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RESEARCH ARTICLE

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Changes in the cortical silent period after repetitive magnetic stimulation of cortical motor areas

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Abstract The physiological mechanisms underlying the lengthening of the silent period (SP) evoked in active upper limb muscles by repetitive transcranial magnetic stimulation (rTMS) of the motor areas were studied in normal subjects. rTMS was delivered at frequencies of 1 Hz, 2 Hz, 3 Hz, 5 Hz, 10 Hz and 15 Hz and at an intensity just above the motor threshold (Mth). Trains delivered at 2 Hz, 3 Hz, 5 Hz, 10 Hz and 15 Hz significantly prolonged the cortical SP, whereas stimuli at 1 Hz did not. The first few stimuli in the train already prolonged the duration of the cortical SP: the other stimuli did not prolong it further. Motor evoked potentials remained unchanged in amplitude regardless of the frequencies and number of stimuli in the train. The effect of intensity of stimulation was studied by delivering trains at suprathreshold intensity (110% and 140% of Mth) and 3-Hz frequency and with trains at subthreshold intensity and 5-Hz and 10-Hz frequencies. SPs had a longer duration at 140% than at 110% Mth intensity. SPs elicited by 3-Hz trains at 140% and 110% Mth intensity lengthened to a similar extent over the course of the train. rTMS delivered at an intensity below Mth did not evoke cortical SPs over the course of the trains. Repetitive stimulation of the cortical forearm motor areas prolonged the duration of the cortical SP in forearm flexor muscles but failed to evoke SPs in the biceps muscles. The maximal single stimulus intensity and less intense stimuli delivered in short trains evoked SPs of similar duration. We propose that rTMS delivered in trains at frequencies higher than 1 Hz and at suprathreshold intensity prolongs the cortical SP mainly through temporal summation of inhibitory interneurones.

Keywords Magnetic stimulation · Motor cortex · Repetitive stimulation · Silent period · Human

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Introduction

Repetitive transcranial magnetic stimulation (rTMS) allows stimulation of cortical motor areas. In the upper limb muscles, the effects of rTMS on the muscle-evoked potentials (MEPs) depend on the number of stimuli in the train and on the frequency and intensity of stimulation. MEPs in response to trains delivered at a frequency of 5 Hz and an intensity of 120% of motor threshold (Mth) increase progressively in size (Pascual-Leone et al. 1994). In an earlier study, we showed that the mechanisms responsible for facilitating the MEPs in hand and forearm muscles during trains of cortical magnetic stimuli originate within the cortex (Berardelli et al. 1998). On the other hand, the size of the MEPs is unchanged if rTMS is delivered while the subjects voluntarily contract the muscles (Berardelli et al. 1999). Presumably, the voluntary contraction that normally facilitates the MEP (see review by Rothwell et al., 1991) masks the facilitatory effect of rTMS. As the frequency and intensity of rTMS is increased, the behavior of MEPs becomes more complex (Pascual-Leone et al. 1994; Jennum et al. 1995).

As well as changing MEPs, rTMS influences the inhibitory phenomena produced by cortical stimulation. In a recent paper we reported that, over the course of trains delivered at frequencies of 3 Hz and 5 Hz and an intensity just above Mth, the cortical silent period (SP), recorded in the forearm muscles during a voluntary contraction, progressively lengthened in duration (Berardelli et al. 1999). The increased duration of the cortical SP did not depend on changes in the preceding MEPs.

Our aim in this paper was to study further the physiological mechanisms underlying the lengthening of the cortical SP observed during rTMS. To see whether the

prolonged SP is related to a specific rTMS frequency, we tested in normal subjects the effects produced by trains of stimuli delivered at lower and higher frequencies than those previously tested (Berardelli et al. 1999). We investigated whether the lengthening of the SP depends on the number of stimuli in the trains and on the stimulation intensity. We also compared the duration of the SP evoked by rTMS with the SP duration produced by single magnetic stimuli.

rTMS could prolong the duration of the SP either by activating a larger number of intracortical inhibitory interneurones (spatial summation) or by activating the same number of interneurones more efficiently (temporal summation). To address this question, we examined whether rTMS delivered over the forearm motor area also activates adjacent cortical areas.

Materials and methods

Subjects

Eight normal subjects (age range 24–45 years) participated in the study. All the subjects gave their informed consent and the study was approved by the local ethics committee.

