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Chronic Treadmill Running Affects Adipose Tissue Metabolism in Spontaneously Hypertensive Rats

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ABSTRACT

Ferreira A, Prímola-Gomes T, Menezes Z, Cruz J, Natali A Chronic Treadmill Running Affects Adipose Tissue Metabolism in Spontaneously Hypertensive Rats. *JEPonline* 2010;13(5): 9-18. We investigated in adipocytes of hypertensive rats (SHR) the effects of chronic treadmill running on parameters influenced by insulin (anti-lipolytic effect, glucose uptake) and on LPL activity. Male SHR were randomly divided into two groups: chronic exercise (CEX-SHR, n=10) and sedentary control (SED-SHR; n=10). Lipolysis was measured under basal, isoproterenol (ISO, 0.1 µM) and insulin (4.3 nM) stimulated conditions. Glucose uptake was measured under basal and insulin (4.3 nM) stimulated conditions. Lipoprotein lipase (LPL) activity was also measured. Lipolytic activity and anti-lipolytic effect of insulin were higher in CEX (0.64 ± 0.06 mM) than in SED group (0.43 ± 0.09 mM). Insulin-stimulated glucose uptake increased in CEX compared to SED group (4.08 ± 0.18 nmol/3 min CEX vs. 3.06 ± 0.23 nmol/3 min SED). LPL activity decreased in CEX compared to SED group (0.22 ± 0.06 nmol [^{3}H]-fatty acid released/min, CEX vs. 0.36 ± 0.04 nmol [^{3}H]-fatty acids released/min, SED). In conclusion, chronic treadmill running increased SHR adipocyte lipolysis response to ISO stimulation and insulin-stimulated glucose uptake with decreased LPL activity at resting conditions.

Key Words: Physical activity, Hypertension, SHR, Adipocyte

INTRODUCTION

The spontaneously hypertensive rats (SHR) is a widely accepted model to study essential hypertension and some of the metabolic dysfunctions that accompany this disease such as hyperinsulinemia, elevated blood glucose and free fatty acid (FFA) concentrations (1-3). These animals exhibit blunted insulin-stimulated glucose uptake in isolated adipocytes, plasma alterations of glucose levels and lipid metabolism (4,5). In addition, defective insulin inhibition of lipolysis (2) and a weak lipolytic response to adrenergic stimulation have been demonstrated in this model [6]. Moreover, the LPL activity is altered during the hypertensive process in SHR (7) and in Dahl salt sensitive rats (8).

Chronic exercise is one of the essentially non pharmacological therapeutic approaches that have been recommended to minimize the undesirable metabolic effects of hypertension (10,11). Improved insulin sensitivity was reported in female SHR submitted to running wheel training (10) and an increase in skeletal muscle glucose uptake was observed in stroke-prone swimming-trained SHR (13), suggesting that exercise training increase the responsiveness of skeletal muscle to insulin. Furthermore, *in vitro* studies demonstrated that exercise training resulted in an increased glucose uptake by skeletal muscle cells (14), even in the obese Zucker rats (13). Besides the effects on glucose metabolism, both acute and chronic exercises also influence the LPL activity (15,16). Despite these beneficial adaptations of skeletal muscle to exercise training, little is known about the direct effects of chronic treadmill running on the adipocyte metabolism of SHR.

The aim of this study was to investigate in SHR adipocytes the tissue-specific effects of chronic treadmill running on parameters that are influenced by insulin, such as anti-lipolytic effect, glucose uptake and LPL activity. We hypothesized that chronic exercise would be effective to improve both the insulin sensitivity and whole metabolism of SHR adipocytes thus, influencing in a tissue-specific manner metabolic pathways that are usually disrupted in the SHR.

