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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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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.

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Keywords

Cervicomedullary stimulation; Transcranial magnetic stimulation; Neural blockade; Central nervous system; Brain

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 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 failure (time from last stimulation to complete termination of cycling exercise: 4 ± 1 s). As soon as possible after task failure (time from failure to assessment: 49 ± 5 s and 63 ± 12 s for CTRL and FENT, respectively; $P = 0.3$), the neuromuscular assessment of quadriceps function was repeated.

2.5. Stimulations

Three forms of stimulations were used during each session: 1) Electrical motor nerve stimulation (MNS), 2) transcranial magnetic stimulation (TMS) and 3) cervicomedullary stimulation (CMS).

2.5.1. MNS—The position of the MNS electrode on the femoral nerve (located high in the femoral triangle) which elicited the biggest compound muscle action potential (M-wave) in VL and quadriceps twitch was determined by delivering low intensity monopolar single pulse stimuli (200 μs pulse width; 100–150 mA) using a cathode probe (with the anode fixed between the greater trochanter and iliac crest) and a constant current stimulator (Model DS7AH, Digitimer Ltd.). Once established, the cathode electrode was fixed at that position using 3-cm round cloth electrodes. Thereafter, the stimulation intensity was increased in 20 mA increments until the size of the maximal twitch and M-wave demonstrated no further increase (i.e. maximal M-wave; M_{max}) at rest. The stimulation intensity was set at 130% of M_{max} intensity at rest (302 ± 21 mA) and checked for supramaximality during a 50% quadriceps MVC. If the M-wave size increased during the 50% MVC, the intensity would have been increased further to ensure plateau; however, this was not necessary in any of the subjects. The supramaximality of this intensity was also checked during a brief (~30 s) cycling bout at 100 W by increasing the stimulation intensity in 20 mA increments above that determined during seated position. This was performed to ensure that a true plateau was attained in the response-intensity curve during cycling (317 ± 23 mA).

2.5.2. CMS—Subjects were asked to perform a 20% quadriceps MVC during the process of establishing the optimal CMS intensities. An electrical percutaneous stimulator was used to activate cervicomedullary junction at the back of the neck to elicit CMEPs in the VL. This was achieved by passing a high voltage pulse (100 μs pulse width, D-185 mark IIa, Digitimer Ltd.) between a set of self-adhesive electrodes (3-cm, round) attached to the skin in the groove between the mastoid processes and the occiput (cathode on the left, contralateral to the right limb muscle). Based on the linear relationship between the increase in contraction strength and the increase in CMEP up to 50% MVC (Martin et al., 2008a; Weavil et al., 2015), the stimulation intensity was set to achieve a CMEP size corresponding to ~20% M_{max} during 20% quadriceps MVC (418 ± 14 V; range 300–520 V).

2.5.3. TMS—Subjects performed a 20% quadriceps MVC during the process of establishing the TMS intensity. A double cone coil (diameter 130 mm, Magstim 200, The Magstim Company Ltd, Dyfed, United Kingdom) was used to elicit MEPs in the VL. The optimal coil position (posterior to anterior direction of current flow in the motor cortex) to preferentially activate the left motor cortex with the biggest representation for the quadriceps (position relative to vertex: ~2–3 cm lateral). This location was marked directly on the scalp for accurate placement throughout the session. The intensity of stimulation (45 ± 4% of maximum) was set to produce a MEP of similar size to CMEP (i.e. ~20% M_{max}) during a 20% MVC. This methodology has been used previously (Sidhu et al., 2012; Weavil et al., 2015). The established TMS (and CMS) intensities were used to measure cortical and motoneuronal excitability during cycling and the pre- and post-exercise assessment of quadriceps function. The rationale for setting the stimulus intensity for excitability measures during the 20% MVC eliciting a small MEP (~20% M_{max}) was to ensure that the response was not close to saturation on the stimulus–response curve (Todd et al., 2003) and to allow for monitoring smaller motoneurons that are active during submaximal contractions (McNeil et al., 2011).

2.6. Neuromuscular assessment of quadriceps function

Subjects were seated comfortably on a custom built chair with full back support, such that the hip and knee were at approximately 120° and 90° of flexion, respectively. A cuff attached to the strain gauge was fixed ~2 cm above the lateral malleolus of the right leg. Three sets of contractions, separated by 1 min, were performed during each assessment. In each set, subjects performed an MVC (~3 s; visual torque feedback provided) during which MNS was delivered to evoke a superimposed twitch (SIT), followed by another MNS to evoke a potentiated quadriceps resting twitch (RT). VA (%) was assessed by expressing SIT as a percentage of RT: $VA = (1 - SIT/RT) \times 100$ (Merton, 1954). Then, for the measurement of corticospinal excitability, in random order, three single TMS pulses, one CMS and one supramaximal MNS (separated by 2–3 s) were delivered during a sustained 20% MVC (adjusted to preceding MVC).

2.7. Set of stimulations during cycling

A set of stimulations during all cycling bouts included three TMS, one CMS and one MNS. As described previously (Sidhu et al., 2012), the order of stimulation type and pedal revolution during which stimulations were delivered was randomised. The crank angle of the

cycle ergometer was monitored continuously via a calibrated linear encoder mounted near the crank shaft. All stimulations during cycling were elicited at a fixed point of the crank cycle (45° after top dead center where quadriceps muscle was active; top dead centre = 0°). Each stimulation was separated by at least five full pedal revolutions.

2.8. Intrathecal fentanyl

Subjects were seated in a flexed sitting position and 1 ml of fentanyl (0.025 mg ml^{-1}) was delivered at the vertebral interspace L3–L4 as previously described (Amann et al., 2009). This drug has been shown to reliably attenuate group III/IV-mediated neural feedback from lower limb muscles in healthy individuals and patients with heart failure and COPD (Amann et al., 2009, 2014; Hilty et al., 2011; Gagnon et al., 2012; Sidhu et al., 2014). The study was completed within 60 min from the time fentanyl was administered.

2.9. Steady-state CO_2 response test and arm cycling

Migration of fentanyl sufficient to reach the brain is a known issue (Amann et al., 2009, 2010) and would negate the significance of our findings since opioid receptors are widely distributed throughout the brain including various areas known to be involved in the regulation of motor function and behavior (Bruijnzeel, 2009). To exclude this possibility, we utilized the fact that binding of fentanyl (applied intrathecally at the lumbar level) on medullary opioid receptors attenuates the ventilatory responsiveness to hypercapnia (Lalley, 2008) and decreases cardiopulmonary responses to arm exercise (Amann et al., 2010). Two tests, including the steady state CO_2 response test and arm cycling (Amann et al., 2010), were used to assess this issue. In case of a sufficient migration of fentanyl to reach the brain, ventilatory responses to both hypercapnia and arm cycling would be attenuated. Eight subjects performed the steady-state CO_2 response tests before and ~10 min after the fentanyl injection using an open circuit technique. Participants were seated in a chair while breathing through a mouthpiece. In addition to eupnoeic air breathing (5 min), ventilatory response to CO_2 (4 min; 70% O_2, 6% CO_2, balance N_2) was measured. Six of the subjects performed constant-load arm cycling (15 W and 30 W, 3 min each) in random order. There was a 2 min break in between each workload and the target cadence was set at 60 rpm (Amann et al., 2010). For both the steady-state CO_2 response test and arm cycling, variables including breathing frequency (f_R; breaths min^{-1}) and tidal volume (V_T; L) were assessed and averaged over the final minute. The same procedures were performed during the control session, but without the injection of fentanyl.

