Effect of Moderate Exercise Training on Peripheral Glucose Effectiveness, Insulin Sensitivity, and Endogenous Glucose Production in Healthy Humans Estimated by a Two-Compartment–Labeled Minimal Model

Yuichiro Nishida,[1] Kumpei Tokuyama,[2] Shoichiro Nagasaka,[3] Yasuki Higaki,[4] Yoko Shirai,[2] Akira Kiyonaga,[1] Munehiro Shindo,[1] Ikuyo Kusaka,[3] Tomoatsu Nakamura,[3] Shun Ishibashi,[3] and Hiroaki Tanaka[1]

For examining the effects of moderate exercise training on peripheral glucose effectiveness (S_g^2*), insulin sensitivity (S_i^2*), and endogenous glucose production (EGP), seven men and one woman (24.8 ± 1.8 years) participated in cycle ergometer training at lactate threshold intensity for 60 min/day, 5 days/week for 12 weeks. Stable-labeled frequently sampled intravenous glucose tolerance tests were performed before and 16 h and 1 week after the last training session. S_g^2* (pre $0.71 \pm 0.03 \times 10^{-2}$, 16 h $0.85 \pm 0.02 \times 10^{-2}$ dl · kg^{-1} · min^{-1}) and S_i^2* (pre $12.6 \pm 2.6 \times 10^{-4}$, 16 h $19.7 \pm 3.3 \times 10^{-4}$ dl · kg^{-1} · min^{-1} · [μU/ml]$^{-1}$), analyzed using the two-compartment minimal model, were significantly elevated 16 h after the last training session. The elevated S_g^2* remained higher despite the cessation of exercise training for 1 week ($1.00 \pm 0.03 \times 10^{-2}$ dl · kg^{-1} · min^{-1}). EGP was suppressed within 20 min after glucose bolus, and the suppression of EGP was followed by their overshoot. The time course of EGP during the intravenous glucose tolerance test remained similar after the training period. In conclusion, moderate exercise training at lactate threshold improves not only peripheral insulin sensitivity but also peripheral glucose effectiveness with no change in the effect of glucose and/or insulin to suppress EGP in healthy humans. *Diabetes* 53: 315–320, 2004

From the [1]Laboratory of Exercise Physiology, Faculty of Health and Sports Science, Fukuoka University, Fukuoka, Japan; the [2]Laboratory of Biochemistry of Exercise and Nutrition, Institute of Health and Sport Sciences, University of Tsukuba, Ibaraki, Japan; the [3]Division of Endocrinology and Metabolism, Department of Medicine, Jichi Medical School, Tochigi, Japan; and the [4]Department of Preventive Medicine, Saga Medical School, Saga, Japan.

Address correspondence and reprint requests to Hiroaki Tanaka, PhD, Laboratory of Exercise Physiology, Faculty of Health and Sports Science, Fukuoka University, 8-19-1 Nanakuma Jonan-Ku, Fukuoka 814-0180, Japan. E-mail: htanaka@fukuoka-u.ac.jp.

Received for publication 3 May 2003 and accepted in revised form 27 October 2003.

Y.N. is currently affiliated with the Molecular Endocrinology and Oncology Research Center, Laval University Medical Center (CHUL), St. Foy, Quebec, Canada.

EGP, endogenous glucose production; FSIGTT, frequently sampled intravenous glucose tolerance test; PCR, plasma clearance rate.

Glucose tolerance is determined by both insulin action and insulin-independent effects; the latter, called glucose effectiveness, represents the action of glucose itself to facilitate the glucose uptake and to suppress endogenous glucose production (EGP) (1). In normal individuals, ~50% of the glucose disposal during an oral glucose tolerance test is due to glucose effectiveness, not to the dynamic insulin response (2). As a result, glucose effectiveness is a component equal to or greater than insulin itself in determining glucose tolerance (2). Using a conventional minimal model, we previously reported that young distance runners and strength-trained men have a 76 and 30% higher glucose effectiveness (S_g) than that of control subjects, respectively (3,4). In addition, we recently showed that a 6-week mild exercise training improves both the S_g and insulin sensitivity (S_i) in healthy men (5). These studies suggest that exercise is one of the unique approaches that may help to increase S_g.

A recently proposed stable-labeled two-compartment minimal model enabled us to single out estimates of glucose uptake from the combined ability of insulin or glucose per se to stimulate glucose uptake and to suppress its own production. This model allowed us to obtain new indexes regarding both the peripheral-specific glucose effectiveness (S_g^2*) and insulin sensitivity (S_i^2*). Furthermore, the combination of a stable-labeled two-compartment minimal model and deconvolution provides a reliable profile of EGP (6–8). Using this new method, we recently found not only S_i^2* but also S_g^2* in exercise-trained middle-aged subjects to be significantly greater than those in sedentary subjects, and both the basal EGP and EGP overshoot during frequently sampled intravenous glucose tolerance tests (FSIGTTs) were also greater in exercise-trained men (9). However, this cross-sectional study has several limitations, including the possibility that exercise-trained men who can run a marathon within 3.5 h (9) may be genetically predisposed to have a higher S_g^2*. In addition, training intensity and/or duration, which induce such an increase in the S_g^2*, could not be elucidated in detail. We therefore decided to study effects of exercise training on S_g^2*, S_i^2*, and EGP in previously sedentary humans,

using the stable-labeled two-compartment minimal model. The present study showed for the first time that moderate exercise training improves not only S_i^{2*} but also S_g^{2*} with no change in the suppressive effect of glucose and/or insulin on EGP in healthy humans.

