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Transcranial magnetic double stimulation: influence of the intensity of the conditioning stimulus

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Abstract

The influence of stimulus parameters on compound muscle potentials evoked by transcranial magnetic double stimulation was systematically investigated. Two magnetic stimulators were discharged via a figure-of-eight-shaped magnetic coil (outer diameter of each circular coil, 7 cm) over the left hemisphere, 6 cm lateral to Cz, using a Bistim interface. Recordings were made from the right first dorsal interosseus muscle. In experiment I, in 12 healthy volunteers the intensity of the conditioning subthreshold stimulus was varied from 0 to 100% of the relaxed motor threshold at an interstimulus interval of 1 ms. In experiment II, interstimulus intervals of 1, 3 and 5 ms were used to investigate the effect of conditioning stimuli of 3 fixed intensities. Maximal reduction of the amplitude of motor evoked potentials was found at a conditioning stimulus intensity of 65% of the relaxed motor threshold (and at an interstimulus interval of 1 ms). Because intensities of the conditioning stimulus higher than 65% reduced amplitudes of motor evoked potentials less effectively than at this intensity, refractoriness of pyramidal neurons can be ruled out as the main mechanism contributing to the observed inhibition. Activation of inhibitory interneurons by intensities lower than is necessary to activate pyramidal neurons is discussed as a possible mechanism for the inhibitory effects evoked by transcranial magnetic stimulation. © 1997 Elsevier Science Ireland Ltd.

Keywords: Conditioning stimulus; Inhibitory interneurons; Stimulus parameters; Transcranial double magnetic stimulation

1. Introduction

Since the introduction of transcranial magnetic stimulation of the human cortex by Barker et al. (1985a,b,c), this method has become an important tool in the assessment of the pyramidal tract (Mills and Murray, 1985; Hess et al., 1986; Meyer and Zentner, 1990; Murray, 1991). Recently, apart from the excitatory effects leading to the activation of spinal motor neurons by repetitive firing of pyramidal neurons (Day et al., 1989), inhibitory effects induced by magnetic stimuli have gained increasing attention. Initially double stimulation was performed with two coils and the effects caused by conduction over associative or commissural fibres, such as the corpus callosum, analysed (Cracco et al., 1990; Ferbert et al., 1992). With the Bistim module, two magnetic stimuli can be applied through the same coil. Studies by Rothwell et al. (1991) and Kujirai et al. (1993) have shown that transcranial magnetic stimuli below the threshold for the activation of spinal alpha motoneurons is able to inhibit responses to above-threshold magnetic stimuli applied a few milliseconds later. The nature of this presumably intracortical inhibitory effect is not known, but an intracortical inhibitory mechanism has been proposed. Initial results concerning the influence of drugs on cortical excitability have been obtained (Ziemann et al., 1995; Inghilleri et al., 1996; Schulze-Bonhage et al., 1996). This present study was designed to investigate the influence of conditioning subthreshold magnetic stimuli in more detail and to shed some light on possible mechanisms underlying inhibition due to magnetic stimuli.

2. Methods and materials

Eighteen normal volunteers, 10 females and 8 males, aged 23–49 years (median 26 years), were examined.

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Two additional subjects were examined but had to be excluded because their motor threshold was too high. None of the subjects suffered from epilepsy and none had an aneurysm clip or a cardiac pacemaker.

In the first experiment the intensity of the conditioning stimulus was varied using a standard interstimulus interval (ISI) of 1 ms in 14 subjects. In the second experiment the conditioning stimulus was varied using additional delays of 3 and 5 ms in 7 subjects, 3 of whom had taken part in the first experiment as well as in a separate session.

EMG responses were recorded from the relaxed right first dorsal interosseus muscle (FDI) with the active silver surface electrode over the motor point and the reference electrode on the metacarpophalangeal joint. Transcranial magnetic double stimulation was performed using two Magstim 200 stimulators. The magnetic stimulators generated a monophasic magnetic field pulse with an increasing time of 100 μs and a maximum duration of 1 ms. The two magnetic stimulators were connected to the same coil through a Bistim module, with which the ISI could be varied between 1 and 1000 ms. We used a figure-of-eight-shaped magnetic coil, with each loop of the coil having an outer diameter of 7 cm (Hallett et al., 1994). The peak magnetic field of the stimulus was 1.75 T below the centre of this coil. However, the Bistim module lead to an approximately 22% reduction of the peak magnetic field.

