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A. E. JEUKENDRUP, M. MENSINK, W. H. M. SARIS, AND A. J. M. WAGENMAKERS
Department of Human Biology, Maastricht University, 6200 MD Maastricht, The Netherlands

Jeukendrup, A. E., M. Mensink, W. H. M. Saris, and A. J. M. Wagenmakers. Exogenous glucose oxidation during exercise in endurance-trained and untrained subjects. *J. Appl. Physiol.* 82(3): 835–840, 1997.—To investigate the effect of training status on the fuel mixture used during exercise with glucose ingestion, seven endurance-trained cyclists (Tr; maximum O_2 uptake 67 ± 2.3 ml·kg^{-1}·min^{-1}) and eight untrained subjects (UTr; 48 ± 2 ml·kg^{-1}·min^{-1}) were studied during 120 min of exercise at ~60% maximum O_2 uptake. At the onset of exercise, 8 ml·kg^{-1}·min^{-1} of an 8% naturally enriched [^{13}C]glucose solution was ingested and 2 ml/kg every 15 min thereafter. Energy expenditure was higher in Tr subjects compared with UTr subjects (3,404 vs. 2,630 kJ; $P < 0.01$). During the second hour, fat oxidation was higher in Tr subjects (37 ± 2 g) compared with UTr subjects (23 ± 1 g), whereas carbohydrate oxidation was similar (116 ± 8 g in Tr subjects vs. 114 ± 4 g in UTr subjects). No differences were observed in exogenous glucose oxidation (50 ± 2 g in Tr subjects and 45 ± 3 g in UTr subjects, respectively). Peak exogenous glucose oxidation rates were similar in the two groups (0.95 ± 0.07 g/min in Tr subjects and 0.96 ± 0.03 g/min in UTr subjects). It is concluded that the higher energy expenditure in Tr subjects during exercise at the same relative exercise intensity is entirely met by a higher rate of fat oxidation without changes in the rates of exogenous and endogenous carbohydrates.

training; carbon 13; breath test; stable isotopes; substrate utilization

FOR MANY YEARS it has been known that substrate utilization during exercise is dependent on the exercise intensity and duration and that both training and diet may affect the relative importance of carbohydrate (CHO) and fat as a fuel (3). As exercise duration progresses, total CHO oxidation decreases while the contribution of plasma glucose and fatty acids to total energy metabolism increases (36). Prolonged exercise at moderate exercise intensities [60–70% maximum O_2 uptake ($\dot{V}O_{2max}$)] results in muscle glycogen depletion and decreased blood glucose concentrations as a result of decreased hepatic glucose production (1, 29).

It has been shown that CHO ingestion may maintain blood glucose availability and high rates of CHO oxidation late in exercise when muscle glycogen levels are low (4, 7, 29). The increased rates of glucose uptake (29) and oxidation (1) may be responsible for the observed improvements in exercise time to exhaustion when CHOs are ingested during exercise (7).

Training is another factor that provokes a large shift in substrate utilization during submaximal exercise (6, 13, 14). After training, the reliance on fat as an energy source is markedly increased, whereas the contribution of CHO decreased, as indicated by a decreased respiratory exchange ratio (RER) value (6, 13, 14, 22) and a slower rate of muscle glycogen breakdown (21). In rats (2) and humans (6), training also decreases blood glucose turnover during moderate-intensity exercise. In addition, Jansson and Kaijser (16) reported lower leg glucose uptake in trained compared with untrained men during exercise at 65% $\dot{V}O_{2max}$ as determined by arteriovenous concentration differences of glucose and estimated blood flow.

Together, these data indicate that the increase in fat oxidation in the trained muscle during exercise reduces both the oxidation of muscle glycogen and of blood glucose. We therefore hypothesized that untrained subjects would also oxidize a larger amount of ingested CHO compared with trained subjects because their rates of total CHO oxidation and glucose turnover are higher.

