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Glucose kinetics during high-intensity exercise in endurance-trained and untrained humans

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Coggan, Andrew R., Comasia A. Raguso, Bradley D. Williams, Labros S. Sidossis, and Amalia Gastaldelli. Glucose kinetics during high-intensity exercise in endurance-trained and untrained humans. *J. Appl. Physiol.* 78(3): 1203–1207, 1995.—In humans, endurance training reduces the rates of glucose production and utilization during moderate-intensity exercise. It is uncertain, however, whether this is also true during high-intensity exercise. Accordingly, we studied eight endurance-trained cyclists and eight untrained subjects during 30 min of cycling at ~80% of maximal oxygen uptake ($\dot{V}O_{2\,max}$). Rates of glucose appearance (Ra) and disappearance (Rd) were determined using a primed, continuous infusion of [6,6-^{2}H]glucose. Average glucose Ra during exercise did not differ in the trained and untrained subjects (34.3 ± 3.6 vs. 36.0 ± 1.7 $\mu mol \cdot min^{-1} \cdot kg^{-1}$; mean ± SE; P, not significant). Plasma insulin, glucagon, norepinephrine, and epinephrine concentrations were also similar in the two groups. In contrast, glucose Rd during exercise was 19% lower in the trained compared with the untrained subjects (27.0 ± 2.6 vs. 33.2 ± 1.5 $\mu mol \cdot min^{-1} \cdot kg^{-1}$; $P < 0.001$). Consequently, during exercise, plasma glucose concentration rose significantly ($P < 0.05$) in the trained subjects but did not change in the untrained subjects. We conclude that utilization of plasma glucose is lower in trained subjects during high-intensity exercise, even when the exercise is performed at the same relative (and therefore a higher absolute) intensity as in the untrained state. Hyperglycemia in trained subjects during intense exercise appears to be due to this lower rate of glucose utilization rather than a higher rate of glucose production.

hepatic glucose production; glucoregulation; hyperglycemia; catecholamines

ONE OF THE HALLMARK adaptations to endurance training is a reduction in the rate of carbohydrate oxidation during submaximal exercise (cf. Ref. 9). This is due, in part, to a slower rate of muscle glycogenolysis during exercise in the trained state (e.g., Ref. 6). However, recent studies have demonstrated that, in humans, training also reduces the rate of glucose uptake during moderate-intensity exercise [i.e., at 45–65% of maximal oxygen uptake ($\dot{V}O_{2\,max}$)] (5, 7, 8, 14, 19, 23). In fact, although sparing of muscle glycogen apparently accounts for most of the training-induced decrease in carbohydrate oxidation during the first ~30 min of moderate-intensity exercise, after this time, the reduction in glucose utilization is quantitatively at least as important (14, 19, 23).

Training, therefore, clearly reduces reliance on plasma glucose as an energy source during moderate-intensity exercise. However, the rate of glucose uptake increases exponentially with increasing exercise intensity (cf. Ref. 4), and trained individuals are capable of exercising at higher absolute intensities than untrained individuals. Furthermore, the maximal capacity of muscle to transport and phosphorylate glucose during exercise is theoretically higher in the trained state, since training increases muscle glucose transporter number (13) and hexokinase activity (6, 14) and reduces the intramuscular glucose 6-phosphate (G-6-P) concentration during exercise (6, 14). Brooks and Mercier (3) have therefore recently hypothesized that there is a "crossover" effect, such that during high-intensity exercise the rate of glucose utilization (and also the rate of glucose production) is actually greater in trained than in untrained subjects. In partial support of this hypothesis, Kjær et al. (15) reported that the tracer-determined rate of glucose appearance (Ra) was higher in endurance athletes than in untrained men during exercise at 60–110% of $\dot{V}O_{2\,max}$. However, the rate of glucose disappearance (Rd) did not differ significantly between the two groups. Moreover, in this study, glucose Ra and Rd were determined during a brief (12 min) incremental exercise test that increased plasma glucose concentration and production approximately twofold and approximately tenfold, respectively. Tracer estimates of plasma glucose kinetics obtained under such extreme non-steady-state conditions may not be accurate (24).

