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ABSTRACT

CORTICAL MODULATION OF SPINAL REFLEXES IN HEALTHY HUMANS

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Considerable evidence suggests that monosynaptic and polysynaptic spinal reflexes are prone to corticospinal inputs. The goal of this study was to establish the cortical modulation of monosynaptic and polysynaptic spinal reflexes in healthy humans. Cutaneomuscular responses were evoked following stimulation of the medial edge of the right foot with a 30 ms pulse train every 10 s via a bipolar electrode and recorded from the ipsilateral tibialis anterior (TA) muscle. Across subjects, medial edge foot stimulation was delivered at 1.2 to 1.5 times the response threshold. The soleus H-reflex was evoked and recorded via conventional methods. The effects of transcranial magnetic stimulation (TMS) applied over left primary motor cortex at 0.7 and 1.2 times the motor evoked potentials (MEPs) resting threshold on the cutaneomuscular TA responses were established at the conditioning-test (C-T) intervals of 0, 25, 50, 70, 90, and 110 ms and on the soleus H-reflex at C-T intervals that ranged from negative 4 to positive 20 ms. We found that the soleus H-reflex was modulated in a similar pattern regardless the intensity of TMS. Subthreshold and suprathreshold TMS induced soleus H-reflex depression at negative C-T intervals and soleus H-reflex facilitation at positive C-T intervals. In contrast, the middle-latency cutaneous TA responses were depressed in all C-T intervals tested. Our findings strongly support

that direct corticospinal and cortico-cortical neuronal pathways affect the excitability of spinal neuronal circuits in healthy humans.

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INTRODUCTION

Evidence in humans and animals support the notion that spinal reflex circuits underlying human movement are susceptible to descending control (Iles and Pisini 1992; Neilsen et al. 1995). Excitation of cutaneous afferents facilitates the soleus motor evoked potentials (MEPs) (Roy and Gorassini 2008), while cutaneous afferents of the foot increase the cortical-mediated excitation of tibialis anterior (TA) long-latency responses (Nielsen et al. 1997). The TA MEPs and peaks of increased firing of single TA motor units evoked by magnetic stimulation of the motor cortex were facilitated when stretch was applied to TA muscle, likely due to increased cortical excitability induced by the muscle stretch itself (Nielsen et al. 1997). Further, motor cortex stimulation in the anesthetized cat increased the depolarization of hindlimb flexor and extensor motoneurons (Lundberg and Voorhoeve 1962). Inhibition from the motor cortex was mediated by Ia inhibitory interneurons while there was simultaneous facilitation produced by stimulation of muscle spindle 1a afferents from the antagonist muscle (Lundberg and Voorhoeve 1962). A similar organization has also been reported for humans (Iles and Pisini 1992). Because corticospinal and cutaneous afferent inputs converge on common α-motoneurons and interneurons in the spinal cord (Bretzner and Drew 2005; Fleshman et al. 1988; Pinter et al. 1982), it is high likely that the cutaneomuscular responses in man are prone to modifications by corticospinal inputs.

Transcutaneous electric stimulation (TES) was the first form of non-invasive brain stimulation that was used before the invention of transcranial magnetic stimulation (TMS) (Rothwell 2012). TMS, which is commonly used to activate supraspinal descending motor pathways, does not stimulate as focally as following electrical stimulation. However, motor cortical output zones can be easily distinguished (Rothwell 2012). Both TES and TMS elicit

muscular contractions through conduction in large diameter corticospinal neurons that have monosynaptic excitatory connections with motoneurons (Rothwell 2012). TES at subthreshold intensity and TMS delivered at 0.95 times the MEP threshold produce a short-latency depression followed by a long-lasting facilitation on the soleus H-reflex (Cowan et al. 1986; Iles and Pisini 1992; Nielsen and Petersen 1995), while the H-reflex in the antagonistic TA muscle is modulated in an opposite pattern to that of the soleus H-reflex (Nielsen et al. 1993). Evidence suggests that the long latency ankle stretch reflex is partly integrated by transcortical circuits (Petersen et al. 1998; Taylor et al. 1995; van Doornik 2004). Subthreshold electric stimulation produced an initially peaked facilitation of the H-reflex in wrist and finger flexor muscles followed by a second facilitation of the H-reflex (Cowan et al. 1986). Further, TMS over the primary motor cortex decreased presynaptic inhibition of soleus Ia afferents (Iles and Pisini 1996). Additionally, the actions of cutaneous and corticospinal pathways completely canceled each other and a spatial facilitation between them was noted (Iles and Pisini 1996). It was concluded that cutaneous and corticospinal axons converge on interneurones that inhibit presynaptic inhibition of group Ia afferents (Iles and Pisini 1992; Nielsen and Petersen 1995).

