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Effect of Transcranial Magnetic Stimulation to Motor Cortex on Pain Perception and Nociceptive Reflex

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Abstract

Noxious stimulation over the foot can evoke a nociceptive flexor reflex (NR) in the lower limb especially for tibialis anterior muscle (TA). Components of NR include the monosynaptic fast latency NRII, and the polysynaptic slow latency NRIII, supposedly a spinal segmental reflex influenced by the supraspinal control. Pain perception is quantified by visual analogous scale (VAS) and has been reported to be related to NRIII. Previous papers have reported the long lasting effect of transcranial magnetic stimulation (TMS), as well as TMS suppressing pain perception. The purpose of this study was to investigate the immediate and prolonged effect of a single-pulse TMS to suppress NR and pain. NRIII was provoked at right TA by a train of electrical stimulation on the right toe in 10 healthy subjects. TMS was delivered over the vertex area to evoke right anterior tibialis muscle activity. A sham TMS from different directions of the coil was performed on the next day. The NRIII amplitude and VAS were measured. As a result, the amplitude of NRIII was significantly decreased than the control 50 ms pre-stimulation (0.20 ± 0.13 mA *vs*. 0.65 ± 0.42 mV, $P = 0.016$), 100 ms pre-stimulation (0.10 ± 0.10 mA *vs*. 0.65 ± 0.42 mV, $P = 0.001$), 15 min post-stimulation (0.12 ± 0.09 mA *vs*. 0.65 ± 0.42 mV, $P = 0.004$), and 30 min post-stimulation (0.41 ± 0.21 mA *vs*. 0.65 ± 0.42 mV, $P = 0.046$). VAS was diminished compared with the control 50 ms pre-stimulation (3.3 ± 0.9 *vs*. 5.4 ± 1.3, $P = 0.002$), 100 ms pre-stimulation (2.6 ± 0.5 *vs*. 5.4 ± 1.3, $P < 0.001$) and 15 min post-stimulation (3.5 ± 0.9 *vs*. 5.4 ± 1.3, $P = 0.046$). The NRIII amplitude was well correlated with VAS in reduction during the TMS condition and 15 min after electrical stimulation ($P < 0.001$). The sham TMS did not suppress NRIII or VAS. In conclusion, our results indicate that NRIII and the nociception can be inhibited by one single pulse TMS and such an effect can last for a period of time.

Key Words: flexor reflex, nociceptive flexor reflex, pain suppression, transcranial magnetic stimulation, visual analogue scale

Introduction

Nociceptive flexor reflex (NR) recorded in the lower limbs in humans is a widely investigated neurophysiological tool. It is a polysynaptic and multisegmental spinal response that produces withdrawal of the stimulated limb. NR is mediated by a complex circuitry modulated at the spinal and supraspinal

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levels. At rest, the NR of the lower limb is usually obtained by stimulating the tibial nerve and by recording from the tibialis anterior (TA) muscle. NR is composed of an early, inconstantly present component, called the fast latency NRII, and a late, larger and stable component, called the NRIII. The NRII is with a latency of 40-60 ms and the latency of NRIII is 85-120 ms. The afferents mediating the NRII are conveyed by large-diameter, low-threshold, non-nociceptive A-beta fibers, while those mediating NRIII are delivered by small-diameter, high-threshold nociceptive A-delta fibers (21, 36). A close relationship between pain and the threshold of NRIII was shown in several human studies (4, 5, 15, 41, 46). It has been suggested that NRIII may be used as an objective measure of pain in human conditions such as for pain mechanism (2, 35, 43), and for pharmacological modulation of pain perception (30, 45). As stated in the guideline of European Federation of Neurology Societies (EFNS), NRIII is used in the physiological and pharmacological studies on modulation of nociception in the lower limb (7). Micalos *et al*. (27) also reported that NRIII and pain thresholds were well correlated and could be applied in experimental pain studies.

