# Metabolic, catecholamine, and endurance responses to caffeine during intense exercise

M. JACKMAN, P. WENDLING, D. FRIARS, AND T. E. GRAHAM

*School of Human Biology, University of Guelph, Guelph, Ontario N1G 2W1, Canada*

**Jackman, M., P. Wendling, D. Friars, and T. E. Graham.** Metabolic, catecholamine, and endurance responses to caffeine during intense exercise. *J. Appl. Physiol.* 81(4): 1658–1663, 1996.—This study examined the possible effects of caffeine ingestion on muscle metabolism and endurance during brief intense exercise. We tested 14 subjects after they ingested placebo or caffeine (6 mg/kg) with an exercise protocol in which they cycled for 2 min, rested 6 min, cycled 2 min, rested 6 min, and then cycled to voluntary exhaustion. In each exercise the intensity required the subject's maximal $O_2$ consumption. Eight subjects had muscle and venous blood samples taken before and after each exercise period. The caffeine ingestion resulted in a significant increase in endurance ($4.12 \pm 0.36$ and $4.93 \pm 0.60$ min for placebo and caffeine, respectively) and resulted in a significant increase in plasma epinephrine concentration throughout the protocol but not in norepinephrine concentration. During the first two exercise bouts, the power and work output were not different; blood lactate concentrations were not affected significantly by caffeine ingestion, but during the exercise bouts muscle lactate concentration was significantly increased by caffeine. The net decrease in muscle glycogen was not different between treatments at any point in the protocol, and even at the time of fatigue there was at least 50% of the original glycogen concentration remaining. The data demonstrated that caffeine ingestion can be an effective ergogenic aid for exercise that is as brief as 4–6 min. However, the mechanism is not associated with muscle glycogen sparing. It is possible that caffeine is exerting actions directly on the active muscle and/or the neural processes that are involved in the activity.

methylxanthines; epinephrine; norepinephrine; glycogen; ergogenic aids; fatigue

A SERIES OF STUDIES by Costill et al. (11), Essig et al. (14), and Ivy et al. (18) stimulated considerable interest in the effects of caffeine ingestion on prolonged exercise (2, 16, 17, 21, 29). In contrast, very few studies have examined brief intense exercise after caffeine ingestion, and the results are equivocal. Studies that used protocols of progressively increasing exercise intensity to maximal $O_2$ consumption ($\dot{V}O_{2\,max}$) have generally demonstrated no effect of caffeine (12, 24, 25). In contrast, protocols in which power output was intense and not controlled (e.g., swimming, running, an anaerobic cycle test) have often (1, 9, 36), but not always (8, 10), resulted in an ergogenic effect of caffeine. In a recent review, Tarnopolsky (31) noted this controversy and concluded that it is unlikely that caffeine is ergogenic in exercise that is so intense that it lasts <15 min.

Frequently, the metabolic consequences of caffeine ingestion followed by prolonged exercise have been explained by increasing fat mobilization and the subsequent sparing of muscle glycogen stores. If this "glycogen-sparing" theory is correct and is the only mechanism by which caffeine influences exercise capacity, then caffeine ingestion should have no impact on short-term intense exercise. Under these conditions, the energy is predominantly derived from anaerobic metabolism and the oxidation of carbohydrates; i.e., fat metabolism is not important (2, 6, 37). Furthermore, muscle glycogen is not limiting in such brief exercise, and thus even if glycogen sparing occurred, it should not have an impact on performance.

There are indications that caffeine is affecting some aspects of the responses to such exercise; there are reports (1, 8–10) of caffeine-related elevations in blood lactate during intense exercise as well as an increase in catecholamines (8, 10). Anselme et al. (1) and Collomp et al. (9) have speculated that the increase in catecholamines in these circumstances enhances muscle glycogenolysis [in contrast to reports (13, 14, 29) of caffeine resulting in a sparing of glycogen during prolonged exercise] and that this generates greater anaerobic metabolism, resulting in greater lactate formation and muscle power output. Interpretation of these studies is difficult in that muscle metabolite data have not been reported. In addition, frequently, direct comparison of the catecholamine and lactate data of placebo and caffeine trials cannot be done with confidence because the power output was different between the open-ended trials (1, 8–10). Nevertheless, it appears that caffeine may increase lactate formation and, possibly, exercise performance during intense exercise.