The purpose of the present study was therefore to determine the effect of endurance training on plasma glucose metabolism during high-intensity exercise in humans. To do so, a primed continuous infusion of [6,6-^{2}H]glucose was used to quantify glucose Ra and Rd in trained and untrained subjects exercising for 30 min at ~80% of $\dot{V}O_{2\,max}$. By selecting intense but not maximal exercise and by increasing the rate of tracer infusion during exercise, variations in plasma glucose concentration and enrichment were minimized, thereby improving non-steady-state determination of glucose Ra and Rd (24).

METHODS

Subjects. Eight endurance-trained cyclists (five men, three women) and eight untrained, sex-matched subjects volun-

teered for this study. Mean (± SE) age, height, weight, and $\dot{V}O_{2\,max}$ (determined as previously described; see Ref. 6) averaged 29 ± 2 yr, 172 ± 3 cm, 63.3 ± 3.8 kg, and 63 ± 2 $ml \cdot min^{-1} \cdot kg^{-1}$, and 26 ± 1 yr, 173 ± 4 cm, 68.9 ± 4.7 kg, and 44 ± 2 $ml \cdot min^{-1} \cdot kg^{-1}$, for the trained and untrained groups, respectively. All subjects were healthy, as indicated by medical history, physician's examination, and standard blood and urine chemistries. The study protocol was approved by the Institutional Review Board of The University of Texas Medical Branch at Galveston.

Experimental protocol. Subjects were instructed to consume a mixed normal diet containing at least 250 g of carbohydrate/day and to refrain from alcohol, caffeine, and strenuous exercise for 48 h. They then reported to the General Clinical Research Center after having fasted overnight (12 h). An indwelling catheter was inserted in a retrograde direction in a dorsal vein of a heated hand for sampling of arterialized venous blood. A second catheter was inserted in an antecubital or forearm vein of the contralateral arm for tracer infusion. After a blood sample was obtained for subsequent determination of background isotopic enrichment, a primed (18.7 $\mu mol/kg$) continuous (0.22 $\mu mol \cdot min^{-1} \cdot kg^{-1}$) infusion of [6,6-^{2}H]glucose (99% enriched; Tracer Technologies, Sommerville, MA) was begun with the use of a syringe pump. The subject rested in a chair for 105 min and then sat quietly on the cycle ergometer (Monark 829E) for 15 min. Blood samples were obtained at 110, 115, and 120 min after the start of tracer infusion and placed in tubes containing sodium fluoride/potassium oxalate or lithium heparin for subsequent determination of plasma glucose and lactate concentrations (YSI 2300A, Yellow Springs, OH) and [6,6-^{2}H]glucose enrichment (8, 19), respectively. Additional blood samples were obtained at 110 and 120 min and placed in tubes containing EDTA/aprotinin or ethylene glycol-bis(β-aminoethyl ether)-*N,N,N',N'*-tetraacetic acid/reduced glutathione for subsequent determination of plasma insulin and glucagon and plasma norepinephrine and epinephrine concentrations, respectively, as previously described (8, 19).

After completion of this baseline sampling, the subject began pedaling the ergometer at a power output intended to elicit ~80% of $\dot{V}O_{2\,max}$. The rate of [6,6-^{2}H]glucose infusion was increased at the onset of exercise and every minute thereafter to mimic a monoexponential function with an asymptote of 0.88 $\mu mol \cdot min^{-1} \cdot kg^{-1}$ at 30 min. [This procedure improves non-steady-state estimates of plasma glucose kinetics by minimizing the rate of change in isotopic enrichment while avoiding the artifact in calculated Ra and Rd that results from a single step change in the rate of tracer infusion (11).] Blood samples were obtained after 5, 10, 15, 20, 25, and 30 min of exercise for subsequent determination of substrate concentrations and glucose enrichment. Additional blood samples were obtained after 15 and 30 min of exercise for subsequent determination of hormone concentrations. Oxygen uptake ($\dot{V}O_2$) and CO_2 production ($\dot{V}CO_2$) were measured after 10, 20, and 30 min of exercise using an Ametek OCM-2 metabolic cart.