Transcranial magnetic stimulation (TMS) is a very useful and non-invasive tool in the study of human brain function (20). It has also been applied to the treatment of Parkinson's disease (11, 24) in recent years. There are several reports using TMS in the treatment of central and peripheral pain, such as endometriosis, thoracic outlet syndrome (16), low back pain (6, 16), reflex sympathetic dystrophy (16), central or thalamic pain (25, 28), musculoskeletal pain syndrome (32), phantom pain (34), pain control (26), pudendal neuralgia (37), and chronic pain (33). Migita *et al*. reported transient antalgic effect of single-pulse TMS in patients with central pain (28). Kanda *et al*. employed paired TMS over different brain areas to modulate pain perception and suggested that TMS over medial frontal cortex could suppress central processing of pain (22). Repetitive TMS (rTMS) over the primary motor cortex could attenuate subjective pain and was used in chronic pain (25, 33), with a long lasting reduction of the pain rating in some chronic pain studies (26, 31).

In this study, we aimed to discover if single pulse TMS produces immediate suppression on NRIII elicited by experimental pain stimulation and if such inhibition can be prolonged. We also measured the change in visual analogous scale (VAS) for analyzing the correlation between the suppression by TMS and the VAS change. Such information allowed us to determine whether single pulse TMS could suppress both the NRIII and the painful perception. In addition, whether such pain suppression effect by single pulse TMS could persist after a period of time was also ascertained.

Materials and Methods

Subjects

A total of 10 healthy subjects without any neurological defect or other major systemic disease such as diabetes mellitus were recruited into our study (6 male, 4 female, age: 28-38) after informed consent was obtained. The study protocol was approved by the hospital's human ethics committee.

Electromyographic (EMG) Recording of NR

We used an EMG machine (MEB-9200, Neuropack*M1*, Nihon Kohden, Tokyo, Japan) and EMG signals were recorded from right TA with two disposable electrodes with 2 cm apart. The active electrode was positioned 15 cm below patella and the reference was placed above the right ankle.

While seated in a chair, subjects were delivered an electrical stimulation of a constant current through the ring electrodes at the second digit of the right foot. The duration of the stimulus was 0.2 ms. Short trains of stimuli were given, typically 8 pulses at 200 Hz. The reflex threshold was defined as the stimulus intensity at which 5 out of 10 consecutive stimuli evoked a muscle response with an amplitude ≥ 50 μV, a duration ≥ 10 ms, and a latency < 180 ms in the relaxed muscle. The intensity of the electrical stimulation was then adjusted to 20% above the threshold and kept constant through the protocol. To avoid habituation, the interval between stimuli was at least one minute. EMG recording was set with a bandpass of 20-3k Hz and a duration of 500 ms. The EMG signals were fully rectified and the onset latencies, duration, and peak amplitudes were measured. As facilitation occurred in conditions of mild voluntary contraction, all subjects were asked to relax themselves to the best of their abilities with the aid of an audio- and visual EMG feedback.

TMS

TMS was delivered through Magstim 200 (Magstim Co. Whitland, UK) with a double cone coil that was applied over the vertex area to elicit the motor evoked potentials (MEP) of the right TA. The magnetic intensity was initially set at 80% and the coil was adjusted for an appropriate position in order to obtain a stable MEP. Later, the magnetic intensity was turned down gradually with a decrement of 2% until the MEP amplitude of the right TA was above 100 μV for at least 5 in 10 tests. Motor threshold

Table 1. Summary of the results in NRIII amplitude and VAS in control, conditioning TMS and sham TMS

	NRIII amplitude (mV)		VAS	
	TMS	Sham TMS	TMS	Sham TMS
Control	0.65 ± 0.42	0.64 ± 0.34	5.4 ± 1.3	5.3 ± 1.0
50 ms precondition	0.20 ± 0.13*	0.51 ± 0.24*	3.3 ± 0.9*	4.8 ± 0.7*
100 ms precondition	0.10 ± 0.10*	0.54 ± 0.24	2.6 ± 0.5*	4.9 ± 0.8
15 min postcondition	0.12 ± 0.09*	0.62 ± 0.28	3.5 ± 0.9*	4.9 ± 1.1
30 min postcondition	0.41 ± 0.21*	0.65 ± 0.36	4.8 ± 0.7	5.1 ± 0.8

*: $P < 0.05$ *vs*. respective control.

(MT) was defined at such magnetic intensity.

