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ORIGINAL ARTICLE

Pain sensitivity is normalized after a repeated bout of eccentric exercise

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Abstract
Purpose The purpose of this study was to investigate the effect of repeated bouts of eccentric exercise on the nociceptive withdrawal reflex (NWR) threshold, a measure of sensitivity in the spinal nociceptive system.
Methods Sixteen healthy students (age 25.7 ± 0.6 years, BMI 24.8 ± 1 kg m^{-2}) participated in this randomized, controlled, crossover study. Two identical bouts of high-intensity eccentric exercises were performed on the tibialis anterior muscle 7 days apart. Control sessions involving no exercise were performed 4 weeks apart the exercise sessions. Pressure pain thresholds (PPT) and the NWR threshold were recorded before, immediately after, and 1 day after both bouts of exercise.
Results Pressure pain thresholds decreased significantly at two of the muscle belly sites on the day after initial bout compared with baseline. NWR threshold decreased by 25 ± 4 % immediately after initial bout and by 30 ± 5 % the next day ($p < 0.05$) as an indication of generalized pain hypersensitivity. On the contrary, no changes were found in both pain thresholds after second bout of eccentric exercise indicating that both localized and generalized pain sensitivity were normalized.
Conclusion In conclusion, this study for the first time documented that an initial bout of unaccustomed high-intensity eccentric exercise, which results in muscle soreness can induce central sensitization. A repeated bout of exercise, however, facilitates inherent protective spinal mechanisms against the development of muscle soreness.

Keywords Eccentric exercise · Central sensitization · Repeated bout effect · Pressure pain threshold · Nociceptive withdrawal reflex

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Introduction

Musculoskeletal pain is the most common cause of pain among young people (Sjogren et al. 2009). It is difficult to treat this type of pain as our knowledge about the neuronal mechanisms mediating and modulating musculoskeletal pain is limited. Alternative approaches for pain treatment are appealing. Exercise-based pain management program is suggested as an effective alternative for relieving musculoskeletal pain (Marinko et al. 2011). For instance, structured exercise induces pain alleviation and improves functional capacity; e.g., it decreases the pain-intensity and pressure pain sensitivity in patients suffering musculoskeletal disorders (Ludewig and Borstad 2003; Marinko et al. 2011). Pain management protocols typically include long-term periods of aerobic exercises or a combination of both aerobic and strength training (Imamura et al. 2009). Single session of resistance exercise alone (O'Connor et al. 2011) has also been suggested to provide pain relief and is especially applicable for people unable to engage in high-intensity or long-term aerobic exercise programs (Ludewig and Borstad 2003; Marinko et al. 2011; O'Connor et al. 2011). However, the pain associated with unaccustomed,

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especially eccentric exercise (ECC) often decreases the ability or willingness to participate in physical activity or therapeutic exercise (Dannecker et al. 2005; van Santen et al. 2002).

Following training programs including an ECC component, subsequent muscle pain and tenderness are peaking at about 24–48 h (MacIntyre et al. 2001) and subsiding within 5–7 days post exercise (Gulick and Kimura 1996; MacIntyre et al. 2001). The phenomenon is called post-exercise muscle damage or more commonly delayed-onset muscle soreness (DOMS). DOMS has been shown to cause localized pressure pain hyperalgesia (Binderup et al. 2010; Hedayatpour et al. 2008) and to decrease the muscle performance, i.e., reduction in range of motion (ROM), muscle strength as well as increased electromyographic (EMG) activity (Madeleine et al. 2011). Hyperalgesia is defined as increased pain from a stimulus that normally provokes pain; it reflects increased pain on suprathreshold stimulation. Current evidence suggests that hyperalgesia is a consequence of perturbation of the nociceptive system with peripheral and/or central sensitization. Hyperalgesia may be seen after somatosensory stimulations like electrical stimulation applied to biological tissues (Cervero and Laird 1996; Merskey and Bogduk 2004).

