Effects of baclofen on motor units paralysed by chronic cervical spinal cord injury

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Baclofen, a gamma-aminobutyric acid receptor agonist, is used to reduce symptoms of spasticity (hyperreflexia, increases in muscle tone, involuntary muscle activity), but the long-term effects of sustained baclofen use on skeletal muscle properties are unclear. The aim of our study was to evaluate whether baclofen use and paralysis due to cervical spinal cord injury change the contractile properties of human thenar motor units more than paralysis alone. Evoked electromyographic activity and force were recorded in response to intraneural stimulation of single motor axons to thenar motor units. Data from three groups of motor units were compared: 23 paralysed units from spinal cord injured subjects who take baclofen and have done so for a median of 7 years, 25 paralysed units from spinal cord injured subjects who do not take baclofen (median: 10 years) and 45 units from uninjured control subjects. Paralysed motor unit properties were independent of injury duration and level. With paralysis and baclofen, the median motor unit tetanic forces were significantly weaker, twitch half-relaxation times longer and half maximal forces reached at lower frequencies than for units from uninjured subjects. The median values for these same parameters after paralysis alone were comparable to control data. Axon conduction velocities differed across groups and were slowest for paralysed units from subjects who were not taking baclofen and fastest for units from the uninjured. Greater motor unit weakness with long-term baclofen use and paralysis will make the whole muscle weaker and more fatigable. Significantly more paralysed motor units need to be excited during patterned electrical stimulation to produce any given force over time. The short-term benefits of baclofen on spasticity (e.g. management of muscle spasms that may otherwise hinder movement or social interactions) therefore have to be considered in relation to its possible long-term effects on muscle rehabilitation. Restoring the strength and speed of paralysed muscles to pre-injury levels may require more extensive therapy when baclofen is used chronically.

Keywords: baclofen; spinal cord injury; muscle paralysis; muscle weakness; axon conduction velocity; intraneural motor axon stimulation

Abbreviations: EMG = electromyograph; F50 = frequency of stimulation that generated half maximal force

Introduction

Muscles paralysed by spinal cord injury are not under voluntary control but do contract involuntarily in response to trivial inputs such as touch of the skin or a change in body position (Thomas and Ross, 1997). These muscle spasms usually begin a few weeks after spinal cord injury (Hiersemenzel et al., 2000) and can be a debilitating feature of the spasticity that is commonly seen after
spinal cord injury, traumatic brain injury or disease. The contractions can interfere with daily activities and hamper social interactions. Thus, many individuals seek to dampen these muscle contractions, either by exercise or by use of medication (Little et al., 1989).

Oral baclofen is commonly used to treat spasticity on a long-term basis (Lewis and Mueller, 1993; Dario and Tomei, 2004). Baclofen is a gamma aminobutyric acid receptor agonist. Although gamma aminobutyric acid receptors are distributed widely throughout the spinal cord (Price et al., 1984; Yang et al., 2001), baclofen largely acts pre-synaptically to decrease release of neurotransmitter from primary afferent terminals, because it binds to pre-synaptic receptors at lower concentrations than it does to post-synaptic receptors. Gamma aminobutyric acid receptors are also more prevalent on primary afferent terminals (Price et al., 1984; Curtis et al., 1997; Yang et al., 2001). Post-synaptically, baclofen acts to increase the total persistent inward current in motoneurons because it increases the sodium current more than it reduces the calcium flow (Li et al., 2004).