Pain Intensity Ratings: Visual Analogue Scale

Rating of the pain intensity in the electrical stimulation was conducted by a 10-cm Visual Analogue Scale (VAS). The scale was marked with "pain threshold" (bottom) and the most intense "pain imaginable" (top).

TMS Conditioning NRIII

Electrical stimulation of the unconditioned NRIII was performed at first to obtain the amplitude as the control. The electrical train stimulation was delivered at an interval of 10 min.

After a rest of 60 minutes, conditioned TMS of 1.2 MT was delivered 50 ms before the two-time electrical train stimulation test with an interstimulus interval (ISI) of one min. Following a rest of 15 min, conditioned TMS was again delivered 100 ms before the electrical train stimulation test twice.

Post TMS Conditioning NRIII

After a 15-min rest, two trains of electrical stimulation were performed with ISI of one minute to reach the NRIII and VAS.

The same procedure was done once again after taking another 15-min rest and to invoke NRIII and VAS. Electrical stimulation over the posterior tibial nerve at the popliteal fossa was delivered to elicit F-wave of TA as the conventional electrophysiological method. The amplitudes of the F-wave at the controlled and different conditions were measured. The H-reflex of soleus was measured by stimulating the tibial nerve immediately after NRIII was recorded.

Sham Test

On the next day, all the experiments were performed as the previous procedure at the same time, except that the magnetic coil was positioned vertically to the skull to avoid stimulating the cortex other than the sound.

Conditioning sham TMS was applied before the electrical stimulation as the experimental procedure on the previous day. The H-reflex and F-wave amplitudes were again measured.

Statistical Analysis

Conditioned and non-conditioned NRIII amplitudes and VAS ratings of each session were analyzed after the test. ANOVA with repeated measurement was used to evaluate the difference between various responses. A value of $P < 0.05$ was defined as statistically significant. For multiple comparisons, we employed the Wilcoxon rank-sum test. Bonferroni correction was applied for multiple comparisons to ensure that the overall rate of type I errors was not greater than 0.05. Correlation between NRIII amplitude and VAS was performed by Pearson correlation.

Results

In this study, we used electrical stimulation to elicit NRIII and correlated it to VAS. Meanwhile, one single-pulse TMS before the electrical stimulation suppressed NRIII and VAS. There was a prolonged suppression of NRIII and VAS in the conditioning TMS. The results are summarized in Table 1. TMS conditioning influenced the NRIII amplitude and VAS more significantly than the control (both $P < 0.001$) but this effect was not seen in the sham TMS conditioning ($P = 0.86$ and $P = 0.81$). In addition, the decrease in NRIII amplitude and VAS at different TMS conditions was significantly different from the sham test ($P < 0.001$). TMS prior to the electrical stimulation reduced the NRIII amplitude and also the VAS (Fig. 1). The mean controlled NRIII amplitude was 0.65 ± 0.42 mV and the mean controlled VAS was 5.4 ± 1.3. The mean NRIII amplitude was 0.20 ± 0.13 mA, 0.10 ± 0.10 mA and the mean VAS was 3.3 ± 0.9, 2.6 ± 0.5 when the conditioning TMS

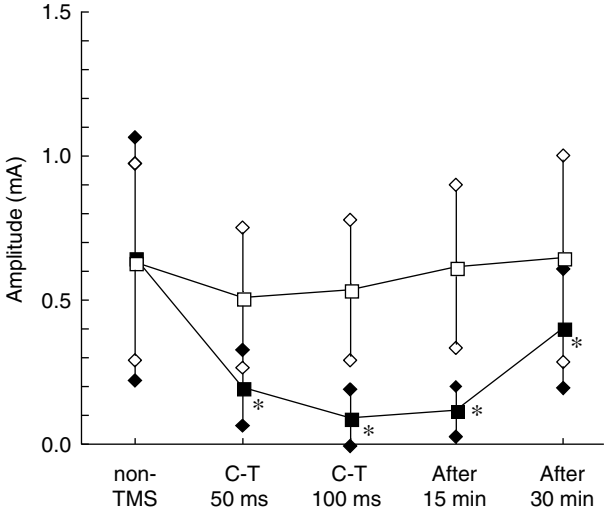

Fig. 1. Amplitudes of nociceptive flexor reflex III (NRIII) in tibialis anterior muscle at different intervals of conditioning test (C-T) of TMS- NRIII. Conditioning TMS was delivered 50 ms and 100 ms before NRIII test (CT 50 ms and CT 100 ms). The amplitude of conditioned NRIII (■, ◆: ± one standard deviation; SD) decreased more significantly than that of the sham test (□, ◇: ± one SD). The NRIII amplitude stayed significantly lowered 15 min and even 30 min after the experiment session (min: minute). *: $P < 0.05$.