Calculations. Glucose Ra and Rd were calculated using the equations of Steele (21) as modified for use with stable isotopes (20). To reduce the influence of random experimental error, data for plasma glucose enrichment and concentration were fit with a spline function (25), and these fitted values were used in the calculation of glucose Ra and Rd. The effective volume of distribution (V) was assumed to be 100 ml/kg body wt (20). However, because of the slow rates of change in plasma glucose enrichment (Table 1) and concentration (Fig. 1) during exercise, similar results were obtained when V was set to 40 or 230 ml/kg, the smallest and largest physiologically plausible limits for V (24). The conclusions of the present study are therefore not dependent on the assumed value of V.

Statistical analyses. Data were analyzed using two-way (group × time) analysis of variance, with statistical significance defined as $P \leq 0.05$. Replicate measurements obtained before exercise did not differ significantly and, therefore, these data were averaged. All data are presented as means ± SE.

RESULTS

The trained and untrained subjects exercised at similar percentages of their respective $\dot{V}O_{2\,max}$ (78 ± 1 vs. 79 ± 2%; P = not significant). In absolute terms, however, the average $\dot{V}O_2$ during exercise was 40% higher in the trained subjects (48.6 ± 1.8 vs. 34.6 ± 2.2 $ml \cdot min^{-1} \cdot kg^{-1}$; $P < 0.001$ by analysis of variance). Despite this greater absolute exercise intensity, the average respiratory exchange ratio (i.e., $\dot{V}CO_2/\dot{V}O_2$) during exercise was significantly lower in the trained men and women (0.94 ± 0.01 vs. 0.97 ± 0.01; $P < 0.05$), as was the average plasma lactate concentration (5.3 ± 0.7 vs. 7.3 ± 0.8 mmol/l; $P < 0.001$).

Plasma glucose concentration and glucose kinetics. Plasma glucose concentration was similar in the trained and untrained subjects at rest (Fig. 1*A*). During exercise, however, plasma glucose concentration rose significantly ($P < 0.05$) in the trained subjects but did not change significantly during exercise in the untrained subjects. Consequently, the mean plasma glucose concentration during exercise tended to be higher in the trained than in the untrained subjects (5.15 ± 0.20 vs. 4.92 ± 0.24 mmol/l; $P = 0.11$).

Basal glucose Ra averaged 10.9 ± 0.5 $\mu mol \cdot min^{-1} \cdot kg^{-1}$ in the trained subjects and rose throughout exercise to a maximum of 47.6 ± 4.8 $\mu mol \cdot min^{-1} \cdot kg^{-1}$ after 30 min (Fig. 1*B*). A similar response was observed in the untrained subjects, with glucose Ra increasing from 11.7 ± 0.6 $\mu mol \cdot min^{-1} \cdot kg^{-1}$ at rest to 54.0 ± 4.9 $\mu mol \cdot min^{-1} \cdot kg^{-1}$ by the end of exercise. Glucose Ra did not differ between the two groups at any time during exercise.

In the trained subjects, glucose Rd during exercise was consistently lower than glucose Ra, reaching a maximum of only 37.2 ± 3.5 $\mu mol \cdot min^{-1} \cdot kg^{-1}$ (Fig. 1*C*). In contrast, glucose Rd in the untrained subjects was very similar to glucose Ra, peaking at 49.0 ± 4.6 $\mu mol \cdot min^{-1} \cdot kg^{-1}$. On average, glucose Rd during exercise was 19% lower in the trained than in the untrained subjects (27.0 ± 2.6 vs. 33.2 ± 1.5 $\mu mol \cdot min^{-1} \cdot kg^{-1}$; $P < 0.001$).

