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Research Report

Neural mechanism of central inhibition during physical fatigue: A magnetoencephalography study

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ABSTRACT

Central inhibition plays an important role in physical performance during physical fatigue. We tried to clarify the neural mechanism of central inhibition during physical fatigue using the magnetoencephalography (MEG) and a classical conditioning technique. Twelve right-handed volunteers participated in this study. Participants underwent MEG recording during the imagery of maximum grips of the right hand guided by metronome sounds for 10 min. Thereafter, fatigue-inducing maximum handgrip trials were performed for 10 min; the metronome sounds were started 5 min after the beginning of the handgrip trials. We used metronome sounds as conditioned stimuli and maximum handgrip trials as unconditioned stimuli to cause central inhibition. The next day, MEG recording during the imagery of maximum grips of the right hand guided by metronome sounds were measured for 10 min. Levels of the fatigue sensation in the right hand and sympathetic nerve activity on the second day were significantly higher than those on the first day. In the right dorsolateral prefrontal cortex (Brodmann's area 46), the alpha-band event-related desynchronization (ERD) of the second MEG session relative to the first session with the time window of 200 to 300 ms after the onset of handgrip cue sounds was identified. The ERD level in this brain region was positively associated with the change in subjective level of right hand fatigue after the conditioning session and was negatively associated with that of the sympathetic nerve activity. We demonstrated that the right dorsolateral prefrontal cortex is involved in the neural substrates of central inhibition during physical fatigue.

1. Introduction

Fatigue can be defined as the difficulty in initiating or sustaining voluntary activities (Chaudhuri and Behan, 2004). Fatigue can be classified as physical or mental, and physical fatigue can be classified as peripheral or central. In contrast to peripheral fatigue, central fatigue is caused at sites proximal to the peripheral nerves and is defined as a progressive decline in the ability to activate muscles voluntarily (Gandevia et al., 1996; Taylor et al., 1996).

Increased inhibition from groups III and IV afferent nerves, which carry sensory information to the central nervous system, to motor neurons in the spinal cord, was reported during physical fatigue (Hayward et al., 1988; Garland et al., 1988;

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Hayward et al., 1991; Garland, 1991; Garland and Kaufman, 1995). The inhibitory input to the motoneuron pool in the spinal cord projects to output neurons in the primary motor cortex (M1) through ascending pathways and the inhibitory input changes the signals of these cells in M1 (Peltier et al., 2005). The inhibitory input from the spinal cord thus seems to contribute to fatigue-related changes in M1.

The supraspinal existence of central fatigue was suggested in a neuroimaging study using Ramachandran's mirror box (Tanaka et al., 2011). Ramachandran's mirror box was constructed by placing a vertical mirror inside a cardboard box with the roof of the box removed; the front of the box had two holes in it through which the participants inserted their arms (Ramachandran et al., 1995). The movement-evoked magnetoencephalography (MEG) response to the imagery of maximum voluntary contractions in the contralateral sensorimotor area was reduced by physical fatigue without the mirror box; however, this reduction completely disappeared with the mirror box. These results confirmed that sensory input was channeled to the ipsilateral M1 using the mirror box, and provided evidence for supraspinal existence of central inhibition (Tanaka et al., 2011).

Recently, we performed a neuroimaging study of classical conditioning of physical fatigue (Tanaka et al., 2013). In this study, metronome sounds were used as conditioned stimuli and physical task trials were used as unconditioned stimuli to cause physical fatigue. Participants underwent MEG measurements during the imagery of maximum handgrips guided by metronome sounds for 10 min. Thereafter, fatigue-inducing physical task trials were performed for 10 min; metronome sounds were started 5 min after the beginning of the task trials. The next day, neural activities during the imagery of maximum handgrips guided by metronome sounds for 10 min were measured. The level of fatigue sensation caused by listening to the metronome sounds on the second day was higher relative to the first day and the equivalent current dipoles (ECDs) in the insular cortex and posterior cingulate cortex were observed only after the conditioning session. These MEG results showed that classical conditioning of physical fatigue took place, and that these brain regions were involved in the neural substrates of physical fatigue related to classical conditioning. However, some brain regions involved in the neural substrates of physical fatigue were thought to have been missed because of limitations of the ECD method. In addition, these brain regions were reported to contribute to fatigue sensation rather than to central inhibition during physical fatigue (Ishii et al., 2012). Therefore, the neural mechanisms of central inhibition during physical fatigue have not been clarified.

