ERGOGENIC, METABOLIC, AND PERCEPTUAL EFFECTS OF LOW DOSES OF CAFFEINE

by

NATHAN THOMAS JENKINS

(Under the Direction of Kirk Cureton)

ABSTRACT

To determine the effects of low doses (1, 2, and 3 mg·kg\(^{-1}\)) of caffeine on cycling performance, differentiated ratings of perceived exertion (D-RPE), quadriceps pain intensity, and metabolic responses to cycling exercise, 13 trained athletes cycled on a stationary ergometer for 15 min at 80% \(\dot{V}O_2\text{peak}\), then completed a 15-min performance ride 60 min after ingesting caffeine or placebo. Work production (kJ·kg\(^{-1}\)) during this ride was the performance outcome measure. D-RPE, pain ratings, and expired gas data were obtained every 3 min, and blood lactate concentrations were obtained at 15 and 30 min. Caffeine had no effect on work production, D-RPE, pain or most metabolic variables. In conclusion, low doses of caffeine do not affect cycling performance or perceptual responses to exercise. Athletes seeking performance benefit should ingest larger doses for which advantageous ergogenic and perceptual effects have been established.

KEY WORDS: ERGOGENIC AID, PERCEIVED EXERTION, PAIN, CYCLE ERGOMETRY
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B.S. Ed., The University of Georgia, 2005

A Thesis Submitted to the Graduate Faculty of the University of Georgia in Partial
Fulfillment of the Requirements for the Degree

MASTER OF SCIENCE

ATHENS, GEORGIA

2007
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DEDICATION

This work is dedicated to my fiancée, Stephanie, for her love, support, constant encouragement, and patience during the preparation of this thesis.
ACKNOWLEDGEMENTS

I thank my friends and fellow graduate students for making this process nearly as much about camaraderie as it was about academics, especially my MBC lab mates, Kevin Bigelman, Arpit Singhal, Jennifer Trilk, and Dr. Jonathan Wingo. I am fortunate to have had such a wonderful group of people to work with everyday. Thanks also to my committee members, Drs. Kevin McCully and Patrick O’Connor, for constantly challenging me to become a better scientist, in the context of both this thesis and the various other works I have done under your instruction. I especially thank my major professor, Dr. Kirk Cureton, for your mentorship in all aspects of this work, from beginning to end, and for your sincere dedication to my present and future academic success.
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CHAPTER 1

INTRODUCTION

It is well known that caffeine enhances exercise performances of greater than 20 minutes in duration (99). It has been suggested that there is a positive dose-response relationship up to approximately 6 milligrams of caffeine per kilogram of body weight (mg·kg\(^{-1}\)) for caffeine’s ergogenic (103) and perceptual (35) effects, but experiments employing lower doses are few. In a recent meta-analysis investigating the ergogenicity of caffeine, Doherty and Smith (34) report that doses of 3 to 13 mg·kg\(^{-1}\) caffeine have a moderate effect (Cohen’s d = 0.4 SD) on exercise performance. Doses of less than 3 mg·kg\(^{-1}\) have received little attention, but there is emerging evidence suggesting that low doses of caffeine are effective for performance enhancement. Cox et al (27) reported that caffeine doses of 1.3 mg·kg\(^{-1}\) and 1.9 mg·kg\(^{-1}\), ingested in the form of a carbonated soft drink, reduced the time to complete a ~30 min laboratory time trial by ~3%. Kovacs et al. (66) reported that a dose of ~2.1 mg·kg\(^{-1}\), ingested in the form of a carbohydrate-electrolyte sports drink, is ergogenic for cycling time trial of ~1 hr duration. There are, however, no systematic investigations of the dose-response in the ergogenic and perceptual effects of low doses of caffeine.

In conjunction with enhanced performance, reduced perception of effort is commonly experienced during submaximal exercise following caffeine ingestion. A meta-analysis found that caffeine ingestion results in average reduced ratings of perceived exertion (RPE) by a magnitude of 0.47 SD compared to placebo, and that 29% of the variance in the ergogenicity of caffeine was explained by the variance of changes in RPE (35). There is considerable evidence suggesting that the underlying physiological mechanism for reduced RPE has to do with the drug’s antagonism of adenosine receptors.
(30, 41), which also appears to account for hypoalgesia of naturally-occurring muscle pain during dynamic exercise (78, 84). To date, however, the implications of reductions in RPE and muscle pain during exercise for enhanced performance remain largely unstudied (35). Furthermore, whether low doses of caffeine affect perceptual responses to exercise, and subsequently enhance exercise performance, remains unknown.

RPE has been assessed primarily by the undifferentiated Borg method (17) in studies of the perceptual effects of caffeine. A model of differentiated ratings of perceived exertion (D-RPE) has been described that incorporates three components of effort sense (85, 86). Central nervous system (CNS) factors, such as motivation, drive, and task aversion determine the overall perception of effort (RPE-O). Local factors, such as strain, force sensation, and fatigue in the working muscles determine the perception of effort in the legs (RPE-L). Cardiorespiratory factors, such as increased heart rate, depth and rate of breathing, and feelings of dyspnea, determine “chest” perceived exertion (RPE-C). The effects of caffeine on these three components of perceived exertion are not yet known. Since ratings of effort sensations are determined by various physiological responses to exercise, D-RPE could provide insight into the important mechanistic actions of caffeine. In addition, a series of recent studies provides evidence that caffeine can reduce sensations of naturally-occurring leg muscle pain during dynamic exercise (78, 79, 84). The hypoalgesic effects were large (Cohen’s d ranging from 0.7-1.2 SD), and occurred in a dose-dependent fashion for young men (84) but not women (79). The authors reason that hypoalgesia may partially explain some of the drug’s ergogenicity; hence, they encouraged future researchers to examine hypoalgesic and ergogenic properties of caffeine. Furthermore, they note that the dose-responsiveness of 5 and 10 mg·kg⁻¹ in men (84) may or may not be realizable with either lower doses, or with doses of tighter intervals.
Purpose of the Study

The primary purposes of this experiment were to determine if low doses of caffeine 1) enhance cycling performance, and 2) alter D-RPE and quadriceps pain ratings in conjunction with improvements in performance. It was hypothesized that low doses of caffeine enhance performance and reduce feelings of discomfort and pain during exercise. A secondary purpose was to collect physiological data that might provide insight into underlying mechanism(s) of ergogenic and/or perceptual effects.

Significance of the Study

This investigation provides experimental evidence as to what may be the smallest effective dose of caffeine that causes changes in performance, metabolic, and perceptual variables. The use of a work-based protocol to measure cycling performance provides data that are applicable to cyclists in competitive situations. The observed effects of caffeine on the physiological responses to exercise provide some clarification to the conflicting literature on this topic. The application of the D-RPE model provides new information regarding the effects of caffeine on the local and central factors involved in perceived exertion. In addition, this study provides new information concerning caffeine’s hypoalgesic effect in conjunction with exercise performance.

Limitations of the Study

The participants in this study were young, male cyclists recruited from local cycling teams, as cycling was the chosen mode of exercise for the experiment. The results therefore may not be applicable to women, elderly, or unfit individuals, or to other modes of exercise such as running or resistance exercise.
In this chapter, the scholarly literature relevant to the ergogenic, metabolic, and perceptual effects of caffeine are reviewed, with a primary focus on the effects of caffeine ingestion on prolonged exercise.

**Ergogenic Effects of Caffeine**

*Protocol issues.* In order to fully understand the ergogenicity of caffeine, it is necessary to first consider issues concerning methodologies used to study exercise performance. Two performance tests have been used: 1) total time to exhaustion (TTE), in which subjects work at a constant rate until volitional fatigue, and 2) total work completion in fixed time or distance. In their meta-analysis of the effects of caffeine on exercise performance test outcomes, Doherty and Smith (34) report that, on average, caffeine elicits moderate effects on TTE and work-based protocols of prolonged exercise performance (Cohen’s $d = .68$ and $.28$ for TTE and work-based protocols, respectively). They suggest that though caffeine has a much larger ergogenic effect for TTE tests compared to work-based tests, this finding has less to do with the effects of the drug than with some peculiarities with TTE protocols. To illustrate this point, Doherty and Smith refer to the meta-analysis of Matson and Tran (73), who found a nearly identical trend for the ergogenic effects of sodium bicarbonate ingestion on TTE vs. work-based protocols. Sodium bicarbonate, like caffeine, resulted in a significantly greater average magnitude of ergogenic effect on TTE compared to work-based tests. Doherty and Smith (34) suggest that the consistent ergogenic effects on TTE tests are inflated. Accordingly, there has been a trend (60) towards the use of work-based protocols for the study of performance with any experimental intervention (e.g., after exercise training, upon
exposure to altitude, in a hot environment, etc). This recommendation comes in light of two key criticisms of TTE protocols. First, the reliability of TTE protocols is disputed, with a coefficient of variation ranging from 6% to 25% (14, 60, 68). Because of this large degree of variability, researchers cannot be entirely certain of any caffeine-induced TTE performance enhancements, unless the magnitude of the caffeine effect is considerably larger than the coefficient of variation between repeated TTE trials. The average enhancement of TTE performance following caffeine ingestion, with a mean performance change of 23.1 ± 12.9% (34), is, unfortunately, approximately equal to the coefficient of variation of 25% (60). Therefore, much of the observed ergogenic effects of caffeine are likely accounted for by the variance associated with repeated bouts of exercise to exhaustion. Second, the applied exercise scientist, athlete, or coach may question the appropriateness of exercising to exhaustion, since there are no competitive situations in which athletes are required to exercise at a constant power output until they can no longer continue. On the other hand, Hinckson and Hopkins (54) maintain that TTE protocols are in fact valid and reliable, and present a differential calculus model that describes maximal duration of exercise as a function of exercise intensity. These authors argue that the TTE approach may in fact be more useful than using work-based performance tests, because a small (e.g., 1-2%) increase in an athlete’s tolerable work rate results in very large (15-20%) increases in time to exhaustion, and also because TTE protocols eliminate the random error associated with the pacing strategies intrinsic to work-based protocols. Further, they argue that TTE protocols may in fact be applicable to training situations, since athletes and coaches often select a constant intensity for training intervals. It is reasonable to argue that if an athlete could tolerate a given training intensity for a longer duration, an increased training volume might be prescribed (either increased number of intervals or increased interval time), thus enhancing the potential training effect. This approach, however, has been met with skepticism (3, 61), and it is thought that the random error associated with TTE arising from the subject’s
motivation to continue or boredom with the exercise task is greater than that associated with pacing strategies during work-based tests (3). Furthermore, inasmuch as pacing strategies are intrinsic to work-based protocols, so they are to successful competition in endurance races, thus the use of a work-based protocol is likely the appropriate choice because of the similarity to athletic competition.