Accordingly, the present study was undertaken to investigate the effects of TMS at different stimulation intensities on cutaneomuscular responses and soleus H-reflex in seated healthy subjects. We hypothesized that the TA medium-latency cutaneomuscular responses are modulated by descending cortical volleys in an opposite pattern to that of the soleus H-reflex.

METHODS

Subjects

All experimental procedures were conducted in compliance with the Declaration of Helsinki after full Institutional Review Board (IRB) approval was granted by the CUNY IRB committee and all participants gave written informed consent to the experimental procedures. Subjects with tooth implants, assistive hearing devices, pacemaker, history of seizures, and medications known to alter central nervous system excitability were excluded from the study. All tests were conducted with subjects seated (hip angle, 120°; knee angle, 160°; ankle angle, 110°) and both feet supported on a foot rest.

Electromyography (EMG) recordings

Following standard skin preparation, single differential bipolar surface EMG electrodes (Motion Lab systems Inc., Baton Rouge, LA, USA) were placed on the medial gastrocnemius (MG), soleus (SOL), and TA of the right leg, and were secured with 3M Tegaderm transparent film (3M, St. Paul, MN, USA). All EMG signals were filtered with a cut-off frequency of 20-1000Hz (1401 plus running Spike 2; Cambridge Electronic Design, Cambridge, UK).

Transcranial magnetic stimulation

Single TMS pulses over the left primary motor cortex (M1) were delivered using a Magstim 200^2 stimulator (Magstim, Whitland, UK) with a double-cone coil (diameter 110 mm) placed so the current of the coil to flow from a posterior to an anterior direction, and according to procedures we have previously utilized (Knikou et al. 2013). The point where the lines between the inion and glabellum, and the left and right ear tragus met was marked on an EEG cap. The

double-cone coil was placed parallel and approximately 1 cm posterior and 1 cm lateral to the left from this intersection point. With the double-cone coil held at this position, the stimulation intensity was gradually increased and the MEPs recorded from the right TA and soleus muscles were observed on a digital oscilloscope (TDS 2014, Tektronix, Beaverton, OR, USA). When in three out of five TMS pulses, MEPs could not be evoked at low stimulation intensities with the subject at rest in the TA muscle only, the magnetic coil was moved by few mm and the procedure was repeated. When the optimal position was determined, the TA MEP resting threshold was established and corresponded to the stimulation intensity that induced repeatable MEPs in size that were approximately 100 μV of peak-to-peak amplitude (Rossini et al. 1994; Rothwell et al. 1999). The MEP resting threshold for subjects participating in soleus H-reflex experiments ranged from 46 to 72 % (52.4 ± 9.32; mean ± SD) and from 42 to 63 % (49.56 ± 6.65; mean ± SD) for subjects participating in cutaneomuscular responses experiments of the maximum stimulator output with subjects seated. All subjects wore a mouth guard and earplugs to minimize discomfort due to TMS.

Cutaneomuscular responses

Two disposable pre-gelled Ag-AgCl electrodes (Supertrace adhesive gel electrodes; Conmed Corporation, NY, USA) were positioned on the medial edge of the right foot. The medial edge of the foot was stimulated with a pulse train of 30 ms duration once every 10 s with a constant current stimulator (DS7A, Digitimer, Hertfordshire, UK) triggered by customized Spike 2 software. Reflex responses were recorded with a single differential electrode placed over the right TA muscle following light mechanical abrasion of the skin. The stimulus intensity during which the initial EMG TA activity was induced was identified as the response threshold. During

testing, medial edge foot stimulation ranged from 1.0 to 1.3 times the reflex threshold across subjects (1.6 ± 0.09 mA). At these intensities, no limb movement was present and subjects reported no pain upon stimulation.

