Prior exercise increases net hepatic glucose uptake during a glucose load

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Galasetti, Pietro, Robert H. Coker, Drury B. Lacy, Alan D. Cherrington, and David H. Wasserman. Prior exercise increases net hepatic glucose uptake during a glucose load. Am. J. Physiol. 276 (Endocrinol. Metab. 39): E1022–E1029, 1999.—The aim of these studies was to determine whether prior exercise enhances net hepatic glucose uptake (NHGU) during a glucose load. Sampling catheters (carotid artery, portal vein, hepatic, and iliac veins), infusion catheters (portal vein and vena cava), and Doppler flow probes (portal vein, hepatic and iliac arteries) were implanted. Exercise (150 min; n = 6) or rest (n = 6) was followed by a 30-min control period and a 100-min experimental period (3.5 mg·kg⁻¹·min⁻¹ of glucose in portal vein and as needed in vena cava to clamp arterial blood glucose at ~130 mg/dl). Somatostatin was infused, and insulin and glucagon were replaced intraportally at fourfold basal and basal rates, respectively. During experimental period the arterial-portal venous (a-pv) glucose gradient (mg/dl) was −18 ± 1 in sedentary and −19 ± 1 in exercised dogs. Arterial insulin and glucagon were similar in the two groups. Net hepatic glucose balance (mg·kg⁻¹·min⁻¹) shifted from 1.9 ± 0.2 in control period to −1.8 ± 0.2 (negative rates represent net uptake) during experimental period in sedentary dogs (Δ3.7 ± 0.5); with prior exercise it shifted from 4.1 ± 0.3 (P < 0.01 vs. sedentary) in control period to −3.2 ± 0.4 (P < 0.05 vs. sedentary) during experimental period (Δ7.3 ± 0.7, P < 0.01 vs. sedentary). Net hindlimb glucose uptake (mg/min) was 4 ± 1 in sedentary animals in control period and 13 ± 2 during experimental period; in exercised animals it was 7 ± 1 in control period (P < 0.01 vs. sedentary) and 32 ± 4 (P < 0.01 vs. sedentary) during experimental period. As the total glucose infusion rate (mg·kg⁻¹·min⁻¹) was 7 ± 1 in sedentary and 11 ± 1 in exercised dogs, ~30% of the added glucose infusion due to prior exercise could be accounted for by the greater NHGU. In conclusion, when determinants of hepatic glucose uptake (insulin, glucagon, a-pv glucose gradient, glycemia) are controlled, prior exercise increases NHGU during a glucose load due to an effect that is intrinsic to the liver. Increased glucose disposal in the postexercise state is therefore due to an improved ability of both liver and muscle to take up glucose.

EXERCISE markedly increases the metabolic demands of the organism, mostly due to increased needs of the contracting muscle (17, 29). Net muscle glucose uptake is greatly enhanced during exercise and remains elevated in the postexercise state to replenish muscle glycogen stores that were depleted during muscle contraction. Increased insulin sensitivity and glucose effectiveness facilitate muscle glucose uptake and glycogen synthesis in the postexercise state (27–29). This process is markedly accelerated if exogenous glucose is administered after the cessation of exercise (15, 26). In fact, the excess whole body glucose uptake measured during glucose infusion after exercise has been ascribed solely to skeletal muscle glucose disposal (17, 29). The liver, on the other hand, even if its glycogen stores are also depleted by prior exercise, remains a net producer of glucose in the immediate postexercise state in fasted animals (32). The liver can become a net consumer of glucose if exogenous glucose is administered after exercise (8). Nevertheless, neither net hepatic glucose uptake (NHGU) nor net hepatic glycogen deposition appears to be different from that measured in the absence of prior exercise (8). In another study, Matsuhisa et al. (20) observed that prior contraction of the rabbit hindlimb caused an increase in the rate of liver deposition of the glucose analog 3-fluoro-3-deoxy-D-glucose (3FDG) during a glucose load. In the aforementioned studies, however, direct hepatic effects of prior exercise were difficult to ascertain, because one or more of the determinants of hepatic glucose uptake [glucose load, arterial-portal venous (a-pv) glucose gradient, pancreatic hormone concentrations] were uncontrolled.

