Original Research Article

Local and Generalized Endogenous Pain Modulation in Healthy Men: Effects of Exercise and Exercise-Induced Muscle Damage

Christopher D. Black, PhD,* Brandon K. Tynes, MS,† Alexander R. Gonglach, MS,* and Dwight E. Waddell, PhD‡

*Department of Health and Exercise Science, University of Oklahoma, Norman, Oklahoma; †Department of Health, Exercise Science and Recreation Management, University of Mississippi, Oxford, Mississippi; ‡Department of Electrical Engineering, University of Mississippi, Oxford, Mississippi, USA

Correspondence to: Christopher D. Black, PhD, Department of Health and Exercise Science, University of Oklahoma, Norman, OK 73069, USA. Tel: (706) 255-3750; Fax: (405) 325-0594; E-mail: cblack@ou.edu.

Abstract

Isometric exercise has been shown to activate endogenous pain inhibitory pathways in healthy adults, but not in some clinical pain populations.

Objective Exercise-induced muscle damage (EIMD) and the associated delayed-onset muscle soreness (DOMS) are a model for studying clinical pain; thus, our purpose was to examine the effects of isometric exercise on pressure pain threshold (PPT) in the presence and absence of DOMS.

Methods Data were collected on 23 males (22.8 ± 2.5 yrs). PPT was assessed in the right (exercising) and left (resting) quadriceps prior to, every 30 seconds during, and 2 and 15 minutes following an isometric contraction of the right quadriceps at 25% of maximal voluntary contraction (MVC) held until fatigue. Unilateral eccentric exercise was performed to induce DOMS in the exercising leg and testing was repeated 48 hours later.

Results DOMS increased (P < 0.001) and resting PPT decreased (P = 0.03) following EIMD. PPTs were elevated during exercise in the exercising (P ≤ 0.002) and resting (P ≤ 0.002) quadriceps but did not differ between the control and EIMD conditions in either leg (P ≥ 0.61). PPT remained elevated 2 and 15 minutes postexercise (P < 0.05) in the exercised quadriceps in both conditions, but values returned to baseline at 2 (P = 0.91) and 15 minutes (P = 0.28) postisometric exercise in the resting quadriceps.

Conclusions Unlike clinical pain, DOMS had no effect on the PPT response during exercise in either the exercising or resting quadriceps. The fact that exercise altered PPT in both quadriceps during exercise suggests a generalized pain inhibitory mechanism was activated. However, the restriction of postexercise effects to the exercised limb suggests localized inhibitory mechanism(s) were activated after exercise.

Key Words. DOMS; Pressure Pain Threshold; Blood Pressure; EMG

Introduction

A growing body of research indicates physical activity plays a role in pain perception. In healthy adults, acute bouts of exercise have been shown to reduce sensitivity to noxious stimuli, often termed exercise-induced hypoalgesia (EIH; for review see [1–3]). EIH manifests as an increase in the pressure, thermal, or electrical stimulus required to elicit pain (i.e., an increased pain threshold) and/or an increase in the amount of time painful pressure or temperatures can be tolerated (i.e., an increase in pain tolerance). The mechanism(s) responsible for EIH are not fully understood, with evidence supporting both generalized and location-specific pain inhibitory mechanisms. Findings of EIH not only in an exercising muscle/limb (e.g., quadriceps or infraspinatus) [4–8], but also in locations distant to the exercising muscle/limb (e.g., the contralateral quadriceps) [5,9,10] suggest generalized or
whole-body pain inhibitory mechanisms may be activated during exercise. The release of endogenous opioids [1,11] and endocannabinoids [12], exercise-induced elevations in heart rate and blood pressure[13], and/or conditioned pain modulation (CPM) [3,14,15] have been proposed as mechanisms of generalized pain inhibition. In addition to generalized pain inhibitory mechanisms, Kosek and Lundberg [5] have demonstrated greater EIH in a contracting muscle compared with the resting contralateral muscle and with a resting distant muscle. These findings suggest local (within a body segment) pain inhibitory mechanisms may act synergistically with generalized mechanisms to produce EIH. Efferent motor activity from the contracting muscle [16] or activation of afferent Aδ and C-fibers within the contracting muscles [17,18] could play a role in inhibiting nociceptive transmission from the contracting muscle and account for the greater EIH in the exercising muscle.

The presence of chronic musculoskeletal pain has been shown to alter endogenous pain inhibitory function and the EIH response. In adults with fibromyalgia, isometric handgrip exercise [19] and isometric exercise of the quadriceps [20,21] have been shown to lead to decreased pressure pain thresholds (PPT) and increased ratings of pain intensity to noxious heat [19] compared with healthy controls in both the contracting muscles and distant muscles. Cycling exercise decreased PPT in the hand, back, and calf muscles in individuals with chronic whiplash disorder [22] and increased ratings of heat pain intensity and unpleasantness, assessed at the thenar eminence, in Gulf War veterans with chronic musculoskeletal pain [23]. Interestingly, alterations in EIH due to chronic musculoskeletal pain have also been shown to be location dependent—both in terms of the pain and the muscle/limb being exercised. In adults with chronic shoulder myalgia, unilateral isometric exercise of the quadriceps led to EIH in the contracting quadriceps, the resting contralateral quadriceps, and the resting contralateral m. infraspinatus [21]. However, when isometric exercise was performed with the painful m. infraspinatus, EIH did not occur in the contracting m. infraspinatus or the resting quadriceps [21]. Similarly, in adults with knee osteoarthritis (OA) upper body (lat pull-down, seated row, and chest press) exercise led to EIH to a pressure stimulus across several upper body (trapezius, biceps) and lower body (tibialis anterior, vastus lateralis) sites [24]. However, in lower body exercise (leg press, leg curl, and calf raise) performed with the painful knee(s), EIH did not occur at any upper or lower body site [24].

