# Metabolic, catecholamine, and exercise performance responses to various doses of caffeine

T. E. GRAHAM AND L. L. SPRIET
*School of Human Biology, University of Guelph, Guelph, Ontario N1G 2W1, Canada*

**Graham, T. E., and L. L. Spriet.** Metabolic, catecholamine, and exercise performance responses to various doses of caffeine. *J. Appl. Physiol.* 78(3): 867–874, 1995.—This study examined the exercise responses of well-trained endurance athletes to various doses of caffeine to evaluate the impact of the drug on exercise metabolism and endurance capacity. Subjects ($n$ = 8) withdrew from all dietary sources of caffeine for 48 h before each of four tests. One hour before exercise they ingested capsules of placebo or caffeine (3, 6, or 9 mg/kg), rested quietly, and then ran at 85% of maximal $O_2$ consumption to voluntary exhaustion. Blood samples for methylxanthine, catecholamine, glucose, lactate, free fatty acid, and glycerol analyses were taken every 15 min. Plasma caffeine concentration increased with each dose ($P < 0.05$). Its major metabolite, paraxanthine, did not increase between the 6 and 9 mg/kg doses, suggesting that hepatic caffeine metabolism was saturated. Endurance was enhanced with both 3 and 6 mg/kg of caffeine (increases of 22 ± 9 and 22 ± 7%, respectively; both $P < 0.05$) over the placebo time of 49.4 ± 4.2 min, whereas there was no significant effect with 9 mg/kg of caffeine. In contrast, plasma epinephrine was not increased with 3 mg/kg of caffeine but was greater with the higher doses ($P < 0.05$). Similarly only the highest dose of caffeine resulted in increases in glycerol and free fatty acids ($P < 0.05$). Thus the highest dose had the greatest effect on epinephrine and blood-borne metabolites yet had the least effect on performance. The lowest dose had little or no effect on epinephrine and metabolites but did have an ergogenic effect. These results are not compatible with the traditional theory that caffeine mediates its ergogenic effect via enhanced catecholamines.

paraxanthine; ergogenic aids; fatigue; fat metabolism; epinephrine

COSTILL AND CO-WORKERS (9, 13, 18) demonstrated that ingestion of the methylxanthine caffeine resulted in increased endurance and power output during prolonged work. These increases were associated with increased catabolism of muscle triglycerides and reduced muscle glycogenolysis. On the basis of these findings together with the results of various investigations of subjects at rest, they proposed (13) that caffeine resulted in an increase in circulating catecholamines, which resulted in enhanced lipolysis. The enhanced availability of free fatty acids (FFA) was thought to cause greater fat metabolism in the active muscle, which in turn inhibited carbohydrate metabolism and resulted in increased exercise capacity.

This model remains unproven; not only have there been several reports that caffeine ingestion did not increase endurance (5, 6, 25) but also in studies in which there was a delay in fatigue with caffeine the complementary data did not always confirm the concepts of the model. For example, our work (15, 26) confirmed that a high dose of caffeine (9 mg/kg) increased endurance, reduced muscle glycogenolysis, and was associated with a large increase in epinephrine. However, there was also an increase in blood lactate that seemed paradoxical in light of the glycogen sparing. More critically, the reduction in glycogenolysis occurred only within the first 15 min of 90 min of exercise, whereas the plasma epinephrine was increased throughout the entire 90 min of exercise. Furthermore, the plasma FFA concentration, the pulmonary respiratory exchange ratio (RER), and the intramuscular acetyl CoA and citrate did not show the changes compatible with the current theories for how enhancement in fat metabolism would inhibit carbohydrate catabolism.

Vestal et al. (29) demonstrated that aminophylline infusion resulted in different circulating concentrations of the methylxanthine theophylline, and there were dose relationships with various metabolic and cardiovascular parameters in resting subjects. Epinephrine and to a lesser extent norepinephrine rose in proportion to the concentration of the methylxanthine as did heart rate, systolic blood pressure, and plasma FFA concentration. If the exercise effects of caffeine are mediated by increases in epinephrine, then there should be a similar dose relationship between caffeine and both the metabolic responses and endurance.

There have been very few studies of exercise and different doses of caffeine. Two studies (11, 23) failed to show any effects of 3–10 mg/kg doses of caffeine on endurance, heart rate, or plasma FFA during progressive exercise tests. Donelly and McNaughton (12) demonstrated that caffeine ingestion increased $O_2$ consumption ($\dot{V}O_2$) during and after prolonged moderate exercise while plasma FFA was increased and RER was decreased. However, there were no differences between 5 and 10 mg/kg doses of caffeine. Cadarette et al. (7) conducted a more systematic study of various doses (2.2, 4.4, and 8.8 mg/kg) of caffeine during prolonged exercise. They found that there was no caffeine effect on RER, plasma FFA, or glycerol, but plasma lactate was positively related to caffeine dose and endurance was increased only with the moderate dose.

