Fructose and glucose co-ingestion during prolonged exercise increases lactate and glucose fluxes and oxidation compared with an equimolar intake of glucose\textsuperscript{1–3}

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ABSTRACT

Background: When fructose is ingested together with glucose (GLUFRU) during exercise, plasma lactate and exogenous carbohydrate oxidation rates are higher than with glucose alone.

Objective: The objective was to investigate to what extent GLUFRU increased lactate kinetics and oxidation rate and gluconeogenesis from lactate (GNGL) and from fructose (GNGF).

Design: Seven endurance-trained men performed 120 min of exercise at \(\sim 60\% \) VO\(_{2}\text{max}\) (maximal oxygen consumption) while ingesting 1.2 g glucose/min + 0.8 g of either glucose or fructose/min (GLUFRU). In 2 trials, the effects of glucose and GLUFRU on lactate and glucose kinetics were investigated with glucose and lactate tracers. In a third trial, labeled fructose was added to GLUFRU to assess fructose disposal.

Results: In GLUFRU, lactate appearance (120 ± 6 \(\mu\)mol \(\cdot\) kg\(^{-1}\) \(\cdot\) min\(^{-1}\)), lactate disappearance (121 ± 7 \(\mu\)mol \(\cdot\) kg\(^{-1}\) \(\cdot\) min\(^{-1}\)), and oxidation (127 ± 12 \(\mu\)mol \(\cdot\) kg\(^{-1}\) \(\cdot\) min\(^{-1}\)) rates increased significantly \((P < 0.001)\) in comparison with glucose alone \((94 ± 16, 95 ± 16, and 97 ± 16 \(\mu\)mol \(\cdot\) kg\(^{-1}\) \(\cdot\) min\(^{-1}\), respectively). GNGF was negligible in both conditions. In GLUFRU, GNGF and exogenous fructose oxidation increased with time and leveled off at \(18.8 ± 3.7\) and \(38 ± 4 \(\mu\)mol \(\cdot\) kg\(^{-1}\) \(\cdot\) min\(^{-1}\), respectively, at 100 min. Plasma glucose appearance rate was significantly higher \((P < 0.01)\) in GLUFRU \((91 ± 6 \(\mu\)mol \(\cdot\) kg\(^{-1}\) \(\cdot\) min\(^{-1}\))\) than in glucose alone \((82 ± 9 \(\mu\)mol \(\cdot\) kg\(^{-1}\) \(\cdot\) min\(^{-1}\))\). Carbohydrate oxidation rate was higher \((P < 0.05)\) in GLUFRU.

Conclusions: Fructose increased total carbohydrate oxidation, lactate production and oxidation, and GNGF. Fructose oxidation was explained equally by fructose-derived lactate and glucose oxidation, most likely in skeletal and cardiac muscle. This trial was registered at clinicaltrials.gov as NCT01128647. Am J Clin Nutr 2010; 92:1071–9.

INTRODUCTION

Regardless of the amount of exogenous glucose intake during exercise, there is a maximal exogenous oxidation rate of \(\sim 1\) g/min. However, adding fructose to glucose during exercise has been shown to further increase exogenous carbohydrate oxidation rate (1–6) up to 1.75 g/min (7). Although the mechanism responsible for this increased exogenous carbohydrate oxidation is unknown, it has been suggested that the major limiting factor of exogenous carbohydrate oxidation is intestinal transport, and that it can be increased if fructose, which uses a molecular absorption pathway distinct from glucose, is co-ingested with glucose (1–3, 6, 8).

Fructose metabolism, however, differs markedly from glucose metabolism. Fructose is essentially taken up by intestinal and liver cells and is rapidly and almost completely converted into triose-phosphates (9). As a result, systemic fructose concentrations only increase marginally after fructose ingestion (10). Furthermore, because nonplancheric cells lack the enzyme fructokinase, and because hexokinase has a markedly lower affinity for fructose than for glucose, it is very unlikely that fructose is directly metabolized in skeletal muscle. Instead, it appears that fructose is essentially converted into glucose and lactate in liver cells to be subsequently oxidized in extrahepatic tissues (11, 12).

It is well established that when fructose and glucose are ingested simultaneously during exercise, plasma lactate concentrations are significantly increased, compared with isoenergetic glucose or glucose polymers ingestion (2, 3, 6–8), which suggests that systemic lactate fluxes increase when mixtures of glucose and fructose are ingested. It was recently shown that when a lactate polymer (polylactate) was ingested simultaneously with glucose and fructose, both polylactate and fructose exhibited similar patterns of oxidation, suggesting rapid conversion of fructose into lactate before oxidation (13).

