doi:10.4149/endo_2009_03_107

EXERCISE TRAINING ATTENUATES LIPECTOMY-INDUCED IMPAIRED GLUCOSE TOLERANCE IN RATS

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Objective. Since visceral adipose tissue (VAT) may account for impaired peripheral and hepatic insulin sensitivity (IS), it has been hypothesized that the partial removal of VAT could result in improved insulin action, while the re-growth of the excised tissue and/or compensatory growth of non-excised depots seems to occur. Thus, it was aimed to investigate whether or not VAT removal and exercise affect IS.

Methods. Male Wistar rats were fed a high-fat diet and subsequently assigned randomly to one of four groups: 1. exercised plus lipectomized (EL), 2. exercised plus sham-lipectomized (ES), 3. sedentary plus lipectomized (CL), 4. sedentary plus sham-lipectomized (CS). After lipectomy, EL and ES animals underwent a 7-consecutive-day training period. Body weight, food intake, basal metabolic rate, fasting glucose, and glucose tolerance were assessed before and after the interventions. Fasting insulin and the HOMA index, body fat mass, and the expression of pro-inflammatory genes were assessed after the interventions.

Results. EL group showed greater insulin sensitivity compared to all other groups. EL and ES groups showed lower fasting insulin levels when compared to CL and CS groups, respectively. The EL group showed improved IS when compared to the remaining groups. The CL group showed impaired glucose tolerance and increased TNF-alpha gene expression. Body weight and fat mass did not differ among the groups. PPAR gamma gene expression was increased in the EL and ES groups. **Conclusions.** These results showed that short-term swimming training improved insulin sensitivity, but failed to prevent fat regain in lipectomized animals. Lipectomy induced impaired glucose tolerance, which is probably related to increased TNF-alpha gene expression. It is possible that a high-fat diet might be implicated in faster regain of adipose tissue after lipectomy. Our results also show that short-term exercise associated with lipectomy could improve insulin sensitivity.

Keywords: Food pattern – OGTT – TNF-alpha – Visceral adipose tissue – Fat removal – Swimming exercise

The number of obese and overweight individuals has increased dramatically over the last decades. Obesity is a risk factor for the development of several diseases and metabolic complications such as insulin resistance, dyslipidemia, diabetes, and atherosclerosis. Obesity and its related diseases are highly associated with high

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fat-diets, which are consumed world-wide (Martin et al. 2006; Mobbs et al. 2007). Although obesity is a very important risk factor for metabolic diseases, the regional distribution of adipose tissue, especially visceral adipose tissue, seems to play an important role in these disorders (Wajchenberg 2000).

Several studies have demonstrated that increased visceral adipose tissue may account for impaired peripheral and hepatic insulin sensitivity, which is often observed in obesity (Einstein et al. 2005). The exact mechanism(s) involved in this process is (are) still not fully elucidated. However, several hypotheses have been studied such as increased portal free fatty acid flux, abnormal expression and secretion of fat-derived peptides (Gabriely et al. 2002), and inflammation (Tilg and Moschen 2008).

Exercise training and lipectomy are two of the strategies most frequently used to reduce adipose tissue mass. It is well established that both exercise training and lipectomy can modulate adipose tissue and insulin action through different mechanisms. Exercise training improves insulin sensitivity (Frosig et al. 2007) and decreases serum free fatty acids (Shojaee-Moradie et al. 2007; Lamontagne et al. 2007) as well as the size of adipocytes (Yan et al, 2007). Additionally, it can reduce the inflammatory state that is typically seen in obesity (Tilg and Moschen 2008). In contrast, lipectomy elicits a reduction in the number of adipocytes, regulates adipokine secretion, and may improve the action of insulin (Gabriely et al. 2002; Barzilai et al. 1999).

There are several factors that modulate insulin action and adiposity. Among the most important regulators are some inflammatory markers such as tumor necrosis factor-alpha (TNF-alpha), interleukin (IL) 6, IL-10, and IL-1 beta (Yu and Ginsberg 2005; Di Gregorio et al. 2005; Plomgaard et al. 2005; Krogh-Madsen et al. 2006). Moreover, there is evidence showing that the nuclear receptors peroxisome proliferators activated receptor (PPAR) alpha and -gamma can modify insulin action and PPAR-gamma can modulate adiposity (van Beekum et al. 2008; Gregoire et al. 1998).

