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How repeatable are the physiological effects of TENS?

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Abstract

Objective: Several studies suggest that transcutaneous electrical stimulation (TENS) can have a variety of effects on the central nervous system (CNS). In this study, we tried to replicate the physiological effects of TENS and to explore its effects on intracortical circuits.
Methods: We used transcranial magnetic stimulation (TMS) and spinal reflex testing to examine excitability of intracortical and spinal cord circuits before and after a 30-min period of TENS over the flexor carpi radialis (FCR) muscle. We measured the amplitude of TMS-evoked muscle responses (MEP), short interval intracortical inhibition (SICI), intracortical facilitation (ICF) and cortical antagonist inhibition (CAI) in flexor and extensor carpial radialis (FCR, ECR) muscles as well as spinal reciprocal inhibition (RI) and presynaptic inhibition (PI) from ECR to FCR.
Results: TENS had no significant effect on any of these measures apart from a reduction in median nerve induced facilitation of FCR when testing CAI.
Conclusions: When compared with previous studies, our results suggest that the effects of TENS are highly variable and unreliable, likely by the difficulty in defining precise parameters of stimulation in individual subjects.
Significance: Care should be taken in assuming that effects after TENS observed in small populations of subjects will apply equally to a wider population.

Keywords: Transcranial magnetic stimulation; Transcutaneous electrical stimulation; Intracortical inhibition; Intracortical facilitation; Spinal excitability

1. Introduction

There is a strong evidence that the excitability of the motor cortex can be modulated by afferent input. In humans, initial experiments concentrated on the immediate effects of sensory input on the amplitude of EMG responses evoked by transcranial magnetic stimulation of motor cortex. Thus, suitably timed electrical stimuli applied to peripheral nerve were found to increase or decrease MEP amplitude, consistent with a short latency afferent influence on motor cortex excitability (Deuschl et al., 1991; Bertolasi et al., 1998; Maertens de Noordhout et al., 1992; Rossini et al., 1996; Tokimura et al., 2000). Later experiments showed that this input also influenced the excitability of intracortical circuits tested with paired pulse TMS protocols (Ridding and Rothwell, 1999; Sailer et al., 2002; Kujirai et al., 1993). More natural inputs, such as muscle vibration, were also shown to modulate motor

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cortical excitability (e.g. Rosenkranz et al., 2003). Recently, the long-term effects of afferent input that outlast the period of stimulation have become an important issue. Thus, in healthy subjects, a prolonged period of peripheral nerve electrical stimulation (10 Hz) at low intensity has been shown to increase corticomotoneuronal excitability in the stimulated body parts (Hamdy et al., 1998; Ridding et al., 2000; Kaelin-Lang et al., 2002).

Transcutaneous electrical nerve stimulation (TENS) has been used for many years as a possible treatment for chronic pain (Hansson and Lundeberg, 1999). Although the mechanism is debated and the results are variable, it is possible that it leads to long-term effects on sensory transmission in the central nervous system. Indeed, TENS has been demonstrated to reduce somatosensory and pain evoked cortical potentials (Hoshiyama and Kakigi, 2000), and when applied over the hand (Mima et al., 2004), can increase sensory thresholds and reduce MEPs in hand muscles. Tinazzi et al. (2005a) reported that 30 min TENS over the flexor compartment of the forearm reduced MEPs in the flexor carpi radialis (FCR) muscle and increased MEPs in the antagonist (ECR) for the following 10–35 min. They postulated that part of this effect might have been via an action of afferent input on the excitability of reciprocal inhibitory connections between antagonist muscles at spinal or cortical levels (Bertolasi et al., 1998). Such effects of TENS on motor excitability may explain the effectiveness of TENS in the treatment of spasticity and dystonia (Foley-Nolan et al., 1990; Bending and Cleeves, 1990; Tinazzi et al., 2005b).

Given the known variation between subjects in the clinical response to TENS, the first aim of this work was to try to confirm the initial observations of Tinazzi et al. (2005a) on modulation of motor cortical projections to forearm muscles. In addition, we hoped to test whether the reciprocal effects on excitability of antagonist muscles were mediated by spinal or by intracortical circuits of reciprocal inhibition.

