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TITLE

EFFECTS OF CAFFEINE, EPHEDRINE AND THEIR COMBINATION ON TIME TO EXHAUSTION DURING HIGH-INTENSITY EXERCISE

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ORIGINAL ARTICLE

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Effects of caffeine, ephedrine and their combination on time to exhaustion during high-intensity exercise

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Abstract This study investigated the effects of acute ingestion of caffeine (C), ephedrine (E) and their combination (C+E) on time to exhaustion during high-intensity exercise. Using a repeated-measures, double-blind design, eight male subjects exercised on a cycle ergometer at a power output that led to exhaustion after about 12.6 min during a placebo (P) control trial. They did this 1.5 h after ingesting either C (5 mg · kg^{-1}), E (1 mg · kg^{-1}), C+E, or P. Trials were separated by 1 week. Venous blood was sampled before and during exercise. The mean (SD) times to exhaustion were 12.6 (3.1) (P), 14.4 (4.1) (C), 15.0 (5.7) (E) and 17.5 (5.8) (C+E) min. Only the C+E treatment significantly increased time to exhaustion compared to P. Oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), minute ventilation ($\dot{V}_E$) and the respiratory exchange ratio (RER) were similar during exercise for all trials. Heart rate during exercise was significantly increased for the C−E and C trials compared to P. Subjective ratings of perceived exertion during exercise were significantly lower after C+E compared to P. All treatments significantly increased lactate levels. Free fatty acid (FFA) levels were significantly increased by C ingestion. Glycerol levels were increased by C+E and C ingestion. Glucose levels were also higher with the drug treatments compared to P. Increased monamine availability after C+E treatment was suggested by measurements of catecholamines and dopamine. In conclusion, the combination of C+E significantly prolonged exercise time to exhaustion compared to P, while neither C nor E treatments alone significantly changed time to exhaustion. The improved performance was attributed to increased central nervous system stimulation.

Key words Ergogenic aids · Metabolism · Fatigue · Methylxanthine · Sympathomimetic

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Introduction

This research is part of a programme evaluating strategies other than physical training that can acutely enhance the physical work capacity of military personnel. Ergogenic aids fall into such a framework, and can be defined as drugs, nutritional strategies, or physiological procedures that cause enhancement of a physical fitness component. Related research has usually focused on eventual applications for competitive athletics. Military combat personnel represent another population for whom the ability to acutely enhance work capacity can be extremely important, perhaps even influencing survival. It is unlikely that most combat personnel will be as physically fit as are the subjects used in much ergogenic aid research, thus the question arises about the feasibility of enhancing the physical performance of moderately fit individuals with ergogenic aids that have been demonstrated to be effective with a fitter population. Moreover, aside from health risks, the ethical concerns of using ergogenic aids banned by sport regulatory bodies are of no relevance to military operations.

Caffeine is a well-established ergogenic aid which soon after ingestion can prolong time to exhaustion during exercise. The studies which have documented such effects have been done primarily with subjects with a high maximal aerobic power and with performance tests that usually, but not always, lasted longer than 30 min (Costill et al. 1978; Graham and Spriet 1991, 1995; Spriet et al. 1992; Trice and Haymes 1995). The extent of improvement appears to be dose related until a dose of 5–6 mg · kg^{-1}, above which no further enhancement occurs (Graham and Spriet 1995; Passman et al. 1995). The ergogenic effects of caffeine ingestion have been attributed to a wide range of physiological factors leading to stimulation of the central nervous system (CNS) and/or energy metabolism in peripheral tissues, including adenosine receptor blockade, improved neuromuscular transmission, increased muscle contractility, and increased catecholamine levels (for

review see Dodd et al. 1993; Nehlig and Debry 1994), although the link between the latter and improved performance has recently been questioned (Chesley et al. 1995; Graham and Spriet 1995).

Ephedrine is a sympathomimetic drug that is both an α- and a β-adrenergic agonist which can stimulate adrenergic receptors in the CNS and peripheral tissues. Like other sympathomimetic drugs ephedrine's mechanism of action is related primarily to "... displacement of norepinephrine from the nerve-ending binding sites to the extracellular fluid, ... where it can then act on effector cells" (Gilman et al. 1990). Although presumed by the International Olympic Committee to induce performance enhancement, we could find no published studies reporting observations that ephedrine improves physical performance. We could find only two relevant studies published in English. Sidney and Lefcoe (1977) reported that a therapeutic dose of ephedrine (24 mg) had no beneficial effects on indicators of physical work capacity. Gillies et al. (1996) reported that a single 120-mg dose of pseudoephedrine had no effect on 40-km simulated time trials in competitive cyclists, on their force generation during a maximal voluntary muscle contraction, or on muscular endurance during repeated isometric muscle contractions.