An adaptive response to one bout of the same or similar ECC exercise is termed the repeated bout effect (RBE) (Kamandulis et al. 2010; Kawczynski et al. 2012; Lavender and Nosaka 2008; Starbuck and Eston 2012). The RBE refers to the protective effect provided by a single bout of ECC exercise against muscle damage of a subsequent ECC bout (Nosaka and Clarkson 1995). Despite a number of studies demonstrating the RBE on isolated ECC contraction of elbow flexors (Paddon-Jones et al. 2000) and knee extensors (Behrens et al. 2012; Kamandulis et al. 2010), the mechanisms behind RBE are only partly understood. Furthermore, the relationship between RBE and muscle pain/soreness has not been fully understood. General increased pain sensitivity has been reported after the first bout of ECC in the presence of DOMS; however, a subsequent bout of ECC did not induce DOMS and had no impact on the pain sensitivity (Kawczynski et al. 2012). There is some evidence suggesting central sensitization after the exercise-induced pain followed by unaccustomed ECC (Nie et al. 2006). Central sensitization is a protective phenomenon defined as increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input (Merskey and Bogduk 2004). The nociceptor-induced sensitization of the somatosensory system is adaptive in that it makes the system hyperalert to conditions in which a risk of further damage is high. This phenomenon is long-lasting but not permanent (Latremoliere and Woolf 2009). It is well known that localized musculoskeletal conditions such as tendinopathy (Fernandez-Carnero et al. 2009) may cause localized and generalized hyperalgesia (central sensitization). However, to our best knowledge, there is no prior study investigating aspects of central sensitization in relation to ECC exercise in healthy people. The nociceptive withdrawal reflex (NWR) is considered to be a reliable electrophysiological outcome for central sensitization (Banic et al. 2004). NWR is a typical defense reaction with the purpose of withdrawing the extremities from potential damaging stimuli. The spinal reflex to nociceptive stimuli is used to evaluate the effect of different interventions and investigate basic pain mechanisms related to central sensitization in humans (Banic et al. 2004).

The objective of the current study was to investigate the effects of two repeated bouts of high-intensity ECC exercise on the NWR threshold as a measure of sensitivity in the spinal nociceptive system and also pressure pain threshold (PPT) as a measure of deep structure sensitivity in a randomized, controlled, crossover design. We hypothesized that the first bout of ECC would induce DOMS and localized muscle hyperalgesia to pressure pain stimulation as well as central sensitization, i.e., facilitation of the NWR. Then, the protective effect induced by hypersensitivity followed by theinitial bout of ECC would modulate DOMS and the associated quantitative pain measures after the second bout.

Methods and subjects

Participants

Sixteen male healthy students fulfilled the entire protocol [age 25.7(0.6) years, body mass 79.9(3.3) kg, height 179.2(1.7) cm, BMI 24.8(1.0) kg m^{-2}]. Informed consent was obtained from each participant. The study was approved by the local ethics committee (no. N-20070019) and conducted in accordance with the Declaration of Helsinki. All the participants were untrained and maintained normal daily activity during the course of the study. None had participated in strength training 6 months prior to entering the study. The inclusion criteria included: no pain, specifically in the lower limb, before the experiment and no history of chronic pain; no caffeine and alcohol drinking during the last 24 h before each experimental session; and no pain medication, no stretching and/or massage exercise nor any attempts to reduce soreness after exercise was allowed.

Study design

In this study, we investigated the effects of two bouts of high-intensity exhausting isokinetic ECC on objective and subjective outcomes of pain in a randomized controlled

crossover manner. NWRT (index of sensitization) was considered the primary outcome while PPT, range of motion and isometric maximum voluntary contraction force (MVC) constituted the secondary outcomes. Participants were familiarized with the protocol and the procedures before data collection. The study was conducted applying two identical bouts of ECC (ECC_1 and ECC_2) separated by 7 days. Control sessions' measurements involving no exercise were also recorded 30 ± 2 days either before or after the ECC bouts. Thirty days seems more than enough to wash out the effect of DOMS on the control measurements results (Gulick and Kimura 1996; MacIntyre et al. 2001). The measurements were conducted before, immediately after, and the day after both ECCs and rest sessions. In the control measurement sessions, instead of the ECC, participants rested quietly for 15 min in the same sitting conditions. The measurements for each participant were performed at the same time of the day.