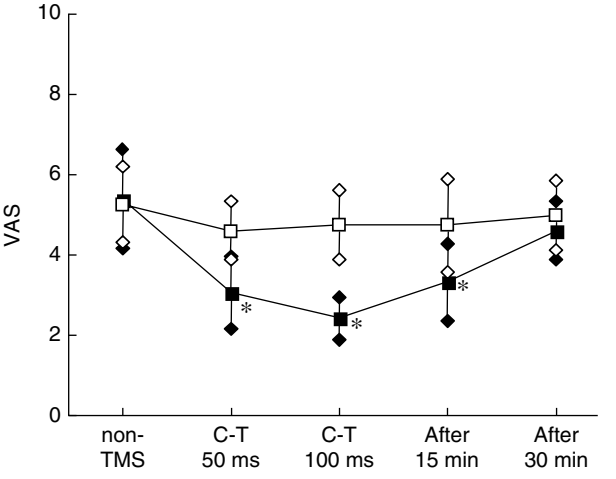

Fig. 2. VAS at CT intervals of 50 ms and 100 ms and electrical stimulations 15 min and 30 min after the conditioning test. The conditioned VAS (■, ◆: ± one SD) decreased more significantly at CT 50 ms and 100 ms than that of the sham TMS (□, ◇: ± one SD) and the reduced VAS lasted for at least 15 min after TMS. The reduction of conditioned NRIII and decreased VAS were well correlated. *: $P < 0.05$.

was 50 and 100 ms before the electrical train stimulation. In both TMS conditions, there was a significant attenuation of the NRIII amplitude ($P = 0.016$ at 50 ms, $P = 0.001$ at 100 ms) and VAS decreasing ($P = 0.002$ at 50 ms, $P < 0.001$ at 100 ms) (Fig. 2). Fifteen min after TMS conditioning, the mean NRIII amplitude (0.12 ± 0.09 mA) and the mean VAS (3.5 ± 0.9) were still significantly inhibited ($P = 0.004$ and $P = 0.005$). Thirty minutes after TMS, the mean NRIII amplitude (0.41 ± 0.21 mA) was again significantly lowered ($P = 0.046$), however, the mean VAS (4.8 ± 0.7) was not different ($P = 0.253$). The reductions in NRIII and VAS during the TMS conditioning and 15 min after the TMS condition were well correlated (correlation coefficient: 0.96, $P < 0.001$). No significant change was found in the H-reflex and F-wave during and after TMS conditioning.

In the sham TMS test, the controlled NRIII amplitude was 0.64 ± 0.34 mV and the controlled VAS was 5.2 ± 1.0. There was no significant difference between the real TMS and sham TMS tests in the controlled NRIII amplitude ($P = 0.95$) or VAS ($P = 0.66$). Decreased NRIII amplitude (0.51 ± 0.24 mV) was only found when sham TMS was 50 ms before electrical stimulation ($P = 0.027$), but no significant change (0.54 ± 0.24 mV) was observed when sham TMS was100 ms before the electrical stimulation ($P = 0.053$). There was no amplitude change 15 or 30 min after the sham TMS conditioning ($P = 0.080$; $P = 0.197$). VAS was significantly decreased only when sham TMS was 50 ms prior to the electrical stimulation (4.8 ± 0.7, $P = 0.033$), but no significant change (4.9 ± 0.8) was found when sham TMS was 100 ms before electrical stimulation ($P = 0.080$) (Fig. 2).

