Preexercise Energy Drink Consumption Does Not Improve Endurance Cycling Performance But Increases Lactate, Monocyte, and Interleukin-6 Response

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Abstract

Phillips, MD, Rola, KS, Christensen, KV, Ross, JW, and Mitchell, JB. Preexercise energy drink consumption does not improve endurance cycling performance but increases lactate, monocyte, and interleukin-6 response. *J Strength Cond Res* 28(5): 1443–1453, 2014—The purpose of this study was to investigate the influence of an energy drink (ED) on cycling performance and immune-related variables. Eleven trained male cyclists (33.4 ± 8.9 years; 81 ± 7.6 kg; maximal $\dot{V}O_2$, 52 ± 3.4 ml·kg^{-1}·min^{-1}) consumed 500 ml of (a) ED (2.0 g taurine, 1.2 g glucuronolactone, 160 mg caffeine, 56 g carbohydrate [CHO], and B vitamins), (b) cola matched for caffeine and CHO (CC), or (c) flavored placebo (PL: sparking water and flavoring) 50 minutes before racing in a randomized, crossover design. Performance was measured as time to complete (TTC) a 25-mile simulated road race. Blood was collected at baseline, 30 minutes after drink consumption, during exercise at miles 5 (M5), 15 (M15), and immediately (POEX) and 30 minutes (30minPO) after exercise. TTC was not different ($p > 0.05$) among trials (ED, 68.6 ± 2.7; CC, 68.9 ± 3.8; PL, 69.6 ± 3.8 minutes). Consumption of CC and ED elicited a mild hypoglycemia elicited a mild hypoglycemia during cycling. POEX interleukin-6 (IL-6) was greatest after ED, whereas CC IL-6 was greater than PL (10.2 ± 1.6, 6.7 ± 0.6, and 4.8 ± 0.7 pg·ml^{-1}, respectively; $p < 0.001$). Cycling increased leukocyte number in all conditions with ED leukocyte number greater than that of PL at M15 (9.8 ± 0.6, 8.5 ± 0.3 × 10^6 cells·mL^{-1}). Energy drink induced an earlier recruitment of monocytes to the blood stream than CC. Mean fat oxidation was greater in PL compared with CC (0.43 ± 0.06 and 0.28 ± 0.04 g·min^{-1}; $p = 0.033$) but did not differ between ED (0.32 ± 0.06) and PL. Lactate was higher in ED compared with CC and PL at M5 and M15 ($p = 0.003$), but there was no significant influence of either ED or CC on performance. Carbohydrate and caffeine consumption before endurance cycling significantly increased the IL-6 release and leukocytosis, and the additional ingredients in ED seem to have further augmented these responses.

Key Words caffeine, taurine, B vitamins, endurance performance, immune response

Introduction

In 2004, Froiland et al. (11) reported that energy drinks (ED) were the most frequently used supplements by collegiate athletes, and it seems that their popularity has continued to grow, particularly in recreational athletes and young persons (16). Researchers have reported improvements in exercise or sport performance with the use of popular EDs (1,13,20), although these findings are not consistent (5). The main ingredients in many EDs are carbohydrate (CHO), caffeine (CAF) and taurine, all of which have been shown to improve performance independently (14,25,27,42). In addition, each of these ingredients may also alter leukocyte and interleukin-6 (IL-6) response to exercise and substrate use.

Exercise of sufficient intensity or duration induces leukocytosis, an increase in circulating leukocyte numbers. Exercise-induced increases in stress hormones (corticosteroids, catecholamines) are largely responsible for leukocytosis and regulate leukocyte trafficking, such as demargination of leukocytes (neutrophils, monocytes, lymphocytes, etc) from vascular walls or from other storage sites (lungs, spleen, etc). In general, a greater elevation in IL-6 or leukocytosis indicates greater physical or metabolic stress or both. Depending on the intensity or duration or both of exercise, leukocyte numbers return to resting levels within 30 minutes to 6 hours after exercise. Leukocytosis is blunted with the ingestion of CHO (23,38) but potentiated by adrenergic stimulation such as that experienced during exercise or after CAF ingestion (22,23). In fact, CHO ingestion attenuated the exercise-induced

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elevation in circulating catecholamines (22) such that coingestion of CHO with CAF resulted in a marked reduction of leukocytosis and a reduced IL-6 response to exercise (38). Interestingly, a meta-analysis recently revealed that coingestion of CHO and CAF provide an ergogenic edge over CHO alone (6).

Interleukin-6 is a pleiotropic inflammatory-related cytokine released from most tissues upon cell activation (stress, damage, infection). It is also known as a myokine because it is released from contracting muscle fibers (31) during both aerobic and resistance exercise (24). Furthermore, postexercise or peak plasma IL-6 response is related to endurance exercise intensity (29) and total work performed during resistance exercise (32). Contraction-induced IL-6 appears to act in an endocrine manner as an energy sensor and substrate regulator increasing lipolysis and hepatic glycogenolysis during exercise, thereby increasing substrate availability (7,31,37). Release of IL-6 is augmented by low muscle glycogen levels (36) and adrenergic stimulation (35), while CHO intake reduces IL-6 and stress hormone response to endurance exercise (26). Carbohydrate and CAF appear to have opposing effects on leukocyte and IL-6 response to exercise with the CHO effect overriding that of CAF (38). In addition, IL-6 production, along with that of other inflammatory cytokines or modulators associated with an inflammatory response, is blunted by taurine (18,34).

The influence of taurine on exercise performance has not been well studied. Taurine is found in relatively high concentrations in leukocytes (20–50 mM) and skeletal muscle (50–60 mM). It has been reported that taurine has significant anti-inflammatory properties (34), reduces oxidative stress (42), acts as a pH buffer in mitochondria (15), and exerts positive effects on sarcoplasmic reticulum Ca^{2+} handling and myocardial contractile function (10,33). Supplementation of taurine (7 days, 60 $mg \cdot day^{-1}$) improved $\dot{V}O_2max$, exercise time to exhaustion (TTE), and maximal workload during cycling ergometry (42), whereas acute ingestion of 1–1.9 mg of taurine did not influence TTE, heart rate, or lactate during a high-intensity run to exhaustion (5). Given the relatively high concentration of taurine in leukocytes and its anti-inflammatory properties, it is possible that taurine may also influence leukocyte and IL-6 response to endurance exercise.