Soleus H-reflex

With the subject seated, a stainless steel plate electrode of 4 cm in diameter was placed and secured proximal to the patella. Rectangular single pulse stimuli of 1-ms duration were delivered by a constant current stimulator to the tibial nerve at the popliteal fossa. The most optimal stimulation site was established via a hand-held monopolar stainless steel head electrode used as a probe (Knikou 2008). An optimal stimulation site corresponded to the site that the M-wave had a similar shape to that of the H-reflex at low and high stimulation intensities, and at the lowest stimulus intensity an H-reflex could be evoked without an M-wave. When the optimal site was identified, the monopolar electrode was replaced by a pregelled disposable electrode (SureTrace, Conmed, Utica, NY) that was maintained under constant pressure throughout the experiment with an athletic wrap. Then, the maximal M-wave was evoked and recorded. The stimulus was adjusted at an intensity that evoked H-reflexes ranging from 10 to 30% of the maximal M-wave.

Experimental Protocol

After the stimulation sites were determined, the effects of TMS on the TA cutaneomuscular responses and soleus H-reflexes were established. TMS (conditioning stimulus) and medial arch or posterior tibial nerve (test stimuli) stimulation were delivered at positive and negative conditioning-test (C-T) intervals. Negative C-T intervals denote that TMS was delivered after the test stimuli. TMS was delivered at 0.7 and 1.0 TA MEP resting threshold at positive C-T

intervals (0, 25, 50, 70, 90, and 110 ms) for the cutaneomuscular responses and C-T intervals ranging from -20 to 20 ms for the soleus H-reflex. For each control and conditioned reflex, 10 responses, each elicited every 10 s, were randomly evoked and recorded.

Data analysis

The control and conditioned reflexes were measured as the area under the full-wave rectified response. For each subject, the conditioned reflex recorded at each C-T interval was expressed as a percentage of the mean size of the control reflex. The mean amplitude of the conditioned reflex from each subject was grouped based on the C-T interval and TMS intensity, and a repeated measures ANOVA was conducted to establish statistically significant differences between the conditioned responses across different TMS intensities and C-T intervals. When a statistically significant difference was found, post hoc Bonferroni tests were applied. Results are presented as mean values along with the standard error of the mean (SEM).

RESULTS

TA MEP Input-Output Curve

In Figure 1, the overall amplitude of the TA MEPs recorded at different stimulation intensities from all subjects are indicated. The TA MEPs are shown as a percentage of the maximal MEP amplitude relative to the multiples of MEP threshold which is shown on the abscissa. The TA MEP input-output curve slope was well defined with a sigmoid function, which gave an $R^2 = 0.98$. Further, the grey bars indicate the level of TMS with respect to multiples of MEP threshold when the TMS was used as a conditioning stimulus. It is apparent that TMS was used when direct corticospinal motoneuronal connections were not activated (i.e., 0.7 × MEP

threshold) and when minimal activity of direct corticomotoneuronal cells were activated (i.e., 1.1 × MEP threshold). The mean latency of the TA MEP, measured with the CUSUM method, ranged from 27.05 to 27.97 ms (31.82 ± 2.89; mean ± SD), while the soleus MEP latency ranged from 27.97 to 39.93 ms (33.59 ± 3.65; mean ± SD). Further, the TA and soleus MEP had an average duration of 53.02 ± 20.44 and 66.9 ± 13.67 ms, respectively.

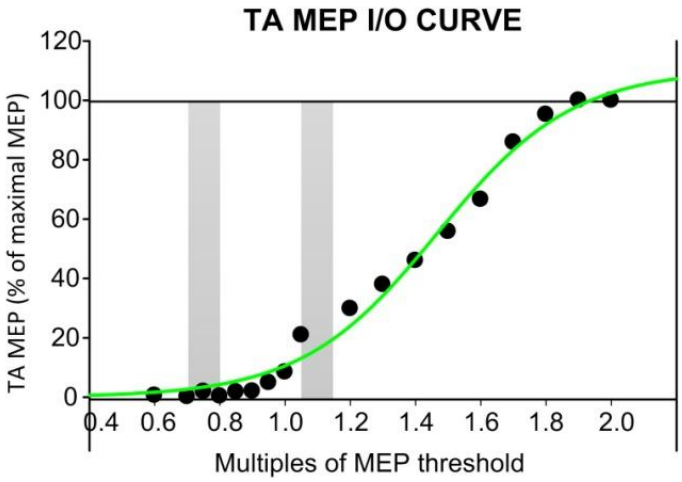

Fig. 1. TA MEP Input-Output Curve. TA MEP peak-to-peak amplitudes recorded from all subjects while seated are plotted against the stimulation intensities, which were normalized to the MEP resting threshold. The vertical grey columns identify the point with respect to the TA MEP input-output curve that TMS was used as a conditioning stimulus to the spinal reflexes.

