Cortical and Spinal Modulation of Antagonist Coactivation During a Submaximal Fatiguing Contraction in Humans

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Lévénez M, Garland SJ, Klass M, Duchateau J. Cortical and spinal modulation of antagonist coactivation during a submaximal fatiguing contraction in humans. J Neurophysiol 99: 554–563, 2008. First published November 28, 2007; doi:10.1152/jn.00963.2007. This study investigates the control mechanisms at the cortical and spinal levels of antagonist coactivation during a submaximal fatiguing contraction of the elbow flexors at 50% of maximal voluntary contraction (MVC). We recorded motor-evoked potentials in the biceps brachii and triceps brachii muscles in response to magnetic stimulation of the motor cortex (MEP) and corticospinal tract (cervicomedullary motor-evoked potentials—CMEPs), as well as the Hoffmann reflex (H-reflex) and maximal M-wave (Mmax) elicited by electrical stimulation of the brachial plexus, before, during, and after the fatigue task. The results showed that although the coactivation ratio did not change at task failure, the MVC torque produced by the elbow flexors declined by 48% (P < 0.01) with no change in MVC torque for the elbow extensors. While the MEP and CMEP areas (normalized to Mmax) of the biceps brachii increased (~50%) over the first 40% of the time to task failure and then plateaued, both responses in the triceps brachii increased (~150–180%) gradually throughout the fatigue task. In contrast to the monotonic increase in the MEP and CMEP of the antagonist muscles, the H-reflex of the triceps brachii exhibited a biphasic modulation, increasing during the first part of the contraction before declining subsequently to 65% of its initial value. Collectively, these results suggest that the level of coactivation during a fatiguing contraction is mediated by supraspinal rather than spinal mechanisms and involves differential control of agonist and antagonist muscles.

INTRODUCTION

During the voluntary contraction of a muscle group, antagonist muscles are usually active. This concurrent activation of agonist and antagonist muscles is referred to commonly as coactivation (De Luca and Mambrito 1987; Psek and Cafarelli 1993). During sustained submaximal isometric contractions, it has been shown that antagonist muscle activity increased in parallel with agonist activity (Ebenblücher et al. 1998; Hunter et al. 2003; Lévénez et al. 2005; Psek and Cafarelli 1993). Because of a slightly greater increase in electromyographic (EMG) activity of the antagonist than the agonist muscles, the coactivation ratio (agonist/antagonist) was found to decrease during fatiguing contractions sustained at a submaximal intensity (Ebenblücher et al. 1998; Psek and Cafarelli 1993). On the basis of this observation, it has been suggested that task failure could be due, in part, by the opposing action of the antagonist muscles. However, the interpretation of EMG activity, in absolute values, to infer change in voluntary drive may be misleading because of amplitude cancellation of the signal that may accompany fatigue (Keenan et al. 2005). In a recent study (Lévénez et al. 2005), in which the EMG activity of the agonist (tibialis anterior) and antagonist (soleus and lateral gastrocnemius) muscles were normalized to their respective postfatigue maximal voluntary contractions (MVCs), the coactivation ratio at the end of the fatiguing contraction was not significantly different from in the prefatigue conditions. Thus when a normalization procedure is used, antagonist coactivation does not appear to contribute to task failure.

The finding of a relatively constant coactivation ratio during a fatiguing contraction indicates that the level of antagonist coactivation is adjusted by the nervous system so that the performance of the agonist muscle is not impeded. De Luca and Mambrito (1987) suggested that coactivation is mediated by a descending “common drive” and that the CNS controls agonist and antagonist muscles as a single motor neuron pool. The alternative hypothesis is that separate central programs control the activation of agonist and antagonist muscles. Such a possibility exists because it has been shown that reciprocal inhibition during simultaneous activation of antagonistic ankle muscles (co-contraction) was less pronounced than in isolated plantarflexion. This observation was explained by an increase in the excitability of the motor neurons of the antagonist muscles resulting from inhibition of interneurons mediating reciprocal Ia inhibition (Nielsen and Kagamihara 1992; Nielsen et al. 1993). Our recent observation (Lévénez et al. 2005) that the amplitude of the H-reflex in the antagonist muscles did not follow the same time course or pattern as the amplitude of the antagonist EMG activation suggests that coactivation might be controlled by supraspinal mechanisms.

The purpose of this study was to investigate the supraspinal and spinal modulation of antagonist coactivation during a submaximal fatiguing contraction of the elbow flexors sustained to task failure. To differentiate cortical and spinal mechanisms in the control of coactivation, we recorded motor-evoked potentials in the biceps brachii and triceps brachii in response to magnetic stimulation of the motor cortex (MEPs) and corticospinal tract (cervicomedullary motor-evoked potentials—CMEPs), and the Hoffmann reflex (H-reflex) in the triceps brachii by electrical stimulation of the brachial plexus. Whereas variations in the size of the MEP reflect changes that can occur at both cortical and spinal levels (Rossini et al. 1994; Rothwell et al. 1991), the CMEP can be used, in awake human
As direct cortical projections to motor neurons appear to lack presynaptic inhibition (Jackson et al. 2006; Nielsen and Petersen 1994), modulation of CMEP responses likely reflects changes at the motor neuron (Martin et al. 2006). Furthermore, and as the H-reflex response is modulated by motor neuron excitability and Ia synaptic transmission, the comparison of its behavior with the CMEP was used to assess possible changes in peripheral input to the motor neuron pool. Because during submaximal sustained contractions, both peripheral mechanisms and suboptimal output from the cortex contribute to limiting the endurance time (Sogaard et al. 2006), we hypothesized that agonist and antagonist muscle activity levels are mediated by supraspinal mechanisms and differentially controlled to keep the coactivation ratio nearly constant.

