Journal of Physiology (1991), **441**, *pp.* 57–72
With 7 figures
Printed in Great Britain

MODULATION OF MOTOR CORTICAL EXCITABILITY BY ELECTRICAL STIMULATION OVER THE CEREBELLUM IN MAN

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(*Received 10 January 1991*)

SUMMARY

1. We have stimulated over the cerebellum of intact human subjects by applying single electrical stimuli through electrodes placed on the back of the head, approximately at the level of the inion. The intensity of stimulation used was below that required to produce direct EMG responses in pre-activated muscles of the hand.

2. In ten subjects the effect of the stimulus over the cerebellum was to reduce the size of the EMG response in first dorsal interosseous muscle evoked by a magnetic stimulus to the cerebral cortex. In all subjects the onset of the period of suppression occurred when the test magnetic cortical shock followed the conditioning cerebellar shock by 5 ms. The duration of the suppression lasted from 3 to 7 ms.

3. The amount of suppression was related to the intensity of stimulation over the cerebellum. At 15% below the threshold for direct motor activation there was no effect; increasing suppression was evident at 10, 5 and 0% below motor threshold.

4. With a conditioning–test interval of 5–6 ms the suppression was the same whether the target muscle was relaxed or active. With longer conditioning–test intervals (12 and 15 ms) the amount of suppression was greater in active than relaxed muscles.

5. The short-latency suppression was greatest when the stimulating anode was ipsilateral to the target muscle and contralateral to the stimulated sensorimotor cortex. The later period of suppression was insensitive to the polarity of stimulation. When the stimulating electrodes were moved 2 cm caudally or cranially the short latency suppression disappeared whereas the longer latency suppression was still observed with the electrodes in the lower position.

6. Different results were obtained when the test EMG response was produced by an electrical (rather than magnetic) stimulus over the sensorimotor cortex. The short latency effect was no longer visible whereas the longer latency effect was the same as when testing with a magnetic cortical stimulus.

7. We suggest that a single electrical stimulus across the base of the skull

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(particularly with the anode over one cerebellar hemisphere) produces a short latency (5–6 ms) disfacilitation of the contralateral motor cortex through activation of cerebellar structures. A later (12 and 15 ms), less specific suppression which is present when testing in active muscles is thought to be mediated by a different mechanism and probably produces its effect at the level of the spinal cord.

INTRODUCTION

Merton & Morton (1980) devised a way of stimulating the cerebral cortex of man through the scalp with a single pulse of electricity. The aim of the present work was to see whether the same method could be used to stimulate the human cerebellum. To our knowledge there has been only one previous report of single pulse stimulation of the cerebellum in man. Levy (1987) directly stimulated the exposed cerebellar cortex during neurosurgery and found it possible to record short-latency descending motor activity in the spinal cord and peripheral nerve. All other human work has employed chronic, repetitive, electrical stimulation through implanted cerebellar electrodes for the relief of epilepsy or spasticity (e.g. Cooper, Amin, Riklan, Waltz & Poon, 1976; McLellan, 1981). Motor effects of such stimuli were said to be minimal.

In a previous paper (Ugawa, Rothwell, Day, Thompson & Marsden, 1991), we showed that single high voltage electrical stimuli across the base of the skull of intact human subjects were capable of activating directly long descending motor pathways at the level of the pyramidal decussation. Since such stimuli activated the brain stem, it seemed possible that shocks at the same site might be capable of activating other nearby structures. Therefore, we used a similar technique in an attempt to stimulate the cerebellum. In order to avoid spread of stimulation to the brain stem, we used only low intensity stimuli, insufficient to evoke direct EMG responses. We did not investigate the possibility of direct cerebellar excitation of spinal motoneurones as reported by Levy.

Despite the lack of direct motor effects, we found that such stimuli were capable of affecting the size of EMG responses evoked by a magnetic shock given 5–6 ms later over the contralateral cerebral motor cortex. For convenience, throughout this paper we shall refer to this form of stimulation as stimulation over the cerebellum. Precisely what structures are activated is addressed in the Discussion. Part of this work has been published in abstract form (Britton, Brown, Day, Marsden, Merton, Rothwell, Thompson & Ugawa, 1990).

METHODS

Subjects were ten healthy volunteers aged 29–73 years, all of whom were members of the Institute staff. They gave their informed consent and the procedures had been approved by the local Ethical Committee. No side effects were noted in any individual.

Surface electromyographic (EMG) activity was recorded from the right first dorsal interosseous muscle (FDI) using silver–silver chloride 9 mm diameter cup electrodes fixed 2–3 cm apart. On some occasions the EMG from left FDI or biceps brachii muscles on both sides also was recorded. Signals were amplified with Digitimer D140 amplifiers with filters set at 80 Hz and 2·5 kHz, and recorded by an Olivetti personal computer using a CED 1401 interface.

High voltage electrical stimulation over the cerebellum was performed using a prototype of the Digitimer D180 stimulator which had been made for us by Mr H. B. Morton. The stimulating

electrodes were fixed with collodion on both sides of the head at the angle made by the posterior edge of the mastoid process and the anterior part of the occipital bone. We shall refer to electrodes in this position as being on the left mastoid and right mastoid. In most experiments, the anode was on the right and the cathode on the left. The intensity of stimulation was usually fixed at around 10% less than the threshold for activation of the descending motor tracts at the pyramidal decussation (Ugawa *et al.* 1991). In this paper we have expressed the intensity of electrical stimulation relative to descending motor tract activation. In some subjects, different stimulation montages were used in order to establish the optimum electrode placement. On some occasions, the cathode was placed on the right and the anode on the left. On others, the electrodes were moved vertically 2 cm above or below the standard position. In other experiments, one of the electrodes was placed in the mid-line whilst the other was maintained laterally (hemispheric stimulation).

