Caffeine lowers muscle pain during exercise in hot but not cool environments

Matthew S. Ganio *, Evan C. Johnson, Rebecca M. Lopez, Rebecca L. Stearns, Holly Emmanuel, Jeffrey M. Anderson, Douglas J. Casa, Carl M. Maresh, Jeff S. Volek, Lawrence E. Armstrong

Abstract

Caffeine (CAF) ingestion may enhance endurance exercise by lowering perceived exertion (RPE) and muscle pain. However, exercise in the heat may be detrimental to performance by increasing RPE and pain. The purpose of this study was to examine if caffeine affects pain and related perceptual responses differently in cool and hot ambient conditions. Eleven male cyclists (mean ± SD; age, 25 ± 6 years; mass, 72.6 ± 8.1 kg; VO2max 58.7 ± 2.9 ml kg−1 min−1) completed four trials in a randomized, double blind design. While remaining euhydrated, subjects cycled for 90 min at 65 ± 7% VO2max followed by a 15-min performance trial. Subjects ingested 3 mg kg−1 of encapsulated caffeine (CAF) or placebo (PLA) 60 min before and 45 after beginning exercise in 12 °C and 33 °C (i.e., 12-CAF, 33-CAF, 12-PLA, and 33-PLA trials). Central, local, and overall perceived exertion (C-, L-, and O-RPE) and pain were measured throughout exercise. Throughout submaximal exercise C-, L-, and O-RPE were significantly greater in 33 °C (P < 0.05) but were not affected by CAF (P > 0.05). Using area-under-the-curve analysis, pain in 33-PLA was increased by 74% vs 12-PLA (P < 0.05). CAF did not reduce pain in 12 °C (P = 0.542), but in 33 °C CAF reduced pain by 27% (P = 0.032). Despite this apparent advantage, CAF improved performance independent of ambient temperature (i.e., non-significant 2-way interaction; P = 0.662). This study found that, although caffeine improves exercise capacity, its effect on leg muscle pain is dependent on ambient temperature. Although exercise in the heat increases pain compared to a cooler environment, caffeine reduces this pain.

Keywords: Environmental temperature, Hyperthermia, Caffeine, Perceived exertion, Muscle pain.

1. Introduction

Although caffeine (CAF) simultaneously affects several organ systems, current evidence suggests that the ergogenic effect of CAF during endurance exercise is due to its actions on the central nervous system [1]. In support of this concept, research indicates that CAF may decrease perceived exertion [2], decrease muscle pain [3–5], and increase vigor [6–8]. Specifically, a meta-analysis by Doherty and Smith [2] concluded that CAF ingestion reduces ratings of perceived exertion (RPE) by an average of 6%. Using regression analysis, they observed that greater reductions in RPE with CAF correlated with larger performance improvements. This reduction in RPE explained 25% of the variance in performance improvement observed with CAF. Decreased RPE with CAF ingestion was primarily a result of local-RPE decreases [9]. Local-RPE is different from central- and overall-RPE in that it originates from feelings or sensations of strain in the exercising muscles and joints. Central-RPE involves ratings of sensations in the cardiopulmonary system, and overall-RPE is an integration of local- and central-RPE [10].

Distinct from RPE, three other relevant CAF findings have been reported. First, perceived muscle pain may be reduced with CAF ingestion during isometric [11] and dynamic [3–5] exercise. This effect of CAF is dose-dependent [5,12] and is independent of sex [3,4]. Although lower muscle pain with CAF ingestion hypothetically contributes to increased performance [5,12], improved performance has been observed in the absence of changes in muscle pain [12]. Second, CAF may decrease feelings of fatigue [8] and increase vigor [6], as measured by the profile of mood states questionnaire (POMS) [13]. However, there is a minimum dose of approximately 260 mg required to observe these changes [7]. Third, moderate levels of CAF (i.e., < 500 mg day−1) do not impair thermoregulation, hydration status, or ratings of thermal sensation and thirst [14–16]. The effect of ambient temperature on a variety of perceptual ratings and mood has been described, but the effect of these changes on subsequent exercise performance has not been elucidated. Ratings of perceived exertion increase in proportion to ambient temperature, especially as exercise duration increases [17–20]. Hypothetically, RPE increases in the heat as a result of hyperthermia and an increased ratio of alpha- to beta-band electroencephalogram (EEG) activity, not muscle electrical activity [21]. This elevated RPE may play a role in decreased exercise performance [18,22]. Also, increased feelings of fatigue and decreased feelings of vigor in the heat may contribute to decreased performance [23].