Although it is well known that TNF-alpha is mainly produced by monocytes in response to inflammatory stimuli, adipose cells are also able to produce and secrete TNF-alpha (Wajchenberg 2000). Recent evidence showed that the expression of TNF-alpha gene is increased in adipocytes in obesity (Segersvard et al. 2008) which can lead to impaired insulin action (Tilg and Moschen 2008). Other studies have shown that TNF-alpha is related to an increased free fatty acid serum concentration (Hotamisligil et al. 1997). It has been shown that IL-6 secretion is increased in the adipocytes of obese subjects (Mohamed-Ali et al. 1997). IL-1beta seems to be involved in type 2 diabetes since it suppresses insulin receptor subtrate-1 (IRS-1) and, therefore, inhibits the insulin-induced glucose transport (Jager et al. 2007). IL-10, which has a protective role in insulin sensitivity, is reduced in insulin-resistant subjects (van Exel et al. 2002).

Despite of the evidence showing positive effects of exercise training (Frosig et al. 2007; Wojtaszewski and Richter 2006; Houmard et al. 2004) and lipectomy on insulin action (Barzilai et al. 1999; Gabriely et al. 2002), no studies have investigated how the exercise training combined with lipectomy can affect insulin sensitivity and adiposity. Additionally, no studies have assessed the effects of exercise training plus lipectomy on inflammatory markers and adipogenic factors. As a result, the purpose of the present study was to investigate the possible synergic effects of exercise training and lipectomy on insulin action and adiposity. We also intended to examine some putative molecular mechanisms involved in the response of those interventions, namely such as TNF-alpha, IL-6, IL-10, IL-1beta, PPAR-alpha, and PPAR-gamma.

Materials and Methods

Animals. Sixty male adult (200-300 g) Wistar rats were kept in individual cages at 25 °C with a fixed 12/12h light-dark cycle. The study was approved by the Ethics and Research Committee of the Physical Education and Sport School (Sao Paulo University – Brazil).

Experimental design. Animals received water and a high-fat diet *ad libitum* for 8 weeks (pre-interventions). The diet contained 41.6 % fat, which has been shown to impair insulin sensitivity and lead to the development of obesity (Buettner et al. 2006). Food intake was measured three times a week. Body weight was measured once a week. At week 8, the first oral glucose tolerance test (OGTT) and basal metabolic rate (BMR) assessment was performed for the animals. One day later, the animals were randomly allocated into either the exercised/lipectomized group (EL), exercised/sham-operated group (ES), control/lipectomized group (CL), or control/sham-operated group (CS). Seven days after surgery, EL and ES animals underwent short-term exercise training for seven days. On week 11 (post-interventions), 48 h after the last exercise train-

ing session, the animals were subjected to the second OGTT and BMR assessment. On the morning of the next day, the animals were sacrificed after a 12-hour fast period. Blood samples were obtained for the subsequent analysis of plasma insulin and glucose, which were used to calculate the HOMA index. Additionally, m. gastrocnemius and epididymal adipose tissue were extracted in order to measure TNF-alpha, IL-6, IL-1beta, IL-10, PPAR-gamma, and PPAR-alpha mRNA expression. The intact carcass was weighed and frozen for posterior body fat mass assessment. Figure 1 depicts the experimental design.

Lipectomy. At week 8, EL and CL rats were anesthetized intraperitoneally (pentobarbital, 50 mg/kg of body weight). A 2 cm incision was made along the *alba linea*, allowing for the removal of as much as possible of the epididymal fat pad, which was weighed after the procedure. The amount of fat removed was not significantly different between groups (5.2 ± 2.9 g for EL and 4.3 ± 1.6 g for CL; $p>0.05$). The muscle incision was stitched with interrupted 3-0 absorbable nylon sutures, and interrupted 3-0 silk nylon sutures were used for the skin incision. In ES and CS animals, an identical incision was made and the intestines and adipose tissue were manipulated, but the fat pads were left intact.

