Interhemispheric Inhibition in Distal and Proximal Arm Representations in the Primary Motor Cortex

Michelle L. Harris-Love, Monica A. Perez, Robert Chen, and Leonardo G. Cohen

1Human Cortical Physiology Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland; and 2Division of Neurology and Toronto Western Research Institute, University of Toronto, Toronto, Ontario, Canada

Submitted 18 December 2006; accepted in final form 5 January 2007

Harris-Love ML, Perez MA, Chen R, Cohen LG. Interhemispheric inhibition in distal and proximal arm representations in the primary motor cortex. J Neurophysiol 97: 2511–2515, 2007. First published January 10, 2007; doi:10.1152/jn.01331.2006. Interhemispheric inhibitory interactions (IHI) operate between homologous distal hand representations in primary motor cortex (M1). It is not known whether proximal arm representations exhibit comparable effects on their homologous counterparts. We studied IHI in different arm representations, targeting triceps brachii (TB, n = 13), first dorsal interosseous (FDI, n = 13), and biceps brachii (BB, n = 7) muscles in healthy volunteers. Transcranial magnetic stimulation test stimuli (TS) were delivered to M1 contralateral to the target muscle preceded 10 ms by a conditioning stimulus (CS) to the opposite M1 at 110–150% resting motor threshold (RMT). IHI was calculated as the ratio between motor-evoked potential (MEP) amplitudes in conditioned relative to unconditioned trials. Mean RMTs were 38.9, 46.9, and 46.0% of stimulator output in FDI, TB, and BB muscles, respectively. IHI was 0.45 ± 0.41 (FDI), 0.78 ± 0.38 (TB), and 0.52 ± 0.32 (BB, P < 0.01) when test MEP amplitudes were matched and 0.28 ± 0.17 (FDI) and 0.85 ± 0.31 (TB, P < 0.05) when TS intensities expressed as percentage RMT were matched. Significant IHI (P < 0.05) was identified with minimal CS intensities (expressed as percentage stimulator output) in the 30 s for FDI, 60 s for TB, and 40 s for BB. Additionally, a CS of roughly 120% RMT suppressed the test MEP but not a test H-reflex in BB, suggesting IHI observed in BB is likely mediated by a supraspinal mechanism. We conclude that IHI differs between different arm muscle representations, comparable between BB and FDI but lesser for TB. This finding suggests the amount of IHI between different arm representations does not strictly follow a proximal-to-distal gradient, but may be related to the role of each muscle in functional movement synergies.

INTRODUCTION

Interhemispheric inhibitory interactions (IHI), expected to contribute to skilled motor functions of the human hand (Duque et al. 2004; Gazzaniga 1964, 1969; Swinnen 2002), are disrupted after lesions in the CNS like stroke and multiple sclerosis (Murase et al. 2004; Schmierer et al. 2002). IHI, tested noninvasively using transcranial magnetic stimulation (TMS; Ferbert et al. 1992), links homologous distal hand representations of the primary motor cortex (M1; Di Lazzaro et al. 1999). The strength of this linkage between other homologous body part representations in humans has not been explored in detail. The existence of morphological and functional differences between proximal and distal arm muscle representations suggests that physiological interactions between these homologous regions may differ. For example, in nonhuman primates transcallosal projections linking proximal muscle representations are more prominent than those connecting distal muscle representations (Gould et al. 1986; Jenny 1979; Pandya et al. 1971; Roullet et al. 1994). One caveat to this finding is that, because of the mosaic-like organization of the arm representation in M1, areas with dense transcallosal projections can be found in both proximal and distal arm representations (Gould et al. 1986). Additionally, corticospinal projections to distal hand muscles are on one hand stronger and more numerous (Kuypers 1978; Palmer and Ashby 1992) and on the other hand more contralaterally distributed (Aglioti et al. 1993; Brinkman and Kuypers 1972; Muller et al. 1997) than those targeting proximal arm muscles, presumably facilitating performance of skilled fractionated finger movements.

These anatomical and physiological differences may support relatively different contributions to motor behavior. Tasks requiring skilled control of distal muscles tend to be more precise, less forceful, often unilateral, requiring more inhibition of mirror activity (Duque et al. 2004; Swinnen 2002). Writing and playing musical instruments are examples of this type of behavior. On the other hand, proximal muscles are often involved in less precise, more forceful, often bilateral symmetrical movements such as lifting, pushing, and carrying, in addition to playing a stabilizing role in performance of more phasic skilled distal hand movements. These differences raise the hypothesis that IHI between proximal and distal arm muscles may differ.

