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Brief Reports

Effects of exercise training on indicators of adipose tissue angiogenesis and hypoxia in obese rats

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ABSTRACT

Objective. To investigate the effects of obesity and exercise training on regional adipose tissue angiogenesis and hypoxia markers in rats.

Methods. Lean (Fa/Fa) and obese (fa/fa) male Zucker rats at 2 months of age were randomly assigned to a sedentary or an exercise training group (lean sedentary: n = 7, lean exercise: n = 8, obese sedentary: n = 7, obese exercise: n = 8). The exercise group walked on a rat treadmill 5 times per week for 8 weeks. Inguinal and epididymal adipose tissue vascular endothelial growth factor A (VEGF-A) and lactate levels were determined.

Results. There were significant effects of obesity in increasing inguinal ($P < 0.001$) and epididymal ($P < 0.05$) adipose tissue VEGF-A, and a significant effect of exercise training in increasing epididymal adipose tissue VEGF-A ($P < 0.05$). There was a significant effect of obesity in increasing inguinal adipose tissue lactate levels ($P < 0.001$). Compared to lean sedentary animals, obese sedentary animals had significantly higher epididymal adipose tissue lactate levels ($P < 0.001$); compared to obese sedentary animals, obese exercise rats had significantly lower epididymal adipose tissue lactate levels ($P < 0.05$).

Conclusions. Exercise training increased adipose tissue VEGF-A, an important factor of tissue angiogenesis, and lowered adipose tissue lactate, an indicator of adipose tissue hypoxia in obese rats. However, these effects are depot-specific and only observed in intra-abdominal adipose tissue.

1. Introduction

Increased adipose tissue mass without an adequate support of vascularization contributes to low oxygenation and chronic inflammation, which are related to an elevated risk of type 2 diabetes [1,2]. VEGF-A plays an important role in stimulating angiogenesis within adipose tissue. An increase in angiogenesis could protect against adipose tissue hypoxia and inflammation in animals [2,3]. Although a few animal studies reported that exercise training altered adipose tissue VEGF-A gene expression [4,5], the regional differences between subcutaneous and intra-abdominal adipose tissue VEGF-A production and the effects of regular exercise on regional adipose tissue VEGF-A production in obesity are still unknown.

Abbreviations: VEGF-A, vascular endothelial growth factor A; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1 alpha.

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There are several markers of adipose tissue hypoxia [6]. Levels of lactate in adipose tissue have been used as a hypoxia indicator. In rodents, intro-abdominal adipose tissue lactate levels increased with obesity and were reduced by caloric restriction [1]. However, it is still unclear if there are regional differences in adipose tissue lactate levels and if exercise training affects regional adipose tissue lactate levels in obesity.

Therefore, the purpose of this pilot/preliminary study was to compare the regional differences in VEGF-A and lactate levels in subcutaneous and intra-abdominal adipose tissue, and to investigate the effects of severe obesity and aerobic exercise training on regional adipose tissue VEGF-A and lactate levels in rats.

2. Methods

2.1. Animals

Male Zucker rats aged 4–5 weeks were purchased from Harlan Laboratories (Indianapolis, IN). The rats were housed one lean (Fa/Fa) and one obese (fa/fa) per cage in the animal facility and were provided with water and lab chow ad libitum. The animals were acclimated to animal facilities for two weeks and then assigned to one of the following groups: lean sedentary (N = 7), lean exercise (N = 8), obese sedentary (N = 7), and obese exercise (N = 8). The sample size was chosen based on results of previously published exercise studies in obese Zucker rats [7,8]. The protocol was approved by the Animal Care and Use Committees at the State University of New York at Buffalo and University of Massachusetts Boston.