At various times after electrical stimulation over the cerebellum, the motor cortex was stimulated using a Novametrix Magstim 200 magnetic stimulator. The coil had a mean diameter of 9 cm and was placed with its centre over the vertex. The current in the coil flowed anti-clockwise as viewed from above in order to activate the motor output from the left hemisphere, and produce muscle responses on the right side. We shall term this magnetic stimulation of the left sensorimotor cortex. In most experiments the intensity of stimulation was adjusted to produce a response of about 1 mV peak-to-peak in relaxed FDI muscles. In some subjects a range of different stimulation intensities was used, and in other subjects the influence of voluntary activation of the target muscle was studied. A short series of experiments also was performed using electric stimulation of the left motor cortex. The cathode was placed at the vertex, and the anode 7 cm lateral on a line joining the vertex with the external auditory meatus.

The design of the experiments was as follows. Electrical stimulation over the cerebellum is referred to as the conditioning shock, and magnetic (or, on occasion, electrical) stimulation of the motor cortex is referred to as the test shock. Trials in which both test and conditioning shocks were given were randomly intermixed with control trials in which only a test shock or only a conditioning shock was given. Six conditions were examined in each block, with eight trials of each condition. The conditions were: test shock alone, conditioning shock alone, and test shock conditioned by the cerebellar shock at four different interstimulus intervals. In some blocks of trials, five different conditioning–test intervals were studied rather than four. The time course of the cerebellar effect was studied by repeating these blocks several times in order to examine the whole range of conditioning–test intervals.

RESULTS

In all subjects, an appropriately timed conditioning stimulus over the cerebellum could decrease the size of EMG responses in the first dorsal interosseous muscle (FDI) to contralateral magnetic cortical stimulation. Figure 1*A* shows a representative example of the average muscle action potentials from the right FDI muscle of one relaxed subject. The conditioning stimulus over the cerebellum was produced by an anode on the right mastoid and a cathode on the left mastoid. When this conditioning shock preceded a magnetic test stimulus to the left sensorimotor cortex by 4 ms the size of the test response was not affected. However, with conditioning–test intervals of 5, 6 or 8 ms, the size of the FDI EMG response was decreased by the conditioning shock over the cerebellum. The time course of this suppression in eight subjects is shown in Fig. 1*B*. In all subjects the onset of the period of suppression occurred with a conditioning–test interval of 5 ms. The duration of inhibition lasted from 3 to 7 ms. Although the conditioning stimulus over the cerebellum caused a contraction of neck muscles, movement of the head, as measured using a linear accelerometer, did not begin until at least 11 ms after the shock. Thus, movement of the head beneath the magnetic stimulating coil could not account for the EMG suppression.

Effect of voluntary pre-activation

The effects described above were obtained in relaxed muscles. However, similar results could be obtained if subjects maintained a steady voluntary contraction (about 5% maximum) throughout the experiment. The mean data with contracting

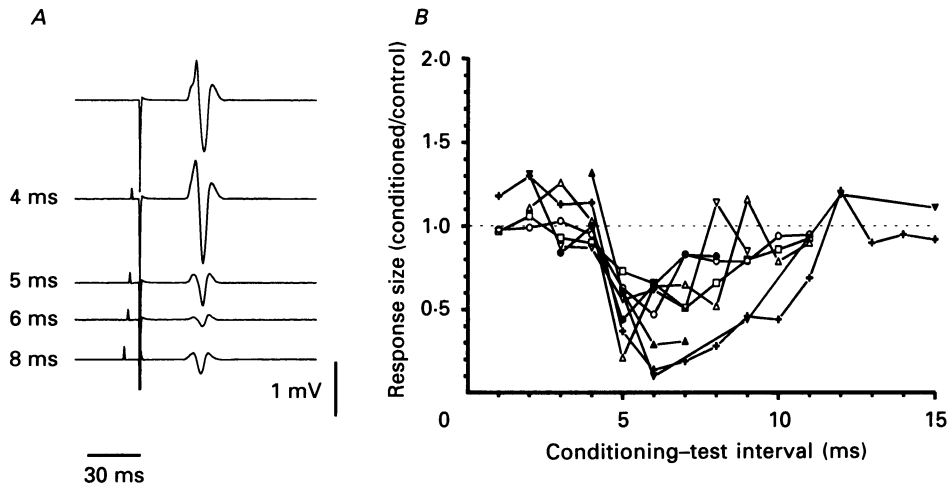

Fig. 1. Suppression of EMG responses in relaxed right FDI muscle following magnetic stimulation of the left sensorimotor cortex by high voltage electrical stimulation over the cerebellum (anode on right mastoid, cathode on left mastoid: see Methods for precise location). The intensity of the conditioning shock over the cerebellum was set to be approximately 10% less than the threshold for direct stimulation of descending motor tracts at the cervico-medullary junction. Control responses to cortical stimulation alone were adjusted to be about 1 mV peak-to-peak in amplitude. The left panel (*A*) shows representative average responses of eight trials in a normal subject. The top trace illustrates the size of control responses produced by the magnetic cortical shock given alone (producing the large stimulus artifact). The four traces below illustrate responses conditioned by a preceding stimulus over the cerebellum given 4, 5, 6 and 8 ms earlier (producing the small stimulus artifact). The right panel (*B*) shows the time course of suppression in eight different subjects. The size of the conditioned response at different intervals has been plotted as a fraction of the size of control responses. In all subjects, suppression began at conditioning–test intervals of about 5 ms, and lasted for 3–6 ms.

muscles from five subjects are shown in Fig. 2 at five different conditioning–test intervals. The depth of suppression in contracting muscles at a conditioning–test interval of 5 ms was very similar to that seen in relaxed muscles. However, at longer intervals the amount of suppression was greater in active than in relaxed muscles. Because of this, and other results noted below, we suggest that suppression at these intervals in the active state was confounded by an additional mechanism different to that producing the early suppression in the relaxed state (see Discussion).

