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Changes in motor evoked potentials in the suprahyoid muscles by repetitive transcranial magnetic stimulation

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ABSTRACT Motor cortical excitability is generally increased by highly frequent repetitive transcranial magnetic stimulation (rTMS) of the motor cortex. However, there are few studies of the effect of high-frequency rTMS on serial changes of motor evoked potentials (MEPs) recorded from swallowing-related muscles. The purpose of this study was to investigate whether facilitation of the suprahyoid muscles is induced by rTMS of the motor cortex. The subjects were 15 healthy adult volunteers, all of whom were right-handed. A total of 150 pulses of rTMS at 5 Hz were applied to the left motor cortex for 30 seconds at the intensity of the resting motor threshold, followed by rest for 30 seconds. This set was repeated 5 times, providing 750 pulses in total. MEPs in the anterior belly of the digastric muscles on both sides were recorded before rTMS, immediately after rTMS, and then every 5 minutes for 60 minutes after rTMS. The mean MEP amplitude for the left muscles was significantly higher than that for the right muscles in all subjects. The MEP amplitude significantly increased immediately after rTMS on both sides. The excitation was 20 to 40% higher than the baseline MEPs and persisted until 35 minutes after rTMS. These results suggest that rTMS intervention induces long-term potentiation in the motor pathway that is conducted to the suprahyoid muscles. This kind of rTMS-evoked plasticity may have an application in treatment of patients with pseudobulbar palsy.

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Key words : **Repetitive transcranial magnetic stimulation, Motor evoked potential, Dysphagia, Facilitation, Long-term potentiation, Neurorehabilitation**

INTRODUCTION

Dysphagia is a common and stressful impairment of unilateral hemispheric stroke that develops in one-third of patients immediately after stroke [1]. Mortality attributed to aspiration pneumonia for stroke patients is notably high in the acute phase. Two-thirds of patients with dysphagia show spontaneous recovery within several weeks, while another third have persistent dysphagia [2]. Therefore, development of effective treatment in neurorehabilitation is required for stroke patients. Transcranial magnetic stimulation (TMS) is a new noninvasive approach that uses direct stimulation of the cerebral cortex. TMS is utilized for evaluation of

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brain function and for treatment to improve cerebral dysfunctions[3-5]. Several studies using different repetitive TMS (rTMS) parameters have reported different modulation of cortical excitability ranging from inhibition to facilitation[6, 7]. A combination of up- and downregulation by rTMS may allow efficient changes in cerebral function. TMS is also a painless and noninvasive technique, and Fregni et al. showed recovery of motor function in stroke patients after low-frequency rTMS of the unaffected hemisphere[8]. Functional recovery has also been reported after application of high-frequency rTMS over the affected hemisphere in order to reactivate hypoactive regions[9].

Several studies of recordings of MEPs from swallowing-related muscles have been performed[6, 7]. Hamdy et al. reported that TMS induced direct corticobulbar projections from the motor cortex to the swallowing-related muscles[10-14]. These projections were bilateral but asymmetric, and were not related to the dominant hand. In most of these studies, electromyographic responses were recorded in the pharyngeal muscles and striated musculature in the upper esophagus using platinum ring electrodes attached to an intraluminal catheter[1, 6, 7, 10, 12, 13, 15-17]. Therefore, there is a need to clarify whether the same projections occur from the motor cortex to the suprahyoid muscles, which play a leading role in the swallowing reflex. There are no studies of the effect of high-frequency rTMS on serial changes of MEPs recorded from the suprahyoid muscles, although a few reports have shown that continuous stimulation of the cerebral cortex facilitates the function of the pharyngeal muscles[11, 14, 17].

In the present study, the TMS-evoked MEPs for the anterior belly of the digastric muscles were determined because these are the most superficial muscles among the suprahyoid muscles. In addition, we investigated whether facilitation of these muscles was obtained by high-frequency rTMS of the motor cortex. Positive results may illustrate the potential for application of rTMS-induced cerebral plasticity in treatment of dysphagia.

