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Contribution of M-Waves and H-Reflexes to Contractions Evoked by Tetanic Nerve Stimulation in Humans

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Klakowicz, Piotr M., Evan R. L. Baldwin, and David F. Collins. Contribution of M-waves and H-reflexes to contractions evoked by tetanic nerve stimulation in humans. *J Neurophysiol* 96: 1293–1302, 2006. First published April 12, 2006; doi:10.1152/jn.00765.2005. Tetanic neuromuscular stimulation evokes contractions by depolarizing motor axons beneath the stimulating electrodes. However, we have shown that extra torque can develop due to the discharge of spinal neurons recruited by the evoked sensory volley. The present experiments investigated whether extra torque in the ankle plantar- and dorsiflexors was associated with enhanced H-reflexes. The tibial and common peroneal nerves were stimulated using 7-s trains (20 Hz for 2 s, 100 Hz for 2 s, 20 Hz for 3 s). Extra torque was defined as significantly more torque during 20-Hz stimulation after the 100-Hz burst ($time_2$) than before it ($time_1$). In 9 of 11 subjects, extra plantarflexion torque developed during stimulation just above motor threshold. In these nine subjects, torque increased from 8 to 13% MVC ($time_1$ to $time_2$), the soleus H-reflex increased from 13 to 19% M_{max} and the M-wave of $\sim 2\%$ M_{max} did not change significantly. To evoke extra dorsiflexion torque, greater stimulation intensities were required. In 6 of 13 subjects, extra torque developed at intensities that evoked an M-wave of 5–20% M_{max} at $time_1$. In these six subjects, torque doubled from 2 to 4% MVC ($time_1$ to $time_2$), whereas tibialis anterior (TA) H-reflexes and M-waves did not change significantly (H-reflex from 0.8 to 2% M_{max} ; M-wave from 12 to 14% M_{max}). In 7 of 13 subjects, extra torque developed at higher stimulation intensities (35–65% M_{max}). In these seven subjects, torque increased from 13 to 20% MVC, whereas TA H-reflexes and M-waves were not significantly different (H-reflex from 0.7 to 1% M_{max} ; M-wave from 49 to 54% M_{max}). Thus enhanced H-reflexes contributed to extra plantarflexion, however, other factors generated extra dorsiflexion.

INTRODUCTION

Electrical stimulation applied over human muscle or nerve can generate contractions to alleviate muscle atrophy and restore motor function after motor pathways are damaged. The stimulation generates contractions by depolarizing motor axons beneath the stimulating electrodes. However, when stimulated using 1-ms pulses delivered at 100 Hz, “extra” torque can develop in addition to the torque due to motor axon stimulation. This extra torque does not develop when the nerve proximal to the stimulation site is blocked with an anesthetic and thus arises from the recruitment of motoneurons in the spinal cord (Collins et al. 2001, 2002). Spinal neurons are recruited by large-diameter afferents because the extra torque can develop at intensities below motor threshold (Collins et al.

2002). Such a synaptic recruitment of motoneurons during electrically evoked contractions may be useful for rehabilitation. The present experiments investigate whether the central contribution to the extra torque is associated with enhanced transmission through the H-reflex pathway.

We have proposed that the extra torque is due to the activation of persistent inward currents in spinal neurons that are triggered by electrically evoked afferent input to the spinal cord (Collins et al. 2001, 2002). Once activated, spinal neurons maintain a sustained discharge that can become dissociated from the stimulus pulse. Despite the strong connection between Ia afferents and soleus motoneurons, motor-unit activity “time-locked” to each stimulus pulse through the H-reflex pathway was initially thought not to contribute (Collins et al. 2001, 2002; Nickolls et al. 2004). H-reflexes are substantially depressed during tetanic stimulation (Burke and Schiller 1976; Crone and Nielsen 1989; Schindler-Ivens and Shields 2000; Taborikova and Sax 1968; Van Boxtel 1986). This postactivation depression is directly related to stimulation frequency (Lloyd 1957; Lloyd and Wilson 1957; Schindler-Ivens and Shields 2000; Van Boxtel 1986), such that relative to H-reflexes evoked at 0.1 Hz, those at 1, 5, and 10 Hz are depressed by more than 65, 75, and 90%, respectively (Schindler-Ivens and Shields 2000). At frequencies between 25 and 100 Hz, H-reflexes were completely abolished (Burke and Schiller 1976). This postactivation depression has been attributed to reduced neurotransmitter release onto spinal motoneurons from previously activated Ia afferents (Hultborn et al. 1996). Given the well-documented depression of H-reflexes during tetanic stimulation, it was initially hypothesized that extra torque was due to “asynchronous” discharge sustained by the activation of plateau potentials in spinal neurons (Collins et al. 2001, 2002; Nickolls et al. 2004). Indeed such asynchronous motoneuron discharge not “time-locked” to the stimuli has been demonstrated during low-intensity tetanic stimulation of the tibial nerve (Burke and Schiller 1976; Collins et al. 2001; Lang and Vallbo 1967). More recently, however, H-reflexes were shown to recover during 2 s of stimulation at 50 Hz (Nozaki et al. 2003). After the initial H-reflex evoked by the first stimulus pulse in the train, there was a period of depression followed by a gradual recovery back to $\sim 20\%$ of the amplitude of the first response. Torque was not recorded in this study, thus it remains unknown whether the recovery of H-reflexes is associated with the development of “extra” torque. Also, the change in H-reflex amplitude may have been due to

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a change in stimulus efficacy rather than altered transmission through the spinal cord, since the stimulation was delivered below motor threshold, without an M-wave to monitor stimulus intensity.

The present study was undertaken to bring together two related findings: first, that extra torque generated by stimulation at 100 Hz involves the activation of spinal motoneurons (Collins et al. 2001, 2002) and second, that H-reflexes can recover during tetanic stimulation of soleus afferents (Nozaki et al. 2003). We hypothesized that when extra torque developed during stimulation at 20 Hz after a 2-s 100-Hz stimulation burst, H-reflexes would be larger than before the burst. H-reflexes were investigated in soleus, a muscle with both robust H-reflexes and extra torque (Collins et al. 2001, 2002; Nickolls et al. 2004) and in tibialis anterior (TA), a muscle with less prevalent H-reflexes (Schieppati 1987; Zehr 2002) and extra torque (Nickolls et al. 2004). For both muscles, M-waves were monitored to evaluate consistency of stimulus and peripheral excitability (Zehr 2002), which were expected to remain unchanged by the 100-Hz stimulation. Parts of these data have been presented previously (Klakowicz et al. 2004, 2005).

METHODS

Subjects

Sixteen neurologically intact persons (21–42 yr old; 11 males and 5 females) participated with informed consent. In total, 11 and 13 subjects received stimulation to tibial and common peroneal (CP) nerves, respectively. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Health Research Ethics Board at the University of Alberta.

Protocol

Only one muscle (soleus or TA) was studied per experimental session, which lasted between 1 and 2 h. All experimental procedures were performed on the right leg. During each experiment, the subject was seated with hip, knee, and ankle at ~90, 110, and 90°, respectively. Both feet were supported, and the right foot was strapped to a footplate configured to record isometric ankle torque (S-type load cell: LCCB-500; Omega, Stamford, CT). The trunk and right thigh were secured to minimize movement.

