Effect of tonic voluntary activity on the excitability of human motor cortex

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1. The threshold for obtaining EMG responses after transcranial magnetic stimulation of the brain is reduced by voluntary contraction of the target muscle. The present experiments tested whether some of this effect is due to increased cortical, as opposed to spinal, excitability during the contraction.

2. Magnetic stimulation was delivered with a figure-of-eight coil oriented with the junction region along the interaural line and also (in 4 of 7 subjects) with a circular coil centred at the vertex. The intensity of the conditioning stimulus was subthreshold for evoking a motor response in the relaxed wrist flexor muscles of the forearm. The presence of a small descending corticospinal volley in both the relaxed and active conditions was detected by measuring the facilitation of test H reflexes elicited in the flexor muscles of the forearm.

3. In all subjects, magnetic stimulation with either coil facilitated the H reflex at conditioning–test intervals of −1 to −3 ms (median nerve stimulus before magnetic). This was followed by a long-lasting facilitation. In three of the seven subjects stimulation with the figure-of-eight coil elicited an additional, earlier peak of facilitation at a conditioning–test interval of −3 to −5 ms.

4. In all subjects, the threshold for obtaining facilitation of the H reflex using a conditioning–test interval of −1 to −3 ms was reduced, and the amount of facilitation was larger, if subjects performed a weak tonic voluntary contraction. In contrast, with a conditioning–test interval of −3 to −5 ms voluntary contraction had no effect on the threshold.

5. It is suggested that H reflex facilitation at the conditioning–test interval of −1 to −3 ms was produced by indirect activation of corticospinal neurones by the magnetic stimulus, whereas at −3 to −5 ms, the facilitation was produced by direct activation of corticospinal axons. It is concluded that tonic voluntary contraction of a target muscle decreases the threshold for indirect activation of corticospinal neurones but not for direct stimulation of their axons.

An important feature of transcranial stimulation of the motor cortex in man, which had not previously been noted in work on animals, is that the threshold for evoking a motor response is higher when subjects are relaxed than when the muscle under test is active (Merton & Morton, 1980). Two main explanations for this phenomenon have been put forward. First, voluntary activation may facilitate spinal motoneurones, making it easier to discharge them with a given descending volley. Alternatively, and not exclusively, voluntary contraction may excite cortical mechanisms so that a given stimulus recruits a larger descending corticospinal volley. In previous experiments, Day *et al.* (1987*a*) used H reflex testing of spinal motoneurone excitability and showed that voluntary activity did not change the threshold for anodal electrical stimulation of the hand area of the motor cortex. They concluded that under these conditions the reduced threshold for evoking EMG responses in active as compared with relaxed hand muscle was produced mainly by an increased excitability at the spinal cord.

The situation may be different when using the newer technique of transcranial magnetic stimulation of the motor cortex. Several lines of evidence suggest that at threshold, at least for corticospinal projections to the hand, magnetic stimulation activates a larger proportion of corticospinal neurones trans-synaptically or at the initial segment than electrical stimulation, which tends to activate corticospinal axons directly in the subcortical white matter (Day *et al.* 1989; Edgley, Eyre, Lemon & Miller, 1990; Berardelli, Inghilleri, Cruccu & Manfredi, 1990; Thompson *et al.* 1991). Thus, responses to magnetic stimulation are more likely to be influenced by the level of

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cortical excitability, which may be raised during a voluntary contraction, than the responses to electrical stimulation. In some subjects, it has been reported that the site at which magnetic stimulation acts may depend on the orientation of the stimulating coil. Usually, a magnetic stimulator is held so as to induce electrical currents which flow posterior–anterior through the hand area of the motor cortex. However, Amassian, Cracco & Maccabee (1989) and Werhahn, Fong, Meyer, Rothwell, Day & Thompson (1993) suggested that if the magnetic stimulus induced an electrical current in the brain which flowed lateromedially up the motor strip, then the site of corticospinal activation could shift, even at relatively low intensities, from the cell body or initial segment down to nodes on the axon within the white matter. Under these conditions, voluntary activity would be expected to have no effect on the threshold for producing corticospinal activation.

The present experiments confirm that in all subjects, there is a component of the corticospinal response to magnetic stimulation which has its threshold lowered by voluntary contraction. In addition, in three of seven subjects, stimulation produced an additional earlier excitation, the threshold of which was unaffected by voluntary contraction.

