International Journal of Sport Nutrition and Exercise Metabolism, 2009, 19, 150-161

Effect of Caffeine on Quadriceps Muscle Pain During Acute Cycling Exercise in Low Versus High Caffeine Consumers

Rachael C. Gliottoni, John R. Meyers, Sigurbjörn Á. Arngrímsson, Steven P. Broglio, and Robert W. Motl

This experiment examined the effect of a moderate dose of caffeine on quadriceps muscle pain during a bout of high-intensity cycling in low- versus high-caffeine-consuming males. College-age men who were low (≤100 mg/day; n = 12) or high (≥400 mg/day; n = 13) habitual caffeine consumers ingested caffeine (5 mg/kg body weight) or a placebo in a counterbalanced order and 1 hr later completed 30 min of cycle ergometry at 75–77% of peak oxygen consumption. Perceptions of quadriceps muscle pain, as well as oxygen consumption, heart rate, and work rate, were recorded during both bouts of exercise. Caffeine ingestion resulted in a statistically significant and moderate reduction in quadriceps muscle-pain-intensity ratings during the 30-min bout of high-intensity cycle ergometry compared with placebo ingestion in both low (d = –0.42) and high (d = –0.55) caffeine consumers. The results suggest that caffeine ingestion is associated with a moderate hypoalgesic effect during high-intensity cycling in college-age men who are low or high habitual caffeine consumers, but future work should consider better defining and differentiating pain and effort when examining the effects of caffeine during acute exercise.

Keywords: adenosine, ergometry, hypoalgesia, sport performance

Pain has been defined by the International Association for the Study of Pain (1979) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (p. 250). There is an expanding body of evidence that acute exercise is a natural stimulus that might transiently, safely, and reliably produce muscle pain (Cook, Jackson, O'Connor, & Dishman, 2004; Cook, O'Connor, Eubanks, Smith, & Lee, 1997; Cook, O'Connor, Oliver, & Lee, 1998; O'Connor & Cook, 1999, 2001). Indeed, moderate- to high-intensity exercise is associated with reports of transient, natu-

Gliottoni, Meyers, Broglio, and Motl are with the Dept. of Kinesiology and Community Health, University of Illinois at Urbana-Champaign. Arngrímsson is with the Center for Sport and Health Sciences, Iceland University of Education, Reykjavik, Iceland.

rally occurring pain in the activated muscles (Cook et al., 1997). The pain is described as exhausting, intense, sharp, burning, tiring, cramping, pulling, and rasping (Cook et al., 1997). Those same descriptors have been used to characterize clinical pain conditions including menstrual pain, arthritic pain, cancer pain, chronic back pain, and fibromyalgia (Cook, 2006). We further note that pain ratings during exercise as measured by the short form of the McGill Pain Questionnaire are nearly 1 standard deviation (*SD*) above the mean scores associated with other laboratory methods of inducing pain (Cook et al., 1997).

Experiments have demonstrated that caffeine, an adenosine-receptor antagonist (Fredholm, Bättig, Holmén, Nehlig, & Zvartau, 1999; Nehlig, Daval, & Debry, 1992), has resulted in a reduction of quadriceps muscle pain during moderate- and high-intensity cycling exercise in low caffeine consumers (Gliottoni & Motl, 2008; Motl, O'Connor, & Dishman, 2003; Motl, O'Connor, Tubandt, Puetz, & Ely, 2006; O'Connor, Motl, Broglio, & Ely, 2004). For example, one experiment indicated that ingestion of a large dose of caffeine (10 mg/kg body weight) reduced quadriceps muscle-pain intensity during moderate-intensity cycling (60% VO_{2peak}) in males who reported low daily caffeine consumption (<100 mg/day; Motl et al., 2003). Another experiment found that ingestion of a moderate (5 mg/kg body weight) and a large (10 mg/kg body weight) dose of caffeine dose-dependently reduced quadriceps muscle-pain intensity during moderate-intensity cycling in males who reported low daily caffeine consumption (<100 mg/day; O'Connor et al.).

One general limitation of those previous experiments was that they examined the effects of caffeine on muscle pain during exercise using low caffeine consumers (≤100 mg/day). Individuals who reported low daily caffeine consumption were recruited in those experiments to minimize tolerance effects associated with habitual consumption of caffeine (Laska et al., 1984). Indeed, one possible mechanism for explaining the caffeine-induced reduction in muscle pain during exercise is that caffeine blocks adenosine A_1 and A_{2a} receptors on the sensory nerve endings in skeletal muscle that can influence pain signaling (Sawynok, 1998). Regular caffeine consumers have an increased production of adenosine receptors in the vascular and neural tissues of the brain (Fredholm et al., 1999; Griffiths & Woodson, 1988; Jacobson, von Lubitz, Daly, & Fredholm, 1996; Nehlig et al., 1992). This suggests that equal doses of caffeine might block a greater percentage of adenosine receptors for low than high caffeine consumers and produce a greater reduction in variables that are mediated by the adenosine neuromodulatory system (Bell & McLellan, 2002). Accordingly, the magnitude of reduction in muscle-pain intensity during exercise after caffeine ingestion might differ based on habitual use of caffeine.