RESEARCH DESIGN AND METHODS

Seven men and one woman (19–33 years) who all were in good health and had not undergone any regular exercise for at least 2 years were examined. All individuals were free from diabetes, and none were taking any medications. All subjects were asked not to change their normal dietary habits and not to engage in any strenuous physical activity. Before the study was begun, the nature, purpose, and risks of the study were explained to all subjects and informed written consent was obtained. The protocol was approved by the local ethical committee of the Jichi Medical School and was conducted in accordance with the Helsinki Declaration.

Body composition and physical fitness. Each subject's percentage of fat was measured by hydrostatic weighing before training and 2 days after the last training session and was estimated on the basis of the hydrostatic density with a correction for the residual lung volume (10). For measuring physical fitness, the graded exercise test on a mechanically braked ergometer (Electric Bicycle Ergometer; Lode's Instrumenten, Groningen, Netherlands) was performed before training and 2 days after the last training session. The work rate was initially set at 10 W and thereafter was increased every 4 s by 1 W. The test was continued until subjective exhaustion was achieved. $V\mathrm{O}_2$ was measured from the mixed expired gas collected in neoprene bags. The volume of the expired gas was quantified with a twin-drum type respirometer (Fukuda Irika CR-20, Tokyo, Japan), and both the O_2 and CO_2 fractions were analyzed by a mass spectrometer (ARCO-1000; ARCO System, Chiba, Japan). Blood samples from an earlobe were obtained every 30 s to measure the blood lactate levels. The blood lactate concentration was plotted against the exercise workload for each subject, and the workload at the first breaking of lactate was used to calculate the exercise training intensity of each subject. The lactate threshold was determined for each subject on the basis of a visual inspection according to the estimations of three experts, who were blinded to the purpose of our study, and the average was used to establish the exercise intensity for training.

Exercise training program. Cycle ergometer training at the lactate threshold level (49.1 ± 2.8% $V\mathrm{O}_{2\mathrm{max}}$ for the first 6 weeks and 49.1 ± 2.2% $V\mathrm{O}_{2\mathrm{max}}$ for the last 6 weeks) was carried out for 60 min/day, five times/week for 12 weeks at our laboratory. Six weeks after starting the training program, each subject underwent a graded exercise test to readjust the training workload. The revised workloads were then used for the next 6 weeks (103.4 ± 5.1 W for the first 6 weeks and 111.0 ± 5.3 W for the last 6 weeks).

Oral glucose tolerance test and FSIGTT. Before starting the exercise training, all subjects were orally given 75 g of glucose after overnight fasting to confirm that they had a normal glucose tolerance according to the Japan Diabetes Society Criteria (11). FSIGTTs were performed before (pre) and both 16 h and 1 week after the last training session. In the morning between 0700 and 0900 after overnight fasting, the subjects were allowed to rest while lying down for at least 30 min before blood sampling commenced. Blood samples were obtained from an antecubital vein in one arm, which was kept in a radiant warmer at 70°C to provide an arterialized blood source. The baseline samples for glucose, insulin, and free fatty acid were obtained, and then glucose isotopically labeled with [6, 6-$^2H_2$]glucose (Aldrich, Milwaukee, WI) was administered in the contralateral antecubital vein (300 mg/kg body wt) within 1 min (9). Regular insulin (Humalin; Shionogi, Osaka, Japan) was infused (20 mU/kg) into an antecubital vein from 20 to 25 min after the glucose bolus. Blood samples for glucose and insulin were frequently obtained up to 180 min. On the day before undergoing the FSIGTT, all subjects were provided with an evening meal consisting of ≥140 g carbohydrate, ≥30 g fat, and ≥33 g protein. FSIGTTs for one female subject were performed at the same phase of her menstrual cycles before and after exercise training.

Biochemical and stable isotope tracer analysis. The plasma glucose levels were measured spectrophotometrically in triplicate using glucose oxidase (Glucose B-test; Wako Pure Chemical, Osaka, Japan). The immunoreactive insulin levels were measured in duplicate using a Phadeseph insulin radioimmunoassay kit (Shionogi, Osaka, Japan). The serum free fatty acid levels were assayed using the standard method (12). Deuterated glucose was analyzed as a penta-acetate derivative using the method by Wolfe (13) as previously described (14). The measurement error associated with the labeled glucose measurement was assumed to be independent, white, and Gaussian, with zero mean and coefficient of variation of 3.0%.

Calculations. The indexes of glucose effectiveness (S_g^{2*}) and insulin sensitivity (S_i^{2*}) specific for peripheral glucose uptake, and plasma clearance rate (PCR) were estimated by a two-compartment minimal model (6,8,15). The model is described in its uniquely identifiable parameterization by the following equation:

$$dq_1/dt = -[k_p + R_{d,0}/Q_1(t) + k_{21}]q_1(t) + k_{12}q_2(t)\ q_1\ (0) = d$$

