Facilitatory I Wave Interaction in Proximal Arm and Lower Limb Muscle Representations of the Human Motor Cortex

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Chen, Robert and Rami Garg. Facilitatory I wave interaction in proximal arm and lower limb muscle representations of the human motor cortex. J. Neurophysiol. 83: 1426–1434, 2000. Transcranial magnetic stimulation (TMS) of the human motor cortex elicits direct and indirect (I) waves in the corticospinal tract. Facilitatory I wave interaction has been demonstrated with a suprathreshold first stimulus (S1) followed by a subthreshold second stimulus (S2). Intracortical inhibition (ICI) and intracortical facilitation (ICF) can be studied by another paired TMS paradigm with a subthreshold conditioning stimulus (CS) followed by a suprathreshold test stimulus. Facilitatory I wave interaction in motor representations other than the hand area and its relationship to ICI and ICF has not been studied. We studied I wave interaction, ICI and ICF in an intrinsic hand muscle (abductor pollicis brevis, APB), in a proximal arm muscle (biceps brachii, BB) and in a lower limb muscle (tibialis anterior, TA) in 11 normal subjects. I wave facilitation was studied by paired TMS at 24 interstimulus intervals (ISIs) from 0.5 to 5.1 ms. For APB and TA, facilitation occurred in three distinct peaks at ISIs of 0.9–1.7, 2.5–3.5, and 4.1–5.1 ms. For BB, facilitation was significant for the first two peaks. The latencies of the peaks were similar among different muscles, but the magnitude of facilitation was much greater for APB and TA compared with BB. For all three muscles, changing the S2 to transcranial electrical stimulation (TES) resulted in much less facilitation of the first peak. For APB, there was significant I wave facilitation with S2 at 72% motor threshold (MT). The same stimulus used as the CS did not elicit ICF at ISI of 15 ms, suggesting that the threshold for eliciting I wave facilitation is lower than that for ICF. For BB and TA, there was no I wave facilitation with S2 at 90% of APB MT, and the same stimulus used as CS led to ICF. Thus in BB and TA the threshold for eliciting ICF is lower than that for I wave facilitation. We conclude that the circuits that mediate I wave interactions are present in the proximal arm and lower limb representations of the motor cortex. I wave facilitation occurs predominately in the cortex and may be primarily related to the monosynaptic corticomotorneuronal (CM) system. The reduced I wave facilitation for BB compared with APB and TA may be related to less extensive CM projection and involvement of other polysynaptic descending pathways. I wave facilitation, ICI, and ICF appears to be mediated by different neuronal circuits.

INTRODUCTION

Electrical stimulation of the exposed motor cortex in cats and monkeys lead to a series of descending volleys in the corticospinal tract, termed the direct (D) and indirect (I) waves (Patton and Amassian 1954). In humans, recordings from spinal epidural electrodes showed that transcranial magnetic stimulation (TMS) of the motor cortex also induced D and I waves (Burke et al. 1990; Di Lazzaro et al. 1998; Kaneko et al. 1996; Nakamura et al. 1997a). Facilitatory I wave interaction has been demonstrated noninvasively by paired-TMS, with a suprathreshold first stimulus (S1) followed by a subthreshold to threshold second stimulus (S2) (Tokimura et al. 1996; Ziemann et al. 1998a). Facilitation was observed at three distinct peaks at interstimulus intervals (ISIs) of 1.0–1.5 ms, 2.3–3.0 ms, and 4.1–5.1 ms. The first peak of facilitation likely occurs in the motor cortex and reflects interactions within the circuits involved in production of I waves in the corticospinal tract (Tokimura et al. 1996; Ziemann et al. 1998a). Previous studies of I wave facilitation concentrated on the hand area of the motor cortex; facilitatory I wave interaction in other motor representations has not been reported.