© 2010 Published by Elsevier Inc.
Although changes in muscle metabolism with increasing exercise intensity lead to increased muscle pain [24,25], it is unknown how changes in metabolism during exercise in heat contribute to muscle pain. Likewise, the increase of central, skin, and muscle temperatures along with changes in blood flow may contribute to perception of muscle pain in a hot environment. Regardless of how environmental temperature influences muscle pain, it is unknown if these perceptual changes will lead to changes in endurance performance.

The purpose of this investigation was to test the effects of CAF on RPE, thirst sensation, thermal sensation, and leg muscle pain during exercise in two ambient temperatures. Although the effect of CAF on these perceptual measures previously has been investigated [3–6,12,14–16], it is unknown if the effects are similar when utilizing CAF in 12 °C and 33 °C. We hypothesized that (a) CAF would lower RPE and pain, and increase feelings of vigor independent of ambient temperature; (b) increased ambient temperature (33 °C) would increase RPE, pain, and feelings of fatigue when ingesting CAF and placebo; and (c) the increased stress due to a high ambient temperature would override the effects of CAF on perceptual parameters during exercise in the heat.

2. Materials and methods

This study was approved by the university’s Institutional Review Board for the use of human subjects in research, and all subjects provided written informed consent prior to testing. Eleven healthy, trained male cyclists were studied using a double blind, randomized experimental design in which each subject served as his own control during four experiments. As determined by medical history, training history and caffeine consumption recall questionnaires, subjects were all current competitive cyclists, had no contraindications to participation in strenuous exercise in the heat, were low daily consumers of caffeine (average 53 ± 39, range 13 to 135 mg day⁻¹), did not smoke or use tobacco products, and did not regularly consume pain medication.

2.1. Familiarization visits

At least one week prior to the first treatment test session, subjects were introduced to the cycling protocol and performance test. At that time, height, body weight and skinfold thickness measures at seven body sites were obtained to estimate body fat percentage. Next, a cycling graded exercise test was conducted on a cycle ergometer (Lode Excalibur Sport V2, Lode BV, Groningen, Netherlands) in a 22 °C environment to measure maximal oxygen uptake (VO₂max). Oxygen uptake (ParvoMedics, Sandy, Utah) and heart rate (chest-mounted monitor, Polar, Inc.; HR) were measured each minute. Rating of perceived exertion was measured every 2 min. At exhaustion, a blood sample (≤2 ml) was collected via a finger-stick to assess blood lactate levels. A follow-up test confirmed that all subjects obtained VO₂max.

After 20 min of rest, subjects practiced elements of the experimental protocol (“first familiarization”). Subjects entered an environmental chamber (Minus-Eleven, Inc.) set at either 12 °C or 33 °C. The temperature was randomly assigned. They then cycled on a stationary ergometer for 15 min at a work rate designed to elicit 60% VO₂max, followed by 15 min at a work rate designed to elicit 70% VO₂max, followed by 15 min of cycling in which the subject practiced the performance test. At least three papers have reported the reliability of the performance test utilized in the present study (i.e., 15 min test following 45–90 min of prior exercise). Doyle [30] reports that test–retest reliability was r = 0.91–0.93 and various studies measure a CV of 3.5–4.0% [30–32]. Sample size calculations, corrected for effect size and repeated measures [29], were performed, and using the means from a similar study [33] for total work (189 and 219 kJ), the average SD (34 kJ), and a reliability of 0.9, the adjusted effect size (d) was 1.79 SD units (−10%) and a sample size of 10 is needed for adequate power to detect changes between conditions.

Body weight was measured on an electronic scale (± 0.1 g, Healthometer® model 349KL, Heathlomet, Inc., Bridgeview, IL) before and after exercise to estimate sweat rate in each environmental condition. Rectal temperature (Tᵣₑ) was continuously monitored via a rectal probe inserted 10 cm past the anal sphincter.

At least 48 h after the first familiarization visit, subjects performed a second familiarization session. If subjects performed the first familiarization at 12 °C, the second practice session occurred at 33 °C, and vice versa.