The aim of the present study was to determine whether prior exercise enhances NHGU in response to controlled changes in arterial glucose, insulin, glucagon, hepatic glucose load, and a-pv gradient. To address this aim, isotopic and arteriovenous-difference techniques were used in the chronically catheterized, conscious dog model after either a prolonged treadmill exercise period or an equivalent period of rest.

MATERIALS AND METHODS

Animals and surgical procedures. Twelve mongrel dogs of either gender (mean weight, 24 ± 2 kg) were studied. Animals were housed in a facility that met American Association for the Accreditation of Laboratory Animals Care guidelines and were fed a standard diet of meat and chow (34% protein, 14.5% fat, 46% carbohydrate, and 5.5% fiber based on dry weight). Experimental protocols were approved by the Vanderbilt University School of Medicine Animal Care and Use Committee. At least 16 days before each experiment, a laparotomy was performed under general anesthesia. Two Silastic catheters (0.03 mm ID) were inserted in the inferior vena cava for tracer and indocyanine green (ICG) infusion. Two more Silastic catheters (0.03 mm ID) were inserted in a jejunal and in a splenic vein (advanced so that the tips were in the portal vein) for intraportal infusion of glucose. Silastic catheters (0.04 mm ID) were also inserted in the portal vein.
Prior Exercise and Net Liver Glucose Uptake

During the 48 h preceding an experiment. Only animals that sedentary or exercise experiment. Dogs were not exercised treadmill running, regardless of whether they were used for a motorized treadmill, so that they would be familiar with regions, respectively.

Doppler flow probes (Transonic Systems, Ithaca, NY) were used to measure portal vein, hepatic artery, and external iliac artery blood flows. A small section of the portal vein, upstream from its junction with the gastroduodenal vein, was cleared of tissue, and a 6.0-mm-ID flow cuff was placed around the vessel and secured. The gastroduodenal vein was isolated and ligated proximal to its coalescence with the portal vein. A section of the main hepatic artery proximal to the portal vein was isolated, and a 3.0-mm-ID flow cuff was placed around the vessel and secured. The external iliac artery was accessed from the abdominal incision, dissected free of surrounding tissue, and fitted with a 4.0-mm-ID flow probe leads and the knotted free catheter ends, with the exception of the carotid artery and the common iliac vein catheters, were stored in subcutaneous pockets in the neck and inguinal regions, respectively. Starting 1 wk after surgery, dogs were exercised on a motorized treadmill, so that they would be familiar with treadmill running, regardless of whether they were used for a sedentary or exercise experiment. Dogs were not exercised during the 48 h preceding an experiment. Only animals that had 1) a leukocyte count <18,000/mm³, 2) a hematocrit >36%, 3) normal stools, and 4) a good appetite (consuming all of the daily ration) were used.

Studies were conducted after a 42-h fast, because this induces a stable minimum in hepatic glycogen content in the dog (11), preventing any effect due to different liver glycogen concentrations between sedentary and exercised animals. On the day of the experiment, the subcutaneous ends of the catheters were freed through small skin incisions made under local anesthesia (2% lidocaine, Astra Pharmaceutical, Worcester, MA) in the abdominal, inguinal, and neck regions. The contents of each catheter were aspirated, and they were flushed with saline. Silastic tubing was connected to the exposed catheters and brought to the back of the dog, where they were secured with quick-drying glue. Saline was infused in the arterial catheters throughout experiments (0.1 ml/min).

