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Absence of effects of contralateral group I muscle afferents on presynaptic inhibition of Ia terminals in humans and cats

Rinaldo André Mezzarane,[1] André Fabio Kohn,[1] Erika Couto-Roldan,[2] Lourdes Martinez,[3] Amira Flores,[4] and Elias Manjarrez[4]

[1]*Biomedical Engineering Laboratory, EPUSP, PTC, University of São Paulo, São Paulo, Brazil;* [2]*Spinal Cord Research Centre, University of Manitoba, Winnipeg, Manitoba, Canada;* [3]*Departamento Neurociencias, CINVESTAV-IPN, Mexico City, Mexico; and* [4]*Instituto de Fisiología, Benemérita Universidad Autónoma de Puebla, Puebla, Mexico*

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Mezzarane RA, Kohn AF, Couto-Roldan E, Martinez L, Flores A, Manjarrez E. Absence of effects of contralateral group I muscle afferents on presynaptic inhibition of Ia terminals in humans and cats. *J Neurophysiol* 108: 1176–1185, 2012. First published June 6, 2012; doi:10.1152/jn.00831.2011.—Crossed effects from group I afferents on reflex excitability and their mechanisms of action are not yet well understood. The current view is that the influence is weak and takes place indirectly via oligosynaptic pathways. We examined possible contralateral effects from group I afferents on presynaptic inhibition of Ia terminals in humans and cats. In resting and seated human subjects the soleus (SO) H-reflex was conditioned by an electrical stimulus to the ipsilateral common peroneal nerve (CPN) to assess the level of presynaptic inhibition (PSI_control). A brief conditioning vibratory stimulus was applied to the triceps surae tendon at the contralateral side (to activate preferentially Ia muscle afferents). The amplitude of the resulting H-reflex response (PSI_conditioned) was compared to the H-reflex under PSI_control, i.e., without the vibration. The interstimulus interval between the brief vibratory stimulus and the electrical shock to the CPN was −60 to 60 ms. The H-reflex conditioned by both stimuli did not differ from that conditioned exclusively by the ipsilateral CPN stimulation. In anesthetized cats, bilateral monosynaptic reflexes (MSRs) in the left and right L_7 ventral roots were recorded simultaneously. Conditioning stimulation applied to the contralateral group I posterior biceps and semitendinosus (PBSt) afferents at different time intervals (0–120 ms) did not have an effect on the ipsilateral gastrocnemius/soleus (GS) MSR. An additional experimental paradigm in the cat using contralateral tendon vibration, similar to that conducted in humans, was also performed. No significant differences between GS-MSRs conditioned by ipsilateral PBSt stimulus alone and those conditioned by both ipsilateral PBSt stimulus and contralateral tendon vibration were detected. The present results strongly suggest an absence of effects from contralateral group I fibers on the presynaptic mechanism of MSR modulation in relaxed humans and anesthetized cats.

H-reflex; soleus; monosynaptic reflex; crossed reflex; commissural interneuron

CROSSED ACTIONS between the right and left limbs via spinal pathways following afferent stimulation have been well documented since the work of Sherrington (1910). The somatosensory influences from both ipsilateral and contralateral origin have a significant relevance to the modulation of reflex responses and shaping of locomotor patterns (Collins et al. 1993; Dietz et al. 2003; Duysens et al. 1991). The study of crossed effects from a variety of sources is useful to understand the functional aspects of motor control involved, for example, in interlimb coordination during locomotion (Haridas and Zehr 2003; Mezzarane et al. 2011).

Cat experiments allow the investigation of specific contralateral actions from different classes of afferents (Baxendale and Rosenberg 1976, 1977; Eccles et al. 1964; Rosenberg 1970). More recently, experiments performed in both humans and cats have provided evidence of prominent crossed actions from group II muscle (Corna et al. 1996; Edgley et al. 2003) and cutaneous (Aggelopoulos and Edgley 1995; Zehr et al. 2001) afferents.

Interestingly, data from animal preparations showed that contralateral group I afferents present a weak direct influence upon the ipsilateral motor nucleus (Harrison and Zytnicki 1984). Subsequent studies indicate that these afferents exert their contralateral influences mainly via commissural interneurons located in laminas VI–VII that synapse on both motoneurons and premotor interneurons (Jankowska et al. 2009), implying the existence of both direct and indirect (via interneurons) crossed actions. Although the absence of effects from contralateral group Ia afferent stimulation on dorsal root potential in the cat was reported previously (Devanandan et al. 1965), it should be stressed that none of the previous work in cats employed direct measurements of these crossed effects on presynaptic inhibition (PSI).

Indirect segmental effects from contralateral group I muscle spindle afferents in both upper and lower limbs of human subjects have been observed through conditioning of the H-reflex. For instance, electric stimulation of contralateral group I afferents [Ia fibers from extensor carpi radialis (ECR)] changed the reciprocal inhibition from ECR to the flexor carpi radialis muscle (Delwaide and Pepin 1991). In lower limb experiments, a presynaptic mechanism has been proposed to explain the observed soleus (SO) H-reflex inhibition in response to activation of contralateral group I muscle afferent by either passive leg pedaling movements (Cheng et al. 1998) or mechanical Achilles tendon stimulation (Koceja and Kamen 1992). It is important to point out that these experiments did not employ any direct evaluation of PSI onto Ia terminals.

Therefore, indirect evidence in the human suggests the possibility that contralateral group I afferents exert influence on the mechanisms subserving monosynaptic reflex (MSR) gain control. PSI of Ia terminals could be a potential target for such crossed effects, as it modulates reflex actions in different motor contexts (Rudomin and Schmidt 1999). For instance, to

Address for reprint requests and other correspondence: R. A. Mezzarane, Biomedical Engineering Laboratory, Escola Politécnica, Univ. of São Paulo, São Paulo, SP, Brazil, Cx.P. 61548, CEP 05424-970 (e-mail: rinaldo@leb.usp.br).

meet the requirements of a variety of motor tasks, the PSI onto Ia terminals can be altered by ipsi- or contralateral peripheral input and descending pathways, in both humans (Hultborn et al. 1987a; Mezzarane and Kohn 2002; Roby-Brami and Bussel 1990) and cats (Gossard and Rossignol 1990; Quevedo et al. 1995).

While several studies have reported weak contralateral influence from group I activation to the ankle extensors in the cat (Harrison and Zytnicki 1984; Holmqvist 1961; Perl 1958), significant crossed effects in human lower limbs have generally been ascribed to group I activation (Cheng et al. 1998; Koceja and Kamen 1992; Stubbs and Mrachacz-Kersting 2009) among other possible influences (e.g., cutaneous and muscle group II) (Iles 1996; Stubbs et al. 2011). However, the crossed effects from contralateral group I activation onto PSI of Ia MSRs remain to be addressed. Hence, in view of the recent human data, it appears worthwhile to reopen the question put forward by Devanandan et al. (1965) and conduct complementary experiments in both cats and humans.

The combination of human and cat experiments can provide a broader view of the neuronal processes within the spinal cord involved in motor control (see, e.g., Hultborn et al. 1987a). This approach was utilized in the present work. To examine whether a presynaptic mechanism mediates crossed influences from group I afferents in humans, the PSI onto SO Ia terminals was conditioned by a vibratory stimulus applied to the contralateral triceps surae tendon. In the cat, two different protocols were used: *1*) stimulation of either ipsilateral or contralateral afferents from posterior biceps and semitendinosus (PBSt) as a conditioning stimulus for the MSR elicited in the ipsilateral gastrocnemius/soleus muscle (GS) and *2*) vibratory stimulus applied to the contralateral tendon of the GS muscle as conditioning for ipsilateral PSI. This last protocol was the same as used in humans. These experimental protocols were expected to reveal a possible presynaptic reflex modulation in response to contralateral group I activation in both species.

METHODS

Human Experiments

Subjects. Eleven subjects (8 men and 3 women) aged 30.27 ± 3.6 yr (mean ± SD) volunteered for the experiments. The protocol was approved by the local ethics committee according to the Declaration of Helsinki. None of the subjects had any history of neurological disorders. Subjects were seated in an armchair with ankle, knee, and hip angles at ~90°.

Data acquisition and stimulation. Surface electrodes (Ag/AgCl with 0.8-cm diameter) were placed bilaterally on the belly of the SO and tibialis anterior (TA) muscles of the right (ipsilateral) leg, with an interelectrode distance of 2 cm. The skin was prepared for electrode placement with an abrasive solution. To obtain the H-reflex of the SO muscle, an electrical rectangular pulse (1-ms duration) was delivered to the ipsilateral posterior tibial nerve (PTN) at the popliteal fossa. The reference amplitude of the H-reflex ranged between 10% and 30% of the maximal direct SO muscle response (M_{max}) (Crone et al. 1990).

