Muscle pain perception and sympathetic nerve activity to exercise during opioid modulation

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The purpose of this experiment was to examine the effects of the endogenous opioid system on forearm muscle pain and muscle sympathetic nerve activity (MSNA) during dynamic fatiguing exercise. Twelve college-age men (24 ± 4 yr) performed graded (1-min stages; 30 contractions/min) handgrip to fatigue 1 h after the ingestion of either 60 mg codeine, 50 mg naltrexone, or placebo. Pain (0–10 scale) and exertion (0–10 and 6–20 scales) intensities were measured during the last 15 s of each minute of exercise and every 15 s during recovery. MSNA was measured continuously from the peroneal nerve in the left leg. Pain threshold occurred earlier [1.8 ± 1, 2.2 ± 1, 2.2 ± 1 J: codeine, naltrexone, and placebo, respectively] and was associated with a lower rating of perceived exertion (RPE) (2.7 ± 2, 3.6 ± 2, 3.8 ± 2: codeine, naltrexone, and placebo, respectively) in the codeine condition compared with either the naltrexone or placebo conditions. There were no main effects (i.e., drugs) or interaction (i.e., drugs × time) for either forearm muscle pain or RPE during exercise [pain: F(2, 22) = 0.69, P = 0.51]. There was no effect of drug on MSNA, heart rate, or blood pressure during baseline, exercise, or recovery. Peak exercise MSNA responses were 21 ± 1, 21 ± 2, and 21 ± 2 bursts/30 s for codeine, naltrexone, and placebo conditions, respectively. Peak mean arterial pressure responses were 135 ± 4, 131 ± 3, and 132 ± 4 mmHg for codeine, naltrexone, and placebo conditions, respectively. It is concluded that neither 60 mg codeine nor 50 mg naltrexone has an effect on forearm muscle pain, exertion, or MSNA during high-intensity handgrip to fatigue.

codeine; rating of perceived exertion; pain perception; autonomic nervous system

CERTAIN TYPES OF MODERATE-TO-HIGH intensity exercise are perceived as painful. For example, reproducible relationships between objective measures of exercise intensity and subjective judgments of leg and forearm muscle pain intensity during cycle ergometry and rhythmic handgrip have been reported (6, 14). Although it is clear that the firing rate of nociceptive afferent fibers (type III and IV) from skeletal muscle is increased in response to noxious stimuli, including exercise, the mechanisms underlying muscle pain during exercise are poorly understood (16, 17).

Endogenous opioids, such as endomorphin, enkephalins, dynorphins, and beta-endorphins have well-established analgesic actions (11, 31, 33), and opioid receptors are found on nociceptive afferent fibers as well as spinal and supraspinal sites involved in pain processing. The endogenous opioid system has been demonstrated to modulate nociceptive afferent fiber activity in both animal and human experiments (10, 26). Consequently, endogenous opioids may be involved in muscle pain during exercise. Peripheral concentrations of endogenous opioids consistently have been shown to increase during moderate and intense exercise (2, 12, 27). Nevertheless, the role of opioids in naturally occurring muscle pain experienced during exercise is unknown.

In addition to their role in pain regulation, endogenous opioids also have been implicated in the modulation of muscle sympathetic nerve activity (MSNA) responses to exercise (8, 22, 23). The opioid antagonist naloxone has been found to either increase (8) or have no effect (23) on MSNA responses to exercise. Specifically, Farrell et al. (8) reported that 1.2 mg intravenous naloxone significantly increased arterial pressure, plasma epinephrine, and muscle sympathetic nerve responses to 3 min of isometric handgrip at 25% maximal voluntary contraction (MVC). However, this finding was not reproduced by Ray and Pawelczyk (23), who did not observe an effect of naloxone on MSNA, arterial pressure, or heart rate. Moreover, preliminary data from Ray et al. (22) showed that morphine (0.075 mg/kg bolus + 1 mg/h maintenance) resulted in increased resting mean arterial pressure but had no