This experiment extended previous research by examining the effect of a moderate dose of caffeine (5 mg/kg body weight) on quadriceps muscle-pain-intensity ratings during high-intensity cycling exercise (i.e., target of 80% VO_{2peak}) in men who reported low or high daily caffeine consumption. We expected that caffeine would be associated with an overall reduction of quadriceps pain-intensity ratings during high-intensity exercise compared with a placebo, and the effect of caffeine on quadriceps muscle pain would be larger in the low than high daily caffeine consumers.

Methods

Participants

The methods were approved by the University of Illinois at Urbana-Champaign Institutional Review Board, and all participants provided written informed consent. We recruited a sample of college-age men who were (a) regular exercisers with above average fitness, (b) nonsmokers, (c) and of average body weight and (d) had no self-reported hypersensitivity to caffeine. Regular exercisers with above average fitness were recruited to ensure the capacity to undertake and complete 30 min of high-intensity exercise. Nonsmokers of average body weight were recruited to avoid the effects of cigarette smoking (Joeres et al., 1988) and obesity (Kamimori, Somani, Knowlton, & Perkins, 1987) on the rate of caffeine metabolism. Participants who reported no hypersensitivity to caffeine were recruited to minimize the potential for extreme anxiety reactions to caffeine ingestion (Charney, Galloway, & Heninger, 1984). The sample included 24 participants who were placed into two groups based on self-reported daily caffeine consumption: low caffeine consumers (≤100 mg/day; n = 12) and high caffeine consumers (≥400 mg/day; n = 12). Characteristics of the overall sample and subsamples based on habitual caffeine use are provided in Table 1.

Materials

Quadriceps Muscle-Pain Ratings. Quadriceps muscle-pain intensity was measured using a categorical scale with ratiolike properties (Cook et al., 1997, 1998). The scale has 12 categories from 0 to 10 with verbal anchors associated with the following numbers: 0 = *no pain at all,* 0.5 = *very faint pain (just noticeable),* 1 = *weak pain,* 2 = *mild pain,* 3 = *moderate pain,* 4 = *somewhat strong pain,* 5 = *strong*

Table 1 Characteristics of the 24 Male Volunteers, *M* ± *SD*

Characteristic	Overall (*N* = 24)	Low users (*n* = 12)	High users (*n* = 12)
Age (years)	25.6 ± 4.6	23.9 ± 4.2	27.2 ± 5.0
Height (cm)	182.0 ± 6.4	182.2 ± 6.8	181.8 ± 5.9
Weight (kg)	77.0 ± 8.0	76.2 ± 6.6	77.8 ± 9.3
Body-mass index (kg/m^2)	23.3 ± 2.1	23.0 ± 2.2	23.5 ± 2.0
DCC (mg/day)	286.7 ± 74.1	40.5 ± 35.7	532.8 ± 112.5
Peak power output (W)	379.7 ± 51.8	388.1 ± 62.5	371.3 ± 41.0
VO_{2peak} (ml · kg^{-1} · min^{-1})	60.2 ± 7.9	61.1 ± 8.8	59.2 ± 7.0
HR_{peak} (beats/min)	188.9 ± 12.9	192.2 ± 10.8	185.5 ± 14.9
RER_{peak}	1.2 ± 0.05	1.2 ± 0.02	1.2 ± 0.07
RPE_{peak}	19.1 ± 1.0	19.4 ± 0.7	18.7 ± 1.2
Peak pain intensity	8.6 ± 3.3	9.9 ± 3.8	7.2 ± 2.7

Note. DCC = daily caffeine consumption; VO_{2peak} = peak oxygen consumption; HR_{peak} = peak heart rate; RER_{peak} = peak respiratory-exchange ratio; RPE_{peak} = peak rating of perceived exertion.

pain, 7 = *very strong pain,* and 10 = *extremely intense pain (almost unbearable).* No verbal anchors are provided in association with numbers 6, 8, and 9. Prior research has demonstrated that scores from this scale are valid and reliable for assessing the perceived intensity of quadriceps muscle pain during exercise (Cook et al., 1997, 1998). The categorical scale was used in the current study both because of the evidence of its reliability and validity and because of its advantages over a visual analog scale used during exercise (e.g., no physical mark needs to be made on a sheet of paper).