METHODS
Animals and exercise protocol
Twenty 16-week old male SHR rats were housed in collective cages under 14-10 h light/dark cycle and had free access to water and standard rodent chow. They were randomly divided into chronic exercise (CEX-SHR, n = 10) and sedentary (SED-SHR, n = 10) groups. The animals from CEX-SHR group were subjected to a low-intensity running program on a motor-driven treadmill (Insight Equipments, SP, Brazil) during 8 weeks, 5 days/week (Monday to Friday). Running speed and duration were set at 12m/min for 15 min/day, 0% grade, in the first week. Then it was progressively increased up to a setting of 14 m/min for 30 min/day in the second week. From the third week on the exercise training protocol was set at 16 m/min, 0% grade, and maintained for 60 min/day (24). The sedentary rats were exposed to the treadmill 5 min/day, 10 m/min and 0% grade to become accustomed to the experimental protocol. Resting blood pressure measurement were obtained at baseline (pre-training period) and 48 hours after the last exercise training session (post-training period) by the tail-cuff method in conscious rat (25). One animal from CEX-SHR died from unknown reasons during the course of the experiment. Three days after the last exercise training session animals were killed by decapitation and tissues (brown and epididymal fat pad, and adrenal glands) were quickly collected and weighed. Plasma was isolated and stored at -20°C for further analysis. All experiments were performed between 8 AM and 10 AM (fasted state, overnight) (26,27) and carried out according to the regulations of the Ethical Committee for the Care and Use of Laboratory Animals at the Federal University of Minas Gerais (Protocol #174/06).

Adipocyte isolation

Pools of isolated adipocytes were prepared from the epididymal adipose tissue of SHR rats (28). Fat pads were enzymatically digested (Collagenase type II at 0.75mg/g adipose tissue, Sigma Chemical Co., USA) and were incubated at 37ºC with constant shaking for 45 min. Cells were filtered through nylon mesh and washed three times with buffer containing (mM): 137 NaCl, 5 KCl, 4.2 NaHCO3, 1.3 CaCl2, 0.5 MgCl2, 0.5 MgSO4, 0.5 KH2PO4, 20 HEPES (pH 7.4), supplemented with 1 % (wt/vol) fatty-acid free bovine serum albumin.

Lipolysis measurements

Lipolysis was measured by following the rate of glycerol release, as previously described (26). After washing, adipocytes were incubated at 37º C in a water bath for 60 min, in the presence or absence of the isoproterenol, a ß-adrenergic agonist (ISO 0.1 μM) and the effects of insulin (4.3 nM) on ISO-stimulated lipolysis were determined. At the end of the incubation period, an aliquot of the infranatant was removed for enzymatic determination of glycerol released into the incubation medium (KATAL, Belo Horizonte, MG, Brazil).

Glucose transport assay

The glucose transport was measured by the adipocyte 2-deoxy-[3H]glucose (2-DOG) incorporation. After isolation, adipocytes were incubated for 45 min at 37º C in the presence or absence of insulin (4.3 nM). The uptake 2-DOG was used to determine the rate of glucose transport as previously described (29). Briefly, glucose uptake was initiated by the addition of 2-DOG (0.2 μCi/tube) for 3 min. Thereafter, cells were separated by centrifugation through silicone oil and the cell associated radioactivity determined by scintillation counting. Nonspecific association of 2-DOG was determined by performing parallel incubations in the presence of 15 mM phloretin, and this value was subtracted of glucose transport activity at each condition.

Lipoprotein lipase activity

Lipoprotein lipase activity was measured as previously described [27]. Briefly, samples of epididymal adipose tissue (50 mg) were homogenized in a detergent solution containing heparin (10 mg/mL), sodium deoxycholate (2 mg/mL), Triton X-100 (0.08 mg/mL), BSA (0.25 M sucrose in tris buffer 0.2M, pH 8.3). Total LPL activity was measured using a [9,10-3H] triolein-containing substrate emulsified with lecithin and 24h fasted rat plasma as a source of apolipoprotein CII. The reaction was stopped by addition of 3.25 mL of methanol-chloroform-heptane 1.41:1.25:1 (v/v/v) followed by 1.05 mL of 0.1 potassium carbonate-borate buffer (pH 10.5). The [3H]-oleic acid released were quantified by liquid scintillation (Biodegradable Couting Scintillant - Amersham). The enzyme activity was expressed as nmol of [3H]-Fatty acid released/min.mg adipose tissue.

Plasma analysis

Plasma triglyceride, total cholesterol, glucose and glycerol were assayed by standard enzymatic methods using kits produced by KATAL (Belo Horizonte, MG, Brazil).

Statistical analysis

Unpaired Student's t-test was used to determine statistical significance between CEX-SHR and SED-SHR for adipose tissue and adrenal gland weights, plasma parameters and LPL activity. Differences in arterial blood pressure, body weight and glucose uptake were tested using two-way ANOVA. Lipolytic activity was tested using repeated measures ANOVA. All reported values are represented as mean ± SEM and were considered significantly different if $P < 0.05$.