Stimulation

rTMS was delivered with a Cadwell high-speed magnetic stimulator (max power 225 J/pulses). A figure-of-eight water-cooled coil was placed over the forearm motor area of the left hemisphere. Mth was calculated at rest using the lowest intensity that produced 5 MEPs with a peak-to-peak amplitude of at least 100 μV in ten trials. Magnetic stimulation was also delivered with a Magstim 200 device able to generate a maximum magnetic field of 2.5 T with a large round coil (outer diameter of 14 cm) placed over the vertex.

Recording

The electromyographic (EMG) activity was recorded with a pair of surface disk electrodes placed over the forearm flexor (FF) muscles or biceps muscle. EMG signals were amplified and filtered by a Digitimer D 160 amplifier, with a time constant of 3 ms and low-pass filter set at 1 kHz, and a personal computer through a 1401 plus AD laboratory interface (Cambridge Electronic Design) and analysed off-line. Subjects exerted a moderate voluntary contraction of the FF muscle (about 30% of maximum muscle activity) monitored with audiovisual feedback.

Measurements of MEPs and SPs

Amplitude of MEPs was measured peak to peak. The duration of cortical SPs was measured from the end of the MEPs to the return of 80% EMG activity. For each subject, data for MEP amplitudes and SP durations were measured from single traces and then averaged. All data were expressed as mean ± SE.

Experimental paradigm

Effects on SPs of rTMS at different frequencies

In eight subjects, trains of 20 magnetic transcranial stimuli were delivered at frequencies of 1 Hz, 2 Hz, 3 Hz, 5 Hz, 10 Hz and 15 Hz and at an intensity of 110% Mth. The intertrain interval was 1–2 min. For each frequency, four trains of repetitive stimuli were delivered and the SP and MEP responses were collected and then averaged.

Effects on SPs of rTMS at different intensities

To investigate the effects of subthreshold repetitive stimuli, trains of 40 magnetic transcranial stimuli were delivered at frequencies of 5 Hz and 10 Hz and at an intensity of 90% Mth (five subjects). The effects of high stimulation intensity were tested with trains of 10 stimuli delivered at 3 Hz and at 140% of Mth (four subjects). We selected this frequency and delivered trains of only 10 stimuli to reduce the unpleasant effects of high-intensity rTMS. The effects on SP duration produced by trains delivered at 140% and 110% Mth intensity were compared.

rTMS and SPs in forearm and biceps muscles

Trains of 10 stimuli were delivered at 5 Hz and 10 Hz over the forearm motor area, and the EMG activity was recorded simultaneously from the forearm flexor and biceps muscles (four subjects). For each subject, the intensity of stimulation was chosen to obtain SPs only in the forearm and not in the biceps muscles and varied from 100% to 110% of the Mth.

Single magnetic stimulation

Four single stimuli delivered with the Cadwell high-speed stimulator were collected and then averaged to collect control SPs. In four subjects, the SP was also recorded after single magnetic pulses delivered at maximal intensity (2,400±5% of Mth) through the Magstim D200 stimulator with the round coil placed over the vertex. Four responses were collected.

Statistical analysis

For each frequency, differences among MEP sizes were tested with a multivariate two-way ANOVA, with repeated measures for the factors frequency and number of stimuli. A two-way ANOVA for repeated measures was used for comparing the SP duration obtained after the last stimulus of the train with a single control stimulus, at all frequencies. At 1-Hz, 2-Hz and 3-Hz frequencies, two-way ANOVA with repeated measures for the factors frequency and number of stimuli was used to evaluate differences in SP duration obtained over the course of trains of 20 stimuli. At frequencies higher than 3 Hz (15 Hz, 10 Hz and sometimes 5 Hz) subsequent magnetic artifacts of the train masked the SP, making it impossible to measure the duration. Differences among SP durations obtained during trains of 11 stimuli delivered at a rate of 3 Hz and at intensities of 110% and 140% Mth were tested with a two-way ANOVA with repeated measures for the factors intensity and number of stimuli. For post hoc analysis we used Tukey's honest-significant-difference (HSD) test. A paired *t*-test was used to compare the last SP obtained after 140% intensity trains and a single control SP recorded after stimulation at maximum intensity of the Magstim stimulator. *P*-values less than 0.05 were considered to indicate significance. All the data are expressed as mean ± SE.