Intensity of conditioning shock over the cerebellum

Figure 3*A* shows a representative example of the effect in the relaxed FDI muscle of one subject at a conditioning–test interval of 5 ms. Control responses (top left hand panel) elicited by magnetic stimulation of the left sensorimotor cortex are

approximately constant in size at around 1 mV peak-to-peak. Responses shown in the right-hand panel were conditioned by a stimulus over the cerebellum (anode on right mastoid, cathode on the left mastoid). When the intensity of the conditioning shock was reduced by 15% (of the maximum output of the stimulator) below that

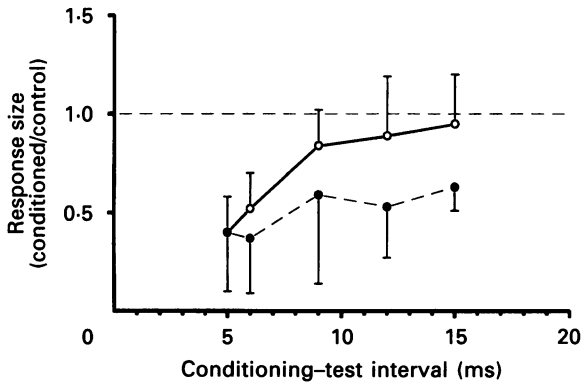

Fig. 2. Comparison of the time course of suppression in active and relaxed muscle. The conditioning stimulus was a shock over the cerebellum (anode on the right, cathode on the left) of constant intensity (−10%). The test shock was a magnetic stimulus over the left sensorimotor cortex, with EMG responses recorded in the contralateral FDI whilst the subject was either completely relaxed (○) or performing a tonic voluntary contraction of about 5% maximum (●). The size of control responses elicited in the active and relaxed states was matched by adjusting the intensity of the sensorimotor test shock. Data are the average (±1 S.D.) from five subjects. The mean amount of suppression at intervals of 9, 12 and 15 ms was larger in the active than in the relaxed state (paired t test; $P < 0{\cdot}05$).

required for direct stimulation of descending motor pathways (−15%), there was no effect on the size of the cortically evoked EMG response. When the conditioning shock was 10 or 5% below threshold (−10, −5%), then the EMG response produced by magnetic stimulation of the left sensorimotor cortex was reduced in size. The maximum effect was seen with shocks over the cerebellum of direct motor threshold intensity (0%). Mean data from four subjects are shown in the bottom graph of Fig. 3*A*. In this figure, the percentage suppression of the test response is plotted at five different conditioning–test intervals for two different intensities of stimulation over the cerebellum (−10, 0%). Conditioning shocks of 0% intensity produced more suppression than shocks at −10%.

Intensity of the magnetic cortical test shock

The percentage suppression produced by a given size of conditioning shock over the cerebellum depended upon the intensity of the magnetic test shock applied to the sensorimotor cortex. The mean data from four subjects is shown in the bottom graph of Fig. 3*B* in which the percentage suppression at five different conditioning–test intervals is plotted for three different sizes of magnetic test shock to the sensorimotor cortex. Raw data from a single subject is plotted above. The intensity of the conditioning shock over the cerebellum was constant, and the muscles were relaxed throughout. The time course, and amount of suppression, was the same whether