This study examined the effect of caffeine ingestion on active muscle metabolism at a power output eliciting $\dot{V}O_{2\,max}$. The protocol included a situation in which power output and duration were controlled as well as circumstances when endurance time was allowed to vary. We hypothesized that, when the power output was controlled, neither muscle and blood lactate concentration nor net glycogenolysis would be influenced by caffeine ingestion. We also hypothesized that caffeine ingestion would result in an increased exercise endurance at a power output requiring $\dot{V}O_{2\,max}$.

## METHODS

*Subjects.* Fourteen young adults who were active recreational or varsity athletes of endurance activities (3 women and 11 men, age $23.5 \pm 2.0$ yr, $\dot{V}O_{2\,max}$ $55.1 \pm 1.8$ ml·kg$^{-1}$·min$^{-1}$) volunteered to take part in the study after they were informed (both verbally and in writing) about the nature of the experiments. The protocol was approved by the Ethics Committee of the University of Guelph.

*Preexperimental protocol.* Each subject reported to the laboratory before the actual experiments and performed an incremental $\dot{V}O_{2\,max}$ test on a cycle ergometer. Subsequently, on a separate day, the subject performed a practice trial consisting of three 2-min exercise bouts at a power output that required the subject's $\dot{V}O_{2\,max}$, with 6 min of rest between

bouts. This served to familiarize the subject with the protocol and to confirm that the chosen power output was appropriate.

*Experimental protocol.* Each subject completed two trials, one with caffeine ingestion and one with placebo. The order was randomized and administered with a double-blind procedure. The subjects abstained from all caffeine-containing foods and beverages for 48 h before the tests and were instructed to prepare for the trials as they would for an athletic competition (i.e., well rested, consuming a high-carbohydrate diet) and to prepare for each test in an identical fashion. To assist in this, the subjects kept a food and activity diary for 48 h before each test. Each subject's tests were conducted at the same time of day, and the trials were separated by 1 wk.

When the subject reported to the laboratory, he or she ingested gelatin capsules containing either caffeine (6 mg/kg body wt) or placebo (dextrose) along with water. After the subject rested quietly for 1 h, the exercise protocol was initiated. The subject performed 2 min of exercise on a cycle ergometer at a power output requiring $\dot{V}O_{2\,max}$, rested seated on the cycle for 6 min, repeated the exercise, rested 6 min, and then exercised at the same power output a third time until voluntary exhaustion without temporal input given. Before leaving the laboratory, the subject completed a brief questionnaire asking whether he or she could predict which treatment had been received.

Eight of the subjects had blood and muscle samples taken during the experiments. In these subjects before ingestion of the capsules, a catheter was placed into a medial antecubital vein, a saline drip (100–175 ml/h) was started to maintain catheter patency, and a resting blood sample was taken. A second blood sample was taken before the onset of the first exercise (referred to as 0 min). Subsequently, blood samples were taken before and during the last 20 s of each work bout (in the third exercise period; if the subject exercised >20 s after a sample was taken, it was discarded and another sample was taken). These eight subjects also had muscle biopsies taken from the vastus lateralis before and immediately after each exercise bout. These were quick-frozen in liquid nitrogen.

*Analyses.* The blood samples (7 ml) were immediately transferred to a sodium-heparinized tube. Hematocrit was measured in duplicate by high-speed centrifugation. A 100-µl portion of the blood sample was added to 500 µl of 0.3 M perchloric acid and centrifuged, and the supernatant was stored at −20°C for lactate analysis (23). A 120-µl aliquot of a 0.24 M solution of ethylene glycol-bis(β-aminoethyl ether)-*N,N,N′,N′*-tetraacetic acid and reduced glutathione was added to the remaining blood. This was centrifuged and the plasma was stored at −80°C for catecholamine analysis (35).