Irrespective of the methodological concerns with TTE performance tests, many investigations of the ergogenic effects of caffeine have utilized such protocols, and the findings of such studies should by no means be discredited or ignored. On the contrary, that caffeine has a moderate to large average effect (.68 SD) may provide some insight into the underlying mechanisms of the drug (discussed below in detail). Furthermore, researchers in Costill’s lab (26) ushered in the modern era of study of caffeine’s ergogenicity with the use of TTE protocol. In this classic study, subjects ingested coffee containing 330 mg caffeine or decaffeinated coffee, with the caffeine treatment resulting in a 26% increase in cycling TTE at 80% \( \dot{V}O_{2\text{max}} \). As a follow-up to that study, investigators of the same laboratory (57) examined the effects of caffeine ingestion on a 2-h performance test during which subjects were instructed to perform as much work as possible. The authors report that subjects increased total work produced by 7.4% compared to control condition, thus providing the first modern contribution to the caffeine literature concerning the drug’s effectiveness on a work-based performance protocol. Taken together, these two studies indicate that caffeine is ergogenic for both TTE and work-based performance tests, and, to a large extent, are the foundation for nearly 30 years of subsequent academic inquiry.

**Effect of caffeine on TTE.** The effect of caffeine on TTE performance has been studied with a variety of experimental manipulations since the classic investigations performed in Costill’s lab. While most reports indicate positive ergogenic effects, it has been shown that caffeine may not increase TTE at a constant rate exercise in a few special situations. For example, TTE at 80-85% \( \dot{V}O_{2\text{max}} \) following exceptionally
prolonged (3-h) cycling exercise at 60% $\dot{V}O_{2\text{max}}$ (107) and a 40km march (40), were unaffected by caffeine ingestion. The effect of caffeine on TTE at workloads corresponding to 10% below the anaerobic threshold can be quite profound (i.e., 43% increase in TTE), but at 10% above the anaerobic threshold, the drug may have no effect (31). Moreover, it has also been demonstrated that while caffeine can increase TTE at 80% $\dot{V}O_{2\text{max}}$ upon acute (1-h) exposure to altitude, the drug was ineffective both at sea level (baseline) and after 2wk acclimatization to 4300m (42). The null result at sea level is of particular interest in light of the fact that the vast majority of caffeine studies report positive ergogenic effects in normal laboratory conditions (34, 99), with the exception of the few unique situations described here.

From the studies that do show positive ergogenic effects on TTE performance, much has been learned regarding some experimental factors thought to influence performance outcomes. It is now known, for example, that caffeine can enhance TTE independent of exercise modality (51), period of caffeine withdrawal (105), age of participants (83, 96), and prior coffee consumption (75). In fact, with regards to caffeine ingestion in the form of coffee, it appears as though some chemical constituent of coffee counteracts the ergogenic effects of caffeine (48), but anhydrous caffeine ingestion is still ergogenic with prior coffee consumption (75). There is no apparent additive effect of repeated caffeine ingestion for repeated TTE protocols in the morning and afternoon (10); the ergogenic effect of caffeine ingested in the morning was retained during afternoon exercise sessions, while ingesting caffeine prior to the afternoon session did not cause further performance enhancement.

Overall, caffeine is effective for increasing TTE performance, yet the dose-responsiveness for performance enhancement is not fully understood. One investigation (50) found that 3 and 6 mg·kg$^{-1}$ increased TTE to the same extent compared to placebo, but, curiously, 9 mg·kg$^{-1}$ did not improve performance. Similarly, Pasman et al. (88) found that caffeine was equally ergogenic at 5, 9, and 13 mg·kg$^{-1}$. From these and similar
findings (11, 48, 105), it is now generally accepted that approximately 6 mg·kg\(^{-1}\) is an optimal dose for moderately prolonging TTE at a constant work rate; above this dose, however, there are no apparent additional ergogenic effects (34).

**Effect of caffeine on work-based exercise performance.** Since the study of Ivy and colleagues (57), the effect of caffeine on endurance exercise performance using non-TTE, work-based protocols have not been widely studied. Only five such studies met the inclusion criteria of Doherty and Smith (34), as compared to 34 studies that used TTE protocols. The ergogenic effect of caffeine is generally smaller in magnitude for work-based tests than for TTE. One investigation (12) found caffeine was not effective for improving 10-km military style running performance (i.e., with a helmet and 11kg backpack), but that treatments of ephedrine and combined caffeine and ephedrine were ergogenic. In contrast, however, a recent investigation (18) found that a small dose of caffeine (3 mg·kg\(^{-1}\)) is ergogenic for 8-km running performance in a field setting. MacIntosh and Wright (71) found a small, but statistically significant, ergogenic effect, with caffeine resulting in 2% faster 1500-m swimming time-trial performance than placebo. Anderson et al. (1) observed enhanced rowing performance in competitive oarswomen, with the interesting outcome that the largest effect was on the first 500-m split of a 2000-m time trial. Cole et al. (21) conducted an elegant experiment in which subjects experienced a much larger ergogenic effect on work-based performance, on the order of 12%. Subjects were instructed to cycle at three different levels of perceived exertion, with total work produced at constant RPE as the main outcome. Caffeine significantly increased work produced at ratings of 9, 12, and 15 on the Borg RPE scale (16). More recently, it was demonstrated that while divided caffeine ingestion has no additive effect on TT performance compared to a single bolus ingestion (24), the ingestion of a cola beverage containing caffeine late in an endurance event is equally effective as ingestion of a caffeine pill (27).
Excepting the studies by Hunter et al. (56) and Jacobson et al. (59), there is evidence that ingestion of caffeinated carbohydrate-electrolyte beverage is more effective than ingestion of a either a carbohydrate-electrolyte beverage or caffeine alone. Sports drinks containing caffeine can improve both ≈1-h (66) and 7 kj·kg\(^{-1}\) (27) time trial performance compared to treatments of water and sports drinks with no added caffeine. Cureton et al. (28) similarly found that a caffeinated sports drink enhanced total work production in 15 min of all-out cycling following 2 h of cycling at oscillating steady state intensities. The magnitudes of the ergogenic effects were 15% compared to a commercially available sports drink and 23% compared to a flavored water placebo beverage.

In general, caffeine is ergogenic for work-based performance tests, albeit to a lesser degree than for TTE (34). Concerning the question of the optimal dose, the studies that investigate the ergogenic effects of caffeine on work-based performance do not provide a conclusive dose-response relationship. A common approach (21, 24, 27, 71) has been to use a 6 mg·kg\(^{-1}\) dose, which generally appears to be effective. Above this dose, performance effects level off. Below this dose, however, it is not clear whether caffeine is of unequivocal ergogenic benefit. Bridge and Jones (18) recently found that 3 mg·kg\(^{-1}\) caffeine is ergogenic for an 8-km running time trial in a field setting, a finding that sheds some light on this problem. Cox et al. (27) found that caffeine ingested in the form of Coca Cola®️, in concentrations of 1.3 mg·kg\(^{-1}\) (study A) and 1.9 mg·kg\(^{-1}\) (study B), enhanced cycling performance on a 7 kJ·kg\(^{-1}\) laboratory time trial. Kovacs et al. (66) reported that a dose of ~2.1 mg·kg\(^{-1}\), ingested in the form of a carbohydrate-electrolyte sports (CES) drink, is ergogenic for cycling time trial of ~1 -h duration. As it is commonplace for athletes to ingest CES and cola beverages during competitive events, the findings of these two studies are certainly applicable to endurance athletes. However, the effects of caffeine alone of similar doses on exercise performance has not yet been
established. At present, the minimal dose required for ergogenicity is unknown, and is an important area for future research.

**Metabolic and Physiological Effects of Caffeine**

*Hypothesized mechanisms of action.* Many investigations of the ergogenic effects of caffeine were designed to also elucidate the underlying physiological mechanisms. Three mechanisms of action have been hypothesized: 1) caffeine promotes lipolysis that results in glycogen sparing; 2) caffeine acts directly on skeletal muscle ryanodine receptors, thereby increasing Ca\(^{2+}\) release from sarcoplasmic reticulum (SR); and 3) caffeine is a competitive inhibitor with adenosine for A1 and A2a receptors, causing a wide range of central nervous system (CNS) responses, such as increased ability to activate muscle, increased motivation to continue, and reduced sensations of effort, muscular strain, pain, and fatigue associated with exercise. In this section, the scientific literature pertinent to these three hypotheses is discussed. In addition, a brief discussion of metabolic and cardiorespiratory responses to exercise is presented.

*Substrate utilization.* That caffeine promotes lipolysis and prolongs the time course of glycogen depletion was the original hypothesized mechanism of ergogenicity. A series of three key papers (26, 39, 57) authored by Costill et al. provide experimental support for this hypothesis. The prolonged TTE (26) and increased work production (57) were observed in conjunction with increased fat oxidation. In each of these studies, caffeine elicited an increase in circulating catecholamines, which in turn increased plasma [FFA] and glycerol, suggesting catabolism of triglyceride in adipocytes into FFA for use as substrate. In addition, caffeine treatments resulted in reduced respiratory exchange ratio (RER), providing further evidence of increased fat oxidation. The authors suggested that because of the increased reliance on FFA for fuel, the rate of muscle glycogenolysis was reduced, prolonging the time to depletion of muscle glycogen. Baldwin et al. (5) had previously demonstrated that increased FFA oxidation at a given intensity was in itself a positive adaptation to endurance exercise training, and could have
positive implications for prolonged exercise in which glycogen depletion limits performance. Hence, it was concluded that because caffeine stimulated an increase in [epi], which in turn promoted FFA oxidation and prolonged the time to glycogen depletion, the ergogenic effects of caffeine were due to attenuated fatigue associated with glycogen sparing (26, 39, 57).

While there are other reports of caffeine’s associations with muscle glycogen sparing (38, 69, 94, 101) and increased circulating catecholamines (38, 104) during exercise, there are some important caveats with the glycogen sparing hypothesis. First, Spriet et al. (101) found that the decrease in the rate of glycogenolysis was only present for the first 15 min of exercise lasting 60-90 min, though the plasma [epi] was increased throughout the exercise bout. The dissociation of increased [epi] and decreased rate of glycogenolysis suggests that persistently elevated [epi] is not a cause of spared glycogen, and that the ergogenic effects may therefore be due to some other effect of caffeine.

Second, several studies have shown ergogenicity with no measurable effects on substrate utilization. Graham and Spriet (50) found caffeine to be ergogenic with no systematic change in [epi], [FFA], or RER. Indeed, several investigations (8, 9, 20, 92) have failed to reproduce the reduction in RER with caffeine ingestion as originally reported by Essig et al. (39). Finally, the numerous findings that indicate caffeine is ergogenic for short-term, high intensity exercise in which neither glycogen depletion nor fat metabolism limit athletic performance capacity (2, 23, 37, 58, 71, 109) is powerful evidence that ergogenicity is mediated by some physiological mechanism unrelated to substrate utilization. Ultimately, since numerous findings fail to support glycogen sparing as an essential mechanism for ergogenicity, there has been a general abandonment of this hypothesis in the literature (45).