The dose relationships of caffeine and metabolism during exercise have not been studied in detail; the few studies seldom used prolonged steady-state exercise and did not measure plasma epinephrine. By examining the endurance, metabolic, and catecholamine responses to various caffeine doses, one could gain a deeper understanding of how the effects of caffeine are mediated in exercising humans. In the present study we investigated the effects of light, moderate, and heavy doses of caffeine on subjects during prolonged exhaustive exercise [85% of maximal $\dot{V}O_2$ ($\dot{V}O_{2\,max}$)]. The blood lactate, glucose, plasma FFA, glycerol, catecholamine, and endurance responses of the subjects were examined to establish whether the ergogenic effect of caffeine is mediated through an increase in circulating catecholamines.

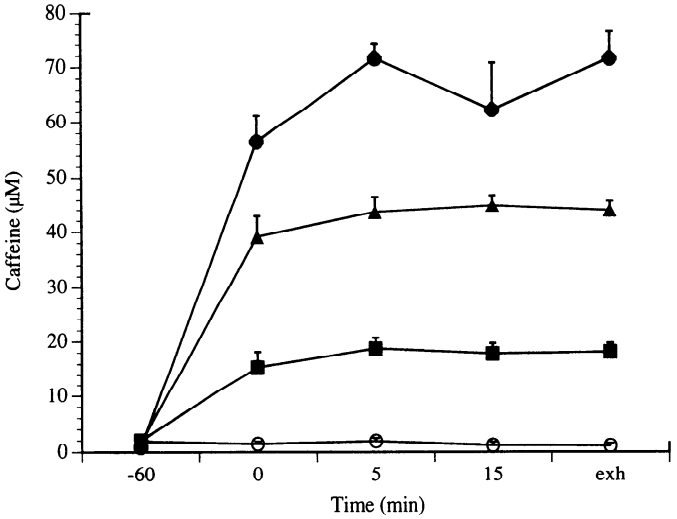


FIG. 1. Plasma caffeine concentration during exercise to exhaustion (exh). Subjects had had no caffeine in their diet for 48 h before the experiment. After a control blood sample (−60 min), the subjects ingested either a placebo (Pl; ○) or caffeine [3 mg/kg (■), 6 mg/kg (▲), or 9 mg/kg (●)]. Bars, SE.

## METHODS

*Subjects.* Eight young adult male volunteers served as subjects for the study. All were well trained distance runners [19–34 yr old, 63.5–83 kg body wt, and 65–76.4 $ml \cdot kg^{-1} \cdot min^{-1}$ $\dot{V}O_{2\,max}$ (determined on the treadmill)]. The subjects were recruited on the basis of their fitness and running ability rather than for uniformity in their caffeine habits. As a result, their daily ingestion of caffeine ranged from 0 to 940 mg/day with two of them being nonusers and three others consuming <200 mg/day. The experimental procedures and the possible risks of the study were explained to each subject both verbally and in writing. All subjects gave their informed consent, and the study was approved by the University's Ethics Committee.

*Preexperimental protocol.* Each subject reported to the laboratory on two occasions before the start of the experiment. On the 1st day the subject performed an incremental $\dot{V}O_{2\,max}$ test on the treadmill. On the 2nd day the subject exercised on the treadmill for 25–30 min at a power output selected to elicit ~85% $\dot{V}O_{2\,max}$. This trial served both to habituate the subject to treadmill running and to confirm that the chosen power output was appropriate.

*Experimental protocol.* Subjects reported to the laboratory four times separated in most cases by 1 wk. For a given subject all trials were conducted at the same time of day. The subjects were instructed to prepare for each test as they would for a race, i.e., to have high-carbohydrate meals and to be well rested. They were told to maintain their normal training schedule and diet. They kept food records and were instructed to eat similar meals and to abstain from all dietary sources of caffeine for 2 days before each trial. Each subject was tested consistently at the same time of day and regulated his diet accordingly.

At the start of each test, a catheter was placed into a medial anticubital vein and a saline drip was started to maintain catheter patency. A resting blood sample was obtained, and the subject consumed gelatin capsules containing 3, 6, or 9 mg/kg of caffeine or placebo (dextrose). The subject rested quietly for 1 h, and a second blood sample was taken. Subsequently the subject warmed up with light running on the treadmill and usually some stretching exercises. On the first trial an accurate record was kept of the duration and intensity of the warm-up, and these were reproduced in each subsequent test. Then the subject ran at a speed and slope that required ~85% $\dot{V}O_{2\,max}$ to the point of voluntary exhaustion. Blood samples and expired air were collected every 15 min and close to exhaustion. All samples were taken while the subject was still exercising. During the trials subjects were given no external clues regarding time (they were told that we would take blood and expired air samples at "various times") and were verbally encouraged to exercise to exhaustion in all trials. Before leaving the laboratory they completed a short questionnaire asking them to state what treatment they believed they had received. The trials were conducted double blind, and the results of the trials were not disclosed to the subjects or the investigators until completion of the tests.

*Analyses.* Expired air samples were analyzed for fractions of $O_2$ and $CO_2$ with an Applied Electrochemical S-3A $O_2$ analyzer and a Sensormedics LB-2 $CO_2$ detector, respectively. Expired volume was determined with a Parkinson-Cowan volumeter. The analyzers were calibrated with gases of known concentrations previously determined by the micro-Scholander technique. The volumeter was calibrated with a Tissot spirometer.