For recordings of the right FDI, the centre of the coil was positioned on the left side of the skull about 6 cm lateral to Cz. Then the optimal coil position with lowest threshold was found. We constructed a special device to fix the coil on the head of the subject, who sat in a comfortable chair with a headrest. This device consisted of two belts (4 cm wide, 100 cm long) which were connected crosswise at their centres. Additionally, there were two small belts for the exact adjustment of the orientation of the coil, which had to be tangential to the head. The belts were made of a stable non-stretchable material; Velcro fasteners were used for fixation.

Responses were recorded by a Nicolet Pathfinder II. The EMG machine was controlled with self-developed programs in the programming language Mecol. EMG signals were filtered between 15 and 8000 Hz. The sensitivity of the amplifier was set to 5 mV and the sweep time was 120 ms.

The individual relaxed motor threshold (Rossini et al., 1992) of each subject was determined by applying single stimuli to the motor cortex. The subject was asked to relax the FDI completely. Possible muscle activity was controlled by a loudspeaker. The field intensity was changed until a block of 16 ensuing stimuli evoked detectable muscle responses with an amplitude of about 0.1 mV with a 50% probability (Caramia et al., 1991). During this procedure the second magnetic stimulator was switched to the stand-by mode. We have expressed stimulus intensity relative to relaxed threshold. After each experiment the relaxed motor threshold was controlled without having changed the position of the coil over the entire experiment.

2.1. Experiment I

In this exploratory experiment we investigated the influence of a conditioning stimulus on a test stimulus by varying the intensity of the conditioning stimulus at as ISI of 1 ms. The test stimulus was set to 110% of the subject's relaxed threshold. The intensity of the conditioning stimuli was varied between 10 and 100% of the threshold.

The 14 different stimulus conditions can be seen in Table 1. In a few subjects we increased the number of stimulus conditions from 14 to 21. In those cases, 9 instead of 6 different conditioning stimulus intensities could be tested. We defined the 14 stimulus conditions by a computer program (see Table 1). In two separate conditions the test stimulus was applied on its own in order to have a quick measure for consistency of the responses during the test. Extensive statistics were performed outside the experimental session. Double stimuli consisting of one of the 6 conditioning stimuli and the test stimulus following an ISI of 1 ms were tested. Because of the exploratory character of this test the intensities of the conditioning stimuli were defined separately for each subject.

2.2. Experiment II

In this experiment the intensities of the conditioning stimuli were set to 95, 65 and 30% of the subject's threshold (relaxed). ISIs of 1, 3 and 5 ms were tested. The basic structure of this program consisted of a block of 14 different conditions, which were applied pseudorandomly as in experiment I. Each condition was repeated 8 times (8×14 stimulus conditions in total). The 14 stimulus conditions can be seen in Table 2.

For each experiment the 8 responses of each condition were superimposed. Because of the frequency of absent potentials (the maximal amount of inhibition), which had

Table 1

Experiment 1: the 14 different experimental conditions

Experimental condition	Explanation
1	ts
2	cs1
3	cs1 + ts
4	cs2
5	cs2 + ts
6	cs3
7	cs3 + ts
8	ts
9	cs4
10	cs4 + ts
11	cs5
12	cs5 + ts
13	cs6
14	cs6 + ts

The test stimulus (ts) was set to 110% of the relaxed threshold and remained unchanged, whereas the conditioning stimulus (cs) had different intensities (cs1, cs2, etc.) between 0 and 100%.