Results

Effects of rTMS on MEP size

rTMS delivered at suprathreshold intensity elicited MEPs whose amplitude remained unchanged over the course of

the trains, regardless of the number of stimuli and frequency. ANOVA showed neither a main effect nor a significant interaction (for frequency, F=1.5; for number of stimuli, F=0.7). rTMS trains delivered at 140% Mth intensity elicited larger-sized MEPs than trains at 110%. During the four trains of eleven stimuli given at 140% Mth intensity, MEPs remained unchanged in amplitude (for number of stimuli, F=2). For all F-values, P>0.05.

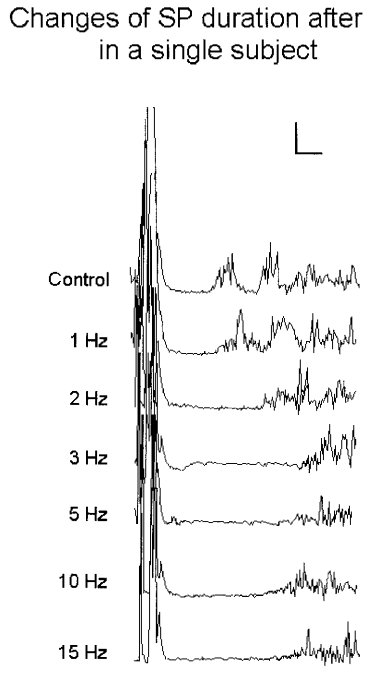

Fig. 1 Duration of the control silent period (*SP*) and of the last SP after suprathreshold repetitive transcranial magnetic stimulation (*rTMS*; 20 stimuli) delivered at 1-Hz, 2-Hz, 3-Hz, 5-Hz, 10-Hz and 15-Hz frequencies in a representative subject. Note the increase in the SP duration at frequencies higher than 1 Hz. Each trace is the mean of four rectified trials. Horizontal calibration is 40 ms and vertical calibration is 0.5 mV

Effects of rTMS at different frequencies on the duration of cortical SPs

The first SPs elicited by trains delivered at 1 Hz, 2 Hz and 3 Hz had a similar duration (F=0.9, P=0.4). At 1 Hz, 2 Hz and 3 Hz, ANOVA showed a main effect of the factors Frequency (F=4.2, P=0.035) and Number of stimuli (F=15.1, P<0.001), with a significant two-way interaction (F=6.7, P<0.001); post hoc analysis showed significant changes in SP duration at 2 Hz and 3 Hz, but not at 1 Hz (1 Hz: F=0.7, P=0.8; 2 Hz: F=14.7, P<0.001; and 3 Hz: F=10.0, P<0.001). The duration of the SPs significantly increased after the sixth stimulus of the 2-Hz train and after the fourth stimulus of the 3-Hz train. At neither frequency did it increase further after the sixth stimulus of train (Figs. 1, 2). Stimulus frequencies higher than 3 Hz made it impossible to measure the duration of the SP after individual stimuli in the train, because the subsequent stimuli coincided with the end of the SP. For this reason, we compared the data for duration of the control SP and the SP obtained by the last stimulus of 1-Hz, 2-Hz, 3-Hz, 5-Hz, 10-Hz and 15-Hz trains. ANOVA disclosed a main effect for the factor Number of stimuli (F=28, P<0.001) and a significant two-way interaction of Frequency by Number of stimuli (F=10.1, P<0.001). Post hoc analysis revealed that for 2-Hz, 3-Hz, 5-Hz, 10-Hz and 15-Hz trains, but not for 1-Hz trains, the last SP had a significantly longer duration than the control SP (Figs. 1, 3).

Effects on SPs of rTMS at different intensities

Subthreshold rTMS evoked no SPs after the first stimulus of the train and no SPs over the course of the train of 40 stimuli. The first SP elicited by rTMS trains delivered at 140% Mth intensity had a longer duration than the first SP elicited by trains at 110% (138±14.4 ms at 140%