METHODS

Subjects

Seventeen right-handed healthy volunteers (ten female, seven male) with an average age of 28.7 ± 5.7 yr participated in the study. All subjects gave their informed consent to the experimental procedure, which was approved by the National Institute of Neurological Disorders and Stroke Institutional Review Board. The study was performed in accordance with the Declaration of Helsinki.

Electromyographic recordings

Subjects were seated in an armchair with their hands resting on a pillow and forearms pronated. Surface electrodes were positioned on the skin overlying the left and right first dorsal interosseous (FDI), triceps brachii (TB), and biceps brachii (BB) muscles in a bipolar montage (interelectrode distance, 2 cm). The amplified electromyo-
graphic (EMG) signals were filtered (band-pass, 20 Hz to 2 kHz), sampled at 5 kHz, and stored on a PC for off-line analysis (LabVIEW version 7.1, CED 1401+ with Signal software, Cambridge Electronic Devices, Cambridge, UK).

Transcranial magnetic stimulation (TMS)

TMS was delivered to the optimal scalp positions for activation of the FDI, BB, and TB muscles. Motor-evoked potentials (MEPs) were elicited by TMS stimuli delivered from a Magstim 200 stimulator (Magstim, Dyfed, UK) through two figure-of-eight coils (loop diameters 8 and 10 cm; type no. SP15560). Measures of cortical excitability included the resting motor threshold (RMT) defined as the lowest intensity of TMS output required to evoke MEPs of ≥50 μV in peak-to-peak amplitude in at least five of ten consecutive trials (Rossini et al. 1994) and IHI. IHI targeting the left (nondominant) arm was measured because inhibition is reported to be strongest from the dominant to the nondominant hemisphere (Leocani et al. 2000).

IHI

IHI was tested following a randomized conditioning-test design previously reported (Ferbert et al. 1992). A suprathreshold conditioning stimulus (CS) was given 10 ms before a test stimulus (TS) delivered to the contralateral side. The CS was always given to the left motor cortex and the TS to the right motor cortex. In 13 subjects, the coils were positioned at the optimal location for activating the left and right FDI and TB, respectively. The magnetic coil for the TS was positioned tangentially over the scalp with the handle pointing backward and perpendicular to the presumed direction of the central sulcus, about 45° relative to the midsagittal line (Werhahn et al. 1994). The CS coil was oriented at 90° relative to the midsagittal line (Sakai et al. 1997; Werhahn et al. 1994). The TS was adjusted to produce an MEP of about 0.3 mV peak to peak in each of the target muscles. The CS was set at 110, 120, 130, 140, and 150% RMT. Stimuli were delivered in five sets of 20 trials (10 conditioned and 10 unconditioned trials randomly intermixed) for each muscle. IHI targeting the left BB was tested in seven subjects in a separate session. In four subjects, IHI in each muscle was measured at five additional interstimulus intervals: 3, 5, 6, 8, and 40 ms, with the CS at 120% RMT and the TS adjusted in each muscle was measured at five additional interstimulus intervals: 3, 5, 6, 8, and 40 ms, with the CS at 120% RMT and the TS adjusted.

H-reflex

To investigate a possible spinal contribution to the effects of the paired-pulse IHI protocol in a proximal muscle we tested the effect of IHI in BB and TB muscles. Motor-evoked potentials (MEPs) were elicited by TMS stimuli delivered from a Magstim 200 stimulator (Magstim, Dyfed, UK) through two figure-of-eight coils (loop diameters 8 and 10 cm; type no. SP15560). Measures of cortical excitability included the resting motor threshold (RMT) defined as the lowest intensity of TMS output required to evoke MEPs of ≥50 μV in peak-to-peak amplitude in at least five of ten consecutive trials (Rossini et al. 1994) and IHI. IHI targeting the left (nondominant) arm was measured because inhibition is reported to be strongest from the dominant to the nondominant hemisphere (Leocani et al. 2000).

Data analysis

IHI (and inhibition of the H-reflex) was calculated as the ratio between the mean peak-to-peak MEP (or H-reflex) amplitude in conditioned versus unconditioned trials. In the initial analysis, Mauchly’s test of sphericity was followed by a repeated-measures ANOVA with factors Muscle and Conditioning Stimulus Intensity. Subsequent planned comparisons between muscles were made using Student’s paired t-test (α = 0.05). In a separate analysis similar to that used by Chen et al. (1998) to examine the absolute CS intensity required to elicit intracortical inhibition in different arm muscle groups, IHI targeting each muscle was grouped by CS intensity expressed as a percentage of maximum stimulator output in 10% increments. For each muscle that had at least three data points at a given CS intensity range, a single-factor t-test with the test value = 1 (i.e., no inhibition or facilitation) was used to determine whether significant inhibition had occurred (α = 0.05). Finally, a Student’s paired t-test was used to compare the effect of CS intensity of 120% RMT on the BB test MEP and BB test H-reflex. The mean and the SE were calculated for each condition.

