Influence of mild exercise at the lactate threshold on glucose effectiveness

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Laboratory of Exercise Physiology, Faculty of Health and Sports Science, Fukuoka University, Fukuoka 814-0133; Department of Community Health Science, Saga Medical School, Saga 849-8501; and Laboratory of Biochemistry of Exercise and Nutrition, Institute of Health and Sport Sciences, University of Tsukuba, Tsukuba, Ibaraki 305, Japan

Sakamoto, Makoto, Yasuki Higaki, Yuichiro Nishida, Akira Kiyonaga, Munehiro Shindo, Kumpei Tokuyama, and Hiroaki Tanaka. Influence of mild exercise at the lactate threshold on glucose effectiveness. J. Appl. Physiol. 87(6): 2305–2310, 1999.—The effect of a single bout of mild exercise on glucose effectiveness (SG) and insulin sensitivity (SI) was studied in six young male subjects by using a minimal model. An intravenous glucose tolerance test was performed under two conditions as follows: 1) 25 min after a bout of exercise on a cycle ergometer at the lactate threshold level for 60 min (Ex) and 2) without any prior exercise (Con). Leg blood flow (LBF) was also measured by strain-gauge plethysmography simultaneously with blood sampling. SI did not significantly change after exercise (18.1 ± 1.5 vs. 17.7 ± 1.9 × 10⁻² min/PμM), whereas SG significantly increased (0.016 ± 0.002 vs. 0.025 ± 0.002 min⁻¹, P < 0.01). The increased blood flow after exercise remained high during the time period for measurement of the glucose disappearance constant and may be a determinant of SG. The incremental lactate area under the curve until insulin loading was also significantly higher in Ex than in Con (2.6 ± 0.9 vs. –3.5 ± 1.5 mM/min, P < 0.05). These results suggest that increased SG after mild exercise may be due, at least in part, to increased LBF and lactate production under a hyperglycemic state.

insulin sensitivity; minimal model; mild exercise

GLUCOSE EFFECTIVENESS (SG), which is analyzed by the minimal model technique, is defined as the effect of glucose per se to normalize its own concentration at basal insulin concentration and is a major determinant of glucose tolerance as well as insulin sensitivity (SI). A recent report on the minimal model suggested that decreased SG might be associated with the development of non-insulin-dependent diabetes mellitus (NIDDM) rather than decreased SI (35). Therefore, increasing SG may be very important because preservation of SG might serve to prevent the development of NIDDM.

Acute exercise is well known to transiently enhance SI in untrained subjects with or without diabetes (20, 30). As far as we know, three studies have studied SG after a single bout of exercise (11, 19, 32); however, the findings are not consistent. Pestel et al. (32) observed no change in SG 2 h after a strenuous ultramarathon run. We have recently reported no change in SG 11 h after mild, hard, and exhaustive exercise (19). On the other hand, Brun et al. (11) reported that SG and SI showed a marked increase 25 min after short-term exercise at 85% of maximal heart rate by using a reduced-sample protocol. A possible explanation for the discrepancies among these results may be the great variability among the exercise intensity, duration, and the time of the intravenous glucose tolerance test (IVGTT) or different methodologies.

Glucose uptake in the postexercise state may be influenced by the time of the IVGTT, because Ivy et al. (21) showed that glucose uptake immediately postexercise caused a 300% increase in the rate of glycogen storage above basal levels during the first 2 h of recovery and a 180% greater rate of storage above basal in the second 2 h of recovery. If the time of the IVGTT was set more immediately after exercise, even more mild-intensity exercise, such as at the lactate threshold level (LT), would be expected to improve glucose uptake, because several reports have suggested that low-intensity exercise as well as high-intensity exercise improves glucose tolerance (9, 10, 41). We therefore designed this study to determine whether LT-intensity exercise improves SG immediately postexercise.

METHODS

Subjects. Six male subjects participated in the present study after giving their informed consent. Subjects had no family history of diabetes or hypertension and were not insulin resistant on the basis of homeostasis model assessment (29). The mean homeostasis model assessment value was 0.81 ± 0.04 (range, 0.74–0.95). The subjects’ characteristics are summarized in Table 1. Body composition was measured by hydrostatic weighing, corrected for residual lung volume (15). The subjects were instructed to abstain from strenuous exercise until the end of the experiment.

Preliminary testing. Maximal oxygen consumption (V̇O₂max) was determined on an electrically braked cycle ergometer by using an incremental exercise protocol; after the subjects cycled at a steady work rate of 10 W for 4 min, the work rate continued and increased gradually by 20 W every 4 min until the subject was unable to continue. Blood samples from the earlobe were obtained just before the end of each stage to determine the blood LT (5, 19). The blood lactate concentrations were plotted against the workload. The LT as the initial break point for blood lactate was determined by visual inspection. The average of the LT determined blindly by three experts was used for exercise intensity.