Exercise training protocol. One week after the surgery, EL and ES animals underwent a 7-day swimming exercise training period. Short-term exercise training has already been shown to improve insulin sensitivity (Black et al. 2005; Tanner et al. 2002; Houmard et al. 2000). Animals exercised with an increasing overload throughout the days (weights attached to the animal's tail), reaching 5 % of the animal's body weight on day 5 (i.e. at the anaerobic threshold for rats during exercise) (Voltarelli et al. 2002). On the first day animals exercised for 15 minutes increasing time throughout the days and reaching 30 minutes on days 6 and 7. Exercise training was performed in 10 individual round tanks (60 cm in depth x 80 cm in perimeter) filled with circulating water maintained at 30 ± 2 °C.

Oral glucose tolerance test (OGTT). The animals were subjected to OGTT after 12-hour overnight fast being administered by gavage the solution of 1.5 g/kg body weight of dextrose was mixed with 0.5 ml of sterile water. Blood samples were taken from the tail at 0, 10, 20, 30, 60, 90, and 120 min after the glucose load for serum glucose determination. The area under the curve (AUC) was calculated for each group according to Matthews et al. (1990). OGTT No.1 was conducted on week 8, one day before surgery, and OGTT No.2 was conducted on week 11 at 48 hours after the last exercise training session.

Homeostasis model of assessment index (HOMA Index). The HOMA index was calculated for fasting blood samples obtained on the day of sacrifice according to (Matthews et al. 1985). Fasting glucose was analyzed by enzymatic method with Celm® kit (São Paulo, Brazil). Fasting insulin was measured by radioimmunoassay by Amersham Buckinghamshire (England).

Basal metabolic rate. The BMR was measured on the day before lipectomy and 48 h after the last exercise training session. Resting oxygen consumption (VO_2) and

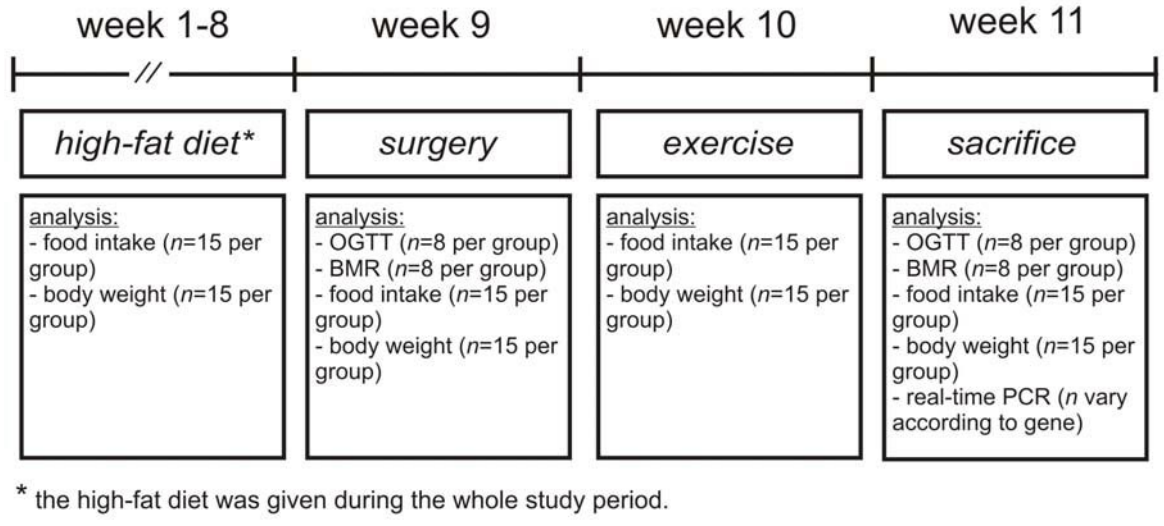

Fig 1 Experimental design

carbon dioxide production were measured in expired air in a closed-circuit respirometer system (Columbus Instruments, Columbus, Ohio, EUA). The BMR was calculated on the basis of the lowest value of energy expenditure per hour. All measurements were carried out over a period of 60 min at room temperature (25 ºC). Animals were maintained in their normal experimental conditions until immediately prior to the measurements. Results were corrected for environmental temperature and atmospheric pressure. They are expressed in terms of milliliters of O_2.body weight (g).min^{-1}.