As such, a beneficial effect of fructose and glucose co-ingestion on muscle performance would be expected because lactate is efficiently oxidized by active muscles during exercise (14, 15). Moreover, oral intakes of lactate polymers have been shown to be as efficient as oral glucose in maintaining glycemia during prolonged exercise (16) and to be oxidized without prior conversion into glucose (17).

The fate of oral fructose administered with glucose during exercise, and more specifically the rate of lactate production elicited after fructose administration, has not been quantitatively assessed. The aim of this study was to assess the metabolic effects

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of ingesting equimolar amounts of glucose or glucose + fructose mixtures in trained athletes during exercise.

SUBJECTS AND METHODS

Ethics

This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Biology and Medicine, University of Lausanne (protocol #59/09).

Participants

Seven healthy, well-trained male endurance cyclists gave written informed consent to participate in this study. Inclusion criteria were age between 20 and 40 y, ≥3 y of cycling endurance training, body mass index (BMI; in kg/m²) between 18 and 25, and taking no medication 1 wk before and during the study. Subjects’ characteristics are shown in Table 1.

Overall study design

The overall study consisted of a preliminary session during which VO_{2max} (maximal oxygen consumption) and maximal aerobic power (MAP) output were assessed, followed by three 120-min submaximal exercise trials performed in a single-blind, randomized, crossover design. Visits were separated by 5–10 d.

The 3 exercise trials aimed at comparing the metabolic effects of oral glucose (ingested at an average rate of 2 g/min) (GLU) or of an oral glucose + fructose (1.2 + 0.8 g/min) mixture (GLUFRU) during exercise. To evaluate glucose and lactate kinetics, total carbohydrate oxidation, and lactate oxidation, subjects were studied during a 2-h exercise protocol with oral administration of a glucose mixture (120 g every hour) or a glucose + fructose (72 + 48 g every hour) mixture. The 6,6-2H₂ glucose and 1³C₃-lactate were infused to calculate glucose and lactate kinetics. Furthermore, indirect calorimetry was performed to measure total carbohydrate oxidation, and expired ¹³CO₂ was monitored to calculate whole-body lactate oxidation.

During the third exercise trial, the same procedures were performed in each subject with repeated administration of oral glucose + fructose labeled with ¹³C₂-fructose to evaluate exogenous fructose metabolic fate and oxidation. Fructose conversion into lactate and glucose were evaluated by monitoring the systemic appearance of plasma ¹³C-labeled lactate and ¹³C-labeled glucose. Total exogenous fructose oxidation was also measured by monitoring ¹³CO₂ production.

TABLE 1

Characteristics of study participants

| Age (y) | 30 ± 5 |
| Height (cm) | 179 ± 6 |
| Weight (kg) | 69.5 ± 3.4 |
| Fat mass (%) | 12.0 ± 2.3 |
| MAP (W) | 365 ± 25 |
| VO_{2max} (L/min) | 5.1 ± 0.3 |
| VO_{2max} (mL · min⁻¹ · kg⁻¹) | 73.4 ± 5.3 |

1 MAP, maximal power output; VO_{2max}, maximal oxygen consumption.

Plasma hormones and substrate concentrations were measured immediately before and throughout the test at 20-min intervals.

Preliminary visit

Within 2 wk of the beginning of the main trials, subjects reported to the laboratory for assessment of their anthropometric characteristics and determination of their VO_{2max}. Volunteers’ body weight and height were measured, and body fat was estimated by skinfold thickness measurements (18). VO_{2max} and MAP were then determined during an incremental test to exhaustion performed on a cycle ergometer (Lode Excalibur; Lode, Groningen, Netherlands). First, subjects sat quietly on the ergometer for 5 min before starting pedaling at 60 W for 5 min. Power output was then increased by 35 W every 3 min until exhaustion. Throughout the incremental test, oxygen uptake (VO₂) and carbon dioxide production (VCO₂) were measured breath-by-breath (SensorMedics Vmax; Sensormedics Corp, Yorba Linda, CA), and heart rate was monitored continuously (Polar S810; Polar Electro Oy, Kempele, Finland). VO₂ was considered as maximal if ≥2 of the following criteria were met: a leveling off of VO₂ with increasing work rate, a respiratory exchange ratio above 1.05, and a maximal heart rate ≤10 beats of the predicted maximal heart rate. In all subjects, ≥2 criteria were met. MAP was calculated from the addition of the last complete step and the fraction of time spent in the following step multiplied by 35 W.

