Plasma glucose kinetics during prolonged exercise in trained humans when fed carbohydrate

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Received 3 October 2001; accepted in final form 8 May 2002

Angus, Damien J., Mark A. Febbraio, and Mark Hargreaves. Plasma glucose kinetics during prolonged exercise in trained humans when fed carbohydrate. Am J Physiol Endocrinol Metab 283: E573–E577, 2002. —Nine endurance-trained men exercised on a cycle ergometer at ~68% peak O2 uptake to the point of volitional fatigue (232 ± 14 (SE) min) while ingesting an 8% carbohydrate solution to determine how high glucose disposal could increase under physiological conditions. Plasma glucose kinetics were measured using a primed, continuous infusion of [6,6-2H]glucose and the appearance of ingested glucose, assessed from [3-3H]glucose that had been added to the carbohydrate drink. Plasma glucose was increased (P < 0.05) after 30 min of exercise but thereafter remained at the preexercise level. Glucose appearance rate (Ra) increased throughout exercise, reaching a peak value of 118 ± 7 µmol·kg−1·min−1 at fatigue, whereas gut Rd increased continuously during exercise, peaking at 105 ± 10 µmol·kg−1·min−1 at the point of fatigue. In contrast, liver glucose output never rose above resting levels at any time during exercise. Glucose disposal (Rd) increased throughout exercise, reaching a peak value of 118 ± 7 µmol·kg−1·min−1 at fatigue. If we assume 95% oxidation of glucose Ra, estimated exogenous glucose oxidation at fatigue was 1.36 ± 0.08 g/min. The results of this study demonstrate that glucose uptake increases continuously during prolonged, strenuous exercise when carbohydrate is ingested and does not appear to limit exercise performance.

METHODS

Subjects. Nine male endurance-trained cyclists/triathletes [33 ± 3 (SE) yr, 78 ± 3 kg] volunteered as subjects for this investigation after being informed of all possible risks and providing written consent. The study was approved by The University of Melbourne Human Research Ethics Committee. Peak pulmonary oxygen uptake (Vo2peak) was determined during incremental exercise to volitional fatigue on an electrically braked cycle ergometer (Lode, Groningen, The Netherlands) and averaged 4.6 ± 0.1 l/min.

Experimental protocol. In the 24 h before the trial, each subject was provided with a food parcel [15.6 MJ, 71% carbohydrate, 15% protein, 14% fat]. Subjects were asked to adhere to the diet and to refrain from exercise and the intake of alcohol, tobacco, and caffeine. On the morning of the trial, subjects arrived at the laboratory in the fasted state. Subjects were weighed, and catheters were inserted into an antecubital vein of one forearm for the collection of blood samples and for the administration of primed, continuous glucose infusions. Subjects were then given an 8% carbohydrate solution at a rate of 0.08 g/min. The results of this study demonstrate that glucose uptake increases continuously during prolonged, strenuous exercise when carbohydrate is ingested and does not appear to limit exercise performance.
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Subjects ingested 1 L/h of an 8% glucose solution throughout exercise. Values are means ± SE. RER was maintained during the first 2 h of exercise but was lower (P < 0.05) than the 30-min value during the latter stages of exercise and at fatigue (Table 1). Estimated carbohydrate oxidation did not change significantly during exercise, although the value at fatigue tended (P = 0.069) to be lower than that at 30 min (Table 1). Plasma glucose increased after 30 min of exercise but thereafter remained at levels similar to those at rest (Fig. 1). Plasma \(^{2}H\) glucose enrichment was 3.6 ± 0.3% immediately before exercise, fell to 1.5 ± 0.1% after 2 h of exercise, but remained at this level until fatigue. Similarly, \(^{3}H\) glucose specific activity increased from 47 ± 4 dmol/µmol at rest to 271 ± 22 dmol/µmol after 2 h of exercise and remained at this level until fatigue. Glucose \(R_{a}\) increased with exercise, reaching its peak value at fatigue (118 ± 7 µmol·kg\(^{-1}\)·min\(^{-1}\)).

Subjects exercised for 232 ± 14 min. Pulmonary RER was maintained during the first 2 h of exercise but was lower (P < 0.05) than the 30-min value during the latter stages of exercise and at fatigue (Table 1). Estimated carbohydrate oxidation did not change significantly during exercise, although the value at fatigue tended (P = 0.069) to be lower than that at 30 min (Table 1). Plasma glucose increased after 30 min of exercise but thereafter remained at levels similar to those at rest (Fig. 1). Plasma \(^{2}H\) glucose enrichment was 3.6 ± 0.3% immediately before exercise, fell to 1.5 ± 0.1% after 2 h of exercise, but remained at this level until fatigue. Similarly, \(^{3}H\) glucose specific activity increased from 47 ± 4 dmol/µmol at rest to 271 ± 22 dmol/µmol after 2 h of exercise and remained at this level until fatigue. Glucose \(R_{a}\) increased with exercise, reaching its peak value at fatigue (118 ± 7 µmol·kg\(^{-1}\)·min\(^{-1}\)).

