Changes in Segmental and Motor Cortical Output With Contralateral Muscle Contractions and Altered Sensory Inputs in Humans

Tibor Hortobágyi, Janet L. Taylor, Nicolas T. Petersen, Gabrielle Russell, and Simon C. Gandevia

1East Carolina University, Biomechanics Laboratory, Greenville, North Carolina 27858; and 2Prince of Wales Medical Research Institute, Barker Street, Randwick NSW 2031, Australia

Submitted 4 November 2002; accepted in final form 27 May 2003

Hortobágyi, Tibor, Janet L. Taylor, Nicolas T. Petersen, Gabrielle Russell, and Simon C. Gandevia. Changes in segmental and motor cortical output with contralateral muscle contractions and altered sensory inputs in humans. J Neurophysiol 90: 2451–2459, 2003; 10.1152/jn.01001.2002. Motor or sensory activity in one arm can affect the other arm. We tested the hypothesis that a voluntary contraction can affect the motor pathway to the contralateral homologous muscle and investigated whether alterations in sensory input might mediate such effects. Responses to transcranial magnetic stimulation [motor-evoked potentials (MEPs)], stimulation of the descending tracts [cervicomedullary MEPs (CMEPs)], and peripheral nerve stimulation (H-reflex) were recorded from the relaxed right flexor carpi radialis (FCR), while the left arm underwent unilateral interventions (5 s duration) that included voluntary contraction, muscle contraction evoked through percutaneous stimulation, tendon vibration, and cutaneous and mixed nerve stimulation. During moderate to strong voluntary wrist flexion on the left, MEPs in the right FCR increased, CMEPs were unaffected, and the H-reflex was depressed. These results are consistent with an increase in excitability of the motor cortex, no effect on the motoneuron pool, and presynaptic inhibition of Ia afferents. In contrast, percutaneous muscle stimulation facilitated both MEPs and the H-reflex. However, muscle contraction produced by a combination of voluntary effort and electrical stimulation also reduced the contralateral H-reflex. After voluntary contractions, the H-reflex remained depressed for 35 s, but after stimulation-evoked contractions, it rapidly returned to baseline. Under both conditions, MEPs recovered rapidly. After voluntary contractions, CMEPs were also depressed for approximately 10 s despite their lack of change during contractions. Wrist tendon vibration (100 Hz) did not affect, and 20-Hz median nerve stimulation or forearm medial cutaneous nerve stimulation mildly facilitated, the H-reflex without affecting MEPs. Voluntary wrist extension, similarly to wrist flexion, increased MEPs and depressed H-reflexes. However, ankle dorsiflexion facilitated the H-reflex akin to the Jendrassik maneuver. These data suggest that a unilateral voluntary muscle contraction has contralateral effects at both cortical and segmental levels and that the segmental effects are not replicated by stimulated muscle contraction or by input from muscle spindles or non-nociceptive cutaneous afferents.

INTRODUCTION

Practice of a motor skill with muscles on one side of the body can improve performance of the skill with the corresponding muscles on the other side of the body (e.g., Schulze et al. 2002; Scripture et al. 1894; Stromberg 1988; Teixeira and Caminha 2003; Wissler and Richardson 1900). Improvements in strength can occur with training with high-force contralateral voluntary contractions or even with mental rehearsal of a contralateral task (e.g., Cannon and Cafarelli 1987; Hortobágyi et al. 1999; Tracy et al. 1999; Yue and Cole 1992). It is not clear what brings about these improvements, but changes in cortical areas associated with motor planning and motor command have been suggested. Voluntary muscle contraction can acutely change the contralateral motor pathway. During unilateral voluntary contractions, as well as activation in the hemisphere contralateral to the contraction, the ipsilateral sensory and motor cortical areas are activated (Cramer et al. 1999; Kristeva et al. 1991; Muellbacher et al. 2000; Stedman et al. 1998; Tinazzi and Zanette 1998). It is less clear whether changes also occur at the motoneuron level on the noncontracting side. In human subjects, H-reflexes and F-waves may increase or remain unchanged (Delwaide et al. 1988; Muellbacher et al. 2000; Stinear et al. 2003). Improvement in contralateral muscle strength can also occur when muscle contractions are evoked by electrical stimulation (e.g., Cabric and Appell 1987; Hortobágyi et al. 1999). Under these conditions,afferent input must drive the improvements in motor function. Again it is unclear which structures or mechanisms are altered. The afferent input associated with the stimulation could exert crossed effects at a cortical level or subcortically, at brain stem, propriospinal or segmental levels. Segmental effects exerted by afferents on the contralateral motoneuron pool have long been described (e.g., crossed-extensor reflex, Sherrington 1910), with later studies suggesting that the crossed effects from afferents are mediated in part by presynaptic and propriospinal paths (Arya et al. 1991; Baxendale and Rosenberg 1976, 1977; Harrison and Zytnicki 1984; Jankowska 1992, 2001; Jankowska and Odutola 1980; McCrea 1986, 2001). Activation of afferents has also been shown to alter function in the ipsilateral motor cortex (Chen et al. 1999; Manganotti et al. 1997).