Subjects duplicated all procedures of the practice session performed in the first familiarization visit.

During both familiarization sessions, subjects were provided instructions and forms to aid in the duplication of dietary intake for the three days prior to each experimental test session. Subjects were allowed to read standard instructions and familiarized with the use of the following perceptual scales used during the experimental trials: Borg’s Rating of Perceived Exertion scale [34] differentiated into central-, local-, and overall-ratings of perceived exertion [10]; thermal sensation [35]; thirst [36]; and leg muscle pain [25,37]. It was carefully explained that local-RPE was not the same as muscle pain, and that the increase in one perception does not preclude an increase in the other and vice versa [24]. Subjects were also familiarized with the computerized version of the Profile of Mood State (POMS) questionnaire [13].

2.2. Experimental test sessions

Subjects completed four test trials; two occurred in 12 °C and two occurred in 33 °C. For one trial in each environmental condition subjects ingested caffeine (CAF); and for the other trial subjects ingested placebo (PLA). Placebo consisted of a non-calicral crystalline solid which had a color and consistency similar to CAF. The contents of capsules for each trial were unknown to the investigators and test subjects. Thus, subjects ingested CAF in a total of 2 trials: 12 °C (12-CAF) and 33 °C (33-CAF); they ingested PLA in a total of 2 trials: 12 °C (12-PLA) and 33 °C (33-PLA). The treatments were presented in a randomized order, separated by at least 5 days (average 8 ± 2 days). Each subject was tested at approximately the same time of day (±1 h) and at least 3 h later after eating. Food records were kept prior to the first experimental test session, and subjects replicated this diet for the 3-day period prior to subsequent trials. Further, the same cycling training was performed for 7 days prior to each test, with no exercise of any form (i.e., weight lifting, cycling, and running) performed within 24 h of each experiment. For the 3 days prior to each test session, subjects abstained from CAF and limited the ingestion of cruciferous vegetables (e.g., broccoli) and flavonoid-containing foods (e.g., onions, apples, citrus and fruits) because they influence caffeine metabolism [38]. Subjects were asked to consume their typical diet (i.e., no carbohydrate loading involving greater than 70% of calories from carbohydrates). Subjects did not take any prescription or over-the-counter pain medicine for at least 3 days prior to each test session.

Subjects reported to the laboratory euhydrated following a minimum 3-h fast. Euhydration was verified by measuring urine specific gravity (U₉). Prior to each cycling experiment, subjects completed a 24-h history questionnaire regarding compliance with pretest instructions and voided the bladder and provided a urine sample. Subjects inserted a rectal temperature probe 10 cm past the anal sphincter. Subjects were not tested if U₉ was greater than 1.025, suggesting dehydration, or if they had an initial Tᵣₑ> 37.8 °C. Subjects were asked to sit quietly and completed the POMS questionnaire. Subjects were then fitted with instrumentation for measurements as part of a larger study. Then, while sitting quietly, subjects were asked their thermal, thirst, and leg muscle pain ratings. Sixty minutes prior to the start of exercise, subjects ingested 3 mg kg⁻¹ body mass of either PLA or CAF in capsule form with 100 ml of water. Body weight was measured on an electronic scale and subjects remained seated in a comfortable 22 °C environment for approximately 40 min. Subjects then entered the environmental chamber and sat on a bicycle
ergometer for 15 min. Subjects wore the same clothing ensemble for each trial. At all times while sitting on the ergometer, a large fan was directed on the subjects and produced an air speed of ~3.3 m·s\(^{-1}\).

After 15 min of seated rest, \(T_{re}\) and skin temperature at the forearm, chest and hip (contact infrared thermometer; Ototemp \(^{TM}\) 3000, Exergen Corp., Newton, MA, \(T_{sk}\)), were obtained along with ratings of thirst, thermal sensation, and perceived muscle pain. This was followed by 90 min of exercise on a stationary cycle ergometer. Subjects began exercise at 60% \(VO_{2max}\) and alternated every 15 min between 60% and 70% \(VO_{2max}\). The power output required to obtain the necessary \(VO_2\) was obtained from preliminary testing (see above). For each subject the programmed watts for 60 and 70% \(VO_{2max}\) was kept identical for each trial. Exercise occurred in an environmental chamber maintained at either 12.3 ± 0.6 °C, 60 ± 5% relative humidity (RH) or 32.9 ± 0.3 °C, 41 ± 2% RH (depending on trial assignment, see above for protocol design). Rectal temperature and \(T_{sk}\) were measured every 15 min during cycling just prior to each change in exercise intensity. Always in the same order, central-, local-, and overall-RPE (C-, L-, and O-RPE, respectively), thirst, thermal, and leg muscle pain ratings were measured every 15 min during cycling just prior to each change in exercise intensity. Perceptual measures were obtained while subjects were wearing nose clips and breathing through a mouthpiece for the measurement of \(VO_2\).