Table 2

Stimulus conditions and results (median, minimum, maximum (μV)) for experiment II

Stimulus condition	Explanation	Median	Minimum	Maximum
1	Test stimulus (t) alone (110% T)	703	332	898
2	Same as above	859	469	1387
3	Conditioning stimulus 95%T (cr95) alone	0	0	469
	Double stimuli: cr95+t			
4	ISI 1 ms	684	410	1367
5	ISI 3 ms	918	332	2070
6	ISI 5 ms	938	508	2207
7	Conditioning stimulus 65%T (cr65) alone	0	0	0
	Double stimuli: cr65 + t			
8	ISI 1 ms	0	0	391
9	ISI 3 ms	0	0	586
10	ISI 5 ms	527	332	703
11	Conditioning stimulus 30%T (cr30) alone	0	0	0
	Double stimuli: cr30 + tr			
12	ISI 1 ms	859	566	1309
13	ISI 3 ms	742	586	1641
14	ISI 5 ms	801	469	1602

T, the subject's individual motor threshold for the relaxed muscle (%T is the percentage of the subject's individual threshold for the relaxed muscle). Interindividual medians of experiment II were calculated from the intraindividual medians of each subject for each stimulus condition (see also Fig. 2).

a different basic distribution from those present, we analysed the results additively with respect to the frequency of the responses present. In the first part of the evaluation, the single responses, the number of present and absent muscle responses was counted. Then the peak-to-peak amplitude of the present muscle responses was measured automatically. The results were analysed with the non-parametric Wilcoxon matched pairs signed rank test for conjuncted two trial problems using the statistical program SPSS (SPSS, 1986) with a significance level of $P = 0.05$.

3. Results

3.1. Experiment I

The aim of the first experiment was to test the influence of conditioning stimuli of different intensities on the response to a following test stimulus.

Fig. 1 shows the results of all 12 subjects in a superimposed mode. The amplitudes of responses to double stimulation are given as intraindividual averages in percent of the test response, which was set to 100%. The intensity of the conditioning stimulus was varied from 10 to 100% of the subject's threshold. Different intensities of conditioning stimuli were used for different subjects to cover the whole range of 10–100%. To calculate an interindividual average, we clustered the data in 15% steps. Motor evoked potentials of smallest amplitude were found when double stimulation was performed with conditioning stimuli of 69–55% of the threshold. The ranges of 100–85% and smaller than 39% of the threshold showed only very small differences in response to double stimulation in comparison to the control condition. The most pronounced effect was seen with conditioning stimuli of medium intensity, whereas stronger or less intense conditioning stimuli had less effect. Graphically the results show a U-shaped curve (Fig. 1).

3.2. Experiment II

In experiment I a subthreshold stimulus was able to reduce the amplitude of a muscle response to a suprathreshold test stimulus applied at an ISI of 1 ms. The question arose as to whether or not the inhibition of the evoked motor potential is the result of refractoriness of cortical pyramidal cells due to the conditioning stimuli. Therefore we examined the dependence of this effect on the ISI in the second

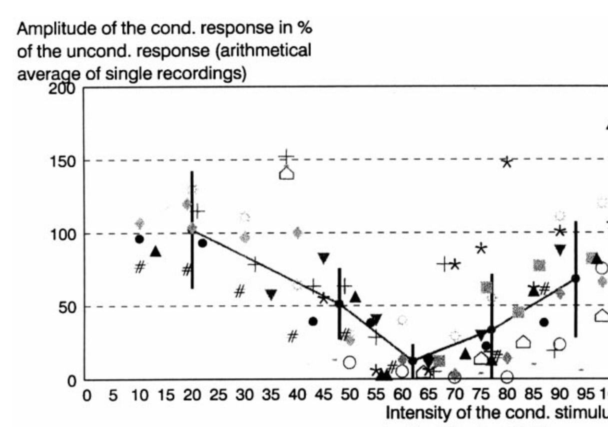

Fig. 1. Experiment I: results of all 12 subjects. The amplitude of the motor evoked potential with double stimulation as percentage of the motor evoked potential after the test stimulus alone as a function of the intensity of the conditioning stimulus (% of threshold) is shown. The intensity of the conditioning stimulus was varied between 0 and 100%T. For a grand average (black line) the data were clustered in 15% segments of stimulus intensity. Marked inhibition can be seen with conditioning stimuli of medium intensity (69–55%T).