Cortical Modulation of Cutaneomuscular Responses

Each subject's characteristics are indicated in Table 1. The latency of the TA cutaneomuscular responses, measured from the onset of the pulse train, following stimulation of the medial edge of the right foot from all subjects was 76.94 ± 7.35 ms (mean ± SD). The TA MEP threshold ranged from 42 to 63 % of the stimulator output (49.56 ± 6.65), while the TMS delivered above and/or below MEP threshold as percentage of the maximum stimulator output for each subject are also indicated. Subthreshold TMS was delivered at 0.72 ± 0.05 of the TA

MEP threshold, while suprathreshold TMS was delivered at 1.16 ± 0.09 of the TA MEP threshold.

Table 1. Subject characteristics participating in flexion reflex experiments.

	Gender	Age	MEPth	Above MEPth	Multiples MEPth	Below MEPth	Multiples MEPth	TA response (ms)	Leg	Arm
S1	M	25	47	47.0	1.00	32.00	0.68	84.57	R	R
S3	F	30	50	52.0	1.04	35.00	0.70	75.80	R	L
S4	F	23	44	53.0	1.20	30.00	0.68	80.38	R	R
S5	M	46	48	58.0	1.21	34.00	0.71	84.61	R	R
S6	M	28	57	68.0	1.19	40.00	0.70	84.64	R	R
S8	F	23	50	60.0	1.20	35.00	0.70	74.98	R	R
S9	M	32	63	68.0	1.08	44.00	0.70	72.22	R	R
S10	F	23	45	54.0	1.20	36.00	0.80	63.00	R	R
S13	F	23	42	54.0	1.29	32.00	0.80	72.22	R	R

MEP threshold (MEPth), above and below MEPth are given as a percentage of the maximum stimulator output, along with multiples of MEPth. Tibialis anterior (TA) response in ms is the latency of the TA responses. Leg, arm: indicates the dominant leg or arm respectively. R=right, L=Left. M=male, F=female.

In Figure 2A, full-wave rectified waveform averages of the TA responses recorded under control conditions and following TMS at 0.7 and 1.0 TA MEP resting threshold are indicated from a representative subject. In the waveform traces, the stimulus train to the medial arch of the foot as well as the TA MEP when TMS was delivered at 1.2 MEP resting threshold at the C-T intervals of 50 ms are easily recognized. In this subject, the conditioned TA responses at the C-T

interval of 50 ms when conditioned with subthreshold and suprathreshold TMS was 80.36 ± 31.96 % and 52.15 ± 11.67 % of control response values, respectively. The average amplitude of the conditioned TA responses from all subjects at 0.72 and 1.16 MEP resting threshold is shown in Figure 2B. The C-T interval is denoted on the abscissa while the conditioned responses are presented as a percentage of control response values regardless the C-T interval tested or TMS intensity strength ($P < 0.05$).