Another technique of paired TMS, with a subthreshold conditioning stimulus (CS) followed by a suprathreshold test stimulus (TS), can be used to study intracortical inhibition (ICI) and facilitation (ICF) (Kujirai et al. 1993). The test responses are inhibited at ISI of 1–4 ms and facilitated at longer ISIs of 8–15 ms. ICI and ICF appear to be mediated by different cortical circuits (Chen et al. 1998b; Ziemann et al. 1996b). Changes in ICI and ICF have been reported in several neurological disorders (Brown et al. 1996; Ridding et al. 1995a,b) and in long-term plasticity (Chen et al. 1998a). ICI and ICF have been demonstrated in the motor representation for proximal arm, trunk, and lower limb muscles (Abbruzzese et al. 1999; Chen et al. 1998a,b; Stokic et al. 1997), in addition to the hand representation. Despite wide differences in motor thresholds (MTs) for different muscles, the CS intensity required to elicit ICI and ICF appears unrelated to MT and the slope of the input-output (MEP recruitment) curve, suggesting that the intracortical mechanisms for inhibition and facilitation are not related to the strength of corticospinal projections (Chen et al. 1998b). It is not known whether the cortical circuits that mediate ICI and ICF are also involved in I wave facilitation.

In the present study, we compared I wave facilitation in a hand muscle (abductor pollicis brevis, APB) to a proximal arm muscle (biceps brachii, BB) and a lower limb muscle (tibialis anterior, TA). We also studied the relationship between ICI, ICF, and I wave facilitation. Our objectives are 1) to determine whether I wave facilitation can be demonstrated in motor representations other than the hand area, 2) to compare the magnitude and latency of I wave facilitation in different motor areas, and 3) to determine whether the thresholds for eliciting ICI, ICF, and I wave facilitation are different. If separate intracortical circuits mediate ICI, ICF, and I wave facilitation,
the stimulus intensities necessary to elicit these phenomena may differ.

METHODS

Subjects

We studied 11 normal volunteers (7 men and 4 women, mean age 40.4 yr, range 25–56 yr) in the main experiments involving I wave facilitation, ICI and ICF. Six subjects (4 men and 2 women, mean age 37.8 yr, range 25–46 yr) participated in studies involving transcranial electrical stimulation (TES). Five subjects participated in both sets of experiments. All subjects gave written informed consent, and the protocol was approved by the University Health Network Committee for Research on Human Subjects.

EMG recordings

The muscles studied were the right APB, BB, and TA. Each muscle was studied separately. Surface EMG was recorded with disposable adhesive disk electrodes placed in a tendon-belly arrangement. The signal was amplified (model 2024F, Intronix Technologies, Bolton, Ontario, Canada), filtered (band-pass 2 Hz to 5 kHz), digitized (Micro 1401, Cambridge Electronics Design, Cambridge, UK), and stored in a laboratory computer for off-line analysis.

Magnetic stimulation

TMS was performed with a 7-cm figure-of-eight coil and two Magstim 200 stimulators connected via a bistim module (The Magstim Company, Dyfed, UK). The coil was placed at the optimal position for eliciting motor-evoked potentials (MEPs) from the target muscle. The optimal position was marked on the scalp to ensure identical placement of the coil throughout the experiment. The handle of the coil pointed backward and was perpendicular to the presumed direction of the central sulcus, ~30° to the mid sagittal line. The direction of the induced current was from posterior to anterior and was optimal to activate the motor cortex transsynaptically (Kaneko et al. 1996; Nakamura et al. 1996; Werhahn et al. 1994). MT was determined at rest to the nearest 1% of the stimulator output and was the minimum intensity required to evoke MEPs of >50 μV in at least 5 of 10 trials.

TES

TES was performed using a Digitimer D180A high-voltage stimulator (Digitimer, Welwyn Garden City, UK) with the time constant set at 100 μs. For stimulation of the APB and BB representations, 1-cm gold-plated electrodes were placed at C3 as the cathode and at the optimal position for TMS of the target muscle (middle of the figure-of-eight coil, ~6–7 cm lateral and 1–2 cm anterior to Cz) as the anode. For stimulation of the TA representation, the cathode was placed 5 cm anterior to Cz, and the anode was placed 2 cm lateral to Cz [lateral anodal stimulation described by Nielsen et al. (1995)]. MT was determined at rest and was the minimum stimulus intensity required to evoke MEPs of >50 μV in more than two of four consecutive trials.

I wave facilitation

We used a paired-TMS paradigm similar to those previously described (Tokimura et al. 1996; Ziemann et al. 1998a). The ISIs ranged from 0.5 to 5.1 ms in steps of 0.2 ms (24 ISIs). Each study consisted of 8 trials for each ISI (192 trials), 16 trials of the S1 alone, and 8 trials of S2 alone delivered 6 s apart in random order controlled by a laboratory computer (Signal software, Cambridge Electronics Design, Cambridge, UK). The S1 was suprathreshold and adjusted to produce MEPs of 0.3–0.6 mV. The MEP amplitude used was lower than that in a previous study in hand muscle (Ziemann et al. 1998a) to obtain similar MEP amplitudes in BB and TA.

