Absence of Local Sign Withdrawal in Chronic Human Spinal Cord Injury

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INTRODUCTION

Local sign withdrawal has been observed in spinal-intact humans in response to electrocutaneous stimuli applied to different regions of skin on the foot and leg (Anderson et al. 1999; Grimby 1963; Hagbarth 1960; Sonnenborg et al. 2001). Local sign withdrawal acts to move the limb from the noxious stimulus. After spinal cord injury (SCI), this organization of the electrocutaneous reflexes has been questioned (Dimitrijevic and Nathan 1968; Grimby 1965). More recently, the skin regions of the spinal-intact human foot have been mapped in detail with regard to the activity of the muscles of the leg, demonstrating a clear pattern of muscle activity consistent with local sign withdrawal from the stimulus site (Anderson et al. 1999, 2001; Sonnenborg et al. 2000, 2001).

The locus of the organization of local sign withdrawal has been associated with the interneurons of the deep dorsal horn of the spinal cord in rats (Schouenborg and Sjolund 1983; Schouenborg et al. 1995). Similarly, these same interneurons have been associated with windup of flexion reflexes (Herrero et al. 2000; Schouenborg and Sjolund 1983). Local sign withdrawal might be preserved after SCI, assuming that the involved interneurons are not overly dependent on descending drive for their organization. Alternately, the local sign could be lost after spinal cord injury as a result of plastic changes in the spinal cord, similar to other reflex behaviors (for review, see Wolpaw and Tennison 2001).

The presence or absence of local sign organization is important for emerging technologies that target microstimulation of the spinal cord (Barbeau et al. 1999). For example, it has been suggested that microstimulation of the deep dorsal horn interneurons could produce targeted, coordinated movements of the leg, based on experiments conducted in the frog, rat, and cat spinal cord that demonstrate novel responses to stimuli applied at different locations within the spinal cord (LeMay et al. 2001; Mushahwar et al. 2002; Tresch and Bizzi 1999). These novel responses depend on an underlying organization of the spinal interneurons, and local sign withdrawal has been used as evidence for their organization and application to human spinal cord injury (Tresch and Bizzi 1999). Despite such promising studies, local sign withdrawal has yet to be addressed in detail in humans with chronic SCI.

For this study, we tested local sign withdrawal in chronic human SCI by applying noxious electrocutaneous stimuli to 4 locations on the foot and 2 locations on the lower leg. The joint torque and electromyogram (EMG) responses were recorded under isometric conditions and compared across stimulus sites. Further, we examined whether common neu-
ronal pathways were involved in the flexion reflexes by applying a series of stimuli, at different locations, with a 1-s delay between stimuli. Because sequences of stimuli result in sequential increases in the reflex response, or windup (Arendt-Nielsen et al. 1994; Hornby et al. 2003), carryover of windup from one stimulus location to another would indicate commonality of the neural pathways of the flexion reflex, possibly located within the deep dorsal horn interneurons or motoneurons.

**METHODS**

**Study description**

This study consisted of ≈2 experimental sessions. Session 1 consisted of tests of withdrawal behaviors at 4 to 6 locations on the lower leg and foot. Session 2 consisted of tests of windup (e.g., see Hornby et al. 2002) at 4 locations on the foot and lower leg, including trials switching test locations in the midst of the windup stimuli. A total of 15 volunteers (12 SCI, 3 spinal-intact) participated in this study, conducted on 2 separate days. Ten SCI subjects and 3 spinal-intact subjects participated in session 1, testing local sign at 4 to 6 locations on the skin of the foot and lower leg. Ten SCI subjects (8 from session 1) participated in session 2, consisting of tests of windup at different skin locations. The SCI study subjects all had clinically “complete” spinal cord injury [American Spinal Injury Association (ASIA) scale A] at levels ranging from C5 to T10 and are summarized in Table 1. Seven of the 12 SCI subjects were taking oral medication for spasms.