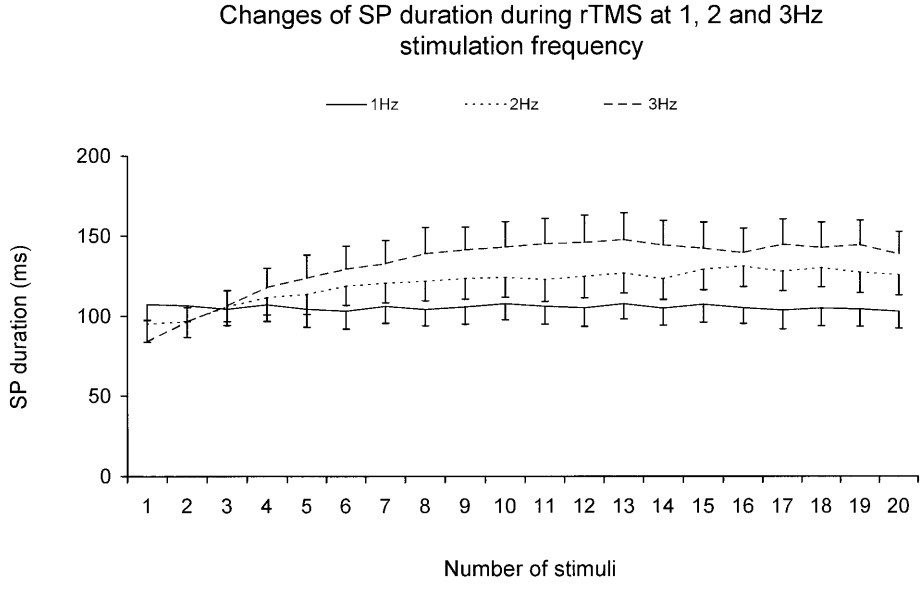

Fig. 2 Changes in the duration of the SP over the course of rTMS delivered in trains of 20 stimuli at frequencies of 1 Hz (*continuous line*), 2 Hz (*dashed line*) and 3 Hz (*broken line*). Each point corresponds to the mean ± SE

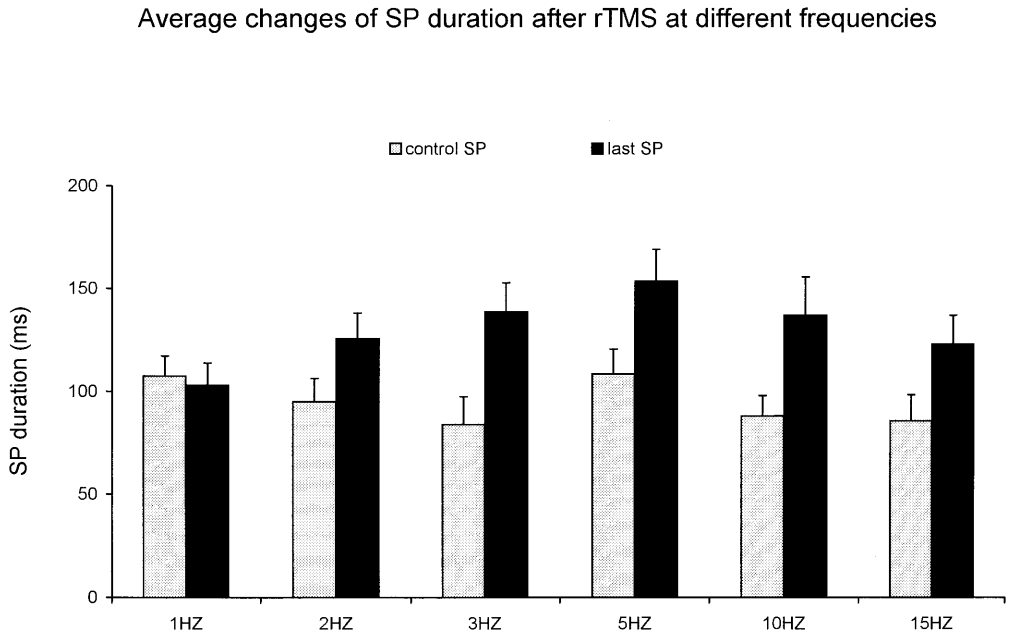

Fig. 3 Comparison between the duration of the SP obtained after the last stimulus of the rTMS trains (*black columns*) and that obtained after a single magnetic stimulus (*grey columns*), at all frequencies studied. Data correspond to mean ± SE

