Effect of graded fructose coingestion with maltodextrin on exogenous $^{14}$C-fructose and $^{13}$C-glucose oxidation efficiency and high-intensity cycling performance

David S. Rowlands,1 Megan S. Thorburn,1 Rhys M. Thorp,1 Suzanne Broadbent,1 and Xiaocai Shi2

1Institute of Food, Nutrition, and Human Health, Massey University, Wellington, New Zealand; and 2Gatorade Sports Science Institute, Barrington, Illinois

Submitted 15 August 2007; accepted in final form 26 March 2008

Rowlands DS, Thorburn MS, Thorp RM, Broadbent S, Shi X. Effect of graded fructose coingestion with maltodextrin on exogenous $^{14}$C-fructose and $^{13}$C-glucose oxidation efficiency and high-intensity cycling performance. J Appl Physiol 104: 1709–1719, 2008. First published March 27, 2008; doi:10.1152/japplphysiol.00878.2007.—The ingestion of solutions containing carbohydrates with different intestinal transport mechanisms (e.g., fructose and glucose) produces greater carbohydrate and water absorption compared with single-carbohydrate solutions. However, the fructose-ingestion rate that results in the most efficient use of exogenous carbohydrate when glucose is ingested below absorption-oxidation saturation rates is unknown. Ten cyclists rode 2 h at 50% peak power then performed 10 maximal sprints while ingesting solutions containing $^{14}$C-maltodextrin at 0.6 g/min combined with $^{14}$C-fructose at 0.0 (No-Fructose), 0.3 (Low-Fructose), 0.5 (Medium-Fructose), or 0.7 (High-Fructose) g/min, giving fructose:maltodextrin ratios of 0.5, 0.8, and 1.2. Mean (percent coefficient of variation) exogenous-fructose oxidation rates during the 2-h rides were 0.18 (19), 0.27 (27), 0.36 (27) g/min in Low-Fructose, Medium-Fructose, and High-Fructose, respectively, with oxidation efficiencies (=oxidation/ingestion rate) of 62–65%. Exogenous-glucose oxidation was highest in Medium-Fructose at 0.57 (28) g/min (98% efficiency) compared with 0.54 (28), 0.48 (29), and 0.49 (19) in Low-Fructose, High-Fructose, No-Fructose, respectively; relative to No-Fructose, only the substantial 16% increase (95% confidence limits ±16%) in Medium-Fructose was clear. Total exogenous-carbohydrate oxidation was highest in Medium-Fructose at 0.84 (26) g/min. Although the effect of fructose quantity on overall sprint power was unclear, the metabolic responses were associated with lower perceptions of muscle tiredness and physical exertion, and attenuated fatigue (power slope) in the Medium-Fructose and High-Fructose conditions. With the present solutions, low-medium fructose-ingestion rates produced the most efficient use of exogenous carbohydrate, but fatigue and the perception of exercise stress and nausea are reduced with moderate-high fructose doses.

dose response; dual-tracer method; substrate metabolism; gastrointestinal distress; fatigue

IT IS NOW WIDELY ACCEPTED that ingestion of carbohydrate solutions can delay fatigue and improve endurance performance during high-intensity exercise of ~60 min or longer (reviewed in Ref. 25). The proposed mechanisms for performance enhancement are related to the prevention of hypoglycemia and the maintenance of high carbohydrate-oxidation rates during the later stages of exercise, when endogenous muscle and liver carbohydrate stores may become depleted (8). For these reasons and for reasons relating to hydration, there is interest from industry, scientists, and athletes in finding the formulation that will best optimize performance.

During exercise, ingested glucose is rapidly absorbed into the circulation and oxidized by the skeletal muscle with high efficiency. In contrast, ingested fructose and galactose are oxidized with lower efficiency probably relating to slower absorption and delays linked to hepatic metabolism (1, 2, 17). However, the contribution of exogenous glucose to energy provision during prolonged high-intensity endurance exercise is limited to ~1.0–1.1 g/min, even when ingested in quantities far exceeded this rate [up to ~3.0 g/min (25)]. The physiological limit to exogenous-glucose oxidation is presently explained by saturation of the sodium-dependent glucose cotransporter (SLGT1), which is responsible for absorption of glucose by active transport across the brush-border membrane of the small intestine (6, 22, 25). Fructose, on the other hand, has been shown to be oxidized at rates of up to 0.38 g/min when ingested in isolation (1, 6) or in combination with glucose (22).

A recent series of studies has shown that the ingestion of solutions containing fructose or sucrose with glucose or maltodextrin at above the saturation rate for the SLGT1 transport (i.e., ≥1.2 g/min glucose or maltodextrin) results in total exogenous-carbohydrate oxidation rates 40–55% higher than when ingesting isoenergetic glucose only or glucose polymer (maltodextrin) solutions (20, 22, 23, 41). While the present paper was in review, Currell and Jeukendrup (11) confirmed that a composite of fructose and glucose ingested at 1.2 and 0.6 g/min, respectively, resulted in substantially enhanced cycling time-trial performance compared with a beverage containing isoenergetic glucose only. The synergism associated with the combined hexoses was reported earlier in intestinal absorption studies by Shi et al. (37), but the increased oxidation of the two hexoses is less marked (21%) at glucose-ingestion rates below saturation (1). Faster absorption and higher total exogenous-carbohydrate oxidation rates with the ingestion of composite carbohydrate solutions could result from the utilization of several different brush-border membrane hexose transport processes, namely SLGT1 for glucose, sodium-independent facilitated passive transport via GLUT5 for fructose (13, 42), and possibly facilitated diffusion via GLUT2, which has a higher affinity for glucose but capacity for fructose and galactose also (42). That is, because glucose and fructose are not competing for the same transporter, more total carbohydrate can be transported into the bloodstream for oxidation, increasing ox-


idation efficiency in comparison to an isoenergetic amount of glucose or fructose alone (22, 37). The coingestion of up to 1.2 g/min of glucose and 1.2 g/min of fructose resulted in an impressive peak combined exogenous-carbohydrate oxidation rate of 1.75 g/min (20). However, in this and in other similar recent studies establishing the upper limits for exogenous-carbohydrate oxidation (19–21, 23), the efficiency of exogenous-carbohydrate oxidation was only 63–73%. High oxidation efficiency is thought to be important to reduce the accumulation of carbohydrate in the gastrointestinal tract, thereby reducing the potential for gastrointestinal problems during exercise (25). Even mild gastrointestinal distress is associated with negative high-intensity endurance performance outcomes (40).