The biopsies were stored at −80°C, and subsequently they were freeze-dried and the nonmuscle elements were discarded. For glycogen analysis, two aliquots (2–3 mg) of muscle were extracted in 2 M HCl at 85°C for 2 h, neutralized with 2 N NaOH, and assayed for glucose (3). An additional 3 mg of tissue were extracted with 0.5 M HClO$_4$ (1.0 mM EDTA), neutralized with 2.2 M KHCO$_4$, and analyzed for total creatine and lactate (23). While these data were expressed per kilogram dry weight, the data were adjusted for differences in total creatine within a given subject's biopsies. Each muscle sample for each subject was corrected by a factor obtained by the ratio between the total creatine concentration of that biopsy to the highest total creatine value obtained for any of the biopsies of that subject. This factor was generally minor (≤1.10) and represents differences between biopsies in nonmuscle tissue that could not be removed by dissection.

*Statistics.* The data were analyzed by two-way analysis of variance for repeated measures. In addition, the decrease in muscle glycogen from rest (before the first exercise) to the end of the second exercise bout was tested in the same way. Differences in all comparisons were accepted as significant if $P \leq 0.05$. In the text and Figs. 1–6, all values cited are means ± SE.

## RESULTS

*Endurance.* The difference in endurance time between the two treatments is presented in Fig. 1. Ten of the 14 subjects increased their endurance during the caffeine test; the mean cycling times were 4.12 ± 0.36 and 4.93 ± 0.60 min for the placebo and caffeine trials, respectively. The difference between treatments was significant, both within the group who had muscle and blood sampling (*subjects 1–8*) and within the subjects who had neither of these procedures. Six subjects correctly identified the treatments, five were wrong, and three felt that they could not make a prediction.

*Plasma catecholamines.* The catecholamine data are summarized in Figs. 2 and 3. The plasma norepinephrine concentration was not different between treatments (Fig. 2). In contrast, caffeine ingestion resulted in an elevation in plasma epinephrine at rest 60 min after ingestion, and this difference continued throughout the duration of the study (Fig. 3).

*Muscle glycogen.* Muscle glycogen was not different between trials before the first exercise or at any point in the experiment (Fig. 4). There was a significant decrease in glycogen during each exercise period, but the decrease in muscle glycogen between treatments was not different for any of the three exercise periods. The net decreases in glycogen between the initial rest sample and the end of the second exercise period (i.e., during the exercises when the power output and exercise time were identical for the 2 treatments) were
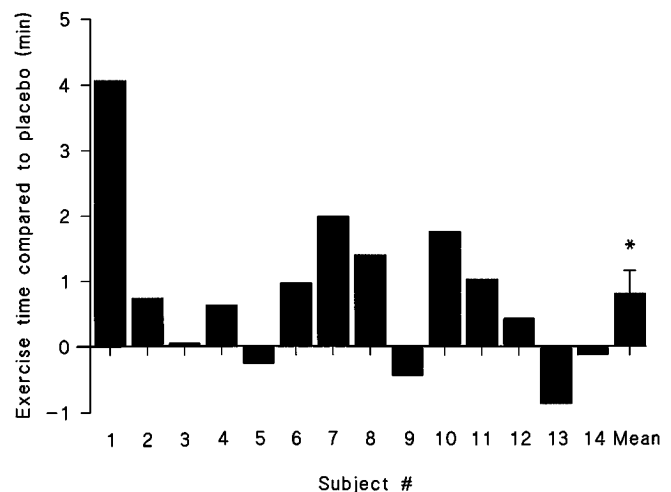


