Neuroscience Research 95 (2015) 59–65

Contents lists available at ScienceDirect

Neuroscience Research

journal homepage: www.elsevier.com/locate/neures

The effect of paired associative stimulation on fatigue resistance

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ARTICLE INFO

Article history:
Received 22 November 2014
Received in revised form 22 January 2015
Accepted 29 January 2015
Available online 7 February 2015

Keywords:
Fatigue
Central fatigue
Motor cortex
Transcranial magnetic stimulation
Paired associative stimulation

ABSTRACT

Paired associative stimulation (PAS) is a non-invasive stimulation method developed to induce bidirectional changes in the excitability of the cortical projections to the target muscles. However, very few studies have shown an association between changes in motor evoked potentials (MEP) after PAS and behavioral changes in healthy subjects. In the present study we hypothesized that the functional relevance of PAS can be seen during fatiguing exercise, since there is always a central contribution to the development of fatigue. Transcranial magnetic stimulation was applied over the motor cortex to measure changes in the MEPs of the soleus muscle before and after PAS. Furthermore, fatigue resistance was tested during 15 s sustained maximal isometric contractions before and after PAS. On average, fatigue resistance did not change after PAS, however the change in excitability correlated significantly with the change in fatigue resistance. *Discussion*: Functionality of PAS intervention was not demonstrated in this study. However, the observed relationship between excitability and fatigue resistance suggests that PAS might have affected central fatigue during short maximal contractions.

1. Introduction

Paired associative stimulation (PAS) is a non-invasive method developed to induce bidirectional changes in the excitability of the cortical projections to the target muscles. PAS combines electrical stimulation of a peripheral somatosensory nerve with transcranial magnetic stimulation (TMS) over the contralateral motor cortex. Depending on the interstimulus interval (ISI), PAS can produce either long-term potentiation (LTP) – or long-term depression (LTD) – like plasticity in the target synapse (Kumpulainen et al., 2012; Stefan et al., 2000; Wolters et al., 2003), showing properties such as rapid onset, associativity, duration, specificity, and NMDA-receptor dependence (Ziemann et al., 2008). Thus, spike-timing dependent plasticity is considered the most likely mechanism behind PAS (Stefan et al., 2000; Wolters et al., 2003). PAS and motor training have been shown to share common neural mechanisms, which suggests that PAS can be used as a test for functionally relevant neuronal circuits within the motor cortex (Jung and Ziemann, 2009; Stefan et al., 2006; Ziemann et al., 2004). However, very few studies have shown functionality of PAS-induced excitability changes in healthy subjects (Frantseva et al., 2008; Jung and Ziemann, 2009; Rajji et al., 2011).

Functional relevance of PAS can probably be seen during fatiguing exercises since it is well known that both central and peripheral factors contribute to the development of fatigue (Gandevia, 2001). Fatigue can be defined as any exercise-induced reduction in the ability of a muscle to generate maximal force or power (Gandevia, 2001). Central fatigue refers to processes proximal to the neuromuscular junction and peripheral fatigue to processes at or distal to it (Gandevia, 2001). The relative contribution of the central and peripheral components depends on the intensity and duration of the fatiguing exercise. Short maximal sustained contractions have been shown to have a substantial central contribution to the development of fatigue (Gandevia et al., 1996; Hunter et al., 2006, 2008; Lentz and Nielsen, 2002; Szubski et al., 2007; Taylor et al., 1996, 1999). Central fatigue has been defined as a progressive reduction in the voluntary activation of a muscle during exercise and it can originate at both spinal and supraspinal levels (Gandevia, 2001). Previous studies suggest that central fatigue at least partially originates from inadequate cortical drive to the motor neurons (Gandevia, 2001; Hunter et al., 2006, 2008).

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http://dx.doi.org/10.1016/j.neures.2015.01.015
0168-0102/

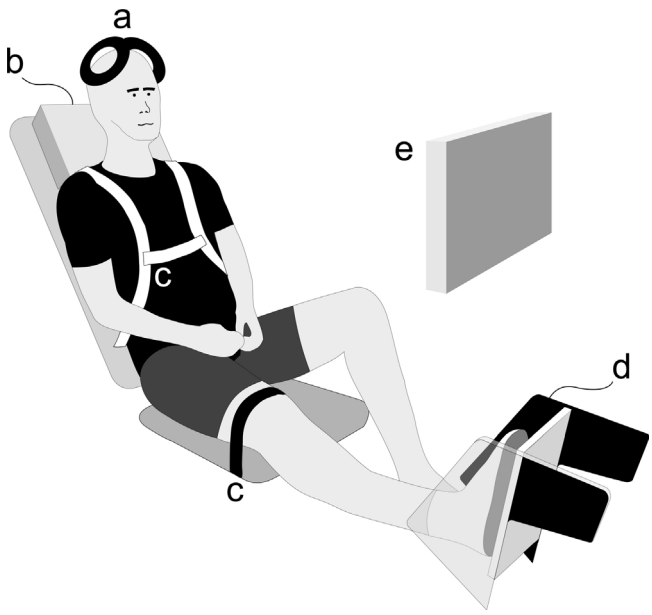

Fig. 1. Schematic of the measurement setup in the ankle dynamometer. (a) A stimulating coil was placed and secured over the left hemisphere and (b) subject's neck was comfortably supported by a head rest. (c) Body movement was restricted with seat belts and a knee strap. (d) Right foot was installed to a force pedal and (e) the force was displayed on a computer screen in front of the subject.