**Test apparatus**

The experimental apparatus used for this study was described previously (Hornby et al. 2002; Schmit et al. 2000). Briefly, each subject was seated in an adjustable chair of a Biodex Rehabilitation/Testing System 2 (Biodex Medical Systems, Shirley, NY); referred to as a Biodex. The foot was clamped to a fixation plate, which was coupled, in turn, to a 6 degrees-of-freedom load cell (Model FT3550, Assurance Technologies) mounted on a modified footplate. The load cell was used to measure the isometric joint torque response to electrocutaneous stimuli. The leg was placed in a comfortable position with the ankle, knee, and hip in approximately midrange of motion, aligned in the sagittal plane. Specifically, the ankle was placed at 100–135° (10–45° of plantar flexion), the knee at 70–130° (110–50° of flexion), and the hip at 75–110° (105–70° of flexion) and 0–10° of abduction. There was no apparent effect of leg position on the responses within these ranges. The distance between the ankle axis of rotation and the load cell reference position was measured along the Cartesian axes of the load cell. The length of the lower leg, between the ankle and knee axes of rotation, and the length of the femur were measured for subsequent calculations of sagittal plane joint torques. A lubricated plate fixture was applied to the medial and lateral surfaces of the knee to prevent frontal plane hip movement.

Surface EMGs were recorded from the tibialis anterior (TA), soleus, medial gastrocnemius (MG), vastus medialis, rectus femoris, and biceps femoris. Active electrodes (Model DE2.1; Delsys, Boston, MA) were applied to the lightly abraded, degreased skin over the respective muscle belly. The leads were attached to a preamplifier/filter system (amplification ×10,000, Delsys Bagnoli 8). All signals were low-pass filtered (500 Hz) and sampled at 1,000 Hz using a data acquisition card (National Instruments, Austin TX) on a personal computer. Custom LabVIEW software (National Instruments) was used for controlling data acquisition and timing of electrical stimuli.

**Stimulation**

Pairs of stimulating electrodes (1 cm diameter; Blue Sensor, N-10-A; Medicotest, Rolling Meadows, IL) were placed at the high point of the medial arch of the foot, on the foot dorsum approximately 3 cm distal to the ankle joint, on the foot dorsum at the base of the 1st and 2nd metatarsals, at the ankle posterior to the lateral malleolus (near the sural nerve), and on the posterior and anterior surfaces of the lower leg midway between the medial malleolus and the knee axis of rotation. Electrodes were placed about 1 cm apart and connected to a bipolar stimulator (Digitimer DS7A; Hertfordshire, UK) when testing the response to an electrocutaneous stimulus. A separate stimulator was connected to a 2nd electrode pair for tests involving multiple test sites (crossover) and command signals to each stimulator were provided by the digital channel outputs of a personal computer. The stimulus consisted of 10 pulses delivered at 2-ms intervals (500 Hz). Each stimulus pulse was 1 ms in duration and the current amplitude ranged from 5 to 50 mA.

**Data analysis**

The EMG and isometric joint torque response to each electrocutaneous stimulus was quantified following the end of the experimental session. All filter processing of the data used the filtfilt function of Matlab (Mathworks, Natick, MA), which filters the data in the forward and reverse directions to eliminate the phase delay. The EMG was band-stop filtered at 55–65 Hz to eliminate line noise using a

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<th>Age</th>
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4th-order Butterworth filter and then rectified. The rectified EMG was then smoothed using a 4th-order low-pass Butterworth filter with a cutoff frequency of 5 Hz.

The isometric joint torques for the ankle, knee, and hip were calculated in the sagittal plane using the measurements obtained from the load cell. The data were multiplied by the transformation matrix described in Schmit et al. (2000), using measurements of load cell location, ankle and knee angles, and tibia and femur lengths. The resulting joint torque data were low-pass filtered at 10 Hz using a 4th-order Butterworth filter and the peak torque values were identified for each joint.