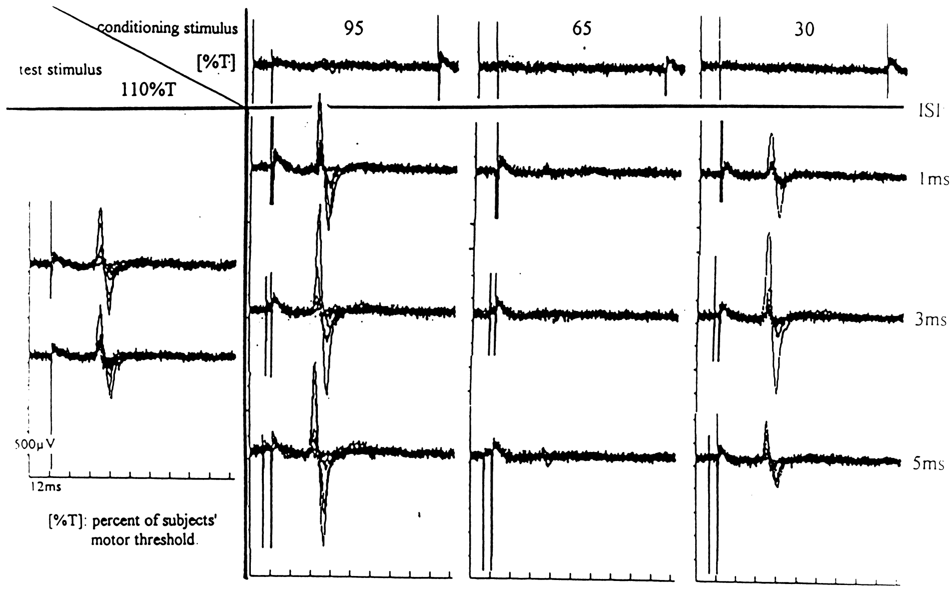

Fig. 2. Experiment II: results of a representative subject are presented. In the top line different intensities of the conditioning stimuli are shown. In the left column the responses to the suprathreshold test stimulus on its own are shown. In the 3 right columns double stimuli with ISIs of 1, 3 and 5 ms are shown. Nearly complete inhibition can be seen with conditioning stimuli of 65%T. The effect wears off with more and with less intensive conditioning stimuli.

experiment. We chose intensities of the conditioning stimulus of 95, 65 and 30% of threshold, each of them applied 1, 3 and 5 ms prior to the test stimulus. Seven normal subjects were examined. The test stimulus was again set to 110% of threshold.

Fig. 2 shows the results of one representative subject. Inhibition of control potentials can be observed in the dependence of the intensity of the conditioning shock (as in experiment I) and of the ISI. The 8 responses of each stimulus condition are superimposed. In the left column two separate blocks of superimposed responses to a test stimulus given on its own are depicted. In the upper line, responses to the conditioning stimuli of different intensities alone are shown. The corresponding double stimuli with delays of 1, 3 and 5 ms follow from top to bottom. Responses conditioned by stimuli of 95% are of similar amplitude to the control response, irrespective of the ISI. No inhibition can be shown with these conditioning stimuli just beyond motor threshold. With conditioning stimuli of 65% the test responses are nearly completely inhibited with each of the ISIs tested. Here the maximum effect was observed; the effect wears off with conditioning stimuli of 30%. Thus, no marked inhibition of the test response was shown with conditioning stimuli of very low intensity.

In Table 2 the interindividual medians of the different intraindividual medians with their maxima and minima are shown. Conditioning stimuli with 65% of threshold have the most pronounced effect with the smallest range, even at an ISI of 5 ms. Using the median of the data, the quantitative amount of inhibition is also considered. In many of the subjects no muscle response was elicited following double stimuli, presumably due to marked inhibition. In performing statistics, it has to be considered that the amplitude of these responses is not equal to zero; it has some kind of distribution around zero that differs from the distribution of present responses. Therefore mainly the number of responses present and the number of responses missing, irrespective of their amplitude, was taken into account for statistical analysis. We used the non-parametric Wilcoxon matched pairs signed rank test for conjuncted two trial problems. The number of muscle responses that occurred under each condition was compared with the number of responses under the control conditions. Table 3 shows that there is maximum inhibition with conditioning stimuli of 65% of threshold. For the other intensities no constant inhibition for all ISIs can be found. Fig. 3 shows the pooled data for all 7 subjects.

