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Cortical excitability changes after high-frequency repetitive transcranial magnetic stimulation for central poststroke pain

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ABSTRACT

Central poststroke pain (CPSP) is one of the most refractory chronic pain syndromes. Repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex has been demonstrated to provide moderate pain relief for CPSP. However, the mechanism underlying the pain relief remains unclear. The objective of this study was to assess changes in cortical excitability in patients with intractable CPSP before and after rTMS of the primary motor cortex. Subjects were 21 patients with CPSP of the hand who underwent rTMS. The resting motor threshold, the amplitude of the motor evoked potential, duration of the cortical silent period, short interval intracortical inhibition, and intracortical facilitation were measured as parameters of cortical excitability before and after navigation-guided 5 Hz rTMS of the primary motor cortex corresponding to the painful hand. Pain reduction from rTMS was assessed with a visual analog scale. The same parameters were measured in both hemispheres of 8 healthy controls. Eight of 21 patients experienced $\geqslant$30% pain reduction after rTMS (responders). The resting motor threshold in the patients was higher than those in the controls at baseline ($P = .035$). Intracortical facilitation in the responders was lower than in the controls and the nonresponders at baseline ($P = .035$ and $P = .019$), and significantly increased after rTMS ($P = .039$). There were no significant differences or changes in the other parameters. Our findings suggest that restoration of abnormal cortical excitability might be one of the mechanisms underlying pain relief as a result of rTMS in CPSP.

1. Introduction

Central poststroke pain (CPSP) is one of the most refractory neuropathic pains caused by the brain lesion of the somatosensory nervous system after cerebrovascular accident, with a reported incidence of 1–8% among poststroke patients [1,3]. These pain symptoms almost always develop within the area of sensory disturbances and have been described as burning, numb, aching, squeezing, or pricking. Medical treatments for CPSP often fail to relieve the pain, and symptoms are persistent in approximately 85% of patients. These pain conditions often disturb poststroke rehabilitation and activities of daily life, thereby reducing the patient's quality of life [18].

For these refractory disease conditions, the electrical motor cortex stimulation (EMCS), whose common target is the precentral gyrus (primary motor cortex; M1), has provided relief in 26–73% of CPSP patients [15,16,33,36,42,43,46]. However, EMCS involves invasive surgery, which requires intracranial electrodes and an implantable pulse generator. In addition, several perioperative complications including stimulation-induced seizure, infection, epidural hematoma, and neurological deterioration have been reported [15,16,33,36,42,43,46]. According to recent reports, noninvasive repetitive transcranial magnetic stimulation (rTMS) can have positive effects in patients with intractable CPSP similar to that of EMCS [2,4,14,17,26,28,41]. Several meta-analyses and systematic reviews have demonstrated that the high-frequency ($\geqslant$5 Hz) rTMS of M1 provides modest and short-lasting effects on neuropathic pain, including CPSP [30,32,34].

The mechanisms underlying rTMS effects on CPSP remain to be elucidated. It has been suggested in several previous reports that EMCS and rTMS of M1 affect the local stimulus sites in M1 and

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the various remote structures that are functionally associated with M1 and involved in chronic pain and pain relief [24,30]. Two positron emission tomography (PET) studies demonstrated that motor cortex stimulation increased the regional cerebral blood flow in the various structures related to pain perception and the emotional aspects of pain, such as the thalamus, insula, limbic system, and upper brain stem [11,19]. Lefaucheur et al. reported that rTMS of M1 restored defective intracortical inhibition in patients with chronic neuropathic pain and proved the alterations within the stimulus site [27]. However, the patient characteristics in these previous reports were heterogeneous. These subjects were patients with CPSP, but some also had neuropathic pain due to spinal or peripheral nerve lesions.

In this study, we concentrated the rTMS effects within M1 in patients with CPSP. A single- or paired-pulse transcranial magnetic stimulation (TMS) allowed us to evaluate the cortical excitability of M1, measuring motor evoked potentials (MEP) [23,47]. The objective of this study was to assess the alterations of cortical excitability in patients with intractable CPSP before and after rTMS of M1.

2. Methods

2.1. Subjects

Subjects were 21 consecutive patients with CPSP (12 men and 9 women), with a mean ± standard deviation age of 59.6 ± 9.0 years and with an average pain duration of 48.1 ± 55.0 months before the experiment. All patients were diagnosed with CPSP according to the following criteria [20]: (1) development of pain after stroke, (2) sensory disturbance corresponding to the cerebral lesion, (3) pain located within the region of sensory disturbance, and (4) exclusion of other causes of pain. All patients had an intractable continuous pain in their hand lasting more than 6 months despite appropriate medical treatments. We excluded patients with severe motor weakness corresponding to less than grade 2 in the manual muscle test because of the insufficient MEP evoked by TMS in the affected hand. The lesions from stroke were located in the thalamus ($n = 8$), putamen ($n = 7$), brain stem ($n = 4$), and subcortex ($n = 2$). All the patients had a sensory deficit in their painful zone and described their pain as burning, aching, squeezing, pricking, or numb; pain occurred in the unilateral body including the hand. Allodynia was observed in 13 patients (62%) and hyperpathia in 4 patients (19%). Patient characteristics and clinical data are summarized in Table 1.

