Total plasma leptin and adiponectin are regulated via chronic Exercise training in streptozocin-induced diabetic rats

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ABSTRACT

The objective of the study was to determine the effects of exercise training on total plasma adiponectin and leptin concentrations in streptozocin-induced diabetic female rats. Thirty, eight week-old female Wistar rats (186 ± 12 g) were randomly assigned to two groups of healthy (n=12) and diabetic (n=18) induced by streptozocin injection, then healthy group were divided into two group of H1 and H2 as healthy control and diabetic group were split up into three groups of D1, D2 as diabetic control and Exe as a exercise training group. Before exercise protocol, samples were obtained from H1 and D1 groups. Exe group performed an 8-week exercise program on treadmill running (28 m/min ~ %70-%75 VO2max) at 0° slope, 1 h/day, and 5 days/week. There were no significant differences induced by time between H1 and H2 group and D1 and D2 group in any variables. Total plasma adiponectin concentration were significantly higher in Exe compared with D2 (P<0.05), also plasma leptin concentration was higher in Exe (P<0.05) but HOMA-IR was not significantly different in Exe compared to D2. In Exe group blood glucose level was lower and insulin concentration was higher compared to D2 but the differences were not statistically significant. Thus, data suggest that 8 week exercise training with moderate intensity for 5 days per week may stimulate adiponectin synthesis and increase total plasma adiponectin concentrations in diabetic female rats.

Key words: adiponectin, leptin, exercise training, Insulin resistance.

Introduction

Leptin and adiponectin, two of the most abundant adipocyte secretions, are believed to link obesity, insulin resistance, and related disorders [51,30].Leptin, an obese gene product, is a 16-kDa protein and is preponderantly expressed in adipose tissue [58]. Leptin regulates body weight by modulating appetite and energy expenditure by affecting the hypothalamus and inhibiting the secretion of neuropeptide Y in mice and humans [18]. Presence levels of leptin will cause a signal to be sent to the central nervous system, which then efforts to assist the subject from obesity by decreasing a petite and increasing energy expenditure, however, most obese subjects have elevated concentrations of leptin [27], suggesting that these people spring up leptin resistance. Meanwhile, studies have also expressed that insulin resistance is especially prevailing in obese human sand have reported an autonomous connection between insulin resistance and raised plasma leptin levels [44,5]. The coinciding plasma leptin levels, plasma insulin levels and body fat propose that leptin might be affect in the connection between obesity and β-cell hypersecretion. Adiponectin (also termed acrp 30, adipoQ, APM-1, GBP28) is an adipocytokine that is generally and abundantly expressed in adipose tissue and directly sensitizes the cells to insulin. Adiponectin structurally is connected with the complement 1q family [22] that plays a crucial function in glucose and lipid metabolism [19]. Low plasma adiponectin levels are associated to insulin resistance and the development of type 2 diabetes [20, 46, 53, and 55]. Activation of AMPK by adiponectin was proved to increase phosphorylation of acetyl-coenzyme A carboxylase (ACC), fatty acid oxidation and glucose uptake via GLUT-4 ensue in a reduced triglyceride content and increased insulin sensitivity [55]. Treatment of streptozocin-induced-diabetic mice with adiponectin gene therapy (hydrodynamic injection of the Adipo gene) has been shown to elevate adiponectin concentrations and reduce hyperglycemia [14]. Exercise has been demonstrated to promote insulin sensitivity in older, obese, insulin resistant, type 2 diabetic and non-diabetic individuals [12, 16, 41]. Many investigations have sought the possible link between plasma
adiponectin levels and insulin-sensitizing effects of exercise, and have reported inconsistent findings. Investigators have proposed that total adiponectin concentration increases [13,24,25], decreases [56] and does not change [6,17,29,57] with exercise training. Recent research suggests that weight loss produced by exercise is an important factor affecting increases in adiponectin expression [57]. The most previous studies have been focused on effect of exercise in obese subjects and because of limitations for diabetic individuals, less attention have been paid to investigate that effect on diabetic patients by changing adiponectin concentration to cope with elevated blood glucose, insulin and insulin resistance. On the other hand recent studies revealed that diabetic patients do not indicate any clear response to exercise training through adiponectin alteration level (32.6.45.36). Hence the aim of the present study is to determine the effect of exercise training on adiponectin concentration in streptozocin-induced diabetic rats.