The findings from shoulder myalgia [21] and knee OA [24] patients suggest localized pain, inflammation, and so on may be able to counterbalance both the generalized and local endogenous pain inhibition responses. To our knowledge, there is no evidence regarding the length of time pain and inflammation localized to a body segment must be present before an alteration in pain inhibitory mechanisms will manifest. To examine this, we sought to induce transient inflammation, edema, and delayed-onset muscle soreness (DOMS) in the quadriceps of healthy men via exercise-induced muscle damage (EIMD). DOMS likely occurs due to the infiltration of macrophages and neutrophils into the damaged muscle followed by the release of inflammatory cytokines, which leads to the sensitization of nociceptors in the damaged muscle [25,26]. EIMD has been proposed to be an ecologically valid model for approximating clinical pain in healthy individuals due to the fact it mimics the strength loss [27], heightened pain sensitivity [27], self-reported disability [28], self-care behaviors [29,30], and impairment to activities of daily living [29,30] reported by clinical pain populations. As such, the primary purpose of the present study was to examine the effects of isometric exercise on endogenous pain inhibitory mechanisms in the contracting quadriceps and contralateral, resting quadriceps of healthy men in the presence and absence of quadriceps EIMD. Blood pressure, efferent motor activity (determined by EMG), and rating of muscle pain and effort during isometric exercise were also assessed in order to examine their contribution to endogenous pain inhibition.

Methods

Participants

Participants consisted of 25 adult males with an average age of 22.8 ± 2.5 years (range: 19–29 years old), an average height of 181.8 ± 7.1 cm, and an average weight of 81.9 ± 18.1 kg. Male participants were chosen to minimize confounding effects of differences in pain sensitivity between men and women [31] and changes in pain sensitivity across the menstrual cycle. Participants had no history of orthopedic injury of the knee, hip, or leg and self-reported not participating in lower body resistance training, defined as resistance training more than 1 day a week at intensities ≥75% 1-RM within the previous 6 months. Potential participants who were taking prescription pain and/or psychiatric medications (including medication for attention deficit hyperactive disorder) were excluded. Participants were asked to refrain from resistance and aerobic exercise, alcohol consumption, and taking NSAIDs or other pain medications for the duration of the study. Caffeine consumption was also prohibited for the 8 hours prior to each testing session. Compliance with these instructions was confirmed by a questionnaire completed prior to each testing session. The experimental methods were approved by a university institutional review board, and all participants provided written informed consent prior to participating. Data from two participants were removed from analysis due to a failure to demonstrate EIMD identified by a lack of isometric force loss. A sample of 23 participants was sufficient to detect a moderate effect of 0.53 SD for the interaction term of a repeated-measures ANOVA at an alpha level of 0.05 and a power of 0.80, assuming a correlation between repeated trials of ≥0.90 [32]. Powering the study to detect an effect of this magnitude was based upon the
idea that changes in pain symptoms of at least 0.50 SD are clinically meaningful [33].

**Experimental Approach**

An overview of the experimental protocol can be seen in Figure 1. Participants were tested on 5 separate days, consisting of 2 days of familiarization and 3 experimental days. During familiarization, participants practiced the assessment of: 1) pressure pain threshold testing of both quadriceps, 2) maximal voluntary isometric strength (MVC) of the right knee extensors, 3) holding an isometric contraction at 25% of MVC for 2 min with their right quadriceps, and 4) blood pressure (BP). Two familiarization sessions were provided, as we have previously demonstrated this increases the reliability of assessments of PPT [34]. On the third testing day (the undamaged, “control condition”) baseline assessments of BP, MVC, and visual analogue scale (VAS; 0–100 mm) assessed muscle soreness (DOMS) and PPT of the right (exercising) quadriceps (PPT-E) and the left resting quadriceps (PPT-R) were determined. Following the baseline assessments, participants performed isometric knee extension exercise with their right quadriceps at a force approximating 25% of MVC until task failure, defined as an inability to maintain a force output within 10% of the target force for 5 consecutive sec. During exercise PPT-E and PPT-R were assessed every 30 sec, ratings of perceived exertion (RPE; Borg 6–20 Scale) and muscle pain intensity (MPI; 0–10 scale) were assessed every 30 sec, and BP was taken every minute. After cessation of exercise, participants rested for 2 min and PPT-E, PPT-R, BP, RPE, and MPI were reassessed. Participants then rested for an additional 13 min (15 min following exercise cessation), whereupon PPT-E, PPT-R, BP, RPE, and MPI were again reassessed. Twenty-four to 72 hours later, the fourth testing day occurred. DOMS was assessed in the right knees extensors to determine if the isometric exercise from testing day 3 had induced soreness. One-repetition maximal strength (1-RM) was then assessed in the right knee extensors. Participants then performed four sets of 10 repetitions of eccentric knee extensions with a weight equal to 120% of 1-RM in order to induce EIMD. The fifth testing day occurred 48 hours after testing day 4 (the EIMD condition). DOMS of the right thigh was assessed, then all testing procedures from testing day 3 were repeated.