Eight healthy volunteers were also enrolled onto this study (8 men; mean age, 52.5 ± 10.0 years). All subjects were right-handed. They had no neurological diseases, and no lesions were evident on magnetic resonance imaging.

2.2. Overview of experiments

A session of 5 Hz rTMS of M1 corresponding to the painful hand was applied to all the patients [14,41]. Cortical excitability within M1 was evaluated by the single- or paired-pulse TMS before and after an rTMS session. Cortical excitability was measured in the same side as rTMS performance. Pain intensity was examined in each patient before and after rTMS using a visual analog scale (VAS). The healthy controls underwent the same single- or paired-pulse TMS measurements in M1 of both hemispheres. We assessed alterations in cortical excitability and the relationship between pain relief and cortical excitability changes.

The ethics committee of Osaka University Hospital approved this study (approval 07099), and written informed consent was obtained from all subjects participating in this study.

2.3. Motor cortical excitability testing

Motor cortical excitability testing was applied by the single- or paired-pulse TMS using a reversed-current, figure-8 double 70-mm coil (Magstim Company, Carmarthenshire, UK) and the Magstim 200 magnetic stimulator (Magstim Company). A Magstim 200 magnetic stimulator provides single monophasic pulses. Two Magstim 200 magnetic stimulators were connected to a Bistim module (Magstim Company) delivering paired pulses. Subjects lay down on the bed to keep their hands relaxed, and their heads were fixed to avoid displacement of the stimulus site during cortical excitability testing and rTMS. The center of the TMS coil was placed on M1 corresponding to the hand using the optical TMS navigation system (Brainsight, Rogue Research Inc, Montreal, Quebec, Canada) and fixed by means of an articulated coil holder. The handle of the reversed-current coil was directed anteromedially so that the intracerebral current was induced to the same direction as the standard double coil handle placed in the posterolateral direction. Finally, the optimal stimulus site was determined on the basis of the highest amplitude MEP in the abductor pollicis brevis (APB) muscles. The MEPs were recorded from surface electrodes placed on the belly and tendon of the contralateral APB muscles through a 20 to 3000 Hz band-pass filter using Neuropack electromyography (MEB-2208, Nihon Kohden, Tokyo, Japan).

Five indices, including (1) resting motor threshold (RMT), (2) MEP amplitude at 120% of RMT (MEP120), (3) cortical silent period (CSP), (4) short interval intracortical inhibition (SICI), and (5) intracortical facilitation (ICF), were measured as parameters of motor cortical excitability. The RMT was defined as the minimum stimulus intensity evoking MEPs of $\geqslant 50$ μV at least 5 of 10 times under complete muscle relaxation [39]. RMT was measured by reducing the stimulus intensity in steps of 1% from the suprathreshold intensity. Complete muscle relaxation was monitored by the electromyograms (EMG) from the APB muscles. Subsequently, 15 MEPs were recorded at 120% of RMT, and the average peak-to-peak amplitude of MEPs was determined as MEP120. CSP was measured by single TMS pulses at 130% of RMT, while subjects executed a continuous maximum voluntary contraction of their APB muscles. To ensure adequate contractions of the target muscle, EMG feedback was provided for the subjects. Eight trials were rectified and superimposed. CSP was defined as the minimum duration from stimulus delivery to the return of voluntary activity [21]. Paired-pulse stimulation was performed in accordance with Kujirai et al. [23]. A conditioning stimulus was set at 80% of RMT, and a test stimulus was set at 120% of RMT. Interstimulus intervals were set at 2 and 4 ms for SICI, and 10 and 15 ms for ICF. Ten trials of each interstimulus interval were randomly intermixed with nonconditioned trials (test stimulus only). Finally, a total of 50 trials were delivered, and the average peak-to-peak MEP amplitude ($MEP_{conditioned}$) was calculated for each condition. SICI and ICF were defined follows: SICI = 100% − ($MEP_{conditioned}/MEP_{nonconditioned}$) and ICF = $MEP_{conditioned}/MEP_{nonconditioned}$. Each stimulation was separated by at least 5 s in order to avoid carryover effects.

2.4. rTMS procedure

The rTMS was applied through a figure-8 coil (MC B-70, Medtronic Functional Diagnostics A/S, Skovlunde, Denmark) and connected to a MagPro magnetic stimulator (Medtronic Functional Diagnostics A/S), which provides repetitive biphasic pulses. The TMS coil was placed with the optical TMS navigation system (Brainsight) and fixed by the coil holder in the same way used for motor cortical excitability testing. The RMT was determined by stimulation of the region of M1 corresponding to the hand representation. A potential equivalent to 90% intensity of RMT was used for repetitive stimulation. Ten trains of 5 Hz rTMS were delivered