that the chronic stimulation techniques presently used to suppress pain and spasticity can be readily adapted to facilitate postural and locomotor control, e.g., encouraging results have been produced by modestly modifying the pattern, level of stimulation strength, and/or the spinal

cord segmental level of ES. ES can generate effective stepping since peripheral afferents can control most of the important features of stepping. For example, a tonic stimulation, i.e., without any temporal pattern modulation, delivered to a general area of the spinal cord can generate relatively effective locomotion. As we learn more about the details of the control of the spinal circuitry associated with these motor tasks, it is highly likely that the ES approach will have even more potential than thought presently.

Since each of these three types of interventions involves mechanisms which have some degree of independence from one another, this provides the opportunity for the combination of interventions to examine potential complementary effects. In fact, our most recent experiments provide a very convincing case that a combination of ES, step training, and the appropriate level of activation of serotonergic neurotransmitter agonists can be used to recover remarkably normal stepping capability after a complete SCI.

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Figure 1.

Locomotor-like EMG patterns induced by epidural stimulation (ES) in an adult complete spinal cord transected (ST) rat stepping at a treadmill speed of 9 cm/sec (A) and in a complete spinal cord injured (SCI) patient (ASIA A) in a supine position (B) are shown. Rhythmic alternating EMG activity induced by ES (40 Hz) at L2 is observed in selected hindlimb muscles in the ST rat six weeks after the injury (A). Rhythmic activity is shown in one leg of the human subject in response to ES (30 Hz) at L2 (B). Abbreviations: RVL, right vastus lateralis; RSt, right semitendinosus; RTA, right tibialis anterior; RMG, right medial gastrocnemius; LMG, left medial gastrocnemius; LEDL, left extensor digitorum longus; Q, quadriceps; A, adductors; TA, tibialis anterior; TS, triceps surae.

Figure 2.

EMG patterns in selected hindlimb muscles induced by ES (4 V) in a ST rat at 30 Hz (A) and 110 Hz (C) and by ES (7 V) in a SCI patient at 30 Hz (B) and 120 Hz (D) are shown. In the ST rat locomotor-like EMG patterns are observed at both stimulation frequencies (A and C). During ES at 110 Hz the locomotor-like rhythm is not changed dramatically, whereas the amplitude and/or duration of the EMG bursts of the LTA and LEDL were decreased. In the SCI patient locomotor-like EMG activity was observed in all muscles with ES (7 V) at L2 at a frequency of 30 Hz (B), but only tonic EMG activity was induced with ES at 120 Hz (D). Abbreviations: K.M., knee movements; all others same as in Fig. 1.

Figure 3.

Differences in the initiation of locomotor-like activity in a ST rat in response to ES (4 V at 40 Hz) at S1 (A) and to ES in the presence of quipazine (0.3 mg/kg) (B) are shown. Vertical arrows indicate the initiation of ES. Note that the locomotor-like rhythm evoked by ES in the presence of quipazine was significantly slower than during ES alone in spite of the fact that the treadmill speed is the same (9 cm/sec) for both conditions. Abbreviations, same as in Fig. 1.

Figure 4.

The effects of hip ischemia on locomotor-like EMG activity induced by ES in an individual with a complete SCI (ASIA A) are shown. EMG recordings from the leg muscles while gradually increasing the intensity of ES from 3.5 V to 5.5 V (in increments of 0.5 V) at L2 are shown in (A). Vertical arrows show the time points at which the stimulus intensity was increased. The transformation from tonic EMG activity into bursting EMG activity occurred at an ES intensity of 5.5 V. After 20 min of ischemia induced by a cuff over the hip, the emergence of the EMG activity while progressively increasing the intensity of ES (shown by arrows) is demonstrated in (B).

Figure 5.

The spectral characteristics of a flexor (TA) and an extensor (MG) muscle in a ST rat (A) and a flexor (TA) and extensor (Sol) muscle in the leg of an individual with a complete SCI (B) during locomotor-like activity induced by ES (S1 at 40 Hz for the rat and L2 at 25 Hz for the human) are shown. The spectral analyses (power-frequency plots) are derived using Fast Fourier Transformation (FFT) procedures and are based on analysis of the burst enclosed in the shaded boxes in each muscle EMG trace. Similar analyses for the left semitendinosus (LSSt), a biarticular muscle having both a flexor (knee flexion) and an extensor (hip extension) function, are shown from a ST rat in (C). Note the dominant spectral peaks that represent the periodicity of the stimulation frequency in those EMG bursts associated with extension,

reflecting a predominance of monosynaptic-evoked potentials. Also note that there are no consistent dominant peaks during the flexor bursts in response to the same stimulation, suggesting that a predominance of polysynaptic-evoked potentials. Abbreviations, same as in Fig. 1.