Blood samples were immediately separated into two aliquots; 3 ml were transferred to a nontreated tube for serum, and 7 ml were transferred to a sodium heparinized tube. Hematocrit was measured in triplicate from the latter sample by using high-speed centrifugation. A modest hemoconcentration occurred in the exercise samples, but there was no difference between trials. A 100-μl aliquot of heparinized blood was added to 500 μl of 0.3 M perchloric acid. A solution of 120 μl of 0.24 M ethylene glycol-bis(β-aminoethyl ether)-*N,N,N′,N′*-tetraacetic acid (EGTA) and reduced glutathione was then added to the remaining heparinized whole blood.

The EGTA- and glutathione-treated plasma was analyzed in duplicate for epinephrine and norepinephrine concentrations by high-performance liquid chromatography (Waters) as described by Weicker (30). Plasma caffeine and dimethylxanthines (paraxanthine, theophylline, and theobromine) were analyzed by first filtering the samples by centrifugation using Ultrafree-MC polysulfone filter units (Millipore UFC3TGC). Then filtered plasma and the internal standard (β-hydroxyethyl)theophylline were injected onto a Radial-Pak cartridge (model 84624, Waters) using a 8-mm × 10-cm Radial Compression Module. Methylxanthines were mea-

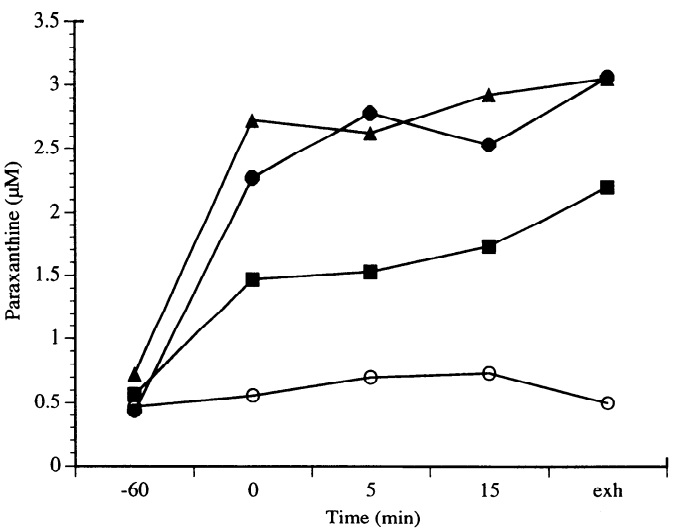


FIG. 2. Plasma paraxanthine during exercise to exhaustion. Paraxanthine is the major metabolite of caffeine. Note that data for 6 and 9 mg/kg trials were very similar, suggesting that this initial step in caffeine metabolism became saturated. ○, Placebo; ■, 3 mg/kg; ▲, 6 mg/kg; ●, 9 mg/kg.

sured at 254 nm and sensitivity range of 0.01 absorbance units full scale. Reagents for standards were obtained from Sigma Chemical. The blood-acid extracts were analyzed enzymatically in duplicate for lactate (16) and glucose (4). Serum was analysed enzymatically in triplicate for FFA (22) and glycerol (14).

*Statistics.* Statistical analysis of the data was complicated by the fact that each subject exercised for a different duration. Therefore complete sets of data were obtained only at −60, 0, 15, and 30 min and at exhaustion. At each time point differences between the four treatments were tested with an analysis of variance. In addition the −60 and 0 min time point data were also compared by analysis of variance for a possible caffeine effect before exercise. If significance ($P < 0.05$) was found, then Duncan's multiple range test was performed. Data are reported as means ± SE.

## RESULTS

*Plasma methylxanthines.* In the placebo condition the subjects had traces (generally <1 μM) of dimethylxanthines in their plasma, and only three of the eight subjects had any detectable plasma caffeine; their values ranged from 1.0 to 3.5 μM. In contrast, during the three caffeine trials the plasma caffeine concentrations rose in a clear dose-related fashion (Fig. 1). In association with this rise, plasma paraxanthine increased progressively with the 3 and 6 mg/kg trials but had no further increase with the 9 mg/kg dose (Fig. 2). The increases in theophylline and theobromine were much lower and more inconsistent (data not shown).

The subjects were not accurate in identifying which test they had completed. For example, only three subjects could positively identify the placebo trial and only one (a nonuser) was able to correctly identify all four tests. Only in 16 of 24 caffeine tests could the subjects correctly identify that they had ingested caffeine, and with the exception of one nonuser none of the subjects correctly guessed the doses. The frequency of correct responses did not appear to increase with dose (e.g., 2 subjects believed that 6 mg/kg of caffeine was placebo) except that everyone believed that the 9 mg/kg dose did have some caffeine in it.

*Pulmonary data.* The pulmonary $\dot{V}O_2$ and RER data had no significant differences due to caffeine. The mean RER data ranged from 0.84 to 0.81 for all time points in all trials.

*Plasma catecholamines.* Every dose of caffeine resulted in a small but significant increase in plasma norepinephrine after 1 h of rest (Fig. 3); the values at this time were greater than the corresponding values preingestion and also greater than those of the placebo condition both pre- and postingestion ($P < 0.05$). During exercise plasma norepinephrine rose to a similar extent after 15 min in all conditions, whereas at 30 min the placebo condition was significantly lower than that of 9 mg/kg of caffeine. At exhaustion all three caffeine trails had greater plasma norepinephrine than that of the placebo condition ($P < 0.05$). At no time point was there a clear indication of a dose-related response other than the general finding that the high caffeine dose was associated with concentrations greater than those of the placebo.