**RESULTS**

**Session 1 procedures**

For session 1 experiments, each stimulus site was tested using 7 different amplitudes: 5, 10, 15, 20, 30, 40, and 50 mA. The order of the stimulus amplitude was randomized and repeated 3 times at 20-s intervals. The peak torque amplitudes and peak smooth rectified TA EMG were obtained for the response to each stimulus and a stimulus-response curve was constructed for the hip torque, ankle torque, and TA EMG. The response to the electrocutaneous stimulus was compared for the different test sites. Because the magnitude of the response varied by stimulus site, comparisons of the pattern of muscle activity for the responses were based on the ratio of peak hip flexion and ankle dorsiflexion torques. The ratios of the peak ankle and hip torques were calculated for each stimulus response and compared across subjects for the arch and dorsum using a paired t-test at the 50-mA stimulus level. The combined effects of stimulus intensity and stimulus site were tested using a 2-factor ANOVA with repeated measures. The ANOVA was applied to the responses of the first 4 stimulus intensities above threshold for the arch and dorsum. Threshold was identified based on visual inspection of raw TA EMG for detectable activity within the first 20 ms after the stimulus.

**Session 2 procedures**

For session 2 experiments, the convergence of electrocutaneous reflex pathways was tested using the windup phenomenon, defined as an increase in flexion withdrawal with repeated stimuli at intervals <3 s. Because repeated stimuli produce progressively larger responses over the first 3 stimuli (Hornby et al. 2002), we sought to determine whether the response to an electrocutaneous stimulus would be greater if preceded by conditioning stimuli at another stimulus site. Because the stimulus sites correspond to different segmental levels, an increased response after conditioning stimuli would suggest convergence of the cutaneous pathways at a level beyond the primary afferent synapse.

Four test sites were considered: the medial arch, dorsum, and anterior and posterior surfaces of the lower leg. A stimulus-response curve similar to the session 1 procedures was obtained, and tests of electrocutaneous windup (see Hornby et al. 2003 for details) were conducted at each stimulus site. A stimulus intensity of 20 mA over threshold (30–70 mA) was used for all tests. For these tests, the electrocutaneous stimulus was repeated at 1-s intervals, with a total of 6 stimuli. Three windup tests were conducted for the arch and dorsum, which were followed by 10 tests in which the stimulus site was switched between the 2nd and 3rd stimuli. For example, 2 test stimuli were applied to the medial arch at a 1-s interval, which were followed 1 s later by 4 test stimuli applied to the dorsum of the foot. Ten switching trials were conducted, alternating between arch to dorsum and dorsum to arch, resulting in 5 trials each. Finally, 3 windup tests (single-stimulus site) were repeated for the arch and dorsum to ensure that there were no systematic changes in the response to the electrocutaneous stimuli.

The mean peak EMG and torque responses were calculated for each stimulus of the windup. The peak values of the 1st and 3rd stimuli of the windup trial at the arch were compared with the 1st stimulus at the arch with 2 preceding conditioning stimuli applied to the foot dorsum using paired t-test. A similar analysis was used for the foot dorsum stimuli.

Windup and preconditioning stimuli were also compared for the anterior and posterior surfaces of the lower leg in 3 of the subjects. These results were compared to determine whether the switching stimuli on the lower leg were consistent with the results from foot stimulation.

**RESULTS**

**Session 1**

A typical SCI response to an electrocutaneous stimulus is shown in Fig. 1 for Subject B. The data were recorded in response to a 50-mA stimulus applied to the medial arch of the foot. A clear EMG response was observed in the TA muscle, with smaller recordings also made in the other muscles of the leg. The resulting joint torques consisted of strong hip and ankle flexion and a small extension moment at the knee. Knee extension torques were generally small compared with ankle and hip torques (<5Nm for 9/10 subjects participating in session 1) and were predominantly in extension (9/10 subjects participating in session 1; Subject G was the exception).