The presence of a constant M-wave in the recordings indicated constant stimulus efficacy to the PTN. However, 3 of 11 subjects did not present an M-wave accompanying the H-reflex within the range of 10–30% M_{max}. Therefore, the stimulus efficacy test for these subjects was achieved by applying between trials an electrical stimulus to the PTN that evoked an M-wave amplitude of 10% M_{max} in the SO muscle. The M-wave amplitude did not change across the trials (for the same stimulus intensity); therefore stimulus efficacy was assumed to be constant.

The H-reflex was conditioned by an electrical stimulus (1-ms duration) applied to the ipsilateral common peroneal nerve (CPN), using a bipolar electrode placed (2 cm apart) at the neck of the fibula to assess the level of PSI. A conditioning-test (C-T) interval of 100 ms (Iles 1996) was selected, and the conditioning stimulus intensity was 1.0 × motor threshold (MT) of the TA (stimuli at 0.9 × MT were also employed in a separate series, see below). Activation of Ia afferents from the TA muscle was assessed before the beginning of the experiment: for those subjects who did not show a detectable H-reflex in the TA muscle in a relaxed state, the stimulus effectiveness at the CPN was confirmed by the presence of an H-reflex during contraction.

To examine whether the induced PSI was not the result of cutaneous afferent stimulation, the conditioning stimulus electrode was moved 2–3 cm distally from the original position on the CPN in two subjects. As previously found (Mezzarane and Kohn 2007), no reduction in the conditioned H-reflex amplitude was observed.

Procedures. The PSI pathway (from the CPN to SO Ia afferents) was conditioned by a brief sinusoidal vibration (3 cycles at 180 Hz) applied to the Achilles tendon of the contralateral (left) leg with a vibratory device (mini-shaker type 4810, Brüel & Kjær). The intensity of the tendon vibration corresponded to the maximal output of the mini-shaker amplifier and was maintained constant across the trial (see below). This stimulus preferentially activates group Ia afferents (Baxendale and Rosenberg 1976) and has been shown to successfully induce PSI (Hultborn et al. 1987a).

Figure 1 depicts a simplified diagram showing the location and time interval of the stimuli (S1 to S3). This protocol was applied in eight subjects. The H-reflex conditioned by electrical CPN stimulation was called "PSI_control" (Fig. 1; gray traces on *right* in Fig. 2*A*). The H-reflex response (elicited by stimulus S1 in Fig. 1 and Fig. 2*A*) conditioned by both a vibratory stimulus to the contralateral Achilles tendon (stimulus S3 in Fig. 1 and Fig. 2*A*) and an electrical stimulus to the ipsilateral CPN (stimulus S2 in Fig. 1 and 2*A*) was called "PSI_conditioned" (black traces in Fig. 2*A*). The negative interstimulus intervals (ISIs) in Fig. 1 indicate that the contralateral vibration (S3) was applied before the electrical stimulus to the CPN (S2). Positive ISIs indicate that the contralateral vibration was applied after the electrical stimulus to the CPN. When the ISI is equal to zero both stimuli were applied simultaneously (see also Fig. 2*A*). The "?" symbol in Fig. 1 represents the unknown commissural neuronal pathway that mediates excitatory/inhibitory effects on the last-order inhibitory interneuron that establishes synaptic contact on Ia terminals of the ipsilateral side.

The efficacy of the vibratory stimulus (applied to the contralateral leg) to activate the corresponding muscle spindle Ia afferents was assessed by comparing the H-reflex amplitudes of the contralateral leg with and without the vibration applied 600 ms before the stimulus to the PTN in the same leg. Twenty responses were obtained every 10 s before the beginning of the experiment. The first 5 responses from the train of 20 were termed "Control 1" (without any conditioning) and were followed by 5 conditioned responses ("Vibration 1"). To achieve full recovery from vibration, this procedure was repeated one more time (after 10 s) to obtain "Control 2" and "Vibration 2" (see Fig. 2*B*), totaling 20 responses. A reduced H-reflex amplitude (e.g., due to homosynaptic depression; Cisi and Kohn 2007; Kohn et al. 1997) suggests that the Ia afferents have been effectively recruited by the brief vibratory stimulus. However, a small contribution from group Ib afferents cannot be excluded (Burke et al. 1983).

The ISI between the conditioning vibratory stimulus to the contralateral tendon and the stimulus applied to the ipsilateral CPN (S3–S2) was chosen pseudorandomly from −60 to 60 ms in steps of 10 ms (Fig. 2*A*). The intervals between the contralateral vibratory stimulus and the test stimulus applied to the PTN (S3–S1) ranged

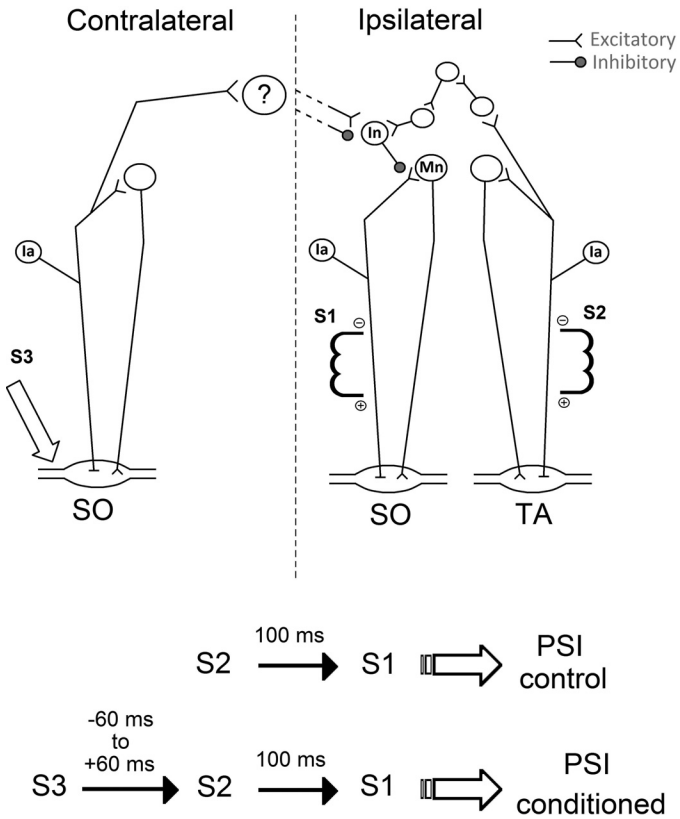

Fig. 1. Simplified schematic showing the locations where the stimuli were applied and the time course of the experiments. The symbol "?" represents the unknown commissural pathway(s) that could mediate crossed actions. The interval between conditioning (S2) and test (S1) stimuli (C-T interval) was fixed at 100 ms. The interstimulus interval (ISI) between S3 and S2 stimuli ranged from −60 to +60 ms in steps of 10 ms (see Fig. 2). S1: stimulus to the posterior tibial nerve (PTN) to obtain soleus (SO) H-reflex; S2: conditioning stimulus to the ipsilateral common peroneal nerve (CPN); S3: contralateral vibratory tendon stimulation; In, last-order inhibitory interneuron; Mn, SO motoneuron; Ia, muscle Ia afferent; PSI, presynaptic inhibition.

from −160 ms to −40 ms (100 ms was subtracted from the ISIs that correspond to the C-T interval between CPN and PTN stimulation).

At the beginning of each trial, five H-reflex responses were elicited every 10 s to bring the central nervous system to a steady state. This procedure was adopted to prevent a possible bias due to a transient change in the spinal cord circuitry. PSI_control and PSI_conditioned responses were obtained for each of the 13 ISIs (gray and black traces, respectively, in Fig. 2*A*) in a pseudorandom alternated fashion. The H-reflex conditioned by CPN stimulation alone (PSI_control) was then compared with the H-reflex conditioned by both CPN stimulation and mechanical stimulus (i.e., PSI_conditioned). In addition, at the end of each trial (after the delivery of the control and conditioned stimuli in all 13 ISIs), five H-reflex responses without any conditioning stimulus (electrical or mechanical) were obtained (this was called "Control") to check for PSI efficacy.

An interval of 10 s was used between consecutive H-reflex responses to minimize the effects of homosynaptic depression (Kohn et al. 1997). Each trial was repeated 10 times, resulting in 260 H-reflex responses (10 PSI_control and 10 PSI_conditioned by vibration for each of the 13 ISIs). Each experiment lasted ~2 h. Subjects were allowed to relax between each 6-min trial (to sprawl, move the head, and stretch the arms, back, etc.) as long as needed.

The protocol described above was repeated at a later date in five subjects with conditioning stimulus intensities of 1.0 × MT and 0.9 × MT to the CPN for two ISIs (−40 ms and −30 ms). These extra experiments were done to explore the possibility that the lack of crossed effects would be due to an already saturated presynaptic inhibitory pathway. In these experiments a different vibration device (Labworks model LW-126-13) was chosen because it was easier to quantify the movement of its tip with an inbuilt accelerometer (see below).