Because changes in plasma glucose concentration were modest, the calculated rate of glucose clearance (i.e., Rd/concn) followed a pattern during exercise similar to that of glucose Rd. Glucose clearance rose from 2.40 ± 0.12 $ml \cdot min^{-1} \cdot kg^{-1}$ at rest to 7.10 ± 0.84 $ml \cdot min^{-1} \cdot kg^{-1}$ after 30 min of exercise in the trained subjects but increased from 2.41 ± 0.12 $ml \cdot min^{-1} \cdot kg^{-1}$ at rest to 9.78 ± 1.04 $ml \cdot min^{-1} \cdot kg^{-1}$ after 30 min of exercise in the untrained subjects. Thus the mean rate of glucose clearance during exercise was 23% lower in the trained than in the untrained subjects (5.31 ± 0.60 vs. 6.94 ± 0.57 $ml \cdot min^{-1} \cdot kg^{-1}$; $P < 0.001$).

TABLE 1. *Plasma glucose enrichment at rest and during exercise (tracer/tracee × 100)*

	Time, min						
	0	5	10	15	20	25	30
Trained	1.91±0.06	2.10±0.09	2.31±0.09	2.26±0.09	2.29±0.12	2.25±0.14	2.22±0.15
Untrained	1.95±0.14	1.99±0.18	2.24±0.17	2.32±0.17	2.33±0.14	2.30±0.14	2.17±0.17

Values are means ± SE for 8 trained and 8 untrained subjects. There were no significant differences over time or between groups.

Plasma hormone concentrations. Basal plasma insulin concentration was similar in the trained and the untrained subjects (Table 2). Plasma insulin concentration decreased ($P < 0.01$) during exercise, particularly in the untrained subjects, but this difference between groups was not significant. Plasma glucagon concentrations were also similar in the trained and untrained subjects at rest and did not change significantly during exercise.

Plasma norepinephrine concentration rose approximately tenfold ($P < 0.001$) during exercise in both the trained and untrained subjects, whereas plasma epinephrine concentration rose approximately fivefold ($P < 0.001$; Table 2). No significant differences were observed between the groups.

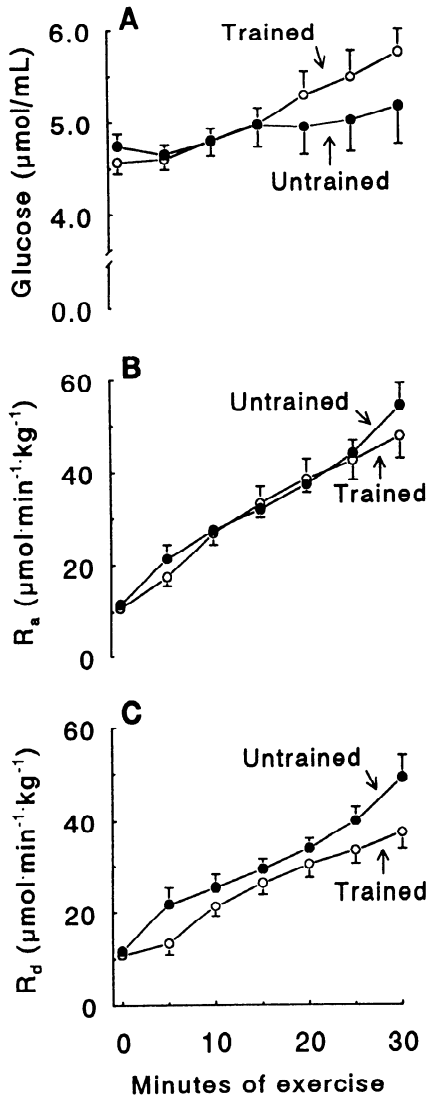

FIG. 1. Concentration (*A*), rate of appearance (Ra; *B*), and rate of disappearance (Rd; *C*) of plasma glucose at rest and during 30 min of exercise at ~80% of maximal oxygen uptake in 8 endurance-trained cyclists and in 8 untrained subjects. Significant main effects for time ($P < 0.05$–0.001) were observed for all 3 variables. In addition, a signficant group main effect was found for Rd ($P < 0.001$), whereas that for concentration approached statistical significance ($P = 0.11$). There were no significant interaction effects. Values are means ± SE.