RESULTS
Control parameters
As shown in table 1, sedentary and exercised SHR gained weight from pre- to post-training period. However, this gain was less pronounced in CEX-SHR (6% CEX-SHR vs. 10% SED-SHR; P<0.05).

After the exercise training period blood pressure did not change in the SED-SHR group and decreased by 7% in CEX-SHR (Table 1; P<0.05). These values were different between groups at the end of exercise period only. By the end of experimental period both adrenal weight and adrenal weight to body weight ratio, increased in CEX-SHR as compared to SED-SHR group. Nevertheless, no differences between groups were observed in adipose tissue weight and plasma parameters (Table 2).

Table 1. Effects of chronic treadmill running on body weight and blood pressure of SED-SHR and CEX-SHR groups.

Conditions	SED-SHR (n=10)		CEX-SHR (n=9_	
	Pre	Post	Pre	Post
BW (kg)	345.9 ±.0.4	379.0 ±.0.4*	344.0 ±.0.4	365.1 ±.0.5**,‡
BP (mm Hg)	162.5 ±.0.3	158.5 ±.0.3	170.6 ±.0.3	159.4 ±.0.5**

Data expressed as mean ± SEM. Abbreviations: BW; body weight, BP; blood pressure, Pre; Pre-Chronic Exercise value, Post; Post-Chronic Exercise value, *; different from SED-SHR Pre (P=0.05), **; different from CEX-SHR Pre (P=0.05), ‡; different from SED-SHR Post (P=0.05).

Lipolysis induced by ß-adrenergic stimulus and anti-lipolytic action of insulin
To study the effect of the chronic exercise on lipolysis, adipocytes were incubated in basal or ISO-stimulated conditions and the insulin responsiveness of lipolysis was measured. Since basal lipolysis is low, the anti-lipolytic action of insulin was tested against ISO-stimulated lipolysis (27). As depicted in Figure 1A, lipolytic activity was not different between groups in basal conditions (0.10 ± 0.01 mM SED-SHR vs. 0.09 ± 0.02 mM CEX-SHR). However, the lipolytic rate stimulated by ISO (0.1 µM) was more prominent in CEX-SHR group (0.64 ± 0.06 mM CEX-SHR vs. 0.43 ± 0.09 mM SED-SHR; P<0.05). Figure 1A also shows that the anti-lipolytic effect of insulin was not different between SED-SHR (0.13 ± 0.01 mM) and CEX-SHR (0.14 ± 0.04 mM).

Table 2. Effects of chronic treadmill running on adipose tissue weight, adrenals glands and plasma parameters of SED-SHR and CEX-SHR groups.

	SED-SHR (n=10)	CEX-SHR (n=9)
	Adipose tissue weight	
Brown (g/100g BW)	0.13 ± 0.01	0.12 ± 0.00
Epididymal (g/100g BW)	0.92 ± 0.04	0.95 ± 0.04
	Adrenals glands	
Weight (mg)	19.3 ± 0.2	22.9 ± 0.3#
Relative weight (mg/g)	0.05 ± 0.01	0.07 ± 0.01#
	Plasma	
Triglyceride (mM)	0.69 ± 0.03	0.71 ± 0.03
Total cholesterol (mM)	1.43 ± 0.08	1.45 ± 0.03
Glucose (mM)	6.82 ± 0.08	7.00 ± 0.15
Glycerol (mM)	0.11 ± 0.01	0.10 ± 0.01

See Table 1 for abbreviations.

Glucose uptake activity stimulated by insulin
The glucose uptake was also evaluated by adipocyte incubation with tritiated 2-DOG which is transported, phosphorylated but not oxidized by the cell (30). Consequently, it accumulates as 2-DOG-6-phosphate inside the cell. The accumulated radioactivity inside the adipocytes is used to evaluate the capacity of glucose uptake in these cells. The insulin action on glucose uptake was also evaluated. As shown in Fig. 1B, the basal glucose uptake was not significantly altered by the chronic exercise (0.87 ± 0.11 nmol/3 min CEX-SHR vs. 0.61 ± 0.07 nmol/3 min SED-SHR). Insulin (4.3 nM) increased the glucose uptake in both groups. However, this increase was higher in CEX-SHR than in SED-SHR group (4.08 ± 0.18 nmol/3 min vs. 3.06 ± 0.23 nmol/3 min, respectively, P<0.05).

