Medical Journal of the
Islamic Republic of Iran

Volume 11
Number 4
Winter 1376
February 1998

MEDIAN NERVE STIMULATION POTENTIATES THE MUSCLE RESPONSES TO TRANSCRANIAL MAGNETIC STIMULATION

A.R. JAMSHIDI FARD AND E.M. SEDGWICK*

*From the Department of Physiology, Arak University of Medical Sciences, Arak, Islamic Republic of Iran, and the *Department of Clinical Neurological Sciences, University of Southampton, Southampton General Hospital, Southampton, SO9 4XY, U.K.*

Abstract

Motor responses evoked by transcranial magnetic stimulation (TMS) or transcranial electrical stimulation (TCS) can be facilitated by a prior conditioning stimulus to an afferent nerve. Two facilitation periods are described; short (SI), when the nerve stimulus is given near 0 to 10 ms after cranial stimulation, and long (LI), when nerve stimulation is given 25-60 ms before the cranial stimulation.[1] These facilitation periods were examined in more detail in 10 normal consenting subjects. The study has ethical committee approval. Focal cortical TMS was applied contralaterally by a figure-of-eight coil over the "hot spot" for the right hand muscles and the strength adjusted to be just above twitch threshold for the relaxed muscle. Conditioning electrical stimuli were applied to the right median nerve at the wrist, again at a strength just suprathreshold for a twitch in APB. The conditioning-test (C-T) interval was varied from -80 to +10 with respect to the magnetic stimulus and 5 magnetic stimuli were tried at each interval. The results confirm the short facilitation period when the C-T interval was -6 to +3 ms. Consideration of the timing indicates that this must occur at the spinal segmental level. The long period of facilitation lasted from 27-70 ms, but it was divided into two periods (27-35 and 55-70 ms) in all subjects, separated by an interval of about 20 ms during which the test response fell to control levels. The long late facilitations may be cortical as the earliest facilitation began at 27 ms having the afferent volley reached the sensory cortex at 20 ms. The long interval facilitation consists of two temporally separate processes, implying separate cortical mechanisms creating a bimodal excitability cycle at the level of motor cortex.

MJIRI, Vol. 11, No. 4, 341-347, 1998.

INTRODUCTION

Since Phillips (1977) hypothesized that proprioceptive feedback may be used by the motor cortex to modulate its own output,[2] a large body of evidence has been reported to support the existence of a trans-cortical reflex pathway involving corticospinal neurons. In humans, there is a definite demonstration that proprioceptive projections provide the neural trail for the afferent limb of the proposed transcortical loop. However, direct evidence that the corticospinal motor output is influenced by the proprioceptive input was missing. Studies of the long latency stretch reflexes,[3] long-loop reflexes,[4] and studies on the mechanism of secondary peak (SP) in firing probability of motoneurons after TMS offered indirect results supporting this view.[5]

In the last decade it has become possible to elicit short latency muscle responses to single electrical stimuli applied to the scalp.[6,7] Transcranial electrical stimulation (TCS) of the motor cortex made possible the objective assessment of the corticospinal pathways. Development of transcranial magnetic stimulation (TMS) introduced by Barker et al.[8] made the technique painless and easier than TCS to perform. In low intensity of the TCS, corticospinal neurons could be activated directly whereas TMS activates them trans-synaptically. Therefore, the latter method would be appropriate for interacting with other afferent inputs to the motor cortex.[9] In both techniques, it has been reported that the latency and amplitude of MEPs can be facilitated by various type of inputs to the cortical motor system such as voluntary activation, vibration, and mechanical and electrical peripheral stimulations.[4,9-12]

Electrical stimulation of the median nerve prior to the focal TMS delivered on corresponding motor cortex explored by mapping experiments[13] showed three periods of facilitation of the MEPs in the APB (abductor pollicis brevis) and ADM (abductor digiti minimi) muscles of normal subjects.[14]

The aim of the present study was to determine firstly the change in the muscle responses to TMS induced by an ascending volley (i.e., stimulation of the median nerve); secondly, to examine the usefulness of the technique of TMS for sensorimotor integration studies.