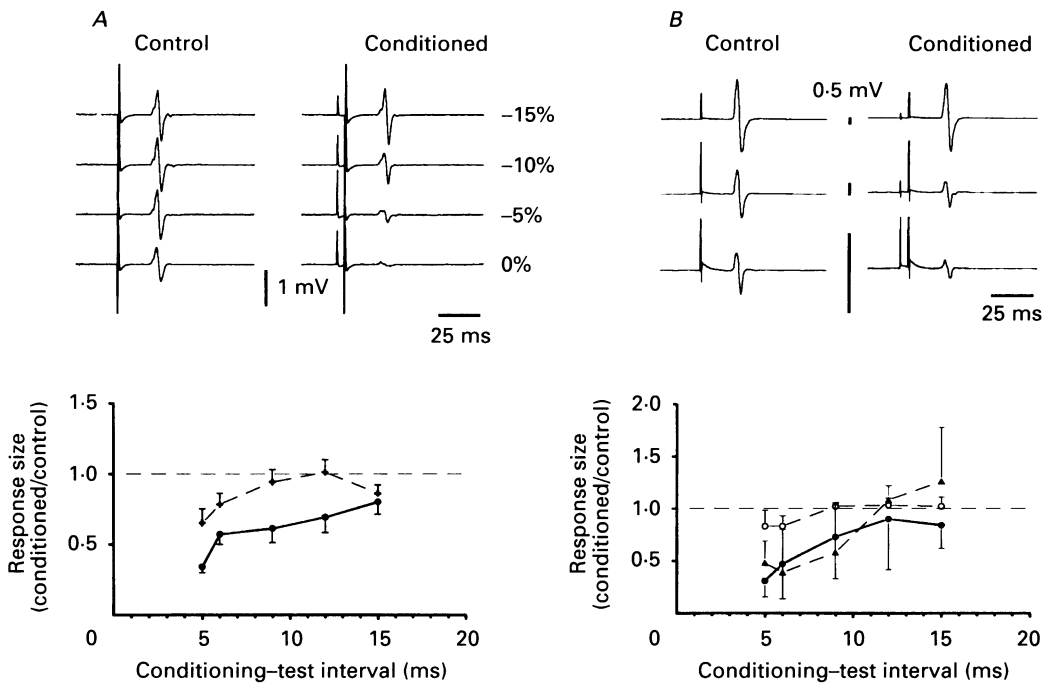

Fig. 3. *A*, effect of intensity of conditioning stimuli over the cerebellum (anode on the right mastoid, cathode on the left mastoid) on the EMG responses evoked in the right FDI muscle by magnetic stimulation of the left sensorimotor cortex. Upper traces are raw data traces (averages of 8 trials each) from one subject showing the effect of different intensities of stimulation over the cerebellum on responses in relaxed FDI using a conditioning–test interval of 5 ms. Control responses are on the left, conditioned responses are on the right. The intensity of the conditioning shock was set to be 15, 10, 5 and 0% below the threshold for direct stimulation of descending motor pathways (−15, −10, −5, 0%, respectively). More suppression is seen at higher intensities. Note that the average control response varies slightly in size from experiment to experiment. The graph below shows average data (±1 S.D.) from seven relaxed subjects showing the time course of suppression of FDI responses at five different conditioning–test intervals. +, shows the time course with a conditioning intensity of −10%; ●, shows the time course with a conditioning intensity of 0%. The average amount of suppression at intervals of 5, 6, 9 and 12 ms was significantly greater ($P < 0{\cdot}05$; paired t test) with a conditioning intensity of 0% compared to −10%. *B*, effect of intensity of motor cortical test stimulus on the amount of suppression seen with a constant intensity (−10%) of conditioning shock over the cerebellum. Upper traces show raw data (average of 8 trials each) from one subject elicited in relaxed FDI muscles by three different intensities of motor cortical stimulation. Control responses are on the left, responses conditioned by a stimulus over the cerebellum (conditioning–test interval = 6 ms) are on the right. Note that the responses have been plotted at different gains. The actual size of responses can be gauged from the 0·5 mV calibration bar given for each pair of responses. The lower graph shows the average (±1 S.D.) time course of suppression in four subjects with three different sizes of control response: less than 2 mV peak-to-peak (●), 2–5 mV peak-to-peak (▲), and more than 5 mV peak-to-peak (○). When the control response was larger than 5 mV, there was an average less suppression at 5, 6 and 9 ms than with test responses of < 2 mV or 2–5 mV peak-to-peak (paired t test; $P < 0{\cdot}05$).

control responses averaged 2–5 mV in size, or less than 2 mV in size. In contrast, when the control responses were greater than 5 mV in amplitude, there was significantly less suppression at intervals of 5, 6 and 9 ms.

The effect of the intensity of the test shock was also investigated in active muscles, but only using a conditioning–test interval of 5 ms and a conditioning shock intensity of −10%. The magnetically evoked EMG responses in the active FDI muscle were reduced to 36±12, 46±25, and 89±9% (mean±S.D.) of their control size when the size of the control response was less than 2, 2–5 and more than 5 mV respectively. In the following section of the results, most studies were performed with control responses in FDI produced by magnetic stimulation of the sensorimotor cortex of about 1 mV in size.

Effects of changing the polarity of stimulation over the cerebellum

We attempted to produce a more localized conditioning stimulus over the cerebellum by placing one of the electrodes at the mid-line on the inion, whilst the other was maintained on either the left or the right side of the base of the skull. We shall refer to this as hemispheric stimulation. The four possible combinations of hemispheric stimulation were studied. Cathode in the mid-line, with anode on the right (R+, M−; right hemispheric anodal), anode in the mid-line with the cathode on the right (R−, M+; right hemispheric cathodal), cathode on the mid-line with the anode on the left (L+, M−; left hemispheric anodal), and anode on the mid-line with the cathode on the left (L−, M+; left hemispheric cathodal). Typical results from one subject using the four different cerebellar stimulation montages are shown in Fig. 4*A*. The responses were evoked in the right relaxed FDI by magnetic stimulation of the left sensorimotor cortex, and the intensity of the hemispheric conditioning stimuli over the cerebellum was the same in all cases (−10%). The conditioning–test interval was 5 ms. Right hemispheric anodal stimulation over the cerebellum was most effective in suppressing the EMG response evoked by activation of left sensorimotor cortex. All other three polarities of conditioning stimulation produced no, or virtually no suppression. The mean data from four subjects for all four forms of hemispheric stimulation over the cerebellum is shown in Fig. 4*B*. The time course of suppression using right hemispheric anodal stimulation was similar to the typical pattern of suppression in relaxed muscles described above. The other three forms of hemispheric stimulation over the cerebellum did not produce significant suppression of the EMG response evoked by activation of left sensorimotor cortex at any of the time intervals studied. In two subjects we investigated the best polarity for suppressing responses in the left FDI muscle by magnetic stimulation of right sensorimotor cortex. Maximal suppression was seen when the anode of the cerebellar conditioning shock was on the left (and cathode on the right).

We also investigated whether the polarity of the stimulus over the cerebellum influenced the amount of suppression in active muscles. The reason for this was the suggestion (see previous section) that 'cerebellar' suppression in the active state reflected two separate processes: an early period of suppression (conditioning–test interval 5–6 ms) similar to that operating in the relaxed state, and a later suppression (conditioning–test interval 12–15 ms) caused by some other mechanism. In these experiments we placed the stimulating electrodes over the cerebellum in their usual

position either side of the mid-line on both mastoids and randomized the polarity of stimuli between anode on the right and anode on the left. As in the relaxed state, responses in the right FDI evoked by magnetic stimulation of left sensorimotor cortex were maximally suppressed at short intervals when the anode was placed on