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METHODS

The primary purpose of this experiment was to examine, in a double-blind setting, the effects of codeine and naltrexone on the perception of forearm muscle pain during and after dynamic handgrip performed to fatigue. On the basis of the known influence of opioids in reducing both the activity of nociceptive afferent fibers and pain, it was hypothesized that the ingestion of codeine would result in lower pain intensity ratings compared with both the naltrexone and placebo conditions and that the ingestion of naltrexone would result in higher pain ratings compared with both the codeine and placebo conditions. The rationale for using a dynamic handgrip stimulus to fatigue was to achieve longer and more intense exercise sessions, thus increasing the likelihood of an endogenous opioid response and 2) allow for the measurement of MSNA. Additionally, rhythmic exercise differs from the isometric protocols employed by previous investigators (8, 23) in that it does not result in continuous muscle ischemia. A second purpose was to examine the effects of codeine and naltrexone on MSNA during and after dynamic fatiguing handgrip. It was hypothesized that the ingestion of codeine would decrease MSNA responses to exercise compared with both the naltrexone and placebo conditions and that naltrexone would increase MSNA responses to exercise compared with both the codeine and placebo conditions.

Participants. A total of 12 college-age (18–35 yr) men who were not on any medication and pain and injury free volunteered to participate in the study. A sample size of 12 provided a statistical power of 0.76 for the primary question concerning the main effect of drug on pain. This value was calculated on the basis of statistical power tables for repeated measures designs (19) and with the following assumptions: an alpha level of 0.05; a one-half SD (0.50) for the drug main effect; a correlation across exercise intensity (trials) of 0.6; and a correlation across conditions (codeine, naltrexone, and placebo) of 0.4. All participants signed a consent form approved by the Institutional Review Board at The University of Georgia. Selected characteristics (means ± SD) were as follows: age (24 ± 4 yr), height (176 ± 5 cm), and weight (75 ± 9 kg).

Procedures. The participants completed three questionnaires: a medical and a 24-h health history, and the multiple affect adjective checklist (MAACL). The 24-h and medical histories were used to inquire about the use of medications and to ensure that the participants were healthy, injury free, able to perform the maximal exercise test, and not allergic to codeine or naltrexone. None of the participants reported any forearm muscle soreness before the exercise sessions. The MAACL was employed to examine the potential role of either codeine, naltrexone, or placebo on the participant’s affective state before exercise and to examine possible relationships between situational affect and muscle pain during exercise. The 132-item MAACL provides valid measures of anxiety, depression, hostility, positive affect, and sensation seeking (34). Participants were given the MAACL before each exercise session exactly 50 min after ingestion of the placebo or active drug.

MSNA. MSNA measurements were made as described by Ray et al. (24). Briefly, multiple nerve fiber recordings of MSNA were made by using a tungsten microelectrode inserted in the peroneal nerve near the head of the fibula. A reference electrode was placed subcutaneously ~2 cm from the recording electrode. Adjustments of the microelectrode were made until a site exhibiting clear spontaneously occurring sympathetic bursts was found. MSNA was expressed as burst frequency (bursts/30 s) and total activity (area/30 s). Total activity was the sum of area of all bursts in a given time period.

Arterial pressure and heart rate were measured continuously by using an Ohmeda Finapres recorder (model 2300, Englewood, NJ). The photoplethysmographic cuff was placed on the middle finger of the nonexercising arm, which was maintained at the level of the heart during testing.

For each exercise test MSNA, arterial pressure, and heart rate data were obtained before (5 min), during (~14 min), and after (5 min) exercise. In the event that the recording electrode came out of the nerve, one of the investigators quickly adjusted the electrode until the MSNA recording was reestablished. This problem occurred once in only one subject during recovery from exercise.