METHODS

The time course and the ratio of the facilitation of the MEPs were examined in 10 healthy volunteers. TMS delivered from a figure-of-eight coil (Magstim 2000, UK) was preceded by a short duration (0.3 ms) electrical pulse applied antidromically (orthodromic for sensory fibers, cathode proximal) on the median nerve at the wrist (Fig. 1). Both conditioning (electrical) and TMS stimulus intensities were at motor threshold. Surface EMG recordings were performed on relaxed APB muscle. Particular care was taken to avoid any voluntary facilitation produced by muscle activation. However, the surface EMG of the muscle was monitored continuously for the subject as a visual feedback to control its relaxation.

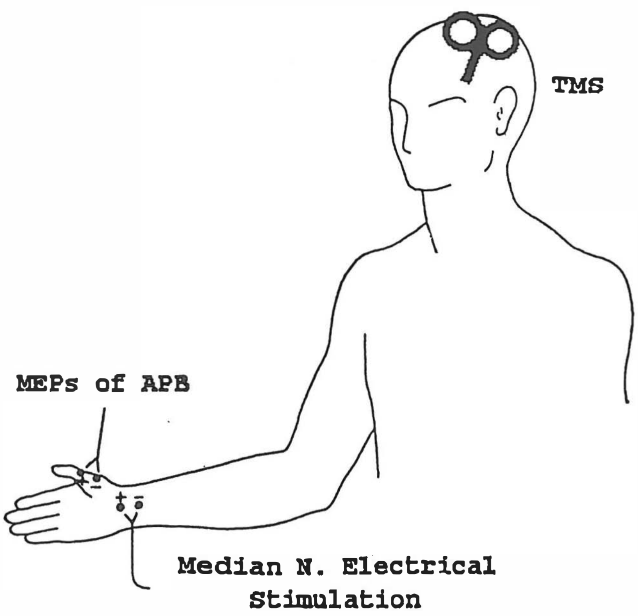


Fig. 1. Schematic drawing of the experimental arrangement.

The unconditioned motor evoked potentials (EMPs) given are the mean ±SD (standard deviation) of 12 trials. In each subject, control MEPs, the mean amplitude ±SD of at least 12 control EMG potentials was calculated, then the conditioning stimulus was applied from 80 ms prior to 10 ms after TMS (C-T intervals of -80 to +10 ms, with respect to magnetic stimulation at 0, Fig. 1. The conditioned response was considered significant if the mean amplitude of 5 trials exceeded mean +3 SD of the unconditioned responses.[15] The C-T intervals were set manually (using a digitimer) and the test stimulations applied randomly to prevent habituation. Particular care was taken to keep optimum relaxation of volunteers in a well-supported semi-lying position.

RESULTS

Our results demonstrate that a sensory volley elicited by electrical stimulation of the median nerve at the wrist evokes three periods of facilitation, with peak potentiation occurring at the short (-6 to +3 ms) intervals (SI facilitation). This potentiation could be observed when the MEP in the EMG trials was overlapped on the H-reflexes produced by median nerve stimulations (Fig. 2).

