Prior Muscular Contraction Enhances Disposal of Glucose Analog in the Liver and Muscle

Munehide Matsuhisa, Hideko Nishizawa, Masahiko Ikeda, Minoru Kubota, Sadao Arai, Ryuzo Kawamori, and Yoshimitsu Yamasaki

To noninvasively investigate in vivo glucose disposal in muscle and liver after exercise, ^{19}F magnetic resonance spectroscopy (^{19}F-MRS) was applied using 3-fluoro-3-deoxy-D-glucose (3FDG) as a metabolic probe. After 30 minutes of muscle contraction of rabbit hindlimb by a 1-Hz electrical stimulation, 3FDG 250 mg/kg was injected intravenously and ^{19}F-MRS was performed on the postcontracted hindlimb or the liver. Rabbits subjected to muscle contraction showed 1.5- and 1.7-fold higher peaks for 3FDG signal intensity in the liver and muscle than those not subjected to it. 3FDG was converted to 3-fluoro-3-deoxy-gluconic acid (3FGA) in the muscle and liver, and 3FDG oxidation was not affected by muscle contraction. During intraportal 3FDG infusion for 120 minutes at a dose of 2 mg · kg^{-1} · min^{-1} after termination of muscle contraction, the postcontracted rabbits showed a continuous increase in the signal intensity of 3FDG and a 2.1-fold higher total signal intensity of 3FDG than those not subjected to muscle contraction. In conclusion, ^{19}F-MRS allows direct noninvasive observation of 3FDG disposal in rabbit muscle and liver. The increased intensity of 3FDG in the liver after muscle contraction suggests that exercise enhances disposal of the glucose analog in the liver, as well as in muscle, and these effects persist for at least 2 hours after exercise.

EXERCISE INCREASES GLUCOSE utilization in muscle and depletes glycogen stores there to produce energy. After exercise, glucose uptake and glycogen synthesis are both increased in skeletal muscle. Therefore, the depleted muscle glycogen store is rapidly repleted during the recovery period.[1] On the other hand, the liver produces glucose by increasing glycogenolysis and gluconeogenesis during exercise, and hepatic glucose production continues in the recovery period.[2] When glucose is administered peripherally after exercise, the liver stores glycogen through direct and indirect pathways.[3] However, it remains to be determined whether exercise can affect the disposal of exogenous glucose in the liver, which may also be depleted stored glycogen during exercise.

Magnetic resonance spectroscopy (MRS) makes it possible to repeatedly and noninvasively analyze the chemical constituents of substances. Among the stable nuclei, ^{19}F has the second-highest magnetic resonance (MR) sensitivity to protons. It has a large range of chemical shifts, and therefore, the metabolic changes of a given substrate are likely to produce large chemical-shift changes that can be easily resolved in vivo. ^{19}F is present in tissues in negligible amounts and hence can be introduced into the system and subsequently traced. The fluorinated glucose analogs 2-fluoro-2-deoxy-D-glucose (2FDG) and 3-fluoro-3-deoxy-D-glucose (3FDG) have been successfully used to study glucose uptake and metabolism for in vitro and in vivo studies.[4-8] Therefore, ^{19}F-MRS can be used to determine the metabolism of fluorinated glucose analog in vivo.

In this study, we examined the acute effect of exercise on glucose analog distribution in the liver and muscle of rabbits and the persistent effect of exercise on hepatic glucose disposal enhanced by portal glucose delivery using ^{19}F-MRS with 3FDG as a metabolic probe.

From the First Department of Medicine, Osaka University School of Medicine, Osaka; Department of Sociology, Kwansei Gakuin University, Nishinomiya; Oriono Hospital, Osaka; and Department of Medicine, Metabolism and Endocrinology, Juntendo University School of Medicine, Tokyo, Japan.

Submitted February 6, 1997; accepted June 17, 1997.

Address reprint requests to Munehide Matsuhisa, MD, PhD, First Department of Medicine, Osaka University School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565, Japan.

0026-0495/98/4701-0009$03.00/0

MATERIALS AND METHODS

The study was approved by the Institute of Experimental Animal Sciences, Osaka University Medical School.