Submaximal exercise trials

For the 48 h before the test, subjects refrained from strenuous exercise. They were asked to record their diets during the 2 d before the first trial and to closely repeat the same dietary intakes before the 2 subsequent trials. It was thus assumed that glycogen concentrations were similar between trials. In addition, they received instructions to avoid foods naturally enriched in ¹³C and to refrain from caffeine and alcohol.

After fasting overnight, subjects reported at 0730 to the laboratory. After arrival, volunteers were asked to void and were then weighed. Next, a catheter was inserted into the antecubital vein (right arm), and an initial blood sample was drawn for baseline determination of plasma metabolites. Expired air samples were collected in quadruplicate for the assessment of baseline expired air ¹³CO₂ isotopic enrichment. A second catheter was inserted into the left arm for stable-isotope tracer infusion.

Ten minutes before the exercise trial started, a primed (11 μmol/kg) constant infusion of 0.11 μmol 6,6-²H₂ glucose · kg⁻¹ · min⁻¹ began. Subjects were asked to sit quietly with VO₂ and VCO₂ being measured breath-by-breath (SensorMedics Vmax; Sensormedics Corp). After 9 min of rest, subjects took their position on the cycle ergometer. The 6,6-²H₂ glucose infusion rate was increased to 0.44 μmol · kg⁻¹ · min⁻¹, and subjects started pedaling at an intensity of 50% of their individual MAP after 1 min. After starting exercise, the mouthpiece was removed, and a 600-mL carbohydrate drink was provided, which had to be consumed within 3 min. To provide a total of 2 L of the drink and 240 g of carbohydrate over the 120 min of exercise, 280 mL of the tested solution was provided thereafter, every 20 min during ≤100 min of exercise.

The test drink contained either 120 g glucose/L (D-Glucose, Fluka Analytic; Sigma Aldrich, Buchs, Switzerland) (GLU) or...
72 and 48 g fructose/L (D-Fructose, Fluka Analytic; Sigma Aldrich) (GLUFRU), as well as 20 mmol NaCl/L and 20 mL lemon juice/L.

For every 20 min of exercise, a measurement of VO2 and VCO2 was performed for 5 min. At this time, a venous blood sample was drawn, ratings of perceived exertion (RPE) were recorded, and a breath sample was obtained before subjects ingested 280 mL of the tested carbohydrate solution. These procedures were thus performed at 15, 35, 55, 75, 95 and 115 min. Participants did not receive any drink at the last time point.

Lactate kinetics were assessed by using a primed (42.5 μmol/kg) constant infusion (2.25 μmol · kg⁻¹· min⁻¹) of [1³C₃]-lactate (Cambridge Isotopes, Andover, MA) during 40–120 min of exercise. Five subjects received the simultaneous primed constant infusion of labeled lactate and deuterated glucose, and 2 subjects underwent the exercise trial with only the infusion of deuterated glucose.

The metabolic fate of fructose was assessed by using identical procedures, without labeled lactate infusion. However, the ingested fructose was labeled with artificially labeled [U¹³C]-fructose (Cambridge Isotopes). The enrichment of fructose in the drink was 1.44837 atom percent. All subjects underwent this trial.

During the trial, heart rate was obtained beat-to-beat (Polar S810; Polar Electro Oy).

At the end of the test volunteers were provided with a carbohydrate-rich snack and could rest.

Analytic procedures

Blood was collected on lithium heparin for measurement of glucose, fructose, lactate and tracers; with EDTA-coated tubes for measurement of insulin, cortisol, and free fatty acids (FFAs); or with EDTA-trasylol for measurement of glucagon. After blood collection, plasma was immediately separated from blood by centrifugation at 4°C for 10 min at 3600 g and stored at −20°C until analysis. Lactate concentration was measured enzymatically by using kits from Boehringer (Boehringer Mannheim, Mannheim, Germany). Plasma glucose concentration was measured by the glucose oxidase method with a Beckman glucose analyzer II (Becton Dickinson, USA). Plasma fructose concentrations were measured by using the glucoamylase–ammonium persulfate (Glucomyo) method (Sigma, St Louis, MO). Plasma lactate and deuterated glucose abundance were measured by gas chromatography–mass spectrometry (GC-MS) (Hewlett-Packard, CA). Plasma fructose concentrations were measured by using the glucokinase method (Sigma, St Louis, MO).

Plasma fructose concentrations were measured by using the protocol from Petersen et al (23). Briefly, 0.1 mL mannitol (0.55 mmol/L) was added per 0.2 mL plasma. The plasma was deproteinized with 0.3 Newton (N) barium hydroxide and 0.3 N zinc sulfate and partially purified by sequential cation-exchange columns. After drying, the samples were derivatized with acetic anhydride and pyridine, and plasma fructose concentrations were measured by using GC-MS with electron impact ionization.