### Table 1. Pulmonary respiratory exchange ratio and estimated carbohydrate oxidation during exercise to fatigue at 68 ± 2% \(V_{O2\ peak}\)

<table>
<thead>
<tr>
<th></th>
<th>30 min</th>
<th>60 min</th>
<th>90 min</th>
<th>120 min</th>
<th>150 min</th>
<th>180 min</th>
<th>Fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>RER</td>
<td>0.95 ± 0.01</td>
<td>0.95 ± 0.01</td>
<td>0.92 ± 0.01</td>
<td>0.92 ± 0.01</td>
<td>0.90 ± 0.01</td>
<td>0.90 ± 0.01</td>
<td>0.89 ± 0.01</td>
</tr>
<tr>
<td>CHOox, g/min</td>
<td>3.40 ± 0.23</td>
<td>3.38 ± 0.18</td>
<td>3.03 ± 0.01</td>
<td>2.97 ± 0.18</td>
<td>2.74 ± 0.15</td>
<td>2.96 ± 0.23</td>
<td>2.65 ± 0.27</td>
</tr>
</tbody>
</table>

Subjects ingested 1 L/h of an 8% glucose solution throughout exercise. Values are means ± SE (n = 9). RER, respiratory exchange ratio; CHOox, carbohydrate oxidation. *P < 0.05, different from 30 min value. †P = 0.069, fatigue vs. 30 min.
during exercise, peaking at $118 \pm 7 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and $23.9 \pm 1.6 \text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, respectively, at fatigue (Fig. 2). Plasma lactate during exercise was not different from the resting value, whereas plasma FFA decreased after 60 min of exercise but then increased to levels higher than rest at 180 min and fatigue (Table 2). Plasma insulin concentrations increased above rest ($P < 0.05$) after the 1st h of exercise and carbohydrate ingestion. After 2 h of exercise, however, plasma insulin concentrations were not different from resting values and then fell to below resting values at the point of fatigue (Table 2). Plasma glucagon was not different from rest during the first 3 h of exercise but was elevated at the point of fatigue (Table 2). Estimated substrate oxidation during the exercise bout is summarized in Fig. 3. With the assumption of 95% oxidation of glucose $R_d$ (14), total carbohydrate oxidation was partitioned into that derived from plasma glucose and that from other carbohydrate sources, primarily muscle glycogen. As exercise duration increased, there was a progressive increase in plasma glucose and fat oxidation and a reduction in the oxidation of other carbohydrates. At the point of fatigue, the contributions of fat, plasma glucose, and other carbohydrates to total energy expenditure were 31, 38, and 31%, respectively.

**DISCUSSION**

The results of the present study demonstrate that trained subjects have a high capacity for glucose uptake during prolonged strenuous exercise when fed carbohydrate. Furthermore, glucose uptake increases throughout exercise and shows no sign of leveling off, even at the point of fatigue. This implies that glucose uptake is not a limiting factor for prolonged exercise performance with carbohydrate ingestion and that the locus of fatigue under these conditions must lie elsewhere.

Carbohydrate ingestion has been shown to delay, but not prevent, fatigue during prolonged strenuous exercise (3, 5). The maintenance of blood glucose availability and glucose uptake in the present study implies that the observed fatigue cannot be due to reduced glucose supply to contracting skeletal muscle. It remains a possibility that intracellular glucose metabolism may be compromised, or that glucose cannot compensate for the declining muscle glycogen availability,
Table 2. Plasma lactate, FFA, insulin, and glucagon levels at rest and during exercise to fatigue at 68 ± 2% VO₂peak

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>60 min</th>
<th>120 min</th>
<th>180 min</th>
<th>Fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate, mmol/l</td>
<td>1.3 ± 0.2</td>
<td>2.2 ± 0.3</td>
<td>1.9 ± 0.3</td>
<td>2.3 ± 0.7</td>
<td>2.7 ± 0.7</td>
</tr>
<tr>
<td>FFA, mmol/l</td>
<td>0.47 ± 0.07</td>
<td>0.30 ± 0.03*</td>
<td>0.42 ± 0.03</td>
<td>0.72 ± 0.04*</td>
<td>0.80 ± 0.04*</td>
</tr>
<tr>
<td>Insulin, pmol/l</td>
<td>67 ± 8</td>
<td>117 ± 16*</td>
<td>72 ± 8</td>
<td>46 ± 6</td>
<td>43 ± 7*</td>
</tr>
<tr>
<td>Glucagon, pg/ml</td>
<td>47 ± 10</td>
<td>70 ± 12</td>
<td>125 ± 45</td>
<td>128 ± 34</td>
<td>185 ± 58*</td>
</tr>
</tbody>
</table>

Subjects ingested 1 l/h of an 8% glucose solution throughout exercise. Values are means ± SE (n = 9). FFA, free fatty acids. *P < 0.05, different from resting value.