Body fat mass assessment. After sacrifice, the carcass (intact body) was immediately frozen for posterior homogenization: distilled water was added to the carcass, which was autoclaved for 30 minutes, followed by homogenization. A sample of the homogenate was added to 3 ml of 30 % (w/v) KOH. The lipid was saponified and the non-esterified fatty acids were extracted (Stansbie et al. 1976). Lipid content is expressed as mg of lipid/ g of tissue (carcass).

Real time RT-PCR. Quantitative real-time PCR was used to analyze TNF-alpha, IL-1 beta, IL-6, and IL-10 gene expression in epididymal fat pads and skeletal muscle (m. gastrocnemius). Total RNA was isolated as previously described using TRIzol® (*Li* et al., 2002). The RNA was then treated with DNAse, and M-MLV reverse transcriptase was used to synthesize cDNA. Thereafter, we performed the real-time PCR using 2 µl of cDNA diluted 1:8 and 2 µl of the following probes: TNF-alpha (Rn00562055) and HPRT (Rn01527838 – Melton et al. 1997) as a control gene, along with 5 µl of the Taqman Master Mix (all from Applied Biosystems) at a final volume of 10 µl. To analyze the other cytokines, the same volume of cDNA was used with 5 µl of SyberGreen PCR Master Mix (Applied Biosystems) and 0.4 µl of each primer (10 pmol/µl) at a final volume of 10 µl.

The primers used were: IL-1 beta (sense 5'CTG TGA CTC GTG GGA TGA TG – 3' and anti-sense 5'GGG ATT TTG TCG TTG CTT GT – 3', Tm 55oC), IL-6 (sense 5'- CCG GAG AGG AGA CTT CAC AG – 3' and anti-sense 5'- ACA GTG CAT CAT CGC TGT TC – 3', Tm 55oC), IL-10 (5'- GGG TCT TGG GAA GAG AAA CC – 3' and anti-sense 5'GCT TTC GAG ACT GGA AGT GG – 3' Tm 58 ºC), PPAR-alpha (sense 5'- TGC TAT AAT TTG CTG TGG AGA TCG– 3' and anti-sense 5'- TGA CTC GGT CTT CTT GAT GAC CT– 3' Tm 56 ºC);

PPAR-gamma (sense 5'- TGT CAT TAT TCT CAG TGG AGA CCG- 3' and anti-sense 5'- CAG CAG GTT GTC TTG GAT GT Tm- 3' 56 ºC), and HPRT (sense 5' CTC ATG GAC TGA TTA TGG ACA GGA C – 3' and anti-sense 5' GCA GGT CAG CAA AGA ACT TAT AGC C – 3' Tm 58oC). All reactions were loaded in the 7300 Real Time System, and analyses were performed using the 7300 System Software (Applied Biosystems) considering the expression of the gene of interest in relation to the expression of the control gene.

Statistical evaluation. Mixed-Model analysis of variance (ANOVA) with repeated measures was performed to compare values between groups for OGTT, energy intake, and body weight. The model was adjusted using the covariance matrix according to Schwarz Bayesian criteria. For insulin, fasting glucose, fasting insulin, and the HOMA index, one-way ANOVA and Tukey's post-hoc test were performed. All values are presented as means ± SD. The level of statistical significance was set a priori at $p \leq 0.05$, and all data analysis was performed using SAS 8.0 software.

Results

All groups were homogeneous for all variables assessed before the interventions ($p > 0.05$). As shown in Table 1, BMR, body weight, and fasting glucose were not affected by the treatments at any timepoint.

Table 1.

Means and standard deviation of baseline data (n=32)

	EL (n=8)	ES (n=8)	CL (n=8)	CS (n=8)
Body weight (g)	499.9±47.3	493.2±35.6	493.6±43.7	491.7±31.8
BMR (mL O_2/min.kg)	32.22±5.58	31.16±4.15	32.9±5.2	32.86±4.86
Fasting glucose (mg.dL^{-1})	87.4±7.2	84.4±15.5	95.1±18.3	83.2±20.0

No significant differences were found among groups for any variable.