After 1 h of rest caffeine ingestion resulted in an

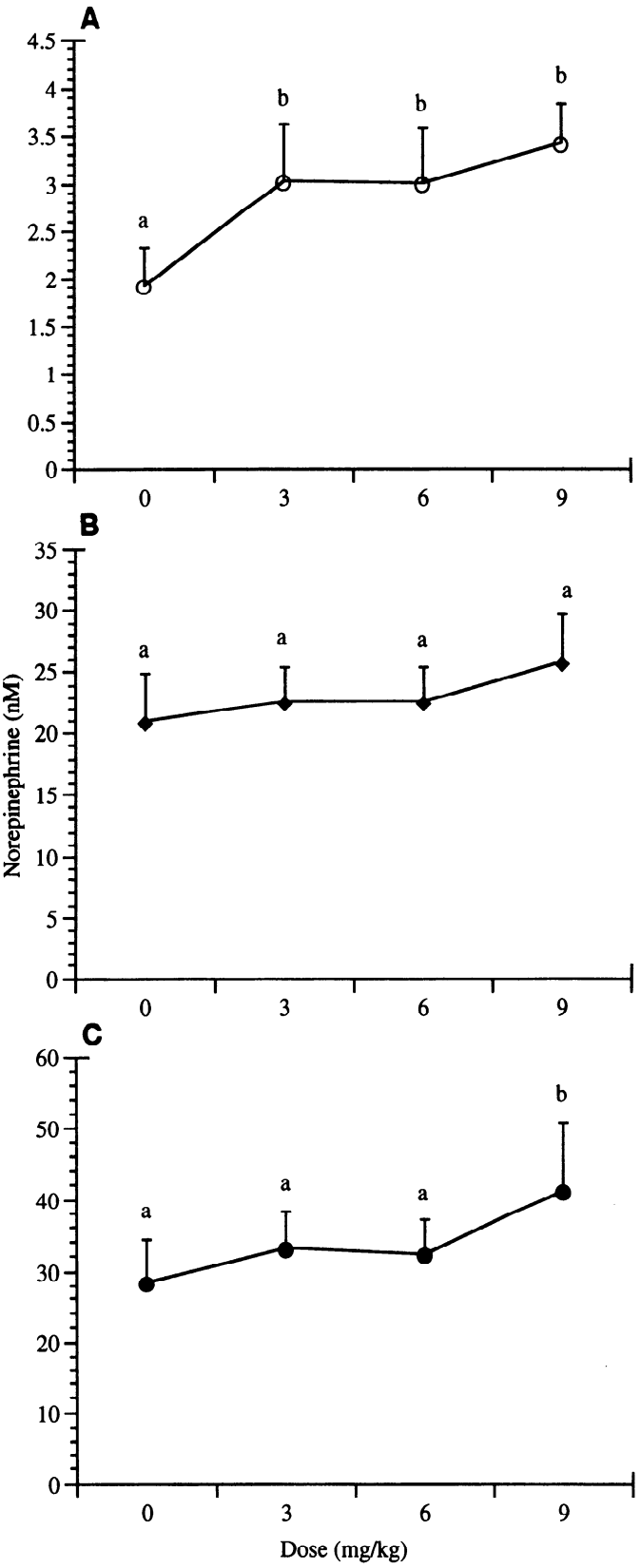


FIG. 3. Plasma norepinephrine during exercise to exhaustion. *A*: data at 0 min. *B*: data at 15 min. *C*: data at 30 min. These data are presented within a time period, i.e., they were obtained on different days because the key issue was whether the data were significantly different among treatments within a time point. Scale of *y*-axis is different for each time point to accommodate the rise during exercise. Those points associated with the same letter were not significantly different from each other.