Although in either case we have no data to support or refute such a suggestion. On the basis of direct measurement of vastus lateralis muscle glycogen levels, previous studies (3, 5) have suggested that the increase in exercise capacity observed with carbohydrate ingestion occurs in the absence of any net muscle glycogen degradation. In contrast, in the present study, the estimated oxidation of other carbohydrates at fatigue (~1.2 g/min), presumably muscle glycogen, still accounted for ~31% of total energy expenditure and ~45% of total carbohydrate oxidation (Fig. 3). It is possible that the estimates of muscle glycogen oxidation from indirect calorimetry and glucose Rₐ in the present study include glycogen use in muscles, other than the vastus lateralis, that may be recruited in the latter stages of prolonged, strenuous exercise. Interestingly, with the assumption of an average muscle glycogen concentration at fatigue of 35 mmol/kg wet wt (3, 5) and an active muscle mass of 8–10 kg, there would still be sufficient muscle glycogen to sustain a carbohydrate oxidation rate of 1.2 g/min for 40–50 min. Thus, it is possible that there may be an absolute requirement for muscle glycogen, either in the type I muscle fibers or at particular locations within muscle fibers, for the maintenance of strenuous exercise. Recently, it has been demonstrated that reduced muscle glycogen availability can impair excitation-contraction coupling within skeletal muscle (2, 23) and that such an effect may be due to an energetic and/or structural requirement for muscle glycogen. Finally, we cannot rule out the possibility that fatigue was the result of impaired muscle function due to mechanisms other than carbohydrate availability and/or reduced neuromuscular activation as a consequence of changes within the central nervous system.

The peak glucose Rₐ during exercise in the present study was 118 ± 7 μmol·kg⁻¹·min⁻¹ or 1.66 ± 0.09 g/min (Fig. 2), a value not that dissimilar from the estimate of ~1.7 g/min obtained by Coyle et al. (5). This represented 55% of total carbohydrate oxidation, with the remaining contribution from other carbohydrate sources, presumably muscle glycogen and lactate. Approximately 90% of the glucose Rₐ was derived from ingested glucose, because HGP did not rise above basal levels and remained at 16 ± 1 μmol·kg⁻¹·min⁻¹ throughout exercise (Fig. 1). Thus we estimate an exogenous glucose oxidation of 1.36 ± 0.08 g/min, a value slightly higher than that which has been suggested to be “maximal” (1–1.1 g/min, see Ref. 13).

Our results clearly demonstrate a high capacity for glucose uptake in trained athletes. It has been suggested that training enhances the capacity for glucose uptake (16), and there are several mechanisms by which this might be achieved. Trained athletes are characterized by higher skeletal muscle GLUT4 protein expression, increased activities of hexokinase and oxidative enzymes, higher proportions of type I skeletal muscle fibers, and greater capillary density, all of which could account for a greater ability to take up glucose in response to both exercise and insulin stimulation (7, 8). It has also recently been suggested that enhanced insulin sensitivity increases glucose uptake during exercise (20). Although the proximal signaling mechanisms responsible for increased muscle glucose uptake in response to insulin stimulation and exercise are generally thought to be different, the above-mentioned morphological and biochemical factors are common to both pathways. These factors, together with progressive muscle glycogen depletion (9) and GLUT4 recruitment to the sarcolemma (17), maintenance of glycemia and insulinemia by carbohydrate ingestion, and a blunting of the rise in plasma FFA (10), could all contribute to the high rates of glucose uptake observed during prolonged, strenuous exercise in trained athletes.

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Fig. 3. Estimated percent contributions from fat, plasma glucose, and other carbohydrates (CHO) to total aerobic energy expenditure during exercise to fatigue at 68 ± 2% VO₂peak until fatigue. Subjects ingested 1 l/h of an 8% glucose solution throughout the trial.

AJP-Endocrinol Metab • VOL 283 • SEPTEMBER 2002 • www.ajpendo.org
A further finding of the present study was that liver glucose output remained at basal levels throughout exercise, even at the point of fatigue. HGP averaged 0.2 g/min, a value similar to that observed in other studies, and this demonstrates that HGP is sensitive to exogenous glucose delivery by either ingestion (14, 15, 18) or infusion (12). Although liver glucose output during exercise is subject to complex and multiple regulatory controls, it appears that classical feedback mechanisms linked to blood glucose availability dominate during prolonged strenuous exercise with carbohydrate ingestion. The appearance of ingested glucose increased throughout exercise, implying no splanchnic limitation to ingested glucose bioavailability. Our feeding regimen produced an average glucose intake of 1.3 g/min during exercise, approximately the same as the estimated upper limit for gastrointestinal glucose absorption, albeit under resting conditions (6). It is possible that ingestion of a larger amount of carbohydrate could result in a splanchnic limitation to ingested glucose appearance, as we have observed with a 10% glucose solution (18). In addition, it has been observed that exogenous carbohydrate oxidation reaches a maximal level despite increases in the amount of ingested carbohydrate (13, 24).

In summary, we have demonstrated that glucose uptake increases continuously during prolonged strenuous exercise and does not appear to limit exercise performance. Furthermore, trained athletes have a high capacity for glucose uptake during prolonged exercise when fed carbohydrate.

We acknowledge the excellent technical assistance of Dominic Caridi.

This study was supported by the National Health and Medical Research Council of Australia.

REFERENCES