Effects of sustained stimulation on the excitability of motoneurons innervating paralyzed and control muscles

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Butler, Jane E., and Christine K. Thomas. Effects of sustained stimulation on the excitability of motoneurons innervating paralyzed and control muscles. J Appl Physiol 94: 567–575, 2003. First published October 11, 2002; 10.1152/japplphysiol.01176.2001.—The excitability of thenar motoneurons (reflected by F-wave persistence and amplitude) and thenar muscle force were measured during a stimulation protocol (90 s of 18-Hz supramaximal electrical stimulation of the median nerve) designed to induce muscle fatigue (force decline). Data from muscles (n = 15) paralyzed by chronic cervical spinal cord injury were compared with those obtained from control muscles (n = 6). The persistence of F waves in both paralyzed and control muscles increased from ~60% to ~76% during the first 10 s of the fatigue protocol. Persistence then declined progressively to ~33% at 90 s. These changes in F-wave persistence suggest that similar reductions occur in the excitability of the motoneurons to paralyzed and control motor units after sustained antidromic activation. Despite this, significantly larger force declines occurred in the paralyzed muscles of spinal cord-injured subjects (~60%) than in the muscles of control subjects (~15%). These data suggest that the decreases in motoneuron excitability for both the spinal cord-injured and control subjects are a result of activity-dependent changes in motoneuron properties that are independent of fatigue-related processes in the muscles.

motoneuron excitability; spinal cord injury; F-wave persistence; paralyzed muscle; electrical stimulation

AFTER SPINAL CORD INJURY (SCI), the motoneurons of paralyzed muscles experience many changes. The balance between the excitatory and inhibitory synaptic inputs may be altered as a result of the removal of descending drive to the motoneurons, interneurons, and presynaptic terminals (e.g., Refs. 3, 26). The motoneurons of paralyzed muscles may receive new inputs from axons that have sprouted from neighboring cells (for reviews see Refs. 5, 32). In humans with chronic SCI, external stimuli such as light touch or muscle stretch often excite the motoneurons of paralyzed muscles more easily. This can result in hyperreflexia or muscle spasm (e.g., Refs. 4, 39, 43). In animals with spinal cord transection, there are alterations in the intrinsic properties of the motoneurons (6, 17, 27). It is less clear whether motoneuron properties also change after human SCI.

The present study was designed to determine whether the excitability of human thenar motoneurons 1) was different for thenar muscles paralyzed chronically by SCI compared with muscles of able-bodied control subjects, 2) changed during sustained electrically stimulated contractions of these paralyzed and control muscles, and 3) paralleled the changes in muscle force during sustained electrically evoked contractions, particularly given the known differences in the fatigability of paralyzed and control thenar muscles (36).

We have assessed the excitability of thenar motoneurons by the analysis of F waves. With electrical stimulation of the peripheral nerve, there is activation of both the target muscle orthodromically and the motoneurons antidromically (1, 10). Antidromic activation can reexcite a proportion of these motoneurons. The reflected impulses travel orthodromically to the muscle and can be recorded as F waves (Ref. 24; for review see Ref. 28). In the present study, the motoneurons of both paralyzed and control muscles experienced the same sustained antidromic activation. This allowed direct comparisons of the changes in motoneuron excitability and muscle fatigue (force decline) in both chronically paralyzed muscles and control muscles independent of voluntary drive.

METHODS

Fifteen people with chronic (>1 yr) cervical-level SCI took part in these studies. The current level of SCI was assessed by using the American Spinal Injury Association criteria (Ref. 25a, Table 1). The thenar muscles of the hand tested were under no voluntary control. That is, no electromyo- graphic (EMG) activity was produced when the subjects were asked to contract these muscles voluntarily, and there was no palpable muscle shortening during a manual examination. Our laboratory’s previous studies on thenar muscles paralyzed by chronic cervical SCI have documented signs of muscle denervation (due to motoneuron death and/or ventral root damage) and reinnervation. For example, motor unit forces and EMG potentials were often larger than usual. In two subjects, >90% of the whole muscle force was produced by

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fewer than five motor units. Approximately one-half of the thenar muscles studied were significantly weaker than control muscles (35). For three subjects who also participated in cases of chronic cervical SCI examined postmortem (15). Thus it is very likely that within this group of SCI subjects there has been partial denervation of the thenar muscles, followed by reinnervation from nearby axons. Six able-bodied subjects with no known neurological disorders also took part as controls (Table 1). Each subject gave informed, written consent to participate in the experiments. All experimental procedures were approved by the local ethics committee and consent to participate in the experiments. All experimental procedures were conducted in accordance with the Declaration of Helsinki.