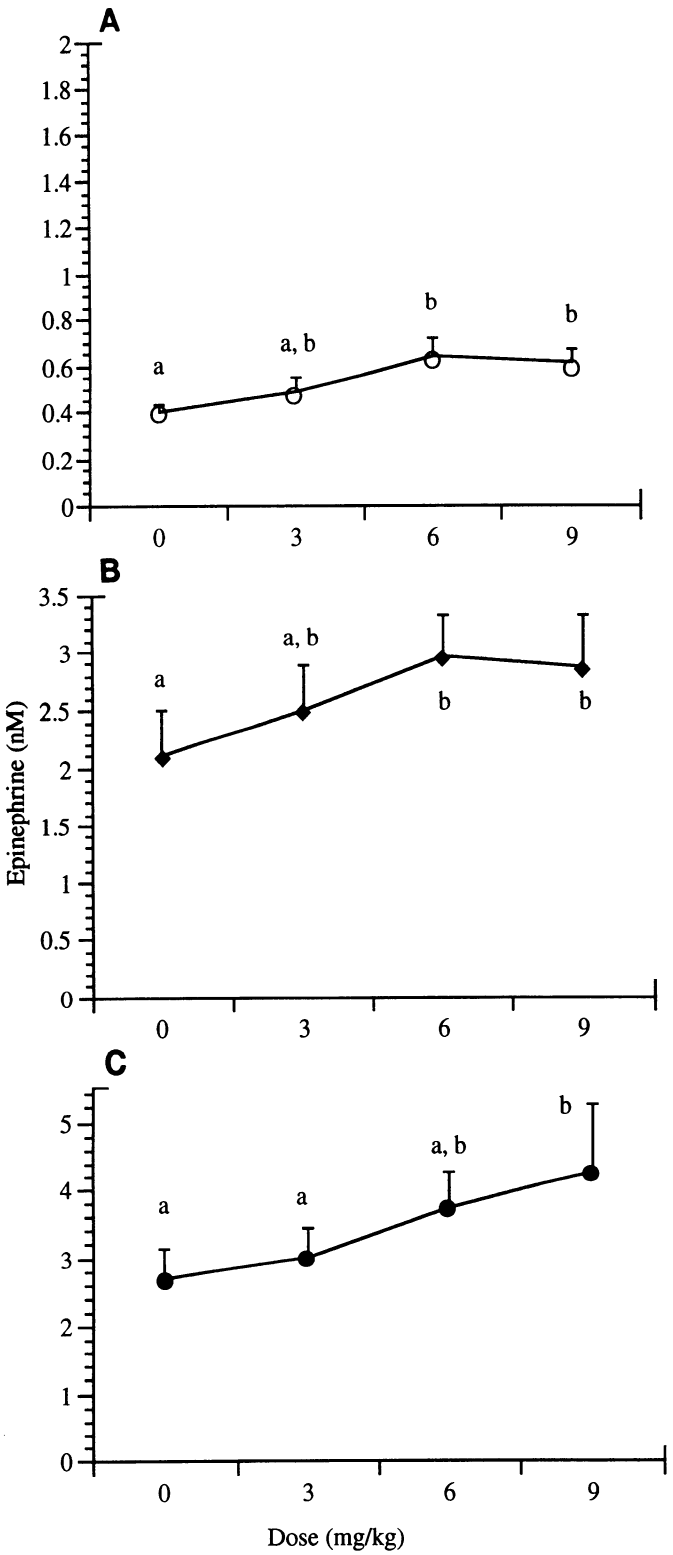


FIG. 4. Plasma epinephrine during exercise to exhaustion. *A*: data at 0 min. *B*: data at 15 min. *C*: data at 30 min. Data were not significantly different between placebo (0 mg/kg) and 3 mg/kg, whereas 9 mg/kg of caffeine resulted in significantly greater plasma epinephrine than placebo. Those points associated with the same letter were not significantly different from each other.

increase in plasma epinephrine such that the concentrations after ingestion of 6 and 9 mg/kg of caffeine were significantly greater than that of the placebo condition (Fig. 4) as well as those values for all conditions preingestion. However, the concentration of plasma epinephrine was not altered after ingestion of the low dose of caffeine. Exercise increased the plasma epinephrine concentration in all trials, and at 15 min the moderate and high caffeine tests had greater levels than placebo ($P < 0.05$). At 30 min the concentration for the 9 mg/kg test was significantly greater than that of both the placebo and the 3 mg/kg experiment. At exhaustion both the moderate and high caffeine doses had epinephrine concentrations greater than placebo ($P < 0.05$). There appeared to be a dose-related response in these data in that the 3 mg/kg dose never caused an increase in epinephrine over placebo, whereas the 9 mg/kg trial produced a greater concentration throughout the experiment ($P < 0.05$). The moderate caffeine dose never resulted in an epinephrine level that was significantly lower than that of the high dose or greater than the low dose, but the data were usually greater than placebo values.

Although there appeared to be a caffeine-epinephrine dose relationship on the basis of the mean data, at an individual level this was not the case. After 15 min of exercise the increase in plasma epinephrine above placebo concentration averaged 96, 181, and 162 pg/ml for the low, moderate, and high caffeine doses, respectively, and the corresponding data for 30 min were 62, 196, and 289 pg/ml. It is tempting to describe these as dose related; however, only one-half of the subjects had their greatest increase with the 9 mg/kg dose and the apparent dose relationship was not consistently demonstrated.

*Blood-borne metabolites*. The data for blood glucose and lactate and serum FFA and glycerol are summarized in Table 1. Blood glucose concentrations were not different between treatments at any time during rest. The concentrations rose during exercise: at 15 and 30 min the concentration was greater in the 6 mg/kg trial than in the placebo condition ($P < 0.05$) and that of the high caffeine dose was greater than placebo at 15 min. At exhaustion the glucose concentration was greater in the 3 mg/kg test than in both the placebo and 9 mg/kg trials ($P < 0.05$); the latter was also lower than the 3 mg/kg data ($P < 0.05$).

Blood lactate rose moderately with exercise, and the concentration during the 9 mg/kg trial was consistently greater than that of placebo ($P < 0.05$; Table 1). There was a distinct trend for both the blood glucose and lactate concentrations to be greater in the caffeine trials.

After ingestion of caffeine the serum FFA concentration was significantly increased by the high dose. However, there were no significant differences between any of the data during exercise. Before exercise caffeine at all three doses elevated the serum glycerol levels above that of placebo. Throughout the exercise the glycerol concentration in the 9 mg/kg test was greater than that in the placebo experiments, but at no time were the data for the other caffeine trials greater than placebo. Thus at rest caffeine ingestion increased serum glycerol and the high dose also resulted in an elevated FFA concentration. During exercise the high dose caused an elevation in glycerol and lactate but no change in FFA.