Recently, a novel possible mechanism of ergogenicity linked to substrate utilization was presented by Yeo et al. (110). During a 2-h cycling bout at ~64% \( \dot{V}O_{2\text{max}} \), 5 mg·kg\(^{-1}\) caffeine was co-ingested with a carbohydrate (CHO) sports drink. They found
a significant increase in both total and exogenous CHO oxidation compared to a CHO drink with no caffeine. The authors reasoned that caffeine likely acts on glucose transporters within the gastrointestinal tract in such a way to enhance glucose uptake into the blood, thereby increasing availability of exogenous glucose for oxidation by skeletal muscle. A particularly unique finding was that in addition to exogenous CHO oxidation, total CHO oxidation increased with the caffeinated beverage, in contrast to others (27, 28, 66) that do not report increased total CHO oxidation. Cureton et al. (28) suggested that this difference may be due to the larger caffeine dose and/or lower work rate used by Yeo et al. (110) compared to other investigations of caffeinated sports drinks. Though an assessment of this novel mechanism is beyond the scope of the present study, future research should aim to 1) determine a precise physiological mechanism by which caffeine might increase exogenous and total CHO oxidation, and 2) investigate whether increased exogenous CHO oxidation due to ingestion of a caffeinated sports drink is of ergogenic benefit per se.

Ryanodine receptors and calcium. Caffeine has long been known to increase release of Ca$^{2+}$ from skeletal muscle sarcoplasmic reticulum (SR) (4, 106), which is, in turn, due to the direct action of caffeine on ryanodine receptors (93). Increased Ca$^{2+}$ release would theoretically increase the force or duration of contraction, and, as Holloszy and Narahara describe (55), increase permeability of the sarcolemma to glucose. Though these phenomena are interesting, it may not be possible to extrapolate them to exercising humans. The increased [Ca$^{2+}$] has resulted from pharmacological (i.e., millimolar) concentrations of caffeine in vitro that are toxic and possibly fatal in humans. The physiological (micromolar) in vivo concentrations have no known effects on the ryanodine receptor or SR Ca$^{2+}$ release (62, 64, 65). The prevailing thought is that the direct effect on muscle tissue is only mildly important (62, 70); accordingly, the present study does not incorporate an analysis of this possible mechanism in its design. Importantly, however, caffeine of micromolar concentrations may have some effect on
skeletal muscle, albeit through some other mechanism (70, 76, 77). With respect to endurance exercise performance, Cureton et al. (28) report that, in addition to the ergogenic effect described previously, a caffèinated sports drink reduced intrinsic muscle fatigue but did not improve the ability to recruit muscle fibers for a maximal contraction. They attribute this finding to some effect of caffeine on skeletal muscle unrelated to Ca\(^{2+}\).

**Adenosine receptor antagonism.** The inhibition of adenosine is now thought to be the primary biochemical mechanistic action of caffèine (41). As a lipid-soluble molecule, caffeine easily crosses the blood brain barrier (74). Accordingly, Davis et al. (30) suggest that their data from exercising rats are therefore important for elucidation of the cause of ergogenic effects observed in humans. These authors found that direct injection of caffeine into the CNS increased running TTE, while injection of the adenosine agonist 5’-N-ethylcarboxamidoadenosine (NECA) reduced TTE, and pretreatment of caffeine before NECA injections attenuated the fatiguing effects of NECA. In addition, intraperitoneal (i.e., peripheral) injection of these treatments had no effect on TTE, suggesting that the effects of caffeine on the periphery are not as important as CNS effects. It is likely, therefore, that CNS adenosine receptor antagonism by caffeine the primary mechanism for the drug’s ergogenicity. The precise physiological pathway that mediates ergogenicity may involve the action of adenosine on excitatory CNS neurotransmitters, particularly dopamine (DA). Adenosine is known to inhibit the release (53) and synthesis (80) of DA in the brain. When accompanied by increased levels of the neurotransmitter serotonin (5-hydroxytryptamine, or 5-HT), decreased levels of DA are associated with central fatigue in humans. Specifically, an increased ratio of 5-HT to DA (5HT/DA) during prolonged exercise is thought to bring about feelings of fatigue, discomfort, boredom, and loss of motivation to continue (29). Because adenosine levels increase with ATP breakdown (41, 67), its inhibitory actions on DA therefore likely contribute to the increase in 5-HT/DA commonly observed during exercise. Hence, inhibition of adenosine receptors by caffeine may somewhat attenuate the increase in 5-
HT/DA, thereby reducing sensations of effort, fatigue, and discomfort associated with prolonged exertion. This mechanism may be related to the large ergogenic effect of caffeine on TTE protocols compared to work-based protocols, because, as described previously, performance on TTE is mainly limited by CNS factors (i.e., boredom) rather than by peripheral factors (i.e., muscular inability to maintain work rate).

In addition to this putative effect on central fatigue, an increase in dopamine activity could account for increased feelings of energy, motivation, and awareness (41). In particular, in regions of the brain with high A2a receptor density, dopaminergic neurons may be indirectly stimulated by caffeine due to A2a receptor antagonism. Barraco et al. (6) have shown that mesolimbic neurons of the nucleus accumbens may be the primary controlling sites for the locomotor depressant effects of adenosine. Specifically, they demonstrated that injection of a selective A2a agonist into the nucleus accumbens suppressed dopaminergic neurons and reduced locomotor activity in rats, while an A1 agonist had no effect. Adenosine binding to A2a receptors in the nucleus accumbens is of particular importance as this brain center is richly innervated with dopaminergic neurons, and is a major player in DA-mediated brain reward processes (6, 44). As described previously, a major physiological function of adenosine is DA inhibition. Accordingly, Graham (44) has suggested that caffeine antagonism of A2a receptors in the nucleus accumbens could indirectly result in increased dopaminergic neuronal activity. Increased DA levels would therefore promote binding of dopamine receptors in brain reward centers such as the nucleus accumbens, as well as in the ventral tegmentum and reticular formation. These areas contain neurons that project to the frontal cortex and limbic system, and are also thought to be key mediators for increased arousal, alertness, motivation, and other associated behavioral effects of caffeine (44). It is important to note that the implications of these central effects for exercise performance are difficult to determine and manipulate in an experimental setting so as to isolate causality, particularly in humans. Nevertheless, it is now widely agreed that the
stimulatory effects of caffeine on the CNS are a primary mechanism by which caffeine enhances exercise performance (33, 44, 45, 49, 63, 72, 100).

In addition to CNS effects, and despite the data of Davis et al. (30) that suggest CNS effects may be the sole mechanism, adenosine receptor antagonism by caffeine may play a role in the peripheral nervous system. It is well known that adenosine has pronociceptive effects via binding of A2 receptors in sensory nerve terminals (98), and, as discussed below, caffeine has been consistently shown to have hypoalgesic effects during prolonged endurance exercise (78, 84). In addition, Graham (44) has presented a theoretical mechanism by which adenosine may act on the neuromuscular junction. ATP is released concurrently with acetylcholine at the neuromuscular junction. Degradation of this ATP produces adenosine, which then binds A1 receptors on the presynaptic membrane, inhibiting further acetylcholine release in a classic negative feedback loop. It is possible that caffeine inhibits this feedback by binding to the A1 receptors, causing increased levels of acetylcholine in the synaptic cleft, thereby enhancing motor unit activation.

Despite widespread dismissal of the substrate utilization and calcium kinetics hypotheses, and though the adenosine receptor antagonism hypothesis is generally accepted, there are several findings that are difficult to explain if caffeine indeed has no direct effect on skeletal muscle. Data that suggest reduced intrinsic muscle fatigue following prolonged cycling (28), as discussed above, provide one such example. The findings of Lopes et al. (70) indicate that caffeine can potentiate force development at a given submaximal electrical stimulation frequency both before and after fatigue. Similarly, two investigations (77, 105) have used spinal cord injured (SCI) patients as a physiological model in which peripheral effects of caffeine can be observed in exercising humans. Both investigations indicated that caffeine elicited effects on peripheral tissues. Mohr et al. (77) found that fictive cycling performance was enhanced following caffeine ingestion by SCI individuals. Clearly, this was independent of any CNS effects, since
upper spinal cord lesions necessarily prevent any outflow from or feedback to the CNS. In addition, the fictive cycling protocol involved rhythmic, alternating electrical stimulation directly applied to the quadriceps, hamstrings, and gluteus muscle groups, and hence bypassed any neural input to the exercise. The finding of enhanced involuntary exercise performance supports the hypothesis that there is some direct effect of caffeine on skeletal muscle.

Cardiorespiratory and metabolic responses to exercise. The effects of caffeine on the cardiorespiratory aspects of exercise have been widely investigated. As discussed briefly in the previous chapter, the findings have been largely equivocal, but some findings indicate that caffeine may influence some gas exchange parameters. In addition, a nearly universal finding is that of increased [La] following caffeine ingestion. This section briefly explores these findings, with particular regard to the implications for effects of caffeine on metabolic variables on exercise performance.

There appears to be no systematic effect of caffeine on $\dot{V}O_{2\text{max}}$ (13, 32, 43, 45), though it has been shown that athletes can better tolerate a given submaximal %$\dot{V}O_{2\text{max}}$, as reflected by either TTE or work-based performance tests. This phenomenon does not appear to be related to effects of caffeine on oxygen uptake kinetics (7, 89) nor to alterations in the lactate threshold (43). Rather, it is thought that subjects are simply able to better tolerate the exercise demands and thereby improve performance primarily via the action of caffeine on adenosine receptors, as discussed above. Interestingly, however, one study (95) has shown that caffeine can attenuate the slow component rise in $\dot{V}O_{2}$ during exercise at a constant running velocity corresponding to 90% $\dot{V}O_{2\text{max}}$. The slow component rise in $\dot{V}O_{2}$, characterized by an increased rate of oxygen uptake at constant submaximal exercise intensity (108), has been associated with increased recruitment of fatigable fast-twitch motor units (97). Santalla et al. (95) suggest that perhaps the findings of ergogenicity by so many authors are due, at least in part, to improved metabolic efficiency as reflected by an attenuated $\dot{V}O_{2}$ slow component rise.
Surprisingly, this hypothesis largely been ignored in the literature since the study by Santalla et al. (95) was published in 2001. It is possible that the attenuated slow component rise is related to the putative actions of caffeine on the neuromuscular junction (44); i.e., if caffeine enhances synaptic acetylcholine release, this may delay motor unit fatigue, and therefore postpone the recruitment of additional motor units.

While several studies report no effect of caffeine on $V_{E}$ during exercise (27, 94, 101), there is evidence to suggest that caffeine could slow $V_{E}$ kinetics at the onset of exercise (7, 90). Birnbaum and Herbst (15) likewise suggest that caffeine enhances respiratory efficiency during exercise in cross-country runners. Brown et al. (19) have shown, with a relatively low caffeine dose of 3.3 mg·kg$^{-1}$, that respiratory efficiency is improved by decreasing the ratio of alveolar dead space to tidal volume, allowing for greater perfusion of alveolar capillaries. Though the mechanism underlying the effects of caffeine on respiratory dynamics remains unclear, the results suggest that caffeine may improve respiratory efficiency, which could contribute to the drug’s ergogenicity.