Materials and Methods

2.1. Animals:

Thirty, eight week-old female Wistar rats (186 ± 12 g) were randomly assigned to two groups of healthy (n=12) and diabetic (n=18) induced by streptozocin injection, then healthy group were divided into two group of H1 and H2 as healthy control and diabetic group were split up into three groups of D1, D2 as diabetic control and Exe as a exercise training group. Before exercise protocol, samples was obtained from H1 and D1 groups. All groups of D1, D2 as diabetic control and Exe as a exercise training group. Before exercise protocol, samples was obtained from H1 and D1 groups. All groups of rats were housed in cages under controlled light/dark (12/12 h) and temperature (22 ± 1 °C) conditions, and were provided with food and water ad libitum. Animals were familiarized with animal lab conditions for 1 week before experiments began. Exercise protocol was approved by post-graduate committee of University of Guilan and other experimental procedures involving animals were approved by the Medical Science University of Jahrom Animal Care and Use Committee. Diabetes was induced by injection of streptozocin (40 mg/kg body mass) through the caudal vein two weeks prior to the initiation of exercise training. Blood was obtained from the tail vein using heparinized microhematocrit tubes. Plasma glucose of all groups was measured weekly. After 2 weeks, animals with plasma glucose level exceeding 16.6 mM were considered as diabetic. Then to recognize time effect, D1 and H1 groups were anesthetized with diethyl ether and sodium pentobarbital (50 mg/kg, intraperitoneal injection) after a 12-h fast their blood was gleaned from the abdominal aorta.

2.2. Exercise training protocol:

The training group was exercised on a rodent motor-driven treadmill at a 0 slope for 60 min/day, 5days/wk for 8 wk. During the 1st wk of training the rats ran at treadmill speed of 10 m/min for 15 min for adaptation. During the 2nd and 3rd wk of training the treadmill speed and exercise duration increased step by step until the animals ran for 60 min/day. The treadmill speed and exercise duration were then held constant for the remainder of the training period. We kept training frequency (5d/wk) and duration (60 min/d) constant and modified training intensity since we were interested in whether increased training stress brought about by aerobic exercise training affected the adiponectin.

2.3. Blood collection and tissue:

Preparation To minimize the effect of acute exercise, the rats were finally anesthetized with diethyl ether and sodium pentobarbital (50 mg/kg, intraperitoneal injection) after a 12-h fast and 32 h after the last training session and their blood was gleaned from the abdominal aorta. Tubes containing plasma sample aliquots were kept frozen at 80 °C until being analyzed.

2.4. Measurements:

Insulin resistance in the fast state was determined by HOMA-IR which was calculated using the below formula: fasting insulin (µU/ml) × fasting glucose (mmol/L)/22.5 [27]. Blood glucose was determined by Accu-Chek Go glucometer. ELISA kits specific for the rat were used to determine plasma insulin (BioVendor, Shibayagi, Japan), total plasma adiponectin and leptin (BioVendor, Czech Republic).

2.5. Statistical analyses:

A Kolmogorov–Smirnov test was applied to determine of normality of distribution of measures which were found to be normally distributed. A one-way analysis of variance (ANOVA) was performed to determine the differences in a parameter among the groups. Significant differences were identified using a least significant difference (Tukey) post-hoc test. All data were expressed as mean ± SD and significance was established at the alpha level p < 0.05.

3. Results:

Comparing control H1 with H2 and control D1 with D2 did not showed significant change in all variables by effect of time although adiponectin concentration was decreased during time. Compared to control H2, body weights of exercise and control D2 were significantly lower after the 8 week experimental protocols, but the differences were not
statistically significant between exercise and control D2. (Table 1). There were significant decrease in insulin concentrations in exercise and control D2 in comparison to control H2 but the difference between exercise group and control D2 was not significant. HOMA-IR was lower in control H2 in comparison to exercise group and control D2 but these differences also were not significant. Plasma concentrations of total adiponectin were significantly higher in control H2 and exercise group than in control (p < 0.05) also plasma leptin concentration was higher in Exe compared with D2 (P<0.05).