$$dq_2/dt = k_{21}q_1(t) - [k_{02} + x(t) + k_{12}]q_2(t)\ q_2\ (0) = 0$$

$$dx/dt = -p_2[\,x(t) - s_k[I(t) - Ib]\}\ x(0) = 0$$

$$g(t) = q_1(t)/V_1$$

where q_1 and q_2 denote labeled glucose masses (mg/kg) in the first (accessible pool) and second (slowly equilibrating pool) compartment, respectively; x(t) is insulin action (min^{-1}), and Ib and I(t) are plasma insulin at the basal level and during the FSIGTT (μU/ml), respectively; $Q_1(t)$ is the glucose mass in the accessible pool (mg/kg), g(t) is the plasma labeled glucose concentration (mg/dl), and d is glucose dose (mg/kg); V_1 is the volume of the first compartment (dl/kg) and k_{21} (min^{-1}), k_{12} (min^{-1}), and k_{02} (min^{-1}) are parameters describing the glucose kinetics; and p_2 (min^{-1}) and s_k ($\mathrm{ml} \cdot \mu\mathrm{U}^{-1} \cdot \mathrm{min}^{-1}$) are parameters describing insulin action. The model structure assumes that insulin-independent glucose disposal takes place in the accessible pool and is the sum of two components, one constant and the other proportional to the glucose mass. $R_{d,0}$ ($\mathrm{mg} \cdot \mathrm{kg}^{-1} \cdot \mathrm{min}^{-1}$) is the constant component of glucose disposal, whereas k_p (min^{-1}) is the proportionality constant between glucose disposal from the accessible compartment and glucose mass in the same compartment. k_P and $R_{d,0}$ were assumed as follows according to a very recent improved version of two-compartment model (15):

$$k_P = 1.14\ k_{21}k_{02}/(k_{02} + k_{12})$$

$$R_{d,0}/Q_1(t) = 1.86\ k_{21}k_{02}Gb/(k_{02} + k_{12})/G(t)$$

where Gb is basal glucose concentration (mg/dl). S_i^{2*} and S_g^{2*} were defined as follows (6,8,15):

$$S_i^{2*} = V_1 s_k k_{21} k_{12}/(k_{02} + k_{12})^2$$

$$S_g^{2*} = V_1[k_p + k_{21}k_{02}/(k_{02} + k_{12})]$$

Given parameters of the two-compartment model and time course of $Q_1(t)$ [$= G(t)V_1$] and insulin, tracee equation described by two-compartment minimal model was solved in each subject to obtain glucose mass in the second compartment ($Q_2(t)$, mg/kg). The glucose disappearance rate [$R_d(t)$] from the accessible pool predicted by the model is determined using the tracer-tracee indistinguishability principle, and time-varying PCR was calculated as $R_d(t)/G(t)$:

$$R_d(t) = [kp + R_{d,0}/V_1G(t) + k_{21}]Q_1(t) - k_{12}Q_2(t),\ Q_2\ (0) = Gb\ V_1\ k_{21}/(k_{02} + k_{12})$$

The precision of parameter estimates (k_{21}, k_{12}, k_{02}, p_2, s_k, V_1) were 22% (range, 7–66%) for k_{21}, 14% (range, 4–31%) for k_{12}, 9% (range, 3–30%) for k_{02}, 13% (range, 6–22%) for p_2, 11% (range, 3–42%) for s_k, and 7% (range, 3–20%) for V_1, and these values were comparable to the previously published results (15). The data were analyzed using the SAAMII software package (SAAM Institute, Seattle, WA).

EGP was estimated by nonparametric deconvolution as previously described (6,14). Computer program for nonparametric deconvolution to estimate EGP was written in Pascal (Borland International, Scotts Valley, CA) on a Macintosh IIcx (Apple Computer, Cupertino, CA). In particular, source programs (ludcmp and lubksb) supplied by Press et al. (16) have been adapted to the particular situation of the nonparametric deconvolution.

The insulin area above the basal level between 0 and 20 min after the administration of glucose was calculated according to a previously described method (3). The glucose disappearance constant (K_G) was calculated as the slope of the least squares regression line related to the natural logarithm of the glucose concentration to the time that samples were drawn between 10 and 19 min after glucose load.

Statistics. All values are shown as the means ± SE. The analyses were performed using the Wilcoxon's signed-rank test. For detecting the effect of 12 weeks of training on body composition and physical fitness level, the data were compared before and after training. For detecting the impact of the 12 weeks of training on metabolic variables, the data were compared before training and 16 h after the last training session (primary end point). Additional comparisons (pre-exercise training versus 1 week: secondary end point) were also made only when a difference between the data before training and 16 h after the last training session was significant. $P < 0.05$ was considered to be statistically significant.

TABLE 1
Characteristics of the subjects

	Before training	After training
Age (years)	24.8 ± 1.8	
Height (cm)	172.5 ± 1.3	
Weight (kg)	68.5 ± 4.6	67.7 ± 4.4
BMI (kg/m^2)	22.9 ± 1.3	22.7 ± 1.2
Fat (%)	15.3 ± 2.1	14.6 ± 1.7
Fat mass (kg)	10.8 ± 1.9	10.1 ± 1.7
LBM (kg)	57.7 ± 3.2	57.7 ± 3.3
$V_{O_{2max}}$ (ml · kg^{-1} · min^{-1})	39.6 ± 2.7	43.8 ± 2.2*
LT-V_{O_2} (ml · kg^{-1} · min^{-1})	18.8 ± 1.1	19.9 ± 0.8
$V_{O_{2max}}$ (ml · kg LBM^{-1} · min^{-1})	47.7 ± 2.6	51.3 ± 1.7*
LT-V_{O_2} (ml · kg LBM^{-1} · min^{-1})	22.2 ± 1.2	23.6 ± 0.6

Data are the means ± SE. LT-V_{O_2}, V_{O_2} at lactate threshold. None of the presented means or SE (except age) included the data from one female subject because the normal ranges in these characteristics are different between men and women. This subject's initial BMI (<25 kg/m^2), percentage of fat (<30%), and $V_{O_{2max}}$ (>31 ml · kg^{-1} · min^{-1}) all were within the normal range for women. Statistical analyses were performed using the data of all subjects (seven men and one woman). *$P < 0.05$ vs. before training. LBM, lean body mass.