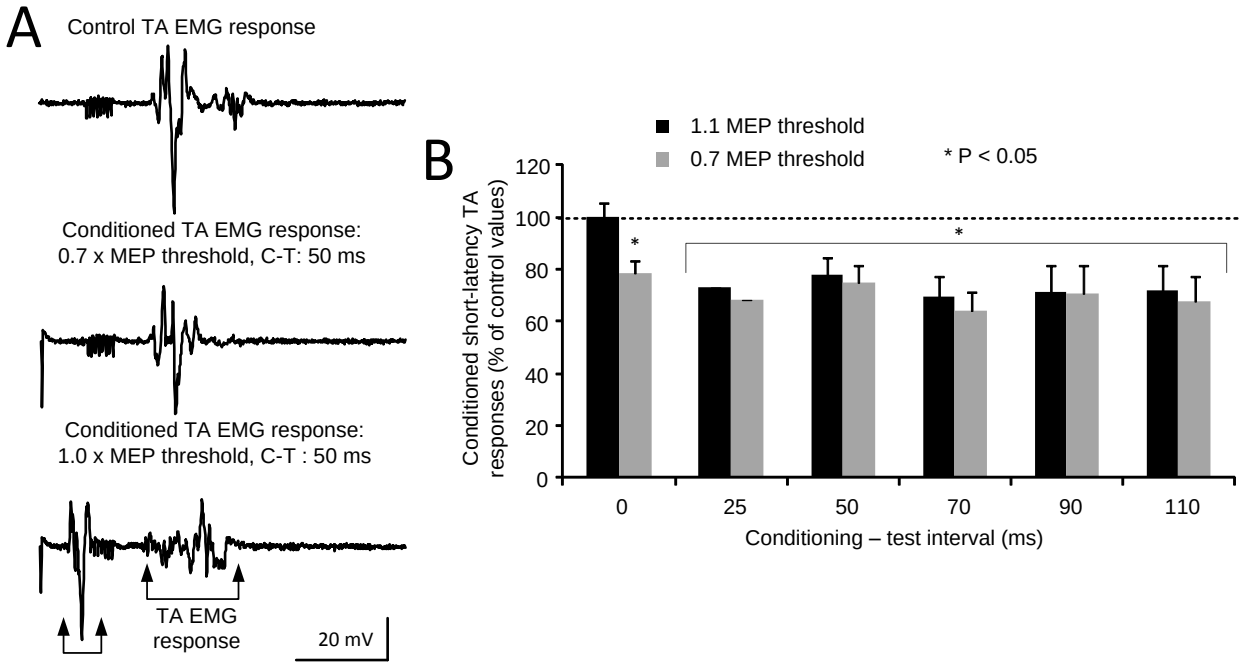

Fig. 2. Cortical modulation of polysynaptic TA responses. A. Non-rectified waveform averages of TA responses from one representative under control conditions and following TMS at subthreshold and suprathreshold intensities. **B**. Amplitude of TA responses from all subjects is indicated for each C-T interval tested. MEP=motor evoked potentials. TA=tibialis anterior.

Cortical modulation of the soleus H-reflex

In this set of experiments, 7 control subjects participated. Each subject's characteristics are indicated in Table 2. The TA MEP threshold ranged from 45 to 73 % of the stimulator output (52.43 ± 9.32), while the TMS delivered above and/or below MEP threshold as percentage of the maximum stimulator output for each subject are also indicated. Subthreshold TMS was delivered

at 0.81 ± 0.09 of the TA MEP threshold, while suprathreshold TMS was delivered at 1.16 ± 0.09 of the TA MEP threshold.

Table 2. Subjects' characteristics participating in H-reflex experiments.

	Gender	Age	MEPth	Above MEPth	Multiples MEPth	Below MEPth	Multiples MEPth	Leg	Arm
S7	M	22	72	72.0	1.00	50.00	0.69	R	R
S11	F	29	45	54.0	1.20	36.00	0.80	R	R
S12	F	36	52	65.0	1.25	52.00	1.00	R	R
S14	M	22	46	56.0	1.22	37.00	0.80	R	R
S15	F	22	46	55.0	1.20	36.00	0.78	R	R
S16	F	30	53	58.0	1.09	42.00	0.79	R	L
S17	M	26	53	60.0	1.13	42.00	0.79	R	R

MEP threshold (MEPth), above and below MEPth are given as a percentage of the maximum stimulator output, along with multiples of MEPth. Leg, arm: indicates the dominant leg or arm respectively. R=right, L=Left. M=male, F=female.

In Figure 3A, rectified waveform averages of soleus H-reflexes recorded under control conditions and following TMS at 0.8 MEP resting threshold and 1.2 MEP resting threshold are indicated from a representative subject. In the waveform traces the M-wave as well as the corresponding H-reflex when TMS was delivered at 0.8 and 1.2 MEP resting threshold at C-T intervals of -2 ms and 20 ms are recognized. In this representative subject, the conditioned soleus H-reflex at the C-T interval of -2 ms when conditioned at 0.8 and 1.2 MEP resting threshold was 54.54 ± 14.62 % and 52.81 ± 16.96 % of control values, respectively. The conditioned soleus H-

reflex at the C-T interval of 20 ms when conditioned at 0.8 and 1.2 MEP resting threshold was 91.17 % and 211.19 % of control reflex values, respectively.

