SG, SI, and EGP of exercise-trained middle-aged men estimated by a two-compartment labeled minimal model

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OVERALL GLUCOSE TOLERANCE is determined by three major physiological factors: insulin secretion, insulin sensitivity (SI), and insulin-independent effect, namely glucose effectiveness (SG), which is the combined ability of glucose per se to stimulate its own uptake and suppress its own production (1). In normal individuals, ~50% of the glucose disposal during an oral glucose tolerance test (OGTT) is attributable to SG but not to insulin action, thus suggesting the importance of SG in determining glucose tolerance (1, 3). Using a minimal model, Welch et al. (50) showed that SG as well as SI decreased in type 2 diabetes mellitus. Moreover, our previous reports (11, 42, 43) demonstrated that SG decreased in Japanese type 2 diabetic patients as well as in subjects with impaired glucose tolerance and type 2 diabetic offspring. Furthermore, an epidemiological study reported that a reduced SI and reduced SG are both strong predictors of type 2 diabetes mellitus (26).

Several studies have investigated the effect of exercise training on SG. Kahn et al. (20) studied healthy elderly men (aged 60–82 yr) before and 6 mo after intensive exercise training and found no effects of exercise training on SG. In addition, no change in SG of middle-aged men after 14 wk of exercise training was observed by Houmard et al. (17). In contrast, we (13, 44) previously reported that young distance runners and strength-trained men have a 76 and 30% higher SG, respectively, than that of controls. Taken together, levels of physical training and/or aging might modify the effect of endurance training on SG. As mentioned above, the one-compartment minimal model has been...
widely used to assess both $S_G$ and $S_I$, whereas this classical method could not single out the estimates of glucose uptake alone from the combined ability of insulin or glucose per se to stimulate glucose uptake and suppress its own production. A recently proposed stable-labeled two-compartment minimal model provides new indexes of glucose uptake-specific glucose effectiveness ($S_G^{(4)}$) and insulin sensitivity ($S_I^{(4)}$). In addition, the combination of a stable-labeled two-compartment minimal model and deconvolution provides a reliable profile of endogenous glucose production (EGP) (7, 29, 30, 48, 49). Furthermore, limitations due to the under-modeling of glucose kinetics in the one-compartment minimal model, as pointed out by several lines of evidence, were overcome by the two-compartment minimal model (8, 9, 10, 12, 47). Because we are aware of no published reports that describe the effect of exercise training on not only the insulin-dependent glucose uptake but also on the insulin-independent glucose uptake and EGP, we decided to study well trained middle-aged people by use of the stable-labeled two-compartment minimal model. The present study shows for the first time that exercise-trained middle-aged men have a greater glucose uptake-specific $S_G$ and $S_I$, and these improvements were seen simultaneously with enhanced EGP.

**RESEARCH DESIGN AND METHODS**

**Subjects.** The characteristics of the subjects are presented in Table 1. Eleven exercise-trained middle-aged men who can run the marathon (42.195 km) within 3.5 h (recent best marathon record: 3.07 ± 0.09 h) were recruited for this study. They had trained for an average of 16.0 ± 2.8 yr (range 4–30 yr). They ran an average of 75.6 ± 8.7 km/wk. An additional 12 age-matched men, who were not engaged in any habitual exercise for ≥2 yr and whose body mass index (BMI) was <24 kg/m² (range 20.7–23.6), were enrolled for comparison with the exercise-trained men. The sedentary subjects were confirmed to be normally glucose tolerant. None of the subjects was taking any medications or supplements. Before this study began, 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 ethics committee of Jichi Medical School and was conducted in accordance with the Helsinki Declaration.

**Physical fitness in exercise-trained middle-aged men.** To measure physical fitness in exercise-trained middle-aged men, the graded exercise test on a treadmill was performed. The running speed was initially set at 140 m/min and thereafter was increased every 4 min by 20 m/min. At each undermaximum stage, the heart rate was measured during the last minute of the stage with a heart rate monitor (Polar Accurex Plus, Tokyo, Japan). When the heart rate reached 70% of the heart rate maximum expected for their age, the running speed was continuously increased every 1 min by 10 m/min until subjective exhaustion was achieved. Oxygen uptake ($V_{O2}$) 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 (Perkin-Elmer 1100, Norwalk, CT).