Three S2 intensities were tested in each muscle. For all three muscles, the first two S2 intensities were 100 and 90% of MT. For BB and TA, the third S2 intensity was 90% of APB MT (equivalent to 71.8 ± 6.7% of BB MT and 47.3 ± 7.6% of TA MT, mean ± SD). This was to allow comparison of I wave facilitation with S2 at the same absolute intensity of the stimulator output among the three muscles. For APB, the third S2 intensity was adjusted to allow comparison between APB and BB at the same percentage of MT for each muscle at a low S2 intensity. It was set at 71.8 ± 6.7% of APB MT, the same percentage of MT as the lowest S2 intensity tested (90% APB MT) for the BB muscle. This intensity will be termed 72% APB MT.

ICI and ICF

ICI and ICF were studied with the paired TMS paradigm described by Kujirai et al. (1993), with a subthreshold CS followed by a suprathreshold TS. ISIs of 2 ms (for ICI) and 15 ms (for ICF) were used. Each study consisted of 10 trials for each ISI, and the test stimuli alone were delivered 6 s apart in random order controlled by a laboratory computer (Signal software, Cambridge Electronics Design, Cambridge, UK). The CS was the same as the lowest intensity of S2 used in each muscle (71.8 ± 6.7% MT for APB, 90% of APB MT for BB and TA). TS was identical to the S1 in the I wave facilitation studies (to produce MEPs of 0.3–0.6 mV).

Comparison of TMS and TES as the S2

To further study the mechanisms of the first I wave facilitation in different muscle representations, we compared the effects of TMS and TES as the S2. Each muscle was studied separately. The S1 was TMS adjusted to evoke MEPs of 0.3–0.6 mV. Three different S2 conditions were tested: 1) TMS at 100% MT with ISI of 1.3 ms, 2) TES at 100% MT with ISI of 1.3 ms, and 3) TES at 100% MT with ISI adjusted for the difference in MEP latency (at ~0.1 mV amplitude) for TMS and TES in each subject. The ISI was calculated as (1.3 ms + MEP latency evoked by TMS − MEP latency evoked by TES). In this condition, the corticospinal waves evoked by TMS should arrive at the spinal cord 1.3 ms before those evoked by TES. Each study consisted of 10 trials of each of the 3 S2 conditions and 10 trials of S1 alone delivered 6 s apart in random order (40 trials).

Data analysis

The peak-to-peak MEP amplitude for each trial was analyzed off-line. The mean MEP amplitude for each ISI was expressed as a percentage of the mean amplitude of S1 given alone (for I wave facilitation) or the test stimulus given alone (for ICI and ICF).

Statistical analysis

The effects of muscle on motor thresholds, S1 intensity and MEP amplitude evoked by S1 alone were analyzed with ANOVA. If ANOVA showed a significant effect of muscle, differences between muscle were analyzed by Games-Howell post hoc test.

For I wave facilitation, the effects of muscle, S2 intensity, and ISI on MEP amplitudes were analyzed with repeated measures ANOVA. ISI was the repeated measure, and muscle and S2 intensity were the independent variables in the ANOVA model. If ANOVA showed a significant effect of ISI, the unpaired t-test was used to identify which ISI differed from control (S1 alone). Bonferroni correction was applied to account for multiple comparison, the uncorrected P value was considered significant if P < 0.002 (0.05/24).

For the experiments comparing TMS and TES as the S2, the effects...
of muscle and the different S2 conditions on MEP amplitude were analyzed by ANOVA. If ANOVA showed a significant effect of muscle or S2 condition, differences among the muscles or S2 conditions were analyzed by Games-Howell post hoc test.

ICI and ICF compared with the control (TS alone) were tested by the unpaired t-test. Unless otherwise stated, values are expressed as means ± SD. Significance level was set as P < 0.05. All statistical analyses were performed with Statview 5.01 software (SAS Institute, Cary, NC).

RESULTS

At maximum stimulator output, adequate MEPs for I wave studies could not be obtained from the BB muscle in one subject and from the TA muscle in two subjects. Therefore the I wave, ICI, and ICF studies were performed on 11 subjects for APB, 10 subjects for BB, and 9 subjects for TA.