Baclofen intake reduces the muscle tone, hyperreflexia and contractions of paralysed muscles associated with spasticity (Pedersen et al., 1970; Penn et al., 1989; Dressnandt et al., 1995; Sköld, 2000; Adams and Hicks, 2005; Taricco et al., 2006), but it is unclear whether these effects are pre- or post-synaptic. A reduction in spasticity may be beneficial in that fewer inappropriate contractions occur making it easier to complete daily tasks (e.g. dressing), reducing the need for assistance and making the individual feel more in control of their body. However, the reductions in muscle activity suggest that baclofen may induce long-term disuse effects in muscle. Indeed, some individuals with spinal cord injury or multiple sclerosis who have taken baclofen for weeks do complain of weakness and reduced voluntary function (Pedersen et al., 1970). However, after only 1 week of medication, baclofen has little impact on objective measures of voluntary muscle strength in people with multiple sclerosis (Smith et al., 1992; Nielsen and Sinkjaer, 2000). Whether baclofen intake over many years has a detrimental effect on the strength, speed or fatigueability of paralysed skeletal muscles is unknown but changes in these parameters may limit use of patterned electrical stimulation to induce behaviours such as grasping.

Since baclofen-induced changes in muscle properties may be detrimental to function, the aim of our study was to determine whether long-term use of baclofen and chronic muscle paralysis from cervical spinal cord injury alters the contractile properties of human thenar motor units more than chronic paralysis alone. The results from two groups of paralysed motor units (termed Paralysis and Baclofen versus Paralysis) were each compared to data from uninjured people (Thomas et al., 1990, 1991a, b, 2006; Westling et al., 1990) because these differences define the amount of change needed to restore the contractile properties of paralysed muscles to uninjured standards. Furthermore, data were collected at the motor unit level because it is difficult to attribute changes in whole muscle properties to one source after spinal cord injury. Whole muscle properties may change with chronic denervation, altered use and/or via drug-mediated effects (Thomas and Zijdewind, 2006).

# Materials and methods

## Subjects

As described previously, intraneural motor axon stimulation was used to examine motor unit properties in 12 people who had a complete, chronic (>1 year), cervical spinal cord injury that resulted in paralysis of the thenar muscles (under no voluntary control), as judged by manual evaluation (Häger-Ross et al., 2006; Klein et al., 2006). Only after all of the data were collected and analysed were the results from spinal cord injured subjects divided into two groups depending on use of baclofen. Since oral baclofen was prescribed a few weeks after injury, the duration of baclofen intake was estimated by years post-injury. Five subjects were assigned to the Paralysis and Baclofen group (1 woman, 4 men; aged 24–47 years). The injury was either at C4 (n=1), C5 (n=1) or C6 (n=3), as defined by American Spinal Cord Injury Association criteria (Maynard et al., 1997), and occurred 1.5–14 years ago during horse riding (n=2), a motor vehicle accident (n=2) or a fall (n=1). The other seven subjects were in the Paralysis group (1 woman, 6 men; aged 25–44 years). Injury was at C4 (n=3), C5 (n=2) or C6 (n=2) and occurred 4–19 years ago from a gunshot (n=1), a motor vehicle accident (n=3) or a diving incident (n=3). Other medications, primarily for management of bowel and bladder, were balanced across the groups. The Investigational Review Board of the University of Miami approved all of the procedures. Informed written consent was obtained from each subject before they participated in the experiment.

## Experimental setup

The subject lay on a bed with the right arm supinated and resting in a vacuum cast (Westling et al., 1990; Häger-Ross et al., 2006; Klein et al., 2006). The whole body was supported with pillows to make the subject comfortable during the 4–6h experiment. These pillows were adjusted regularly in an attempt to prevent muscle spasms because any movement usually changed the position of the needle electrode in the median nerve. The hand was stabilized in Therputty with the palm up. The fingers were held against the putty with metal hoops. The thumb was extended and aligned against a transducer at the interphalangeal joint for measurement of force at right angles in the directions of abduction and flexion. The electromyographic (EMG) activity evoked by intraneural motor axon stimulation was recorded from the distal and proximal ends of the thenar muscles with surface electrodes taped across the muscles. All single pulses and the first pulse in a train were synchronized to the pulse pressure waves, which were monitored using an optical detector (Astro-Med, West Warwick, RI, USA), wrapped around the middle finger of the right hand. To minimize baseline fluctuations from the pulse pressure further, the force was reset to a predetermined baseline just prior to stimulus delivery, which occurred 50–100ms after peak pulse pressure (Westling et al., 1990). Skin temperature was monitored on the forearm (52K/J thermometer; Fluke, Everett, WA, USA).

