Neuroscience 339 (2016) 655–666

DIFFERENTIAL RESPONSES OF SPINAL MOTONEURONS TO FATIGUE INDUCED BY SHORT-LASTING REPETITIVE AND ISOMETRIC TASKS

ANTONIO MADRID,[a] JOSEP VALLS-SOLÉ,[b] ANTONIO OLIVIERO,[c] JAVIER CUDEIRO[a,d] AND PABLO ARIAS[a]*

[a] *Universidade da Coruña, NEUROcom (Neuroscience and Motor Control Group) and Biomedical Institute of A Coruña (INIBIC), Department of Medicine-INEF Galicia, A Coruña, Spain*

[b] *EMG Unit, Neurology Service, Hospital Clinic, Department of Medicine, University of Barcelona, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain*

[c] *FENNSI Group, Hospital Nacional de Parapléjicos, SESCAM, Toledo, Spain*

[d] *Centro de Estimulación Cerebral de Galicia, A Coruña, Spain*

Abstract—Compared to isometric activities, the neural basis of fatigue induced by repetitive tasks has been scarcely studied. Recently, we showed that during short-lasting repetitive tasks at the maximal possible rate (finger tapping for 10 and 30 s), tapping rate and maximal voluntary contraction (MVC) force decrease at the end of finger tapping. We also observed larger silent periods (SP) induced by transcranial magnetic stimulation during MVC *post* finger tapping. However, if SP were induced by cervicomedullary stimulation (CMS) they remained unchanged. This suggested a supraspinal origin of fatigue for repetitive tasks. Nevertheless, CMS SP only partially explore spinal excitability; therefore, to evaluate a spinal origin of fatigue it is essential to know the features of the CMS-evoked potentials (CMEP). Herein, we evaluated (n = 15) the amplitude of the CMEP during MVC executed immediately (no gap) after a short-lasting finger tapping task; we also evaluated the compound muscle action potential (CMAP) so that the amplitude of the CMEP was expressed as a function of the CMAP amplitude. Indices of fatigue obtained during finger tapping were compared with those obtained during short-lasting maximal isometric tasks. While indices of excitability increased initially in both tasks, they decreased with the isometric task only when the task was prolonged to 30 s. We suggest that the inability to maintain increased levels of spinal excitability during task execution is a neurophysiological mark of fatigue. Our results suggest that the origin of fatigue induced by brief and fast repetitive tasks is not spinal.

Key words: fatigue, repetitive movements, human, spinal cord.

*Corresponding author.
E-mail address: pabloarias.neurocom@udc.es (P. Arias).

Abbreviations: AMT, active motor threshold; ANOVA, analysis of variance; CMAP, compound muscle action potential; CMS, cervicomedullary stimulation; MVC, maximal voluntary contraction; SP, silent periods.

http://dx.doi.org/10.1016/j.neuroscience.2016.10.038

INTRODUCTION

The understanding of fatigue of the human motor system is of paramount importance in the fields of ergonomics, sport and neurology. The neural basis of fatigue has been studied extensively in the case of isometric contractions, either maximal or submaximal (Gandevia, 2001; Duchateau et al., 2002; Maluf and Enoka, 2005; Klass et al., 2008; Taylor and Gandevia, 2008; Williams et al., 2014), and there is strong evidence that isometric fatiguing tasks induce a reduction in the excitability of circuitry in both the spinal cord (Taylor et al., 1996; Duchateau et al., 2002; Butler et al., 2003; Klass et al., 2008) and motor cortex (Gandevia et al., 1996; Taylor et al., 1996; Di Lazzaro et al., 2003). The evaluation of evoked potentials in response to transcranial magnetic stimulation (TMS) and electric or magnetic cervicomedullary stimulation (CMS) has permitted the localization of the sites where excitability of the motor system has been modified during fatigue. While TMS is used to evaluate intracortical and corticospinal excitability (Hallett, 2000, 2007), the potentials induced by CMS (i.e. CMEP) are adequate to explore the excitability of the spinal cord circuits (Ugawa et al., 1991; Taylor and Gandevia, 2004; McNeil et al., 2013).

Fatiguing isometric contractions of maximal effort increase the duration of the silent periods (SP) induced by CMS and reduce muscle force during maximal voluntary contraction (MVC) (Taylor et al., 1996), an effect already present after 10 s of MVC in the small muscles of the hand (Arias et al., 2015). This is an indication of longer lasting decreased spinal motoneuronal excitability, which is partly due to recurrent inhibition and after-hyperpolarization (Inghilleri et al., 1993; Brasil-Neto et al., 1995). Fatigue also induces neurophysiological changes that reveal adaptations of intracortical motor circuits: an increase of TMS-SP, mediated by GABA receptors (Taylor et al., 1996; Arias et al., 2015); a reduction in the descending volleys in the corticospinal tract (Di Lazzaro et al., 2003); and a increase in cortico-cortical inhibition to paired-pulse TMS (McNeil et al., 2009).

