Effect of Mild Exercise Training on Glucose Effectiveness in Healthy Men

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OBJECTIVE — To detect whether mild exercise training improves glucose effectiveness (SG), which is the ability of hyperglycemia to promote glucose disposal at basal insulin, in healthy men.

RESEARCH DESIGN AND METHODS — Eight healthy men (18–25 years of age) underwent ergometer training at lactate threshold (LT) intensity for 60 min/day for 5 days/week for 6 weeks. An insulin-modified intravenous glucose tolerance test was performed before as well as at 16 h and 1 week after the last training session. SG and insulin sensitivity (SI) were estimated using a minimal-model approach.

RESULTS — After the exercise training, V02max and V02 at LT increased by 5 and 34%, respectively (P < 0.05). The mild exercise training improves SG measured 16 h after the last training session, from 0.018 ± 0.002 to 0.024 ± 0.001 min⁻¹ (P < 0.05). The elevated SG after exercise training tends to be maintained regardless of detraining for 1 week (0.023 ± 0.002 min⁻¹, P = 0.09). SI measured at 16 h after the last training session significantly increased (pre-exercise training, 13.9 ± 2.2; 16 h, 18.3 ± 2.4, ×10⁻³ · min⁻¹ · pmol⁻¹, P < 0.05) and still remained elevated 1 week after stopping the training regimen (18.6 ± 2.2, ×10⁻³ · min⁻¹ · pmol⁻¹, P < 0.05).

CONCLUSIONS — Mild exercise training at LT improves SG in healthy men with no change in the body composition. Improving not only SI but also SG through mild exercise training is thus considered to be an effective method for preventing glucose intolerance.

Glucose effectiveness (SG), which is the ability of hyperglycemia to promote glucose disposal at basal insulin, is a component of importance equal to or greater than insulin itself when determining glucose tolerance (1,2). In normal individuals and in insulin-resistant obese individuals, ~50 and ~80%, respectively, of the glucose disposal during an oral glucose tolerance test is attributable to SG and not to the secreted insulin (2). Welch et al. (3) demonstrated that patients with type 2 diabetes have low SG as well as low insulin sensitivity (SI). Moreover, recent reports have shown that Japanese type 2 diabetic patients, offsprings with impaired glucose tolerance, and the type 2 diabetic offspring all have a decreased SG (4–6). These studies suggest that a reduction in SG is closely associated with an onset of type 2 diabetes. In addition, Martin et al. (7) demonstrated that a reduced SI and a reduced SG are both strong predictors of future type 2 diabetes. Improving SG could, therefore, be important for preventing type 2 diabetes.

Although the effect of exercise training on insulin action has been well documented (8,9), little is known about the effect of exercise training on SG. Kahn et al. (8) did the first longitudinal study that assessed the effect of physical training on SG. They studied healthy men (60–82 years of age) before and 6 months after intensive exercise training and found no effects of exercise training on SG (0.014 ± 0.001 vs. 0.015 ± 0.002 min⁻¹). No change in the SG of middle-aged men after 14 weeks of moderate to intensive exercise training (0.020 ± 0.002 vs. 0.023 ± 0.002 min⁻¹) was also observed by Houmard et al. (9). On the other hand, we previously reported that young distance runners have a 76% higher SG than that of the control subjects (10). Based on the findings of these studies, a beneficial effect of exercise on SG would be expected only in young subjects or in those who are in a very high physically trained state, such as distance runners. We recently demonstrated that mild exercise at the lactate threshold (LT) for 60 min is sufficient to increase SG in men immediately after the exercise (11). Of note, the increase in SG immediately after mild exercise is similar to the level in trained subjects. It is therefore of great interest to see whether the repetition of the exercise corresponding to the LT, which can be easily and safely performed, could therefore possibly lead to a long-term improvement in SG. We therefore investigated whether mild exercise training increases SG in healthy men. The present results suggest that mild exercise training improves not only SI but also SG in healthy men.

RESEARCH DESIGN AND METHODS

Subjects.
Eight healthy men (18–25 years of age) who had not performed any regular exercise for at least 2 years were examined. All
individuals were free of diabetes and none was taking any medications. None of the subjects were smokers. All subjects were asked not to change their normal dietary habits and not to engage in any strenuous physical activity. The study protocol was conducted in accordance with the Helsinki Declaration. Before beginning the study, the nature, purpose, and risks of the study were explained to all subjects, and informed written consent was obtained.