The efficiency of exogenous glucose oxidation is likely to be greatest at ingestion rates below the absorption-saturation rate and the most efficient fructose coingestion rate, and the effect of fructose dose on metabolism, gastrointestinal distress, and performance remains to be established. Therefore, the aims of this study were to determine the effect of increasing fructose dose on the oxidation efficiency of exogenous fructose and glucose, endogenous substrate metabolism, gastrointestinal distress and fatigue ratings, and intermittent high-intensity endurance cycling performance.

**MATERIALS AND METHODS**

**Participants**

Ten male cyclists and triathletes aged 33 y (SD 10) and with a body mass of 77 kg (SD 9) completed the study. All participants had been cycling 8 or more hours per week and competing regularly for more than 12 mo. Maximal oxygen uptake (VO$_{2\text{max}}$) and power (W$_{\text{max}}$) were 61 ml·kg$^{-1}$·min$^{-1}$ (SD 6) and 360 W (SD 39), respectively. Cyclists were screened for contraindications to exercise and were fully informed of the purpose and risks associated with procedures before beginning experimentation. This study was approved by the Central Regional Ethics Committee Protocol Number CEN/06/03/015.

**Experimental Design**

The study design was a randomized, double-blind, four-way crossover in which the effects of the ingestion of fructose and glucose polymer (maltodextrin) solutions on metabolic and performance outcome measures were compared against a solution containing maltodextrin alone. Each cyclist made nine visits to the laboratory over 5 wk. The first visit on week 1 consisted of an incremental test to establish VO$_{2\text{max}}$ and W$_{\text{max}}$ followed by a familiarization ride of the performance test. On weeks 2–5, a weekly pattern was established whereby exercise training was standardized and a 2-h background ride was followed 2 days later by the experimental trial consisting of a 2-h ride and performance test (see below for description of the exercise tests). To reduce the endogenous $^{13}$C background, participants were provided with extensive lists and instructed not to eat foods with components derived from plants with a C$_{4}$ photosynthetic cycle, which are naturally enriched in $^{13}$C (maize, sugar cane, or sugar beet) from at least 10 days before the first background trial to reduce the background $^{13}$C enrichment. To standardize diet, cyclists recorded their diet for 6 days during week 1 starting 4 days before the first background ride and were asked to replicate their diet on a daily basis for the following 3 wk to minimize the effect of any diet change on outcome measures. Cyclists modified their training program during weeks 2–5 where day 1 was a long duration ride (3–4 h), days 2 and 3 a medium duration ride (2–3 h), day 4 the background test, and day 6 the 2-h ride and performance test; days 5 and 7 were rest and recovery ride (1–2 h) days, respectively. For a given participant, all laboratory tests were conducted at the same time of day starting between 05:00 and 08:00 to control for circadian variance. Cyclists reported to the laboratory following an overnight fast. No strenuous activity or alcohol consumption was experienced in the 24-h prior to a laboratory test.

**Protocols**

**Incremental test and familiarization.** VO$_{2\text{max}}$ and W$_{\text{max}}$ were measured using a progressive exercise protocol on an electronically braked cycle ergometer (VeloTron Racer Mate, Seattle, WA) as described elsewhere (40). VO$_{2\text{max}}$ was measured online with a calibrated SensorMedics Vmax Spectra Series gas analyzer (SensorMedics, Yorba Linda, CA) and taken as the highest attained 20-s average oxygen uptake. W$_{\text{max}}$ was defined as the last completed work rate plus the fraction of time spent in the final non-completed work rate multiplied by the 25 W step work rate increase. Following the incremental test, participants rested for 10 min before completing the performance test for procedural familiarization. An 8% carbohydrate-based solution was ingested every 20 min, and participants practiced recording gastrointestinal distress and ratings of relative perceived exertion on the scales to be used in the experiments. During all rides, environmental conditions were maintained at 21–22°C and 50–55% humidity by air conditioning.

**Background.** A 2-h ride at 50% W$_{\text{max}}$ was performed in the lab on the 2nd day of each week of the experiment to establish background $^{13}$C enrichment required for later calculation of glucose oxidation. On reporting to the lab, participants were asked to toilet, and body mass was measured. Participants then mounted their cycle ergometers (VeloTron Racer Mate). Expired breath was collected into a Douglas bag for 90 s for calculation of oxygen consumption and carbon dioxide production rates and then directed through a 5-liter mixing chamber for an additional 90 s when samples were collected into 3 × 10-ml evacuated tubes (Exeter, Labco, High Wycombe, UK) for breath $^{13}$C enrichment and subsequent calculation of exogenous-glucose oxidation rates (see below). Background solutions were ingested at rest and every 15 min during exercise immediately following the breath sampling.