Before and after every 15 min during exercise, after perceptual ratings were obtained, subjects drank a volume of water equal to 80% of estimated sweat losses (i.e., subjects drank a total of 1.72 ± 0.37 and 1.02 ± 0.37 l in 33 °C and 12 °C, respectively). The total volume was estimated from the sweat rate measured in the corresponding familiarization session (i.e., sweat rate measured in the 12 °C familiarization was used to estimate the volume of water needed in the two 12 °C experimental trials; likewise for the 33 °C conditions). Fluid ingestion after 45 min of exercise included the ingestion of a second dose of either CAF or PLA equal to 3 mg·kg\(^{-1}\) body mass in capsule form.

After 90 min of cycling, subjects immediately completed a 15-minute performance test at their maximal effort, as practiced in the familiarization trials. The total work performed (kilojoules, KJ) during the test was used as a measure of performance. Financial incentives based on performance relative to body size helped encourage maximal effort in each trial. At the end of exercise, \(T_{re}\), \(T_{sk}\), C-, L-, O-RPE, thirst, thermal, and pain ratings were measured. After exercise, subjects exited the environmental chamber, wiped his body with a towel, voided the bladder, and had post-exercise body weight measured. Approximately 15 min after the end of exercise, subjects sat and completed the computerized POMS questionnaire.

Sweat rate during exercise was calculated from the change in body weight, corrected for excreted urine weight, estimated respiratory water losses, and weight gain due to fluid ingestion. Mean skin temperature (\(T_{sk}\)) was calculated using a modification of the Burton formula [39]:

\[
T_{sk} = (0.14 \times T_1) + (0.5 \times T_2) + (0.5 \times T_3)
\]

where \(T_1\), \(T_2\), and \(T_3\) were forearm, chest, and hip sites, respectively.

### 2.3. Statistical analyses

Statistical analyses were performed using SPSS v.11 for Windows and v.17 for Macintosh (SPSS, Inc., Chicago, IL). Data are reported as means ± standard deviation (SD). An alpha level of 0.05 was used for all significance tests. Perceptual responses were examined during steady state exercise (i.e., from the beginning of exercise to 90 min).

To examine the effects of ambient temperature on caffeine ingestion, a two-way (treatment × time) repeated-measures analysis of variance (ANOVA) was used to test the significance of mean differences. Greenhouse–Geisser corrections were made when the assumption of sphericity was violated. Follow-up repeated-measures t-tests and the Bonferroni alpha correction were used when appropriate. In order to quantify the overall magnitude of C-, L-, O-RPE, and perceived muscle pain prior to the performance test, area under the curve (AUC) was calculated utilizing the trapezoidal method for responses during submaximal exercise [40].

### 3. Results

#### 3.1. Subjects

The eleven subjects had a mean age, height, mass, percent body fat, and \(VO_{2max}\) of 25 ± 6 years, 179.1 ± 9.2 cm, and 72.6 ± 8.1 kg, 10.4 ± 2.3%, 4.25 ± 0.48 l·min\(^{-1}\) (58.7 ± 29 ml·kg\(^{-1}\)·min\(^{-1}\)), respectively. Subject hydration status before and after exercise was similar in all trials as indicated by non-significant differences in pre- and post-exercise body mass and \(U_{sg}\) (pre and post combined average of all trials: 71.87 ± 8.19 kg and 1.009 ± 0.006, respectively; \(P>0.05\)). At the end of exercise subject body mass loss, expressed as percent of pre-exercise body mass, was not significantly different between conditions (−0.28 ± 0.62, −0.33 ± 0.70, −0.64 ± 0.57, and −0.82 ± 0.61, in 12-PLA, 12-CAF, 33-PLA, and 33-CAF, respectively; \(P=0.060\)).

