Effect of prior exercise on glucose metabolism in trained men

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Rose, Adam J., Kirsten Howlett, Douglas S. King, and Mark Hargreaves. Effect of prior exercise on glucose metabolism in trained men. Am J Physiol Endocrinol Metab 281: E766–E771, 2001.—Several studies have demonstrated that oral glucose tolerance is impaired in the immediate postexercise period. A double-tracer technique was used to examine glucose kinetics during a 2-h oral glucose (75 g) tolerance test (OGTT) 30 min after exercise (Ex, 55 min at 71 ± 2% of peak O2 uptake) and 24 h after exercise (Rest) in endurance-trained men. The area under the plasma glucose curve was 71% greater in Ex than in Rest (P = 0.01). The higher glucose response occurred even though whole body rate of glucose disappearance was 24% higher after exercise (P = 0.04, main effect). Whole body rate of glucose appearance was 25% higher after exercise (P = 0.03, main effect).

There were no differences in total (2 h) endogenous glucose appearance (RaE) or the magnitude of suppression of RaE, although RaE was higher from 15 to 30 min during the OGTT in Ex. However, the cumulative appearance of oral glucose was 30% higher in Ex (P = 0.03, main effect). There were no differences in glucose clearance rate or plasma insulin responses between the two conditions. These results suggest that adaptations in splanchnic tissues by prior exercise facilitate greater glucose output from the splanchnic region after glucose ingestion, resulting in a greater glycemic response and, consequently, a greater rate of whole body glucose uptake.

Methods

Subjects. The study group consisted of six healthy, endurance-trained male volunteers (29.2 ± 0.0 ± 2.0 yr, 72.9 ± 3.7 kg, 1.77 ± 0.03 m). All subjects had been exercising regularly (6.2 ± 0.4 days/wk, 1.1 ± 0.2 h/day) for at least the prior 6 mo, and physical training frequently involved cycling or running. Written information about the purpose, nature, and potential risks relating to experimental procedures was given to the subjects before they provided consent to participate. The protocol was reviewed and approved by the Deakin University Human Ethics Committee.

Preexperimental protocol. Subjects were instructed to maintain their normal exercise regimen throughout the entire trial period and refrain from exercise (other than that required for normal living), smoking, and the consumption of alcohol or caffeine for 24 h before testing. Initially, participants completed an incremental cycle exercise test to volitional exhaustion to determine peak rate of pulmonary O2 uptake (V̇O2 peak). V̇O2 peak and peak power output were 65.4 ± 2.8 ml·kg−1·min−1 and 5.91 ± 0.24 W/kg, respectively. This test and the subsequent exercise session were conducted on an electromagnetically braked cycle ergometer (Lode, Groningen, The Netherlands). During exercise, expired air was analyzed using a metabolic cart (Gould 2900 Metabolic System), and heart rate (HR) was recorded (Polar Electro). Before each use, the flowmeter and chemical sensors of the metabolic cart were calibrated using a syringe of known volume and gases of known composition.

The glycemic response to ingested carbohydrate is greater in the period immediately after exercise (2, 3, 15, 20), whereas the insulineemic response may be greater (15), not different (2), or lower (20, 21). Although these results indicate a relative reduction in whole body insulin action in the period immediately after exercise, the physiological bases of this response remain unclear. King et al. (15) suggested that this apparent insulin resistance may be due to elevations in hormones and metabolites after exercise, which may act to impede peripheral glucose uptake, particularly in skeletal muscle. Indeed, others have observed that nonexercised muscle is insulin resistant after exercise (6). However, other studies have revealed that net glucose output from the splanchnic (liver/gut) tissues during a gut glucose load is greater in the period immediately after exercise than in the rested state (12, 16). Therefore, the roles of peripheral uptake and splanchnic output of glucose in altering glucose tolerance during the period immediately after exercise are not clear.

The aim of the present study was to examine the effect of prior exercise on three primary determinants of oral glucose tolerance. Our approach was to use the double-tracer technique to determine the rate of appearance of exogenous glucose (RaE), endogenous glucose production, and whole body glucose uptake after exercise. To distinguish between the transient effects of acute exercise on glucose tolerance and insulin action in humans who habitually exercise, we chose to examine glucose kinetics in endurance-trained individuals.