Our interest is in prolonging the ability to sustain exercise that leads to exhaustion in 10–20 min, a duration that is unlikely to be limited by depletion of energy substrate stores. Thus, in contrast to others who have hypothesized that caffeine, for example, can prolong exercise time by reducing the rate of carbohydrate oxidation during exercise, we are interested in prolonging exercise at an intensity at which increased arousal is probably more important than substrate availability. In light of the CNS effects of both caffeine and ephedrine (Nehlig et al. 1992), the present study was designed to evaluate the effects of caffeine and ephedrine, individually and in combination, on exercise that leads to exhaustion in about 15 min. The combining of caffeine and ephedrine is based on the speculation that caffeine induces a "permissive" action on ephedrine, both lowering the threshold concentration required for physiological effects and potentiating the physiological effects of a given ephedrine concentration (Astrup et al. 1991; Dulloo et al. 1992).

The purpose of this experiment was to evaluate the effects of caffeine, ephedrine and their combination on time to exhaustion during intense exercise. This study was designed to test the hypothesis that a combination of caffeine and ephedrine would have a greater ergogenic effect than would either caffeine or ephedrine alone.

Methods

Subjects

Informed consent was obtained from 12 healthy male volunteers. Four of these subjects vomited during the exercise trial involving combined caffeine and ephedrine treatment; their data are not presented. The mean (SD) physical characteristics of the remaining eight subjects were: age 31 (5) years, body mass 81.4 (8.4) kg, height 1.77 (0.06) m, peak oxygen consumption ($\dot{V}O_{2peak}$) during cycle exercise 47 (7) ml · kg^{-1} · min^{-1}. The subjects were familiar with exhaustive exercise but were not trained athletes. Participation was restricted to individuals who had been consuming the caffeine equivalent of at least seven cups of caffeinated coffee per week for at least the preceding 6 months. This inclusion criterion was implemented because of the eventual application of the findings to military personnel, the vast majority of whom consume caffeine regularly.

Procedures

A pilot study was carried out to determine the approximate time at which ephedrine, caffeine and the combination of caffeine and ephedrine would produce peak plasma concentrations after ingestion, and to determine the time required between trials to ensure that the drug was cleared. Based on these pilot data it was decided to begin exercise testing 1.5 h post drug ingestion, and that a minimum of 2 days was needed between trials.

During the study the subjects visited the laboratory on six separate occasions. During visit no. 1 they were medically screened, and had their $\dot{V}O_{2peak}$ determined during exercise on an electronically braked cycle ergometer. After a 1-h recovery they exercised in a progressive, step-wise incremental fashion for 4 min at each of four submaximal intensities estimated to be equivalent to 50%, 60%, 75%, and 85% of $\dot{V}O_{2peak}$. The rate of oxygen consumption ($\dot{V}O_2$) was measured between the 3rd and 4th min at each intensity and the linear regression equation between power output and $\dot{V}O_2$ was calculated for each individual subject. This equation was used to calculate the intensities equivalent to 50% and 85% $\dot{V}O_{2peak}$ for subsequent exercise testing. During the subsequent testing the 50% intensity was used for 5 min of warm-up and the 85% intensity was chosen because pilot investigations showed that subjects were exhausted within the desired time framework of about 10–20 min at this intensity.

During visit no. 2 the subjects were familiarized with the experimental procedures and the exercise performance test. During this familiarization session a venous catheter was inserted in an antecubital vein (Insyte, Deseret) and a 1-ml blood sample was taken prior to exercise. The subjects then did the exercise performance test which would be subsequently used in all treatment trials. This consisted of exercising for 5 min at a power output calculated to elicit 50% $\dot{V}O_{2peak}$, followed immediately by exercising to exhaustion at an intensity calculated to initially correspond to about 85% $\dot{V}O_{2peak}$. The subjects were instructed to maintain pedalling rate between 60 and 80 rev · min^{-1} during all trials. The ride ceased when the pedalling rate dropped below 50 rev · min^{-1}. Blood was again sampled at the 5-min mark of the 85% $\dot{V}O_{2peak}$ ride. These two blood samples ("pre" and "5 min") during visit no. 2 were not assayed; their purpose was simply to familiarize the subjects with the blood sampling procedures.