METHODS

Stimulation and recording techniques

The experiments were performed on normal volunteers. All subjects gave informed consent and the procedures were approved by the local ethical committee.

All recordings were made from the flexor muscles of the wrist in the left forearm. Surface EMGs were obtained via two 9 mm diameter Ag–AgCl electrodes placed 1·5 cm apart over the mid-belly of the flexor carpi radialis muscle. EMGs were amplified and filtered by D150 amplifiers (Digitimer, Welwyn Garden City, Herts) with a time constant of 10 ms and a low-pass filter set at 3 kHz. Data were collected on a computer and stored on floppy disk for later analysis using a CED 1401 A–D converter (Cambridge Electronic Design, Cambridge, UK) sampling at 7–8 kHz per channel.

Magnetic stimulation was performed with a high power Magstim 200 (Magstim Co., Whitland, Dyfed). In most experiments, a figure-of-eight coil with external loop diameters of 9 cm, was held on the right side of the scalp with current in the junction region directed medial to lateral along the interaural line. This stimulus should therefore induce current in the brain flowing in the lateral to medial direction up the motor strip, and activate muscles in the left arm and hand. Intensities were expressed as a percentage of the maximum output of the stimulator. Subthreshold stimuli were defined as shocks below the intensity needed to produce a liminal motor-evoked response (MEP) ($> 50\ \mu V$ in 50 % of trials) in totally relaxed muscles. This ranged from 40 to 55 % of the maximum stimulator output. In four subjects, the experiments were also performed using a 13 cm external diameter coil centred at the vertex with the electrical current flowing clockwise in the coil so as to produce preferential activation of the right motor cortex. Such a stimulus should induce posterior to anterior current flow in the brain across the hand/arm area of motor cortex.

With the subject seated and relaxed, H reflexes were elicited by electrical stimulation of the median nerve in the cubital fossa with 0·5 ms square wave pulses at about motor threshold intensity. Stimuli were given every 6 s or so and were intermixed at random with subthreshold shocks to the scalp so that the subjects could not predict the occurrence of brain stimulation.

Experimental protocol

First, the effect of the conditioning magnetic shock on the test H reflex size was investigated. Magnetic stimulation with the figure-of-eight coil was performed in all seven subjects; stimulation with the circular coil in four of them. The cortical stimulus intensity used was usually 5–10 % of the stimulator output below the threshold for a MEP at rest. Eight to twelve trials each of control H reflexes and H reflexes conditioned by a scalp shock were collected at different conditioning–test intervals. The time of the conditioning scalp shock was taken as 0 ms; so if the H reflex test stimulus was given first, the conditioning–test interval was negative. When we had determined the minimum interval for magnetic facilitation of the H reflex, blocks of trials were conducted with varying intensities of magnetic stimulation in order to find the threshold for the effect. Experiments were conducted when the muscle was completely relaxed and silent, and also when the subject exerted a small background voluntary contraction (approximately 5–10 % of maximum) of the wrist flexor muscle. The EMG of the contracting muscle was monitored continuously on an oscilloscope. The size of control H reflexes under the active and relaxed conditions were matched by adjusting the intensity of the median nerve stimulus.

The peak-to-peak size of the conditioned H reflex was expressed as a percentage of the control H reflex size. The size of the maximum motor response (M_{max}) was measured in order to express the size of the H reflex as a percentage of the M_{max}. Differences between conditioned and control H reflexes were assessed using a two-tailed Student's t test.

RESULTS

The effect of scalp magnetic stimulation on the H reflex of relaxed forearm flexor muscles

For the purpose of our experiments, it was essential to investigate the time course of the initial effect of the cortical descending volley on the forearm flexor muscle motoneurone pool. Cowan, Day, Marsden & Rothwell (1986) showed that a submotor threshold scalp electrical shock facilitated FCR H reflexes at a minimum interval of −4 to −5 ms (i.e. H reflex stimulus precedes magnetic cortex shock). This initial peak lasted 1–2 ms and was followed by a later period of facilitation starting at −2 to −1 ms and lasting 10–20 ms. In the present experiments, subthreshold magnetic stimulation also produced facilitation of the H reflex, but the interval for the initial peak was usually shorter than that seen after electrical stimulation and averaged −2 ms (see Fig. 1). This peak was followed by