The other ingredients in the ED examined here were glucuronolactone and various B vitamins. Glucuronolactone is purported to provide additional fuel and improve performance, but there is no research to substantiate this claim (16). The B vitamins, especially niacin (41), have anti-inflammatory properties and are important for metabolism and adaptation to training. However, their ergogenic potential, when ingested before exercise, is thought to be minimal (40). It is believed that the combination of all the ingredients in an energy beverage may provide an ergogenic edge over coingestion of CAF and CHO alone. We sought to test this hypothesis and to examine potential perturbations in basic immune-related variables, including circulating IL-6 and leukocyte numbers, and indicators of substrate metabolism because it is partially regulated by contraction-induced IL-6.

Therefore, the purpose of this article was to examine the influence of one 500 ml serving of a popular ED (Red Bull, Red Bull GmbH, Santa Barbara, CA, USA) on endurance performance, substrate metabolism, IL-6 levels, and leukocyte trafficking during a 25-mile simulated cycle road race. Specifically, we matched CHO and CAF content of a control beverage (cola; CC) to that of the ED to determine if the added ingredients in the ED influence performance or other dependent variables or both. We hypothesized that both the ED and CC trials would result in improved performance and a reduction in both IL-6 and leukocytosis compared with the placebo (PL) trial. We also hypothesized that there would be no differences in outcomes between ED and CC for performance or substrate metabolism but that ED would result in a lower IL-6 and leukocyte response compared with CC as a result of the inclusion of taurine and B vitamins (particularly niacin) in the ED.

Methods

Experimental Approach to the Problem

This study was designed to test the hypothesis that common ingredients (taurine, B vitamins, glucuronolactone) in EDs provide ergogenic benefits above that of coingestion of CAF and CHO, alone, when consumed before a 25-mile simulated cycling road race. In addition, we sought to determine the influence of the additional ED ingredients on circulating IL-6 and leukocyte concentrations, and substrate utilization because IL-6 is a regulator of substrate availability. At least 5 days after preliminary testing (body composition, graded test for maximal oxygen consumption, etc), all participants completed 3 separate experimental trials, where they consumed 1 of 3 beverages (ED, CC, or PL) before the simulated race. Gas exchange variables were measured and analyzed to determine oxygen consumption and substrate oxidation, while blood samples were obtained throughout the experimental trials to examine circulating variables including glucose, lactate, glycerol, pH, bicarbonate, IL-6, and a complete blood count with a 5-part differential analysis.

Subjects

Eleven recreationally trained male cyclists (mean age, 33.4 ± 8.9 years; body mass, 81 ± 7.6 kg; height, 181 ± 7.2 cm; maximal $\dot{V}O_2$, 4.2 ± 0.07 $L \cdot min^{-1}$, 52 ± 1 $ml \cdot kg^{-1} \cdot min^{-1}$; peak power output, 360 ± 7.8 W) volunteered to participate in a blinded, randomized, crossover design study with 3 experimental conditions. All participants were informed about the risks and procedures of the study and provided written informed consent to participate. This study was approved by an Institutional Review Board at the Texas Christian University. A habitual CAF consumption questionnaire was used to exclude potential participants who consumed less than 80 mg or greater than 350 mg of CAF per day to avoid the influence of novel or excessive CAF use.

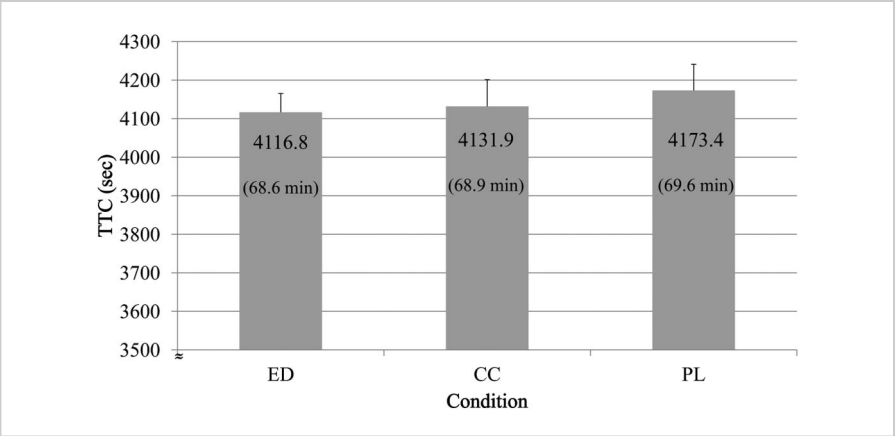

Figure 1. Time to completion (TTC) expressed in seconds. ED = energy drink; CC = caffeine and carbohydrate control; PL = placebo. $p > 0.05$.

Preliminary Procedures

Preliminary testing was conducted a minimum of 5 days before the experimental trials and consisted of body composition assessments, maximal oxygen uptake ($\dot{V}O_2max$), daily CAF intake questionnaire, dietary intake, and an acclimation ride (10 mile). Body mass was measured to the nearest 0.1 kg, and height was measured to the nearest 1 mm. Body composition was assessed using a 7-site skinfold technique with the Siri equation for body density.

Maximal oxygen consumption was determined using a continuous incremental exercise test performed on an electronically braked cycle ergometer (Velotron DynaFit Pro, Seattle, WA, USA) until volitional fatigue. Participants began cycling at a work rate of 100 watts, with increasing increments of 50 watts every 3 minutes for the first 3 stages after which the work rate was increased every 2 minutes by 35–50 W until physical exhaustion. Expired gases were continuously analyzed using open circuit spirometry with automated O_2 and CO_2 analyses (ParvoMedics True One 2400, Sandy, UT, USA). Heart rates were monitored continuously using short-range telemetry (Polar Systems, Kempele, Finland) and recorded every 2 minutes. Following the $\dot{V}O_2$ max test, after a 30-minute rest period, participants completed a 10-mile acclimation ride to allow them to familiarize themselves with the Velotron components. This process allowed each participant to personalize their seat and handle bar heights, pedals, and gear preferences, so that the experimental race simulated a road race as closely as possible.