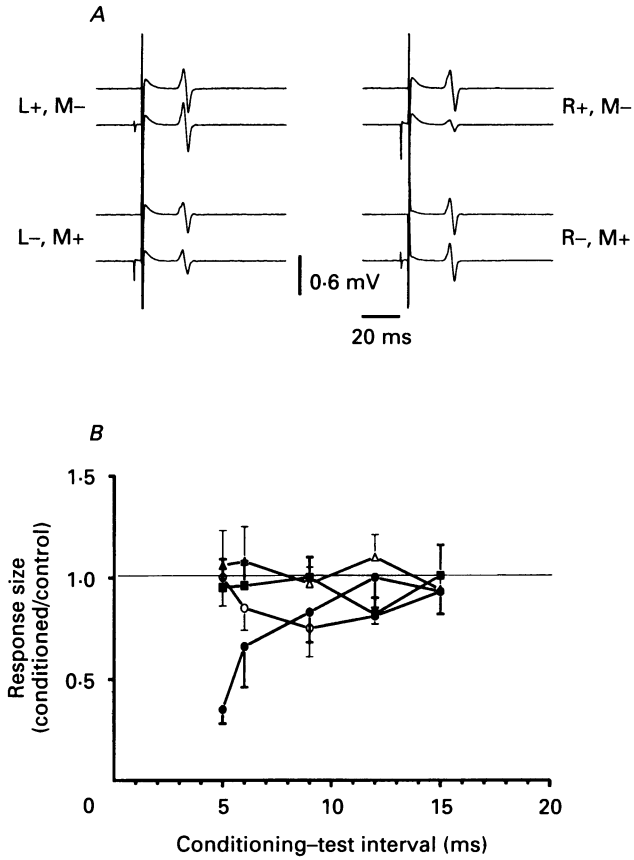

Fig. 4. Effect of hemispheric stimulation over the cerebellum (+ = anode, − = cathode, with electrodes over inion in mid-line (M) and mastoid to left (L) or right (R)) on EMG responses in the relaxed right FDI muscle evoked by magnetic stimulation of the left sensorimotor cortex. The top panels (*A*) show raw data from one subject at a conditioning–test interval of 5 ms. The four pairs of traces in *A* consist of a control response (above) to sensorimotor cortical stimulation alone, and a conditioned response (below) with hemispheric stimulation over the cerebellum preceding sensorimotor activation. Each trace is the average of eight trials. Note that the size of the control response is slightly different in each of the four conditions. The intensity of conditioning stimulation was set to be −10%. The lower panel (*B*) shows the time course of suppression at five different conditioning–test intervals in four subjects (mean ± 1 S.D.). All four stimulation polarities are shown: anode on the left, cathode on the mid-line (*A*, top left; *B*, ○); cathode on the left, anode on the mid-line (*A*, bottom left; *B*, ■); anode on the right, cathode on the mid-line (*A*, top right; *B*, ●); cathode on right, anode on mid-line (*A*, bottom right; *B*, △). At conditioning–test intervals of 5 ms suppression was only seen when the anode was on the right (paired *t* test; $P < 0{\cdot}05$).

the right side of the head. However, at conditioning–test intervals of 12 and 15 ms, suppression was seen with either polarity of stimulus (Fig. 5).

We conclude that the best short latency (conditioning–test intervals of 5–6 ms) suppression of EMG responses evoked by magnetic stimulation of sensorimotor

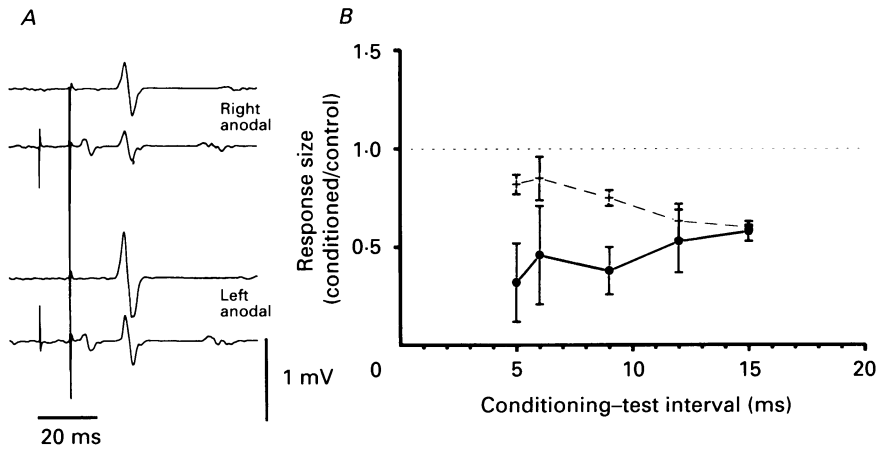

Fig. 5. Comparison of the effect of two different polarities of conditioning shock over the cerebellum on EMG responses in the right FDI produced by magnetic stimulation of the left sensorimotor cortex. This experiment was performed with the target muscle pre-activated with a voluntary contraction of about 5% of maximum force. The conditioning shock was either right anodal (upper trace in *A*; ● in *B*) (anode on right mastoid, cathode on left mastoid), or left anodal (lower trace in *A*; + in B) (anode on left, cathode on right). *A* shows average (of 8 trials) results from one subject using a conditioning–test interval of 12 ms. The two pairs of traces show control responses above and conditioned responses below. Note that in this example the cerebellar stimulation intensity was just above the threshold (approximately 2%) for direct muscle activation leading to a small EMG response which can be seen in the lower trace of each pair. At this timing, the control response was suppressed equally well whether the anode was on the right or left of the head. The graph in *B* plots the time course of suppression (mean ± 1 S.D.) from 4 subjects. Both polarities of stimulation gave suppression at conditioning–test intervals of 12 and 15 ms. In contrast, at conditioning–test intervals of 5, 6 and 9 ms right anodal conditioning shocks gave more suppression than left anodal shocks (paired *t* test at each timing; $P < 0{\cdot}05$).

cortex is seen when the anode of the conditioning stimulus over the cerebellum is placed ipsilateral to the muscle under investigation and contralateral to the sensorimotor cortex stimulated. However, the late phase of suppression (12 and 15 ms) seen in active muscles, is relatively insensitive to the polarity of the conditioning shock.

Changing the vertical position of the conditioning electrodes

The best inhibitory effects of the conditioning shock over the cerebellum were seen when the electrodes were in the standard position on the base of the skull on both mastoids. An example of this from a single subject is shown in Fig. 6 using a conditioning stimulus intensity of 10% (of the maximum output of the stimulator) below motor threshold. If the electrodes were fixed 2 cm above or below this position,

and the conditioning stimulus intensity kept constant, then no suppression of the cortical response was apparent at conditioning–test intervals of 5 ms. In contrast to this lack of effect at an interval of 5 ms, suppression of cortically evoked test responses was observed at conditioning–test intervals of 12 and 15 ms (not shown) when the conditioning electrodes were placed in the lower position.