**Assessment of Quadriceps PPT**

PPT of the right and left quadriceps was assessed using a digital pressure algometer (FDIX, Force One, Wagner Instruments, Greenwich, CT) with a circular rubber tip (1 cm in diameter). Participants were seated with their hip at ~90° of flexion and their knee held at an angle of 60° below horizontal. Two marks were placed approximately 1 inch apart on each thigh over the belly of the rectus femoris, measured as half the distance from the top of the ASIS to the proximal patella. These marks served as a reference site for all future measurements. The algometer head was placed over the mark and mechanical pressure was gradually applied at a rate of ~60 kPa/sec until the applied pressure was perceived as painful. The transition from "uncomfortable" pressure to "painful" pressure was noted by the participant saying, "pain." Three assessments, which alternated between the two assessment sites, were performed prior to the bout of isometric exercise (baseline) and averaged. Assessments were performed prior to isometric exercise on test day 3 and test day 5 and prior to eccentric exercise on test day 4. During exercise, a single measurement was performed every 30 sec on both the right and left quadriceps with the measurement location alternating between each marked location.

**Induction and Assessment of EIMD**

Concentric 1-RM strength of the right knee extensors was determined on a seated knee extension machine adjusted to each participant essentially as described previously [35]. The participants were seated on the machine with their hip positioned at a ~90° angle and their back resting flat against a pad. Position was adjusted such that the center of rotation of the knee was aligned with the center of rotation of the extension lever arm. Participants first performed a set of 10 unilateral (right leg only) concentric/eccentric repetitions using a light weight (~10–20 kg depending on participant size) as a warm-up. Participants then performed a unilateral knee extension at a weight estimated to be 80–90% of maximal, moving from a knee angle of 90 degrees below horizontal to full extension. Five sec were allowed to move the lever arm through a complete range of motion. Researchers assisted in the lowering of the weight after each attempt. If an attempt was completed in the prescribed time period, with proper form (full range of motion, back and gluteal muscles remaining in contact with the seat), then the weight was increased by 5% until it could not be completed. Three min of rest were provided between each attempt. Three to five lift attempts were typically required, with the heaviest recorded as 1-RM. Following assessment of 1-RM, eccentric exercise was performed to induce muscle damage. Forty eccentric muscle actions (four sets of 10 repetitions) were performed using the right knee extensors with an initial weight of 120% of concentric 1-RM as described previously [35]. Two researchers positioned the lever arm to the starting position (full knee extension) and the participant then lowered the lever arm through a ~90° range-of-motion in 3 sec. The researchers then returned the lever arm to the starting position and exercise proceeded. Three min of rest was provided between each set. If the participant could no longer perform the eccentric contractions in a controlled manner, then resistance was reduced by 5% and exercise continued until all contractions of that set were completed.

Maximal voluntary isometric strength and ratings of muscle soreness were used to indirectly assess whether EIMD occurred. Strength loss has been suggested to be the one of the most valid and reliable indirect
methods to assess EIMD [36]. In order to do this, MVC of the right knee extensors was determined prior to the exercise protocol on test day 3 and was reassessed prior to exercise on test day 5. MVC was determined as described previously [37] using a modified knee extension/leg curl machine (model GLCE-365; Body Solid, Forest Park, IL) with a force transducer (model SBO- 750; Transducer Technologies Temecula, CA) fixed to the lever arm parallel to the line of pull allowing for assessment of isometric torque with the knee held at an angle of 60° below horizontal when the participant’s right ankle was secured to the lever arm. The transducer was connected to a data acquisition system (model AHP 214; iWorx Systems Incorporated, Dover, NH) and torque data were sampled at 5 kHz and analyzed using a custom written program (Waddell, 2012) using MatLab software (Mathworks, Natick, MA).

Participants performed three maximal isometric efforts with their right knee extensors; 3 min of rest were provided between each effort. MVC was determined as the average of the two best efforts. If MVC did not differ between test day 3 and test day 5, it was assumed EIMD did not occur.

Muscle soreness was assessed prior to exercise on test day 3, day 4, and test day 5. A VAS was used to assess muscle soreness and pain by placing a vertical line along a 10-cm line with anchors of “no pain” and “worst pain imaginable” from left to right, respectively. A series of three concentric/eccentric right knee extensor actions (~3 sec “up,” ~3 sec “down”) were performed using a weight equal to 50% of concentric 1-RM. Participants were asked to rate on the VAS the perception of pain experienced during the eccentric portion of the exercise. There was a 1-min rest period between each contraction. A total of three ratings were performed and averaged to determine the criterion measure of muscle soreness.

**Isometric Exercise**

Unilateral isometric exercise was performed until task failure using right knee extensors. Participants were seated on the modified knee extension/leg curl machine (described above) with the hip at 90° of flexion, the knee fixed at 60° below horizontal, and the ankle fixed to the extension lever arm via inelastic straps. Participants were provided visual feedback and asked to match and maintain a target force equal to 25% of their previously determined MVC. Verbal encouragement was provided and exercise continued until task failure, defined as an inability to maintain a force output within 10% of the target force for 5 consecutive sec.