Experimental Trials

Each participant was instructed to refrain from CAF use beginning at noon on the day before his or her experimental trials. They were also instructed to refrain from structured physical activity and to record their dietary intake during the 24 hours before the first experimental trial and to follow this routine (same dietary macronutrient intake) in the 24 hours before their second and third trials, to standardize their nutritional status and activity levels.

The participants reported to the laboratory after an overnight fast (10–12 hours) on 3 different occasions, separated by at least 5 days. Participants were blinded to the conditions and were randomly assigned 1 of 3 different 500 ml beverages. The ED consisted of a commercially available product (RedBull), which contained 160 mg CAF, 56 g CHO (11.2% CHO), 2.0 g taurine, 1.2 g glucuronolactone, 40 mg niacin, 10 mg pantothenic acid, 10 mg vitamin B6, and 10 μg vitamin B12. The second beverage was a control drink consisting of a traditional cola product, which was matched

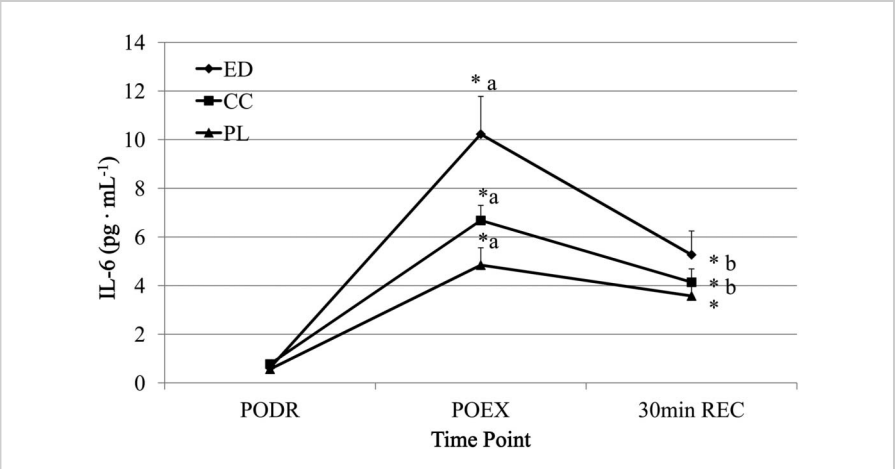

Figure 2. Plasma IL-6 response. *Greater than PREX ($p = 0.001$); a = different than other conditions at POEX; b = lower than POEX within condition ($p < 0.05$). ED = energy drink; CC = caffeine and carbohydrate control; PL = placebo. PODR = 30 minutes after drink ingestion at rest; POEX = immediately after exercise; REC = 30-minute recovery from exercise.

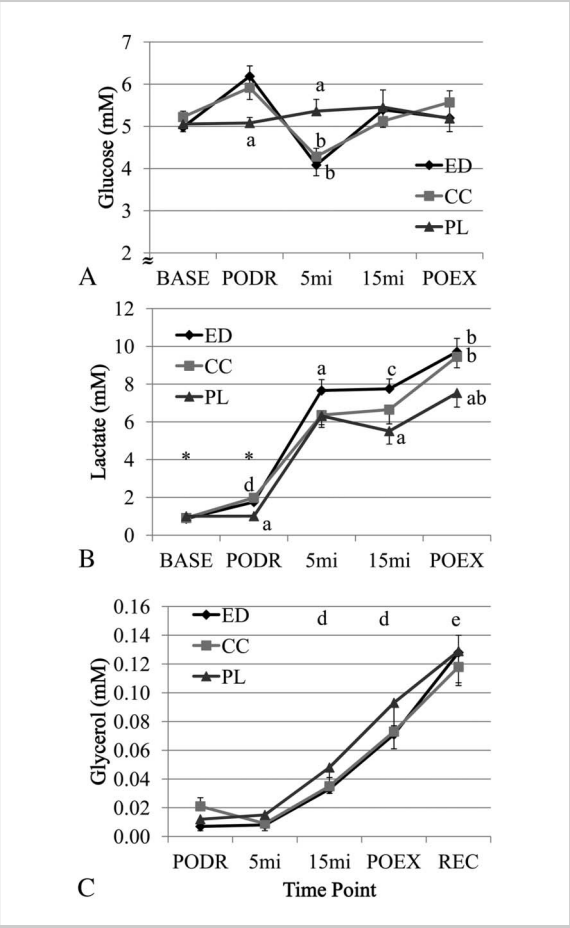

Figure 3. A) Blood glucose level (in millimoles) from BASE to POEX. a = different than other conditions at same time point ($p = 0.015$); b = different than PODR within condition ($p = 0.015$). B) Blood lactate level (in millimoles) from BASE to POEX. *BASE and PODR less than other time points within condition ($p = 0.003$); a = different than other conditions at same time point ($p = 0.003$); b = greater than 5 mi and 15 mi within condition; c = greater than CC at 15 mi ($p \leq 0.05$); d = PODR greater than BASE in ED and CC. C) Blood glycerol level (in millimoles) from PODR to REC. d = time point mean different than PODR, 5 miles, and REC ($p < 0.04$); e = time point mean greater than all other time points. ($p \leq 0.025$). ED = energy drink; CC = caffeine and carbohydrate control; PL = placebo; BASE = baseline after 15-minute supine rest; PODR = 30 minutes after drink ingestion at rest; 5 mi = 5 mile time point; 15 mi = 15 mile time point; POEX = immediately after exercise; REC = 30 minutes recovery from exercise.