METHODS
Two experiments were performed to assess responses elicited by stimulation of the motor cortex (MEP) and descending corticospinal pathways (CMEP) during a submaximal isometric fatiguing contraction of the elbow flexor muscles. A third experiment was conducted to analyze the contribution of spinal adjustments (H-reflex) on the activity of the antagonist muscles. A total of 13 subjects (7 men and 6 women), aged between 23 and 47 yr [30.8 ± 7.5 (SD) yr], volunteered to participate in this investigation. All subjects were well accustomed to electrical stimulation and transcranial and cervicomedullary magnetic stimulation. None of the subjects presented signs of neurological or orthopedic disorders. The Local Ethics Committee approved this study and the subjects gave their informed consent prior to participation in the investigation. All the experimental procedures were performed in accordance with the Declaration of Helsinki.

Experimental setup and mechanical recording
Subjects were seated in an adjustable chair with the right wrist positioned in a custom apparatus that was tightly secured to the force transducer. The right forearm was horizontal, and in neutral supination/pronation, with the upper arm vertical. Two straps were placed around the wrist to restrain and stabilize the forearm. The isometric torque exerted by the flexor muscles of the extensor muscles was recorded by a strain-gauge transducer (TC 2000-500, linear range: 0–2,200 N, sensitivity: 30 mV/N; Kulite, Basingstoke, UK). The signal was amplified (bandwidth: DC–300 Hz; AM 502, Tektronix, Beaverton, OR), displayed on an oscilloscope, and stored on a personal computer.

EMG recordings
Voluntary and electrically induced EMG activity in the biceps brachii and triceps brachii were obtained by means of bipolar surface electrodes (8-mm-diam silver disk electrodes). One electrode was positioned over the mid-belly of each muscle, and a second electrode was placed 3 cm (center to center) distal to the first one, with the ground electrode placed over a bony prominence on the right elbow. All EMG signals were amplified (1,000 ×), and filtered (10 Hz to 1 kHz) by a custom-made differential amplifier. The signals were acquired on a personal computer at a sampling rate of 2 kHz with a data-acquisition system and analyzed off-line by using the AcqKnowledge analysis software (Model MP 150, Biopac Systems, Santa Barbara, CA).

Stimulation
BRACHIAL PLEXUS STIMULATION. Stimuli (rectangular pulses, 0.2-ms duration) were delivered to the brachial plexus at Erb’s point to evoke the maximal M-wave (Mmax) with a stimulator (Grass S88K, Astra-Med) that was triggered by a digital timer (Master-8, AMPI, Jerusalem, Israel). The cathode (8-mm-diam silver disk electrode) was located in the supravacuicular fossa and the anode (8-mm-diam silver disk electrode) over the acromion. The electrical stimulus delivered by the stimulator was increased gradually until the M-wave of the biceps brachii and triceps brachii reached a plateau while the subject was at rest. The level of stimulation was then set >20% above this point to ensure a maximal activation of these muscles. The H-reflex was evoked in the triceps brachii by submaximal electrical stimulation with the same electrode positions as for the M-wave recording. Because the H-reflex was difficult to elicit in relaxed muscle at the relatively weak stimulus intensity required for it to be clearly distinguishable from the M-wave, it was therefore recorded during a steady isometric contraction of the biceps brachii at 20% MVC. Stimulus (rectangular pulses, 0.5-ms duration) intensity was set close to motor threshold and delivered at a constant rate of 3 Hz. Up to 30 responses were averaged to eliminate the background EMG activity and thereby to allow clear definition of the onset latency. In each subject, the H-reflex was identified by the criteria proposed by Miller et al. (1995): appearance at lower stimulus intensity and longer latency than the M-wave, disappearance of the putative reflex response on relaxation of the contracting muscle when stimulus intensity was sufficient to induce the reflex response but not the M-wave, and occlusion as stimulus intensity increased and the M-wave grew in amplitude.

TRANSCRANIAL MAGNETIC STIMULATION. A circular coil (130 mm OD) positioned over the cortex elicited MEPs recorded from biceps brachii and triceps brachii (Magstim 200 stimulator, Dyfed, UK). The direction of current flow in the coil preferentially activated the left motor cortex. The head of the subjects was secured in a custom-made headrest that ensured stable positioning of the coil during the experiment. Stimulus intensity was increased in 5% steps of maximum stimulator output while the subject maintained a ∼3-s contraction at 20% MVC of the elbow flexor muscles with the aid of visual feedback. Threshold was defined as the intensity at which three of four evoked responses were discerned above background EMG levels (Sacco et al. 1997). Stimulus intensity was standardized at 30% of stimulator output above threshold level (range for all subjects, 70–90% of maximal stimulator output) for all subsequent recordings and remained constant throughout the protocol.