In order to estimate voluntary efferent motor activity to the quadriceps during the isometric exercise protocol, electromyographic (EMG) signals were collected during MVC and isometric exercise via unipolar electrodes placed over the belly of the vastus medialis with an interelectrode electrode distance of ~2 cm. Placement sites were shaved, abraded, and cleaned with alcohol prior to electrode placement, and the sites were marked with indelible ink to ensure similar placement across multiple testing sessions. Analog EMG signals were collected at 5 kHz, digitized, and stored for data analysis (model AHP 214; iWorx Systems Incorporated, Dover, NH). EMG signals from each MVC and the isometric exercise bout were then processed using a custom written program (Waddell, 2012) using MatLab software (Mathworks, Natick, MA). Signals were divided into 1-sec epochs, and the root mean square (RMS) of the signal was calculated for each epoch. To normalize for differences among participants and among testing sessions, data from isometric exercise were normalized (expressed as a percentage) to the value from the corresponding MVC during that testing session.

Increases in blood pressure during exercise have been implicated as a possible mechanism of EH. As such, blood pressure was assessed in the left brachial artery prior to, during, and following isometric exercise using an automated cuff (Omron HEM-907XL Pro Blood Pressure Monitor; Lake Forest, IL) placed over the left brachial artery. Assessments were performed every 60 sec during exercise and at 2 and 15 minutes post exercise.
**Muscle Pain and Perceived Effort During Isometric Exercise**

Ratings of perceived exertion and quadriceps muscle pain intensity were obtained every 30 sec during the isometric exercise bout using the Borg 6–20 scale [38] and a specially designed and validated 0–10 pain intensity scale [39]. Before exercise, participants were given standard instructions [38,39] as to the proper use of both scales.

**Statistical Analysis**

To determine whether EIMD had occurred, mean values for MVC were examined using a dependent t-test (Control vs EIMD) and DOMS was examined using a one-way repeated measures analysis of variance (ANOVA) across the three assessment time points (day 3: control; day 4: eccentric exercise; and day 5: EIMD). Additionally, pre-exercise PPT was compared using a two-condition (control and EIMD) × two-leg (exercising leg, PPT-E; resting leg, PPT-R). To examine changes in pain sensitivity during and following exercise, all measures obtained during isometric exercise were first normalized to the measurement occurring at or closest to 25%, 50%, 75%, and 100% of time-to-task failure. Values for PPT-E and PPT-R were then normalized to resting values to minimize differences between legs and between testing days (due to DOMS). Once they were normalized, PPTs were then analyzed using a two-condition (control and EIMD) × seven-time (pre, 25%, 50%, 75%, 100% of time to task failure, 2 minutes postexercise, and 15 minutes postexercise) completely within repeated measures ANOVA. Similar analysis was performed for MAP. To examine changes in physiological and perceptual variables during isometric exercise, mean values for EMG RMS, RPE, and MPI were analyzed using a two-condition (control and EIMD) × four-time (25%, 50%, 75%, and 100% of time to task failure) completely within repeated measures ANOVA. If significant interactions were found, one-way repeated measures ANOVAs were performed and, if significant, planned contrasts (using dependent t-tests) were used to test for differences in means at individual time points. Main effects were interpreted only in the absence of a significant interaction. If main effects were found, main comparisons were then performed using Fisher’s least significant difference (LSD). Pearson correlation coefficients were calculated to evaluate bivariate relationships between the percent change in PPT-E, PPT-R, MPI, RPE, SBP, DBP, MAP, and EMG RMS. Significance was set a priori at an α level of P ≤ 0.05 for a two-tailed test. Effect sizes were calculated as a Cohen’s d statistic, as the difference in means divided by the pooled standard deviation of the means. As a general guideline, effects of ~0.20 SD are judged to be small, ~0.50 SD are judged to be moderate, and ≥ 0.80 SD are judged to be large. All data are presented as mean ± SD and all testing was performed using SPSS (version 19).

**Results**

**Assessment of EIMD**

Ratings of muscle soreness did not differ from test day 3 to test day 4 (P = 0.14; Figure 2A), but were increased on test day 5 (P < 0.001; d = 2.6 SD compared with test day 3 and P < 0.001; d = 2.6 SD compared with test day 4). A significant condition × interaction (Figure 2B; P = 0.03) was found for absolute values of resting (pre-exercise) PPT. Quadriceps PPT decreased in the leg that underwent eccentric exercise (P = 0.03; d = -0.47), but did not change in the leg that did not undergo eccentric exercise (P = 0.28). MVC decreased 8.0% from 333.2 ± 74.1 Nm to 306.5 ± 75.3 Nm (P = 0.005; d = -0.36 SD) from test day 3 to test day 5. The presence of DOMS, decreased PPT, and the decrease in MVC were interpreted as evidence EIMD occurred. Time-to-task failure during isometric exercise at 25% of MVC decreased 20% from 360 ± 138 seconds to 288 ± 109 seconds (P = 0.004; d = -0.52 SD) on test day 5 compared with test day 3.

**Normalized Pressure Pain Threshold During Exercise**

Normalized (to resting values) data from the assessment of PPT-E are shown in Figure 3A. There was not a significant condition × time interaction (P = 0.76) or a significant main effect for condition (P = 0.50). There was a main effect for time (P = 0.001) with pressure pain threshold values at 25% (d = 0.55 SD), 50% (d = 0.56 SD), 75% (d = 0.64 SD), and 100% (d = 0.67 SD) of time-to-task failure being elevated compared with baseline (P ≤ 0.002). Pressure pain threshold at 2 (P = 0.016; d = 0.40 SD) and 15 minutes postexercise (P = 0.038; d = 0.43 SD) were also elevated compared with baseline. Data from the assessment of PPT-R are shown in Figure 3B. There was no significant condition × time interaction (P = 0.61) or a main effect for condition (P = 0.76). There was a main effect for time (P ≤ 0.001) with values at 25% (d = 0.41 SD), 50% (d = 0.55 SD), 75% (d = 0.64 SD), and 100% (d = 0.79 SD) of time-to-task failure being elevated compared with baseline (P ≤ 0.002). However, values at 2 (P = 0.91; d = 0.05 SD) and 15 minutes postexercise (P = 0.28; d = 0.16 SD) did not differ from assessments made at baseline.