RESULTS

The 12-week exercise program produced a training effect as demonstrated by a 9.9% increase in $V_{O_{2max}}$ ($P < 0.05$; Table 1). The body weight, percentage of fat, fat mass, and lean body mass remained unchanged with the training (Table 1). The fasting (arterialized venous) glucose concentration did not significantly change after exercise training (Table 2). The fasting insulin concentrations 16 h after the last training session tended to be lower than the pretraining level ($P = 0.080$) but returned to the pretraining level 1 week after the training regimen was stopped. The K_G values were similar when evaluated before training and 16 h and 1 week after the training (Table 2, Fig. 1*A*). An integrated area of insulin during the first 10 min of the FSIGTT, as an index of first-phase insulin secretion, significantly decreased at both 16 h and 1 week after the training (Table 2, Fig. 1*B*).

The exercise training significantly increased the peripheral glucose effectiveness (S_g^2*) measured 16 h after the last training session (Table 2). The elevated S_g^2* after the training remained higher than the pretraining level regardless of detraining for 1 week. The insulin sensitivity (S_i^2*) increased significantly 16 h after the last training session but returned to the pretraining level 1 week after the training regimen was stopped. The time course of exogenous and endogenous glucose concentrations during FSIGTT before and after (16 h and 1 week) training is shown in Fig. 1*C* and *D*. The PCRs increased immediately after glucose infusion and several minutes after insulin infusion before and 16 h and 1 week after training, and the PCRs after the 12-week training (both 16 h and 1 week after the training) were greater than those of before training throughout FSIGTT (Fig. 1*E*).

The averages of basal EGP increased after the training, although the increase was not statistically significant (Table 2). The EGP was similarly suppressed within 20 min, and the differences in the EGP between the basal level and the bottom did not change after the training regimen (pre 0.91 ± 0.10, 16 h 0.94 ± 0.10, and 1 week 1.22 ± 0.10 mg · kg^{-1} · min^{-1}, respectively; NS; Fig. 1*F*).

TABLE 2
Metabolic parameters before (pre) and after (16 h and 1 week) the exercise training

	Pre	16 h	1 week
n	8	8	8
Basal glucose (mg/dl)	97.4 ± 3.5	95.2 ± 1.7	97.2 ± 2.3
Basal insulin (μU/ml)	5.5 ± 1.0	4.5 ± 0.7	5.9 ± 0.8
Basal FFA (mEQ/l)	0.38 ± 0.08	0.57 ± 0.05	0.46 ± 0.06
K_G (% min^{-1})	2.30 ± 0.20	1.87 ± 0.27	2.09 ± 0.19
Insulin area (μU · ml^{-1} · min) 0–10 min	490 ± 107	282 ± 76*	364 ± 63*
Insulin area (μU · ml^{-1} · min) 0–20 min	745 ± 157	409 ± 115*	542 ± 91
S_g^2 (× 10^{-2} dl · kg^{-1} · min^{-1})	0.71 ± 0.03	0.85 ± 0.02*	1.00 ± 0.03*
S_i^2 (× 10^{-4} dl · kg^{-1} · min^{-1}) [μU/ml]$^{-1}$)	12.6 ± 2.6	19.7 ± 3.3*	14.2 ± 3.3
Basal EGP (mg · kg^{-1} · min^{-1})	1.30 ± 0.10	1.50 ± 0.04	1.81 ± 0.06
Basal PCR (ml · kg^{-1} · min^{-1})	1.32 ± 0.06	1.58 ± 0.05*	1.87 ± 0.05*

Values are the means ± SE. FFA, free fatty acids. *$P < 0.05$ vs. before training.

The suppression of EGP was followed by their overshoot, and the EGP overshoot remained unchanged after training (peak EGP: pre 1.68 ± 0.14, 16 h 1.89 ± 0.16, and 1 week 1.97 ± 0.13 mg · kg^{-1} · min^{-1}, respectively; NS; Fig. 1*F*). The difference in the EGP between the peak and the bottom also did not change after the training (pre 1.29 ± 0.15, 16 h 1.33 ± 0.12, and 1 week 1.38 ± 0.10 mg · kg^{-1} · min^{-1}, respectively; NS). S_g^2*, S_i^2*, and EGP corrected for lean body mass displayed similar results to the data corrected for body weight (data not shown).

The estimated parameters of the two-compartment minimal model are summarized in Table 3. A volume of glucose distribution in the first pool (V_1) significantly increased after the training. The model incorporated mixing parameters (k_{21} and k_{12}) between the glucose pools (q_1 and q_2) and did not change after the training. k_{02} and k_p tended to increase after 1 week of detraining, although the increase was not statistically significant ($P = 0.069$ and $P = 0.093$, respectively). A parameter s_k also tended to increase 16 h after the training ($P = 0.093$), but it returned to the basal level after 1 week of detraining, whereas another parameter, p_2, remained unchanged after the training (Table 3).

