Short-Latency Crossed Inhibitory Responses in the Human Soleus Muscle

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Stubbs PW, Mrachacz-Kersting N. Short-latency crossed inhibitory responses in the human soleus muscle. J Neurophysiol 102: 3596–3605, 2009. First published October 7, 2009; doi:10.1152/jn.00667.2009. Even though interlimb coordination is critical in bipedal locomotion, the role of muscle afferent mediated feedback is unknown. The aim of this study was to establish if ipsilateral muscle generatedafferent feedback can influence contralateral muscle activation patterns in the human lower limb and to elucidate the mechanisms involved. The effect of ipsilateral tibial nerve stimulation on contralateral soleus (cSOL) responses were quantified. Three interventions were investigated, 1) electrical stimulation applied to the tibial nerve at stimulation intensities from 0 to 100% of maximal M-wave (M-max) with the cSOL contracted from 5 to 15% of maximal voluntary contraction (MVC) and 15 to 30% MVC, 2) ipsilateral tibial nerve stimulation at 75% M-max prior to, during, and following the application of ischemia to the ipsilateral thigh, 3) Electrical stimulation applied to the ipsilateral sural (SuN) and medial plantar nerves at stimulation intensities from 1 to 3 times perceptual threshold. A short-latency depression in the cSOL electromyogram (EMG; onset: 37–41 ms) was observed following ipsilateral tibial nerve stimulation. The magnitude of this depression increased (P = 0.0005 and P = 0.000001) with increasing stimulus intensities. Ischemia delayed the time of the minimum of the cSOL depression (P = 0.04), SuN and medial plantar nerve stimulation evoked a longer latency depression [average; 91.2 ms (SuN); 142 ms (medial plantar nerve)] and therefore do not contribute to the response. This is the first study to demonstrate a short-latency depression in the cSOL following ipsilateral tibial nerve stimulation. Due to its short latency, the response is spinally mediated. The involvement of crossed spinal interneurons receiving input from low-threshold muscle afferents is discussed.

INTRODUCTION

During split belt treadmill walking where the left and right legs are moving at different velocities, the stepping pattern is maintained at a ratio of 1:1, which may indicate that the neural circuits controlling each leg are coupled (Reismann et al. 2005). Although it is not known if this coupling is generated spinally or supraspinally, there is evidence that spinocerebellar pathways are involved (Reismann et al. 2007).

In an effort to understand these mechanisms, several noninvasive techniques have been implemented to perturb one side of the body and observe the generated responses in the muscles of the contralateral leg (cLEG). For example, following trains of electrical stimuli at different stimulation intensities applied to the ipsilateral inferior tibial nerve and sural nerve (SuN) at the ankle, a contralateral soleus (cSOL) facilitation has been reported at a latency of 72–105 ms in the early stance phase of walking. This decreased in magnitude in the late stance phase and was absent during the swing phase of the cLEG in the gait cycle (Duyens et al. 1991). Similarly, a facilitation has been reported in the contralateral medial gastrocnemius at an onset latency of 93–112 ms following unexpected backward perturbations of the ipsilateral leg (iLEG) when standing on a split belt treadmill (Dietz et al. 1989). However, such mechanical stimuli may have altered the position of both legs such that the observed responses may have originated from the cLEG itself. Contralateral responses following ipsilateral perturbations have been attributed to spinal mechanisms. However, because it is known that supraspinal pathways can contribute to ipsilateral lower limb reflexes at latencies of ≥79 ms (Petersen et al. 1998), the possibility remains that the responses observed in the cLEG have a supraspinal origin.

In animal studies, evidence has emerged for circuitry located at the spinal level that connects muscles of opposite limbs. For example, commissural interneurons, a group of interneurons linking the two sides of the body, have been directly identified in the cat. These originate in the dorsal horn of laminae IV, V, and VIII within the mid-lumbar region of the spinal cord (Edgley and Jankowska 1987; Edgley et al. 2003; Jankowska and Noga 1990). Commissural interneurons project to motoneurons, ipsilateral and contralateral interneurons at the same level. They also project caudally (via descending tracts) or rostrally (via ascending tracts) (Bannatyne et al. 2003). They receive supraspinal input from the ipsilateral medial longitudinal fasciculus, the ipsilateral lateral vestibular nucleus, and pyramidal tract (Jankowska et al. 2005a, 2006) and peripheral input from group Ia, group II (Jankowska et al. 2005a), and cutaneous afferents (Edgley and Aggelopoulos 2006). Aggelopoulos et al. (1996) reported that inhibitory post synaptic potentials (IPSPs) mediated by commissural interneurons were abolished following transection of the spinal cord, suggesting that a tonic descending drive is required for activation of the commissural interneurons. Functionally, through invasive peripheral nerve recordings, short-latency IPSPs followed by excitatory post synaptic potentials, mediated by commissural interneurons, have been observed during cat locomotion with the authors proposing that these short-latency responses are a way of synchronizing the electromyographic (EMG) responses between the two legs (Frigon and Rossignol 2008). These studies demonstrate that commissural interneurons have a variety of inputs with a number of output effects. Their identification has provided a framework for studies of similar circuitry in humans.