Depending on the muscle tested (soleus or TA), the peak torque was measured over a 1 s period during a single 3- to 5-s maximal voluntary contraction (MVC) of ankle plantar- or dorsiflexor muscles. A practice MVC was performed before data were collected. Subjects were provided with visual feedback of their EMG activity and received verbal encouragement to perform a maximal attempt. The maximal peak-to-peak M-wave amplitude (M_{\max}) to a supramaximal pulse was obtained from the relaxed muscle. Transcutaneous tetanic electrical stimulation was delivered to the tibial or CP nerve to evoke extra torque (see following text). Subjects were instructed to relax during the stimulation and not to contribute to the evoked contraction; they were encouraged to attend to other tasks (e.g., read or to listen to music). The mean amplitudes of torque, M-waves and H-reflexes were quantified before and after a 2-s 100-Hz stimulation burst.

Electromyography

Surface EMG was recorded from the right soleus and TA with bipolar (2.25 cm²) Ag-AgCl electrodes (Vermed Medical, Bellows Falls, VT). EMG signals were preamplified 200–500 times and band-pass filtered 10–1,000 Hz (AMT-8, Bortec Biomedical, Calgary, AB).

Nerve stimulation

The right tibial and CP nerves were stimulated in the popliteal fossa and at the caput fibulae, respectively, at the site that evoked a response (M-wave or H-reflex) at the lowest stimulation intensity. In cases when CP nerve stimulation resulted in eversion, the stimulation site was adjusted to preferentially activate TA, as determined by monitoring the muscle contraction and evoked torque. One-millisecond rectangular pulses were delivered via bipolar surface electrodes from a Grass S88 stimulator (Grass Instruments, AstroMed, West Warwick, RI), connected in series with a CCU1 constant current unit and a SIU5 insulator unit. Stimulation current was measured (mA-2000 Noncontact Milliammeter, Bell Technologies, Orlando, FL).

Induction of extra torque

Extra torque was generated using a continuous stimulation train adapted from a previous study (Collins et al. 2001): 20 Hz for 2 s to 100 Hz (burst) for 2 s to 20 Hz for 3 s (i.e., 20-100-20 Hz for 7 s). Five such stimulation trains, 10 s apart, were included in a single trial for each subject. Extra torque was considered to be present if torque was larger after the 100-Hz burst than before it. This definition was established in previous experiments that showed an increase in torque is absent when the nerve is blocked proximal to the stimulation site (Collins et al. 2001, 2002). Stimulation intensity was initially set at motor threshold, evoking a small and stable M-wave by a single stimulus. If extra torque was not observed through visual inspection during the trial, then additional trials were initiated at increased stimulation intensities until extra torque was observed or the experiment was terminated. Each increase in stimulation intensity was approximately double the current of the previous trials. For CP nerve stimulation, trials were obtained both at lower and higher intensities. In all cases, if the stimulation was reported to be painful, the experimental session was terminated. For each subject, no more than three trials were collected with tibial nerve stimulation; three to six trials were collected with CP nerve stimulation with each trial at different stimulation intensities. Stimulation intensity is reported as the size of the mean M-wave just prior to the 100-Hz burst (averaged over the interval 1–2 s into the stimulation; time₁ see following text) at which point consecutive M-waves were most consistent. The presence of extra torque was confirmed after the experiment by statistical evaluation of the changes in amplitude from before to after the 100-Hz burst (see following text). Data were included in the analysis if the elevation in torque after the 100-Hz burst was significant, and if M-waves were present during the 20-Hz stimulation (in some trials an initially small M-wave was absent during the stimulation train). Additional trials involving five trains at 20 Hz for 7 s (no 100-Hz burst) were recorded at the same stimulation intensity as the individual's single trials with the 100-Hz burst. In total, such a comparison between trials with and without the 100-Hz burst was implemented during tibial and CP nerve stimulation in six and four subjects, respectively.

Data acquisition and analysis

Data were sampled at 2 kHz using a custom-written program (LabView, National Instruments) and stored on computer for analysis. Torque was normalized to the MVC for each subject. The amplitude of each M-wave and H-reflex during periods of 20-Hz stimulation was measured peak-to-peak and normalized to M_{\max} . EMG responses were not evaluated during the 100-Hz stimulation since the stimulus artifact typically contaminated the signal (the artifact in Fig. 1 is atypically small).

Torque, M-wave and H-reflex amplitudes for each subject were averaged over the five successive stimulation trains that were part of a single trial. Group data were obtained by pooling these mean data from each subject. For CP nerve stimulation, when trials were col-

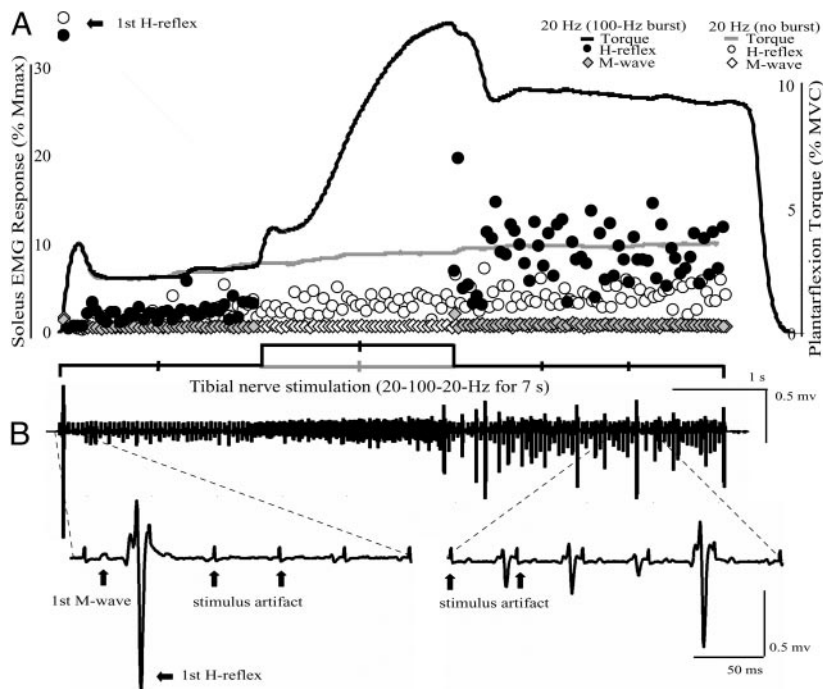


FIG. 1. Plantarflexion torque and electromyographic (EMG) responses evoked by tibial nerve stimulation in a single subject. *A*: normalized isometric torque generated by the 20-100-20-Hz stimulation, and normalized amplitude of each H-reflex and M-wave during 20-Hz stimulation before and after the 100-Hz burst. Also shown are torque, H-reflexes, and M-waves evoked by 20-Hz stimulation for 7 s. Data are averaged from 5 trains applied in a single trial. Stimulation pattern with the 100-Hz burst (black line) and without the burst (gray line) are represented beneath the plot. *B*: EMGs from a single 20-100-20-Hz stimulation train and beneath on an expanded time scale. Mean responses before and after the 100-Hz burst are represented for this subject in Fig. 3*B* (gray triangle).

lected at different stimulation intensities data were analyzed separately for responses occurring at lower ($<20\% M_{\max}$) and higher ($>20\% M_{\max}$) stimulation intensities. For both individual and group data, the mean size of EMG responses and torque during 20-Hz stimulation were compared before (time₁ = 1–2 s from stimulation onset) to after the 100-Hz burst (time₂ = 5–6 s from stimulation onset) during the 7-s stimulation train. Thus mean values over the interval 1–2 s into the initial 20-Hz stimulation were compared with mean values at the same time into the second phase of 20-Hz stimulation after the 100-Hz burst.