MT, S1 intensity, and MEP evoked by S1 alone

The resting MTs were 48.2 ± 6.6% for APB, 60.5 ± 7.6% for BB, and 83.4 ± 11.6% for TA. ANOVA showed significant effect of muscle (P < 0.0001), and post hoc comparison showed significant difference among all three muscles. The S1 intensities used, expressed as a percentage of the resting MT, were 114.7 ± 9.3% for APB, 134.9 ± 11.2% for BB, and 108.4 ± 5.4% for TA. The effect of muscle on S1 intensity was significant (ANOVA, P < 0.001), and post hoc comparison showed that the S1 intensities used were significantly higher for BB than APB and TA, whereas APB and TA were not significantly different. The MEP amplitude evoked by S1 alone was 0.449 ± 0.22 mV for APB, 0.342 ± 0.127 mV for BB, and 0.53 ± 0.276 mV for TA. ANOVA showed that the effect of muscle was not significant.

I wave facilitation

I wave facilitation at different S2 intensities for APB, BB, and TA are shown in Figs. 1–3. Representative trials from one subject are shown in Fig. 4. For the APB muscle (Fig. 1), the effects of ISI (P < 0.0001) and S2 intensity (P = 0.0005) on the conditioned MEP amplitudes were significant. Post hoc comparison showed significant difference among all three S2 intensities used. The interaction between ISI and stimulus intensity was also significant (P < 0.0001), indicating that the effect of ISI was different at different stimulus intensities. ANOVA performed separately for each S2 intensity showed significant effect of ISI for all three S2 intensities tested (P < 0.0001). With S2 at 100% MT, Bonferroni corrected multiple t-tests showed three distinct periods of significant facilitation at ISIs of 0.9–1.7 ms (peak 1.5 ms), 2.5–3.1 ms (peak 2.9 ms), and 4.5–5.1 ms (peak 4.5 ms). With S2 at 90 and 70% of MT, the first period of facilitation (1.1–1.7 ms, peak 1.5 ms for 90% MT; 1.1–1.7 ms, peak 1.3 ms for 70% MT) was significant, but the second and third periods were not significant. Thus reduction of S2 from 100% of MT to 90 or 70% of MT led to a greater reduction of I wave facilitation for the second and third peak than the first peak (Fig. 1).

For the BB muscle (Fig. 2), the effect of ISI (P < 0.0001) was significant, but the effect of S2 intensity was not. When ANOVA was performed separately for each S2 intensity, the effect of ISI was significant for S2 at 100% MT (P = 0.0031) and 90% MT (P = 0.0125), but not for S2 at 90% APB MT. Bonferroni corrected multiple t-test showed that the first two periods of facilitation were significant with S2 at 100 and 90% MT (1.5, 2.5, and 2.7 ms for 100% MT, 1.3 and 2.7 ms for 90% MT; Fig. 2).

For the TA muscle (Fig. 3), the effects of both ISI (P < 0.001) and S2 intensity (P = 0.0001) were significant. Post hoc
testing showed significant difference among all three S2 intensities tested. The interaction of ISI and stimulus intensity was also significant ($P < 0.0001$). When ANOVA was performed separately for each S2 intensity, the effect of ISI was significant with S2 at 100% MT ($P < 0.0031$) and 90% MT ($P < 0.0125$), but not with S2 at 90% APB MT. With S2 at 100 and 90% MT, there were also three distinct periods of significant MEP facilitation. The first period was at 1.1–1.9 ms for 100% MT and 1.3–1.7 ms for 90% MT. The second period was at 2.9–3.5 ms (peak 2.9 ms) for 100% MT and 2.9 ms for 90% MT. The third period was at 4.1–5.1 ms (peak 4.7 ms) for 100% MT and 4.7–4.9 ms (peak 4.7 ms) for 90% MT. Reduction of S2 from 100% MT decreased all three periods of I wave facilitation (Fig. 3).

**FIG. 2.** I wave facilitation at different intensities of the 2nd stimulus for biceps brachii (BB) muscle. Averaged data from 10 subjects. Error bars represent standard error. Asterisks indicate significant difference from control values ($t$-tests with Bonferroni correction). The magnitude of I wave facilitation was considerably less than that for APB (Fig. 1).