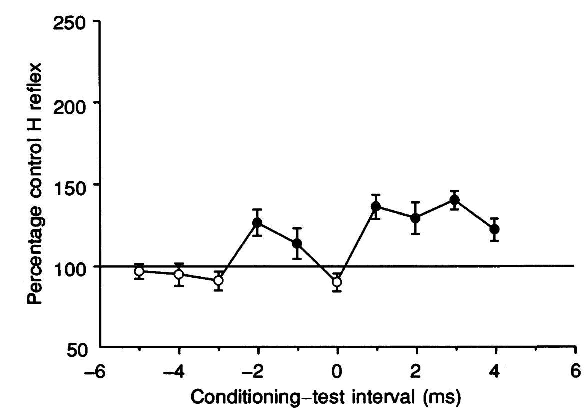

Figure 1. Time course of the effect of a submotor threshold scalp magnetic stimulus (given at time zero) on the H reflex evoked in relaxed wrist flexor muscles of the left arm in a representative subject

A circular coil centred at the vertex (current flowing clockwise in the coil) was used to deliver the magnetic shock with a stimulus intensity of 40 % of the maximum output of the stimulator (about 5 % below the threshold for obtaining a motor evoked response at rest in this subject). A similar time course was obtained in this subject when a figure-of-eight coil (junction region placed on the right side of the scalp along the interaural line) was used with the same intensity as above. ●, indicate conditioning–test intervals at which the conditioned H reflex was statistically different from control H reflex size ($P < 0{\cdot}05$). Control H reflex size is represented by the horizontal line. Each point represents the mean of eight measurements; standard errors of the mean are expressed by the bars.

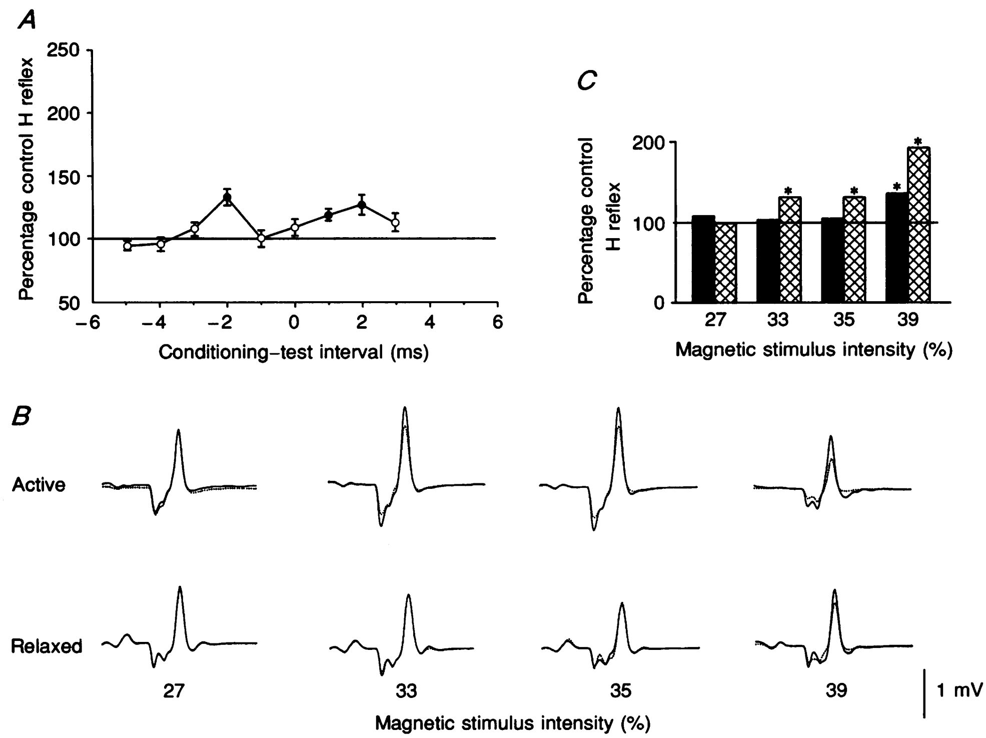

Figure 2.