To our knowledge, there is only one study that investigated the effect of physical training on exogenous glucose oxidation. Krzentowski et al. (23) measured the oxidation of orally ingested glucose during exercise at the same absolute intensity (40% of the pretraining $\dot{V}O_{2max}$) before and after a 6-wk training program. Although endurance training is known to cause a large shift from predominantly CHO oxidation toward fat oxidation (6, 13, 14), in their study Krzentowski et al. (23) observed no changes in total CHO or fat oxidation. Yet, exogenous glucose oxidation was increased by 17% by the training. These findings are in contrast to a major body of literature and to the above-formulated hypothesis.

Until now, no study has investigated the effect of training on the composition of the fuel mixture oxidized during exercise at the same relative exercise intensity when CHOs are ingested. Therefore, the present study was undertaken to investigate the differences in total fat and CHO oxidation and in the contribution of exogenous and endogenous CHO oxidation between endurance-trained and untrained subjects at the same relative, moderate intensity.

MATERIALS AND METHODS

Subjects. Two groups of subjects with different training backgrounds participated in this study: eight well-trained (Tr) cyclists or triathletes and seven healthy untrained (UTr) subjects. The Tr subjects trained at least 4 times a week for 2 h or more and had a training history of at least 5 yr. The UTr subjects were healthy young adults who were not active in any sport and had no history of endurance training. Subjects' characteristics are listed in Table 1. After the nature and the risks of the experimental procedures were explained to the subjects, their written informed consent was obtained. The study was approved by the local Ethical Committee (Maastricht University).

Pretesting. Subjects' $\dot{V}O_{2max}$ was measured on an electronically braked cycle ergometer (Lode Excalibur, Groningen, The Netherlands) during an incremental exhaustive exercise test

Table 1. *Subject characteristics*

	Untrained ($n = 7$)	Trained ($n = 8$)
Age, yr	20.9 ± 0.5	25.1 ± 1.4
Height, cm	183 ± 3	182 ± 2
Weight, kg	75.4 ± 3.8	72.3 ± 1.2
BMI, m/k^2	22.6 ± 0.9	22.0 ± 0.5
Wmax, W	291 ± 12	414 ± 14*
$\dot{V}O_{2max}$, l/min	3.5 ± 0.1	5.2 ± 0.1*

Values are means ± SE; n = 15 subjects. BMI, body mass index; Wmax, maximum workload; $\dot{V}O_{2max}$, maximum O_2 uptake. *Significantly different between trained and untrained subjects, $P < 0.001$.

(24) 1 wk before the first experimental trial. The results of this test were used to determine the 50% maximum workload (Wmax; ~60% $\dot{V}O_{2max}$) that was later used in the experimental trials.

Experimental trials. Each subject performed two exercise trials, each separated by at least 7 days. The order of the trials was counterbalanced. Each trial consisted of 120-min cycling at 50% Wmax (~55–60% $\dot{V}O_{2max}$). During one test, subjects ingested a glucose solution with a high natural abundance of ^{13}C to study oral glucose oxidation. The second test was employed with ingestion of a glucose solution with a low natural abundance of ^{13}C to allow correction for changes in breath $^{13}CO_2$ background enrichment during exercise. To avoid background shifts, standard procedures were followed (18, 19). Subjects were instructed not to consume any products with a high natural abundance of ^{13}C during the entire experimental period. This was done to minimize a shift in background enrichment due to changes in endogenous substrate utilization. Furthermore, subjects were instructed to keep their diet as constant as possible the days before the trials.

Protocol. Subjects reported to the laboratory at 8:00 AM after an overnight fast, and before all trials a small standardized breakfast of two crackers with cheese was provided [(in g) 14 CHO, 4 fat, 6 protein]. A Teflon catheter (Baxter Quick Cath DuPont) was inserted into an antecubital vein, and at 8:30 AM a resting blood sample was drawn. Two subjects were tested on the same day, starting the protocol 10 min apart (i.e., the second subjects started the protocol 10 min later). Resting breath gases were collected (Oxycon β, Meinhardt, Mannheim, Germany), and vacutainer tubes were filled directly from a mixing chamber in duplicate to determine the $^{13}C/^{12}C$ ratio in expired CO_2. At 8:50 AM, the first subject started a warm-up of 5 min at 100 W, followed by 5 min at 40% Wmax. At 9:00 AM, the workload was increased to 50% Wmax for 120 min. During the first minute, subjects drank an initial bolus (8 ml/kg) of an 8% glucose solution. Thereafter, every 15 min a beverage volume of 2 ml/kg was provided. The average amount of glucose provided during the 120 min of exercise was 127 ± 2 g in Tr subjects and 132 ± 7 in UTr subjects. Blood samples were drawn at 30-min intervals until the end of exercise. Expiratory gases were collected every 15 min.