2.10. Data analysis

Peak-to-peak amplitude and area of MEPs, CMEPs and M_{max} were measured between cursors placed to encompass all phases of evoked potentials in VL. As amplitude and area revealed similar changes, only area is reported. The area of each MEP and CMEP was normalized to that of M_{max} elicited in the same set to account for activity – dependent changes in muscle sarcolemmal excitability. To indicate changes at the motor cortical cells, MEPs were expressed relative to CMEPs (i.e. MEP/CMEP). The duration of the cortical silent period (cSP) during 20% MVC performed pre- and post-exercise was determined as the interval from the stimulus to the return of the continuous EMG by automated script written to detect EMG exceeding ± 2 SD of pre-stimulus EMG for at least 100 ms (Goodall

et al., 2010). The cycling EMG signal was rectified and waveform average analysis was performed on a 10-s segment just prior to the stimulation set during both non-fatiguing and fatiguing exercise. The reference point for overlaying and averaging was taken as 45°, the same point on the crank angle that was used to elicit stimulations. Average EMG during each revolution was measured across a 100 ms window (50 ms pre and 50 ms post point of stimulation) (Sidhu et al., 2012). In order to quantify background EMG during the isometric muscle contractions performed pre- and post-exercise, root mean squared electromyogram (EMG_{rms}) was measured from a 100-ms segment prior to the point of stimulation. This was measured to document the fatigue-related changes in central drive at a given relative torque from pre-post exercise. Pre-exercise MVC, VA, RT and area of evoked potentials represent the average from the three sets performed. Post-exercise measurements are reported as three separate sets performed at 56 ± 5 s (post-1), 146 ± 5 s (post-2), and 236 ± 5 s (post-3) after exercise so as to monitor recovery. During non-fatiguing cycling, responses from the 80% W_{peak} bouts were averaged. To address our main question as to whether corticospinal responsiveness changed during sustained cycling in CTRL and FENT conditions, we compared responses at task “failure” to the “start” of exercise.

2.11. Statistical analysis

Normality of the data was confirmed by Shapiro–Wilk W test. Two-way repeated measures ANOVAs were used to examine the effect of fentanyl-blockade (i.e. CTRL and FENT sessions) on MVC, VA and RT from baseline across time (“post-1”, “post-2”, “post-3”). Paired t-tests were also conducted to directly compare the relative (percent) changes from baseline between CTRL and FENT sessions. This allowed any additional fatigue induced by the afferent blockade to be dissociated from intact feedback. Two-way repeated measures ANOVAs were used to examine the effect of fentanyl-blockade on cycling EMG, M_{max}, MEP (%M_{max}), CMEP (% M_{max}) and MEP/CMEP across fatigue cycling exercise (“start” and “failure”). Two-way repeated measures ANOVAs were used to examine the effect of fentanyl-blockade on EMG, M_{max}, MEP (% M_{max}), CMEP (%M_{max}) and MEP/CMEP during the pre- and post-exercise 20% MVC. If the data did not conform to the assumption of sphericity, the *P*-value was Greenhouse–Geisser corrected. When ANOVA revealed a significant interaction or a main effect, Holm-Sidak post hoc tests were performed and corrected for the number of comparisons. In cases where interactions are not significant, only main effects are indicated, whereas if interactions are significant, relevant main effects are also reported. Students paired t-tests were used to determine differences in (a) responses from pre- vs. post-fentanyl administration in the non-fatiguing exercise workload (b) resting responses obtained during static contractions pre- vs. post-fentanyl administration and (c) resting ventilatory responses to CO_2 from pre- vs. post-fentanyl administration. Cohen’s effects sizes (d_z) were calculated with G * Power software. Data are given as mean ± S.E.M. Statistical significance was set at $P \leq 0.05$.

3. Results

3.1. Effect of fentanyl administration on resting ventilatory responses to CO_2 and arm cycling (Tables 1 and 2)

As reflected by lack of a difference in breathing patterns, eupneic air breathing was not altered in any of the subjects following fentanyl injection ($t_7 < 0.300$; $P > 0.200$, $d_Z < 1.104$). Furthermore, exposure to 6% CO_2 resulted in no difference in ventilatory responses in all subjects ($t_7 < 0.900$; $P > 0.300$, $d_Z < 0.988$). Throughout the arm cycling exercise, ventilatory responses were unaltered in all subjects following fentanyl administration ($t_5 < 1.956$; $P > 0.108$, $d_Z < 1.550$).

3.2. Effect of fentanyl administration on resting quadriceps function

Fentanyl had no effect on pre-fatigue quadriceps MVC, RT and VA ($t_9 < 1.248$; $P > 0.243$, $d_Z < 0.926$). Furthermore, fentanyl administration had no effect on EMG_{rms} (~0.105 mV; $t_9 = 0.137$; $P = 0.894$, $d_Z = 0.389$), M_{max} (~0.050 mV.s; $t_9 = 0.232$; $P = 0.822$, $d_Z = 0.509$), MEP (~26% M_{max}; $t_9 = 1.241$; $P = 0.246$, $d_Z = 0.923$), CMEP (~21% M_{max}; $t_9 = 0.878$; $P = 0.403$, $d_Z = 0.799$) and MEP/CMEP during the 20% MVC (~122%; $t_9 = 1.281$; $P = 0.232$, $d_Z = 0.937$).

3.3. Effects of blocking group III/IV muscle afferents on time to exhaustion, exercise-induced quadriceps fatigue (Fig. 2), and the cardiopulmonary responses to exercise

3.3.1. Time-to-exhaustion—Exercise time to exhaustion was not different between both conditions (CTRL: 8.9 ± 0.7 min; FENT: 8.1 ± 0.7 min; $t_{13} = 1.412$; $P = 0.182$, $d_Z = 0.994$).