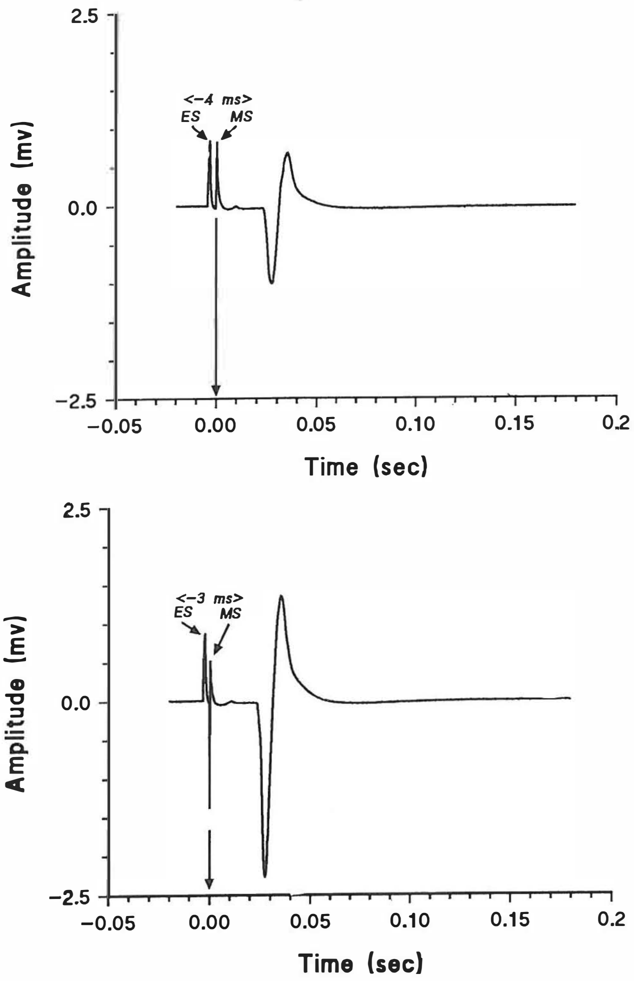


Fig. 2. Two averaged MEPs of APB, conditioned with an electrical stimulation of median nerve 3 and 4 ms prior to TMS (n=4). Considering the H reflex latency and MEP latency in this subject at 3 ms C-T interval, two electrically evoked ascending volleys and magnetically induced descending volleys have met each other probably in the C8 motor pool.

Two other windows of facilitation periods were observed, beginning after long intervals (LI) of 27-35 ms and 55-70 ms. The maximum facilitation observed was 734% (range 422-734) for the short period, and 386% (range 295-386) during the long period of facilitation (Fig. 5). The pooled data from 10 subjects are also plotted in Fig. 4. The pattern of facilitation, based on the control level of MEPs amplitude value (100%) is shown in a staircase line formed to link the data points implying trimodal facilitation with no inhibition period during these intervals. It must be noted that the LI facilitations were separated by an interval of about 20 ms during which the test response fell to control levels (Figs. 4,5).

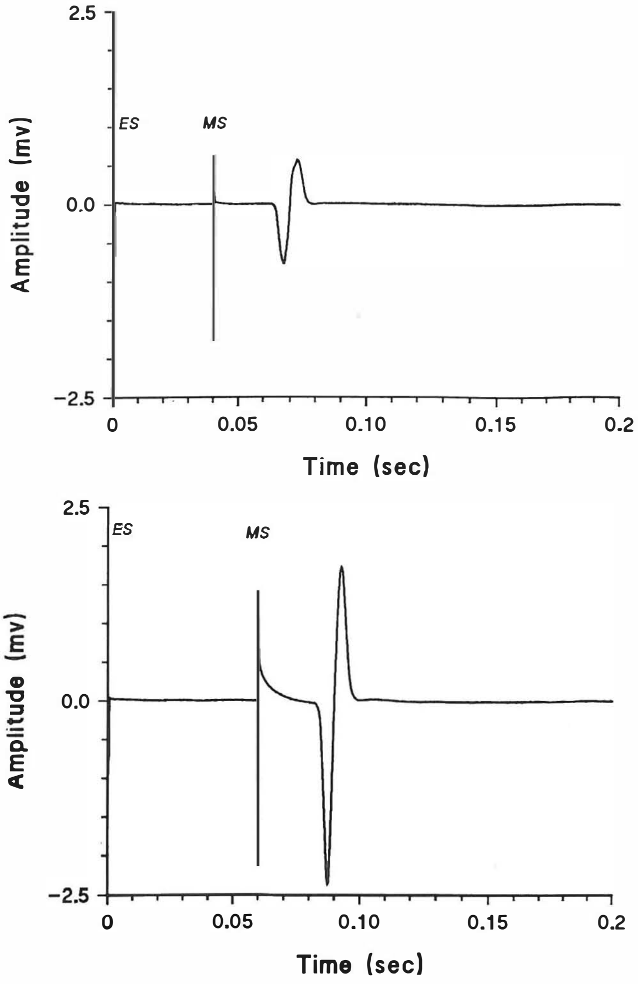


Fig. 3. Two averaged MEPs of APB, conditioned with an electrical stimulation of median nerve 40 and 60 ms prior to TMS (n=5). The long interval facilitation (27-70 ms) was divided to 2 windows by a fall in MEPs amplitudes recorded in C-T intervals of around 40 ms.

The influence of the conditioning stimulus was found not to be limited to the median nerve myotome (Fig. 5, dotted traces). A similar pattern of changes also happened in amplitudes of MEPs recorded from ADM (abductor digiti minimi), a synergistic muscle whose peripheral nerve, the ulnar nerve, had not been stimulated. These facilitations, however, were not significant.