The first aim of this study was to establish if muscle generated afferent feedback can influence interlimb coordination in the human lower limb at latencies that are likely spinal in origin. The second aim was to elucidate the possible ipsilateral afferent pathways involved in the observed cSOL response. To meet the first aim, the tibial nerve of the iLEG was
stimulated at different stimulation intensities while the cSOL was precontracted to various contraction levels. Two levels of contraction were investigated to observe if changing tonic descending drive to the muscle alters the responses in the cSOL. To meet the second aim, the SuN and medial plantar nerve were stimulated at different intensities to examine whether the evoked crossed responses could be due to these afferents within the tibial nerve. Ischemia was applied to the ipsilateral thigh to reduce the effect of large-diameter, low-threshold afferents of the iLEG, to the cSOL response.

**Methods**

**Subjects**

A total of 23 subjects (10 males and 13 females) aged 22–59 [mean age: 31.1 ± 10.2 yr (SD)] participated in this study. Four experiments were conducted (for a total of 36 experimental sessions) and two subjects participated in all four experiments. At the time of the study, all subjects were free of any known physical or neurological disorders. All subjects provided written informed consent to participate in this study. Approval was given by the Scientific Ethics Committee of Nordjylland and conformed to the standards of the Declaration of Helsinki.

**Apparatus and Instrumentation**

Surface electrodes (20 mm Blue Sensor Ag/AgCl, AMBU A/S, Denmark) recorded the EMG activity of the SOL of the right and left legs for all aspects of the experiments. The electrodes were placed in accordance with the recommendations of Cram et al. (1998). All data were sampled at a frequency of 4 kHz. The EMG signals were amplified and band-pass filtered at 20 Hz to 2 kHz.

**General experimental setup**

In all experiments, the hip and knee were positioned at an angle of 100° and the ankle at 110°. The left (contralateral to the stimulated leg) and right (ipsilateral) feet were positioned on two separate footplates aligned parallel to each other. The subjects were asked to perform a maximum voluntary contraction (MVC) of the left SOL (cSOL). For the cSOL MVC, the subjects were instructed to push down on a footplate so the soles of the feet remained flat on the footplate to ensure that the force produced was a result of the rotation at the ankle joint. The subjects were asked to avoid contraction of proximal leg muscles while performing the MVC. If the subjects recruited proximal leg muscles, they were asked to repeat the MVC measurement. A total of three MVC measurements were recorded with 1-min rest between trials. During the four experimental conditions, the percentage of maximal EMG to be contracted to was assessed every 5–7 s at the 15cSOL contraction level. Once the MVC was precontracted to various contraction levels, the SuN and medial plantar nerve were stimulated at different intensities to examine whether the evoked crossed responses could be due to these afferents within the tibial nerve. Ischemia was applied to the ipsilateral thigh to reduce the effect of large-diameter, low-threshold afferents of the iLEG, to the cSOL response.

**Experiment 1—electrical stimulation of the ipsilateral tibial nerve**

Twelve subjects (4 males and 8 females; mean age: 30.9 ± 9.9 yr) partook in this experiment. One subject was excluded as the maximal M-wave (M-max) could not be established due to subject discomfort during electrical stimulation. Eleven subjects participated with the cSOL contracted from 5 to 15% of the MVC (15cSOL condition), and 10 subjects participated with the cSOL contracted from 15 to 30% of the MVC (30cSOL condition). Ten subjects participated in both conditions. The electrical stimulus was provided by an “isolated stimulator” (Noxitest IES 230). A monopolar stimulation of the tibial nerve of the right leg was elicited by the cathode (PALs platinum round electrode, Model No. 879100, 3.2 cm diam, Axelgaard Man) located in the popliteal fossa and the anode (PALs platinum rectangular electrode, Model No. 895340, 7.5 × 10 cm, Axelgaard Man) on the anterior aspect of the knee at the level of the patella. The cathode was adjusted to minimize the movement artifact in the ipsilateral SOL (iSOL) and to optimize the observed M-wave. Stimuli were delivered every 5–7 s, and the stimulus intensity was increased until an M-wave was observed. This was deemed the motor threshold (MT). Following this, the M-max was established. The electrical stimulus intensity was increased in 5-mAmp increments. At each trial, the preceding M-wave peak-to-peak amplitude was compared with the new M-wave peak-to-peak amplitude. A total of three trials at each stimulus intensity were recorded. Once the preceding M-wave peak-to-peak amplitude and new M-wave peak-to-peak amplitude had plateaued for the three trials, the electrical stimulus was decreased to the previous stimulation intensity and labeled the M-max. The electrical stimulation intensity corresponding to the M-max was divided into 10 equal segments with each segment being 10% of stimulation intensity used to elicit the M-max. For each experimental condition (15cSOL and 30cSOL), 30 pulses were administered for each of the 10 stimulus intensities (for a total of 300 stimuli for each contraction level) every 5–7 s. The subjects were given 5-min rest between conditions, rest breaks every 100 stimuli, and were able to pause the experiment at any time if they reported fatigue.