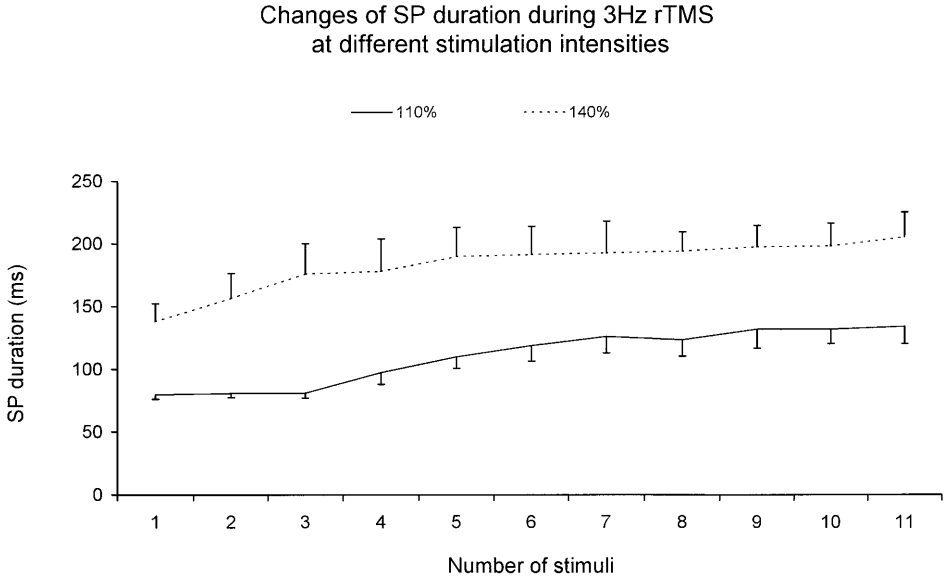

Fig. 4 Changes in the duration of the SP over the course of rTMS trains (11 stimuli) delivered at 3-Hz frequency and intensities 140% (*dashed line*) and 110% (*continuous line*) of motor threshold. Each point corresponds to the mean ± SE

vs 80±3.5 ms at 110%; P=0.07). SPs elicited by both stimulus intensities lengthened to a similar extent over the course of the train. ANOVA showed a main effect of the factors Intensity (F=27.3, P=0.01) and Number of stimuli (F=19.0, P<0.001), but no significant two-way interaction (F=1.1, P=0.38; Fig. 4).

rTMS and SPs in forearm and biceps muscles

rTMS delivered at 5-Hz and 10-Hz frequencies significantly increased the duration of the SPs recorded from the forearm muscles. At 5 Hz, the first SP lasted 31.5±3.3 ms and the last 42.5±4.5 ms (for factor Number of stimuli, F=5.01, P=0.0005). At 10 Hz, the first SP lasted 28.4±3.7 ms and the final SP lasted 42.8±4 ms (for factor Number of stimuli, F=7.4, P=0.05). Simultaneous recordings of EMG activity over the biceps and forearm muscles showed that neither the first nor subsequent stimuli in the trains evoked SPs in the biceps (Fig. 5).

Comparison between the duration of the cortical SP after single high-intensity magnetic stimulation and after rTMS

The SP after single magnetic stimuli delivered at maximal intensity (240±5% Mth) and the last SP after rTMS delivered in trains of 11 stimuli at 140% had a similar

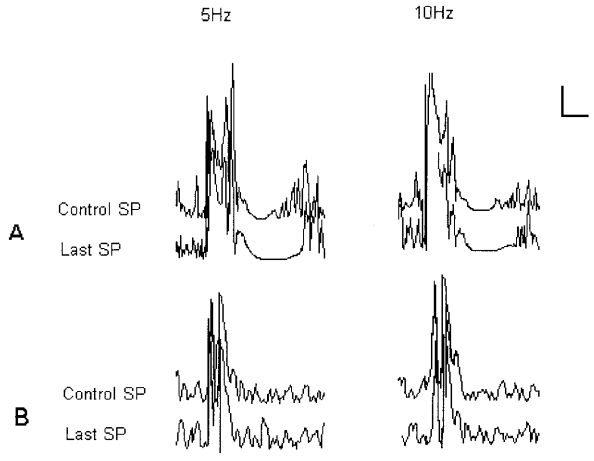

Fig. 5A, B Duration of the control SP and of the last SP after suprathreshold rTMS (ten stimuli) in forearm (**A**) and biceps muscles (**B**) delivered at 5-Hz and 10-Hz frequencies in a representative subject. rTMS prolonged the duration of the cortical SP in forearm flexor muscles but failed to evoke SPs in the biceps muscles. Each trace is the mean of five rectified trials. Horizontal calibration is 25 ms and vertical calibration is 0.5 mV

mean duration (205±19.8 ms vs 197±26.2 ms; P=0.65 by Student's paired t-test).