Adipose tissue LPL activity

Circulating triglyceride-fatty acid uptake was estimated by measuring LPL activity, the enzyme that hydrolyzes the core of triglyceride-rich lipoproteins into FFA and monoglyceride in epididymal fat pads. The results showed a 37% decrease in LPL activity in epididymal adipose tissue from CEX-SHR (0.22 ± 0.06 nmol [^{3}H]-FAR/min) when compared to that of SED-SHR (0.36 ± 0.04 nmol [^{3}H]-FAR/min, P<0.05) (Fig. 1C).

DISCUSSION

The purpose of this study was to investigate in SHR adipocytes the tissue-specific effects of chronic treadmill running on parameters that are influenced by insulin. The main findings were that the adipocytes from SHR submitted to chronic exercise exhibited a framework of increased ISO-stimulated lipolysis and anti-lipolytic effect of insulin associated to higher insulin response on glucose uptake and to decreased LPL activity at resting conditions.

Chronic exercise is known as a stressor that increases the adipocyte response to catecholamine in normotensive rats (31). Such adjustments are made at the adrenal gland and sympathetic control levels and act through the ß-adrenergic receptors coupled with the adenylate cyclase system to assist with the energy supply to the active muscles and other tissues (32). The experiment using ISO allowed us to mimic the stimulation performed by catecholamine in adipose tissue and to evaluate the ability of this tissue to release substrates to circulation by means of lipolysis as reported elsewhere (26). While previous reports have demonstrated that SHRs have defective catecholamine-mediated lipolysis (2), our chronic exercise program helped to enhance the sensitivity of adipocytes from SHR to ISO resulting in a higher degree of lipolysis at resting conditions. Our data showed that chronic exercise increased the adipocyte response to adrenergic agonists (32 %) on lipolysis. Although the sympathoadrenergic system responds to both low- and high-intensity exercise with even higher response to high-intensity exercise, Shepherd et al. (33) reported that adipocytes from female SHR submitted to high-intensity treadmill running training were minimally responsive to ISO. Our data give support to the idea that low-intensity chronic exercise is also efficient to restore catecholamine-mediated lipolysis in adipocytes from SHR.
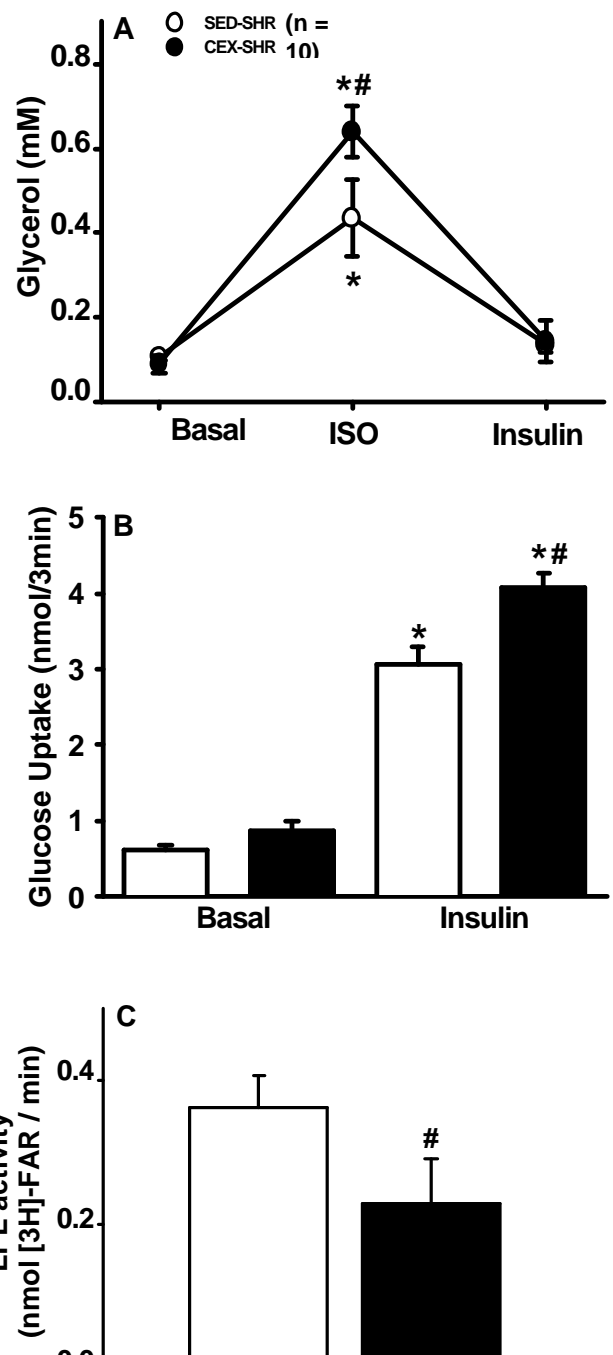