**Experiment 2—ipsilateral electrical stimulation with ischemia**

Seven subjects (2 males and 5 females; mean age: 26.4 ± 5.9 yr) partook in this experiment. The 15cSOL contraction level was used for the experiment and maintained during iSOL H-reflex collection. Prior to ischemia, the iSOL M-max and cSOL MVC were established. Initially, 20 H-reflexes of the ipsilateral tibial nerve were induced every 5–7 s at 20–30% of the M-max, followed by 40–60 electrical stimuli administered every 5–7 s at 75% M-max. Ischemia to the iLEG was induced at the distal thigh, slightly proximal to the knee joint, where a blood pressure cuff was inflated to 200–220 mmHg. The H-reflex of the iSOL was assessed at 5, 10, and 15 min post cuff inflation. Fifteen minutes following cuff inflation, the H-reflex was assessed every 5–7 s at the 15cSOL contraction level. Once the H-reflex was depressed to 25% of its pre-ischemia value (for most subjects ~20–22 min), 40–60 electrical stimuli were delivered at the pre-ischemia intensity level. The H-reflex size of 25% of the pre-ischemia value was chosen as Uysal et al. (2009) demonstrated that this level of ischemia blocks ~50% of group Ia afferents (assessed with tendon tap) without affecting the group II afferents. The M-wave was monitored on-line to ensure that the alpha motoneurons were not blocked. Once the M-wave began to decrease, electrical stimulation was ceased and the cuff was deflated. Fifteen minutes post-ischemia, the H-reflex of the iSOL was recorded to ensure it had returned to pre-ischemia levels. Once this had occurred, 60 electrical stimuli were applied at 75% M-max to the ipsilateral tibial nerve for the 15cSOL contraction level to ensure that the response in the cSOL had returned to its preischemia value. The data were analyzed off-line to ensure no reduction in the peak-to-peak M-wave amplitude occurred while administering the electrical stimuli during ischemia. If an M-wave reduction was observed, the subsequent trials were removed from the analysis.

**Experiment 3—cutaneous nerve stimulation: medial plantar and sural nerve**

Eleven subjects (7 males and 4 females; mean age: 32.7 ± 10.1 yr) partook in these experiments. Eight subjects participated in the ipsilateral SuN stimulation experiment, and eight subjects participated in the ipsilateral medial plantar nerve stimulation experiment. Five
subjects participated in both experiments. The SuN and medial plantar nerve adjoin the tibial nerve distal to the stimulation site and were stimulated to exclude these cutaneous afferents as a source of the cSOL short-latency depression. In both experiments, 60 trains of stimuli were applied; three shocks, 3-ms interval, 1-ms duration (see Nielsen et al. 1997) every 5–7 s at 1, 1.5, 2, 2.5, and 3 times perceptual threshold (PT). For all PT levels the 15cSOL contraction level was used (see experiment 1). In the experiments, electrical stimulation was applied to the medial plantar nerve and SuN at the ankle. The stimulating electrodes (PALs platinum round electrode, Model No. 879100, 3.2 cm diam, Axelgaard Man) were attached posterior and inferior to the medial malleolus for medial plantar nerve stimulation and posterior and inferior to the lateral malleolus in the notch between the lateral malleolus and calcaneal tendon for SuN stimulation. The medial plantar nerve stimulation elicited a triangularly spreading sensation toward the first and second metatarsal on the plantar side of the foot, and the SuN stimulation elicited a sensation on the lateral side of the foot toward the fifth metatarsal. The subjects were asked to describe the sensation, and the electrodes were adjusted accordingly until the required sensation was elicited. The order of the intensity of PT stimulation was randomized. To avoid fatigue subjects were rested every 60 electrical stimuli.