## Experimental protocol

The path of the median nerve above the elbow was located by monitoring contractions in median innervated muscles whilst stimulating through the skin. A single stimulus (200µs duration) was then applied via an uninsulated tungsten electrode as it was advanced towards the median nerve 10–15cm above the elbow. This electrode served as a guide for positioning an insulated electrode in the median nerve.
The insulated electrode was moved in fine steps within the nerve until it was beside a motor axon that innervated the thenar muscles (0.2 mm diameter electrode, ≥1 MΩ impedance; FHC, Bowdoinham, ME, USA). The criteria to verify the all-or-none stimulation of a single motor axon were described by Westling et al. (1990). Briefly, the current was increased then decreased slowly while monitoring the evoked EMG and force on oscilloscopes to establish the range of current over which a single thenar axon could be stimulated. The current was set to the middle of this range for the delivery of all subsequent stimuli. Each axon was stimulated according to the protocols used in uninjured control subjects so that the two datasets could be compared (Thomas et al., 1990, 1991a, b; Westling et al., 1990): (i) 20 single pulses, synchronized to the pulse pressure wave, to elicit twitches; (ii) trains of pulses at 5, 8 and 10 Hz for 2 s; 15, 20, 30, 40 and 50 Hz for 1 s and 100 Hz for 0.5 s to examine the evoked force at different frequencies; (iii) 5–10 single pulses to evaluate potentiation of the twitch force; and (iv) 13 pulses at 40 Hz each second for 2 min to assess fatigue (Burke et al., 1973). One advantage of using 40 Hz to test fatigue is that this frequency is high enough for complete fusion of human thenar motor unit forces, and action potentials are maintained throughout the protocol (Klein et al., 2006). After all of these stimuli, the electrode was moved within the nerve to identify and stimulate another thenar motor axon.

Data collection and analysis

Surface EMG (distal and proximal), force (abduction and flexion), pulse pressure and stimulus current were sampled online at 3000, 375, 375 and 94 Hz, respectively, to an SC/Zoom system (Department of Integrative Medical Biology, Physiology Section, Umeå University, Sweden). All data analyses were completed off-line.

The EMG and force responses to 10 single pulses were averaged. Measurements from the distal and proximal EMG included latency (time from stimulus pulse to EMG onset), as well as the duration, peak-to-peak amplitude and area of the first 2 phases, as defined by isoelectric crossings. Axon conduction velocity was estimated from EMG latency and the conduction distance from the stimulus point to the common EMG electrode, with correction for the neuromuscular delay (Westling et al., 1990; Häger-Ross et al., 2006). EMG duration was used as an estimate of conduction along the muscle fibres. Resultant force was calculated from the abduction and flexion forces. Measurements made from the resultant force included peak twitch force, contraction time (time from force onset to peak force) and half-relaxation time (time for the force to fall from its peak to half peak force), both before and after trains of pulses at 5–100 Hz. Peak force was also measured for the responses evoked by different stimulus frequencies (5–100 Hz) and each response was normalized to the maximal tetanic force. The frequency that generated half maximal force (F50) was calculated from the linear regression equation that best fit the forces measured for three consecutive stimulus frequencies that spanned half maximal force (e.g. 5, 8 and 10 Hz or 8, 10 and 15 Hz) as the force–frequency relationship is close to linear in this frequency range (Thomas et al., 1991a, b). During the fatigue protocol, peak force was measured every 20 s. The fatigue index was calculated every 20 s by dividing each force measurement by the initial force. To estimate the effect of motor unit weakness on whole muscle fatigue, the median number of motor units that had to be stimulated to produce 1 N of force was computed from the force measured every 20 s during the fatigue test. This contraction level was chosen because uninjured people exert about 1 N of force (5% of maximum) with their thenar muscles during many daily activities (Thomas et al., 2005).