Experimental design. Subjects consumed a meal containing 57% carbohydrate, 15% protein, and 28% fat calories at 6:00-
Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>22.7 ± 0.3</td>
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<tr>
<td>Height, cm</td>
<td>172.2 ± 2.3</td>
</tr>
<tr>
<td>WHR</td>
<td>0.81 ± 0.02</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>64.6 ± 1.4</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>21.8 ± 0.2</td>
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<tr>
<td>Body fat, %</td>
<td>11.9 ± 1.6</td>
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<tr>
<td>Maximal O₂ uptake, ml·kg⁻¹·min⁻¹</td>
<td>44.1 ± 1.5</td>
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Values are means ± SE; n = 6 subjects. WHR, waist-to-hip circumference ratio.

7:00 PM on the evening previous to each IVGTT. A 12- to 13-h fast was imposed on the subjects. They stayed at the laboratory one night before each IVGTT and woke at 7:00 AM. An 18-gauge catheter was placed in an antecubital vein in one arm for blood sampling, and a similar catheter was placed in the opposite arm for administration of intravenous solutions; patency of the catheters was maintained with an infusion of saline (40–50 ml/h) throughout the experiment. Leg blood patency of the catheters was maintained with an infusion of saline (40–50 ml/h) throughout the experiment. Leg blood flow (LBF) was measured for the resting state three times with an infusion of insulin (Humalin, Shionogi, Osaka, Japan) was administered (20 mU/kg) via the antecubital vein from 45 to 60 min after insulin injection (14). An additional infusion of insulin (Humalin, Shionogi, Osaka, Japan) was administered (20 mU/kg) via the antecubital vein from 45 to 50 min. Two IVGTTs were scheduled in a randomized design through chemiluminescence (Shimadzu CL-760, Kyoto, Japan). A mercury rubber strain gauge (Vasculab, Medasonics) was wrapped around the calf at the level of the widest circumference. The relative change in the volume of the calf segment under the strain gauge was registered on a chart recorder and was separated by at least 1 wk.

LBF. The knee joint was bent slightly, and supporting pillows were placed under the thigh and Achilles tendon. A mercury strain gauge was registered on a chart recorder and was used for calculations of plethysmographic blood flow according to the principle outlined by Whitney (39), including calibration. The occlusion cuff was placed around the thigh. The cuff pressure used was 50 mmHg. LBF was measured simultaneously with blood sampling during the IVGTT.

Analytic methods. Plasma glucose concentrations were measured in triplicate spectrophotometrically with glucose oxidase (glucose B test, Wako Pure Chemical, Osaka, J apan). The measurement error of glucose was assumed to be "white," with a Gaussian value of zero mean and a coefficient of variation of 1.5%. Immunoreactive insulin was measured in duplicate by using a Phadeseph insulin radioimmunoassay kit (Shionogi, Osaka, Japan). Coefficients of variation were 4% for >180 pM insulin and 7% for <180 pM insulin. Blood lactate was measured by flow-injection analysis with the use of immobilized enzyme (lactic oxidase) columns with detection by chemiluminescence (Shimadzu CL-760, Kyoto, J apan) (34). The coefficient of variation of this assay was within 2% of the established standard lactate solutions (1.0–10.0 mmol/l).

Data analysis. The glucose disappearance constant (K0) value was calculated as the slope of the least squares regression line relating the natural logarithm of the glucose concentration to time from five samples drawn between 10 and 19 min. Endogenous plasma lactate responses were expressed as the area under the insulin curve during the first 10 min, calculated by using the trapezoidal method (14). The area under the lactate curve was determined by using the trapezoidal method for 20 min before the insulin injection or the period after the insulin injection. S0 and Sc were estimated by the minimal model approach (6–8, 12, 35). In this analysis, fluctuations in circulating glucose levels over time are described by the following differential equations: dG(t)/dt = -p1[G(t) - Gb] - X(t)G(t) and dX(t)/dt = -p3X(t) + p2[I(t) - I0], where G(t) is the plasma glucose concentration, I(t) is the plasma insulin concentration, and Gb and I0 are baseline concentrations; p1, p2, and p3 are model parameters; and X(t) represents the time course of the peripheral insulin effects (expressed as min⁻¹). X(t) is increased by p3 in proportion to the change in plasma insulin above the basal level and decreases by a first-order process proportional by p2 to X(t) itself. Parameter p1 represents the effect of glucose per se, at basal insulin, to normalize its own concentration in plasma independent of increased insulin. This parameter, known as Sc, has been verified through comparison with studies in which the insulin secretory response in normal dogs was suppressed with somatostatin infusion (1) or in which insulin-dependent diabetes mellitus patients received basal insulin infusion during IVGTT (37). Sc is comprised of the following two components: a non-insulin-dependent component and a basal insulin component. The basal insulin component of Sc (BIE) can be calculated as the product of I0 and S0; BIE = I0 × S0 (24). Therefore, the contribution of the non-insulin-dependent component (S0 at 0 insulin, GEZI) is the difference between total Sc and BIE; GEZI = S0 - (I0 × S0) (24). The p2-to-p3 ratio defines the S0 index, which represents the increase in the net glucose disappearance rate dependent on a rise in insulin above basal. The S0 index has been validated by comparison with a direct measure of SI from glucose-clamp experiments in humans (4, 12). The minimal model program was written in Pascal (Borland, Scotts Valley, CA) on a Macintosh 11cx (Apple Computer, Cupertino, CA) as described previously (14, 35).