**FIG. 3.** I wave facilitation at different intensities of the 2nd stimulus for tibialis anterior (TA) muscle. Averaged data from 9 subjects. Error bars represent standard error. Asterisks indicate significant difference from control values ($t$-tests with Bonferroni correction). The magnitude of I wave facilitation was similar to that for APB (Fig. 1) and considerably greater than that for BB (Fig. 2).
Comparison of I wave facilitation among different muscle representations

I wave facilitation among different muscle representations were examined in two ways. First, the S2 intensities were matched as a percentage of the rest MT for each muscle. Studies with S2 at 100 and 90% MT were analyzed, because these intensities were similar to control (S1 alone) values. ANOVA showed significant effects of muscle (P < 0.0001) and ISI (P < 0.0001). Post hoc comparison showed that the three muscles were significantly different from each other. The interaction of ISI and muscle was also significant (P < 0.0001). Figures 1–3 showed that I wave facilitation was much more prominent for APB and TA compared with BB. The first peak was similar for APB and TA, but the second and third peaks were more prominent for TA than APB.

The second way to examine the effect of muscles was to match the S2 as an absolute percentage of the stimulator output. S2 at 90% APB MT was tested in all three muscles (Fig. 1B, Fig. 2C, and Fig. 3C). ANOVA showed significant effects of muscle (P = 0.031), ISI (P < 0.001) and muscle × ISI interaction (P < 0.001). Post hoc comparison showed significant difference between APB and BB and between APB and TA, but not between BB and TA. Figures 1–3 showed that with S2 at 90% APB, I wave facilitation was only evident for APB but not for BB nor TA.

ICI and ICF

The results are shown in Fig. 5. For APB with CS at 70% MT, there was significant inhibition at ISI of 2 ms (P = 0.0001) and 15 ms (P = 0.0037), and no facilitation was observed. When the same CS was used as the S2 in I wave studies, there was significant facilitation at the first peak (Fig. 1C). For BB and TA with the CS at 90% APB MT, there was significant inhibition at ISI of 2 ms (P = 0.0007 for BB, P = 0.0054 for TA). ISI of 15 ms showed no significant inhibition nor facilitation. With the same CS used as the S2 in I wave studies, there was no I wave facilitation for BB and TA (Figs. 2C and 3C).

Comparison of TMS and TES as the S2

Because TMS is painful, some subjects did not have all three muscles studied. Data were available from five subjects for APB and BB, and from four subjects for TA. TES evoked MEPs of shorter latencies in all subjects. The differences in

FIG. 5. Intracortical inhibition (ICI) and facilitation (ICF). Paired transcortical magnetic stimulation (TMS) paradigm with conditioning stimulus (CS) followed by test stimulus (TS) was used. ISI of 2 ms was used for ICI and ISI of 15 ms was used for ICF. The CS was 71.8 ± 6.7% MT for APB and 90% APB MT for BB and TA. The TS was identical to that used in the I wave facilitation studies (to elicit MEPs of 0.3–0.6 mV). MEP amplitudes are expressed as percentages of that evoked by the test pulse alone. Asterisks represent significant difference (t-test) from control (test pulse alone). There was significant ICI in all 3 muscles, but no significant ICF.

FIG. 6. Comparison of TMS and transcranial electrical stimulation (TES) as the S2. The MEP amplitudes, expressed as percentages of the MEP amplitude evoked by the S1 alone, are plotted against the different S2 conditions for the 3 muscles studied. Error bars represent standard errors. The S1 was TMS adjusted to produce MEPs of 0.3–0.6 mV, and the S2 was TMS or TES at 100% rest MT. In the ISI adjusted condition, the ISI was adjusted for the differences in MEP latencies evoked by TMS and TES. The ISI was calculated as 1.3 ms + MEP latency evoked by TMS − MEP latency evoked by TES. There was much more facilitation with the S2 as TMS than with the S2 as TES.
latencies are 2.4 ± 0.7 ms for APB, 2.0 ± 1.0 ms for BB, and 2.2 ± 0.8 ms for TA. The results are shown in Fig. 6. With S2 as TMS at ISI of 1.3 ms, there was marked MEP facilitation in all subjects. With S2 as TES at ISI of 1.3 ms and at ISI adjusted for the difference in latency between TMS and TES, there was mild facilitation in some subjects and no facilitation in others. ANOVA showed a significant effect of S2 condition ($P = 0.0016$). Post hoc comparison showed significant differences in MEP amplitude between S1 alone and S2 as TMS at ISI of 1.3 ms and between S1 alone and S2 as TES at ISI of 1.3 ms. The difference between S1 alone and S2 as TES with ISI adjusted for differences in MEP latency was not significant.