**Blood Pressure**

There was not a significant condition × time interaction for SBP (P = 0.20; Table 1) or a significant main effect for condition (P = 0.32). There was a main effect for time (P < 0.001) with values from 25–100% of exercise time and 2 minutes postexercise differing from baseline (P ≤ 0.001); however, SBP had returned to resting levels by 15 minutes postexercise (P = 0.056). SBP rose during exercise with values at 50–100% of exercise time being greater than values at 25% (P ≤ 0.001), and values from 75% and 100% of time being greater than values from 50% (P ≤ 0.02). Values from 75% and 100%
of exercise time did not differ from each other ($P = 0.17$). Similar results were observed for DBP (Table 1) as the group × time interaction was not significant ($P = 0.19$) and there was no main effect for condition ($P = 0.18$). A main effect for time was observed ($P < 0.001$) with values from 25–100% of exercise time differing from baseline ($P < 0.001$). Assessment from both 2 and 15 minutes postexercise did not differ from baseline values ($P \geq 0.10$). DBP rose during exercise with values at 50–100% of exercise time being greater than values at 25% ($P \leq 0.001$), and values at 75% were greater than values at 50% ($P = 0.03$). Values from 100% percent of exercise time did not differ from values at 50–75% of exercise time ($P \geq 0.09$). There was no condition × time interaction for MAP ($P = 0.16$; Table 1), nor was there a main effect for condition ($P = 0.15$). There was a main effect for time ($P < 0.001$), with values from 25–100% of exercise time ($P \leq 0.001$) and values from 2 minutes postexercise ($P = 0.009$) being elevated from baseline. By 15 minutes postexercise, MAP had returned to baseline levels ($P = 0.18$). MAP rose during exercise, as values from 50–100% differed from those at 25% ($P \leq 0.001$), and values from 75% and 100% were greater than those at 50% ($P \leq 0.02$).
Table 1  Selected physiological and perceptual variables during and after isometric exercise

<table>
<thead>
<tr>
<th>Variable</th>
<th>Condition</th>
<th>Resting</th>
<th>25%</th>
<th>50%</th>
<th>75%</th>
<th>100%</th>
<th>2 min post</th>
<th>15 min post</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>Control</td>
<td>122 ± 8</td>
<td>142 ± 15a</td>
<td>152 ± 20ab</td>
<td>153 ± 13abc</td>
<td>157 ± 23abc</td>
<td>126 ± 15a</td>
<td>119 ± 10</td>
</tr>
<tr>
<td></td>
<td>EIMD</td>
<td>122 ± 10</td>
<td>136 ± 12a</td>
<td>144 ± 13ab</td>
<td>155 ± 14abcd</td>
<td>158 ± 5abcd</td>
<td>128 ± 9a</td>
<td>118 ± 9</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>Control</td>
<td>76 ± 9</td>
<td>95 ± 10d</td>
<td>103 ± 11abc</td>
<td>104 ± 7abcd</td>
<td>109 ± 14ab</td>
<td>78 ± 11</td>
<td>76 ± 10</td>
</tr>
<tr>
<td></td>
<td>EIMD</td>
<td>76 ± 6</td>
<td>90 ± 8d</td>
<td>100 ± 9abc</td>
<td>107 ± 10abcd</td>
<td>102 ± 19abcd</td>
<td>78 ± 10</td>
<td>75 ± 8</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>Control</td>
<td>91 ± 7</td>
<td>111 ± 11a</td>
<td>120 ± 13abc</td>
<td>120 ± 8abcd</td>
<td>125 ± 16abcd</td>
<td>94 ± 11a</td>
<td>91 ± 9</td>
</tr>
<tr>
<td></td>
<td>EIMD</td>
<td>91 ± 6</td>
<td>106 ± 7a</td>
<td>115 ± 9abc</td>
<td>123 ± 8abcd</td>
<td>121 ± 13abcd</td>
<td>95 ± 9a</td>
<td>89 ± 5</td>
</tr>
<tr>
<td>MPI (0–10 scale)*</td>
<td>Control</td>
<td>–</td>
<td>2.0 ± 1.6d</td>
<td>3.8 ± 2.7d</td>
<td>5.3 ± 3.1f</td>
<td>6.8 ± 3.1d</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>EIMD</td>
<td>–</td>
<td>2.0 ± 1.4d</td>
<td>3.7 ± 2.0d</td>
<td>5.7 ± 2.4f</td>
<td>7.7 ± 2.6dg</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>RPE (6–20)*</td>
<td>Control</td>
<td>–</td>
<td>12.1 ± 3.0f</td>
<td>15.4 ± 3.3f</td>
<td>17.4 ± 3.1f</td>
<td>18.9 ± 2.3f</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>EIMD</td>
<td>–</td>
<td>11.1 ± 2.2f</td>
<td>14.9 ± 1.9f</td>
<td>17.7 ± 1.8f</td>
<td>19.2 ± 1.0f</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>EMG RMS (% of MVC RMS)*</td>
<td>Control</td>
<td>–</td>
<td>21.1 ± 9.9d</td>
<td>25.4 ± 11.5d</td>
<td>28.8 ± 13.8abc</td>
<td>36.3 ± 18.0b,c,d</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>EIMD</td>
<td>–</td>
<td>17.3 ± 7.7d</td>
<td>21.2 ± 7.9d</td>
<td>25.3 ± 13.5c,d</td>
<td>32.3 ± 18.4b,c,d</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; MPI = rating of muscle pain intensity; RPE = ratings of perceived exertion; EMG RMS = root mean square of EMG amplitude.