Protocol 1

Ten male rabbits weighing 1.9 to 2.2 kg were allowed free access to food and water before the experiments. Under light general anesthesia induced by a minimal-dose intravenous bolus injection of pentobarbital sodium (≤25 mg/kg), an angiocatheter was inserted percutaneously into the right saphenous vein for sampling. To prevent interference from the ^{19}F-MRS of 3FDG in urine from occurring in the muscle, a catheter was inserted into the bladder. The rabbit was then held in place in a paper box to prevent movement. To simulate mild exercise, increased contractile activity in a hindlimb was produced by electrical stimulation. Electrodes were inserted subcutaneously into both the medial and lateral sides of the posterior thigh. Electrical stimulation (SEN-3201; Nihon Kohden, Tokyo, Japan) was delivered at 1 pulse/s, with each pulse having a duration of 20 milliseconds, and the voltage was applied to tolerance. After 30 minutes of muscle contraction or rest, the rabbits were immediately administered a single injection of 3FDG 250 mg/kg through the ear vein. ^{19}F-MRS was performed for the liver (n = 5) or the contracted hindlimb (n = 5) for the next 120 minutes. These measurements were performed twice with a 7-day interval after the rabbits were fasted overnight and then subjected to 30 minutes of rest or muscular contraction in randomized order.

Protocol 2

Seven days before the first experiment, five male rabbits weighing 1.9 to 2.2 kg underwent a laparotomy with general anesthesia (pentobarbital sodium 25 mg/kg). A Silastic catheter (Fuji Systems, Tokyo, Japan) was inserted into the portal vein and then filled with saline containing heparin, with the free end being knotted and placed in a subcutaneous pocket. On the day of the experiment, the subcutaneous end of the catheter was freed through a small skin incision under light general anesthesia. An angiocatheter for sampling venous blood and a urinary catheter were inserted, and the rabbits were fixed as described in animal protocol 1. After 30 minutes of muscle contraction or rest, 3FDG was infused intraportally at a rate of 2 mg · kg^{-1} · min^{-1} for 120 minutes. Measurements of hepatic ^{19}F-MRS during intraportal 3FDG infusion

were performed twice with a 7-day interval after the rabbits were made to fast overnight and then subjected to 30 minutes of rest or muscular contraction in randomized order.

In Vivo ^{19}F-MRS Measurement

All in vivo MRS data were collected on a Siemens (Erlangen, Germany) MR system, Magnetom, operating at 1.5 T. After the bolus intravenous injection or during intraportal infusion of 3FDG, the rabbit fixed in a harness was positioned in the coil. ^{19}F-MRS measurements for muscle and liver were obtained by attaching the surface coil to the posterior thigh and the epigastric region, respectively. Homogeneity over the sample volume was maximized by shimming on the proton signal of tissue water to the proton line width in the range of 30 to 35 Hz. The MR signal was obtained at 59.8 MHz using a one-pulse sequence. Files were blocked at every 512 free-induction decays. The sequence parameters were optimized in phantom experiments. Chemical shifts were referred to an external 5-fluorouracil (5FU) standard. Signal intensity was determined from the area of each resonance calculated by an integration program. 3FDG signal intensity was determined as the combined area of α and β anomers. Total 3FDG accumulation in each organ was determined as the combined area of 3FDG and 3-fluoro-D-gluconic acid (3FGA). The MR signal was obtained every 5 minutes for the initial 30 minutes, and then every 10 minutes during the following 90 minutes. In protocol 2, we determined the initial velocity of hepatic 3FDG disposal (IV_{3FDG}) from the formula, $IV_{3FDG} = [3FDG]_{30}/30$ (mV · ppm · min^{-1}), where $[3FDG]_{30}$ is 3FDG intensity at 30 minutes.