DISCUSSION

Results of the study indicate that three windows of facilitation times could be observed in MEPs conditioned with an afferent sensory volley elicited by electrical

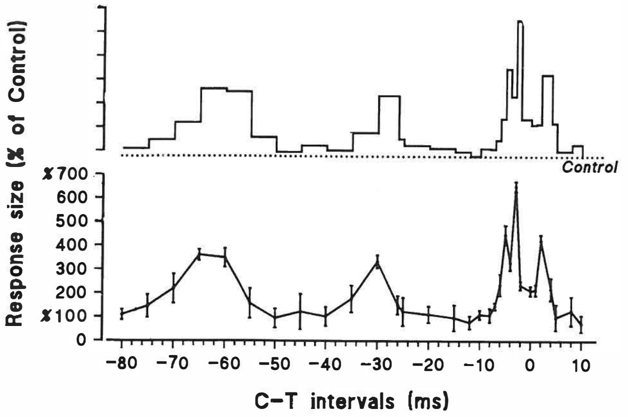
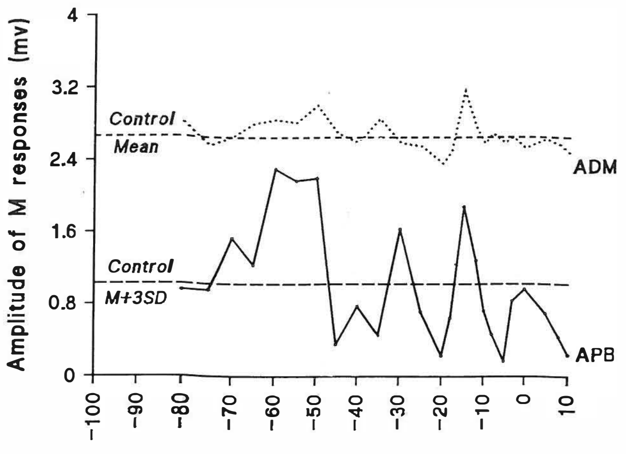
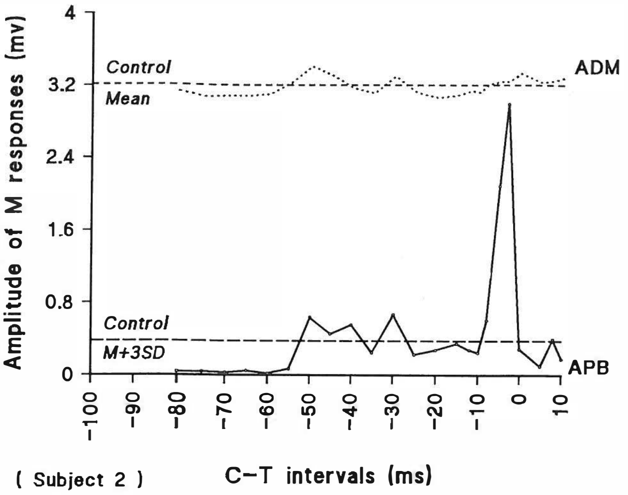


Fig. 4. Pooled data from 10 subjects showing the mean (±SEM) EMG response size of TMS at around motor threshold intensity when combined with an afferent volley at different intervals. The MEP sizes are expressed in percentage when the mean amplitude of unconditioned MEPs was considered to be 100. Three windows of facilitation are re-drawn in staircase form relative to the control level to give a summary of the results.



(Subject 1)



(Subject 2)

Fig. 5. Average of 5 MEP amplitudes recorded from APB and ADM in two individual subjects at C-T intervals of -80 to +10 ms. Subject 1 showed maximum long interval facilitation (LI) and subject 2 showed maximum short interval facilitation (SI) among normal subjects. Similar pattern of changes also occurred in amplitudes of MEPs recorded from ADM, a synergistic muscle whose peripheral nerve, the ulnar nerve, had not been stimulated. This facilitation however, was not significant.

stimulation of the median nerve; one at short C-T intervals (SI) and two other periods of facilitation after longer intervals (LI). LI facilitation had already been reported as a long-lasting period of facilitation by others using TCS (transcranial electrical stimulation) and TMS.

Our data seem different from those of Troni et al.[16] who used transcranial electrical stimulation and described only one long lasting period of facilitation in time intervals of 28-100 ms or with those reported by Deletis et al.,[1] who also found one long period of late facilitation lasting 25-60 ms with TCS. When they used TCS as test stimuli, the maximum facilitation observed in APB was 1399% in SI and 350% in LI. They also reported facilitations at C-T intervals of 4,7,30, and 35 ms when the TMS was applied by a big (9.5 cm) circular coil instead of TCS, 2 cm anterior to the vertex and over the scalp as a test stimulus, but only at those time intervals. Their results in short interval facilitation are almost similar to our data.