2. Materials and methods

2.1. Subjects

Eight healthy subjects (25–33 years old) were studied. All subjects gave a written informed consent to study, which was approved by the Research Ethics Committee of the Institute of Neurology. Subjects were comfortably seated in an armchair with the right forearm positioned on a moulded armrest in a supinated position while the forearm and hand muscles were relaxed. Parameters of motor excitability were recorded before and after 30 min transcutaneous electrical nerve stimulation over the flexor carpi radialis.

2.2. EMG recording

Surface electromyographic (EMG) recordings in a belly-to-tendon montage were made from the flexor carpi radialis (FCR) and the extensor carpi radialis (ECR) muscles. The raw signal was amplified and filtered with a band-pass filter of 30 Hz to 1 kHz (Digitimer Ltd). Signals were digitized at 2 kHz (CED Power1401, Cambridge Electronic Design, Cambridge, UK) and stored on a laboratory computer for off-line analysis.

2.3. Transcranial magnetic stimulation (TMS)

TMS was performed using two MAGSTIM 200 stimulators connected by a Y-cable to a figure-of-eight-shaped coil with an internal wing diameter of 7 cm (Magstim, Dyfed, UK). The coil was held with the handle pointing backwards and laterally approximately perpendicular to the central sulcus, to evoke anteriorly directed current in the brain, and was optimally positioned to obtain MEPs in the contralateral FCR and ECR muscles. Stimulation intensities are quoted in the text as a percentage of maximal stimulator output. The position of the coil was marked on the scalp so that it could be kept at exactly the same site along the session. Motor threshold (MT) was determined in the FCR as the main target muscle. MTs were defined as the lowest stimulus intensity that evoked an MEP with an amplitude >50 μV in at least five of the 10 successive trials in muscles at rest.

Short interval intracortical inhibition (SICI) and intracortical facilitation (ICF) were recorded using techniques which have been previously described (Kujirai et al., 1993; Ridding and Rothwell, 1999). Paired magnetic stimuli at different interstimulus intervals (ISI) were applied at the optimal scalp site for evoking responses in FCR and ECR while the subject was at rest. The test (second) stimulus was set to intensity sufficient to evoke a response in the target muscles (FCR and ECR) of approximately 1–1.5 mV. The conditioning (first) stimulus was at intensity 70% of stimulator output below the passive threshold for the target muscle. The interval between conditioning and test stimuli was 2 and 3 ms for the investigation of SICI and 10, 15 ms for the investigation of ICF. Inhibitory, excitatory timings and TMS alone were incorporated into a single block of 60 stimuli. Therefore, in total there were 12 trials for each condition, and the orders of presentation of the conditions were randomised.

Cortical antagonist inhibition was studied by a protocol which has been previously described (Bertolasi et al., 1998). The protocol involves peripheral nerve stimulation as a conditioning stimulus followed by a TMS test pulse. Bipolar electrical stimulation (cathode proximal) was delivered to the median nerve at the elbow (interelectrode distance, 20 mm; diameter of each stimulating electrode, 9 mm) with a square pulse of 0.1 ms and at an intensity producing a minimum activation of motor axons as monitored by the presence of a small M wave (generally smaller than an isoelectric peak amplitude of 50 μV in forearm flexors) that was used to confirm consistency of the stimulation during each experimental session. The conditioning-test intervals were 13, 15 and 19 ms. The intensity of TMS test pulse

was set to evoke an MEP of 1–1.5 mV in the FCR and ECR. Twelve trials for each conditioning stimulus and 12 trials for TMS alone were presented randomised in a single block.