CERVICOMEDULLARY MAGNETIC STIMULATION. A double-cone coil (110 mm OD) positioned over the back of the head elicited CMEPs recorded from the same muscles (Magstim 200 stimulator). The coil was maintained against the head of the subject by an experimenter during the whole experiment. The subject was wearing a bathing cap on which the position of the coil was marked precisely. The center portion of the coil was placed slightly laterally and caudally to the inion with the current going downwards, according to Taylor (2006). In that orientation, activation occurs at the cervicomedullary junction (Taylor and Gandevia 2004) and evokes short-latency responses in arm muscles. The stimulus intensity was increased while the subject maintained a contraction at 20% MVC of the elbow flexor muscles with the aid of visual feedback. For all subjects, stimulus intensities ranged between 85 and 95% of maximal stimulator output. The intensity of stimulation was set to evoke a CMEP response in the triceps brachii of comparable amplitude to the MEP obtained by TMS for the same subject.
Although less painful than electrical stimulation, several practical difficulties can be encountered with cervicomedullary magnetic stimulation. A major problem is that CMEP cannot be obtained in all subjects because of morphological factors. Indeed, even with the use of a double-cone coil, the distance from the inion to the spinal cord at the foramen magnum is at the limit of effective stimulation in some subjects (see Taylor and Gandevia 2004). Furthermore, as with
electrical stimulation, another difficulty is the possible stimulation of axons in the motor roots (Taylor 2006; Taylor and Gandevia 2004). With increased intensity of stimulation, activation of axons in the motor roots can be detected by an abrupt reduction in onset latency of ~2 ms (Taylor and Gandevia 2004). To detect this potential problem, we carefully monitored the latencies of the responses throughout the experiment to ensure that high stimulation intensities did not activate the motor axons at or near the ventral roots. We are confident that we were stimulating the descending tracts because the latency of the CMEP was consistently 2–3 ms shorter than the MEP latency, and 2–3 ms longer than the latency of the Mmax.

**Muscle fatigue and testing procedure**

**EXPERIMENT 1.** The first experiment investigated the effects of a submaximal fatiguing contraction on the size of the MEPs in agonist and antagonist muscles ($n = 13$). Each experimental session began with the subject performing at least two MVCs with the elbow flexor muscles and two MVCs with the elbow extensor muscles. Each MVC had a total duration of 4–5 s and there was 2- to 3-min rest between successive trials. Thereafter the intensity of the electrical and magnetic stimulation needed to evoke Mmax and MEP, respectively, was determined. This part of the experiment took 15–20 min. To avoid fatigue, a 20% MVC of the elbow flexor muscles was held while the MEP stimulus intensities were determined. Once a stable recording condition was reached (variation in amplitude of <5% during 3 successive responses), control responses for MEPs and Mmax (2–3 responses each) were then recorded during two brief submaximal contractions sustained at 50% MVC and averaged to obtain a mean value.

The fatigue task consisted of a sustained isometric contraction of the elbow flexor muscles at 50% MVC. A cortical stimulus (MEP), followed by brachial plexus stimulus (Mmax), were delivered every 15 s during the fatigue task. The fatigue task ended when the subject was unable to maintain the required force level (50% MVC) for a period of 5–10 s (task failure). At the end of the fatigue task and without any transition (relaxation), the subjects produced a 3–4 s MVC with the elbow flexor muscles followed immediately by a 3–4 s MVC with the elbow extensor muscles (Fig. 1A). To assess the recovery from fatigue, MEPs and Mmax were elicited during a 3-s contraction at 50% MVC every minute during the first 5 min and after 10 min. In a subset of experiments, subjects performed an MVC with the elbow flexor muscles and the elbow extensor muscles at 4, 5, and 10 min after the end of the fatigue task to investigate the recovery of the maximal torque and average EMG (aEMG) of the elbow flexor and extensor muscles ($n = 9$). During the brief MVCs, eight of the nine subjects received a single cortical stimulus (MEP) followed by a brachial plexus stimulus (Mmax), before and after the fatiguing contraction and during the recovery phase.

**EXPERIMENT 2.** In 6 of the 13 subjects, we were able to record a consistent CMEP response concurrently in the agonist and antagonist muscles. Subjects performed an identical protocol to experiment 1 except that stimulation was applied at the cervicomedullary junction to evoke short-latency responses (CMEPs) in the arm muscles. During these experiments, Mmax responses were also elicited by brachial plexus stimulation after each CMEP.

**EXPERIMENT 3.** The recording of a clear stable H-reflex in the triceps brachii during the contraction of the biceps brachii was possible in 6 of the 13 subjects. The fatiguing protocol was similar to experiment 1 except that a train of stimuli (3 Hz), followed by a maximal brachial plexus stimulation (Mmax) were delivered every 20 s during the fatigue task.

**Measurements**

For both the elbow flexor and extensor muscles, the MVC torque and associated aEMG activity, recorded before and after the fatigue task, were determined for a 2-s period during the torque plateau. Before the fatigue task, the trial that yielded the largest MVC torque was taken as the control value. To exclude fatigue-related changes in the propagation properties of the muscle fiber membrane, each aEMG was normalized to the average amplitude (area divided by time) of the rectified Mmax response recorded during the same MVC. The aEMG amplitude of the agonist and antagonist muscles during the fatiguing contraction was measured for a 2-s duration, every 15 s before the stimuli were delivered. These values, as well as postfatigue values, were normalized to the aEMG recorded during maximal elbow flexor contraction and during the recovery phase.

