Aerobic training increases the expression of adiponectin receptor genes in the peripheral blood mononuclear cells of young men

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ABSTRACT: Little is known about the effect of exercise training on the expression of adiponectin receptor genes in peripheral blood mononuclear cells (PBMCs). In this study, we investigated the effects of aerobic training on the expression of AdipoR1 and AdipoR2 mRNAs in PBMCs, whole body insulin sensitivity, and circulating adiponectins in men. Thirty young men were randomly assigned to either a control (n = 15) or an exercise (n = 15) group. Subjects assigned to the exercise group underwent a 12-week jogging and/or running programme on a motor-driven treadmill at an intensity of 60%-75% of the age-based maximum heart rate with duration of 40 minutes per session and a frequency of 5 days per week. Two-way mixed ANOVA with repeated measures was used to test any significant time-by-group interaction effects for the measured variables at p = 0.05. We found significant time-by-group interaction effects for waist circumference (p = 0.001), VO2max (p < 0.001), fasting insulin (p = 0.016), homeostasis model assessment for insulin resistance (HOMA-IR) (p = 0.010), area under the curve (AUC) for insulin response during the 75-g oral glucose tolerance test (p = 0.002), high-molecular weight (HMW) adiponectin (p = 0.016), and the PBMC mRNA levels of AdipoR1 (p < 0.001) and AdipoR2 (p = 0.001). The exercise group had significantly increased mRNA levels of AdipoR1 and AdipoR2 in PBMCs, along with increased whole body insulin sensitivity and HMW adiponectin, decreased waist circumference, and increased VO2max compared with the control group. In summary, the current findings suggest that exercise training modulates the expression of AdipoR1 and AdipoR2 mRNAs in PBMCs, implying that manipulation of the expression of these genes could be a potential surrogate for lifestyle intervention-mediated improvements of whole body insulin sensitivity and glucose homeostasis.

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INTRODUCTION

Adiponectin, an adipocyte-derived protein that is abundantly present in circulating plasma, plays a critical role in energy homeostasis by promoting glucose uptake into skeletal muscle and stimulating fatty acid oxidation [11]. Hypoadiponectinaemia is associated with metabolic complications such as obesity, metabolic syndrome and type-2 diabetes mellitus (T2DM) [2-3]. Thus, both pharmacologic and non-pharmacologic strategies to enhance insulin-sensitizing actions of adiponectin have been employed to enhance the insulin-sensitizing actions of adiponectin. Many of these strategies have been effective in improving the metabolic conditions commonly associated with insulin resistance and hyperinsulinaemia [4-7].

Using expression cloning, Yamauchi et al. [8] were the first to describe two specific surface receptors for adiponectin, termed adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2). AdipoR1 is primarily expressed in tests, heart and skeletal muscle, whereas AdipoR2 is highly expressed in liver, tests and small intestine. AdipoR1 and AdipoR2 serve as receptors for globular and full-length adiponectin, thus regulating adiponectin-mediated fatty acid oxidation, glucose uptake, and anti-inflammation actions. Consequently, adiponectin signalling has become extensively studied in the context of obesity-linked diseases such as insulin resistance, T2DM, and atherosclerosis [8-9].

Both AdipoR1 and AdipoR2 are expressed on the surface of peripheral blood mononuclear cells (PBMCs) [10]. The expression of adiponectin receptors on PBMCs is modulated by clinical conditions such as being overweight with coronary artery disease [11], severe obesity [12-13], T2DM [14] and patients with end-stage kidney disease [15]. These observations indicate a possible link between adiponectin signalling and metabolic diseases.

PBMCs are circulating immune cells that are increasingly used in gene expression studies because they can be easily collected multiple times in sufficient quantities. In contrast, adipose, muscle, and liver tissue samples require more invasive sampling. Thus, PBMCs have been used as a surrogate for tissues that are not easily accessible in gene expression studies investigating the molecular mechanisms underlying several human diseases [16]. Importantly, the gene
expression profiles in PBMCs and other cell types have been shown to be remarkably similar (80% concordant) [17]. Moreover, PBMCs exhibit altered expression of genes involved in energy homeostasis [18] and sterol metabolism [19] in response to acute changes in the feeding conditions of rats.

Exercise training has an insulin sensitizing effect like adiponectin in that exercise training also promotes glucose uptake into skeletal muscle and stimulates fatty acid oxidation [6]. Although changes in metabolic conditions are known to alter adiponectin receptor expression levels in PBMCs [11-15], little is known regarding whether lifestyle interventions, including exercise and/or exercise training, modulate the expression of AdipoR1 and AdipoR2 genes in PBMCs. In this study, therefore, we investigated whether aerobic exercise training in healthy, untrained young men modulates: 1) the expression of AdipoR1 and AdipoR2 mRNAs in PBMCs, and 2) whole body insulin sensitivity.