Experimental procedures. Animals were either exercised at a moderate intensity (100 m/min, 12% grade) on a motorized treadmill (n = 6) or remained sedentary (n = 6) from t = −180 to −30 min (Fig. 1). The exercise duration and intensity used in these experiments have been shown previously to result in a twofold increase in heart rate and an increase in O₂ uptake to 50% of maximum (22). A period of exercise recovery or continued rest followed (−30 to 100 min). At time = −70 min, a primer of [3-³H]glucose (30 μCi) was given, followed by venous infusions of [3-³H]glucose (0.3 μCi/min) and ICG (0.1 mg/min), which were continued for the duration of the study. ICG was used as a backup for the Doppler method of flow measurement. After a 10-min transition period (t = −30 to −20 min), from t = −20 to 0 min (basal period), three blood samples were drawn for assessment of basal levels of metabolic variables. From t = 0–100 min (experimental period), glucose was given via a constant intraportal infusion (3.5 mg·kg⁻¹·min⁻¹) and by a variable infusion into the inferior vena cava to clamp the arterial blood glucose at 130 mg/dl. From t = 0–100 min, endogenous pancreatic hormone secretion was also suppressed via a continuous somatostatin infusion into the inferior vena cava (0.8 μg·kg⁻¹·min⁻¹). Insulin and glucagon were replaced via intraportal infusions of 1.2 nl·kg⁻¹·min⁻¹ (4-fold basal) and 0.5 ng·kg⁻¹·min⁻¹ (basal), respectively. Arterial samples were drawn at 5-min intervals from t = −20 to 100 min. Portal, hepatic, and common iliac venous samples were drawn at t = −20, −10, 0, 60, 70, 80, 90, and 100 min. Portal vein, hepatic artery, and external iliac artery blood flows were recorded continuously from the frequency shifts of the pulse sound signal emitted from the Doppler flow probes (9, 10).

Processing of blood samples. Plasma and deproteinized blood samples that were not analyzed the day of the study were stored at −70°C after the completion of the experiment. Plasma glucose levels were determined during experiments by the glucose oxidase method with a glucose analyzer (Beckman Instruments, Fullerton, CA). For the determination of plasma [3-³H]glucose radioactivity, samples were deproteinized with barium hydroxide and zinc sulfate, the supernatant was evaporated, and the residue was dissolved in 1 ml of water and 10 ml Ecolite (ICN Biomedicals, Irvine, CA). Radioactivity was then determined by liquid scintillation counting with a Beckman LS 5000TD counter. Whole blood (samples deproteinized by 1:3 dilution in 4% perchloric acid) lactate, glyceral, alanine, glucose, and plasma free fatty acids were measured by enzymatic methods (18) on a Technicon autoanalyzer (Tarrytown, NY) or on a Monarch 2000 centrifugal analyzer (Instrumentation Laboratories, Lexington, MA).

Immunoreactive insulin was measured with a double antibody system (interassay coefficient of variation (CV) of 10%;
Ref. 21]. Immunoreactive glucagon was measured in plasma samples containing 50 µl of 500 Kallikrein-inhibitor units/ml Trasylol (FBA Pharmaceuticals, NY) with a double antibody system (CV of 7%) modified from the method developed by Morgan and Lazarow (21) for insulin. Insulin and glucagon antisera, standard glucagon and insulin, and the 125I-Trasylol (FBA Pharmaceuticals, NY) with a double antibody were obtained from Linco Research (St. Charles, MO).

Calculations. The tracer-determined total rate of glucose appearance (GIR) was determined by steady-state equations for isotope ([3-3H]glucose) dilution (3). Endogenous glucose GIR was calculated by subtracting the glucose infusion rate (portal vein + vena cava) from the total glucose GIR.

Net hepatic balances of lactate, glucose, alanine, FFA, and glycerol were determined by the following formula: HAF × ([H] − [A]) + PVF × ([H] − [P]), where [A], [P], and [H] are the arterial, portal venous, and hepatic vein blood or plasma substrate concentrations, respectively, and HAF and PVF are the hepatic artery and portal vein blood or plasma flows, respectively, determined with Doppler flow probes. The load of a substrate reaching the liver was calculated as follows: [P] × PVF + [A] × HAF. Net hepatic substrate fractional extraction was calculated as the ratio of net hepatic balance to hepatic load.