It is an established phenomenon that active neural structures show a lower threshold to stimulation than when the same structures are at rest. This could be most easily shown via MEPs elicited in pre-activated muscles (e.g. the effect of voluntary contraction on the threshold of MEPs in both TCS and TMS techniques). This facilitation has been explained based on the activation of descending corticospinal fibers which directly or indirectly through spinal interneurons, evoke a discharge from the spinal motoneurons whose threshold is decreased and their excitability level has been increased due to the ongoing voluntary muscle contraction,[17] or possibly from the activated cortical structures responsible for the voluntary drive (cortical motor system). On the other hand, it is well established in the literature that feedback from the muscle afferents to the spinal motor motoneuron pool has also a facilitating effect on MEPs amplitude.[11,12]

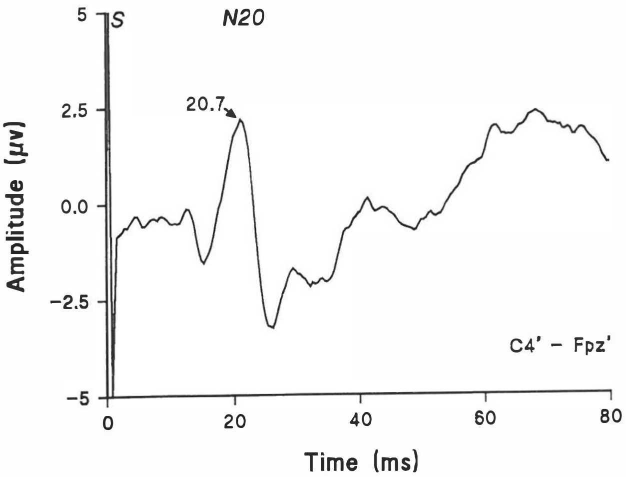


Fig. 6. SEP recorded from the contralateral sensory cortex after application of our conditioning electrical stimulation to the median nerve at the wrist in one subject. (average of 256 responses recorded from C4'-Fpz'-Gain 10 μv, Frequency bandwidth 0-2 KHz).

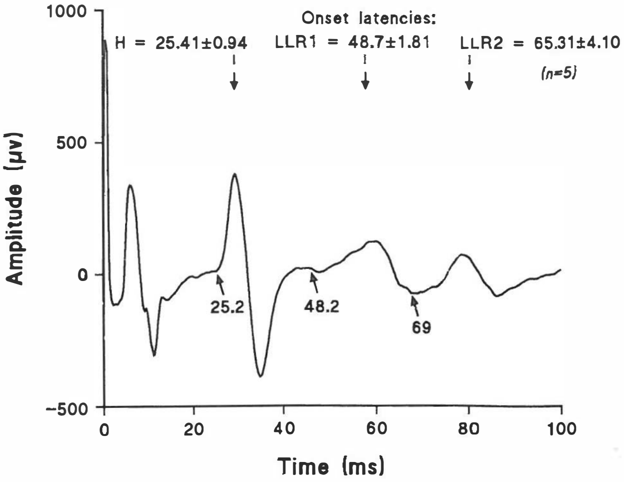


Fig. 7. Long loop responses recorded from slightly activated APB after median nerve stimulation at the wrist (average of 64 sweeps). Except evoked H reflexes (the second component), two other late components appear in the surface EMG.

Two main questions should be answered to explain the results; 1) which type of afferent fibers are stimulated with conditioning electrical stimulations? 2) Where are the anatomical levels of the facilitation, are they spinal or supraspinal?

Troni et al.[16] in a similar experiment performed with TCS, applied cutaneous stimulation to the median nerve dermatome of fingers. With stimulation of the exteroceptive component of the median nerve, they did not observe any significant potentiation and implied that the proprioceptive fibers, particularly the primary spindle afferents with a possible contribution of Ib fibers, had been stimulated with their conditioning stimuli (1 ms duration). We used shorter durations of electrical pulses, i.e., 0.3 ms which, at motor threshold intensity, probably has stimulated mainly the fast proprioceptive (Ia) fibers.