The present study was designed to investigate what changes occur in the motor pathway during strong contralateral voluntary contractions and therefore might mediate improvements in performance. We sought evidence for changes at a segmental level as well as at the motor cortex and also examined whether such changes could be reproduced by electrically induced...
muscle contractions. We examined the effect of a voluntary contraction of the wrist flexor muscles on responses evoked in the resting contralateral muscle (flexor carpi radialis). Motor-evoked potentials (MEPs), which are influenced by both cortical and motoneuron excitability, were elicited through transcranial magnetic stimulation. Cervicomedullary MEPs (CMEPs), which largely depend on motoneuron excitability, were elicited through electrical stimulation between the mastoid processes. H-reflexes, which primarily test the connection of Ia afferents with the motoneurons, were also examined. In addition, we looked at whether voluntary contractions of other muscles (wrist extensors, ankle dorsiflexors) would also alter responses in the resting contralateral wrist flexor. Finally, to determine the crossed effects of afferent input, we tested MEPs and H-reflexes during contralateral percutaneous muscle stimulation, mixed peripheral nerve stimulation and cutaneous nerve stimulation, and during activation of muscle spindles by tendon vibration.

METHODS

Four studies were carried out to examine how contraction of muscles and/or stimulation of afferents in the left arm affected MEPs, H-reflexes and CMEPs recorded from the right arm (see Table 1). A total of 16 healthy volunteers (age, 20–47 yr, 5 females) participated. Six subjects participated in more than one study. Experiments were approved by the local human ethics committee and were conducted according to the Declaration of Helsinki. In a preliminary session, potential subjects were tested for the presence of an H-reflex in the flexor carpi radialis (FCR) when relaxed and were familiarized with the equipment and procedures.

Experimental setup

In each study, the subject sat comfortably at a table with the left arm and hand held, in a neutral position, in an isometric myograph that measured flexion and extension forces about the wrist (strain gauge linear to 350N, Xtran, Melbourne, Australia). Visual feedback of force was provided to the subject on an oscilloscope. The right arm rested on the table in a position that allowed the subject to relax most effectively. EMG activity was recorded from right the FCR with surface electrodes (Ag-AgCl discs, 10 mm diam) fixed over the muscle. The subject was earthed via a large flexible strap. EMG signals were amplified and filtered (1.6 Hz–1 kHz, Model 1902, Cambridge Electronic Design, Cambridge, UK).

Protocol

Each study consisted of a number of blocks of trials that all followed a similar pattern. Each block consisted of five trials that were performed in a continuous fashion. Each trial lasted for 1 min. During each trial, a “test” stimulus was delivered at regular intervals to evoke motor responses in the relaxed right FCR. In one 5-s period of the trial, an experimental intervention on the left side of the body was also carried out. The test stimuli and the 5-s left-sided intervention were timed so that one test stimulus was delivered in the middle of the intervention on each side. Other stimuli were delivered when the subject was completely at rest. Test stimuli included transcranial magnetic stimulation to evoke MEPs, median nerve stimulation to evoke H-reflexes, and stimulation of the corticospinal tract at the cervicomedullary level to evoke CMEPs. Interventions included voluntary contractions of different muscle groups on the left side of the body and afferent stimulation and stimulated muscle contractions in the left arm. In each block of trials, the effect of one intervention on one type of test response was examined. In each study, the order of presentation of the blocks of trials was varied between subjects.

The subject received standard instructions 10 s prior to each intervention. For example, in experiments that required voluntary contraction, the instructions were: “Get ready to contract on the left and completely relax the right side.” In addition, the subject was frequently reminded to relax other muscles. Auditory feedback of EMG activity from the FCR muscle on the right side also helped the subject to maintain relaxation in the right arm throughout each block of trials.

Test stimuli

In different experimental protocols, we recorded H-reflexes, CMEPs, or MEPs from the relaxed right FCR.