**FIG. 1.** Flexion reflex response to cutaneous stimulus is shown for SCI Subject B. Stimulus parameters: 1-ms pulsewidth, 50 mA, 10 pulses, 500 Hz. Stimulus was applied to arch of foot. A: electromyogram (EMG) responses of tibialis anterior, medial gastrocnemius, rectus femoris, and medial hamstrings are shown. These results are typical of other subjects all of whom elicited dominant EMG response in tibialis anterior. B: joint torque responses of hip, knee, and ankle are shown. Stimulus is indicated by pulse at time = 50 ms. For this subject, strong hip and ankle flexion was observed with a simultaneous weak knee extension. This pattern of joint torques was typical.
In all of the SCI subjects tested, there was no clear change in joint torque pattern of response with stimuli applied to the foot dorsum or the medial arch. This observation contrasted with local sign withdrawal observed in spinal-intact controls. Two exemplary cases are shown in Fig. 2. Subject G produced a clear flexion of the hip, knee, and ankle at both test locations, whereas the hip and ankle torques changed sign in the spinal intact subject, with arch stimulation producing hip and ankle flexion, whereas dorsum stimulation produced extension in both joints. Changes in joint torque for spinal-intact subjects consisted of a large decrease in hip flexion (mean 73%) and ankle dorsiflexion (mean 78%) and a modest decrease in knee flexion torque (mean 17%) in comparing the responses of the foot dorsum stimulus to the medial arch responses. These results are consistent with differences in muscle activity (EMG) patterns; for example, the TA EMG decreased dramatically in response to dorsum stimulation in the spinal-intact subjects. Conversely, the TA and MG EMGs were comparable for the SCI subject. In all 10 SCI subjects tested, the torque never changed from flexion to extension, or from extension to flexion, at any joint, by changing the stimulus location.

The stimuli were also tested at a stimulus site over the sural nerve and at the toes, with results for Subject H shown in Fig. 3. The responses were comparable at each stimulus location, with no apparent difference in the pattern of torque generation. Similarly, a comparison between the torque response associated with stimulation applied to the anterior and posterior skin of the lower leg (considering the 5 subjects with ankle torques >2 Nm) also demonstrated comparable patterns of torque generation. An example is shown in Fig. 4, for Subject G. The torque was produced in the same direction for each stimulus site, for each test subject; however, we noted that the magnitude of response was comparable at each test location.
Session 2

Convergence of cutaneous afferent inputs from different regions of the limb onto common neuronal pathways was assessed in 10 subjects using the windup/crossover design. Windup, which is an increase in the flexion reflex response when preceded by conditioning stimuli, has been observed in chronic SCI (Hornby et al. 2003). We postulated that the similarity of the response to skin stimuli at different locations might be the result of convergence of afferent inputs onto a common interneuronal pathway (possibly located in 2nd- or 3rd-order interneurons or motoneurons). Subjects were tested using a series of 6 stimuli, applied at 1-s intervals. The responses to repeated stimuli at one location were compared with the response when the stimulus was preceded by conditioning stimuli at another skin location. An example is shown in Fig. 6 for Subject D. Figure 6A shows the results from dorsum stimulation, overlaid on the response with 2 preconditioning stimuli applied to the medial arch. Note that the response to the 3rd stimulus is identical for both conditions. Similarly, the response to medial arch windup was comparable to the response with 2 preconditioning stimuli applied to the foot dorsum (see response to 3rd stimulus in Fig. 6B). These results were consistent across all subjects tested, with the 3rd through 6th responses identical for windup and windup with preconditioning.

Averaged data for the first 3 pulses for all subjects are summarized in Fig. 7. The mean peak ankle and hip torque was calculated for arch stimulation, dorsum stimulation, and trials in which the stimulation was changed from one location to the other (between the 2nd and 3rd pulses). Mean peak torques were calculated for each stimulus, for each subject. These data were then averaged across subjects, for each stimulus number. Note that windup occurred, with the response to the 2nd and 3rd stimuli being larger than the 1st stimulus for arch or dorsum stimuli alone. When the stimulus site was switched, the...
response to the 3rd stimulus was similar to the stimulus obtained after windup alone at the 2nd stimulus, and was consistent across all subjects (Fig. 7).

Paired t-tests were used to compare the responses to the windup stimuli. For trials in which no switching was applied, there was a significant difference between the 1st and 3rd stimuli for ankle and hip peak torque responses at the arch ($P < 0.05$). Similarly, peak hip torque responses to the 1st and 3rd stimuli were significantly different during stimulation of the foot dorsum ($P < 0.05$); however, the peak ankle torque was not significantly different despite a mean increase. The response to the 1st crossover stimulus was also compared with the 1st and 3rd stimuli of the single-site test. Again, significant differences were observed in all comparisons except for ankle peak torques with stimuli applied to the foot dorsum.