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Subjects were instructed to complete an exercise bout (45–75 min) at 70–80% of their peak HR 24 h before each trial. In addition, they were provided with a food package for consumption containing ~14 MJ (~80% carbohydrate) on the day before each trial, and they were instructed to consume 5 mL of water per kilogram of body mass on waking in the morning of the trial to ensure adequate hydration. Subjects were studied after a 12-h overnight fast.

**Experimental protocol.** Subjects presented to the laboratory for two separate trials: an exercise (Ex) and a 24-h postexercise (Rest) trial. Before the commencement of each trial, a Teflon catheter was inserted into a forearm vein of one arm for blood sampling and the contralateral arm for infusion. The catheter for blood sampling was kept patent throughout each trial by periodic injection of 0.9% saline containing a small amount of heparin. Immediately after a blood sample was obtained, a priming dose of [6,6-2H]glucose (3.3 mmol; Cambridge Isotope Laboratories, Cambridge, MA) was administered, and a continuous infusion (0.4 μmol/min) of the same isotope was started and maintained throughout the duration of a trial. Each trial had an initial 2-h infusion period, during which subjects rested in the seated position to allow tracer equilibration.

In Rest, an oral glucose tolerance test (OGTT) was performed at the end of the 2-h rest period. In Ex, after the 2-h rest period, subjects exercised on a cycle ergometer at a work rate approximating 70% $V_{\text{O}_2}$ peak for 60 min (which included a 5-min warm-up at ~50% $V_{\text{O}_2}$ peak). The OGTT was started 30 min after completion of the exercise bout. During exercise, expired air was collected and analyzed for $O_2$ consumption and $CO_2$ production, and HR was recorded at 15-min intervals. The 2-h OGTT commenced with the ingestion of 75 g of glucose tolerance test solution (300 ml) to which 60 μCi of [3-3H]glucose (Du Pont Biotechnology Systems, Wilmington, DE) had been added. No food or liquid was consumed throughout either of the trials other than the glucose drink. The resting trial was staggered such that the ingestion of the glucose drink in the two trials occurred at approximately the same time of day to account for diurnal variation in hormonal and metabolic responses. Trials were counterbalanced between subjects.

Venous blood was sampled at 5-min intervals during the last 10 min of the exercise bout and 10 min before each OGTT to determine baseline levels. During each OGTT, blood was sampled at 15-min intervals for 2 h after ingestion of the glucose load. Blood samples for glucose, isotopically labeled glucose, and lactate were collected at each sampling point for both trials. Samples for nonesterified fatty acids (NEFA) and insulin were collected at 30-min intervals during the OGTT. Samples for hematocrit (Hct) were collected immediately before the exercise bout in Ex and at 0, 60, and 120 min of the OGTT for both trials.

**Analytic techniques.** Samples for glucose, lactate, and insulin were collected in lithium heparin tubes, and NEFA samples were collected in tubes containing 30 μl of EGTA and reduced glutathione. All blood samples were immediately spun, and the plasma was stored on ice for the remainder of each experiment. Thereafter, samples were stored at −20°C until analysis. Whole blood was collected in lithium heparin tubes and placed on ice for subsequent analysis of Hct.

Plasma glucose and lactate concentrations were measured using an automated analyzer (model EML 105, Radiometer). Plasma insulin concentrations were determined by RIA (Phadeseeph, Pharmacia and Upjohn). Plasma NEFA concentrations were determined using an enzymatic-colorimetric method (NEFA C test kit, Wako Chemicals). Hct was determined by the microcapillary centrifugation method. Plasma, drink, and infusion [3H]glucose and [3H]glucose were analyzed using a modified method as described in detail previously (18). Briefly, plasma aliquots were deproteinized, and the protein-free supernatant was evaporated to remove labeled water. To determine [3H]glucose radioactivity, the dried product was reconstituted with distilled water, scintillant was added, and the samples were counted by a liquid scintillation counter (model LS 3801, Beckman). To determine [3H]glucose enrichment, a derivatization solution (2:3 pyridine-acetic anhydride) was added to the dried product and measured by gas chromatography-mass spectrometry (5890 series 2 gas chromatograph and 5971 mass spectrophotometer detector, Hewlett-Packard, Avondale, PA).