**Frequently sampled intravenous glucose tolerance test and OGTT.** On the day when a frequently sampled intravenous glucose tolerance test (FSIGTT) was performed, in the morning between 0700 and 0900 after overnight fasting, the subjects were allowed to rest while laying down for ≥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 (FFA) were obtained, and then glucose isotopically labeled with [6,6-$^2$H$_2$]glucose (Aldrich, Milwaukee, WI) was administered in the contralateral antecubital vein (300 mg/kg body wt) within 1 min (27). Regular insulin (Humulin; 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, insulin, and FFA 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 of carbohydrate, ≥30 g of fat, and ≥33 g of protein. The FSIGTTs on the exercise-trained men were performed 48 h after the last training session.

The sedentary subjects were orally given 75 g of glucose after overnight fasting to confirm them as being normally glucose tolerant. Blood samples were obtained before and 30, 60, 90, and 120 min after the load, and plasma glucose and serum insulin levels were both measured. All subjects were asked not to change their normal dietary habits and not to engage in any strenuous physical activity or hard exercise training for ≥1 wk before the FSIGTT and OGTT. The OGTT and FSIGTT were performed ≥7 days apart.

**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). The serum FFA levels were assayed using the standard method (41). Deuterated glucose was analyzed as a pentaacetate derivative by use of the method of Wolfe (53), as previously described (27). The measurement error associated with the labeled glucose measurement was assumed to be independent, white, and Gaussian, with a zero mean and a coefficient of variation of 3.0%.

**Calculations.** The indexes of glucose effectiveness ($S_G^{(4)}$) and insulin sensitivity ($S_I^{(4)}$) specific for glucose uptake were estimated by a two-compartment minimal model (7). The model is described in its uniquely identifiable parameterization by the following equations (46)

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

\[
\frac{dq_2}{dt} = -[k_{22} q_2(t) - k_{21} q_1(t) + k_{12} q_1(t)]q_2(0) = 0
\]

\[
\frac{dx}{dt} = -k_x x(t) + k_y [l(t) - lb]
\]

\[
x(0) = 0
\]

\[
g(t) = q_1(t)/V_l
\]

\[
k_p = 3k_{22} k_{29} (k_{29} + k_{12}) - R_{d,0}/V_j G_b
\]

where $q_1$ and $q_2$ denote labeled glucose masses (mg/kg) in the first (accessible pool) and second (slowly equilibrating pool)
The insulin area above the basal level between 0 and 20 min after the administration of glucose was calculated according to the previously described method (44). 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 from samples drawn between 10 and 19 min.

**Statistics.** All values are shown as means ± SE. To evaluate the differences between the exercise-trained middle-aged men and the control subjects, the data were analyzed by Mann-Whitney’s U-test. The significance of the relationship between variables was assessed by the Pearson correlation coefficient. A P value < 0.05 was considered to be statistically significant.

**RESULTS**

As indicated in Table 1, the trained and sedentary subjects differed significantly in body weight and BMI. The high-level maximal VO_2 (V_O2 max) of exercise-trained middle-aged men in the present study (52.1 ± 1.4 ml·kg⁻¹·min⁻¹), which corresponds to the previously reported V_O2 max in exercise-trained middle-aged men (54.4 ± 1.6 ml·kg⁻¹·min⁻¹) (17), provided evidence that they were all well trained. Although the basal glucose levels were similar in both groups, the basal serum insulin levels were lower in the exercise-trained middle-aged men than in the sedentary controls (Table 2). K_G values were similar in both groups (Table 2 and Fig. 1A). The integrated area of insulin during the first 20 min after glucose injection in the trained tended to be lower (P = 0.065) than that of sedentary men (Table 2 and Fig. 1B).

The volume of the glucose distribution in the first pool (V₁) was identical in untrained and trained subjects [sedentary vs. trained men: 1.10 ± 0.16 vs. 1.18 ± 0.22 dl/kg, not significant (NS)]. The model incorporated mixing parameters, i.e., k₂₁ and k₁₂, between the glucose pools (q₁ and q₂) were also similar between the two groups (k₂₁: 0.102 ± 0.012 vs. 0.114 ± 0.018 min⁻¹, NS; k₁₂: 0.117 ± 0.013 vs. 0.116 ± 0.013 min⁻¹, NS; respectively). Two param-

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**Table 2. Metabolic parameters of subjects**