4. Discussion

In all 18 subjects investigated, an inhibition of muscle responses to suprathreshold test stimuli was found by applying subthreshold conditioning stimuli 1, 3 and 5 ms in advance. This is in line with results obtained by Rothwell et al. (1991) and Kujirai et al. (1993) who first observed this effect. This inhibition was shown to depend on the interstimulus interval as well as on the intensity of the conditioning stimuli. We observed the strongest inhibition with conditioning stimuli of moderate intensity; with stronger or weaker conditioning stimuli the effect decreased.

Kujirai et al. (1993) found the best suppression with conditioning stimuli of 0.7–0.9 times the relaxed motor threshold in a smaller number of subjects. As this technique has found broad application since then, we addressed the issue of optimal stimulus conditions in a larger number of sub-

Table 3

Results of the Wilcoxon matched pairs rank test for not conjuncted two trial problems (*P*-values)

Conditioned stimulus (%T)	ISI (ms)		
	1	3	5
95	0.0431	0.1088	0.5930
65	0.0180	0.0180	0.0277
30	0.1775	0.0277	0.0431

In addition to the amplitude measurements, we calculated the number of missing responses that occurred through inhibition after double stimulation. Missing responses in the control and the double stimulus condition were compared using the Wilcoxon matched pairs signed rank test for not conjuncted two trial problems (experiment II). The number of responses to the unconditioned stimulus is tested against the number of responses to double stimulation; for example, a ts on its own produced significantly more responses (regardless of their amplitudes) than a ts preceded by a cs of 65%T due to complete suppression of the responses in the latter condition.

jects and a wider range of stimulus intensities. The stimulus intensity producing maximal inhibition in our study was somewhat lower (65% of the relaxed motor threshold). For future studies we would suggest using a stimulus intensity of 65–70% of the relaxed motor threshold. This intensity is clear below the threshold intensity for the mildly preinnervated muscle. The motor threshold for the active muscle is usually 10–20% below that of the relaxed muscle.

The Magstim 200 generates a monophasic magnetic pulse with the coil current reaching its maximum after 0.1 ms. The pulse has a total duration of some 1 ms (Jalinous, 1991). As it has a slow asymptotic decay the coil current reaches less than 10% of its peak within 0.6 ms. Therefore the residual field after 1 ms is minimal and interstimulus intervals of 1 ms can be used without significant influence on the second stimulus.

Could partial refractoriness of pyramidal tract neurons also account for the reduced muscle responses to the second stimulus? If refractoriness of pyramidal tract neurons was the major factor responsible for a reduced motor evoked potential amplitude to the suprathreshold stimulus, the degree of inhibition would be expected to increase in parallel with the intensity of the conditioning stimulus applied. The latter expectation could be backed by results showing that higher stimuli produce more peaks in the post-stimulus time histogram than weaker ones (Day et al., 1989). A parallel increase of the inhibitory effect alone with the increasing intensity of the conditioning stimulus, however, was not found in our study. In contrast, only when stimulating at low intensities of conditioning stimuli did the degree of inhibition increase when higher intensities were applied. At stimulus intensities above 65% of motor threshold, increasing the intensity of the conditioning stimulus would decrease the inhibition observed. Thus, refractoriness of pyramidal neurons is very unlikely to be the only explanation for reduced motor responses after conditioned stimuli. Further arguments against refractoriness as the sole cause of inhibition can be derived from epidural recordings with electrical double stimulation showing that the amplitude of the volley onto the second stimulus is reduced by only 50% in the ISI of 1 ms and recovers completely in the ISIs of 3 and 5 ms (Inghilleri et al., 1989, 1990).