*Indicates a significant (P ≤ 0.05) main effect for time.

aIndicates a significant difference (main comparison; P ≤ 0.05) from value during rest.
bIndicates a significant difference (main comparison; P ≤ 0.05) from value at 25% of time-to-task failure.
cIndicates a significant difference (main comparison; P ≤ 0.05) from value at 50% of time-to-task failure.
dIndicates a significant difference (main comparison; P ≤ 0.05) from value at 75% of time-to-task failure.
eIndicates a significant condition × time interaction (P ≤ 0.05).
fIndicates a significant difference (simple comparison; P ≤ 0.05) from values at all other time points.
gIndicates a significant difference (simple comparison; P ≤ 0.05) between conditions at that time point.

Values are mean ± SD.

MAP did not differ between 75% and 100% of exercise time (P = 0.36).

Ratings of Muscle Pain and Effort During Exercise

A significant group × time interaction was found for MPI (P = 0.009; Table 1). A one-way ANOVA for time was significant for both the control and EIMD condition (P ≤ 0.001), with all tested time points (25%, 50%, 75%, and 100% of exercise time) differing (P ≤ 0.001) from each other in both the control and EIMD conditions. Simple comparisons between conditions at each testing time point revealed that MPI was elevated (P = 0.049) only at the end of exercise (100%) in the EIMD condition. Similarly, for RPE, a significant condition × time interaction was found (P = 0.024; Table 1) and the one-way ANOVA for time was significant in both the control (P ≤ 0.001) and EIMD (P ≤ 0.001) conditions. RPE increased over time in both conditions, with each time point differing from all others (P ≤ 0.001). RPE did not differ between conditions at any time point (P ≥ 0.07).

EMG RMS During Exercise

There was not a significant condition × time interaction for EMG RMS when expressed as a percentage of the peak value during MVC (P = 0.98; Table 1) or a main effect for condition for EMG RMS (P = 0.11). There was a main effect for time for EMG RMS (P < 0.001), with RMS increasing over time such that each time point differed from the others (P ≤ 0.002).

Relationship Between PPT, Physiological, and Perceptual Variables

Pearson correlation coefficients for the relationships between PPT-E and PPT-R and rating of muscle pain, perceived exertion, blood pressure variables, and EMG amplitude during the fatiguing isometric contractions are shown in Table 2. The changes in PPT-E and PPT-R were significantly correlated (P < 0.001). Small but statistically significant relationships were also found between the changes in PPT-E and MPI (P = 0.001) and RPE (P = 0.007) during exercise. No relationship was found between the change in PPT-R and the SBP (P = 0.56), DBP (P = 0.18), MAP (P = 0.18), or EMG RMS (P = 0.08). The change in PPT-R was correlated to MPI (P = 0.014), RPE (P = 0.01), DBP (P = 0.024), MAP (P = 0.023), and EMG RMS (P = 0.002), but to SBP (P = 0.45).

Discussion

Exercise activates endogenous pain inhibitory mechanisms and leads to hypoalgesia during and following
Table 2  Pearson correlation coefficients between change in selected variables during isometric exercise

<table>
<thead>
<tr>
<th>Variable</th>
<th>%ΔPPT-E</th>
<th>%ΔPPT-R</th>
<th>MPI</th>
<th>RPE</th>
<th>%ΔSBP</th>
<th>%ΔDBP</th>
<th>%ΔMAP</th>
<th>EMG RMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>%ΔPPT-E</td>
<td>–</td>
<td>0.30**</td>
<td>0.24**</td>
<td>0.20**</td>
<td>–0.04</td>
<td>–0.10</td>
<td>–0.10</td>
<td>0.13</td>
</tr>
<tr>
<td>%ΔPPT-R</td>
<td>–</td>
<td>0.18*</td>
<td>0.23**</td>
<td>0.06</td>
<td>0.17*</td>
<td>0.17*</td>
<td>0.23**</td>
<td></td>
</tr>
<tr>
<td>MPI</td>
<td>–</td>
<td>0.78**</td>
<td>0.38**</td>
<td>0.32**</td>
<td>0.32**</td>
<td>0.24**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPE</td>
<td>–</td>
<td>0.41**</td>
<td>0.41**</td>
<td>0.41**</td>
<td>0.41**</td>
<td>0.24**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>%ΔSBP</td>
<td>–</td>
<td>–</td>
<td>0.42**</td>
<td>0.42**</td>
<td>0.42**</td>
<td>0.17*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>%ΔDBP</td>
<td>–</td>
<td>–</td>
<td>0.98**</td>
<td>0.98**</td>
<td>0.98**</td>
<td>0.27**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>%ΔMAP</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMG RMS</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05 (two-tailed).
**P < 0.01(two-tailed).