Glucose solutions. To quantify exogenous glucose oxidation, solutions were prepared from corn-derived glucose (Amylum), which has a high natural abundance of ^{13}C. The ^{13}C enrichment of the glucose was −11.2 δ/mil (‰) vs. Pee Dee Bellemnitella (PDB; −0.01259 atom percent excess) and was determined by on-line combustion-isotope ratio mass spectrometer (Carlo Erba-Finnigan MAT 252, Bremen, Germany). During the control trial, subjects ingested an 8% solution prepared from potato-derived glucose (AVEBE). This glucose had a ^{13}C enrichment of −26.1 δ‰ vs. PDB (−0.02934 atom percent excess), which is similar to the ^{13}C enrichment of expired air of European subjects (39).

Analysis. Blood (5 ml) was collected into EDTA-containing tubes and centrifuged for 4 min at 4°C. Aliquots of plasma were frozen immediately in liquid nitrogen and stored at −40°C until analysis of glucose (Uni Kit III, 0710970, La Roche, Basel, Switzerland), lactate (9), and free fatty acid (FFA; Wako NEFA-C test kit, Wako Chemicals, Neuss, Germany) concentrations that was performed with the COBAS FARA semiautomatic analyzer (La Roche). Insulin was analyzed by radioimmunoassay (Linco Ultra-Sensitive Human Insulin radioimmunoassay kit). From indirect calorimetry [RER, O_2 uptake ($\dot{V}O_2$)], and stable-isotope measurements (breath $^{13}CO_2/^{12}CO_2$; isotope ratio mass spectrometer, Finnigan MAT 252), total energy expenditure and oxidation rates of total fat, total CHOs, and exogenous glucose were calculated.

Calculations. From CO_2 uptake ($\dot{V}CO_2$) and $\dot{V}O_2$, total CHO and total fat oxidation rates were calculated (32)

$$\text{glucose oxidation} = 4.585\ \dot{V}CO_2 - 3.226\ \dot{V}O_2$$

$$\text{fat oxidation} = 1.695\ \dot{V}O_2 - 1.701\ \dot{V}CO_2$$

The isotopic enrichment was expressed as the δ‰ difference between the $^{13}C/^{12}C$ ratio of the sample and a known laboratory reference standard, according to the formula of Craig (8)

$$\delta^{13}C‰ = \left[\left(\frac{^{13}C/^{12}C\ \text{sample}}{^{13}C/^{12}C\ \text{standard}}\right) - 1\right]\cdot 10^3$$

The $\delta^{13}C$ was then related to an international standard, PDB.

The amount of ingested glucose oxidized was calculated according to the formula

$$\text{exogenous glucose oxidation} = \dot{V}CO_2 \cdot \left(\frac{\delta_{exp} - \delta C}{\delta_{ing} - \delta C}\right)\left(\frac{1}{k}\right)$$

in which δC is the ^{13}C enrichment of expired air in the control test (C; background), δ_{exp} is the ^{13}C enrichment of expired air during exercise at different time points, δ_{ing} is the ^{13}C enrichment of the ingested glucose, and k is the amount of CO_2 (in liters) produced by the oxidation of 1 g glucose (k = 0.7467 l CO_2/g glucose).

In the present study and in previous studies (20, 34, 37, 39), it was shown that instructing the subjects not to eat any products of high natural ^{13}C abundance during the experimental period was effective in reducing the background shift (change in $^{13}CO_2$) from endogenous substrate stores in European subjects (39). However, although the background shift was small in the present study, background correction was made by using the ^{13}C enrichment of breath samples in the CHO trial.