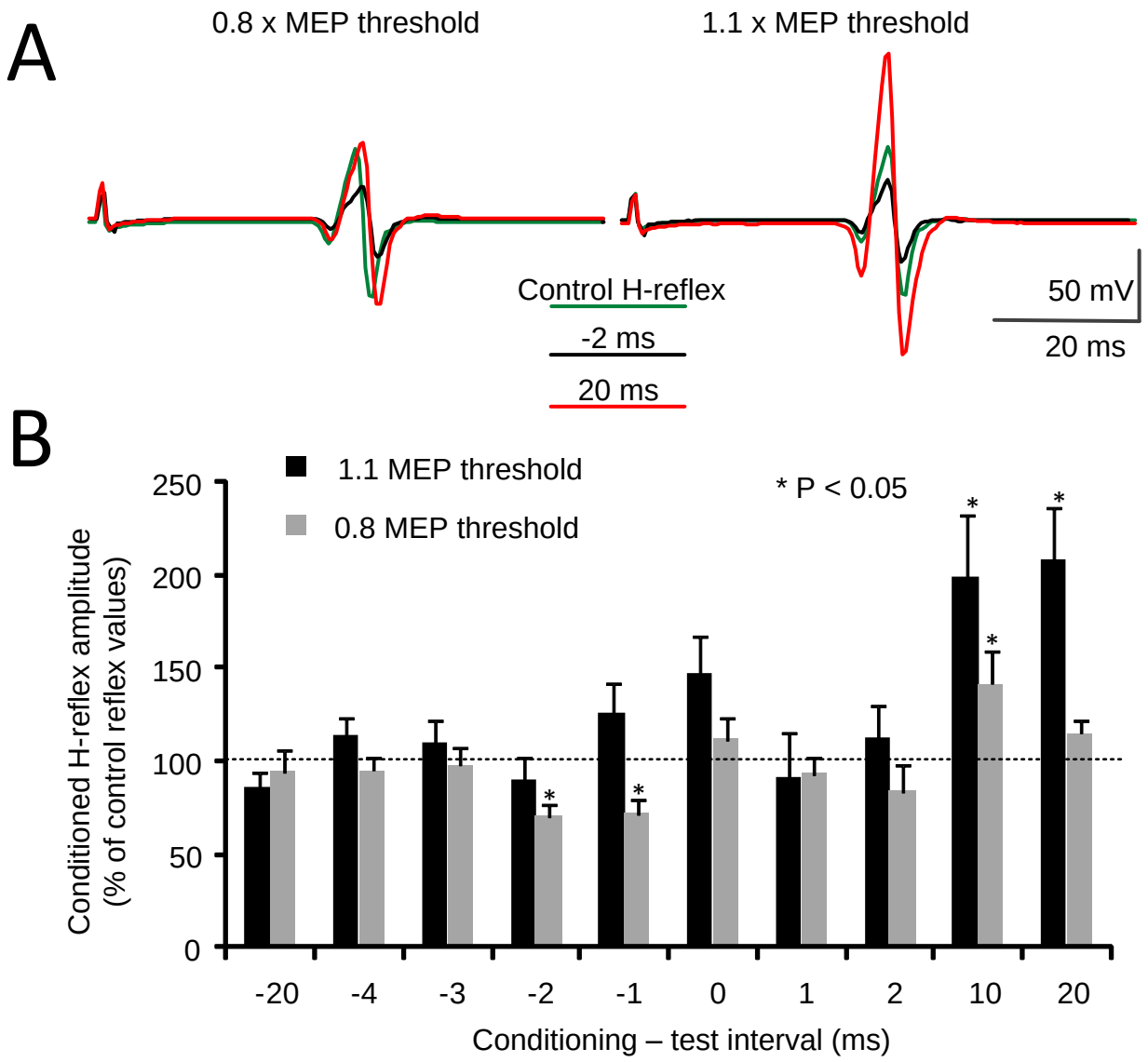

Fig. 3. Cortical modulation of the soleus H-reflex. A. Full waveform rectified averages of the control and conditioned H-reflex following stimulation at .8 MEP resting threshold TMS stimulus intensity and 1.2 MEP resting threshold TMS stimulus intensity of a representative subject **B**. Amplitude of Soleus H-reflex responses from all subjects (n= 7) is indicated for each C-T interval tested.