Statistics

Non parametric statistics were performed using Statistical Package for the Social Sciences software, with statistical significance set at P < 0.05. Medians, ranges and percentiles (25% and 75%) are reported. Differences between group medians and distributions for twitch force, contraction time, half-relaxation time, tetanic forces, F50, fatigue index, axon conduction velocity and EMG duration were assessed using Mann–Whitney and Kolomorov–Smirnov tests, respectively. Spearman’s evaluations were used to examine the significance of correlations between injury duration and the measured parameters. After logarithmic transformation of data that were not distributed normally, a repeated measures ANOVA was used to examine whether the number of units that had to be activated to produce 1 N of force differed across time and groups.

Results

EMG and force were recorded from 48 thenar motor units that have been paralysed chronically because of cervical spinal cord injury. When the data analyses were complete, the results were separated into two groups according to whether or not the person uses baclofen to reduce symptoms of spasticity. Data from 23 of these units were obtained from five subjects who take baclofen to manage involuntary muscle contractions and have done so for a median of 7 years (range 1.5–14 years), termed the Paralysis and Baclofen group. The remaining 25 paralysed units were from seven individuals who have not taken anti-spasm medication for a median of 10 years (range 6–19 years), termed the Paralysis group. Data from each group of paralysed motor units were compared to 45 units obtained from 12 uninjured subjects (Uninjured group).

Force and fatigability

Chronic baclofen weakened the maximal tetanic forces of paralysed motor units significantly [median (range) 35 mN (9–135 mN)] compared to the values measured for units from uninjured subjects [100 mN (27–209 mN)] P = 0.001; Fig. 1A]. The forces of the units in the Paralysis group [45 mN (12–270 mN)] were also weaker than units in the Uninjured group, but the differences were not significant (P = 0.15). In contrast, the twitch forces of units in the Paralysis and Baclofen [13 mN (2–40 mN)] and Paralysis group were similar [19 mN (5–70 mN)] P = 0.11, but significantly stronger than those in the uninjured group [8 mN (3–32 mN)] P < 0.05; Fig. 1B]. For stimulus frequencies between 10 Hz and 100 Hz, the absolute forces produced by units in the Paralysis and Baclofen group were significantly lower than units in the Uninjured group (P ≤ 0.04, Fig. 1C]. Although the median forces for units in the Paralysis group were weaker than those of the Uninjured group in response to stimulation at 8–100 Hz, they did not differ statistically. The forces recorded for each of the paralysed groups did not differ at any frequency.

Weaker tetanic forces and stronger twitch forces for each group of paralysed units resulted in significantly higher twitch/tetanic force ratios for paralysed units [Paralysis and Baclofen 0.35 (0.11–0.58); Paralysis 0.35 (0.21–0.58) compared to Uninjured
units [0.12 (0.03–0.24) both \( P < 0.001 \)]. After the delivery of a series of pulse trains at frequencies between 5 and 100 Hz, the median relative increases in twitch force were 17% (−32 to 110%) for the Paralysis and Baclofen group, 2% (−20 to 50%) for the Paralysis group and 39% (−23 to 304%) for the Uninjured group. This resulted in a higher twitch/tetanic ratio for units in the Paralysis and Baclofen group [0.44 (0.20–0.59)] compared to units in the Paralysis group [0.35 (0.17–0.48)] but the ratios were not significantly different (\( P = 0.07 \)).