**FIG. 1.** Torque and electromyography (EMG) during a sustained elbow flexor contraction at 50% of maximal voluntary contraction (MVC). A: recordings from 1 subject of torque (a), biceps brachii EMG (b), and triceps brachii EMG (c). For clarity, the artifacts and the responses related to the maximal stimulation have been truncated. The overshoot and undershoot of the torque signal (a) at the end of the fatigue task are due to the MVCs of the flexor and extensor muscles, respectively. B: means ± SE average EMG (aEMG), expressed as percentage of prefatigue values, for the biceps brachii (○) and triceps brachii (●) during the fatiguing task and recovery for all 13 subjects. Significant differences from initial value: *, $P < 0.05$; **, $P < 0.01$. 

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muscle (agonist) or elbow extensor muscle (antagonist) contraction that were performed prior to the fatigue task to follow the time course of change in aEMG relative to its maximum. The aEMG recorded at the end of the fatigue task was also normalized to the aEMG of the postfatigue MVC. This procedure was used to control for whether the decrease in aEMG with fatigue was due to amplitude cancellation that occurs when overlapping positive and negative phases of muscle action potentials are summed (Keenan et al. 2005). With such normalization, modulations in aEMG can be used with confidence to infer change in voluntary drive than with prefatigue normalization alone (Lévénez et al. 2005). The level of coactivation was quantified by computing the ratio between the normalized agonist and antagonist aEMG activity (Lévénez et al. 2005). For each muscle, the peak-to-peak amplitude and the area of MEPs, CMEPs, H-reflex, and Mmax were measured before, during, and after the fatigue task. To measure the area, the signal was first rectified and measured between cursors that encompassed the evoked potentials. Because peak-to-peak amplitude and area showed similar change for these parameters, only areas are reported for MEP and CMEP. In contrast, we measured (see Fig. 5) the changes in peak-to-peak amplitude for the H-reflex to compare the current data with those of our previous study (Lévénez et al. 2005). The amplitude of the increment in force evoked by each single motor cortical stimulus during the brief isometric MVCs (suprathreshold twitch) was measured and used as an index of the output from the motor cortex (Gandevia et al. 1996; Todd et al. 2003; Taylor 2006). The latency of MEP, CMEP, and H-reflex responses, defined as the time between the stimulus artifact and the onset of the evoked potential, was also determined. To exclude fatigue-related changes of the muscle fiber membrane and to assess the supraspinal, motor neuronal, and spinal adjustments during the task, the MEP, CMEP, and H-reflex areas were normalized, at each time point, to their corresponding Mmax areas. The duration of the silent periods following transcranial and cervicomедullary magnetic stimulation were measured in the contracting muscles and were taken as the intervals from the stimulus to the return of continuous EMG. Because the time to failure differed from subject to subject, all data were normalized as percentage of the time to task failure (endurance time). Every 20% of endurance time is presented in Figs. 1–3, 5; we selected the closest response to each percent endurance time. When two responses were spaced similarly around the percent endurance time, the two values were averaged.

Statistical analysis
The MVC torque of the elbow flexor and extensor muscles, the superimposed twitch, and the EMG parameters (aEMG amplitude; H-reflex, Mmax, MEP, and CMEP areas and amplitudes; silent period duration) from the biceps brachii and triceps brachii that were observed before, during, and after the fatigue task were analyzed by a one-way ANOVA with repeated measures (% endurance time). To compare the behavior of the aEMG, MEP, and CMEP over time between the biceps brachii and triceps brachii or the time course of change of the MEP and CMEP, data were analyzed by a two-way ANOVA with repeated measures on two factors (muscle or stimulation condition × time). When significant main effects were observed, Dunnett’s test was used for post hoc analysis. A probability of $P < 0.05$ was chosen as significant for all analyses. Data are reported as means ± SD within the text and means ± SE in the figures.

RESULTS
Time to task failure, MVC torque, and corresponding aEMG after fatigue
The average time to task failure for all subjects was $122.4 ± 41.2$ s (range: $90–211$ s). Immediately after the fatigue task, the MVC torque produced by the elbow flexor muscles decreased by $48.0\%$ (55.7 ± 22.3 to 28.7 ± 10.8 Nm; $P < 0.01$) of the prefatigue values, whereas the elbow extensor MVC torque did not change significantly (26.1 ± 10.6 vs. 25.7 ± 9.6 Nm, before and after fatigue, respectively). The time course of recovery for the elbow flexor muscles was quite rapid. The MVC torque of the elbow flexors returned to its prefatigue value within 10 min.

At task failure, the peak-to-peak amplitude of the Mmax for the biceps brachii recorded during the MVC did not change significantly compared with prefatigue value (101.1 ± 25.3%; $P > 0.05$), but because of the slowing of the conduction velocity, its area displayed a significant increase of $34.7 ± 37.2\%$ (from 55.5 ± 1.5 to 73.8 ± 39.6 $\mu$V.s before and after fatigue, respectively; $P < 0.01$). In contrast, the Mmax area for the antagonist muscle (triceps brachii) did not change $(72.3 ± 41.8$ vs. $67.4 ± 42.5 \mu$V.s; $P > 0.05$). The Mmax of the biceps brachii returned to its control value within 1 min after the end of the fatigue task. The aEMG for the biceps brachii during the brief MVCs of the elbow flexor muscles recorded immediately after the fatigue task decreased by $29.8 ± 26.5\%$ ($P < 0.01$) from the prefatigue values. In contrast, the aEMG for the triceps brachii recorded during the brief MVCs of the elbow extensor muscles did not change significantly from its prefatigue values ($–6.3 ± 20\%$; $P > 0.05$).