A, time course of the effect of a submotor threshold scalp stimulus (delivered with a figure-of-eight coil) on the H reflex evoked in relaxed wrist flexor muscles from another subject. The stimulus intensity was 39 % of the maximum output of the stimulator (about 10 % below the motor threshold at rest). *B*, the effect of different intensities of cortical magnetic stimulation expressed as a fraction of the maximum output of the stimulator (figures at bottom of each column) on the size of H reflexes evoked at rest and during voluntary activity in the flexor muscles of the forearm using a conditioning–test interval of −2 ms (i.e. the test H reflex stimulus was given before the magnetic conditioning shock) in the same subject. Each record shows superimposed control (dotted line) and conditioned (continuous line) H reflexes over a 10 ms period starting 10 ms after the median nerve stimulus. *C*, graph of the raw data shown in *B*. The histograms show the percentage facilitation of control (100 %) H reflexes by a magnetic stimulus, measured by comparing peak-to-peak amplitudes of the average response ($n = 8$) when the muscle was relaxed (filled bars) or active (cross-hatched bars). Asterisks refer to significant differences between the size of conditioned and of control H reflexes ($P < 0{\cdot}05$).

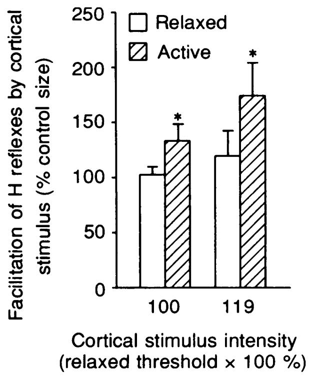

Figure 3. Effect of voluntary contraction on threshold and amount of facilitation of the wrist flexor H reflex produced by a scalp magnetic stimulus using a conditioning–test interval of −2 ms

Mean (+ 1 S.D.) data from 7 subjects. H reflex size when given in conjunction with a cortical stimulus has been expressed as a percentage of the peak-to-peak control H reflex size. To normalize cortical stimulation strength between different subjects, intensity is given as a percentage of the average intensity (indicated as 100 %) which produced no effect or a just identifiable facilitation (not significant) of the H reflex in the relaxed individuals. The contraction was 5–10 % of maximum force. Asterisks refer to significant differences between control and conditioned H reflexes ($P < 0.05$).

later facilitation lasting up to 20 ms, which was not analysed in detail in the present experiments.

Changes in the threshold for H reflex facilitation during voluntary contraction

The data reported in this section refer to the main purpose of the present investigation, namely whether the threshold for magnetic activation of corticospinal tract is the same during a voluntary contraction as at rest.

Figure 2 shows the results from a typical individual. Using a conditioning–test interval of −2 ms, which was the minimum interval for H reflex facilitation in this case (see time course in Fig. 2*A*), the threshold intensity of cortical stimulation needed to produce a significant minimal facilitation of the H reflex at rest was 39 %. In contrast, significant facilitation in the active state occurred with a stimulus intensity of only 33 %. Increasing the intensity of cortical stimulation increased the amount of facilitation in both relaxed and active muscles but the amount of facilitation of the H reflex was larger during voluntary effort. Similar results were obtained in all the other subjects tested with conditioning–test intervals corresponding to