Visits 3–6 were the various drug and placebo trials. These were separated by a minimum of 1 week. All subjects ingested all drugs and the treatments were randomized and double blind. After an overnight fast the subjects drank a 473-ml bottle of Gatorade as their breakfast; it is advertised to contain 28 g of carbohydrate. They then reported to the laboratory 2 h later. A venous catheter was inserted. This was followed by drug ingestion with a 250-ml glass of water. Then the subjects rested for 90 min after which a 10-ml blood sample was taken just before the exercise test. Blood was again sampled at the 5 and 10 min marks of 85% $\dot{V}O_{2peak}$ exercise and at exhaustion. From each 10-ml blood sample 5 ml was expelled into a tube treated with ethylenebis(oxonitrilo)-tetraacetate (EGTA, 90 mg · ml^{-1}) and glutathione (60 mg · ml^{-1}) (Cat-A-Kit, Upjohn, Kalamazoo, Mich., USA) and the remainder was expelled into an EDTA-treated tube (EDTA is ethylenediaminetetraacetate). The EGTA-treated sample was used for catecholamine and drug analysis, the EDTA for all other analyses. Between samples the catheter was kept patent by flushing it with heparinized saline (10 IU · ml^{-1}).

l · ug and placebo administration

All treatments were ingested in opaque gelatin capsules. At 90 min before exercise the subjects consumed either 5 mg · kg^{-1} of caffeine (C), 1 mg · kg^{-1} ephedrine (E), a combined 5 mg · kg^{-1} caffeine plus 1 mg · kg^{-1} of ephedrine (C + E), or a placebo (P). P consisted of the same number of capsules as used for the other treatments, which contained dietary fibre (Metamucil).

Measurements

$\dot{V}O_{2peak}$ was determined as the peak $\dot{V}O_2$ during a progressive incremental test to exhaustion on an electronically braked cycle ergometer (Siemens Ergomed RE 930, Sweden). The test began with subjects pedalling at a power output of 75 W, and exercise intensity was increased by 37.5 W · min^{-1} until the subject was unable to maintain a pedalling rate of 50 rev · min^{-1}. The final 30–60 s of respiratory gases expired were collected in a 350-l wet spirometer (Collins Gasometer, Braintree, Mass., USA). After determining the volume and temperature of the expired gas, a sample line directed a sample from the spirometer to oxygen and carbon dioxide analysers (Ametek models S3A and CD3A, Pittsburgh, Pa., USA) for the determination of gas fractions. During the treatment trials respiratory gas exchange variables were measured continuously during exercise using an automated metabolic cart (OCM-2, AMETEK, USA). Heart rate was monitored throughout the exercise (Vantage XL, Polar, USA). Subjects were asked to rate their perceived exertion (RPE) just prior to the blood sampling during exercise using a 10-point scale (Borg 1982). Plasma was obtained from aliquots of each blood sample and assayed for glucose (GOD-PAP, Boehringer Mannheim, Germany), free fatty acids (FFA, NEFA C kit, Wako, USA), norepinephrine, epinephrine and dopamine (negative ion chemical ionization gas chromatography-mass spectrometry) (Zamecnik 1997). Another aliquot of each whole-blood sample was immediately deproteinized and subsequently assayed fluorometrically for glycerol (Boobis and Maughan 1983) and lactate (Maughan 1982). In addition pre-exercise plasma samples were assayed for their caffeine and ephedrine concentrations by mass spectrometry (GC-MS) electron-impact, selective-ion monitoring.

Data analysis

For the ride times to exhaustion a one-way repeated-measures analysis of variance was used to compare the changes in the dependent variables across treatment trials. For all other variables a two-way repeated-measures analysis of variance was used to compare the changes in the dependent variables across treatments and time. Commercially available statistical software was used (Gagnon et al. 1989). When a post-hoc comparison was required a means-comparison contrast technique was employed (Gagnon et al. 1989), and the Huyn-Feldt-epsilon factors were used to adjust degrees of freedom for multiple comparisons. Statistical significance was accepted at the $P \leq 0.05$ level. Values at exhaustion were used in the analysis but the reader should note that those values correspond to varying times to exhaustion among the subjects.