DISCUSSION

The main finding of the present study is that the 12-week exercise training at the lactate threshold significantly increased both the peripheral glucose effectiveness (S_g^2*) and insulin sensitivity (S_i^2*), which were derived by a two-compartment–labeled minimal model. These results suggest that moderate exercise training improves not only insulin-dependent glucose uptake but also insulin-independent (glucose-dependent) glucose uptake in healthy humans. Although the effect of exercise training on insulin sensitivity has been well documented using the glucose clamp method (17), only one previous study, which was

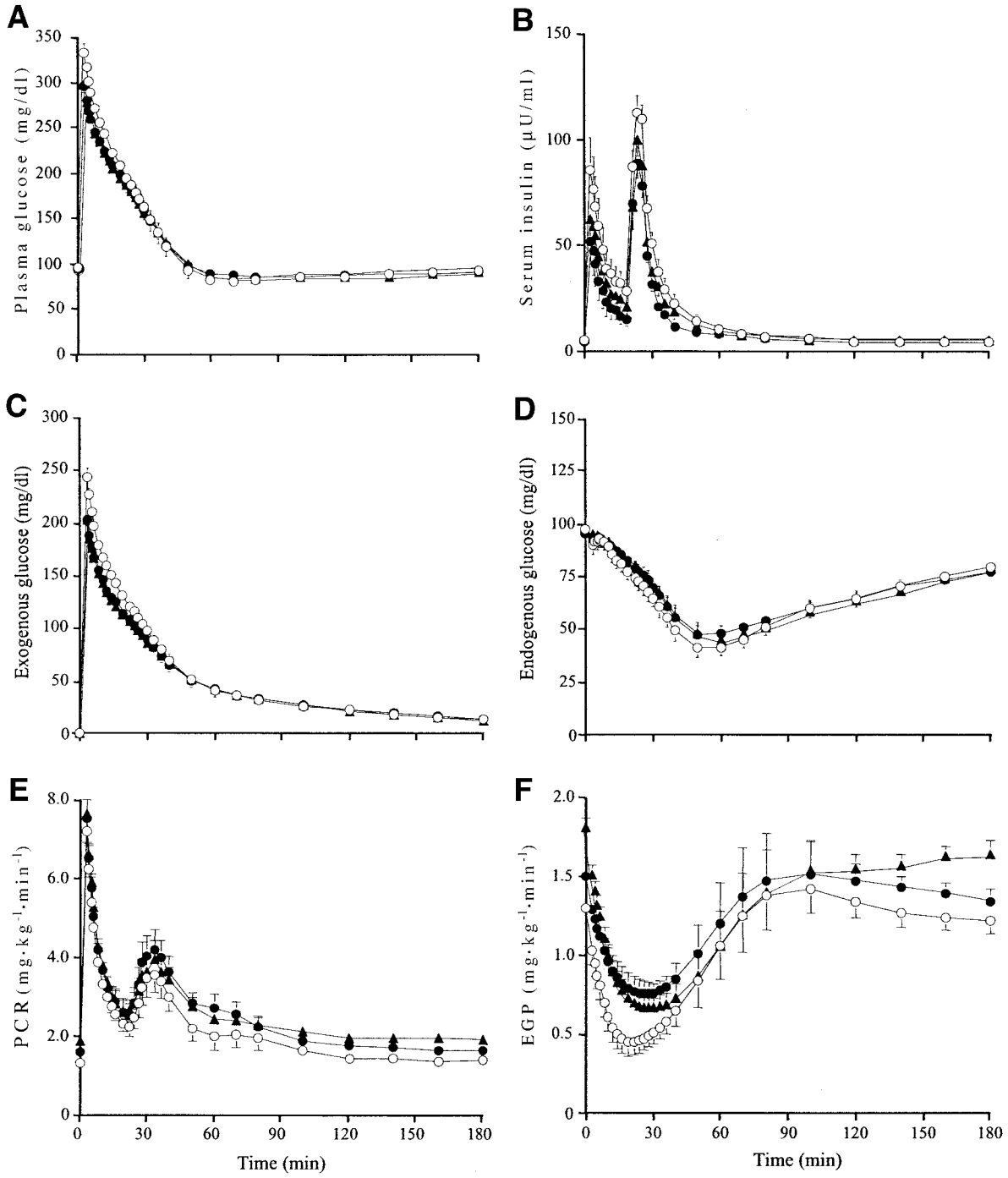

FIG. 1. The time course of plasma glucose concentration (*A*), insulin concentration (*B*), exogenous glucose concentration (*C*), endogenous glucose concentration (*D*), PCR (*E*), and EGP (*F*) during the FSIGTT before (○) and at 16 h (●) and 1 week (▲) after the 12-week exercise training. Values are the means ± SE.

conducted by us, reported the effect of exercise training on S_g^{2*} and EGP in men (9). This cross-sectional study showed that exercise-trained men have a greater S_g^{2*} and EGP (9). The present longitudinal study provided the first evidence that a 12-week moderate exercise training program improves the S_g^{2*} with no change in the ability of glucose and/or insulin to suppress EGP in previously sedentary humans.