MATERIALS AND METHODS

Subjects

A total of 15 healthy adult volunteers (13 males and 2 females) with a mean age of 23 years old participated in the study. All of the subjects were right-handed. Persons with neurological disorders or epilepsy, those with a history of neurosurgical procedures, and those with implanted metal medical devices including implants and pacemakers were excluded from the study.

Device

The Dantec Magstim (Dantec, Denmark) and a round-shaped coil (Dantec, Denmark) were used for magnetic stimulation. The largest magnetic field was generated locally immediately beneath the center hall of this coil. The electromyographic response to left cortical stimulation was recorded on the anterior belly of the digastric muscles on both sides using silver chloride electrodes. A ground electrode was positioned on the mental protuberance. Recordings were made using Neuropack-μ (Nihon Kohden Corporation, Japan) with the sensitivity set at 50 μV/division and the filter at 1-1,000 Hz. This study was approved by the Ethics Committee of Kawasaki Medical School. The subjects gave informed consent after receiving a full explanation of the study.

Procedures

The subjects were seated in a comfortable armchair. The CZ point was determined on the top of the head in accordance with the International 10-20 System Electrode Placement Criteria[18]. Recording electrodes were put on the skin of the neck just above the anterior belly of the digastric muscles on both sides. TMS was given on the left cerebral hemisphere for determining the intensity of the resting motor threshold (RMT). The site where the maximum MEP was evoked from the target muscle by a single weak stimulus was found by moving a ring-shaped coil in the left lateral and anteroposterior directions on the scalp in steps of 1 cm. The site with the maximum MEP was defined as the optimally stimulated site and named the motor hot-spot. The RMT was defined as the lowest stimulation intensity evoking an MEP $\geq 50\ \mu V$ on the motor hot-spot 5 times in 10 stimulation trials. Changes of MEPs were measured with a single stimulus at 120% RMT.

A baseline MEP was recorded prior to rTMS. A total of 150 pulses of rTMS at 5 Hz were then applied to the left motor cortex for 30 seconds at an intensity of 100% RMT, followed by rest for 30 seconds. This set was repeated 5 times, providing 750 stimuli in total. This process was referred to as 5-minute rTMS intervention. MEPs were recorded immediately after rTMS, and then every 5 minutes for 60 minutes after rTMS. The amplitude of each MEP was measured as a peak-to-peak value. The distance between the CZ point and the optimally stimulated site in anteroposterior and lateral directions and the stimulus intensity were also examined. Statistical analysis was performed using a paired t-test.

RESULTS

The MEP waves potentiated by rTMS in Subject 1 are shown in Fig. 1. The baseline MEP in the left anterior belly of the digastric muscle was larger than

-200 μV/10ms

Fig. 1. Baseline MEPs and MEPs potentiated by rTMS in Subject 1. MEP waves at rest, immediately after rTMS, and every 5 minutes for 60 minutes after rTMS are shown serially from left to right. The upper and lower MEP waves are those evoked from the left and right anterior belly of the digastric muscles.