Isometric MVC

Before and after completion of both ECCs, the participants performed six trials of isometric dorsi flexion (DF) MVCs (100 % MVC) to define the relative level of the ECC exercise intensity. The six repetitions of the MVC lasting 5 s each were performed with three repetitions at 90° and three at 85°, respectively, and with 60 s of rest between each repetition. The average of the six repetitions was recorded as the isometric MVC force for each of the trials. The MVC assessments were obtained before, after, and the day after ECCs.

Exhausting isokinetic eccentric exercise

A Kin-Com isokinetic dynamometer (KINETIC COMMUNICATOR 125 AP, Software Version 4.03, Chattecx Corp., Chattanooga, TN, 37405, USA) and a plantar/dorsi attachment (P N. 54708) was used for the ECC of the tibialis anterior (TA) muscle by moving the ankle from 5° of DF to 25° of plantar flexion (PF). A 90° angle between the foot and the leg was defined as neutral position (0°); DF degrees were defined as positive and PF degrees as negative. The angular velocity was set at $10° \ s^{-1}$, and the minimum load was set as 80 % MVC measured before the ECC1. After acclimatization, the participants were told to perform at their maximum force level during the ECC protocol. The dynamometer would stop whenever the participants produced less than 80 % MVC force during both the ECCs. The participants performed six repetitions per set, with 20 s of rest in between the sets. The exercise continued for as many sets as required to achieve a condition where participants were no longer able to maintain an adequate ECC ankle DF. This protocol was used to induce at least 50 % reduction of the isometric MVC force at the measurement immediately after ECC. A reduction of 40 % in muscle strength is regarded as one of the most valid and reliable indicators of the extent of muscle damage in humans (Warren et al. 1999). The protocol used in our study was supposed to induce more than 40 % declines in muscle strength. It has been shown that such an ECC protocol can produce DOMS, and reduction in range of motion for several days following the exercise (Prasartwuth et al. 2005). The participants were provided with visual feedback of the force during the ECCs and were verbally encouraged to maintain their maximal force by the experimenter.

Muscle soreness and pain

Muscle soreness was measured using a 0–10 score scale, where 0 indicated "no soreness or tenderness", while 10 corresponded to "worst soreness or tenderness". Participants were instructed to score soreness intensity while walking. Muscle pain was measured using the 0–10 scale, where 0 indicated "no pain", while 10 was anchored with "worst pain imaginable". Participants scored their pain intensity while the investigator palpated the mid-belly of the TA muscle. Using the distal portions of the index and forefingers, palpation was performed in a circular motion over the site by the same investigator for all the participants (Muthalib et al. 2011).

Pressure pain threshold

Pressure pain threshold recordings were made to investigate deep structure sensitivity to pressure pain. PPTs were assessed at five sites on the TA muscle with the participants in supine position. The five sites were equally interspaced between the distal and proximal musculotendinous junction of the tibialis anterior. The sites were marked using a permanent marker to replicate the exact recording sites during the whole period of study. The PPTs were measured using an electronic hand-held pressure algometer (Somedic Algometer type 2, Sweden) with a round, flat 2 mm thick rubber tip, with an area of $1 \ cm^2$. The pressure was increased at a constant rate of 30 kPa/s and was applied perpendicularly to the skin surface. Each recording was repeated three times randomly between the stimulation sites. The distance among adjacent points and the elapsed time between consecutive PPT recordings prevented spatial and temporal summation. The mean value of the three recordings was used as the PPT value. For points with a coefficient of variance equal to 0.2 or more, a fourth or fifth recording was obtained to reduce the intra-individual variation, and the mean value of all three, four or five recordings was then used as the PPT value for each site

(Binderup et al. 2010). Pain sensitivity maps of the TA muscle were generated using the averaged PPT values over the five locations based on measured horizontal and vertical positions of each point. The interpolation was performed using an inverse distance weighted interpolation to obtain an easy reading of the PPT distribution (Binderup et al. 2010).