For individual and group data, paired *t*-tests were used to assess significant differences between mean values from time₁ to time₂. Data for individual subjects and the group are reported as mean \pm SD, and for group data 95%-confidence intervals are shown. To identify differences between responses in a trial with the 100-Hz burst to those in a trial without the burst, the mean data recorded at time₁ and time₂ were compared between trial with and without the burst using separate paired *t*-test. For all comparisons, there were no significant differences between torque at time₁. An α level of $P < 0.05$ was used to evaluate statistical significance.

RESULTS

Tetanic stimulation both of tibial and CP nerves produced extra torque. The 20-Hz stimulation generated significantly more torque after a 2-s 100-Hz burst (at time₂) than before it (at time₁). However, the extent to which H-reflexes contributed to extra plantarflexion and dorsiflexion was different. H-reflexes contributed predominantly during tibial nerve stimulation but not during CP nerve stimulation.

In total, extra torque was generated in 9 of 11 and 10 of 13 subjects during stimulation of the tibial and CP nerves, respectively. Extra torque did not develop in 1 and two subjects during tibial and CP nerve stimulation, respectively. Two additional experiments (1 each for tibial and CP nerve stimulation) were prematurely terminated due to participant discomfort. Only results that demonstrated extra torque were included for analysis because the objective was to investigate the con-

tribution of H-reflexes to these contractions. Current was measured in all experiments and was consistent throughout each stimulus train.

Tibial nerve stimulation

The intensity of tibial nerve stimulation required to evoke extra plantarflexion was just above motor threshold. The mean M-wave amplitude at time₁ ranged from 0.3 to 4% M_{\max} among the subjects.

Figure 1 shows data recorded from a subject in whom there was a large initial H-reflex followed by a period of depressed H-reflexes during the initial 20-Hz stimulation and then increased H-reflexes contributing to extra plantarflexion after the 100-Hz burst. The peak-to-peak amplitude of each H-reflex and M-wave during 20-Hz stimulation and torque generated by the 20-100-20-Hz stimulation train are represented in Fig. 1*A*. Also shown are amplitudes of EMG responses and torque evoked by the 20-Hz stimulation for 7 s (no 100-Hz burst). These data are the average of five successive stimulation trains. EMG activity for a single 20-100-20-Hz stimulation train is shown in Fig. 1*B*. The first H-reflex was largest, measuring $34 \pm 8\%$ (SD) M_{\max} as indicated by the arrow in Fig. 1*A*, and the initial torque was $\sim 4\%$ MVC. After the first response, H-reflexes were immediately depressed and remained so during the initial 20-Hz stimulation. From time₁ to time₂ (from before to after the 100-Hz burst), the mean H-reflex tripled from $3 \pm 0.4\%$ M_{\max} to $9 \pm 0.8\%$ M_{\max} ($P < 0.001$), whereas the relatively smaller mean M-wave was elevated from $0.6 \pm 0.1\%$ M_{\max} to $0.9 \pm 0.1\%$ M_{\max} ($P < 0.01$). The corresponding torque more than tripled from $3 \pm 0.4\%$ MVC to $10 \pm 0.8\%$ MVC ($P < 0.001$). During the trial with 20-Hz stimulation for 7 s (no 100-Hz burst), the mean H-reflex and torque gradually increased ($P = 0.01$ and $P = 0.02$, respectively). However, in the trial with the 100-Hz burst, the mean H-reflex at time₂ was two times larger ($P < 0.01$) and the torque was nearly three

times larger ($P < 0.001$) than in the intensity-matched trial without the 100-Hz burst.

In most subjects, the extra torque was accompanied by increased H-reflexes; however, in two subjects, small extra torque was not accompanied by significant changes in H-reflexes and M-waves. To evaluate the effect of the 100-Hz burst, trials with and without the burst were compared at matched stimulation intensities in six subjects. Figure 2A shows pooled results from three subjects in which the 100-Hz burst was effective at inducing significant changes in both torque and H-reflex amplitude: mean H-reflex and torque at time₂ were 165% ($P = 0.01$) and 137% ($P = 0.045$) of responses without the burst, respectively. In contrast, Fig. 2B shows pooled results from another three subjects in whom data from the trial with the 100-Hz burst were not significantly different from intensity-matched trials without the burst. Two of these subjects exhibited considerably different results (individual values for all 6 subjects are shown in Fig. 3B). One subject had the largest initial H-reflex (83% M_{\max}) followed by an immediate depression and a rapid and substantial recovery during the initial 20-Hz stimulation (recovering up to $\sim 40\%$ M_{\max}), whereas the overall torque was among the largest ($\sim 30\%$ MVC). The other subject had the smallest initial H-reflex (26% M_{\max}) that remained depressed throughout ($\sim 3\%$ M_{\max}), whereas the overall torque was among the smallest ($\sim 4\%$ MVC). In both these subjects, the change in torque was small and gradual after the 100-Hz burst, whereas M-waves were not significantly different from time₁ to time₂. After the stimulation ended, some EMG activity continued (not shown) as evident by the more gradual decline in torque (Fig.

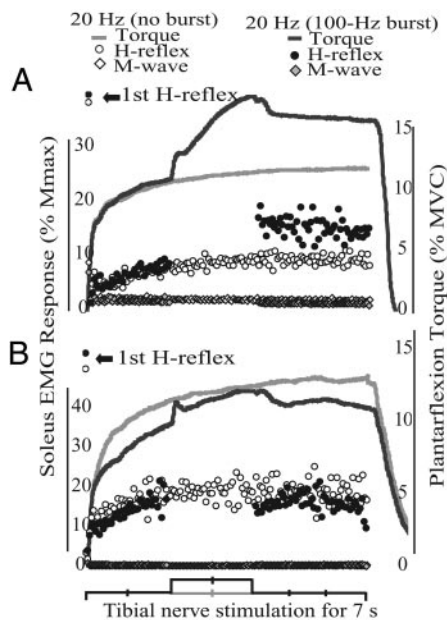


FIG. 2. Effectiveness of the 100-Hz burst for increasing amplitude of H-reflexes and torque, compared with 20-Hz stimulation alone in a group of subjects. A: pooled results of 3 subjects that demonstrated increased H-reflexes after the 100-Hz burst. Mean responses, before and after the burst, are represented for each of these subjects in Fig. 3B (dark square, dark diamond, and gray triangle). Torque (gray line) from 20-Hz stimulation alone is truncated at 7 s because stimulation was 10 s in 1 subject. B: pooled results of other 3 subjects that demonstrated the ineffectiveness of the 100-Hz burst at further increasing H-reflexes, relative to stimulation without the 100-Hz burst. Mean responses for each of these subject are represented in Fig. 3B (gray square, white triangle, and white circle).

2B). Such sustained activity, however, was observed only in two subjects. In all other subjects, for both tibial and CP nerve stimulation, torque and EMG promptly returned to prestimulus levels after the stimulation ended.