Figure 1 – A) Effects of chronic treadmill running on lipolysis in Basal, ISO (0.1 µM) and Insulin (4.3 nM) stimulated conditions. B) Effects of chronic treadmill running on glucose uptake C) Effects of chronic treadmill running on LPL activity. Data expressed as *mean ± SEM*. *, $P < 0.05$ versus Basal and Insulin conditions for both groups; #, $P < 0.05$ versus SED-SHR ISO condition.

The exact pathway involved in this increased response to catecholamine in SHR adipocytes remains unclear. The increases in the response to catecholamine stimulated by ISO and adrenal hypertrophy found in the present study agree with previous evidences showing that exercise training increases the capacity of the sympathoadrenergic system to mobilize energy, at the adipose tissue level, to supply active muscles (31,34). So, it is reasonable to point out that changes associated with circulating levels of catecholamine and to alterations in the sympathetic activity itself may influence sub cellular pathways (31, 32, 34, 35). It was recognized that the defective control of lipolysis by catecholamine is under the predominant control of a single gene locus at chromosome 4 in SHR (2). Despite the evidence that the adipocyte receptor signaling of SHR and normotensive rats are responsive to exercise training, there are no differences in either ß-adrenergic receptor density or affinity, even after the training period (33).

The SHR phenotype is characterized by increased insulin resistance at the whole body and adipocyte levels (1). The chronic exercise protocol used in the present study enhanced the sensitivity of adipocytes from SHR to insulin leading to an increased glucose uptake at resting conditions. This effect of chronic exercise has been shown in SHR voluntarily exercised in running wheels (10). Hajri and colleagues (37) and others (1, 38) showed that SHR exhibited deficient fatty acid transporter CD36 expression which impairs FA oxidation to a larger extent than it impairs FA esterification. This disruption on FA oxidation has been coupled with both reduced (37) and augmented (1) rates of glucose utilization. Our results suggest that chronic treadmill running stimulates independent sub cellular pathways related to insulin action, particularly glucose uptake.

In the present study, the effect of chronic exercise on insulin-stimulated glucose uptake measured in the adipose tissue was lower than one would expect for trained skeletal muscle. Accordingly, exercise training increases the whole body glucose clearance and this adaptive response is more prominent in skeletal muscle than in adipose tissue from normotensive rats (39). However, such increases cannot be addressed exclusively to the skeletal muscle (40). Other tissues, including adipose tissue, have been ascribed as important contributors to the increases in whole body glucose clearance induced by chronic exercise (40). The results of the present study give support to the importance of adipose tissue to insulin-stimulated glucose uptake in SHR.

Our data showed that LPL activity was reduced in adipocytes from CEX-SHR. Earlier studies demonstrated that LPL activity in adipose tissue of normotensive Spreague-Dawley rats was responsive neither to long-term treadmill exercise training (16) nor to acute exercise bout, as measured 24 h post exercise (15). It is important to consider the fact that LPL activity is regulated in a tissue specific manner and may be linked to both pre- and post-transcriptional controls (15, 16). Sambandam and colleagues (7) showed that LPL activity was reduced and possibly coupled with significantly diminished FFA supply to the SHR myocardium. It may be possible that the reduction in LPL activity found in the present study promotes a drift of FA to other tissues, particularly skeletal muscle, apparently an important target for the effects of chronic exercise and hypertension on LPL (15, 16, 41). In fact, it is well established that chronic exercise improves the lipid oxidation capacity (31).

Finally, our chronic exercise program helped to enhance glycerol release with ISO stimulation and insulin-stimulated glucose uptake associated with decreased LPL activity. This lower LPL activity would suggest less lipid storage which coincides with greater glycerol release with ISO. The increased rate of lipolysis associated to decreased LPL activity may have contributed to the reduction of body weight observed in exercised rats.

CONCLUSIONS

The findings of the present study show that adipocytes from SHR are sensitive to chronic treadmill running. The exercise program used here increased SHR adipocyte ISO-stimulated lipolysis and anti-lipolytic effect of insulin associated to higher insulin response on glucose uptake and to decreased LPL activity at resting conditions.

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