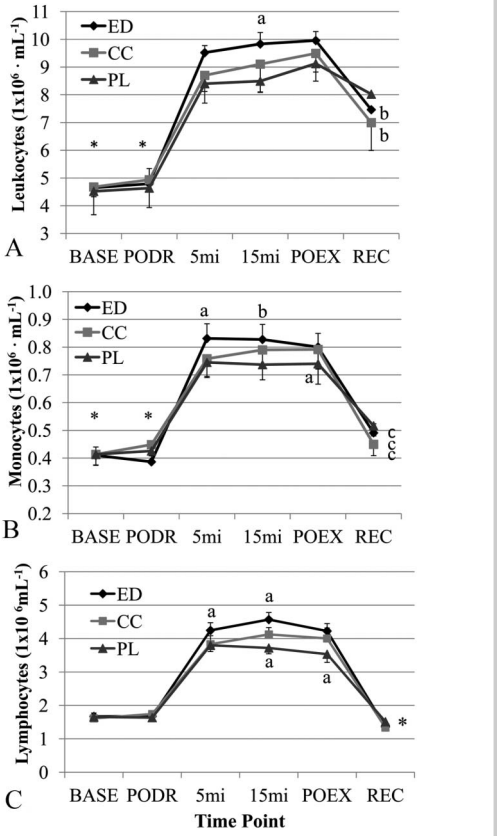

Figure 4. A) Leukocyte number from BASE to REC. *BASE and PODR less than all other time points within condition. a = greater than PL at 15 mi; b = less than 5 mi, 15 mi, and POEX within condition ($p = 0.012$). B) Monocyte number from BASE to REC. *BASE and PODR less than all other time points within condition; a = different from other conditions at same time point; b = greater than PL at 15 mi; c = less than 5 mi, 15 mi, and POEX within condition. ($p = 0.002$). ED = energy drink; CC = caffeine and carbohydrate control; PL = placebo. BASE = baseline after 15-minute supine rest, PODR = 30 minutes after drink ingestion at rest; 5 mi = 5 mile time point; 15 mi = 15 mile time point, POEX = immediately after exercise; REC = 30-minute recovery from exercise.

for CAF and CHO (CC drink) to that of ED. The placebo drink (PL) was made up of sparkling water and noncaloric flavoring. Participants were provided the drinks in opaque, colored containers and consumed each beverage in its entirety within 5 minutes after which time they rested for 40 minutes before warm-up.

Participants were asked to complete a 25-mile simulated road race as fast as possible on the Velotron cycle ergometer. Performance was measured as time to complete the fixed distance (time to completion, TTC). The course was designed to mimic a traditional road race on a relatively flat course with various inclines and descents of ±2%. Participants watched a computer screen that revealed the simulated course on which they were riding. Grade was maintained at zero percent during gas and blood collection. Average percent grade for the 25-mile distance was zero. Water was allowed ad libitum during the first trial for each subject. The volume consumed was measured and allowed for the subsequent 2 trials. All simulated races were preceded by 10-minute warm-up period, including cycling and stretching.

Blood Analysis

Blood was collected from an indwelling catheter inserted into an antecubital vein at baseline (after 15-minute supine rest, before consuming the beverage [BASE]), 30 minutes after consumption of the drink (PODR), during exercise at

Table 1. Neutrophil number.*

($1 \times 10^6 \cdot ml^{-1}$)	Condition	BASE	PODR	5 mile	15 mile	POEX	REC
Neutrophil number	ED	2.32 ± 0.21	2.50 ± 0.25	4.0 ± 0.43	4.01 ± 0.39	4.51 ± 0.36	5.41 ± 0.62
	CC	2.43 ± 0.032	2.53 ± 0.32	3.71 ± 0.45	3.98 ± 0.45	4.20 ± 0.42	5.02 ± 0.56
	PL	2.21 ± 0.13	2.29 ± 0.17	3.47 ± 0.20	3.62 ± 0.19	4.31 ± 0.18	5.81 ± 0.69
	Time point mean ± SE	2.32 ± 0.20†	2.44 ± 0.21†	3.72 ± 0.31	3.87 ± 0.28	4.34 ± 0.27†	5.41 ± 0.56†

*BASE = baseline after 15 minutes supine rest; PODR = 30 minutes after drink ingestion at rest; POEX = immediately post-exercise; REC = 30 minutes recovery from exercise; ED = energy drink; CC = caffeine and carbohydrate control; PL = placebo.
†Different than all other time points ($p < 0.001$).

mile 5 (M5), mile 15 (M15), and immediately after (POEX) and 30 minutes after (30minPO) exercise. Blood was collected into (a) room temperature untreated tubes used for glucose and glycerol, (b) chilled untreated tubes for IL-6, and (c) room temperature EDTA tubes used for lactate, and a complete blood count and 5-part differential analysis (ActDiff 5 Hematology Analyzer; Beckman Coulter, Miami, FL, USA). Blood samples from untreated tubes were centrifuged (2,000*g*, 12 minutes, 4° C) and stored at −80° C until analysis. Interleukin-6 was analyzed via a high-sensitivity enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN, USA). Glucose and lactate were assessed enzymatically via spectrophotometry. Glycerol was analyzed with a quantitative colorimetric kit per manufacturer's instructions (BioAssay Systems, Hayward, CA, USA). Blood bicarbonate and pH levels were assessed via an automated analyzer (ABL 77 series; Radiometer, Copenhagen, Denmark).

Gas Analysis and Ratings of Perceived Exertion

Analyses of expired gases were initiated at mile points 4, 14, and 24. Analyses continued through the completion of miles 5, 15, and 25. Mean oxygen consumption and respiratory exchange ratio (RER) were recorded for each time point. Based on respiratory gas analyses, CHO and lipid oxidation were calculated at each of the time points. Ratings of perceived exertion (RPE; Borg scale 6–20) were obtained to determine if central perception of effort was affected by the beverages. Ratings of perceived exertion was obtained every fourth mile beginning at mile 4 and ending at mile 24.

Statistical Analyses

Data were analyzed using a 2-way repeated measures analysis of variance (ANOVA). The first factor was condition with 3 levels (ED, CC, and PL), and the second factor was time, which had different levels, depending on the variable. The Shapiro-Wilk test was used to check normality of the data, and the Mauchly's test of sphericity was used. If the sphericity test confirmed that the covariance assumption was not satisfied, the Huynh-Feldt adjustment was used to correct degrees of freedom. When the ANOVA detected significant main effects, pairwise comparisons using the Bonferroni adjustment were used to determine where the differences existed. When the ANOVA identified significant interactions, a Newman-Keuls test was used post hoc. Descriptive information is expressed as mean ± *SD*, and dependent variables are presented as mean ± standard error. Threshold for significance was set at $p \leq 0.05$.