In our volunteers, short interval facilitation occurred when the MEPs evoked by TMS in the EMG trials were overlapped on the H reflexes produced by median nerve electrical stimulations. On the other hand, these time intervals correspond to the arrival of both the conditioning electrical stimuli and the corticospinal descending volley evoked following TMS to the spinal cord.[13] Therefore, this early potentiation period is likely to occur at the spinal cord level. Based on this hypothesis, the range of C-T interval for examining the spinal summation of C-T stimulations in a subject could be estimated from the following formula;

SI, C-T interval estimate= (H latency + DML 2)-CMCT

H reflex latency and distal motor latency (DML) of APB could be acquired from the median nerve conditioning stimuli, and central motor conduction time could be measured based on MEP latency from test TMS.

In our data, the maximum facilitation observed was 734% for the short period and 386% during the long period indicating that the late cortical or supraspinal loop facilitation is considerably weaker than the spinal one. We postulated that the amount of facilitation is somehow influenced by the different population of the fibers projecting to these levels, although many other factors may be involved.

Consideration of the timing indicates that early SI facilitation must occur at the spinal segmental level due to the summation of the two stimuli at the motor pool. Based on the time of occurrence, there are two possible explanations for long late facilitation; 1) They may be cortical as the earliest facilitation in the motor cortex began at 27 ms but the afferent volley from median nerve stimulation at the wrist reaches the sensory cortex at 20 ms (Fig. 6). 2) They may happen at the spinal level and the excitability of the motoneurons changes in three windows of time after receiving one set of ascending volley.

It is unlikely that these facilitations occur at the spinal level due to summation of the afferent volley with a volley in the small, slow conductive corticospinal fibers. The near threshold magnetic stimulus is unlikely to excite the small corticospinal fibers, directly or indirectly, and there are no reports of magnetically induced volleys in these fibers. The second assumption could not be the case, because application of a short duration, near threshold single pulse could only produce H reflexes and polysynaptic responses could not be seen in EMG trial without facilitation. Also, in 1982, Marsden, Merton and Morton studied the difference between the long latency stretch reflex and the tendon-jerk latencies. They measured the latencies of these two responses in masseter, flexor hallucis longus and flexor pollicis longus muscles and subtracted the latency of the jerk response of these muscles from their long latency stretch reflex latencies. The differences were 5 ms for the jaw, 22 ms for the thumb and 38 ms for the big toe. These excess latencies are clearly related to the distance of the motoneurons of the relevant muscle from the cerebral cortex.

There is supportive evidence, both in anatomy[18] and in electrophysiology[18] that the neural activity of muscle afferents reaches the motor cortex possibly through a fast pathway from hand and digits to area 4 (examined in monkeys by Lemon, 1979), and indirectly from the sensory cortex. If these connections to the motor cortex exist, either directly or indirectly, it is likely to anticipate a window of facilitation which coincides with the activation of these sensorimotor pathways. In monkeys, there is evidence of clear bimodal responses recorded directly from area 4 neurons after median nerve electrical stimulation.[18] He suggested a slower afferent pathway to the motor cortex or a re-afferentation from the periphery caused by the muscle twitch evoked after the nerve stimulation, as possible origins of these bimodal responses. Studies by Delitis and Beric[1] on long-loop reflexes, Mills et al.[5] on the mechanism of secondary peak (SP) in firing probability of motoneurons after TMS and Troni et al.[16] on the effect of TCS on long latency reflexes, offered indirect evidence supporting that cortical mechanisms may be involved in the facilitation of MEPs. On the other hand, the long loop responses, elicited in our subjects by the conditioning electrical stimuli applied on the median nerve at the wrist, recorded from APB during slight voluntary contraction of the muscle, also showed a bimodal long loop response (Fig. 7).

Another piece of evidence which supports a supraspinal or cortical origin of the long interval facilitation is notified by Deletis et al.[1] who used a C-T paradigm to examine the relative timing of the facilitation periods after peripheral nerve stimulations for both upper and lower limbs. A greater C-T interval for the onset of facilitating periods in the lower limb MEPs which is relatively consistent with the conduction time for the arrival of the orthodromic afferent volley at the cortical level implies transcortical or supraspinal involvement. If this hypothesis is correct, then the long interval facilitation consisted of two temporally separate processes implying separate cortical mechanisms creating a bimodal excitability cycle at the level of the motor cortex.

