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Delextrat, A. et al.: ACETAMINOPHEN INGESTION IMPROVES REPEATED SPRINT CYCLING PERFORMANCE IN FEMALES: A RANDOMIZED CROSSOVER TRIAL

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Abstract:
The aim of this study is to investigate the effect of acute acetaminophen (ACT) ingestion on eight maximal 30-second cycling bouts, interspersed with two-minute rests. Seven recreationally active females (N=7, 22.8±6.7 years of age, with a stature of 163.4±5.8 cm, and body mass of 58.9±5.9 kg) participated in a placebo-controlled, randomized crossover design. Pain perception, heart rate, and power profiles were analyzed using a time x condition repeated measures ANOVA. Blood lactate after the eighth bout and total work done were analyzed using the paired samples t-test. Participants achieved a significantly greater (p=.007, =.725) peak power output during the ACT trials (402.9±73.8 W, 95% CI=334.6–471.1 W) when compared to the placebo (PLA) trials (378.7±64.6 W, 95% CI=319.0–438.4 W). Supplementation of ACT had no effect on mean power output, blood lactate accumulation, pain perception, or total work done after eighth bouts (p>.05). Data presented here suggest females can improve peak power output during repeated Wingate tests with ACT ingestion. It is proposed that the altered afferent feedback may have caused these alterations in power output.

Key words: acetaminophen, pain, perception, power output, Wingate test

Introduction
The capacity to repeat high-intensity efforts is crucial to performance in a variety of sports, including team and racket sports (Fernandez-Fernandez, Zimek, Wiewelhove, & Ferrauti, 2012; Mendez-Villanueva, Hamer, & Bishop, 2007). Several types of training have been proven beneficial for performance in these sports, including repeated sprint training (sprint ≤10 seconds, separated by recovery periods ≤60 seconds), intermittent sprint training (sprint ≤10 seconds, separated by recovery periods ≥60 seconds), or sprint interval training (sprint ≥30 seconds, separated by recovery periods ≥60 seconds), (Bishop, Girard, & Mendez-Villanueva, 2011; Buchheit & Laursen, 2013). Investigations concerning determinants of sprint interval training (SIT) performance have revealed that fatigue taking place between the initial and final sprints is multifactorial, and may be induced by various peripheral and central factors (Buchheit & Laursen, 2013). While peripheral factors, including muscle excitability, metabolite accumulation, and ionic disturbances have been extensively studied (Mohr, et al., 2004; Sahlin & Ren, 1989), less research has focused on the potential role of central fatigue (Foster, Taylor, Chrismas, Watkins, & Mauger, 2014). A recent study suggested that SIT performance may be limited by neural drive and the central regulation of motor unit recruitment (Ross, Gregson, Williams, Roberston, & George, 2010). Recently, interrelationships between central and peripheral factors of fatigue during SIT have been investigated (Amann, Sidhu, Weavil, Mangum, & Venturelli, 2015; Stone, et al., 2012; Swart, et al., 2009). Tucker (2009) proposed an association between the development of peripheral fatigue and...
central motor drive through alterations in afferent neural feedback from the myofibrils to the central nervous system (CNS). These changes may be related to nociceptive feedback following exercise-induced pain. Indeed, various metabolites (e.g., hydrogen and potassium ions) released during high-intensity exercise increase nociceptive signals to the central nervous system (CNS) through the stimulation of type III and type IV afferent muscle fibres, which in turn could regulate the central regulation of motor unit recruitment (Amann, Proctor, Sebranek, Pegelow, & Dempsey, 2009).

Since exercise-induced pain is a limiting factor of performance during high-intensity activities (Foster, et al., 2014), the consumption of analgesic substances, such as aspirin, caffeine or amphetamines has become common practice among athletes (Tscholl, Alonso, Dolle, Junge, & Dvorak, 2010). However, it is difficult to dissociate the analgesic effects of these drugs from their other actions, including anti-inflammatory, metabolic or psychological. In contrast, acetaminophen (ACT) is a non-steroidal non-opioid analgesic available over-the-counter associated with limited effects other than pain inhibition. The analgesic properties of ACT rely on various mechanisms, including the inhibition of the enzyme cyclooxygenase (responsible for the synthesis of prostaglandins), and a modulation of afferent and efferent pain pathway (Andersson, et al., 2011).