Reflex detection

Nociceptive withdrawal reflex recording was obtained using surface EMG recordings. The electrodes (Ambu® Neuroline 720, ref: 72001-K/12, Denmark) for EMG recording were placed over the shaved, abraded, and cleaned skin of the TA muscle. The EMG activity was amplified (variable between 500 and 5,000 times), band-pass filtered [5–500 Hz], digitized (12 bits A/D converter, 2 kHz), and stored on a disk. The electrodes were fixed at a constant inter-electrode distance of 20 mm, and located in relation to anatomical landmarks according to the recommendations by SENIAM. The criterion used to determine the NWR threshold (NWRT) was if at least one significant different peak occurred in the 60–200 ms post-stimulation interval of the signals recorded from the TA muscle. The NWR was recorded after the electrical stimulation using surface electrodes (Ambu® Neuroline 700, ref: 70001-K/12, Denmark) placed at the arch of the foot. Using an ascending/descending staircase method, the current intensity was increased by 1-mA increments until an NWR was detected and then the intensity was decreased at the same increments until the reflex was no longer detected. The procedure was repeated three times and the average of the six points (three peaks and three troughs) was used for NWRT estimation.

Statistical analysis

Power analysis was performed considering a full factorial repeated measures and using a small effect size ($\eta = 0.25$), confidence level ($\alpha = 0.05$), and desired power (80 %). The required total sample size was calculated as 16 participants. A linear mixed model analysis of variance with factors of time (before, immediately after, and the day after ECCs and rests) and treatments (ECC_1, ECC_2, $Rest_1$, $Rest_2$) was performed. Dependent variables included NWRT, PPTs, MVC, and ROM. Bonferroni adjustment for multiple comparisons was used for post hoc test. Shapiro-Wilk and Q-Q plots test confirmed normal distribution of the dataset. The reliability of the NWRT, and PPT measures were analyzed using intra-class correlation coefficient (ICC). We used measurements of the control sessions over 1 day (within day), 2 consecutive days (between days), and 2 days with 7 days in between (within week) from the same 16 subjects. The within day, between days, and within week R values of ICC were 0.94, 0.90, and 0.90 for NWRT, and 0.96, 0.94, and 0.82 for PPT, respectively. In all tests, $p \leq 0.05$ was considered as statistically significant difference. The data are presented by the mean value and the standard error of the mean (SEM).

Results

All the participants completed their own specific training protocol at both the bouts. In average, 57 (5) sets and 344 (32) [mean (SEM)] repetitions were performed. As shown in Fig. 1, NWRT only decreased immediately after and the day after ECC_1 ($p < 0.05$). In contrast to ECC_1, there was no significant effect of the ECC_2 on NWRT neither immediately after nor the day after ECC_2.

The PPT values at the muscle belly site (sites 2 and 3) only decreased significantly the day after ECC_1 compared with the baseline ($p < 0.05$, and $p < 0.01$ for sites 2 and 3, respectively). In contrast to ECC_1, there was no significant effect of the ECC_2 on PPT the day after ECC_2 (Fig. 2).

Maximum voluntary contraction force decreased significantly immediately after both ECC_1 and ECC_2 ($p < 0.001$, and $p < 0.01$, respectively). The MVC force was significantly decreased the day after ECC_1 ($p < 0.001$) and did not change the day after ECC_2. Similarly, ROM decreased significantly immediately after both the ECC_1 and ECC_2 ($p < 0.001$, and $p < 0.001$, respectively). Further, ROM only decreased the day after ECC_1 ($p < 0.05$) and did not change the day after ECC_2 (Table 1).