Discussion

Our study showed that rTMS delivered over the cortical motor areas in trains at different frequencies and at an intensity just above Mth in normal subjects lengthened the duration of the cortical SP. But it invariably left MEPs unchanged in amplitude. These findings confirm our previous observation that rTMS modifies SPs and MEPs independently (Berardelli et al. 1999).

We now report for the first time the changes in the duration of the cortical SP induced by varying the frequency, number of stimuli and intensity of rTMS. The SP began to lengthen at frequencies higher than 1 Hz and the increase remained evident at 3 Hz. Higher frequencies (5, 10 and 15 Hz) failed to prolong it further. Equally important in changing the duration of cortical SPs were the number of stimuli delivered. Already after the fourth stimulus in a train delivered at 3 Hz and after the sixth stimulus in a 2-Hz train the SP had significantly lengthened; its duration then reached a plateau. The lengthening of the SP during rTMS had no relation to stimulus intensity.

The SP is almost entirely generated by cortical mechanisms. Many studies have investigated the physiological mechanisms underlying the SP evoked by non-repetitive TMS. Studying normal subjects, Fuhr et al. (1991), Inghilleri et al. (1993), Roick et al. (1993) and Taylor et al. (1996) provided evidence that the activation of cortical inhibitory interneurones plays a major role in generating the cortical SP. Peripheral changes may intervene, but do so only in the early part of the cortical SP. Support for the cortical origin comes also from changes in the duration of the SP seen in patients with cortical lesions (Uozumi et al. 1991; Haug et al. 1992; von Giesen et al. 1994; Inghilleri et al. 1998). In humans, the observation that SP changes can also be seen in patients affected by basal ganglia diseases (Priori et al. 1994a; Ikoma et al. 1996), and in normal subjects after the administration of dopaminergic and GABAergic drugs (Priori et al. 1994b; Inghilleri et al. 1996) support the idea that the thalamocortical connection plays a role in generating the SP. The duration of the cortical SP in humans is similar to the long-lasting cortical neuronal inhibition (more than 200–250 ms) induced by single electrical stimulation of the cat brain surface (Krnjevic et al. 1964). Electrical stimulation of the cortex probably activates the inhibitory basket cells widespread in layers III, IV and V of the cortex, and the inhibition is probably caused by the release of GABA (Krnjevic et al. 1964).

During rTMS the cortical SP could have been prolonged by a decrease in the excitatory drive produced by repetitive stimulation. This is unlikely, however, because the size of the MEPs, which reflects the excitatory drive, did not decrease over the course of the trains.

The lengthening of the cortical SP after rTMS could be explained by at least two mechanisms. The first is a more efficient inhibition generated, during rTMS, by the same intracortical inhibitory interneurones through a temporal summation mechanism. Our data show that the lengthened duration of SPs evoked by rTMS is evident only at frequencies higher than 1 Hz. At this frequency, the interstimulus interval is too long to allow temporal summation of inhibitory post-synaptic potentials, which last approximately 250 ms (Dreifuss et al. 1969). When rTMS is delivered at a frequency of 2 Hz or higher, the intervals between stimuli (500 ms at 2 Hz or less) approach the duration of the inhibitory post-synaptic potentials. Subsequent stimuli can therefore generate a temporal summation of post-synaptic potentials, thus producing a long-lasting inhibitory action and ultimately more efficient inhibition. To prolong SPs significantly, trains at 2 Hz (500-ms interstimulus intervals) need six stimuli, whereas trains at 3 Hz (333-ms interstimulus intervals) need only four. With trains delivered at higher frequencies (5 Hz, 10 Hz and 15 Hz), the duration of the SP after individual stimuli in the train cannot be tested, as explained above.

The second hypothesis is that rTMS activates a larger number of cortical inhibitory interneurones. To address this question, using simultaneous recording of the SPs in forearm flexors and biceps muscles, we investigated whether focal rTMS, delivered over the forearm flexor cortical areas, activates interneurones impinging on cortical cells targeting nearby muscles (biceps). Although at cortical level the representation of the hand muscles is interspersed in a discontinuous mosaic form with that of the more proximal muscles, studies with TMS mapping of muscle representation in human motor cortex showed a somatotopic progression on the scalp of proximal to distal muscles along a postero-medial to antero-medial

axis (Wassermann et al. 1992). In our experiments, although rTMS elicited a prolonged SP in forearm muscles, it elicited no SPs in the biceps muscles. This suggests that rTMS did not produce a widespread activation of cortical interneurones in adjacent cortical areas (spatial summation from lateral to medial cortical motor area). Therefore, at the frequencies and intensities used here, rTMS probably elicits prolonged SPs through local mechanisms of temporal summation. A contribution of a progressively larger number of inhibitory interneurones, recruited at a local scale, impinging on the cortical cells targeting the forearm muscles, cannot be excluded.