#### 3.2. Performance

Total work (KJ) accumulated during the performance test, independent of treatment, was greater in 12 °C than 33 °C (237 ± 191 ± 35, respectively, \(P<0.001\)). Likewise, for each ambient temperature, CAF did not significantly differ in PLA (219 ± 44 vs 209 ± 42, respectively; \(P=0.006\)). However, performance differences with CAF (vs PLA) were not dependent on ambient temperature (i.e., non-significant interaction; \(P=0.062\))

#### 3.3. Body temperature

Rectal temperature from 15 to 90 min averaged 38.10 ± 0.55, 38.18 ± 0.55, 38.41 ± 0.74, and 38.55 ± 0.75 °C in 12-PLA, 12-CAF, 33-PLA, and 33-CAF, respectively. In 33-CAF \(T_{re}\) was significantly greater than 12-CAF at min 30 and 45 (average 38.41 ± 0.31 and 38.07 ± 0.33 °C in 33-CAF and 12-CAF, \(P=0.004\)). From 60 to 105 min, \(T_{re}\) was greater in 33 °C than 12 °C independent of treatment (39.57 ± 0.37 vs 39.11 ± 0.45 °C, \(P<0.05\)). At all time points, \(T_{sk}\) was significantly greater in 33 °C than 12 °C (33.02 ± 1.38 and 24.30 ± 2.36 °C, respectively; \(P<0.05\)). Within each ambient temperature, CAF did not significantly influence \(T_{re}\) or \(T_{sk}\) compared to PLA (\(P>0.05\)).

#### 3.4. Perceptual measures and profile of mood states

The only mood domain differences between trials were in vigor activity and fatigue (Table 1). In 33-CAF, post-exercise vigor-activity was greater than 33-PLA (\(P<0.01\)), however this same CAF effect was not present in 12 °C (\(P>0.05\)). Post-exercise vigor-activity in 33-PLA was less than 12-PLA (\(P<0.05\)). Vigor-activity decreased from pre- to post-exercise in 33-PLA only (\(P<0.05\)). As anticipated, in all conditions exercise increased fatigue, however post-exercise fatigue was greater in 33-PLA vs 12-PLA (\(P<0.05\)). This same temperature effect on fatigue was not observed with CAF ingestion (Table 1).

Thirst, independent of treatment, was significantly greater in 33 °C than 12 °C from 15 to 75 min (\(4±1\) and \(2±1\), respectively, \(P<0.05\)). At min 90, thirst was significantly greater in 33-PLA vs 12-PLA (\(5±2\) vs \(3±1\), \(P=0.032\)) but did not differ between 33-CAF and 12-CAF (\(5±3\) vs \(3±1\), \(P=0.068\)). Thirst did not differ with CAF ingestion (vs PLA) at any point before or during exercise (\(3±1\) vs \(3±2\), \(P>0.05\)). Thermal sensation, independent of treatment, was significantly greater in 33 °C than 12 °C from 0 to 90 min (\(5.5±0.9\) vs \(3.5±1.2\), \(P<0.05\)) but did not differ between CAF and PLA (\(4.5±1.4\) vs \(4.5±1.5\), \(P>0.05\)).
At individual time points the only C-, L-, and O-RPE differences between trials were at min 60. Local-RPE was significantly greater in 33-PLA than 12-PLA ($P=0.038$), and O-RPE was significantly greater in 33-CAF vs 12-CAF ($P=0.017$). However when examining the overall effect of RPE with AUC analysis, C-, L-, and O-RPE was significantly greater in 33 °C vs 12 °C independent of treatment ($P<0.05$, Fig. 1). In 12 °C, CAF did not decrease C-, L-, or O-RPE AUC ($P=0.401, 0.527$, and $0.185$; effect size ($\eta^2$) = 0.080, 0.046, and 0.187, respectively). In 33 °C, CAF did not decrease C-, L-, or O-RPE AUC ($P=0.548, 0.059$, and $0.099$; $\eta^2=0.042, 0.342$, and 0.274, respectively).