There are many reports of increased [La] at a given exercise stimulus following caffeine ingestion (22, 50, 52, 94, 101). Lactate is a metabolite associated with hydrogen ion accumulation thought to cause fatigue under some conditions. Thus, increased [La] is a somewhat paradoxical effect of a drug that is generally considered to be efficacious for performance. Despite the near universality of this finding, this phenomenon is rarely discussed with regards to caffeine’s metabolic actions (46). In an interesting exception, Graham et al. (47) addressed this problem in 2000. They found that while arterial [La] was increased, there was no effect on muscle lactate levels following caffeine ingestion. They speculated that this was possibly due impaired lactate clearance from the blood by the liver. Given that many studies reporting ergogenic effects of caffeine also report increased [La], it is clear that increased [La] is not detrimental to the physical work capacity of exercising humans.
Perceptual Effects of Caffeine

*Effects of caffeine on perception of effort.* Nearly all studies investigating the effect of caffeine on prolonged exercise report a reduction in perception of effort. Some investigations have found increased work output at a given RPE (21, 57, 89); more commonly, others have reported reduced RPE at a given exercise intensity (20, 26, 36, 37). A recent meta-analysis by Doherty and Smith (35) examined the effect of caffeine on perceived exertion across 21 studies from which 109 effect sizes were calculated. The authors report a mean effect size of -0.47 SD across these studies, and conclude that caffeine has a quantifiable impact on RPE that is significantly different from zero. A dose of ~6 mg·kg$^{-1}$ appears to be consistently effective, though, as with caffeine’s effect on performance, this is also the most frequently used dose. The efficacy of lower doses remains uncertain. A regression analysis revealed that reduction in RPE during exercise accounted for nearly one third of the variance of improvement in performance following caffeine ingestion ($r^2 = .29$). It is therefore of interest to measure RPE in studies that investigate the ergogenic effects of caffeine, as the change in RPE is at least moderately related to the change in performance.

Differentiated ratings of perceived exertion. Perceived exertion is a complicated phenomenon, involving multiple sensory inputs from the body (82). During aerobic activities such as cycling or running, effort sensations result from both peripheral and central afferent pathways (91). The central (i.e., CNS) component involves mental aspects of exercise, including motivation, drive, and aversion to the task. In addition, discomfort and strain associated with breathing ($\dot{V}_E$) and relative metabolic demand (i.e., %$\dot{V}O_2$max) are very important in regulating the subjective intensity of the exercise task. The peripheral component of perceived exertion involves local discomforts associated with working muscle fatigue, pain, and strain in the joints of the moving limbs.

Pandolf (85, 87) has described a model of perceived exertion, termed differentiated ratings of perceived exertion (D-RPE), that isolates the CNS, breathing,
and peripheral aspects of RPE. Subjects are asked to rate the sensations of each component individually: overall RPE (RPE-O), reflecting the overall level of effort the subject feels he or she is putting into the exercise task; breathing effort, or “chest” RPE (RPE-C), reflecting the subject’s feelings of dyspnea, breathlessness, and breathing rate and depth; working muscle, or “leg” RPE (RPE-L), representing feelings of muscular force, strain, pain, and joint discomfort in the legs. While it has not been widely used in investigations of the perceptual effects of caffeine, use of the Pandolf D-RPE model would provide insight as to which component(s) are most influenced by caffeine, which could, in turn, provide new evidence as to what may be the important underlying mechanisms of action. Brief discussions of each component of this model are presented below, with particular reference to the possible consequences of caffeine ingestion on the various aspects of perceived exertion.

Most studies reporting that caffeine reduces steady-state RPE and enhances work-based performance indicate that caffeine does not necessarily influence motivation or reduce aversion to the task. For example, Cureton et al. (28) found that RPE was reduced at constant submaximal intensities, with the difference in RPE between caffeinated and non-caffeinated sports drinks increasing as exercise duration progressed. This difference in RPE was eliminated during the ensuing performance ride such that RPE increased to the maximal tolerable level (Borg 6-20 category scale rating ≈19 at end of performance ride for all beverages). The authors suggest that a lower RPE just prior to the performance ride may have provided a greater reserve for increasing power output to the maximal tolerable level, but the sensation of “maximal effort” did not differ between treatments. The finding that caffeine increased work performance at a given level of RPE is in agreement with previous research (21, 57). However, as discussed previously, the profound ergogenic effects on TTE protocol are strong evidence in favor of a CNS effect of caffeine. Caffeine may indirectly enhance DA activity, resulting in increased drive and motivation to continue in spite of discomfort. Nearly all of the investigations to date
have used the Borg 6-20 RPE scale (17). Because of its all-inclusive nature, the use of
the Borg 6-20 category scale does not permit an isolated analysis of subjects’ motivation
or central drive, and hence the findings of reduced RPE and coincident TTE cannot be
conclusively attributed to CNS effects based on RPE data alone. Despite a large
literature indicating that CNS effects of caffeine are important, the effect of caffeine on
CNS component of perceived exertion has not been widely examined.

As discussed above, caffeine may enhance the efficiency of the respiratory system
(15, 19). In addition, Supinski et al. (102) found that caffeine reduced breathing effort
sensation and respiratory muscle endurance during loaded breathing. It is interesting that
in a regression analysis, Noble et al. (81) found that depth and rate of breathing, key
sensory cues to which subjects are attentive during exercise (82), account for the greatest
portion of the variance in RPE. Thus, it is possible that the effects of caffeine on RPE
and exercise performance may be in part due to the effects on $\dot{V}_E$ and breathing
sensations, yet this hypothesis has received little attention in the literature.

Caffeine’s actions on the CNS are probably responsible for reduced sensations of
strain, fatigue, and muscular effort during exercise. Adenosine receptor antagonism
inhibits afferent feedback from the periphery (41), which is likely the chief mechanism
responsible for increased work production at a given RPE. In addition, the hypothesis
that caffeine may enhance acetylcholine activity at the neuromuscular junction (44) may
account for some effect peripheral sensations during exercise. Therefore, it is also
possible that the effects of caffeine on undifferentiated RPE may be partly accounted for
by the drug’s effects on the peripheral component of RPE.

*Effects of caffeine on perception of working muscle pain.* While related to
perceived exertion, working muscle pain should be considered as a separate entity. The
valid measurement of naturally occurring leg muscle pain during cycling exercise has
been described by Cook et al. (25). Recent studies by Motl et al. (78, 79) and O’Connor
et al. (84) have investigated the effects of caffeine ingestion on working muscle pain
during prolonged endurance exercise. These experiments involved recreationally active participants with moderate levels of fitness who performed 30 minutes of cycling at 60% \( \dot{V}O_{2\text{max}} \). The main finding of the first experiment was that a large dose (10 mg·kg\(^{-1}\)) of caffeine yielded significantly lower ratings of muscle pain in the quadriceps muscles during cycling (.47 SD). In the second study (84), the authors found a dose-dependent relationship between caffeine consumption and hypoalgesic effects. A large dose (10 mg·kg\(^{-1}\)) of caffeine had a large hypoalgesic effect (d = .90), while a moderate dose (5 mg·kg\(^{-1}\)) had a moderate hypoalgesic effect (d = .56), compared to placebo. Recently, Motl et al. (79) duplicated this study using all female subjects. They found large magnitudes of hypoalgesia for both 5 mg·kg\(^{-1}\) (1.23 SD) and 10 mg·kg\(^{-1}\) (.78 SD). There was no apparent dose-dependence of the effect since 5 mg·kg\(^{-1}\) resulted in such a large degree of hypoalgesia; nevertheless, the authors demonstrated that caffeine is hypoalgesic for both men and women. They speculate that the hypoalgesia is related to the ergogenicity of caffeine, and indeed their findings are likely relevant for competitive endurance athletes. There are, however, no studies that have measured endurance performance and muscle pain. Consequently, the authors call for investigations of the interactive effects of caffeine on working muscle pain and athletic performance.
CHAPTER 3

LOW DOSES OF CAFFEINE: NO EFFECT ON PERCEPTUAL RESPONSES TO EXCERCISE AND CYCLING PERFORMANCE¹.

¹ Jenkins NT, Trilk JL, Singhal AS, O’Connor PJ, Cureton KJ. To be submitted to the International Journal of Sports Nutrition and Exercise Metabolism.
Abstract

The purpose of this experiment was to learn whether low doses of caffeine have ergogenic, perceptual, and metabolic effects during cycling exercise. To determine the effects of 1, 2, and 3 mg·kg⁻¹ caffeine on cycling performance, differentiated ratings of perceived exertion (D-RPE), quadriceps pain intensity, and metabolic responses to cycling exercise, 13 trained athletes cycled on a stationary ergometer for 15 min at 80% \( \dot{V}O_{2\text{peak}} \), then completed a 15-min performance ride 60 min after ingesting caffeine or placebo. Accumulated energy (kJ·kg⁻¹) during the performance ride was used as a measure of performance. D-RPE, pain ratings, and expired gas data were obtained every 3 min, and blood lactate concentrations were obtained at 15 and 30 min. Caffeine yielded no ergogenic effects, nor were there any effects on D-RPE or pain. Selected metabolic variables were affected by low doses of caffeine, but these are likely of little consequence for performance or perceptual outcomes. It is concluded that low doses of caffeine have no effect on cycling performance or perceptual responses to exercise. Athletes seeking benefit in competitive settings should ingest larger doses for which advantageous ergogenic and perceptual effects have been established.

**KEY WORDS:** ERGOGENIC AID, PERCEIVED EXERTION, PAIN, CYCLE ERGOMETRY


Introduction

Caffeine is known to enhance prolonged exercise performance (37). More specifically, caffeine doses of 3 to 13 mg·kg\(^{-1}\) caffeine improve exercise performance by 0.41 standard deviations (14). Doses of less than 3 mg·kg\(^{-1}\) have received little attention, but some studies suggest that low doses of caffeine are effective for performance enhancement. Caffeine doses of 1.3 mg·kg\(^{-1}\) and 1.9 mg·kg\(^{-1}\), ingested in the form of a carbonated soft drink, reduced the time to complete laboratory time trial lasting ~30 min by ~3% (12). Also, a dose of ~2.1 mg·kg\(^{-1}\), ingested in the form of a carbohydrate-electrolyte sports drink, is ergogenic for cycling time trial of ~1 hr duration (26). There are, however, no investigations of the dose-response in the ergogenic and perceptual effects of low doses of caffeine alone.

Reduced perception of effort is commonly experienced during submaximal exercise following caffeine ingestion. A meta-analysis found that caffeine ingestion results in average reduced ratings of perceived exertion (RPE) by a magnitude of 0.47 SD compared to placebo, and that 29% of the variance in the ergogenicity of caffeine was explained by the variance of changes in RPE (15). There is evidence that the underlying physiological mechanism for reduced RPE has to do with the drug’s antagonism of adenosine receptors (13, 17), which also appears to account for hypoalgesia of naturally-occurring muscle pain during dynamic exercise (27, 29). To date, however, the implications of reductions in RPE and muscle pain during exercise for enhanced performance remain largely unstudied (15). Furthermore, whether low doses of caffeine affect perceptual responses to exercise, and subsequently enhance exercise performance, remains unknown.