**Measurements recorded**

The cSOL EMG was quantified as the minimum value within a 30–to 60-ms time window following ipsilateral tibial nerve stimulation. However, it should be noted that in some subjects, low stimulus intensities did not elicit any response. The minimum value was expressed as a percentage of the cSOL background EMG, recorded in the 90 ms preceding the electrical stimulus to the ipsilateral tibial nerve. When a depression was observed, the depression onset, duration, and time of the minimum value were recorded. A longer-latency facilitation was observed in some subjects, but due to its variability, the onset, duration, maximum value, and time of maximum were assessed using visual inspection. Further analysis on this facilitation was not performed.

For experiment 2, the peak-to-peak H-reflex and M-wave of the iSOL were established pre-ischemia, during, and 10–15 min post-ischemia. For the 75% M-max stimulus intensity, the cSOL depression magnitude, onset time, duration, and time of minimum were assessed within the same time window as for experiment 1.

For experiment 3, the minimum value during medial plantar nerve and SuN stimulation, as a percentage of the background EMG, was recorded within a 38–to 68-ms time window. A delay of 8 ms was added as the medial plantar nerve and SuN are stimulated at the ankle and the tibial nerve is stimulated at the popliteal fossa. Assuming the velocity of the low-threshold (Aβ) cutaneous afferents is 45–62 m s⁻¹ (Willer et al. 1978), with a tibial leg length of ~0.4 m, a delay of 8 ms would be expected when compared with electrical stimulation applied at the popliteal fossa. As there was no cSOL depression in the defined time window during SuN and medial plantar nerve stimulation but a longer-latency depression followed by a facilitation, the onset and duration of this depression and facilitation were assessed using visual inspection.

**Statistical analysis**

For experiment 1, repeated-measures ANOVA (rmANOVA) were performed for the response variables (depression magnitude, onset, duration, and time of minimum). The within factor variables were 0% M-max (defined as the stimulus intensity immediately prior to the stimulus intensity eliciting an M-wave), 25% M-max, 50% M-max, 75% M-max, and 100% M-max. When significant differences were identified the Fishers’ t-test conducted post hoc revealed a significant increase in the depression magnitude between the 0% M-max condition and the 25, 50, 75, and 100% M-max conditions (P < 0.001) and between both the 25 and 50% M-max conditions and the 100% M-max condition (P < 0.01). For the 30cSOL condition, there was a significant increase in the depression magnitude between the 0% M-max condition and the 25, 50, 75, and 100% M-max conditions (P < 0.001) and between both the 25 and 50% M-max conditions and the 100% M-max condition (P < 0.05).

**Onset of depression, length of depression, and time of minimum**

In the 0% M-max condition, only three subjects showed a short-latency depression, and therefore the 0% M-max condi-
tion was removed from the rmANOVA. For the 15cSOL condition, rmANOVA’s revealed no significant differences for the onset time of depression \[P = 0.60, \ F(3,33) = 0.64\], duration of depression \[P = 0.92, \ F(3,33) = 0.16\], or time of minimum \[P = 0.30, \ F(3,33) = 1.29\]. Similarly, for the 30cSOL condition, rmANOVA’s revealed no significant differences for the onset time of depression \[P = 0.07, \ F(3,30) = 2.68\], duration of depression \[P = 0.37, \ F(3,30) = 1.09\], or time of minimum \[P = 0.22, \ F(3,30) = 1.57\]. The proportion of MT (of the iSOL) in which the cSOL depressive response commenced for all subjects varied between 0.75 × MT–2.8 × MT in the 15cSOL (mean: 1.2 × MT) and 30cSOL (mean: 1.2 × MT) conditions.

Figure 3, A and B, displays the iSOL peak-to-peak M-wave (○) and the minimum value of the cSOL EMG activity (in the 30- to 60-ms time period) as a percentage of background EMG activity (●) in relation to the stimulation intensity (mAmps) for two subjects. Figure 3A demonstrates a depression commencing at 26 mA (corresponding to 1 × MT) and Fig. 3B demonstrates a depression commencing at 20 mA (corresponding to 2.8 × MT). Figure 3C displays the average ± SD of the EMG activity (in the 30- to 60-ms time period) as a percentage of background EMG activity.
Prior to and 15 min following ischemia, all subjects showed a short-latency depression. In one subject, ischemia completely abolished the depression, and in two subjects (one subject shown in Fig. 4, A and B), the onset of the depression was delayed markedly by 11 ms (Fig. 4B) and 20 ms. All available

background EMG activity in relation to the stimulation intensity for all subjects ($n = 11$).

Table 1 summarizes the means ± SD for the 25, 50, 75, and 100% M-max conditions for the depression onset, duration, and time of minimum. Two tailed $t$-tests revealed no significant difference ($P < 0.05$) for the depression onset, duration, and time of minimum between the 15$cSOL$ and 30$cSOL$ conditions for any M-max percentage level.