3.3.2. MVC—Pre-exercise MVCs were not different across the three sets during both CTRL and FENT ($t_9 < 1.154$; $P > 0.277$, $d_Z < 0.895$). In addition to a significant interaction effect ($F_{3,27} > 6.631$; $P = 0.002$), there were significant main effects of time ($F_{3,27} = 17.631$; $P < 0.001$) and fentanyl-blockade ($F_{1,9} = 13.433$; $P = 0.005$) on quadriceps MVC. MVC at post-1, post-2 and post-3 was attenuated compared to baseline during both CTRL and FENT sessions ($P < 0.006$, $d_Z > 1.782$). Pre- to post-exercise percent reduction in MVC was larger following FENT vs. CTRL at post−1 (−24 ± 3% vs. 11 ± 1%; $t_9 = 3.041$; $P = 0.014$, $d_Z = 1.577$) and post-2 (−20 ± 2% vs. 9 ± 1%; $t_9 = 3.927$; $P = 0.004$, $d_Z = 1.921$). This change was not significant following FENT vs. CTRL at post-3 (−17 ± 2% vs. −13 ± 2%; $t_9 = 1.048$; $P = 0.322$, $d_Z = 0.858$).

3.3.3. RT—In addition to an interaction effect ($F_{3,27} = 3.023$; $P = 0.047$), there was a main effect of time ($F_{3,27} = 46.538$; $P < 0.001$) and fentanyl-blockade ($F_{1,9} = 33.863$; $P < 0.001$) on RT. RT at post-1, post-2 and post-3 were attenuated compared to baseline during both CTRL and FENT sessions ($P < 0.001$, $d_Z > 2.262$). Pre- to post-exercise percent reduction in RT was greater following FENT vs. CTRL at post-1 (−51 ± 4% vs. −38 ±3%; $t_9 = 2.408$; $P = 0.039$, $d_Z = 1.342$) and post-2 (−48 ± 4% vs. −38 ± 2%; $t_9 = 2.344$; $P = 0.044$, $d_Z = 1.315$). At post-3, there was a trend for greater reduction following FENT vs. CTRL (−45 ± 3% vs. −36 ± 3%; $t_9 = 1.998$; $P = 0.076$, $d_Z = 1.192$).

3.3.4. VA—In addition to an interaction effect ($F_{3,27}$ = 2.945; P = 0.050), there was a main effect of time ($F_{3,27}$ = 5.042; P = 0.007) and a main effect of session for VA ($F_{1,9}$ = 6.039; P = 0.036). VA was attenuated at post-1, post-2 and post-3 in CTRL, (P < 0.023, d_Z > 1.462) but not in FENT (P > 0.870, d_Z < 0.439). Pre-to post exercise percent reduction in VA was greater following CTRL vs. FENT at post-1 (−14 ± 3% vs. 0 ± 1%; t_9 = 2.946; P = 0.016, d_Z = 1.546) and post-2 (−9 ± 2% vs. 1 ± 1%; t_9 = 2.688; P = 0.025, d_Z = 1.444). The difference was not significant following CTRL and FENT at post-3 (−3 ± 1% vs. 1 ± 1%; t_9 = 1.310; P = 0.223, d_Z = 0.947).

3.3.5. Heart rate and ventilatory response—Fentanyl blockade significantly attenuated cardiopulmonary responses to constant-load exercise to exhaustion. The compromised ventilatory response was mediated by a blockade-induced decrease in breathing frequency since tidal volume remained unaltered throughout the trial. A detailed illustration of the cardiopulmonary response during CTRL vs. FENT can be found in the Supplementary Fig. S1.

3.4. Effect of group III/IV muscle afferents on the excitability of corticospinal pathway to the quadriceps during non-fatiguing locomotor exercise (Fig. 3)

Fentanyl-blockade had no effect on quadriceps EMG (0.36 ± 0.03 mV; t_{13} = 1.959; P = 0.072, d_Z = 0.984), M_{max} (0.05 ± 0.00 mV.s; t_{13} = 0.219; P = 0.830, d_Z = 0.422), and MEPs during the short non-fatiguing cycling bouts (t_{13} = 0.191; P = 0.851, d_Z = 0.397; Fig. 3A). However, fentanyl-blockade increased CMEPs (t_{13} = 3.003; P = 0.011, d_Z = 1.299; Fig. 3B). Consequently, MEP/CMEP was reduced following fentanyl-blockade (t_{13} = 2.184; P = 0.048, d_Z = 1.052; Fig. 3C).

3.5. Effect of group III/IV muscle afferents on the excitability of corticospinal pathway to the quadriceps during fatiguing locomotor exercise (Fig. 1D, Fig. 4)

3.5.1. EMG and M_{max}—There was a main effect of time ($F_{1,13}$ = 6.266; P = 0.026) on cycling EMG. EMG at failure of both CTRL and FENT exercise was greater than at the start of exercise (average of both sessions; Start: 0.32 ± 0.02 mV; Failure: 0.39 ± 0.03 mV; P < 0.011, d_Z > 1.286). There was no interaction and no main effects of time ($F_{1,13}$ = 1.599; P = 0.228) or session ($F_{1,13}$ = 2.680; P = 0.126) on M_{max} (average across all trials: 0.05 ± 0.01 mV·s) during cycling.

3.5.2. MEP(%M_{max}), CMEP(%M_{max}) and MEP/CMEP—MEP and CMEP at the start of fatiguing cycling were large relative to M_{max} (~80% M_{max}) indicating the two stimulation types activated a large pool of the knee extensor motor units during cycling. At start of exercise, MEPs and CMEPs were equivalent in terms of relative size in both conditions (t_{13} < 1.470; P > 0.165, d_Z < 0.843). There was an interaction between session and time ($F_{1,13}$ = 4.534; P = 0.039) and a main effect of time ($F_{1,13}$ = 4.450; P = 0.050) on MEP during fatigue cycling. Compared to the start of CTRL exercise, MEPs were unchanged at exhaustion (P = 0.630, d_Z = 0.558). During FENT, MEPs were 13 ± 3% greater at exhaustion compared to the start (P = 0.006, d_Z = 1.383). There was no interaction or main effect of time ($F_{1,13}$ = 0.041; P = 0.842) or session ($F_{1,13}$ = 0.560; P = 0.468) on CMEP during fatigue cycling. There was an interaction between session and time on MEP/CMEP

($F_{1,13}$ = 5.010 P = 0.050). Compared to the start of exercise, a 25 ± 6% increase in MEP/CMEP was seen at failure during FENT (P = 0.040, d_Z = 1.080), but not during CTRL (P = 0.855, d_Z = 0.392).

3.6. Effect of group III/IV muscle afferents on pre- to post-exercise changes in corticospinal excitability of the quadriceps during a 20% MVC (Fig. 5)

3.6.1. EMG_{rms} and M_{max}—Although there was no interaction between session and time ($F_{3,27}$ = 2.288; P = 0.101), there was a main effect of time ($F_{3,27}$ = 5.382; P = 0.005) on background EMG_{rms} during 20% MVC. EMG_{rms} at post-1, post-2, and post-3 was greater compared to pre-exercise baseline in FENT (P < 0.009, d_Z > 1.683). In CTRL, EMG_{rms} at post-1 and post-2 remained unchanged from baseline (P > 0.487, d_Z < 0.746), but at post-3, it was greater compared to pre-exercise baseline (P = 0.036, d_Z = 1.360). There was no interaction ($F_{3,27}$ = 2.175; P = 0.114) and no main effects of time ($F_{3,27}$ = 1.063; P = 0.381) or session ($F_{1,9}$ = 0.563; P = 0.472) on M_{max} from pre- to post-exercise.