Plasma ^{19}F-MRS Measurement

In separate experiments to determine 3FDG intensity in a blood sample, 20-mL blood samples were taken from the rabbits at 0, 15, 30, 60, and 120 minutes after a 250-mg · kg^{-1} 3FDG injection or during a 2-mg · kg^{-1} · min^{-1} 3FDG infusion. 5FU (Hoffman-LaRoche) was added to the samples as an internal reference. The ^{19}F-MR spectrum of each sample in an 8-cm-diameter nuclear magnetic resonance tube was obtained at room temperature at 59.8 MHz using a one-pulse sequence. The radiofrequency (RF) probe was a double-turn surface coil tunable to the resonance frequencies of the proton and ^{19}F placed over the center of the MR tube. ^{19}F-MRS of blood samples was obtained using the 1.5-T MRS system magnetometer. Sequence parameters were optimized in phantom experiments (repetition [TR] time, 1,000 milliseconds; RF time, 150 microseconds; number of scans, 512).

Data Analysis

To measure plasma glucose and insulin concentrations, plasma samples were taken every 15 minutes for the initial 60 minutes and every 30 minutes for the next 60 minutes. Plasma glucose levels were determined by a glucose oxidase method using the Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Plasma insulin levels were analyzed by radioimmunoassay (Amersham, Buckinghamshire, England). All data are presented as the mean ± SEM. Between-group comparisons were evaluated by a Wilcoxon single-rank test. One-way ANOVA was used for comparison within each group. Statistical significance was accepted at P less than .05.

RESULTS

Protocol 1

Plasma glucose levels in rabbits with and without muscle contraction reached a peak at 30 minutes and decreased gradually until 120 minutes (Fig 1). There was no significant difference between the two groups. Plasma insulin levels were comparable between the groups (Table 1). Three resonances with discrete chemical shifts were resolved in the liver (Fig 2). The chemical shifts of resonances −26.1, −31.0, and −40.2 ppm resolved in vivo coincided with those of the β and α anomers of 3FDG and 3FGA, respectively[4] (Fig 2).

^{19}F-MRS showed that in vivo hepatic signal intensity of 3FDG reached a peak immediately and decreased gradually for 120 minutes. On the other hand, the signal intensity of 3FGA increased gradually. Comparing ^{19}F-MR spectra from the rabbits not subjected to muscle contraction showed that total hepatic accumulation of 3FDG increased significantly until 20 minutes and then tended to remain at that level over the next 100 minutes in the postcontracted rabbit (Fig 3). The peak of hepatic 3FDG disposal was 1.5 times higher in rabbits subjected to muscle contraction versus those not subjected to it.

In comparison to the ^{19}F resonance obtained from rabbits not subjected to muscle contraction, 3FDG accumulation in postcontracted muscle increased significantly until 30 minutes and the peak of total 3FDG disposal was 1.7 times higher (Fig 4). The signal intensity of 3FGA in muscle increased gradually independently of muscle contraction.

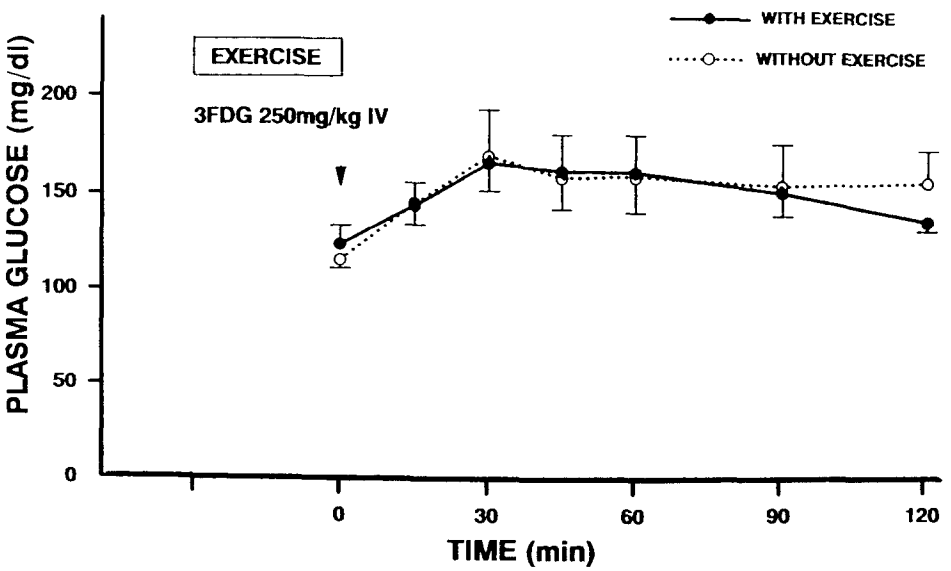

Fig 1. Plasma glucose (mg/dL) in rabbits with and without muscle contraction after intravenous injection of 3FDG 250 mg/kg. Values are means ± SEM (n = 5).