RIGHT MEDIAN NERVE STIMULATION FOR H-REFLEX. Single electrical stimuli were delivered with saline-soaked gauze-covered button electrodes, the cathode 5 cm proximal to the anode, in the cubital space (duration 1 ms, Digitimer DS7, Welwyn Garden City, Hertfordshire, UK) with the subject at rest. First, we determined the appropriate stimulating electrode location and identified the H-reflex in the FCR based on its latency and recruitment curve. Next, we increased stimulation intensity to produce a maximal compound action potential. The average amplitude of the maximal M-waves was 10.8 ± 3.9 (SD) mV. The average amplitude of the maximal H-reflex was 4.2 ± 2.4 mV. Finally, the stimulation intensity was set to produce an H-reflex that corresponded to approximately 50% of the maximal H-wave. During blocks of trials, H-reflexes were evoked at 5-s intervals.

TRANCRANIAL MAGNETIC STIMULATION OF THE MOTOR CORTEX. Excitatory responses (MEPs) were evoked by a figure of eight–shaped coil (diameter of each wing 90 mm) connected to a Magstim 200 magnetic stimulator (Magstim, Dyfed, UK). The intersection of the coil was placed tangentially to the scalp with the handle pointing backward and laterally at approximately 45° away from the midline. The optimal coil position to elicit maximal responses in the right FCR was marked on the scalp. Motor threshold was assessed with the subject relaxed, and in subsequent studies, the intensity was set at

### Table 1. Summary of the experimental protocols

<table>
<thead>
<tr>
<th>Left-Sided Intervention</th>
<th>Responses Tested in Right FCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1 (6 subjects)</td>
<td></td>
</tr>
<tr>
<td>75% MVC of L. wrist flexors</td>
<td>H-reflex MEP</td>
</tr>
<tr>
<td>75% MVC of L. ankle dorsiflexors</td>
<td>H-reflex MEP</td>
</tr>
<tr>
<td>75% MVC of L. wrist extensors</td>
<td>H-reflex MEP</td>
</tr>
<tr>
<td>Study 2 (6 subjects)</td>
<td></td>
</tr>
<tr>
<td>75% MVC of L. wrist flexors</td>
<td>H-reflex MEP</td>
</tr>
<tr>
<td>Tendon vibration of L. FCR</td>
<td>H-reflex MEP</td>
</tr>
<tr>
<td>Cutaneous stimulation of L. forearm</td>
<td>H-reflex MEP</td>
</tr>
<tr>
<td>Mixed nerve stimulation at L. wrist</td>
<td>H-reflex MEP</td>
</tr>
<tr>
<td>Study 3 (7 subjects)</td>
<td></td>
</tr>
<tr>
<td>50% MVC of L. wrist flexors</td>
<td>H-reflex MEP</td>
</tr>
<tr>
<td>75% MVC of L. wrist flexors</td>
<td>H-reflex MEP</td>
</tr>
<tr>
<td>Muscle stimulation of L. wrist flexors to produce force of 50% MVC</td>
<td>H-reflex MEP</td>
</tr>
<tr>
<td>Muscle stimulation + voluntary contraction of L. wrist flexors to produce force of 75% MVC</td>
<td>H-reflex MEP</td>
</tr>
<tr>
<td>Study 4 (4 subjects)</td>
<td></td>
</tr>
<tr>
<td>75% MVC of L. wrist flexors</td>
<td>CMEP</td>
</tr>
</tbody>
</table>

MEP, transcranial magnetic stimulation evoked motor potential; CMEP, cervicomedullary junction stimulation evoked motor potential; MVC, maximal voluntary isometric contraction; L, left, FCR, flexor carpi radialis muscle. In each experiment, the conditions were randomized. The order of H-reflex and MEP recordings under each condition was also systematically alternated between subjects.
150% of this value. During blocks of trials, MEPs were evoked at 5-s intervals.

CERVICOMEDULLARY STIMULATION. Single electrical stimuli were delivered via two 9-mm Ag-AgCl electrodes fixed over the left (cathode) and right (anode) mastoid processes and filled with conductive paste (100 μs duration, ~750 V; Digitimer D180) (Gandevia et al. 1999; Ugawa et al. 1991). This stimulation activates axons in the corticospinal tract (Petersen et al. 2002; Taylor et al. 2002) and so evokes muscle responses (CMEPs). The stimulation intensity ranged from 46 to 55% of stimulator output (51.0 ± 3.4%) and produced a mean compound potential in the right FCR of 22.3 ± 4.6% of the maximal M-wave. The maximal M-wave was elicited by supramaximal electrical stimulation over the brachial plexus. (Further details of these procedures are given in Gandevia et al. 1999). As cervicomедуllary stimulation causes some local discomfort, fewer CMEPs than other test responses were evoked during trials (see Study 4).

