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Group III/IV locomotor muscle afferents alter motor cortical and corticospinal excitability and promote central fatigue during cycling exercise

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HIGHLIGHTS

- In the absence of fatigue: Group III/IV muscle afferents facilitate motor cortex.
- In presence of fatigue: Group III/IV muscle afferents disfacilitate motor cortex.
- Group III/IV muscle afferents promote central fatigue during endurance exercise.

ABSTRACT

Objective: To investigate the influence of group III/IV muscle afferents on the development of central fatigue and corticospinal excitability during exercise.
Methods: Fourteen males performed cycling-exercise both under control-conditions (CTRL) and with lumbar intrathecal fentanyl (FENT) impairing feedback from leg muscle afferents. Transcranial magnetic- and cervicomedullary stimulation was used to monitor cortical versus spinal excitability.
Results: While fentanyl-blockade during non-fatiguing cycling had no effect on motor-evoked potentials (MEPs), cervicomedullary-evoked motor potentials (CMEPs) were 13 ± 3% higher ($P < 0.05$), resulting in a decrease in MEP/CMEP ($P < 0.05$). Although the pre- to post-exercise reduction in resting twitch was greater in FENT vs. CTRL (−53 ± 3% vs. −39 ± 3%; $P < 0.01$), the reduction in voluntary muscle activation was smaller (−2 ± 2% vs. −10 ± 2%; $P < 0.05$). Compared to the start of fatiguing exercise, MEPs and CMEPs were unchanged at exhaustion in CTRL. In contrast, MEPs and MEP/CMEP increased 13 ± 3% and 25 ± 6% in FENT ($P < 0.05$).
Conclusion: During non-fatiguing exercise, group III/IV muscle afferents disfacilitate, or inhibit, spinal motoneurons and facilitate motor cortical cells. In contrast, during exhaustive exercise, group III/IV muscle afferents disfacilitate/inhibit the motor cortex and promote central fatigue.
Significance: Group III/IV muscle afferents influence corticospinal excitability and central fatigue during whole-body exercise in humans.

1. Introduction

Strenuous whole body endurance exercise has been documented to induce central fatigue in the physically active human (Sidhu et al., 2009; Weavil et al., 2016). Central fatigue is defined as an exercise-induced attenuation in the degree to which the central nervous system (CNS) activates skeletal muscle and is manifested in a diminished output from spinal motoneurons and a

Abbreviations: CMEP, cervicomedullary evoked potential; CMS, cervicomedullary stimulation; CNS, central nervous system; cSP, cortical silent period; CTRL, control; EMG, electromyogram; FENT, fentanyl; MEP, motor evoked potential; M_{max}, maximal M-wave; MNS, motor nerve stimulation; MVC, maximal voluntary contraction; RT, resting twitch; SIT, superimposed twitch; TMS, transcranial magnetic stimulation; VA, voluntary activation; VL, vastus lateralis; W_{peak}, peak power output.

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concomitant decrease in voluntary muscle activation (VA) (Bigland- Ritchie et al., 1978; Taylor et al., 2016). Although several factors have been identified to contribute to exercise-induced central fatigue and the restriction in motoneuronal output during intense exercise (Nybo and Secher, 2004), existing evidence suggests a role of group III/IV muscle afferents in this phenomenon (Kennedy et al., 2014; Sidhu et al., 2014).

Contraction-induced mechanical and chemical stimuli activate molecular receptors on the terminal end of both thinly myelinated (group III) and unmyelinated (group IV) nerve fibers located within skeletal muscle. The activation of these receptors, which progressively increases during fatiguing contractions, raises the spontaneous discharge of group III/IV muscle afferents (Kaufman and Rybicki, 1987; Adreani et al., 1997; Kaufman et al., 2002). Via the dorsal horn of the spinal cord (Craig et al., 2000), these sensory neurons project directly, and/or indirectly, to various sites within the CNS including areas which have been linked with central fatigue (e.g. α-motoneurons, motor cortex, insular or cingulate cortex) (Craig et al., 1994; Liu et al., 2002, 2003; Klass et al., 2008). Strong feedback from these muscle afferents, as present during muscle fatigue, restricts motoneuronal output and muscle activation by limiting voluntary descending drive from 'upstream' of the motor cortex and depressing the excitability of the corticospinal pathway including the motor cortex and spinal motoneurons (Martin et al., 2008b; Sidhu et al., 2014). Despite existing evidence from single-joint exercise, little is known about the effects of group III/IV lower limb muscle afferents on the excitability of corticospinal projections to the leg muscles during locomotor exercise.

In the context of whole body endurance exercise, changes in VA from pre- to post-exercise can be quantified by a twitch interpolation technique based on peripheral motor nerve stimulation (MNS) (Merton, 1954). To provide a measure of cortical and motoneuronal excitability during exercise and/or changes from pre- to post-exercise, transcranial magnetic stimulation (TMS) of the motor cortex and electrical stimulation of the cervicomedullary junction, evoking short latency motor evoked potentials (MEPs and CMEPs, respectively), have been used (Hoffman et al., 2009; Sidhu et al., 2012).