Net limb balances were calculated as follows: LF × ([A] − [I]). LF is limb blood flow through the external iliac artery, and [I] is the substrate level in the common iliac vein. Limb fractional substrate extraction was calculated as the limb substrate uptake divided by the limb substrate load (LF × [A]). Blood levels and flows were used for the calculation of all hepatic and limb balances, with the exception of FFA balances for which plasma concentrations and flows were used. The ratio of blood to plasma glucose was calculated for the basal period and the glucose infusion period for each dog at each of the five sampling sites. Plasma glucose values were then multiplied by their corresponding ratio (i.e., blood glucose to plasma glucose) to convert to blood glucose concentrations. The advantage of plasma glucose measurements is that a large number of replicates can be obtained quickly and at little added cost. The ability to measure replicate samples reduces the measurement CV. The conversion to blood values alleviates the need for assumptions regarding the equilibration of substrates between red cell and plasma water.

When glucose is infused in the slow, laminar flow of the portal vein, mixing of the glucose in the blood can be problematic. To assess whether at a given time point during intraportal glucose infusion good mixing of glucose was present, we used the following equation

\[ \text{GIR}_{\text{pv}} / \text{PVBF} - [G]_{a-pv(t)} - [G]_{a-pv(basal)} \]

where GIRpv is the infusion rate of glucose in the portal vein, PVBF is the portal venous blood flow, and [G]_{a-pv(t)} and [G]_{a-pv(basal)} are the a-pv glucose gradients at time t or at baseline (i.e., in the presence and in the absence of portal glucose infusion), respectively. With this method, the difference between the two terms of the equation equals zero in the presence of perfect glucose mixing. Samples were considered unmixed if the result of the above equation was >140% or <60% of the following equation: [G]_{a-pv(t)} - [G]_{a-pv(basal)}. Animals were excluded from the study if poor mixing, according to the above definition, occurred in more than two out of the five time points of the experimental period.

Data are expressed as mean ± SE. Data in some instances are expressed as the mean of three measurements for the basal period (20 to 0 min) and of five measurements for the glucose steady-state portion of the experimental period (60-100 min). Statistics were performed with SuperAnova (Abacus Concepts, Berkeley, CA) on a Macintosh PowerPC. Statistical comparison between groups and over time was made with ANOVA designed to account for repeated measures. Specific time points were examined for significance with contrasts solved by univariate repeated measures. Pooled data from basal and glucose infusion periods were compared with unpaired t-tests. Statistics are reported in the corresponding table or figure legend for each variable. Differences were considered significant when P values were <0.05.

RESULTS

Arterial blood glucose, a-pv glucose gradient, and pancreatic hormone levels. Arterial blood glucose was similar between the two groups at baseline and rose by ~80% during the experimental period in both groups (Fig. 2). The a-pv glucose gradient was positive in both groups at baseline (3.1 ± 0.4 in sedentary and 4.3 ± 0.4 mg/dl in exercised dogs) and became markedly negative during the experimental period (~17.9 ± 1.8 in seden-
ory and −19.3 ± 3.4 mg/dl in exercised dogs). There were no differences in the a-pv glucose gradient between the two groups.

As expected, arterial plasma insulin at baseline was slightly lower in the exercised than in the sedentary dogs. Insulin levels rose by about threefold during the experimental period and were similar in the two groups. Arterial plasma glucagon was higher at baseline in exercised compared with sedentary dogs. During the experimental period, the pancreatic clamp equalized glucagon levels in the two groups. The presence of a metabolic steady state was reflected by the stability of the measurements described previously during the last 40 min of the experimental period.