Statistics. Results are presented as means ± SE. Statistical comparison between control and exercise conditions was performed by Student’s t-test. P < 0.05 was considered significant.

RESULTS

Neither basal plasma glucose nor plasma insulin concentrations before IVGTT showed a significant difference between control and exercise conditions (Table 2). The plasma glucose, insulin, and lactate concentrations during IVGTT are illustrated in Fig. 1. The plasma glucose concentration is significantly lower in the exercise condition than in the control condition at 26, 28, 30, 36, 40, and 50 min, respectively (P < 0.05, Fig. 1). No significant difference in the plasma insulin concentration was observed between both conditions. The plasma lactate concentration gradually increased in both conditions after glucose loading. The incremental lactate area under the curve before insulin injection was significantly higher in the exercise condition than...
in the control condition (2.6 ± 0.9 vs. -3.5 ± 1.5 mM/min, P < 0.05) but not after injection.

K_G was significantly higher in the exercise condition than in the control condition (Table 2). There was no significant difference in the integrated area of plasma insulin between conditions (Table 2). S_G did not significantly change after exercise (Table 2, Fig. 2). S_G is significantly higher after exercise than in the control condition (P < 0.05, Table 2, Fig. 2). LBF was significantly higher in the exercise condition than in the control condition (at 8, 14, and 16 min, P < 0.05, Fig. 3). During the corresponding time (10–19 min) for calculation of K_G, LBF in the exercise condition was significantly higher than in the control condition (P < 0.05, Fig. 4).

**DISCUSSION**

The major finding of the present study was that mild exercise at the LT leads to a marked increase in S_G immediately postexercise. We have previously shown that endurance- or strength-trained athletes, respectively, have higher S_G than do sedentary subjects (13, 36). In the present study, an increase in S_G immediately after a single bout of mild exercise is similar to the level in trained subjects.

The five comparable studies on non-insulin-mediated glucose uptake (2, 11, 19, 28, 32) have reported inconsistent findings. Marin et al. (28) examined the effect of glycogen-depleting exercise on hyperglycemic clamp-derived glucose uptake in premenopausal women. In this study, non-insulin-mediated glucose uptake was not increased 24 h after exercise, but insulin-mediated glucose uptake was increased. We have recently reported that S_G was not increased in sedentary subjects 11 h after three types of exercise (exercise at LT, exercise at 4-mM lactate level, or exhaustive exercise), whereas S_G was increased only after exhaustive exercise (19). Pestell et al. (32) studied the effect of a strenuous ultramarathon run on glucose tolerance 2 h after exercise in highly trained subjects, but both S_G and S_I were not significantly increased. However, S_G in the present study was increased 25 min after exercise, in agreement with the finding by Brun et al. (11). They found that S_G was increased 25 min after exercise at 85% of maximum heart rate (11). Taken together, these findings indicate that the effect of a single bout of exercise on S_G could rapidly decreased in a time-dependent way.

Araujo-Vilar et al. (2) have demonstrated that there was a significant 45% increase in S_G during exercise at 50% of VO_{2max}, which is similar to the exercise intensity of our study. Our findings show similar increases in S_G even after exercise compared with their study. The increased S_G is due to either the increased glucose disposal in tissue or an augmented effect to suppress hepatic glucose production. Possible residual effects of

### Table 2. Metabolic parameters

<table>
<thead>
<tr>
<th>Control</th>
<th>Exercise</th>
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<tr>
<td>Basal glucose, mg/dl</td>
<td>94.5 ± 1.3</td>
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<tr>
<td>Basal insulin, pM</td>
<td>26.3 ± 1.6</td>
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<tr>
<td>K_G value, %/min</td>
<td>1.68 ± 0.37</td>
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<tr>
<td>Insulin area, pM·min</td>
<td>1650 ± 267</td>
</tr>
<tr>
<td>S_G, min⁻¹</td>
<td>0.016 ± 0.002</td>
</tr>
<tr>
<td>BIE, min⁻¹</td>
<td>0.004 ± 0.000</td>
</tr>
<tr>
<td>GEZI, min⁻¹</td>
<td>0.012 ± 0.002</td>
</tr>
<tr>
<td>S_I, ×10⁻¹·min⁻¹·pM⁻¹</td>
<td>18.8 ± 1.6</td>
</tr>
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</table>