**MATERIALS AND METHODS**

**Subjects.** Healthy, untrained male students (N=50) who replied to flyers placed on the department and dormitory boards of our institution underwent an initial phone interview. After the initial interview, a total of 45 participants were invited for a physician-based health evaluation, which included medical history and overall health screening, body composition measurement, and assessment of metabolic risk factors.

Thirty out of the 45 initial participants met the inclusion criteria, which included being between 20 and 30 years old and a non-smoker. Moreover, participants were required to be free of any kind of disease that would not permit them to take part in this study such as cardiovascular, metabolic, and musculoskeletal disorders. Exclusion criteria included abnormal liver enzymes, microalbuminuria, poorly controlled diabetes (> 10% glycated haemoglobin (HaA1C), acute illness and infection, heart failure, and use of thiazolidinediones, which have been shown to independently increase AdipoR expression on monocytes [20]. In addition, participants who took any medication and supplements were excluded. Since all participants ate at the university restaurant, they consumed an identical diet. Then, after giving required information about the details of the study, each participant meeting the appropriate inclusion criteria without any exclusion criteria (N=30) agreed to participate in the study. Participants were randomized to the exercise training (n=15) or control group (n=15).

The sample size for each group was determined so that the study would be sufficiently powered to detect group differences in the primary outcome of this study, which was the change in total serum adiponectin level. Based on our preliminary data, we calculated that a sample size of 12 subjects per group would provide a power of 85% (a probability of 0.05) for detecting a statistically significant difference between the groups on our primary outcome. The Institutional Research Ethics Review Committee reviewed and approved the study. After receiving written informed consent from each participant, the clinical evaluation was performed.

**Exercise training**

Subjects assigned to the exercise group underwent a 12-week supervised jogging and/or running programme on a motor-driven treadmill (Quinton, USA) at an intensity of 60%-75% of the age-based maximum heart rate with duration of 40 minutes per session and a frequency of 5 days per week. Each exercise session started with 5 minutes of warm-up, followed by 30 minutes of jogging and/or running at the predetermined 60-75% HRmax and ended with 5 minutes of cool-down. Subjects were instructed to maintain their exercise heart rate within 5 beats/min of their targeted heart rate by using a heart rate monitor (POLAR Accurex Plus, Finland). As the fitness level of each subject improved, the running velocity required to maintain the desired exercise intensity was increased. Subjects assigned to the control group were asked to maintain their current lifestyle and dietary intakes during the study period.

**Glucose tolerance test and biochemical analyses**

Glucose, total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDLc) levels were measured in duplicate from fasting blood samples using an Ektachem DT-60 II analyzer (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, NY, USA). Insulin levels were measured in duplicate using an enzyme-linked immunosorbent assay kit (ALPCO Diagnostics, Salem, NH, USA). The index of insulin resistance was assessed using the homeostasis model of assessment for insulin resistance (HOMA-IR), as HOMA-IR = (fasting insulin (µU/ml) x fasting glucose (mM))/22.5 [21]. The intra- and inter-assay coefficients of variation for insulin were 2% and 5%, respectively.

In addition, the oral glucose tolerance test (OGTT) was conducted as an index of whole body insulin sensitivity. In brief, each subject was asked to eat a balanced diet consisting of at least 150 g of carbohydrate per day for 3 days before the test. Fruits, breads, cereals, grains, rice, crackers, and starchy vegetables such as potatoes, beans, and corn are good sources of carbohydrate. Participants were asked not to eat, drink, smoke, or exercise strenuously for 10-12 hours before their first blood sample was taken. Then, a 2-h OGTT was performed. The test involved consumption of a liquid glucose bolus (75 g) after an 8-h fast, followed by sample collection for the measurement of glucose and insulin concentrations both at baseline (before glucose consumption) and at 30, 60, 90, and 120 min after glucose consumption.

The circulating levels of total and HMW adiponectins were determined in the serum of all subjects, using Human Total and HMW Adiponectin/Acrp30 Quantikine ELISA Kits (R&D Systems, Inc., Minneapolis, MN, USA). The intra- and inter-assay coefficients of variation for total adiponectin were 3.9% and 6.4%, respectively. The intra- and inter-assay coefficients of variation for HMW adiponectin were 3.5% and 8.5%, respectively.