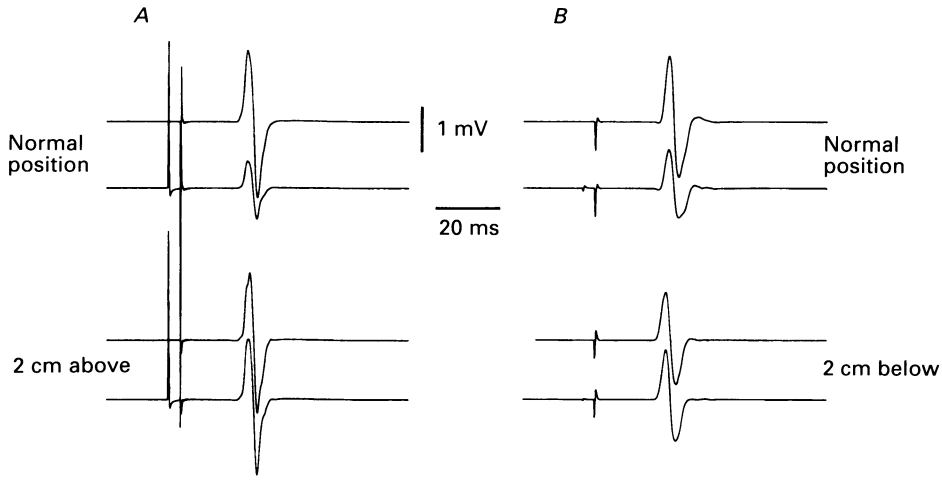

Fig. 6. Effect of changing the position of the conditioning stimulating electrodes over the cerebellum (with the anode on the right mastoid and cathode on the left mastoid) on suppression of EMG responses in the relaxed right FDI muscle evoked by magnetic stimulation of the left sensorimotor cortex. Conditioning stimulation intensity was −10% for all responses. Each pair of traces shows an average (of 8) control responses (upper trace), and responses conditioned by a cerebellar stimulus given 5 ms earlier (lower trace). Note that the control response varies slightly in size from experiment to experiment. The left traces (*A*) show the effect of moving both conditioning electrodes 2 cm above the normal position, traces on the right (*B*) show the effect of moving the electrodes 2 cm lower than their normal position. Moving the conditioning electrodes up or down prevents suppression of the response to sensorimotor cortical stimulation.

Comparison between magnetic and electrical test shocks over the motor cortex

All the data described above were obtained using a magnetic test shock over the sensorimotor cortex. In order to provide some evidence as to whether the suppression we had been observing was occurring at a cortical or a spinal level, we compared the effect of the conditioning shock over the cerebellum on EMG responses evoked by electrical as opposed to magnetic cortical stimulation of cerebral motor cortex (see Discussion). In order to ensure a relatively pure direct activation of pyramidal tract neurones by electrical cortical stimulation, we performed these experiments in active muscles using a just suprathreshold anodal electric stimulation over the sensorimotor cortex. A typical example of the results is shown in Fig. 7. This figure shows that a conditioning shock over the cerebellum at an intensity of about 0% was capable of inhibiting the EMG response to magnetic stimulation of sensorimotor cortex with conditioning–test intervals of 5, 6 and 15 ms. In contrast, the same conditioning shock over the cerebellum had no effect on the responses to electrical stimulation of the sensorimotor cortex with conditioning–test intervals of 5 and 6 ms. It should be noted that, as usual, the onset latency of the control responses to magnetic cortical