Fig. 1. Endurance time for each subject. Difference in endurance time during final exercise period (*exercise 3*) between placebo and caffeine trials is shown. Positive number indicates that time was greater in caffeine test. *Subjects 1–8* were in biopsy trials, whereas *subjects 9–14* did not have muscle biopsies taken. Mean data (Mean) represent all 14 subjects and were significantly greater (* $P < 0.05$) than placebo data. Large response of *subject 1* did not bias result in that difference remains significant even without this data set.
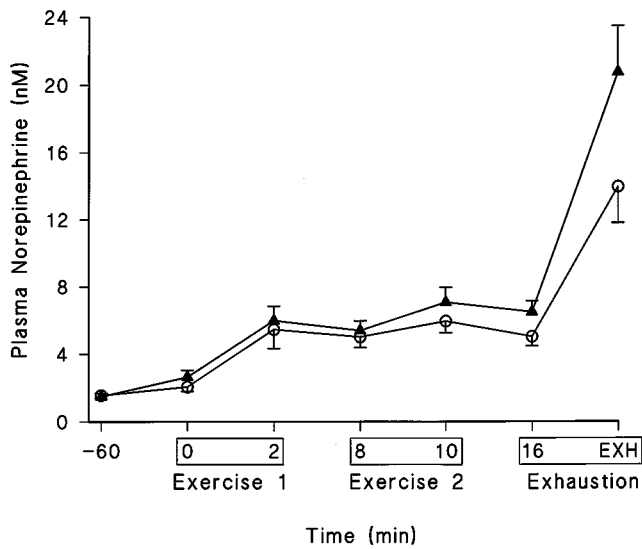
Fig. 2. Responses of venous plasma norepinephrine concentration to exercise and to caffeine ingestion. Data are means ± SE. ▲, Caffeine trial; ○, placebo tests. Boxes on *x*-axis indicate periods of exercise, and −60 min is data point before ingestion of capsules, which was followed by 1 h of rest. EXH, exhaustion. In exercise states, blood was always sampled before cessation of exercise.



Fig. 4. Responses of muscle glycogen concentration to exercise and to caffeine ingestion. Organization is the same as for Fig. 2, with the exception that data were not obtained at −60 min. Lowercase letters indicate significant ($P \le 0.05$) time effect; data with same letter are not significantly different from each other.

116 ± 23 and 125 ± 31 mmol/kg dry wt for the placebo and caffeine trials, respectively. At the end of the third bout of exercise, i.e., at exhaustion, the mean muscle glycogen values were 281 ± 42 and 237 ± 53 mmol/kg dry wt for the caffeine and placebo tests, respectively.

*Blood and muscle lactate.* Exercise resulted in significant increases in blood lactate before and after the second exercise period (Fig. 5). In addition, before and after the third exercise, the blood lactate was significantly greater than the earlier data. Despite the mean data being consistently greater during the caffeine trial, there was no significant treatment effect. Muscle lactate concentrations rose significantly with each exercise, and caffeine ingestion resulted in a significantly
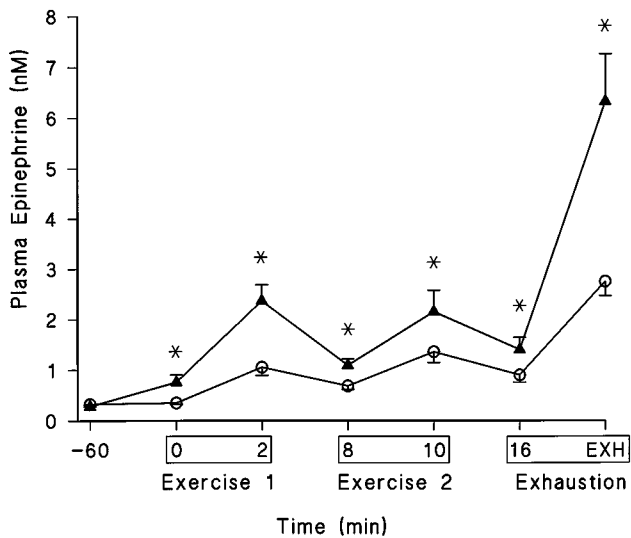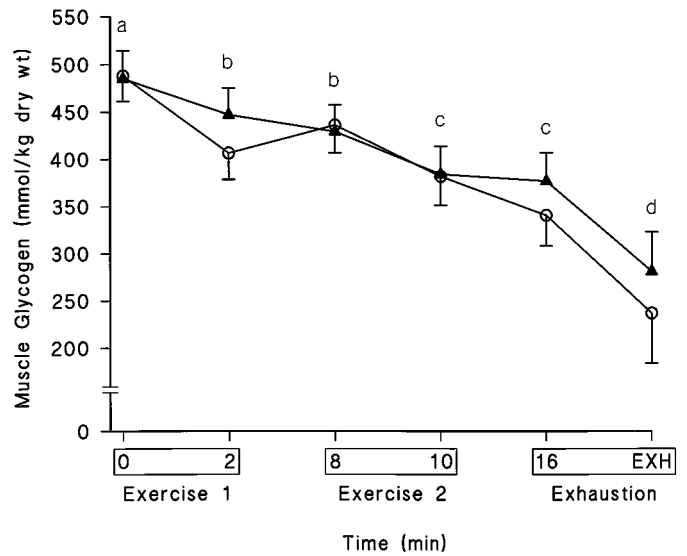
greater muscle lactate concentration in the first two exercise periods (Fig. 6).