Codeine/naltrexone/placebo conditions. In the codeine condition the participants received 60 mg of codeine in one capsule. Studies using similar doses have demonstrated the analgesic effectiveness of 60 mg of codeine to experimental pain stimuli (18, 29), whereas others have reported little or no side effects when a single oral dose is taken (1, 20). The codeine was ingested with 8 oz of water 60 min before exercise, and consumption was witnessed by one of the investigators. The timing of drug administration was based on previous reports that maximal plasma concentrations of codeine occur ~1 h after a single oral dose of 60 mg (11, 20). The capsule was identical to the capsules used in the placebo and naltrexone conditions, a procedure designed to blind the participant as to the condition. In the naltrexone condition the participants received 50 mg of naltrexone in one capsule taken orally. Naltrexone is an opioid antagonist that exhibits no agonist effects. The naltrexone was administered with 8 oz. of water 60 min before exercise in a manner identical to the codeine and placebo condition (lactose capsule). Naltrexone taken orally has a peak plasma concentration within 60 min and has been reported to produce sustained effects for up to 24 h from a single oral dose (11). To ensure a double-blind administration, one investigator, who did not conduct the exercise tests (P. J. O’Connor), distributed the capsules to a second investigator (D. B. Cook). The second investigator, who was unaware of what the capsules contained, administered all the capsules and conducted all of the exercise tests. The order in which the participants completed the conditions was randomized and counterbalanced.
Graded handgrip protocol. Each participant completed a minimum of three graded, dynamic handgrip exercise tests to fatigue. The exercise sessions were performed on 3 separate days. Before exercise the participants received either codeine, naltrexone, or placebo in a randomized, counterbalanced order. Exercise was performed with the dominant hand while the participants were in a supine position. The dominant hand and arm were extended laterally (60–90° angle) from the body and fully supported. Handgrip was performed at a rate of 30 contractions/min with the aid of a calibrated metronome. The first minute of exercise was done with no load. For each subsequent 1-min stage, the weight was increased by 1.13 kg until an exercise stage could not be completed. The participants were given 15 s of rest every minute while one of the investigators added 1.13 kg to the weight-support bar.

Pain and exertion assessment. Forearm muscle pain intensity was assessed by using a category scale with ratio properties. The pain intensity scale ranges from 0 (no pain at all) to 10 (extremely intense pain, almost unbearable). With this scale, if the subjective intensity increases above 10, the subject is free to choose any number larger in proportion to 10 that describes the proportionate growth of the sensation. Prior work with this instrument has provided evidence for both the validity and reliability of this tool for quantifying naturally occurring muscle pain during exercise (6).

The participants listened to a taped set of instructions, which informed them that they would be repeatedly asked to rate the intensity of the pain and exertion in their forearms and that they were to report aloud the number that corresponds to that intensity. Additionally, participants were instructed to remember to say the word “pain” when the pain in their forearm became just noticeable (pain threshold). An investigator recorded the minutes and seconds from a digital timer that was started at the beginning of exercise, and this quantified pain threshold.

Ratings of perceived exertion (RPE) were assessed during and after exercise by using Borg's 6–20 category scale (4) after explicit audiotaped and oral instructions (cf. 6). Our previously employed instructions were modified to obtain local ratings of forearm muscle exertion. A second scale for measuring perceived exertion [0–10 category-ratio scale; Borg, (3)] was employed to examine the relationship between ratings of pain and RPE by using scales that were both based on ratio-scaling methods.

During the graded exercise test forearm muscle pain and exertion ratings were obtained during the last 15 s of every 1-min exercise stage. At the point of fatigue (i.e., failure to maintain a handgrip contraction rate of 30 repetitions/min), the test was stopped, and the participants were asked to immediately stop contracting their forearm. Pain and exertion ratings were obtained every 15 s for 5 min during the recovery period to assess the abatement of pain and exertion perceptions.

Posttest information. Within 5 min after the completion of the exercise test, participants indicated in writing the reason they stopped exercising. Thereafter, they completed the short-form of the McGill Pain Questionnaire (MPQ) (15) to provide a multidimensional description of the forearm muscle pain experienced during the exercise test.