Tracer-determined total and endogenous glucose Ra was not significantly higher in the exercised compared with the sedentary animals at baseline (4.0 ± 0.5 vs. 2.8 ± 0.3 mg·kg⁻¹·min⁻¹). Total Ra (endogenous + exogenous) became significantly greater in the exercised animals during the experimental period (11.1 ± 0.8 vs. 7.0 ± 0.5 mg·kg⁻¹·min⁻¹). Endogenous glucose Ra was completely suppressed during the experimental period in both groups.

**Hepatic glucose metabolism.** The basal hepatic glucose load was 23 ± 1 mg·kg⁻¹·min⁻¹ in the sedentary dogs and 25 ± 1 mg·kg⁻¹·min⁻¹ in the exercised dogs (Fig. 3). It increased to 36 ± 2 mg·kg⁻¹·min⁻¹ in sedentary and to 40 ± 1 mg·kg⁻¹·min⁻¹ in exercised dogs during the experimental period. Exercised dogs had a significantly higher basal net hepatic glucose output compared with sedentary animals (4.2 ± 0.3 vs. 1.9 ± 0.2 mg·kg⁻¹·min⁻¹, P < 0.01). Animals in both groups shifted to NHGU during the experimental period. There was significantly more net glucose uptake in exercised than in sedentary dogs (−3.2 ± 0.4 vs. −1.8 ± 0.2 mg·kg⁻¹·min⁻¹, P < 0.05). The total change in net hepatic glucose balance from baseline to the experimental period was therefore 3.7 ± 0.5 mg·kg⁻¹·min⁻¹ in sedentary dogs and 7.3 ± 0.7 mg·kg⁻¹·min⁻¹ in exercised animals (P < 0.001 vs. sedentary). The net hepatic fractional extraction of glucose during the experimental period was greater in the exercised than in the sedentary dogs (0.08 ± 0.01 vs. 0.05 ± 0.01, P < 0.02).

**Hindlimb glucose metabolism.** The basal net hindlimb glucose uptake was 4.0 ± 0.9 mg/min in the sedentary dogs and 8.4 ± 0.9 mg/min in the exercised dogs (P < 0.05 vs. sedentary). During the experimental period, it rose to 13.2 ± 1.4 mg/min in sedentary dogs and to 32.8 ± 3.5 mg/min in exercised dogs (P < 0.01 vs. sedentary). Net hindlimb glucose fractional extraction paralleled the response of net hindlimb glucose uptake (2.6 ± 0.5% in sedentary dogs and 4.6 ± 0.4% in exercised dogs at baseline, P < 0.05; 4.7 ± 0.5% in sedentary dogs and 13.4 ± 1.0% in exercised dogs during the experimental period, P < 0.05).

Blood levels and hepatic and hindlimb balances of gluconeogenic precursors. Arterial lactate concentrations were similar at baseline and increased by ~80% in both groups (Fig. 4). Exercised animals displayed significantly more basal net hepatic lactate uptake (−12.5 ± 1.2 vs. −7.3 ± 1.7 μmol·kg⁻¹·min⁻¹, P < 0.05). During the experimental period, all animals shifted to net hepatic lactate output, with no significant difference between the two groups. The basal net hindlimb lactate output was −21.8 ± 4.0 and −13.8 ± 4.7 μmol/min (P > 0.05; nonsignificant) in exercised and sedentary dogs, respectively. During the experimental period, net hindlimb lactate output was suppressed in both groups.

Net hepatic alanine and glycerol uptakes were higher at baseline in exercised dogs; similar values of hepatic
uptake of both metabolites were detected during the experimental period (data not shown).

Blood flows. Although basal hepatic artery blood flow was higher in the exercised dogs than in the sedentary dogs ($P < 0.05$), total splanchnic blood flow was similar between the two groups throughout the study (Table 1). The external iliac artery blood flow was similar between groups throughout the study.