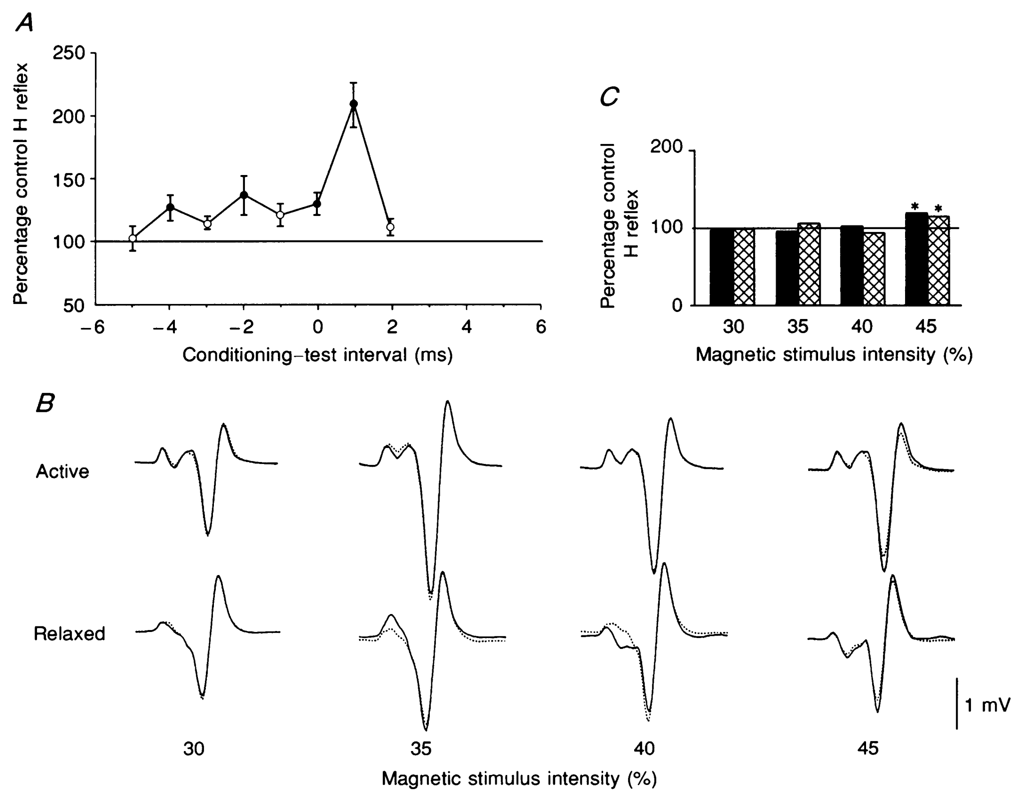

Figure 4.

A, time course of the effect of a submotor threshold scalp stimulus (delivered with a figure-of-eight coil) on the H reflex evoked in relaxed wrist flexor muscles from another subject. In this case, the earliest facilitatory effect occurred at conditioning–test intervals of −4 ms. The stimulus intensity was 45 % of the maximum output of the stimulator (about 10 % below the motor threshold at rest). *B* and *C*, as in Fig. 2 using a conditioning–test interval of −4 ms.

the onset of excitation (from −3 to −1 ms). The group data obtained in seven subjects is shown in Fig. 3. Since the motor threshold cortical stimulus intensity varied between subjects, the cortical stimulus intensity is expressed as a percentage of the average liminal intensity (indicated as 100 %) for a just identifiable facilitation of the H reflex in relaxed individuals. Thus, at 100 % the cortical stimulus is virtually ineffective in the relaxed condition. However, during voluntary activation of the muscles, the same cortical stimulus produced a significant facilitation of the H reflex in all the subjects (paired t test: $t = -6{\cdot}466$, $P = 0{\cdot}001$). An increase in the strength of the cortical stimulus to about 20 % above the threshold value produced a clear facilitation in the relaxed condition which was significantly augmented during voluntary activation (paired t test: $t = -4{\cdot}868$, $P = 0{\cdot}003$). The difference in the degree of facilitation between the two active conditions is also significant (paired t test: $t = -4{\cdot}317$, $P = 0{\cdot}005$). Similar results were obtained in the four of the subjects who were tested using a circular stimulating coil centred at the vertex of the scalp.

In two subjects, increasing the cortical stimulus intensity close to the threshold for obtaining a MEP in the active muscle, produced a very large facilitation of the H reflex (about 200 %) at rest. In this condition, there was no extra facilitation during voluntary contraction: the size of the conditioned H reflex was facilitated by only about 175 %.

An early H reflex facilitation in three subjects

In three of the seven subjects, stimulation with the figure-of-eight coil, but not with the round coil at the vertex, produced H reflex facilitation which began earlier than that discussed above, at conditioning–test intervals of −4 ms. This is approximately the same timing as reported by Cowan *et al.* (1986) and Day *et al.* (1987*a*) for electrical stimulation of motor cortex. Like the early facilitation evoked with electrical stimulation (Day *et al.* 1987*a*), the threshold for this early magnetic facilitation was not changed by voluntary contraction of the target muscle. Figure 4 illustrates the effect of different intensities of cortical stimulation on the size of FCR H reflexes evoked at rest and during voluntary activity in the flexor muscles of the forearm in a representative subject. In this case, the conditioning–test interval was −4 ms (see time course in Fig. 4*A*). At rest, the threshold for cortical facilitation of the H reflex was 45 % of the maximum output of the stimulator. This was approximately 10 % of the stimulator output below the stimulus intensity required to evoke a MEP when relaxed and was motor threshold level when contracting. Activating the muscle made no difference to the threshold or the amount of cortical facilitation of the H reflex. Similarly, for the other two subjects in whom it was possible to obtain an early (−4 ms) phase of excitation at rest, the threshold and the amount of facilitation of the H reflex did not change with voluntary activation of the muscle.