<table>
<thead>
<tr>
<th></th>
<th>Sedentary</th>
<th>Trained</th>
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</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Basal glucose, mg/dl</td>
<td>98.8 ± 1.9</td>
<td>102.1 ± 2.1</td>
</tr>
<tr>
<td>Basal insulin, μU/ml</td>
<td>5.9 ± 0.6</td>
<td>3.4 ± 0.2*</td>
</tr>
<tr>
<td>Basal FFA, mEq/L</td>
<td>1.06 ± 0.28</td>
<td>0.27 ± 0.03*</td>
</tr>
<tr>
<td>K_G, % min⁻¹</td>
<td>1.8 ± 0.17</td>
<td>1.95 ± 0.20</td>
</tr>
<tr>
<td>Insulin area, μU·ml⁻¹·min⁻¹</td>
<td>318 ± 54</td>
<td>216 ± 53</td>
</tr>
<tr>
<td>(0-10 min)</td>
<td></td>
<td></td>
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<tr>
<td>Insulin area, μU·ml⁻¹·min⁻¹</td>
<td>513 ± 9.1</td>
<td>296 ± 69</td>
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<tr>
<td>(0-20 min)</td>
<td></td>
<td></td>
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<tr>
<td>SI_G, % 10², d/kg·min⁻¹·min⁻¹</td>
<td>0.60 ± 0.05</td>
<td>0.81 ± 0.08*</td>
</tr>
<tr>
<td>SI_P, % 10², d/kg·min⁻¹·min⁻¹</td>
<td>11.9 ± 2.4</td>
<td>24.6 ± 3.0*</td>
</tr>
<tr>
<td>Basal EGP, mg/kg·min⁻¹·min⁻¹</td>
<td>1.59 ± 0.05</td>
<td>1.82 ± 0.08*</td>
</tr>
<tr>
<td>Basal PCR, dl/min·kg⁻¹·min⁻¹</td>
<td>0.016 ± 0.001</td>
<td>0.024 ± 0.006</td>
</tr>
</tbody>
</table>

Values are means ± SE. FFA, free fatty acids; K_G, glucose disappearance constant; SI_G, glucose uptake-specific glucose effectiveness; SI_P, glucose uptake-specific insulin sensitivity; EGP, endogenous glucose production; PCR, plasma clearance rate. * P < 0.05 vs. sedentary controls.
eters concerning glucose disposal from the second compartment, $k_2$ and $k_{O_2}$, were similar between the sedentary and trained subjects ($k_2$: $0.124 \pm 0.012 \text{ vs. } 0.094 \pm 0.005 \text{ min}^{-1}, \text{NS}; k_{O_2}: 0.00464 \pm 0.00041 \text{ vs. } 0.00424 \pm 0.00027 \text{ min}^{-1}, \text{NS}$), whereas another parameter, $k_a$, was significantly greater in trained men than in sedentary men ($0.000157 \pm 0.000027 \text{ vs. } 0.000220 \pm 0.000023 \text{ ml} \cdot \text{U}^{-1} \cdot \text{min}^{-2}, P < 0.05$). The fractional parameters describing the insulin-independent glucose uptake, i.e., $k_p$, tended to be greater in trained men than in sedentary men ($0.00157 \pm 0.000027 \text{ vs. } 0.000220 \pm 0.000023 \text{ ml} \cdot \text{U}^{-1} \cdot \text{min}^{-2}, P < 0.05$). Tissue-specific glucose effectiveness ($S_{G^2}$) and insulin sensitivity ($S_{I^2}$) were significantly greater in the trained men (Table 2). PCR was obviously greater in the trained men than in the sedentary men throughout the FSIGTT, and it increased immediately after the glucose infusion and several minutes after insulin infusion (Fig. 1F).

The basal EGP in the trained men was significantly greater than that in the controls (Table 2 and Fig. 1F). A significant positive correlation between $S_{G^2}$ and the basal EGP was found ($r = 0.98, P < 0.01$; Fig. 2). The EGP of sedentary subjects and the exercise-trained men was similarly suppressed by $\sim 70\%$ within 10 min, followed by an additional suppression after insulin infusion (Fig. 1F). The EGP returned to the basal level at $\sim 60$ min in the trained men and at $100$ min in the controls, followed by its overshoot, which was significantly greater in the trained men than in the controls (sedentary vs. trained men, peak EGP: $1.81 \pm 0.10 \text{ vs. } 2.35 \pm 0.27 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}, P < 0.01$). The serum FFA concentrations during the FSIGTTs of trained subjects were lower than those of the sedentary subjects (Table 2 and Fig. 3). As shown in Fig. 3, FFA in the sedentary men began to recover at $70$ min and then returned to the basal level at $100$ min. On the other hand, FFA in the trained men began to recover at $40$ min and rapidly returned to the basal level at $140$ min and thereafter showed a clear overshoot at $180$ min.