To verify the variability of the mechanical stimulus, an experiment focusing on the mini-shaker tip displacement was performed. The stimulus intensity (corresponding to the maximal output of the mini-shaker amplifier) was measured by the displacement of the mini-shaker tip when in contact with the tendon (~0.6 mm). In this experiment, the displacement of the mini-shaker tip was measured by a kinematic analysis system (Optotrak Certus, Northern Digital) that detected the movement of an active optical marker attached to the tip at a sample frequency of 800 Hz. To assess the consistency of the mini-shaker tip displacement, the movement during 28 vibratory stimuli applied to the tendon with an interval of 1 s was recorded. The same procedure could not be adopted to evaluate the displacement during a complete trial because of the overheating of the active markers. In these experiments, an accelerometer (ADXL193; Analog Devices) was attached to the main cylinder located inside the armature of the shaker (LW-126-13) whose tip remained in contact with the contralateral triceps surae tendon (similar procedure was employed by Fornari and Kohn 2008). The consistency of mechanical stimulation could be assessed throughout the trial, as acceleration directly corresponds to displacement.

Signal processing and data analysis. The EMG signals were amplified and filtered (10 Hz to 1 kHz) by a MEB 4200 system (Nihon-Kohden). The signals were fed into the PC-based acquisition and processing system WorkBench (DataWave Technologies) that sampled each signal at 2,500 Hz. Two independent stimulators (of the MEB 4200 system) delivered the electrical stimuli, triggered by the PC-based signal acquisition system. This system also triggered the vibratory stimulus at the appropriate timings. The resulting data files in ASCII were processed by programs written in MATLAB (MathWorks).

To ensure that the induced PSI was effective, the last five responses of a given trial (the "Control" response without any conditioning, either electrical or mechanical, described in *Procedures*) were compared to the PSI_control (reflex responses conditioned by only CPN stimulus). An average of all 13 values (corresponding to the 13 ISIs) of PSI_control was computed for each trial and compared to the average of 5 Control responses obtained in the respective trial. The average of all PSI_control and Control reflexes, evaluated for all 10 repetitions (dashed and solid traces, respectively, in Fig. 3*A*), was estimated for each subject to calculate the overall PSI effect shown in Fig. 3*B*.

Cat Experiments

Preparation. Experiments were performed on 17 adult cats (weight range 2.2–4.0 kg) initially anesthetized with pentobarbital (35 mg/kg ip). Blood pressure was monitored through the carotid artery. The left radial vein was also cannulated to administer additional doses (10 mg/kg) of pentobarbital to maintain deep anesthesia. Guidelines contained in the National Institutes of Health *Guide for the Care and Use of Laboratory Animals* (85-23, revised 1985) were strictly followed.

The lumbo-sacral and low thoracic spinal segments were exposed, and the dura mater was removed. After the surgical procedures, the animal was restrained in a stereotaxic apparatus with spinal and pelvic clamps. L_5–L_7 ipsilateral and contralateral ventral roots were dissected and sectioned. Pools were formed with the skin around the exposed tissues, filled with mineral oil (after placement of the electrodes), and maintained at a constant temperature (37°C). Blood pressure was continuously monitored and maintained at 100–120 mmHg.

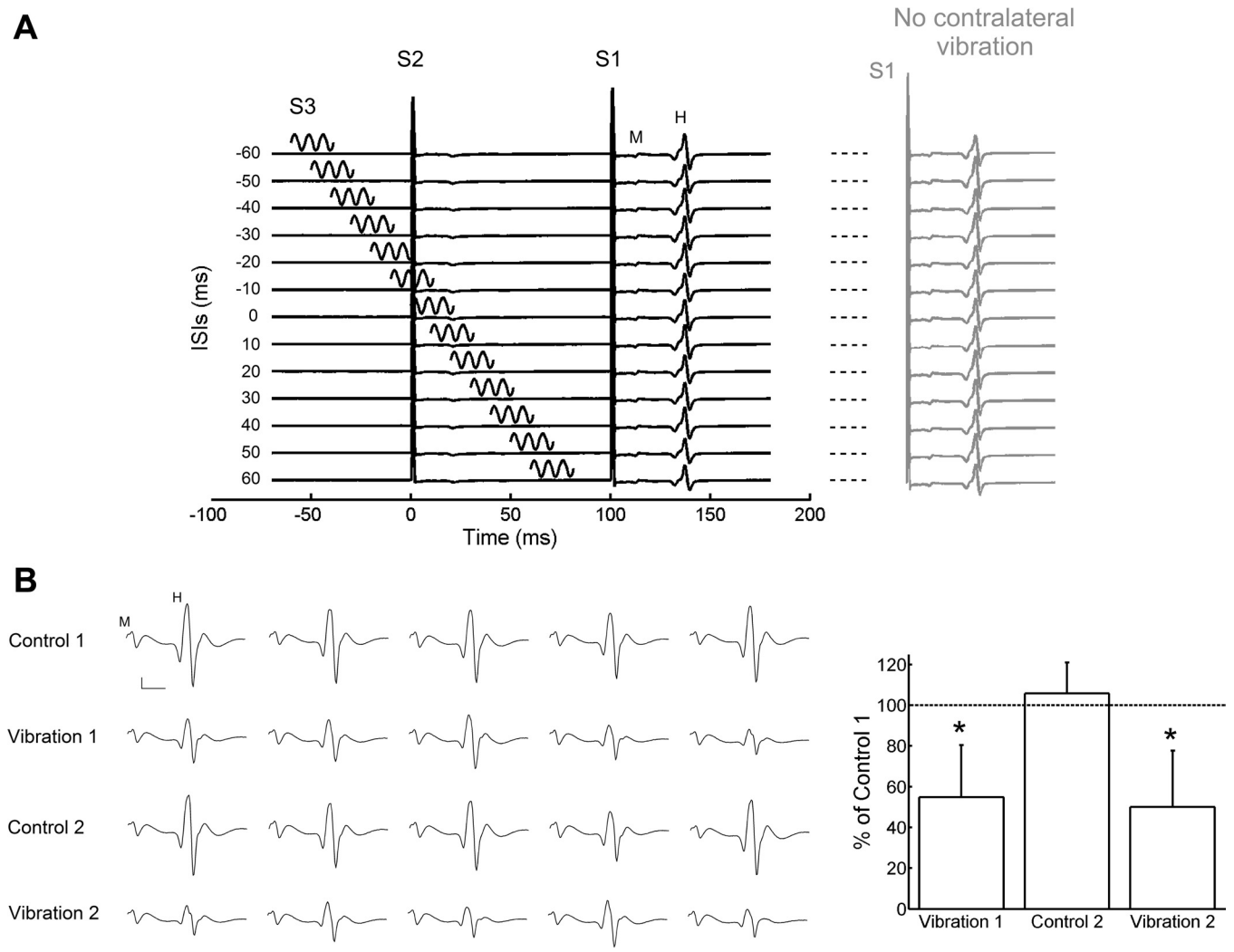

Fig. 2. *A*: timing of stimuli S1, S2, and S3. The sinusoidal cycles indicate the timing of contralateral vibration (S3) ranging in latency from −60 to +60 ms from the electrical conditioning stimulus to the CPN (S2). Each trace in black represents the average of 10 PSI_conditioned responses (conditioned by both S2 and S3 at the appropriate ISIs) obtained in the ipsilateral SO. Each trace in gray (on *right*) shows the average of 10 PSI_control responses (conditioned by S2 only). The C-T interval between S2 and S1 was always 100 ms. Note that the amplitude of PSI_control and the PSI_conditioned were almost the same throughout the 13 ISIs for this subject. H, H-reflex; M, respective M-wave. *B*: raw signals from a representative subject showing the H-reflexes obtained without (Control 1 and 2) and with (Vibration 1 and 2) conditioning vibration applied 600 ms before PTN stimulation. The vertical and horizontal calibration are, respectively, 0.2 mV and 10 ms. Bar graph on *right* shows the significant effect of vibration (mean of 5 subjects) in reducing the H-reflex amplitude and the full recovery after 10 s from the end of the vibratory stimulus (see text for details). *Significant differences from Control 1 and 2 ($P < 0.001$). Error bars are SD.