Values are means ± SE. BIE, the basal insulin component of glucose effectiveness (S_G), which is calculated as the product of basal insulin and insulin effectiveness; GEZI, the difference between total S_G and the BIE. *Significantly different from control condition, P < 0.05 by paired t-test.
the exercise that may cause increased $S_G$ are increased blood flow or increased glucose transporter in the plasma membrane.

Hespel et al. (18) showed that glucose uptake in muscle is stimulated by increased blood flow in the absence of insulin. In this study, we found that increased blood flow in skeletal muscle, a major site of glucose disposal, remains significantly elevated until the corresponding time to determine $K_G$, that is significantly correlated to $S_G$ (25). Thus we speculated that the increased blood flow, which enhances glucose delivery to peripheral tissue, may contribute to the increased $S_G$. In addition to the increase in blood flow, our results show an increase in the integrated blood lactate area during the same period, suggesting that a significant component of $S_G$ can be derived from the metabolism of glucose to lactate (38).

Goodyear et al. (16) reported that 30 min after exercise both the number of plasma membrane glucose transporters and glucose transport activity remain elevated (1.6- and 1.8-fold above baseline, respectively), even though glycogen concentrations had returned to baseline concentrations. This may also contribute to the increased $S_G$. In addition, the effect of exercise on hepatic glucose production may be a reason for the change in $S_G$. Further study is needed to clarify these topics by using the stable-labeled, minimal model approach.

It is well known that a single bout of exercise causes an increase in $S_I$ (19, 28, 30). Brun et al. (11) also demonstrated that $S_I$ as well as $S_G$ were significantly increased immediately after exercise at 85% of maximum heart rate (70–80% of $V_O^{2,max}$, as predicted by age). In contrast to these studies, we observed no significant increase in $S_I$ immediately after mild exercise at LT intensity (45.4 ± 3.1% of $V_O^{2,max}$) for 60 min. The reasons for this discrepancy remain obscure, but the differences in exercise intensity may contribute to the contradictory results. The factor responsible for the increase in $S_G$ could be an increase in capillary insulin transport and/or an increase in insulin action at the target cell (7). Yang et al. (40) have shown that transcapillary insulin transport is a rate-limiting step for insulin action on its target tissues. Insulin as well as exercise can directly induce an increase in LBF in humans (3, 23). However, as shown in Fig. 3, LBF under both conditions did not change significantly after the glucose and insulin boluses, which elevate the plasma insulin levels. The results suggest that blood flow is elevated only by the effect of exercise. Furthermore, blood flow enhancement through exercise lasts until 25 min after the glucose bolus. Increased blood flow in the $K_G$-determined period may have contributed less to $S_I$, because $S_I$ does not correlate with $K_G$ (25). LBF during exercise has been shown to be positively

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**Figure 2.** Insulin sensitivity ($S_I$; A) and glucose effectiveness ($S_G$; B) in control (open bars) and mild exercise condition (solid bars). Symbols represent individual subjects. *Significantly different from control condition, $P < 0.05$.

**Figure 3.** Time course of leg blood flow (LBF) during intravenous glucose tolerance test. Vertical dotted line, time of insulin injection (20 mU/kg). Values are means ± SE. *Significantly different from control condition, $P < 0.05$.

**Figure 4.** LBF corresponding time to glucose disappearance constant between control (open bar) and mild exercise condition (solid bar). *Significantly different from control condition, $P < 0.05$. 

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correlated with exercise intensity (23). Thus we speculate that the blood flow might have remained higher longer in the study of Brun et al. (11) than in the present study, resulting in increased $S_I$.

An alternative explanation for this discrepancy could be related to glucose transporter concentration, because insulin-stimulated glucose transport has been found to be proportional to glucose transporter GLUT-4 protein concentration (17). Recent evidence has shown an increase in GLUT-4 protein expression immediately after a single but prolonged strenuous-exercise bout in an animal study (22). Thus it is possible that the exercise in this study may not have increased the GLUT-4 protein concentration, because the exercise intensity was not high enough.

In conclusion, the present study suggests that the mild exercise at LT intensity could be one of the physiological conditions that improves $S_I$, indicating acute improvement in glucose tolerance. Our results may lead to effective exercise therapy not only for hypertension (26, 27) and hyperlipidemia (31, 33) but also for patients with glucose intolerance.

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