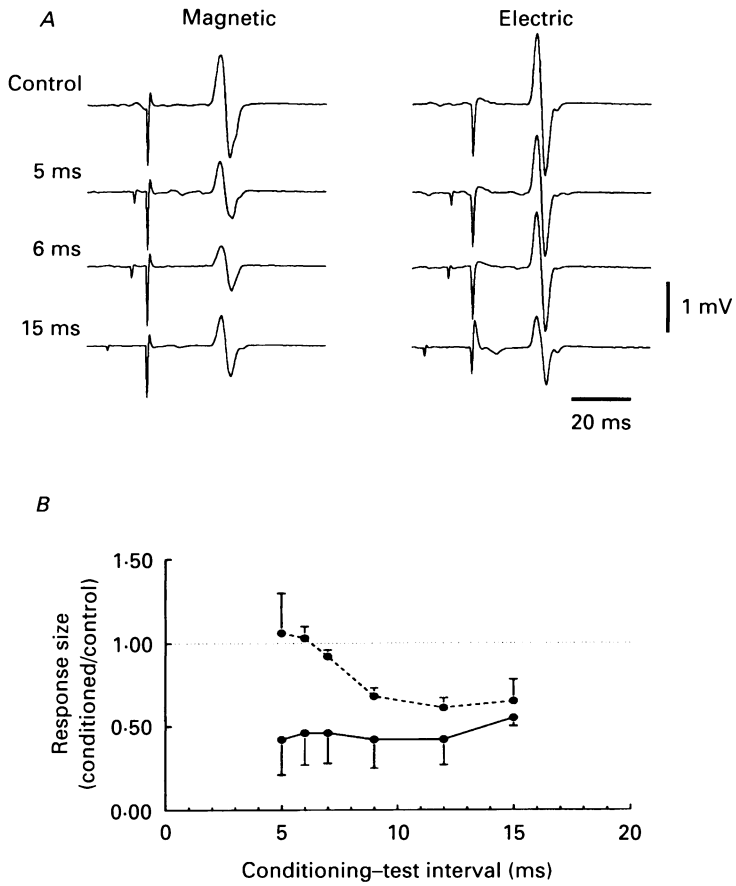

Fig. 7. Comparison between effects of stimulation over the cerebellum (anode on right mastoid, cathode on left mastoid just below motor threshold intensity) on responses evoked in active right FDI muscle by magnetic or anodal electrical stimulation of left sensorimotor cortex. *A*, shows raw data from one subject. Each trace is the average of eight trials; traces on the left illustrate responses to a magnetic test shock, those on the right to an electric test shock. The top trace shows the size of the control response to the test stimulus given alone; the traces beneath were obtained with a conditioning shock given 5, 6 or 15 ms earlier. The response to an electric test shock is suppressed only at 15 ms. (Note that when electric shocks were used, the conditioning–test interval was 2 ms longer than when magnetic test shocks were given. This compensates for the difference in latency of EMG responses evoked by the two forms of stimulation. See text.) *B*, mean (±1 S.D.) time course of suppression in three subjects of the responses evoked by electric (●----●) or magnetic (●——●) stimulation of the sensorimotor cortex. The intensity of the conditioning shock over the cerebellum was adjusted to be just below motor threshold. Stimulation over the cerebellum inhibited the responses to magnetic stimuli at all conditioning–test intervals. In none of the three subjects was there any inhibition of the responses to electric test shocks at conditioning–test intervals of 5, 6 or 7 ms ($P > 0{\cdot}05$ in paired t tests on the data of each individual). Significant inhibition of the electrically elicited responses was observed at one or more of the later intervals (9, 12 or 15 ms) in every subject. (Note that as in *A*, when electrical test shocks were given, the conditioning–test interval was adjusted to compensate for the difference in latency of magnetic and electrically evoked EMG responses.)

stimulation was about 2 ms longer than the onset latency of the responses to electrical stimuli (Day, Dressler, Maertens de Noordhout, Marsden, Nakashima, Rothwell & Thompson, 1989). In order to compensate for this, the actual conditioning–test intervals when electric stimulation of the sensorimotor cortex was used were 7, 8 and 17 ms. Mean data from three subjects are shown in Fig. 7*B*. In this figure, the responses were obtained using conditioning stimuli of motor threshold. This graph shows the usual suppression of EMG responses evoked by magnetic stimulation of sensorimotor cortex. Although this size of conditioning shock did not suppress electrically evoked test responses produced by electrical stimulation of sensorimotor cortex at conditioning–test intervals of 5 and 7 ms, there was significant suppression at 9, 12 and 15 ms. As noted above, this differential effect of a relatively high intensity conditioning shock over the cerebellum at early and late intervals indicates that the suppression at these timings is produced by different mechanisms.

DISCUSSION

We have shown in a previous report that high voltage electrical stimulation across the base of the skull is capable of activating descending motor pathways at about the level of the pyramidal decussation (Ugawa *et al.* 1991). In this paper we have found that stimuli sub-threshold for any such direct effect on descending motor pathways are nevertheless capable of decreasing the size of EMG responses evoked by magnetic stimulation of the cerebral sensorimotor cortex. The effect is large, and has been seen in all subjects so far studied. The time course of this suppression suggests that it consisted of two phases: an early phase with conditioning–test intervals of 5 or 6 ms, and a later phase appearing at conditioning–test intervals of 12 and 15 ms. The differences between these two phases are summarized in Table 1.

Mechanisms of the early phase of suppression

The early phase of suppression at conditioning–test intervals of 5–6 ms was seen in all subjects with relatively low intensities of conditioning shocks over the cerebellum. A stimulus such as this would have activated many cutaneous afferents from the back of the head and it is possible that the resulting cutaneous afferent volley was responsible for the observed effects (e.g. Day, Dressler, Maertens de Noordhout, Marsden, Nakashima, Rothwell & Thompson, 1988). However, the fact that the polarity and site of stimulation was critical suggests that the effect was due to stimulation of a specific CNS structure rather than to some non-specific inhibition of reflex origin. Two questions arise: which structure is responsible for producing the suppression of EMG responses evoked by magnetic stimulation of sensorimotor cortex, and where does the suppression take place?

We suggest that electrical stimulation over the base of the skull reduces the size of responses evoked by magnetic stimulation of the sensorimotor cortex by suppression at the level of the cerebral cortex. The argument is as follows: both electrical and magnetic cerebral stimuli are thought to produce EMG responses by activation of the corticospinal tract. If the suppression seen in the present experiments was at a spinal level, the responses to both electrical and magnetic cerebral stimulation should be affected equally. Since only magnetically evoked

responses were suppressed, this explanation is unlikely to be true. There is a difference in latency between responses to the two forms of stimulation, and Day *et al.* (1989) have suggested that the latency difference arises because electrical cerebral stimuli activate pyramidal tract neurones directly whereas magnetic cerebral stimuli activate the same pyramidal tract neurones trans-synaptically. An alternative

TABLE 1. Comparison of suppression of motor responses to stimulation of the sensorimotor cortex following conditioning stimulation over the cerebellum at conditioning–test intervals of 5 and 6 ms, and at intervals of 12 and 15 ms

	5 and 6 ms	12 and 15 ms
Effect of voluntary activation of target muscle	Inhibition present whether active or relaxed	Inhibition usually only seen in active muscle
Best polarity of conditioning shock	Anode ipsilateral to target muscle	Anodal or cathodal stimulation equally effective
Best position of conditioning electrodes	At level of inion	Lower than inion
Magnetic *vs.* electric test shocks	Only magnetically evoked responses inhibited	Magnetic and electrically evoked responses equally affected

hypothesis put forward by Edgley, Eyre, Lemon & Miller (1990), based on experiments performed on the macaque monkey, is that both forms of scalp stimulation activate the corticospinal neurones directly; the electrical stimulus at a deep level and the magnetic stimulus more superficially at the initial segment. Both hypotheses, however, predict that a change in cortical excitability would influence the response to a magnetic stimulus, whether it activates the corticospinal neurones trans-synaptically or at the initial segment, but have little effect on the response to a low intensity electrical stimulus which activates the axons of corticospinal neurones at the nodes. Both Day, Riescher, Struppler, Rothwell & Marsden (1991), and Datta, Harrison & Stephens (1989) have used this argument previously to localize excitability changes to the level of the sensorimotor cortex during the stretch reflex and during different types of voluntary movement. It is likely, therefore, that in the present experiments suppression of the magnetically induced EMG response occurred at a cerebral cortical level.