Regarding the site where subthreshold stimuli exert their inhibitory effect, it has been shown that magnetic conditioning stimuli inhibit only the effect of magnetic but not electrical anodal test stimuli. In addition, conditioning stimuli at intensities used in this study have been shown not to change H reflex amplitudes (Rothwell et al., 1991; Kujirai et al., 1993). In contrast, subthreshold electrical anodal stimuli could be shown to produce facilitation of the H reflex (Cowan et al., 1983, 1986; Rothwell et al., 1984). Moreover, Davey et al. (1994) found inhibitory effects of subthreshold magnetic stimuli on both agonist and antagonist muscles. Although projections of pyramidal tract neurons to spinal inhibitory interneurons exist (Jankovska et al., 1976), all these findings are not easily explained by a spinal mechanism underlying inhibition, but suggest an intracortical inhibitory effect of subthreshold magnetic stimuli. In contrast, as electrical stimuli have their site of action at least in part at the axon hillock or deeper in the white matter, spinal effects are common. Facilitation of the H reflex can only be produced by suprathreshold magnetic stimuli (Nielsen et al., 1993; Nielsen and Peterson, 1995). Task-related changes in the H reflex could only be observed in magnetic but not in electrical stimulation.

Electrical stimulation excites predominantly deeper lying structures, such as pyramidal tract axons (Patton and Amassian, 1954, 1960; Amassian et al., 1987; Day et al., 1987a,b, 1989; Rothwell et al., 1987). In contrast, magnetic stimulation activates mainly intracortical intraneurons. Pyramidal tract neurons are probably activated only indirectly (Caramia et al., 1988; Amassian et al., 1989; Rothwell et al.,

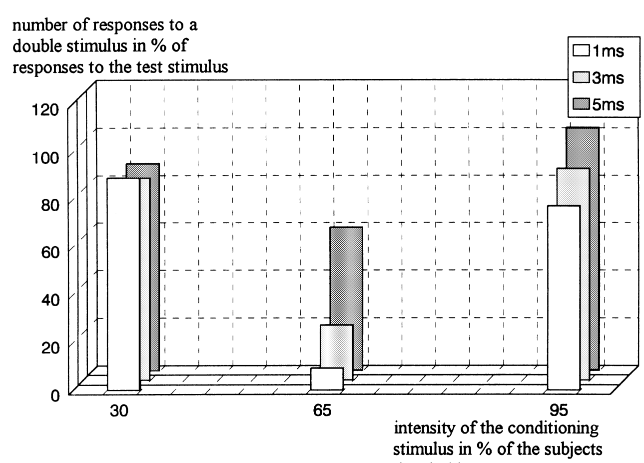

Fig. 3. Pooled data of experiment II. The number of present responses to a double stimulus in percent responses to the test stimulus as a function of the intensity of the conditioning stimulus (%T) is shown for the ISIs 1, 3 and 5 ms. As in experiment I, a U-shaped curve can be seen. The most pronounced inhibition is present with a conditioning stimulus of 65%T and an ISI of 1 ms.

1989). Because of this effect on cortical interneurons, responses to magnetic stimulation can be influenced by various conditioning stimuli either of the same site of the brain or from other sites in the contralateral hemisphere or the cerebellum (Datta et al., 1989; Rothwell et al., 1991; Ugawa et al., 1991; Ferbert et al., 1992; Davey et al., 1993; Flament et al., 1993; Kujirai et al., 1993). Also modulatory effects of a conditioning peripheral sensory input onto the excitability of the motor cortex are thought to be of cortical origin (Mariorenzi et al., 1991). From the mechanism of action of magnetic fields, transcranial magnetic stimulation is supposed to excite primarily horizontally orientated fibres in the upper and middle cortical layers. Epstein et al. (1990) found a maximum of the electrical field induced by magnetic stimulation on the crown of the gyrus near the level of the grey-white junction. Thus, excitatory afferents to the distal dendritic spines as well as inhibitory interneurons terminating on dendritic shafts arc to be expected to discharge in responses to a transcranial magnetic stimulus. At subthreshold levels, the integration of these afferents makes pyramidal tract neurons fire at a rate not sufficient to activate spinal alpha motor neurons. Day et al. (1991) found excitation of motor evoked potentials with magnetic but not with electrical transcranial stimuli using a peripheral muscle stretch as conditioning stimulus. Deletis et al. (1992) observed facilitation of muscle evoked potentials using an electrically induced peripheral afferent volley as conditioning stimulus with an electrical as well as a magnetic transcranial test stimulus. This discrepancy may be due to stimulation of different intracortical pathways using different experimental paradigms.