Study 1

Subjects (n = 6) completed six blocks of five trials. The effects on the MEP and the H-reflex of contraction of three different contralateral muscle groups (left wrist flexors, left wrist extensors, left ankle dorsiflexors) were examined. Each left-sided contraction was performed in two blocks of trials. In one, MEPs were evoked in the relaxed right FCR, and in the other, H-reflexes.

During blocks of wrist flexion trials, the subject produced voluntary isometric force with the left wrist flexors with visual feedback of force displayed on an oscilloscope. Based on several brief maximal voluntary isometric contractions (MVCs), a target corresponding to a 5-s 75% MVC was presented on the second channel of the oscilloscope. After a few practice trials, the subject had no difficulty in matching the voluntary force signal with the target. In other blocks of trials, voluntary contractions of 75% maximal force of the left wrist extensors were made in a similar way with the left arm in the same myograph as for wrist flexion. For blocks of ankle dorsiflexion trials, the left foot was fastened with a wide strap to a footrest with the ankle joint in neutral position. Surface EMG electrodes were placed over the tibialis anterior muscle. The EMG signal was rectified, integrated, and displayed on an oscilloscope in front of the subject. As for the wrist experiments, the subject followed a target that appeared on the second channel of the oscilloscope. Here, the target was scaled to 75% of the maximal EMG activity. A separate experiment in six subjects showed that the surface EMG activity of the tibialis anterior muscle and dorsiflexion force at 25, 50, 75, and 100% MVC are well correlated (r = 0.93, P < 0.0001). Throughout all blocks of trials, subjects maintained relaxation of the right wrist flexors.

Study 2

Subjects (n = 6) performed eight blocks of five trials. The effects of contralateral tendon vibration, cutaneous nerve stimulation, and mixed nerve stimulation were compared with the effects of a 75% MVC of the contralateral wrist flexors on the MEP and the H-reflex in the relaxed right FCR. Each 5-s left-sided intervention was used in two blocks of trials. In one, MEPs were tested, and in the other, H-reflexes.

The four interventions in this study are listed. 1) Subjects performed 5-s voluntary contractions of the left wrist flexors (75% MVC) as described in study 1. 2) The left FCR tendon was vibrated at 100 Hz using a commercially available vibrator (displacement approximately 1–2 mm). With the subject’s hand in the myograph, the cone-shaped end of the vibrator was positioned at a 90° angle on the FCR tendon and held for 5 s. 3) The left medial cutaneous nerve of the forearm was stimulated at 20 Hz for 5 s. With the subject’s left hand in the myograph, the stimulating electrode (5 × 15 mm) was placed over the medial aspect of the upper arm, 2–5 cm proximal to the myograph, the stimulating electrode (5 × 15 mm) was placed over the medial aspect of the upper arm. 2–5 cm proximal to the medial epicondyle of the elbow. Pulse duration was 1 ms, and stimulus intensity was adjusted to produce strong radiating paresthesia over the anterioomedial aspect of the forearm, including the area over FCR. 4) The left median nerve was stimulated at 20 Hz for 5 s via a pair of surface electrodes (Ag-AgCl, 10-mm diam) just proximal to the wrist. Pulse duration was 0.2 ms, and stimulus intensity was set to produce strong radiating paresthesia. This type of stimulation activates muscle, joint, and skin afferents.

Study 3

Subjects (n = 7) completed eight blocks of five trials. The effects of two strengths of contralateral voluntary wrist flexion on MEPs and H-reflexes in the relaxed right FCR were examined. These were compared with the effects of contralateral wrist flexion brought about by percutaneous muscle stimulation or by a combination of voluntary effort and muscle stimulation. The effect of each 5-s left-sided intervention on MEPs was tested in one block of trials and on H-reflexes in another block.

There were four interventions in this study. 1) Subjects performed 5-s voluntary contractions of the left wrist flexors to a target force of 75% MVC as in studies 1 and 2. 2) Subjects performed weaker 5-s voluntary wrist flexions to a target force of 50% MVC. 3) Percutaneous muscle stimulation was used to produce left wrist flexion with a force of 50% MVC. Two pairs of stimulating electrodes (3–5 cm long, 2–3 cm wide) were cut from flexible electrodes (3M product) and positioned 1 cm apart along the belly of the left FCR and flexor carpi ulnaris (FCU). The electrodes from each muscle were connected to a two-channel therapeutic muscle stimulator (Metron Multistim, MA-100, Metron Medical, Carrum Downs, Australia). FCR and FCU were simultaneously stimulated for 5 s with a 1-s on-ramp and 0 s off-ramp at 2 kHz modulated at 50 Hz up to maximal stimulator output of 80 mA. Such stimulation parameters can produce forces up to 100% MVC with relatively little discomfort in arm muscles (Horobagyi et al. 1992). Pilot experiments revealed that stimulation producing 50% maximal wrist flexion altered the H-reflex on the contralateral side and to minimize subject discomfort, this level of evoked force was used. 4) Percutaneous muscle stimulation of the left wrist flexors was used in combination with voluntary effort to give a summed force of 75% of maximal wrist flexion. In this condition, the muscle stimulator was set to produce force of about 30–40% MVC, and the subject voluntarily exerted additional force to reach the target set at 75% MVC.