**DISCUSSION**

This is the first demonstration that paired TMS, with a suprathreshold S1 followed by a subthreshold to threshold S2, resulted in I wave facilitation in motor representations other than in the hand area. We also directly compared I wave facilitation, ICI and ICF at the identical stimulus intensities.

**Nature of I wave facilitation**

Because the first peak of I wave facilitation is within the refractory period of corticospinal (Tokimura et al. 1996) and corticocortical fibers (Amassian et al. 1998), the facilitation by the S2 is related to excitation of neuronal elements not directly excited by S1. We used TMS and TES to examine whether the first peak of I wave facilitation occurs in the cortex or in subcortical structures and found much greater facilitation with TMS as the S2 compared with TES as the S2 for all three muscles studied (Fig. 6). This is similar to previous studies in hand muscles using TES as the S2 (Tokimura et al. 1996; Ziemann et al. 1998a). With the induced current flowing from posterior to anterior, TMS predominately elicits I waves in both the arm and the leg areas (Edgley et al. 1997; Houlden et al. 1999; Nakamura et al. 1997b). At active MT intensity, anodal TES predominately elicits D waves through direct activation of corticospinal fibers within the white matter and is therefore not sensitive to changes in cortical excitability (Amassian et al. 1990; Rothwell 1997). At higher intensities, TES may also recruit I waves (Di Lazzaro et al. 1998). Because we use TES at rest MT (higher intensity than active MT), the mild facilitation with TES as the S2 in some subjects is probably due to generation of I waves. The latency of anodal TES of the leg representation depends on the location of the electrodes (Nielsen et al. 1995). We confirmed the findings of Nielsen et al. (1995) that TES with anode 2–3 cm lateral to the vertex evoked MEPs with latencies ~2 ms earlier than MEPs evoked by TMS.

Our findings suggest that the first peak of I wave facilitation occurs predominately at the cortex not only for the hand representation, but also for the proximal arm and leg representations. However, we cannot rule out a small subcortical contribution. The nature of the second and third peaks of facilitation has not been studied in detail, but the similarity of the intervals with the periodicity of I waves also suggests that this later facilitation also occurs in the cortex. The neuronal circuits responsible for I wave facilitation are not known. One proposed mechanism is the arrival of multiple excitatory postsynaptic potentials (EPSPs) on the corticospinal neuron through a chain of cortical interneurons, with the initial segment of cortical interneurons as the site of excitation by the S2 (Amassian et al. 1998). An alternative mechanism is repetitive discharge of the corticospinal neuron due to sustained depolarization produced by the S1 (Ziemann et al. 1998a).

Previous studies used search coils to examine whether the amplitude of the second stimulus is influenced by the first stimulus (Tokimura et al. 1996; Ziemann et al. 1998a). At ISIs of 0.5–1.2 ms, the current induced by the second stimulus was slightly increased and started in the undershoot of the first pulse. However, with the coil in lateromedial direction, which activates corticospinal fibers directly (Kaneko et al. 1996; Werhahn et al. 1994), there was little or no facilitation at these ISIs (Tokimura et al. 1996; Ziemann et al. 1998a). Therefore the slightly higher amplitude of S2 at ISIs <1.2 ms probably does not contribute significantly to the facilitation observed. In any case, the peaks of I wave facilitation occur at ISIs >1.2 ms, when the amplitude of the second stimulus was unaffected by the first stimulus.

**Extent of I wave facilitation among different muscle representations**

With S2 set at the same percentage of rest MT (90–100%), the magnitude of I wave facilitation was much lower for BB compared with APB and TA (Figs. 1–3). In addition, with S2 set at the same percentage of stimulus output (at 90% APB MT), I wave facilitation was still more prominent for APB (Fig. 1B) than BB (Fig. 2C). Can variations in the S1 intensities used account for this difference? The S1 was adjusted to evoke similar sizes of unconditioned MEPs in the three muscles tested. Expressed as percentage of the rest MT, the S1 intensities were higher for BB than APB and TA. This implies that the input-output or recruitment curve (the rise in MEP amplitude with increasing stimulus intensities) is steeper for APB and TA than for BB, confirming the results of previous studies (Abbruzzese et al. 1999; Chen et al. 1998b). However, this difference in S1 intensity (expressed percentage of rest MT for the muscle being tested) cannot explain reduced MEP facilitation in BB, because higher S1 intensity in the same muscle leads to increased rather than decreased MEP facilitation (Ziemann et al. 1998a).