Paralysed motor units were fatigable irrespective of whether baclofen was taken chronically (fatigue indices at 2 min: 0.36, 0.15–0.60) or not (0.28, 0.08–0.57, \( P = 0.53 \)) compared to units in the Uninjured group (0.85, 0.41–0.95, both \( P < 0.001 \); Fig. 2A). Although baclofen did not change the relative declines in paralysed motor unit force over time, weak motor units will be likely to result in weaker muscles and greater whole muscle fatigue (Thomas and Zijdewind, 2006). To illustrate this issue, 41 motor units would have to be stimulated tetanically to produce an initial 1 N of force in paralysed muscles of people who take baclofen when calculations are made using the median force of units for which we measured fatigue (24 mN). In contrast, only 18 units would be needed to produce 1 N of force in paralysed muscles of those who do not use baclofen and 12 units in muscles of uninjured subjects (median tetanic forces: 55 and 80 mN, respectively). To maintain 1 N of force after 2 min of intermittent 40 Hz stimulation, 87, 66 and 17 units would have to be activated in these respective groups (Fig. 2B). The number of units that needed to be stimulated increased over time (\( F = 26.0; P < 0.001 \)) for each group (\( F = 9.3; P < 0.001 \)). The increase in unit numbers over time was also greater for the Paralysis and Baclofen group compared to the Uninjured group (group by time interaction, \( F = 18.8; P < 0.001 \) but not for the Paralysis group. Even if a lower frequency was used for each group during fatigue (e.g. median F50), twice as many units would have to be activated to generate the initial 1 N so the group differences in the initial number of units would remain.

**Contractile speed**

Overlays of the twitch force recorded from six motor units, three from the Paralysis and Baclofen group and three from the Paralysis group show that units of comparable amplitude reached peak force at similar times but the force relaxation was slower with paralysis and baclofen (Fig. 3A). For the group data, twitch contraction times were similar irrespective of whether chronic paralysis was accompanied by baclofen use [median (range) 59 ms (49–82 ms)] or not [56 ms (33–102 ms, \( P = 0.30 \))] but significantly longer than those of units from uninjured subjects [48 ms (37–73 ms) both \( P < 0.006 \); Fig. 3C]. In contrast, chronic paralysis and baclofen resulted in significantly longer twitch half-relaxation times [66 ms (41–105 ms)] than recorded from
units in either the Paralysis group (49 ms, 21–150 ms, \( P = 0.001 \)) or the Uninjured group [55 ms (22–82 ms) \( P = 0.002 \); Fig. 3D].

The stimulus frequency needed to produce half maximal force (F50) was significantly lower in paralysed units influenced by baclofen [7 Hz (1–13 Hz)] compared to units in the Uninjured group [12 Hz (5–18 Hz) \( P = 0.002 \)]. F50 values were also lower for units in the Paralysis group [9 Hz (1–18 Hz)] compared to the Uninjured group, but the differences were not significant (\( P = 0.06 \), Fig. 3B). The median F50 was similar for each group of paralysed units (\( P = 0.57 \)).

**Conduction velocity**

Axon conduction velocity differed across groups. Paralysis alone resulted in the slowest median axon conduction velocity [42 m/s (26–54 m/s)]. Conduction velocity was intermediate for units influenced by chronic Paralysis and Baclofen [50 m/s (30–65 m/s)] and fastest for units in the Uninjured group [58 m/s (47–78 m/s) all \( P \leq 0.004 \), Fig. 4A]. However median EMG durations, an estimate of muscle conduction velocity, were comparable for paralysed units irrespective of whether baclofen was used chronically [12 ms (5–16 ms)] or not [10 ms (6–21 ms) \( P = 0.24 \)] but longer than for units in the Uninjured group [9 ms (6–15 ms) both \( P \leq 0.003 \); Fig. 4B].

**Motor unit characteristics in relation to level and duration of spinal cord injury**

For each group of paralysed motor units, there were no significant relationships between injury duration and twitch forces, tetanic forces, twitch contraction times, half-relaxation times or F50. Similarly, there were no obvious trends between injury level and each of the measured physiological parameters.

**Discussion**

Our data show that thenar motor units were weaker than usual in muscles subjected to the long-term effects of baclofen and chronic muscle paralysis due to cervical spinal cord injury. Weakness at the motor unit level is likely to reduce the strength and increase fatigue of whole paralysed muscles. The combination of paralysis and baclofen also prolonged motor unit relaxation more than paralysis alone, but resulted in less slowing of axon conduction velocity. These results suggest that baclofen has differential effects on nerve and muscle. None of these changes can be explained by differences in injury level, injury duration, temperature or chronic denervation. Nor can they be detected with whole nerve or muscle analysis. Thus, the weakness, slowing in relaxation and intermediate axon conduction velocity we show for thenar motor units after cervical spinal cord injury may reflect the reduction in daily muscle activity that occurs both as a consequence of baclofen use and as a result of chronic paralysis.