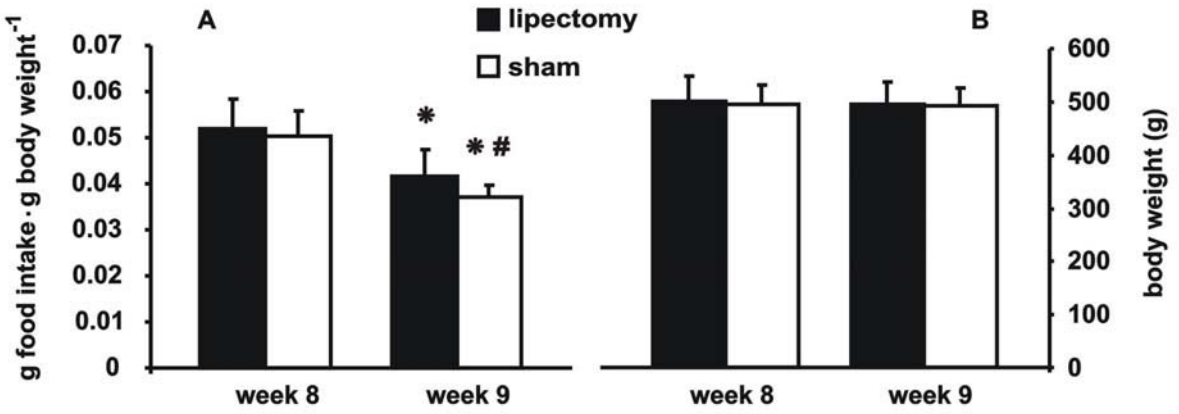

Fig 2 Mean ± standard deviation (SD) of food intake (panel A) and body weight (panel B) at weeks 8 and 9. * significantly different from week 8 (p<0.05); # significant different from lipectomy (p<0.05).

Post-intervention BMRs were neither different from baseline data nor among the groups (33.06±7.11 for EL; 30.61±10.18 for ES; 31.28±3.74 for CL and 32.81±3.30 for CS; p>0.90). Body weight was not affected by lipectomy, exercise training, or the combination of both (p>0.05). As expected, food intake was decreased after surgery compared with pre-surgery (p<0.05), but lipectomized rats showed 11% increased food intake compared to sham rats on week 9 (Fig. 2). On week 10 (exercise training) and 11 there were no significant differences on food intake (week 10 – EL 0.054 ± 0.011, CL 0.054±0.014, ES 0.051±0.022, CS 0.046±0.012; on week 11 – EL 0.052±0.010, CL 0.059± 0.200, ES 0.063±0.031, CS 0.073±0.017; all values expressed in kcal/g body weight). Despite this, body fat mass was not significantly different between the groups post-interventions (p>0.05).

The pre-intervention area under the curve (AUC) of OGTT did not differ between groups, but CL showed greater glucose intolerance at post-intervention compared to pre-intervention and greater glucose intolerance at post-intervention compared to ES, EL, and CS (Fig. 3).

After the interventions, both exercised groups (EL and ES, 6.8 ± 1.4 μU/ml and 8.8 ± 2.6 μU/ml respective-

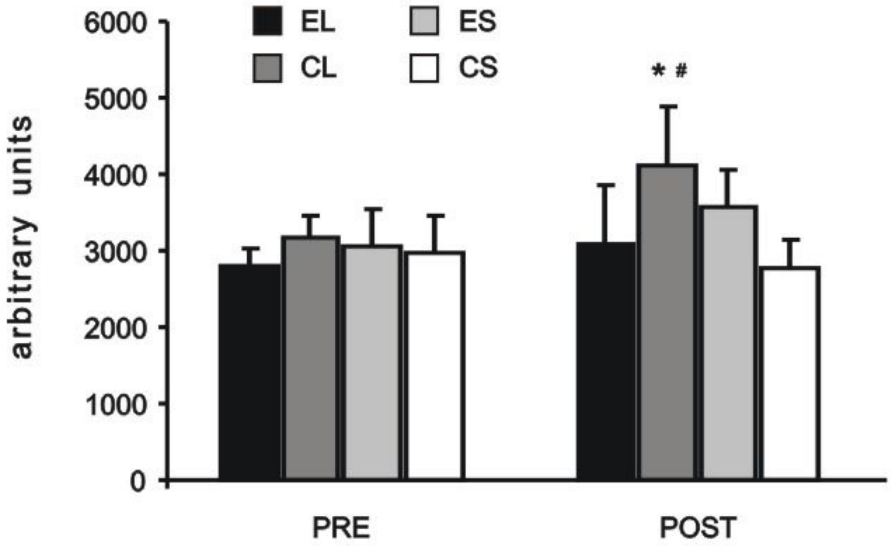

Fig 3 AUC (glycaemic curve) response from OGTT at PRE and POST interventions. # Significantly different from EL, ES and CS post (p< 0.01).

