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Neuroscience Letters 286 (2000) 199–202

Neuroscience Letters

www.elsevier.com/locate/neulet

Loss of the muscle silent period evoked by transcranial magnetic stimulation of the motor cortex in patients with cervical cord lesions

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Received 17 April 2000; accepted 24 April 2000

Abstract

The silent period following motor evoked potentials in small hand muscles after transcranial magnetic stimulation (TMS) of the human motor cortex is considered to be cortical origin. The authors report three patients with cervical spinal cord lesions who showed loss of the cortical silent period (CSP) after TMS. One patient had traumatic cervical cord injury, and the other two patients had cervical spondylosis. All the patients had cervical cord compression on magnetic resonance imaging. TMS study showed loss of the CSP in both the hand and foot muscles in two patients and only in the foot muscle in one patient. Paired TMS study in one patient with pseudoathetotic hands showed reduced inhibition within the motor cortex. The hand weakness or interrupted sensory afferents might have caused motor cortical reorganization or hyperexcitability, leading to the loss of the CSP.

Keywords: Transcranial magnetic stimulation; Cortical silent period; Cervical cord lesion; Cortical excitability; Cortical reorganization; Paired cortical stimulation

Transcranial magnetic stimulation (TMS) of the human motor cortex during voluntary muscle contraction induces inhibition of muscle activity (cortical silent period: CSP) after the motor evoked potentials (MEPs) in small hand muscles [1,4,7]. Although various neurological disorders shorten or lengthen the CSP, loss of the CSP was reported only in a case of a small ischemic stroke localized in the motor cortex [9]. We herein report three patients with cervical spinal cord lesions who showed loss of the CSP, and discuss its pathomechanism and cortical plasticity after spinal cord damages.

We examined three patients with cervical cord lesions using TMS. Patient 1 was a 30-year-old woman with Machado–Joseph disease. She fell in November 1997, and then, tetraparesis developed because of a cervical cord injury. Cervical magnetic resonance imaging (MRI) showed protrusion of C4/5 and C5/6 intervertebral discs with intramedullary signal changes (Fig. 1A). Cervical discectomy and anterior vertebral fusion were performed. Thereafter, the tetraparesis gradually improved, but bilateral pseudoathetotic hand postures, hand muscle atrophy, right forearm sensory deficit, and spastic paraparesis remained. Median and tibial nerve somatosensory evoked potentials (SSEP) showed loss of bilateral cervical spinal and cortical components. Patient 2 was a 55-year-old man with myelopathy due to multiple protrusions of cervical discs with cord compression (Fig. 1B). He had brisk reflexes in the four limbs and sensory disturbances in bilateral legs as a symptom of cervical myelopathy, but no weakness. Nerve conduction study was unremarkable, but tibial nerve SSEP showed central conduction delay. He underwent cervical posterior decompressive laminoplasty. Patient 3 was a 50-year-old man with radiculopathy due to cervical spondylosis with spinal canal stenosis (Fig. 1C). He showed weakness and decreased reflexes in the left upper extremity without sensory disturbances. SSEP was unremarkable to median nerve stimulation, but showed central conduction delay to tibial nerve stimulation. He was treated conservatively. TMS was performed three months after the operation in patient 1, and four months postoperatively in patient 2.

We obtained the informed consent of the patients for the following examination, after the approval by the local ethics committee. MEPs were recorded using surface electrodes from unilateral (right in patient 1; left in patients 2 and 3) first dorsal interosseus (FDI) and flexor hallucis brevis (FHB) muscles after TMS via a figure-of-eight coil (mean diameter of 70 mm) connected to a Magstim 200 stimulator (Magstim Company, Whitland, Dyfed, UK). The coil was

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0304-3940/00/$ - see front matter
PII: S0304-3940(00)01125-3

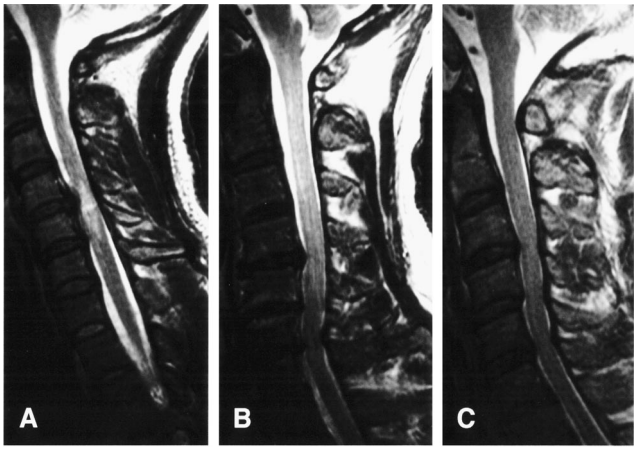

Fig. 1. T2-weighted MRIs of the cervical spine and spinal cord in patients 1 (A), 2 (B) and 3 (C).