Because in measures of performance the null hypothesis test (and associated p value) may fail to identify practical significance, we also used inferential statistics based on interpretation of magnitude of effects (3). The mean effects of the 3 drink conditions and their 90% confidence limits were estimated using the method of Hopkins (17). The method (spreadsheet) computes quantitative and qualitative chances that the true effects of the drinks were beneficial, trivial, and harmful when a value for the smallest worthwhile change is

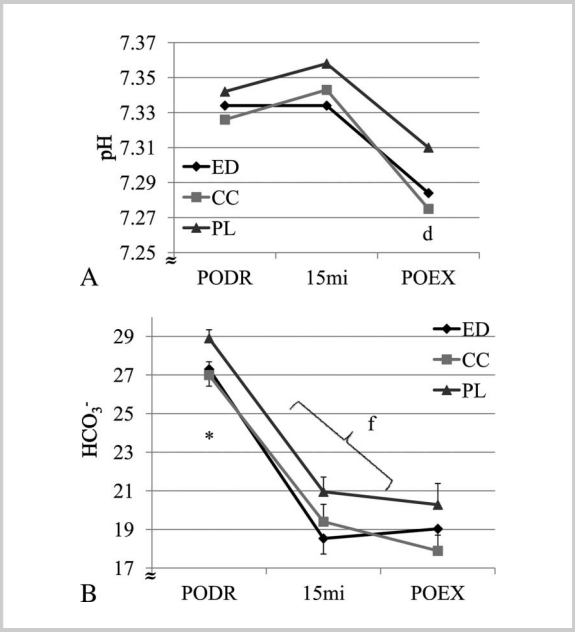

Figure 5. A) Blood pH level ($n = 8$). d = POEX mean less than 15 mi ($p = 0.01$). B). Bicarbonate level (HCO_3^-). *PODR mean greater than 15 mi and POEX means ($p < 0.001$); f = PL mean greater than means of ED and CC (condition effect, p = 0.010). ED = energy drink; CC = caffeine and carbohydrate control; PL = placebo. PODR = 30 minutes after drink ingestion at rest; 15 mi = 15 mile time point; POEX = immediately after exercise.

entered (17). We used a value of 0.6% (25 seconds) for TTC because it represents the smallest worthwhile enhancement for cyclists in road time trials lasting approximately 69 minutes (30). Here, we show the qualitative assessment of the chances of benefit when the chances of benefit were >5% and the chances of harm <5%.

Results

Time to Completion

In the ED condition, TTC was 15.1 and 56.6 seconds faster compared with CC and PL, respectively, whereas CC TTC was 41.5 seconds faster than PC. However, the differences among conditions were not statistically significant ($p > 0.05$; Figure 1). Six participants had the fastest performance in the ED trial, 4 in the CC, and 1 in the PL. Using the spreadsheet to calculate clinical and mechanistic magnitude-based inferences, we found that the differences between each condition were most unlikely harmful, but most unlikely beneficial in respect to race performance (clinical inference, 17). The 90% confidence limits were as follows: ED vs. PL = 3.2 ± 1.8, CC vs. PL = 2.9 ± 1.8, and ED vs. CC = 2.2 ± 1.8. In addition, performance enhancement by either of the CAF-containing beverages was 100% negligible or trivial using the mechanistic inferences (3,17). Therefore, we conclude that ED had no significant practical effect on race performance in the current study.

Blood Analyses

Serum IL-6 was significantly elevated POEX and remained greater than PODR at 30 minutes of recovery in all conditions (Figure 2). There was a condition × time interaction ($p = 0.001$) where POEX IL-6 was different among all conditions, and IL6 at 30 minutes recovery was less than POEX in ED and CC (Figure 2).

Serum glucose did not significantly change during the PL condition; however, both ED and CC resulted in a significant increase in glucose from BASE to PODR such that these values were greater than PL at PODR (30 minutes after drink ingestion) (Figure 3A). Glucose significantly decreased in ED and CC at 5 miles where it was less than that of PL, then returned to baseline levels by 15 miles (Figure 3A). Both ED and CC increased circulating lactate concentration at rest, 30 minutes after drink ingestion, where it was greater in these conditions compared with PL (Figure 3B). During exercise, lactate increased in all conditions as indicated in Figure 3B. Lactate was greater in ED compared with CC and PL at 5 miles and 15 miles. In addition, PL lactate was less than that of CC at 15 miles and less than both ED and CC immediately after exercise. A main effect of time revealed that serum glycerol concentration increased throughout the exercise trials and REC, as indicated in Figure 3C ($n = 8$). When later staged exercise (mean of 15 miles and postexercise) glycerol concentrations were compared, there was a tendency ($p = 0.055$) for PL (0.070 ± 0.011 mM) to be greater than ED and CC (0.052 ± 0.006, 0.054 ± 0.013, mM, respectively).

Circulating leukocyte number was significantly greater at all time points during and after exercise compared with BASE and PODR (Fig. 4A). At the 15-mile time point, leukocyte number was significantly greater in ED compared with PL. During recovery from exercise, leukocyte number dropped in ED and CC to lower than that at 5 miles, 15 miles, and POEX, but remained significantly elevated above resting values (Fig. 4A). Monocyte number in circulation significantly increased by 5 miles and remained elevated above BASE and PODR through 30-minute recovery from exercise in all conditions (Fig. 4B). Monocyte number was greater in ED compared with CC and PL at 5 miles, and greater than PL at 15 miles. By the POEX time point, monocyte number was greater in both ED and CC compared with PL. During recovery from exercise, monocyte number decreased below exercise values, but remained significantly elevated above BASE and PODR in each condition.

Cycling increased lymphocyte number, which returned to baseline by REC (Fig. 4C). Energy drink induced the greatest lymphocyte response as lymphocyte number was significantly greater in ED compared with CC and PL at 5 miles. Furthermore, at the 15-mile time point, lymphocyte number was significantly different among all 3 conditions with ED being the greatest, followed by CC and PL. At POEX, PL was significantly lower than ED and CC (Fig. 4C). Neutrophil numbers are shown in Table 1. There was a main effect