2.4. Parameters of electrical stimulation

For continuous somatosensory stimulation, TENS was delivered to the forearm flexor muscles by means of an electrical generator (Digitimer DS7A, Welwyn Garden City, Hertfordshire, UK) and applied over the belly of the FCR by a pair of plastic electrodes (2 × 3 cm). The current frequency was set at 150 Hz, with pulse duration of 0.1 ms and delivered in a symmetrical rectangular monophasic waveform. Strength intensity was below the motor threshold and produced a tingling sensation in the stimulated area without muscle twitch or pain. Stimulation was administered throughout each 30-min session in 2-s trains at 150 Hz (300 stimulus/train) separated by 2-s pauses. This parameter of stimulation was chosen in reference to the work of Tinazzi et al. (2005a) in which a long-lasting modulation was reported.

2.4.1. Complementary experiment 1

This complementary experiment was performed to check possible changes at the spinal level. In five subjects M and H waves, reciprocal inhibition (RI) and presynaptic inhibition (PI) were recorded from FCR muscle before and after the TENS. The parameters of the TENS were the same as used in the main experiment. Maximum M wave was elicited during supramaximal stimulation in the median nerve (rectangular pulse with duration of 1 ms and intervals interpulse 5 s) and the intensity was modulated to obtain the maximal H wave amplitude. The amplitude of the H wave was measured peak-to-peak and expressed as percentage of maximum M wave. For RI and PI, we used an H-reflex conditioning-test paradigm. Radial electrical stimulation (1 ms rectangular pulse) was delivered 2 ms (for RI) and 20 ms (for PI) before the median nerve stimulation. Ten conditioned and 10 test H-reflex were averaged before and after the TENS. The amplitude of conditioned H-reflex was expressed as percentage of the test H-reflex.

2.4.2. Complementary experiment 2

We conducted a separate set of experiments on ten subjects in whom we increased the width of the electrical pulse used in TENS from 100 to 500 μs in order to activate more selectively large diameter sensory afferents. According to calculations of Panizza et al. (1992), for a stimulus duration of 100 μs, the threshold for sensory fibers is 56 ± 49% higher than motor fibers, while for a duration equal to or greater than 500 μs, the threshold for sensory fibers is lower than for motor fibers. Ten subjects who did not participate in any previous experiment were stimulated by TENS with a width pulse of 500 μs. The frequency and the trains were the same as those in the main experiment. MEP size, SICI and ICF were recorded before and after 30 min of TENS.

2.5. Data analysis

Motor thresholds were expressed as percentage of maximal stimulator output. Changes in the size of MEPs after single TMS pulses before and after TENS were analyzed by a paired *t*-test. For SICI and ICF, single trial peak-to-peak MEP amplitudes were measured and averaged for each ISI separately. Size (peak-to-peak amplitude) of the conditioned mean MEP was expressed as a percentage of the mean test MEP. Analysis of variance (ANOVA) using repeated measures was performed with muscle (FCR, ECR), TENS (before, after) and ISI (2, 3, 10, 15 ms) as within subject factors. The same procedure was performed for the cortical antagonist inhibition but the factor ISI was reduced to three levels (13, 15, 19 ms). Changes in H-reflex, RI and PI were analyzed by paired *t*-test.

3. Results

3.1. Motor threshold and size MEP

The relaxed motor threshold (rMT) in the FCR (43 ± 9% of maximal stimulator output) was unchanged after TENS (42 ± 2%). Before TENS, the intensity required to obtain an MEP in FCR of around 1 mV was 57% (±15%). The amplitude of the MEP evoked by this stimulus was the same after TENS (Fig. 1).

3.2. Intracortical inhibition and facilitation

Fig. 2 shows the amplitude of MEPs in FCR and ECR at the different interstimulus intervals. Both muscles showed inhibition at shorter ISI (2 and 3 ms) and facilitation for longer ISI (10 and 15 ms). These effects were unchanged after TENS.