A significant correlation between BMI and $S_{I^2}$ was observed ($r = 0.43, P < 0.05$), whereas the correlation between BMI and $S_{G^2}$ was not statistically significant ($r = 0.36, \text{NS}$).
DISCUSSION

Using the stable-labeled two-compartment minimal model, we found that glucose uptake-specific glucose effectiveness (SG2*), insulin sensitivity (SI2*), and PCR in exercise-trained middle-aged subjects were significantly greater than those of sedentary subjects. In addition, the basal EGP and EGP overshoot during FSIGTT were also greater in the trained men. These results suggest that trained middle-aged men demonstrated both enhanced insulin-dependent glucose uptake and insulin-independent glucose uptake to maintain glucose homeostasis.

An acute rise in plasma glucose concentration has a marked effect of increasing skeletal muscle non-insulin-dependent glucose uptake in healthy humans (2). In an animal study, acute hyperglycemia induced an approximately twofold increase in the skeletal muscle plasma membrane GLUT4 content independent of insulin, thus suggesting that glucose per se activates specific glucose transporter proteins (14). Middle-aged endurance-trained men have a 1.8-fold greater concentration of GLUT4 protein compared with sedentary controls (16). Likewise, Houmard et al. (17) reported that only a 14-wk physical training regimen increased the skeletal muscle GLUT4 protein concentration 1.8-fold in previously sedentary middle-aged men. On the basis of these reports, it is possible that a training-induced augmentation in GLUT4 protein concentration in skeletal muscle might be one of the reasons for the enhanced SG2* observed in the present study. A previous study reported GLUT1, a ubiquitous glucose transporter located in the cell sarcolemma and the perineurial sheaths within the skeletal muscle, transports glucose independently of insulin (25). An increased GLUT1 with exercise training has been observed in the rodent muscle (33). In addition, an increased expression of GLUT1 in human skeletal muscle after exercise training (60% VO2max for 1 mo) was also reported (31). It is therefore conceivable that GLUT1 may contribute to the greater SG2* in the exercise-trained middle-aged men.

Prolonged increases in FFA availability result in a marked impairment in the ability of insulin to promote skeletal muscle glucose transport and/or phosphorylation and also in the accumulation of end products of the hexosamine biosynthetic pathway (15). In addition, in the absence of insulin, FFA was able to reduce muscle glucose uptake in vitro (36). A sharp reduction in FFA levels increased the muscle non-insulin-mediated glucose uptake by 10%; conversely, an acute increase diminished the glucose uptake by 26% (32). These results suggest that FFA could inhibit non-insulin-mediated glucose uptake in human skeletal muscle. In this study, the FFA levels during FSIGTT in exercise-trained middle-aged men were far lower than in the sedentary controls (Fig. 3). A lower level of FFA could also explain the greater SG2* in these trained men.

The basal EGP level correlated with the fasting plasma glucose level and increased substantially in the type 2 diabetic patients who had a fasting plasma glucose >180 mg/dl (18). Surprisingly, the EGP in exercise-trained middle-aged men was also significantly greater compared with that of the untrained controls. Our result as estimated by the two-compartment minimal model was consistent with the results of previous human and animal studies that employed the model-independent method. By using the constant-rate tracer infusion technique, Kjaer et al. (24) showed that the basal EGP tended (P > 0.1) to be higher (15%) in trained than in sedentary men under similar basal glucose concentrations. Turcotte and Brooks (45) also showed that trained animals have a significantly higher basal EGP with the use of [14C]lactate and

![Fig. 2. Relationship between glucose uptake-specific glucose effectiveness (SG2*) and basal EGP in sedentary subjects (○) and exercise-trained middle-aged men (●) (r = 0.98, P < 0.01).](http://ajpendo.physiology.org/)

![Fig. 3. Time course of serum free fatty acid (FFA) concentration during FSIGTT for sedentary subjects (○; n = 12) and exercise-trained middle-aged men (●; n = 11). Values are means ± SE.](http://ajpendo.physiology.org/)
insulin infusion, namely at 10 insulin levels were maintained at the same levels by insulin concentration after exercise training. When the Segal et al. (39) observed an unchanged or decreased dent determinant of EGP in nondiabetic subjects (28). of the basal EGP to exercise training seems to be diabetes mellitus, after physical training. The response men, or even decreased EGP in patients with type 2 onstrated an unchanged EGP in both lean and obese of the basal glucose disappearance is noninsulin medi-
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[3H]glucose. On the other hand, Segal et al. (39) demonstrated an unchanged EGP in both lean and obese men, or even decreased EGP in patients with type 2 diabetes mellitus, after physical training. The response of the basal EGP to exercise training seems to be related to the difference in the basal insulin level, because basal insulin concentration was an independ-
ent determinant of EGP in nondiabetic subjects (28).