Study 4

Subjects (n = 4) performed one block of trials in which the effect of a contralateral voluntary contraction on CMEPs recorded from the relaxed right FCR was examined. In each trial subjects performed a 5-s voluntary contraction of the left wrist flexors to a target force of 75% MVC as previously described. Cervicomедуllary stimulation was delivered in the middle of the contralateral contraction and at 5, 10, 20, 30, 40, and 50 s later to evoke responses in the right FCR.

Data recording and analysis

Force and EMG signals were collected at 5 kHz (CED 1401 interface, Cambridge Electronic Design) for off-line analysis using customized software. The area and peak-to-peak amplitude of each potential was measured automatically between cursors. Because the two measurements showed similar changes with the various experimental interventions, we report the data only as area. The cursor positions were the same for each type of response throughout each study. The latency of each response was determined by eye aided by a cursor. Relaxation in the right FCR was defined as the absence of EMG activity exceeding a background level of 20 μV.

J Neurophysiol • VOL 90 • OCTOBER 2003 • www.jn.org
**Statistical analysis**

Two main analyses were performed. One was a one-way ANOVA with repeated measures to compare the responses between conditions and relative to the normalization value of 1. A second analysis was a condition by time repeated measures ANOVA to determine if the recovery responses were different between the four conditions (BMDP 2V subroutine, BMDP PC-90, Los Angeles, CA). When the F value was significant, Tukey’s post hoc contrasts were used to determine the means that were significantly different at $P < 0.05$.

**RESULTS**

Unilateral voluntary wrist flexion produced different changes in the H-reflex, the responses to stimulation of the corticospinal tract (CMEP), and the responses to transcranial magnetic stimulation of the motor cortex measured in the FCR muscle on the contralateral (right) side. The H-reflex decreased and CMEPs were unchanged, while the MEPs increased. Wrist extension also increased the MEPs and decreased the H-reflex elicited on the contralateral side. However, contraction of the ankle dorsiflexors muscles significantly increased the H-reflex and slightly increased the MEPs.

Figure 1 shows examples of the effects of unilateral voluntary contractions of the left wrist flexors on the H-reflex, MEPs, and CMEPs recorded from the right FCR. Contraction of the left wrist flexors at 25% MVC slightly reduced the H-reflex. When the strength of the contraction on the left was increased to 50 and 75% MVC, the H-reflex on the right was further reduced (by 22 ± 18% and 50 ± 17% of control values, $F = 175.6, P = 0.0001$, Fig. 2). Contraction of the left wrist extensors also reduced the H-reflex by 33 ± 29%, but left ankle dorsiflexion increased it by 22 ± 52% (both $P < 0.05$).

In contrast to the effect on the H-reflex, voluntary contraction increased MEPs. Figure 2 shows that voluntary contraction of the left wrist flexors at 50 and 75% MVC increased MEPs to 176 ± 57% and 215 ± 85% of control values (see also Fig. 1B). MEPs also increased (201 ± 96% of control) with contraction of the left wrist extensors at 75% MVC and to a lesser extent (138 ± 25%) with contraction of the left ankle dorsi flexors.

**FIG. 1.** Effect of left voluntary wrist flexion on the H-reflex (A), motor-evoked potentials (MEPs) (B), and cervicomedullary junction stimulation-evoked potentials (CMEPs) (C) recorded in the relaxed right flexor carpi radialis muscle (FCR) of 1 subject. Each panel contains 5 superimposed potentials. Note in A that voluntary contraction at 25% MVC had little effect on the H-reflex evoked in the right FCR. Stronger contractions produced a progressive reduction in the H-reflex. In contrast, MEPs in the right FCR doubled in size (B). Voluntary contraction of the left ankle dorsiflexors muscles at 75% MVCs slightly increased both the H-reflex and MEP. The control responses were recorded at complete rest 2.5 s before the start of each voluntary contraction. C: CMEPs recorded in the right FCR were not affected during voluntary left wrist flexion at 75% MVC.
contraction of the left wrist fl contraction, CMEPs were reduced significantly at the control level (P < 0.05; Fig. 2; see also Fig. 1C).