Research concerning the role of ACT on exercise performance is limited to its antipyretic properties, with significant improvements in the time to exhaustion during running performed in the heat following acute ingestion (Bartscher, et al., 2013). To our knowledge, only two experimental trials have focused on the analgesic effects of ACT on exercise performance in thermoneutral conditions (Foster, et al., 2014; Mauger, Jones, & Williams, 2010). Mauger and colleagues (2010) reported improved self-paced 10-mile (16.1 km) time trial performance in trained male cyclists (26 minutes 15 seconds vs. 26 minutes 45 seconds for ACT and placebo conditions respectively). Foster et al. (2014) reported that, compared to a placebo, ingestion of 1.5 g ACT prior to eight bouts of 30 s Wingate Anaerobic Tests (WAnTs) significantly increased mean power output in the final three sprints, resulting in a significantly greater overall mean power output and a lower percentage power decrement. Changes were accompanied by the unaltered pain perception, peak power output, and heart rate between ACT and placebo (PLA) conditions.

It is well established that men and women have dissimilar pain responses, with women characterized by a lower pain tolerance (Naugle, Naugle, Fillingim, & Riley, 2014; Tashani, Alabas, & Johnson, 2010). Gender differences are attributable to hormonal responses, blood pressure and body size (Tashani, et al., 2010). As a result, analgesic efficacy of ACT may be altered in females compared to males. Moreover, a lack of female participants in sports medicine research has recently been reported (Costello, Bieuzen, & Bleakley, 2014) and therefore, the aim of the present investigation was to investigate the influence of ACT on RSE in females. It was hypothesized ACT would improve power profiles during eight 30-second WAnTs.

Methods
Participants
Seven females (22.8±6.7 years of age, with a stature of 163.4±5.8 cm, and body mass of 58.9±5.9 kg) participated in the present investigation. Participants were recreationally active (they exercised for an average of 6.1±3.1 h·wk⁻¹), but were not well trained. Participants abstained from alcohol, caffeine and exercise for 24 hours prior to the investigation. Participants arrived at the laboratory in a 4 hour fasted condition as requested according to self-reporting. To increase reliability, participants were allocated the same appointment time on all visits to the laboratory to attenuate diurnal variations (Hayes, Bickerstaff, & Baker, 2010). Preceding the data collection and exercise, participants completed a Physical Activity Readiness Questionnaire (PAR-Q) and gave their full written consent to participation. The study was approved by the London Metropolitan University Ethics Committee.

Experimental design
After an initial familiarization session to get accustomed to measurement tools, participants reported to the laboratory on two separate occasions separated by a minimum of 48 hours. A placebo-controlled, randomized crossover design was used. Upon arrival at the laboratory, participants ingested an orange flavoured drink (300 ml) containing either an additional 1.5 g ACT or nothing additional to风味ing (PLA [as used by Foster et al. (2014)])]. Thirty minutes were allowed between ingestion and commencement of exercise to allow for peak plasma ACT levels to occur (Grosser, Smyth, & Fitzgerald, 2011). Participants completed a standardized three minute warm-up involving pedalling at 60 rpm interspersed with three 2-3-second all-out sprints on a stationary cycle ergometer (Monark 874, Monark, Sweden). A recovery period of five minutes was allowed between the warm-up and the test. Participants completed eight WAnTs against a load corresponding to 5% body mass applied to the flywheel, each separated by two minutes of active recovery. This schedule was chosen to cause increased pain due to limited metabolite clearance (Sinoway, Hill, Pickar, & Kaufman, 1993) and has been previously used in male participants (Foster, et al., 2014). Power output...
was calculated per second for the duration of each WAnT and peak power output, mean power output (both in W), and total work done (kJ) were calculated using WAnT software test package for Monark 874 (version 2.2). Heart rate (b·min⁻¹) was recorded during the last 1-2 seconds of each WAnT. After 20 seconds of each sprint, participants selected a score on a ten-point scale accompanied by verbal descriptions to assess perceived pain between conditions (Cook, O’Connor, Eubanks, Smith, & Lee, 1997). This was chosen since high intra-class correlations (r=0.88-0.98) suggest this scale is a reliable measure of pain intensity during exercise.