**DISCUSSION**

It is well established that prior exercise increases insulin sensitivity and glucose effectiveness (12), leading to enhanced rates of net muscle glucose uptake and glycogen synthesis (7, 8, 14). By comparison, far less is known about how prior exercise affects NHGU. In the present study, the influence of prior exercise on the net hepatic uptake of an intraportal venous glucose load was investigated in conscious dogs in which circulating glucose, insulin, glucagon, a-pv glucose gradient, and hepatic glucose load were carefully controlled. Prior exercise led to a 74% greater NHGU and a 58% greater net hepatic glucose fractional extraction compared with sedentary controls. The total change in net hepatic glucose balance from the basal period to the glucose infusion period was 3.7 and 7.3 mg·kg$^{-1}$·min$^{-1}$ in sedentary and exercised dogs, respectively. Whole body glucose uptake was 57% greater in exercised compared with sedentary animals. It could be calculated that 26 and 28% of the whole body glucose uptake could be accounted for by NHGU in the sedentary and exercised dogs, respectively. Although the exercised dogs consumed more glucose, the percent contribution of hepatic and nonhepatic tissues to whole body glucose uptake was similar.

The hypothesis that liver glucose uptake could be stimulated by prior exercise is consistent with previous studies in humans (16) and rabbits (20). Kawamori et al. (16) showed that the splanchnic disposal of an oral glucose load during a euglycemic-hyperinsulinemic clamp was about twice as high after exercise as after rest in non-insulin-dependent diabetes mellitus patients. In this study, glucagon levels were not controlled or even measured, and only an indirect estimate of the NHGU was made. Matsuhisa et al. (20) measured the accumulation of phosphorylated 3FDG in the liver of anesthetized rabbits after 30 min of electrical stimulation of the hindlimb muscles. The accumulation of phosphorylated 3FDG in the liver was approximately twofold greater after muscle contraction compared with nonelectrically stimulated control rabbits. The effect of prior exercise directly on the liver was difficult to assess because the animals that underwent muscle contraction had higher circulating insulin. Although the stud-