Incremental Exercise Test. Participants performed an incremental exercise test on an electronically braked, computer-driven cycle ergometer (Lode BV, Groningen, The Netherlands) to measure VO_{2peak}. Initially, they were fitted to the cycle ergometer. They were then provided with standardized, tape-recorded instructions for correctly using the quadriceps muscle-pain (see Appendix A in Cook et al., 1997, or Methods of Cook et al., 1998) and overall perceived-exertion (Borg, 1998) scales. After listening to the instructions while viewing the scales, all participants articulated that the pain scale was measuring the intensity of hurt in the quadriceps muscles of the legs during exercise, whereas the perceived-exertion scale was measuring the overall amount of effort during exercise. The maximal-exercise-test procedures were described by an investigator, and participant questions were answered. After inserting a mouthpiece to collect expired gases, the participants performed a 5-min warm-up at 25 W. The initial work rate for the exercise test was 50 W, and the work rate continuously increased at a rate of 24 W/min until the participant reached volitional fatigue. Using an open-circuit spirometry system (TrueOne, Parvo Medics, Sandy, UT), ventilation, oxygen consumption (VO_2), carbon dioxide production (VCO_2), and respiratory-exchange ratio were measured every 20 s. Heart rate was continuously displayed using a Polar heart-rate monitor (Polar Electro Oy, Kempele, Finland). Heart rate, rating of perceived exertion, work rate, and perceptions of quadriceps muscle pain were recorded every minute during the test of VO_{2peak}. VO_{2peak} was defined as the highest recorded VO_2 value when two of three criteria were satisfied: respiratory-exchange ratio ≥1.10, peak heart rate within 10 beats/min of age-predicted maximum (i.e., ~1 *SD*), or peak rating of perceived exertion ≥18.

Procedures

Participants completed 1 day of preliminary testing and 2 days of experimental testing. The 2 days of experimental testing were separated by 1 week. Experimental testing was conducted in the morning (7 a.m. ± 1 hr). Consistent with previous research (Gliottoni & Motl, 2008; Motl et al., 2003, 2006; O'Connor et al., 2004), participants were asked to abstain from caffeine consumption for 12 hr, alcohol consumption for 24 hr, and eating a large meal and exercising for 12 hr before the experimental testing.

Preliminary Day. Before incremental exercise testing, the participants completed a 7-day caffeine recall questionnaire (James, Bruce, Lader, & Scott, 1989) and a medical-history questionnaire. The medical-history questionnaire was used to identify contraindications to caffeine consumption and exercise testing. The incremental exercise test provided an opportunity for participants to experience and

rate cycle-ergometry-induced quadriceps muscle pain throughout the full range of possible stimulus intensities.

Experimental Days. On the experimental days, participants ingested capsules that contained caffeine (5 mg/kg body weight) or placebo with ~250 ml of water and then sat and read quietly. One hour after ingesting the capsules, a time that consistently has coincided with peak plasma caffeine concentrations (Charney et al., 1984; Kamimori et al., 1995,1987; Kaplan et al., 1997), the participants performed 30 min of cycling on an ergometer at a target intensity of 80% VO_{2peak}. Participants' perception of quadriceps muscle-pain intensity, work rate, and heart rate were recorded every 5 min during the exercise bouts. Expired gases were analyzed using open-circuit spirometry after 5, 15, and 25 min of exercise. An investigator reduced the work rate every 5 min consistent with previous research (Gliottoni & Motl, 2008; Motl et al., 2003, 2006; O'Connor et al., 2004) so that each participant exercised at a target intensity of approximately 80% VO_{2peak} throughout the first exercise bout. The reduction in work rate was not based on pain or heart rate, but rather our collective experience, and was confirmed for maintaining the target intensity based on expired gases after 5, 15, and 25 min of exercise. This procedure was adopted to control for O_2 drift and thereby ensure that participants would complete the entire 30-min bout of cycling exercise. The work rate during the second day of experimental tests was identical as a means of controlling the physical stimulus associated with quadriceps muscle pain.

Drug Delivery and Content. Caffeine (Caffeine Anhydrous, USP/NF, Gallipot, St. Paul, MN) and placebo were delivered in gelatin capsules (No. 1, Eli Lilly & Co., Indianapolis, IN). The dose of caffeine (5 mg/kg body weight) was moderate and equivalent to consuming approximately two and a half to three 8-oz cups of ground roasted coffee (Barone & Roberts, 1996). The dose of placebo was an equal number of gelatin capsules containing white, all-purpose flour. Caffeine was administered using a double-blind procedure to protect against possible participant and experimenter expectancy effects. The order of drug administration was counterbalanced.