**2-h ride.** On day 6 of each week cyclists rode for 2 h at 50% W$_{\text{max}}$ (average VO$_{2}$ 2.92 l/min, SD 0.28) to examine the effect of the test solutions on metabolic and perceptual outcome measures; this ride was followed by the performance test (see below). On arrival at the laboratory, riders toileted, and then a 20-gauge cannula was inserted into the antebrachial vein of the cyclist’s forearm (Becton Dickinson Medical, Singapore). A two-way stopcock valve (Becton Dickinson Medical) was connected to the cannula to allow for blood sampling at this point and during exercise. Cyclists then mounted the cycle ergometer and resting expired breath samples were collected. During the 2-h ride, the following outcome variables were collected every 15 min in the order of psychometric variable rating, breath into a Douglas bag (90 s) then through the mixing chamber (see above), then three breaths into a 6-liter anesthetic bag, and finally a blood sample. Experimental solutions were ingested at rest and every 15 min during exercise immediately following the breath sampling. Expired breath collected into the anesthetic bag was used for the analysis of $^{14}$CO$_{2}$ activity. Following collection, gas from the bag was bubbled through a CO$_{2}$ trapping solution, containing 1 ml hyamine hydroxide in 1 M methanol (Nuclear Enterprises, Sighthill, Edinburgh, Scotland), 2 ml of 96% ethanol (VWR International, Poole, England), and 1–2 drops of phenolphthalein (Ajax Finechem, Mt. Wellington, Auckland, NZ) until the pink-colored solution became clear, at which point exactly 1 mmol of CO$_{2}$ was trapped. Seventeen milliliters of scintillation cocktail (Ultima Gold, Perkin Elmer, Boston, MA) was then added to the trapping solution. Swabs of the equipment (drink bottles, mixing chamber, anesthetic bags, and tubing) were taken twice during the
experimental period and tested for $^{14}$C. All tests revealed no residual $^{13}$C build-up on the equipment.

**Performance test.** Following the 2-h ride, cyclists dismounted for body mass measurement and toileting before beginning the performance test. No breath data were collected during the performance test, but the experimental solutions continued to be ingested on a per serving basis every 15 min and ingested ad libitum. The performance test consisted of ten maximal sprint efforts, interspersed and beginning with a recovery interval at 40% Wmax. The internal work to be done (kilocalories) during the sprint (2–3 min) and recovery (5–6 min) periods was determined by individual Wmax (kilocalories = 0.125 × Wmax). Fixed linear workloads approximately equivalent to the load created by riding a 28, 39, or 48 front chain ring and a 10-sprocket, 21- to 11-tooth rear cluster were selected from the Velotron software. An up-or-down gear switch was positioned on the end of the right handlebar brake hood to provide convenient changing of the gearing. Cyclists self-selected cadence and gearing but were instructed to sprint as fast as possible until the required kilocalories were acheived. No verbal encouragement was provided to the participants; the only information provided during the sprints was elapsed work completed (kilocalories) shown on a computer screen. Participants were given a verbal countdown in preparation for the start of each sprint and at 20, 10, 5, and 2 kilocalories to go in preparation for the end of each sprint. Test characteristics are described elsewhere (35). During the performance test, psychometric data and blood was collected immediately following sprints 1, 4, 7, and 10.

**Carbohydrate Solutions**

Immediately before exercise, participants ingested a 400-ml bolus of test solution, followed by 200 ml at 15-min intervals throughout the 2-h ride and performance test. Four different carbohydrate and appropriate background solutions were prepared for ingestion during exercise. All four solutions contained 4.5% maltodextrin ingested at a rate of 0.6 g/min during exercise. The control solution (No-Fructose) contained maltodextrin only. The three experimental solutions also contained 2.25% (Low-Fructose), 3.75% (Medium-Fructose), and 5.25% (High-Fructose) fructose, representing respective fructose ingestion rates of 0.3, 0.5, and 0.7 g/min. The fructose ingestion rates were chosen so that the pre-study predicted fructose oxidation maxima of 0.4 g/min would be clearly identified by a plateau in the oxidation rate in the 0.5 and 0.7 g/min fructose conditions. Upon completion of the main experiment, one subject volunteered to conduct a trial with the ingestion of maltodextrin at 0.6 g/min and fructose at 1.2 g/min as a pilot to explore the limits to exogenous-fructose oxidation. The maltodextrin powder used in the drink supplements was maize derived (Star-Dri 10, Tate & Lyle, Decatur, IL) and had a $^{13}$C enrichment of $-10.69\,\%$ vs. PDB. The fructose solutions were labeled with 4.2 kBq of U-14C6-fructose (Amersham Biosciences, Buckingham, UK) per gram of fructose ingested during the 2-h lab test. All solutions contained 1.17 g NaCl (20 mmol/l Na+) and lime flavoring for palatability. Osmolalities (mosmol/kg) of the four experimental solutions were 80 for No-Fructose, 208 for Low-Fructose, 280 for Medium-Fructose, 379 for High-Fructose. The solutions used in the background rides contained all ingredients except the maltodextrin and U-14C6-fructose. The U-14C6-fructose was omitted from the solutions ingested during the performance test to minimize unnecessary exposure.

**Psychometric Scales**

Perception ratings were recorded during the 2-h ride and the performance test to score the effect of fructose dose on physical exertion, gastrointestinal distress, and drink characteristics. For the full cohort of 10 cyclists, ratings were obtained for leg muscle tiredness, perceived exertion, nausea, and abdominal cramps. Several weeks into data collection, ratings of drink sweetness and palatability were added, but for these outcomes a full dataset was obtained for only seven cyclists. Perception was quantified using scales modeled from Borg’s CR10 (4). Verbal descriptors were associated with the scale: 0, nothing; 1, very weak/mild; 2, weak/mild; 3, moderate; 5, strong; 7, very strong; 10, extremely strong; and 13.5, absolute maximum/unnbearable. Participants were instructed to make a pen mark on a continuous scale rating the strength of their exertion or distress. The numerical value for each verbal anchor was not displayed on the scale charts, so as not to distract the participant from their rating, as the numerical value increased factorially in accordance with the CR10 scale by $1^k$. The CR10 scale used to construct the psychometric scales for this study has previously been shown to be reliable and valid (4) and the CVs for most markers on the present scales ranged from 0.20 to 0.96 of a scale unit (35).