At individual time points the only differences in leg muscle pain ratings were at min 60 and 90. At both time points perceived pain was lower in 12-PLA vs 33-PLA (average $2\pm2$ and $4\pm2$ for 12- and 33-PLA, respectively, $P<0.05$). However, with AUC analysis, there was a significant reduction in muscle pain with CAF ingestion that was dependent on environmental condition (Fig. 2). Specifically, pain in 33-PLA was increased by 74% vs 12-PLA ($P<0.05$). The ingestion of CAF did not reduce pain in 12 °C ($P=0.542$), but in 33 °C, CAF reduced pain by 27% ($P=0.032$, Fig. 2). The reduction in pain with caffeine ingestion in the heat resulted in pain values that were similar between 33-CAF and 12-CAF ($P<0.05$, Fig. 2). In order to identify if the differences between pain in 33 °C and 12 °C correlated with performance, we performed a Pearson correlation between pain AUC and KJ performance; there was no correlation ($r=−0.193, P=0.209$).

4. Discussion

To test the effects of CAF at different ambient temperatures, subjects exercised for 105 min in 12 °C and 33 °C environments while hydration and nutritional status were controlled prior to and throughout testing. At rest, before and after exercise, mood was assessed with a POMS questionnaire. Prior to and throughout exercise, the C-RPE, L-RPE, and O-RPE, thirst sensations, thermal sensations, and pain ratings were measured. The main finding of this study was that CAF ingestion reduced muscle pain in 33 °C but not 12 °C (Fig. 2). Despite this apparent advantage in 33 °C, improvements in a 15-min performance test with CAF were independent of temperature (i.e., caffeine improves performance in both 12 °C and 33 °C). Further, there was no correlation between pain ratings and performance.

Using standardized perceptual scales and instructions, we observed a degree of variability similar to others [3,4]. However, the lack of CAF effects on RPE and pain at individual time points may be explained in three ways. First, the effect of ambient temperature on perceptual scale variability is unknown; variability may be increased because heat tolerance and cardiorespiratory fitness varies from individual to individual. Second, the alternating exercise intensity every 15 min likely contributed to increased variability at each time point. Last, although total CAF ingested in the present protocol is similar to other studies examining CAF and pain [25,37], our providing CAF in two smaller doses over the long duration exercise, opposed to one large dose at the beginning of exercise, may have resulted in smaller differences in perceptual measures at individual time points but the same overall effect. Therefore, in an effort to reduce the possibility of a type-II error at individual time points and to gain a greater understanding of the overall effect of temperature and CAF on perceptual measures, we incorporated an area-under-the-curve (AUC) analysis. This type of analysis has been used by others and provides an accurate assessment of the overall effect of a treatment on perceptual measures like pain [40,41]. Therefore AUC analysis allows for a more sensitive assessment of the overall effect of temperature and CAF on perceptual measures in the present protocol.

4.1. Effects of ambient temperature

Exercise in 33 °C provided a greater thermoregulatory challenge than in 12 °C, as evidenced by increased $T_{es}$ and $T_{ve}$. Thermal sensation also was greater throughout 33-PLA and 33-CAF (vs 12-PLA and 12-CAF). This

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Profile of mood states (POMS) pre-ingestion of caffeine (CAF) or placebo (PLA) capsules and post-exercise. Measures pre-ingestion occurred in 22 °C and post-exercise occurred in 22 °C after 105 min of exercise in 12 or 33 °C.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-ingestion Post-exercise</td>
<td>Pre-ingestion Post-exercise</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Placebo</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11±4</td>
</tr>
<tr>
<td>Tension</td>
<td>19±5</td>
</tr>
<tr>
<td>Anxiety</td>
<td>24±7</td>
</tr>
<tr>
<td>Depression</td>
<td>16±4</td>
</tr>
<tr>
<td>Anger</td>
<td>26±6</td>
</tr>
<tr>
<td>Hostility</td>
<td>20±7</td>
</tr>
<tr>
<td>Vigor</td>
<td>17±5</td>
</tr>
<tr>
<td>Activity</td>
<td>23±6</td>
</tr>
<tr>
<td>Fatigue</td>
<td>25±6</td>
</tr>
<tr>
<td>Confusion</td>
<td>5±1</td>
</tr>
</tbody>
</table>

Note: Values are mean±SD. Significantly different than 33-PLA at the same time point. **$P<0.01$; ***$P<0.001$.}

Please cite this article as: Ganio MS, et al, Caffeine lowers muscle pain during exercise in hot but not cool environments, Physiol Behav (2010), doi:10.1016/j.physbeh.2010.12.005
Fig. 1. Central-, Local-, and Overall-Rating of perceived exertion (C-RPE, L-RPE, and O-RPE, respectively) area under the curve (AUC) involving 0 to 90 min of exercise. †Significantly different from the opposite treatment of the same temperature (i.e., main temperature effect; $P<0.05$).