It should be noted that in the use of $^{13}CO_2$ in expired air to calculate exogenous substrate oxidation is the trapping of exogenous $^{13}CO_2$ in the bicarbonate pool, a very large and slowly exchanging pool in which an amount of CO_2 arising from decarboxylation of energy substrates is temporarily trapped each minute (35). However, during exercise, the CO_2 production increases severalfold so that a physiological steady-state situation will occur, and $^{13}CO_2$ in expired air will be equilibrated with the $^{13}CO_2/H^{13}CO_3^-$ pool. The dilution of $^{13}CO_2$ becomes negligible, and recovery of $^{13}CO_2$ approaches 100% after 60 min of exercise (31). Therefore, in the present study, data from the initial 60 min were not used for the calculation of exogenous glucose oxidation.

Statistics. An unpaired *t*-test was used to compare the differences in substrate utilization and blood parameters between Tr and UTr subjects. Analysis of variance for repeated measures was performed to study differences over time within each group. Scheffé's post hoc test was applied in case of a significant ($P < 0.05$) *F*-ratio to locate the differences.

RESULTS

$\dot{V}O_2$ and heart rate. The workload at 50% Wmax was 207 ± 7 W in the Tr subjects and 146 ± 6 W in the UTr subjects. Over the entire exercise period, $\dot{V}O_2$ was significantly higher in the Tr compared with UTr subjects ($P < 0.01$). On average, $\dot{V}O_2$ was 38 ml/kg in Tr subjects and 29 ml/kg in UTr subjects, respectively, which corresponded to 57 and 60% $\dot{V}O_{2max}$, respectively. Despite the higher absolute work rate, the Tr subjects exercised at a significantly lower heart rate. In Tr subjects, heart rate increased from 127 ± 3 to 130 ± 3 beats/min (bpm) and in UTr subjects from 129 ± 4 to 147 ± 4 bpm, respectively, toward the end of exercise.

Total CHO and fat oxidation. After 15 min of exercise, RER was 0.87 ± 0.01 in Tr subjects and 0.91 ± 0.01 in UTr subjects, respectively ($P < 0.05$), and after 120 min of exercise the RER was 0.85 ± 0.01 and 0.89 ± 0.01 in Tr and UTr subjects, respectively ($P < 0.05$). Total fat oxidation calculated over the second hour of exercise (60–120 min) was significantly higher in Tr compared with UTr subjects (37.4 ± 2.3 g in Tr subjects vs. 22.5 ± 1.4 g in UTr subjects; Fig. 1). No differences were observed in the absolute amounts of CHO oxidized in this period (116.3 ± 7.5 vs. 113.7 ± 3.6 g in UTr subjects; Fig. 1).

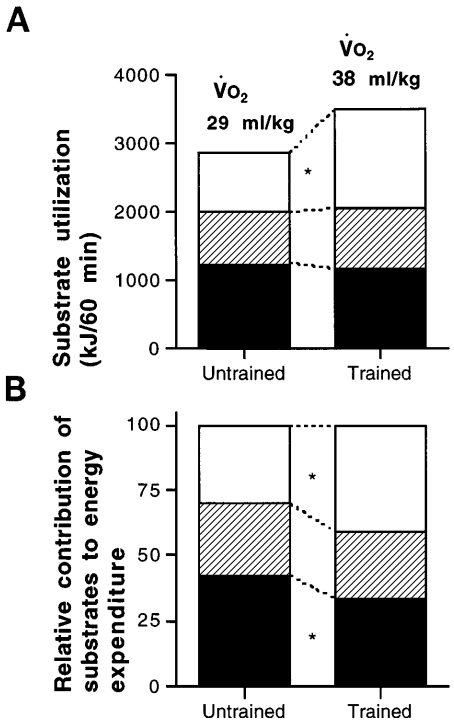

Fig. 1. Absolute (kcal/60 min; *A*) and relative (%; *B*) contributions of substrates to energy expenditure in trained and untrained subjects. Open bar segments, fat; hatched bar segments, oral carbohydrates; filled bar segments, endogenous carbohydrates. $\dot{V}O_2$, O_2 uptake. *Significant difference between trained and untrained subjects, $P < 0.05$.