**Expired Breath**

**Analysis.** Breath samples were transferred from syringe into 7 ml lithium heparin vactuators (Becton Dickinson, Franklin Lakes, NJ) and centrifuged at 2,000 g, 4°C for 12 min. Plasma was aspirated into Eppendorf tubes and stored at $-30^\circ$C until analysis. Lactate, glucose, and electrolyte concentrations were analyzed using an automated analyzer (Bayer Rapidlab 800, Bayer HealthCare, Tarrytown, NY).

**Calculations.** Total fat and carbohydrate oxidation rates (g/min) were calculated using the non-protein respiratory quotient (24): carbohydrate oxidation (g/min) = 4.210 · $\dot{V}_{CO_2}$ – 2.962 · $\dot{V}_{O_2}$; fat oxidation (g/min) = 1.695 · $\dot{V}_{O_2}$ – 1.701 · $\dot{V}_{CO_2}$. Conversion factors of 15.64 kJ/g (12) for carbohydrate and 40.81 kJ/g (31) for fat oxidation were used to estimate the contribution to energy expenditure. Oxidation rates (g/min) of exogenous glucose were calculated from $^{13}$C enrichment and indirect calorimetry measurements. Isotopic enrichment of expired air was expressed as the delta per million difference ($\delta_{\text{CO}_2}$) between $^{13}$C/$^{12}$C ratio of the sample and a known laboratory reference standard (PDB) according to the formula: $\delta^{13}$C = [(14CO2/g/min) – (13CO2/g/min)]/[(13CO2/g/min) – (12CO2/g/min)] × 1000‰, where, $^{13}$C/$^{12}$C standard = 0.112372 (9). The amount of glucose oxidized was then calculated according to the formula: exogenous glucose oxidation (g/min) = $\dot{V}_{CO_2}$ · ($\delta_{\text{Ingestion}}$ – $\delta_{\text{Bkg}}$)/($\delta_{\text{Bkg}}$ – $\delta_{\text{Ingestion}}$)k, in which $\delta_{\text{Ingestion}}$ is the $^{13}$C enrichment of expired air in the 2-h background trial, $\delta_{\text{Bkg}}$ is the $^{13}$C enrichment of expired air during the 2-h ride with $^{13}$C-enriched glucose ingestion, $\delta_{\text{Bkg}}$ is the $^{13}$C enrichment of the carbohydrate supplement, and k is the volume of $\text{CO}_2$ (liters) produced via oxidation of 1 g of glucose (k = 0.7467). The rate of exogenous fructose oxidation (EFO) was calculated according to the formula: EFO = $\dot{V}_{CO_2}$ · [(14CO2/g/min) – (13CO2/g/min)]/16, where, $^{14}$CO2 is the radioactivity of 1 mmol of expired $\text{CO}_2$ (pmol/mmol) multiplied by 6, because there are six carbon atoms per molecule of [U-14C]fructose; SA Fruc is the specific activity of the ingested fructose (pmol/mmol); and k is the volume of $\text{CO}_2$ (liters) produced by the oxidation of 1 g of fructose (k = 0.7467). The percent efficiency of exogenous-carbohydrate metabolism was: oxidized/ingested rate × 100.

Calculation of exogenous substrate oxidation is affected by the delayed equilibration of $^{13}$CO2 and $^{14}$CO2 with the large endogenous $\text{HCO}_3^-$ pool. However, a physiological steady-state condition occurs relatively rapidly during exercise, and $^{13}$CO2 and $^{14}$CO2 in the expired air will be equilibrated with $^{13}$CO2/$^{12}$CO2 and $^{14}$CO2/$^{12}$CO2.
pools, respectively, from ~60 min of steady-state exercise (33). As a consequence, the main outcome measures for substrate oxidation were from 60 to 120 min of exercise.

Statistical Analysis

**General method for analysis of experimental outcomes.** The effects of fructose ingestion rate on outcomes were estimated with mixed modeling (Proc Mixed, SAS Version 9.1, SAS Institute, Cary, NC). Most dependent variables, except psychometric parameters and raw data expressed as a percent, were analyzed after natural log transformation to reduce effects of nonuniformity of error and to express changes as percents. Mixed linear models were applied independently to the 2-h ride and the performance data sets. For all datasets, treatment was the primary fixed effect and for the performance and psychometric analyses an order term was included to account for the familiarization or fatigue effect between consecutive trials common to most physical performance and psychological measures; the order term, however, was omitted from the analysis of drink sweetness and palatability because of insufficient sample size for interaction to run and therefore the uncertainty for these estimate is greater. Sample time or sprint number were modeled as numeric predictors (as in linear regression).

The random effect variances included in the models were: 1) subject identity, 2) the interaction between subject identity and exposure to the three different fructose conditions (i.e., allowing for individual variation in response to treatment), 3) the interaction between subject identity and slope (time or sprint number), and finally 4) the additional slope variation associated with fructose condition. The within-subject sample standard deviation was estimated from the residual variance.

**Presentation of data.** Subject descriptive and some outcome data are raw means and standard deviations. Unless otherwise noted, means derived from the analysis of log-transformed variables are back-transformed least-squares means, with the associated between-subject spread represented by the coefficient of variation, which can be converted to a unit value by conversion to a factor. For example, for a plasma-glucose concentration of 5.0 mmol/l with a coefficient of variation of 20%, the variation is 5.0 × 1.20 to 5.0 ÷ 1.20, or 6.0 to 4.2 mmol/l. Means and outcomes are presented generally to two significant digits.