Real-time quantification of AdipoR1 and AdipoR2 mRNA in PBMCs.
Blood samples were available from 15 participants in the exercise training group and 15 participants in the control group. Venous blood collected in EDTA was diluted 1:1 with RPMI-1640 (Sigma-Aldrich, St. Louis, MO, USA) at room temperature. Up to 25 ml of the diluted blood was layered on 15 ml Lymphocyte-H (Cederlane, Burlington, NC, USA) at room temperature. After centrifugation at 800 g for 20 minutes, PBMCs were removed from the interface using a Pasteur pipette and transferred into a new 50 ml Falcon tube. The cell pellet was washed twice in RPMI then centrifuged at 800 g for 10 minutes to pellet the lymphocytes, and the supernatant was discarded. The pellets were then suspended in 10 ml of RPMI.

Total RNA was isolated using TRIzol reagent (Invitrogen, Carlsbad, CA, USA). For quantitative polymerase chain reaction (qPCR), total RNA was reversed transcribed using random hexamer primers and RevertAid reverse transcriptase (Fermentas, Life Sciences, Ontario, Canada). First-strand cDNA was synthesized using SuperScript III reverse transcriptase (Invitrogen). Relative mRNA expression levels were expressed as the ratio to hypoxanthine-guanine phosphoribosyl transferase 1 (HPRT1). Briefly, 4.5 μl of each cDNA (about 1 μg) served as a template in 10 μl of PCR mixture containing 5 μl of TaqMan universal polymerase master mix (Applied Biosystems, Foster City, CA) and 0.5 μl of TaqMan probe. Three probes were used (Applied Biosystems): ADIPOR1 (mRNA NM_015999.2, Hs00360422_m1), ADIPOR2 (mRNA NM_024551.2, Hs00226105_m1), HPRT1 (probe exon location 6–7, 4326321E, Hs99999909_m1, as endogenous control) was labelled with VIC. Amplification was carried out in the ABI PRISM 7500 Real-Time PCR System (Applied Biosystems) under the following conditions: 2 min at 50°C, 10 min at 95°C, followed by 40 cycles of 15 s at 95°C, and 1 min at 60°C. Adiponectin, ADIPOR1, and ADIPOR2 quantities were normalized to the amount of HPRT1 cDNA. Results were analyzed using SDS 2.3 software (Applied Biosystems) by the 2-ΔΔCT method.

**Statistical analyses**

Data are expressed as mean ± SD. Normality of distribution for dependent variables was assessed using the Shapiro-Wilk test. If the data were not normally distributed, outcome variables were logarithmically transformed prior to statistical analyses. A two-factor (time: pre and post; group: control and exercise) with mixed-design ANOVA followed by an LSD post-hoc test was performed for all the continuous variables to evaluate the effect of exercise in different groups. In addition, effect sizes (i.e., Cohen’s d) were calculated by dividing the post-pre change over the course of exercise training by the pooled standard deviation of the pre test scores for the specific group (i.e., control vs. exercise training group). Thus, effect sizes for the exercise or control group were calculated by the post-pre change for that specific group by the pooled standard deviation of the pre test scores for the entire group. All statistical analyses were performed using Statistical Package for the Social Sciences (version 18.0; SPSS, Inc., Chicago, IL), with a type I error rate of α = 0.05.

**RESULTS**

Table 1 summarizes changes in body fatness and cardiorespiratory fitness in response to 12 weeks of aerobic exercise training. Significant time-by-group interactions were found for waist circumference (p=0.003) and VO2 (p<0.001); these interactions were not found for BMI (p=0.184) or percent body fat (p=0.162). Subjects in the exercise group had a significantly decreased waist circumference (p=0.001) and an increased VO2 (p<0.001) after 12 weeks of exercise training, compared with subjects in the control group.

Table 2 represents changes in haemodynamics and metabolic parameters in response to 12 weeks of aerobic exercise training. Significant time-by-group interactions were found for fasting insulin (p=0.016), HOMA-IR (p=0.010), and AUC for insulin (p=0.002), with no such interactions for systolic blood pressure (p=0.351), diastolic blood pressure (p=0.084), TG (p=0.249), TC (p=0.879), HDLC (p=0.904), fasting glucose (p=0.125), and AUC for glucose (p=0.077). Compared with subjects in the control group, subjects in the exercise group had significantly decreased fasting insulin (p<0.001) and HOMA-IR (p=0.001) after 12 weeks of aerobic exercise training. Moreover, subjects in the control group had a significantly increased AUC for insulin during the OGTT (p=0.023) compared with subjects in the exercise group, following the same experimental period.