Data Analysis

Descriptive statistics are presented in text and table as $M \pm SD$ and in figures as $M \pm SEM$. The work-rate data recorded during exercise were analyzed with a 2 (group: low users and high users) × 6 (time: 5, 10, 15, 20, 25, and 30 min) mixed-model ANOVA based on the univariate F statistic; drug was not included in the model because the work rate was identical between the two experimental exercise sessions. The VO_2 data were analyzed with a 2 (group: low users and high users) × 2 (drug: 5 mg/kg body weight caffeine and placebo) × 3 (time: 5, 15, and 25 min) mixed-model ANOVA based on the univariate F statistic. The heart rate and quadriceps muscle-pain-intensity data recorded during exercise were analyzed with 2 (group: low users and high users) × 2 (drug: 5 mg/kg body weight caffeine and placebo) × 6 (time: 5, 10, 15, 20, 25, and 30 min) mixed-model ANOVAs based on the univariate F statistic. Within all analyses, group was a between-participants factor, whereas drug and time were within-participant factors. The judgment of significance of the main effects and interactions in the mixed-model

ANOVAs was based on the univariate F statistic, and we used the Greenhouse–Geisser adjustment when violating the assumption of sphericity based the significance of Mauchly's test of sphericity. Effect sizes for F statistics were expressed as eta-squared (η^2). Effect sizes for mean differences were expressed as Cohen's d (Cohen, 1988).

Results

Effect of Caffeine on Absolute and Relative Exercise Intensity

The work-rate and heart-rate data are presented in Figure 1. The 2 × 6 mixed-model ANOVA indicated no statistically significant group main effect on work rate (p = .46), but there was a statistically significant Group × Time interaction, $F(1.3, 27.7) = 3.98$, p = .05, $\eta^2 = 0.15$. The interaction indicated that there was a larger reduction in work rate across time in the group of low caffeine users (d = –1.12; ~41-W reduction over time) than high caffeine users (d = –0.89; ~31-W reduction over time). The 2 × 2 × 6 mixed-model ANOVA indicated that there were neither statistically significant main effects for group (p = .15) and drug (p = .33) nor statistically significant interactions for Group × Drug (p = .78), Group × Time (p = .10), Drug × Time (p = .42), and Group × Drug × Time (p = .55) on heart rate.

The next analysis examined the effects of group and drug on oxygen consumption (VO_2) during the exercise sessions. The 2 × 2 × 3 mixed-model ANOVA indicated no statistically significant main effects for group (p = .38) and drug (p = .62) on VO_2. There were no statistically significant interactions for Group × Drug (p = .90), Group × Time (p = .20), Drug × Time (p = .31), and Group × Drug × Time (p = .92) on VO_2. The mean VO_2 values during exercise after ingestion of caffeine and placebo were 46.9 ± 6.1 and 46.5 ± 6.1 ml · kg^{-1} · min^{-1}, respectively, for the low caffeine users; the corresponding values for the high caffeine users

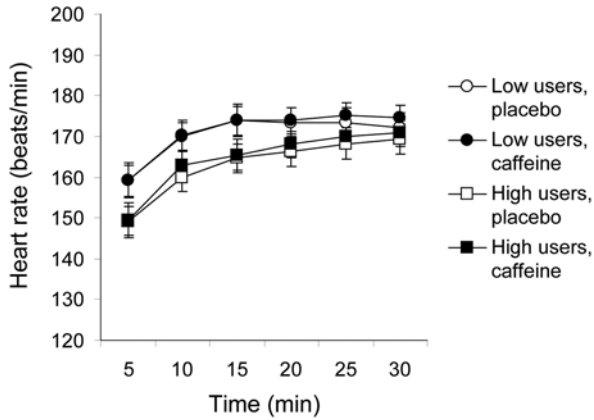

Figure 1 — Work rate and heart rate recorded during 30 min of high-intensity cycling exercise (75–77% VO_{2peak}), M ± SE.

were 44.7 ± 5.8 and 44.4 ± 6.6 ml · kg^{-1} · min^{-1}, respectively. Those VO_2 values represented relative exercise intensities of 77% and 76% VO_{2peak} for the caffeine and placebo conditions, respectively, for the low caffeine users and relative exercise intensities of 76% and 75% VO_{2peak} for the caffeine and placebo conditions, respectively, for the high caffeine users. Those values fall within a range that would classify the intensity of exercise as hard or vigorous (American College of Sports Medicine, 2006).