Primary statistical analyses. Pain ratings, RPE, and MSNA were analyzed by using a two-way [condition (codeine, naltrexone, placebo) × trials] repeated-measures ANOVA. The trials factor ranged from 5 different intensities for data obtained in association with exercise intensity [20, 40, 60, 80, and 100% of peak work (J)] to 20 time points associated with recovery (ratings obtained every 15 s for 5 min). When appropriate, eta2 was used as a measure of the magnitude of an association among variables. Rough guidelines for the strength of association for a given eta2 value are that 0.01 is considered a small effect, 0.09 medium, and 0.15 large. Pain threshold, peak pain, and baseline MSNA, arterial pressure, and heart rate among conditions were analyzed by using a one-way repeated-measures ANOVA. Significant main effects were followed up by simple contrast analysis to further delineate where the significant differences occurred. T-tests were used to analyze baseline MSNA, arterial pressure, heart rate, and selected pain threshold and peak variables between the control and placebo conditions. Pearson correlations were used to examine relationships between and among arterial pressure, MSNA, pain, and RPE. Effect sizes (d) were calculated according to the method described by Cohen (5) (mean 1 – mean 2/pooled SD) to provide a measure of the magnitude of the differences between selected variables. All table values are expressed as means ± SD, and all graphic values are means ± SE.

RESULTS

Pain threshold. Forearm muscle pain threshold data for codeine, naltrexone, and placebo conditions are presented in Table 1. One-way repeated-measures ANOVA revealed significant main effects for the amount of work completed at pain threshold and the perceived exertion using both the 0–10 and the 6–20 scales. Contrast analysis revealed that pain threshold was reported at a lower weight and RPE ratings were lower in the codeine condition compared with both the naltrexone and placebo conditions.

Peak exercise data. Peak exercise data for the codeine, naltrexone, and placebo conditions are shown in Table 2. There were no significant differences across conditions for any of the variables measured at peak exercise. Data based on verbal reports obtained postexercise indicated that six individuals, in at least one of three exercise tests, stopped exercising due in part to the pain they felt in their forearms. Overall, pain was a factor in the decision to stop exercising in 10 of the 36 exercise tests, whereas fatigue was indicated in 34 of

<p>| Table 1. Measures of exercise intensity at pain threshold for codeine, naltrexone, and placebo conditions |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>Codeine (mean ± SD)</th>
<th>Naltrexone (mean ± SD)</th>
<th>Placebo (mean ± SD)</th>
<th>F Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work, J</td>
<td>1.8 ± 1</td>
<td>2.2 ± 1</td>
<td>2.2 ± 1</td>
<td>5.1 (22)</td>
<td>0.01</td>
</tr>
<tr>
<td>Perceived exertion (0–10)</td>
<td>2.7 ± 2</td>
<td>3.6 ± 2</td>
<td>3.8 ± 2</td>
<td>5.4 (22)</td>
<td>0.01</td>
</tr>
<tr>
<td>Perceived exertion (6–20)</td>
<td>10.2 ± 3</td>
<td>11.4 ± 2</td>
<td>11.9 ± 3</td>
<td>4.3 (22)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 12 men.
36 tests (both pain and fatigue were reported by some subjects).

**Pain during exercise.** Pain intensity ratings at 20, 40, 60, 80, and 100% of peak work (J) are shown in Fig. 1, top. Pain increased as a positively accelerating function of percent peak work (J) during maximal handgrip exercise \(F(2, 22) = 55.7, P < 0.001\). There was no significant main effect for condition or interaction.

**Perceived exertion during exercise.** Perceived exertion ratings at 20, 40, 60, 80, and 100% of peak work (J) are illustrated in Fig. 1, middle and bottom. Perceived exertion ratings using both the 0–10 and 6–20 scales increased as a function of percent peak work (J) \[0–10\] scale: \(F(2, 22) = 179.9, P < 0.001\); \[6–20\] scale: \(F(2, 22) = 455.9, P < 0.001\]. There were no significant main effects for condition or interactions for either scale.