Table 1. Arterial Plasma Insulin (μmol/L) in Rabbits With and Without Muscle Contraction After Intravenous Injection of 3FDG 250 mg/kg (mean ± SEM, n = 5)

	Time (min)						
	0	15	30	45	60	90	120
Protocol 1							
EX(−)	10.1 ± 1.7	11.0 ± 1.5	10.6 ± 1.4	10.8 ± 1.7	10.7 ± 1.7	10.6 ± 1.2	10.8 ± 1.8
EX(+)	8.7 ± 0.6	14.6 ± 1.2	15.8 ± 2.3	11.3 ± 0.5	10.7 ± 1.3	10.2 ± 0.4	9.5 ± 1.4
Protocol 2							
EX(−)	7.9 ± 1.3	8.8 ± 0.6	9.4 ± 1.2	8.0 ± 0.7	7.6 ± 0.4	7.7 ± 0.6	7.5 ± 0.6
EX(+)	6.7 ± 1.1	7.5 ± 0.8	8.8 ± 1.4	10.2 ± 1.2	11.0 ± 1.0	10.6 ± 1.2	12.2 ± 1.7

Abbreviations: EX(−), without exercise; EX(+), with exercise.

Protocol 2

Plasma glucose concentrations increased gradually up to 120 minutes independently of muscle contraction (Fig 5). No significant differences in plasma glucose and insulin levels were observed between the two groups at any time during intraportal infusion of 3FDG (Table 1).

In rabbits subjected to muscle contraction, 3FDG signal intensity continued to increase during intraportal infusion of 3FDG at a dose of 2 mg · kg^{-1} · min^{-1} (Fig 6). In rabbits not subjected to muscle contraction, the signal intensity of 3FDG increased until 90 minutes and then remained at a plateau during the next 30 minutes. 3FDG signal intensity from 100 to 120 minutes after muscle contraction was significantly larger than that obtained from rabbits not subjected to it. The initial velocity of hepatic 3FDG disposal after muscle contraction was significantly higher than at rest (0.92 ± 0.18 *v* 0.37 ± 0.18 mV · ppm · min^{-1}, $P < .05$).

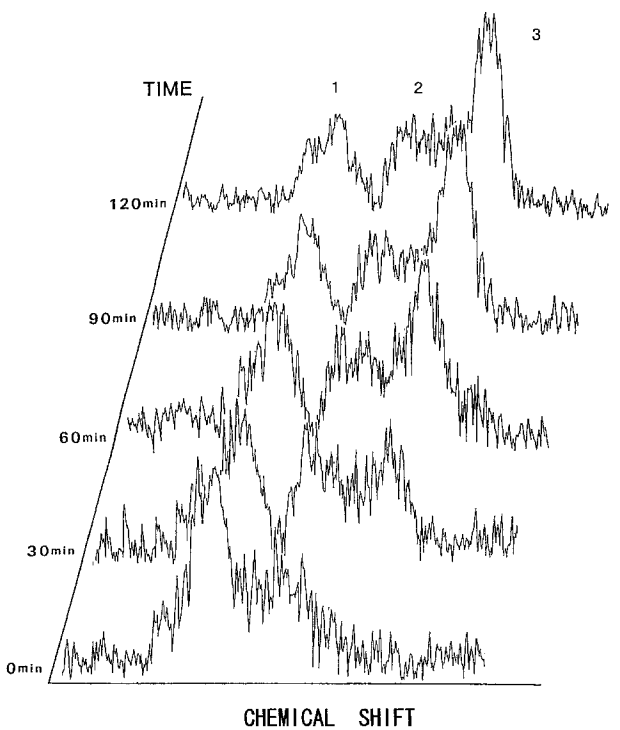

Fig 2. Representative stack plots of 5 consecutive ^{19}F-MR spectra in the liver after intravenous injection of 3FDG 250 mg/kg. Spectra at −26.1, −31.0, and −40.2 ppm represent the β and α anomers of 3FDG and 3FGA, respectively.