Pooled results of all nine subjects who demonstrated extra plantarflexion torque during 20-100-20-Hz stimulation of the tibial nerve are shown in Fig. 3A. The first H-reflex was largest, measuring $48 \pm 18\%$ M_{\max} , with subsequent H-reflexes depressed by $\sim 85\%$ in the first half second (down to $<10\%$ M_{\max}). From time₁ to time₂ (indicated by the boxes in Fig. 3A), the mean H-reflex increased 51%, from $13 \pm 12\%$ M_{\max} to $19 \pm 12\%$ M_{\max} ($P = 0.046$), while the mean M-wave of $2 \pm 1\%$ M_{\max} did not change significantly. The corresponding torque increased 61%, from $8 \pm 8\%$ MVC to $13 \pm 8\%$ MVC ($P = 0.001$). Changes in mean torque and EMG responses from time₁ to time₂ for each of the subjects are shown in Fig. 3B. To demonstrate the depression of H-reflexes and changes after the 100-Hz burst, mean values of EMG responses at time₁ and time₂ were normalized to the mean of the first response of each train. The amplitude of this first response as a % M_{\max} is shown in parenthesis next to the symbol for each subject. For instance, the subject in Fig. 1 is represented by the shaded triangle. The mean H-reflex at time₁ and time₂ was ~ 0.1 and ~ 0.3 of the first H-reflex of 34% M_{\max} , respectively. Extra torque was accompanied by larger H-reflexes after the 100-Hz burst in seven of nine subjects. Although M-waves were significantly different in four subjects (decreased in 2) after the 100-Hz burst, the pooled mean M-waves were not significantly different ($\sim 2\%$ M_{\max}). Across subjects the mean M-wave at time₂ (range: 0.3–4% M_{\max}) was between 5 and 20 times smaller than the H-reflex (range: 3–40% M_{\max}).

Overall, tibial nerve stimulation initially evoked a small M-wave and a larger H-reflex. After the immediate depression of H-reflexes, the amplitude recovered partially during the initial 20-Hz stimulation and was even more elevated after the 100-Hz burst. In contrast, M-wave amplitude remained small and was not significantly different from time₁ to time₂. Each time H-reflex amplitude recovered the torque also increased significantly.

CP nerve stimulation

Stimulation intensities for the CP nerve required to generate extra dorsiflexion torque, as reflected by the mean M-wave at time₁, varied between subjects and was typically much higher (5–100% M_{\max}) than with tibial nerve stimulation ($<5\%$ M_{\max}). Therefore data were divided into two groups according to the intensity of CP nerve stimulation. The “lower” intensity included intensities that evoked mean M-waves between 5 and 20% M_{\max} ; at the “higher” intensity, the mean M-waves ranged 35–65% M_{\max} . Extra dorsiflexion torque was found in 10 of 13 subjects. In six subjects, extra torque developed at the lower intensities; in two of these subjects, the stimulation evoked mean M-waves of $<10\%$ M_{\max} . Extra torque was found in seven subjects at higher intensities, five of whom also exhibited extra torque at lower intensities and were included in both groups. In the remaining two subjects, maximal stimulation intensities were required to generate extra dorsiflexion, thereby evoking maximal M-waves and very strong contractions ($\sim 50\%$ MVC). Even though the stimulation was not reported to be painful, these results were excluded from further com-

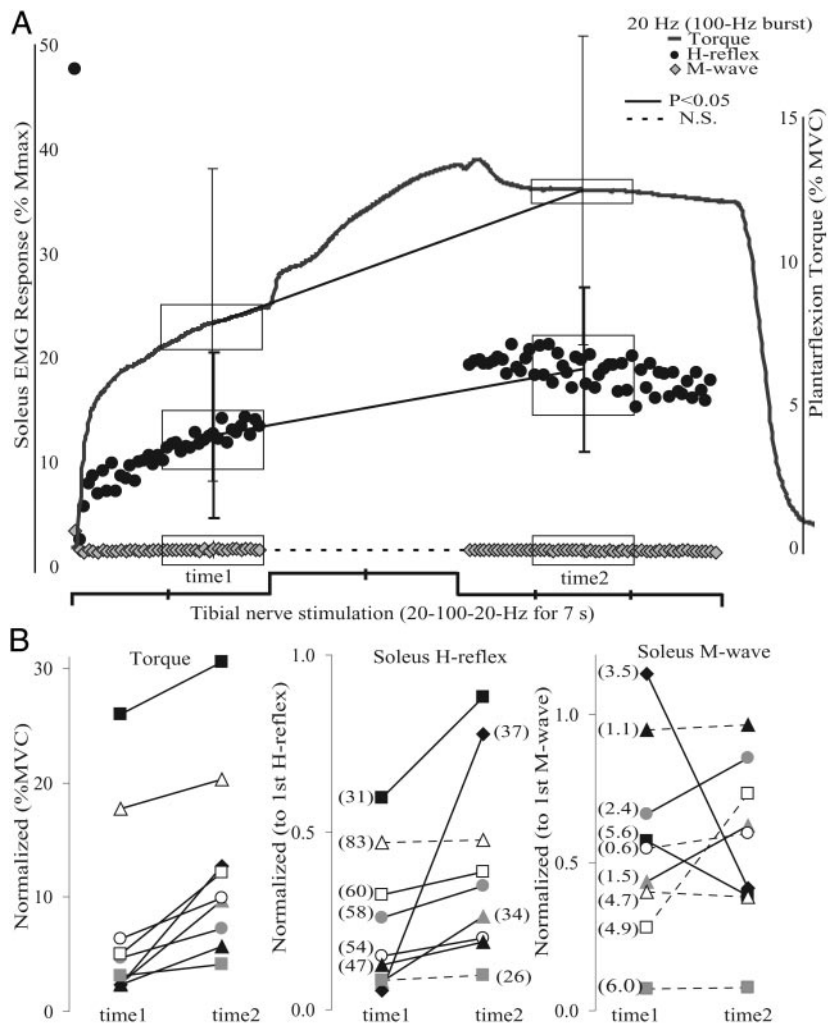


FIG. 3. Group results of tibial nerve stimulation at 20-100-20 Hz for 7 s. *A*: pooled results of 9 subjects (error bars represent 95% confidence interval). *B*: mean responses before (time₁) and after the 100-Hz burst (time₂) for individual subjects. Individuals' mean H-reflex and M-wave are normalized to 1st response in the stimulation train; amplitude of this response is shown in parenthesis next to the symbol for each subject. For pooled and individual data, significant change ($P < 0.05$) from time₁ to time₂ are denoted by solid line, as well as N.S. changes by dashed lines.

parison because of the large difference in intensity required to produce extra dorsiflexion (mean M-wave in the groups at lower and higher intensity was 7 and 50% M_{\max} , respectively).