However, cortical and spinal adaptations to fatigue are known to be task dependent (Enoka and Stuart, 1992; Barry and Enoka, 2007; Enoka and Duchateau, 2008; Enoka et al., 2011). While neural mechanisms related to fatigue during isometric tasks have been thoroughly studied, those related to fatigue during repetitive movements have been much less studied. One fundamental point during the study of the neural basis of fatigue is to control (or to avoid) the recovery of the system at the time of testing

(Taylor et al., 2000). This is relatively simple in the case of isometric activities where the stimulation of the brain can be performed during the task without stopping the activity. On the other hand, the study of fatigue induced by repetitive movements has been traditionally performed at rest, after the fatiguing activity (Brasil-Neto et al., 1993; Arias et al., 2012; Teo et al., 2012), which would not allow for the assessment of fast recovering forms of fatigue. This could be the case with fatigue developed during short-lasting repetitive movements executed at maximal possible rate. Recently, we have developed a protocol that allowed us to evaluate cortical and spinal adaptations to muscle fatigue when performing a repetitive finger tapping task (*ft*) with no time for recovery (Arias et al., 2015). The study involved the evaluation of TMS and CMS SPs during brief (2 s) episodes of MVC, which were executed immediately after maximal rate *ft* (10 or 30 s). When fatigued, subjects were unable to maintain the maximal tapping rate and their force was decreased during MVC, this was accompanied by an increase SP induced by TMS but not by CMS (Arias et al., 2015); those results advocate for a cortical locus of fatigue for fast rate *ft*. On the contrary, the reduction in force after short isometric MVC was accompanied by an increase in both CMS-SP and TMS-SP (Arias et al., 2015).

Therefore, the findings only partially ruled out the development of fatigue at spinal circuitry during maximal rate *ft* because we only evaluated CMS-SP duration but not the CMEP amplitude. A meaningful interpretation of the CMEP amplitude can only be achieved if considered in relation to the amplitude of the compound muscle action potential (CMAP) in response to supramaximal stimulation of the corresponding nerve (at the same time of testing the CMEP). This is fundamental because the CMAP reflects the efficiency of transmission in the periphery (Rich, 2006).

In the present work, we have modified our previous protocol to examine the spinal mechanisms of fatigue during maximal rate *ft* by mean of CMEP amplitude evaluation. We have been careful in exploring spinal and neuromuscular transmission at the time of fatigue, without allowing time for recovery. For comparison, we also explored the responses induced by a fatiguing isometric (*iso*) task. In all cases the tasks were short lasting, 10 or 30 s. We predict that spinal motoneurons will behave differently depending on the task employed.

EXPERIMENTAL PROCEDURES

Experimental protocols conformed to the Helsinki declaration and were approved by our institution Ethics Committee. All subjects were screened for incompatibility with brain stimulation protocols. All were medication free during the week preceding testing and signed a voluntary informed consent.

Subjects

The experiment included 15 healthy subjects (all men, age range 18–40 years). In all subjects the spinal excitability was evaluated with stimulation at the level of the cervicomedullary junction during several 2.5-s MVCs. Electrical stimulation was used in seven subjects, while magnetic stimulation using a double cone coil was used in the remaining eight subjects (who refused to participate if the stimulation was electrical due the produced discomfort). All subjects underwent both *ft* and *iso* fatigue testing sessions, 15 days apart.

Protocol

The two sessions were identical except for the type of *task* executed. In one of the session, participants were asked to perform index *ft*. In the other session they executed continuous index finger *iso* against a force sensor; the force direction was ‘‘toward” *flexion* of the first metacarpophalangeal joint. In all cases participants wore a small and light goniometer to monitor movements of the index finger metacarpophalangeal joint; we used also a metal ring attached at the distal phalanx of the index. Participants tapped or pressed over a thin metal plate located on the force sensor.

For both *ft* and *iso* sessions, subjects performed the tasks in three modes: comfort rate-effort (*comfort* mode) for 30 s; 10 s at maximal rate-effort (*10 max* mode); and finally 30 s at maximal rate-effort (*30 max* mode). Each mode was repeated four consecutive times (i.e., sets); rest periods between sets lasted 1 min 40 s. The decrease in frequency or amplitude (for *ft*), or in force output (for *iso*) defined the presence of fatigue.

For the *comfort-ft*, subjects were asked to ‘‘*tap at their most comfortable rate without feeling fatigued*” for as long as the set lasted. *Comfort-ft* is reliable (Arias et al., 2012) and paced about 1/3 of *ft* maximal rate. During *comfort-ft* the metabolic activity in the sensorimotor cortex is lower than at faster (> 3 Hz) or slower (< 1 Hz) rates (Jancke et al., 1998; Lutz et al., 2005), showing its suitability as control condition in our protocol. Participants were asked to press ≈1/3 MVC for *comfort-iso*; and visual feedback was provided. For maximal modes, subjects were encouraged to tap/press as fast/hard as they could from the very beginning to the end of the set.

The participants also executed 2.5-s MVCs before (*pre*) and right after (no gap allowed) task-execution (*post*), either after *ft* or *iso*, for all modes and sets (Fig. 1). The magnitudes of 2.5-s MVCs were analyzed to monitor fatigue (Bigland-Ritchie and Woods, 1984). During the 2.5-s MVCs the CMS was applied (at 1.5 s), and we recorded the SP duration and CMEP amplitudes (Taylor et al., 1996). The peripheral transmission of the potentials during the same 2.5-s-MVCs was also evaluated (at 2.2 s) with the amplitude of the CMAP (Rich, 2006). We calculated the ratio CMEP/CMAP to evaluate spinal excitability accounting for the state of the periphery; this was always performed with the CMEP and CMAP acquired in the same MVC. Thus the stimulation pulses (CMS, and 700 ms later supramaximal to the ulnar nerve) were applied during the 2.5-s MVC. A practice sessions was scheduled (Gandevia, 2001).