**TABLE I.** Changes in body fat composition and cardiorespiratory fitness after 12 weeks of aerobic training (means ± SDs).

| Parameter | Control group (n=15) | Exercise group (n=15) |
|-----------|----------------------|-----------------------|
|           | PRE                  | POST                  | ES        | PRE                  | POST                  | ES        |
| BMI (kg·m⁻²) |          |                      | 24.5±2.1 | 24.9±2.2 |          |                      | 24.2±1.9 | 0.36 |
| BF (%)    | 21.3±2.5            | 20.6±3.0              | 0.23     | 23.2±3.6            | 21.4±4.3              | 0.59     |
| WC (cm)   | 82.7±7.3            | 82.5±7.9              | 0.03     | 87.1±6.8            | 83.1±6.0              | 0.57     |
| VO₂ (mL·kg⁻¹·min⁻¹) | 46.8±3.2 | 47.8±3.0              | 0.38     | 45.9±2.1            | 54.5±2.2              | 3.24     |

Time-by-group interaction effects: (1) p=0.184 for BMI, (2) p=0.162 for BF, (3) p=0.003 for WC, and (4) p<0.001 for VO₂.

BMI: body mass index; BF: body fat; WC: waist circumference.

ES: effect sizes (Cohen’s d) were calculated by dividing the pre-post change over the course of exercise training by the pooled standard deviation of the pretest scores for the specific group (i.e., control vs. exercise training group).
TABLE 2. Changes in haemodynamic and metabolic parameters after 12 weeks of aerobic training (means ± SDs).

| Parameter | Control group (n=15) | Exercise group (n=15) |
|-----------|----------------------|-----------------------|
| SBP (mmHg) | 131.4±15.4 | 129.0±8.1 |
| DBP (mmHg) | 75.7±8.9 | 73.3±4.5 |
| HR (beats·min⁻¹) | 76.6±2.7 | 60.9±2.3 |
| TC (mmol·L⁻¹) | 4.04±0.54 | 4.73±1.35 |
| HDLC (mmol·L⁻¹) | 1.17±0.16 | 1.50±0.37 |
| TG (mmol·L⁻¹) | 0.91±0.32 | 1.29±0.67 |
| Glucose (mmol·L⁻¹) | 4.87±0.24 | 4.98±0.38 |
| Insulin (mU·mL⁻¹) | 7.58±1.08 | 8.06±1.22 |
| HOMA-IR | 1.65±0.30 | 1.80±0.40 |
| AUC for GLU (mg·mL⁻¹·hr⁻¹) | 429.1±50.6 | 422.9±77.2 |
| AUC for INS (mg·mL⁻¹·hr⁻¹) | 99.3±23.2 | 99.7±40.0 |

Note: Time-by-group interactions: (1) p=0.351 for SBP, (2) p=0.084 for DBP, (3) p=0.071 for HR, (4) p=0.879 for TC, (5) p=0.904 for HDLC, (6) p=0.249 for TG, (7) p=0.125 for insulin, (8) p=0.016 for HOMA-IR, (9) p=0.001 for AUC for glucose, and (10) p=0.002 for AUC for insulin.

Significant treatment effects (post-pre) compared with the control group. DBP: diastolic blood pressure; HR: heart rate; TC: total cholesterol; HDLC: high-density lipoprotein cholesterol; TG: triglycerides; HOMA-IR: homeostasis model assessment for insulin resistance; AUC: area under the curve; GLU: glucose; INS: insulin.

DISCUSSION

Circulating adiponectin promotes whole body insulin sensitivity as well as glucose and fatty acid metabolism. Adiponectin exerts these effects via its cellular receptors, AdipoR1 and AdipoR2, which are expressed in liver, heart, testis, skeletal muscle, and other tissues. AdipoR1 and AdipoR2 have been cloned [8] and expressed in PBMCs [10]. The expression of these receptors is modulated by various metabolic diseases such as insulin resistance and T2DM [7, 13]. However, it was previously unknown whether the expression levels of AdipoR1 and AdipoR2 in PBMC are also modulated in response to lifestyle modifications such as exercise training. This study is the first to report that a lifestyle modification (i.e., 12 weeks of aerobic exercise training) upregulates AdipoR1 and AdipoR2 expression in PBMCs. In addition, this lifestyle modification led to increased levels of HMW adiponectin, whole body insulin sensitivity, and cardiorespiratory fitness, as well as decreased waist circumference, in this study population.