Lower intensity CP nerve stimulation

The effect of stimulating the CP nerve at lower intensity (mean M-wave of $<20\%$ M_{\max}) for an individual who demonstrated extra dorsiflexion accompanied by small yet increased H-reflexes after the 100-Hz burst is shown in Fig. 4. In this subject, M-waves also increased after the burst and were ≥ 10 times larger than H-reflexes. The EMG activity shown at the bottom of Fig. 4 demonstrates that peak-to-peak amplitude of M-wave was measurable, separate from the stimulus artifact (shown truncated). The first M-wave was $9 \pm 1\%$ M_{\max} and the H-reflex was smaller, measuring $1 \pm 2\%$ M_{\max} . From time₁ to time₂, the mean M-wave increased 41%, from $7 \pm 1\%$ M_{\max} to $10 \pm 1\%$ M_{\max} ($P = 0.01$), and the mean H-reflex increased from $0.3 \pm 0.3\%$ M_{\max} to $1 \pm 0.2\%$ M_{\max} ($P = 0.02$). The corresponding torque increased 98%, from $4 \pm 0.3\%$ MVC to $7 \pm 0.9\%$ MVC ($P = 0.001$). Compared with responses in a trial during 20-Hz stimulation alone (no burst), after the 100-Hz burst, torque and M-wave and H-reflex amplitude were larger ($P = 0.001$).

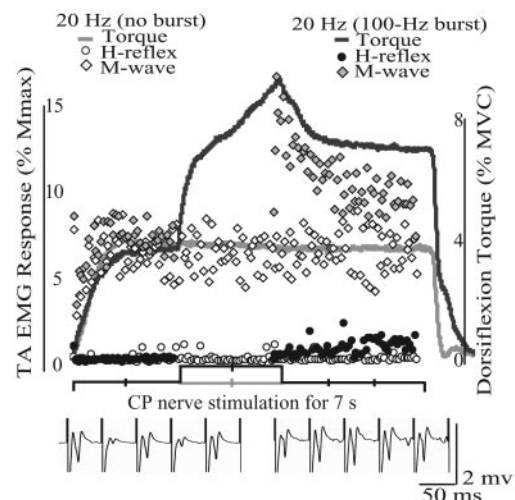


FIG. 4. Common peroneal (CP) nerve stimulation at lower intensity in a single subject with extra dorsiflexion accompanied by increased tibialis anterior (TA) M-waves and H-reflexes after the 100-Hz burst. Electromyograms are shown from a single train during 20-Hz stimulation at onset (*left*) and after the 100-Hz burst (*right*). The amplitude of each M-wave was measurable apart from the stimulus artifact (truncated). Mean responses before and after the 100-Hz burst are represented for this subject in Fig. 5*B* (gray triangle).

Pooled results from six subjects for CP nerve stimulation at 20-100-20 Hz using lower intensity stimulation are shown in Fig. 5A. The first M-wave was $17 \pm 8\%$ M_{max} and the first H-reflex was $5 \pm 10\%$ M_{max} . From time₁ to time₂, the mean M-wave and H-reflex increased from $12 \pm 5\%$ M_{max} to $14 \pm 6\%$ M_{max} ($P = 0.130$) and from $0.8 \pm 0.8\%$ M_{max} to $2 \pm 2\%$ M_{max} ($P = 0.074$), respectively; however, these changes were not significant. Nevertheless, the corresponding torque doubled from $2 \pm 1\%$ MVC to $4 \pm 2\%$ MVC ($P = 0.02$). Although the group EMG responses were not statistically different from time₁ to time₂, individual differences were evident as shown in Fig. 5B. Extra torque was accompanied by increased mean M-waves and H-reflexes in three subjects. In the other three subjects, despite M-waves and H-reflexes not being significantly elevated after the 100-Hz burst, extra dorsiflexion of $\sim 2\%$ MVC was generated. However, the largest extra dorsiflexion torque (of $\sim 4\%$ MVC) was accompanied by significant changes in the mean M-wave and the relatively smaller H-reflex (see filled triangle and diamond in Fig. 5B). Across subjects the magnitude of the mean H-reflex (range: 0.3–4% M_{max}) at time₂ was between 2 and 50 times smaller than the concurrent mean M-wave (range: 6–24% M_{max}). Overall, low-intensity CP nerve stimulation produced extra torque with no consistent changes in the amplitude of M-waves and H-re-

flexes. Unlike the results of tibial nerve stimulation, during CP nerve stimulation H-reflexes were small and M-waves predominated.

Higher-intensity CP nerve stimulation

The effect of stimulating the CP nerve at higher intensity is shown in Fig. 6 for a subject who exhibited large extra dorsiflexion torque. From time₁ to time₂ torque doubled from $17 \pm 7\%$ MVC to $34 \pm 4\%$ MVC ($P = 0.001$). The corresponding mean M-wave increased from $49 \pm 7\%$ M_{max} to $55 \pm 5\%$ M_{max} ($P = 0.01$), while the nearly absent mean H-reflex was slightly elevated from $0.3 \pm 0.1\%$ M_{max} to $0.5 \pm 0.1\%$ M_{max} ($P = 0.036$). In this case, however, M-waves were not significantly different from responses in the intensity-matched trial without the 100-Hz burst. In comparison to the trial without the burst, the extra dorsiflexion of $\sim 17\%$ MVC therefore occurred without elevated EMG responses. In contrast, in another subject the extra torque was accompanied by increased M-waves and relatively smaller H-reflexes after the 100-Hz burst (subject represented by dark square in Fig. 7B), which was similar to the results of the subject shown in Fig. 4.

Pooled results of seven subjects with 20-100-20-Hz stimulation of the CP nerve at higher intensity are shown in Fig. 7A.