Results

Plasma caffeine levels [mean (SD)] just prior to exercise and 90 min after treatment ingestion were similar in the C and C + E trials [50.5 (10.1) and 39.9 (8.4) μM, respectively]. Plasma ephedrine levels were also similar just prior to exercise in the E and C + E trials [0.394 (0.091) and 0.329 (0.116) μM, respectively].

The calculation of the regression equations between $\dot{V}O_2$ and power output resulted in a mean slope of 10.3 ml · min^{-1} · W^{-1}, a mean intercept of 624 ml · min^{-1}, and a mean correlation coefficient of 0.99. For the endurance ride to exhaustion the mean power output settings were 131 (20) W for the first 5 min and then 233 (40) W for the remainder of the test. Table 1 shows that there was a significant main effect of drug treatment on the time to exhaustion and no order effect. Time to exhaustion was significantly longer after the C + E treatment when compared to the P or C treatments.

During exercise $\dot{V}O_2$, carbon dioxide production ($\dot{V}CO_2$), and minute ventilation ($\dot{V}_E$) were similar in all trials and increased during exercise (Table 2). Heart rate increased significantly during exercise at the 85% $\dot{V}O_{2peak}$ intensity. The drugs significantly altered the heart rate response to exercise: heart rates after C + E and C treatments were higher than those after P (Table 3). RPE values increased significantly during exercise at the 85% $\dot{V}O_{2peak}$ intensity, and were also significantly affected by drug treatment: C + E values were lower compared to P and C values (Table 3).

Blood variables

For plasma norepinephrine there was a significant time by treatment interaction, which is attributed to the value at exhaustion being significantly greater for both the C + E and E trials compared to both the P and C trials (Table 4).

There were significant effects of both treatment and time on plasma epinephrine levels, which increased significantly during exercise. The C + E and C plasma epinephrine levels were similar but significantly higher than the P and E trials. P and E levels were similar (Table 4).

Pre-exercise plasma dopamine concentrations were significantly higher in C + E compared to P and C trials. By 10 min of exercise both C + E and E values were similar and significantly greater than the P and C values and this significant difference was also observed in the sample taken at exhaustion (Table 4).

Table 1 Effect of treatment and of trial order on time to exhaustion during exercise. Values are mean (SD) for 8 subjects. (*C + E* Caffeine plus ephedrine)

Effect	Time to exhaustion (min)
Treatment:	
Placebo	12.6 (3.1)
C + E	17.5 (5.8)*
Caffeine	14.4 (4.1)
Ephedrine	15.0 (5.7)
Order:	
Trial 1	14.0 (5.0)
Trial 2	15.3 (4.0)
Trial 3	14.3 (4.7)
Trial 4	15.9 (6.1)

* Effects of C + E significantly different from those of placebo and caffeine ($P < 0.05$)

Table 2 Effect of treatment on oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), and minute ventilation ($\dot{V}_E$) during the exercise at the 85% $\dot{V}O_{2peak}$ intensity. Values are mean (SD) for 8 subjects

	Treatment	Time (min) elapsed since start of exercise:				End exercise
		1	3	5	7	
$\dot{V}O_2$* ($l \cdot min^{-1}$)	Placebo	2.46 (0.34)	3.03 (0.35)	3.21 (0.45)	3.28 (0.41)	3.41 (0.48)
	C+E	2.50 (0.34)	2.95 (0.33)	3.14 (0.38)	3.29 (0.33)	3.56 (0.48)
	Caffeine	2.48 (0.31)	3.04 (0.39)	3.25 (0.40)	3.27 (0.34)	3.33 (0.50)
	Ephedrine	2.39 (0.31)	2.94 (0.35)	3.09 (0.28)	3.25 (0.29)	3.52 (0.51)
$\dot{V}CO_2$* ($l \cdot min^{-1}$)	Placebo	2.48 (0.31)	3.36 (0.37)	3.46 (0.50)	3.46 (0.42)	3.54 (0.48)
	C+E	2.44 (0.27)	3.21 (0.28)	3.33 (0.27)	3.43 (0.25)	3.53 (0.33)
	Caffeine	2.49 (0.27)	3.30 (0.33)	3.46 (0.31)	3.44 (0.29)	3.49 (0.44)
	Ephedrine	2.41 (0.26)	3.26 (0.31)	3.37 (0.18)	3.51 (0.22)	3.62 (0.37)
$\dot{V}_E$* ($l \cdot min^{-1}$)	Placebo	62.9 (8.3)	91.0 (12.5)	101.0 (13.8)	108.9 (13.5)	122.9 (14.0)
	C+E	64.6 (6.9)	88.4 (12.5)	98.6 (13.4)	106.5 (13.4)	128.9 (14.0)
	Caffeine	65.9 (9.5)	90.4 (13.7)	102.4 (14.1)	108.5 (17.7)	125.0 (14.5)
	Ephedrine	62.0 (8.3)	86.5 (13.1)	97.9 (13.2)	109.9 (15.0)	126.1 (16.7)