**Baclofen slows the relaxation of motor units paralysed by spinal cord injury**

Baclofen and paralysis slowed the twitches of motor units more than paralysis alone due to increases in half-relaxation
times (Fig. 3D). This prolonged relaxation suggests that baclofen reduces the rate of calcium uptake by the sarcoplasmic reticulum, possibly as a consequence of greater disuse (Duchateau and Hainaut, 1987). In contrast, baclofen seems to have little influence on the amount of calcium released during a single pulse, or the sensitivity of the myofilaments to calcium, because twitch forces and contraction times were greater in both groups of paralysed units compared to the units from uninjured controls. The slowing of relaxation in combination with a long contraction time and a high twitch/tetanic force ratio could explain why units influenced by paralysis and baclofen reached half maximal force at lower stimulation frequencies than units in the Uninjured group (Fig. 3B).

**Baclofen reduces the slowing of axon conduction velocity that occurs with spinal cord injury**

Axon conduction velocities were faster for the Paralysis and Baclofen group versus Paralysis alone, but the median value for each group was slower than for control data (Fig. 4A). There were no temperature discrepancies between experiments that could explain these differences. However, EMG durations were comparable for each group of paralysed units, an estimate of muscle conduction velocity (Fig. 4B). These results suggest that baclofen reduces the amount to which axon conduction velocities slow with chronic paralysis rather than altering muscle conduction velocity.

Baclofen may work directly on the axon-Schwann cell unit. Gamma aminobutyric acid B receptors are present on Schwann cells in culture (Magnaghi et al., 2004), but it is unclear whether the high levels of baclofen needed to activate these receptors influence myelination and thus conduction along peripheral axons. Another possibility is that baclofen indirectly affects axons by changing action potential traffic. Involuntary activation of motor units at slow rates is common in paralysed thenar muscles (Zijdewind and Thomas, 2001). Similar firing behaviour, chronic low frequency stimulation at 10 Hz, slowed motor axon conduction velocity in cats (Gordon et al., 1997; Munson et al., 1997). Reductions in motor axon conduction velocity also occur with operant down conditioning of the H-reflex in rats (Carp et al., 2001) and monkeys (Carp and Wolpaw, 1994). Both groups of paralysed motor units are likely to be down conditioned (less active than muscles of uninjured people), consistent with the observed reductions in axon conduction velocity. The greater slowing of axon conduction velocity with chronic paralysis alone may reflect the presence of more low frequency activity. Halter et al. (1995) suggest that a decrease in axon conduction velocity relates best to the voltage dependence of sodium channel activation rather than myelination. Since the range of conduction velocities was similar across groups (Paralysis and Baclofen: 35 m/s, Paralysis: 28 m/s, Uninjured controls: 31 m/s), we do not believe that we have a systematic group bias in remyelination or motoneuron death to account for the different shifts in the conduction velocity distributions.