DISCUSSION

Time course of H reflex facilitation

In most subjects, subthreshold magnetic stimulation facilitated H reflexes in the FCR muscle at conditioning–test intervals of about −2 ms. If we assume that the H reflex is predominantly monosynaptic and that the major pathway tested by transcranial stimulation is the monosynaptic component of the corticospinal tract to spinal motoneurones (see Rothwell, Thompson, Day, Boyd & Marsden, 1991), then this effect was presumably caused by interaction at the motoneuronal membrane of a subthreshold excitatory volley from the cortex with an H reflex input from the periphery. The onset of facilitation was about 2 ms later than that observed by Cowan *et al.* (1986) using subthreshold electrical stimulation of motor cortex. This is the same as the difference in latency to onset of surface EMG responses in hand and forearm muscles after electrical and magnetic brain stimulation (Day, Thompson, Dick, Nakashima & Marsden, 1987*b*). It probably reflects the difference in timing of the earliest descending volleys produced by the two forms of stimulation at threshold (Berardelli *et al.* 1990; Thompson *et al.* 1992). Why this difference should arise is still debated. Most authors believe that both electrical and magnetic forms of stimulation activate the large-diameter component of the corticospinal tract (Edgley, Eyre, Lemon & Miller, 1992). If so, then the responses to electrical stimulation occur earlier because (i) electrical stimulation activates corticospinal axons deeper within the brain than magnetic stimulation, or (ii) because magnetic stimulation activates the corticospinal pathway indirectly, via a synaptic relay. Edgley *et al.* (1990) have shown in the monkey that magnetic stimulation cannot spread deep into the brain, and that even at maximum intensities, activation occurs in the grey matter. If so, the fact that it is possible in man to obtain responses in most muscles at the same latency as when using electrical stimulation with high intensity and/or appropriately directed magnetic stimulation of the motor cortex (see Amassian *et al.* 1989; Day *et al.* 1989; Amassian, Quirk & Stewart 1990; Rothwell, Day & Amassian, 1992; Werhahn *et al.* 1993) appears to support the suggestion that the 2 ms difference in the latency of the earliest excitatory effect depends on whether pre- or postsynaptic structures of pyramidal tract neurones are activated by magnetic stimulation.

Effects of voluntary contraction on cortical facilitation of the H reflex

In all seven subjects, the threshold of the cortical stimulus needed to produce H reflex facilitation was decreased, and the amount of facilitation at low intensities of cortical stimulation was larger when subjects were active than when they were relaxed. We suggest that tonic voluntary contraction increased cortical excitability to magnetic stimulation, so that a given stimulus evoked a larger descending corticospinal volley.

However, before attributing these effects to variations in the level of cortical excitability, the possibility of changes in spinal cord excitability should be taken into account. It has been shown that the sensitivity of monosynaptic test reflexes to facilitation varies as a function of the size of the control test reflex itself (Crone, Hultborn, Mazieres, Morin, Nielsen & Pierrot-Deseilligny, 1990). This is unlikely to have been of importance in the present experiments for two reasons. First, comparable sizes of test H reflexes were elicited in both relaxed and active conditions by adjusting the intensity of the H reflex stimulus. Second, the size of the test H reflexes in the present seven subjects studied was remarkably large (for the flexor carpi radialis muscle), being of the order of 30% of the maximum M-wave amplitude. At least for the selection of individuals used here, we should have been within the range of H reflex size where the sensitivity to facilitation has been shown to remain fairly constant (Crone *et al.* 1990).