Voluntary EMG activity during the fatiguing task
As illustrated for one subject in Fig. 1A, the aEMG activity for the biceps brachii increased progressively throughout the fatiguing contraction. Relative to the prefatigue value, the aEMG of the biceps brachii increased by $165.6\%$ ($P < 0.01$) at the end of the fatigue task (Fig. 1B). Similar to the agonist muscles, the aEMG of the antagonist muscle increased throughout the fatiguing contraction leading to an increase of $123.7\%$ ($P < 0.01$) at task failure (Fig. 1B). Expressed as percentage of its maximum value during an MVC, it increased from $5.6 ± 2.9\%$ at the beginning of the contraction to $11.5 ± 5.5\%$ ($P < 0.01$) at task failure. At this stage, the aEMG of the biceps brachii and triceps brachii reached $80.9 ± 27.7$ and $86.8 ± 20.7\%$ of their respective aEMG recorded during the postfatigue MVCs of the elbow flexors. This similar increase in EMG of both muscles led to a comparable agonist-to-antagonist ratio (0.98 ± 0.32 vs. 0.94 ± 0.27 before and after fatigue, respectively; $P > 0.05$). The aEMG during recovery returned to control values within 2 min of rest for the biceps brachii and 1 min of rest for the triceps brachii (Fig. 1B).

Changes in MEP and CMEP during the fatiguing task
During the sustained submaximal isometric contraction of the elbow flexor muscles, the size of MEP and CMEP increased in both the agonist and antagonist muscles (Fig. 2). In the prefatigue control contractions of $50\%$ MVC, the average MEP area, expressed as percentage of the Mmax area, was $80.9 ± 29.6$ and $7.7 ± 6.5\%$ for the biceps brachii and triceps brachii, respectively. The latency of the MEP was the same in the prefatigue contractions as at task failure in biceps brachii ($11.8 ± 1.6$ vs. $11.8 ± 1.3$ ms) and triceps brachii ($12.6 ± 2.3$ vs. $12.8 ± 2.1$ ms).

The increase of the MEP exhibited a different time course in the agonist and antagonist muscles (Fig. 3A). The increase in
the MEP area, expressed at each time point relative to the Mmax, for the biceps brachii occurred over the first 40% of the time to failure and remained constant during the remaining part of the task, reaching 144.3 ± 61.4% (P < 0.01) of its prefatigue values. In contrast, the normalized MEP area of the triceps brachii increased gradually over the course of the task, reaching 279.1 ± 148.3% (P < 0.01) of its control value at task failure. The areas of the normalized MEP for the biceps brachii and the triceps brachii recovered within 1 min after the end of the fatigue task.

The MEP area, normalized to its corresponding Mmax, during the brief MVCs (n = 8), recorded immediately after the brief MVCs (n = 8), recorded immediately after the brief MVCs (n = 8), recorded immediately after the brief MVCs (n = 8).
fatigue task, did not change significantly from their prefatigue values (89.8 ± 30.5 vs. 88.5 ± 32.5 and 49.8 ± 20.8 vs. 50.9 ± 18.4% in biceps brachii and triceps brachii, respectively). The superimposed twitch evoked in the elbow flexors by the motor cortical stimulation during the brief MVC (n = 8) increased significantly (P < 0.01) at task failure (9.8 ± 8.3% MVC) compared with prefatigue values (3.3 ± 1.5% MVC).

The average CMEP areas, expressed as percentage of the Mmax area during the control contractions at 50% MVC, were 43.7 ± 22.4 and 6.5 ± 4.5% for the biceps brachii and triceps brachii, respectively. As for the MEPs, these responses increased in size during the course of the fatigue task in both the agonist and antagonist muscles (Fig. 3B). The normalized CMEP area of the biceps brachii increased to an average value of 154.8 ± 51.5% (P < 0.05) over the fatigue task with most of the increase occurring during the first half of the fatiguing contraction. The normalized CMEP area of the triceps brachii increased progressively up to the end of the fatigue task, reaching 246.2 ± 149.1% (P < 0.01) of the control values (Fig. 3B). Similar to the MEP, the areas of the normalized CMEP for the biceps brachii and the triceps brachii recovered within 1 min after the end of the fatigue task (Fig. 3). There was also no significant change in the CMEP latency, respectively, at task failure compared with prefatigue values for the biceps brachii (8.6 ± 0.9 vs. 8.4 ± 0.8 ms) or the triceps brachii (9.9 ± 1.6 vs. 9.5 ± 0.7 ms). The CMEP area, normalized to its corresponding Mmax, during the brief MVCs (n = 6), recorded immediately after the fatigue task, did not change significantly from their prefatigue values (66.9 ± 17.2 vs. 58.9 ± 13.5 and 26.5 ± 6.6 vs. 28.9 ± 8.8% in biceps brachii and triceps brachii, respectively).

As illustrated in Fig. 3, the pattern of response was similar for the MEP and CMEP within each muscle (ANOVA; biceps: P = 0.72; triceps: P = 0.66). Furthermore, no statistical difference (ANOVA; biceps: P = 0.71; triceps: P = 0.49) was observed when the time course of change of the MEPs and CMEPs was obtained from the same six subjects.