%ΔPPT-E = percent change in pressure pain threshold in the exercised quadriceps; %ΔPPT-R = percent change in pressure pain threshold in the resting quadriceps; MPI = ratings of muscle pain intensity; RPE = ratings of perceived exertion; %ΔSBP = percent change in systolic blood pressure; %ΔDBP = percent change in diastolic blood pressure; %ΔMAP = percent change in mean arterial pressure; EMG = root mean square of EMG amplitude.

Exercise (see [1–3] for review) in healthy individuals (see [1–3] for review), but not in chronic musculoskeletal pain patients [19–24]. EIMD is accompanied by a well-characterized inflammatory response [25,26], leading to sensitization of nociceptors in and around the damaged muscle—manifesting as DOMS. Because of this, EIMD is thought to be an ecologically valid model for approximating acute clinical pain in healthy individuals. Given the paucity of data on the length of time pain must be present to alter the EIH response and that localized, inflammatory-based pain (e.g., knee OA and shoulder myalgia) in the exercising muscle/limb may also influence the generalized and local EIH response [27,28], the purpose of this study was to examine the effects of fatiguing isometric exercise in the presence and absence of EIMD on generalized and local endogenous pain inhibition. The primary findings were: 1) PPTs in the contracting and resting contralateral quadriceps were increased during exercise to a similar extent in the control and EIMD conditions, and 2) whether the limb was exercised, but not whether EIMD was present, affected PPTs postexercise, as EIH was observed at both 2 and 15 minutes postexercise in the contracting quadriceps, but not in the resting contralateral quadriceps.

EIH During Exercise

In the present study, DOMS had no effect on endogenous pain modulation to a pressure stimulus during exercise. In contrast to our findings, the EIH response is altered in several clinical populations such as fibromyalgia [19–21], whiplash disorder [22], chronic shoulder myalgia [21], and knee OA [24]. There is evidence of central sensitization (i.e., heightened neural signaling in the CNS resulting in hypersensitivity to noxious stimuli) occurs in fibromyalgia [40], whiplash disorder [41], shoulder myalgia [42], and knee OA [43]. However, central sensitization was not apparent in our participants, as pain sensitivity at rest and during exercise was not altered in the nondamaged leg. This finding adds to the growing body of literature that central sensitization, rather than acute changes in localized pain sensitivity, may be required to alter the endogenous pain inhibitory response.

Interestingly, data from shoulder myalgia [21] and knee OA [24] indicate a normal EIH response occurs when the exercise is performed by a nonpainful muscle/limb, but that the EIH response is attenuated when the exercise is performed using a painful muscle/limb. Contrary to this idea, data from the present study indicate that localized soreness in the exercising muscle did not alter the EIH response during exercise. This finding further supports the idea of an interaction between central sensitization, pain facilitation, and the EIH response. Prolonged noxious inputs from chronically painful muscles and joints may result in changes in spinal and supraspinal (such as the PAG and rostral ventromedial medulla [RVM]) areas, leading to greater pain facilitation when an already painful muscle/limb is exercised, thus overriding endogenous pain inhibition [21,24]. This could explain the lack of EIH when painful muscles are exercised in knee OA and shoulder myalgia, but “normal” EIH response when a nonpainful muscle is exercised. Given the apparent importance of central sensitization in the balance of pain inhibition and facilitation, the ability of acute pain models such as EIMD and hypertonic saline to approximate clinical pain deserves further study.

EIH Following Exercise

An interesting finding of the present study was that while EIH occurred in the exercising and contralateral resting quadriceps during the isometric exercise protocol, EIH only persisted after exercise in the exercising limb. Several previous studies [9,10,15,24] have found EIH in locations distant to the exercising muscle/limb following an isometric exercise protocol similar to the
present study. These studies used 

\[9,10,15,24\] a Forgione-Barber pressure stimulator to assess pain sensitivity. However, similar to our findings, several other studies \[21,44\] have also demonstrated no postexercise effect of isometric exercise at locations distant to the exercised muscle assessed. Interestingly, these studies assessed PPT using a pressure algometer, as was done in the present study. These disparate findings suggest if generalized pain modulation occurs after exercise, it may depend not only on the type of noxious stimuli applied (pressure, thermal, etc.), but also on the type of assessment performed (threshold, tolerance, etc.). Additionally, our findings indicate postexercise EIH in the exercised muscle/limb was not affected by the presence of localized inflammation and soreness consequent to EIMD, unlike findings from chronic pain patients with fibromyalgia \[7\], knee OA \[24\], and shoulder myalgia \[21\]. Lannersten and Kosek \[21\] assessed PPT in the exercised and resting quadriceps following isometric exercise and found EIH persisted in the exercised quadriceps, but not in the resting contralateral quadriceps in healthy adults, similar to the present study. Together these findings suggest localized endogenous pain inhibition may play a role in the length of time EIH may persist following cessation of exercise. This could be the result of efferent motor activity from the contracting muscle \[16\] or activation of afferent Aδ and C-fibers \[17,18\] within the contracting muscles leading to inhibition of nociceptive transmission.