**Experimental setup.** The subject sat in a chair with the test arm to the side. The forearm was held stable in a rigid vacuum cast, and the hand was supinated (see Refs. 35, 36). The dorsum of the hand was stabilized in modeling clay, and the fingers were restrained from moving by a metal plate strapped over their surface. The thumb was extended and rested with ~0.5 N passive force against a custom-made force transducer that permitted flexion and abduction forces to be measured separately at right angles to one another. The forces recorded with the hand in this experimental position are produced by all median-innervated thenar muscles (abductor pollicis brevis, flexor pollicis brevis, and opponens pollicis). The forces were amplified and filtered (direct current to 100 Hz; model 2310, Measurements Group, Raleigh, NC) and sampled to a computer at 400 Hz (SC/Zoom data acquisition system, Dept. of Physiology, University of Umeå, Umeå, Sweden). The resultant force that was used for the analyses was calculated off-line by using the following equation

\[
\text{Resultant force} = \sqrt{\left(abduction \text{ force}\right)^2 + \left(flexion \text{ force}\right)^2}
\]

Three electrodes (flexible braided strands of silver-coated copper wires) were used to record surface EMG activity from the proximal and distal portions of the thenar muscles. The common electrode was placed over the belly of the thenar muscles between the two other electrodes. One electrode was placed proximally over the base of the thenar eminence, while the other was distal over the metacarpal-phalangeal joint of the thumb. The differential signals between the common and proximal electrodes, and between the common and distal electrodes, were amplified, filtered (30 Hz to 1 kHz; Grass P511 amplifier, Astro-Med, West Warwick, RI), and sampled to a computer at 3,200 Hz.

The thenar muscles were activated transcutaneously by supramaximal electrical stimulation of the median nerve with a stimulating electrode placed just proximal to the wrist (250-µs pulse width, 100–150 V; Grass S88, Astro-Med). The anode and cathode were 3 cm apart and 1 cm in diameter. The stimulator was triggered by computer-generated pulses. The pulse patterns were programmed by using commercially available software (Fystat, Datalid, Umeå, Sweden). The stimuli were delivered at a voltage that was ~15% higher than that required to produce a maximal M wave in the muscles. Both the proximal and distal EMG signals were monitored on an oscilloscope throughout the experiment.

**Experimental protocol.** Isometric contractions of the paralyzed and control thenar muscles were evoked by supramaximal electrical stimulation of the median nerve at 18 Hz for 90 s. This frequency of stimulation was chosen because it results in largely fused muscle contractions. It was also the mean motoneuron firing frequency observed at the end of a sustained (fatiguing) maximal voluntary contraction of the thenar muscles (36).

Both before and immediately after the 90 s of stimulation at 18 Hz, five single supramaximal stimuli were delivered at 1 Hz to assess the twitch force. The maximal tetanic force of the thenar muscles was evoked by delivering stimuli at 50 Hz for 1 s (Fig. 1).

**Data analysis.** The latency and peak-to-peak amplitude of each F wave (when present) were measured for 20 consecutive stimuli at 0, 10, 25, 45, 65, and 89 s because, for the median nerve, assessment based on 20 trials is considered to be clinically adequate (28). This constituted a total of 120 measurements for the six periods. F waves were only measured if they were clearly visible above the noise associated with the surface EMG. On average, the peak-to-peak noise was 18 ± 3 (SD) μV, whereas the smallest F waves measured for SCI and control subjects were 23 and 32 μV, respectively. The onset latency of F waves, when present, ranged from ~21 to 45 ms depending on the subject. The range of F-wave latencies for each subject from the entire experiment (n = 120 stimuli) was used to calculate the F-wave chronodispersion. The chronodispersion depends on the range of conduction velocities of the activated motor axons (23, 28).