*Endurance*. With the placebo treatment the subjects

TABLE 1. *Summary of blood metabolite data*

| Measure Caffeine Dose | Time, min | | | | |
|---|---|---|---|---|---|
| | −60 | 0 | 15 | 30 | Exh |
| Glucose, mM | | | | | |
| Pl | 3.39±0.47 | 3.35±0.29 | 3.91±0.33† | 4.74±0.25† | 4.94±0.82†§ |
| 3 mg/kg | 3.59±0.34 | 3.27±0.26 | 4.51±0.35†‡ | 5.35±0.30†‡ | 5.83±0.34‡ |
| 6 mg/kg | 3.83±0.30 | 3.62±0.27 | 4.99±0.37‡ | 5.89±0.41‡ | 5.51±0.76‡ |
| 9 mg/kg | 3.26±0.29 | 3.95±0.17 | 5.32±0.44‡ | 5.09±0.51†‡ | 4.54±0.19§ |
| Lactate, nM | | | | | |
| Pl | 1.09±0.12 | 1.08±0.12 | 3.00±0.59† | 3.66±0.64† | 4.44±0.54† |
| 3 mg/kg | 1.10±0.07 | 1.21±0.17 | 3.97±0.55†‡ | 4.16±0.54† | 5.32±0.77†‡ |
| 6 mg/kg | 1.34±0.33 | 1.64±0.38 | 3.33±0.45‡ | 4.26±0.69† | 5.22±0.97†‡ |
| 9 mg/kg | 0.84±0.08 | 1.24±0.15 | 4.16±0.53‡ | 5.35±0.82‡ | 6.26±0.8‡ |
| FFA, mM | | | | | |
| Pl | 0.42±0.09 | 0.38±0.07† | 0.44±0.09 | 0.42±0.08 | 0.46±0.08 |
| 3 mg/kg | 0.39±0.07 | 0.67±0.15†‡ | 0.51±0.07 | 0.49±0.05 | 0.47±0.06 |
| 6 mg/kg | 0.33±0.05 | 0.67±0.17†‡ | 0.45±0.06 | 0.43±0.06 | 0.47±0.05 |
| 9 mg/kg | 0.55±0.18* | 0.96±0.27‡ | 0.55±0.07 | 0.58±0.07 | 0.60±0.06 |
| Glycerol, mM | | | | | |
| Pl | 0.18±0.01 | 0.14±0.02† | 0.25±0.02† | 0.35±0.03† | 0.41±0.05† |
| 3 mg/kg | 0.18±0.02 | 0.21±0.03‡ | 0.36±0.06†‡ | 0.43±0.04†‡ | 0.46±0.06†‡ |
| 6 mg/kg | 0.16±0.01 | 0.20±0.03‡ | 0.31±0.03†‡ | 0.37±0.04† | 0.52±0.07†‡ |
| 9 mg/kg | 0.19±0.03* | 0.23±0.03‡ | 0.49±0.11‡ | 0.46±0.04‡ | 0.56±0.05‡ |

Values are means ± SE. Dose of caffeine is indicated as placebo (Pl) or 3, 6, or 9 mg/kg. Exh, exhaustion. Values not having the same symbol are significantly different from each other ($P < 0.05$). * Data at 0 min are significantly different from corresponding data at −60 min within a given treatment.

ran for 49.4 ± 4.2 min; their endurance was significantly increased to ~60 min with either 3 or 6 mg/kg of caffeine (Fig. 5), which represented a 22.0 ± 9.0 and 21.9 ± 7.2% increase over the placebo data, respectively. In contrast, endurance with 9 mg/kg of caffiene was more variable and the increase (6.2 ± 6.2 min or 10.9 ± 12.6%) was not significantly different from placebo. Only two subjects, both caffeine users, had their best result with 9 mg/kg of caffeine, whereas three subjects actually ran longer with placebo than with 9 mg/kg of caffeine. There did not appear to be any relationship between caffeine habits and optimal dose; for example, the heaviest user had his longest run after 3 mg/kg of caffeine but the two nonusers had their best endurance with 6 mg/kg of caffeine. Subjectively, some subjects, especially the lightest users and nonusers, complained of mental confusion, the inability to "focus" on the task, and so on, with the highest dose. One subject had been tested in our laboratory previously and with 9 mg/kg of caffeine had run 25.2 min longer than with placebo. Two years later at the same power output he ran 21.15 min longer.

## DISCUSSION

This study examined the exercise responses of well-trained endurance athletes to various doses of caffeine to evaluate the impact of the drug on plasma catecholamines, the circulating concentration of FFA, and endurance. The results demonstrated that ingesting higher doses of caffeine resulted in a progressive increase in circulating plasma caffeine, but there was a clear upper limit in the concentration of paraxanthine, caffeine's main metabolite. Caffeine was associated with no change in epinephrine at the low dose but with significant increases after the moderate and high doses. Only the highest caffeine dose resulted in increases in serum glycerol and FFA concentrations. Despite the apparent ineffectiveness of the low dose and the apparent strong response of the high dose, endurance was improved with the former but not with the latter.