Mechanisms of EIH

In the present study, isometric exercise to fatigue resulted in moderate-to-large (effect sizes ranging from \(\sim 0.40\) to \(\sim 0.80\) SD) increases in PPT, indicating reduced pain sensitivity in both the contracting and resting contralateral quadriceps during exercise. These findings are similar to previous investigations demonstrating reduced pain sensitivity during \[5\] or following \[9,10\] a bout of exercise in both the exercising muscle/limb and in a distant muscle/limb—suggesting exercise activates generalized pain inhibitory mechanism(s). Several potential mechanisms have been proposed to underlie generalized EIH in healthy individuals. Elevations in blood pressure during exercise may lead to activation of arterial baroreceptors \[13,45\] and subsequently activate brain areas such as the periaqueductal grey (PAG), insula, and anterior cingulate cortex (ACC), which are implicated in pain modulation \[46\]. Although the present study was not specifically designed to determine the effects of changes in blood pressure on PPTs, SBP, DBP, and MAP all rose during exercise in a time-dependent manner. However, no relationship was observed between changes in SBP, DBP, or MAP and changes in PPTs in the exercising quadriceps. Additionally, changes in DBP and MAP were only weakly correlated to changes in PPT in the resting quadriceps \((r = 0.17, r^2 = 0.03)\)—potentially explaining only 3% of the variance in PPT. This was likely due to the lack of a time effect on the increases in PPT in the present study. These findings are at odds with those of Ring et al. \[45\], who found changes in blood pressure were associated with changes in sensitivity of the nociception flexion reflex (R-III reflex). Other studies have found no relationship between changes in blood pressure and changes in sensitivity to pressure \[6\] and thermal \[14\] stimuli, as we demonstrated in the present study. Caution should be taken in interpreting the lack of relationship given the narrow range of values for SBP, DBP, and MAP, as our sample was healthy, normotensive young men and that beat-to-beat assessments of blood pressure were not made. It is also possible elevations in blood pressure may affect sensitivity to different noxious stimuli to a greater (R-III reflex) or lesser (pressure) extent.

Conditioned pain modulation, where an initial painful stimulus (conditioning stimulus) leads to inhibition of pain to a subsequent noxious stimulus applied to a different location has also been suggested to affect the EIH response \[9,14,15\]. The isometric exercise employed in the present study was perceived as painful by our participants, and muscle pain ratings increased as a function of exercise time. A weak positive relationship was found between ratings of muscle pain intensity during exercise and changes in PPTs—providing further evidence CPM may play a role in EIH. Our findings of a weak relationship between EIH and pain experienced during exercise were similar in magnitude to that found by Lemley et al. \[15\] and, taken together with previous work demonstrating EIH during nonpainful exercise \[14\], suggests factors other than CPM likely also contribute to EIH. Efferent motor output from the contracting muscle \[16\] has also been hypothesized to inhibit nociceptive transmission. The observed increase in EMG RMS over time during exercise provides clear evidence motor output also increased as participants began to fatigue. Despite this increase, RMS values were not correlated with changes in PPT in the exercising limb and were only weakly correlated with changes in PPT in the resting limb—similar to the findings for blood pressure and muscle pain during exercise. Although not measured, it is also possible pain sensitivity was altered during exercise simply via distraction \[47\] or by the exercise leading to the release of endogenous opioids \[1,11\] and endocannabinoids \[12\], which have also been implicated in the EIH response. It remains unresolved how these mechanisms work independently or in concert to produce EIH. Future studies attempting to independently manipulate these variables could provide greater insight into the contribution of each to the EIH response.

This study has several experimental considerations. Our use of a nonrandomized study design does increase the chance of an “order” or “learning” effect occurring. In addition to the prolonged recovery period required following EIMD, an initial bout of EIMD leads to an adaption that reduces damage from subsequent bouts of eccentric exercise \[48\]. This “repeated-bout” effect has been shown to last for 6–9 months \[49\] and to occur not only in the muscle that was damaged, but also in the homologous contralateral muscle \[50\]. As such,
randomizing the order of the EIMD and control conditions, while experimentally preferable, was infeasible in practice. Our findings of no changes in baseline PPT in the unexercised leg lends support that an order effect likely did not occur in one of the primary dependent measures of the study. This study used only college-aged men, and therefore caution should be taken in generalizing our findings to women and/or older adults. Additionally, chronic pain conditions often result in long-term pain and functional limitations as well as anxiety/fear or movement or fear of reinjury—all of which are not present in the EIMD model.

In conclusion, this study found the short-term increase in pain sensitivity (i.e., DOMS) associated with EIMD did not alter endogenous pain inhibition during or following a bout of fatiguing isometric exercise. This finding supports the idea that central sensitization, rather than more acute localized pain, likely contributes to the lack of endogenous pain inhibition observed in clinical pain populations. Additionally, our finding that EIH persisted only after cessation of exercise in the exercised muscle suggests a localized pain inhibitory mechanism(s) may be acting after exercise to produce EIH. As such, the endogenous inhibitory mechanism(s) acting to produce EIH during and following exercise may differ.

References


19 Staud R, Robinson ME, Price DD. Isometric exercise has opposite effects on central pain mechanisms in fibromyalgia patients compared to normal controls. Pain 2005;118:176–84.


21 Lannersten L, Kosek E. Dysfunction of endogenous pain inhibition during exercise with painful muscles.


28 Bishop MD, Horn ME, George SZ, Robinson ME. Self-reported pain and disability outcomes from an endogenous model of muscular back pain. BMC Musculoskelet Disord 2011;12:35.


33 Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life–The remarkable universality of half a standard deviation. Med Care 2003;41:582–92.