placed tangentially to the scalp, with the handle pointing backward for FDI and perpendicular to the parasagittal line for FHB. The scalp stimulation was delivered on the site where the largest MEPs were obtained for each FDI or FHB. The threshold was determined in tonically active muscles as the minimum stimulation intensity (%) that evoked a clearly distinguishable MEP from the background EMG. Then MEPs were recorded from FDI or FHB during contraction with about half of the maximum force. The stimulus intensity was 100% of the stimulator's output. CSP was measured as the interval between the time of TMS and visible resumption of EMG following the CSP with a gain of 0.2 mV/cm. We calculated the averages of peak-to-peak MEP amplitude and CSP of eight consecutive responses. Furthermore, ten patients with Machado–Joseph disease (six women and four men; mean age 45.2 years) were also similarly examined for comparison with the results in patient 1.

Next, for patient 1, we investigated intracortical inhibitory function using the paired TMS technique [5]. We used a figure-of-eight coil and two Magstim 200 connected to a Bistim device. The target muscle was the right relaxed FDI. The conditioning stimulus intensity was 5% below the threshold and the test stimulus intensity was set at the intensity that evoked MEPs of approximately 0.5 mV amplitude. Interstimulus intervals (ISIs) varied from 1 to 10 ms. Non-conditioned (control) and conditioned test stimuli were randomly intermixed. We collected eight conditioned and non-conditioned responses for each ISI, and measured peak-to-peak MEP amplitudes. Thereafter, the amplitude of the conditioned response was expressed as a percentage to that of the control response (MEP amplitude ratio). We used multiple analysis of variance (MANOVA) for the statistical analysis for amplitude inhibition of conditioned test MEPs for each ISI. The result was also compared with the data of ten healthy control subjects (four women and six men; mean age 32.3 years). The level of significance was set at five percent.

The thresholds in patients 1 to 3 were 32, 42 and 46% for FDI, and 48, 58 and 58% for FHB, respectively. All the patients showed clearly visible MEPs for FDI and FHB. In patient 1, there was no definite CSP for FDI, and for

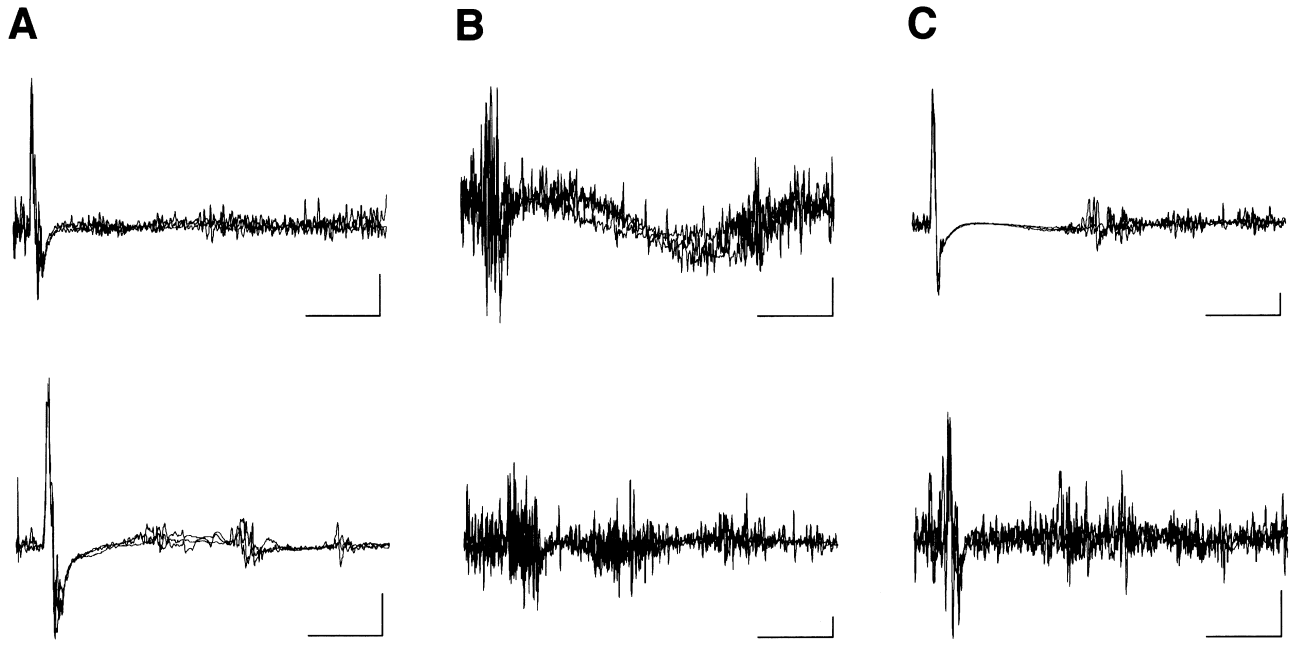

Fig. 2. MEP waveforms and cortical silent period during voluntary contraction of the first dorsal interosseus (upper column) and flexor hallucis brevis (lower column) muscles in patients 1 (A), 2 (B) and 3 (C). Three recordings were superimposed for each muscle. The points of magnetic stimulation were at the beginning of each trace. Horizontal bars represent 100 ms for each patient. Vertical bars represent 1 mV for patients 1 (A) and 3 (C), and 0.2 mV for patient 2 (B).