The effect of caffeine on RPE has been assessed primarily by the use of undifferentiated ratings (6). A model of differentiated ratings of perceived exertion (D-RPE) has been described that incorporates three components of effort sense (30, 31). Central nervous system (CNS) factors, such as motivation, drive, and task aversion...
determine the overall perception of effort (RPE-O). Local factors, such as strain, force sensation, and fatigue in the working muscles determine the perception of effort in the legs (RPE-L). Cardiorespiratory factors, such as increased heart rate and depth and rate of breathing determine “chest” perceived exertion (RPE-C). The effects of caffeine on these three components of perceived exertion are not yet known. Since ratings of effort sensations are determined by various physiological responses to exercise, D-RPE could provide insight into possible mechanisms by which caffeine produces ergogenic effects. In addition, there is evidence that caffeine in 5 and 10 mg·kg\(^{-1}\) reduces sensations of naturally-occurring leg muscle pain during dynamic exercise (27-29). The hypoalgesic effects were large and occurred in a dose-dependent fashion for young men (29). The authors reasoned that hypoalgesia may partially explain some of the drug’s ergogenicity; hence, they encouraged future researchers to incorporate examinations of both hypoalgesic and ergogenic properties of caffeine. Furthermore, they noted that the dose-responsiveness of 5 and 10 mg·kg\(^{-1}\) in men (29) may or may not be realizable with lower doses.

The primary purposes of this experiment were to determine if low doses of caffeine 1) enhance cycling performance, and 2) alter D-RPE and quadriceps pain ratings in conjunction with improvements in performance. It was hypothesized that low doses of caffeine enhance performance and reduce D-RPE and pain during exercise. A secondary purpose was to collect metabolic data that might provide insight into underlying mechanism(s) of ergogenic and/or perceptual effects.

**Methods**

*Participants.* Twenty-one male cyclists were recruited by word-of-mouth, flyers, and email lists of local cycling teams and clubs. Of these, 8 either did not meet inclusion criteria (n = 2), or withdrew prior to starting the experimental trials for personal reasons (n = 6). The final sample size n = 13 was determined *a priori* to be adequate to detect moderate ergogenic and perceptual effects of .4 SD, assuming a mean test-retest
correlation of 0.9 for preloaded work-based protocols (24), with statistical power of 0.8 at a 0.05 $\alpha$ level of significance (34).

Participants completed physical activity and dietary caffeine questionnaires to assess training volume and caffeine consumption. Participants cycled a mean ± SEM of 207 ± 31.5 km·wk$^{-1}$ and were habitual consumers of caffeine (132 ± 41 mg caffeine·d$^{-1}$). None of the participants indicated any history of medical conditions that would predispose them to injuries or risks of negative side effects associated with strenuous exercise or caffeine ingestion, as assessed by medical history and caffeine sensitivity questionnaires (29). Selected characteristics of the 13 cyclists are presented in Table 1. The University of Georgia Institutional Review Board approved the experimental procedures of this experiment, and all participants provided written informed consent.

**Preliminary Procedures**

*Baseline measures.* Participants completed 24-hr history questionnaires to assess adherence to pretest instructions, and 7-day caffeine recall questionnaires to assess habitual caffeine ingestion (3). Height and weight were measured, and seven skinfold thicknesses were assessed to estimate body density (23), from which body fatness was estimated using the Siri equation (36). Participants gave a urine sample to ensure adequate hydration, and tympanic temperature was measured. Urine specific gravity was measured by a refractometer (Atago Co., Ltd., Bellevue, WA, model URC-PN) was used as a maker of hydration status (2). Testing was rescheduled if participants had a fever (tympanic temp $\geq$ 37.1°C) or if urine specific gravity was $\geq$ 1.021 (2). Upon completion of questionnaires and preliminary measurements, participants performed a 10-min warm up at a low intensity [100-125 Watts (W)], followed by a graded exercise test (GXT) to exhaustion on an electrically-braked cycle ergometer to determine peak oxygen uptake ($\dot{V}O_{2\text{peak}}$) (Lode Excalibur Sport 2000, Lode B.V., Groningen, The Netherlands). The GXT began at a power output of 200 W, increasing 25 W every 2 min until participants reached volitional exhaustion. $\dot{V}O_2$, carbon dioxide production ($\dot{V}CO_2$), pulmonary
ventilation ($\dot{V}E$), and respiratory exchange ratio (RER) were determined by indirect calorimetry using a Parvo Medics TrueOne 2400 Metabolic Measurement System (Parvo Medics, Inc., Salt Lake City, UT). Heart rate (HR) was monitored continuously using a Polar® Vantage XL heart rate monitor (Polar Electro, Inc., Woodbury, NY, model 145900). Undifferentiated RPE was obtained at the end of every stage using the 10-point Borg category scale with ratio properties (5). Three min following the $\dot{V}O_2$peak test, a capillary blood sample was obtained for determination of peak $[La]$ (Lactate Pro™ Blood Lactate Test Meter; Arkray, Inc.; Kyoto, Japan). All 13 cyclists met at least two of the following criteria of maximal effort: increase in $\dot{V}O_2$ (l·min$^{-1}$) between the last two stages of less than half of the expected increase (0.135 l·min$^{-1}$), RER $\geq$ 1.10, $[La] \geq$ 7.0 mmol·l$^{-1}$, or RPE $\geq$ 9 on the Borg CR-10 scale.

**D-RPE and leg muscle pain rating instruction.** During recovery from the GXT, participants were given detailed instructions as to how the D-RPE and leg muscle pain scales were to be used in the experimental trials. The instructions for the pain scale were as described previously (10). D-RPE instructions were developed from the Pandolf model (31) and are presented in the Appendix. D-RPE was obtained using the 10-point Borg category scale with ratio properties (5). This scale was used because of its similarity to the quadriceps pain intensity scale (10). To ensure that participants understood the procedure, they were then asked to explain the D-RPE and pain scales and instructions in their own words back to the investigators. We were especially careful to ensure that participants understood the differences between RPE-L and sensations of quadriceps pain [i.e., that RPE-L involves sensations of muscular strain, force, and perceptions from all working muscles of the legs, while pain ratings are solely asking for the degree of hurt felt in the quadriceps (10, 31)].

**Protocol familiarization.** Following this instruction, participants performed a practice ride to familiarize themselves with the exercise tasks of the remaining trials and to verify the cycling intensity prescription of 80%$\dot{V}O_2$peak. In addition, they were asked to
periodically give D-RPE and pain ratings, so as to become familiar with the assessment of their perceptual responses to the exercise. For 15 min, they cycled at the work rate estimated to elicit 80% \( \dot{VO}_2\text{peak} \), which was calculated using the American College of Sports Medicine metabolic equation for gross \( \dot{VO}_2 \) during cycle ergometry (1):

\[
\dot{VO}_2 = (10.8 \times W \times M^{-1}) + 7,
\]

where \( \dot{VO}_2 \) is gross O\(_2\) consumption (ml·kg·min\(^{-1}\)), \( W \) is power output in Watts, and \( M \) is body mass in kg. After 4 min active recovery (unloaded cycling), participants performed a 15-min cycling protocol during which they were instructed to maintain the highest possible intensity. For this ride, the ergometer was set to the linear mode, whereby the work rate increased linearly as a function of pedaling cadence. They were instructed to maintain as high a cadence, (i.e., perform as much work) as possible.

**Experimental Procedures**

*Research design and protocol.* A double-blind, placebo-controlled, repeated-measures experimental design was employed in which all participants were tested under all treatment conditions. As described above, participants refrained from strenuous exercise for the 24 h and from caffeine for 48 h prior to testing, and completed 24-h history and 7-d caffeine recall forms to assess compliance with pretest instructions. Urine specific gravity was measured to ensure euhydration. Tympanic temperature was measured to ensure the absence of a fever. With 450 mL water, participants ingested a pill containing a placebo (white flour), or one of three treatments: 1 mg·kg\(^{-1}\), 2 mg·kg\(^{-1}\), 3 mg·kg\(^{-1}\) caffeine. Following treatment ingestion, participants sat quietly for 60 min to allow for peak blood concentrations of caffeine (25).

After the 60 min quiet rest, participants performed a cycling protocol identical to the familiarization session. The first portion of the pre-loaded exercise test was 15 min of cycling at a work rate estimated to elicit 80% \( \dot{VO}_2\text{peak} \). During the ride, \( \dot{VO}_2 \), \( \dot{VE} \), and RER were measured via open circuit spirometry as described above. The slow component rise in \( \dot{VO}_2 \) was calculated as the difference in \( \dot{VO}_2 \) (l·min\(^{-1}\)) between min 15
(end of exercise) and min 3 (approximate end of fast component rise in \( \dot{V}O_2 \)). At 3 min intervals (min 3, 6, 9, 12, and 15), participants were asked for the D-RPE ratings (RPE-L, RPE-C, RPE-O) and intensity of quadriceps pain. Following the 15 min of exercise, a blood sample was obtained via fingerstick and was analyzed for [La].

After 4 min active recovery (unloaded cycling), participants were instructed to ride as hard as possible for 15 min, to simulate an extended all-out effort at the end of a race. This procedure was identical to the one practiced on the preliminary visit. This method of assessing performance in prolonged exercise is preferred over time-to-exhaustion protocols because of the ecological validity associated with work-based performance tests (24); that is, a protocol where cyclists perform the greatest amount of work possible closely replicates competitive situations. Work production on this ride was expressed relative to participants’ body weight (kJ·kg\(^{-1}\)), which was used as a measure of cycling performance. The physiological and perceptual measures for the performance test portion of the ride are identical to the methods described above for exercise at the constant work rate. Metabolic measures were obtained throughout the 15-min performance ride, and a fingerstick was performed to determine [La].

*Success with blinding of treatment.* Upon completion of all experimental trials, participants were asked to guess the order in which they received the treatments. The following measures were determined upon completion of all data collection: 1) the number of participants who correctly named the placebo trial, 2) the number of participants who attributed the greatest dose of caffeine with the trial in which they produced the most work, and 3) the number of participants who correctly guessed the sequence of treatments.

*Statistical Analysis.* A univariate, one-way repeated measures analysis of variance (ANOVA) was used to test the significance of mean differences among treatments in work production (kJ·kg\(^{-1}\)) performed during the performance ride. Physiological (%\( \dot{V}O_2\)peak, \( \dot{V}E \), RER, and HR) and perceptual (RPE-L, RPE-C, RPE-O, and
ratings of pain intensity) outcomes were analyzed using a $4 \times 5$ (Treatment $\times$ Time) ANOVA with repeated measures on both factors. [La] obtained following exercise was analyzed using a one-way ANOVA with repeated measures. The constant load and performance ride portions of the exercise were analyzed separately for all variables. The Greenhouse-Geisser adjustment to degrees of freedom was utilized for all repeated-measures ANOVA tests. If the omnibus test revealed a significant $F$ ratio, paired sample $t$-tests were used to test individual differences between treatments and time points. The Hochberg (21) $\alpha$ adjustment for multiple comparisons was applied for all post hoc comparisons to protect the overall $\alpha$ level of 0.05. Effect sizes are presented as partial eta-squared ($\eta^2_p$) for overall $F$-ratios and as Cohen’s $d$ for individual mean differences (9). All analyses were performed using SPSS v. 13.0 for Windows (SPSS, Inc., Chicago, IL).