Ischemia

Figure 4, A and B, displays the cSOL EMG traces following ipsilateral tibial nerve stimulation for an average of 60 stimuli (Fig. 4A) and 40 stimuli (B), pre-ischemia (A) and during ischemia (B). Figure 4A displays a depression onset time of 38 ms and a time of minimum of 52 ms versus $B$, which displays a depression onset time of 49 ms and a time of minimum of 56 ms.

FIG. 2. Average depression magnitude of the cSOL for different iSOL stimulation intensities. Mean and SD of the cSOL EMG activity as a percentage of background EMG over the 30– to 60-ms time window following ipsilateral tibial nerve stimulation across all subjects. Data are for different iSOL M-max intensities. The graphs represent a cSOL contraction level from 5–15% maximal voluntary contraction (MVC, $A$) and 15–30% MVC ($B$). * , **, and *** significant differences to $P < 0.05$, $P < 0.001$, and $P < 0.001$, respectively.

FIG. 3. Comparison of the iSOL peak-to-peak M-wave, magnitude of depression and stimulation intensity. $A$ and $B$: peak-to-peak iSOL M-wave ($\circ$) and cSOL EMG activity as a percentage of background EMG ($\bullet$) for 2 individual subjects (subjects 2 and 3). Each data point represents a different stimulation intensity and is the average of 30 stimuli. Subjects maintained a precontraction level of 5–15% MVC. $C$: average and SD of the cSOL EMG activity as a percentage of background EMG in relation to the stimulation intensity for all subjects ($n = 11$).
TABLE 1. *Onset of depression, time of minimum value, and length of depression*

<table>
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<th>M-max, %</th>
<th>15cSOL</th>
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<td>51 ± 4</td>
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<td>24 ± 14</td>
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<td>38 ± 4</td>
<td>38 ± 3</td>
<td>47 ± 6</td>
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<td>40 ± 5</td>
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<td>24 ± 8</td>
<td>27 ± 16</td>
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<td>100</td>
<td>40 ± 6</td>
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Values are the means ± SD. Onset of depression, time of minimum value, and the length of depression for the 15cSOL and 30cSOL contraction levels for 25, 50, 75, and 100% M-max. n = 11 (15cSOL) and n = 10 (30cSOL).

data were analyzed using the rmANOVA. For the subject with complete suppression, only the amplitude data were used as the timing could not be determined. The rmANOVA’s revealed a significant difference in the time of minimum value \( P = 0.04, F_{(2,12)} = 4.48 \) for the short-latency depression pre- (50 ± 3 ms), during (57 ± 7 ms), and post-ischemia (49 ± 6 ms; Fig. 4C). Post hoc analysis using a Fishers LSD multiple comparison test revealed a significant difference \( P < 0.05 \) between the during ischemia condition and both the pre- and post-ischemia conditions. There was no significant difference \( P > 0.05 \) between the pre- and post-ischemia time of minimum. The rmANOVA’s revealed no significant difference among pre-ischemia, during, and post-ischemia conditions for the magnitude of the depression \( P = 0.11, F_{(2,14)} = 0.45 \); pre: 77.85 ± 6.43%, during: 81.13 ± 10.41%, post: 80.39 ± 11.66%, duration of the depression \( P = 0.35, F_{(2,12)} = 1.16 \); pre: 25 ± 8 ms, during: 20 ± 5 ms, post: 22 ± 8 ms, or onset of depression \( P = 0.36, F_{(2,12)} = 1.13 \); pre: 40 ± 3 ms, during: 44 ± 11 ms, post: 40 ± 4 ms. Figure 4C displays the time of the minimum value pre-ischemia, during, and post-ischemia for the six subjects showing a depression during ischemia and indicates where the significant differences exist.

Cutaneous stimulation

Figure 5 shows traces for the cSOL responses following ipsilateral tibial nerve (Fig. 5, A–C), SuN (D), and medial plantar nerve (E) stimulation and is an average of 30 (A–C) and 60 (D and E) stimuli. Figure 5F displays the mean ± SD of the minimum cSOL EMG as a percentage of background EMG for all subjects 38–68 ms following the stimulation of the ipsilateral medial plantar nerve and SuN (for all stimulation intensities). Figure 5, A and B, displays the cSOL EMG for subjects 5 and 6 for the 75% M-max condition and C–E display the cSOL EMG for subject 7 following ipsilateral tibial nerve (C), SuN (D), and medial plantar nerve (E) stimulation. For subject 7, the three stimulation protocols were conducted on separate occasions. Following SuN stimulation, a depression can be observed in subject 7 with an onset of 91 ms (Fig. 5D). If the distal stimulation site is considered and ~8 ms is subtracted, the depression observed with SuN only stimulation is also observed during tibial nerve stimulation at comparable latencies (see Fig. 5C). Although subjects 5 and 6 were not subjected to SuN stimulation, a possible depression from the stimulation of the SuN, as part of the tibial nerve, can be observed in Fig. 5B, and in A, there is a possible combination of the short-latency depression and the longer-latency SuN depression (as observed in Fig. 5D). Figure 5E shows ipsilateral medial plantar nerve stimulation and a slight facilitation with an onset of 73 ms and duration of 86 ms followed by a longer latency depression in the cSOL. From Fig. 5E, it appears that the medial plantar nerve does not contribute to the short-latency depressive effects of the cSOL. From Fig. 5, A–D, it can be observed that the depression evoked by SuN stimulation is likely observed in direct stimulation of the tibial nerve; however, there is a distinct shorter-latency cSOL de-