The extent of I wave facilitation appears to be better correlated with the slope of the input-output curve than with MT. The effects of I wave facilitation by paired TMS may be similar to using higher stimulus intensities for single pulse. Thus I wave facilitation may be less for BB than the APB and TA because the input-output curve is less steep for BB. The relatively flat input-output curve may also explain the absence of a significant effect of S2 intensity on I wave facilitation in BB over the range of stimulus intensities we tested. It has been suggested that MT is in part influenced by the excitability of a core region of neurons. Increasing the stimulus intensity not only increases the number of discharges from the core neurons, but also recruit neurons that are less excitable or those spatially further away from the center of activation by TMS (Hallett et al. 1999; Ridding and Rothwell 1997). Our finding is consistent with the suggestion that I waves are generated by chains of cortical interneurons at some distance away from the core region of neurons projecting into the corticospinal neuron (Amassian et al. 1987). Another possible explanation is that the...
difference in input-output curve may represent variations in the
strength of corticomotoneuronal (CM) projection. The higher
MT for TA than BB may be because the leg representation is
on the medial surface of the motor cortex, further away from
the stimulating coil than the proximal arm representation. This
may also explain the absence of I wave facilitation for TA at
the low S2 intensity of 90% APB MT (Fig. 3C), although ICI
can be elicited at the same intensity (Fig. 5). The intracortical
circuits for I wave facilitation in TA are likely further from the
coil than the circuits for APB and BB.

The magnitude of I wave facilitation between BB and APB
is likely related to the differences in the organization of the CM
system for proximal and distal arm muscles. In the monkey,
the maximal CM EPSP is considerably larger for motoneurons
innervating the hand muscles than those supplying proximal
arm muscles (Phillips and Porter 1964; Porter and Lemon
1993). Similarly, single-unit studies in humans showed that
TMS evoked short-latency EPSPs in motoneurons sup-
plying hand muscles than those innervating the BB muscle
(Palmer and Ashby 1992). These studies suggested that the
direct, monosynaptic CM projections are more prominent for
hand muscles than for the BB muscle. For lower limb repre-
sentations, single-motor-unit studies in humans showed that the
CM projection is more prominent for TA motoneurons than for
motoneurons innervating other more proximal or distal lower
limb muscles (Brouwer and Ashby 1992). The estimated
EPSPs elicited by TMS just below active threshold in TA
motoneurons were similar to that in motoneurons projecting to
intrinsic hand muscles (Brouwer and Ashby 1992; Palmer and
Ashby 1992). In contrast to the findings for the monosynaptic
EPSP, a phase of facilitation later than the monosynaptic
response was found to be more prominent for motoneurons
supplying proximal arm muscles than for hand muscles in the
monkey (Bernhardt and Bohm 1954) and in humans (Colebatch
et al. 1990; Palmer and Ashby 1992). The late facilitation may
be mediated by small diameter corticospinal fibers or by indi-
rect, polysynaptic routes. It has also been shown in the monkey
that slow pyramidal tract neurons are predominately related to
proximal muscle contraction (Matsunami and Hamada 1981).
It may be postulated that I wave facilitation as demonstrated by
paired TMS is primarily related to the monosynaptic CM
system. The reduced I wave facilitation for BB may be due to
desynchronization of I waves related to involvement of cortical
neurons and CM fibers of different sizes, or activation of other
polysynaptic descending pathways.

Timing of I wave facilitation among different muscle
representations

Despite wide differences in motor thresholds and the mag-
nitude of I wave facilitation, the timing of the peaks was
similar for the three muscles studied. This finding suggests that
the mechanisms responsible for timing of I wave generation are
similar among different representations of the motor cortex.
This is consistent with the observation that the interpeak la-
tencies of the I waves evoked from the leg area (Houlden et al.
1999) are similar to those evoked predominately from the hand
and arm areas (Di Lazzaro et al. 1998; Kaneko et al. 1996;