Plasma ^{19}F-MRS Measurement

Plasma 3FDG intensity increased to 0.382 mV · ppm · mL^{-1} 15 minutes after 3FDG injection and decreased to an undetectable range 30 minutes later. During 3FDG infusion, plasma 3FDG could not be measured for 120 minutes.

DISCUSSION

The present findings demonstrate that muscle contraction increases the accumulation of the glucose analog 3FDG, not only in the contracted muscle but also in the liver. Similar to D-glucose, 3FDG is readily transported by a sodium ion–

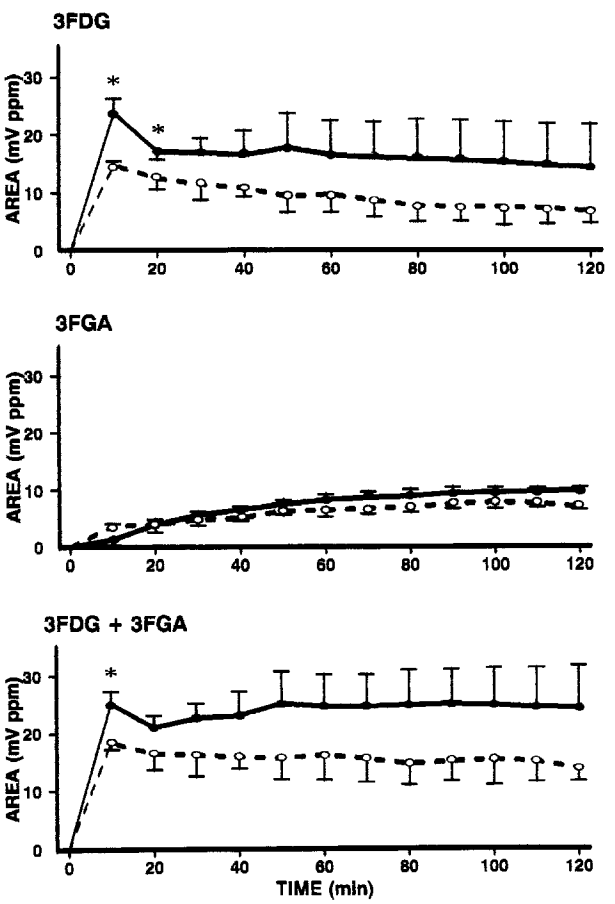

Fig 3. Time course of signal intensity of 3FDG and 3FGA in the liver of rabbits with (●) and muscle contraction (○) without after intravenous injection of 3FDG 250 mg/kg. Values are the mean ± SEM (n = 5). *$P < .05$, with *v* without muscle contraction.