Hyperglycemia per se increases glucose utilization (18–20) and stimulates the disposal of glucose by oxidative and nonoxidative metabolism (21,22). An acute rise in the plasma glucose concentration has a marked effect of increasing the non–insulin-dependent glucose uptake in human skeletal muscles (23). In a rodent study, stimulation of myotubes with glucose was also shown to induce an approximately twofold increase of the GLUT4 content in the plasma membrane independent of insulin, providing first evidence that glucose per se activates the specific glucose transporter proteins (24). In addition, a recent study reported that glucose, independent of insulin, does in fact increase GLUT4 translocation/glucose transport in skeletal muscle and adipose tissues through the activation

TABLE 3
Estimated parameters of the two-compartment minimal model before (pre) and after (16 h and 1 week) the training

	Pre	16 h	1 week
V_1 (dt/kg)	0.90 ± 0.04	1.13 ± 0.06*	1.13 ± 0.05*
k_{21} (min^{-1})	0.1269 ± 0.0095	0.1083 ± 0.0136	0.1062 ± 0.0093
k_{12} (min^{-1})	0.1387 ± 0.0186	0.1242 ± 0.0117	0.1212 ± 0.0085
k_{02} (min^{-1})	0.00411 ± 0.00032	0.00444 ± 0.00051	0.00500 ± 0.00024
p_2 (min^{-1})	0.091 ± 0.015	0.088 ± 0.009	0.093 ± 0.007
s_k ($ml \cdot \mu U^{-1} \cdot min^{-1}$)	0.00167 ± 0.00038	0.00244 ± 0.00061	0.00164 ± 0.00044
k_p (min^{-1})	0.0042 ± 0.0002	0.0041 ± 0.0002	0.0048 ± 0.0003

Values are the means ± SE. V_1, volume of the first compartment; k_{21}, k_{12}, and K_{02}, glucose kinetic parameters; p_2 and s_k parameters describing insulin action; k_p, proportional effect of glucose mass in the first compartment on glucose disposal from the same compartment. *$P < 0.05$ vs. before training.

of protein kinase C-ζ/λ (25). Because longitudinal studies show that exercise training increases skeletal muscle GLUT4 protein content in healthy humans (26,27), it is possible that a training-induced increase in GLUT4 protein in skeletal muscle could be one of the mechanisms for the enhanced S_g^{2}* after the training. Another glucose transporter, GLUT1, which is located in the cell sarcolemma of skeletal muscle, transports glucose independent of insulin (28). Endurance exercise training (60% $V\text{O}_{2\text{max}}$ for 4 weeks) was shown to induce an increase in the skeletal muscle GLUT1 protein content in humans (27). Therefore, it is also possible that an enhanced S_g^{2}* after the training regimen could be due in part to a training-induced increase in the GLUT1 content in skeletal muscle.

Our result that an elevated S_i^{2}* 16 h after exercise training returned to the basal level after 1 week of detraining, which was estimated by the two-compartment minimal model, was consistent with the results of several human studies using the glucose clamp method, which showed that the increased insulin action as a result of exercise training disappears after 7–10 days of detraining (29,30). Conversely, the S_g^{2}* remained elevated after 1 week of detraining. The GLUT4 content in the muscle of endurance-trained runners remained elevated regardless of detraining for 14 days (31). In addition, an elevated mitochondrial ATP production rate as an index of individual mitochondrial enzymatic activities in human skeletal muscle after 6 weeks of endurance training remained 37–70% above pretraining levels after longer periods (3 weeks) of detraining (32). The persistent increase in S_g^{2}* after 1 week of detraining may be associated with the increased GLUT4 content and/or mitochondrial enzymatic activities in skeletal muscle, but these possibilities all require further investigation.

A single bout of exercise is also known to increase S_g in men (33). In contrast to the effects of chronic exercise training on the S_g^{2}*, as shown in the present study, an increase in the glucose effectiveness after an acute bout of exercise could rapidly disappear within at most several hours (34–36), whereas an increase in insulin sensitivity can last for several days (37). Further study is needed to elucidate the precise and detailed mechanisms responsible for alterations in glucose effectiveness after chronic exercise training and an acute bout of exercise.

We have previously shown that improvements in the S_g^{2}* and S_i^{2}* are associated with an increased basal EGP and an enhanced EGP overshoot in exercise-trained middle-aged men (9). The increase in basal EGP and EGP overshoot in exercise-trained men seemed to be an adaptation to compensate for their high insulin-dependent and -independent peripheral glucose uptake to prevent hypoglycemia (9). In this study, we observed a significant increase in the indexes for glucose uptake, but the change in the basal EGP and EGP overshoot after 12-week training did not reach statistical significance. The differences observed in the EGP between these two studies may be associated with the difference in the indexes for the glucose uptake observed in the trained men (9) and in our participants in this study. The levels of S_g^{2}* after this training regimen (16 h 0.85×10^{-2} and 1 week 1.00×10^{-2} $dl \cdot kg^{-1} \cdot min^{-1}$, respectively) were similar to those of exercise-trained men, which were measured 48 h after the last training session (0.81×10^{-2} $dl \cdot kg^{-1} \cdot min^{-1}$). However, the levels of S_i^{2}* after the training (16 h 19.7×10^{-4} and 1 week 14.2×10^{-4} $dl \cdot kg^{-1} \cdot min^{-1} \cdot [\mu U/ml]^{-1}$, respectively) were far lower than those of trained men (24.6×10^{-4} $dl \cdot kg^{-1} \cdot min^{-1} \cdot [\mu U/ml]^{-1}$). As a result, the increase in S_i^{2}* after this training may not be sufficient to induce a significant change in EGP. Another possible explanation for the difference in EGP between these two studies is the duration of exercise training—namely, 12 weeks in the present study versus 4–30 years in our previous study (9). An adaptation of the liver and/or kidney to the exercise training–induced increase in insulin-dependent and -independent peripheral glucose uptake could be achieved after a longer period of exercise training. In the present study, similar K_G and plasma total glucose profile were observed despite increased PCR after the exercise training. This may be explained by the persistently increased level of EGP throughout FSIGTT after the training (see Fig. 1*F*), although the increase was modest. Consistently, increased PCR and EGP but identical K_G and plasma total glucose profiles were clearly observed in exercise-trained men (9).