The aim of our present study was to identify the neural mechanisms of central inhibition related to classical conditioning during physical fatigue. We tried to identify the neural substrates of central inhibition through the comparison of neural activities during the imagery of maximum handgrips between conditioned and unconditioned states, as the difference between these conditions has been shown to be limited to the presence and absence of central inhibition (Tanaka et al., 2012; Shigihara et al., 2013a; Tanaka et al., 2013). In addition to having a high temporal resolution, MEG has an advantage of measuring brain activity using time–frequency analyses (Stam, 2010). Oscillatory brain rhythms are considered to originate from synchronous synaptic activities of a large number of neurons (Brookes et al., 2011). Synchronization of neural networks may reflect integration of information processing, and such synchronization processes can be evaluated using MEG time-frequency analyses; multiple, broadly distributed, and continuously interacting dynamic neural networks are achievable through the synchronization of oscillations at particular time–frequency bands (Varela et al., 2001). In particular, event-related desynchronization (ERD) of alpha frequency band (8–13 Hz) was reported to be associated with fatigue in the central nervous system (Shigihara et al., 2013b; Ishii et al., in press). Alterations of the decreased MEG alpha power densities in some brain regions induced by classical conditioning during the imagery of maximum handgrips may provide valuable clues to identify the neural mechanism of central inhibition. In addition, the correlation analyses between the MEG variables and changes of subjective and physiological parameters after classical conditioning may provide important clues regarding the roles of MEG variables on physical fatigue.

2. Results

To assess changes in the subjective level of fatigue after the 10-min maximum handgrip trials, two-way analyses of variance (ANOVAs) for repeated measures were performed. Significant main effects of hand [$F(1,11)=63.43$, $P<<0.001$] and time course [$F(1,11)=35.21$, $P<<0.001$] and a hand × time course interaction effect [$F(1,11)=39.18$, $P<<0.001$] were shown. The level of subjective fatigue of the right hand after the handgrip trials was significantly higher than before the handgrip trials (Fig. 1A). However, the level of subjective fatigue of the left hand was not altered after the handgrip trials (Fig. 1A). The handgrip force of the right hand after the handgrip trials was significantly lower than that before the trials (Fig. 1B).

To assess changes in the subjective level of fatigue after the conditioning session, comparisons of fatigue scores before and after the first and second MEG sessions were performed. Although the main effect of conditioning [$F(1,11)=2.80$, $P=0.122$] was not shown, a significant main effect of time course [$F(1,11)=11.83$, $P<<0.001$] and a conditioning × time course interaction effect [$F(1,11)=7.45$, $P=0.019$] were shown in the right hand. The main effects of conditioning [$F(1,11)=0.18$, $P=0.681$] and time course [$F(1,11)<<0.01$, $P=1.000$] and a conditioning × time course interaction effect [$F(1,11)=3.48$, $P=0.089$] were not shown in the left hand. Subjective levels of right hand fatigue after the second MEG session was higher than that after the first MEG session (Fig. 2A), although the subjective level of left hand fatigue after the second MEG session was not different from that after the first MEG session (Fig. 2B).

We also assessed changes in high-frequency (HF) power and low-frequency (LF) power/HF power ratio after the conditioning session. Although HF was not altered after the conditioning session (Fig. 3A), LF/HF ratio was significantly increased after the conditioning session (Fig. 3B).

To identify the brain region associated with the central inhibition during physical fatigue, the decreased oscillatory power, that is, ERD, for alpha frequency band in the second