Body composition and physical fitness.
Each subject’s percent fat was measured by hydrostatic weighing before training and 2 days after the last training session and was estimated based on the hydrostatic density with a correction for the residual lung volume. To measure physical fitness, the graded exercise test on a mechanically braked ergometer (Electric Bicycle Ergometer; Lode’s Instrumenten B.V., Groningen, the 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 1 min by 15 W. The test was continued until submaximal exhaustion was achieved. VO₂ 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 O₂ and CO₂ fractions were analyzed by a mass spectrometer (Perkin-Elmer 1,100, Norwalk, CT). 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; the workload at the first breaking of lactate was used to calculate the exercise training intensity of each subject. The LT was determined for each subject based on the estimations of three experts, who were blinded to the purpose of our study, and was used to establish the exercise intensity for training.

Exercise training program.
Bicycle ergometer training at the LT level (the first 3 weeks, 42.3 ± 2.1% VO₂max; the latter 3 weeks, 54.2 ± 2.9% VO₂max) was carried out for 60 min/day, 5 times/week for 6 weeks at our laboratory. Three weeks after the training program started, each subject underwent a submaximal graded exercise test to readjust the training workload. The revised workloads were then used for the next 3 weeks. All participants completed the entire training protocol.

Intravenous glucose tolerance test.
Intravenous glucose tolerance tests (IVGTTs) were performed before (i.e., pre) and both 16 h and 1 week after the last training session. Because one subject caught a cold, an IVGTT after 1 week of detraining could not be performed on that subject. In the morning (between 0700 and 0900 h) after overnight fasting, the subjects were allowed to rest lying down for at least 30 min before blood sampling commenced. Blood samples were obtained from an antecubital vein in one arm that was kept in a radiant warmer at 70°C to provide an arterialized blood source. Baseline samples for glucose and insulin were obtained, and then glucose was administered in the contralateral antecubital vein (300 mg/kg body wt) within 2 min. Subsequent samples were obtained at frequent intervals until 180 min as previously described. Insulin (Humalin; Shionogi, Osaka, Japan) was infused (20 mU/kg) into an antecubital vein from 20 to 25 min after the administration of glucose. On the day before they underwent the IVGTT, all subjects were provided with an evening meal consisting of ≈140 g carbohydrate, ≈30 g fat, and ≈33 g protein.

Data analysis.
The incremental insulin between 0 and 20 min after the administration of glucose was calculated as the area under the curve using the trapezoidal rule. The glucose disappearance constant (KGl) 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. The S₁ and S₀ were estimated using a minimal-model approach (1–11). The S₁ index represents the increase in the net glucose disappearance rate, which, in turn, depends on the rise in insulin above the basal level. S₀ represents the effect of glucose per se, at basal insulin, to normalize its own concentration independent of the secreted insulin. The basal insulin component of (BIE) can be calculated as the product of basal insulin (Ib) and S₁ as follows: BIE = Ib · S₁. The contribution of the noninsulin-dependent component (St at zero insulin [GEZI]) is the difference between the total S₀ and the BIE: GEZI = S₀ − (Ib · S₁). The minimal-model program was written in Pascal (Borland International, Scotts Valley, CA) on a Macintosh IICx (Apple Computer, Cupertino, CA).

Analytical methods.
The plasma glucose levels were measured in triplicate spectrophotometrically 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).

Statistics.
All values are shown as means ± SEM. The analyses were performed using Wilcoxon’s signed-rank test. To detect the effect of 6 weeks of training on body composition and physical fitness level, the data were compared before and after training. To detect the impact of the 6 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 vs. 1 week; secondary endpoint were made only when a difference between the data before training and 16 h after the last training session was significant. A P value <0.05 was considered to be statistically significant.

RESULTS
Level of physical training and body composition.
The mild 6-week exercise program produced a training effect as demonstrated by a 5.5% increase in VO₂max from 41.6 ± 1.2 to 43.9 ± 1.2 ml · kg⁻¹ · min⁻¹ (P < 0.05). VO₂ at LT also increased by 34% (P < 0.05) with exercise training. The body weight and the relative percentage of body fat remained unchanged with exercise training (Table 1).

Fasting glucose and insulin levels.
Fasting (arterialized venous) glucose concentration was significantly lower at 16 h after the last training bout (90.5 ± 2.2 mg/dl, P < 0.05) than the pretraining level (94.9 ± 1.8 mg/dl) but not 1 week...
after stopping the training regimen (92.9 ± 2.1 mg/dl). The fasting insulin concentrations did not change after exercise training (pre, 28.6 ± 1.3; 16 h, 27.9 ± 3.5; 1 week, 30.2 ± 3.0 pmol/l).

$S_G$ and $S_I$.