**Motor unit tetanic forces are weaker with chronic paralysis and baclofen**

Baclofen is prescribed chronically for various neuromuscular conditions. Our data suggest that the strength of whole muscles that have been paralysed by spinal cord injury will be reduced by the use of baclofen over many years because the tetanic forces of motor units in these muscles were significantly lower than the forces of uninjured control units (Fig. 1A). In contrast, maximal muscle force may be little affected after acute baclofen intake based on a limited number of studies on people with multiple sclerosis or spinal cord injury (Burke et al., 1971; Smith et al., 1992; Nielsen and Sinkjaer, 2000). Motor unit weakness due to chronic paralysis and baclofen intake may reflect decrements in the size of muscle fibres, often a 30%-55% decrease after paralysis alone, and possibly by declines in specific tension (maximal force per unit area) (Cope et al., 1986, 1986). The data regarding changes in specific tension after spinal cord injury remain equivocal. Specific tension was reduced in cat hind limb motor units months after spinal transection (Cope et al., 1986; Munson et al., 1986), increased in rat soleus (Lieber et al., 1986), but unchanged in spastic rat tail muscles (Harris et al., 2006) and in fibres taken from human vastus lateralis after chronic spinal cord injury (Malisoux et al., 2007). Studies in animals that have compared muscle activity after spinal transection versus spinal isolation show that maximal force and specific tension decline more when disuse is greater (Davis and Montgomery, 1977; Alaimo et al., 1984; Roy et al., 2002, 2007; Talmadge et al., 2002; Ohira et al., 2006). It is conceivable that chronic use of baclofen causes further deterioration in neuromuscular properties over and above that attributable to paralysis alone by reducing levels of muscle activity. Weakness of motor units due to paralysis and baclofen may have resulted from a reduction in the number of strong spasms, reducing the high motor unit firing rates needed to maintain muscle strength. In contrast, the residual tonic motor unit discharge, largely at slow rates, may have been inadequate to maintain the fatigue resistance of units in either group of spinal cord injured subjects (Kernell et al., 1987a, b; Westgaard and Lomo, 1988; Thomas and Ross, 1997; Zijdewind and Thomas, 2001). Previous investigators have found that EMG activity during sleep, the self-reported number of spasms, and spasticity were all reduced in most spinal cord injured people following oral or intrathecal baclofen administration for periods lasting one day to eight weeks (Pedersen et al., 1970; Burke et al., 1971; Hugenholtz et al., 1992; Kravitz et al., 1992). Our preliminary data also indicate that baclofen intake reduces the amount of daily muscle activity. Long-term (24 h) EMG recordings from the paralysed thenar muscles of two of the subjects with a complete spinal cord injury at C4 which occurred either 7 or 8 years ago show that daily muscle activity was reduced to 6% and 22% of the levels measured in uninjured control subjects. The lower level of muscle activity was present in the person who had taken baclofen since injury. In the hour after baclofen was taken each time (40 mg, three times) versus the hour before medication intake, there was a 63% reduction in muscle activity. Hence, reductions in activity from paralysis...
and baclofen, relative to uninjured activity levels, may ultimately translate into long-term deficits in motor unit force. This action of baclofen on peripheral tissues would seem clinically undesirable in paralysed muscles or in muscles that can be controlled voluntarily.

Twitch forces, which largely reflect the amount of calcium released during a single pulse, the sensitivity of the myofilaments to calcium and muscle stiffness, were comparable for each group of paralysed units and greater than units from uninjured controls. Thus, twitch forces seem more influenced by paralysis than baclofen. Similarly, post-tetanic twitch potentiation occurred in all three groups of motor units, although paralysed units demonstrated smaller relative increases in twitch force compared to units in the Uninjured group, possibly reflecting less phosphorylation of myosin light chains (Celichowski et al., 2006; Harris et al., 2006; Macintosh et al., 2008). Less post-tetanic potentiation of unit twitch force in muscles paralysed chronically by spinal cord injury can therefore be attributed largely to paralysis alone. Similar results have been obtained following reductions in muscle stiffness (Westgaard and Lomo, 1988) and support the contention that the sensitivity of the myofilaments to calcium during contractions was unimpaired by baclofen (Tubman et al., 1997; Macintosh et al., 2008).

Studies that evaluate chronic effects of medication are prone to nonspecific effects