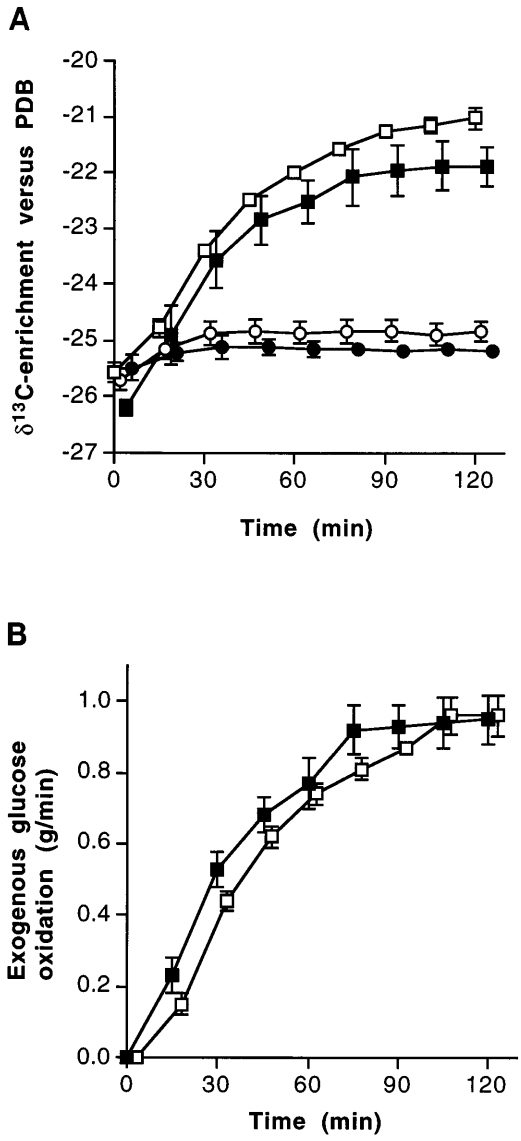

Fig. 2. *A*: breath $^{13}CO_2/^{12}CO_2$ ratio [δ‰ vs. Pee Dee Bellemnitella (PDB)]. Values are means ± SE; $n = 15$ subjects. □, PDB in untrained subjects; ○, ^{13}C enrichment in untrained subjects; ■, PDB in trained subjects; ●, ^{13}C enrichment in trained subjects. *B*: no difference was observed in exogenous glucose oxidation in endurance-trained (■) and untrained subjects (□) at same relative exercise intensity.

Exogenous glucose oxidation. Background ^{13}C enrichments measured from the resting breath samples were comparable for the Tr and UTr subjects (−26.2 ± 0.2 δ‰ vs. PDB in Tr subjects and −25.6 ± 0.2 δ‰ vs. PDB in UTr subjects, respectively). Changes in isotopic composition of expired CO_2 in response to exercise are shown in Fig. 2. With ingestion of the corn-derived glucose in CHO tests, the rise in ^{13}C was significant, reaching an enrichment difference of ~4 δ‰ toward the end of 120-min exercise (compared with resting breath sample). The changes in background enrichment during exercise in the control trial were minimal and not statistically significant. A background correction was

made for the calculation of exogenous glucose oxidation by using the data from the control trial. In line with the breath isotopic enrichment, exogenous glucose oxidation showed a gradual increase over time (Fig. 2). Peak oxidation rates were reached at the end of exercise (120 min) and were 0.95 ± 0.07 and 0.96 ± 0.03 g/min in Tr and UTr subjects, respectively. This difference was not statistically significant. The amount of exogenous glucose oxidized over the 60- to 120-min period was slightly, but not significantly, higher in Tr compared with UTr subjects (49.5 ± 1.5 vs. 44.8 ± 2.6 g; Fig. 1). Endogenous glucose oxidation, as calculated from total CHO oxidation minus exogenous glucose oxidation, was also similar in Tr and/or UTr subjects (68.9 ± 2.7 g in Tr and 66.8 ± 6.8 g in UTr subjects, respectively; Fig. 1).