The exercise training significantly increased the $S_G$ measured at 16 h after the last training session (pre, 0.018 ± 0.002; 16 h, 0.023 ± 0.001 min$^{-1}$, $P < 0.05$, Fig. 1). The elevated $S_G$ after the training tended to be higher than the pretraining level regardless of detraining for 1 week (0.023 ± 0.002 min$^{-1}$, $P = 0.09$, Fig. 1). Neither GEZI (pre, 0.014 ± 0.002; 16 h, 0.019 ± 0.001 min$^{-1}$) nor BIE (pre, 0.004 ± 0.001; 16 h, 0.005 ± 0.003 min$^{-1}$) changed after exercise training. $S_I$ measured at 16 h after the last training session significantly increased (pre, 13.9 ± 2.2; 16 h, 18.3 ± 2.4, ×10$^{-3}$ · min$^{-1}$ · pmol/l$^{-1}$, $P < 0.05$) and still remained elevated 1 week after stopping the training regimen (18.6 ± 2.2, ×10$^{-3}$ · min$^{-1}$ · pmol/l$^{-1}$, $P < 0.05$, Fig. 2). The $K_G$ remained unchanged (pre, 2.4 ± 0.2; 16 h, 2.3 ± 0.2%/min). The incremental insulin response during the first 20 min did not change after training (pre, 3,610 ± 727; 16 h, 3,022 ± 502; 1 week, 3,335 ± 570 pmol · l$^{-1}$ · min$^{-1}$).

**Table 1—Characteristics of subjects**

<table>
<thead>
<tr>
<th></th>
<th>Before training</th>
<th>After training</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>21.9 ± 0.8</td>
<td>—</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170.3 ± 1.1</td>
<td>—</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.4 ± 2.8</td>
<td>61.0 ± 2.8</td>
</tr>
<tr>
<td>Percent fat</td>
<td>12.7 ± 1.3</td>
<td>13.5 ± 1.4</td>
</tr>
<tr>
<td>$V_{O_{2max}}$ (ml · kg$^{-1}$ · min$^{-1}$)</td>
<td>41.6 ± 1.2</td>
<td>43.9 ± 1.2*</td>
</tr>
<tr>
<td>$V_{O_{2max}}$ (ml/min)</td>
<td>2551 ± 134</td>
<td>2677 ± 140*</td>
</tr>
<tr>
<td>LT-$V_{O_{2}}$ (ml · kg$^{-1}$ · min$^{-1}$)</td>
<td>17.7 ± 1.3</td>
<td>23.7 ± 1.1*</td>
</tr>
</tbody>
</table>

Data are means ± SEM. *$P > 0.05$ vs. before training. $LT-V_{O_{2}}$: $V_{O_{2}}$ at lactate threshold.

**CONCLUSIONS** — The main finding of the present study was that mild exercise training for 6 weeks improved $S_G$ in healthy young men. A longitudinal follow-up study showed that a high $S_G$ protected to some degree against the development of type 2 diabetes, whereas a low $S_G$ together with a low $S_I$ produced the greatest cumulative risk of developing the disease (7). Therefore, improving not only $S_I$ but also $S_G$ through mild exercise was thus, for the first time, found to have a preventative effect on glucose intolerance.

By measuring $S_G$ 16 h after the last training bout, we showed exercise training to have a sustained effect on $S_G$, and this effect was found to occur independently of the metabolic effect of a single bout of exercise. Brun et al. (13) observed an increase in $S_G$ 25 min after 15 min of intensive exercise, whereas no influence on $S_G$ 120 min after 2 h of intensive exercise was reported by Pestell et al. (14). We recently demonstrated that a single bout of mild exercise using the same regimen as that used in the present study increased $S_G$ 25 min after completing the exercise (11). However, improved $S_G$ immediately after the same mild exercise was not ob-

![Figure 1—Changes in $S_G$ with 6 weeks of mild exercise training. Three IVGTTs were performed before (pre, n = 8) and 16 h (n = 8) and 1 week (n = 7) after the last training session.](image-url)
served 11 h after exercise (15). Taken together, these findings indicated that the effect of a single bout of exercise on $S_G$ could thus rapidly decrease in a time-dependent manner.

The improved $S_I$ observed after our program correlated with previous findings using a minimal-model approach performed in middle-aged or older men in which endurance training resulted in a 36–62% increase in $S_I$ (8,9). However, neither of these studies observed any significant effect on $S_G$ (8,9). Kahn et al. (8) studied healthy older men (61–82 years of age) before and 60 h after intensive exercise training for 6 months and found no effects on $S_G$ (0.014 ± 0.001 vs. 0.015 ± 0.002 min$^{-1}$). In addition, Houmard et al. (9) found no change in $S_G$ in middle-aged men (40–65 years of age) 48 h after moderate to intensive exercise training for 14 weeks (0.020 ± 0.002 vs. 0.023 ± 0.002 min$^{-1}$). However, there are several possible explanations for the differences between their observations and ours.