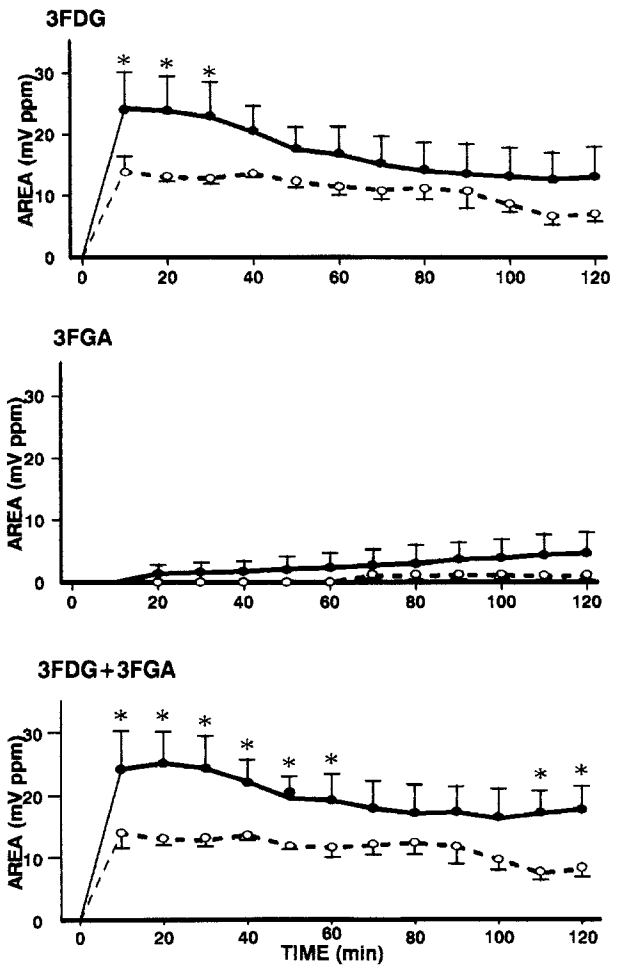

Fig 4. Time course of signal intensity of 3FDG and 3FGA in the muscle of rabbits with (●) and muscle contraction (○) without after intravenous injection of 3FDG 250 mg/kg. Values are the mean ± SEM (n = 5). *$P < .05$, with *v* without muscle contraction.

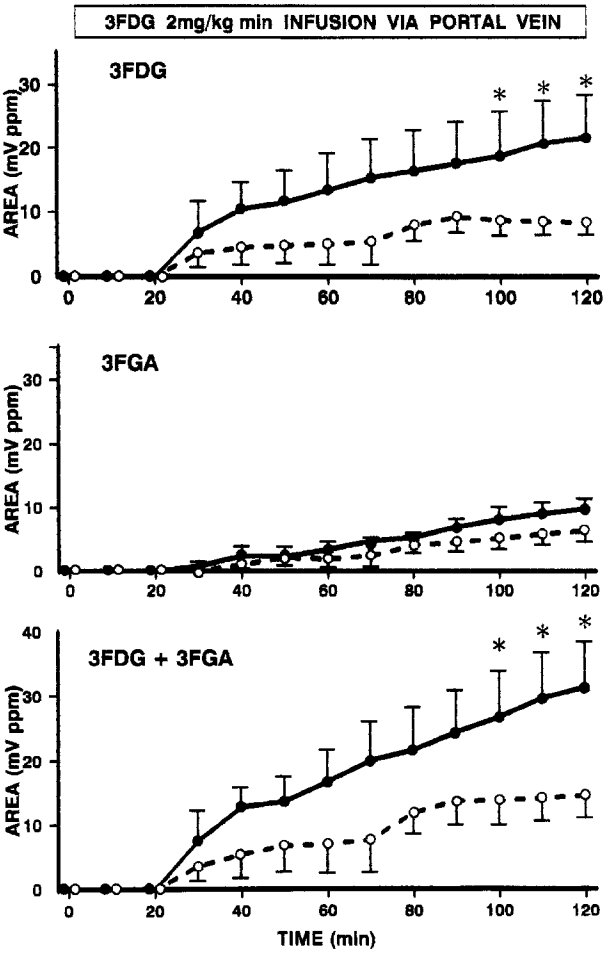

Fig 6. Time course of signal intensity of 3FDG and 3FGA in the muscle of rabbits with (●) and muscle contraction (○) without during intraportal infusion of 3FDG 2 mg · kg^{-1} · min^{-1} for 120 minutes. Values are the mean ± SEM (n = 5). *$P < .05$, with *v* without muscle contraction.