Blood parameters. Plasma glucose concentrations remained stable during exercise, between 4.5 and 4.9 mmol/l. No differences between the two groups were observed (Fig. 3*A*). Plasma FFA levels were also similar, although there was a tendency for the Tr subjects to have slightly higher plasma FFA concentrations (Fig. 3*B*). Plasma lactate concentrations were significantly higher in the UTr compared with the Tr subjects throughout the entire exercise period (Fig. 3*C*). In both trials, plasma insulin levels decreased during exercise from values of ~10–11 μU/ml to values of ~4–5 μU/ml. There were no differences between the Tr and UTr subjects (Fig. 3*D*).

DISCUSSION

We studied the composition of the fuel mixture and oxidation rates of exogenous glucose oxidation in subjects with different training backgrounds. A group of Tr and UTr subjects showed large differences in Wmax and $\dot{V}O_{2max}$ (Table 1). Therefore, endurance-trained subjects exercised at a 42% higher absolute work rate, whereas relative exercise intensity was the same. As a result, energy expenditure was also 29% higher in the Tr group. One of the main adaptations to endurance training is a reduction in the rate of CHO oxidation during exercise and a concomitant increased rate of fat oxidation. This effect has been observed at both the same absolute and relative exercise intensities (5, 6, 12, 14–16). Also, in the present study a higher rate of fat oxidation and an increased relative contribution of fat were observed in Tr compared with UTr subjects when they exercised at the same relative exercise intensity. However, despite markedly higher rates of fat oxidation, Tr subjects displayed similar rates of exogenous, endogenous, and total CHO oxidation. Although the absolute work rate in the Tr group was higher, endogenous CHO utilization was similar in Tr and UTr groups.

A more appropriate way to look at the data during exercise at the same relative exercise intensity may be by expressing substrate utilization relative to energy expenditure (Fig. 1). The contribution of fat is higher in

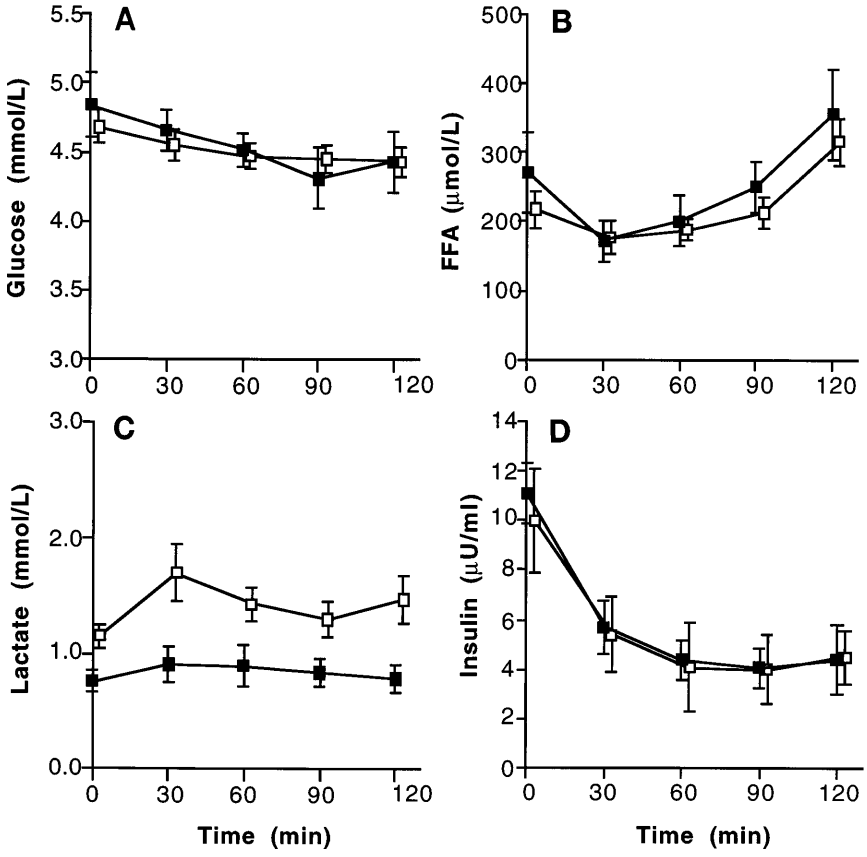

Fig. 3. Plasma glucose (*A*), free fatty acid (FFA; *B*), lactate (*C*), and insulin concentrations (*D*) in trained (■) and untrained subjects (□) during 120 min of exercise. *Significant difference between 2 groups, $P < 0.05$.