**Calculations and statistics.** The integrated areas under the plasma glucose and insulin curves were calculated using the trapezoidal model (15). Rates of plasma glucose appearance ($R_a$) and disappearance ($R_d$) were calculated using a modified monocompartmental non-steady-state model (26) with the assumption that the apparent glucose space was 25% body weight and pool fraction was 0.65. The metabolic clearance rate (MCR) of glucose was calculated by dividing $R_d$ by the corresponding plasma glucose concentration. The $R_d$ of oral glucose ($R_o$) and endogenous glucose ($R_{E}$) were calculated using the method of Steele et al. (25) as used with stable glucose isotope (23). To calculate an insulin sensitivity index, the glucose $R_a$ values at 30, 60, and 90 min were divided by the corresponding plasma insulin concentration and the mean of these values was taken. The data from the two trials were compared by ANOVA for repeated measures. Specific differences were located with the Student-Newman-Keuls post hoc test. A paired t-test was used to locate differences in areas under the response curves between the two conditions. Values are means ± SE.

**RESULTS**

In Ex, subjects exercised at a work rate requiring $71 ± 2\% V_{\text{O}_2}$ peak for 55 min on a cycle ergometer, which corresponded to 57 ± 1% peak power output and 82 ± 2% peak HR. Venous plasma lactate was 3.9 ± 0.8 mmol/l during the final 10 min of exercise.

Plasma glucose was not significantly different before glucose ingestion between Rest and Ex (Fig. 1A). The integrated area under the plasma glucose curve was 71% greater in Ex than in Rest ($P = 0.01$; Fig. 1A). Whole body glucose $R_a$ increased to a greater extent after oral glucose in Ex ($P = 0.03$, main effect). The total $R_a$ during the 2 h after glucose ingestion was 25% greater in Ex ($P = 0.02$; Fig. 1B). Whole body glucose $R_d$ rose to greater levels after glucose ingestion in Ex ($P = 0.04$, main effect), with total glucose uptake during the 2 h after glucose ingestion being 24% greater ($P = 0.03$; Fig. 1C). The MCRs of glucose were not different between Rest and Ex before or after glucose ingestion (Fig. 2A). Although $R_{E}$ was 8.6 μmol·kg$^{-1}$·min$^{-1}$ greater in Ex than in Rest in the preingestion period, this difference did not reach statistical significance ($P = 0.22$). However, $R_{E}$ was significantly higher from 15 to 30 min during the OGTT in Ex than in Rest (Fig. 2B). Despite this early difference, there were no differences in the cumulative $R_{E}$ (Fig. 2B) or the magnitude of suppression of $R_{E}$ during the OGTT between Rest (43 ± 4%) and Ex (48 ± 11%). $R_o$ was significantly greater during the OGTT in Ex ($P = 0.03$, main effect).
main effect), with the cumulative $R_{a0}$ being 30% greater in Ex ($P = 0.03$, Fig. 2C). Thus the greater increase in whole body $R_a$ when glucose was ingested after exercise was due, at least in part, to a greater $R_{a0}$.

Plasma insulin was not different between Ex and Rest before and during the OGTT (Table 1). The integrated areas under the insulin curves were also not different between Ex and Rest (13,320 ± 1,751 and 12,759 ± 1,810 pmol·l$^{-1}$·min, respectively). There was a significantly higher insulin sensitivity index (glucose $R_d$ divided by insulin concentration) in Ex than in Rest (0.49 ± 0.07 vs. 0.35 ± 0.04 μmol·kg$^{-1}$·min$^{-1}$·pmol$^{-1}$·l, $P = 0.02$), despite no difference in glucose MCR. Plasma NEFA concentration was significantly higher before glucose ingestion in Ex but was reduced to similar concentrations in Ex and Rest during the OGTT (Table 1). There were no differences in the plasma lactate response before and during the OGTT between Ex and Rest (Table 1). There were no differences in Hct before and during the OGTT between Ex and Rest (data not shown).

**DISCUSSION**

The results demonstrate an exaggerated glycemic response to oral glucose ingested in the period immediately (30 min) after exercise compared with that ingested 24 h after exercise. This finding is consistent with several similar studies in untrained (2) and moderately trained (15) middle-aged people as well as endurance-trained men (20). This greater glycemic response could be due to an effect of prior exercise to increase whole body glucose $R_a$, decrease whole body glucose uptake, or a combination of both. In the present study, whole body glucose $R_a$ was 25% higher when glucose was ingested after exercise. Similarly, Maehlum et al. (16) observed a 50–300% greater net glucose output from splanchnic tissues over a 3-h period after ingestion of 100 g of glucose subsequent to exhaustive...
to intraduodenal glucose infusion is augmented after exercise (22). Regardless of the mechanism, the higher SBF may be a contributing factor to the higher RaO observed after exercise in this study. In contrast, the increase in gut glucose absorption (i.e., hepatic arterial-portal venous glucose gradient, glycemia, insulin, and glucagon) were controlled, suggesting that intestinal permeability to glucose is higher after exercise. Although the mechanism for increased intestinal permeability after exercise is not clear, carrier-mediated intestinal glucose absorption may be decreased during exercise in trained men (27), possibly attributable to the reduction in SBF during high-intensity activity. To our knowledge, there are no studies that have examined carrier-mediated glucose transport in the postexercise state. Interestingly, however, there is evidence that paracellular permeability is increased after high-intensity (80% \( \dot{V}O_2 \) peak) running exercise (22). Regardless of the mechanism, the present results are compatible with a previously observed finding that the gut glucose output in response to intraduodenal glucose infusion is augmented after exercise in dogs (12).