* All variables increased progressively during exercise ($P < 0.05$), but there was no difference among treatments

Table 3 Effect of treatment on heart rate and ratings of perceived exertion (*RPE*) (Borg scale units) during the exercise at the 85% $\dot{V}O_{2peak}$ intensity. Values are mean (SD) for 8 subjects

	Treatment	Time (min) elapsed since start of exercise:		End exercise
		5	10	
Heart rate (beats · min^{-1})	Placebo	170 (11)	177 (10)	181 (10)
	C+E*	176 (11)	183 (11)	187 (9)
	Caffeine	174 (12)†	181 (9)	185 (8)
	Ephedrine	174 (11)	179 (11)	183 (8)
*C+E > placebo = ephedrine; †caffeine > placebo ($P < 0.05$)				
RPE	Placebo	5.6 (1.3)	8.3 (1.1)	8.4 (1.4)
	C+E*	4.7 (0.8)	6.1 (1.1)	8.4 (1.4)
	Caffeine	5.3 (0.7)	8.1 (1.5)	9.0 (1.2)
	Ephedrine	4.9 (1.0)	7.3 (1.8)	8.5 (1.7)
*C+E < placebo = caffeine ($P < 0.05$)				

* Both variables increased progressively during exercise ($P < 0.05$)

Table 4 Effect of treatment on plasma catecholamines before and during the exercise at the 85% $\dot{V}O_{2peak}$ intensity. Values are mean (SD) for 8 subjects

	Treatment	Pre-exercise	Time elapsed since start of exercise (min):		End exercise
			5	10	
Norepinephrine* (nM)	Placebo	3.3 (0.7)	13.2 (2.4)	21.6 (6.0)	27.3 (8.6)
	C+E	3.7 (0.8)	12.1 (3.4)	23.2 (5.7)	34.3 (7.0)†
	Caffeine	3.0 (1.0)	11.9 (2.3)	21.5 (4.8)	29.2 (6.3)
	Ephedrine	3.0 (1.0)	13.5 (2.3)	24.1 (6.2)	33.7 (7.4)†
†Drug by time interaction ($P < 0.05$): C+E = ephedrine > caffeine = placebo at end of exercise					
Epinephrine* (nM)	Placebo	0.29 (0.16)	1.19 (0.43)	2.11 (0.72)	2.77 (1.04)
	C+E	0.50 (0.22)*†	1.47 (0.69)	2.73 (1.07)	3.53 (1.63)
	Caffeine	0.45 (0.17)	1.52 (0.66)	2.91 (1.60)	4.16 (2.16)
	Ephedrine	0.30 (0.16)	1.01 (0.48)	1.94 (1.79)	2.42 (1.66)
Treatment effect ($P < 0.05$): C+E = caffeine > ephedrine = placebo					
Dopamine* (nM)	Placebo	0.47 (0.14)	0.56 (0.14)	0.79 (0.26)	0.96 (0.27)
	C+E	0.65 (0.18)*	0.68 (0.15)	1.07 (0.37)†	1.71 (0.69)†
	Caffeine	0.48 (0.11)	0.59 (0.11)	0.79 (0.15)	1.12 (0.48)
	Ephedrine	0.50 (0.11)	0.67 (0.08)	1.04 (0.36)†	1.57 (0.58)†
†Drug by time interaction ($P < 0.05$): C+E > C = P pre-exercise; †C+E = E > C = P at min 10 and end of exercise					