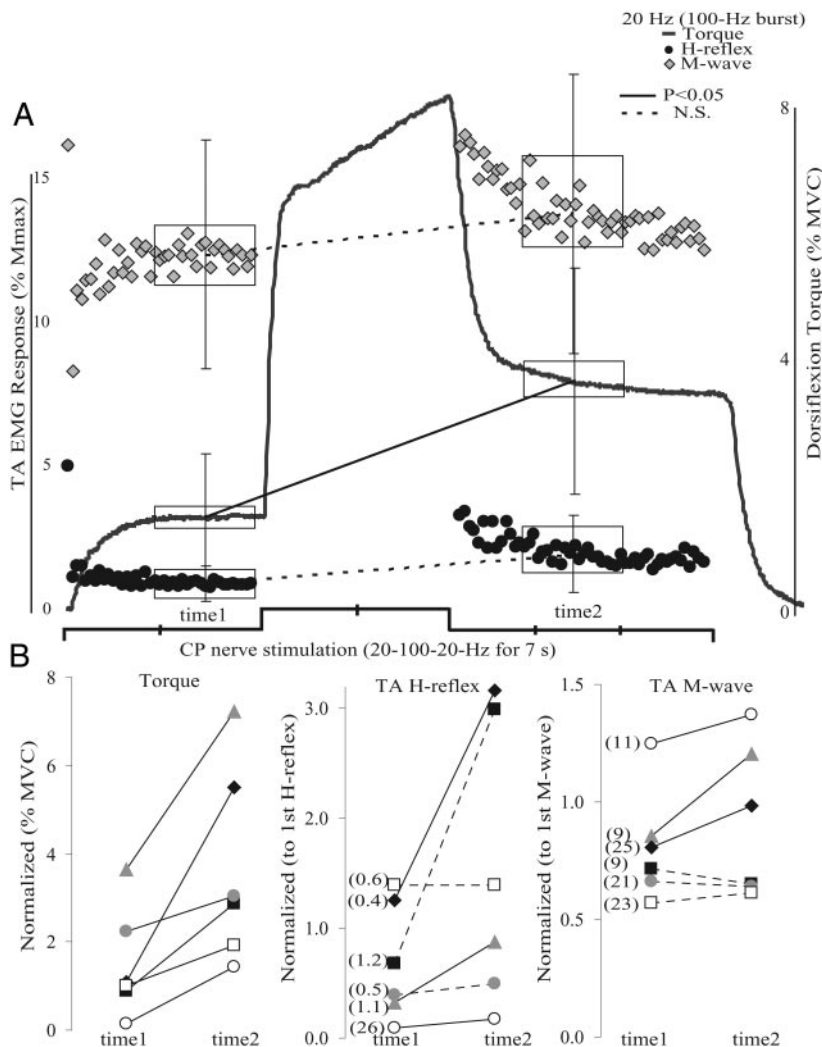


FIG. 5. Group results of CP nerve stimulation at 20-100-20 Hz for 7 s at lower stimulation intensity (mean M-waves at time₁ were between 5 and 20% M_{max}). A: pooled results of 6 subjects (error bars represent 95% confidence interval). B: mean responses before (time₁) and after the 100-Hz burst (time₂) for individual subjects. Individuals' mean H-reflex and M-wave are normalized to 1st response in the train; amplitude of this response is shown in parenthesis next to the symbol for each subject. For pooled and individual data, significant change ($P < 0.05$) from time₁ to time₂ are denoted by solid line, as well as N.S. changes are denoted by dashed lines ($P = 0.130$ and $P = 0.074$ for pooled mean M-wave and H-reflex, respectively).

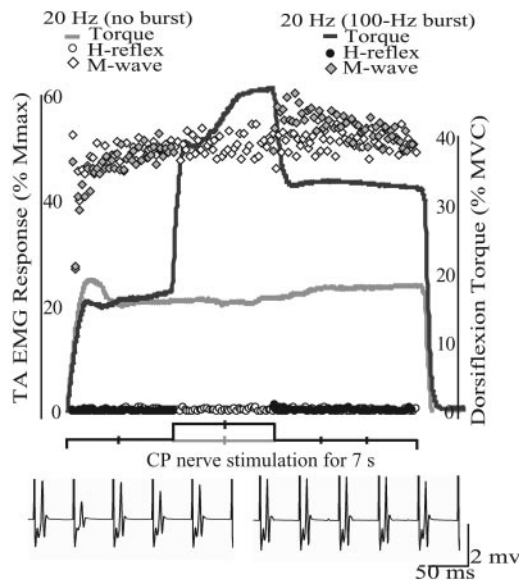


FIG. 6. CP nerve stimulation at higher intensities in a single subject with extra dorsiflexion without sufficiently increased EMG responses after the 100-Hz burst. Extra torque was not associated with increased M-waves or H-reflexes, relative to EMG responses during 20-Hz stimulation alone. Mean responses before and after the 100-Hz burst are represented for this subject in Fig. 7B (white circle).

The first M-wave was $45 \pm 18\% M_{\max}$ and the H-reflex was $1 \pm 0.5\% M_{\max}$. From time₁ to time₂, the mean M-wave and H-reflex were not significantly different although the M-wave increased from $49 \pm 10\% M_{\max}$ to $54 \pm 14\% M_{\max}$ ($P = 0.065$) and the H-reflex increased from $0.7 \pm 0.4\% M_{\max}$ to $1 \pm 0.8\% M_{\max}$ ($P = 0.128$), respectively. The corresponding torque increased 55%, from $13 \pm 7\% MVC$ to $20 \pm 9\% MVC$ ($P = 0.007$). Although the group EMG mean responses were not statistically different after the 100-Hz burst, individual changes in mean values from before to after the 100-Hz burst are shown in Fig. 7B. Extra dorsiflexion was accompanied by significantly increased mean M-waves in three subjects and increased H-reflexes in five subjects. Across subjects, the magnitude of the mean H-reflex at time₂ (range: 0.4–3% M_{\max}) was between 20 and 100 times smaller than the concurrent mean M-wave (range: 34 and 75% M_{\max}). Overall, with CP nerve stimulation at higher intensities, H-reflexes were small and M-waves dominated. However, the extra dorsiflexion torque was not consistently accompanied by changes in M-waves or H-reflexes.

DISCUSSION

The objective of the present study was to determine whether H-reflexes recover from postactivation depression during te-

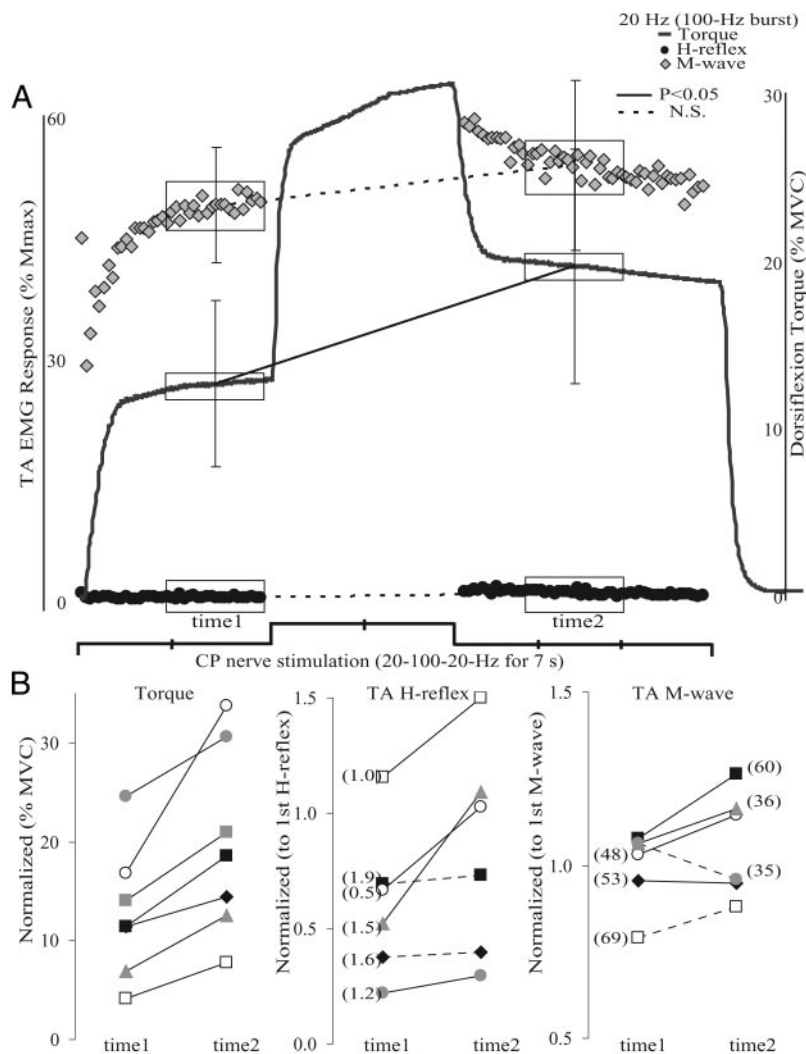


FIG. 7. Group results of CP nerve stimulation at 20-100-20 Hz for 7 s at higher stimulation intensity (mean M-waves at time₁ were between 35 and 65% M_{\max}). A: pooled results of 7 subjects (error bars represent 95% confidence interval). B: mean responses before (time₁) and after the 100-Hz burst (time₂) for individual subjects. Individuals' mean H-reflex and M-wave are normalized to 1st response in the train; amplitude of the response is shown in parenthesis next to the symbol for each subject. For pooled and individual data, significant change ($P < 0.05$) from time₁ to time₂ are denoted by solid line and N.S. changes are denoted by dashed lines ($P = 0.065$ and $P = 0.128$ for pooled mean M-wave and H-reflex, respectively). Note: for reasons of scale, mean EMG responses are not shown for 1 subject (gray square): at time₁ and time₂, the mean M-wave was 3 and 4 ($P = 0.18$), respectively, normalized to the first M-wave (16% M_{\max}), and the mean H-reflex was 0.3 and 2.7 ($P = 0.005$), respectively, normalized to the first H-reflex (0.7% M_{\max}).