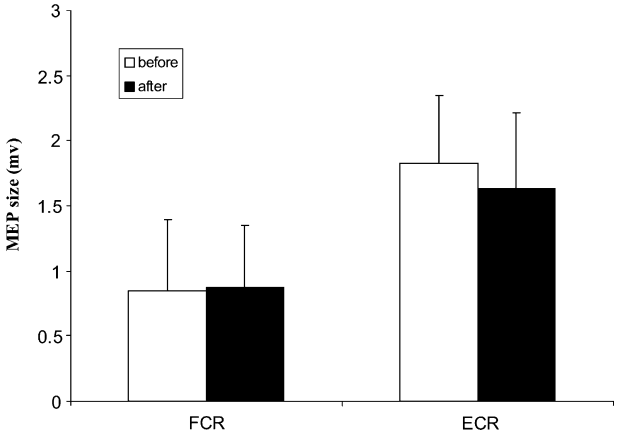

Fig. 1. Means (± SD) of MEP amplitudes obtained for FCR and ECR. Both muscles showed no significant MEP change after the application of TENS.

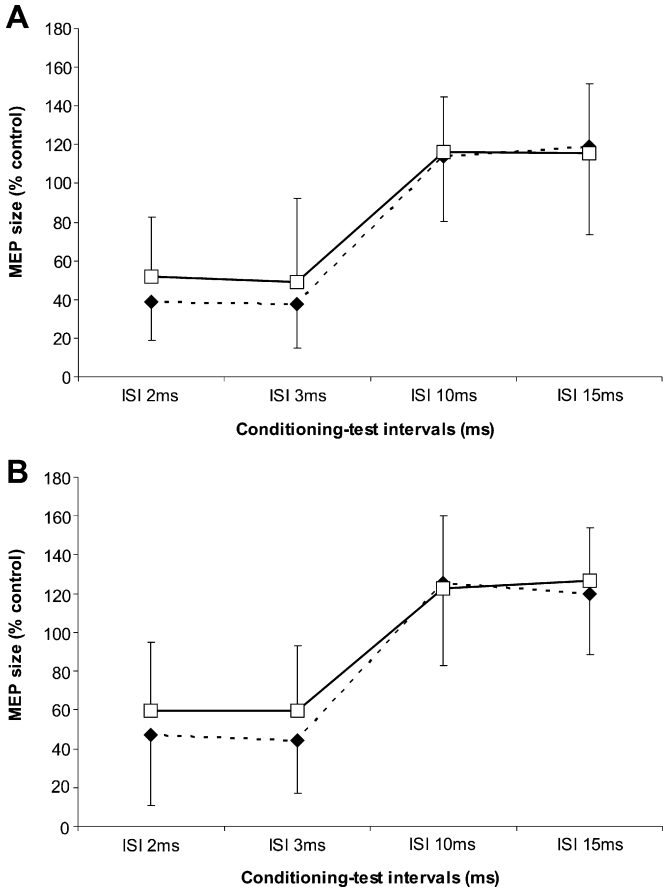

Fig. 2. Time course of short intracortical inhibition (SICI) and facilitation (ICF) in the FCR (A) and ECR (B) muscles. The *abscissa* indicates the ISIs studied and the *ordinate* the amplitude of the conditioned response as a percentage of the test response alone. The dotted lines show the MEP amplitude before TENS and the black line after TENS. No significant changes of MEPs size were observed after TENS.

3.3. Cortical antagonist inhibition

The ANOVA showed a significant main effect of muscle ($F_{1,7} = 5.11$, $p = 0.05$) as well as a muscle $*$ TENS interaction ($F_{1,7} = 6.92$, $p = 0.027$). Since there was no effect of the factor ISI, the data from the interstimulus intervals (13, 15, 19 ms) were averaged for the next part of the analysis. Two separate ANOVAs for each muscle showed that after TENS the effect of the median nerve volley was unchanged for ECR, whilst there was a significant reduction in the FCR ($F_{1,7} = 6.61$, $p = 0.04$, Fig. 3). Indeed there was now no longer a difference in the effect of median nerve stimulation on responses in FCR and ECR: both were reduced compared with control MEPs given alone.