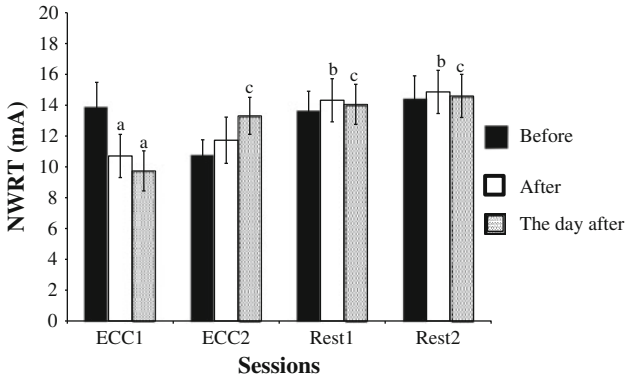

Fig. 1 Mean values (SEM) of nociceptive withdrawal reflex threshold (NWRT) at before, after, and the day after first bout of ECC exercise (ECC_1), second bout of ECC exercise (ECC_2), and control (Rest1 and 2) sessions ($N = 16$). **a** Significantly different from session before ECC1; **b** significantly different from session after ECC_1; **c** significantly different from the day after ECC_1; $p \leq 0.05$

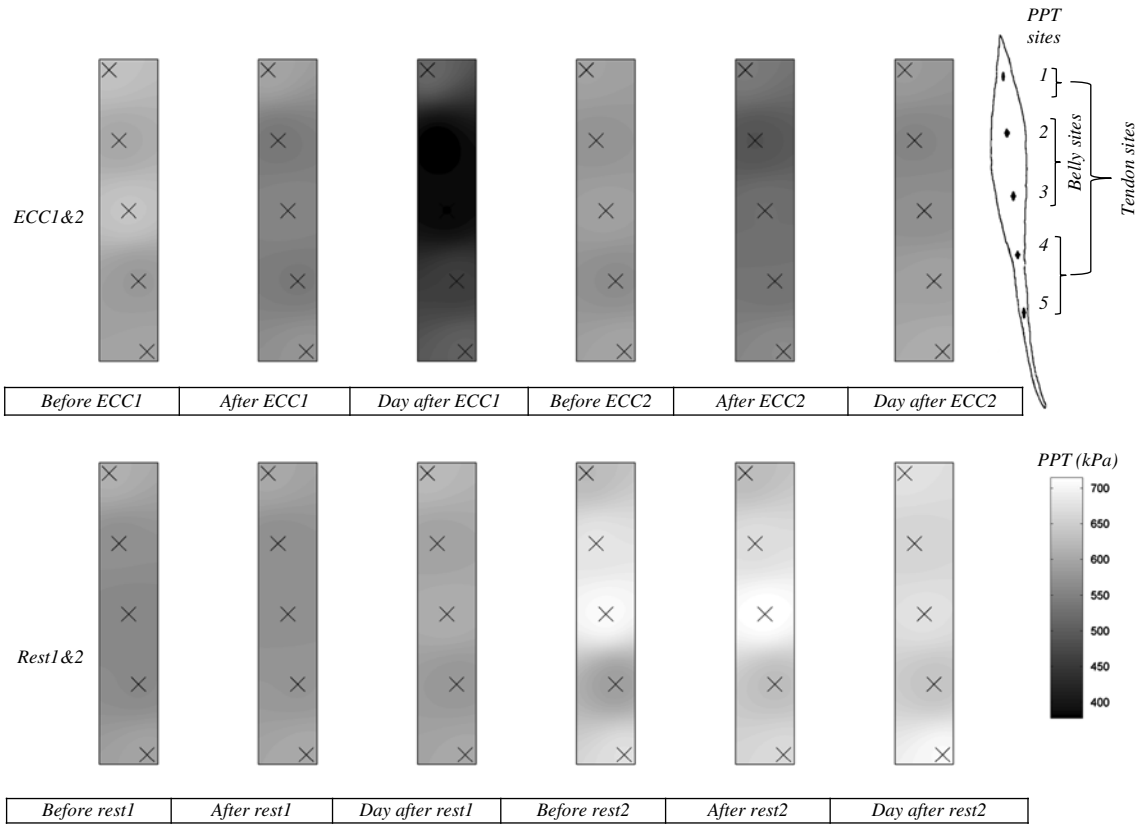

Fig. 2 Pressure pain threshold (PPT) maps from the tibialis anterior muscle before, after, and the day after first ECC exercise (ECC_1), second ECC exercise (ECC_2) and Control (Rest1 and 2) sessions ($N = 16$). Points 1–5 correspond to PPT sites

Table 1 Mean values (SEM) of MVC and ROM before, immediately after and the day after ECC exercises (ECC_1 and ECC_2), and control sessions (Rest1 and Rest2); *Force MVC* force measured during maximum voluntary contraction, *ROM* range of motion.

$N = 16$	ECC_1			ECC_2			Control ($rest_1$)		Control ($rest_2$)	
	Before	After	Day after	Before	After	Day after	Before	Day after	Before	Day after
Force $_{MVC}$ (N)	257.2 (12.4)	56.8 (6.2)[a]	134.7 (13.3)[a,b]	220.1 (14.7)	160.1 (11.0)[c]	207.2 (13.2)	256.9 (12.8)	244.4 (11.1)	259.1 (9.4)	264.2 (11.6)
ROM (°)	44.3 (1.8)	11.9 (2.2)[a]	17.3 (1.5)[a,b]	36.3 (2.0)	21.8 (2.0)[c]	31.0 (2.4)	43.7 (1.4)	45.3 (1.5)	45.2 (1.4)	45.4 (1.3)
Pain (score 0–10)	0	3.6 (0.5)[a]	5.4 (0.5)[a,b]	0.8 (0.2)	1.3 (0.1)	0.4 (0.1)	0	0	0	0
Soreness (score 0–10)	0	6.2 (0.6)[a]	6.6 (0.3)[a,b]	1.6 (0.5)	2.7 (0.4)	1.3 (0.2)	0	0	0	0

[a] Significantly different from session before ECC_1

[b] Significantly different from session after ECC_1

[c] Significantly different from before ECC_2

$p \leq 0.05$

Discussion

The reliability of the NWRT and PPT within day, between days, and within-week was high. The day after ECC_1, NWRT and PPTs decreased indicating that the ECC produced DOMS-related muscle hyperalgesia and enhanced generalized pain hyperexcitability (central sensitization). The day after ECC_2, a normalization of PPTs compared with the day after ECC_1 were seen supporting