The hepatic cytochrome *P*-450 oxygenases play a major role in the primary metabolism of caffeine to the dimethylxanthines; the majority of the caffeine is demethylated at the 1, 3, and 7 positions, resulting in theobromine, paraxanthine, and theophylline, respectively. Paraxanthine represents 80–85% of the metabolism (20, 21), and it has been suggested that paraxanthine may be involved in FFA mobilization (17). Our data do not support this hypothesis; although the paraxanthine concentrations in our study were in the same range (1.5–7 μM) as those reported by Hetzler et al. (17), the serum FFA and glycerol data in the present study increased significantly only with the high caffeine dose. In contrast, the paraxanthine concentration was elevated with even the low dose, and its concentration during the 9 mg/kg caffeine trial did not increase above that seen with 6 mg/kg of caffeine. Thus there was a complete dissociation between the circulating paraxanthine and FFA concentrations.

These paraxanthine and caffeine data also demonstrate an important aspect of caffeine metabolism. Cytochrome *P*-450 1A2 is the isoform that is the sole mediator of 3-demethylation, i.e., the production of paraxanthine. Both Kotake et al. (21) and Denaro et al. (10) have suggested that this enzyme can be saturated with caffeine; their data demonstrated that a caffeine dose between 3 and 5 mg/kg was sufficient to cause saturation. Our data are in full agreement with this conclusion, as in both the 6 and 9 mg/kg trials paraxanthine reached concentrations of ~3 μM while the high dose of caffeine resulted in a 50% increase in plasma caffeine over that observed with the moderate dose.

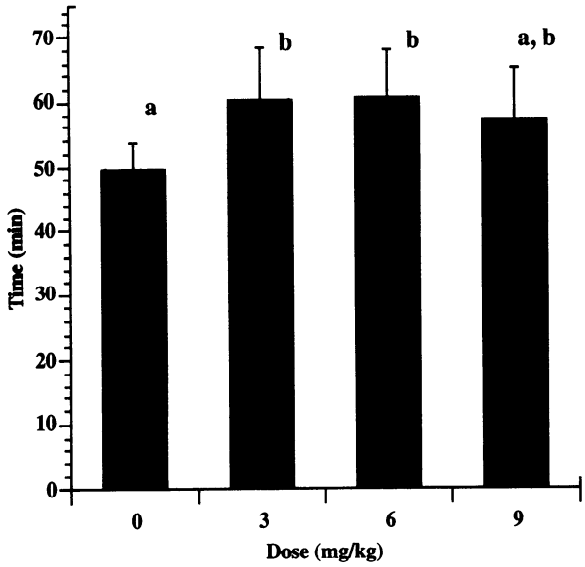


FIG. 5. Exercise time during exercise to exhaustion. Data are mean data for exercise duration after placebo (0 mg/kg) or 3, 6, or 9 mg/kg of caffeine. Histogram bars with the same letter are data not significantly different from each other. Note that 0 and 3 mg/kg trials were significantly different despite lack of difference in plasma epinephrine (Fig. 4) and, conversely, that 0 and 9 mg/kg exercise times were not significantly different, although these trials had quite different plasma epinephrine data (Fig. 4).

The actions of caffeine could be the direct result of the plasma caffeine or could be due to the increase in plasma epinephrine. Vestal et al. (29) found that increasing concentrations of theophylline in the range of the caffeine concentrations used in the present study resulted in a dose-related increase in epinephrine. However, they demonstrated this only with the mean data for their subjects. The mean data in the present study also tend to demonstrate such a relationship, but within individual subjects there was variation across caffeine doses. This result together with the data for both performance and blood-borne metabolites (see below) lead us to conclude that the rise in epinephrine is not essential for the caffeine responses. Previously van Soeren et al. (28) found that groups of caffeine users and nonusers had very similar metabolic responses to caffeine ingestion before exercise despite having very different plasma epinephrine responses. Similarly, Bangsbo et al. (3) found that 6 wk of increased caffeine intake dampened the epinephrine response to caffeine but had no impact on exercise metabolism. In these previous studies it is possible that the different responses between groups and/or treatments were due to differences in either liver metabolism of caffeine or differences in peripheral tissue sensitivity to caffeine and/or epinephrine. However, in the present study these long-term adaptations could not be a factor, and we can conclude that the different epinephrine concentrations had no detectable effect on metabolism.

In contrast, previous studies (19, 24, 27) demonstrated that elevation of circulating epinephrine concentrations via infusion resulted in an increase in muscle glycogenolysis in the active muscle and an increase in glycogen phosphorylase $a$. However, the increases in epinephrine in these investigations were very large, far exceeding the increase associated with the caffeine trials in the present experiments. This finding suggests that whereas epinephrine is obviously a potent metabolic hormone, there are many redundancies in the systems and a perturbation in one parameter does not need to lead to a response unless the perturbation is large.

The results for exercise endurance also support the conclusion that caffeine does not need to assert its effects through a catecholamine mechanism. The low dose of caffeine caused a significant increase in endurance, but there was no change in epinephrine. Similarly the high dose of caffeine did not significantly increase endurance, yet there was a large increase in plasma epinephrine. On the basis of subjective reports of some subjects it would appear that at the high dose the caffeine may have stimulated the central nervous system to the point at which the usually positive ergogenic responses were overridden.