3.6.2. MEP(%M_{max}), CMEP(%M_{max}) and MEP/CMEP—There was a main effect of time ($F_{3,27}$ = 8.713; P < 0.001) on MEP. MEP at post-1 and post-3 was greater compared to baseline during FENT (P < 0.019, d_Z > 1.506). During CTRL, MEP at post-1 and post 3 was not altered from baseline (P > 0.185, d_Z < 0.991), but at post-2 it was greater compared to baseline (P = 0.038, d_Z = 1.348). There was a main effect of time ($F_{3,27}$ = 5.833; P = 0.003) on CMEP. CMEP at post-1, post-2 and post-3 was greater compared to baseline during CTRL (P < 0.026, d_Z > 1.277). During FENT, CMEP was unchanged from baseline at post-1, post-2 and post-3 (P > 0.206, d_Z < 0.795). There was no interaction ($F_{3,27}$ = 1.689; P = 0.193) and no main effect of time ($F_{3,27}$ = 0.368; P = 0.777) but a trend for a main effect of session ($F_{1,9}$ = 3.728; P = 0.086) on MEP/CMEP.

3.6.3. cSP—There was an interaction between session and time ($F_{3,27}$ = 3.241; P = 0.038) and a main effect of session ($F_{1,9}$ = 4.680; P = 0.050) on cSP. cSP at post-1 during FENT was shorter compared to baseline (P = 0.027, d_Z = 1.269) and was different from CTRL (SP during CTRL greater than FENT; P = 0.003, d_Z = 1.782).

4. Discussion

4.1. Main findings

We utilized a pharmacological approach to attenuate group III/IV-mediated feedback during locomotor exercise and provide direct evidence that these sensory neurons contribute to the development of central fatigue during this type of physical activity. Furthermore, although our findings reflect a disfacilitating, or inhibitory, influence of group III/IV muscle afferents on motor cortical cells during *fatiguing* exercise, they have no effect on the excitability of motoneurons innervating knee-extensors. In contrast, during intense but *non-fatiguing* locomotor exercise, group III/IV-mediated feedback facilitates motor cortical cells but disfacilitates, or inhibits, knee-extensor motoneurons with no consequence for the overall excitability of the corticospinal pathway. These observations combined indicate that exercise-induced fatigue modulates the influence of group III/IV muscle afferent feedback on the excitability of the corticospinal pathway. Finally, the present findings may support the

hypothesis that the group III/IV-mediated disfacilitation (or inhibition) of the corticospinal pathway is a potential contributor to the development of central fatigue during exhaustive endurance exercise (Sidhu et al., 2014).

4.2. Group III/IV muscle afferents facilitate central fatigue during locomotor exercise

The significant decrease in VA following CTRL exercise reflects the development of central fatigue during strenuous endurance exercise. The novel aspect of the present study is the identification of group III/IV muscle afferent feedback as a significant contributor to this decrease. Specifically, when the exercise causing considerable central fatigue under CTRL conditions was repeated with impaired neural feedback, the exercise-induced decrease in VA was significantly attenuated (Fig 2C).

The current findings contrast with our previous studies documenting no pre- to post-exercise decrease in VA under conditions of intact feedback (Amann et al., 2009, 2011a). Since central fatigue can recover within 3 min (Bigland-Ritchie et al., 1986; Pageaux et al., 2015), this discrepancy is likely explained by the up to 5 min delay between the end of the exercise and the beginning of the post-exercise VA assessment in our previous studies. This procedure was optimized for the current study and we were able to quantify post-exercise VA within 1–2 min after task failure. This enabled us to capture, although likely still underestimated, a considerable degree of exercise-induced central fatigue during the immediate recovery period.

Despite the reduction in central fatigue, cycling time was not prolonged with fentanyl blockade in neither the current nor our recent study (Sidhu et al., 2014). Previous work has suggested that the theoretically positive effect (on performance) of reducing central fatigue via afferent blockade could be counterbalanced, or even outweighed, by the associated exaggeration of peripheral fatigue (mainly accounted for by the fentanyl-induced hypoventilation and the attenuated muscle O_2 transport; see Supplementary Fig. S1) (Amann et al., 2011a). Specifically, since additional peripheral fatigue (Fig 2), requires increased muscle activation to maintain a given power, the gain in voluntary drive (i.e. decreased central fatigue) is apparently not sufficient to sustain the workload for too long with the net effect of similar endurance times in CTRL and FENT. The exact mechanisms accounting for the increase in neural drive during cycling exercise with blocked group III/IV muscle afferents are not fully understood. One simple explanation could be that the afferent block attenuates the discomfort associated with fatigued locomotor muscle which may enable the exercising human to ‘push’ harder.

The situation is different in well-trained endurance athletes which are characterized by a clearly compromised performance during constant-load cycling exercise executed with fentanyl blockade (Amann et al., 2011a). Although the present data cannot address this discrepancy, the diversity is likely related to different effects of fentanyl blockade on arterial oxygenation in well-trained endurance athletes vs. untrained individuals. Briefly, considering the closer proximity to the steep part of the oxyhemoglobin dissociation curve during intense endurance exercise in trained vs. untrained individuals (Dempsey et al., 1999), a given fentanyl-induced fall in alveolar ventilation and PO_2 causes a greater fall in arterial oxygenation in the endurance trained. In this population, as arterial oxygenation is a

key determinant of endurance performance and fatigue (Amann and Calbet, 2008; Goodall et al., 2014), the impact of fentanyl on arterial oxygenation and associated consequences might outweigh the gain in voluntary drive with a net effect of a compromised endurance performance (Amann et al., 2011a).

Interestingly, it has recently been suggested that, in contrast to whole body endurance exercise, muscle afferent feedback might only play a small role in central fatigue-related impairments in cycling sprint performance (Torres-Peralta et al., 2015). Although this finding confirms the notion that strong motivation might briefly outweigh the sensory feedback-mediated inhibitory influence on motoneuronal output during whole body exercise such that short sprints can still be performed relatively unimpaired (Amann, 2011; Noakes, 2011), other studies (Hureau et al., 2014, 2016) challenge this hypothesis. The role of group III/IV muscle afferent feedback in impairing sprint performance therefore remains elusive.

