RAPID COMMUNICATION

Relationship between Exercise Training-Induced Increase in Insulin Sensitivity and Adiponectinemia in Healthy Men

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Abstract. Circulating concentrations of adiponectin, an adipocyte-derived protein, are increased by thiazolidinediones and by weight reduction, accompanied with improvement in insulin sensitivity. The effect of exercise training, another therapy to increase insulin sensitivity (SI), on adiponectinemia is currently unclear. The present study was undertaken to clarify whether exercise training-induced increase in SI is related to changes in adiponectinemia in healthy men. Twelve healthy non-obese men 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 and at 16 h and 1 week after the last training session to determine SI using a minimal-model approach. Serum levels of adiponectin were determined at the same time. After the exercise training, VO2max and LT were significantly increased by 7.2% and 22.3% (P<0.01), while BMI and body fat mass remained unchanged. SI was significantly increased at 16 h after the last training session (from 7.0±3.1 to 9.6±3.6 [×10⁴·(μU/ml)×·min⁻¹], P<0.01), but returned toward the basal levels at 1 week after the cessation of the training. Serum adiponectin concentrations before the training (20.9±7.4 μg/ml) were positively correlated with SI. The concentrations were slightly but significantly decreased at 16 h (17.2±6.6 μg/ml, P<0.05), and returned to the basal values at 1 week after the training. From these results, it can be concluded that exercise training-induced increase in SI is not dependent on the increase in adiponectinemia in healthy men.

Key words: Adiponectin, Exercise training, Insulin sensitivity, Minimal model

CIRCULATING concentrations of adiponectin, the product of adipose most abundant gene transcript 1 (apM1) gene, are decreased in subjects with obesity, type 2 diabetes mellitus, and coronary heart disease [1, 2]. In a cross-sectional study involving varying degrees of glucose tolerance, hypoadiponectinemia is strongly associated with insulin resistance [3]. Adiponectin replacement therapy dramatically reverses insulin resistance and glucose intolerance in obese diabetic mice [4, 5] and in adiponectin-knockout mice [6]. These results indicate that the increase in adiponectinemia and/or adiponectin sensitivity would be of therapeutic use in insulin resistant and glucose intolerant states.

As a pharmacological approach to insulin resistance, thiazolidinediones are known to increase serum adiponectin concentrations in humans [7–9]. It is therefore likely that the improvement in insulin sensitivity by thiazolidinediones would be in part due to the increase in adiponectinemia. As a non-pharmacological approach, body weight reduction also increases circulating levels of adiponectin, and the increase in adiponectinemia is associated with the decrease in body mass index (BMI) and the improvement in insulin sensitivity [10]. As another therapy to increase insulin sensitivity along with weight reduction, exercise train-
ing might also affect adipocyte metabolism and result in changes in adiponectinemia. However, the relationship between exercise training and adiponectinemia is not known at present. Exercise training is often accompanied with the reduction of body fat, which could obscure the effects of exercise training on adiponectinemia. The present study was undertaken to clarify whether exercise training-induced increase in insulin sensitivity is related to changes in adiponectinemia in healthy men, who showed no change in BMI and body fat mass during 6 weeks of the training program.

Materials and Methods

Subjects

Twelve non-obese healthy men (18 to 33 years of age) who had not performed any regular exercise for at least 2 years were enrolled. They were free of diabetes mellitus and none was taking any medication. The nature, purpose, and risks of the study were explained to all subjects, and informed written consent was obtained. The study was approved by the local ethics committee of Jichi Medical School and was conducted in accordance with the Helsinki Declaration.

Methods

Bicycle ergometer training at the lactate threshold (LT) level was carried out for 60 min/day, 5 times/week for 6 weeks at the laboratory in Fukuoka University. Dietary intake was not restricted throughout the training period. To measure physical fitness, the graded exercise test on a mechanically braked ergometer was performed before the 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 subjective exhaustion was achieved. V̇O₂ was measured from the mixed expired gas collected in neoprene bags. The volume of the expired gas was quantified with a respirometer (Fukuda Irika CR-20, Tokyo, Japan). O₂ and CO₂ fractions were determined by a mass spectrometer (Perkin-Elmer 1100, Norwalk, CT). Blood samples from an earlobe were obtained every 30 s to measure blood lactate levels, which were determined by a flow injection analysis using immobilized enzyme (lactate oxidase) columns with detection made by chemiluminescence (Shimadzu CL-760, Kyoto, Japan). The blood lactate levels were 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 LT was determined for each subject based on a visual inspection, and was used to establish the exercise intensity for training. Three weeks after the training program started, each subject underwent the graded exercise test to readjust the training workload. The revised workloads were then used for the next 3 weeks. The details of the protocol were described elsewhere [11].