2.2. Procedures

Exercise training and sample collection were performed as previously described [7,8] with slight modifications [9]. The training began with the rats exercising on a treadmill for 10 m/min, 20 min per day, 5 days per week, and then gradually built up to 20 m/min, 60 min per day, 5 days per week for 8 weeks [9]. On the sample collection day, animals were sacrificed by cardiac puncture, and inguinal (subcutaneous) and epididymal (intra-abdominal) adipose tissue samples were collected and incubated as previously described [9,10]. Adipose tissue VEGF-A release levels were determined by using a Milliplex assay (Millipore, St. Charles, MO). Frozen adipose tissue samples were homogenized in Tris buffer, and adipose tissue lactate levels were determined with an assay kit (Cayman Chemical, Ann Arbor, MI) per the manufacturer's instructions. In addition, protein concentrations in adipose tissue were determined by the micro Lowry method (Sigma-Aldrich, St. Louis, MO).

2.3. Statistical analyses

Statistical analyses were performed using JMP 10 for Windows (SAS, Cary, NC). A paired t-test was used to compare differences in regional adipose tissue variables. A two-way analysis of variance was used to determine the main effects of obesity, the main effects of exercise and any obese and exercise interactions. Once an obesity and exercise interaction was identified, LSD post-hoc tests were used to compare individual group differences. Data were expressed in mean ± SE and a significance level of $P < 0.05$ was used.

3. Results

In the whole cohort, VEGF-A secretion levels were higher in epididymal (13.20 ± 3.93 ng/g protein) compared to inguinal (6.41 ± 1.18 ng/g) adipose tissue ($P < 0.01$). However, lactate levels were higher in inguinal (10.32 ± 1.21 ng/g protein) compared to epididymal (5.63 ± 0.82 ng/g) adipose tissue ($P < 0.001$).

There was a significant main effect of obesity ($P < 0.01$), but no main effect of exercise training, on inguinal adipose tissue VEGF-A levels, indicating that obesity increases inguinal adipose tissue VEGF-A release (Fig. 1A). There were main effects of obesity and exercise training on epididymal adipose tissue VEGF-A secretion (both $P < 0.05$), indicating that both obesity and exercise training increase epididymal adipose tissue VEGF-A secretion; therefore, obesity increased epididymal adipose tissue VEGF-A levels, and this increase was more exacerbated by exercise training (Fig. 1B).

Similar to the results of adipose tissue VEGF-A, there was a significant main effect of obesity ($P < 0.01$), but no main effect of exercise training, in increasing inguinal adipose tissue lactate levels ($P < 0.001$) (Fig. 2A). However, there was a significant obesity and exercise interaction on epididymal adipose tissue lactate levels ($P < 0.001$) (Fig. 2B). Compared to the lean sedentary group, the obese sedentary group had significantly higher lactate levels ($P < 0.001$). Compared to the obese sedentary group, the obese exercise group had significantly lower lactate levels ($P < 0.05$).

4. Discussion

This study investigated how obesity and exercise training alter regional adipose tissue VEGF-A and lactate levels in male Zucker rats. Our findings support that obesity up-regulate adipose tissue VEGF-A and lactate levels in both inguinal (subcutaneous) and epididymal (intra-abdominal) adipose tissue in the rats. Surprisingly, exercise training only altered VEGF-A and lactate levels in epididymal, but not inguinal adipose tissue.

Previous animal studies indicated that, dietary-induced obesity increased VEGF-A mRNA levels in epididymal adipose tissue [1]. In human studies, overweight/obese subjects had lower VEGF-A mRNA levels in subcutaneous abdominal adipose tissue [11], and obese subjects with higher BMI had lower adipose tissue VEGF-A release [12]. Our findings, for the first time, indicate that severe obesity up-regulates VEGF-A release in both subcutaneous and intra-abdominal adipose tissue in Zucker rats. Although previous studies reported that that exercise increases adipose tissue VEGF-A gene expression in animals [4,5], our study is the first to report that the obesity-related increase in rat adipose tissue VEGF-A protein levels is more exacerbated by exercise training and this effect is fat-depot specific. One previous study reported that exercise training increased VEGF-A gene expression in epididymal adipose tissue of rats [4], and another study reported that exercise increased VEGF-A mRNA, but did not change its protein levels in subcutaneous adipose tissue of rats [5].