Our result of a lack of a significant increase in endurance after the ingestion of 9 mg/kg of caffeine is contrary to our recent work (15, 26) in which this dose resulted in a 44% increase in elite runners and a 27% increase in fit recreational athletes. The present subjects would certainly be comparable to the those of the latter investigation, and the protocol as well as the diet and exercise control before the test were identical. The reason for the difference may lie in their caffeine habits. In all three studies the subjects had a wide range of caffeine use. The previous studies had fewer light and/or caffeine nonusers than the present study did. The present results for the high caffeine dose were quite variable: three subjects (all caffeine users) had large increases in endurance relative to placebo, three others had their shortest exercise with this dose, and one had a very modest increase over his placebo time. Two of these subjects were nonusers, and one was a very light user. There is no clear direct relationship between their caffeine habits and the response to this high dose, but generally the lightest users had a weak or negative response and complained of mental "confusion."

Perkins and Williams (23) could not demonstrate an ergogenic response with 4, 7, or 10 mg/kg doses of caffeine, but their protocol lead to exhaustion in 5 min. Only Cadarette et al. (7) studied dose responses of caffeine during prolonged exhaustive exercise. Their plasma caffeine concentrations and exhaustion times were similar to those in the present study, and the moderate dose (4.4 mg/kg) was optimal for endurance, as it was in this experiment. However, they attributed this result to one subject's data and implied that generally there was little effect of caffeine. It is difficult to compare their results with those of the present study, because they did not measure catecholamines and, more importantly, we are uncertain about their preexperimental control of caffeine. They asked their subjects to withdraw from caffeine for 48 h (the regular caffeine habits of the subjects are not given), but they report a placebo or preingestion plasma caffeine concentration of almost 22 $\mu$M. Our subjects had little or no caffeine ($<3.5$ $\mu$M) in their plasma after a 48-h withdrawal, and even after ingesting 3 mg/kg of caffeine their concentrations were $<22$ $\mu$M; yet, there was a

significant improvement in endurance with this caffeine dose. Therefore the plasma caffeine concentration in their placebo condition could very well have resulted in a positive endurance performance.

The endurance data have serious implications for sports-governing bodies. Currently the maximal concentration of caffeine acceptable by the International Olympic Committee is 12 $\mu$g caffeine/ml urine. We did not measure urinary caffeine in this study, but in other investigations (15, 26) we found that in identical protocols even a dose of 9 mg/kg resulted in a urinary concentration below this limit. Thus the present data imply that a caffeine dose ~33% of what is acceptable has an ergogenic effect.

The data of the blood-borne metabolites are difficult to interpret both because they are only concentrations and do not always reflect flux and also because fats are very energy dense and important physiological changes may not always be measurable. Nevertheless the data had certain consistencies: significant differences were associated almost exclusively with the high caffeine dose. With it the resting FFA concentration was elevated and glycerol was increased throughout the experiment. These findings suggest that adipose triglycerides were mobilized. However, it is ironic that this response, which is fundamental to the theory of Essig et al. (13), should occur only in the experiment in which there was no improvement in endurance. As mentioned above, it also occurred when there was no further increase in plasma paraxanthine concentration. Previously several investigators (7, 11, 12) also reported the lack of a dose response of FFA to caffeine. Our data do not permit us to conclude whether the FFA-glycerol response to the high caffeine dose was due to the large increase in epinephrine or to a direct action of caffeine on the adipose tissue.

We also observed a trend in the lactate data to be greater with each caffeine dose, and this trend reached significance with the 9 mg/kg dose. Cadarette et al. (7) reported an identical finding, and previously we found (15, 26) that 9 mg/kg of caffeine elevated blood lactate during strenuous prolonged exercise. Similarly, there are reports that caffeine increased blood lactate during brief intense exercise (2, 8). This is paradoxical, since caffeine has been shown to result in reduced muscle glycogenolysis during prolonged exercise (13, 26). We cannot conclude that the blood lactate increase was due to increased production, as changes in release and/or clearance could affect the data; however, we are aware of no evidence that either caffeine or epinephrine could increase muscle lactate release or decrease blood lactate clearance. In fact, recently Ahlborg and Juhlin-Dannfelt (1) reported that $\beta$-receptor blockade decreased splanchnic lactate clearance during exercise. Their observation suggests that the elevated epinephrine associated with caffeine ingestion could increase, not decrease, blood lactate clearance. Thus it appears that there may be an increased muscle lactate production despite a decreased muscle glycogenolysis. It seems unlikely that muscle glucose uptake compensates glycolysis, as there were no caffeine effects on the blood glucose concentration. This is an area that merits more investigation.

In summary, this study demonstrated that increasing doses of caffeine resulted in increasing circulating concentrations of caffeine. The lack of a progressive increase in paraxanthine implies that the initial metabolic step may be saturated. Endurance performance was enhanced by low and moderate doses of caffeine when there was no accompanying changes in blood FFA and/or epinephrine. These data suggest that the caffeine effects on endurance, blood paraxanthine, epinephrine, and FFA are not all directly dependent on each other and may reflect differential actions of the drug on different tissues at different caffeine concentrations.

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Address for reprint requests: T. E. Graham, Human Biology, Univ. of Guelph, Guelph, Ontario N1G 2W1, Canada.

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