Because PAS can be used to systematically alter the responsiveness of neurons in the primary motor cortex, the current study was designed to investigate the effect of two different PAS interventions on fatigue resistance during 15 s sustained maximal isometric contractions. The PAS interventions targeted the soleus muscle (SOL) as this is an important antigravity muscle during standing and a major contributor to force production during the impact phase of walking and running (Ishikawa et al., 2005). It was hypothesized that after PAS_{LTP} fatigue resistance would increase whereas after PAS_{LTD} fatigue resistance would decrease.

2. Materials and methods

2.1. Ethical approval and subjects

Thirty healthy subjects volunteered for the study and were divided into two groups: PAS induced LTP-like plasticity group (PAS_{LTP}; 9 females and 6 males, 25 ± 4 years, 62 ± 10 kg, 168 ± 11 cm) and LTD-like plasticity group (PAS_{LTD}; 9 females and 6 males, 25 ± 4 years, 63 ± 7 kg, 168 ± 7 cm). Subjects were blinded to the PAS intervention they were undergoing and thus the PAS_{LTP} and PAS_{LTD} were considered as each other's control. None of the subjects had any history of neuromuscular or orthopedic diseases and all subjects were naïve to the experiments. Before testing, subjects were informed about the procedures and gave written consent. The study was approved by the ethics board from the University of Jyväskylä and was performed in conformity with the latest revision of the declaration of Helsinki.

2.2. Experimental design

Participants were positioned on a custom built ankle dynamometer (University of Jyväskylä, Finland) with the hip at 110°, the knee in an extended position at 180°, the ankle at 90° and the right foot resting on a pedal (Fig. 1). A seat belt restricted movement of the upper body and straps secured the right leg and foot. Hands were resting in the lap during all measurements. Prior to the measurements, the participants performed three maximal isometric plantar flexions with a 3 min rest interval between trials. The highest force value was considered as the maximal voluntary contraction (MVC). The experimental protocol is shown in Fig. 2; the upper panel represents the main protocol and the lower panel the additional procedures for sub-groups. The main protocol included transcranial magnetic stimulation (TMS) to measure changes in the motor evoked potentials (MEPs) of SOL before (pre) and twice after the PAS intervention; immediately after (post0) and 15 min after (post15) PAS. The fatigue resistance tests were performed before (pre) and after all TMS measurements (post15). To test for changes at the spinal level, SOL Hoffman reflexes (H-reflexes) were elicited in a subgroup at the pre, post0 and post15 measurements. Fatigue, MEP and PAS procedures were conducted so that fatigue would not affect MEPs or PAS intervention. To avoid possible fatigue effects there was at least 40 min between the last fatiguing contraction and the PAS intervention in the pre measurements. In the post measurements, fatigue resistance was measured after all the MEPs were recorded but within 25 min of the PAS protocol, because LTP/LTD effects have been shown to last for a minimum of 30 min (Kumpulainen et al., 2012; Mrachacz-Kersting et al., 2007; Stefan et al., 2000; Wolters et al., 2003).

2.3. Recordings

For electromyographic (EMG) measurements, a pseudomonopolar electrode placement protocol was used where one surface electrode of a pair (Unilect, Ag/AgCl, Unomedical Ltd., Redditch, UK) was placed on the right SOL and the other over a bony surface of the tibia. A ground electrode was placed over the lateral malleolus (Hoffman et al., 2009). The pseudomonopolar setup allowed MEPs of higher amplitude to be recorded, which in turn also decreased the intensity of the stimulus needed to evoke a detectable MEP. Prior to electrode placement, the skin was shaved, abraded and cleaned with alcohol to reduce resistance below 5 kΩ. EMG signals were amplified (100×), band-pass filtered (10–1000 Hz) and sampled at 5 kHz (Neural Systems NL 900D and NL 844, Digitimer Ltd., Hertfordshire, UK). EMG data and reaction forces from the pedal were collected with a computer via 16-bit AD converter (CED power 1401, Cambridge Electronics Design Limited, UK) and stored for later analysis.

2.4. Procedures

A rectangular current pulse with a duration of 1 ms was delivered to the common tibial nerve using a constant-current stimulator (DS7AH, Digitimer Ltd., Hertfordshire, UK) for the PAS protocol in addition to evoking H-reflexes and maximal M-waves (M_{max}). A circular cathode with a pickup area of 77 mm^2 (Unilect short-term ECG Electrodes, Ag/AgCl, Unomedical Ltd., UK) was placed over the tibial nerve on the popliteal fossa and an oval shaped (5.08 cm/10.16 cm) anode (V-trodes neurostimulation electrodes, Mattler Electronics Corp., USA) was placed above the patella. Motor threshold (MT) was defined as the minimal intensity that induced a visually identifiable muscle twitch in SOL. To quantify reliable M_{max}, supramaximal stimulus intensity was used, being 150% of the current needed to elicit maximal stimulus response.

For the fatigue test subjects were instructed to produce their maximal isometric plantar flexion force and maintain it for 15 s (Fig. 3), during which the force declined toward the end. Verbal encouragement was given throughout the trial. At the end of the fatiguing contraction, neural deficit was estimated using the interpolation twitch technique (ITT); a supramaximal (M_{max} intensity) double pulse with 10 ms interval was delivered to the tibial nerve to quantify possible increment in force (superimposed twitch).