The elevated net splanchnic glucose output observed by Maehlum et al. (16) persisted when measured 12 h after exercise, during which the subjects were starved. In addition, it has been demonstrated that gut glucose output is greater during an identical intestinal glucose load in 42-h- vs. 18-h-fasted dogs (8). Thus whether this effect is the result of exercise per se or simply the result of inducing a greater negative energy balance is unclear.

Burke et al. (3) suggested that the greater splanchnic glucose output observed after exercise by Maehlum et al. (16) is related to a selective hepatic insulin resistance. Indeed, there is indirect evidence that prior exercise may reduce the absolute rate of hepatic glucose uptake during a gut glucose load. Hamilton et al. (12) observed no change in net hepatic glucose uptake and a greater suppression of endogenous glucose production during intraduodenal infusion in exercised dogs. If the contribution of the kidneys to endogenous glucose production is assumed to be minor (4), then this finding suggests that the absolute rate of hepatic glucose uptake was reduced after exercise. In contrast to this indirect finding, studies in diabetic humans (14) and in animal models (8, 17) indicate that prior exercise augments hepatic glucose uptake. In particular, a study in dogs by Galassetti et al. (8) revealed that when the primary determinants of net hepatic glucose uptake (i.e., hepatic arterial-portal venous glucose gradient, glycemia, insulin, and glucagon) were controlled, prior exercise augmented net hepatic glucose uptake. Thus it is unclear whether the absolute rate of hepatic glucose uptake was reduced in the present study. Furthermore, because the extraction of glucose by the liver on first pass from the portal circulation contributes only ~5% to total disposal (7), any reduction in hepatic glucose disposal probably cannot quantitatively contribute to the 30% greater increase in \( R_{s,o} \) observed after exercise.

A reduced suppression of \( R_{s,E} \) would also contribute to the greater rise in total \( R_s \) after glucose ingestion in the postexercise period. In the present study, \( R_{s,E} \) was significantly higher from 15 to 30 min after oral glucose in Ex. The reason behind this response is unclear but may be related to elevated glucagon after exercise (12). Although exercise reduces hepatic glycogen stores (13),

### Table 1. Plasma insulin, NEFA, and lactate responses during a 75-g OGTT immediately after exercise and 24 h after exercise

<table>
<thead>
<tr>
<th>Time, min</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
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</thead>
<tbody>
<tr>
<td>Plasma insulin, pmol/l</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Rest</td>
<td>41 ± 11</td>
<td>223 ± 52</td>
<td>188 ± 17</td>
<td>138 ± 30</td>
<td>88 ± 23</td>
</tr>
<tr>
<td>Ex</td>
<td>31 ± 4</td>
<td>169 ± 34</td>
<td>200 ± 32</td>
<td>140 ± 21</td>
<td>78 ± 27</td>
</tr>
<tr>
<td>Plasma NEFA, mmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>0.41 ± 0.04</td>
<td>0.37 ± 0.04</td>
<td>0.27 ± 0.01</td>
<td>0.24 ± 0.01</td>
<td>0.23 ± 0.01</td>
</tr>
<tr>
<td>Ex</td>
<td>0.66 ± 0.08*</td>
<td>0.42 ± 0.04</td>
<td>0.28 ± 0.02</td>
<td>0.26 ± 0.02</td>
<td>0.31 ± 0.04</td>
</tr>
<tr>
<td>Plasma lactate, mmol/l</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Rest</td>
<td>1.1 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>1.5 ± 0.1</td>
<td>1.4 ± 0.1</td>
<td>1.3 ± 0.2</td>
</tr>
<tr>
<td>Ex</td>
<td>1.3 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>1.5 ± 0.1</td>
<td>1.5 ± 0.1</td>
<td>1.2 ± 0.1</td>
</tr>
</tbody>
</table>