Participants were verbally encouraged throughout the test to avoid pacing and to sustain their supramaximal effort throughout the test. Post exercise blood lactate (mmol·L⁻¹) was measured two minutes following the completion of the final WAnT (Lactate Pro, Arkray, Inc., Kyoto, Japan), in accordance with previous studies (e.g. Robach, et al., 1997).

Statistical analysis
Data were analyzed using SPSS version 21 (IBM North America, New York, NY, USA). Conventional methods, mean and standard deviations (SD) were used to analyze descriptive data. Data were tested for normal distribution by Shapiro-Wilk’s test and for homogeneity of variance using Levene’s test. Following confirmation of parametricity, a two-way analysis of variance (ANOVA [condition × bout]) with repeated measures was used to test for differences in mean power output, peak power output, pain and HR. Where a main effect was observed, a Sidak post-hoc test was used to locate significant differences. Differences in total work done and post exercise blood lactate were analysed using a paired t-test. Also, 95% confidence intervals (CI) and effect size (ES) are presented. Significance was set a priori at p<.05 and observed power was .909 for peak power output.

Results
No significant effect of condition (ACT vs. PLA) existed for mean power output (p=.103; =.380); however a moderate effect was observed. ANOVA revealed a significant, large, main effect for bout number on mean power output (p<.001, =.938). Post-hoc analysis revealed mean power output during bout one was significantly greater than subsequent bouts (p<.05). Participants achieved a significantly greater (p=0.007, =.725) peak power output during the ACT trials (402.9±73.8 W, 95% CI=334.6-471.1 W) when compared to the PLA trials (378.7±64.6 W, 95% CI=319.0-438.4 W), associated with a large effect size. ANOVA revealed a main, large, effect of bout number on peak power output (p<.001, =.871). Post-hoc analysis revealed peak power outputs during bouts 4-8 were significantly lower than during bout one (p<.05). Heart rate was not significantly different between conditions or bouts (respectively for ACT and placebo: 172±9 vs. 161±26, 174±10 vs. 166±22, 175±9 vs. 174±13, 173±9 vs. 173±14, 174±9 vs. 171±14, 172±10

Figure 1. Power output profiles during eight 30-second Wingate anaerobic tests following consumption of acetaminophen (ACT) and placebo (PLA). ACT resulted in a greater peak power output than PLA (p<.05). Mean power output was not significantly different between groups (p>.05). *Significantly different between conditions for an individual bout. Data are presented as M±SEM for clarity.
Discussion and conclusions

For the first time, we report the efficacy of 1.5 g ACT ingestion to enhance SIT performance in females. Peak power output was significantly improved over eight WAnTs with the ingestion of ACT. However, no significant changes in mean power output, pain perception or physiological parameters (heart rate, blood lactate) were found between ACT and PLA conditions.

Our results differ from those concerning recreationally active males where no difference in peak power output was reported, whilst a bout x condition interaction for mean power output was observed, indicating only the final three bouts of eight WAnTs improved with ACT supplementation (Foster, et al., 2014). These discrepancies suggest that the analgesic effect of ACT ingestion may allow females to perform closer to their physiological maximum from the start of the SIT, while the effect of ACT in men starts later because these latter have a higher pain threshold (Tashani, et al., 2010). However, it may be suggested these data reflect gender differences in fatigue resistance (Hunter, 2014). As fatigue resistance is greater in women than men, it is not entirely surprising that ACT improves fatigue resistance in men but not in women. Interestingly, the variation in mechanical power between ACT and PLA conditions occurred without any change in physiological parameters, which is in agreement with the findings from Foster and colleagues (2014). As stated by these authors, a limitation of their study was the absence of blood lactate measurement. Within this context, the present study included post-exercise blood lactate sampling, showing high values but not significantly different between the conditions (14.3±1.7 vs. 14.3±1.2 mmol·L⁻¹, respectively for ACT and PLA conditions). Hydrogen ions (linked to lactate) are amongst the metabolites known to increase nociceptive signals to the CNS through the stimulation of type III and type IV afferent muscle fibres. Consequently, we can hypothesize that for similar concentrations of lactate (and thus of hydrogen ions), ACT may have played a role in the nociceptive signal and decreased inhibition of the central motor drive usually observed with pain (Aman, et al., 2009), thus allowing an increase in peak power output. Interestingly, Mauger and colleagues (2010) previously reported altered blood lactate concentra-

ions and heart rate responses to ACT when compared to PLA. However, this was during a 10-mile cycling time trial rather than SRE, which highlights the specificity of SRE exercise.