## DISCUSSION

This study examined the impact of caffeine ingestion on muscle glycogen and lactate metabolism during intense exercise when power output was controlled (*exercises 1* and *2*) as well as the effect on endurance during intense exercise performed until voluntary exhaustion (*exercise 3*). The major findings were that in *exercises 1* and *2* after caffeine ingestion both muscle lactate and plasma epinephrine concentrations were increased even though the power output, the total work done, and the net muscle glycogenolysis were unaffected. In addition, the exercise endurance was en-



Fig. 3. Responses of venous plasma epinephrine concentration to exercise and to caffeine ingestion. Organization is the same as for Fig. 2. *Significant treatment effect, $P \le 0.05$.
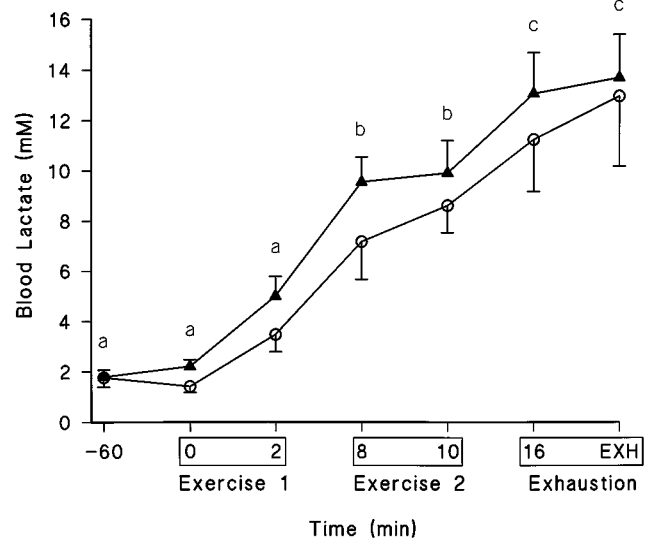


Fig. 5. Responses of venous blood lactate concentration to exercise and to caffeine ingestion. Organization is the same as for Figs. 2 and 4.
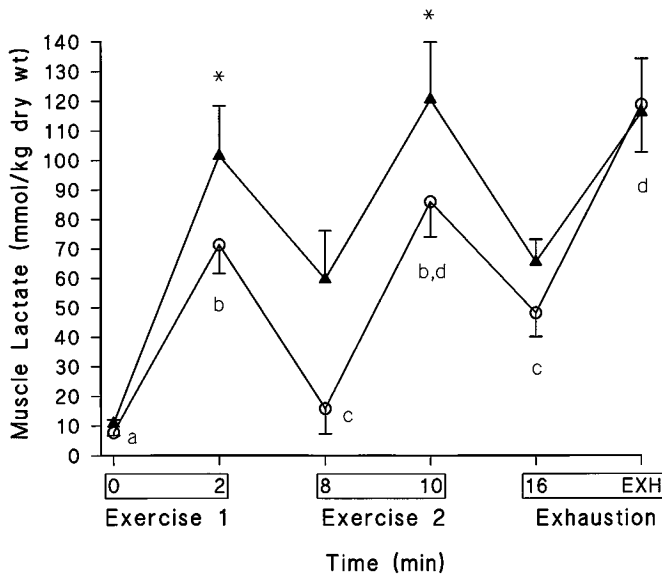
Fig. 6. Responses of muscle lactate concentration to exercise and to caffeine ingestion. Organization is the same as for Figs. 2 and 4. *Significant treatment effect, $P \leq 0.05$.

hanced by caffeine under circumstances when muscle glycogen availability was not a limiting factor. These findings strongly suggest that the actions of caffeine are complex, involving physiological mechanisms beyond that of glycogen sparing.

