Exercise Physiology

Interval or continuous aerobic exercise performed 3 days a week increases endothelium-dependent relaxation in female rats fed with fructose

Anderson Gregorio Joaquim[1], Leandro Kansuke Oharomari[2], Gabriel Tavares do Vale[3], Carlos Renato Tirapelli[3], Camila de Moraes[1]

[1]Universidade de São Paulo, Escola de Educação Física e Esporte de Ribeirão Preto, Ribeirão Preto, SP, Brazil; [2]Universidade Estadual Paulista "Júlio de Mesquita Filho", Escola de Ciências Farmacêuticas de Araraquara, Departamento de Alimentos e Nutrição, Araraquara, SP, Brazil; [3]Escola de Enfermagem de Ribeirão Preto, Departamento de Enfermagem Psiquiátrica e Ciências Humanas, Laboratório de Farmacologia, Ribeirão Preto, SP, Brazil.

Associate Editor: Katia de Angelis. [1]Universidade Federal de São Paulo, São Paulo, SP, Brazil, [2]Graduate Program in Translational Medicine, Universidae Nove de Julho, São Paulo, SP, Brazil. E-mail: prof.kangelis@yahoo.com.br.

Abstract - Aim: We investigated the effects of continuous or interval aerobic exercise training on vascular reactivity of female rats fed with fructose. **Methods:** Female Wistar rats (8-wk old) were divided into: sedentary (SD), continuous training (CTR), and interval training (ITR). Moderate intensity training protocols consisted of running 3 days/week for 7 weeks. CTR ran 40 min at 30%−40% of the maximal speed (MS) and TRI consisted of 7 sets of 1 min at 70% of MS followed by 3 min at 35% of MS. Animals were fed with standard chow and fructose (10%) in drinking water. Concentration-response curves to acetylcholine and phenylephrine, and oxidative stress biomarkers, were determined in the aorta. Body weight gain, visceral fat, and plasma triglycerides and glucose were also evaluated. **Results:** Endothelium-dependent relaxation was significantly increased by both exercise regimens (CTR: Emax = 85 ± 6% and ITR: Emax = 84 ± 1%) compared to sedentary rats (SD: Emax = 62 ± 5%). The contractile maximal response was not different but phenylephrine potency was increased in CTR (pEC_{50}: 8.41 ± 0.19) and reduced in ITR (pEC_{50}: 7.06 ± 0.11) compared to SD (pEC_{50}: 7.77 ± 0.08). In addition, the generation of superoxide was lower in trained groups as compared with sedentary (about −28% in CTR and −22% in ITR). TBARS and nitrate/nitrite levels were not modified. Compared to the SD group, ITR gained 39% less body weight and CTR has 29% less visceral fat. Glucose and triglycerides were not modified. **Conclusion:** CTR and ITR, carried out 3 days/week, were efficient to improve endothelium-dependent relaxation and reduce superoxide generation in the aorta from female rats fed with fructose.

Keywords: interval exercise, fructose, vascular reactivity, endothelium, oxidative stress.

Introduction

It has been demonstrated that high fructose diet consumption is associated with an increase in adipose tissue[1]. Even before the excessive body fat gain, animals fed fructose-rich diets show a significant rise in blood triglycerides, low-density lipoproteins, insulin resistance, hyperglycemia, and impairment of endothelium-dependent relaxation[2,3]. Decreased NO availability is only one of the mechanisms associated with endothelial dysfunction[4], which increases the susceptibility to the development of cardiovascular diseases. It has been documented that estrogen is protective against vascular dysfunction in premenopausal females when compared to age-matched males[5]. However, it would seem that estrogen's protection is lost when women are exposed to poor behaviour (poor nutrition habits, high-caloric diet, smoking, alcohol consumption). Roberts et al.[6] reported that long-term high fat, high refined-carbohydrate diet induces endothelial dysfunction and decreases plasma antioxidant capacity in female rats, even before the onset of hypertension.

On the other hand, exercise is well recognized as a non-pharmacological approach to preventing and treating vascular disorders. It has been reported in both humans[7] and animals[8] that endothelium-mediated vasodilatation is improved after aerobic exercise training. Moreover, aerobic exercise reduces oxidative stress in the aortic artery of obese animals[9,10] and improves the production of NO, which is the main endothelium-derived relaxing factor[11].

Currently, the determination of optimal training variables to improve vascular function is an emerging

challenge in exercise science. The influence of different methods, intensities, and the ideal frequency of exercise sessions have not been determined. Most of the animal studies were carried out using moderate-intensity continuous training[9,11-13] In humans, it has been proposed that high-intensity interval training is considered a time-efficient alternative to improve cardiometabolic health[14,15]. However, the short duration of high-intensity efforts carried out in different animal models is still controversial. For example, greater endothelium-dependent relaxation of the mesenteric artery was observed in rats fed with a high-fat high-carbohydrate diet and submitted to physical training five times a week for 12 weeks[16]. In contrast, a pathological adaptation in the left ventricle was observed in hypertensive rats caring out five times a week of high-intensity exercise training[17], and no significant effects in the antioxidant defense were observed in healthy Wistar rats which had trained six times a week[18].