The results of our study could, however, be explained by suggesting a lower or similar threshold for the activation of inhibitory neurons as compared to excitatory afferents by magnetic stimuli. If this was the case, inhibitory neurons would be activated when low stimulus intensities are chosen. Inhibition at spinal and muscular level would increase as long as the recruitment of inhibitory interneurons outbalances the increase in excitatory afferent input to pyramidal tract neurons. At some intensity, activation of excitatory afferents would supervene that of inhibitory neurons, and the inhibitory effect of the conditioning stimulus would decline again (Fig. 4). Thus, the U-shaped curve of inhibition with respect to the intensity of magnetic conditioning stimuli shown in Fig. 1 could be explained. A similar effect with simultaneous activation of excitatory and inhibitory afferents to pyramidal tract neurons has been attributed to intracortical, possibly GABAergic, inhibitory interneurons (Krnjevic et al., 1966a,b,c; Chagnac-Amitai and Connors, 1989; Jacobs and Bonoghue, 1991). Such afferents to pyramidal tract neurons might lead to maximal inhibition, for example during the presence of GABA-A induced chloride currents induced by cortical interneurons such as basket cells (DeFelipe et al., 1986; Gatter et al., 1987).

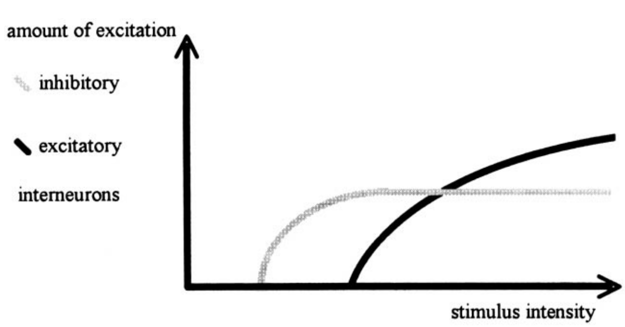

Fig. 4. Hypothetical curve of recruitment of inhibitory and excitatory intracortical interneurons as a function of stimulus intensity. With low stimulus intensities inhibitory interneurons are activated. With increasing stimulus intensity the activation of inhibitory interneurons is saturated, whereas excitatory ones start to be active. With more intensive stimuli the activation of excitatory interneurons predominates, and the stimulus is then suprathreshold.

Experimental evidence for the activation of inhibitory interneurons exists in the case of electrical cortex stimulation at single cell level. Creutzfeld et al. (1956) observed inhibition of tonically firing cortical pyramidal cells to epicortical anodal stimulation even at intensities insufficient to increase the firing rate in part of the cortical neurons. From the relative contribution of I and D waves to the activity in the pyramidal tract, magnetic stimulation has been shown to activate pyramidal neurons only indirectly at the intensities applied in our study (Day et al., 1989; Thompson et al., 1991). The preferential activation of superficial horizontally orientated fibres by magnetic stimulation may thus give the effect of a preponderance of inhibitory interneurons in the upper cortical layers over excitation at certain intensities, as suggested by the results of this study. This mechanism would also explain the results of Davey et al. (1994) showing that low subthreshold intensities of transcranial magnetic stimuli reduced voluntary tonic muscle activity.

In summary, the results of this study provide evidence against refractoriness of pyramidal tract neurons as the main mechanism underlying the inhibitory effects of subthreshold conditioning stimuli. The results may thus serve a better understanding of the mechanisms involved as discussed above. In addition, the study provides information regarding the optimal intensities and interstimulus intervals to apply when using the transcranial double magnetic stimulation paradigm.

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