First, the participants of their studies were much older than those in our study. Some studies demonstrated that glucose tolerance in older people does not significantly improve regardless of the duration or type of exercise training performed (8,16). These results suggest that aging per se may mask the effect of physical exercise on $S_G$.

A second possibility may also be due to differences in methodology. Whereas Houmard et al. (9) used venous blood sampling during IVGTT, we used arterialized venous sampling. Although many studies using a minimal-model technique used venous blood sampling (1–7), we believe arterialized sampling to be a more accurate method for measuring $S_G$. We recently assessed the effect of arterialized sampling on $S_G$ in one subject whose plasma glucose level from venous blood showed a distinctive blunt peak after the rapid injection of glucose throughout the three trials (17). As the arterialized venous blood was sampled, we observed the general response of the plasma glucose, which has a sharp peak immediately after the glucose challenge and an 1.8-fold increase in $S_G$ with no alteration in $S_I$ (17). Because the $S_G$ at least partly depends on the initial state of plasma glucose during the IVGTT, $S_G$ estimated from venous samples may be underestimated. Based on these findings, venous blood sampling may not be suitable for the accurate measurement of $S_G$.

Martin et al. (18) demonstrated that a prolonged infusion of epinephrine enhanced hepatic glucose production (HGP) and inhibited glucose uptake, thus resulting in a decreased $S_G$. Although Kahn et al. (8) reported that the catecholamine concentrations obtained in the morning did not change after exercise training, dynamic epinephrine secretion is thus speculated to be secreted in trained subjects a long time after undergoing the intensive exercise training (19). Third, the repetition of epinephrine exposure induced by intensive exercise, such as that reported in the study by Kahn et al., may therefore mask the effect of exercise training on $S_G$.

Finegood and Tzur (20) showed the minimal-model method to have an artifact that underestimates $S_G$, particularly when the insulin release decreases. Although Houmard et al. (9) did not show the results of integrated area of insulin after the glucose load, Kahn et al. (8) found a significant decrease in the acute insulin response to glucose after exercise.
determined by multiplying the fasting in-
1012
S
induced augmentation in these proteins
result, it is possible that a training-
program (60%

somewhat harder than that used in our
study (24). Phillips et al. (23) reported
intensive exercise training in an animal
study. Interestingly, mild exercise train-
ing increases the GLUT4 protein concen-
tration to the same extent as that of
GLUT1 in human skeletal muscle in-
creased after moderate
training. This is important because if the increase is
in GEZI (35%) was similar to that seen in
BIE (28%), GEZI, which accounts for
78% of S
G (22% of the remainder is BIE,
both before and after exercise), increased
after exercise in seven of eight subjects. As
a result, these data tend to show that most of
the change in S
G occurs in GEZI.

Skeletal muscle is the predominant
site of insulin-dependent and noninsulin-
dependent glucose disposal in humans
(21). Recently, Galante et al. (22) demonstrated
that acute hyperglycemia induced an
increase in the GLUT4 content in the
plasma membrane of skeletal muscle in-
dependent of insulin in vivo and in vitro.
Some studies have reported that physical
training increases the GLUT4 protein
concentration in human skeletal muscle
(9,23). Interestingly, mild exercise train-
ing increases the GLUT4 protein con-
tent to the same extent as that of
intensive exercise training in an animal
study (24). Phillips et al. (23) reported
that the expression of GLUT1 in human
skeletal muscle increased after moderate
exercise training—training that was
somewhat harder than that used in our
program (60% \(V_{\text{O2max}}\) for 1 month). As
a result, it is possible that a training-
induced augmentation in these proteins
in skeletal muscle is one of the reasons for
S
G to increase after mild exercise training.

S
G represents the effect of glucose on
the net glucose disappearance, i.e., the
total sum of glucose’s ability to enhance glu-
ose uptake and inhibit HGP. Ader et al.
(1) postulate that 54% of S
G could be ex-
plained by the effect of glucose on periph-
eral glucose uptake, whereas 46% results
from the glucose-mediated suppression of HGP. Unfortunately, our study was not
designed to distinguish between the abil-
ity of glucose per se to increase the pe-
ripheral glucose uptake and the ability of
that of glucose per se to suppress HGP.
Future studies will clarify whether improved S
G is attributable to the ability of glucose per
se to increase peripheral glucose uptake
and/or suppress HGP using a stable-
labeled minimal model.

The present results show, for the first
time, direct evidence that physical train-
ing induces an increase in S
G in previ-
ously sedentary men. Improving not only
S
G but also S
I through mild exercise train-
ing at LT is thus considered to be an
effective method for preventing glucose
intolerance.

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