Table 1: Effects of exercise training programs on plasma measures in different groups.

<table>
<thead>
<tr>
<th>variables</th>
<th>Control H2</th>
<th>Control D2</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>258.62±14.95</td>
<td>131.62±11.22</td>
<td>146.12±16.25</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.19 ± 0.16</td>
<td>22.96 ± 6.25</td>
<td>20.55±2.82</td>
</tr>
<tr>
<td>Insulin (µU/mL)</td>
<td>9.72 ± 0.05</td>
<td>3.14±0.18</td>
<td>3.34 ± 0.28</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.26 ± 0.09</td>
<td>3.20±0.90</td>
<td>3.12 ± 0.60</td>
</tr>
<tr>
<td>Plasma total adiponectin (µg/mL)</td>
<td>1.62 ± 0.10</td>
<td>0.94±0.056</td>
<td>1.14 ± 0.03*</td>
</tr>
<tr>
<td>Plasma total leptin (pg/ml)</td>
<td>129.10± 5.85</td>
<td>74.87± 9.32</td>
<td>90.79± 7.16*</td>
</tr>
</tbody>
</table>

*p < 0.05 vs. D2

(*)Significant compared with control D (P ≤ 0.05)

Fig. 1: Weight (A), glucose (B), insulin (C), HOMA-IR (D), plasma adiponectin (E), plasma leptin (F) Exercise interventions in streptozocin-induced diabetic rats. P ≤ 0.05.

4. Discussion:

This research is one of the first evidence that proved aerobic exercise training, even in the presence of weight gain, can improve plasma adiponectin concentration in diabetic female rats. Data found in the present study proposed that a substantial change in body weight induced by exercise training is not necessarily necessitated to elicit increased adiponectin levels. These findings are adverse to previous reports suggesting that weight loss is required to heighten circulating adiponectin levels [4], although there are some studies that have proved exercise training combined with reduction in body mass had no effect on adiponectin concentrations [21,35]. At the end of the present study, the body weight differentiation of exercise and control D group were not significant but plasma total adiponectin concentrations in the exercise groups were significantly greater than those in the control D. Thus, exercise training appears to be important parameters affecting the endocrine adaptation of total adiponectin and there seems to be a possible effect for exercise training on adiponectin. Adiponectin is expressed and released predominantly by adipose tissue [19]. Hence, it appears that the raised plasma
adiponectin concentration in this study is a direct manifestation of training-induced increases of adiponectin production in adipose tissue. In a previous study, obese subjects training 3 d/wk, 60–75 min/session ensued no change in circulating total adiponectin concentrations, however, in a group that followed a hypocaloric diet and another group that exercised and followed a hypocaloric diet, raised in circulating total adiponectin were found [47]. This differs from the present study in which animals were not obese but diabetic and completed greater weekly exercise than in the previous study. O’leary et al. [47] also reported no change in circulating total adiponectin in obese adults who exercised 5d/wk at ∼ 70–75% VO2max for 12 wk. The exercise intensity was similar to the exercise intensity group in the study; nevertheless, the animals in the present study were not obese. In the present study there was no significant change in body mass with training. Although most studies do disclose weight or fat loss with concomitant increase in circulating adiponectin, and there is evidence that adiponectin concentrations are inversely related to fat cell size [2], various studies have not found this pattern. For instance, it was reported that training considerably reduced abdominal fat with no succeeding change in adiponectin concentrations in middle age men with type II diabetes [8], plus there are other reports of no alteration in circulating adiponectin with exercise-training-induced weight loss [41,49]. A very possible explanation for these findings is that the increases in adiponectin with training are due to the arousal of adipocyte mitochondrial biogenesis. Mitochondrial function in adipocytes is crucial for adiponectin synthesis with impaired mitochondrial function reducing adiponectin synthesis and raised mitochondrial biogenesis increasing adiponectin synthesis [23]. It has been shown that a high fat diet cut down mitochondrial function in adipocytes which also reduces adiponectin concentrations [8]. Moreover, it has been shown that exercise training will stimulate mitochondrial biogenesis in white adipose tissue [48]. In summary, this investigation is the first to demonstrate there is an effect for exercise training for the adaptation of circulating total adiponectin concentrations.

Acknowledgment

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References

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