**Pain and exertion during recovery from handgrip exercise.** Pain intensity ratings during recovery from maximal handgrip are shown in Fig. 2. Two-way repeated-measures ANOVA revealed no significant main effect for condition \(F(2, 22) = 2.5, P = 0.10\); however, a significant interaction was detected \(F(38, 418) = 1.5, P = 0.026, \text{eta}^2 = 0.12\). The SE bands in Fig. 2 show greater variability in the placebo condition. Inspection of individual responses revealed one influential subject exhibiting ratings that were \(>2\) SD above the group mean at trials 3, 4, and 6–14 in the placebo condition. There were no significant main effects or interactions for RPE during recovery (0–10 or 6–20 scales).

**MPQ data.** MPQ data for the codeine, naltrexone, and placebo conditions are presented in Table 3. There were no significant main effects or interactions for RPE during recovery (0–10 or 6–20 scales).

### Table 2. Peak exercise data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Codeine</th>
<th>Naltrexone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak pain (0–10)</td>
<td>7.7 ± 3</td>
<td>8 ± 4</td>
<td>8.2 ± 4</td>
</tr>
<tr>
<td>Peak RPE (0–10)</td>
<td>9.9 ± 1</td>
<td>10.3 ± 2</td>
<td>11.4 ± 4</td>
</tr>
<tr>
<td>Peak RPE (6–20)</td>
<td>19.7 ± 1</td>
<td>19.3 ± 1</td>
<td>19.4 ± 1</td>
</tr>
<tr>
<td>Peak work, J</td>
<td>4.9 ± 1</td>
<td>4.6 ± 1</td>
<td>4.9 ± 1</td>
</tr>
</tbody>
</table>

Values are means ± SD; \(n = 12\) men. RPE, rating of perceived exertion.

Fig. 1. Pain intensity (0–10 scale; top) and rating of perceived exertion [RPE; 0–10 (middle) and 6–20 scales (bottom)] at 20, 40, 60, 80, and 100% of peak work (J) during maximal handgrip for codeine, naltrexone, and placebo conditions (\(n = 12\)).

Fig. 2. Pain intensity ratings (0–10 scale) during recovery from fatiguing handgrip for codeine, naltrexone, and placebo conditions (\(n = 12\)).

### Table 3. McGill Pain Questionnaire data for codeine, naltrexone, and placebo conditions

<table>
<thead>
<tr>
<th>Variable</th>
<th>Codeine</th>
<th>Naltrexone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cramping pain</td>
<td>1.7 ± 1</td>
<td>1.6 ± 1</td>
<td>1.5 ± 1</td>
</tr>
<tr>
<td>Hot-burning pain</td>
<td>1.8 ± 1</td>
<td>1.8 ± 1</td>
<td>1.9 ± 1</td>
</tr>
<tr>
<td>Aching pain</td>
<td>1.9 ± 1</td>
<td>1.7 ± 1</td>
<td>1.8 ± 1</td>
</tr>
<tr>
<td>Tiring-exhausting pain</td>
<td>2.4 ± 1</td>
<td>2.2 ± 1</td>
<td>2.4 ± 1</td>
</tr>
</tbody>
</table>

Values are means ± SD and represent the average pain ratings based on scores of 1) mild, 2) moderate, and 3) severe. The table represents the 4 verbal descriptors that were used most frequently and given the highest mean rating when the participants recalled the forearm muscle pain experienced during maximal handgrip exercise.
were no differences among the conditions for any of the verbal descriptors chosen to describe the forearm muscle pain, or its intensity, experienced during maximal handgrip.

**Baseline cardiovascular and MSNA data.** Preexercise baseline values for MSNA, heart rate, and mean arterial pressure are shown in Fig. 3. MSNA, heart rate, and mean arterial pressure were not significantly different across conditions before exercise.

**MSNA, heart rate, and arterial pressure during exercise.** MSNA burst frequency (bursts/30 s) and total activity (area/30 s) during handgrip for codeine, naltrexone, and placebo conditions are illustrated in Fig. 4. MSNA burst frequency increased during handgrip exercise (trial main effect: $F(4, 44) = 65.1, P < 0.001$); however, there was no main effect for condition or interaction. Total MSNA increased during exercise (trial main effect: $F(4, 44) = 10.6, P < 0.001$), but there was no main effect for condition or interaction. A similar pattern of response, both physiologically and in terms of the ANOVA results, was observed for heart rate (peak values: codeine = 136 ± 16, naltrexone = 130 ± 10, placebo = 135 ± 14) and mean arterial pressure (peak values: codeine = 79 ± 14, naltrexone = 78 ± 12, placebo = 81 ± 9).