Silent period following motor cortical stimulation

The silent period duration following motor cortical stimulation lengthened during the sustained submaximal fatiguing contraction (Fig. 4A). The duration of the silent period at the beginning of the fatiguing contraction was 95.0 ± 23.5 and 91.6 ± 25.1 ms for the biceps brachii and the triceps brachii, respectively. The silent period increased progressively during the fatigue task and reached 144.8 ± 39.9 and 127.5 ± 42.0 ms (P < 0.01) in biceps and triceps brachii, respectively, at the end of the contraction (Fig. 4B). When normalized relative to their initial values, the duration of silent periods for the biceps brachii and triceps brachii increased, respectively, by 53.4 and 43.2% (P < 0.01 for both muscles). The magnitude of this increase for both muscles did not differ significantly (ANOVA; P = 0.28). The first cortical stimulus, delivered 1 min after the end of the fatigue task, elicited a silent period which had returned to control duration (Fig. 4).

A silent period also followed each CMEP during the contraction at 50% MVC. Its average duration was less than for the MEP and corresponded to 63.6 ± 7.0 and 59.3 ± 11.3 ms for the biceps brachii and the triceps brachii, respectively. The silent period increased significantly by 23.6% (P < 0.01) and

32.7% (P < 0.05) during the sustained submaximal contraction and reached 77.8 ± 2.3 and 76.1 ± 6.8 ms in biceps and triceps muscles, respectively, at task failure (Fig. 4). The recovery was very fast, and 1 min after the end of the fatiguing contraction, the silent period had returned to control values.

When silent periods were measured during the brief MVCs of the elbow flexor muscles, before and after the fatigue task, they also increased significantly from 86.4 ± 14.1 to 123 ± 46.3 ms (P < 0.01) and from 54.2 ± 11.1 to 70.6 ± 11 ms (P < 0.05) for MEP and CMEP, respectively. However, it is interesting to note that during the elbow extension MVCs that
followed the fatigue task, when the triceps brachii was acting as an agonist, the silent periods associated with the MEP in this muscle did not change significantly compared with their pre-fatigue values (78.0 ± 13.9 vs. 75.7 ± 9.2 ms; P > 0.05).

Changes in the H-reflex of the antagonist muscle during the fatiguing task

The amplitude of the H-reflex in the triceps brachii showed a biphasic time course during the sustained submaximal fatiguing contraction with the elbow flexors (ANOVA, P < 0.01; Fig. 5). The peak-to-peak amplitude of the H-reflex superimposed on the 50% MVC of biceps brachii in the pre-fatigue condition was 7.3 ± 5.3% of Mmax. Its amplitude increased slightly but not significantly (8.3 ± 12.1%) during the first 20% of the fatiguing contraction before declining gradually during the remaining part of the task, reaching 64.7 ± 23.5% of the pre-fatigue value (P < 0.05). The absence of significant change for the initial increase of the normalized H-reflex is, however, due to the different time course of its biphasic modulation in the different subjects. Indeed, when the peak of H-reflex was averaged for all subjects, irrespective of the time at which it was obtained, the amplitude and area were increased by 17.1 ± 13.0 and 22.8 ± 21.7% (P < 0.05), respectively. Similarly, the maximum reduction of the H-reflex amplitude and area at the end of the fatiguing contraction reached, respectively, 52.4 ± 18.0% (P < 0.01) and 63.6 ± 11.6% (P < 0.01) of the prefatigue values. There was no significant change in the H-reflex latency for the triceps brachii at task failure compared with pre-fatigue values (9.5 ± 0.4 vs. 9.4 ± 0.3 ms).

DISCUSSION

The purpose of this study was to investigate the control mechanisms of antagonist coactivation during a submaximal sustained isometric contraction. To differentiate cortical and motor neuronal mechanisms in the control of coactivation, MEPs and CMEPs were recorded in the agonist and antagonist muscles. To probe a possible modulation in peripheral input to the motor neuron pool, the time course of change of the H-reflex and CMEP were compared in the antagonist muscle. The main finding of this study is that the MEP, CMEP, and the H-reflex of the antagonistic triceps brachii muscle each showed different changes during the fatiguing contraction of the agonist biceps brachii muscle, although the coactivation ratio between the two muscles was unchanged at task failure. Collectively, these data are consistent with the concept of a supraspinal and differential control of agonist-antagonist muscles during coactivation.

Fatigue in the agonist muscle

As classically described (Duchateau et al. 2002; Fuglevand et al. 1993; Garland et al. 1994; Hunter et al. 2003; Lösher et al. 1996; Psek and Cafarelli 1993; Sogaard et al. 2006), the EMG activity of the agonist muscles increases progressively during the sustained submaximal contraction. As evidenced by the recruitment of motor units during sustained submaximal contractions (Carpentier et al. 2001; Garland et al. 1994; Griffin et al. 2001), the increase in aEMG during such tasks is usually considered to indicate an enhancement of the central drive to the motor neuron pool to maintain a constant level of force (Bigland-Ritchie et al. 1986; Fuglevand et al. 1993; Hunter et al. 2003; Lösher et al. 1996; Sogaard et al. 2006).