F-wave persistence (the number of F waves present out of each set of 20 responses) was used as our primary measure of motoneuron excitability. Because F waves occur with the same incidence in both low- and high-threshold motoneurons (9, 23, 37), the F-wave amplitude is an indication of the number of motoneurons activated. Hence, amplitude can also reflect the excitability of the motoneuron pool (12). To measure F-wave amplitude, the EMG records were first high-pass filtered (70 Hz) to remove the tail end of the maximal M

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**Table 1. Subject data for control and SCI groups**

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<th>Cause</th>
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Control

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<tr>
<td>Mean ± SE</td>
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SCI, spinal cord injury; MVA, motor vehicle accident; M, male; F, female.
wave on which the F wave could occur, particularly toward the end of the 90 s of stimulation because of slowing of the M wave. This filtering procedure did not significantly affect the peak-to-peak amplitude of the F waves at the beginning or the end of the fatigue protocol. F-wave amplitudes were expressed relative to the amplitude of the maximal M wave measured at around the same time (within 1.1 s; 0 (Mmax1), 10 (Mmax2), 25 (Mmax3), 45 (Mmax4), 65 (Mmax5), and 89 s (Mmax6)) and averaged across each set of 20 stimuli. If F waves were not present by visual inspection, the amplitude was considered to be zero. Zero values were included in the mean calculation because this gave an average amplitude across 20 stimuli, which is representative of the average response of the motoneuron pool.

Maximal M waves were also measured every 5 s throughout the 90 s of 18-Hz stimulation. We measured the onset latency, peak-to-peak amplitude, area, and duration of the first two phases of the potential from either the distal or proximal portion of the muscle. For every subject, each maximal M wave measured was normalized to the maximal M wave at the beginning of the 90 s of 18-Hz stimulation. The peak resultant forces were measured at the same time points as the M waves. In addition, twitch force and 50-Hz tetanic force were measured before and immediately after the sustained stimulated contraction.

**Statistics.** For SCI and control subjects, data were averaged across the group for F-wave persistence, F-wave amplitude (%Mmax1 to %Mmax6), maximal M-wave area, and amplitude (% initial), and force (% initial). Data are expressed as means ± SE. Significant changes in these variables across the 90 s of 18-Hz stimulation and significant differences between paralyzed and control muscles were assessed by using a two-way ANOVA with Student-Newman-Keuls post hoc all-pairwise comparisons. A Kruskal-Wallis one-way ANOVA on ranks was used with Dunnett’s method post hoc all-pairwise comparisons to determine any changes in the variables over time within a subject group. Twitch and 50-Hz forces evoked before and after the 90-s stimulation at 18 Hz were compared by using paired t-tests. Pearson product-moment correlations were used to establish whether there were significant relationships between different variables. Statistical significance was set at $P < 0.05$. Overlap between male and female muscle force for SCI and control subjects allowed data to be pooled across gender (40).

**RESULTS**

**Changes in F waves.** Figure 2 shows maximal M waves and the subsequent F waves recorded from the paralyzed thenar muscles of one SCI subject during the first and last second of the 90 s of 18-Hz stimulation. The maximal M wave decreased in amplitude after 90 s of stimulation, although the area of the response remained constant (Fig. 2A, see Changes in maximal M waves). Therefore, F-wave amplitudes were always expressed relative to the amplitude of the maximal M wave recorded at approximately the same time. The same traces are shown in Fig. 2B at a higher gain to depict the F-wave responses (small late responses between dashed lines). The decrease in the occurrence of F waves is evident in the last second of stimulation by the more frequent absence of responses (Fig. 2B, right). Notice the variability in the F-wave amplitudes and latencies compared with the consistency of the maximal M waves (Fig. 2B).

F-wave persistence (a reflection of motoneuron excitability) was calculated as the proportion of trials in which an F wave was present (regardless of size) from a sample of 20 consecutive stimuli beginning at 0, 10, 25, 45, 65, and 89 s. Initial F-wave persistence was similar for paralyzed and control muscles (67 ± 10 and 53 ± 10%, respectively; Fig. 3A). The changes in persistence were also similar over time. After 10 s of stimulation, the persistence had increased for both SCI and control subjects (to 77 ± 9 and 75 ± 11%; not significant (NS)). F-wave persistence then began to decline progressively. Significant reductions from the maximum value at 10 s occurred at 65 s for both paralyzed and control muscles. By 90 s, F-wave persistence had fallen to 32 ± 9 and 33 ± 5% initial, respectively, values that were also significantly different from persistence at 10 s.