4.3. Influences of group III/IV muscle afferents on the corticospinal pathway during non-fatiguing exercise

Group III/IV muscle afferent feedback during short intense, but non-fatiguing cycling disfacilitates spinal motoneurons while facilitating motor cortical cells – with the net effect of an unchanged corticospinal excitability (Fig 3). The disfacilitating effect of group III/IV afferents on the excitability of the motoneuron pool during non-fatiguing exercise is possibly modulated through presynaptic inhibition of Ia afferents (Rossi-Durand et al., 1999) and the associated reduction in reflex facilitation of the motoneurons (Macefield et al., 1993). Interestingly, earlier investigations using intramuscular hypertonic saline in a muscle performing a non-fatiguing submaximal contraction to activate nociceptive group III/IV muscle afferents found that these sensory neurons facilitate motoneurons while depressing motor cortical cells (Martin et al., 2008b). It is important to note that, compared to present observations, these findings reflect the exact opposite effect of group III/IV-mediated feedback on cortical and spinal excitability. This discrepancy might be explained by the involvement of two different subtypes of group III/IV muscle afferents (nociceptive vs. non-nociceptive) (Light et al., 2008) and/or potential activity-related differences in the excitability of the corticospinal pathway (Sidhu et al., 2013).

The exact mechanism(s) accounting for the observed group III/IV-mediated facilitation of the motor cortex during non-fatiguing exercise remains elusive. However, it has been suggested that increases in sympathetic nervous activity, which are largely determined by group III/IV muscle afferent feedback (Mark et al., 1985), facilitate cortical excitability (Buharin et al., 2013, 2014). It could therefore be speculated that the observed facilitating effect of group III/IV muscle afferents on cortical excitability might be mediated through their influence on sympathetic nervous activity.

4.4. Influences of group III/IV muscle afferents on the corticospinal pathway during fatiguing exercise

The excitability of both spinal motoneurons and motor cortical cells remained unchanged during CTRL (Fig 4). Although afferent blockade during the same exercise did not affect CMEPs, MEP/CMEP significantly increased suggesting a disfacilitating, or inhibitory,

influence of group III/IV muscle afferents on the excitability of the motor cortex during fatiguing locomotor exercise. As such, the overall increase in the excitability of the corticospinal pathway during FENT (Fig. 4A) is likely accounted for by the increased motor cortical excitability. Consequently, the lack of an overall facilitation of the corticospinal pathway during CTRL is, at least in part, related to the depressing influence of group III/IV muscle afferents on motor cortical cells which could be accounted for by the role of these afferents in increasing intracortical inhibition (Schabrun and Hodges, 2012). Interestingly, it has recently been documented that this depressing effect can also spill-over and affect corticospinal excitability of a rested muscle not directly involved in the fatiguing exercise (Sidhu et al., 2014).

As a side note, since increases in EMG have been documented to facilitate motoneurons during cycling exercise, the unchanged CMEPs during CTRL (which was characterized by a substantial increase in EMG from start to exhaustion) indirectly suggest a depressing effect of fatigue on motoneuronal excitability (Weavil et al., 2015, 2016). As fentanyl blockade had no effect on CMEPs at exhaustion, this depression might not be accounted for by group III/IV muscle afferents. Instead, the repetitive activation of motoneurons, which can change intrinsic motoneuron properties leading to insufficient neurotransmitter release or compromised synaptic efficacy, could account for the compromised motoneuronal excitability (Gandevia et al., 1999; Petersen et al., 2003; Rossi et al., 2012).

In the presence of fatigue, the role of group III/IV muscle afferents in determining corticospinal excitability appears to be different during locomotor compared to single joint exercise. In contrast to the present findings during whole body exercise, studies based on fatiguing single muscle contractions using post-exercise cuff occlusion have documented a dissociation between corticospinal excitability and group III/IV discharge (Gandevia et al., 1996; Taylor et al., 2000). However, *in the absence of fatigue*, studies using hypertonic saline infusion during exercise involving a single muscle group agree with the current findings (during fatigue) and document an inhibitory effect of these afferents on the cortex, but a facilitatory effect at the spinal level (Martin et al., 2008b). These inconsistencies might be explained by a host of reasons including the difference in contractile regimes (Sidhu et al., 2013), the differential effect of group III/IV afferents on extensors vs. flexors (Martin et al., 2006), the presence/absence of fatigue, and/or differences in the approach to manipulate neural feedback (Amann et al., 2015).

Finally, increases in sympathetic nervous activity evoked via lower body negative pressure have been documented to facilitate cortical excitability of a non-fatigued, resting hand muscle (Buharin et al., 2013, 2014). As blood pressure during cycling exercise with fentanyl blockade is compromised (Amann et al., 2010), potential baroreceptor-mediated increases in sympathetic nervous activity during FENT (Amann et al., 2011b; Sidhu et al., 2015) could have contributed to the increase in corticospinal excitability during exercise (Fig. 4A). However, although the difference in sympathetic nervous activity between cycling exercise with fentanyl-blockade and control conditions is unknown, it is likely that the difference, if any, is rather small (Amann et al., 2011b).

4.5. Effect of group III/IV muscle afferent feedback after fatiguing locomotor exercise

Within the first minute after CTRL exercise, the net excitability of the corticospinal pathway was similar to pre-exercise, but was increased following FENT (Fig. 5C). While the excitability of motoneurons was increased after CTRL exercise, it remained similar to baseline following FENT exercise. Although only detected as a trend ($P = 0.08$), this difference resulted in a ~27% higher cortical excitability after FENT compared to CTRL (Fig. 5E). This trend supports our findings *during* exercise and suggests that group III/IV muscle afferents may continue to disfacilitate motor cortical excitability for a short duration after exercise.

Some of the changes in the excitability of corticospinal projections to knee extensors following exhaustive endurance exercise differ from those following fatiguing single muscle contractions. Specifically, the excitability of both the corticospinal pathway (Taylor et al., 2000; Maruyama et al., 2006; Takahashi et al., 2009) and spinal motoneurons (Butler et al., 2003) is reduced following fatiguing single-joint exercise. Additionally, post single joint exercise responses have been suggested to be dissociated from group III/IV afferent feedback (Gandevia et al., 1996; Taylor et al., 2000). Again, the disparity in the effect of group III/IV muscle afferents on corticospinal excitability following whole body vs. single joint exercise likely arises from a host of potential physiological (see above) and methodological differences which complicate a direct comparison.

Finally, post-exercise cSP, which has both cortical and spinal components, was significantly shorter following FENT vs. CTRL, a blockade-induced effect that has also been observed following isometric knee-extension exercise (Hilty et al., 2011). Since the lengthening of the cSP is, although recently challenged (McNeil et al., 2009), attributed to $GABA_B$ inhibitory brain circuits (Inghilleri et al., 1993; Siebner et al., 1998), the blockade-induced shortening of cSP suggests that group III/IV muscle afferents may enhance cortical inhibition.