tanic stimulation and thereby contribute to the development of "extra torque" in the ankle plantar- and dorsiflexors. Extra torque was defined as significantly more torque during stimulation at 20 Hz after a 2-s 100-Hz stimulation burst than during 20-Hz stimulation before the burst. The recovery of H-reflexes, with no change in M-wave amplitude, during tibial nerve stimulation supports earlier proposals that a spinal mechanism contributes to the development of extra torque in the plantarflexors (Collins et al. 2001, 2002; Nickolls et al. 2004). However, extra dorsiflexion torque during CP nerve stimulation was not accompanied by enhanced reflexes and thus is due to either unmeasured central factors or peripheral mechanisms. The possibility of a peripheral contribution contrasts with previous findings that extra dorsiflexion was abolished during proximal block of the CP nerve (Collins et al. 2002).

Reflexive contribution to extra torque

The recovery of H-reflexes accompanied by stable M-wave amplitude was most apparent during tibial nerve stimulation, hence this discussion of the reflexive contribution to extra torque is most relevant for the generation of extra plantarflexion torque during tibial nerve stimulation.

Relative to the first H-reflex of each stimulus train, soleus H-reflexes were depressed by 85% during the first half second of stimulation at 20 Hz; this is in accord with the well-known postactivation depression during tetanic stimulation (Burke and Schiller 1976; Lang and Vallbo 1967; Lloyd 1957; Lloyd and Wilson 1957; Schindler-Ivens and Shields 2000; Van Boxtel 1986) (see INTRODUCTION). However, the amplitude of soleus H-reflexes recovered and was significantly larger during 20-Hz stimulation after a 100-Hz burst than before it. In some subjects, a pronounced recovery back to ~50% of the first H-reflex occurred during the initial 20-Hz stimulation. This was similar to the partial recovery of H-reflexes up to ~20% of the first response during 2-s, 50-Hz stimulation of tibial nerve afferents (Nozaki et al. 2003). Thus in our experiments, the 100-Hz burst enhanced the recovery of H-reflex amplitude but was not always necessary for some recovery to occur. Nonetheless, the present results demonstrate for the first time that the recovery of H-reflex amplitude is associated with the development of extra torque and is not due to changes in stimulus efficacy because M-wave amplitude remained stable.

Other studies that employed tetanic tibial nerve stimulation (1-ms pulses at 25–100 Hz) demonstrated that H-reflexes remained depressed throughout the stimulation even though asynchronous motoneuron discharge emerged (Burke and Schiller 1976; Lang and Vallbo 1967). Such discrepancy in H-reflex behavior from the present study may be explained by the size of the afferent volley. In the present study, the stimulation was delivered above motor threshold, and in the former studies, stimulation was below motor threshold. The depression during 2-Hz stimulation is inversely related to the size of the initial H-reflex (Van Boxtel 1986). Moreover, the ability to induce synchronized motoneuron discharge with muscle vibration but not with low-intensity tetanic stimulation can be partially attributed to differences in the size of the afferent volley (Burke and Schiller 1976; Van Boxtel 1986). In animal studies, large monosynaptic reflexes undergo less attenuation than smaller reflexes, nevertheless, even large reflexes are progressively depressed at frequencies >10 Hz

(Lloyd and Wilson 1957). Likewise in humans, large H-reflexes (20–50% M_{max}) undergo almost complete depression during 10-Hz stimulation (Schindler-Ivens and Shields 2000). Although the extent of H-reflex recovery may depend on the strength of the induced afferent volley, a clear relation between the size of the initial H-reflex and the extent of recovery was not obvious among the subjects in the present study.

Multiple mechanisms could bring about the recovery of H-reflex amplitude in the present study. First, inadvertent or voluntary activation of motoneurons would increase H-reflex amplitude (Zehr 2002); however, several pieces of evidence suggest this was not the case. Subjects did not perceive the stimulation as uncomfortable or painful and remained relaxed. Moreover, similar extra torque develops in persons with clinically complete SCI (Nickolls et al. 2004). Second, reduced presynaptic inhibition may contribute since it is a potent modulator of H-reflex amplitude (Zehr 2002). Third, the initial postactivation depression of the H-reflex attributed to reduced neurotransmitter release may have been partially offset by posttetanic potentiation (PTP) through an increased mobilization and release of neurotransmitter from Ia afferent terminals (Van Boxtel 1986). However, the 2-s 100-Hz stimulation burst in this study is shorter than stimulation periods typically employed for PTP of H-reflexes (tens of seconds to minutes) (Kitago et al. 2004; Van Boxtel 1986). Fourth, temporal summation of excitatory postsynaptic potentials could account for changes in H-reflexes, as shown for monosynaptic reflexes with stimulation >60 Hz (Lloyd 1957; Lloyd and Wilson 1957); however, this is unlikely because the 20-Hz stimulation was probably too low for temporal summation to be maintained. Last, the activation of plateau potentials may generate the drive for extra torque (Collins et al. 2001, 2002; Nickolls et al. 2004), resulting in the discharge of some motor units "time-locked" to the stimulus pulses as H-reflexes (Nozaki et al. 2003), whereas other motor units may remain discharging independent of the stimulation (Burke and Schiller 1976; Collins et al. 2001). In the present study, such asynchronous activity could not be distinguished from the surface EMG due to the stimulus artifacts, M-waves, H-reflexes, and their associated silent periods. Therefore the extent to which the extra torque in the plantarflexors arises from reduced presynaptic inhibition, potentiated transmission at the Ia-motoneuron synapse and the development of plateau potentials in spinal neurons remains to be determined.

Regardless of the mechanism of recovery, the extra plantarflexion torque recorded in the present study was due at least in part to greater reflexive recruitment of motor units. The relationship between H-reflex amplitude and torque is demonstrated in the data where an initially large H-reflex, followed by a period of depression, results in an initial peak in torque that then subsides. Maffiuletti et al. (2000) have estimated that torque generated by an H-reflex is greater than that by a M-wave of equal amplitude. This contribution from H-reflexes to extra torque is consistent with our previous finding that extra torque did not develop while the reflex pathway was transiently blocked by an anesthetic (Collins et al. 2001, 2002). Although elevated soleus H-reflexes were always accompanied by extra plantarflexion, the relative contributions to the extra torque made by increased transmission through the H-reflex pathway and other mechanisms stands to be quantified.