3.4. Complementary experiment 1: measure of spinal excitability

Fig. 4 shows the values obtained for H-reflex, RI and PI. The RI at 2 ms was 73.31% before and 58.18% after TENS, and the PI at 20 ms was 93.36% before vs. 104% after TENS. None of these effects was statistically significant

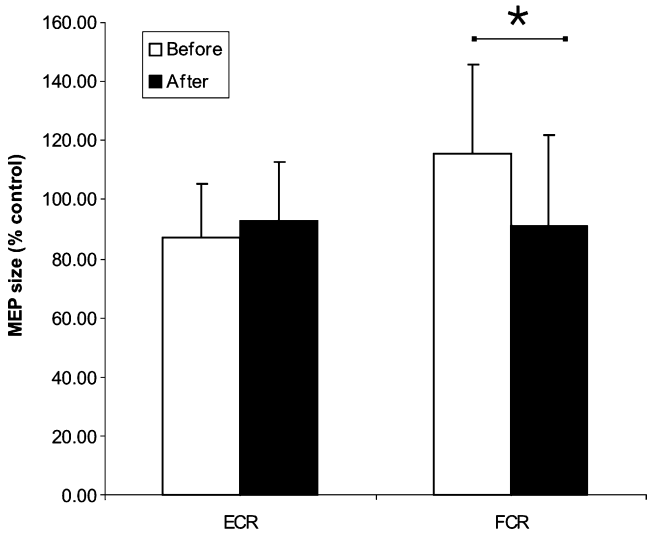

Fig. 3. Response to median electrical stimulation in the ECR and FCR muscles. Since there was no significant effect of ISI we group the ISI data to represent the mean effect in the two muscles before and after TENS. The FCR showed a significant decrease in amplitude after TENS ($F = 6.61$, $p = 0.04$) without significant changes in the ECR. $^{*}p < 0.05$.

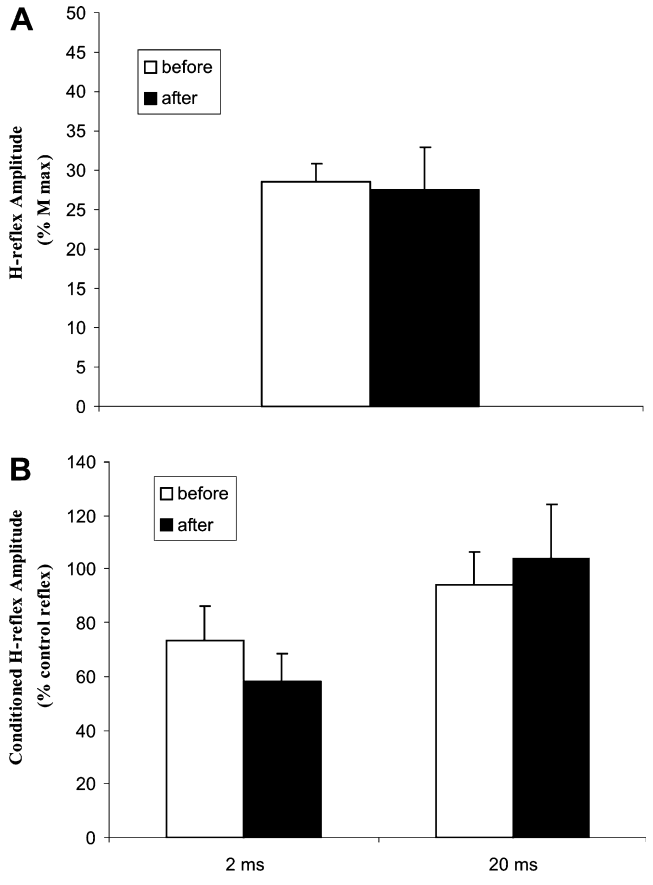

Fig. 4. Effects of TENS over different parameters of spinal excitability. No significant change was reported. (A) H-reflex. (B) Reciprocal inhibition (2 ms) and presynaptic inhibition (20 ms).

($t = 1.07$, $p = 0.36$ and $t = 0.88$, $p = 0.44$ for RI and PI, respectively).

3.5. Complementary experiment 2: effect of TENS pulse width

The lack of effect of TENS on MEPs and SICI/ICF contrasted with the positive effects that had been reported by Tinazzi et al. (2005a). Even with a wide of the electrical pulse of 500 μs, this form of TENS failed to change the MEP size for any muscle; neither did it have any effect on SICI or ICF.