Effect of Caffeine on Ratings of Quadriceps Muscle-Pain Intensity

The quadriceps muscle-pain-intensity ratings recorded during the exercise sessions are provided in Figure 2. The 2 × 2 × 6 repeated-measures ANOVA indicated a statistically significant drug main effect on pain-intensity ratings, $F(1, 22) = 12.57$, $p = .002$, $\eta^2 = 0.36$, but no statistically significant interactions for Drug × Group ($p = .62$), Drug × Time ($p = .10$), and Drug × Group × Time ($p = .72$). The mean pain-intensity scores during exercise after ingestion of caffeine and placebo were 3.00 ± 1.6 and 3.8 ± 1.7, respectively. Ingestion of caffeine resulted in a moderate reduction in quadriceps muscle-pain-intensity ratings compared with the placebo ($d = –0.48$), and this effect size was similar in magnitude between the groups of low caffeine users ($d = –0.42$) and high caffeine users ($d = –0.55$).

Discussion

This experiment involved an examination of the role of habitual caffeine consumption in moderating the hypoalgesic effect of caffeine during high-intensity cycling exercise in men. The primary finding was that both low and high habitual caffeine consumers reported a significant and moderate reduction in quadriceps

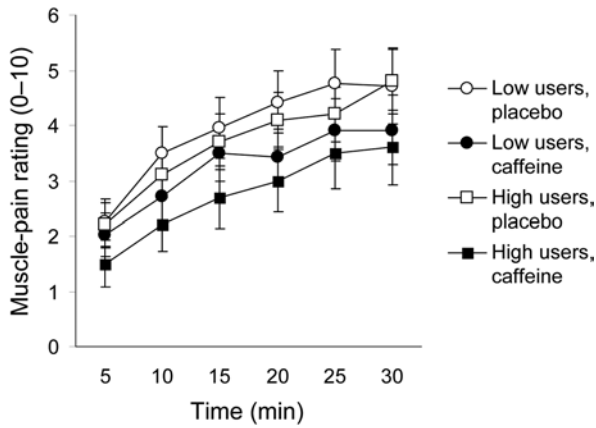

Figure 2 — Quadriceps muscle-pain-intensity values recorded during 30 min of high-intensity cycling exercise (75–77% VO_{2peak}), *M* ± *SE*.

muscle-pain-intensity ratings during high-intensity cycling exercise after ingestion of a moderate dose of caffeine.

The results of the current study did not support our expectation that the effect of caffeine ingestion on muscle-pain-intensity ratings during exercise might be moderated by habitual use of caffeine. The expectation of a moderated effect by habitual caffeine use was based on literature showing that caffeine operates as an adenosine A_1- and A_{2a}-receptor antagonist (Sawynok, 1998) and that regular caffeine consumption is associated with an up-regulation of adenosine receptors (Fredholm et al., 1999; Griffiths & Woodson, 1988; Jacobson et al., 1996; Nehlig et al., 1992). We reasoned that an equivalent dose of caffeine might block a greater percentage of adenosine receptors for low than high habitual caffeine users and, thus, potentially produce a greater reduction in muscle-pain intensity during exercise. We do not have an explanation for the discrepancy between our expectations and actual results. One possibility is that high users actually had a higher plasma concentration of caffeine than nonusers during exercise, consistent with previous research (Bell & McLellan, 2002). If indeed there was a difference in plasma caffeine concentrations between users and nonusers, this would undermine the basis of our argument that equivalent doses of caffeine would block a greater percentage of adenosine receptors in nonusers and thereby yield a larger reduction in muscle pain during exercise; the possibility of a high plasma concentration of caffeine in users would potentially equilibrate the percentage of adenosine-receptor blockade. Another possibility is that the groups were similar in caffeine sensitivity as a result of our screening criteria for avoiding paniclike attacks associated with caffeine ingestion in susceptible individuals. Some researchers have suggested that differences in sensitivity to caffeine might account for differences in the ergogenic effects of caffeine between users and nonusers (Bell & McLellan). Another possibility is the inconsistent findings of caffeine tolerance on physiological, psychological, and perceptual variables. For example, tolerance has been reported for the actions of caffeine on blood pressure and heart rate, diuresis, plasma catecholamine levels, renin activity, and nervousness and jitteriness but not alertness and wakefulness or cerebral glucose metabolism (Nehlig, 1999). The inconsistent findings for caffeine tolerance might be linked with individual differences in susceptibility to and tolerance of caffeine-induced effects and might be overcome with large enough doses of caffeine (Nehlig). Therefore, a possible explanation for our findings is that either muscle pain does not exhibit tolerance or the dose of caffeine was not sufficient to overcome tolerance effects.