Fig. 2. Perceived muscle pain area under the curve (AUC) involving 0 to 90 min of exercise. †Significantly different from the opposite treatment of the same temperature (i.e., main temperature effect; $P<0.05$).

Increased thermal sensation in the heat was likely due to the differences in skin temperature and not differences in core body temperature [42]. Thirst ratings, after 15 min of seated rest in each test temperature, were not different between trials. However, at the beginning of and throughout the exercise, thirst was greater in 33 °C vs 12 °C. Thirst is known to increase with dehydration and hyperosmolality [43], but in the current study subjects began and maintained euhydration throughout each trial by ingesting more water in 33 °C vs 12 °C. Thirst also correlates strongly with RPE [44] and, in the present study, the increased RPE in 33-PLA and 33-CAF (Fig. 1) may have influenced thirst ratings. It also is possible that arginine vasopressin (AVP), a recognized hormonal correlate of thirst, was greater in the heat [45]. Although we did not measure AVP, the increases in pain that we observed in 33-PLA may have increased AVP and stimulated thirst; this phenomenon may occur in the absence of plasma osmolality differences (i.e., in situations of similar hydration status) [46]. Future studies should examine the interactions of pain, thirst, and AVP in different environments.

Central-, L-, and O-RPE, AUC was greater in 33 °C vs 12 °C ($P<0.05$; Fig. 1). The increase in RPE with ambient temperature is well-documented and is positively and linearly correlated with core body temperature and the ratio of alpha- to beta-band EEG activity [17–20]; it is not associated with increased muscular fatigue in the heat [21]. Crewe et al. [18] observed that, at a variety of ambient temperatures and exercise intensities, RPE was significantly correlated with $\text{T}_{\text{R}}$ ($r^2=0.85$). In the same study, exercise duration during a test-to-exhaustion was significantly correlated to the rate of increase in RPE. In the present study, exercise in 33 °C increased $\text{T}_{\text{R}}$ and RPE to a greater degree than 12 °C. We also observed decreased total work in 33 °C vs 12 °C. Therefore, our data support the hypothesis that increased RPE in the heat during submaximal exercise contributes to decreased endurance performance.

Increased pain in 33-PLA vs 12-PLA (Fig. 2) may have been due to an increased proportion of anaerobic metabolism [47], which can result in a buildup of metabolites that increase muscle pain (e.g., hydrogen ions and bradykinin) [25]. Future experiments should confirm these findings with analyses of these metabolites in muscle biopsies. Regardless, the increased pain in 33-PLA (vs 12-PLA) may have contributed to performance differences observed between trials, due to aversive sensations.

Subjects reported reduced perceived exertion and pain during submaximal exercise in 12 °C (vs 33 °C). In 12 °C, subjects were able to exercise at a higher intensity and accomplish a greater amount of work during the performance test (vs 33 °C). It is possible that the reduced perceived exertion and pain during the submaximal exercise in 12 °C resulted in a self-selected pace during the performance test that was greater in intensity, and thus resulted in increased performance (i.e., total work) in 12 °C vs 33 °C [2].

4.2. Effects of caffeine

Although thermal sensation, thirst, and C-, L-, and O-RPE increased in 33 °C, CAF ingestion did not alter these measures significantly. Our laboratory recently exposed subjects to treadmill walking for 90 min in 38 °C, after the ingestion of three CAF treatments of 0, 3, or 6 mg kg$^{-1}$.
body mass [15]. The data from the present study support our earlier findings; CAF does not alter thirst or thermal sensations. Further, Doherty and Smith, [2] using meta-analysis techniques, concluded that CAF reduces RPE during exercise an average of 6%; this may partially explain improvements in performance. In the present study although the 4 and 7% reductions of O-RPE AUC in 12-CAF and 33-CAF (vs PLA) were not statistically different (Fig. 1), CAF improved performance in both temperatures. Therefore it is possible that improved performance with CAF ingestion is partly explained by reductions of RPE [2].