Stimulation. In a group of 12 animals contralateral and ipsilateral GS afferents were stimulated with single pulses of 1.2–1.4 times the threshold level of afferent volleys recorded on the cord dorsum (Fig. 4*A*). Conditioning stimuli (3 electrical pulses at 100 Hz; Enriquez-Denton et al. 2004) were applied to ipsi- or contralateral PBSt afferents (Fig. 4*A*). Figure 4, *B* and *C*, *right*, show the ipsilateral GS-MSR conditioned by stimulation to both the ipsilateral and contralateral PBSt nerves, respectively. C-T intervals from 0 to 120 ms were analyzed. The frequency of stimulation was adjusted to 0.5 Hz. A Master-8 system (and TTL pulses) was used to produce simultaneous pulses of stimulation. In a group of five animals a brief conditioning vibration (3 cycles at 180 Hz with a Chubbuck mechanical stimulator transducer) was applied to the contralateral GS tendon in order to activate the corresponding muscle Ia afferents (see Fig. 5). Conditioning ipsilateral PBSt stimulation consisted of a train of 3 pulses at 100 Hz (Enriquez-Denton et al. 2004). The ISIs between contralateral tendon vibration and ipsilateral PBSt stimulus varied from −60 to +60 ms. Negative ISIs indicate that the vibratory stimulus was delivered before the conditioning electrical stimulus to the PBSt nerve (to induce PSI on the ipsilateral side). These negative ISIs were considered for statistical analysis. This procedure was analogous to that implemented for the human experiments. The C-T interval between the electrical stimulus to the ipsilateral PBSt and GS nerves was fixed at 25 ms.

Electrophysiological recordings. Bilateral MSRs were recorded simultaneously from proximal L_6 ventral roots. When a stimulus was applied to the ipsilateral GS nerve no reflexes were evoked in the contralateral ventral root.

Bilaterally evoked afferent volleys and spontaneous cord dorsum potentials were recorded at L_6 by using two silver ball electrodes placed on the cord dorsum. Another electrode was inserted in the back muscles as a reference. Low-noise and high-gain differential amplifiers (Grass model P511) were used to amplify the potentials.

Statistical Analyses

A two-tailed paired *t*-test was used to detect the PSI effect in humans by comparing H-reflex of SO with (PSI_control) and without (Control) conditioning by ipsilateral CPN stimulation. In the cat, the

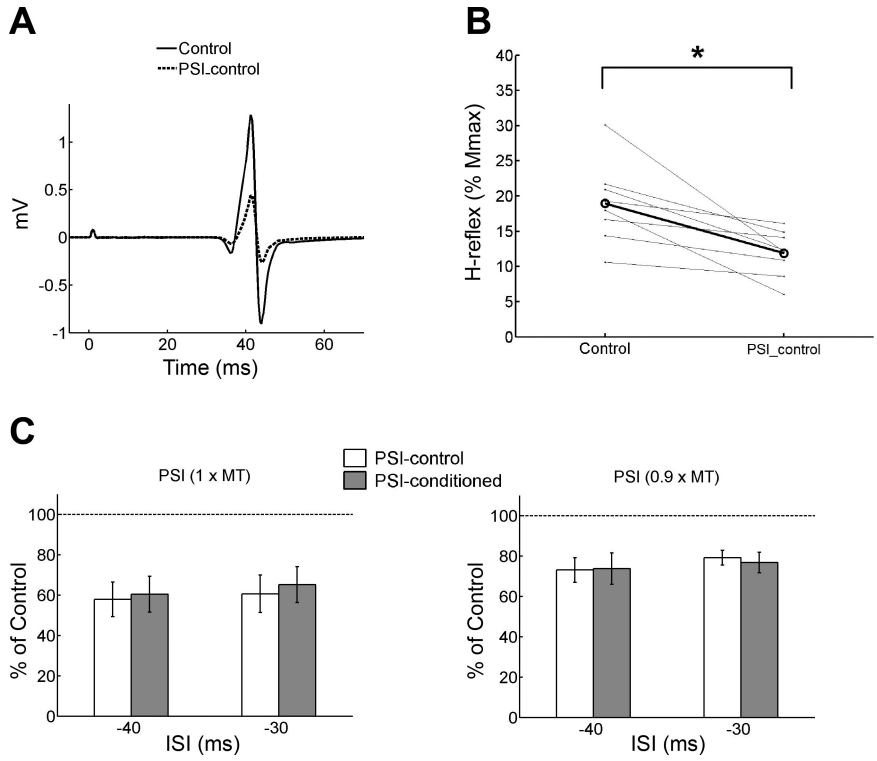

Fig. 3. *A*: averaged H-reflexes obtained from 1 subject (the one who produced the lowest PSI_control amplitude in *B*). The dashed waveform is the average of 130 PSI_control sweeps. The solid waveform is the average of 50 Control sweeps. *B*: pairwise comparison between H-reflex amplitudes obtained with (PSI_control) and without (Control) CPN stimulation from all subjects. Thick black line represents the averaged value. The conditioned H-reflex responses were significantly different from control (*significant difference, $P < 0.05$). *C*: averaged PSI_control and PSI_conditioned responses obtained from 5 subjects with 2 ISIs, −40 ms and −30 ms. No significant differences between both responses (for the ISIs investigated) were detected for both intensities of conditioning to the CPN 1.0 × motor threshold (MT) and 0.9 × MT.

PSI effect was detected by comparing the MSR of GS with and without conditioning by either ipsilateral or contralateral PBSt stimulation. The same test was used to detect possible differential effects of contralateral tendon vibration on reflex responses conditioned by ipsilateral PSI across the 13 ISIs in humans and 6 ISIs in cats. The statistical package SPSS (v. 16.0) was used to perform the analyses. A significance level was set as being lower than 5%.

RESULTS

Human Experiments

Figure 2*A* shows typical records obtained from one subject during an experiment. The black traces are the EMG recorded from the SO muscle representing the PSI_conditioned responses (mean of 10 repetitions), i.e., the H-reflexes conditioned by both S2 (ipsilateral CPN electrical pulse applied 100 ms before the PTN) and S3 (contralateral tendon vibration at the 13 ISIs) stimuli. The gray traces in Fig. 2*A*, *right*, represent the averaged reflex responses with no contralateral vibration (PSI_control).

The amplitudes of these responses (PSI_conditioned and PSI_control), which look very similar to each other as in the example of Fig. 2*A*, were compared as previously described. Indeed, considering all subjects, there were no significant differences between PSI_control and PSI_conditioned amplitudes for each of the 13 ISIs (Table 1). These results indicate an absence of effect from contralateral vibration on the ipsilateral PSI, i.e., there is no effect from the contralateral Ia afferents on the PSI of the ipsilateral Ia SO terminals in relaxed humans. The difference between PSI conditions are of near-borderline significance at ISIs of −30 ms and 20 ms ($P = 0.056$ and $P = 0.062$, respectively). However, the P values at neighboring ISI values were not marginal (0.98/0.52 and 0.46/0.88, respectively), indicating absence of a possible physiologically significant difference between conditions. Additionally, the repetition of the experiment for ISIs of −30 ms and −40 ms (Fig. 3*C*) confirmed the lack of effects at these latencies (see below).

Figure 6*A* shows EMG recordings from the SO muscle in one subject. The dotted, solid, and dashed lines represent the averaged Control, PSI_control, and PSI_conditioned reflexes, respectively. There is a clear effect of the CPN conditioning in this subject. Figure 6*B* demonstrates the same effect in all subjects. Both individual and overall data show an absence of differences ($P > 0.05$) between PSI_control and PSI_conditioned for the ISIs depicted (Fig. 6).

The comparison between PSI_control and the H-reflex amplitudes obtained at the end of each trial (Control) for all subjects showed that the overall effect from CPN stimulation was significant ($P < 0.05$) (Fig. 3, *A* and *B*). The conditioned H-reflex decreased by ~40% from its control value (Fig. 3*B*).

Conditioning stimuli. To examine the possibility that the induced level of PSI by CPN conditioning was saturated (i.e., reached a maximum value), the experiment was repeated in five human subjects with two different conditioning intensities to the CPN (1.0 × MT and 0.9 × MT) at 2 ISIs (−40 ms and −30 ms) (Fig. 3*C*). The results presented in Fig. 3*C* show a lack of contralateral effects at both conditioning intensities. Moreover, the 0.9 × MT conditioning stimulus effect was less than that observed with 1.0 × MT. These findings suggest that the absence of crossed effects is not a result of saturation in the inhibitory pathway.