4.6. Conclusion

During locomotor exercise performed in the absence of fatigue, group III/IV muscle afferent feedback facilitates motor cortical cells while depressing motoneuronal excitability. In contrast, during leg exercise in the presence of fatigue, feedback from the same afferents disfacilitates, or inhibits, the excitability of motor cortical cells without affecting motoneurons and promotes the development of central fatigue. The differential effect of group III/IV muscle afferents on the corticospinal pathway during the absence vs. the presence of fatigue suggests that fatigue-related factors (e.g. alterations in intrinsic motoneurone properties and/or the cortical circuitry) might alter the net effect of group III/IV-mediated feedback on cortical and motoneuronal excitability during locomotor exercise. These findings have implications for our understanding of exercise limitations in healthy humans and are likely of great relevance for populations characterized by an altered afferent feedback mechanism, for example, patients with heart failure (Amann et al., 2014).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clinph.2016.10.008.

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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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.

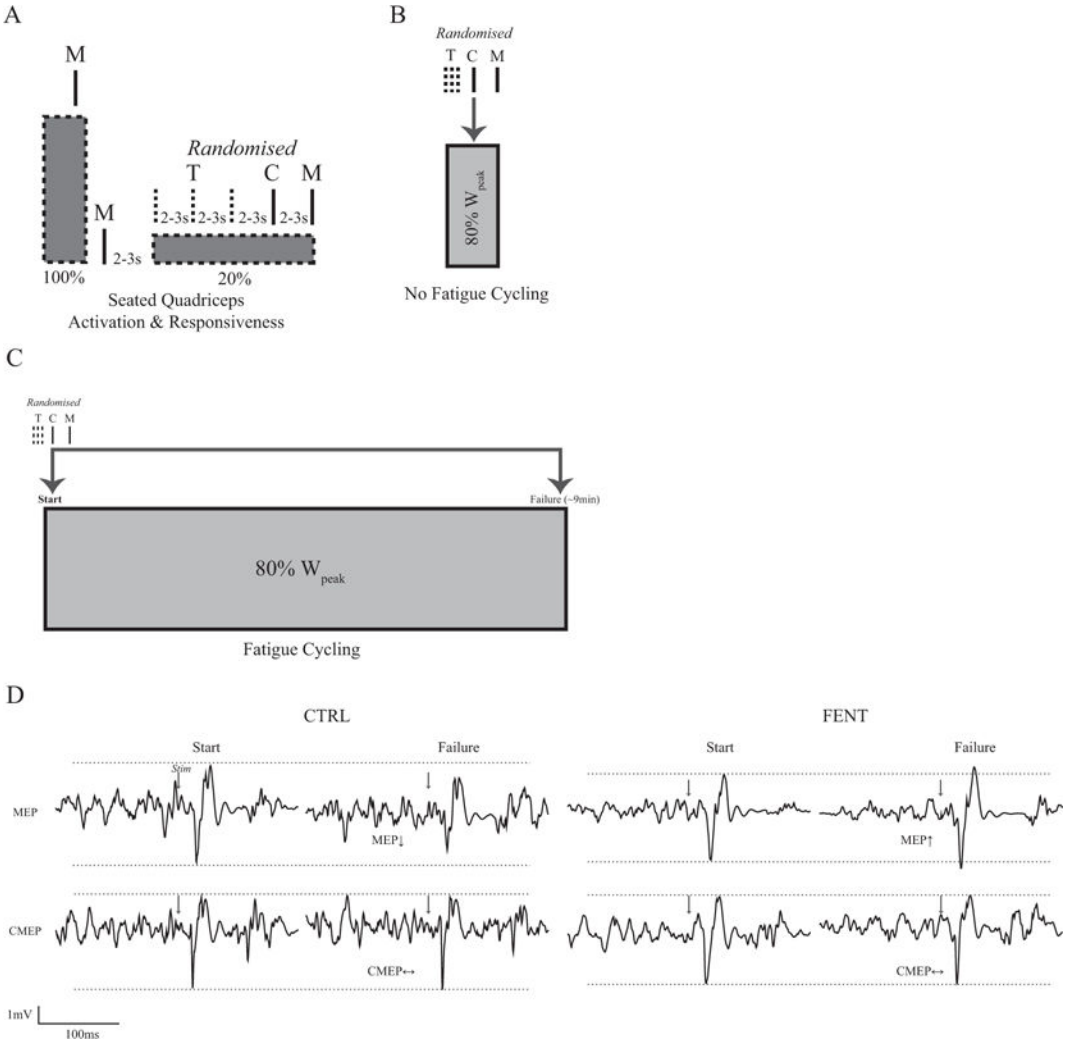

Fig. 1.

Schematic of the main components of study protocol and raw traces of TMS and CMS evoked potentials from a representative subject. A: Femoral motor nerve stimulation (M) delivered during maximum voluntary contraction (MVC; 100%) and at rest in order to calculate voluntary activation (VA). Three transcranial magnetic stimulation (T), one cervicomedullary stimulation (C) and one M were also delivered during a 20% MVC in a randomised order to measure corticospinal pathway excitability. B: Subjects performed short (~1 min each) non-fatiguing cycling bouts at 80% W_{peak} (i.e. 246 ± 13 W) during which three T, one C and one M was delivered. Subjects repeated (A) and (B) following the administration of intrathecal fentanyl. C: Subjects then sustained 80% W_{peak} cycling exercise to task failure during which the same set of stimulations was delivered at the start and at task failure. D: Representative raw traces of T- and C-evoked electromyographic (EMG) responses from a single subject during control (CTRL) and fentanyl (FENT) sessions. Note the reduction in MEP (↓) in CTRL, the increase in MEP (↑) in FENT, and the absence of an effect on CMEPs (↔) from start of exercise to task failure.