RBE. This is in agreement with previous finding of decreased pain sensitivity after ECC_2 with respect to ECC_1 as evidence for RBE (Kawczynski et al. 2012). Further, a clear hyperalgesia in the TA muscle belly sites to pressure pain stimulation was found after ECC_1 in line with Fernandez-Carnero et al. (2010). Moreover, in the current study, DOMS and RBE were detected for the first time by NWRT modulation as a measure of spinal cord hyperexcitability. The use of the NWRT enabled to detect neural changes in

relation to repeated ECC, and that the repetition of ECC exercise may further facilitate inherent protective spinal mechanisms against the development of DOMS.

Repeated bout effect has generally been attributed to three main theories of neural, connective tissue, and cellular adaptations. Considering the demonstration of a protective/adaptive effect of ECC on the subsequent bouts even prior to full recovery (Mair et al. 1995; Nosaka and Clarkson 1995), neural adaptation and its underlying central modulation have been suggested as the most likely mechanism explaining RBE (McHugh et al. 1999). In the present study, the performances, i.e., number of sets and repetition as well as the relative load were kept constant over the two bouts of ECC. We found a decrement in ROM, MVC, PPT, and consequently significantly less DOMS developed after ECC_2 compared to ECC_1 indicate the presence of an RBE. Further, the lower level of MVC and ROM before starting ECC_2 compared with their baseline level indicates that the second bout of ECC was performed prior to full recovery. Therefore, the present findings confirm the fact that the protective/adaptive effect of ECC is not dependent on full recovery (Kawczynski et al. 2012; Mair et al. 1995; Nosaka and Clarkson 1995). Furthermore, a light load ECC exercise that does not significantly change markers of muscle damage also confer protection against a subsequent bout of more demanding ECC exercise performed after 2 days (Lavender and Nosaka 2008). It seems that muscles can be preconditioned even by a light ECC exercise resulting in protection towards subsequent damage caused by high ECC.