**Results**

*Effects of caffeine on cycling performance.* The performance data are presented in Figure 1. Performance values (mean ± SEM) relative to body mass were 2.96 ± 0.16, 2.94 ± 0.12, 3.08 ± 0.16, 3.05 ± 0.17 kJ·kg$^{-1}$ for placebo, 1 mg·kg$^{-1}$, 2 mg·kg$^{-1}$, and 3 mg·kg$^{-1}$ caffeine, respectively. The omnibus one-way repeated measures ANOVA revealed a significant main effect ($F_{3,36} = 3.65, p = 0.031, \eta^2_p = 0.233$). Analysis of the magnitude of mean differences indicated that 2 mg·kg$^{-1}$ resulted in 4.4% (d = 0.26) and 4.3% (d = 0.20) increases in performance compared to 1 mg·kg$^{-1}$ and placebo. Additionally, there was a small (2.9%) mean increase in performance with 3 mg·kg$^{-1}$ compared to placebo (d = 0.14). There was no effect of 1 mg·kg$^{-1}$ on performance compared to placebo (d = -0.01). The post hoc analysis revealed no significant mean differences in performance among treatments when the familywise error rate was controlled with the Hochberg $\alpha$ level adjustment. The inter-individual range for performance change with caffeine compared to placebo was -7.9% (1 mg·kg$^{-1}$) to 17.8% (2 mg·kg$^{-1}$).
Effects of caffeine on perceptual responses to exercise. Perceptual responses to exercise are summarized in Figure 2 (D-RPE) and Figure 3 (pain). During cycling at 80% \( \dot{V}O_2^{\text{peak}} \), there was no Treatment \( \times \) Time interaction effect on RPE-C (\( F_{12, 144} = 0.505, p = 0.754, \eta^2_p = 0.04 \)), RPE-L (\( F_{12, 144} = 1.123, p = 0.358, \eta^2_p = 0.086 \)), RPE-O (\( F_{12, 144} = 1.506, p = 0.209, \eta^2_p = 0.111 \)), or quadriceps pain intensity ratings (\( F_{12, 144} = 1.683, p = 0.156, \eta^2_p = 0.123 \)). Analysis of marginal means revealed no Treatment main effect on RPE-C (\( F_{3, 36} = 0.375, p = 0.729, \eta^2_p = 0.030 \)), RPE-L (\( F_{3, 36} = 1.981, p = 0.149, \eta^2_p = 0.142 \)), RPE-O (\( F_{3, 36} = 0.912, p = 0.419, \eta^2_p = 0.071 \)), or quadriceps pain intensity ratings (\( F_{3, 36} = 1.939, p = 0.159, \eta^2_p = 0.139 \)). There was a significant Time effect for all variables (\( p < 0.05 \)).

During the performance ride, there was no Treatment \( \times \) Time interaction effect on RPE-C (\( F_{12, 144} = 0.727, p = 0.723, \eta^2_p = 0.057 \)), RPE-L (\( F_{12, 144} = 0.623, p = 0.820, \eta^2_p = 0.049 \)), RPE-O (\( F_{12, 144} = 0.873, p = 0.455, \eta^2_p = 0.068 \)), or quadriceps pain intensity ratings (\( F_{12, 144} = 0.612, p = 0.647, \eta^2_p = 0.049 \)). Analysis of marginal means revealed no Treatment effect for RPE-C (\( F_{3, 36} = 1.133, p = 0.346, \eta^2_p = 0.086 \)), RPE-L (\( F_{3, 36} = 1.522, p = 0.237, \eta^2_p = 0.013 \)), RPE-O (\( F_{3, 36} = 0.813, p = 0.474, \eta^2_p = 0.063 \)), or quadriceps pain intensity ratings (\( F_{3, 36} = 1.441, p = 0.253, \eta^2_p = 0.107 \)) on the omnibus two-way repeated measures ANOVA. There was a significant Time effect for all variables (\( p < 0.05 \)), but no Treatment \( \times \) Time interaction (\( p > 0.05 \)).

Effects of caffeine on cardiorespiratory and metabolic responses to exercise. The physiological responses to cycling at 80% \( \dot{V}O_2^{\text{peak}} \) are presented in Table 2. The two-way repeated measures ANOVA revealed no significant Treatment \( \times \) Time interaction effect on %\( \dot{V}O_2^{\text{peak}} \) (\( F_{12, 144} = 1.080, p = 0.378, \eta^2_p = 0.083 \)), \( \dot{V}_E \) (\( F_{12, 144} = 0.764, p = 0.686, \eta^2_p = 0.06 \)), RER (\( F_{12, 144} = 0.698, p = 0.751, \eta^2_p = 0.055 \)), or HR (\( F_{12, 144} = 0.197, p = 0.743, \eta^2_p = 0.016 \)). Analysis of marginal means revealed no Treatment effect on %\( \dot{V}O_2^{\text{peak}} \) (\( F_{3, 36} = 1.083, p = 0.356, \eta^2_p = 0.083 \)), \( \dot{V}_E \) (\( F_{3, 36} = 2.844, p = 0.072, \eta^2_p = 0.192 \)), RER (\( F_{3, 36} = 2.170, p = 0.125, \eta^2_p = 0.153 \)), or HR (\( F_{3, 36} = 0.477, p = 0.594, \eta^2_p = 0.038 \)). For each of
these variables, there was significant Time effect (all $p > 0.05$). There was no main effect of caffeine on the slow component rise in $\dot{V}O_2$ during the constant-rate exercise ($F_{3, 36} = 1.102, p = 0.359, \eta^2_p = 0.084$). The one-way repeated measures ANOVA revealed a significant treatment effect on [La] ($F_{3, 36} = 3.844, p = 0.038, \eta^2_p = 0.243$), though post hoc comparisons with the Hochberg adjustment to the overall $\alpha$ level revealed no significant mean differences in [La] among treatments (all $p > 0.05$).

The metabolic responses to the performance ride are presented in Table 3. The omnibus two-way repeated measures ANOVA revealed no Treatment $\times$ Time interaction effect on $\% \dot{V}O_{2peak}$ ($F_{12, 144} = 1.394, p = 0.246, \eta^2_p = 0.104$), $\dot{V}E$ ($F_{12, 144} = 1.326, p = 0.278, \eta^2_p = 0.099$), RER ($F_{12, 144} = 1.987, p = 0.097, \eta^2_p = 0.142$), or HR ($F_{12, 144} = 1.464, p = 0.226, \eta^2_p = 0.109$). Analysis of marginal means revealed a significant Treatment effect on $\%\dot{V}O_{2peak}$ ($F_{3, 36} = 6.718, p = 0.002, \eta^2_p = 0.359$). Hochberg comparisons indicated that $\%\dot{V}O_{2peak}$ was elevated at 9 min with 2 mg·kg$^{-1}$ caffeine compared to 1 mg·kg$^{-1}$ by 4.9 ± 1.4% (95% CI: 1.8% to 8.0%; $p = 0.005, d = 0.91$) and placebo by 5.2 ± 1.2% (95% CI: 2.6% to 7.8%; $p = 0.001, d = 0.71$). $\%\dot{V}O_{2peak}$ remained elevated at 12 min and 15 min for 2 mg·kg$^{-1}$ compared to placebo, by 5.1 ± 1.6% (95% CI: 1.6 to 8.6%; $p = 0.008, d = 0.81$) and 7.3 ± 2.2% (95% CI: 2.5 to 12.2%; $p = 0.005, d = 0.93$), respectively. The omnibus test also indicated a significant overall Treatment effect on $\dot{V}E$ ($F_{3, 36} = 6.55, p = 0.004, \eta^2_p = 0.353$). Post hoc comparisons with the Hochberg adjustment indicated that at 9 min, $\dot{V}E$ was elevated by 8.3 ± 2.0 l·min$^{-1}$ (95% CI: 3.9 to 12.7 l·min$^{-1}$; $p = 0.001, d = 0.52$) for 2 mg·kg$^{-1}$ compared to 1 mg·kg$^{-1}$. The omnibus tests of Treatment main effects for RER ($F_{3, 36} = 1.923, p = 0.156, \eta^2_p = 0.143$) and HR ($F_{3, 36} = 2.944, p = 0.058, \eta^2_p = 0.109$) were not significant. There was a significant Time effect for each of these variables ($p < 0.05$). [La] was significantly increased with caffeine ($F_{3, 36} = 4.336, p = 0.020, \eta^2_p = 0.265$), with the follow-up Hochberg comparisons indicating a significant increase for 3 mg·kg$^{-1}$ compared to placebo by 2.5 ± 0.5 mmol·l$^{-1}$ (95% CI: 1.3 to 3.6 mmol·l$^{-1}$; $p < 0.001, d = 0.90$).
Success with blinding of treatment. Five of the 13 participants correctly identified the placebo trial, 8 attributed their best performance to the 3 mg·kg\(^{-1}\) dose (2 of whom were correct), and no participants correctly guessed the sequence of treatments.

Discussion

The present study provides the first experimental investigation of the ergogenic, perceptual, and metabolic effects of low doses of caffeine (1, 2, and 3 mg·kg\(^{-1}\) body weight). Caffeine had little effect on cycling performance, perceptual responses, and metabolic variables. These findings are important for athletes seeking to maximize performance gains from caffeine ingestion prior to a prolonged bout of training or a competitive event. Our findings are also relevant for future researchers who attempt to address many remaining important research questions concerning the physiological, perceptual, and ergogenic effects of caffeine.

With regard to the primary outcome variable, cycling performance, the main finding is that although 2 and 3 mg·kg\(^{-1}\) elicited average ergogenic effects of 4.3% (d = 0.20) and 2.9% (d = 0.14) compared to placebo, respectively, the individual changes were highly variable (see Figure 1), and not greater than chance, as indicated by the post hoc comparisons of mean differences. Therefore, the observed ergogenic effects of caffeine in the present study are of little substantive meaning for competitive endurance athletes. An unusual finding was that compared to placebo, %\(\dot{V}O_2\)\(_{\text{peak}}\) was significantly elevated by \(\approx 5-7\%\) at 9, 12, and 15 min of the performance ride with 2 mg·kg\(^{-1}\) caffeine (d = 0.71, 0.81, and 0.93, respectively), suggesting that the participants were able to tolerate an increased metabolic intensity with caffeine. However, the elevated \(\dot{V}O_2\) may be of limited practical applicability. These effects, though statistically significant and of large magnitude, did not translate into an increase in cycling performance.