Figure 3 compares the effects of contralateral afferent stimulation on the H-reflex and MEP with those of voluntary contraction. Whereas voluntary contraction of the left wrist flexors reliably reduced the H-reflex in the right FCR, tendon vibration at the left wrist had no effect, and innocuous stimulation of the median nerve at the left wrist or of the medial cutaneous nerve at the left elbow marginally increased the H-reflex (P = 0.060). The MEP, which was increased by voluntary contraction, was unaffected by the afferent stimulation.

In contrast to the weak effects from electrical stimulation of the median nerve and the medial cutaneous nerve, strong percutaneous muscle stimulation of the left wrist flexors, with its associated stimulation of the overlying skin, increased the

H-reflex and MEPs in the right FCR. However, when a voluntary contraction was added to this electrical stimulation, the facilitation of the H-reflex reverted to a depression. Figure 4 shows records of the H-reflex from one subject and the boxed portion of Fig. 5A shows the group data during these interventions. Percutaneous muscle stimulation that produced a force of 50% MVC from the left wrist flexors increased the size of the H-reflex by 30 ± 16% (P < 0.05), but voluntary contraction at the same absolute force reduced it by 22 ± 18%. When subjects produced wrist flexion of 75% MVC by combined voluntary effort and percutaneous muscle stimulation, H-reflex size was reduced by 37 ± 33%. Voluntary contraction at 75% MVC further reduced the H-reflex size by 51 ± 17%. MEPs increased significantly under all four conditions compared with control values (P < 0.05).

After contralateral voluntary contractions, the H-reflex recovered slowly with continued depression for more than 30 s.
Figure 5 displays the time course for the recovery of the H-reflexes and MEPs with stimulated (50% MVC), voluntary (50% and 75% MVC), and the combined voluntary plus stimulated (75% MVC) contractions. The MEP recovered quickly in all conditions, but for the H-reflex the condition-by-time repeated measures ANOVA revealed a significant interaction ($F = 3.34, P = 0.001$). The H-reflex recovered rapidly from facilitation to control level after percutaneous muscle stimulation, but the depression after a voluntary contraction of the left wrist flexors recovered more slowly, over 10–15 s after a 50% MVC and over 35 s after a 75% MVC. After the combined voluntary plus stimulated contraction, recovery of the H-reflex from depression took approximately 15 s.

Occasionally, the subjects were not able to fully relax the right FCR, and inadvertent background EMG activity occurred when an H-reflex, MEP, or CMEP was recorded. However, the data in Figs. 1–5 contain observations in which there was no more than 20 $\mu$V of background EMG. Indeed, the H-reflex depression associated with voluntary contractions on the contralateral side was so robust that the H-reflex recorded with background EMG (10% of the observations) was still significantly less than the control value ($72 \pm 12\%$ of control, $t = 2.9, P = 0.015$).

**Discussion**

We have shown that voluntary contraction of the left wrist flexors increased the size of responses to magnetic cortical stimulation (MEPs) in a wrist flexor of the other arm. This contraction did not affect responses to stimulation of the corticospinal tract (CMEPs) but reduced the size of H-reflexes in the resting arm. The depression of the H-reflex was long-lasting and persisted for more than 30 s after the end of the contraction. An additional novel finding was that, in contrast to voluntary contraction, strong stimulation of the muscle and overlying skin increased both MEPs and H-reflexes. Both returned quickly to control levels postcontraction. Vibration of the tendons of the left wrist flexors did not affect the H-reflex on the right, but focal cutaneous or mixed nerve stimulation mildly facilitated it without affecting the MEP. These data suggest that a unilateral voluntary muscle contraction has crossed effects at both cortical and segmental levels. Furthermore, the segmental effects associated with voluntary contractions are not replicated by stimulated muscle contraction or by input from muscle spindles or nonnociceptive cutaneous afferents.

As transcranial magnetic stimulation activates corticospinal neurons both directly and transsynaptically, the size of the MEP is influenced by the excitability of neurons in the motor cortex as well as by the excitability of the motoneuron pool (Rothwell et al. 1991). Here, we found that MEPs in the right FCR increased in size during left wrist flexion. However, CMEPs did not change in size. CMEPs were elicited through stimulation of the descending tracts at a subcortical level and activate many of the same axons as transcranial magnetic stimulation (Gandevia et al. 1999; Taylor et al. 2002; Ugawa et al. 1991). The lack of change of the CMEP suggests that the excitability of the motoneuron pool changed little with the contralateral contraction. Thus it is likely that the increase in size of the MEP came about through increased excitability in the motor cortex. These results are consistent with previous findings reported for hand muscles (Cramer et al. 1999; Kris- teva et al. 1991; Muellbacher et al. 2000; Stedman et al. 1998; Tinazzi and Zanette 1998). The increase in the size of the MEP in the right wrist flexors was graded with the strength of voluntary effort but was not specific for contraction of the homologous muscles on the left. It also occurred with contractions of the antagonists, and to a lesser degree, with contractions of the ankle dorsiflexors. Thus it may indicate a general increase in motor cortical excitability with strong voluntary contractions. A contribution of afferent input to this increase in cortical excitability cannot be ruled out. Although muscle spindle activation through tendon vibration and non-noxious stimulation of a cutaneous or a mixed nerve did not alter MEP size, the MEP was increased during the muscle contractions elicited by strong percutaneous electrical stimulation.