Initial mean F-wave amplitudes (%Mmax1; derived from the F-wave responses to the first 20 stimuli of the fatigue protocol) were not significantly different between SCI subjects (4.9 ± 1.7 Mmax1, range 0–26.5% Mmax1) and control subjects (1.9 ± 0.9 Mmax1, range 0.4–6.3% Mmax1; Fig. 3B). If no F wave was present, an amplitude of zero was included in the mean. Whether the zero-amplitude F waves were included in the means or not, there was no significant difference between initial F-wave amplitudes of SCI subjects and control subjects. This may relate to the large variability in F-wave amplitude across SCI subjects.

For SCI subjects, mean F-wave amplitude increased in the first 10 s (from 4.9 ± 1.7% Mmax1 to 5.8 ± 1.2% Mmax2; NS). From this increased level, there was a significant decrease in F wave amplitude by 65 s (to 2.8 ± 0.9% Mmax5) and at 89 s (to 3.6 ± 1.7% Mmax6). The SCI subjects with the largest F-wave amplitudes also showed the lowest average persistence of F waves.
They often, but not always, had the weakest maximum forces and therefore probably had the fewest remaining motor units. Despite this, these subjects showed changes in F-wave amplitude and persistence across the stimulation protocol that were consistent with the group data. For the control group, F-wave amplitude did not change significantly across the 90 s of 18-Hz stimulation, although the trends were similar to those seen for the SCI group (F-wave amplitudes were 1.9 ± 0.9% \(M_{max1}\), 2.8 ± 1.0% \(M_{max2}\) at 10 s, 3.0 ± 1.4% \(M_{max3}\) at 25 s, 2.5 ± 1.1% \(M_{max4}\) at 45 s, 2.1 ± 0.9% \(M_{max5}\) at 65s, and 1.5 ± 0.7% \(M_{max6}\) at 89 s; Fig. 3B).

When group mean F-wave persistence (%initial) and group mean F-wave amplitude (%initial) at each time point measured across the 90 s of 18-Hz stimulation were compared, there were significant positive correlations between these two parameters for both SCI and control subjects (\(r^2\) = 0.90 and \(r^2\) = 0.83, respectively). These results suggest that both of these measures, F-wave persistence and F-wave amplitude, reflect motoneuron excitability similarly.

The mean latency to the onset of the F waves (averaged across all measured F waves) was significantly longer for paralyzed muscles (31.2 ± 0.9 ms) than for control muscles (27.0 ± 0.6 ms). However, the minimum F-wave latency (1 value per subject) was not different between SCI and control subjects (26.0 ± 0.6 and 25.2 ± 0.6 ms, respectively). Mean F-wave chronodispersion was significantly higher for the paralyzed muscles (8.7 ± 1.1 ms) than for the control muscles (4.2 ± 0.4 ms).

Changes in maximal M waves. Initially, the amplitude of the maximal M wave for paralyzed muscles (10.0 ± 2.0 mV, coefficient of variation 0.78) was significantly smaller and more variable across subjects than that measured from control muscles (20.1 ± 2.1 mV, coefficient of variation = 0.65; Fig. 4A). However, the amplitudes of the maximal M waves recorded from

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Fig. 2. Electromyographic responses during the fatigue protocol from a SCI subject with paralyzed thenar muscles. A: 20 maximal M waves recorded at the beginning (left) and end (right) of the 90 s of 18-Hz stimulation are overlaid. B: raster of the same 20 traces as in A displayed at a different gain to show F-wave responses (between dashed lines).
and 13.7 ± 1.9 N of force in control thenar muscles. The mean absolute force evoked by 18-Hz stimulation was similar for SCI and control subjects but was more variable within SCI subjects (Fig. 4B; coefficient of variation = 0.88 for SCI subjects and 0.35 for controls). These forces corresponded to 87 ± 2 and 74 ± 6% of the maximal tetanic force generated in muscles of SCI and control subjects by 50-Hz stimulation (10.9 ± 2.3 and 18.8 ± 3.0 N, respectively). For the paralyzed muscles, the initial relative force produced by 18-Hz stimulation was significantly larger than that evoked from control muscles. However, for each subject group, there was no correlation between the proportion of maximal force (or the absolute force) produced initially by the 18-Hz stimulation and the amount of muscle force loss at the end of the protocol (i.e., fatigue).

After 90 s of stimulation at 18 Hz, the force had declined to 38 ± 3% of the initial force for paralyzed muscles and to 85 ± 4% of the initial force for control muscles (P < 0.05; Fig. 4B). For SCI subjects, the force declined significantly in the first 10 s, whereas, for control subjects, force potentiated initially (NS). The force decline in control muscles was not significant until after 65 s (Fig. 4B).