The initial ECC caused a significant decrease of the NWRT immediately and the day after ECC_1 (Fig. 1). The decrease in NWRT is considered to reflect hyperexcitability of the spinal nociceptive system (Banic et al. 2004). Hence, it is likely that the decrease in NWRT was caused by central sensitization after a strong stimulus induced by ECC_1 while this was not observed after ECC_2. The M wave amplitudes of trapezius, vastus medialis, vastus lateralis, and rectus femoris have recently been reported to be unchanged after exercise-induced muscle soreness (Behrens et al. 2012; Vangsgaard et al. 2013). This may indicate that altered contractile properties after ECC_1 have not caused the reported decrease in NWRT immediately and the day after ECC_1. The observed modulation of the NWRT is therefore most likely reflecting central changes in the reflex pathway suggesting hyperexcitability of the spinal nociceptive pathways.

A reduction in the H-reflex of the trapezius muscle evoked by a submaximal stimulation immediately after and the day after ECC has recently been reported (Vangsgaard et al. 2013). This indicates a decrease in the excitability of the motoneuron pool in presence of DOMS. In contrast, the central sensitization inferred by a decrease in the NWRT in the present study is probably a result of facilitation of the sensory part of the reflex arc after performing ECC_1. Muscle inflammation and chemical stimulation of the muscle nociceptors (group III/IV afferents) are reported to activate other afferents in the reflex pathways, i.e., low threshold mechanoreceptors, cutaneous nociceptive afferents, group II muscle afferents as well as joint afferents (Mense 1993). These afferents together develop a widespread multisensorial convergence onto common interneurons in the spinal cord (Schomburg 1990). Interaction of afferents input at an interneuronal level, presumably in the dorsal horn of the reflex pathway (Andersen et al. 2000) furnishes a plausible explanation of the NWRT modulation by ECC as well as muscle hyperalgesia and soreness.

Unlike the ECC_1, there was no decrease in the PPTs or NWRT immediately after and the day after ECC_2. Actually, the levels of NWRT increased the day after ECC_2 compared with the day after ECC_1 indicating a protective effect of ECC and RBE (Fig. 1). Exercise training has been suggested to modulate various neurotrophins at central and peripheral levels (Ying et al. 2003) leading to a synaptic efficacy (Hutchinson et al. 2004) of sensory motoneurons and signal transduction receptors (Ying et al. 2003). Given the result for NWRT after ECC_1 and ECC_2, it seems possible that ECC_1 could provide a sufficient physiological stimulus to cause central sensitization and therefore manifestation of a remarkable plasticity of the somatosensory nervous system (Latremoliere and Woolf 2009). This central facilitation in response to ECC_1 provided an opportunity for rapid functional plasticity that could lead to treating with ECC_2 more efficiently, hence suggesting the importance of centrally mediated changes in relation with the RBE.

Conclusion

The present randomized controlled cross-over study highlighted that high-level unaccustomed ECC causing DOMS led to central sensitization depicted by lower NWRT. Central sensitization induced by ECC_1 probably played a key role behind pain/soreness. A lack of central sensitization was observed after ECC_2. Conditioning professionals should consider consecutive bouts of ECC in training and rehabilitation programs as a way to limit the effects of central sensitization behind DOMS.

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Conflict of interest The authors declare that they have no conflict of interest.

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