TABLE 3. Changes in serum adiponectin and PBMC AdipoR mRNAs after 12 weeks of aerobic training (means ± SDs).

| Parameter | Control group (n=15) | Exercise group (n=15) |
|-----------|----------------------|-----------------------|
| Total adiponectin (mg·mL⁻¹) | 5.09±1.85 | 4.97±0.85 |
| HMW adiponectin (mg·mL⁻¹) | 1.29±0.61 | 1.05±0.65 |
| AdipoR1 mRNA (arbitrary unit) | 0.75±0.15 | 0.72±0.21 |
| AdipoR2 mRNA (arbitrary unit) | 0.93±0.28 | 0.68±0.23 |

Note: Time-by-group interaction effects: (1) p=0.263 for total adiponectin, (2) p=0.008 for HMW adiponectin, (3) p<0.001 for AdipoR1 mRNA, and (4) p<0.001 for AdipoR2 mRNA.

Significant treatment effects (post-pre) compared with the control group. PBMC: peripheral blood mononuclear cells; HMW: high molecular weight; AdipoR: adiponectin receptor.

ES: effect sizes (Cohen's d) were calculated by dividing the pre-post change over the course of exercise training by the pooled standard deviation of the pretest scores for the specific group (i.e., control vs. exercise training group).
Exercise and insulin sensitivity

Our results are consistent with previous findings. In a lifestyle intervention study involving a hypocaloric diet and a moderate-intensity treadmill exercise, Pang et al. [10] found that responders who had achieved an increase in VO2max greater than 10% or weight loss greater than 5% after the intervention had significantly increased expression of AdipoR1 and AdipoR2 genes compared with subjects who did not achieve these goals. Chan et al. [22] reported that at baseline, obese Zucker rat had significantly lower levels of the AdipoR1 gene and protein in soleus muscle than lean littermates. Moreover, 8 weeks of aerobic exercise training reversed these decreases in AdipoR1 expression and protein production in the soleus muscle; these changes were not seen in the lean littermates. Huang et al. [2] observed that at baseline, obese/diabetic KKAY mice had significantly lower levels of AdipoR1 in the liver and lower AdipoR1 and AdipoR2 in white adipose tissue, and higher levels of AdipoR2 in skeletal muscle compared with C57BL/6 mice. Following 8 weeks of exercise training, the KKAY mice had significantly increased levels of AdipoR1 in the skeletal muscle and liver and decreased levels of AdipoR2 in the liver. However, no significant changes were observed in the adipose tissue levels of AdipoR1 or AdipoR2. Together, these findings indicate a link between adiponectin signalling and whole body insulin sensitivity.

In addition, cross-sectional studies have suggested a potential link between adiponectin signalling and metabolic diseases. For example, Rigamonti et al. [13] found that obese individuals had significantly higher serum levels of adiponectin and higher levels of AdipoR2 expression in leukocytes compared with their lean counterparts. Weigert et al. [7] reported that obese control and T2DM patients both had significantly higher levels of AdipoR1 and AdipoR2 expression in monocytes compared with the normal weight controls. Sohn et al. [23] reported that children with Prader-Willi syndrome who were treated with growth hormone had significantly higher expression of AdipoR2 compared with their counterpart children who were not receiving growth hormone treatment. Moreover, Shen et al. [15] reported that patients with end-stage kidney disease had significantly higher levels of AdipoR1 and AdipoR2 in PBMCs. Thus, it will be interesting to investigate whether exercise and/or exercise training modulate the adiponectin receptor expression in PBMCs after 12 weeks of exercise training.

This study has several limitations. A primary limitation of our study is that expression of AdipoRs was not measured at the protein level, not only in PBMC but also in liver and skeletal muscle, where AdipoR1 and AdipoR2 are expressed in a tissue-specific manner and AdipoR1 and AdipoR2 genes are changed in the liver and skeletal muscle by fasting and re-feeding [25]. Consequently, additional research will need to include the quantification of AdipoRs at both gene and protein levels to address the implication(s) of AdipoRs’ responses to exercise training in a more meaningful way. Second, additional work would benefit from the inclusion of individuals at risk for insulin resistance and/or T2DM, since those with metabolic complications would be likely to have greater room for responses of adiponectin receptors as well as whole body insulin sensitivity to exercise training. Finally, the low-to-moderate-sized effects of exercise training on primary (i.e., AUCs for both glucose and insulin during the OGTT) and secondary (i.e., percent body fat, waist circumference) measures provide an important foundation for future work examining the efficacy of exercise training as a treatment for hyperadiponectinaemia and/or insulin resistance.

**CONCLUSIONS**

In conclusion, the data presented here suggest that exercise training might modulate the expression of AdipoR1 and AdipoR2 in PBMCs. Thus, adiponectin receptor genes in PBMCs might serve as a surrogate for lifestyle intervention-mediated improvements in whole body insulin sensitivity and glucose homeostasis.

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