4. Discussion

This is the first study to investigate the after-effects of 30 min TENS on the excitability of corticospinal, corticocortical and spinal motor circuits. Although the parameters and sites of TENS were the same as in a previous study (Tinazzi et al., 2005a), we failed to reproduce the reported effects on MEP amplitude. In fact, we found no effect of TENS on MEP, SICI/ICF or spinal and cortical reciprocal inhibition. The only positive result was a reversal of the usual effect of median nerve effect on MEPs in FCR from facilitation to suppression.

The lack of influence of TENS on the amplitude of MEPs in FCR and ECR muscles was unexpected. Given the size of the effect reported by Tinazzi et al. (2005a), we had calculated that we had more than 90% chance of seeing a similar result with the initial sample of 8 subjects that were examined in the main set of experiments. The fact that no significant changes in MEP were seen in the supplementary sample of 10 subjects suggests that the size of the effect observed by Tinazzi et al. (2005a) was by chance much larger than the expected mean. We conclude that if TENS has an effect on MEPs in forearm muscles, then it is more likely to be of the order of 15% or less, rather than the 50% or more reported previously. The contrast between the results also implies that any effect is likely to be highly variable between subjects. This was also noted by Charlton et al. (2003) who found that TENS over the motor point for the FDI increased MEP size in 7 subjects, decreased it in 4 subjects while in 11 subjects there was no change. The authors argued that part of this variation could be due to the difficulty in defining criteria used to set and maintain the stimulus intensity. We tried to explore this with our second supplementary experiment, in which we used a wider pulse width of TENS to obtain a more specific activation of large diameter sensory afferents (Panizza et al., 1992), but this also failed to reveal any lasting influence of TENS on MEP excitability.

As with the MEPs, there was no change in intracortical inhibition (SICI) and facilitation (ICF) after TENS. A short-term modulation of intracortical inhibition and facilitation has been documented after low amplitude vibration of forearm and hand muscles (Rosenkranz and Rothwell, 2003; Rosenkranz et al., 2003), but not after the application of electrical stimulation (Kaelin-Lang et al., 2002).

Prior to TENS, low-intensity stimulation of the median nerve at the elbow suppressed MEP responses evoked in forearm extensor muscles, whereas it increased MEPs in the forearm flexor muscles. On the basis of the respective timings of each effect as well as H-reflex studies, Bertolasi et al. (1998) suggested that the former is due to activation of a reciprocal connection between antagonist muscles within the motor cortex, whereas the latter is likely to result from facilitation of flexor muscle reflexes at a spinal level. TENS had no effect on the extensor inhibition. However, it reversed the FCR facilitation into suppression. The difference in the effects is clearly compatible with the idea that the median nerve effects on FCR and ECR utilise separate pathways, but the mechanism is unclear.

The data show that TENS had no effect on MEPs in FCR; in addition, TENS had no effect on FCR H-reflexes or on reciprocal inhibition of FCR from afferents in the radial nerve. The conclusion is that if the median nerve facilitation of FCR is due to a spinal mechanism, then TENS must have a very specific influence on this pathway, to the exclusion of effects on spinal motoneurones and reciprocal inhibitory neurones. It is possible, for example that the pathway mediating median nerve facilitation of FCR is related to the more general flexor reflex pathways. If so, then it may account for the success of TENS in treating some forms of spasticity.

One question not yet addressed in the literature is whether attention to the sensation during application of TENS could influence its effects in central nervous system. However, we were specifically trying to replicate the Tinazzi et al.'s (2005a) study, where the attention was not controlled and indeed TENS itself is never applied clinically with any specific instructions about focussing attention on the sensation.

In summary, although changes in cortical and spinal levels have been reported after the application of TENS, these changes could not be replicated in the present study. In addition, we demonstrated an unexpected change in median nerve/MEP conditioning of FCR. The results imply that TENS is a variable and unreliable conditioning stimulus, and that care should be taken in assuming that effects observed in small populations of subjects will apply equally to a wider population.

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