Calculations

Plasma glucose and rates of lactate appearance and disappearance and metabolic clearance rate (MCR) were calculated from plasma 6,6-²H₂ glucose and [1³C₃]-lactate isotopic enrichment (IE), respectively, by using the Steeles' equations for non–steady state conditions (24). The volume of distribution was considered to be 180 mL/kg for glucose and 100 mL/kg for lactate (25, 26).

The rate of appearance of lactate from fructose (RaLF) (μmol·kg⁻¹·min⁻¹) was calculated from the lactate Ra (RaL), [1³C₃]-lactate, and [1³C]-fructose isotopic enrichment as follows:

$$\text{RaLF} = \frac{\text{lactate IE} \cdot \text{RaL}}{\text{fructose IE}}$$

where lactate IE and fructose IE are the enrichment of plasma lactate and ingested fructose, respectively.

Gluconeogenesis from lactate was calculated from lactate incorporation into glucose (27, 28)

$$\text{GNGL} = \frac{\text{glucose IE} \cdot \text{glucose Ra}}{\text{lactate IE} \cdot k}$$

where GNGL (μmol · kg⁻¹·min⁻¹) was the gluconeogenesis from lactate, and glucose IE and lactate IE are the isotopic enrichment of plasma glucose and lactate, respectively. k represents the correction factor for the loss of carbon labels in the tricarboxylic acid cycle during GNGL, which was assumed to be 0.67.

Gluconeogenesis from fructose (GNGF) was calculated as

$$\text{GNGF} = \frac{\text{glucose IE} \cdot \text{glucose Ra}}{\text{fructose IE} \cdot k}$$

where GNGF (μmol·kg⁻¹·min⁻¹) is the gluconeogenesis from fructose, and glucose IE and fructose IE are the isotopic enrichments of plasma glucose and fructose, respectively. k represents the correction factor for the loss of carbon labels in the tricarboxylic acid cycle during GNGF, which was assumed to be 0.67.

Substrate oxidation

Carbohydrate and fat oxidation rates (g/min) were calculated from respiratory gas exchange (29).

Lactate oxidation rates were calculated from [¹³C] abundance in expired CO₂ and plasma lactate. Plasma lactate oxidation rate (μmol·kg⁻¹·min⁻¹) was calculated without taking into account secondary labeling of glucose because gluconeogenesis was almost negligible (see Results) (25).

$$\text{Plasma lactate oxidation} = \frac{\text{VCO}_2}{\text{lactate IE}} \cdot \frac{\text{CO}_2 \text{ IE}}{180} \cdot \frac{1}{22.4 \cdot 3}$$

where CO₂ IE and lactate IE are the isotopic enrichment of expired CO₂ and plasma lactate; 22.4 3 corresponds to the volume of CO₂ per mol of lactate oxidized. Recovery of metabolic [¹³C]CO₂ in breath was considered to be complete.

Exogenous fructose oxidation was calculated as follows (20):

$$\text{Exogenous fructose oxidation (g/min)} = \text{TrCO}_2 \cdot \frac{\text{CO}_2 \text{ IE}}{\text{fructose IE} \cdot 0.8} \cdot \frac{\text{VCO}_2}{10^6}$$

where CO₂ IE and fructose IE are the isotopic enrichment of breath CO₂ and ingested fructose expressed in atom percent.
excess (APE), \( \dot{V}CO_2 \) is the total respiratory CO2 (mL/min), 0.8 is the recovery of \(^{13}\text{C}\) from fructose in breath CO2, 0.134 is the volume of CO2 (mL) produced by oxidation of 1 \( \mu \text{mol} \) fructose, 180 is the molar weight of fructose, and \( 10^6 \) represents the conversion from micrograms to grams.

Total gluconeogenesis from fructose and lactate and lactate production and oxidation from fructose were calculated over the last 40 min of exercise, assuming that fructose absorption had reached steady state and was equal to the intake (ie, 0.8 g/min). Nonoxidative fructose disposal was considered to be the difference between fructose absorption and oxidation rates.

Heart rate data were averaged every 5 s from beat-to-beat signal by using linear interpolation after removal of artifacts using “R” (30).

**Statistical analysis**

Data for the 2 GLUFRU trials were averaged; skewed distributions were log-transformed before statistical calculations. Analysis of the effect of treatment (GLU compared with GLUFRU) over time on metabolic variables and substrate kinetics was performed by using a 2-factor (time \( \times \) condition) repeated-measures analysis of variance (ANOVA). When applicable, Tukey post hoc tests were performed.