A surprising finding was that, although MEPs increased in size during the contralateral voluntary contraction, H-reflexes were depressed and remained depressed for many seconds after the contraction. This result contrasts with the well-known
facilitation of the H-reflex by the contraction of remote muscles in the Jendrassik maneuver (Delwaide et al. 1988). The depression was graded with the intensity of unilateral muscle contraction. It was minimal or absent at 25% MVC and large at 50% MVC, and at 75% MVC, it was so large that in some cases the reflex was abolished (Fig. 1). The observation that a weak voluntary contraction causes little depression is consistent with the lack of depression previously reported with passive and active wrist or finger movements (Delwaide et al. 1988). However, contralateral H-reflex depression may be limb- and task-specific as passive or active pedaling with one leg does depress the H-reflex in the other leg (Brooke et al. 1988). Therefore, contralateral H-reflex depression may be necessary for the depression to occur. The depression of the H-reflex showed more specificity than the increase in the MEP. Contraction of the dorsiflexors of the ankle did not depress the H-reflex in the other leg (Brooke et al. 1997; Collins et al. 1993). Such contralateral projections may form part of a central pattern generator that aids in coordination between legs (Arya et al. 1991; Harrison and Zytynicki 1984; Jankowska and Odutola 1980; McCrea 1986, 2001). In the arms, voluntary contraction at least moderate intensity is necessary for the depression to occur. The depression of the H-reflex showed more specificity than the increase in the MEP. If the H-reflex were not depressed despite some background EMG activity that would be expected to facilitate the reflex (Burke et al. 1989). These results suggest that the H-reflex depression associated with contralateral voluntary contraction occurs via a presynaptic mechanism. Furthermore, this mechanism only operates with voluntary efforts. Whereas voluntary contraction depressed the H-reflex on the contralateral side, muscle contractions evoked through percutaneous electrical stimulation facilitated it (Fig. 4). We suspect that the strong cutaneous afferent input associated with this stimulation may underlie the contralateral facilitatory effect on the H-reflex. The weak facilitation resulting from stimulation of the median nerve at the wrist, or of a purely cutaneous nerve in the forearm, at nonpainful levels is consistent with this proposal. Addition of a voluntary effort at the same time as the percutaneous muscle stimulation to generate a combined force of 75% MVC not only abolished the facilitation of the contralateral H-reflex but resulted in a depression approaching that in a voluntary 75% MVC without percutaneous stimulation. These results suggest that there is a strong presynaptic inhibition of Ia afferents brought about by descending activity associated with a contralateral voluntary contraction.

Presynaptic inhibition of Ia afferents is known to be modulated by corticospinal inputs. In humans, both facilitation and depression of the inhibition have been described with different tasks and in different motoneuron pools. In the wrist flexors, presynaptic inhibition is reduced by both voluntary flexion and extension of the ipsilateral wrist but can be facilitated by the corticospinal volley evoked by a transcranial magnetic stimulus (Aymard et al. 2001; Meunier and Pierrot-Deseilligny 1998). However, presynaptic inhibition lasts for hundreds of milliseconds, whereas the depression of the H-reflex described in the current study took more than 30 s to return to control levels after a 5-s contralateral contraction. Changes of such long duration have not previously been described. Postactivation depression is of longer duration than axo-axonal presynaptic inhibition but has still largely recovered in 10 s (Crone and Nielsen 1989; Hultborn et al. 1996). Furthermore, this type of presynaptic depression is homosynaptic. That is, the depression occurs at Ia terminals that have been active. In the current study, it is unlikely that activity in the contralateral arm could result in firing of muscle spindle afferents in a relaxed muscle. Wilson et al. (1999) reported that a strong contralateral hand-grip could evoke firing of muscle spindles in the wrist extensors but only when it also evoked muscle activity. In our study, the relaxed right FCR remained electrically completely silent in the trials we included in the analysis. Thus the long duration of the H-reflex depression is difficult to explain. One observation suggests that depression of the H-reflex after the voluntary contraction may involve an additional mechanism to that during the contralateral effort. While CMEPs were unchanged during the contraction, their size was reduced in the 10 s after the contraction. This reduction suggests that a decrease in the excitability of the motoneuron pool occurs following the contralateral contraction, and this may contribute to the continued depression of the H-reflex.