After the 90 s of stimulation, the tetanic force produced by 1 s of 50-Hz stimulation was reduced to 75 ± 5 and 97 ± 7% prefatigue values in SCI and control subjects, respectively. Twitch force was reduced to 45 ± 7 and 96 ± 17% prefatigue values (initially 2.1 ± 0.4 and 1.7 ± 0.2 N) in SCI and control subjects, respectively. The decline in muscle force production (fatigue) assessed by 18-Hz, 50-Hz, and twitch force was significantly greater in the paralyzed vs. control thenar muscles. The force loss in the paralyzed muscles was greater for the twitches and the 18-Hz stimulation than for the 50-Hz stimulation. This was not the case for the control muscles.

Changes in F-wave persistence and muscle force. Figure 5 illustrates the dissociation between F-wave persistence (motoneuron excitability) and muscle fatigue. For both groups, the reduction in F-wave persistence was of a similar magnitude, whereas muscle force loss was about four times greater in paralyzed muscles than in control muscles. This suggests that the changes in motoneuron excitability (as indicated by F-wave persistence) were independent of fatigue-related events in the muscles.

**DISCUSSION**

These data confirm other reports that show thenar muscle force declines more in paralyzed muscles than in control muscles during electrically stimulated contractions (36). Despite this, the motoneurons that innervated the paralyzed or control muscles behaved similarly with respect to their excitability. The mean F-wave persistence reached ~76% for both groups of subjects in the first 10 s of stimulation. Thereafter, F-wave persistence progressively declined to ~33% for both groups. These results suggest that the significant decreases in the excitability of motoneurons innervat-
ing paralyzed or control muscles that occur with sustained antidromic activation at 18 Hz are dissociated from the fatigue processes that take place in the muscles.

Motoneuron excitability. The potential for rearrangements in synaptic inputs to motoneurons (Ref. 26, 39; for reviews see Refs. 5, 32) and/or alterations in the intrinsic properties of motoneurons and muscle unit types after SCI (6, 17, 27) could lead one to suspect that the F-wave behavior during fatigue may be different between paralyzed and control muscles. However, the similarity in F-wave persistence for these two groups of subjects suggests that the intrinsic threshold for antidromic excitation of motoneurons has not altered significantly after chronic muscle paralysis (Refs. 1, 10; see also Refs. 6, 17, 27). This is in contrast to the large changes observed in muscle fiber properties after chronic paralysis.

After 90 s of 18-Hz stimulation, F-wave persistence was reduced in both SCI and control subjects. The changes in F-wave persistence and amplitude tended to parallel each other, although the amplitude changes over time were not significant for control subjects. This may be a consequence of the large variability in F-wave amplitude within a set of 20 measurements (Fig. 2; Refs. 9, 23, 37). Although these decreases in F-wave persistence probably reflect a reduction in the excitability of the motoneurons as a result of prolonged antidromic activation (see Refs. 20, 21, 31), a number of alternatives need to be considered.

First, the afferent input to a motoneuron pool evoked by stimulation may distort the amplitude and persistence of F-wave responses. Use of supramaximal nerve
stimulation (28), as employed here, normally avoids afferent influences on F waves. Moreover, postactivation homosynaptic depression of Ia afferents occurs with 18-Hz stimulation (e.g., Refs. 3, 18), so this should markedly diminish reflex activation of the motoneurons by these afferents. Similar processes probably occur in other large-diameter afferents. Thus large-diameter afferent input to motoneurons or changes in this input either due to the SCI itself or from muscle reinnervation (7) are unlikely to influence the persistence or amplitude of the present F waves. The similar reductions in motoneuron excitability observed here for both SCI and control subjects, even though the paralyzed muscles were fatigued to a much greater extent, also suggest that the F-wave changes are not directly mediated by feedback from small-diameter muscle afferents. Small-diameter afferents that are activated by the accumulation of muscle metabolites during fatigue (19) are considered to be responsible for the decreased H reflexes (14) and decreased motoneuron firing rates associated with fatigue in control muscles (30, 41). In contrast, the present data are consistent with other studies that have shown that prolongation of the firing of small-diameter muscle afferents does not decrease motoneuron excitability when tested with short-latency reflex responses (42), responses to transmastoid stimulation during relaxation (34), or during voluntary contractions (Ref. 2; for reviews see Refs. 13, 33).