An H-reflex was evoked in the contralateral leg 600 ms after the vibration to establish whether the conditioning mechanical stimulus used in the present experiments was enough to activate Ia afferents. The traces in Fig. 2*B*, *left*, are the raw data from one representative subject showing the 20 reflex responses elicited within 10-s intervals. The aver-

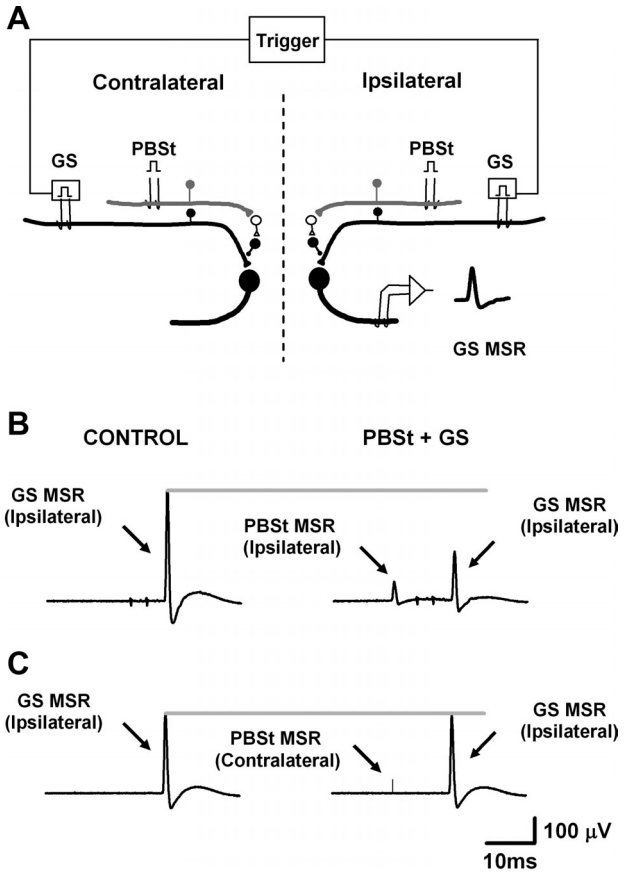

Fig. 4. *A*: diagram of the experimental arrangement in cats. Black, gastrocnemius/soleus (GS); gray, posterior biceps and semitendinosus (PBSt). The conditioning stimulus was applied to either the ipsilateral or contralateral PBSt nerve as indicated. The test stimuli were applied to the contralateral and ipsilateral GS nerves to produce monosynaptic reflexes (GS-MSR). *B*: in this example, conditioning stimulation was applied to the ipsilateral PBSt nerve at a 10-ms ISI. *Left*: MSR control response to the test stimulus applied to ipsilateral GS nerve without conditioning. *Right*: the ipsilateral PBSt conditioning stimulation produced a significant reduction in the amplitude of the GS-MSR. *C*: same as *B*, but with the conditioning stimulation applied to the contralateral PBSt nerve. Note that the contralateral PBSt conditioning stimulation did not produce a significant decrease in the amplitude of the GS-MSR.

age peak-to-peak reflex responses conditioned by the mechanical stimulus are presented in Fig. 2*B*, *right*. The depression was significant for all subjects tested ($P < 0.001$). A full recovery of reflex amplitude after the 10-s interval (compare Vibration 1 with Control 2) is evident in the bar graph. The overall reflex depression in response to vibration was 47%.

The mechanical stimuli (tendon vibration with 3 cycles at 180 Hz) were very consistent along the experiment. The mean ± SD displacement of the tip of the mini-shaker in contact with the tendon in response to the application of 28 stimuli (evoked at 1-s intervals) was 0.56 ± 0.008 mm, yielding a very small coefficient of variation (CV = 1.4%). Experiments with the second shaker system (adjusted to give similar tip displacements) also yielded a very small CV (3.5%), with a measured acceleration of 25 g (where g is the acceleration of gravity). This value corresponded to a displacement of ~0.7 mm (Hultborn et al. 1987a).

Cat Experiments

Figure 4*B* shows that the conditioning stimulation (around 10 ms of C-T time interval) to the ipsilateral PBSt nerve was associated with a statistically significant reduction ($P < 0.05$, *t*-test) in amplitude of the GS-MSR. On the other hand, no change was observed in GS-MSR amplitude when the conditioning stimulus was applied to the contralateral PBSt nerve (Fig. 4*C*). Similar results were obtained when the sides were switched, i.e., when the test reflex was recorded from the contralateral GS (not shown).

The open circles in Fig. 7 illustrate measurements of GS-MSR amplitudes for one cat for all values of C-T time intervals described in METHODS, but similar results were obtained in the other 11 cats. The filled circles in Fig. 7 show the GS-MSR mean values from the 12 cats, conditioned by either ipsilateral (Fig. 7, *top*) or contralateral (Fig. 7, *bottom*) stimuli to the PBSt nerve at 20 ms of C-T time interval. There was a significant decrease ($P < 0.05$, 12 cats) in the mean GS-MSR amplitude when the conditioning stimulus was applied to the ipsilateral PBSt nerve (Fig. 7, *top*). Conversely, there was no detectable change ($P > 0.05$, 12 cats) in the GS-MSR amplitude when the conditioning stimulus was applied to the contralateral PBSt nerve (Fig. 7, *bottom*).

The experiments using conditioning vibratory stimulation of the contralateral tendon in the cat, as illustrated in Fig. 5, yielded results similar to those obtained in humans. The pooled data for five animals are illustrated in Fig. 8. The filled bars in Fig. 8 show the mean amplitude of GS-MSRs under PSI of the ipsilateral PBSt afferents (PSI_control). The open bars show the mean amplitude of GS-MSRs during both electrical stimulation of ipsilateral PBSt and contralateral tendon vibration (i.e., activation of contralateral group Ia afferents) (PSI_conditioned). Figure 8 also shows the effects of this contralateral conditioning stimulation to the tendon for different ISIs (from −60 to 0 ms). In summary, the conditioning vibratory stimulation (S3) of the contralateral group Ia afferents was not associated with significant ($P > 0.5$) changes in amplitude of the GS-MSR (S1) subjected to PSI by the ipsilateral PBSt afferents (S2).

DISCUSSION

Crossed influences from afferent inputs of the contralateral limb can adjust the excitability of reflex pathways via pre- and postsynaptic mechanisms. The present study focused on the crossed effect of group I afferents from the contralateral SO onto ipsilateral PSI of Ia afferents in resting human subjects and anesthetized cats. The results obtained from experiments in both species seem to corroborate and extend previous findings in cats that contralateral group I activation does not affect ipsilateral mechanisms of reflex gain control via presynaptic interneurons (Devanandan et al. 1965). The range of ISIs was probably wide enough to include the latencies necessary for an eventual crossed effect at the spinal cord level. The neurophysiological aspects of the contribution of group I afferents to crossed effects and probable pathways are discussed below.

Evidence for Group I Afferents in Mediating Crossed Effects

In general, crossed reflexes have been extensively studied in humans and animal preparations. The current view is that

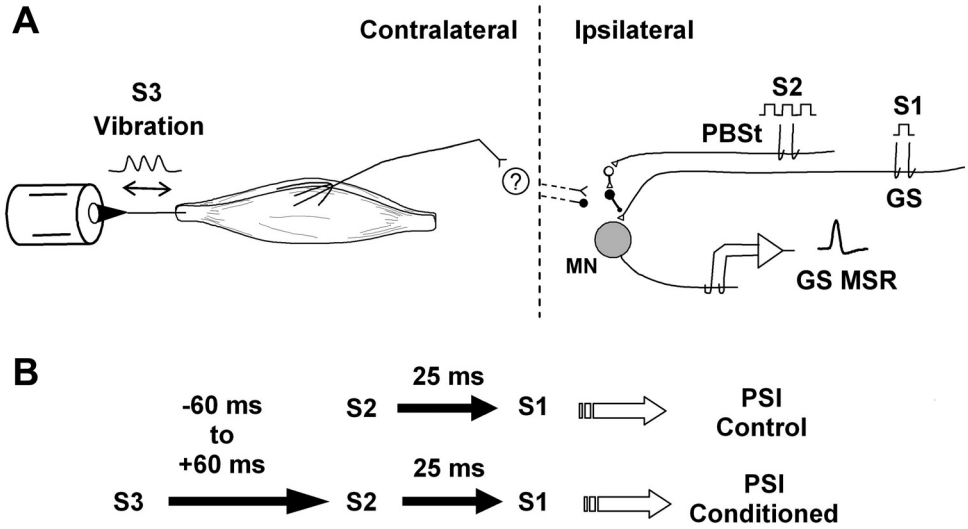

Fig. 5. *A*: diagram of the experimental arrangement to explore the effects of contralateral group Ia afferents on PSI of the GS-MSR. Conditioning stretching stimulation (S3) was applied on the contralateral GS tendon (3 vibratory cycles). Conditioning electrical stimulation (S2) was applied on the ipsilateral PBSt nerve (3 electrical pulses), and the test stimulus (S1) was applied on the ipsilateral GS nerve (1 electrical pulse). The symbol "?" represents the unknown commissural pathway(s) that could mediate crossed actions. *B*: the stimulation sequence was similar to the stimulation illustrated in Fig. 1, but with C-T interval (between S2 and S1) of 25 ms instead of 100 ms used in the human experiments.

high-threshold afferent fibers convey the strongest contralateral effects. However, there is some evidence from experiments in both cat and human suggesting group I afferents in crossed reflexes acting directly onto motoneurons (Curtis et al. 1958; Jankowska et al. 1978, 2009) or indirectly via excitatory and inhibitory interneurons (Bannatyne et al. 2009; Delwaide and Pepin 1991; Jankowska et al. 2009).