**Estimate precision and statistical inference.** In keeping with recent trends in inferential statistics (3, 39) and APS guidelines (10), we report uncertainty of outcomes as 95% confidence limits (CL) or interval (CI) and make probabilistic magnitude-based inferences about the true (large-sample) values of outcomes by qualifying the likelihood that the true effect represents a substantial change as described below and elsewhere (3). In our analysis, the threshold for a substantial change for metabolic and psychometric outcomes was the conventional smallest standardized (Cohen) change of 0.20 times the between-subject SD for the control condition (7); whereas for performance, it was 1.1% (for derivation, see Ref. 40). To provide probability-based practical inference, an effect was described as mechanistically unclear if its confidence interval includes both substantial positive and negative values (>2.5% chance that the true value are both substantially positive and negative). Otherwise, the probability of a substantial increase or decrease was calculated from the two-tailed Student’s t-distribution using a published spreadsheet (15) and inferred for 95% CI as: <0.5%, almost certainly not; 0.5–2.5%, very unlikely; 2.5–12.5%, unlikely; 12.5–87.5%, possible; 87.5–97.5%, likely; 97.5–99.5%, very likely; >99.5%, almost certain. In the case where the majority (>95%) of the confidence interval lies between the threshold for a substantially positive and negative effect, the likelihood of the effect being trivial (negligible) is qualified.

**RESULTS**

**Stable and Radioactive Isotope Measurements**

Breath $^{14}$CO$_2$ radioactivity and $^{13}$C enrichment during the 2-h ride are shown in Fig. 1.

**Substrate Oxidation**

Oxidation rates are presented in Fig. 2, oxidation efficiencies are in Fig. 3, and the proportional contributions of substrate to energy expenditure is illustrated in Fig. 4. A summary of average substrate-oxidation rates and oxidation efficiency are presented in Table 1, and the corresponding statistical comparisons are in Table 2.

**Exogenous fructose oxidation.** A clear dose response to fructose ingestion was observed (Fig. 2; Table 1). From regression, for every 0.2 g/min increase in the rate of ingested fructose, exogenous-fructose oxidation increased by 0.09 g/min, illustrating the degree of reduced oxidation efficiency with increased fructose dose. Average exogenous-fructose oxidation efficiency was greatest in Low-Fructose and was substantially higher than in Medium-Fructose and High-Fructose (Table 2). A plateau in the peak fructose-oxidation rate indicating a physiological limit was not identified.

From the 60th to 120th min of the 2-h ride, there were clear increases in the rate of exogenous fructose oxidation of 16%, 25%, and 39% in the Low, Medium, and High-Fructose conditions (Fig. 2). The corresponding changes in fructose oxidation efficiency were 7.2%, 11.1%, and 15.7%, respectively (Fig. 3). In terms of differences between conditions, the increase in fructose oxidation rates in the Medium-Fructose and High-Fructose conditions were 8% (95% CL: ±10%, increase possible) and 20% (±11%, almost certain) greater than in Low-Fructose; and in High-Fructose, rates were 11% greater.
(±12%, likely) than in Medium-Fructose. In terms of efficiency, only the 8.4% increase (±5.1%, very likely) in the High-Fructose condition, relative to the increase in the Low-Fructose condition was clear.

Raw peak exogenous-fructose oxidation rates in the Low, Medium, and High-Fructose conditions, respectively, were 0.20 (SD 0.02; range 0.16 to 0.24), 0.30 (0.03; 0.24 to 0.36), and 0.42 (0.05; 0.34 to 0.50) g/min occurring at the 120 min sampling point. In the exploratory pilot (n = 1), the outcome from the ingestion of fructose at 1.2 g/min with maltodextrin was a peak fructose-oxidation rate of 0.8 g/min.

Exogenous-glucose oxidation. Relative to No-Fructose, there were clear substantial increases in the average exogenous glucose oxidation rate and efficiency in the Medium-Fructose condition only (Tables 1 and 2). Exogenous-glucose oxidation and efficiency in the High-Fructose condition was not clearly different to that in No-Fructose but tended lower relative to that in the Low and Medium-Fructose conditions (Figs. 2 and 3), but the difference was clear cut relative to Medium-Fructose only (Table 2).

From the 60th to 120th min of the 2-h ride, the rate of exogenous glucose oxidation increased 29 to 32% in all four drink conditions; however, there were no clear differences between conditions.

Total exogenous-carbohydrate oxidation. The rate of total exogenous-carbohydrate oxidation is the sum of exogenous fructose and glucose (maltodextrin) oxidation and it was increased by fructose ingestion (Table 1). For the fructose comparison, values were greatest in the Medium-Fructose condition, but a substantial difference was likely relative to Low-Fructose only (Table 2). When expressed as oxidation efficiency there was a substantial reduction in the High-Fructose condition relative to the Low-Fructose, Medium-Fructose,
Perceived exertion and muscle tiredness. Perceived exertion was rated light to moderate during the 2-h ride and very hard to extremely hard during the performance test (Fig. 5). Perceived exertion was reduced during the 2-h ride with High-Fructose relative to the No-Fructose and Low-Fructose conditions and in the Medium-Fructose relative to the Low-Fructose conditions (Table 3), but during the performance test the differences were mostly trivial (Table 3), which is consistent with the instructed application of rider effort. From sprint 1 to 10, perceived exertion increased by 1.0 to 1.7 units, but there were no clear differences between the conditions. The perception of muscle tiredness was reduced during the 2-h ride with increasing fructose dose, with substantial reductions in High-Fructose relative to the No-Fructose and Low-Fructose conditions, and in the Medium-Fructose relative to the Low-Fructose condition (Table 3). The attenuating effect of the High-Fructose condition was maintained during the performance test relative to the No-Fructose condition, but was largely unclear for the remaining comparisons (Table 3). Muscle tiredness increased by 1.0 to 1.6 units during the 2-h ride and by 2.4 to 4.2 units during the performance test, but there were no clear differences between the conditions.