**MSNA, heart rate, and arterial pressure during recovery from handgrip exercise.** No significant main effects or interactions were observed during recovery from maximal handgrip for any of the MSNA, heart rate, or arterial pressure data.

**Selected relationships of interest.** A strong negative relationship between forearm muscle pain ratings and systolic arterial pressure at 100% of peak exercise intensity in the placebo condition was observed ($r = -0.84$) and is illustrated in Fig. 5. Correlations between pain ratings and systolic arterial pressure during submaximal exercise ranged from $-0.27$ to $0.17$. A significant negative correlation between pain and arterial pressure at 100% of peak exercise in the naltrexone condition was also observed ($r = -0.64$), whereas a significant positive correlation between pain and arterial pressure at 100% of peak exercise ($r = 0.74$) was observed in the codeine condition.

Nonsignificant bivariate correlations in the placebo condition indicated that pain was nonsignificantly related to exertion (0–10) during exercise ($20\% r = 0.25$, $40\% r = -0.04$, $60\% r = 0.06$, $80\% r = 0.14$, $100\% r = -0.02$). Relationships between pain and MSNA in the placebo condition also were low and nonsignificant (pain and burst frequency: $20\% r = -0.04$, $40\% r = -0.14$, $60\% r = -0.44$, $80\% r = 0.24$, $100\% r = 0.20$; pain and area: $20\% r = 0.12$, $40\% r = -0.22$, $60\% r = -0.21$, $80\% r = -0.08$, $100\% r = 0.24$).

**DISCUSSION**

The primary findings of the present investigation are that 1) post-pain threshold, neither codeine nor nalt-
Naltrexone altered the perception of forearm muscle pain and 2) neither drug had an effect on MSNA burst frequency or total activity.

**Muscle pain.** The lack of an effect for either codeine or naltrexone on muscle pain during exercise would seem to be at odds with what is known about type III and IV afferent fiber activity and the role that opioids play in regulating their activity. However, it is worth emphasizing that pain is a complex phenomenon that involves multiple systems working in parallel to regulate nociceptive activity. The simple act of inhibiting one of the modulatory systems may not result in an alteration in the subjective experience because of the redundancy of the system. Bradykinin, potassium, serotonin, and histamine, all of which have been shown to be released during exercise, act directly on type IV fibers, resulting in an increased firing rate. These algesics also sensitize the type III fibers that respond to the increased intramuscular pressure during exercise. There are also a population of small afferent fibers reported to become active only during muscular contractions and that respond linearly to the force of the contraction. Combined, these algesic mechanisms increase the likelihood that the afferent nociceptive signal will be transmitted to supraspinal sites that are important in pain perception even when one possible mechanism is eliminated.

The timing of the administration of both drugs was based on reports that peak plasma concentrations of both codeine (and its O-demethylation to morphine) and naltrexone occur ~1 h after oral administration. We chose a dosage that is double that frequently prescribed for mild-to-moderate pain. Moreover, we did not want to exceed 60 mg because it has been reported that codeine administered at doses above this amount increases the likelihood of unwanted side effects, which in and of themselves could have altered pain responses. Other researchers consider the dose of naltrexone used in this study to be large, consequently, the naltrexone dose should have been adequate for the purposes of the present investigation. Thus the present results suggest that the endogenous opioid system, particularly the mu receptor-mediated portion, does not play a major role in the perception of muscle pain during exercise.