In conclusion, we found that a 12-week moderate exercise training program at the lactate threshold significantly increased the S_g^{2}* (both 16 h and 1 week after training cessation) and S_i^{2}* (16 h after training cessation), which were estimated by a two-compartment–labeled minimal model. These results suggest that moderate exercise training could enhance not only the peripheral insulin-dependent glucose uptake but also the peripheral insulin-independent glucose uptake with no change in the ability of glucose and/or insulin to suppress EGP in healthy humans.

ACKNOWLEDGMENTS

This work was partially supported by grants from the Japanese Ministry of Education, Culture, Sports, Science, and Technology (10770574, 11480005, and 12671123), the Central Research Institute of Fukuoka University, Japan Diabetes Foundation, the Institute for Adult Disease Asahi Life Foundation, and the Jichi Medical School Young Investigator Award.

We thank all subjects who participated in this study. In addition, we thank the Department of Pharmacy of Jichi Medical School for compounding the sterile-labeled glucose solutions.

REFERENCES

1. Ader M, Pacini G, Yang YJ, Bergman RN: Importance of glucose per se to intravenous glucose tolerance: comparison of the minimal-model prediction with direct measurements. *Diabetes* 34:1092–1103, 1985
2. Best JD, Kahn SE, Ader M, Watanabe RM, Ni T-C, Bergman RN: Role of glucose effectiveness in the determination of glucose tolerance. *Diabetes Care* 19:1018–1030, 1996
3. Tokuyama K, Higaki Y, Fujitani J, Kiyonaga A, Tanaka H, Shindo M, Fukushima M, Nakai Y, Imura H, Nagata I, Taniguchi A: Intravenous glucose tolerance test-derived glucose effectiveness in physically trained humans. *Am J Physiol* 265:E298–E303, 1993
4. Fujitani J, Higaki Y, Kagawa T, Sakamoto M, Kiyonaga A, Shindo M, Taniguchi A, Nakai Y, Tokuyama K, Tanaka H: Intravenous glucose tolerance test-derived glucose effectiveness in strength-trained humans. *Metabolism* 47:1–5, 1998
5. Nishida Y, Higaki Y, Tokuyama K, Fujimi K, Kiyonaga A, Shindo M, Sato Y, Tanaka H: Effect of mild exercise training on glucose effectiveness in healthy men. *Diabetes Care* 24:1008–1013, 2001
6. Caumo A, Cobelli C: Hepatic glucose production during the labeled IVGTT: estimation by deconvolution with a new minimal model. *Am J Physiol* 264:E829–E841, 1993
7. Nicolao DG, Sparacino G, Cobelli C: Nonparametric input estimation in physiological system: problems, methods and case studies. *Automatica* 33:851–870, 1997
8. Vicini P, Caumo A, Cobelli C: The hot IVGTT two-compartment minimal model: index of glucose effectiveness and insulin sensitivity. *Am J Physiol* 273:E1024–E1032, 1997
9. Nishida Y, Tokuyama K, Nagasaka S, Higaki Y, Fujimi K, Kiyonaga A, Shindo M, Kusaka I, Nakamura T, Ishikawa S, Saito T, Nakamura O, Sato Y, Tanaka H: S_G, S_I, and EGP of exercise-trained middle-aged men estimated by a 2-compartment labeled minimal model. *Am J Physiol* 283:E809–E816, 2002
10. Goldman RF, Buskirk ER: A method for underwater weighing and the determination of body density. In *Techniques for Measuring Body Composition.* Brozek J, Hershel A, Eds. Washington, DC, National Research Council, 1961, p. 78–89
11. Kuzuya T, Nakagawa S, Satoh J, Kanazawa Y, Iwamoto Y, Kobayashi M, Nanjo K, Sasaki A, Seino Y, Ito C, Shima K, Nonaka K, Kadowaki T: Committee of the Japan Diabetes Society on the diagnostic criteria of diabetes mellitus: report of the committee on the classification and diagnostic criteria of diabetes mellitus. *Diabetes Res Clin Pract* 55:65–85, 2002
12. Sugo S, Matsumoto Y, Yamaoka T, Sakurabayashi I: Improved enzymatic method for determining free fatty acids in serum, with use of 3-octanoic acid. *Clin Chem* 36:163, 1990
13. Wolfe RR: *Radioactive and Stable-Isotope Tracers in Biomedicine: Principles and Practice of Kinetic Analysis.* New York, Wiley-Liss, 1992
14. Nagasaka S, Tokuyama K, Kusaka I, Hayashi H, Rokkaku K, Nakamura T, Kawakami A, Higashiyama M, Ishikawa S, Saito T: Endogenous glucose production and glucose effectiveness in type 2 diabetic subjects derived from stable-labeled minimal model approach. *Diabetes* 48:1054–1060, 1999
15. Toffolo G, Cobelli C: The hot IVGTT two-compartment minimal model: an improved version. *Am J Physiol* 284:E317–E321, 2003