* All variables increased progressively during exercise ($P < 0.05$)

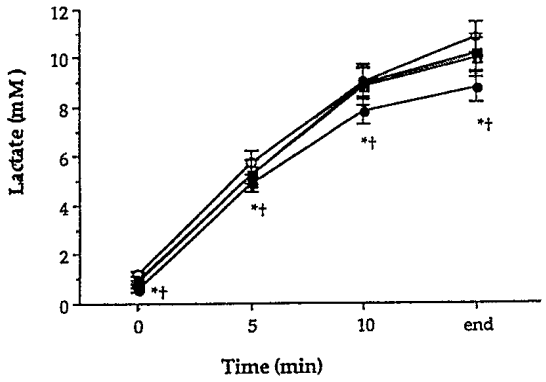

Fig. 1 Lactate concentration in deproteinized whole blood before and during the exercise at the 85% peak oxygen consumption ($\dot{V}O_{2peak}$) intensity. Values are mean (SEM), (O Caffeine plus ephedrine ($C+E$), ■ caffeine, △ ephedrine, ● placebo). *Significant drug effect: C+E = caffeine = ephedrine > placebo. †Significant time effect: end > 10 min > 5 min > 0 min

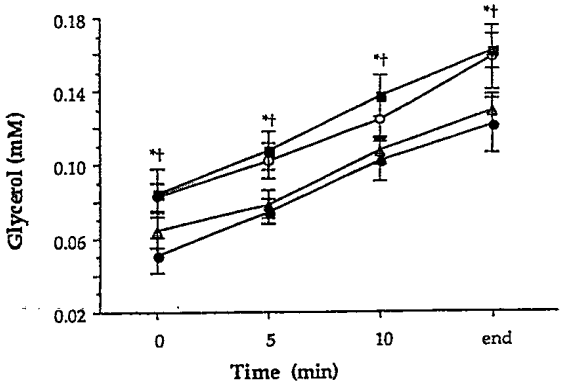

Fig. 3 Glycerol concentration in deproteinized whole blood before and during the exercise at the 85% $\dot{V}O_{2peak}$ intensity. Values are mean (SEM). (O C+E, ■ caffeine, △ ephedrine, ● placebo). *Significant drug effect: C+E = caffeine > ephedrine = placebo. †Significant time effect: end > 10 min > 5 min > 0 min

Blood lactate concentration increased significantly during exercise, and all drug treatments significantly increased lactate concentrations compared to those obtained after P treatments, both pre-exercise and during exercise (Fig. 1).

Plasma FFA concentrations were significantly changed only by C treatment; they were higher both before and during exercise compared to the other trials (Fig. 2).

Blood glycerol also increased significantly in concentration during exercise (Fig. 3), and there were significant main effects of treatment: C and C+E treatments led to similar and higher glycerol levels compared to those measured after P and E treatments (Fig. 3).

The blood sample taken at exhaustion had a significantly higher glucose concentration than that taken pre-exercise. There was also a main effect of drug treatment: C+E treatment led to a significantly higher level than the E, C and P treatments, and C and E values were similar to each other and higher than P levels (Fig. 4).

Discussion

The main finding of this investigation was that the combined C+E treatment increased time to exhaustion during high-intensity exercise by untrained subjects by about 38% compared to P treatment. Since neither the C nor the E treatments alone changed time to exhaustion, the hypothesis was accepted that the ingestion of the combination of C+E would enhance performance more than ingesting either substance alone.

It was decided a priori that a 20% increase in time to exhaustion would be a significant increase. Statistical power calculations were then done based on the anticipated mean time to exhaustion with P treatment and a desired power ($1-\beta$) of at least 0.70. These calculations indicated that 9–10 subjects would suffice; thus, 12 subjects were recruited for the experiment in anticipation of normal subject attrition rates. The relatively high incidence of nausea, which reduced our sample size to eight subjects, was not expected and resulted in a de-