In contrast to the long-lasting depression of the H-reflex with the contralateral voluntary efforts, the facilitation of the H-reflex that occurred with the stimulated muscle contraction was observed only during the contraction. MEPs were facilitated at the same time. Our observations cannot identify more closely the site or sites of facilitation, which might be cortical or segmental. No afferent groups are known to have direct crossed effects on the contralateral motoneuron pool but act by modulating the excitability of interneurons (Arya et al. 1991; Harrison and Zytynicki 1984; Jankowska and Odutola 1980; McCrea 1986, 2001). Strong percutaneous muscle stimulation includes activation of both cutaneous and muscle afferents and subjects report discomfort from both the skin stimulation and the muscle contraction. Activation of more specific afferent classes showed less dramatic changes. Activation of muscle spindles through vibration of the tendons of the wrist flexors had no apparent effect at the cortical or segmental level, whereas non-noxious cutaneous stimulation or mixed nerve stimulation tended to facilitate the H-reflex weakly. This is consistent with facilitation of the soleus H-reflex reported after stimulation of the posterior tibial nerve in the other leg (Robinson et al. 1979).

In interpreting our findings, we have used comparison of MEPs, CMEPs, and H-reflexes to infer changes in the excitability of motor cortical neurons and of the motoneuron pool, but this relies on the different stimuli activating the same population of motor units. There is evidence that both transcranial magnetic stimulation and Ia afferent stimulation initially recruit small motor units, in the same order as voluntary activation (Awiszus and Feistner 1993; Gandevia and Rothwell 1987; Hugon 1973; Pierrot-Deseilligny and Mazelet 2000; Rothwell et al. 1991). In addition, stimulation of the corticospinal tract activates many of the same descending axons as
magnetic cortical stimulation so that it probably also recruits small motor units first (Taylor et al. 2002). Thus it is likely that the three stimuli recruit similar populations of motoneurons. A possible problem is that transcranial magnetic stimulation and stimulation of the corticospinal tract probably activate neighboring muscles as well as the targeted FCR, so that surface-recorded MEPs and CMEPs may have contributions from other flexors in the forearm. However, the similar shapes of the responses suggest similar sites of the contributing motor units and this similarity makes it probable that a significant component of the MEP and CMEP, as well as the H-reflex, emanates from FCR. Furthermore, as the conditioning voluntary contractions on the contralateral side involved all wrist flexors, there is no reason to expect different behavior from motor units in FCR compared with its neighboring muscles.

Unilateral voluntary muscle contractions in one arm produced complex changes in the motor pathway controlling the other arm. During the contraction, the excitability of the motoneuron pool appears unaffected while the motor cortex has increased excitability, and H-reflex changes suggest that there is a substantial decrease in muscle spindle input to the motoneurons. After the contraction, the H-reflex remains depressed, and motoneuron excitability is decreased. The balance of these changes may be task-specific. In a study examining bilateral interactions in the first dorsal interosseus, subjects were not instructed to relax the contralateral muscle during unilateral MVCs. They generated approximately 8% of maximal EMG activity in the “resting” muscle and this coactivity increased with fatigue (Zijdewind and Kernell 2001). We instructed subjects to concentrate on relaxing the muscles of the right arm despite the contralateral contraction, and subjects were largely successful at this task. Although there are no data to suggest that the H-reflex can be altered voluntarily, cortical output can influence presynaptic inhibition and primates, including humans, can modulate H-reflex size with operant conditioning (Wolpaw 1987).

The present results extend existing evidence that unilateral motor and sensory activity affect structures bilaterally to produce “crossed effects.” Comparison of the effects of stimulated muscle contractions and voluntary contractions on the MEP and H-reflex shows that both afferent activity and motor commands to contract on one side can alter the contralateral motor pathway.

We thank R. B. Gorman for assistance with data analysis and Drs. Leonardo Cohen, Paul DeVita, Mark Hallett, and Jean Lambert for comments on an earlier draft.

DISCLOSURES

This research was supported by the National Health and Medical Research Council (3206). It was also supported in part by a short-term travel fellowship (SF0052/2000-B-1) from the International Human Frontier Science Program, a Research and Creative Activity grant from the Division of Research and Graduate Studies, and a Faculty Travel Grant from the Thomas W. Rivers Endowment Fund, East Carolina University to T. Hortobágyi.

REFERENCES