Nausea and abdominal cramps. During both the 2-h ride and performance test, nausea and abdominal cramp (not shown) ratings were between nothing and very mild (Fig. 5). There were small increases in nausea during the 2-h ride in the Low-Fructose condition relative to No-Fructose (Table 3). During the performance test, average nausea was reduced in the Medium- and High-Fructose conditions relative to the Low-Fructose condition (Table 3). Nausea increased by 1.0 to 1.7 units from sprints 1 to 10, but there were no clear differences between conditions. There was a slight increase in abdominal cramp rating within the extremely mild range during the 2-h ride in the High-Fructose condition, but this effect was clear relative to the Low-Fructose condition only (Table 3).

Drink sweetness and palatability. During the 120-min ride, the Medium- and High-Fructose solutions were substantially sweeter relative to the No-Fructose solution, and the High-
### Table 2. Summary of the effect of solution composition on substrate oxidation from the 60th to 120th min period of the 2-h ride

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Oxidation Rate</th>
<th>Oxidation Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exogenous fructose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exogenous glucose</td>
<td>10.4 ± 16.6 uncertain</td>
<td></td>
</tr>
<tr>
<td>Total exogenous carbohydrate</td>
<td>48 ± 20 almost certain</td>
<td></td>
</tr>
<tr>
<td>Endogenous carbohydrate</td>
<td>−1.3 ± 10.6 likely trivial</td>
<td></td>
</tr>
<tr>
<td>Total carbohydrate</td>
<td>11 ± 9 likely</td>
<td></td>
</tr>
<tr>
<td>Endogenous fat</td>
<td>−7.7 ± 2.9 possibly trivial</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean Effect Comparisons (%) with 95% CL and Qualitative Inference</td>
<td></td>
</tr>
<tr>
<td>Exogenous fructose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exogenous glucose</td>
<td>0.4 ± 16.6 uncertain</td>
<td></td>
</tr>
<tr>
<td>Total exogenous carbohydrate</td>
<td>48 ± 20 almost certain</td>
<td></td>
</tr>
<tr>
<td>Endogenous carbohydrate</td>
<td>−1.3 ± 10.6 likely trivial</td>
<td></td>
</tr>
<tr>
<td>Total carbohydrate</td>
<td>11 ± 9 likely</td>
<td></td>
</tr>
<tr>
<td>Endogenous fat</td>
<td>−7.7 ± 2.9 possibly trivial</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Perceived exertion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.2 ± 0.2 likely</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.0 ± 0.2 uncertain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.6 ± 1.6 likely</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.2 ± 0.2 uncertain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.2 ± 0.2 uncertain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.5 ± 1.6 likely</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.8 ± 1.1 likely</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drink palatability</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.2 ± 0.2 uncertain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.2 ± 0.2 uncertain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.5 ± 1.6 likely</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.8 ± 1.1 likely</td>
<td></td>
</tr>
</tbody>
</table>

Values are ±95% confidence limit (CL); add and subtract this number to the mean effect to obtain the 95% CLs for the true difference. Thresholds for assigning qualitative terms to chances of substantial effects were as follows: <0.5%, very unlikely; <2.5%, unlikely; <12.5%, unlikely; <87.5%, possible; >87.5%, likely; >97.5%, very likely; >99.5%, almost certain. An effect is unclear if its confidence interval includes both substantial increases and decreases. Cell text styles represent the certainty of a substantial outcome: **bold** is almost certain, very likely, or likely; *italic* is possible; and regular is unclear. Arrow symbols indicate an increase (↑) or decrease (↓).

### Table 3. Summary of the effect of solution composition on exertional parameters, gastrointestinal distress, and drink characteristics during the 2-h ride and the performance test

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean Effect Comparisons (Likert Scale Units) with ±95% CL and Qualitative Inference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low-Fructose Minus</td>
</tr>
<tr>
<td>Muscle tiredness</td>
<td>0.1 ± 0.5 uncertain</td>
</tr>
<tr>
<td>Perceived exertion</td>
<td>−0.3 ± 0.5 uncertain</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.2 ± 0.2 likely</td>
</tr>
<tr>
<td>Abdominal cramp</td>
<td>0.0 ± 0.0 trivial</td>
</tr>
<tr>
<td>Drink sweetness</td>
<td>1.0 ± 0.2 uncertain</td>
</tr>
<tr>
<td>Drink palatability</td>
<td>−1.6 ± 1.6 likely</td>
</tr>
</tbody>
</table>

Values are ±95% CL; add and subtract this number to the mean effect to obtain the 95% CLs for the true difference. Thresholds for assigning qualitative terms to chances of substantial effects were as follows: <0.5%, very unlikely; <2.5%, unlikely; <12.5%, unlikely; <87.5%, possible; >87.5%, likely; >97.5%, very likely; >99.5%, almost certain. An effect is unclear if its confidence interval includes both substantial increases and decreases. Cell text styles represent the certainty of a substantial outcome: **bold** is almost certain, very likely, or likely; *italic* is possible; and regular is unclear. Arrow symbols indicate an increase (↑) or decrease (↓).
Fructose solution was substantially sweeter than the Low-Fructose solution (Table 3). During the performance test, the fructose drinks were all substantially sweeter than the No-Fructose solution, and the High-Fructose solution was substantially sweeter than the Low- and Medium-Fructose solutions (Table 3). Sweetness rating increased during the 120 min ride, but there were no clear treatment effects. The Low- and Medium-Fructose solutions were rated more palatable relative to the No-Fructose solution during both the 120-min ride and the performance test (Table 3). All other comparisons were unclear.