Moreover, the present results imply also that rTMS produces different effects on MEPs and SPs. Previous investigators (Pascual-Leone et al. 1994; Berardelli et al. 1998) showed that the rTMS-induced facilitation of the MEP outlasts the duration of the trains, whereas the effects on SPs do not (Berardelli et al. 1999). Pascual-Leone et al. (1994) observed that, with the coil situated over the optimal scalp position for activating distal upper limb muscles, rTMS led to a spread of facilitation, inducing progressively larger MEPs in distant muscles. Conversely, we have now found that focal rTMS, at the frequencies and intensities used here, did not produce a spread of activation to inhibitory interneurones in adjacent cortical areas. All these data show that rTMS produces different effects on the inhibitory and excitatory responses.

The prolonged cortical SP after trains of magnetic stimulation in human subjects is difficult to compare with the inhibitory phenomena elicited by stimulation of presynaptic cortical neurones in animal experiments. In these experiments prolonged stimulation of the cortex (up to 10 min) at a stimulus frequency between 1 and 3 Hz induces long-term reduction of activities of excitatory cortical synapses. It probably does so by acting on excitatory cortical synapses (Dudek and Bear 1992; Mulkey and Malenka 1992; Hess and Donoghue 1996). In contrast, TMS produces an SP by exciting cortical inhibitory interneurones (Rothwell et al. 1991; Inghilleri et al. 1993; Roick et al. 1993).

The changes seen in the duration of the SP after we varied the frequency of stimulation provide useful information that might add to our knowledge of the physiological features of the interneuronal net mediating the SPs. The cortical SPs induced by rTMS do not habituate; their prolonged duration reaches maximum after few stimuli; and, as we have previously shown, the lengthening does not outlast the train (Berardelli et al. 1999). These physiological features resemble those of the SP1 component of the masseter inhibitory reflex. The SP1 originates from activation not of a polysynaptic but of an oligosynaptic circuit (Cruccu et al. 1984). Moreover, contrary to the habituation of the polysynaptic reflexes after repetitive stimulation of peripheral nerves, for example the masseter reflex SP2 (Cruccu et al. 1984), the cortical SP during rTMS becomes longer rather than shorter. If the masseter reflex and cortical SP can be compared, then our findings support the concept that the circuit underlying the cortical SP is a simple oligosynaptic inhibitory network.

To see how the intensity of stimulation influences the SP, we studied the effects of lower and higher intensity rTMS. We found that subthreshold rTMS did not lead to progressive recruitment of forearm muscle SPs. rTMS therefore prolongs the SP when the SP is already present from the beginning of the train. This finding is in line with the hypothesis discussed above that cortical inhibitory interneurones profit from temporal rather than from spatial summation. Using suprathreshold rTMS, we compared trains of magnetic stimuli (11 shocks) at a 3-Hz frequency and at 110% Mth with trains delivered at the same frequency and with higher suprathreshold intensity (140% of Mth). The higher stimulation intensity produced longer SPs. The increased duration at higher intensities is a well-known phenomenon (Inghilleri et al. 1993), related to the recruitment of a larger number of cortical inhibitory cells. In the present experiments, rTMS trains delivered at 140% and 110% Mth intensity elicited a similar percentage increase in the lengthening of each SP in the train. Hence, the magnitude of cortical facilitation does not depend on the number of inhibitory cells first recruited. Our experiments specified that the last SPs after short trains delivered at 140% Mth intensity and the SP evoked by a single shock at maximal intensity (240% Mth) had a similar mean duration. These experiments imply that single shocks delivered at maximum stimulator output and stimuli delivered in trains at low intensities elicit similar inhibition.

In conclusion, rTMS at frequencies from 1 to 15 Hz prolongs the duration of the cortical SP. This phenomenon is therefore not specific for a single rTMS frequency. The lengthening of the SP during rTMS depends on the frequency of stimulation as well as on the number of stimuli in the train. It has no relation to stimulus intensity. As the physiological mechanism underlying the lengthening of the cortical SP, we propose that rTMS produces a more efficient inhibition mainly through temporal summation of inhibitory interneurones.

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