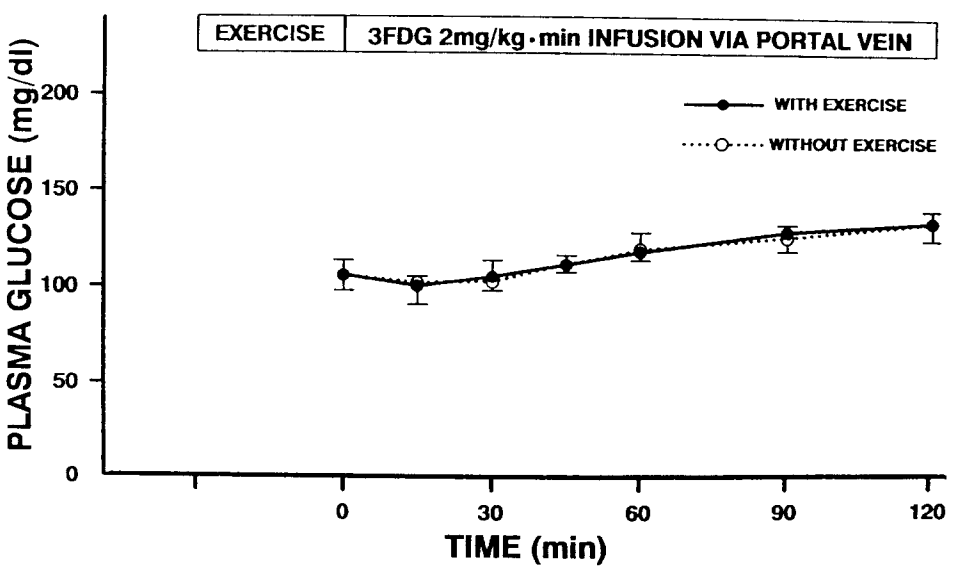

Fig 5. Plasma glucose (mg/dL) in rabbits with and without muscle contraction during intraportal infusion of 3FDG 2 mg · kg^{-1} · min^{-1} for 120 minutes. Values are means ± SEM (n = 5).

dependent active transport system in hamster intestine[9] and by the facilitated systems in human erythrocytes,[10,11] rat adipocytes,[12] and rat brain.[13] 3FDG competes with glucose for transport into heart cells[14] and rat synaptosomes.[13] Moreover, 3FDG uptake is inhibited by the glucose transport inhibitor cytochalasin B and/or phloretine in human erythrocytes[15] and rat brain.[13] Facilitative glucose transport is mediated by a family of membrane proteins, the glucose transporters. Their isoforms are considered to recognize substrates in a similar manner but with different affinities for sugar.[16] Therefore, 3FDG, which is transported into human erythrocytes with a K_i and Vmax similar to those of D-glucose,[10,11] may be extracted by muscle cells and hepatocytes via the glucose transporter.

In contrast to its transport property, 3FDG is a poor substrate for the hexokinase reaction[17] and subsequent metabolic pathways such as glycolysis,[11] glycogen synthesis,[18] and the pentose phosphate shunt.[11] Although some conflicting reports have shown the phosphorylation of 3FDG in rat heart[14] and brain,[13] the major enzymes in 3FDG catabolism may be aldose reductase and glucose dehydrogenase. 3FDG is converted to 3-fluoro-3-deoxy-D-sorbitol (3FDSL) by aldose reductase and 3FDSL is metabolized to 3-fluoro-3-deoxy-D-fructose in rat brain,[5] lens,[6] and testes.[7] 3FDG is oxidized to 3FGA by glucose dehydrogenase in rabbit liver and kidney cortex.[4] 3FGA is metabolized to 3FGA-6-phosphate by gluconokinase in rabbit liver.[4] Our study showed that oxidation is also a major metabolic pathway of 3FDG in rabbit muscle. The physiological significance of glucose dehydrogenase is not clear, but this enzyme is considered to work in hyperglycemia because of its high K_m (31 mmol/L).[19] This may be why in our experiments glucose dehydrogenase activity was low and 3FGA signal intensity did not differ regardless of whether the rabbits were subjected to muscle contraction.

To determine the contribution of blood 3FDG to the MR spectra, 20-mL blood samples were taken in a separate experiment and the MR spectra were measured. MR spectra of 3FDG could be distinguished 15 minutes after 3FDG injection. Although muscular blood flow increases and hepatic blood flow decreases during exercise, blood flow immediately reverses to resting levels after exercise.[2] Therefore, it is unlikely that 3FDG in the blood and a hemodynamic change in the blood flow contribute to an increase in 3FDG intensity in the liver and muscle 15 minutes after muscular contraction. To confirm the validity of in vivo muscular and hepatic ^{19}F-MRS, MR spectra obtained from the muscle and liver were compared with those from the isolated tissue samples after the experiment. The spectra for the intact organs were similar to those for the tissue samples (data not shown). Therefore, the signal intensity of 3FDG obtained from muscle and liver by ^{19}F-MRS was speculated to represent the disposal of 3FDG in these organs.