FHB, background EMG was suppressed but not completely after MEP (Fig. 2A). Patient 2 showed no CSP for either FDI or FHB (Fig. 2B). In patient 3, FDI showed CSP, but there was no CSP in FHB (Fig. 2C). Among ten patients with Machado–Joseph disease, there were no patients who showed loss of CSP. In the paired stimulation study in patient 1, significant MEP inhibition was noted only at ISI of 3 ms, whereas the control subjects showed significant inhibition at ISIs of 1 to 5 ms (Fig. 3).

The silent period after TMS consists of an early component affected by decreased spinal motor neuron excitability and a delayed component due to suprasegmental, presumably intracortical, mechanisms [12]. Recent investigators, however, reported that the entire CSP might be of cortical origin [7,9]. In fact, selected patients with focal ischemic lesions showed loss of the CSP despite intact MEP sizes, suggesting that both the early and late components of the CSP may originate within the motor cortex [7,9]. In addition, the silent period can appear without any appreciable excitation after cortical stimulation, indicating that such inhibition is cortical in origin and independent of muscle excitation [14].

Our patients presented here had no cortical lesions, and the losses of the CSP were unlikely to have originated from cortical lesions. Although patient 1 had Machado–Joseph disease, our experience in ten other patients with Machado–Joseph disease ruled out its relation to the loss of the CSP. Motor cortical excitability and inhibitory actions in the motor cortex can be influenced by various conditions such as ipsilateral motor cortical stimulation, and transcallosal or somatosensory activation [3,8,10,11]. Sensory deprivation of the skin over the FDI muscle reduces the size of motor cortical representation [8]. In contrast, peripheral sensory nerve stimulation shortens the CSP [3].

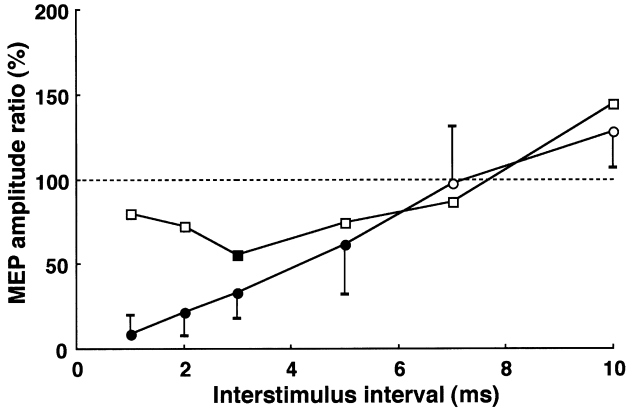

Fig. 3. Effect of subthreshold conditioning stimulation as percentages of the mean conditioned to non-conditioned MEP amplitude for relaxed first dorsal interosseus muscle in the paired stimulation study in patient 1 (square) and ten control subjects (circle). Values below 100% represent inhibition. Vertical bars represent SD. Closed square and circles represent significant inhibition (MANOVA, $P < 0.05$). Control MEP amplitudes are represented by a horizontal dashed line.

Considering that all the patients had cervical cord compression on their MRIs and that patients 2 and 3 had no overt sensory disturbances in the hands, abnormal ascending impulses produced by the cervical cord lesions, not disruption of sensory afferents, might have induced secondary motor cortical hyperexcitability, resulting in the CSP loss. The pseudoathetotic hands in patient 1 might also have been associated with the cortical hyperexcitability. The result of the paired TMS study also supported this hypothesis. The influence of Machado–Joseph disease itself on the motor cortical inhibition was unlikely, because cortical inhibitory function by this paradigm has been reported to be usually normal in patients with spinocerebellar degeneration [15].

The other candidate for the CSP loss is hyperexcitability of spinal motor neurons. The pseudoathetotic hands in patient 1 might have resulted from disturbance of propriospinal inhibitory interneurons, resulting in abnormal firing of spinal motor neurons. However, this is not sufficient to explain the CSP loss, which was also observed in the foot muscles.

Spinal cord injury, complete or incomplete, has been reported to induce reorganization of motor cortical function [2,6,13]. Motor responses to TMS are enhanced in proximal muscles to paretic hands or at rostral levels to spinal cord lesions [6,13]. Cortical inhibition also becomes weak or absent as a cortical plasticity to corticospinal tract dysfunction, and may contribute to restoration of useful motor function [2]. The loss of the CSP in our patients is compatible with those reports. The reorganized, disinhibited motor cortical function might have participated in the relative preservation of motor function, especially in patients 1 and 3, who showed hand weakness. The loss of the CSP in patients with cervical cord damages may be ascribable to plastic nature of the motor cortex.

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