The main aim of this study was to investigate the effect of lower limb muscle afferent feedback on the development of central fatigue and the excitability of corticospinal projections to the knee-extensors during cycling exercise. Specifically, we used lumbar intrathecal fentanyl to attenuate group III/IV locomotor muscle afferents with the purpose of evaluating their role in modulating post-exercise VA and the excitability of the motor cortex and spinal motoneurons during fatiguing and non-fatiguing cycling exercise. We tested the hypotheses that feedback from group III/IV locomotor muscle afferents alters the excitability of motor cortical cells during whole body cycling exercise and contributes to the development of central fatigue quantified via the pre- to post-exercise decrease in VA.

2. Methods

2.1. Subjects

Fourteen active males [maximal O_2 consumption: 53 ± 2 ml kg^{-1} min^{-1}; peak power output (W_{peak}): 311 ± 11 W; age: 23 ± 1 years; body mass: 75 ± 3 kg; height: 177 ± 2 cm] not involved in regular athletic activities, volunteered to participate in the study. All subjects were healthy with no known neurological or cardiovascular diseases. Written informed consent was obtained from each participant. All experimental procedures were approved by the University of Utah and Salt Lake City Veterans Affairs Medical Center Institutional Review Boards and conformed to the Declaration of Helsinki. All participants refrained from intense exercise at least 48 h prior, and caffeine ingestion at least 12 h prior to each visit.

2.2. Torque and electromyogram recordings

Quadriceps torque was measured using a calibrated linear strain gauge (MLP 300; Transducer Techniques, Temecula, CA). Force signals were amplified (1000 times) and sampled at 2000 Hz using a 16-bit Micro 1401 mk-II and Spike 2 data collection software (Cambridge Electronic Design Ltd, Cambridgeshire, England) via custom written program scripts. Electromyogram (EMG) recordings were recorded with surface electrodes (Ag-AgCl, 10 mm diameter) placed over the muscle belly of the vastus lateralis (VL) in a bipolar configuration (centre-to-centre distance of 2 cm). EMG signals were amplified (1000 times; Neurolog Systems, Digitimer Ltd., Welwyn Garden City, Hertfordshire, England), band-pass filtered (50–1000 Hz; NL-844, Digitimer Ltd) and analog to digitally converted at a sampling rate of 2000 Hz using the CED data acquisition software.

2.3. Cycle ergometer set-up

Subjects were positioned on the cycle ergometer with their feet fastened securely to the pedals and their hands holding onto a bar secured on a table in front of them. A mouthpiece, connected to a metabolic cart (Medgraphics Ultima CFX, MGC Diagnostics, Saint Paul, MN, USA) to measure pulmonary ventilation and gas exchange, was mounted onto a horizontal bar. This set-up ensured that the upper body and head were kept stable during stimulations and allowed the consistent application of TMS.

2.4. Experimental Protocol

Subjects were thoroughly familiarized with the experimental procedures during two preliminary visits and participated in a total of four sessions. Subjects were provided with verbal encouragement during cycling exercise and asked to maintain a constant rpm of 80. During the first preliminary visit, subjects performed a maximal incremental exercise test [20 W + 25 W min^{1}] (Amann et al., 2004) on a bicycle ergometer (Velotron, Elite Model, Racer Mate, Seattle, WA) for the determination of maximum workload (W_{peak}) and maximal oxygen consumption. During the second preliminary visit, subjects practiced constant-load bicycle exercise (80% W_{peak}, 250 ± 8 W) to task failure (i.e. pedal frequency dropped below 80% of target for >10 s, despite vocal encouragement). On two additional study days, in counter-balanced order, subjects repeated the same exercise either under control conditions (i.e. no injection; CTRL) or with intrathecal fentanyl applied through the L3–L4 vertebral interspace (FENT) (Amann et al., 2009). In both sessions, neuromuscular assessment of the quadriceps muscle was conducted on 10 of the 14 subjects before and as soon as possible after exercise. Subjects were initially asked to perform 3 maximal voluntary contractions (MVC) of the right knee extensors (with 1 min rest between each contraction). Thereafter, optimal stimulation intensities were established and neuromuscular quadriceps function was assessed while subjects were seated on a custom made chair. Subjects then moved to the cycle ergometer where they performed four short (~40 s each; 2 min of rest in between) non-fatiguing exercise bouts, two 100 W (warm-up) bouts and two 80% W_{peak} bouts in each session (Fig. 1). Both the assessment of quadriceps function (Fig. 1A) and the non-fatiguing exercise bouts (Fig. 1B) were repeated after fentanyl administration. One set of stimulations was elicited during the non-fatiguing exercise bouts (40 s at 80% W_{peak}) to assess corticospinal excitability. During fatiguing cycling (80% W_{peak} to exhaustion), a set of stimulations was elicited at the start and when the subjects reached task