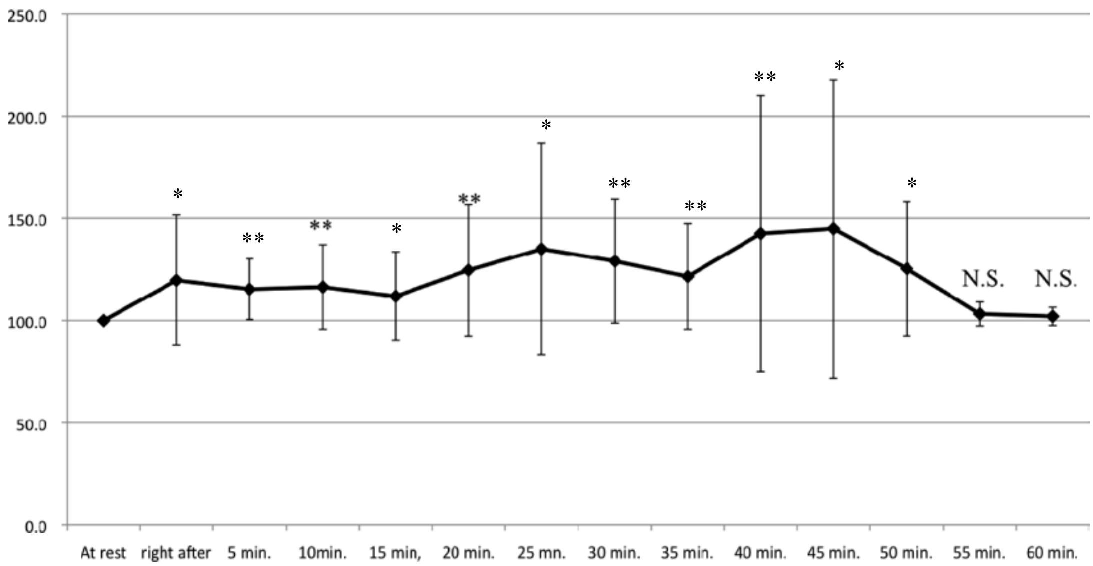

Fig. 2. Changes in MEP amplitude of the left anterior belly of the digastric muscle in all subjects. Excitability refers to the relative amplitude of MEPs (MEP / baseline MEP). A paired t-test was used for statistical analysis. * p<0.05, ** p<0.01, N.S.: not significant.

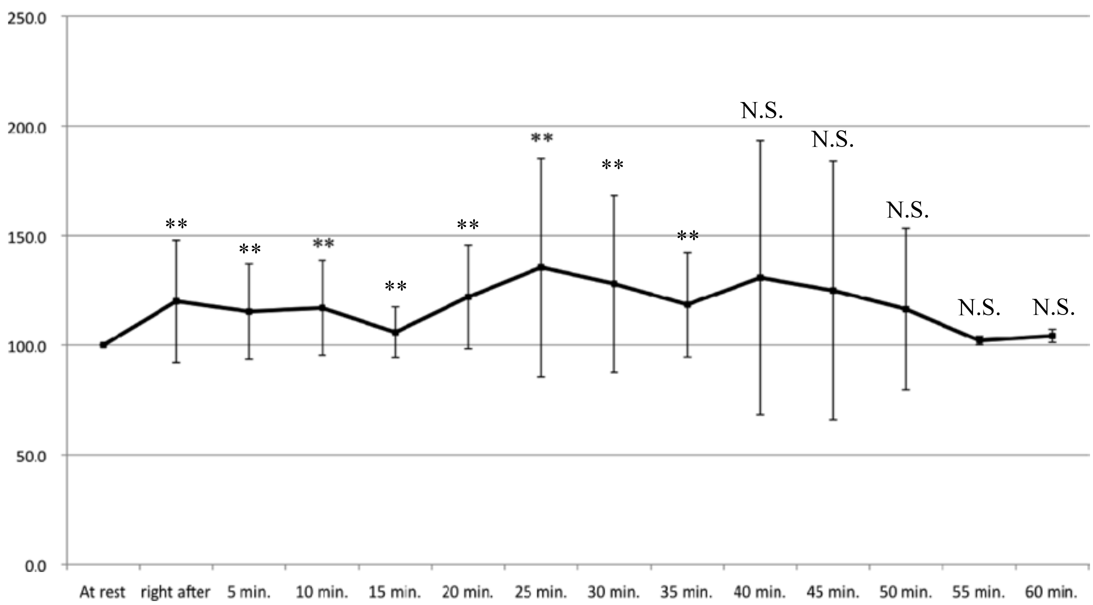

Fig. 3. Changes in amplitude of MEPs for the right anterior belly of the digastric muscle in all subjects. Excitability refers to the relative amplitude of MEPs (MEP / baseline MEP). A paired t-test was used for statistical analysis. * p<0.05, ** p<0.01, N.S.: not significant.

that in the right muscle. While the MEP amplitude increased on both sides after rTMS, the amplitude of every MEP on the left was larger than on the right. Excitation was sustained until 60 minutes after rTMS.