FIG. 4. The effect of ischemia of the ipsilateral thigh on the cSOL response. A: pre-ischemia cSOL EMG trace (average of 60 stimuli of the ipsilateral tibial nerve); B: during ischemia cSOL EMG trace (average of 40 stimuli). Raw data are for 1 subject (subject 4). •, the ipsilateral tibial nerve stimulus onset; ••••, 40 ms post stimulus onset; •••, the time of the minimum value of the short-latency depression during ischemia. C: mean and SD (n = 6) for the time of minimum pre-ischemia, during and post-ischemia. *, a significant difference to \( P < 0.05 \).
Depression was preceded by a shorter-latency facilitation in zero to five subjects (dependent on the proportion of PT) with an average onset of 60 ± 18 ms and an average length of 35 ms and followed by a longer-latency facilitation in four to five subjects (dependent on the proportion of PT) with an average onset latency of 119 ± 15 ms and an average length of 36 ± 13 ms. The cSOL depression was the most consistent response in medial plantar nerve stimulation and observed in six to seven subjects (depending on proportion of PT). The cSOL responses to ipsilateral medial plantar nerve stimulation were at longer latencies than those of SuN stimulation. The depression occurred at an average onset of 142 ± 22 ms and had an average length of 42 ± 15 ms. Similarly to SuN stimulation, this depression was preceded by a shorter-latency facilitation in four to six subjects (dependent on the proportion of PT) with an average onset of 74 ± 21 ms and average length of 41 ± 12 ms and was followed by a longer-latency facilitation in four to eight subjects (dependent on the proportion of PT) with an onset of 206 ± 26 ms and an average duration of 45 ± 17 ms.

**Discussion**

The aim of this study was to observe if muscle afferent generated feedback can influence interlimb coordination in the cSOL following ipsilateral tibial nerve stimulation. Further, if this feedback was mediated at latencies that may be spinal in origin. The second aim was to elucidate on the possible mechanisms mediating this response.

This is the first time a short-latency depression has been observed in the cSOL following electrical stimulation of the ipsilateral tibial nerve while the cSOL is tonically contracted. The onset latencies of the cSOL depressive response were between 37 and 41 ms and are therefore too short to be mediated by supraspinal pathways (Petersen et al. 1998). Ischemia significantly delayed the onset of the response. Stimulation of the SuN and medial plantar nerve did not produce a short-latency response, suggesting that lower threshold muscle afferents of the iLEG are the source to the short latency depression. Stimulation intensity and cSOL precontraction level did not alter the depression onset, duration, or time of minimum.

**Latencies of the cSOL response**

Central latencies must be considered when assessing the cSOL responses. The average onset latency of the cSOL response was 37–41 ms (Table 1) following ipsilateral tibial nerve stimulation. In Fig. 1, B and C, the H-reflex occurred at 30 ms and the cSOL response occurred at 37.5–41 ms (B–E), implying that in this subject there is a 7.5- to 11-ms delay in the cSOL depression and iSOL reflex responses. The 7.5- to 11-ms delay must account for the afferent nerve conduction time, spinal nerve conduction time, and central synaptic delays between spinal interneurons. Given this, the cSOL response is likely spinally mediated.

**Previous human experiments**

To date, no studies have reported cSOL responses at the short latencies observed in the current study. This may be related to the type or intensity of stimulation as typically, the strongest response suppression could only be observed at...
higher electrical stimulation intensities. In addition, electrical stimulation creates a synchronous volley of electrical activity, whereas previous mechanical perturbation studies investigating crossed body responses (Bachmann et al. 2008; Berger et al. 1984; Dietz et al. 1986, 1989) would have elicited asynchronous afferent volleys from muscle spindles, Golgi tendon organs, or cutaneous afferents. These asynchronous volleys provide phasic stimuli to the spinal cord and may not provide the necessary temporal summation to stimulate the inhibitory spinal interneurons to create an impetus large enough to provide a depressive effect to the cLEG. Further, it is known that electrical stimulation and mechanical stretch of a muscle may exert different effects on spinal circuitries and mechanisms, for example, presynaptic inhibition (Morita et al. 1998). It cannot be ruled out that these short-latency depressive responses are eliminated once a more functional task is imposed or perhaps are dependent on the phase of the gait cycle as shown by cLEG facilitatory responses (Dietz et al. 1986; Duyuens et al. 1991).