In accordance with our previous research examining leg muscle pain during maximal cycle ergometry, forearm muscle pain increased as a function of the exercise stimulus. Pain threshold in the placebo condition occurred on average at ~46% (6.6 kg) of the peak exercise intensity (14.3 kg), which is comparable to leg muscle pain threshold (~50%) observed during ramped maximal cycling exercise. Peak forearm muscle pain ratings averaged 8.2 on the 0–10 scale, a value identical to the average peak leg muscle pain reported in our previous cycle ergometry study. Moreover, the MPQ verbal descriptors most frequently used to describe forearm muscle pain were tiring-exhausting, aching, hot-burning, and cramping pain, which are also the same descriptors that were used to describe leg muscle pain during exercise. These results provide additional support for the reliability and validity of the 0–10 pain intensity scale used to quantify muscle pain during exercise. Moreover, these findings suggest that the intensity and quality of muscle pain experienced during graded or ramped maximal exercise tests are similar whether a large or small muscle mass is employed.

In the codeine condition, pain threshold occurred earlier and corresponded with lower exertion ratings than both the naltrexone and placebo conditions. The difference represented about one exercise stage (1.13 kg or 1 min of exercise) and corresponded to a moderate effect (~0.5) for both comparisons. It is unclear why such an effect occurred. This effect, however, did not translate into altered pain ratings or performance during exercise or altered pain ratings during recovery. Therefore, simply altering someone’s threshold for pain detection does not necessarily mean that the individual will experience changes in pain intensity above pain threshold. This is important because pain threshold is usually of little concern in sports. For example, with endurance athletes the greater concern is how long they can tolerate an intense bout of exercise.

There is a great deal of literature showing relationships between arterial pressure and pain. It has been reported that both chronic hypertension and acute experimental increases in arterial pressure are associated with reduced pain sensitivity. Experimental stimulation of arterial and cardiopulmonary baroreceptors (e.g., neck suction, physiological volume expansion, or pharmacological sympathetic stimulation) results in antinociceptive behavior in both animals and humans. Conversely, significant and parallel relationships between the degree of ischemic forearm muscle pain (produced during a sub-
maximal-effort tourniquet test) and arterial pressure have been reported (14).

In the present investigation, there was a significant negative relationship between pain ratings and systolic arterial pressure, but only at the highest exercise intensity (100% of peak exercise intensity) and only in the placebo and naltrexone conditions. It is unclear why this occurred only at the peak of exercise. This finding does suggest a link between elevated arterial pressure and pain inhibition and is in agreement with previous research demonstrating that arterial baroreceptor stimulation inhibits pain in rats and humans (7, 13, 21). However, given our sample size and lack of consistency across conditions, these results should be interpreted with caution. Nevertheless, this observation, if found to generalize, would have potentially important clinical implications. For example, it might aid in our understanding and identification of those at risk for “silent” myocardial infarctions during exercise.

**Perceived exertion.** There was no effect of drug on perceived exertion during exercise or in recovery. This is not surprising given the lack of an effect of drug on the perception of pain and performance. In our previous work examining pain and exertion during exercise, we chose to employ the Borg 6–20 category scale for the measurement of perceived exertion and a 0–10 category-ratio scale to assess pain. The goal of that research was to determine the extent to which the constructs of pain and exertion could be differentiated during exercise. During the cycle ergometry protocol, perceived effort ratings were reported at low exercise intensities, but naturally occurring leg muscle pain typically did not occur until a moderate intensity of ~50% of peak power output was reached. Moreover, leg pain was only moderately related to exertion during exercise. From that study, it was concluded that pain and exertion were two separate, albeit related, constructs (6). However, the Borg 6–20 category scale is theoretically and empirically distinct from the 0–10 category-ratio scale, and the use of the two different scales may have made the original comparison less compelling. Therefore, in the present investigation we chose to add a measure of RPE and use Borg’s 0–10 category-ratio scale (3). The pain and RPE 0–10 category-ratio scales are designed to overcome limitations of category scales (e.g., ceiling effects) by allowing users to choose a number above 10 when necessary. These scales are not only designed to have ratio properties (i.e., possessing a true 0 and unbounded), but they have been shown to perform similarly compared with ratio scaling methods (3, 6). The low correlations observed (r = −0.04 to 0.25) between pain (0–10) and RPE (0–10) in this experiment, and the occurrence of exertion before pain, again support the contention that pain and exertion are two separate constructs. The distinction between pain and exertion is potentially important because it allows researchers to determine the role of pain in various types of exercise performance. It also allows researchers to learn whether pain per se influences exertional perceptions.