Student’s paired \( t \) tests were used to identify differences between single parameters for normally distributed data, and Wilcoxon’s signed rank tests were used for nonnormally distributed data.

The respective change of exogenous fructose oxidation rate and gluconeogenesis from fructose was analyzed with a one-factor ANOVA. When applicable, multiple comparisons were performed with a Tukey post hoc test.

All statistical computations were made by using “R,” an open source statistical software (30). \( P \) values < 0.05 were considered significant. All data are expressed as means ± SDs.

**RESULTS**

**Tracers**

\(^{13}\text{C}\) Enrichments of plasma lactate and glucose and expired CO2 are presented in Figure 1. Plasma lactate enrichment was significantly \((P < 0.01)\) higher in GLU compared with GLUFRU during \(^{13}\text{C}\)-lactate infusion, reaching \(^{2.5}\) and \(^{2}\) molar percent excess (MPE), respectively (Figure 1A). With \(^{13}\text{C}\)-fructose ingestion, \(^{13}\text{C}\)-lactate enrichment reached steady state between 40 and 120 min at 0.39 ± 0.06 MPE (Figure 1D). Glucose \(^{13}\text{C}\) enrichment remained low when labeled lactate was infused, reaching 0.03 and 0.02 APE in GLU and GLUFRU.

**FIGURE 1.** Mean (±SD) isotopic enrichment of plasma lactate (A and D), plasma glucose (B and E), and expired (Exp.) carbon dioxide (CO2) (C and F) during \(^{13}\text{C}\)-labeled lactate infusion (A, B, and C; \( n = 5 \)) and during \(^{13}\text{C}\)-fructose ingestion (D, E, and F; \( n = 7 \)). Enrichment of plasma lactate is expressed as molar percent excess (MPE). Enrichment of plasma glucose and expired CO2 are expressed as atom percent excess (APE). Open triangles represent glucose-alone (GLU) and black squares represent glucose + fructose (GLUFRU) conditions during the lactate turnover trial. Black squares represent the GLUFRU condition with ingestion of \(^{13}\text{C}\)-fructose. Note that the scales for the y-axis for the \(^{13}\text{C}\)-lactate trials (panels A, C, and E) and for the \(^{13}\text{C}\)-fructose trials (panels B, D, and F) are different. All analyses were performed by 2-factor repeated-measures ANOVA in panels A–C. A: \( P < 0.01 \) for treatment, \( P < 0.001 \) for time, and \( P < 0.01 \) for treatment \( \times \) time interaction. B: \( P = 0.01 \) for treatment, \( P < 0.001 \) for time, and \( P = 0.13 \) for treatment \( \times \) time interaction. C: \( P = 0.34 \) for treatment, \( P < 0.001 \) for time, and \( P < 0.21 \) for treatment \( \times \) time interaction. D–F: \( P < 0.001 \) for time (one-factor ANOVA with repeated-measures). **Significant difference between GLU and GLUFRU: *\( P < 0.05 \), **\( P < 0.01 \) (Tukey post hoc test).”

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respectively (Figure 1B). Plasma glucose enrichment was significantly higher in GLU. In contrast, when $^{13}$C-fructose was ingested, glucose enrichment increased to 0.2 APE (Figure 1E) at 100 min of exercise. With $^{13}$C-lactate infusion, expired $^{13}$CO₂ enrichment was 0.37 ± 0.02 and 0.36 ± 0.02 APE in GLU and GLUFRU, respectively (Figure 1C). With $^{13}$C-fructose ingestion, $^{13}$CO₂ enrichment increased with time to reach a plateau of ~0.15 APE after 100 min (Figure 1F).

**Plasma metabolites**

At rest, plasma lactate concentration was 1.27 ± 0.36 and 1.27 ± 0.39 mmol/L in GLU and GLUFRU, respectively (Figure 2). It decreased slightly (1.21 ± 0.26 mmol/L) and remained stable during exercise in GLU. As expected, plasma lactate concentration increased to 1.75 ± 0.40 mmol/L in GLUFRU, which was significantly higher (2-factor repeated-measures ANOVA: treatment, $P < 0.001$; time, $P < 0.001$; treatment × time, $P < 0.01$) than in GLU (Figure 2A).

Plasma glucose concentration increased at the onset of exercise in both conditions and was, on average, 6.2 ± 0.9 mmol/L in both conditions (Figure 2B) with no difference between GLU and GLUFRU.

Plasma fructose concentration was close to zero at the onset of exercise and increased significantly with time, reaching a plateau of 0.47 mmol/L after 80 min of exercise in GLUFRU (Figure 2D).