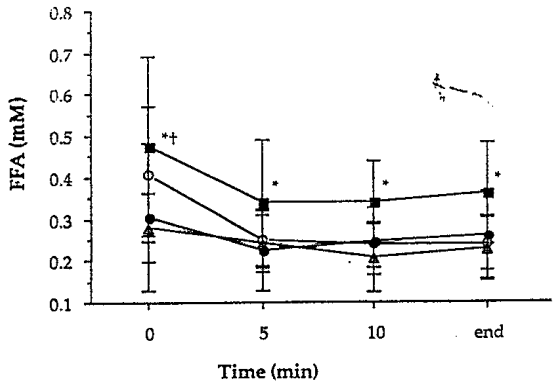

Fig. 2 Plasma free fatty acid (*FFA*) concentration before and during the exercise at the 85% $\dot{V}O_{2peak}$ intensity. Values are mean (SEM). (O C+E, ■ caffeine, △ ephedrine, ● placebo). *Significant drug effect: caffeine > C+E = ephedrine = placebo. †Significant time effect: 0 min > 5 min = 10 min = end

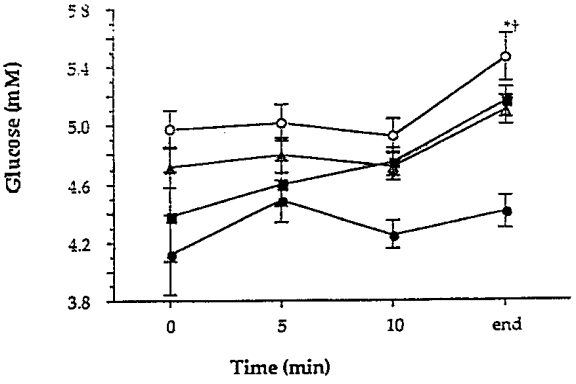

Fig. 4 Plasma glucose concentration before and during the exercise at the 85% $\dot{V}O_{2peak}$ intensity. Values are mean (SEM). (O C+E, ■ caffeine, △ ephedrine, ● placebo). *Significant drug effect: C+E > caffeine = ephedrine > placebo. †Significant time effect: end > 10 min = 5 min = 0 min

crease in power to 0.63. Thus, it can be expected that 63% of the time experiments with a similar sample size of eight subjects would result in finding a significant effect of treatment, if indeed the null hypothesis is false.

The reproducibility of the time to exhaustion variable is a viable concern (McLellan et al. 1995), but an experimental design involving four repeated measurements of a variable is extremely robust to type-I statistical errors. If anything, the lack of reproducibility of time to exhaustion in our subjects should have resulted in an increased risk of a type-II error, i.e. accepting the null hypothesis when in fact it is false, and therefore concluding that there was no difference between trials. In contrast, the difference was systematic; all eight subjects had significantly longer times to exhaustion during the C+E trial compared to the P trial, thus the statistical significance of the finding. The repeated-measures design of this study should have adequately controlled for concern about the reproducibility of the time to exhaustion variable.

C treatment alone did not significantly prolong time to exhaustion. Although the possibility of a type-II error cannot be precluded, such results are similar to those of Butts and Crowell (1985) who employed cycle ergometer tests to exhaustion and similar caffeine doses. The present results, however, are contrary to most of the work done with endurance type activity (Costill et al. 1978; Graham and Spriet 1991; Ivy et al. 1979; MacIntosh and Wright 1995). Our untrained subjects were exhausted after just 14 min after caffeine ingestion. This time is far shorter than the times that the trained subjects of Costill et al. (1978) and Graham and Spriet (1991) lasted, i.e. 90 min and 59 min, respectively. These authors used a similar cycling exercise and intensity. Even when performance times were closer to those of the present study, such as those of MacIntosh and Wright (1995) who studied 1500 m swimmers, training state seems important. Their trained swimmers improved performance after caffeine treatment compared to placebo. Thus, it appears that the state of training of the subjects is a definite factor that can account for some of the differences among the studies.

Our shorter times to exhaustion may also be a result of our methodology. Our power outputs, calculated to be equivalent to 85% $\dot{V}O_{2peak}$, were determined from submaximal 4-min steps. This is too short a step to obtain steady-state during cycle exercise, especially in untrained subjects. Figure 5 shows that 85% $\dot{V}O_{2peak}$ was reached after 5 min, but then continued to increase until exhaustion, when $\dot{V}O_2$ ranged from 88 to 94% with a mean value of 91% $\dot{V}O_{2peak}$.

The possibility also exists that the present subjects were less sensitive to caffeine, as all were required to be caffeine users. Previous studies (Essig et al. 1980; Fisher et al. 1986; Nehlig et al. 1992) have shown that habitual caffeine users have a blunted effect of caffeine ingestion on physical performance.