The current findings both replicate and extend previous work on caffeine and naturally occurring muscle pain during exercise. Previous experiments have demonstrated that ingestion of large (10 mg/kg) and moderate (5 mg/kg) doses of caffeine reduced quadriceps muscle-pain-intensity ratings during moderate-intensity cycling exercise in low-caffeine-consuming males and females (Motl et al., 2003, 2006; O'Connor et al., 2004) and during high-intensity cycling exercise in low- to moderate-caffeine-consuming females (Gliottoni & Motl, 2008). This experiment demonstrated that ingestion of a moderate (5 mg/kg) dose of caffeine reduced quadriceps muscle-pain-intensity ratings during high-intensity cycling exercise in males who were either low or high habitual caffeine users. Some previous researchers have reported no reduction in quadriceps muscle-pain-intensity ratings after ingestion of low doses of caffeine (1, 2, and 3 mg/kg) during 15 min

of high-intensity cycling exercise (target intensity of 80% VO_{2peak}) in males who were low to moderate caffeine users (Jenkins et al., 2008). We further note that the pain-intensity ratings in that study were substantially higher than those reported in the current study using a similar target intensity (80% VO_{2peak}). The higher pain-intensity ratings in that study might be explained by the lower fitness level of the participants or a difference in the actual intensity of cycling between that previous research (~87% VO_{2peak} in placebo condition) and the current study (75–76% VO_{2peak} in placebo condition). The emerging evidence suggests that ingestion of moderate or large, but not small, doses of caffeine is associated with a moderate to large reduction in pain-intensity ratings in the quadriceps during moderate- and high-intensity cycling exercise in both high- and low-caffeine-consuming individuals.

The findings from this experiment have implications for several future lines of research. This study only examined the effects of a moderate dose of caffeine on muscle pain during high-intensity exercise in men who were low and high caffeine consumers. We selected high-intensity exercise (i.e., 80% VO_{2peak}) to examine the effects of caffeine on changes in leg-muscle pain for low and high caffeine consumers because it should produce stronger perceptions of pain in the activated muscles than moderate-intensity exercise (i.e., 60% VO_{2peak}), and we do not have any information about such effects with a moderate exercise intensity. Possible benefits of evoking stronger perceptions of muscle pain involve (a) avoiding the possibility of floor effects (i.e., limited room for improvement in reducing pain) when examining caffeine's effect on muscle pain during acute exercise; (b) examining the effect of caffeine on pain using an exercise stimulus that might more closely represent the demands of athletic performance, although we did not actually measure performance; and (c) further characterizing the nature of the acute exercise stimulus for which caffeine might exert an effect on perceptions of muscle pain. Future research would benefit from an examination of the effects of both small and large doses of caffeine on muscle pain during high-intensity exercise in males and females who are low and high habitual caffeine consumers. Future investigations might consider examining the synergistic effects of caffeine and other agents on muscle pain during exercise. This is based on the observation that nonexercise clinical studies have demonstrated that larger doses of an analgesic substance are as effective in reducing pain as smaller doses of the same substance combined with caffeine (Laska et al., 1984). For example, one substance of interest might be aspirin. Although previous research has reported that ingesting aspirin had no effect on muscle pain during an incremental maximal exercise test (Cook et al., 1997), aspirin plus caffeine might demonstrate larger effects on muscle pain during exercise than either drug in isolation. Such results might have further implications for understanding the mechanisms of hypoalgesia during exercise and identifying safe, legal, effective methods of reducing pain that naturally occurs as a consequence of exercise.

This study did not examine the mechanisms that might explain the effect of caffeine on muscle pain during exercise. One of the more plausible explanations is that caffeine acts on peripheral or central adenosine A_1 and A_{2a} receptors involved in the nociceptive system (Sawynok & Liu, 2003). Indeed, many of the pharmacological actions of caffeine are linked with adenosine-receptor blockade (Fredholm et al., 1999; Griffiths & Woodson, 1988; Jacobson et al., 1996; Nehlig

et al., 1992), and adenosine A_1 and A_{2a} receptors are located on sensory nerve endings in skeletal muscle that can influence pain signaling (Sawynok, 1998). The peripheral actions of adenosine on A_1 and A_{2a} receptors seem to be receptor specific and result in antinociceptive and pronociceptive effects, respectively (Sawynok). Caffeine might reduce muscle pain during exercise by blocking the pronociceptive effects of A_{2a} receptors on sensory afferents, and such an effect would likely exceed the blockade of the antinociceptive effects of A_1 receptors. Clearly, one major future research direction involves mechanistic examinations of the effect of caffeine on muscle pain during acute exercise.