The mean amplitude of the baseline MEPs on the left (609 ± 365 μV) in all subjects was significantly higher than that on the right (278 ± 188 μV). The mean latencies of the baseline MEPs were 4 ± 1 ms on the left and 5 ± 0 ms on the right, with no significant difference between these values. Changes in the MEP amplitude of the left anterior belly of the digastric muscle in all subjects are shown in Fig. 2. The amplitude of MEPs significantly increased after rTMS. The excitation was approximately 20 to 40% higher than the baseline MEP, and this condition persisted until 50 minutes after rTMS. Changes in the MEP amplitude in the right anterior belly of the digastric muscle in all subjects are shown in Fig. 3. The amplitude also significantly increased after rTMS in the right MEPs, and the excitation was approximately 20 to 30% higher than the baseline MEPs and persisted until 35 minutes after rTMS.

The optimal stimulation site was located 15 ± 2 cm outward and 0 ± 2 cm forward from the CZ point, and the mean stimulation intensity was 18 ± 3% of the maximum stimulator output.

DISCUSSION

The results of the present study showed that TMS-evoked MEPs for the bilateral anterior belly of the digastric muscles can be recorded using surface electrodes. Hamdy et al. and Khedr et al. recorded MEPs mainly in the pharyngeal muscles and striated musculature in the upper esophagus using platinum ring electrodes attached to an intraluminal catheter[1, 6, 7, 10, 12, 13, 15－17]. Consequently, it was unclear from which muscles MEPs were derived, since contamination by volume conduction was not verified. While the anterior belly of the digastric muscles is known to be the most superficial of the suprahyoid muscles, we have shown that MEPs using surface electrodes have the same latency as potentials recorded from a needle electrode inserted into the muscle (unpublished data).

Several studies have shown that the primary motor cortex is involved in evoking of voluntary swallowing, while others have indicated that voluntary swallowing is evoked by the insular, cingulate cortex or supplementary motor area [13, 15, 20]. Some studies have also suggested that the regions of the motor cortex related to the swallowing muscles could be stimulated by TMS, and have indicated that swallowing has bilateral but asymmetric interhemispheric associations within the motor and premotor cortex[5, 7－10]. The latency of MEPs measured in our study was faster than that in previous studies, which made it highly unlikely that TMS activated these areas; however, it could not be ruled out that TMS activated neurons in the brainstem or the direct corticobulbar projection. In addition, the MEP amplitude was somewhat larger than that in previous studies, and was found to be higher on the same side of the stimulation than on the opposite side. The results also suggest that TMS evokes potentials distal to the motor cortex, although TMS was applied to the left cerebral hemisphere. Specifically, it may be possible to stimulate the central pattern generator in the swallowing center, including the reticular formation, nucleus of the solitary tract, ambiguous nucleus, and trigeminal motor nucleus, through certain interneurons. Further studies are needed to identify the precise point of stimulation.

There are no reports on the effect of high-frequency rTMS on serial changes of MEPs recorded from suprahyoid muscles, although it has been shown that continuous stimulation of the cerebral cortex at 5 Hz facilitates the pharyngeal muscles[11, 14, 17]. In the present study, the amplitude of MEPs recorded from the bilateral anterior belly of the digastric muscles significantly increased after rTMS, and the excitation was approximately 20 to 30% higher than the baseline MEPs. Our results suggest that rTMS intervention induces long-term potentiation in the motor pathway that is conducted to the suprahyoid muscles. This kind of rTMS-evoked plasticity may be effective for treatment of dysphagia in patients with pseudobulbar palsy. Further studies are required to confirm the effectiveness of treatment using rTMS.

In conclusion, short latency and high amplitude MEPs were recorded from the bilateral anterior belly of the digastric muscles using surface electrodes, and the amplitude on the same side as the TMS was found to be higher than that on the opposite side. Long-term potentiation in MEPs recorded from bilateral muscles was induced by rTMS, and the excitation was approximately 20 to 30% higher than the baseline MEPs.

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