Second, during repetitive nerve stimulation, there are activity-dependent changes that occur in peripheral motor (and sensory) axons that can reduce their excitability (e.g., Ref. 22). Again, these changes are normally avoided by the use of supramaximal nerve stimulation. This is one advantage of measuring F waves rather than H reflexes to assess motoneuron excitability during repetitive stimulation. However, in terms of F-wave initiation, the excitability of the axon hillock may be critical. Although activity-dependent changes in the axon hillock have never been studied directly in humans, it would be reasonable to assume that the axon hillock and peripheral motor axon properties will change in a similar manner. Therefore, it is possible that the decrease in F-wave persistence that we have observed in the present study may incorporate changes in the excitability of the axonal hillock and motor axons. F-wave persistence (and amplitude) changes for the two groups of subjects were not significantly different across the fatigue protocol. This suggests that any changes in motoneuron excitability and/or motor axons are similar for SCI and control subjects during prolonged antidromic activation.

Third, with low-frequency supramaximal stimulation of the whole median nerve in humans, abductor pollicis brevis F-wave persistence is ~80–100%, whereas mean F-wave amplitude is ~5% of the maximal M wave (11, 28). However, stimulation at interstimulus intervals of 50 ms reduces the amplitude and persistence of F waves after the second stimulus. This reduction is believed to result from the activation of recurrent inhibitory pathways (11, 25). At 18 Hz (interstimulus interval of 55.6 ms), our initial F-wave persistence and amplitude are, therefore, probably influenced by recurrent inhibition. However, the effects of prolonged stimulation at 18 Hz on the occurrence of F waves are not known. As a result, it may be difficult to distinguish whether the decreases in F-wave persistence over time are a consequence of prolonged antidromic activation of the motoneurons, the cumulative effects of sustained activation of recurrent inhibitory circuits, or both these processes. Nonetheless, the F-wave changes were not different for SCI and control subjects.

Finally, muscle reinnervation may influence the excitability of motoneurons. We have documented for some of the SCI subjects studied here that there has been partial denervation and reinnervation of the thenar muscles. This mixture of lower and upper motoneuron damage is particularly obvious in subjects with low maximal tetanic forces (35, 38). F-wave amplitudes were particularly large (relative to the maximal M wave) in some subjects with very low muscle forces. F-wave persistence was also lower in these subjects. These data are consistent with a lower number of motor units. Nevertheless, the changes in the excitability of the motoneurons were similar across the group of SCI subjects regardless of the initial muscle force, initial F-wave amplitude, or initial F-wave persistence. In addition, there were no significant correlations between the changes in the F waves and initial muscle force. Thus it does not seem that the SCI subjects with clear evidence of muscle reinnervation have unusual motoneuron properties, as assessed by the persistence and amplitude of F waves.

In summary, the changes in the F waves observed here most likely represent progressive changes in the intrinsic properties of the motoneurons associated with their sustained antidromic activation during the stimulation protocol.

F-wave latencies. The mean F-wave latencies and chronodispersion were significantly longer and higher, respectively, for the SCI vs. control subjects in the present study. However, minimum F-wave latencies were the same for the two groups. These data indicate that the fastest conducting motor axons were similar in SCI and control subjects. However, there may be a larger number of axons with slower conduction velocities in SCI subjects. Slowed conduction velocity may be due to the presence of thinly myelinated, large-diameter motor axons in human ventral roots near the site of SCI (15) or may reflect changes in the conduction properties of intact motor axons after a partial peripheral nerve lesion (16).

Conclusions. Changes in the excitability of motoneurons in human subjects during periods of prolonged activation have not been previously reported, other than by measuring motor unit firing rates during voluntary contractions. In the present study, F-wave analysis during sustained antidromic activation of the thenar motoneuron pools revealed reductions in motoneuron excitability that were similar in both SCI and control subjects. This was despite obvious differences
in their muscle fatigue and the potential for large differences in muscle afferent feedback to the spinal cord. Thus, if motoneuron excitability is reduced by sustained activation, any given input (reflex or voluntary) would have a reduced capacity to activate the motoneurons innervating both paralyzed and control muscles. These data suggest that the decreases in motoneuron excitability for both the spinal cord-injured and control subjects are a result of activity-dependent changes in motoneuron properties that are independent of fatigue-related processes in the muscles. This comparison between control and SCI subjects also suggests that chronic paralysis has changed the activity-dependent properties of the muscle fibers much more than it has influenced the excitability of the motoneurons.

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REFERENCES