Overall, our performance data are in contrast to the findings of others in the literature. The finding that 3 mg·kg\(^{-1}\) was not ergogenic was unexpected, particularly in light of the evidence that this dose is sufficient for enhancing endurance exercise.
performance. For example, 3 mg·kg\(^{-1}\) is known to be effective for increasing exercise time to exhaustion at 85% \(\dot{V}O_{2peak}\) (20) and for decreasing 8-km running time in a field setting (7). Our data are also not in agreement with the findings of two studies that have shown ergogenic effects of doses lower than 3 mg·kg\(^{-1}\). One investigation found that caffeine ingested in the form of Coca Cola\(^\circ\), in concentrations of 1.3 mg·kg\(^{-1}\) (study A) and 1.9 mg·kg\(^{-1}\) (study B), enhanced cycling performance on a 7 kJ·kg\(^{-1}\) laboratory time trial by \(\sim\)3% (12). Kovacs et al. (26) reported that a dose of \(\sim\)2.1 mg·kg\(^{-1}\), ingested in the form of a carbohydrate-electrolyte sports drink, is ergogenic for cycling time trial of \(\sim\)1 hr duration. As it is commonplace for athletes to ingest sports drinks and cola beverages during competitive events, the practical applications of ingesting caffeine in these vehicles are recognized. However, the aim of our study was to investigate the effects of caffeine \textit{per se}; we therefore chose pills as the vehicle of administration rather so as to isolate the effects of the drug itself. We did not replicate the ergogenic effects of the approximately equivalent doses of caffeine used by previous experiments. Thus, our data do not support the hypothesis that caffeine doses of 1, 2 and 3 mg·kg\(^{-1}\) are ergogenic.

The present experiment must also be considered in light of the recent finding that a placebo effect associated with caffeine administration may be ergogenic in itself (4). Cyclists increased power output during a simulated 10-km time trial by \(\sim\)2 to 3% when they believed they had ingested caffeine compared to when they believed they had ingested a placebo, although no caffeine was actually consumed (all conditions were placebo). It has been suggested that an increase in cycling power output of \(\sim\)1.5% is the smallest beneficial improvement for a road cyclist (33). Beedie et al. (4) therefore suggest that even with a double-blind, placebo-controlled experimental design, some of the observed ergogenicity may be explained by participants’ beliefs or expectations of caffeine’s putative performance enhancing effects, and these placebo effects may be erroneously interpreted as “meaningful.” If our performance data are expressed as average power output, as in the study of Beedie et al. (4), performance was increased by
4.6% and 3.1% during 2 and 3 mg·kg$^{-1}$, respectively, compared to placebo. On one hand, the blind was successfully retained in the present study, since none of the 13 participants correctly identified the order of their treatments. On the other hand, however, 8 of 13 cyclists believed that they had in fact received the highest dose of caffeine on the day that corresponded with their personal best performance, and only 2 of these 8 actually received 3 mg·kg$^{-1}$ on the day of their best performance. Hence, it is likely that some portion of our observed increases in performance were due to participants’ belief that they had received caffeine, and that this placebo-belief phenomenon contributed to the variability in our performance outcome.

Overall, there is ample scientific literature in support of caffeine as an effective ergogenic aid (14, 18). Thus, the present findings are in contrast with the current thought regarding the ergogenicity of caffeine. Doses of 1, 2, and 3 mg·kg$^{-1}$ may not provide adequate stimulus to enhance high-intensity endurance exercise performance. Athletes seeking to gain maximal performance benefits would do well to ingest a dose of greater than 3 mg·kg$^{-1}$.

A possible explanation for the present study’s failure to support that caffeine enhances cycling performance with low doses is that the metabolic demand of the steady state portion of the exercise was quite severe. A power output corresponding to 80% $\dot{V}O_2$peak was chosen so as to resemble a high-intensity bout of bicycle training or racing. We reasoned that any ergogenic effects of caffeine following 15 min of cycling at this intensity would be of practical application to our target population. The metabolic intensity (%$\dot{V}O_2$peak) of the exercise increased steadily throughout the cycling bout, with no differences in %$\dot{V}O_2$peak among Treatments at any individual points in Time. There was no effect of caffeine on the slow component rise in $\dot{V}O_2$, contrary to previous findings (35). Indeed, at the end of the first 15 min, participants were cycling at ~90% $\dot{V}O_2$peak, indicating that the prescribed exercise intensity was above that for which a steady state in $\dot{V}O_2$ was attainable. The severe demands of the exercise task were also
reflected by [La] of ~9 mmol·l$^{-1}$, clearly well above the cyclists’ lactate threshold. Several previous investigations have shown that caffeine enhances performance at similar intensities (11, 32, 38). Nevertheless, it is probable that for the present sample, the severity of the exercise was great enough to cause substantial fatigue, thus overwhelming the potential ergogenicity of caffeine.

Caffeine had no apparent effects on RPE-C, RPE-L, RPE-O, or quadriceps pain during cycling exercise at a power output corresponding to 80% $\dot{V}O_{2peak}$. This finding is in contrast to the hypothesis that caffeine would attenuate these perceptual responses to exercise, perhaps because the intensity prescription of the constant-rate exercise was severe enough to reduce the likelihood of reduced D-RPE and pain. Caffeine is now widely known to mediate perception of effort and muscle pain via central nervous system adenosine receptor antagonism (17), which appears to be the primary mechanism underlining the typically observed moderate ($d \approx 0.5$) reduction in RPE (15). However, adenosine is only one of several other metabolites (e.g., H$^+$ ions, bradykinin, substance P) associated with high intensity exercise that contribute to sensations of discomfort and pain. Caffeine, however, has no known effects on these metabolites. In our experiment, adenosine receptor antagonism apparently did not occur to the extent necessary to attenuate feelings of discomfort and pain. In addition, the deleterious effects of these other metabolites were probably present due to the severe intensity. The combination of high intensity exercise and low caffeine doses likely reduced the chance of attenuated sensations of muscular effort, dyspnea, central drive, and quadriceps muscle pain.

Three recent investigations provide convincing evidence that caffeine attenuates naturally occurring leg muscle pain during cycling exercise (27-29). In each of these investigations, the authors called for future research to investigate the possibility of concomitant hypoalgesia and ergogenicity. In addition, there is a need to address the supposed dose-dependence of caffeine-induced hypoalgesia, as well as whether caffeine is hypoalgesic at intensities of greater than the prescribed intensity of 60% $\dot{V}O_{2peak}$ in the
three previous investigations. The present investigation was an attempt to address these research problems, from which we conclude that caffeine is not hypoalgesic in doses of 1, 2, and 3 mg·kg⁻¹ at 80% \( \dot{V}O_{2\text{peak}} \). Again, it is likely that the severity of the exercise intensity caused rapid accumulation of various metabolic byproducts, thereby limiting the likelihood of hypoalgesic effects of caffeine. Motl et al. (unpublished observations) recently found that 5 mg·kg⁻¹ caffeine is hypoalgesic during cycling at 80% \( \dot{V}O_{2\text{peak}} \). Therefore, it may be that 5-6 mg·kg⁻¹ is the minimum effective hypoalgesic dose, which may not be surprising in light of the evidence for this dose as being consistently ergogenic (14). Nonetheless, the question of whether hypoalgesia is partly responsible for the widely shown ergogenicity has by no means been completely addressed. Future investigation of this important question is warranted.

Caffeine had no measurable effects on the metabolic and cardiorespiratory responses to exercise during the constant-rate phase of the test. Metabolic and cardiorespiratory measures were obtained to provide insight into the hypothesized effects of caffeine on performance, D-RPE and quadriceps pain intensity ratings. As expected, there were no effects of caffeine on RER, which, if reduced, would indicate a decreased relative utilization of carbohydrate as substrate for the production of ATP, and theoretically, a sparing of muscle glycogen. While early studies (11, 16, 22) supported the glycogen-sparing hypothesis, it has been repeatedly shown that ergogenicity is largely independent of effects on substrate utilization (18), thus this hypothesis is now largely rejected in the literature. For this reason, the present study incorporated a relatively short exercise duration of a total of 30 min (for which glycogen depletion is not limiting), to assess changes in cycling performance independently of this supposed mechanism.

The performance ride data provide further insight into the possible metabolic effects of caffeine. The finding that [La] was increased with 3 mg·kg⁻¹ compared to placebo at the end of the performance ride (\( p < 0.001, d = 0.90 \)) suggests that lactate metabolism is influenced by caffeine at this dose. This is in agreement with Bridge and
Jones (7), who found that [La] was increased with 3 mg·kg⁻¹ during an 8-km running time trial. However, these authors did not investigate doses of less than 3 mg·kg⁻¹. Hence, the present study provides the first experimental evidence that the mechanism for increase [La] is operative at 3 mg·kg⁻¹, but probably not at a lower dose. With regards to an underlying physiological mechanism, our experimental design does not allow for substantive insight into what may be the cause of increased [La]. Despite nearly ubiquitous findings of increased [La] with caffeine (18), there is a dearth of literature with regards to a specific mechanism. The two studies (8, 19) that have addressed this problem have shown that arterial, but not muscle, [La] is increased during submaximal steady state exercise, suggesting that caffeine possibly inhibits lactate clearance from the blood by the liver. We did not address this plausible mechanism, and future investigations might utilize doses similar to those in the present study to test the hypothesis that hepatic lactate clearance may be inhibited by caffeine. Based on our data, it appears that whatever the mechanism, 3 mg·kg⁻¹ caffeine may be a threshold dose to detect the effects of caffeine on [La].

**Conclusion**

In summary, caffeine of doses lower than those administered in previous studies did not influence cycling performance, metabolic variables, or perceptual responses. There were no effects of caffeine on RPE-C, RPE-L, RPE-O, or quadriceps muscle pain during exercise. Future investigations should assess D-RPE and quadriceps pain to elucidate caffeine’s perceptual effects, specifically in light of concomitant ergogenic effects. Athletes seeking performance enhancement are likely to gain greatest benefit from larger caffeine doses than 3 mg·kg⁻¹, as the ergogenicity of greater doses has been consistently demonstrated in the literature (14).
Acknowledgements

We gratefully acknowledge Chike Akoh and Victor Maridakis for assistance in data collection and preparation of caffeine treatments. We are indebted to Dr. Jonathan Wingo for sharing his technical expertise.
References


Table 1. Participant characteristics.