The conditioning stimulus also showed some influences on surface EMGs recorded from ipsilateral ADM, a muscle from the APB neighbourhood, both in hand and the somatotopic organization of the motor cortex (homunculus). This observation suggests a spinal and cortical sensorimotor organization which is strongly biased toward facilitating the neural circuitry associated with an individual agonistic muscle and which does not provide significant facilitatory interactions with the other synergistic muscles.

Since the results, regardless of the uncertainty about the sites and mechanisms of the facilitation, could be obtained by intact sensory and motor projections and processing, the TMS with the figure-of-eight coil with such a C-T paradigm could be used for clinical assessment of spinal and cortical sensorimotor integration in a manner which is not possible through isolated assessment of ascending or descending pathways using standard evoked potential techniques.

REFERENCES

1. Deletis V, Schild JH, Beric A, Dimitrijevic MR: Facilitation of motor evoked potentials by somatosensory afferent stimulation. Electroenceph Clin Neurophysiol 85: 302-310, 1992.
2. Phillips CG, Porter RR: Corticospinal Neurones. Academic Press, London, U.K., 1977.
3. Marsden CD, Merton PA, Morton HB: Direct electrical stimulation of corticospinal pathways through the intact scalp in human subjects. Adv Neurol 39: 387-91, 1983.
4. Deletis V, Beric A: Electrically evoked long loop responses (LLR): normative data for upper and lower extremities. Electromyogr Clin Neurophysiol 29: 433-437, 1989.
5. Mills KR, Boniface SJ, Schubert M: Origin of the secondary increase in firing probability of human motor neurons following transcranial magnetic stimulation. Brain 114: 2451-2463, 1991.
6. Merton PA, Morton HB: Stimulation of the cerebral cortex in the intact human subjects. Nature 285: 227, 1980.
7. Levy WJ, York DM, McCaffrey M, Tamzer F: Motor evoked potentials from transcranial stimulation of the motor cortex in humans. J Neurosurg 15: 287-302, 1989.

8. Barker AT, Jalinous R, Freeston IL: Non-invasive magnetic stimulation of human motor cortex. Lancet 1: 1106-1107, 1985.

9. Day BL, Marsden CD, Rothwell JC: Contrasting effects of muscle stretch on the response to magnetic and electrical cortical stimulation in man. J Physiol 414: 13P, 1989.

10. Hess CW, Mills KR, Murray NMF: Magnetic stimulation of human brain: facilitation of motor responses by voluntary contraction of ipsilateral and contralateral muscles with additional observation on amputee. Neuroscience Letters 71: 235-240, 1986.

11. Claus D, Mills KR, Murray NMF: Facilitation of muscle responses to magnetic brain stimulation by mechanical stimuli in man. Exp Brain Res 71: 273-278, 1988.

12. Day BL, Riescher H, Struppler A, Rothwell JC, Marsden CD: Changes in the response to magnetic and electrical stimulation of the motor cortex following muscle stretch in man. J Physiol 433: 41-57, 1991.

13. Jamshidi Fard AR: PhD thesis, Clinical Neurological Sciences, University of Southampton, U.K. 1994 (see Table I and II for CMCTs).

14. Jamshidi Fard AR, Bagust J, Sedgwick EM: Muscle responses elicited by transcranial magnetic stimulation (TMS) in the human hand after electrical activation of afferent volleys in median nerve. Brain Res Assoc Abst 11: 96, 1994.

15. Armitage P, Berry G: Statistical Methods in Medical Research, 2nd Ed., Blackwell Scientific Publications, Oxford, UK, PP. 94-97, 1988.

16. Troni W, Cantello R, DeMattei M, Bergamini L: Muscle responses elicited by cortical stimulation in the human hand: differential conditioning by activation of the proprioceptive and exteroceptive fibers of the median nerve. In: Rossini MP, Marsden CD (eds.), Non-invasive Stimulation of Brain and Spinal Cord: Fundamentals and Clinical Applications. New York: Alan R. Liss, Inc. pp. 73-83, 1988.

17. Day BL, Rothwell JC, Thampson PD, Dick GPR, Cowan JM, Berardelli A, Marsden CD: Motor cortex stimulation in intact man. 2. Multiple descending volleys. Brain 110: 1191-1209, 1987a.

18. Lemon RN: Short-latency peripheral inputs to the motor cortex in conscious monkeys. Brain Res 161: 150-155, 1979.