FIG. 5. Change in H-reflex of the triceps brachii during the sustained contraction of the elbow flexor muscles at 50% MVC. A: H-reflexes recorded in the triceps brachii in response to electrical stimulation of the plexus brachial of 1 subject at the beginning (a), and at 20% (b) and 100% (c) of the time to task failure (after). B: group data (means ± SE; n = 6) are expressed as a percentage of their prefatigue values. Significant differences from prefatigue value: *, P < 0.05.
The progressive increase of the aEMG in the biceps brachii during the course of the fatigue task was accompanied by an augmentation of both normalized MEP and CMEP areas. However, these responses increased during the first 40% of the time to task failure and plateaued during the remaining part of the fatiguing task. This increase in MEP and CMEP areas are consistent with an increasing voluntary drive (Sacco et al. 1997; Sogaard et al. 2006). Indeed it has been shown that enhanced voluntary effort results in augmented motor neuronal and cortical excitability that leads to increased MEPs and CMEPs for contractions ≤50–70% MVC in the elbow flexor muscles (Di Lazzaro et al. 1998; Martin et al. 2006; Todd et al. 2003; Ugawa et al. 1995; current study). However, the reduced aEMGs (~20%), normalized to the postfatigue MVC, in the biceps brachii at the end of the fatigue task is consistent with the presence of central fatigue (Löschner et al. 1996; Sacco et al. 1997; Sogaard et al. 2006; Zijdewind et al. 1998). This conclusion is supported by the significant decrease in aEMG (normalized to Mmax) of the biceps brachii recorded immediately after the fatigue task and the larger superimposed twitch in response to cortical stimulation during the brief MVCs of the elbow flexor muscles, compared with the prefatigue condition. The latter observation indicates the presence of supraspinal impairment (Gandevia et al. 1996; Löschner et al. 2002; Todd et al. 2003). Although the MEP size of the triceps reached ~17% of Mmax at the end of the fatigue task, the increment in elbow flexion torque evoked by the cortical stimulation may have been underestimated due to an antagonist extension twitch and consequently, central fatigue may be underestimated (Sogaard et al. 2006).

**Antagonist coactivation during fatigue**

At the beginning of the fatigue task, the antagonist coactivation was ~10% of its maximum for the triceps brachii, a value which is similar to that observed in other studies of comparable contraction level for the same muscle (Hunter et al. 2003; Todd et al. 2003). As previously reported (Ebenblicher et al. 1998; Hunter et al. 2003; Levenez et al. 2005; Psek and Cafarelli 1993), the EMG activity of the antagonist muscle increased progressively during submaximal contraction of the elbow flexors. In the current study, this enhanced antagonist coactivation occurred without any fatigue of the antagonist muscles as attested by the similar MVC torque of the elbow extensors at the beginning and end of the fatiguing task. The relatively comparable increase in aEMG, normalized to the EMGs of postfatigue MVCs, for the agonist muscle (biceps brachii) and antagonist muscle (triceps brachii), led to the fact that at task failure, the coactivation ratio was not significantly changed as compared with initial values. This observation, consistent with our previous study for the ankle muscles (Levenez et al., 2005), indicates that task failure cannot be attributed to the opposite action of the antagonist muscles as a consequence of a greater increase in activation compared with the agonist muscles.

The central adjustment of the antagonist muscles activity during fatiguing contractions was investigated by recording MEP and CMEP responses in the triceps brachii. Our data showed that both MEP and CMEP areas increased gradually and nearly linearly during the fatigue task. This increase is consistent with a progressive enhancement of the voluntary drive to the antagonist muscles. This linear increase in the MEP and CMEP in the antagonist muscle, although these responses saturated in the agonist muscle, is presumably due to their smaller size and the lower level of activation (Taylor et al. 1997). The saturation in MEP and CMEP size during contractions of 50% and more can be due to changes in the intrinsic properties of the motor neurons, the trajectory of their afterhyperpolarization, and the change in afferent input (Martin et al. 2006; Todd et al. 2003). Interestingly, the MEP and CMEP responses of the triceps brachii augmented similarly during the course of the fatigue task and reached comparable augmentation of the aEMG at task failure (~150–180%). This is even more evident when MEP and CMEP, acquired from the same subjects, are compared. The parallel increase in both MEP and CMEP presumably reflects the change in motor neuron excitability. The absence of change in MEP area, normalized to Mmax, in the triceps brachii during the brief MVCs of the elbow extensors at the end of the fatigue task compared with prefatigue values is consistent with the EMG data and indicates that the excitability of the antagonist muscles was not affected by fatigue of the agonist muscles.

The potential contribution of spinal adjustments on the activity of the antagonist muscles during the fatiguing contraction by the agonist muscles was analyzed by recording the H-reflex in the triceps brachii. Contrary to the CMEP that increased monotonically during the course of the contraction, the H-reflex displayed a biphasic modulation. The amplitude and area of the H-reflex were augmented during the first part of the fatigue task before declining progressively until the end of the contraction. Because the changes in H-reflex were observed when the CMEP is increasing, the reduction in H-reflex cannot be due to a decreased excitability of the motor neuron pool of the triceps brachii. In contrast, our results indicate that the modulation of the H-reflex in the antagonist muscles during a fatiguing contraction by the agonist muscles is likely caused by modulation in presynaptic inhibition. This mechanism is under the influence of diverse afferent inputs and closely controlled by central mechanisms (Hultborn et al. 1987; Meunier and Pierrot-Deseilligny 1998; Nielsen and Petersen 1994).

**Change in the silent period of the agonist and antagonist muscles during fatigue**

The silent period elicited by cortical stimulation during the fatiguing contraction increased gradually in both agonist and antagonist muscles. At task failure, the silent period was augmented concurrently by 53.4 and 43.2% in the biceps brachii and triceps brachii, respectively. This lengthening was transient and recovered within 1 min after the end of the fatigue task. Such progressive prolongation of the silent period in the agonist muscle and its rapid recovery have been described previously during sustained and intermittent contractions at submaximal and maximal intensities (Sacco et al. 1997; Sogaard et al. 2006; Taylor et al. 1996, 2000) but was not observed in all studies (Ljubisavljevic et al. 1996; Löschner and Nordlund 2002). However, our result of a similar time course of change for the silent period in the antagonist as in the agonist muscles is a new finding.