Body Weight Change and Frequency of Stops to Urinate

Mean body weight loss ranged 0.27 to 0.33 kg and 0.10 to 0.17 kg during the 2-h ride and performance test, respectively; the effect of solution was likely trivial or inconclusive. Only three subjects needed to stop to toilet during the 2-h ride and there was no pattern relating to solution composition. No riders needed to toilet during the performance test.

Plasma Glucose, Lactate, Electrolytes, and Bicarbonate

The effect of solution on plasma glucose and lactate concentrations is shown in Fig. 6. During the 2-h ride, lactate was 31% (±18%, very likely) and 24% (±18%, very likely) higher in the Medium- and High-Fructose conditions, relative to the No-Fructose condition. The outcomes for the remaining glucose and lactate comparisons and for sodium, potassium, and bicarbonate were qualified as possible substantial increases or decreases, or unclear, and are not shown for brevity.

Performance

The effect of solution composition on overall sprint mean power (position effect) was unclear (Fig. 7). However, the Medium- and High-Fructose conditions substantially attenuated the decline in sprint mean power over the course of the ride.
performance test (fatigue) relative to the No-Fructose condition by 6.2% (±3.4%, very likely) and 5.3% (±3.8%, likely); fatigue was also less in the Medium-Fructose relative to the Low-Fructose condition by 3.8% (±3.5%, likely).

DISCUSSION

In this study we employed a subsaturation glucose-ingestion rate of 0.6 g/min and examined the effect of increased fructose-ingestion rate on carbohydrate metabolism and performance. Under these conditions, exogenous fructose oxidation increased with ingestion rate to reach a peak of 0.42 g/min in the High-Fructose condition, but a plateau indicating physiological maxima was not attained. Interestingly, we found the highest efficiency of exogenous-glucose oxidation (from the ingested maltodextrin) and total exogenous-carbohydrate oxidation rate with a medium-fructose dose; surprisingly, with the high-fructose dose glucose oxidation efficiency substantially declined. Endogenous carbohydrate oxidation was not affected by fructose ingestion, but fat oxidation was reduced in the Medium- and High-Fructose conditions. These metabolic responses were associated with substantially lower perceptions of muscle tiredness and exertion ratings during the 2-h ride, and although overall the effect of solution composition on sprint mean power was unclear, there was evidence for attenuated fatigue and nausea over the course of the performance test in the Medium-Fructose and High-Fructose conditions.

The highest exogenous-glucose oxidation efficiency occurring in the medium-fructose condition is perhaps one of the more important findings of the present study: it agrees with previous findings for enhanced glucose absorption (37) and oxidation when coingested with fructose (1), but also suggests that under the current solution characteristics (tonicity and concentration, carbohydrate type and form, ingestion rate) an ingested fructose:maltodextrin molar ratio of around 0.8 may lead to the most efficient exogenous-carbohydrate delivery and oxidation. To confirm this suggestion, other ingestion rates with the same molar ratio would need to be trialed, although it is unlikely that the relationship would hold at glucose-ingestion rates above ~1.0 g/min because of SLGT1 transport limitations. Why glucose oxidation efficiency dropped at the highest fructose-ingestion rate is not clear but a physiological explanation for it might be found at one of several processes: gastric emptying, intestinal absorption, liver metabolism, and skeletal muscle uptake and oxidation. Before moving on to explanations, however, a comment is warranted regarding the magnitude of the glucose-oxidation efficiency values in the Low-Fructose and Medium-Fructose conditions with standard deviations implicating seemingly impossible individual values over 100% (Table 1). We can provide three explanations. First, as a characteristic of the tracer method, the 13CO2/H13CO2 ratio in the bicarbonate pool requires ~1 h of 13C flux to reach equilibrium between input (metabolism) and output (breath 13CO2) (33). Second, there is a physiological delay from ingestion of a given quantity of 13C-labeled glucose to its oxidation of unknown duration (e.g., 5–25 min). The combined consequence is that a proportion of the ingested 13C-labeled substrate taken during the first hour of exercise will be measured as 13CO2 in the breath during the second hour—the period during which the oxidation efficiency calculations are made. The 29–32% increase in glucose oxidation efficiency from 60 to 120 min during the 2-h ride (Fig. 3) is likely to be partially due to these methodological and physiological features. Finally, following similar studies, substrate oxidation rates were calculated from the non-protein respiratory exchange ratio. Previously we quantified protein oxidation to account for 7–8% of energy expenditure during prolonged endurance exercise in well-trained athletes (34). True CO2 output from exogenous-carbohydrate oxidation is therefore likely to be overestimated due to the non-protein assumption, but by only a small amount (e.g., 0.005 g/min). Despite these issues, the magnitude of the treatment effect on the efficiency outcome is likely to be real, because the methodological features outlined above will be nearly identical between conditions.