Another possible explanation for the larger facilitation of the H reflex during voluntary contraction is that the distribution of synaptic excitation during voluntary effort is not the same as when subjects are at rest. As a result, the same magnetic conditioning volley may differentially facilitate the test H reflex in the two conditions. However, if this were the case, then it would be difficult to explain the results at conditioning test intervals of −4 ms (see below), where there was no difference in the degree of facilitation in both relaxed and active states. Likewise, using the same protocol as for the present experiments, the earliest descending volley to *electrical* stimulation of the motor cortex was reported to be of the same size in both relaxed and active conditions (Day *et al.* 1987*a*). We conclude that changes in the excitability of the motor cortex during voluntary contraction were responsible for the significant increase in facilitation of the forearm H reflexes after magnetic stimulation of the brain. In effect, this implies that the magnetic conditioning stimulus can interact with cortical neurones involved in a tonic voluntary contraction. Whether the same is true for the corticospinal projection to all muscles is unknown. In the leg, results similar to those presented here were reported briefly by Nielsen, Petersen & Deuschl (1992). However, Maertens de Noordhout, Pepin, Gerard & Delwaide (1992) used a different technique and were unable to find evidence that voluntary contraction of leg muscles decreased the cortical threshold for magnetic stimulation.

The intensity of the cortical conditioning stimulus was important in determining whether voluntary contraction would increase the amount of H reflex facilitation. In two subjects, the usual additional facilitation of the H reflex at a conditioning–test interval of −2 ms was abolished when the cortical stimulus intensity was raised. The intensity used was sufficient to produce a large facilitation at rest and a just identifiable direct motor response during activation. One possible explanation is that saturation or occlusion occurs at the cortical level when the conditioning magnetic shock evokes too large a response at rest. This would be supported by the fact that voluntary contraction had produced a consistent extra facilitation of the conditioned response when the intensity of the cortical stimulus was reduced. Such occlusion or saturation has been shown to operate at the level of the spinal cord in man (Rossi & Mazzocchio, 1988; Iles & Pisini, 1992). Occlusion at the level of the human motor cortex might account for the results of Brouwer, Ashby & Midrioni, (1989) who found that the facilitation of motoneurones produced by a constant magnetic stimulus was greater during a weak contraction than during a strong contraction.

Early facilitation of the H reflex with magnetic stimulation

In three subjects, stimulation with a figure-of-eight coil placed on the lateral scalp with the junction region oriented lateromedially, produced earlier facilitation of the H reflex than with a circular coil at the vertex. The timing of this facilitation was very similar to that seen after electrical stimulation of the brain (−4 ms; Cowan *et al.* 1986). Voluntary activity had no effect on the threshold for producing this peak. The same result was observed by Day *et al.* (1987*a*) using a similar conditioning–test interval between a cortical electrical shock and forearm H reflexes. We conclude that voluntary activity has no effect on the excitability of the site responsible for initiating the earliest corticospinal volley after magnetic stimulation with a laterally placed figure-of-eight coil. This site may therefore be close to, or the same as that activated by transcranial electrical stimulation (see also Rothwell, Day & Amassian, 1992).

In conclusion, we have found that in most subjects magnetic stimulation of the brain at threshold produces the earliest H reflex facilitation in forearm flexor muscles at −2 ms. The threshold for eliciting this facilitation is reduced during voluntary contraction of the target muscle. Such a phenomenon is consistent with the hypothesis that the major volleys evoked by magnetic stimulation are produced by trans-synaptic (I-waves) or initial segment activation of pyramidal tract neurones. This mechanism would allow for summation of magnetic and other inputs as suggested by a number of previous studies (Datta, Harrison & Stephens, 1989; Day, Riescher, Struppler, Rothwell & Marsden, 1991; Ugawa, Day, Rothwell, Thompson, Merton & Marsden, 1991; Ferbert, Priori, Rothwell, Day, Colebatch & Marsden, 1992). This finding may have important implications when comparing data obtained from intact, awake subjects with those obtained from anaesthetized subjects in whom the baseline cortical excitability may be different (Thompson *et al.* 1991; Hicks, Burke, Stephen, Woodforth & Crawford, 1992). As the present results suggest, the threshold for indirect activation of corticospinal neurones is critically dependent upon the pre-existing state of excitation of those neurones whereas the threshold for direction activation is relatively insensitive to change in cortical excitability.

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