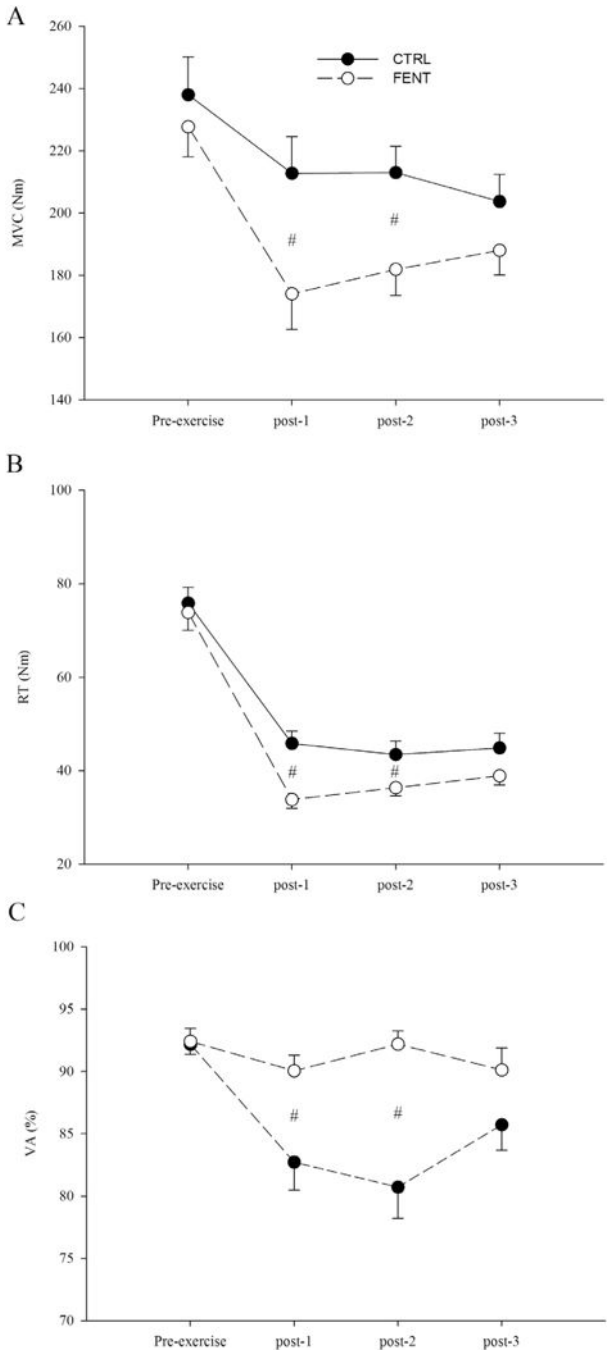

Fig. 2.

Exercise-induced quadriceps fatigue. Pre- to post-exercise (post-1: 56 ± 5 s; post-2: 146 ± 5 s; post-3: 236 ± 5 s) changes in maximal voluntary contraction torque (MVC; panel A), resting twitches (RT; panel B) and voluntary activation (VA, panel C) during exercise. #Significantly different across sessions.

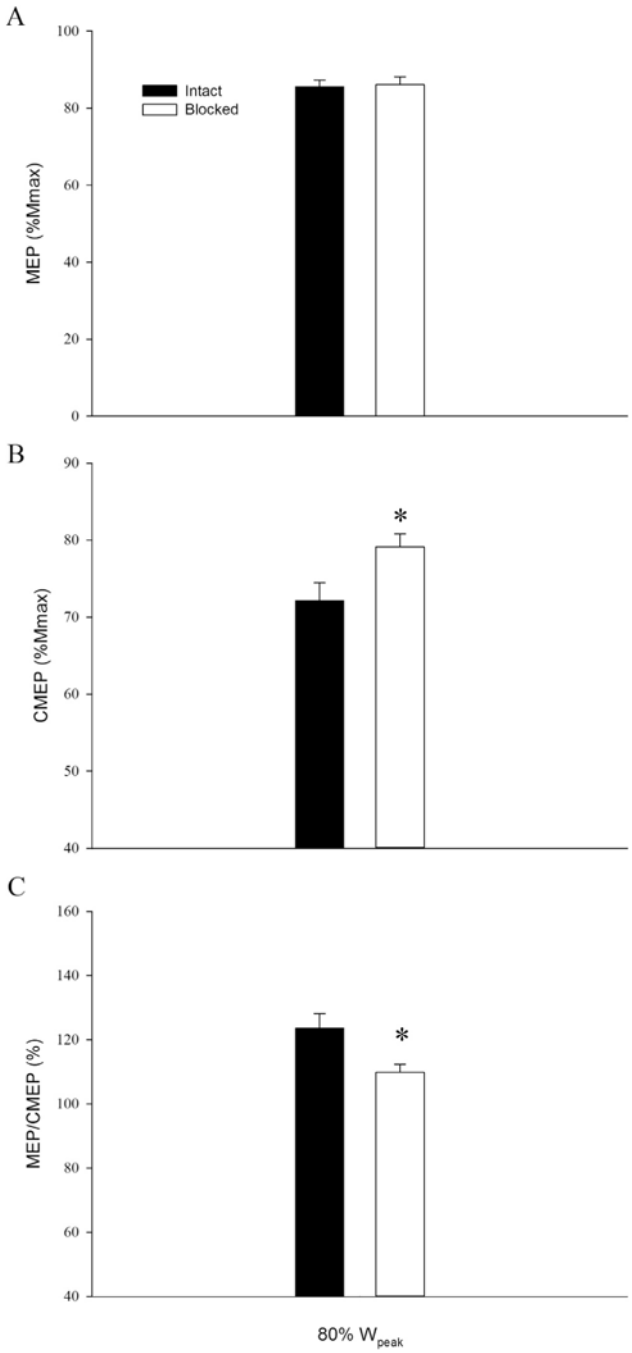

Fig. 3.

Corticospinal excitability during non-fatiguing exercise. Figure illustrates motor-evoked potentials (MEP normalized to M_{max}; panel A), cervicomedullary-evoked potentials (CMEP normalized to M_{max}; panel B) and MEP/CMEP (panel C) during non-fatiguing cycling bouts performed for ~40-s at 80% W_{peak} (~246 W) with intact (black bars) and blocked (white bars) group III/IV locomotor muscle afferents. *Significantly different from intact feedback.

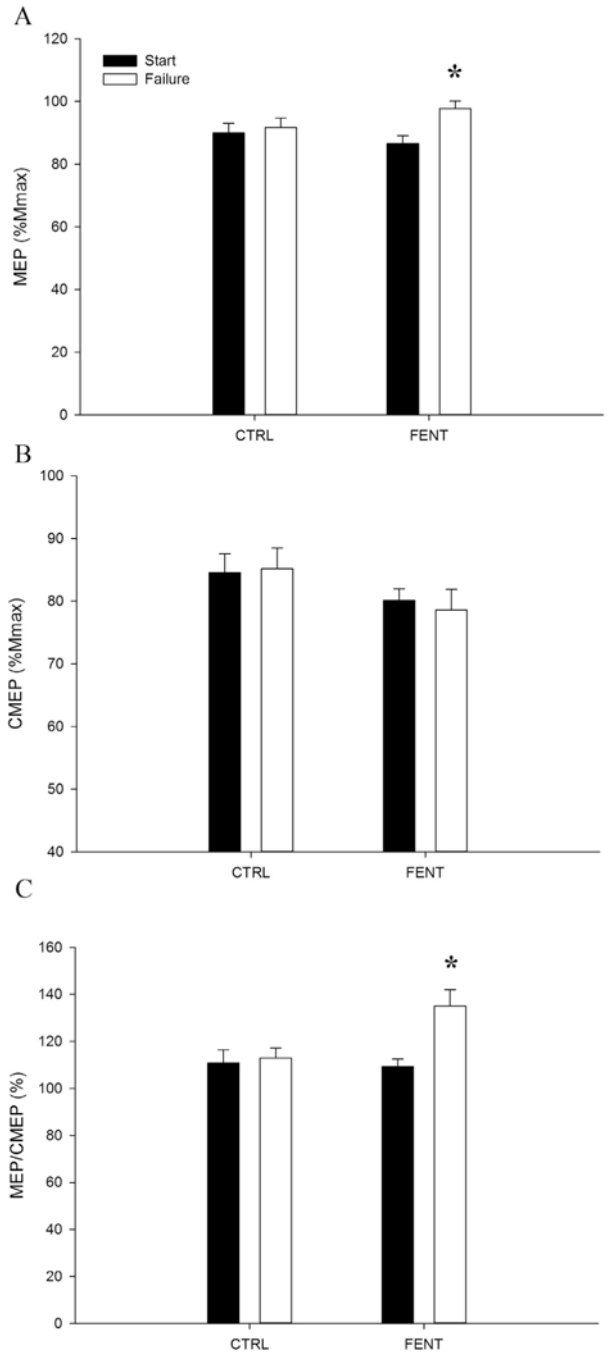

Fig. 4.