**MSNA.** The results of the present experiment, while not directly comparable, appear to be in contrast to previous results obtained by Farrell et al. (8), who showed an augmentation of naloxone on MSNA during moderate-intensity, brief-duration, isometric handgrip. However, the results are in agreement with Ray and Pawelczyk (23), who showed no effect of naloxone on MSNA during moderate-intensity, brief-duration, isometric handgrip.

It is not immediately clear why different results were obtained in the earlier works by Ray and Pawelczyk (23) and Farrell et al. (8). However, one criticism of prior work attempting to examine the influence of the endogenous opioid system on MSNA responses to exercise has been the use of exercise stimuli that were of low intensity, short duration, and involved static contractions. Thus the exercise stimulus itself may not have been sufficient to stimulate the endogenous opioid system. Alternatively, it may be that the exercise stimulus used previously was not painful and thus negated the potential effects of naloxone. The strength of the present experimental design was that we employed painful, high-intensity, and dynamic exercise to fatigue while examining the MSNA responses after administration of both an opioid agonist and antagonist. Rhythmic exercise is different from isometric exercise used in our earlier studies because rhythmic exercise does not elicit continuous ischemia. Therefore, our results extend our previous findings to rhythmic exercise and strongly suggest that the endogenous opioid system does not modulate MSNA during handgrip.

No prior studies have adequately determined whether pain and MSNA are related. One study, in which muscle pain was poorly assessed and experienced by only 3 of 25 subjects, reported no relationship between pain and MSNA (32). In the present investigation, pain ratings during exercise were weakly or moderately related to MSNA burst frequency or total activity (pain and burst frequency: r = −0.44 to 0.24 and pain and total activity: r = −0.21 to 0.23). This lack of a strong relationship is not surprising given that nociceptive signals are modified at spinal and supraspinal sites that are independent of the sympathetic nervous system. Moreover, pain perception was not altered in the present study, which may have limited the potential for observing stronger relationships between MSNA and pain.

The present study could not definitively assess whether pain perception during exercise was altered by central mechanisms (i.e., higher brain systems). It is possible that “central command,” associated with volitional effort, may have interacted with afferent feedback from the muscle to modulate pain perception. Future studies using postexercise muscle ischemia, which eliminates central command, may be useful in addressing this issue. In the present study, postexercise muscle ischemia was not assessed because it would have confounded our postexercise responses.

In summary, the results from this study indicate that the ingestion of either 60 mg of codeine or 50 mg
of naltrexone does not alter the perception of forearm muscle pain or exertion during maximal handgrip exercise to fatigue. Additionally, neither drug had an effect on MSNA when expressed in terms of burst frequency nor total integrated activity. We conclude that codeine and naltrexone, in practical doses, do not have an effect on naturally occurring muscle pain, exertion, or MSNA during exercise. Whether this finding generalizes to other opioid agonists and different modes of exercise remains to be tested.

**Perspectives**

The experience of muscle pain during exercise is a common phenomenon: the runner rounding the final curve and sprinting toward the finish of the 1,500 m at the Olympic Games, the 90-yr-old great-grandmother climbing a flight of stairs, and the patient with peripheral vascular disease simply walking to the grocery store all can experience intense muscle pain during exercise. These perceptions of pain provide strong motivation. Pain motivates the athlete, the great-grandmother, and the peripheral vascular disease patient all to slow down, presumably so they do not seriously injure themselves. By learning more about the mechanisms underlying this type of exercise-generated muscle pain, we may eventually be able to improve both well-being and athletic performance. We are surprised that muscle pain is one of the least studied types of pain and urge applied physiologists interested in muscle to consider including the perception of pain as a dependent measure in their future investigations involving exercise.

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