<table>
<thead>
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<th>Variable</th>
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<tr>
<td>Age (y)</td>
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<td>Ht (cm)</td>
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<td>Wt (kg)</td>
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<td>% fat</td>
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<td>$\dot{\text{VO}}_{2\text{peak}}$ (L·min$^{-1}$)</td>
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<tr>
<td>$\dot{\text{VO}}_{2\text{peak}}$ (ml·kg$^{-1}$·min$^{-1}$)</td>
<td>55.2 ± 7.2</td>
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<tr>
<td>80% $\dot{\text{VO}}_{2\text{peak}}$ power output (W)</td>
<td>260.4 ± 34.9</td>
</tr>
</tbody>
</table>
Table 2. Physiological responses to cycling at 80% VO
2peak. Values are mean ± SEM.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
</tr>
</thead>
</table>
| %VO
2peak | Placebo  | 80.3 ± 1.0 | 86.2 ± 1.1 | 88.4 ± 1.3 | 89.1 ± 1.1 | 89.9 ± 1.3 |
|         | 1 mg·kg⁻¹ | 80.5 ± 1.0 | 86.6 ± 1.0 | 87.7 ± 1.4 | 89.1 ± 1.4 | 89.7 ± 1.4 |
|         | 2 mg·kg⁻¹ | 81.4 ± 1.2 | 86.1 ± 1.4 | 88.4 ± 1.4 | 90.1 ± 1.8 | 91.3 ± 1.9 |
|         | 3 mg·kg⁻¹ | 80.4 ± 1.0 | 87.5 ± 1.2 | 89.2 ± 1.2 | 90.8 ± 1.3 | 91.5 ± 1.3 |
|         | 1 mg·kg⁻¹ | 80.5 ± 1.0 | 86.6 ± 1.0 | 87.7 ± 1.4 | 89.1 ± 1.4 | 89.7 ± 1.4 |
|         | 2 mg·kg⁻¹ | 81.4 ± 1.2 | 86.1 ± 1.4 | 88.4 ± 1.4 | 90.1 ± 1.8 | 91.3 ± 1.9 |
|         | 3 mg·kg⁻¹ | 80.4 ± 1.0 | 87.5 ± 1.2 | 89.2 ± 1.2 | 90.8 ± 1.3 | 91.5 ± 1.3 |
|         | 1 mg·kg⁻¹ | 75.3 ± 3.9 | 86.0 ± 3.6 | 91.2 ± 4.2 | 95.1 ± 5.0 | 99.0 ± 5.8 |
|         | 2 mg·kg⁻¹ | 76.0 ± 4.0 | 86.5 ± 4.9 | 92.8 ± 4.9 | 96.8 ± 5.7 | 101.1 ± 6.0 |
|         | 3 mg·kg⁻¹ | 75.8 ± 4.2 | 88.7 ± 4.1 | 94.0 ± 4.5 | 99.8 ± 4.7 | 104.7 ± 5.5 |
|         | 1 mg·kg⁻¹ | 1.05 ± 0.01 | 1.02 ± 0.01 | 1.00 ± 0.01 | 0.99 ± 0.01 | 0.99 ± 0.01 |
|         | 2 mg·kg⁻¹ | 1.03 ± 0.02 | 1.01 ± 0.01 | 1.00 ± 0.01 | 0.98 ± 0.01 | 0.98 ± 0.01 |
|         | 3 mg·kg⁻¹ | 1.05 ± 0.02 | 1.03 ± 0.01 | 1.01 ± 0.01 | 1.00 ± 0.01 | 0.99 ± 0.01 |
|         | 1 mg·kg⁻¹ | 155 ± 5.8   | 167 ± 2.8   | 173 ± 3.0   | 176 ± 3.1   | 179 ± 3.1   |
|         | 2 mg·kg⁻¹ | 154 ± 6.1   | 168 ± 3.4   | 174 ± 3.4   | 177 ± 3.5   | 180 ± 3.6   |
|         | 3 mg·kg⁻¹ | 158 ± 3.7   | 168 ± 3.4   | 174 ± 3.4   | 178 ± 3.2   | 181 ± 3.4   |
| [La]*   | Placebo  | 8.2 ± 0.7   | 9.0 ± 0.7   | 9.0 ± 0.8   | 9.7 ± 0.7   |
|         | 1 mg·kg⁻¹ | 8.2 ± 0.7   | 9.0 ± 0.7   | 9.0 ± 0.8   | 9.7 ± 0.7   |
|         | 2 mg·kg⁻¹ | 8.2 ± 0.7   | 9.0 ± 0.7   | 9.0 ± 0.8   | 9.7 ± 0.7   |
|         | 3 mg·kg⁻¹ | 8.2 ± 0.7   | 9.0 ± 0.7   | 9.0 ± 0.8   | 9.7 ± 0.7   |

Significant omnibus F ratio indicated by *. Post-hoc Hochberg pairwise comparisons for [La] not significant.
Table 3. Physiological responses to performance ride. Data are mean ± SEM.

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<th>12</th>
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<td>[La]</td>
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<td>2 mg·kg(^{-1})</td>
<td>8.8 ± 0.7</td>
<td></td>
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<tr>
<td></td>
<td>3 mg·kg(^{-1})</td>
<td>9.9 ± 0.7(^{a})</td>
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</table>

Significant omnibus F ratio indicated by *.

\(^{a}\)Different from placebo; \(^{b}\)different from 1 mg·kg\(^{-1}\) (p < 0.05).
Figure Legends

Figure 1. Effect of caffeine on cycling performance for individual participants. Large open circles connected by solid line represent treatment means ± SEM.

Figure 2. Differentiated ratings of perceived exertion during 80% $\dot{V}O_{2\text{peak}}$ (left column) and performance ride (right column). Y-axes are RPE-chest (RPE-C), RPE-legs (RPE-L), and RPE-Overall (RPE-O).

Figure 3. Ratings of quadriceps pain intensity during cycling at 80% $\dot{V}O_{2\text{peak}}$ (left) and performance ride (right).
Figure 1.
Figure 2.
Figure 3.
CHAPTER 4
SUMMARY AND CONCLUSIONS

Summary

Nearly 30 years of research have produced an extensive literature in support of caffeine as an effective ergogenic aid. However, the minimal effective dosage of caffeine needed to produce an ergogenic effect is not known. In addition, caffeine is widely reported to reduce perceived exertion and working muscle pain during exercise, though neither the minimal effective dose nor the implications of this effect for exercise performance are clearly understood. Furthermore, the effects of caffeine on perceived exertion have not been studied with the differentiated model (85). The present experiment was designed to determine the effects of low doses of caffeine on differentiated ratings of perceived exertion, leg muscle pain, and cycling performance.

Thirteen trained athletes were tested in this study. In a randomized, double-blind, placebo controlled research design, participants received treatments of 1, 2, and 3 mg·kg$^{-1}$ caffeine, and a placebo. Sixty min following ingestion, 13 trained male cyclists performed 15 min of cycling at 80% $\dot{V}O_{2\text{peak}}$ followed by a 15 min performance ride in which they performed as much work as possible. These doses had no ergogenic benefit on a pre-loaded, work-based protocol. Doses corresponding to 2 mg·kg$^{-1}$ and 3 mg·kg$^{-1}$ increased cycling performance, as measured by work production relative to body weight (kJ·kg$^{-1}$) during the 15 min performance ride, by 4.3% and 2.9% compared to placebo. While this was a large enough effect for the one-way ANOVA to result in a significant overall $F$ ratio, follow up analysis of mean differences with the Hochberg adjustment for multiple comparisons did not reveal any significant differences among treatments. Thus, the observed changes in cycling performance were too variable to conclude that these doses have a consistent ergogenic effect.
Caffeine had no effect on perceptual responses to exercise. This may have been because of the severe intensity of the first portion of the exercise test, or because the small doses did not provide an adequate degree of adenosine receptor antagonism, or some combination thereof. The D-RPE model should be used in future studies to assess the relationship between caffeine’s perceptual and ergogenic effects. In addition, the present study is in contrast to a growing literature to support the hypoalgesic effects of caffeine. The low doses of caffeine were likely inadequate to elicit hypoalgesia, suggesting that for intensities corresponding to ~80% \( \overline{V}O_2 \text{peak} \) or greater, the threshold dose for hypoalgesia is above 3 mg·kg\(^{-1}\).

Metabolic variables were collected to gain insight into the underlying physiological actions of caffeine. Caffeine had little effect on \( \dot{V}O_2 \), \( \dot{V}E \), or \([La]\) during cycling at 80% \( \overline{V}O_2 \text{peak} \), which was, in general, in contrast to the literature. During the performance ride, 2 mg·kg\(^{-1}\) caffeine elicited an increase in the sustainable metabolic intensity. However, this finding is probably of little practical applicability, because cycling performance was not significantly enhanced. Finally, \([La]\) was increased with 3 mg·kg\(^{-1}\) during the performance ride, suggesting that 3 mg·kg\(^{-1}\) may be a threshold to detect the widely observed increase in \([La]\) resulting from caffeine ingestion.

**Conclusions**

From the data collected in the present experiment, it is concluded that:

1. Caffeine in doses of 3 mg·kg\(^{-1}\) or less have little systematic effect on cycling performance and perceptual responses to exercise.

2. Athletes seeking performance enhancement are likely to benefit from larger caffeine doses larger than 3 mg·kg\(^{-1}\), as the ergogenicity of greater doses has been consistently and repeatedly demonstrated (34).
References


47. **Graham, T.E., J. W. Helge, D. A. Maclean, B. Kiens and E. A. Richter.**


Appendix. D-RPE scale and instructions.

Borg’s CR-10 RPE Scale and Instructions for Differentiated RPE

While exercising we want you to rate your perception of exertion, i.e., how heavy and strenuous the exercise feels to you. We will ask you to rate your perception of exertion in three different contexts: 1) local, or muscular, perceived exertion; 2) central, or respiratory, perceived exertion, and 3) overall perceived exertion. The local perceived exertion depends on the degree to which you feel strain and fatigue in your quads, including muscle aches, cramps, tremors, and sensations of heaviness or shakiness that are due to the exercise. When asked for your central rating of perceived exertion, we want you rate the effort based on your breathing sensation. This focus should be on your perceived intensity of breathing. Finally, for the overall perception of exertion, report the total, overall effort that you are putting into the exercise task.

Look at this rating scale; we want you to use this scale from 0 to 10, where 0 means “no exertion at all” and 10 means “almost maximal exertion.”

1 corresponds to “very weak” exercise. For a normal, healthy person it is like walking slowly at his or her own pace for some minutes.

4 on the scale is “somewhat strong” exercise, but it still feels OK to continue.

7 “very strong” is very strenuous. A healthy person can still go on, but he or she really has to push him- or herself. It feels very heavy, and the person is very tired.

10 on the scale is an extremely strenuous exercise level. For most people this is the most strenuous exercise they have ever experienced.

If you give a truly maximal effort you can give a number above 10 that is in relation to 10. A 20 would be twice as intense as 10 and 15 would be 1.5 times as intense as 10.

You can give half numbers such as 5.5.
Try to appraise your feeling of exertion as honestly as possible. Don’t underestimate it, but don’t overestimate it either. It’s your own feelings that are important. Look at the scale and the expressions and then give a number.

Any questions?
<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
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<tbody>
<tr>
<td>0</td>
<td>Nothing at all</td>
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<tr>
<td>½</td>
<td>Extremely weak (just noticeable)</td>
</tr>
<tr>
<td>1</td>
<td>Very weak</td>
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<tr>
<td>2</td>
<td>Weak (light)</td>
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<td>3</td>
<td>Moderate</td>
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<td>4</td>
<td>Somewhat strong</td>
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<td>5</td>
<td>Strong (heavy)</td>
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<tr>
<td>7</td>
<td>Very strong</td>
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<tr>
<td>9</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Extremely Strong (almost max)</td>
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<tr>
<td>•</td>
<td>Maximal</td>
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