Peripheral contributions to extra torque

During CP nerve stimulation, TA H-reflexes were generally small and did not increase significantly during periods of extra torque after the 100-Hz stimulation burst. Moreover, when an increase did occur, it was usually associated with enlarged M-waves, making interpretations about changes in transmission through the TA H-reflex pathway difficult to ascertain. However, an increase in M-waves, as well as the relatively smaller H-reflexes, probably contributed to extra dorsiflexion torque in some individuals (see Figs. 4, 5B, and 7B). CP nerve stimulation required higher stimulation intensities to evoke extra torque than tibial nerve stimulation, resulting in larger M-waves. Thus in addition to the predisposition for smaller H-reflexes in TA (Zehr 2002), larger M-waves would also reduce the likelihood of a reflex contribution to the evoked contraction in the dorsiflexors due to antidromic collision in motor axons. Although unmeasured central contributions, such as the asynchronous motoneuron discharge, may be involved in generating extra torque in the dorsiflexors, several peripheral mechanisms should also be considered.

First extra dorsiflexion was associated with enlarged TA M-waves after the 100-Hz burst in 6 of 13 cases (Figs. 4, 5B, and 7B). Some change in the amplitude of both M-wave and H-reflex could be expected due to changes in muscle architecture beneath the recording electrodes consequent to muscle shortening during the contraction (McComas et al. 1994). However, with no joint movement this effect should be small and would not contribute to increased torque. Otherwise, a larger M-wave would be associated with increased Ca^{2+} release, thereby affecting Ca^{2+} -dependent excitation-contraction coupling that would translate to increased force production by the muscle (Klass et al. 2004; O'Leary et al. 1997). Comparable potentiation of M-waves has been shown under similar stimulation parameters (2 s at 100 Hz) with nearly maximal activation of motor axons (McComas et al. 1994). Likewise, the potentiated M-waves in the present study may have reflected changes in excitation of the muscle fiber membrane (Cupido et al. 1996; McComas et al. 1994; O'Leary et al. 1997) due to an enhancement of electrogenic $\text{Na}^+ - \text{K}^+$ active-transport mechanism (Cupido et al. 1996; Hicks and McComas 1989; McComas et al. 1994). This paradoxical finding that potentiated M-waves may have contributed to extra dorsiflexion torque and the absence of augmented torque during proximal anesthetic block of the CP nerve (Collins et al. 2002) may be explained by a peripheral mechanism that depends on intact spinal mechanisms. Indeed, norepinephrine released from intramuscular sympathetic nerve fibers is one probable stimulus to increase the electrogenic capacity of $\text{Na}^+ - \text{K}^+$ active-transport mechanism, which would thereby amplify M-waves (Kuiack and McComas 1992; McComas et al. 1994).

In 5 of 13 subjects, extra dorsiflexion torque was not accompanied by significantly increased M-waves or H-reflexes. This was most prevalent when M-waves and torques were large prior to the 100-Hz stimulation burst (M-waves $>50\%$ M_{max} ; torque $>10\%$ MVC; see Figs. 5B, 6A, and 7B). Such observations could be explained by changes beyond the muscle fibers' membrane (O'Leary et al. 1997; Vandervoort and McComas 1983). Potentiated muscle twitches of the ankle dorsiflexors without changes in M-waves following maximal tetanic stimulation (100 Hz for 7 s) has been attributed to

enhanced excitation-contraction coupling and/or myosin-actin interaction (O'Leary et al. 1997). Because intensity, frequency, and duration of stimulation can influence potentiation (Brown and von Euler 1938; Grange et al. 1993), the extent to which potentiation of muscle twitches contributed to extra dorsiflexion under the present stimulation paradigm is not clear. Perhaps at sufficiently high stimulation intensities, extra dorsiflexion would have developed in the previous investigations during nerve block conditions (see Collins et al. 2002).

The striking difference in the reflexive contribution to extra torque between the plantarflexors (soleus) and dorsiflexors (TA) may relate to two main differences between these muscles. First the H-reflex is more predominant in soleus than in TA (Zehr 2002). Second, muscles with high proportions of fast-twitch fibers, such as TA, more prevalently exhibit both M-wave potentiation (McComas et al. 1994) and muscle potentiation (Belanger et al. 1983; Brown and von Euler 1938; O'Leary et al. 1997). Peripheral changes were probably not involved for extra plantarflexion because the soleus M-waves remained small and unchanged and the potentiation capacity of soleus is minimal (Vandervoort and McComas 1983). An additional characteristic of skeletal muscle that is common to both fiber types is the catch-like property, whereby doublet or triplet pulses (5- to 10-ms interpulse intervals) delivered early in a stimulus train can enhance the force generated by the subsequent constant-frequency stimulation. This effect, however, declines over 300 ms and is nearly absent during stimulation >25 Hz (Binder-MacLeod and Kesar 2005) and probably does not contribute appreciably to the extra torque in the present experiments. Whether recovering H-reflexes contribute to some of the torque enhancement of previous catch-like stimulation studies has so far not been entirely excluded.

Implications

Electrical stimulation of human muscle is commonly used to restore movement and to reduce the muscle atrophy that arises from disuse (Popovic et al. 2001). Compared with conventional constant frequency stimulation, generating contractions using bursts of high-frequency, wide-pulse stimulation may be advantageous for several reasons (Collins et al. 2001). Motor units activated reflexively should be recruited according to the size principle (Henneman and Olson 1965), with fatigue-resistant muscle fibers activated first (Awiszus and Feistner 1993; Buchthal and Schmalbrunch 1970; Henneman and Olson 1965). On the contrary, conventional motor axon stimulation recruits motor units in a reversed (Enoka 2002) or more random (Gregory and Bickel 2005) order, and so involves a greater proportion of fast-fatigable fibers. Thus augmenting electrically evoked contractions by recruiting motoneurons reflexively may improve the fatigue resistance of such contractions. This may help to slow muscle atrophy and the transformation from slow to fast twitch fiber types that commonly occurs after a spinal cord injury (Burnham et al. 1997). So far extra torque has been demonstrated in muscles that flex and extend the ankle (Collins et al. 2002; Nickolls et al. 2004) and flex the wrist (Baldwin et al. 2004). Whether extra torque can be generated in other muscles remains to be investigated and will determine the generalizability of this technique for rehabilitation. The potential to reflexively generate extra torque may require substantial H-reflexes in the muscle (for preva-

lence of H-reflexes in muscles, see Zehr 2002) and may also be limited by the stimulation intensity—large enough to overcome H-reflex depression and small enough to avoid antidromic collision (large M-waves). Moreover, harnessing the larger than expected H-reflexes during tetanic stimulation in persons with chronic SCI (Schindler-Ivens and Shields 2000) may recruit spinal motoneurons to a greater extent than in neurologically intact persons. Similar extra torque has been reported in persons with SCI (more frequently in plantarflexor than in dorsiflexor muscles) without any obvious links to hyper-reflexia and spontaneous spasms (Nickolls et al. 2004). For muscles in which H-reflexes are small and larger M-waves are required, as with the TA muscle, extra torque may still be advantageous. Muscle fatigue may be reduced by asynchronous motoneuron discharge initiated via afferent inputs to spinal neurons or by the enhanced muscle fibers' electrogenic (McComas et al. 1994) and contractile capacities (Cooper et al. 1988; Matsunaga et al. 1999). Together these mechanisms could result in additional recruitment of nonfatigued muscle fibers during prolonged stimulation.

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