Plasma FFAs were comparable in GLU and GLUFRU at rest (0.36 ± 0.12 and 0.33 ± 0.15 mmol/L, respectively). Plasma FFAs decreased significantly with time during exercise (2-factor repeated-measures ANOVA: time effect, $P < 0.001$) and were on average significantly lower in GLUFRU (0.12 ± 0.07 mmol/L) than in GLU (0.23 ± 0.09 mmol/L) (2-factor repeated-measures ANOVA: treatment main effect, $P < 0.01$; Figure 2C).

Plasma insulin concentrations (Figure 2E) were 6.1 ± 1.9 and 6.1 ± 1.2 μU/mL at rest in GLU and GLUFRU, respectively, and increased over time in response to carbohydrate ingestion ($P < 0.001$) with no difference between conditions. After 120 min, insulin concentrations were 8.1 ± 1.9 and 9.3 ± 2.6 μU/mL in GLU and GLUFRU, respectively.

Plasma glucagon concentrations (Figure 2F) were comparable in GLU and GLUFRU at rest (44.2 ± 11.4 and 45.9 ± 11.6 pg/mL). During exercise, plasma glucagon concentrations increased slightly in both groups but were marginally lower in GLUFRU than in GLU (2-factor repeated-measures ANOVA: treatment, $P < 0.01$; time, $P < 0.001$; treatment × time, $P = 0.31$).

Plasma cortisol concentration was similar between GLU and GLUFRU at rest (420 ± 87 compared with 470 ± 90 pmol/L) and during exercise (382 ± 124 compared with 378 ± 112 pmol/L).

**Substrate oxidation and kinetics**

In the GLU condition, total carbohydrate and fat oxidations were 3.1 ± 0.4 and 0.35 ± 0.16 g/min, respectively (not shown in tables or figures).

Lactate rate of appearance (Ra) was 94 ± 16 μmol · kg⁻¹ · min⁻¹, lactate rate of disappearance (Rd) was 95 ± 16 μmol-

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**FIGURE 2.** Mean (±SD) plasma substrate concentrations in response to ingestion of glucose alone (GLU) or glucose + fructose (GLUFRU). For all variables, $n = 7$. All analyses were performed by 2-factor repeated-measures ANOVA in panels A–C, E, and F. A: $P < 0.001$ for treatment, $P < 0.01$ for time, and $P < 0.01$ for treatment × time interaction. B: $P = 0.78$ for treatment, $P < 0.001$ for time, and $P = 0.87$ for treatment × time interaction. C: $P < 0.001$ for treatment, $P < 0.001$ for time, and $P < 0.28$ for treatment × time interaction. D: $P < 0.001$ for time (one-factor repeated-measures ANOVA). E: $P < 0.001$ for treatment, $P < 0.001$ for time, and $P = 0.068$ for treatment × time interaction. F: $P < 0.01$ for treatment, $P < 0.001$ for time, and $P = 0.31$ for treatment × time interaction. **Significant difference between GLU and GLUFRU treatments: *P < 0.05, **P < 0.01 (Tukey post hoc test). 3Significant difference between 0, 20, 40, and 60 min ($P < 0.05$, Tukey post hoc test). FFA, free fatty acids.
kg \cdot min^{-1}, and its oxidation was 97 ± 16 μmol \cdot kg^{-1} \cdot min^{-1} (Figure 3). In GLU, lactate MCR was observed to be 75 ± 13 mL \cdot kg^{-1} \cdot min^{-1}. Oxidized Rd lactate was 102 ± 12% in these conditions. Glucose Ra, Rd, and MCR were, on average, 75.9 ± 9.5 μmol \cdot kg^{-1} \cdot min^{-1}, 77.7 ± 10.4 μmol \cdot kg^{-1} \cdot min^{-1}, and 12.9 ± 2.8 mL \cdot kg^{-1} \cdot min^{-1}, respectively (Figure 4). Data obtained during the 13C3-lactate infusion indicated that liver gluconeogenesis from lactate (GNGL) was negligible, at most 2.0 μmol \cdot kg^{-1} \cdot min^{-1} (Figure 5).