DISCUSSION

Endurance training reduces the rate of glucose uptake during moderate-intensity exercise (5, 7, 8, 14, 19, 23). Trained individuals, however, are capable of exercising at higher absolute intensities than untrained individuals. Furthermore, training increases muscle glucose transporter number (13) and hexokinase activity (6, 14) and reduces intramuscular G-6-P concentrations during exercise (6, 14). Brooks and Mercier (3) have therefore recently hypothesized that training actually increases reliance on plasma glucose as an energy source during intense exercise. In contrast to this hypothesis, however, we found that glucose Rd was significantly lower in trained than in untrained subjects during exercise at ~80% of $\dot{V}O_{2\,max}$. This was true, even though the absolute exercise intensity was considerably higher in the trained men and women. Given the cross-sectional nature of the present study, it is possible that at least some of this difference in glucose Rd was due to factors other than training per se (e.g., genetics). However, this finding is consistent with previous longitudinal studies of lower intensity exercise (5, 8, 19). The present data also do not exclude the possibility that training enhances the rate of glucose uptake during exercise at >80% of $\dot{V}O_{2\,max}$. Kjær et al. (15), however, found that the rate of glucose clearance (although not glucose Rd) tended to be lower in endurance athletes than in untrained men during exercise at 100–110% of $\dot{V}O_{2\,max}$. As indicated previously, tracer estimates of plasma glucose kinetics obtained under such extreme non-steady-state conditions must be viewed with caution. Nevertheless, the data of Kjær et al. (15) suggest that training may inhibit utilization of plasma glucose even during maximal or supramaximal exercise. We therefore find no evidence in trained humans for a "crossover" in glucose utilization during high-intensity exercise as proposed by Brooks and Mercier (3).

The present results are thus the first to clearly show that glucose uptake is lower in trained subjects during high-intensity exercise, as has been previously observed during moderate-intensity exercise (5, 7, 8, 14, 19, 23). They do not, however, provide any insight into

TABLE 2. *Plasma hormone concentrations at rest and during exercise*

	Time, min		
	0	15	30
Insulin, pmol/l			
Trained	26±3	20±5	20±5
Untrained	33±6	17±3	13±1
Glucagon, pmol/l			
Trained	64±5	60±4	69±5
Untrained	64±7	74±7	72±6
Norepinephrine, nmol/l			
Trained	2.13±0.21	12.74±1.12	24.30±4.14
Untrained	2.65±0.18	9.63±1.19	20.98±5.30
Epinephrine, nmol/l			
Trained	0.38±0.04	0.99±0.14	1.58±0.33
Untrained	0.29±0.05	0.85±0.16	1.48±0.36

Values are means ± SE for 8 subjects/group. Significant main effects for time were observed for insulin ($P < 0.01$), norepinephrine ($P < 0.001$), and epinephrine ($P < 0.001$). There were no significant group or interaction effects.

the mechanism by which this occurs. Because training increases muscle hexokinase activity and attenuates the rise in muscle G-6-P concentration during exercise, though, it seems likely that the decrease in plasma glucose use with training is the result of a reduction in the rate of glucose transport, not in the rate of glucose phosphorylation (cf. Ref. 6 for discussion). Furthermore, the slower rate of glucose utilization during exercise in fit compared with unfit subjects is closely correlated with the higher muscle respiratory capacity of the former (7, 18). Still, it remains unclear exactly how an increase in muscle mitochondrial content with training might lead to less activation of the glucose transport process during exercise.