Caffeine ingestion also may influence mood by decreasing fatigue [8] and increasing vigor [6]. Fatigue ratings significantly increased from pre-ingestion to post-exercise in each trial; CAF had no effect (Table 1). Decreases in fatigue (i.e., drowsiness) with CAF, as observed by others [8], may only occur during periods of sleep-deprivation. Our data show that CAF ingestion does not affect muscular fatigue during high intensity exercise (Table 1), in that CAF ingestion in 33 °C resulted in a greater vigor-activity rating post exercise than PLA.

Contrary to this, post-exercise vigor-activity was similar in 12 °C when ingesting CAF and PLA. The implications for this difference are unclear because CAF improved performance independent of ambient temperature, and suggests the possibility that CAF improved performance in 12 and 33 °C via different mechanisms.

4.3. Interactions of caffeine and ambient temperature

Contrary to our initial hypothesis, pain AUC was reduced in 33-CAF but not 12-CAF (Fig. 2). As discussed above, the 74% increase of pain AUC in 33-PLA (vs 12-PLA; Fig. 2) may have resulted from altered metabolism in active skeletal muscles with subsequent increases in metabolites that increase the perception of pain (e.g. bradykinin, serotonin, and histamine) [24]. However, the effect of CAF on pain was dependent on ambient temperature. In 33 °C CAF reduced pain 27% (vs 33-PLA; P < 0.05). This may have been a result of either peripheral or central effects of CAF. Although adenosine receptor antagonism on the muscle membrane can result in attenuated feedback inhibition such that the CNS does not receive detrimental stimuli [11], recent evidence suggests that CAF acts centrally by crossing the blood-brain-barrier and antagonizing adenosine receptors directly on the brain [48]. This can affect central pain pathways and reduce sensations of muscle pain [3]. Specifically, adenosine receptor antagonism (due to CAF ingestion) at the insular anterior cingulate and midcingulate brain regions may decrease feelings of pain [11,42]. Interestingly, activation of these brain areas also occurs with skin warming [42]. This suggests that increased brain activation due to greater thermal stress and muscle pain in 33 °C was reduced by CAF intake, possibly due to adenosine receptor antagonism in brain regions that are activated by pain and thermal stress [3].

Caffeine has been previously shown to decrease leg muscle pain during exercise [3,4]. However the effect of ambient temperature on CAF and muscle pain has not previously been examined. Although not stated, it is assumed that previous research was conducted in mild ambient temperatures (i.e., 20–22 °C). In those conditions leg muscle pain was reduced from 2.5 ± 1.5 in PLA to 1.8 ± 1.6 with CAF [3]. Our lack of CAF effect on pain in 12 °C may be explained by the already low pain ratings in the PLA condition (i.e., 1.2 ± 1.2; Fig. 2). Therefore, we propose that the lack of CAF effect in 12 °C was due to a lack of threshold activation in pain and thermal sensory neurons, which CAF is known to influence [11,42].

Despite reductions in the leg muscle pain during 33-CAF and not 12-CAF (compared to PLA), performance improvements were independent of temperature. Thus, our data suggest that performance improvements in 12 °C occurred because CAF favorably affected an aspect of performance other than pain. Performance is affected by multiple perceptual and physiological variables, and it is likely that limiting factors to performance differed in 12 and 33 °C.

5. Conclusions

Our data demonstrate that thermal, C-RPE, and L-RPE, and O-RPE increased due to elevated air temperature (33 °C vs 12 °C). Perceived muscle pain AUC was reduced with CAF ingestion in 33 °C but not 12 °C. Future studies should focus on other interactions of CAF, pain, and ambient temperature that are relevant to human performance.

Acknowledgements

We thank the test subjects for their persistence and motivation during this investigation. The authors gratefully acknowledge the technical assistance of Jim Alvarez, Katie Beasley, Jillian Block, Julie DeMartini, Michael Eckert, Kalyn Henry, Ben Keegan, Jennifer Klau, Elaine Lee, Garrett Manthey, Stefania Marzano, Brendon McDermott, Emily Perillo, Greg Rannali, Jennifer Rivera, Katie Sanders, Amanda Travis, Angie West, and Linda Yamamoto. This study was funded in part by the University of Connecticut Doctoral Student Extraordinary Expense Award.

References