Higher epinephrine concentrations were measured in the present study after both the C and C+E treatments.

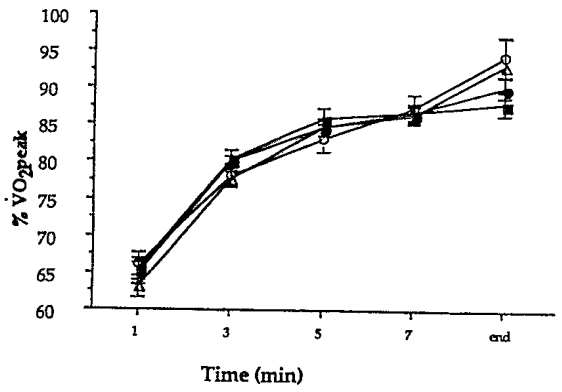

Fig. 5 % $\dot{V}O_{2peak}$ during exercise at a power output equivalent to 85% $\dot{V}O_{2peak}$. (○ C+E, ■ caffeine, △ ephedrine, ● placebo)

This observation is consistent with many (Bellet et al. 1968; Graham and Spriet 1991; Leblanc et al. 1985; Robertson et al. 1978), but not all (Tarnopolsky et al. 1989), previous reports of higher epinephrine levels at rest and during exercise after caffeine ingestion. Higher epinephrine levels could stimulate lipolysis, which would explain the higher FFA and glycerol concentrations during the C and C+E trials in the present study. Spriet et al. (1992) reported that muscle glycogenolysis was significantly reduced during the first 15 min of exercise at about 80% $\dot{V}O_{2max}$ after caffeine ingestion. There is no indication, however, that the increased availability of circulating lipid substrate was exploited in the present investigation, since blood lactate levels were higher after both C and C+E treatments.

The results of the measurements of norepinephrine, epinephrine and their precursor dopamine suggest that monamine availability was increased after C+E treatment. Such increased availability would likely have effects on both peripheral and CNS adrenergic receptors. The blood measurements suggest effects of the various drug treatments on energy metabolism, but there is no indication that energy substrate availability or delivery limited time to exhaustion during the P trial. Thus, increased circulating stores of glucose or lipid are not likely to be advantageous during the exercise test used in this study. Evidence of a CNS effect of the C+E treatment in the present study is found in the RPE for the C+E trials, which were significantly reduced compared to those of the P or C trials. Thus, it can be speculated that a perceptual masking of fatigue allowed the subjects to continue to exercise for longer.

The physiological mechanisms underlying the suggested synergistic pharmacological effects of combining caffeine and ephedrine cannot be fully explained by the data collected in the present investigation. Attributing the effects primarily to increased stimulation of CNS-mediated function is attractive because combined application of caffeine and ephedrine has been demonstrated previously to be synergistic for functions which, in contrast with exercise, are involuntary in nature. Vallerand et al. (1989) reported that the metabolic rate

was significantly higher in resting shivering subjects after combined caffeine and epinephrine treatment than with either caffeine or epinephrine alone. Similarly, Astrup et al. (1991) reported similar results for average daily energy expenditure over several weeks in a clinical trial of combined caffeine and ephedrine used to treat obese individuals.

It is important to note that 4 of the original 12 subjects stopped exercising during the C+E trial because of nausea. Their nausea was stimulated by the exercise and was not reported by the subjects prior to commencing exercise. We presume that it was the interaction of the high-intensity exercise with the caffeine and ephedrine which caused the nausea since these subjects were able to complete all the other trials uneventfully. The nausea was not expected and the scope of this experiment is not sufficient to facilitate identification of the cause. Although caffeine has been known to induce gastric distress in sensitive individuals, no nausea was reported in studies that used far higher doses of caffeine ingested before exercise (Graham and Spriet 1995; Chesley et al. 1995). Whether or not the interaction of ephedrine with caffeine stimulates nausea should be investigated systematically before any application of these findings is pursued.

In conclusion, the combined C+E treatment significantly improved time to exhaustion during high-intensity exercise in untrained subjects, whereas this was not the case with either C or E treatment alone. The ergogenic effect of the C+E treatment is not attributed to changes in muscle energy metabolism, but primarily to CNS-mediated factors.

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