Segal et al. (39) observed an unchanged or decreased EGP level simultaneously with no change in the basal insulin concentration after exercise training. When the insulin levels were maintained at the same levels by insulin infusion, namely at 10 µU/ml, the basal EGP in physically trained subjects was lower than that in the sedentary controls (37). On the basis of these studies, the basal EGP may decrease if the basal insulin levels are maintained at the pretraining levels after training.

However, the fasting insulin levels in the exercise-trained middle-aged men who took part in our study were far lower than those of sedentary men (Table 2), thus suggesting that the basal insulin had less of a restraining effect on the basal EGP in trained subjects.

Another possible explanation for the greater basal EGP in our trained subjects might be enhanced gluconeogenesis. In rats, gluconeogenesis accounts for 50% of glucose production at basal conditions (38), and the rate of glucose synthesis from the labeled lactate in incubated liver slices declined with age; however, exercise training partially offsets this decline (34). In addition, training has also been reported to signifi-
cantly increase the activity of some enzymes involved in gluconeogenesis (19). Although in humans the rate of gluconeogenesis that accounts for basal glucose pro-
duction is lower (~20%) than in rats (40), the increased gluconeogenic capacity as a result of exercise training may, in part, contribute to the enhanced basal EGP in trained men.

The question arises as to whether or not EGP is geared to match glucose utilization. Eighty percent of the basal glucose disappearance is noninsulin mediated in healthy men (2), and insulin-independent glucose removal under basal conditions is assumed to be three times greater than insulin-dependent removal in the model that we used. As expected, we found a very strong positive correlation between $S_{Ω}^{*}$ and basal EGP; $S_{Ω}^{*}$ and basal EGP of the trained men were greater than those of sedentary controls. This relationship and comparison may suggest that trained men had a higher turnover rate of glucose under basal conditions through the higher insulin-independent glucose up-
take.

Another interesting finding of the present study is the significantly greater EGP overshoot observed in trained middle-aged men. The difference in the EGP overshoot between trained men and sedentary subjects may reflect the difference in the plasma glucose concen-
tration. The nadir of glucose levels during the FSIGTTs was deeper (trained men: $-25.4 \pm 2.8$ mg/dl; controls: $-20.8 \pm 3.0$ mg/dl compared with the basal glucose level) and was earlier (trained men: $68.2 \pm 4.2$ min; controls: $94.2 \pm 10.3$ min after glucose ingestion) in the trained men. Kjaer et al. (24) demonstrated that, during insulin-induced hypoglycemia, despite identical plasma glucose concentrations, epinephrine and growth hormone reached higher levels (98 and 52%, respectively) in the trained men than in the untrained controls. In this study, a deeper decline in the plasma glucose concentration may therefore elicit a greater counterregulatory hormonal response in trained middle-aged men. In addition, FFA in the sedentary men slowly returned to the basal level at the end of the FSIGTT, whereas FFA in the trained men rapidly returned to the basal level, and a clear overshoot was also observed at 180 min (Fig. 3). These results also imply a higher counterregulatory hormonal response in the trained men.

In this study, the endogenous insulin area above the basal insulin (0–20 min) in trained men tended to be smaller ($P < 0.1$) than that in sedentary men (Table 2). On the other hand, the exogenous insulin areas above insulin levels at 19 min (20–40 min) were similar between the two groups (sedentary vs. trained: $608 \pm 53 \text{ vs. } 561 \pm 50 \mu U \cdot \text{ml}^{-1} \cdot (\mu U / \text{ml})^{-1} \cdot \text{min}^{-1}, P = 0.44$, NS). We thus speculate that slightly reduced insulin area in response to glucose challenge in exercise-trained men was primarily due to changes in insulin secretion, consistent with previous reports (22, 23). It has generally been observed that insulin-sensitive sub-
jects secrete less insulin in response to glucose chal-
lenge (21). However, the detailed mechanisms for such an adaptation remain to be elucidated. At least one group of investigators (51, 52) has suggested that endurance training results in an enhanced clearance of insulin from plasma that accounts in part for the lower insulin area to glucose administration. Because we could not assess insulin clearance in the studied subjects directly, such a possibility cannot be fully ruled out.

In conclusion, using the two-compartment labeled min-
al model and deconvolution, we found that exercise-
trained middle-aged had a significantly greater $S_{Ω}^{*}$, $S_{Ω}$, basal EGP, and EGP overshoot than sedentary subjects had. These results suggest that not only insulin sensitivity but also glucose effectiveness specific for glucose up-
take were enhanced in exercise-trained middle-aged men. For keeping glucose homeostasis, their higher basal EGP and greater EGP overshoot appear to compensate well for the higher ability of the insulin-dependent and -independent glucose uptake.

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