Figure 3B shows the average conditioned H-reflex amplitude from all subjects at TMS stimulus intensities 0.8 MEP resting threshold and 1.2 MEP resting threshold. The C-T interval

is denoted on the abscissa while the conditioned responses are presented as a percentage of control response values. A two-way ANOVA showed that the conditioned soleus H-reflexes varied significantly with respect to the C-T intervals tested and TMS intensity level ($F_{9,1} = 7.68$, $P < 0.001$). The soleus H-reflexes conditioned by TMS at 0.8 MEP resting threshold and C-T intervals of -2 ms, -1 ms, and 10 ms were 70.78 ± 16.70 %, 71.69 ± 22.21 %, and 141.86 ± 44.70 % of control soleus H-reflexes respectively. TMS stimulus intensity at 1.2 MEP resting threshold and C-T intervals of 10 ms and 20 ms produced a significant facilitation on the soleus H-reflex, which reached overall amplitude of 198.38 ± 88.36 % and 207.83 ± 73.48 % of control soleus H-reflexes, respectively.

DISCUSSION

This study demonstrated that subthreshold and suprathreshold TMS stimulation affected soleus H-reflex excitability in a biphasic pattern and depressed medium-latency TA cutaneomuscular responses in healthy subjects while seated. The same effects were observed regardless the TMS intensity. These findings support for cortical modulation of spinal neuronal circuits in humans.

The TMS-induced modulation of the soleus H-reflex seen in this study is consistent with other studies. It has been previously shown that low intensities of TMS elicit a short-latency inhibition of the soleus H-reflex followed by a long-latency facilitation (Nielsen and Petersen 1995; Cowan et al. 1986). Furthermore, subthreshold TMS stimulation induces a significant depression of soleus motoneuron activity at - 0.8 ms and -1.5 ms C-T intervals (Iles and Pisini 1992). In addition, significant soleus H-reflex facilitation was reported at the C-T intervals of +5 and +6 ms (Kudina et al. 1993). In this study, inhibition and facilitation of the soleus H-reflex

were apparent regardless the TMS intensity (i.e., subthreshold and suprathreshold) (Fig. 3B). This finding suggests that both cortico-cortical and corticospinal descending pathways can affect spinal reflex excitability in humans.

We had hypothesized in this study that cutaneomuscular responses will modulate in an opposite pattern to that observed for the soleus H-reflex. The TA cutaneomuscular responses were reduced following subthreshold and suprathreshold TMS (Fig. 2B). TMS and electrical stimulation of the superficial peroneal nerve depressed TA EMG activity in cats (Bretzner and Drew, 2005), while long-latency forearm reflexes evoked by radial superficial nerve stimulation are facilitated following TMS at C-T intervals that ranged from 40 to 50 ms (Deuschl et al. 1991). Further, TA MEPs were inhibited by tibial nerve stimulation at 35 ms C-T interval and facilitated by TMS at 45 and 60 ms C-T interval (Roy and Gorassini 2008). These findings along with our current findings strongly support for corticospinal control of spinal reflex circuits in humans.

Subthreshold TMS can suppress the MEP evoked by a subsequent suprathreshold TMS, the EMG responses produced by TMS, and the excitability of spinal motoneurons (Di Lazzaro et al. 1998; Davey et al. 1994; Ferbert et al. 1992; Kujirai et al. 1993). These effects were ascribed to changes of cortical excitability rather than to changes of spinal excitability, on the basis that upon paired TMS, epidural electrodes placed at high cervical levels did not record any descending activity (i.e., I-waves) and anodal electric stimulation failed to induce any suppression (Kujirai et al. 1993; Di Lazzaro et al. 1998). Therefore, the spinal reflex depression and or facilitation observed below MEP threshold could have been mediated by cortico-cortical neurons that decreased the corticospinal output of spinal cord circuitry.

In pyramidal cats and non-human primates, intracellular recordings demonstrate that a single-pulse stimulation of the M1 produces excitatory postsynaptic potentials and subsequent inhibitory postsynaptic potentials on spinal α-motoneurons (Preston and Whitlock 1960). Similar effects have been demonstrated in man, with the initial facilitation to be mediated likely by monosynaptic excitation of rapidly-conducting cortico-motoneuronal axons based on the short latency (Marsden et al. 1982). The subsequent inhibition is attributed to monosynaptic corticospinal projections to Ia inhibitory interneurons (Rothwell et al. 1984; Cowan et al. 1986).

CONCLUSION

We demonstrate in this study, for the first time, that spinal interneurons mediating cutaneous reflexes are prone to corticospinal modulation in healthy humans. Further, a bimodal modulation pattern of the soleus H-reflex was evident. These effects were present regardless the TMS intensity, suggesting that direct and indirect corticospinal volleys affect the spinal reflex circuitry in a similar manner. The relative cortical control of spinal reflexes during movement and functional motor tasks in humans warrants further investigation.

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