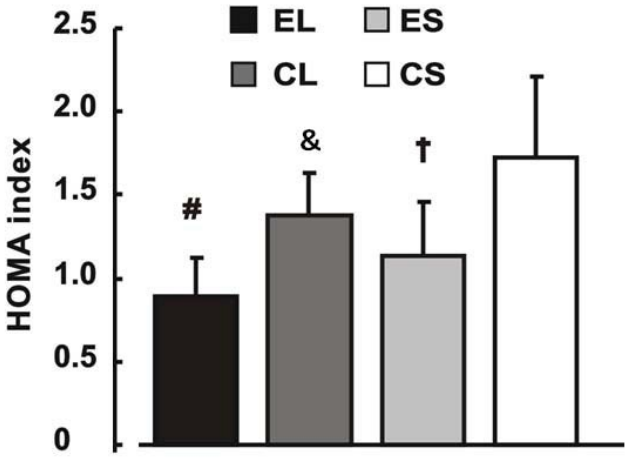

Fig 4 Homa Index (IR and %S) comparison across groups. # indicates EL versus CL, ES, CS (p<0.05); & indicates CL versus ES, CS (p<0.05); † indicates ES versus CS (p<0.05) (EL n=8; CL n=9; ES n=8; CS n=8).

ly) showed reduced fasting insulin when compared to non exercised groups (CL and CS, 11.6 ± 4.1 μU/ml and 11.7 ± 5.2 μU/ml respectively). Additionally, EL showed significant increased insulin sensitivity (assessed by HOMA index) when compared to all other groups. ES showed increased significant insulin sensitivity compared to CL and CS groups. CL displayed significantly increased insulin sensitivity than CS group. as assessed by the HOMA index (Fig. 4).

The CL group showed increased TNF-alpha gene expression in skeletal muscle when compared to all other groups (p<0.01; Fig. 5). There were no significant differences in PPAR-alpha gene expression in the skeletal muscle between groups. The EL group showed significant decreased PPAR-gamma gene expression in skeletal muscle compared to control CS (p<0.05), and the CL and ES groups presented decreased PPAR-gamma gene expression in visceral adipose tissue compared to the EL and CS groups.

IL-1beta, IL-6, and IL-10 gene expression did not differ among the groups after exercise or lipectomy (p>0.05).

Discussion

The aim of this study was to verify the effects of lipectomy and exercise training on insulin sensitivity and adiposity of animals fed a high fat-diet. To our knowledge, the present study is the first to find that lipectomy alone may impair glucose tolerance in rats fed a high fat-diet, while exercise training can prevent glucose intolerance. Furthermore, lipectomized animals seemed to compensate for adipose tissue removal, since total body fat was similar among groups at the end of the study. We also investigated the underlying mechanisms involved in these responses.

An important finding was the lack of significant difference in body fat mass among the groups post-intervention. These data suggest that, after removal of visceral adipose tissue, the lipectomized animals compensated for the adipose tissue that was removed. The higher energy intake observed in lipectomized groups (11% increment) may have contributed to the regain in adipose tissue. The increased food intake represents an excess of 63 kcal in lipectomized groups, which, in turn, may account for an increase of 7 g of fat in lipectomized groups (the fat removal was approximately 5.2 g per animal). The compensation for or re-growth of excised adipose tissue was already described by others (Mauer and Bartness 1997; Michel and Cabanac, 1999; Harris et al. 2002). Such a phenomenon is often seen 4 to 16 weeks after surgery depending on the species (Mauer et al., 2001), whereas a similar response was found after only 2 weeks in the present study. This difference in the time response was probably due to the high-fat diet used in our study, as other studies have used the standard control diet (Mauer and Bartness 1994; Barzilai et al. 1999; Kim et al. 1999; Gabriely et al. 2002). Therefore, a high-fat diet seems to accelerate the compensation for or re-growth of adipose tissue after lipectomy. We chose a high-fat diet in order to mimic regular human food patterns (Doucet and Tremblay 1998). In fact, Lavoie et al. (2005) reported that a high-fat diet increases the rate of pre-adipocyte replication, which contributes to