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**Table 1. External iliac artery, hepatic artery, portal vein, and total splanchnic blood flows**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Experimental Period</th>
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</thead>
<tbody>
<tr>
<td>External iliac artery, ml/min</td>
<td>209 ± 18</td>
<td>200 ± 12</td>
</tr>
<tr>
<td>Sedentary</td>
<td>241 ± 21</td>
<td>185 ± 21</td>
</tr>
<tr>
<td>Exercised</td>
<td></td>
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<tr>
<td>Hepatic artery, ml·kg$^{-1}$·min$^{-1}$</td>
<td>6.7 ± 0.4</td>
<td>8.1 ± 0.5</td>
</tr>
<tr>
<td>Sedentary</td>
<td>10.4 ± 0.7*</td>
<td>10.1 ± 1.2</td>
</tr>
<tr>
<td>Exercised</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Portal vein, ml·kg$^{-1}$·min$^{-1}$</td>
<td>22.1 ± 1.8</td>
<td>16.7 ± 1.4</td>
</tr>
<tr>
<td>Sedentary</td>
<td>22.4 ± 2.7</td>
<td>17.8 ± 1.4</td>
</tr>
<tr>
<td>Exercised</td>
<td></td>
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</tr>
<tr>
<td>Total splanchnic, ml·kg$^{-1}$·min$^{-1}$</td>
<td>28.9 ± 1.8</td>
<td>24.8 ± 1.3</td>
</tr>
<tr>
<td>Sedentary</td>
<td>32.8 ± 2.4</td>
<td>27.9 ± 1.0</td>
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<tr>
<td>Exercised</td>
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Data are means ± SE; $n = 6$/group. Dogs were 42 h fasted and were studied after 150 min of either rest or moderate exercise. Baseline values are average of 3 measurements (~20 min–0 min), and experimental period value is mean of 5 steady-state measurements (60–100 min). *$P < 0.05$, exercised vs. sedentary.
ies previously cited provide indirect support for the hypothesis that prior exercise stimulates NHGU, in none were the factors that are known to influence NHGU controlled nor was NHGU measured directly. Hamilton et al. (8) showed that rates of NHGU were similar in exercised dogs and in sedentary controls, when glucose was infused intraduodenally at 8 mg·kg$^{-1}$·min$^{-1}$. Because a greater suppression of endogenous R$_E$ was seen in exercised animals at a time when rates of NHGU were similar to sedentary controls, unidirectional hepatic glucose uptake must also have been reduced by prior exercise. Endogenous pancreatic hormone secretion was not suppressed in the study by Hamilton et al., and circulating glucagon levels were greater in the exercised dogs. Because glucagon can antagonize NHGU (13), the higher glucagon levels may have masked a NHGU response in the exercised dogs. Maehlum et al. (19) have reported that a greater proportion of an oral glucose load escapes hepatic retention in exercised than in sedentary humans. Although this finding may appear contrary to the findings from the present study, it should be noted that in the work by Maehlum et al. the experimental setting was significantly different from ours. The human subjects in their study were administered glucose orally in a bolus. In this situation, the glucose load reaching the intestine is the same in the two experimental groups, but the load reaching the liver is greater in the exercised subjects, as exercise enhances the ability of the gut to absorb ingested glucose (5, 8). Because this exercise-induced increase in hepatic glucose load is greater than the increase in NHGU, a greater amount of glucose leaves the splanchnic region in response to oral glucose after exercise. All factors known to stimulate NHGU were controlled in the present study. It could be argued, however, that other extrahepatic determinants such as catecholamines, cortisol, and growth hormone, which were not measured, may also have influenced liver metabolism. Arterial catecholamine levels have been previously demonstrated to increase two- to threefold during an exercise bout comparable with that used in this study (2). Nevertheless, the experimental period started 30 min after the cessation of exercise, at which time catecholamine levels have been shown to return to basal levels (2). Further, catecholamines mainly affect liver glucose metabolism by increasing the availability of gluconeogenic precursors from the periphery. In this study, the net liver uptake of glyceraldehyde and alanine and the net liver output of lactate were similar in exercised and sedentary dogs. Cortisol and growth hormone levels are also increased during exercise; their influences on hepatic glucose metabolism, nevertheless, have not to date been clearly defined. It should be noted, however, that the increased secretion of the aforementioned counter regulatory hormones favors net glucose output by the liver, not NHGU. Controlling the levels of these hormones should, if anything, have enhanced the effect of prior exercise on NHGU.

A strong positive correlation exists between NHGU and both insulin concentration and hepatic glucose load (23, 24). Increased sensitivity to one of these factors, or both, may cause the increase in NHGU after exercise. A positive correlation also exists at rest between NHGU and the magnitude of a negative a-pv glucose gradient until values of approximately −20 mg/dl, above which no further enhancement of NHGU was observed (25). The a-pv glucose gradients measured in our study (−18 and −19 mg/dl) were very close to the value that maximally stimulates NHGU (25). It is possible, however, that prior exercise increases the sensitivity or responsiveness of NHGU to the a-pv glucose gradient. At the cellular level, glucose transport across the hepatocyte membrane is primarily mediated by the GLUT-2 isoform of the glucose transporter family. Once in the cytoplasm, glucose is phosphorylated through a reaction catalyzed by the enzyme glucokinase (GK). GLUT-2 is not believed to play a limiting role in the movement of glucose from the extracellular to the intracellular space of the hepatocyte. GK activity, on the other hand, is thought to be rate limiting for glucose uptake in the liver and can be regulated in response to different stimuli, such as glucose, fructose, and glucagon concentrations (1). An increase in GK activity occurs because of the translocation of GK from the nucleus of the hepatocyte to the cytosol and the loss of the inhibitory binding with its regulatory protein. Although the effect of exercise on GK activity has not been completely elucidated, a significant increase in GK activity has been reported after exercise in rats (4). Hamilton et al. (8) observed that GK activity was not significantly different in exercised and sedentary dogs after an intraduodenal glucose load. In these previous studies, GK analysis was performed on crude liver tissue homogenates, and enzymatic movement from the nuclear membrane into the cytosol could not be detected. In addition, other determinants of liver glucose uptake were not controlled.