Caffeine ingestion consistently increased the plasma epinephrine concentration in the present study both at rest and throughout the exercise, whereas norepinephrine concentration was unaffected. In studies of caffeine ingestion and exercise, plasma catecholamines have seldom been measured; however, the published data are consistent. Graham and Spriet (16, 17) and Spriet et al. (29) have repeatedly found that caffeine increases plasma epinephrine both at rest and during prolonged exercise, whereas norepinephrine is unaffected. This is in contrast with Tarnopolsky et al. (32) but is generally in agreement with Collomp and co-workers (8, 10). Collomp and co-workers found that caffeine ingestion combined with brief intense exercise elevated the plasma concentration of both catecholamines. The difference between studies for the norepinephrine data may be due to some protocol differences; e.g., they frequently did not control the power output between conditions. However, the present data confirm the caffeine effect on epinephrine, and these catecholamine data are the most complete that have been reported for intense exercise; previous studies (8, 10) from other laboratories have not determined the temporal aspects of the response but rather have only taken samples pre- and postexercise.

Although the rise in plasma epinephrine seems to be a reliable indicator of a caffeine effect on the body, the ramifications that this has on metabolism are uncertain. It has been used frequently to explain the assumed enhanced fat metabolism and muscle glycogen sparing and increased endurance in prolonged exercise. However, Spriet et al. (29) have found that the muscle glycogen sparing only occurred in the initial phase of

prolonged exercise, whereas the plasma epinephrine was increased throughout the exercise. In addition, the ergogenic effects of caffeine on prolonged exercise were found even when the dose of caffeine was insufficient to elevate plasma epinephrine (17). Furthermore, van Soeren et al. (33) have found that quadriplegic subjects at rest responded to caffeine ingestion with a rise in plasma free fatty acids even though there was no increase in epinephrine. Thus the metabolic impact of the increase in epinephrine concentration is uncertain.

In contrast to the theory that the epinephrine would indirectly cause muscle glycogen sparing, previous investigations (19, 26, 30) that infused epinephrine to generate high circulating concentrations found metabolic responses such as increased muscle glycogenolysis and elevations in muscle glycogen phosphorylase *a*. Anselme et al. (1) and Collomp and co-workers (8–10) have frequently found that during intense exercise caffeine resulted in increased blood lactate concentration, and in some studies, Collomp and co-workers (8, 9) found an increase in power output. Collomp and co-workers (9) speculated that the caffeine-induced increase in epinephrine caused an increase in anaerobic metabolism that in turn facilitated a greater power output during intense exercise situations. However, Chesley et al. (7) recently reported that when they infused epinephrine into subjects exercising at 80% $\dot{V}O_{2 \, max}$ to generate concentrations very similar to those created by caffeine ingestion, they could measure no impact on muscle glycogenolysis, lactate, creatine phosphate, or ATP concentrations despite an increase in the mole fraction of glycogen phosphorylase *a*. The present data are in agreement with this finding.

The present study addresses some of the limitations of previous investigations that have used intense exercise conditions. For example, none of these studies had data for intramuscular metabolites, and in almost every case where endurance was studied, the power output was not controlled (1, 8, 9, 36). It is virtually impossible to compare catecholamine and/or metabolic data between caffeine and placebo conditions when the power output is not controlled. Previous investigations of both prolonged (16, 17, 29) and intense (1, 8–10) exercise have reported that caffeine ingestion was associated with increased blood lactate concentrations. This could indicate that there was an increased production by the active muscle, but it could also be due to decreased blood clearance. The present data demonstrated that caffeine ingestion increased muscle lactate during the exercise bouts of fixed power output and duration; this strongly suggested that there was an increased lactate production.