This study is not without additional limitations. One of those is that we might not have adequately defined pain and differentiated it from effort for the participants in this study. As noted in the Introduction, pain has been defined by the International Association for the Study of Pain (1979) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" p. 250). We defined pain for the participants as the intensity of "hurt," and this is consistent with the second part of the aforementioned definition of pain. We further provided participants with standardized, tape-recorded instructions for correctly using the quadriceps muscle-pain (see Appendix A in Cook et al., 1997, or Methods of Cook et al., 1998) and overall perceived-exertion (Borg, 1998) scales, and all participants articulated that the pain scale was measuring the intensity of hurt in the quadriceps muscles of the legs during exercise, whereas the perceived-exertion scale was measuring the overall amount of effort during exercise. Nevertheless, future work should consider better defining and differentiating pain and effort when examining the effects of caffeine during acute exercise. This might be done by providing the definition of pain offered by the International Association for the Study of Pain. This future work might further benefit from an attempt to detect actual tissue damage (e.g., rise in blood CK unrelated to exercise-induced hemoconcentration) as a method of verifying the occurrence of muscle pain during acute exercise.

Another limitation is that we did not measure plasma caffeine concentrations and cannot rule out the possibility that differences in plasma caffeine concentrations between groups masked the possible moderating role of habitual caffeine use on the caffeine-induced hypoalgesia during exercise. We further note that this research was conducted in a laboratory under controlled conditions using cycle ergometry, and we cannot be certain that similar results would be observed during athletic events or in sports requiring arm motion (e.g., running) or predominantly upper extremity movements (e.g., swimming). An additional limitation is that we did not examine withdrawal symptoms (e.g., headaches), and such symptoms could influence leg-muscle pain during exercise. This should be addressed in future research.

Overall, the results of this experiment add to the body of evidence suggesting that caffeine ingestion influences muscle pain during exercise and provide novel evidence that caffeine is associated with a reduction in muscle pain in both habitual users and nonusers of caffeine. Additional research might examine the role of varying doses of caffeine on muscle pain during high-intensity exercise in individuals who differ in habitual caffeine consumption, the interactive effects of caffeine with other analgesic substances, and mechanisms that might explain the effect of caffeine on muscle pain during exercise. Such investigations will highlight

factors that might influence and underlie the effect of caffeine on naturally occurring muscle pain during acute exercise.

References

American College of Sports Medicine. (2006). ACSM's guidelines for exercise testing and prescription (7th ed.). Baltimore: Lippincott Williams & Wilkins.

Barone, J.J., & Roberts, H.R. (1996). Caffeine consumption. *Food and Chemical Toxicology, 34,* 119–129.

Bell, D.G., & McLellan, T.M. (2002). Exercise endurance 1, 3, and 6 h after caffeine ingestion in caffeine users and nonusers. *Journal of Applied Physiology, 93,* 1227–1234.

Borg, G. (1998). *Borg's perceived exertion and pain scales*. Champaign, IL: Human Kinetics.

Charney, D.S., Galloway, M.P., & Heninger, G.R. (1984). The effects of caffeine on plasma MHPG, subjective anxiety, autonomic symptoms and blood pressure in healthy humans. *Life Sciences, 35,* 135–144.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (3rd ed.). New York: Academic Press.

Cook, D.B. (2006). Physical activity and pain. In E.O. Acevedo & P. Ekkekakis (Eds.), *Psychobiology of physical activity* (pp. 203–217). Champaign, IL: Human Kinetics.

Cook, D.B., Jackson, E.M., O'Connor, P.J., & Dishman, R.K. (2004). Muscle pain during exercise in normotensive African American women: Effect of parental hypertension history. *Journal of Pain, 5,* 111–118.

Cook, D.B., O'Connor, P.J., Eubanks, S.A., Smith, J.C., & Lee, M. (1997). Naturally occurring muscle pain during exercise: Assessment and experimental evidence. *Medicine and Science in Sports and Exercise, 29,* 999–1012.

Cook, D.B., O'Connor, P.J., Oliver, S.E., & Lee, Y. (1998). Sex differences in naturally occurring leg muscle pain and exertion during maximal cycle ergometry. *The International Journal of Neuroscience, 95,* 183–202.

Fredholm, B.B., Bättig, K., Holmén, J., Nehlig, A., & Zvartau, E.E. (1999). Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacological Reviews, 51,* 83–133.