The effects of changing the stimulus site were also examined.

**FIG. 6.** Responses to repeated stimuli, with crossover of stimulus sites, are shown for Subject D. Stimuli with 1-ms pulsewidth, 50 mA amplitude, 10 pulses, 500 Hz, were applied at 1-s intervals. **A**: gray traces indicate response to stimulation of foot dorsum at 1-s intervals. Black traces demonstrate response to 2 stimuli applied to arch, with stimulus site switched to dorsum of foot for remaining stimuli. Last 4 responses overlapped completely with dorsum-only responses, suggesting that responses to 3rd and later stimuli were independent of site of first 2 stimuli. **B**: similar results were obtained with arch stimulation (gray) and switching of stimulus site from dorsum to arch on 3rd stimulus (black). Again, 3rd response and later were virtually identical.
with stimulation of the lower leg in 3 subjects that produced torque responses >1 Nm at the hip. Example data are shown in Fig. 8. These data were qualitatively similar to the responses elicited by test stimuli on the foot, with similar responses obtained at each test site.

**DISCUSSION**

Electrocutaneous stimuli applied to different locations on the skin of the leg in human SCI produced similar joint torque responses in 10/10 subjects. This absence of local sign with-
drawal differs from the response in spinal-intact subjects in which the leg responds in a manner that removes the skin from a noxious stimulus (see Fig. 2, Hagbarth 1960). As a result, the interneuronal processing of cutaneous stimuli is altered in chronic human spinal cord injury either directly by the release of descending influences or indirectly throughout plasticity in the neuronal pathways after injury. The follow-up experiments using windup and crossover of stimulus locations suggest that the musculotopic organization of the flexion reflexes, typically associated with deep dorsal horn interneurons, is lost in chronic human spinal cord injury.

Comparisons of electrocutaneous reflex responses in spinal-intact and SCI subjects

One of the primary observations of the current experiments was an absence of local sign withdrawal in chronic SCI. These results differ from observations of electrocutaneous reflex organization in animals and in spinal-intact humans. In the rat, each hindlimb muscle has an organized, “nocireceptive” field on the skin associated with the withdrawal reflex (Schouenborg and Kalliomaki 1990). These reflex activations act to move the limb in a direction away from the stimulus for the standing rat (Schouenborg et al. 1994). As a result, a “modular organization” of the spinal cord based on a musculotopic mapping of spinal interneurons has been suggested. (Musculotopic mapping refers to cells that are associated with the activity of specific muscles, rather than regions of the skin.)

The modular organization, or local sign withdrawal, has also been documented in spinal-intact humans in marked contrast to the SCI data that we have observed. For example, the plantar surface of the foot has been tested for both excitation and inhibition of different muscles at ≥16 different test sites, with results indicating that there is both an excitatory and inhibitory map (generally organized as agonist/antagonist; Andersen et al. 1999; Sonnenborg et al. 2000, 2001). Local sign is maintained for both flexion/extension and inversion/eversion muscle groups. Similarly, human local sign withdrawal has been demonstrated using 11 stimulus sites on the skin of the dorsum of the foot including responses producing plantarflexion movements (Sonnenborg et al. 2001). These results contrast the stereotyped single-response type that we observed in subjects with chronic SCI. In fact, we did not observe plantarflexion of the ankle for any of the stimulus sites. Further, the ankle response to dorsum stimulation had a similar proportion to hip flexion as the reflex response to stimulation applied to the skin of the arch.

Spinal locus of windup in chronic human SCI

The locus of flexion reflex windup is unknown, but a number of factors suggest that the 2nd order, or deep dorsal horn neurons, as well as motoneuronal pools, may be involved. Windup was originally noted in cat dorsolateral spinal columns, with axon origination in the dorsal horn (Rexed lamina IV) in response to activation of skin afferents (Mendell 1966). The deep dorsal horn neurons have also been associated with windup or central sensitization to pain stimuli in rats (Morisset and Nagy 1998; Schouenborg and Sjolund 1983; Woolf 1983; reviewed by Herrero et al. 2000). These same cells are intercalated within the flexion reflex (Schouenborg and Sjolund 1983) and many exhibit intrinsic membrane properties consistent with windup (Morisset and Nagy 1998, 2000). As a result, deep dorsal horn neurons are appealing candidates for windup of human flexion reflexes.