In the GLUFRU condition, and compared with GLU, total carbohydrate oxidation was significantly (P < 0.05) higher by ~7%, reaching 3.3 ± 0.3 g/min, whereas fat oxidation rate was lower, on average 0.27 ± 0.18 g/min (P < 0.05, not shown in tables or figures). Significantly higher lactate kinetics and oxidation rate (2-factor repeated-measures ANOVA: treatment main effect, P < 0.001) as well as glucose kinetics (P < 0.01) were observed in GLUFRU as compared with GLU. On average, lactate Ra, Rd, and oxidation rate were higher by ~30%, at 120 ± 6, 121 ± 7, and 127 ± 12 μmol \cdot kg^{-1} \cdot min^{-1}, respectively (Figure 3, A–C). In GLUFRU, lactate MCR (71 ± 15 mL \cdot kg^{-1} \cdot min^{-1}) was, however, not different from that in GLU (Figure 3D). Oxidized Rd lactate was 104 ± 11% in GLUFRU and 102 ± 12% in GLU.

Glucose Ra and Rd were, on average, higher (2-factor repeated-measures ANOVA: treatment main effect, P < 0.01) in GLUFRU compared with GLU (Figure 4) by ~10%, at 83 ± 13 and 84 ± 15 μmol \cdot kg^{-1} \cdot min^{-1}, respectively. In addition, glucose MCR was higher by 8%, at 13.7 ± 2.6 mL \cdot kg^{-1} \cdot min^{-1}. Despite the higher lactate kinetics and plasma lactate concentration in GLUFRU, GNGL remained negligible (Figure 5).

With the use of labeled fructose, total exogenous fructose oxidation reached 38 ± 4 μmol \cdot kg^{-1} \cdot min^{-1} or ~0.48 ± 0.1 g/min during the later stages of the exercise trial (ie, after 100 min). Gluconeogenesis from fructose (GNFR) increased with time and reached 19 μmol \cdot kg^{-1} \cdot min^{-1} after 100 min of exercise. Fructose conversion into plasma lactate (calculated with lactate Ra of the test with 13C3-lactate infusion, see section entitled “Calculations”) was 35.4 ± 2.9 μmol \cdot kg^{-1} \cdot min^{-1}.

Other variables

Mean VO2, VCO2, and respiratory exchange ratio (RER) at rest and during exercise are shown in Table 2. RER was significantly higher in GLUFRU during exercise (P < 0.05, Wilcoxon’s signed-rank test).

Mean heart rate was comparable between conditions, at 134 ± 7 beats/min in GLU compared with 133 ± 7 beats/min in GLUFRU (P = NS) (Table 2).

After 20 min of exercise, RPE was 9.1 ± 1.1 and 9.7 ± 1.1 in GLU and GLUFRU, respectively. RPE increased significantly

FIGURE 4. Mean (±SD) glucose (Gluc.) rates of appearance (Ra; A), rates of disappearance (Rd; B), and metabolic clearance rate (MCR; C) in glucose-alone (GLU) and glucose + fructose (GLUFRU) conditions. All analyses were performed by 2-factor repeated-measures ANOVA. A: P < 0.001 for treatment, P < 0.01 for time, and P = 0.86 for treatment × time interaction. B: P = 0.01 for treatment, P = 0.01 for time, and P = 0.71 for treatment × time interaction. C: P = 0.08 for treatment, P < 0.01 for time, and P = 0.91 for treatment × time interaction. For all variables, n = 7.
Repeated-measures ANOVA.

Significant difference between 20, 40, 60, and 80 min of exercise (GNGLactate; PO (W) — — 182

Average power output (PO), oxygen consumption (VO2), carbon dioxide production (VCO2), respiratory exchange ratio (RER), heart rate (HR), and perceived exertion (RPE) at rest and during exercise.

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<th>Rest</th>
<th>Exercise</th>
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<td>GLU</td>
<td>GLUFRU</td>
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<tr>
<td>PO (W)</td>
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<tr>
<td>VO2 (L/min)</td>
<td>0.374 ± 0.09</td>
<td>0.403 ± 0.06</td>
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<tr>
<td>VCO2 (L/min)</td>
<td>0.308 ± 0.07</td>
<td>0.331 ± 0.05</td>
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<td>RER</td>
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<td>HR (beats/min)</td>
<td>57 ± 7</td>
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Values are means ± SDs. GLU, glucose alone; GLUFRU, glucose + fructose; F × E, Fructose × Exercise interaction. P values were derived by 2-factor repeated-measures ANOVA.

DISCUSSION

To our knowledge, this study provides the first detailed assessment of fructose metabolism during high-dose glucose + fructose ingestion during exercise. We showed that oxidation of fructose co-ingested with glucose is explained equally by lactate oxidation produced from fructose cleavage and by glucose oxidation derived from fructose and direct fructose oxidation in splanchnic tissues.