The percent body fat was measured by hydrostatic weighing with simultaneously measuring residual volume by O₂ rebreathing method before the training and 2 days after the last training session.

To determine insulin sensitivity, frequently-sampled intravenous glucose tolerance tests were performed before and at both 16 h and 1 week after the last training session as described previously [11]. In brief, baseline samples for glucose and insulin were obtained before the injection of 0.3 g/kg glucose. The glucose solution was administered to the antecubital vein, and an additional infusion of regular insulin (Humulin, Eli-Lilly, Kobe, Japan) was performed (20 mU/kg) from 20 to 25 min after the glucose bolus. Blood samples were frequently obtained up to 180 min. The incremental insulin between 0 and 20 min after the glucose bolus and the glucose disappearance constant (Kg) were calculated, and insulin sensitivity index (SI) was estimated using a minimal model approach [12].

Biochemical analysis

Plasma glucose concentration was measured using glucose oxidase method (Glucose B-test, Wako Pure Chemical, Osaka, Japan). Serum insulin level was determined by radioimmunoassay (Shionogi, Osaka, Japan). Fasting sera, which were kept at −70°C, were used to measure serum adiponectin concentrations by radioimmunoassay (Linco Research, St. Charles, MO). The intra- and inter-assay coefficients of variation for adiponectin were less than 5%.

Statistical analysis

All data are presented as means ± SD. Simple linear regression analysis was performed to calculate a corre-
loration. Wilcoxon signed rank test was used to evaluate time-course changes in indices. The statistical package StatView (Abacus Concepts, Berkeley, CA) for Macintosh version 5.0 was used for these analyses. A P value less than 5% was considered significant.

**Results**

**Determinants of SI at baseline**

Baseline SI of the participants was weakly correlated with percent body fat \((r = -0.612, P = 0.0345)\) and with body fat mass \((r = -0.557, P = 0.0598)\), but not with BMI \((r = -0.178, P = 0.5801)\). The SI was also marginally associated with VO\textsubscript{2max} \((r = 0.546, P = 0.0664)\) and VO\textsubscript{2} at LT \((r = 0.562, P = 0.0570)\), respectively.

**Training effects (Table 1)**

The 6 week exercise program produced a training effect as demonstrated by a 7.2% increase in VO\textsubscript{2max} and a 22.3% increase in VO\textsubscript{2} at LT. BMI and body fat mass remained unchanged.

Fasting glucose concentrations were significantly lower at 16 h after the last training bout than the before training levels. Fasting insulin concentrations and Kg values did not change after the exercise training. SI was significantly increased at 16 h after the last training session, but returned toward the basal levels at 1 week after the cessation of the training. The incremental insulin area between 0 and 20 min after the glucose bolus was simultaneously decreased at 16 h in accordance with the increase in SI. The disposition index (the product of the insulin area and SI) remained unchanged after the exercise training (data not shown).

The increase in VO\textsubscript{2max} and VO\textsubscript{2} at LT was not directly related to the change in SI (data not shown).

**Adiponectinemia**

Basal levels of serum adiponectin were between 11.0 and 32.0 \(\mu\text{g/ml} \) (20.9 ± 7.4 \(\mu\text{g/ml} \)), and positively correlated with SI before the training (Fig. 1). Basal adiponectin levels were not associated with BMI, percent body fat and body fat mass in these 12 non-obese subjects (data not shown).

At 16 h after the last training session, serum adiponectin concentrations were slightly but significantly decreased, and returned to the basal values at 1 week after the training (Table 1). As shown in Fig. 1, SI was increased and serum concentrations of adiponectin were decreased in most of the subjects. The change in adiponectinemia during the 6 week training period was not directly associated with the changes in VO\textsubscript{2max}, VO\textsubscript{2} at LT, fasting glucose, SI, BMI, percent body fat and body fat mass (data not shown).