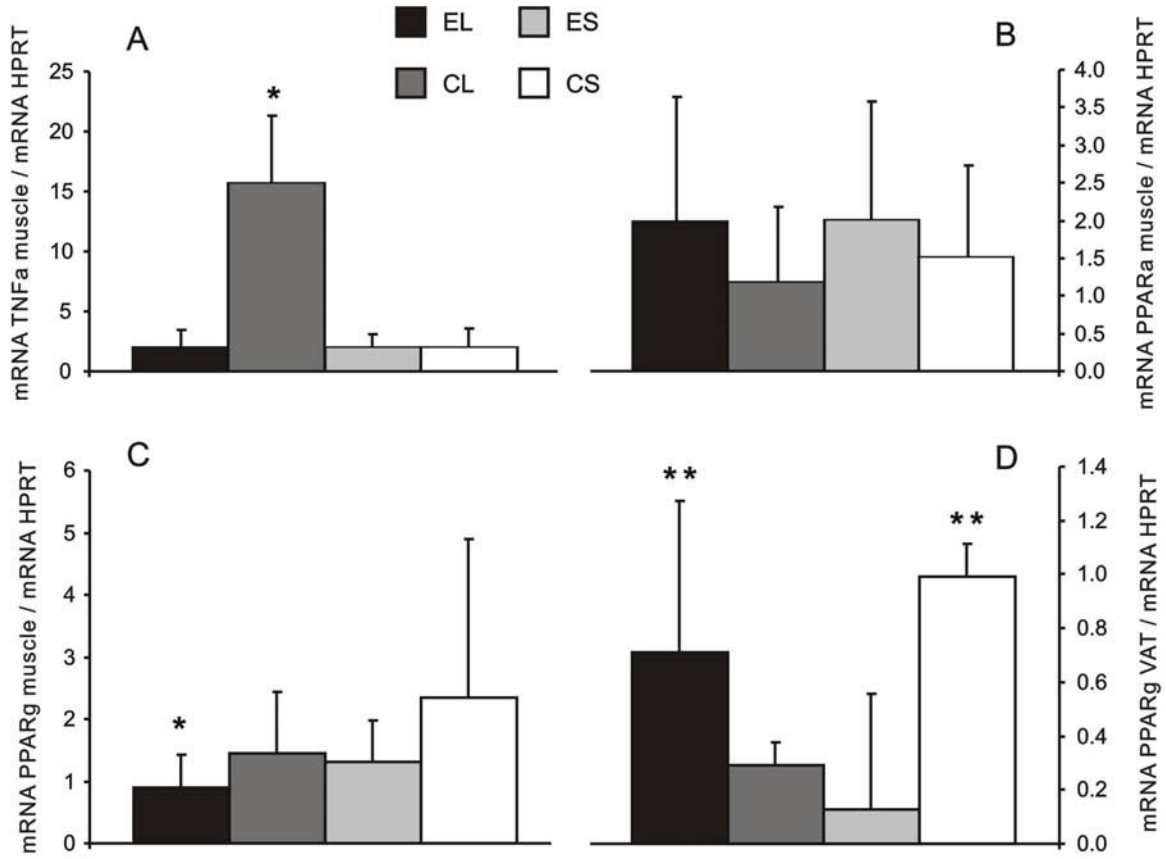

Fig 5 Gene expression responses to experimental procedures. Panel A -TNF-alpha gene expression in skeletal muscle *significantly different from all other groups ($p<0.01$); Panel B – PPAR-alpha gene expression in skeletal muscle (no significant differences were found); Panel C – PPAR-gamma gene expression in skeletal muscle *significantly different from CS ($p<0.05$); Panel D – PPAR-gamma gene expression in visceral adipose tissue **significantly different from CL and ES ($p<0.05$).

a more effective lipogenesis. Another study found that after 2 months of a high-fat diet, male rats had both increased body weight and body fat mass compared to those subjected to a control diet (Marotta et al. 2004). Taken together, these data can partially explain the rapid regain of adipose tissue observed in our study.