Because liver glycogen content and synthetic rates were not measured in the present study, it is impossible to specify the intrahepatic fate of the excess glucose taken up by the liver in response to a glucose load in the postexercise state. The net hepatic balances of the gluconeogenic precursors lactate, alanine, and glycerol, on the other hand, were similar in sedentary and exercised animals. This suggests that glycogen storage was probably the preferential pathway through which the liver of exercised dogs directed the excess glucose taken up compared with sedentary animals.

Prior exercise induced greater net hindlimb glucose uptake during glucose infusion, despite similar hindlimb glucose and insulin loads in exercised and sedentary animals. This is consistent with numerous previous studies in which prior exercise led to greater net skeletal muscle glucose fractional extraction due to enhanced muscle insulin sensitivity (28, 30) as well as increased insulin-independent glucose uptake (6, 29). The greater net glucose uptake by the skeletal muscle has been previously shown to result in greater rates of intramuscular glycogen synthesis (19, 29). Although muscle glycogen was not measured in the present study, these previous reports are consistent with our
observation that net muscle lactate output was similar in sedentary and exercised animals.

As stated previously, the contribution of the liver to whole body glucose uptake is quantitatively smaller than that of the skeletal muscle (in the present study the liver accounted for 26–28% of whole-body glucose uptake, whereas the large majority of the remainder could be accounted for by total whole-body glucose uptake). The importance of the liver as a contributor to glucose uptake. The importance of the liver as a contributor to glucose uptake, whereas the large majority of the remainder could be accounted for by total whole-body glucose uptake. The importance of the liver as a contributor to glucose uptake, whereas the large majority of the remainder could be accounted for by total whole-body glucose uptake. The importance of the liver as a contributor to glucose uptake, whereas the large majority of the remainder could be accounted for by total whole-body glucose uptake. The importance of the liver as a contributor to glucose uptake, whereas the large majority of the remainder could be accounted for by total whole-body glucose uptake. The importance of the liver as a contributor to glucose uptake, whereas the large majority of the remainder could be accounted for by total whole-body glucose uptake. The importance of the liver as a contributor to glucose uptake, whereas the large majority of the remainder could be accounted for by total whole-body glucose uptake. The importance of the liver as a contributor to glucose uptake, whereas the large majority of the remainder could be accounted for by total whole-body glucose uptake. The importance of the liver as a contributor to glucose uptake, whereas the large majority of the remainder could be accounted for by total whole-body glucose uptake. The importance of the liver as a contributor to glucose uptake, whereas the large majority of the remainder could be accounted for by total whole-body glucose uptake. The importance of the liver as a contributor to glucose uptake, whereas the large majority of the remainder could be accounted for by total whole-body glucose uptake.

In summary, the work presented here provides for the first time clear evidence that prior exercise can directly influence liver carbohydrate metabolism by significantly increasing net glucose uptake by this organ. This result was obtained by strictly controlling the fundamental determinants of NHGU (concentrations of glucose and pancreatic hormones, a-pv glucose gradient, hepatic glucose load), thereby isolating effects of prior exercise per se. In this setting, prior exercise resulted in a 74% increase in NHGU and in a 58% increase in net hepatic glucose fractional extraction compared with sedentary controls. NHGU comprised one-third of the added whole body glucose uptake after exercise. Our data show that the liver is a major site of glucose removal when a carbohydrate load is administered in the postexercise state.

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