Values are means ± SE (n = 6). NEFA, nonesterified fatty acid; OGTT, oral glucose tolerance test; Ex, immediately after exercise; Rest, 24 h after exercise. *Significantly different from Rest, \( P < 0.05 \).
EXERCISE AND ORAL GLUCOSE TOLERANCE

the liver remains a net producer of glucose in the postabsorptive state after exercise (1). In the present study, we observed no significant difference in the cumulative $R_{\text{aE}}$ and magnitude of suppression of $R_{\text{aE}}$ during the OGTT. This finding is consistent with a study using a graded, hyperinsulinemic-euglycemic clamp technique, which demonstrated no significant difference in the sensitivity or responsiveness of insulin to suppress $R_{\text{aE}}$ in the period immediately after exercise compared with 15 h after exercise in trained men (19).

The greater $R_a$ during the OGTT after exercise would, via mass action, increase whole body glucose uptake. There was a 24% greater increase in whole body glucose $R_a$ during the 2-h OGTT after exercise, which is likely to be mainly attributable to greater glucose disposal in previously active muscle (12). King et al. (15) demonstrated an apparent insulin resistance in moderately trained middle-aged people immediately after exercise and suggested that elevations in counterregulatory hormones and metabolites may impede glucose $R_a$ in the immediate postexercise state. Indeed, elevated levels of plasma NEFA and triglycerides produce muscle insulin resistance and impair glycogen synthesis in the postexercise state (5). However, in the present study, although the plasma NEFA were higher after exercise immediately before the OGTT, by 30 min NEFA had returned to concentrations that were not different from those observed in the rested condition during the OGTT. The rapid decrease in plasma NEFA in the present study may be related to the high level of fitness of the subjects in this study, since endurance training augments the suppression of adipocyte lipolysis by insulin (24).

Because the glucose MCRs and plasma insulin responses were not different between exercised and rested conditions, it is unlikely that whole body insulin sensitivity was altered after exercise. Similarly, Mikines et al. (19) demonstrated no difference in whole body insulin insulin action in the period immediately after exercise vs. 15 h after exercise in trained men. However, a negative hepatic arterial-portal venous glucose gradient, which is not present during a clamp situation, can impede peripheral glucose uptake in resting dogs (11). Interestingly, prior exercise eliminates the inhibitory effect of the portal signal on peripheral glucose disposal, particularly in contracted skeletal muscle (10). Thus it is conceivable that prior exercise alters the balance between splanchnic and peripheral glucose disposal after glucose ingestion, perhaps for preferential synthesis of glycogen in contracted skeletal muscle. However, there was no difference in the balance between hepatic and peripheral glucose disposal between exercised and rested dogs during portal glucose infusion (10). Conversely, in the present study, a higher intestinal absorption rate after exercise may create an effect whereby the glucose load reaching the liver saturates the rate at which the liver can take up glucose, thereby facilitating enhanced splanchnic glucose escape. Thus, as demonstrated by the present study and previous studies (12, 16), adaptations to splanchnic tissues by prior exercise facilitate the delivery of ingested glucose to the systemic circulation, thereby enhancing peripheral glucose disposal.

Some authors have attributed the impaired glucose tolerance after exercise to a reduced insulin response (20, 21), whereas others have demonstrated no difference (2) or higher (15) insulin responses after exercise. The results of the present study also show a lower insulin response relative to the increase in plasma glucose; nevertheless, there was a greater increase in glucose $R_a$ with no difference in glucose clearance, and a higher insulin sensitivity index when glucose was ingested after exercise. Thus the present data suggest that it is unlikely that a lower insulin response contributes to the apparent glucose intolerance after exercise.

In summary, the greater glycemic response when glucose is ingested after exercise is mediated by a greater $R_a$, the majority of which is due to a greater $R_{aO}$. This heightened $R_{aO}$ is probably due to exercise effects on splanchnic tissues to increase intestinal absorption and/or reduce hepatic uptake of glucose. Because there were no differences in plasma insulin or glucose clearance rate between exercised and rested states, the greater whole body glucose uptake appears to be mediated by the exaggerated glycemic response to oral glucose after exercise. This study demonstrates that, along with adaptations within active muscle itself, adaptations in splanchnic tissues by prior exercise may facilitate whole body glucose disposal and the resynthesis of muscle glycogen.

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