Corticospinal excitability during fatiguing exercise. Figure illustrates motor-evoked potentials (MEP normalized to M_{max}; panel A), cervicomedullary-evoked potentials (CMEPs normalized to M_{max}; panel B) and MEP/CMEP (panel C) at the start of exercise (black bars) and at exhaustion (white bars) during control (CTRL) and fentanyl (FENT) sessions. *Significantly different from start of exercise.

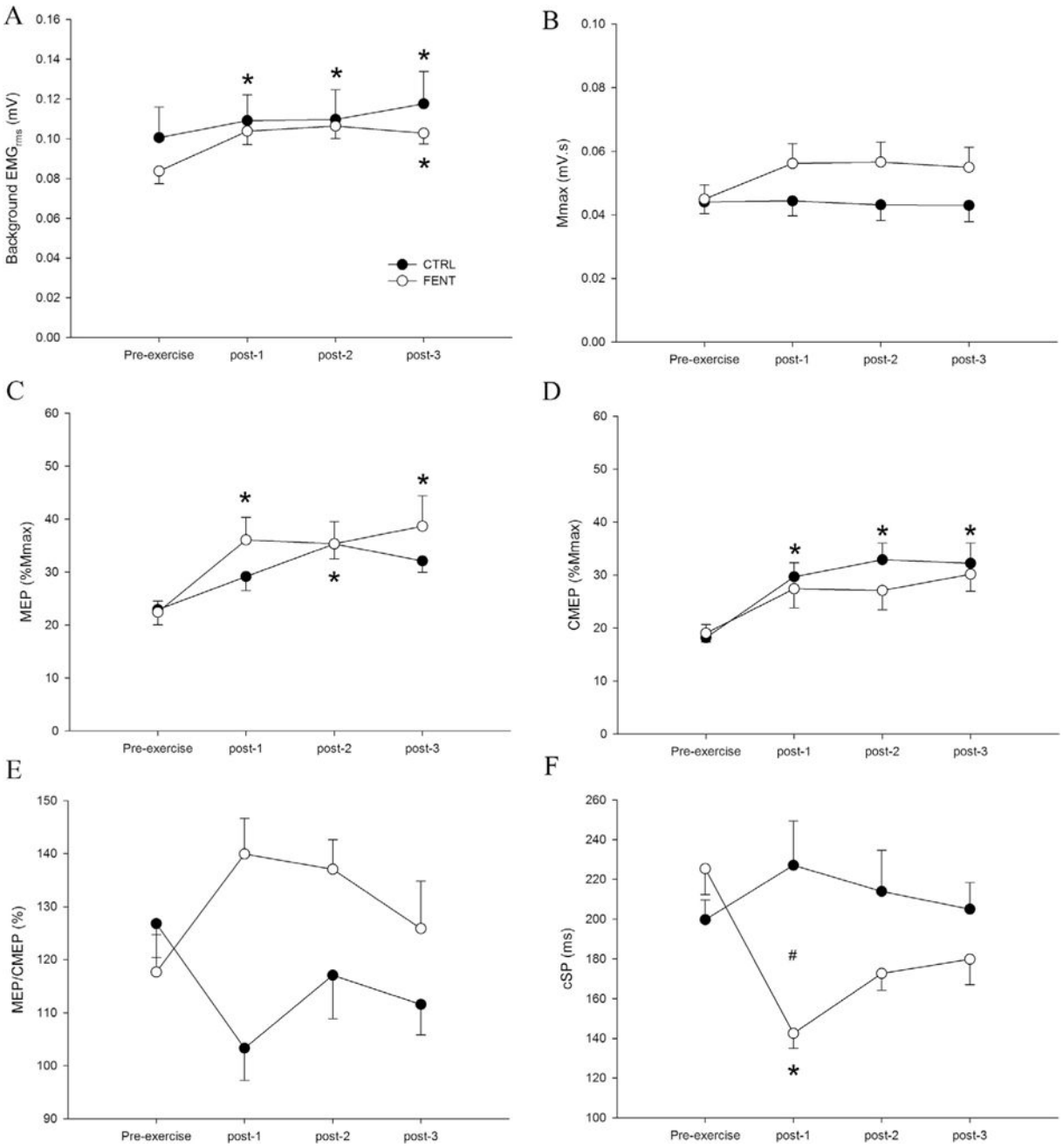

Fig. 5.

Pre- to post-exercise changes in corticospinal excitability. Pre- to post-exercise (post-1: 56 ± 5 s; post-2: 146 ± 5 s; post-3: 236 ± 5 s) changes in background root mean squared electromyogram (EMG_{rms}; panel A), maximal compound muscle action potential (M_{max}; panel B), motor-evoked potentials (MEPs normalized to M_{max}; panel C), cervicomedullary-evoked potentials (CMEPs normalized to M_{max}; panel D), MEP/CMEP (panel E) and cortical silent period (cSP; panel F) during 20% MVC (adjusted to instantaneous MVC).

Measurements were taken during control (CTRL) and fentanyl (FENT) sessions.
*Significantly different from pre-exercise. #Significantly different across sessions.

Table 1

Ventilatory response to CO_2 at rest. $N = 8$. Data are means ± SE.

F_iCO_2 (%)	Breathing frequency (breaths/min)		Tidal volume (L)	
	Pre-FENT	Post-FENT	Pre-FENT	Post-FENT
0.04	12.4 ±1.5	12.5 ± 1.7	1.0 ± 0.2	1.1 ±0.3
6	15.1 ± 1.6	14.4 ±1.9	1.6 ± 0.1	1.8 ±0.2

Table 2

Ventilatory response during the last minute of arm cycling exercise at two different workloads. $N = 6$. Data are means ± SE.

Workload	Breathing frequency (breaths/min)		Tidal volume (L)	
	CTRL	FENT	CTRL	FENT
15 W	27.5 ± 2.6	25.4 ± 2.3	1.7 ± 0.2	1.7 ± 0.1
30 W	29.2 ± 2.4	27.3 ±2.0	2.0 ± 0.1	2.1 ± 0.1