16. Press WH, Flannery BP, Teukolsky SA, Vetterling WT: *Numeral Recipes in Pascal.* Cambridge, U.K., Cambridge University Press, 1989
17. Koivisto VA, Yki-Jarvinen H, DeFronzo RA: Physical training and insulin sensitivity. *Diabetes Metab Rev* 1:445–481, 1986
18. Best JD, Taborsky GJ Jr, Halter JB, Porte D Jr: Glucose disposal is not proportional to plasma glucose level in man. *Diabetes* 30:847–850, 1981
19. Verdonk CA, Rizza RA, Gerich JE: Effects of plasma glucose concentration on glucose utilization and glucose clearance in normal man. *Diabetes* 30:535–537, 1981
20. DeFronzo RA, Ferrannini E, Hendler R, Felig P, Wahren J: Regulation of splanchnic and peripheral glucose uptake by insulin and hyperglycemia in man. *Diabetes* 32:35–45, 1983
21. Yki-Jarvinen H, Bogardus C, Howard BV: Hyperglycemia stimulates carbohydrate oxidation in humans. *Am J Physiol* 253:E376–E382, 1987
22. Thorburn AW, Gumbiner B, Brechtel G, Henry RR: Effect of hyperinsulinemia and hyperglycemia on intracellular glucose and fat metabolism in healthy subjects. *Diabetes* 39:22–30, 1990
23. Baron AD, Brechtel G, Wallace P, Edelman SV: Rates and tissue sites of non-insulin- and insulin-mediated glucose uptake in humans. *Am J Physiol* 255:E769–E774, 1988
24. Galante P, Mosthaf L, Kellerer M, Berti L, Tippmer S, Bossenmaier B, Fujiwara T, Okuno A, Horikoshi H, Häring HU: Acute hyperglycemia provides an insulin-independent inducer for GLUT4 translocation in C_2C_{12} myotubes and rat skeletal muscle. *Diabetes* 44:646–651, 1995
25. Bandyopadhyay G, Sajan MP, Kanoh Y, Standaert ML, Quon MJ, Reed BC, Dikic I, Farese RV: Glucose activates protein kinase C-ζ/λ through proline-rich tyrosine kinase-2, extracellular signal-regulated kinase, and phospholipase D: a novel mechanism for activating glucose transporter translocation. *J Biol Chem* 276:35537–35545, 2001
26. Houmard JA, Shinebarger MH, Dolan PL, Leggett-Frazier N, Bruner RK, McCammon MR, Israel RG, Dohm GL: Exercise training increases GLUT-4 protein concentration in previously sedentary middle-aged men. *Am J Physiol* 264:E896–E901, 1993
27. Phillips SM, Han X-X, Green HJ, Bonen A: Increments in skeletal muscle GLUT-1 and GLUT-4 after endurance training in humans. *Am J Physiol* 270:E456–E462, 1996
28. Klip A, Paquet MR: Glucose transport and glucose transporters in muscle and their metabolic regulation. *Diabetes Care* 13:228–243, 1990
29. Burstein R, Polychronakos C, Toews CJ, MacDougall JD, Guyda HJ, Posner BI: Acute reversal of the enhanced insulin action in trained athletes: association with insulin receptor changes. *Diabetes* 34:756–760, 1985
30. King DS, Dalsky GP, Clutter WE, Young DA, Staten MA, Cryer PE, Holloszy JO: Effects of exercise and lack of exercise on insulin sensitivity and responsiveness. *J Appl Physiol* 64:1942–1946, 1988
31. Houmard JA, Hortobagyi T, Neufer PD, Johns RA, Fraser DD, Israel RG, Dohm GL: Training cessation does not alter GLUT-4 protein levels in human skeletal muscle. *J Appl Physiol* 74:776–781, 1993
32. Wibom R, Hultman E, Johansson M, Matherei K, Constantin-Teodosiu D, Schantz PG: Adaptation of mitochondrial ATP production in human skeletal muscle to endurance training and detraining. *J Appl Physiol* 73:2004–2010, 1992
33. Sakamoto M, Higaki Y, Nishida Y, Kiyonaga A, Shindo M, Tokuyama K, Tanaka H: Influence of mild exercise at the lactate threshold on glucose effectiveness. *J Appl Physiol* 87:2305–2310, 1999
34. Garetto LP, Richter EA, Goodman MN, Ruderman NB: Enhanced muscle glucose metabolism after exercise in the rat: the two phases. *Am J Physiol* 246:E471–E475, 1984
35. Pestell RG, Ward GM, Galvin P, Best JD, Alford FP: Impaired glucose tolerance after endurance exercise is associated with reduced insulin secretion rather than altered insulin sensitivity. *Metabolism* 42:277–282, 1993
36. Higaki Y, Kagawa T, Fujitani J, Kiyonaga A, Shindo M, Taniguchi A, Nakai Y, Tokuyama K, Suzuki M, Tanaka H: Effects of a single bout of exercise on glucose effectiveness. *J Appl Physiol* 80:754–759, 1996
37. Mikines KJ, Sonne B, Farrell PA, Tronier B, Galbo H: Effect of physical exercise on sensitivity and responsiveness to insulin in humans. *Am J Physiol* 254:E248–E259, 1988