Table 2. Gas analyses and heart rate.*

	Condition	5 mi	15 mi	25 mi	Condition mean ± SE
$\dot{V}O_2$ (L·min^{-1})	ED	3.42 ± 0.09	3.25 ± 0.09	3.61 ± 0.12	3.43 ± 0.09
	CC	3.35 ± 0.07	3.27 ± 0.11	3.73 ± 0.13	3.45 ± 0.09
	PL	3.45 ± 0.11	3.22 ± 0.09	3.62 ± 0.13	3.43 ± 0.09
	Time point mean	3.41 ± 0.09†	3.25 ± 0.08†	3.66 ± 0.11†	
Heart rate (b·min^{-1})	ED	162 ± 4 0.1	165 ± 3.9	175 ± 3.8	167.2 ± 3.7
	CC	159 ± 3.6	161 ± 4.6	175 ± 4.0	165.3 ± 3.9
	PL	158 ± 3.8	158 ± 3.6	168 ± 3.5	161.5 ± 3.2‡
	Time point mean	159.8 ± 3.6	161.3 ± 3.8	172.8 ± 3.5†	
Respiratory exchange ratio	ED	0.97 ± 0.01	0.92 ± 0.01	0.97 ± 0.02	0.95 ± 0.010
	CC	0.95 ± 0.01	0.93 ± 0.01	0.99 ± 0.02	0.96 ± 0.009
	PL	0.94 ± 0.01	0.90 ± 0.01	0.96 ± 0.01	0.94 ± 0.010
	Time point mean	0.95 ± 0.008	0.92 ± 0.009†	0.97 ± 0.012	
Carbohydrate oxidation (g·min^{-1})	ED	3.58 ± 0.14	2.78 ± 0.18	3.75 ±0.28	3.37 ± 0.17
	CC	3.41 ± 0.15	2.97 ± 0.19	4.12 ± 0.25	3.50 ± 0.16
	PL	3.35 ± 0.18	2.56 ±0.21	3.75 ± 0.21	3.22 ± 0.12
	Time point mean	3.45 ± 0.13	2.77 ± 0.14†	3.87 ± 0.21	
Lipid oxidation (g·min^{-1})	ED	0.27 ± 0.06	0.46 ± 0.08	0.24 ± 0.08	0.32 ± 0.06
	CC	0.28 ± 0.05	0.42 ± 0.06	0.15 ± 0.06	0.28 ± 0.04
	PL	0.40 ± 0.07	0.61 ± 0.06	0.28 ± 0.07	0.43 ± 0.06§
	Time point mean	0.31 ± 0.05†	0.50 ± 0.06†	0.22 ± 0.05†	

*Values are expressed as mean ± standard error. ED = energy drink; CC = caffeine and carbohydrate control; PL = placebo; 5 mi = 5 mile time point; 15 mi = 15 mile time point.
†Different than all other time points ($p \leq 0.05$).
‡Different than ED and CC ($p = 0.007$).
§Different than CC ($p = 0.033$).

of time for circulating neutrophil concentration which increased at PODR compared with baseline. Mean neutrophil number continued to increase during exercise and recovery as indicated in Table 1.

A time effect indicated that mean blood pH decreased immediately after exercise compared with that at 15 miles (Figure 5A). There were main effects of both time point and condition for blood bicarbonate level. Bicarbonate significantly decreased at 15 miles compared with PODR and remained lower than PODR and POEX. The PL drink resulted in a greater mean bicarbonate level than ED and CC (Figure 5B).

Ratings of Perceived Exertion and Gas Analysis

A time effect ($p = 0.001$) for RPE revealed that it significantly increased at mile 12, compared with earlier time points. Ratings of perceived exertion further increased at mile 20 and was greatest at mile 25. The time effect was based on a range of values from 12 to 17.5; however, there was only a tendency for a condition × time interaction ($p = 0.065$) where it seems that RPE values may have been approaching significance among groups at the end of exercise (24 miles: ED 15.8 ± 0.48, CC 16.2 ± 0.48, PL 16.8 ± 0.49).

Table 2 shows gas analysis data and heart rate. Mean oxygen consumption was lower at 15 miles compared with 5 miles and was greatest at 25 miles. There was no effect of condition on oxygen consumption. However, mean heart rate was lower in PL compared with ED and CC. Heart rate at 25 miles was greater than that at 5 miles and 15 miles. Respiratory exchange ratio was lower at 15 miles compared with the other 2 exercise time points, but condition had no significant effect on RER. There was a tendency for a condition effect ($p = 0.095$) for steady-state RER (mean of 5- and 15-mile RER) where RER tended to be lower in PL compared with the other 2 conditions. Carbohydrate oxidation was also lower at 15 miles compared with 5 miles and 25 miles, but there was no effect of condition. Mean lipid oxidation was greater in PL compared with ED (Table 2). Lipid oxidation significantly increased from 5 miles to 15 miles, then it significantly decreased at 25 miles to less than that at 5 miles. Average exercise intensity was 82, 83, and 81% $\dot{V}O_2$max in ED, CC, and PL, respectively ($p > 0.05$).

Discussion

Both ED and CC resulted in higher plasma IL-6 and circulating leukocyte concentrations, when compared with PL, in a 25-mile simulated cycling road race, with the greatest changes occurring in the ED condition. These results do not support our hypotheses, as we expected that the additional ingredients in ED would reduce the exercise-induced inflammatory response when compared with CC.

Furthermore, neither ED nor CC significantly improved performance. These results are also in opposition to our original hypotheses but are in agreement with some studies (5) while contradicting others (1,13) where the same or similar drinks were consumed. Timing of drink consumption, inclusion of CHO, and different exercise protocols may explain the differences in outcomes among studies.

In regard to sport performance, timing of preexercise supplement consumption is a key variable to consider. It has been known for sometime that consumption of precompetition CHO should be timed to avoid a large insulin response during exercise (9,19). If CHO is consumed 30–60 minutes before exercise, it induces the expected hyperinsulinemia which, if occurring at the onset of exercise, may lead to a "hypoglycemic rebound" where the effects of muscle glucose uptake during exercise and insulin (reduced hepatic glucose output and increased tissue uptake) result in temporary hypoglycemia (9,21). Elevated insulin levels also inhibit lipolysis resulting in reduced release of free fatty acids during exercise (9). We observed a trend for higher exercise glycerol concentrations in PL compared with the other conditions, which is consistent with insulin's suppression of lipolysis in ED and CC. It seems that the ED and CC conditions also elicited a mild hypoglycemic rebound. In the ED condition, the 5-mile glucose value was $\leq$3.5 mM in 3 subjects with a total of 6 subjects' glucose $\leq$ 4.0 mM. In CC, 2 subjects were below 3.5 mM with a total of only 3 subjects' blood glucose $\leq$ 4.0. No participants experienced a change in glucose in the PL condition. Although there was no apparent negative effect of the mild hypoglycemia on performance in our subjects, the reduced CHO availability may have contributed to the elevated IL-6 observed in both ED and, to a somewhat lesser extent, CC.