We observed that exercised groups (EL and ES) showed decreased fasting insulin when compared with controls (CL and CS). Moreover, we calculated the HOMA index, which allows for estimation of insulin resistance. Exercised groups presented decreased insulin resistance compared to their control groups. These data show that 7 days of consecutive swimming training can improve insulin sensitivity.

Importantly, we also observed improved insulin sensitivity in the EL group compared to all other groups. These results indicate an associative effect of training and lipectomy on insulin sensitivity compared to lipectomy or exercise training alone.

Interestingly, the CL group showed increased TNF-alpha gene expression compared to all other groups. Ishikawa et al. (2006) reported that subcutaneous fat modulates insulin sensitivity in mice by regulating TNF-alpha expression in the visceral fat. In their study, mice were subjected to subcutaneous lipectomy and, afterwards, developed insulin resistance, which was correlated with greater TNF-alpha gene expression. In our study, the increased TNF-alpha gene expression in the CL group may explain the decline in glucose tolerance observed in the same group.

The EL group did not show impaired glucose tolerance, which is probably due to the protective effect of exercise training preventing high-fat diet-induced impairments in insulin action. According to Yaspelkis et al. (2007), endurance exercise training improves insulin

action in animals fed a high-fat diet through activation of components of the insulin signaling cascade in skeletal muscle. Another specific finding of our study was the greater expression of PPAR-gamma mRNA observed in the EL group. There is acceptable evidence to suggest that the PPAR-gamma gene is associated with greater adipogenesis (Staels and Fruchart 2005). Moreover, the EL group showed greater insulin sensitivity compared to all other groups at POST interventions. It is well known that PPAR-gamma also stimulates the synthesis of adipocytes that are more insulin sensitive (Wajchenberg 2000). Increased PPARgamma activity and gene expression are directly associated to greater body weight and adiposity (Nadeau et al. 2007; Harrington et al. 2007). Thus, it is not surprising to observe increased PPARgamma mRNA expression in CS group, considering that control animals were fed a high fat diet and were kept sedentary. Furthermore, EL showed greater PPARgamma mRNA expression compared to ES and CL groups. It has been demonstrated that lipectomy is able to induce local and peripheral adipogenesis (Bueno et al. 2005). In this context, the increased PPARgamma mRNA expression in EL group could be interpreted as a homeostatic response against the abrupt reduction in adipose tissue content as a result of lipectomy combined to exercise training, leading for a possible medium to long-term adipose tissue regain. Intriguingly, however, the same trend was not seen in exercised only or lipectomized only groups, which suggests an additive effect of lipectomy and exercise on PPAR gamma mRNA response. Indeed, PPARgamma is a putative candidate to explain adipose tissue compensation and greater insulin sensitivity, but only when the lipectomy was combined with exercise.

PPAR-alpha gene expression was not altered either by lipectomy or exercise training. Our results are in agreement with previous studies conducted by Helge et al. (2007) and Kannisto et al. (2006), indicating that this gene is not related to the glucose tolerance and insulin sensitivity responses observed in our study.

Finally, the apparent mismatch between OGTT and HOMA data (i.e. CL vs. CS groups) deserves a few comments. The inherent limitations of the methods applied in the current study could partially explain the divergent results. It is important to highlight that we were not able to assess insulin response during OGTT, such that it mainly reflected glucose tolerance, whereas its capacity to estimate insulin sensitivity is debatable. Therefore, in order to provide a broader view of insulin sensitivity, we calculated the HOMA index, which considers both fasting insulin and glucose to estimate insulin sensitivity. Even though, caution should be exercised because this method is not a gold standard measure of insulin sensitivity, so further investigations should address this question using more accurate techniques, such as the clamp technique.

In conclusion, we showed that lipectomy, when accompanied by a high-fat diet, results in adipose tissue regain and impaired glucose tolerance. TNF-alpha is probably involved in the impaired glucose tolerance, while the high-fat diet may explain the fat regain. Exercise training can prevent glucose tolerance impairment and when exercise is associated with lipectomy, it can improve insulin sensitivity. A possible mechanism that may explains the adipose tissue compensation and greater insulin sensitivity observed after lipectomy combined with exercise is the increase in PPAR-gamma gene expression.

Acknowledgements

This research was supported by FAPESP 04/11291-7.

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