An important issue is whether paralysis and baclofen use have more impact on motor unit properties than many other variables that are difficult to control. We can address bias during subject selection, stimulation of motor axons or data analysis and do not consider that these factors explain our results. Thenar muscle paralysis due to spinal cord injury was an inclusion criterion but use or non-use of medication was not. Data were only separated according to baclofen use after all of the analyses were complete. In terms of sample bias, the range of axon conduction velocities was similar for all three groups. The entire axon velocity distribution for each group of paralysed units also shifted in parallel to the uninjured distribution which was representative for the entire range of thick myelinated fibres in the median nerve (Johansson and Vallbo, 1983; Westling et al., 1990). Thus, the slowing of axon conduction velocity with paralysis and baclofen use, or paralysis alone was likely to be distributed across axons with different diameters. Different injury levels or durations do not explain the data either. The data for each parameter overlapped considerably for different injury levels and durations. Individuals with an injury at C4, C5 or C6 were included in each group. The relationship between each measured parameter and injury duration was also insignificant, as expected, because the largest changes in the force, speed and fatigue of whole paralysed muscles occur in the first 6 months post-injury (Shields and Dudley-Javoroski, 2006). Furthermore, the median injury duration was less for the Paralysis and Baclofen group versus the Paralysis group. Even so, the tetanic force, half-relaxation time and F50 data were only different for the Paralysis and Baclofen group versus the Uninjured group. Together, all of these results indicate that the combination of baclofen and paralysis shifts motor unit properties further away from uninjured values, changes that may have implications for muscle function.

Functional implications

The weakening of motor unit tetanic forces with paralysis and baclofen use (Fig. 1A) is likely to reduce whole muscle strength, which in turn, will exacerbate fatigue of the whole muscle when electrical stimulation is used to produce functional behaviours. Since uninjured people exert about 1 N of force (5% of maximum) with their thenar muscles during many daily activities (Thomas et al., 2005) it is reasonable that similar forces would need to be generated in paralysed thenar muscles during patterned electrical stimulation. Progressively more motor units have to be stimulated tetanically to produce this force over time in all groups of units but the increase in unit numbers over time is greater for paralysed muscles of people who take baclofen compared to that needed in muscles of uninjured subjects (Fig. 2B). This same trend was evident when comparisons were made between paralysed muscles influenced by baclofen versus those that were not, although the difference in the number of motor units was not statistically significant (P = 0.06). Nevertheless, in some cases of spinal cord injury that involve paralysis and baclofen or paralysis alone, the number of motor units needed to generate 1 N of force may exceed the total number of thenar motoneurons that survive the injury (Yang et al., 1990; Thomas et al., 2002; Thomas and Zijdewind, 2006), limiting task performance. The difference between the numbers of paralysed and uninjured units that have to be activated would arise even if the units were stimulated at their respective F50 values. Hence, despite the potential metabolic benefit of using fewer pulses for units in the Paralysis and Baclofen group compared to the Uninjured group when using the F50, the large number of units needed to reach 1 N may negate this possibility. Furthermore, such low stimulus frequencies may generate unsteady forces, limiting their use for completing specific tasks. Moreover, if these effects of baclofen use and paralysis arise from less muscle use, the resultant weakness and fatigability are likely to occur whether baclofen is administered intrathecally or orally.

To introduce behaviours by functional electrical stimulation, a certain absolute force is usually needed over time for task performance as well as smooth contractions. The optimal stimulus parameters necessary to achieve these requirements over time in a weak and fatigable muscle remains a critical issue. We know the final absolute forces were similar in paralysed thenar muscles when intermittent stimulation was delivered at 20 Hz for 4 min or 40 Hz for 2 min, irrespective of the initial forces (Thomas et al., 2003). Whether use of lower frequencies (<20 Hz) would offset fatigue needs to be addressed. Besides optimizing stimulus parameters, chronic weakness and fatigue may be reduced through training. Early, long-term, high frequency stimulation of paralysed muscle against resistance can reduce muscle weakness and fatigue (Kernell et al. 1987a; Shields and Dudley-Javoroski, 2006).

In summary, our findings suggest caution in treatment with baclofen, particularly if it causes loss of function. Chronic baclofen use may weaken residual voluntary force, force generated during
patterned electrical stimulation and muscle spasms. Thus, the acute effects of baclofen, whether positive or negative, have to be weighed carefully in relation to its potential long-term impact on neuromuscular properties. Restoring the strength and speed of paralysed muscles toward pre-injury levels may require rehabilitation to be tailored differently in terms of stimulus intensity and frequency, as well as training duration, when baclofen is used chronically.

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