Observations of windup of flexion reflexes in human SCI are consistent with a windup site involving the deep dorsal horn neurons. Comparisons of the windup in dorsal horn neurons suggest that the deep dorsal horn neurons, particularly those with wide dynamic range (responding to A- and C-fiber stimulation), show windup more than superficial dorsal horn neurons responding to the same types of stimuli (Schouenborg and Sjolund 1983). Previous tests of windup of the flexion reflex in human SCI demonstrated a decrease in latency of the flexion reflex with repeated stimuli, an observation consistent with windup of wide dynamic range interneurons (see Hornby et al. 2002 for discussion). The deep dorsal horn neurons (lamina III–V) have also been implicated in the spatial organization of withdrawal reflexes in the spinal rat, being assigned a “musculotopic” arrangement (Schouenborg et al. 1995). This suggests that the deep dorsal horn neurons may receive inputs from multiple spinal segments, as would be required for the windup crossover observed in the present study. The superficial dorsal horn neurons also receive inputs from cutaneous afferents; however, they are arranged in a somatotopic arrangement (Light and Durkovic 1984), which would make them unsusceptible to windup crossover. As a result, the loss of local sign, coupled with carryover of windup excitability from sites at different segmental levels, indicates that deep dorsal horn neurons may be the site of windup.

In the present experiments, the response to the 3rd stimulus in the crossover trials was similar to the response of the 3rd stimulus in the windup trials. Most of the similarity could be attributed to windup caused by stimulation at the original site, although significant differences remained. In particular, crossover from dorsum to arch stimuli resulted in a response that was smaller than the response to the 3rd stimulus of windup at the arch. Conversely, crossover from arch to dorsum resulted in a response that was significantly larger than the response to the 3rd stimulus of windup at the dorsum for data at the hip; however, the ankle differences were not significant. One possible explanation for these differences may be that arch stimulation generally resulted in larger responses than foot dorsum stimulation resulting in greater windup of the motoneuronal pool for crossover trials from the arch to the dorsum.

The small differences in the crossover stimuli suggest that ankle and hip flexor motoneurons may also exhibit properties contributing to windup. The presence of windup in human motoneurons has been observed as a decrease in the threshold of motor unit recruitment with repeated voluntary contractions at intervals less than about 6 s (Gorassini et al. 2002a). Related observations of force fluctuations with low levels of electrical stimulation (Collins et al. 2001) and nonlinearities in motor unit recruitment/derecruitment (Gorassini et al. 2002b) coincidentally indicate the presence of plateau potential behaviors in human motoneurons. Plateau potentials have been associated with windup in reduced animal preparations (rat: Morisset and Nagy 2000; cat: Bennett et al. 1998; turtle: Russo and Hounsgaard 1994; Svirks and Hounsgaard 1997), indicating a possible role for motoneuronal plateau potentials in windup of the flexor reflex observed in the current study. Acutely after spinal cord injury, plateau potential behavior of motoneurons is lost...
(rat: Bennett et al. 2001b; cat: Hounsgaard et al. 1988); however, the motoneurons of chronically spinalized rats again show evidence of plateau potential behaviors, which has been suggested to contribute to hyperreflexia in chronic spinal cord injury (Bennett et al. 2001a).

For the current study, motoneuronal windup may be less of a factor than deep dorsal horn interneuron windup based on the following rationale: when stimulating the arch, a large flexor motoneuron activation was noted; therefore we might expect that the 3rd pulse of the windup would be larger for arch stimulation than for crossover from the dorsum, which elicits much smaller responses. Similarly, we might expect that the 3rd pulse of the windup sequence for the dorsum would be smaller than crossover from the arch. Although there was a slight trend in this direction (Fig. 7), it could not account for the majority of windup effects. We cannot, however, exclude the role of flexor motoneuronal plateaus in the contribution of windup in our present results.