An electrophysiological study conducted by Harrison and Zytnicki (1984) showed that the crossed effects from Ia afferents onto motoneurons are weak in the cat, but these afferents can modulate the level of reciprocal inhibition by acting on Ia inhibitory interneurons. This result indicates an indirect rather than a direct crossed action onto the motoneuronal pool. Although previous studies described inhibitory effects from contralateral triceps surae tendon vibration on both ankle extensors and flexors in the cat (Baxendale and Rosenberg 1976, 1977), no explanation of the putative underlying mechanisms mediating these crossed effects was provided. Using parameters of contralateral mechanical conditioning stimulation similar to those of Baxendale and Rosenberg (1976), the present work did not identify changes in the PSI of Ia terminals from contralateral group I activation in the cat, suggesting that the inhibitory effects were not mediated by a presynaptic mechanism.

In humans, it has been speculated that the inhibitory effects of a conditioning mechanical stimulation (single tap) to the contralateral Achilles tendon on the ipsilateral H-reflex responses were conveyed by Ia afferents and mediated by a presynaptic inhibitory mechanism (Koceja and Kamen 1992). Similarly, it has been reported that passive cycling movements of the contralateral leg induced ipsilateral H-reflex inhibition that was dependent on the speed but not on the phase (limb position) of movement (Cheng et al. 1998; Collins et al. 1993). The velocity dependence is an indication of the involvement of group Ia afferents from the moving limb. The presence of contralateral reflex inhibition both in the relaxed muscle and during voluntary contraction of the stationary limb suggests the involvement of a presynaptic mechanism mediating the crossed effect. Again, these authors did not provide direct evaluation of the possible mechanisms contributing to this inhibitory effect.

In contrast to the view of the crossed reflex modulation operating via presynaptic mechanism, it was previously suggested that activation of group I afferents on the contralateral side of the cat did not produce an inhibitory presynaptic action onto ipsilateral Ia afferents (Devanandan et al. 1965). The present results extended these findings and explicitly demonstrate a lack of PSI modulation of Ia MSRs from contralateral group I afferents in both cats and humans. Therefore, the results from Koceja and Kamen (1992), using contralateral mechanical conditioning, and from Cheng et al. (1998), using contralateral passive leg cycling, might not be fully explained by presynaptic inhibitory mechanisms acting on ipsilateral Ia terminals.

A second mechanism, probably postsynaptic, could be operative in the mediation of the effects from contralateral group I afferent activation. A postsynaptic mechanism can also explain the reduction of ongoing ipsilateral SO EMG at latencies around 40 ms after contralateral PTN electrical stimulation (Stubbs and Mrachacz-Kersting 2009), but these authors did not explore this possibility. One must consider that in previous studies (Cheng et al. 1998; Koceja and Kamen 1992; Stubbs and Mrachacz-Kersting 2009) other classes of afferents could

Table 1. *Percentage of inhibition of H-responses conditioned by both stimuli (S2 and S3) and by CPN stimulation (S2)*

	ISI, ms												
	−60	−50	−40	−30	−20	−10	0	10	20	30	40	50	60
% PSI_conditioned	42	35	32	29	31	33	30	32	35	35	32	33	33
% PSI_control	44	31	32	38	34	32	33	35	31	35	35	33	35
P values	0.876	0.210	0.982	0.056	0.519	0.654	0.458	0.460	0.062	0.885	0.621	0.856	0.398

Values are % of inhibition of the H-responses conditioned by both stimuli (S2 and S3), termed PSI_conditioned, and by the common peroneal nerve (CPN) stimulation (S2), termed PSI_control. *P* values are from the 2-tailed paired Student's *t*-test. This test was used to detect differences between PSI_conditioned and PSI_control for all 13 interstimulus intervals (ISIs) between stimulus S3 (tendon vibration) and S2 (electrical pulse to the CPN).

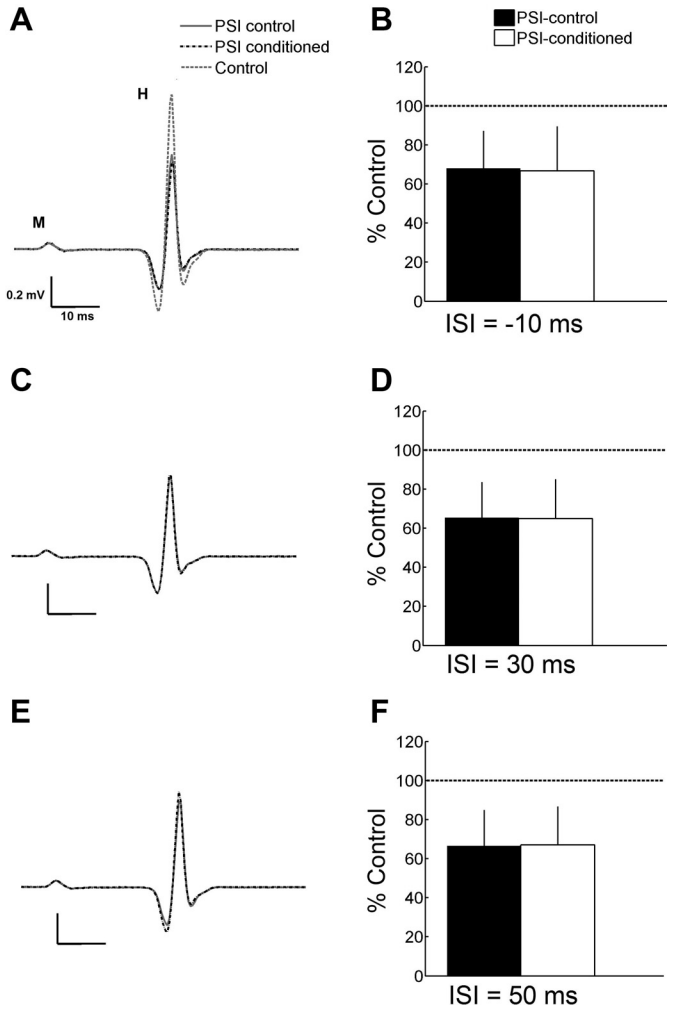

Fig. 6. Averaged (10 trials) reflex responses obtained from 1 representative subject across 3 different ISIs [−10 ms (*A*), 30 ms (*C*), 50 ms (*E*)]. Dotted trace in *A* is the averaged (mean of 50 responses) Control H-reflex, i.e., without any kind of conditioning. Solid and dashed traces in *A*, *C*, and *E* are the averaged PSI_control and PSI_conditioned responses, respectively. The mean peak-to-peak amplitude evaluated for all subjects is shown in *B*, *D*, and *F*. Filled and open bars are averaged PSI_control and PSI_conditioned responses, respectively, as % of the Control H-reflex (horizontal dashed lines). Error bars are SD.

also be contralaterally activated (e.g., cutaneous and group II) (Iles 1996; Stubbs et al. 2011); hence the crossed effects would not be only associated with contralateral Ia afferents.

Even though Devanandan et al. (1965) anticipated an absence of postsynaptic influence from contralateral Ia afferents onto motoneurons, later studies documented changes in excitability of the Ia inhibitory interneuron in response to contralateral group I stimulation in cat hindlimbs (Harrison and Zytnicki 1984) and in the upper limbs of humans (Delwaide and Pepin 1991). With respect to the latter study, one can speculate that Ia inhibitory interneurons could mediate these crossed influences in human lower limbs as well. Nevertheless, any comparison of crossed effects on reciprocal inhibition (or PSI) between upper and lower limbs would be speculative because of the lack of available data.

Altogether, these findings suggest that the influence of contralateral group I afferents onto interneurons involved in PSI of Ia terminals is feeble or absent. Reciprocal inhibitory pathways (postsynaptic action) might be relevant in the mediation of these crossed effects.

It is important to mention that, despite the very low intensity of vibratory stimulus, a recruitment of cutaneous afferents cannot be fully discarded in the present experiments in humans. A significant crossed effect on PSI from contralateral cutaneous activation has been reported (Iles 1996). One may argue that the train of four electrical shocks (1.5 × perceptual threshold) used by Iles (1996) is probably much more effective in firing cutaneous afferents than the vibration applied to the skin over the Achilles tendon as used in the present research. Thus putative cutaneous crossed effects should be expected to be of a lesser magnitude here than in Iles's (1996) experiments.