Differences in metabolic pathway contributions may explain the discrepancy between cardiorespiratory parameters in the present investigation and those of Mauger and colleagues (2010) – the participants in the latter were exercising for approximately 26 minutes and would therefore rely on glycolytic and oxidative metabolism; whereas in the present investigation, participants were primary metabolizing intramuscular stores initially. However, considering the interval length (30 s), constrained recovery (two minutes) and repeated bouts it is likely that the work bouts were primarily reliant on oxidative metabolism. When two 30-second sprints were separated by four minutes of recovery, there was a 25% reduction in work performed in the second sprint, and an increase in oxidative metabolism such as this pathway met up to 43% of the energy demand (Bodansan, Nevil, Boobis, & Lakomy, 1996). Considering the present investigation employed less recovery and more sprints, it is likely that a large portion of energy demand was met by oxidative metabolism. Regardless of the exact mechanism, the findings of the present investigation add to the increasing body of evidence (Aman, & Dempsey, 2008; Noakes, 2012), suggesting that human muscle fatigue does not reside solely in the muscle (Ganevia, 2001) and that the CNS regulates both the prolonged (Noakes, 2011; Stone, et al., 2012; Swart, et al., 2009), intermittent (Foster, et al., 2014) and, in the case of the present investigation, short duration (as peak power output is typically reached ~5 seconds, [Herbert, Sculthorpe, Baker, & Grace, 2015]) exercise performance. It is worthwhile noting however that our investigation concerned females, and therefore replication in males may not result in the same performance enhancement.

Several factors may explain the gender-specific responses to ACT during SRE. It is well-known that females have a greater sensitivity to pain and a lower pain threshold than males (Hunter, 2014; Tashani, et al., 2010). Within this context, the lower pain threshold of our participants could partly explain the quicker effects of ACT on power output compared to males, with the differences between ACT and PLA conditions observed in peak power output from the start of SRE in our study, whereas delayed effects of ACT were reported in males (Foster, et al., 2014).

The main physiological parameters that could explain the gender differences in pain threshold, and thus the contrasting effects of ACT, include body size and blood pressure. It is interesting to note that effects of ACT observed in the present study were different from the study of Foster et al. (2014), and besides the gender differences, our participants
were considerably lighter (59±6 kg compared to 75±14 kg). Therefore, although our 1.5 g dosage was the same as in Foster et al. (2014), the relative dose was greater, which could explain the greater effects of ACT observed in the present study. However, it should be noted that positive effects of ACT on pain perception and performance have not always been reported, and very large doses should be avoided. Indeed, despite an abundance of evidence suggesting that depression of pain perception or peripheral feedback enhances performance (Foster, et al., 2014; Mauger, et al., 2010; Stone, et al. 2012), Amann and colleagues (2009) reported that complete blocking of lower limb afferent feedback actually reduced performance due to an overly aggressive start to a time trial and therefore a depletion of the curvature constant parameter \((W')\). (Skiba, Chidnok, Vanhatalo, & Jones, 2012).

The main limitation of the present study was a relatively small sample size (N=7). However we mostly reported moderate to large effect sizes, which suggests that our results can be applied to larger populations.

In conclusion, the present study showed benefits of ACT ingestion on RSE capacity in females, with an improvement of peak power output generated during each sprint, with no significant difference in mean power output, heart rate, blood lactate, or pain perception observed between the conditions. Although we do not endorse chronic supplementation of ACT, acute doses prior to competition may enhance performance. This information has applications for sprint coaches and athletes alike. However, it is important to acknowledge that the current work was performed in recreational and not highly trained females. Therefore, those working with highly trained females should treat these findings with caution. Future research may wish to concern whole body exercise to determine whether a greater magnitude of influence is exerted by ACT.

References


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