Comparison with previous studies of I wave facilitation

We found three distinct periods of facilitation in the APB
muscle, separated by troughs that the S2 has no significant
effect on MEP amplitude. The timing of the peaks and the
extent of facilitation were similar to two previous studies of
facilitatory I wave interaction in hand area of the human cortex
(Tokimura et al. 1996; Ziemann et al. 1998a). The magnitude
of the peaks increased with higher S2 intensities, similar to the
finding of Ziemann et al. (1998a). However, we observed that
decreasing S2 intensities from 100 to 90% rest MT or lower
abolished the second and third peak (Fig. 1), whereas Ziemann
et al. (1998a) found facilitation at all three peaks with S2 as
low as 90% of active MT. The likely explanation for the
different findings is that the MEP evoked by S1 alone is
smaller (0.45 mV) in our study than in the study of Ziemann
et al. (1998a) (~1 mV). With the induced current in the posterior-
anteor direction in both studies, the I1 wave is first recruited,
and the later I waves appear at higher stimulus intensities (Di
Lazzaro et al. 1998; Kaneko et al. 1996; Nakamura et al.
1997a). The relatively low S1 intensity in our study likely
activated the circuits for I1 more strongly than those for the
later I waves. Therefore facilitation for the first peak occurred
at lower S2 intensities than the later peaks.

Relationship between I wave facilitation, ICI, and ICF

We used low CS intensities to study ICI and ICF to deter-
mine the thresholds for I wave facilitation, ICI, and ICF. The
finding of significant ICI but no ICF in all three muscles
examined is consistent with previous studies that demonstrated
higher thresholds for ICF than ICI (Chen et al. 1998b; Ziemann
et al. 1996b). This supports the suggestion that ICI and ICF are
due to separate mechanisms (Ziemann et al. 1996b).

Several of our findings indicate that the neuronal circuits
mediating I wave facilitation are different from those for ICI
and ICF. First, the significant I wave facilitation with S2 at
72% of rest MT for APB (Fig. 1C) and absence of ICF with the
CS at the same intensity (Fig. 5) suggests that I wave facilita-
tion is different from ICF. Second, the significant ICI in both
BB and TA with CS at 90% APB MT (Fig. 4) and the absence
of I wave facilitation with S2 at the same intensity (Figs. 2C
and 3C) suggests that neuronal network mediating I wave
facilitation is also separate from that for ICI. Therefore ICI
appears to have the lowest threshold, followed by I wave
facilitation, and ICF seems to have the highest threshold. It
should be pointed out that I wave facilitation and ICI may be
testing different population of motoneurons. I wave facilita-
tion is due to activation of motoneurons in addition to those re-
cruited by the S1, whereas ICI is due to derecruitment of
motoneurons that would have been activated if the test stimulus
(ideal to the S1) was given alone. However, this difference
is unlikely to account for our findings. Previous studies showed
that ICI is stable over a large range of test stimulus intensities
(Ridding and Rothwell 1999; Ridding et al. 1995c) and I wave
facilitation increases with higher S1 intensities (Ziemann et al.
1998a). These results predict that the motoneurons recruited at
high TMS intensities have relatively lower threshold for I wave
facilitation than ICI, compared with motoneurons recruited at
low TMS intensities. This is opposite to our finding of lower
threshold for ICI than I wave facilitation.
Another observation is that the threshold for eliciting I wave facilitation appears to be lower for muscles with low MT, because strong I wave facilitation was evident for APB with S2 at 90% APB MT (Fig. 1B), but there was no significant I wave facilitation with the same S2 (as absolute percentage of stimulator output) for BB (Fig. 2C) and TA (Fig. 3C). Similarly, at the low S2 intensity of 72% MT for the muscle being studied, there was significant I wave facilitation for APB (Fig. 1C) but not for BB (Fig. 2C). This is different from the finding for ICI and ICF, because the thresholds (expressed as absolute percentage of stimulator output) for eliciting ICI and ICF in different muscle representations are not related to MTs (Chen et al. 1998b).

The hypothesis for different circuits mediating I wave facilitation, ICI, and ICF is also supported by the effects of drugs (Ziemann et al. 1996a, 1998b) on these phenomena. GABAergic neurons appear to be involved in all three systems, because drugs that enhance the effect of GABA (such as lorazepam and vigabatrin) increase ICI, and decrease ICF and I wave facilitation. However, other drugs (such as gabapentin) may change ICI and ICF but have no effect on I wave facilitation, indicating that some neurons are involved in ICI and ICF but not I wave facilitation.

In conclusion, we showed that I wave facilitation can be obtained from the proximal arm and leg representations of the human motor cortex. The timing of I wave facilitation is similar in different motor areas. However, the magnitude of facilitation varies considerably and may be related to the organization of the CM system. ICI, ICF, and I wave facilitation are likely mediated by different neuronal circuits.

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