| Table 1. | Training effects of the subjects |
| --- | --- | --- |
| | Before training | Just after training | 1 week after training |
| BMI (kg/m\(^2\)) | 20.8 ± 2.1 | 20.7 ± 2.1 | — |
| Body fat mass (kg) | 8.1 ± 3.3 | 8.1 ± 2.8 | — |
| VO\textsubscript{2max} (ml/kg\(^{-1}\)·min\(^{-1}\)) | 41.4 ± 5.1 | 44.4 ± 4.3* | — |
| LT-VO\textsubscript{2} (ml/kg\(^{-1}\)·min\(^{-1}\)) | 18.4 ± 3.5 | 22.5 ± 2.9* | — |
| Fasting glucose (mg/dl) | 95.5 ± 5.6 | 91.9 ± 6.0* | 94.7 ± 6.9 |
| Fasting insulin (\(\mu\text{U/ml}\)) | 4.7 ± 1.3 | 4.5 ± 1.4 | 5.4 ± 1.6 |
| Kg (%/min) | 2.5 ± 0.5 | 2.1 ± 0.7 | 2.1 ± 0.4 |
| SI \times 10^4 ([\(\mu\text{U/ml}\)]\(^{-1}\)·min\(^{-1}\)) | 7.0 ± 3.1 | 9.6 ± 3.6** | 7.8 ± 3.1 |
| Insulin area ([\(\mu\text{U/ml}\) 20 min] | 643 ± 289 | 417 ± 213* | 579 ± 254 |
| Serum adiponectin (\(\mu\text{g/ml}\)) | 20.9 ± 7.4 | 17.2 ± 6.6** | 20.9 ± 9.0 |

Data are mean ± SD. *P<0.01, **P<0.05. LT-VO\textsubscript{2}: VO\textsubscript{2} at lactate threshold.
Fig. 1. Individual changes in adiponectinemia and insulin sensitivity index (SI) before and at 16 h after 6 weeks of the exercise training. Closed circles denote the data before the training, and the regression line shows the correlation between serum adiponectin concentrations and SI ($r = 0.628$, $p = 0.0288$). Open circles denote the data at 16 h after the training.

Discussion

In the present study, mild exercise training for 6 weeks increased insulin sensitivity accompanied with the decrease in acute insulin response to glucose bolus. Simultaneously, serum adiponectin concentrations were decreased just after the training. At 1 week after the cessation of the training, insulin sensitivity index decreased toward the basal levels, and serum adiponectin concentrations also returned to the basal values. During the 6 weeks of training, BMI and body fat mass of the subjects remained unchanged. These data clearly indicate that exercise training-induced increase in insulin sensitivity is not due to the increase in adiponectinemia in healthy men.

Several preliminary abstracts show that exercise-induced improvement in insulin sensitivity is associated with the increase in adiponectinemia in middle-aged subjects with coronary risk factors [13] and in type 2 diabetic subjects [14]. As a slight but significant decrease in BMI was noted in these studies [13, 14], in contrast to the present study, it seems likely that the weight reduction has a considerable effect on the increase in adiponectinemia [8]. Otherwise, exercise training can increase circulating adiponectin concentrations in a state of preexisting hypoadiponectinemia, which is often observed in subjects with type 2 diabetes mellitus or dyslipidemia [2, 15].

As for the mechanisms of the decrease in serum adiponectin levels just after the exercise training, several possibilities can be discussed. First, insulin sensitivity was increased after the exercise training, while fasting insulin levels remained unchanged, suggesting increased insulin action. The increased insulin action per se may suppress expression and/or secretion of adiponectin from adipocytes. In accordance with this assumption, Faehre et al. [16] reported that insulin reduces adiponectin mRNA levels in vitro adipocytes in a dose- and time-dependent manner. Second, the decrease in fasting glucose just after the training may play a role on the decrease in adiponectinemia. Although serum adiponectin levels are decreased in hyperglycemia [2], the effects of a slight decrease in normal fasting glucose on adiponectinemia are currently unknown. Since adiponectin has a significant insulin-sensitizing effect [4–6], secretion of adiponectin may be suppressed to avoid further decrease in glycemia. This possibility requires further investigation such as an examination of adiponectinemia in hypoglycemic disorders. Third, although the exercise intensity was rather mild in the present study, recurrent activation of catecholamines during the exercise training may have a suppressive effect on adiponectin gene expression, as demonstrated in vitro [17].
Baseline insulin sensitivity in Japanese healthy men was weakly correlated with body fat and physical fitness estimated by exercise testing, consistent with a previous observation in Caucasians [18]. Insulin sensitivity and physical fitness were concomitantly increased after the exercise training. Although there was no direct correlation between the increase in these two parameters, this may be possibly due to the small sample size (n = 12) of the present study. Several mechanisms have been proposed for the increase in insulin sensitivity after exercise training; for instance, an increase in capillary density among muscle fibers, a shift of muscle fiber type to type IIa fiber, and an improvement in intracellular signaling of insulin, etc [19, 20]. It seems possible that those mechanisms also contribute to the increased aerobic capacity after exercise training.

We conclude that exercise training-induced increase in insulin sensitivity is not dependent on the increase in adiponectinemia in healthy men. It remains to be elucidated whether the changes in adiponectinemia are related to the exercise-induced increase in insulin sensitivity in subjects with type 2 diabetes and metabolic syndrome.

References