Even considering the possibility of the interference from low-threshold cutaneous afferents (Hultborn et al. 1987a; Perl 1957), it is very unlikely that a cutaneous effect would counteract any possible group I crossed effect for all the ISIs used in the present study. The complementary experiments in the cat

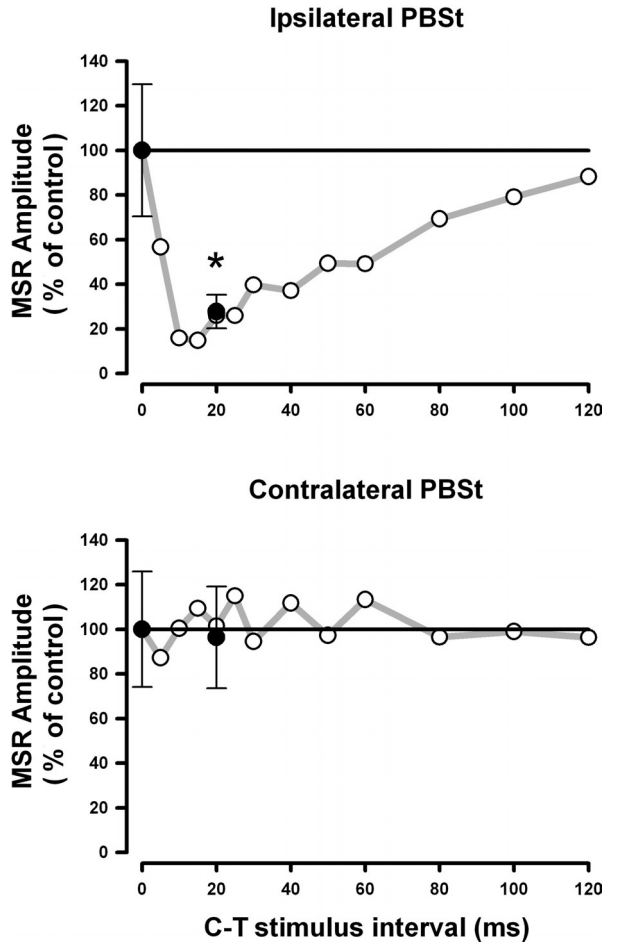

Fig. 7. GS-MSR amplitude as a function of the ipsilateral or contralateral PBSt C-T interval. Open circles show results for 1 experiment. Filled circles show the mean GS-MSR amplitude for all the experiments in cats for control (test stimulus, 0 ms) and 20 ms of either ipsilateral or contralateral PBSt C-T interval. *Top*: MSR amplitude obtained when the test GS-MSR was conditioned by stimulation of the ipsilateral PBSt nerve. *Statistically significant change ($P < 0.05$, *t*-test) between the control (test GS-MSR) and the GS-MSR conditioned by the ipsilateral PBSt nerve at C-T interval of 20 ms. *Bottom*: GS-MSR was conditioned by stimulation of the contralateral PBSt nerve. The contralateral PBSt conditioning stimulation (C-T interval of 20 ms) did not produce a statistically significant change in the amplitude of the GS-MSR ($P > 0.05$, *t*-test). Error bars are SE.

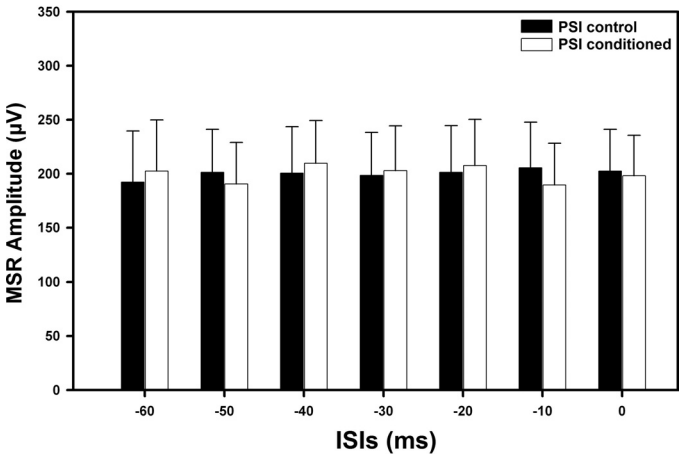

Fig. 8. GS-MSR amplitude (average of 5 cats) obtained by the stimulation protocol illustrated in Fig. 5. Filled bars, mean amplitude of the GS-MSR conditioned by the ipsilateral electrical stimuli to the PBSt nerve, i.e., ipsilateral PSI (PSI_control). Open bars, mean amplitude of the GS-MSR conditioned by both the vibratory stimuli to the contralateral GS tendon and the ipsilateral electrical stimuli to the PBSt nerve, i.e., contralateral conditioning of the ipsilateral PSI (PSI_conditioned). Note that the contralateral conditioning vibratory stimulation to group I afferents did not produce a statistically significant change in amplitude of ipsilateral GS-MSRs under PSI for ISIs from −60 to 0 ms ($P > 0.05$, *t*-test). Error bars are SE.

(which produced the same results as in humans) support this hypothesis since the conditioning electrical stimulation was applied directly on group I PBSt nerves (without the participation of cutaneous afferents) and the vibratory conditioning was applied exclusively to the isolated tendon (without the skin).

Possible Commissural Interneurons Conveying Crossed Effects

Commissural interneurons that convey the signals from contralateral synaptic inputs are not homogeneous, and their characterization is complex (Edgley and Aggelopoulos 2006; Jankowska et al. 2005, 2009; Jankowska and Edgley 2010).

An important target for monosynaptic input from group I afferents are the commissural interneurons located within laminae VI–VII (Bannatyne et al. 2009; Jankowska et al. 2009). Among these intermediate zone interneurons, those that project to contralateral motor nuclei have only contralateral axons and those that project bilaterally send axons to areas located outside the motor nuclei, indicative of targets other than motoneurons (Jankowska et al. 2009). These bilaterally projecting interneurons are of special interest, as one may speculate that they form contact with interneurons interposed in presynaptic inhibitory pathways, i.e., they also project to ipsilateral lamina VI, where the occurrence of GABAergic presynaptic synapses on Ia terminals has been reported (Maxwell et al. 1990) and where few GABAergic interneurons (probably primary afferent depolarization mediated) have been found (Bannatyne et al. 2009).

Therefore, commissural interneurons from the contralateral intermediate zone could be strong candidates to convey crossed effects from group I afferents and modulate PSI in the ipsilateral side. However, while PSI on group I afferents has been suggested to be a mechanism to select intermediate zone interneurons (with or without crossed axonal projections) according to the motor task (Liu et al. 2010), no morphological study has provided evidence of synaptic connections between these commissural neurons and ipsilateral last-order presynaptic inhibitory interneurons. Previous studies were also unable to confirm the existence of crossed oligosynaptic (or polysynaptic) pathways leading to modulation of PSI of Ia terminals. Absence of such crossed pathways could explain the present results obtained in humans and cats.

It is important to emphasize, however, that the general pattern of neuronal connectivity within the human spinal cord might be considerably different from that described in animal preparations. Thus, given the relatively long time course of PSI in humans (~100 ms; Hultborn et al. 1987b) and in cats (see Fig. 7), the use of a long range of ISIs in the present study was necessary to unravel possible crossed actions on ipsilateral PSI mediated by crossed pathways.

Future Directions

A complementary characterization of group I contralateral influences in humans could come from the analysis of motor units with different synaptic input thresholds within the SO motoneuronal pool. In the present experiments only the earliest recruited motor units were investigated by evoking test reflexes at around 20% M_{max}. Hence, it is conceivable that contralateral effects could be differentially manifested for a wider range of motor unit types, i.e., there could be an uneven distribution of effects (perhaps task dependent) throughout the pool of motoneurons belonging to the SO motor nucleus (Mezzarane et al. 2011). This possibility remains to be explored by performing an analysis based on a wider spectrum of H-reflex amplitudes.

Additionally, possible crossed effects conveyed by group I afferents from heteronymous muscles onto Ia PSI regulation deserve further investigation.

Conclusion

The present results from anesthetized cats and humans in a resting state suggest that the contribution of contralateral group I afferents to reflex modulation via PSI of Ia terminals is minimal or absent. If we can generalize the results obtained here for the specific pathways investigated, one may conclude that *1*) the weak crossed effects found in cats in previous studies are not mediated by a presynaptic inhibitory mechanism and *2*) if there is a group I crossed influence in humans, it is not mediated by PSI. Therefore, the presynaptic mechanism subserving reflex gain control is not triggered or regulated by contralateral group I afferent activation. One alternative mechanism operational in both species could be a postsynaptic reflex modulation.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: R.A.M. and E.M. conception and design of research; R.A.M., E.C.-R., L.M., and A.F. performed experiments; R.A.M., E.C.-R., L.M., and A.F. analyzed data; R.A.M., A.F.K., and E.M. interpreted results of experiments; R.A.M. and E.M. prepared figures; R.A.M. drafted manuscript; R.A.M., A.F.K., and E.M. edited and revised manuscript; R.A.M., A.F.K., and E.M. approved final version of manuscript.

REFERENCES

Aggelopoulos NC, Edgley SA. Segmental localisation of the relays mediating crossed inhibition of hindlimb motoneurones from group II afferents in the anaesthetized cat spinal cord. *Neurosci Lett* 185: 60–64, 1995.

Bannatyne BA, Liu TT, Hammar I, Stecina K, Jankowska E, Maxwell DJ. Excitatory and inhibitory intermediate zone interneurons in pathways from feline group I and II afferents: differences in axonal projections and input. *J Physiol* 587: 379–399, 2009.

Baxendale RH, Rosenberg JR. Crossed reflexes evoked by selective activation of muscle spindle primary endings in the decerebrate cat. *Brain Res* 115: 324–327, 1976.