What structures are activated by the conditioning stimulus in order to produce this cortical suppression? One possibility is that long ascending or descending pathways are activated in the brain stem. Antidromic firing of pyramidal tract axons could cause cortical inhibition via extensive recurrent collaterals (e.g. Stefanis & Jasper, 1967). Similarly, it is possible to imagine that the orthodromic stimulation of certain classes of afferent fibre could produce motor cortical inhibition. Ugawa *et al.* (1990) have shown that electrical stimulation at the base of the skull can indeed activate descending motor pathways. However, there are three reasons why this seems an unlikely explanation for the present results. First, the stimulus intensity of the conditioning shock was set to be below threshold for producing direct EMG activation through stimulation of descending motor pathways. Second, even if a very small number of fibres, incapable of producing detectable EMG response were activated by a low intensity stimulus, it is known that the polarity of stimulation is unimportant in activating brain stem motor pathways. In contrast, in the present

experiments, the polarity of stimulation was highly important in producing the cortical suppression. Third, the best point for evoking direct motor tract stimulation was 2 cm lower than the best point found for producing cortical suppression in the present experiment.

In view of the importance of the polarity of stimulation (anodal stimulation over the cerebellum produces greatest short latency suppression of EMG responses evoked by magnetic stimulation over the opposite sensorimotor cortex), and the results of hemispheric stimulation over the cerebellum (unilateral anodal stimulation was most effective), it seems likely that the conditioning shock activated a lateralized structure. The cerebellar hemispheres lie close to the stimulating anode. In cats, surface anodal stimulation of the cerebellar cortex selectively activates Purkinje cells by direct depolarization (Granit & Phillips, 1957). This causes inhibition of deep cerebellar nuclei (Ito, Yoshida, Obata Kawai & Udo, 1970). In the monkey, deep cerebellar nuclei are known to be tonically active when the animal is awake and at rest (Thach, 1968). Since the dentato-thalamo-cortical pathway is known to be excitatory (Allen & Tsukahara, 1974), Purkinje cell activation would therefore cause disfacilitation of motor cortex. The polarity of stimulation in the present experiment is consistent with this explanation. An anode on the right side would cause cerebellar disfacilitation of the left motor cortex and suppression of evoked EMG responses in muscles on the right side of the body.

The time of onset of cortical suppression might also be appropriate for a cerebello-thalamo-cortical pathway. Inhibition of EMG responses evoked by magnetic stimulation of the cerebral cortex began 5 ms after the cerebellar conditioning shock. If we suppose (1) that the inhibition is directed to sensorimotor cortical pyramidal tract cells, and (2) that it takes about 1 or 2 ms for scalp magnetic stimulation to activate these pyramidal tract cells (Day *et al.* 1989), then the maximum time available for cerebello-cortical inhibition is 6–7 ms. In the cat, Purkinje cells discharge 0·7 ms after anodal stimulation (Granit & Phillips, 1957). Conduction time to the cerebellar nuclei is about 1·0 ms (Ito *et al.* 1970), time from cerebellum to thalamus is 1·3 ms (Uno, Yoshida & Hirota, 1970), and the time from thalamus to motor cortex about 2–3 ms (Phillips & Porter, 1977). Thus, the time in the cat from stimulation of the cerebellum to a change in motor cortical excitability is 5–6 ms. Given that the distance is longer in man, our estimate of 6–7 ms seems a reasonable possibility. For comparison, a pathway of similar length, with two interposed synapses, is that from the dorsal columns to the sensorimotor cortex. Sensory evoked potential measurements of the N14–N20 interval suggest that the conduction time through this pathway is of the order of 6 ms (see Jones, 1982).

Mechanisms of the later phase of suppression

Suppression of EMG responses evoked by electrical stimulation of sensorimotor cortex by stimulation over the cerebellum at conditioning–test intervals of 12 and 15 ms was seen only when the subject voluntarily pre-activated the target muscle. In contrast to the earlier suppression, responses to both electrical and magnetic stimulation of the sensorimotor cortex were equally inhibited. Following the reasoning above, this suppression may have been produced by spinal mechanisms, such as postsynaptic inhibition of α-motoneurones, or presynaptic inhibition of the terminals of corticospinal tract fibres. Many structures may have been activated by

such a relatively large shock, such as cerebellar outflow pathways to descending systems originating in the brain stem, cervical nerve roots and pain receptors around the stimulating electrodes. All could produce inhibition by spinal mechanisms, and it would be unwise to speculate further on which mechanism may be involved. The important point is that this relatively non-specific inhibition which probably operates at a spinal level is quite different from the earlier suppression, which we have proposed to involve cerebellar suppression of structures in the cerebral cortex.

In conclusion, it is our hypothesis that in the present experiments electrical stimuli across the base of the skull were capable of producing short latency suppression of motor cortex through an effect on cerebellar structures. In active muscles, a later suppression of EMG activity was also provoked by stimuli at the same site, but this was thought to be due to a non-specific suppression at the level of the spinal cord.

We should like to thank Mr Richard Bedlington for his invaluable assistance in building and maintaining much of the equipment used in the present experiments. Data collection programs had been kindly modified to suit our purposes by Dr J. G. Colebatch. Dr Ugawa was supported by a Wellcome Japanese Training Fellowship. Special thanks are due to Dr T. Britton and Dr P. Brown for help in the initial experiments of this series.

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