In the ED trial, IL-6 was more than twofold greater when compared with PL, and 52% greater when compared with CC. These are quite significant differences. Low blood glucose during exercise influences both muscle fiber IL-6 release and demargination of leukocytes into the vascular pool when compared with exercise with CHO feedings, when blood glucose is maintained (23,38). Furthermore, hypoglycemia is known to stimulate the hypothalamic-pituitary-adrenal axis, resulting in the release of stress hormones. In fact, the CAF-related increase in exercise IL-6 was completely blunted when CAF was coingested with CHO (38). In part, the influence of low blood glucose and CAF on immunological variables is because of the increases in cortisol and epinephrine, both of which stimulate IL-6 release and increase circulating leukocyte number (23,35,38), independent of exercise (22). In addition, low blood glucose may increase reliance on muscle glycogen as fuel, and low glycogen levels are associated with increased IL-6 release (36). The metabolic roles of contraction-induced IL-6 release include lipolysis and glycogenolysis, as IL-6 acts as a substrate regulator acting to increase substrate availability (31,37). The CHO-induced hyperinsulinemia and associated, temporary hypoglycemic rebound measured at mile 5 (approximately 14 minutes of exercise) in the ED and CC trials most likely contributed to the elevated IL-6 response in these conditions by reducing available glucose to working muscles, inhibiting lipolysis, and increasing stress hormone response and reliance on muscle glycogen. We did not measure stress hormones or muscle glycogen in the current study, but the influence of "lower" blood glucose during exercise on stress hormone response is known (26), as is the potential of reduced free fatty acid availability to increase reliance on muscle glycogen.

Mechanisms responsible for increased IL-6 release also likely played a role in leukocyte alterations during exercise, particularly for monocyte and lymphocyte number. Circulating monocyte number was greater in ED and CC immediately post-exercise, compared to PL, whereas, lymphocyte number was greater in ED compared to CC or PL at several time points. Both low blood glucose (23,38) and stress hormones (22,23) increase demargination of leukocytes into the vascular pool. Increased metabolic rate, body temperature, insulin-like growth factor, heat shock proteins, oxidative stress, and other factors associated with exercise alter cell trafficking and induce leukocytosis, as well (39). We thought that the additional ingredients (taurine, niacin, and CHO) in the ED, and just CHO in CC might attenuate the exercise-induced leukocytosis normally observed in the fasted state, even in the presence of caffeine ingestion. This was not the case. In fact, we observed the opposite response. The addition of taurine and other ED ingredients did not blunt leukocytosis in our study protocol. Instead, ED elicited a a greater recruitment of monocytes and lymphocytes into the bloodstream compared to CC and PL. If time to completion had been significantly improved in the ED and CC conditions, we could have partially ascribed the elevations in IL-6 and leukocytes to exercise intensity. Exercise intensity directly influences both IL-6 production and leukocyte trafficking (28), but there was no statistical difference in TTC among conditions.

In the ED condition, TTC was 15.1 and 56.6 seconds faster compared with CC and PL, respectively, whereas CC TTC was 41.5 seconds faster than PL. Although these TTC values were not statistically different from one another, it could be argued that a 15–56 seconds improvement in TTC could significantly improve race results. Even after using the Batterham and Hopkins (3) technique to calculate clinical and mechanistic magnitude-based inferences, we found that a 56.6-second difference in race time was beneficial $<$5% of the time, based on a smallest worthwhile enhancement of TTC in cyclists of 0.6% (during a cycling bout lasting approximately 69 minutes) (30). It is possible that the 0.6% may have overestimated the difference in race time required to make a meaningful improvement in TTC in the current study because only 1 study has thus far assessed the smallest worthwhile change in cycling of approximately 70 minutes (30). Interestingly, there were no differences among conditions in RER or $\dot{V}O_2$ during exercise, indicating similar

exercise intensities among the 3 groups. However, heart rate was significantly lower in PL compared with ED and CC. The known CAF-related elevation in stress hormones may be responsible for elevating exercise heart rates in ED and CC. The elevated heart rate response observed here is consistent (20) or not in agreement (13) with other reports where the same volume of the same ED was used. The differences may be the result of the timing of ED consumption or exercise protocol used. Similar to our study, Ivy et al. (20) administered the ED 40 minutes before exercise and observed an elevated heart rate during the ED trial along with an increase in epinephrine compared with their placebo. Geiβ et al. (13) did not administer the drink until after 30 minutes of steady-state exercise, before an additional 30 minutes of exercise followed by an incremental test to exhaustion. In contrast to our findings and those of Ivy et al. (20), heart rate was lowest in the ED trial of Geiβ et al. (13). Their subjects did not experience a hypoglycemic rebound because subjects had been cycling for 30 minutes before EB consumption.

Plasma CAF levels begin to increase after 15–45 minutes with peak concentrations occurring approximately 1 hour after consumption (14). Hence, the timing of drink consumption may explain why Geiβ et al. (13) did not report an elevated heart rate. Geiβ et al. (13) attributed the observed reduced heart rate to taurine in the ED. Taurine is inotropic for cardiac muscle when exposed to Ca^{2+} (9) and may increase cardiac contractility (stroke volume) in endurance-trained subjects (4). Baum and Weiβ (4) hypothesized that the increased stroke volume in their ED trial would account for the lower exercise heart rates reported by Geiβ et al. (13). We did not measure stroke volume, but our results for exercise heart rate do not support this hypothesis, at least not using a single taurine dose of 2 mg (~25 $mg \cdot kg^{-1}$). Ivy et al. (20) also did not report a reduction in heart rate after a taurine-containing ED. Taurine content in popular EDs is below the doses expected to elicit a therapeutic benefit (16). Indeed, performance was enhanced after 7 days taurine supplementation (6 $g \cdot day^{-1}$, 40) but not after a single dose of 1–1.9 mg (5). Both Ivy et al. (20) and Geiβ et al. (13) reported an improvement in performance after ED, but in neither study was there a drop in blood glucose during exercise. Some athletes are more susceptible to a hypoglycemic rebound than others (21), so this response may, at least partially, explain our divergent performance findings, along with timing of drink consumption.