Gastric emptying was not measured, but the pattern for reduced oxidation efficiency of both fructose and glucose in the High-Fructose condition coupled with a slight but detectable increase in abdominal cramps vs. Low-Fructose provide indirect evidence that delayed gastric emptying might be a causal factor contributing to the reduced oxidation efficiency. Two possible explanations are solution hyperosmolality and solution energy density. Most studies have reported no statistically clear effect of solution osmolality on gastric emptying (5, 18, 29, 32), but there is some comparative evidence that osmolality of composite carbohydrate solutions might affect gastric delivery. In a recent study (41), higher average total exogenous-carbohydrate oxidation rates (1.32 g/min) were observed with the ingestion of a 260 mosmol/kg solution containing maltodextrin (1.2 g/min ingestion rate) and fructose (0.6 g/min ingestion rate) compared to a similar study using a 866 mosmol/kg glucose and fructose solution (1.16 g/min oxidation rate) (22). Others have also suggested that coingestion of fructose and glucose promotes faster solution gastric emptying than an equicaloric glucose-only solution (30, 38). With respect to energy density, there is evidence for a negative relationship between carbohydrate content and gastric emptying with mildly hypertonic solutions (330 mosmol/kg) (5).

At the level of the duodenaljejunum, carbohydrate absorption was found to be greater with beverages containing two or three transportable substrates (glucose and fructose or sucrose) than with isoenergetic beverages containing a single transportable carbohydrate (glucose or maltodextrins), suggesting that adding a second transportable substrate to a glucose solution stimulates additional transport mechanisms (36, 37). Enhanced monosaccharide transport will increase water absorption by osmosis, which may increase permeability via the opening of tight junctions, leading to additional free hexose transport through the paracellular pathway (36, 37). It is difficult to explain the reduced oxidation of exogenous glucose in the High-Fructose condition on the basis of a brush-border membrane transport mechanism, except for the possibility that increasing fructose ingestion from 0.5 to 0.7 g/min increased the competition for a shared transport mechanism with glucose (e.g., GLUT2 and paracellular pathway). Other mechanisms are also possible: the hypertonic or high-caloric nature of the High-Fructose solution may have delayed gastric emptying of maltodextrin into the small intestine, and there may be relative absorption delays associated with osmotic equilibrium in the lumen.

Relative to the high exogenous-glucose oxidation efficiency with ingested maltodextrin (81–98%), fructose oxidation effi-
ciency was less and declined with dose from 62 to 52%. These data suggest significant retention or non-oxidative metabolism of fructose. In the first published dual tracer study in this area, Jenjens et al. (22) reported a similar average fructose oxidation efficiency of 63%. Likewise, others have reported 64–85% lower exogenous-fructose oxidation during prolonged exercise relative to isocaloric quantities of exogenous glucose (1, 17, 27–29), although recently Burelle et al. (6) reported only ~4% less exogenous fructose oxidized vs. glucose. Lower efficiency for fructose relative to glucose could be due to slower intestinal uptake relating to transporter affinity (42), partial entrapment, storage or metabolism of fructose in the liver, or to preferential uptake and oxidation in contracting tissues (2, 6, 16). While unconfirmed with primary-level data, the circumstantial weight of evidence points to SLGT1 transport as the most important factor limiting exogenous-glucose oxidation to ~1.0–1.1 g/min at exercise intensities up to 70% $\dot{V}O_2_{max}$ (25), whereas the liver appears the most influential site for the lower fructose-oxidation efficiency. There is little hepatic metabolism of exogenous glucose during exercise (26) and nearly all infused glucose (up to 3.0 g/min) is oxidized by the muscle during exercise (14). On the other hand, skeletal muscle expresses GLUT5 (16), but because of the presence of fructokinase in the liver, fructose delivered into the circulation could be preferentially taken up by hepatic tissues during exercise. With fructose infusion (1.5 g/min) during 90 min of exercise at 30% $\dot{V}O_2_{max}$ follow by 20-min rest, Ahlborg and Borkman (2) reported that 28% of the fructose was taken up by contracting muscle; a further 28% was taken by resting muscle and 45% by the liver. During infusion, arterial lactate and pyruvate rose two- to threefold, and these substrates were released from splanchnic tissues and taken up by exercising and resting muscle. Splanchnic release of lactate, pyruvate, and glucose accounted for 78% of fructose uptake during exercise (2). Interestingly, 28% of the infusion rate suggests a muscle fructose-oxidation rate of 0.42 g/min, similar to the maximal fructose-oxidation rate in present study. In another study, 55–60% of exogenous $^{13}$C-fructose ingested during 3-h of running at 45% $\dot{V}O_2_{max}$ was seemingly taken up by the liver and converted to $^{13}$C-glucose that was released into the plasma during the last 90–180 min of exercise and likely subsequently oxidized by the muscle (17). From these studies, it appears that ingested fructose is less immediately available to the skeletal muscle than glucose, but the liver acts as a reservoir for releasing fructose-derived metabolites that are utilized by the muscle later as a carbon source for oxidation.

The addition of fructose to maltodextrin had little effect on endogenous carbohydrate oxidation, but increased total carbohydrate oxidation and decreased endogenous-fat oxidation in the Medium-Fructose and High-Fructose conditions. The reduction of endogenous fat oxidation is a common observation in response to exogenous carbohydrate ingestion, but any sparing of endogenous carbohydrate oxidation with a composite carbohydrate solution might be limited to very high ingestion rates. In a series of studies, the high ingestion rates of glucose or maltodextrins of 1.2–1.8 g/min with fructose or sucrose coingested at 0.6 g/min or above, showed 10–33% reductions in the rate of oxidation of endogenous carbohydrate relative to the ingestion of isocaloric glucose or maltodextrin only (19–23, 41). In contrast, another group using ingestion rates of composite carbohydrates below the physiological max-

\[ \text{ACKNOWLEDGMENTS} \]

We thank Dr. Kevin Schmidt and Ian Ross for assistance with $^{13}$C license requirements and Sheinach Dunn for laboratory assistance. We also thank the cyclists for their valued contribution.

\[ \text{GRANTS} \]

This work was supported by a grant from Gatorade Sport Science Institute, Chicago, IL.

\[ \text{REFERENCES} \]