Gliottoni, R.C., & Motl, R.W. (2008). Effect of caffeine on leg muscle pain during intense cycling exercise: Possible role of anxiety sensitivity. *International Journal of Sport Nutrition and Exercise Metabolism, 18,* 103–115.

Griffiths, R.R., & Woodson, P.P. (1988). Caffeine physical dependence: A review of human and laboratory animal studies. *Psychopharmacology, 94,* 437–451.

International Association for the Study of Pain. (1979). Pain terms: A list with definitions and notes on usage. *Pain, 6,* 247–252.

Jacobson, K.A., von Lubitz, D.K., Daly, J.W., & Fredholm, B.B. (1996). Adenosine receptor ligands: Differences with acute versus chronic treatment. *Trends in Pharmacological Sciences, 17,* 108–113.

James, J.E., Bruce, M.S., Lader, M.H., & Scott, N.R. (1989). Self-report reliability and symptomatology of habitual caffeine consumption. *British Journal of Clinical Pharmacology, 27,* 507–514.

Jenkins, N.T., Trilk, J.L., Singhal, A., O'Connor, P.J., & Cureton, K.J. (2008). Ergogenic effects of low doses of caffeine in cycling performance. *International Journal of Sport Nutrition and Exercise Metabolism, 18,* 328–342.

Joeres, R., Klinker, H., Heusler, H., Epping, J., Zilly, W., & Richter, E. (1988). Influence of smoking on caffeine elimination in healthy volunteers and in patients with alcoholic liver cirrhosis. *Hepatology (Baltimore, Md.), 8,* 575–579.

Kamimori, G., Lugo, S.I., Penetar, D.M., Chamberlain, A.C., Brunhart, G.E., Brunhart, A.E., et al. (1995). Dose-dependent caffeine pharmacokinetics during severe sleep deprivation in humans. *International Journal of Clinical Pharmacology and Therapeutics, 32,* 182–186.

Kamimori, G.H., Somani, S.M., Knowlton, R.G., & Perkins, R.M. (1987). The effects of obesity and exercise on the pharmacokinetics of caffeine in lean and obese volunteers. *European Journal of Clinical Pharmacology, 31,* 595–600.

Kaplan, G.B., Greenblatt, D.J., Ehrenberg, B.L., Goddard, J.E., Contreau, M.M., Harmatz, J.S., et al. (1997). Dose-dependent pharmacokinetics and psychomotor effects of caffeine in humans. *Journal of Clinical Pharmacology, 37,* 693–703.

Laska, E.M., Sunshine, A., Mueller, F., Elvers, W.B., Siegel, C., & Rubin, A. (1984). Caffeine as an analgesic adjuvant. *Journal of the American Medical Association, 251,* 1711–1718.

Motl, R.W., O'Connor, P.J., & Dishman, R.K. (2003). Effect of caffeine on perceptions of leg muscle pain during moderate intensity cycling exercise. *Journal of Pain, 4,* 316–321.

Motl, R.W., O'Connor, P.J., Tubandt, L., Puetz, T., & Ely, M.R. (2006). Effect of caffeine on leg muscle pain during cycling exercise among females. *Medicine and Science in Sports and Exercise, 38,* 598–604.

Nehlig, A. (1999). Are we dependent upon coffee and caffeine? A review on human and animal data. *Neuroscience and Biobehavioral Reviews, 23,* 563–576.

Nehlig, A., Daval, J.L., & Debry, G. (1992). Caffeine and the central nervous system: Mechanisms of action, biochemical, metabolic and psychostimulant effects. *Brain Research. Brain Research Reviews, 17,* 139–170.

O'Connor, P.J., & Cook, D.B. (1999). Exercise and pain: The neurobiology, measurement, and laboratory study of pain in relation to exercise in humans. In J.O. Holloszy (Ed.), *Exercise and sport sciences reviews* (pp. 119–166). Baltimore: Lippincott Williams & Wilkins.

O'Connor, P.J., & Cook, D.B. (2001). Moderate-intensity muscle pain can be produced and sustained during cycle ergometry. *Medicine and Science in Sports and Exercise, 33,* 1046–1051.

O'Connor, P.J., Motl, R.W., Broglio, S.P., & Ely, M.R. (2004). Dose-dependent effect of caffeine on reducing leg muscle pain during cycling exercise is unrelated to systolic blood pressure. *Pain, 109,* 291–298.

Sawynok, J. (1998). Adenosine receptor activation and nociception. *European Journal of Pharmacology, 347,* 1–11.

Sawynok, J., & Liu, X.J. (2003). Adenosine in the spinal cord and periphery: Release and regulation of pain. *Progress in Neurobiology, 69,* 313–340.