Implications of a loss of local sign in human spinal cord injury

The loss of local sign in chronic human SCI raises questions about interventions designed to produce targeted movements using microstimulation of spinal cord. Microstimulation of the acute spinalized frog (Tresch et al. 1999) or chronic (3 wk) spinalized rat (Tresch and Bizzi 1999) produces directional movement of the hindlimb. Because these same spinal locations respond to stimulation of specific regions of the skin and the pattern of movement from microstimulation of the cord is consistent with local sign withdrawal (Tresch and Bizzi 1999), a link has been made between directional specificity of electrocutaneous reflexes and basic functional groupings of muscle activity (Tresch et al. 1999). The present data indicate that the directional specificity of different parts of the spinal cord have been lost after injury (or never existed at the spinal level in humans). As a result, microstimulation of the spinal cord may not produce a set of unique basic groupings of muscle activation.

Plasticity of spinal electrocutaneous reflexes

The absence of local sign in chronic human SCI suggests that either the flexion reflex organization has undergone significant plastic change in the period after injury, or that the organizational center of local sign is located in supraspinal structures in humans. In rats, the modular organization of the electrocutaneous reflexes is retained after spinalization (<12 h) (Schouenborg et al. 1992), although the region of excitation expands (Schouenborg et al. 1994). Similarly, targeted inhibitory reactions are observed in the rat hindlimb within 12 h of spinalization (Weng and Schouenborg 1996), supporting the notion that a spinal organization of reflexes in acutely spinalized rats is maintained. These studies suggest that the organization of local sign flexion reflexes in humans must either reside in supraspinal centers or the human spinal cord undergoes plastic changes in the organization of this reflex. Although species-dependent differences in the spinal organization of flexion reflexes have been demonstrated in the reflex sensitivity of the extensor digitorum longus in cats compared with rats (possibly because of differences in the biomechanics of standing in the 2 species) (Levinsson et al. 1999), many cases of spinal plasticity have been observed, making reorganization of the spinal reflexes a feasible explanation for the loss of local sign.

A number of plastic changes in the spinal organization of flexion reflexes have been documented. For example, in the neural development of rats, immediately after birth (days 1 and 5), rats produce poorly organized flexion reflex responses, which develop into the known modular organization in adults (3 wk old) (Holmberg and Schouenborg 1996). In the tail of the rat, spinal intact and spinalized (24 h) rats demonstrate markedly different responses to noxious heat stimuli of different regions of the skin (Cleland and Bauer 2002). Similarly, receptive fields of rat spinal interneurons intercalated within the flexion reflex pathways demonstrate changes in their receptive fields in response to conditioning stimuli (Cook et al. 1987) and motor units of the biceps femoris demonstrate a decrease in threshold and increase in receptive field after a peripheral tissue injury (Woolf 1983). One example of spinal plasticity that may be of particular interest is the expansion of the receptive cutaneous fields of the muscles of the rat spinal cord after transection (out to 12 h) (Schouenborg et al. 1992), which, if they expanded far enough, could explain the present results.

An increase in sensitivity of the flexion reflexes could mask an underlying local sign organization. For example, slight differences have been observed with different stimulus intensities applied to the human foot sole (Sonneborg et al. 2000). However, in general, the responsive areas for specific muscles are restricted, regardless of the amplitude of the stimulus (Anderson et al. 2001). Our data suggest that stimulus intensity is a small factor in the flexion reflex response, with ankle recruitment occurring at lower stimulus intensities than hip recruitment (indicated by increasing hip:ankle torque ratios in Fig. 5). Furthermore, this dependency on stimulus intensity is the same for both medial arch and dorsum stimuli.

Based on the results of this study, we conclude that a modular organization of the spinal cord to produce local sign withdrawal is lost in chronic human SCI. These changes may be the result of a reorganization of the spinal interneurons of the deep dorsal horn, which may also contribute substantially to windup properties of the flexion reflex.

DISCLOSURES

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REFERENCES