Tr subjects (42.3 vs. 30.2%). The reduction in the relative contribution is mostly explained by a lower contribution of endogenous glucose (33.7 vs. 42.3%), whereas exogenous glucose contribution is about equal in the Tr and UTr subjects (25.0 vs. 27.5%). Therefore, we could not confirm our hypothesis that UTr subjects have higher rates of exogenous CHO oxidation compared with Tr subjects.

To our knowledge, there is only one other study (23) that investigated the effect of training on exogenous CHO oxidation rates. In a comparison of our data with the findings of the study of Krzentowski et al. (23), there seem to be some striking differences. In their study, six subjects trained 60 min, 5 times/wk at a low intensity (30–40% $\dot{V}O_{2max}$), and oral CHO oxidation was investigated at the same absolute exercise intensity before and after a 6-wk training program. A training-induced increase in $\dot{V}O_{2max}$ of 29% was reported, whereas CHO and fat oxidation changed little. Fat oxidation seemed to be slightly higher after training, but during the later stages of exercise this difference was not statistically significant. Exogenous CHO oxidation, however, was increased by 17% after training.

The difference in $\dot{V}O_{2max}$ between the Tr and UTr subjects was much larger in the present study (46% in this study vs. 29% reported by Krzentowski et al.) (23), and the exercise intensity was higher (56–60% $\dot{V}O_{2max}$ in this study vs. 40% $\dot{V}O_{2max}$ reported by Krzentowski et al.). Despite the larger difference in training status, the Tr subjects did not have an increased exogenous glucose oxidation, so we cannot confirm the suggestion brought about by Krzentowski et al. that training leads to an increased capacity to oxidize ingested CHO. For both groups in our study, peak oxidation rates of the ingested glucose were 0.95–0.96 g/min. These values are close to the maximum oxidation rate of orally ingested CHO, which is believed to be ~1.0 g/min (10, 38).

Of interest are also a paper by Massicotte et al. (26) and one by Pirnay et al. (33). They looked at the effect of increasing exercise intensity on exogenous glucose oxidation. With increasing exercise intensity, the rate of oral CHO oxidation increases (26, 33), although, at high work rates, oxidation rates may level off (33). Apparently, the present study is not in line with these findings: we found slightly but not significantly higher oxidation rates for subjects exercising at $\dot{V}O_2$ of 38 and 29 $ml \cdot kg^{-1} \cdot min^{-1}$. The work rate in the UTr subjects in the present study was below the value at which leveling off of the relationship between work rate and oral glucose oxidation, as reported by Pirnay et al. (33), occurred. Thus training seems to change the relationship between exercise intensity and exogenous glucose oxidation.

The oxidation of orally ingested CHO has been extensively investigated by using either stable or radioactive tracers. Both methods revealed information regarding the factors that influence exogenous CHO oxidation rates (see Ref. 10 for review). Among these factors are the type (11, 25, 27, 30, 37) and the amount of CHO ingested (34, 38), the feeding schedule (10), glycogen availability (17, 28), and the exercise intensity (26, 33). Here we observed no differences in exogenous glucose oxidation at ~60 $\dot{V}O_{2max}$ in subjects with a different training status. This may imply that UTr and Tr subjects may equally benefit from CHO ingestion.

In conclusion, the present study demonstrates that exogenous and endogenous glucose oxidation rates during similar relative submaximal exercise intensities were not different in Tr and UTr subjects, even with large differences in the relative contribution of CHO and fat. One of the most profound observations in this study was the higher fat oxidation rates in the Tr subjects. The increase in energy expenditure in the Tr subjects was entirely met by this increase in fat oxidation without changes in the oxidation rates of total, endogenous, and ingested CHOs.

Address for reprint requests: A. E. Jeukendrup, Dept. of Human Biology, Maastricht University, PO Box 616, NL-6200 MD Maastricht, The Netherlands (E-mail: A.Jeukendrup@HB.UNIMAAS.NL).

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