In comparison, TMS significantly lowered the NRIII amplitude than the sham TMS, both at 50 ms and 100 ms before conditioning, $P < 0.001$), and 15, and 30 min after the conditioning ($P = 0.002$; $P = 0.004$). VAS was also significantly decreased by TMS than by the sham TMS 50 ms and 100 ms prior to electrical stimulation ($P = 0.002$; $P < 0.001$) and 15 min after conditioning test ($P = 0.018$), but not 30 min after the conditioning test ($P = 0.35$).

Discussion

In the study, we found that the NRIII might be suppressed under single pulse TMS condition (50 ms and 100 ms before the electrical stimulation). The pain suppression effect (decreased VAS at 2 points) was noted in TMS conditioning and could last for at least 15 min after TMS. Meanwhile, the subjective painful perception was also attenuated along with the NRIII suppression. The prolonged suppression of NRIII and pain should not be considered a placebo effect since the sham TMS could not produce a similar effect.

NRIII is originated from multi-afferent convergence to the interneurons in the spinal cord with

a spatial and temporal interaction between the intraspinal signals. It is also known that supraspinal structures such as cerebral cortex, cerebellum, and brain stem are all involved in the modulation of NR (38). There are clinical reports indicating that supraspinal structures can influence NRIII (1, 9, 10). There exits a high correlation between the pain threshold and NRIII threshold, the pain intensity stimulus-response curve and the reflex size stimulus-response curve (5, 8, 15, 46), suggesting that NR may be an "objective" measure of experimental pain (18, 42).

We used this pain-NRIII correlation to evaluate the suppression effect of single pulse TMS to motor cortex, and observed an immediate pain suppression after single pulse TMS that lasted for a period of time. As it is already known that, most of the studies that described rTMS to the motor cortex as having transient pain relief effect (23, 26, 31), but no report has mentioned a similar effect by single pulse TMS. A long session of rTMS could produce a long effect according to the number of stimulation, the frequency, and the intensity. It is confirmed that a small number of suprathreshold rTMS can induce a transient change of the motor cortex for seconds to minutes (3, 12), whereas longer period of rTMS produced a longer effect (29, 40). There have been no reports on if one single TMS could attenuate pain and if there is a prolonged effect on the cerebral cortex. However, there may still be a similar behavior of a single pulse TMS as rTMS to reduce the pain ratings and also the long lasting effect though it may be less apparent as rTMS. A single session of rTMS to the motor cortex was able to reduce pain shortly (26, 31) and repeated sessions of motor cortex rTMS may prolong the pain relief effect (23).

Repetitive electrical stimulation may induce a gradual decrease of NRIII that is known as "habituation" (13, 39). This phenomenon occurs more easily at lower stimulation intensities (13), at a stimulation frequency of 0.3-1 Hz (14), and at an interstimulus interval (ISI) of 5 sec (17). In contrary, there was no habituation at ISI 25 sec (17) and even a facilitating effect at a higher stimulation frequency (2). We used a high frequency electrical stimulation with a relative high intensity. Also, we delivered the electrical stimulation at a relatively long interval to avoid NRIII habituation. Another issue in our study is the placebo effect of TMS. We applied the sham TMS that only one sound was elicited. There was a mild placebo effect of the sham test both in NRIII and VAS. This was also found in other studies of rTMS (23, 26). However, the pain reduction of real TMS was still more significant than the sham test.

The mechanism of the antalgic effect by TMS on motor cortex stays unknown. An activation of the motor cortex may modulate the projection to thalamus, sensory cortex and other part of cerebrum. Therefore, motor cortex activation may modulate the pain perception structures *via* affecting other sensation related structures. During motor cortex stimulation, there was an increase of blood flow in the ipsilateral thalamus, orbitofrontal and cingulated gyri, and the upper brain stem (19).

In conclusion, we found that one single pulse TMS to motor cortex before electrical painful stimulation over lower limb may suppress the NRIII amplitude as well as VAS. The suppression of NRIII amplitude was well correlated with the decrease in VAS. Furthermore, there was a prolonged effect of pain suppression by single pulse TMS. This indicates that an external stimulation to the cerebrum may change the plasticity of the brain. The mechanism of prolonged pain suppression of TMS to motor cortex remains unclear and needs further neurophysiological investigation.

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