In the present study, to increase contractile activity of the muscle, 1 Hz of electrical stimulation was applied to a hindlimb for 30 minutes. Such muscular contraction has been reported to increase glucose transport[20] and decrease glycogen[20,21] and phosphocreatine (PCr)[21] in the contracted muscle. This muscular contraction was considered to be very mild, because the decrease of PCr was much smaller than observed during a 5-Hz electrical stimulation and the contraction was performed only for a hindlimb.

Glucose transport is the rate-limiting step of glucose utilization in skeletal muscle at rest[22] and after exercise.[23] Contractile activity can stimulate translocation of the glucose transporter GLUT-4 from an intracellular pool to the plasma membrane,[24] and enhances glucose uptake in the absence of insulin.[25] Increased glucose uptake induced by muscular contraction persists for several hours following exercise.[22] In the present study using ^{19}F-MRS, 3FDG uptake in muscle was shown to increase about twofold after muscle contraction. Two mechanisms were suggested to enhance muscular glucose uptake following exercise.[26] The first occurs independent of insulin until muscle glycogen stores are repleted to resting values. The other mechanism involves increased insulin sensitivity that enhances glycogenesis and leads to glycogen storage beyond the resting level. These mechanisms are both considered to be associated with the increased ability of muscle to synthesize glycogen following exercise.[23,27,28] Therefore, muscular glycogen depletion may enhance glucose uptake in muscle by an increased capacity to dispose of glucose via conversion to glycogen.

Moreover, we found that this type of mild exercise could enhance hepatic glucose disposal in rabbits for at least 2 hours during portal glucose analog infusion. Kawamori et al[29] demonstrated similar findings in non–insulin-dependent diabetic patients by using a euglycemic-hyperinsulinemic clamp combined with an oral glucose load. In the liver, the high-K_m facilitated glucose transporter (GLUT-2) and the glucose-phosphorylating enzyme, glucokinase, are key regulators of the rate of glucose metabolism. GLUT-2 is assumed to play a permissive role by allowing rapid equilibration of intracellular and extracellular glucose. Therefore, the hepatic level of 3FDG reflects the level in the hepatocyte and extracellular fluid. However, since the exercise-induced decrease of hepatic blood flow returns to the resting level immediately after exercise,[2] prior muscle contraction might enhance glucose disposal in the liver independently of hemodynamic change.

Wasserman et al[30] reported that in the postexercise period, the direct pathway (glucose → glucose-6-phosphate [G-6p] → glycogen) for hepatic glycogen deposition becomes active and the indirect pathway (gluconeogenic precursors → G-6P → glycogen) is relatively less important. Therefore, after exercise, circulating glucose is used directly to rebuild hepatic glycogen, and hepatic glucose uptake might be augmented by increased hepatic glucose utilization. To maintain glucose homeostasis during exercise, the sum of changes in glycogenolytic and gluconeogenic processes in the liver must be equivalent to the accelerated muscular glucose uptake. In the postexercise period, increased hepatic gluconeogenesis persists and glucose production decreases gradually.[30,31] Therefore, the net hepatic glucose balance might be in the output state. Under the present experimental conditions, since measurement of hepatic glucose uptake using arteriovenous glucose difference or tracer methods would have been interrupted by hepatic glucose production, we used ^{19}F-MRS with 3FDG as a metabolic probe to observe hepatic glucose disposal.

In contrast to our findings, several investigators have reported

that splanchnic glucose output increased after glucose feeding during the postexercise period in humans[32] and dogs.[33] Possible reasons for the disagreement are differences in the exercise intensity and the method. The intensity of exercise in the present study was very mild and performed only by a hindlimb, whereas it was of heavy or moderate intensity in the other studies. The ^{19}F-MRS procedure we used is a highly sensitive and direct method for determining hepatic glucose disposal.

In conclusion, ^{19}F-MRS allows for direct noninvasive measurement of 3FDG metabolism in rabbit muscle and liver. Disposal of the glucose analog determined by ^{19}F-MRS was augmented by muscular contraction in the liver and the contracted muscle. Our results suggest that the liver, as well as the muscle, acts as a glucose disposal organ after muscular contraction of a hindlimb.

ACKNOWLEDGMENT

The authors gratefully acknowledge the collaboration of Dr R. Morita and Dr A. Yoshikawa and the technical assistance of M. Kawakami.

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