In contrast to the short-latency depression, a longer-latency facilitation has consistently been reported in previous studies. This facilitation is independent of the type of perturbation and task; however, onset latencies vary across studies and range from 65 to 112 ms (Bachmann et al. 2008; Berger et al. 1984; Dietz et al. 1986, 1989). In the current study, facilitatory cSOL responses following tibial nerve stimulation occurred at 63.3 ± 12.7 ms. However, these were not always observed, and in some subjects, the facilitation may have been suppressed by the short- and medium-latency cSOL depressive responses (compare Fig. 5, B and C with A). These results are in agreement with the onset latencies in Berger et al. (1984) and Dietz et al. (1986), who propose spinal pathways as mediators of the response. However, they are different from the onset latencies observed in Dietz et al. (1989) and Bachmann et al. (2008). These studies report onset latencies of >79 ms and therefore the responses may be mediated by cortical and subcortical pathways (Petersen et al. 1998).

Cutaneous afferents

In the current study, the tibial nerve was stimulated. This contains afferents from the SuN (only cutaneous) and medial plantar nerve (muscular and cutaneous). These nerves were investigated as they adjoin the tibial nerve distal to the stimulation site and may contribute to the short-latency responses observed from direct tibial nerve stimulation. Previous studies stimulating the SuN have revealed cSOL depressive responses with an onset latency of ~80 ms followed by facilitatory responses (Burke et al. 1991). Others have only reported a medium-latency facilitatory response with an onset latency of ~70–110 ms (Bussel et al. 1989; Delwaide et al. 1981; Duyuens et al. 1991). In the current study, stimulation of the SuN resulted in a depressive response with an average onset of 93 ms followed, in most cases, by a longer onset latency facilitation (consistent with Burke et al. 1991). During gait, stimulation of the posterior tibial nerve at the ankle produced a facilitation commencing at ~70 ms followed by a depression (Duyuens et al. 1991) as observed in the current study on humans at rest.

In none of the studies did stimulation of the SuN and medial plantar nerve cause a cSOL depressive response at latencies of 37–41 ms (or 45–49 ms if the distal cutaneous stimulation site is considered) as seen with direct stimulation of the tibial nerve (see Fig. 5F; compare A–C with D and E). Also, the cSOL EMG traces from tibial nerve stimulation demonstrate a depression of the EMG, likely mediated by cutaneous afferents, at a longer latency than the initial short latency depression (compare Fig. 5A–C with the vertical dot dash line extending from D). Therefore from the results of the current and previous studies the short-latency cSOL depressive response is not likely to be cutaneous in origin.

Possible pathways

Due to the short onset latencies of the cSOL depression, it is speculated that the response is mediated by crossed spinal interneurons. Although these have not been directly identified in humans, invasive electrical stimulation studies of ipsilateral nerve afferents and commissural interneurons in the cat spinal cord may provide insight to the responses observed in the current study (Arya et al. 1991; Baxendale and Rosenberg 1976; Holmquist 1961; Jankowska et al. 2005a, b, 2006; Perl 1958). In cats, group I and group II afferents have been reported to project onto crossed spinal interneurons (Arya et al. 1991; Baxendale and Rosenberg 1976; Holmquist 1961; Jankowska et al. 2005a; Perl 1958) in addition to cutaneous afferents from the sural, saphenous and superficial peroneal nerves (Edgley and Aggelopoulos 2006). In the current study, an ischemic block of the distal thigh delayed the time of the minimum of the short-latency cSOL depression, indicating that the low-threshold, larger-diameter, group I afferents of the iLEG, contribute to this response. Despite ischemia of the iLEG, the response was not abolished, indicating that smaller-diameter, higher-threshold, group II afferents, may also be involved in the short-latency depressive response. These results are consistent with the findings in the cat reporting inhibitory connections from ipsilateral group I (Baxendale and Rosenberg 1976; Jankowska et al. 2005a; Perl 1958) and group II afferents (Arya et al. 1991; Jankowska et al. 2005a; Perl 1958). In addition, when Perl (1958) stimulated ipsilateral group I muscle afferents and recorded in the same muscle group of the cLEG, a depression was followed by a more prominent facilitation. This finding was also observed in the present study. However, contrary to the findings in the current study, Perl (1958) reported weak crossed spinal connections from the ipsilateral gastrocnemius/soleus to the contralateral gastrocnemius/soleus. The different role, due to quadrupedal versus bipedal locomotion, afferent projections and afferent conduction velocities could possibly account for the differences between cat and human studies (Dietz 2002; Nielsen 2003; Zehr and Stein 1999).