In regard to exercise intensity, we measured $\dot{V}O_2$ at 3 time points during the TTC trials. $\dot{V}O_2$, and thus exercise intensity, may have been greater in CC, and particularly ED where average heart rate was greatest, during segments of the "race" when $\dot{V}O_2$ was not collected. Therefore, we cannot completely discount the possibility that the ED or CC improved effort by the subjects, leading to a slight increase in intensity, not statistically detectable by the TTC performance data. Supporting the possibility of a slight increase in exercise intensity is that bicarbonate was lower in ED and CC compared with PL, with no differences in pH, indicating greater buffering requirement for H^+ liberated from hydrolysis of adenosine triphosphate and glycogenolysis. Furthermore, lactate was also greatest early in the ED condition, possibly indicating a greater reliance on glycolysis.

The combination of no change in RPE, higher heart rates and lactate, and slightly faster (ns) finishing times in ED and CC may indicate that there was a mild effect of the caffeinated beverages or other ingredients in the ED on exercise effort. It is possible that ED and CC influenced central fatigue. This is supported by no change in RPE among groups, even though TTC was almost a minute faster in the ED compared with PL, and 41.5 seconds faster in CC than PL. The absence of a difference in RPE among conditions with a 1-minute reduction in TTC (ED vs. PL) is consistent with CAF's known effects on perception of effort. Many authors have used higher doses (3–9 $mg \cdot kg^{-1}$) of CAF when central effects were observed (2,14), whereas others have observed positive central effects using the same dose of ED used here. In the current and other studies where there was no influence of CAF or EDs on performance, the dose of CAF may not have been great enough to elicit a significant response. Caffeine dose in 500 ml of ED and CC was 160 mg (~2 $mg \cdot kg^{-1}$), which is at the lower end of what has been shown to improve endurance performance. In fact, at least 3–6 $mg \cdot kg^{-1}$ is apparently required to consistently improve physical or mental performance (2,14,19).

It is interesting that we observed a significantly greater lipid oxidation in PL compared with CC, but no difference existed between that of PL and ED. These observations lend us to speculate that the additional ingredients in the ED may have tended to increase lipid oxidation in working muscle and be related to the increased IL-6 release. Lipid oxidation and glycerol concentrations between ED and CC, however, were not different, so it is difficult to make this claim. It will be interesting to further explore the influence of energy beverages on substrate metabolism, including the role of IL-6.

Especially interesting in the current study was that not only were the results from ED and CC contrary to our hypotheses but also ED elicited the greatest IL-6 response and earlier monocytosis, indicating an effect of the additional ingredients in the ED, although there was no significant effects on performance. Given the data discussed above, our best explanation is that there was an effect of the additional ingredients in the ED on (a) overall inflammatory response to exercise, (b) substrate metabolism generating increased IL-6 release, or (c) the nonsignificant reductions in "race" time translated to higher exercise intensities, which could account for the observed increases in immunological variables. An increased inflammatory response to taurine, B vitamins, or glucuronolactone, however, would not be expected. In fact, both taurine (34) and B vitamins, especially niacin (41), have anti-inflammatory functions. Consequently, it is difficult to explain these results. There is a possibility that

the anti-inflammatory actions of taurine (34) or niacin (8,41) or both reduced adhesion molecule response to exercise (12) in leukocytes, resulting in greater circulating leukocyte numbers, particularly monocytes. Regardless, the ED elicited earlier recruitment of monocytes to circulation and the greatest IL-6 response possibly indicating a greater systemic inflammatory response, substrate challenge in muscle, or slightly higher exercise intensity. It is likely that hypoglycemia, as discussed earlier, contributed to the findings observed in immunological variables in the ED and CC conditions. More investigation will be necessary to confirm or refute these hypotheses.

Here, we show that there was only a 15-second difference (not significant) in TTC when preexercise consumption of a popular ED was compared with cola matched for cola matched for caffeine and carbohydrate. Consumption of both ED and CC approximately 55 minutes before beginning a 25-mile simulated road race resulted in significant hypoglycemia in several subjects. Although both CAF and CHO have been shown to improve performance independently, the suggested timing of their consumption is not the same. Coadministration of caffeine and carbohydrate 30–60 minutes before exercise may not be advised because of the hypoglycemia effect of stacking high insulin and exercise-induced glucose uptake. As shown in the previous literature, it is recommended that preexercise CHO consumption occur either immediately or 2–3 hours before the onset of exercise (9), while the maximum effects of CAF are observed approximately 1 hour after consumption (14). The combination of CAF and CHO in EDs or other beverages, therefore, may not be practical for use as a preexercise ergogenic aid.

We are the first to investigate the immune-related responses to ED consumption during exercise. We studied relatively young, recreational athletes, as they are a group that frequently uses supplements for performance enhancement. We simulated an actual road race in the laboratory so that our results would be applicable to current practice but well controlled. Previous reports of the ergogenic potential of taurine, or other ingredients in the ED, were not evident in the current study, even though our subjects consumed the equivalent of 2 single servings (500 ml) of the ED. There was no significant benefit of the ingredients in the ED over and above those of CAF and CHO on performance in the current study. In fact, the ED resulted in greater IL-6 release and perturbation in leukocyte response to exercise, particularly monocytes. The mechanisms are unclear and will require additional work to understand those involved in our findings.

Practical Applications

The popularity of EDs in athletic populations has continued to increase since their development. The recommended serving size of the ED examined here is 250 ml (16) but is sold in single cans of larger volumes (500 ml). In some studies, they have improved both psychological and physical performance, and many athletes, both recreational and highly trained, consume them before competition. The present data do not support an ergogenic potential of a popular ED, above that of coconsumption of CHO and CAF, even when using a 2-serving dose (500 ml), if consumed approximately 50 minutes before race. In addition, the data indicate that the ED induced greater inflammatory-related responses than did CC (just CAF and CHO) or PL. Coaches and sports medicine personnel should be cognizant of recommended CHO and CAF doses, consumption timing before competition, and remember that EDs contain a significant glucose load (11% CHO in current ED) and CAF.

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