While the rate of uptake of plasma glucose during exercise was lower in the trained than in the untrained subjects, the rate of glucose production was similar in the two groups. Consequently, plasma glucose concentration rose significantly during exercise in the trained but not in the untrained subjects. The latter results are consistent with prior investigations demonstrating a greater rise in plasma glucose concentration in trained than in untrained individuals during strenuous exercise (1, 12, 15). Previously, Kjær et al. (15) ascribed this to a greater rate of glucose production in trained subjects, resulting from a training-induced increase in epinephrine secretion. In the present study, however, plasma epinephrine (as well as norepinephrine, glucagon, and insulin) concentrations during exercise were similar in the two groups. It is possible that long-term training enhances epinephrine secretion and glucose production only during exercise at intensities greater than these used in the present experiments, i.e., only during exercise at >80% of $\dot{V}O_{2\,max}$. Most studies, however, have not found epinephrine levels to be higher in trained than in untrained subjects during maximal or near-maximal exercise (1, 10, 16, 17, 22). Alternatively, it is possible that an exaggerated epinephrine response to strenuous exercise develops only after many years of training. All of the athletes in the present study had been training intensely for >4 yr, however, and several had been training for >15 yr. Thus the reason for these discordant findings is not readily apparent. In any case, it should be noted that the present results differ from those obtained during moderate-intensity exercise performed at the same absolute intensity in the untrained and trained states (5, 7, 8, 19). Under these conditions, training markedly attenuates the glucoregulatory hormone response to exercise, resulting in a lower glucose Ra. Recent data indicate that this is due to reductions in both the rate of hepatic glycogenolysis and the rate of gluconeogenesis during exercise (8).

Although the kinetics of plasma glucose are best described by a multiple-pool model, in the present study (as in most previous studies), glucose Ra and Rd were calculated using the single-pool approximation of Steele (21). The accuracy of this approach depends in part on the selection of an appropriate value for V, the effective volume of distribution. Since V is usually not known and in fact may not even be constant over time, the use of an assumed fixed value for V can lead to large errors in the estimated Ra and Rd when plasma glucose enrichment and concentration are changing rapidly (24). In the present study, however, changes in plasma glucose enrichment were greatly minimized by appropriate increases in the rate of tracer infusion during exercise. As a result, the values obtained for Ra were essentially independent of the assumed V. For example, in the trained subjects, Ra during exercise averaged 34.8 ± 2.3, 34.3 ± 3.6, and 34.0 ± 4.3 $\mu mol \cdot min^{-1} \cdot kg^{-1}$ when calculated with a V of 40, 100, or 230 ml/kg, respectively. The corresponding values in the untrained subjects were 36.5 ± 1.4, 36.0 ± 1.7, and 35.8 ± 2.2 $\mu mol \cdot min^{-1} \cdot kg^{-1}$. The calculated Rd was somewhat dependent on V, however, because plasma glucose concentration rose during exercise, particularly in the trained men and women. Specifically, in the trained subjects, Rd during exercise averaged 33.0 ± 2.1, 27.0 ± 2.6, and 23.9 ± 3.0 $\mu mol \cdot min^{-1} \cdot kg^{-1}$ when calculated with a V of 40, 100, or 230 ml/kg, respectively, whereas in the untrained subjects the corresponding values were 35.8 ± 1.3, 33.2 ± 1.5, and 31.9 ± 2.7 $\mu mol \cdot min^{-1} \cdot kg^{-1}$. Regardless of the assumed V, however, glucose Rd was significantly lower ($P < 0.001$) in the trained than in the untrained subjects.

To summarize, the present data clearly demonstrate that the rate of utilization of plasma glucose is lower in trained than in untrained subjects during high-intensity exercise, even when the exercise is performed at the same relative (and, therefore, a higher absolute) intensity as in the untrained state. Hyperglycemia in trained subjects during intense exercise appears to be due to this lower rate of glucose utilization rather than a higher rate of glucose production.

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