RESULTS

The test of sphericity revealed that sphericity assumptions were not violated—therefore sphericity is assumed in subsequent reporting of P values. A repeated-measures ANOVA revealed a trend toward a main effect of muscle (F = 3.5, P = 0.08), a significant main effect of conditioning stimulus intensity (F = 4.8, P = 0.01), and a significant interaction between muscle group and conditioning stimulus intensity (F = 3.1, P = 0.01). The results of subsequent planned comparisons are as follows:

IHI in FDI and TB

RMTs were lower in FDI (38.9 ± 9.8%) than in TB (46.9 ± 10.1%; P < 0.01). On average, IHI was deeper in FDI (0.45 ± 0.41) than in TB (0.78 ± 0.38; P < 0.01) with matched-test MEP absolute amplitudes of about 0.3 mV (Fig. 1). In three subjects in whom TS intensities expressed as percentage of RMT for FDI and TB muscles were comparable (115 ± 19 and 124 ± 22% RMT, respectively), IHI was also deeper in the FDI (0.28 ± 0.17) than in TB (0.85 ± 0.31; P < 0.05) muscles.

IHI in BB and TB

In six of the seven subjects in whom BB IHI was tested, TB IHI was also tested. Despite the finding that RMTs were not different between the TB (44.8 ± 8.2%) and the BB (46.0 ± 9.3%; ns, n = 6), IHI was deeper in BB (0.52 ± 0.32) than in TB (0.80 ± 0.26; P < 0.05).

Threshold for IHI across muscle representations

When examining IHI in each muscle at conditioning stimulus intensities expressed as a percentage of RMT, we observed that IHI for FDI, TB, and BB could be elicited at CS intensities of ≥120% RMT (Fig. 2A); yet it remained apparent that the depth of IHI differed between the muscles (Fig. 1). This difference in IHI between muscles was also observed when the absolute CS intensity required to elicit significant IHI was examined (Fig. 2B). Clearly, IHI was elicited in different muscles at different CS intensities (expressed as percentage of maximum stimulator output; Fig. 2B). Specifically, minimum
CS intensities of 30–39 or 40–49% maximum stimulator output were required to elicit significant IHI in the FDI and BB, respectively, but minimum intensities of ≥60% were required to elicit significant IHI in TB. Because the lowest CS intensity used to test IHI was 110% RMT and the RMT for BB and TB tended to be >40%, there are no data to report for BB or TB at CS intensities of 30–39% of stimulator output (Fig. 2B).

Varying interstimulus intervals (ISIs)

For the BB and TB, the strongest IHI was observed at the 10-ms ISI (Fig. 3). Deep IHI was observed in the FDI at both the 8- and 10-ms ISIs.

Effect of CS on the test H-reflex and test MEP evoked in the ipsilateral BB

The size of the BB test MEP (11.1 ± 2.6% of M-max) and test H-reflex (13.8 ± 3.7% of M-max) were comparable (P = 0.3). The CS elicited clear and prominent IHI in the BB in all individual subjects in the absence of changes in H-reflexes. A paired t-test showed that the CS suppressed the test MEP amplitude (IHI = 0.47 ± 0.08) to a significantly larger extent than the test H-reflex (inhibition = 1.02 ± 0.03; P = 0.01; Fig. 4B).

DISCUSSION

The main finding of this study was that IHI between different arm muscle representations in the M1 differed. IHI was

FIG. 1. With matched test motor-evoked potential (MEP) amplitudes (left side of graph), deeper interhemispheric inhibition (IHI) was observed targeting the first dorsal interosseous (FDI) and biceps brachii (BB) than the triceps brachii (TB) muscle (right side of graph). This difference between muscles did not arise simply from differences in motor threshold because the FDI and BB had very different motor thresholds (see subplot), yet both showed significantly more IHI than the TB.

FIG. 2. IHI targeting FDI, TB, and BB muscles as a function of conditioning stimulus (CS) intensity expressed (A) as percentage resting motor threshold (% RMT) and (B) as percentage of stimulator output. A: significant inhibition for FDI, TB, and BB at CS intensities of ≥120% RMT, yet the depth of inhibition appears to be different between the muscles. B: significant inhibition in the FDI and BB at CS intensities of 30–39 and 40–49% of stimulator output, respectively, whereas no significant inhibition was observed in the TB until CS intensities reached ≥60%. *Significant difference from 1 (1 = no inhibition or facilitation).