The silent period in the ongoing voluntary EMG activity after a MEP is usually considered to result principally from interruption of the corticomotor output, and its duration is
thought to be an indicator of the level of the inhibition in the motor cortex (Di Lazzaro et al. 2002; Fuhr et al. 1991; Inghilleri et al. 1993). Indeed, the first 60–70 ms of the silent period reflects events at a spinal level (see CMEP results) such as afterhyperpolarization and recurrent inhibition of the motor neurons (Chen et al. 1999; Fuhr et al. 1991; Garland and Miles 1997; Inghilleri et al. 1993), whereas the remaining part results from inhibition of voluntary cortical output (Di Lazzaro et al. 2002). In our fatigue task, the prolongation of the silent period following the CMEP is less than that occurring after the MEP (see also McKay et al. 1996; Taylor et al. 1996), suggesting that the increase in duration after the MEP probably includes extra inhibition at cortical level. Although the exact mechanisms underlying the prolongation of the silent period are unknown (Benwell et al. 2006, 2007; Taylor and Gandevia 2001), the finding of a similar time course of the modulation of the silent period in both agonist and antagonist muscles indicates that the cortical changes represented by the lengthening of the silent period are not directly related to fatigue of the corresponding muscle because the triceps brachii did not fatigue in our experimental conditions. Although some studies have reported that a change in the silent period is restricted to muscles producing intense contractions (Taylor et al. 1996), it has been shown to lengthen in contralateral muscles during a sustained MVC of the ipsilateral ankle dorsiflexor muscles (McKay et al. 1996). As recently suggested by Benwell and coworkers (2006, 2007); these changes might be part of a central adaptive process to optimize motor output and motor control rather than a process of central fatigue as such. Our observation that at the end of the fatiguing contraction when the antagonist muscles acted as an agonist and performed an MVC, the alteration of the silent period instantaneously disappeared and its duration became comparable to the prefatigue conditions is consistent with this hypothesis.

Possible mechanisms underlying constant coactivation ratio during fatigue

The potential contribution of cortical and motor neuronal mechanisms in the regulation of antagonist coactivation was analyzed by recording the MEP and CMEP responses in the antagonist muscle. As already mentioned, in the absence of Mmax impairment, the gradual and similar increase in size of both MEP and CMEP indicates that the excitatory drive to the motor neuron pool of the antagonist muscle is increased at the same time that central fatigue developed in the agonist muscles. Because there is no reason to believe that changes in the intrinsic properties of the triceps brachii motor neurons would limit their activation at such low level of activation (~10%), as could be the case during fatigue (Gandevia 2001; Kornell and Monser 1982; Nordstrom et al. 2007), the modulation of the motor neuron excitability may be mainly attributed to changes in the supraspinal and/or spinal drive to the motor neuron pool. The current observation that the H-reflex does not change linearly despite a progressive increase in CMEP during the course of a fatigue task involving the elbow flexor muscles indicates that the peripheral excitatory drive cannot by itself mediate the level of antagonist coactivation during sustained contractions. In contrast, this finding and the observation that supraspinal fatigue occurred in the agonist but not in the antagonist at task failure support the concept that coactivation is mediated by supraspinal rather than spinal mechanisms (De Luca and Mambrito 1987; Lévénez et al. 2005; Psek and Cafarelli 1993). Furthermore, the observation of a constant coactivation ratio suggests that the agonist and antagonist muscles are controlled differently, either directly by the descending drive to the motor neuron pool of the agonist and antagonist muscles or most probably through a specific modulation of the reciprocal inhibitory interneurons (Crone and Nielsen 1994) and presynaptic inhibition of Ia afferent (current study) rather than by a common descending drive to the motor neuron pool of both set of muscles (De Luca and Mambrito 1987). As the lengthening of the silent period during fatiguing contractions for both agonist and antagonist muscles is similar, this suggests that there might be one mechanism by which the supraspinal level controls the balance of the increased drive between agonist and antagonist muscles (Benwell et al. 2006, 2007). Indeed an increased cortical inhibition to the antagonist muscles would compensate for the enhanced excitability at the spinal level (as attested by CMEP growth), possibly due in part to a reduced reciprocal inhibition, to maintain a constant agonist-antagonist ratio. Without control by supraspinal mechanisms, the torque produced by the antagonist would increase as the excitability increases because it is not fatigued and would counteract that of the agonist. The absence of this inhibition when the antagonist acted as agonist is consistent with this suggestion.

In conclusion, a sustained contraction held at 50% MVC torque with the elbow flexors is accompanied by a progressive increase in aEMG activity of the antagonist muscle (triceps brachii). Because the coactivation ratio was the same at the onset and end of the fatigue task, there is no evidence that task failure is due to the opposite action of the antagonist muscles. The gradual and similar increase in both MEP and CMEP of the triceps brachii indicate that the excitatory drive to the motor neuron pool of the antagonist muscle is increased during fatigue of the agonist muscle. The different behavior of the H-reflex and CMEP during the fatiguing contraction in the antagonist muscle, suggests that the level of coactivation is likely under the control of supraspinal rather than spinal mechanisms. The results further indicate a differential control of the two sets of muscles during coactivation.

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References