It appears that the low-threshold afferents mediate part of the response in the current study. However, the average proportion of MT that elicited a cSOL depression was 1.2 × MT, and only three subjects showed a depression commencing <1 × MT. Previous studies have reported that at 0.6 × MT, group Ia afferents are activated (Hultborn et al. 1987) and at 0.95 × MT, group Ib afferents are activated (as in Pierrot-Deseilligny et al. 1981a). If these afferents were mediators of this response, a short-latency depression might be expected in all subjects at lower stimulus intensities. Although group I afferents are preferentially stimulated at lower stimulation intensities, they have been shown to be activated at stimulation intensities of
vestigial or neonatal reflex (such as those observed in Pang and response. Furthermore, whether the response is strong enough bursts of activity, such as during walking, may alter the extension would be inappropriate (Arya et al. 1991). However, between the limbs during limb flexion when contralateral limb mechanisms may signal contralateral limb extension during its short-latency pathways may provide communication in the spinal cord may be exposed resulting in an inhibition to the cSOL EMG.

Separating group Ia and group Ib selectively recruiting or abolishing group Ib afferents is difficult (Pierrot-Deseilligny and Burke 2005), and proposing group Ia in favor of group Ib afferents as a source or mediator of the cSOL response can only be speculative. Ischemia has been reported to abolish Ia afferent input initially and 5 min later, abolish the group Ib afferents (Pierrot-Deseilligny et al. 1981b). In the current study, where ischemia was induced at 25% of the initial iSOL H-reflex magnitude and when the 40–60 electrical stimului had been completed, there is the possibility that both low-threshold group Ia and group Ib afferents were blocked indicating that both may mediate the cSOL depressive response. Due to the limitations of ischemia, the only conclusion that can be drawn is that low-threshold afferents mediate part of the cSOL short-latency depressive response. The cSOL depression reported here occurred at 1.2 × MT and larger stimulation intensities evoked a larger cSOL depression. This could indicate group II afferents as the source of the response, as stimulus intensities of >1 × MT are more likely to recruit group II afferents (Marque et al. 1996). This would concur with findings in the cat that show strong group II inhibitory projections to contralateral motor neurons (Arya et al. 1991; Jankowska et al. 2005a; Perl 1958). In addition, at higher electrical stimulation intensities a greater number of smaller diameter, higher threshold, group II afferents would be recruited that may indicate these afferents as a source of the cSOL depression. Another explanation of the short-latency depression (also proposed by Arya et al. 1991; Perl 1958) is that low-threshold group I afferents mediate the initial depressive response and group II afferents mediate the later component of the response. In the cat, it appears that group I afferents partly mediate the crossed response. However, as there are a limited number of group Ia afferents projecting onto commissural interneurons (Jankowska et al. 2005a), the role of group I afferents to the crossed spinal response may be limited.

Functional implications in humans

Although the functional implications are speculative, the possible connections reported here may have implications in walking, standing, and sitting to standing. An explanation provided by Edgley and Jankowska (1987) and furthered by Arya et al. (1991) suggests that these short-latency inhibitory mechanisms may signal contralateral limb extension during its role in switching from extension to flexion. It is also proposed that the short-latency pathways may provide communication between the limbs during limb flexion when contralateral limb extension would be inappropriate (Arya et al. 1991). However, as the depression was only observed in sitting, more phasic bursts of activity, such as during walking, may alter the response. Furthermore, whether the response is strong enough to influence the gait pattern is unknown. It may be a remnant vestigial or neonatal reflex (such as those observed in Pang and Yang 2001; Yang et al. 1998, 2005), that has no function in the adult human or may have implications during gait. With this in mind, more research needs to be conducted during functional tasks.

Conclusion

The first aim of this study was to establish if muscle generated afferent feedback can influence interlimb coordination in the human lower limb at latencies that could be spinal in origin. From the current study, it can be concluded that the cSOL EMG responses are modulated by electrical stimulation to the ipsilateral tibial nerve and that in all subjects, the cSOL response to tibial nerve stimulation was a short-latency depression when the cSOL was tonically contracted. The second aim of the study was to elucidate on the possible mechanisms for the observed interlimb coordination. Although this study cannot provide definite conclusions as to the mechanisms, pathways, or afferents mediating this interlimb response, it provides a body of evidence that suggests the cSOL response is likely not cutaneous in origin and that at least a part of the response is mediated by low-threshold group Ia, Ib, or II afferents, or a combination of some or all of these. Future in depth studies are required to further elucidate on the source and pathways of this response and its functional implications in humans.

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