FIG. 3. IHI targeting FDI, TB, and BB muscles measured at different interstimulus intervals (ISIs). Note that the strongest inhibition for both the TB and BB occurred at an ISI of 10 ms. *Significant difference from 1 (1 = no inhibition or facilitation).
Third, expression of CS intensity as a percentage of maximum was comparable, the same result was observed: more profound comparable RMTs, yet BB showed greater IHI (Fig. 1). Sec-

explained by differences in RMT. First, the BB and TB had than between TB representations. These results could not be more prominent between FDI and BB muscle representations because the strongest IHI in the TB, as well as BB, was because IHI was measured at a suboptimal ISI for the TB does not appear likely that these results were observed simply comparable CS intensities for the FDI and BB muscles despite substantial differences RMTs. Therefore these results could not be accounted for by differences in RMT across muscles. It also does not appear likely that these results were observed simply because IHI was measured at a suboptimal ISI for the TB because the strongest IHI in the TB, as well as BB, was observed at the 10-ms ISI (Fig. 3), the interval at which all of the between-muscle comparisons were made. Finally, our finding that a CS suppressed the size of the BB test MEP in the paired-pulse IHI protocol but not the BB test H-reflex (Fig. 4) suggests a predominantly supraspinal mechanism mediating IHI, consistent with previous reports in distal arm muscles (Ferbert et al. 1992; Gerloff et al. 1998).

Previous studies suggested that the strength of inhibition between homologous muscle representations may differ along a stereotyped proximal–distal gradient (Sohn et al. 2003). Our results suggest that such a difference can indeed be observed between proximal and distal representations when comparing certain muscle groups (e.g., FDI and TB) but not others (e.g., FDI and BB). For example, IHI between BB muscle representations was comparable to that between FDI, a distal hand muscle. Consistent with this finding, similar CS intensities induced significant IHI between distal FDI and proximal BB (Fig. 2B), but not between TB. Clearly TB representations appear to exhibit a different threshold for expressing IHI than the other two muscles. These results are consistent with those of Chen et al. (1998). These authors found that the absolute CS intensity required to induce intracortical inhibition was relatively similar among different proximal and distal arm muscles despite widely varying RMTs, concluding that the mechanisms governing intracortical inhibition are not related to RMT or to the strength of corticospinal projections. The present results suggest that a similar conclusion can be drawn for IHI.

Cortical inhibitory processes like IHI are thought to underlie the ability to produce skilled, finely controlled movements. If this is the case, one would expect that IHI is operationally important in performance of ecologically focal and skilled motor tasks. Recent work by Graziano et al. (2002, 2004) showed that intracortical stimulation of M1 in monkeys elicited a stereotyped flexion of the elbow accompanied by a grasping hand posture moving toward the opening mouth in a feeding gesture. Stimulation of a different M1 area resulted in eye closing with head turning away, raised arm, and elbow extended, in a massive muscle response mimicking a protective posture. The first type of movement (feeding) engaged unilateral biceps and distal hand muscles and had a very precise and repeatable final posture (Graziano et al. 2002, 2004), whereas the second (more protective) engaged less focal, massive, and perhaps more bilateral activity with active involvement of TB. It is possible that in our experimental design, greater IHI observed between BB and FDI representations could contribute to performance of more precise, skilled motor actions geared to inhibit mirroring, whereas the lesser IHI between TB representations could be ecologically meaningful to secure bilateral rapid, massive protective responses as required for defensive arm movements. More experiments are required to determine whether such differential organization of IHI across body part representations may represent one of the strategies by which human and nonhuman primates modulate aspects of motor control required for survival. Finally, with magnetic stimulation of M1, Palmer and Ashby (1992) showed an initial inhibitory response in contralateral triceps and deltoid motor units in contrast to the short-latency facilitation observed in contralateral BB and FDI motor units. These findings further suggest a possible difference in control of movement synergies involving the different muscle groups, with more direct inhibition to the triceps and deltoid from the contralateral motor cortex, whereas control of synergies involving BB and FDI may rely more on IHI.

Acknowledgments

We thank C. Nicholas for assistance with data collection.

Grants

This research was supported by a National Institute of Neurological Disorders and Stroke (NINDS) intramural postdoctoral fellowship to M. Harris-Love and the Intramural Research Program of the NINDS, National Institutes of Health.

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