Baxendale RH, Rosenberg JR. Crossed reflexes evoked by selective activation of tendon organ afferent axons in the decerebrate cat. *Brain Res* 127: 323–326, 1977.

Burke D, Gandevia SC, McKeon B. The afferent volleys responsible for spinal proprioceptive reflexes in man. *J Physiol* 339: 535–552, 1983.

Cheng J, Brooke JD, Misiaszek JE, Staines WR. Crossed inhibition of the soleus H reflex during passive pedalling movement. *Brain Res* 779: 280–284, 1998.

Cisi RL, Kohn AF. H-reflex depression simulated by a biologically realistic motoneuron network. *Conf Proc IEEE Eng Med Biol Sci* 2007: 2713–2716, 2007.

Collins DF, McIlroy WE, Brooke JD. Contralateral inhibition of soleus H reflexes with different velocities of passive movement of the opposite leg. *Brain Res* 603: 96–101, 1993.

Corna S, Galante M, Grasso M, Nardone A, Schieppati M. Unilateral displacement of lower limb evokes bilateral EMG responses in leg and foot muscles in standing humans. *Exp Brain Res* 109: 83–91, 1996.

Crone C, Hultborn H, Mazières L, Morin C, Nielsen J, Pierrot-Deseilligny E. Sensitivity of monosynaptic test reflexes to facilitation and inhibition as a function of the test reflex size: a study in man and the cat. *Exp Brain Res* 81: 35–45, 1990.

Curtis DR, Krnjevic K, Miledi R. Crossed inhibition of sacral motoneurones. *J Neurophysiol* 21: 319–326, 1958.

Delwaide PJ, Pepin JL. The influence of contralateral primary afferents on Ia inhibitory interneurones in humans. *J Physiol* 439: 161–179, 1991.

Devanandan MS, Holmqvist B, Yokota T. Presynaptic depolarization of group I muscle afferents by contralateral afferent volleys. *Acta Physiol Scand* 63: 46–54, 1965.

Dietz V. Spinal cord pattern generators for locomotion. *Clin Neurophysiol* 114: 1379–1389, 2003.

Duysens J, Tax AA, van der Doelen B, Trippel M, Dietz V. Selective activation of human soleus or gastrocnemius in reflex responses during walking and running. *Exp Brain Res* 87: 193–204, 1991.

Eccles RM, Holmqvist B, Voorhoeve PE. Presynaptic inhibition from contralateral cutaneous afferent fibres. *Acta Physiol Scand* 62: 464–473, 1964.

Edgley SA, Aggelopoulos NC. Short latency crossed inhibitory reflex actions evoked from cutaneous afferents. *Exp Brain Res* 171: 541–550, 2006.

Edgley SA, Jankowska E, Krutki P, Hammar I. Both dorsal horn and lamina VIII interneurones contribute to crossed reflexes from feline group II muscle afferents. *J Physiol* 552: 961–974, 2003.

Enriquez-Denton M, Manjarrez E, Rudomin P. Persistence of PAD and presynaptic inhibition of muscle spindle afferents after peripheral nerve crush. *Brain Res* 1027: 179–187, 2004.

Fornari MC, Kohn AF. High frequency tendon reflexes in the human soleus muscle. *Neurosci Lett* 440: 193–196, 2008.

Gossard JP, Rossignol S. Phase-dependent modulation of dorsal root potentials evoked by peripheral nerve stimulation during fictive locomotion in the cat. *Brain Res* 537: 1–13, 1990.

Haridas C, Zehr EP. Coordinated interlimb compensatory responses to electrical stimulation of cutaneous nerves in the hand and foot during walking. *J Neurophysiol* 90: 2850–2861, 2003.

Harrison PJ, Zytnicki D. Crossed actions of group I muscle afferents in the cat. *J Physiol* 356: 263–273, 1984.

Holmqvist B. Crossed spinal reflex actions evoked by volleys in somatic afferents. *Acta Physiol Scand* 52: 1–66, 1961.

Hortobágyi T, Taylor JL, Petersen NT, Russell G, Gandevia SC. Changes in segmental and motor cortical output with contralateral muscle contractions and altered sensory inputs in humans. *J Neurophysiol* 90: 2451–2459, 2003.

Hultborn H, Meunier S, Morin C, Pierrot-Deseilligny E. Assessing changes in presynaptic inhibition of Ia fibres: a study in man and the cat. *J Physiol* 389: 729–756, 1987a.

Hultborn H, Meunier S, Pierrot-Deseilligny E, Shindo M. Changes in presynaptic inhibition of Ia fibres at the onset of voluntary contraction in man. *J Physiol* 389: 757–772, 1987b.

Iles JF. Evidence for cutaneous and corticospinal modulation of presynaptic inhibition of Ia afferents from the human lower limb. *J Physiol* 491: 197–207, 1996.

Jankowska E, Bannatyne BA, Stecina K, Hammar I, Cabaj A, Maxwell DJ. Commissural interneurons with input from group I and II muscle afferents in feline lumbar segments: neurotransmitters, projections and target cells. *J Physiol* 587: 401–418, 2009.

Jankowska E, Edgley SA. Functional subdivision of feline spinal interneurons in reflex pathways from group Ib and II muscle afferents; an update. *Eur J Neurosci* 32: 881–893, 2010.

Jankowska E, Edgley SA, Krutki P, Hammar I. Functional differentiation and organization of feline midlumbar commissural interneurones. *J Physiol* 565: 645–658, 2005.

Jankowska E, Padel Y, Zarzecki P. Crossed disynaptic inhibition of sacral motoneurones. *J Physiol* 285: 425–444, 1978.

Koceja DM, Kamen G. Contralateral influences on triceps surae motoneuron excitability. *Electroencephalogr Clin Neurophysiol* 85: 177–182, 1992.

Kohn AF, Floeter MK, Hallett M. Presynaptic inhibition compared with homosynaptic depression as an explanation for soleus H-reflex depression in humans. *Exp Brain Res* 116: 375–380, 1997.

Liu TT, Bannatyne BA, Jankowska E, Maxwell DJ. Properties of axon terminals contacting intermediate zone excitatory and inhibitory premotor interneurons with monosynaptic input from group I and II muscle afferents. *J Physiol* 588: 4217–4233, 2010.

Maxwell DJ, Christie WM, Short AD, Brown AG. Direct observations of synapses between GABA-immunoreactive boutons and muscle afferent terminals in lamina VI of the cat's spinal cord. *Brain Res* 53: 215–222, 1990.

Mezzarane RA, Klimstra M, Lewis A, Hundza SR, Zehr EP. Interlimb coupling from the arms to legs is differentially specified for populations of motor units comprising the compound H-reflex during "reduced" human locomotion. *Exp Brain Res* 208: 157–168, 2011.

Mezzarane RA, Kohn AF. Bilateral soleus H-reflexes in humans elicited by simultaneous trains of stimuli: symmetry, variability, and covariance. *J Neurophysiol* 87: 2074–2083, 2002.

Mezzarane RA, Kohn AF. Control of upright stance over inclined surfaces. *Exp Brain Res* 180: 377–388, 2007.

Perl ER. Crossed reflexes of cutaneous origin. *Am J Physiol* 188: 609–615, 1957.

Perl ER. Crossed reflex effects evoked by activity in myelinated afferent fibers of muscle. *J Neurophysiol* 21: 101–112, 1958.

Quevedo J, Eguibar JR, Jiménez I, Rudomin P. Raphe magnus and reticulospinal actions on primary afferent depolarization of group I muscle afferents in the cat. *J Physiol* 482: 623–640, 1995.

Roby-Brami A, Bussel B. Effects of flexor reflex afferent stimulation on the soleus H reflex in patients with a complete spinal cord lesion: evidence for presynaptic inhibition of Ia transmission. *Exp Brain Res* 81: 593–601, 1990.

Rosenberg ME. Synaptic connexions of alpha extensor motoneurones with ipsilateral and contralateral cutaneous nerves. *J Physiol* 207: 231–255, 1970.

Rudomin P, Schmidt RF. Presynaptic inhibition in the vertebrate spinal cord revisited. *Exp Brain Res* 129: 1–37, 1999.

Sherrington CS. Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing. *J Physiol* 40: 28–121, 1910.

Stubbs PW, Mrachacz-Kersting N. Short-latency crossed inhibitory responses in the human soleus muscle. *J Neurophysiol* 102: 3596–3605, 2009.

Stubbs PW, Nielsen JF, Sinkjær T, Mrachacz-Kersting N. Phase modulation of the short-latency crossed spinal response in the human soleus muscle. *J Neurophysiol* 105: 503–511, 2011.

Zehr EP, Collins DF, Chua R. Human interlimb reflexes evoked by electrical stimulation of cutaneous nerves innervating the hand and foot. *Exp Brain Res* 140: 495–504, 2001.