In addition, during these two exercise periods the net decrease in muscle glycogen was not affected by caffeine administration. While this has not been previously examined in intense exercise, investigations of prolonged exercise (13, 14, 29) have demonstrated that caffeine results in reduced muscle glycogenolysis. It appears that with the high-energy demands of the intense exercise, the metabolic signals negate the mechanism(s) by which glycogen sparing is induced in

less intense metabolic conditions. This may be due to factors such as greater changes concentrations of intracellular modulators such as calcium and hydrogen ions, free ADP and AMP, and different motor unit recruitment during the intense exercise. Why it appeared that lactate production was increased when there was no measurable elevation in glycogenolysis is completely speculative. The glucose uptake response is unknown, but it has been reported (5, 34) that methylxanthines can influence contraction-induced glucose uptake in the rat hindlimb. However, Vergauwen et al. (34) found a 20–25% reduction in glucose uptake in the presence of a physiological concentration of caffeine. Obviously if this occurred in the present study, it would not enhance muscle lactate production.

In the final portion of the present protocol the subjects exercised to voluntary exhaustion. Caffeine ingestion resulted in a significant increase in endurance. Studies using a progressive exercise protocol have often (12, 25), but not always (15), failed to demonstrate an ergogenic effect of caffeine. In contrast, several investigations using shorter and more intense exercise conditions (1, 9, 36) have reported a positive ergogenic effect of caffeine administration. Our study confirmed this finding, but the glycogen and lactate data failed to support the theory that the cause was metabolic in nature. For example, even at the end of the exhaustive exercise, the subjects had ample stores of muscle glycogen.

There are a number of possibilities that could explain this result. It is well known that caffeine affects the central nervous system (27, 31). This in turn could influence motor control, resulting in a more optimal motor recruitment. In addition, the voluntary decision to stop exercising is processed in the central nervous system; perhaps caffeine causes the brain to ignore or overrule fatigue signals for a longer time during the exercise. While these are certainly possible, the fact that the majority of the subjects could not correctly identify the caffeine trial suggests that any effect of caffeine on the nervous system was not obvious to the subjects themselves.

There are also possible effects that involve the muscle itself. Silinsky and Redman (28) reported that at the myoneural junction ATP is released concurrently with acetylcholine. The ATP is degraded, producing adenosine, which binds to the motoneuron's $A_1$ receptors to inhibit further neural transmitter release. Caffeine is known to be an adenosine antagonist and thus could disinhibit this response. Previously, the probability of caffeine affecting calcium mechanisms has been discounted because of the high dose of caffeine required to obtain an effect. It has recently been reported that cyclic ADP-ribose, a naturally occurring metabolite of NAD (20), can potentiate the effect of caffeine on the action of caffeine on the calcium-induced calcium-release mechanism. This could mean that physiological doses of caffeine could effect calcium availability possibly via ryanodine receptors. This in turn would affect excitation-contraction coupling and possibly metabolic pathways (4, 21, 22, 31).

In addition, Lindinger et al. (21) reported that caffeine ingestion resulted in less increase in plasma potassium during prolonged exercise. They speculated that this was the result of a greater potassium uptake by resting muscle. This could possibly lead to greater removal of potassium from the t tubules and help to delay the onset of fatigue processes. These possibilities remain as mere theories. One fundamental aspect that needs to be explored is that if caffeine can directly affect the muscle, what is the nature of the mechanism and/or receptor?

The present study demonstrated that caffeine ingestion can result in an increase in muscle endurance during intense exercise that leads to fatigue in ~5 min. Caffeine resulted in increases in muscle lactate concentrations, suggesting an increased lactate production. In addition, despite an increase in plasma epinephrine, there is no impact on muscle glycogen stores associated with the caffeine administration, and, at the point of voluntary fatigue, the stores do not appear to be limiting. These findings lead us to conclude that caffeine-induced ergogenesis can occur through mechanisms in addition to glycogen sparing and raise the possibility that there are direct actions on the muscle itself and/or the myoneural junction and/or the central nervous system.

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