We observed that fructose co-ingested with glucose led to a slight, but significant, increase in the rate of glucose appearance. In contrast, previous observations have shown that in resting conditions, fructose administration did not change total glucose production due to an auto-regulation of glucose production, in which increased GNG is compensated for by decreased hepatic glycogenolysis (31). Differences between studies performed in resting conditions and exercise may be explained by the fact that exercise stimulates glucagon secretion (32) and that hyperglucagonemia impairs auto-regulation of glucose production, most likely by stimulating glucose-6-phosphate hydrolysis and hepatic glucose release (33, 34). Increased glucose utilization may be induced by fructose ingestion through an increase in glucokinase activity induced by fructose-1-P in hepatic cells (35). Although plasma glucose concentration did not change significantly in our study, this may be due to the relatively small increase in total glucose fluxes, which were insufficient to produce a significant increase in glycemia, or because fructose simultaneously increased glucose utilization to some extent. Such an increase in glucose utilization may indeed be induced by fructose ingestion through an increase in glucokinase activity induced by fructose-1-P in hepatic cells (35).

Fructose ingestion led to an increase in total lactate Ra (+ 30% in GLUFRU compared with GLU). This increased lactate production, together with the low plasma fructose concentrations, suggests that part of the ingested fructose was extracted at first pass by the splanchnic tissues and released into the bloodstream as lactate (11, 36). Assuming that the difference in lactate Ra between GLUFRU and GLU corresponds to fructose conversion into lactate, our results indicate that this pathway accounted for approximately half of the fructose oxidation. The other half could be accounted for by GNGI.

Total lactate oxidation was also increased in GLUFRU compared with GLU. This most likely corresponds to lactate oxidation in active muscle fibers (37). Part of lactate oxidation may also take place in heart muscle, because lactate is efficiently used as an energy fuel in cardiomyocytes during exercise (38). Approximately 100% of lactate Rd was oxidized both with GLU and GLUFRU. Our figure is somewhat higher than previous reports (14, 25, 39, 40) showing that 80% of lactate Ra was oxidized during exercise. It is likely that the high oxidative capacity of our highly trained subjects, reflected by their high VO2max values, accounted for this difference (15). It is also possible that our data slightly overestimated the relative lactate oxidation, because lactate kinetics were measured in non-arterialized venous blood, which is known to lead to a slight underestimate of lactate kinetics (41). Nonetheless, our data clearly indicate that oxidation was the major fate of the lactate production, whether from exogenous or endogenous glucose or from exogenous fructose.

Hepatic lactate uptake and conversion into glucose contributes substantially to total lactate disappearance under fasting conditions. Increased lactate availability, produced by exogenous lactate infusion, increases fractional (42, 43) and total glucoseogenesis from lactate (GNGI) during prolonged exercise in fasted conditions (43). In contrast, our results show that GNGI,
was very low, most likely as a consequence of carbohydrate intake and suppression of gluconeogenesis by hyperinsulinemia (44), although our subjects were well trained and had high GNG capacity (27). A reduction of liver blood flow, which occurs during strenuous exercise, may also contribute to lower hepatic gluconeogenesis (45).

In agreement with previous studies, a peak oxidation rate of \( \approx 0.45 \) g exogenous fructose/min occurred after 100 min of exercise (2, 6, 7, 46). Because fructose conversion into lactate and oxidation was estimated to be 35 and 31 \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \), corresponding to 28% and 25% of the fructose load, respectively, and because fructose-derived glucose released into the systemic circulation was estimated to be 29% of the fructose load (Table 1), one can conclude that both the lactate and glucose released by the liver were essentially oxidized, presumably in active skeletal muscles (14, 15, 40) and the heart (38). Our data also indicate that, by the end of the exercise, \( \approx 40\% \) of the labeled carbons of fructose had not been recovered in expired air (Table 3). Similar observations have been reported previously (3, 46), and it has been suggested that the liver may act as a carbon reservoir after fructose ingestion, which rapidly releases lactate while temporarily retaining part of the glucose synthesized as glycogen (46).

Our study has several limitations. First, measurements of lactate kinetics and of fructose disposal were performed only during exercise but not at rest; furthermore, all measurements were performed in subjects after having received the glucose or co-ingestion of fructose with glucose not only allows the increase of total carbohydrate oxidation beyond what may be obtained with increasing glucose doses but also provide an additional oxidative fuel to active skeletal muscles during exercise.

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The authors' responsibilities were as follows—VL, PS, and LT: designed the study; VL, RB, PS, GC, and GPM: performed the experiments; VL: performed the statistical analysis and wrote the manuscript; and LT, RB, YS, PS, GC, and GPM: edited the manuscript. None of the authors had any conflicts of interest.

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