Although the responses of aerobic exercise training in vascular function are well documented in male experimental models as mentioned above, it was still unclear whether exercise training affects female rats' vasculature responses. The improvement in endothelium-dependent response was shown in non-ovariectomized hypertensive rats after 6 weeks of swimming exercise (1 h/day, 5 days/wk)[19], and after 6 weeks of voluntary running (30% of maximal aerobic velocity, 7 days/wk)[20]. To date, we did not identify studies on the possible effect of physical exercise in preventing endothelial dysfunction in fructose-fed female rats. Thus, we aimed to investigate the effects of continuous versus interval exercise training on vascular responsiveness of fructose-fed non-ovariectomized female rats. In addition, considering the importance of translational research we carried out an exercise protocol with three sessions per week, which is similar to observed exercise behaviour in humans.

Methods

Animals

Twenty-four female Wistar rats (Rattus norvegicus, 60 days) were divided into 3 groups: sedentary (SD), continuous training (CTR), and interval training (ITR). Animals were housed in collective polypropylene cages (41×34×30 cm) (four animals/cage) and kept on a 12 h light/dark cycle with free access to standard chow and fructose (10%) in drinking water. Food and fructose solution intake were daily assessed, and body weight was measured weekly. After 7 weeks, animals were submitted to overnight fasting (about 8 h), anesthetized (Thiopental Sodium 35 mg/kg, i.p.), and exsanguinated by the descendent aorta. The thoracic aorta was carefully removed and the visceral fat pad (retroperitoneal and perirenal fat) was excised and weighted.

All procedures were reviewed and approved by the Ethics Committee on Animal Use in Research (CEUA/PUSP-RP protocol number 14.1.874.53.7) in compliance with the "Principles of Laboratory Animal Care" (NIH publication Nº 86-23, revised 1985) and the National Law (CONCEA publication Nº 11.794, 2008).

Incremental maximal treadmill test and exercise training protocol

Animals were submitted to treadmill adaptation, which consisted of one week of running at 10 m/min for 30 min daily. After this, all rats underwent an incremental treadmill test, beginning at 11.6 m/min followed by progressive increases of 1.6 m/min every 2 min until 20 m/min. Subsequently, the speed was increased by 3.2 m/min with rats running until exhaustion (determined when the animal touched the bottom of the treadmill five times within one minute). The exhaustion speed was used to determine maximal speed (MS) using the following equation: MS = W1 + (W2 x t/120), where W1 = exhaustion speed, W2 = speed increase (1.6 m/min or 3.2 m/min), t = duration of the incomplete test stage. Exhaustion speed was considered as a parameter of animals' running ability and was used for the allocation of animals in the CTR and TRI groups to guarantee that the animals' ability of running was similar between groups.

Physical exercise training

The two exercise protocols began concomitantly with the consumption of fructose and were carried out for 7 weeks, 3 times a week (Monday, Wednesday, and Friday) in the morning. Aerobic continuous exercise training (CTR) consisted of a five-min warm-up (running at 30% of MS) followed by 40 min of running and a 5-min cooldown. Running velocity was progressively increased over the weeks of training, beginning at 30% until 40% of MS. The aerobic interval exercise training (TRI) consisted of a five-min warm-up (running at 30% of MS) followed by 28 min of running (1 min at 70% of MS and 3 min of active rest at 35% of MS) and a 5-min cooldown. Running velocity was also progressively increased over the weeks of training. The training loads were equalized to isolate the effect of exercise intensity, that is, the total volume of work performed by each group was matched, the only difference being the type of stimulus (continuous or interval).

Concentration-response curves

Thoracic aorta was placed in freshly prepared Krebs solution containing (mM): NaCl, 118; $NaHCO_3$, 25; glucose, 5.6; KCl, 4.7; KH_2PO_4, 1.2; $MgSO_4$, 1.17 and $CaCl_2$, 2.5. The arteries were cleaned of all adherent tissue and cut into rings of approximately 2 mm. Each ring was suspended between two wire hooks and mounted in 5-mL organ chambers with Krebs solution at 37 °C, pH 7.4, and continuously gassed with a mixture of 95% O_2 and 5%

CO_2 under a resting tension of 10 mN. The tissue's isometric tension was recorded by a force-displacement transducer (UgoBasile, Varese, Italy) connected to a PowerLab 400™ data acquisition system (ADInstruments MA, EUA). After 1 h of the stabilization period, cumulative concentration-response curves to acetylcholine (ACh, 10 mM-100 µM) were obtained in endothelium intact aortic rings were pre-contracted with phenylephrine (2 µM). Relaxing responses have been calculated as percentages of the contraction induced by phenylephrine. The contractile response was assessed by concentration-response curves to phenylephrine (PHE, 1 nM − 3 µM). Emax represents the maximal response that the agonist produced and was represented in percentage. The equation used was: (tension ∗ 100) / resting tension) − 100. Nonlinear regression analyses to determine the maximal response (Emax) and the agonist concentration required to induce the half of maximal response (EC50) using GraphPad Prism (GraphPad Software, San Diego, CA, USA).

Plasma glucose and triglycerides

Blood samples were taken from the descendent aorta, plasma and serum were immediately separated by centrifugation (8000*g*). Glucose and triglycerides concentrations were measured using specific kits (colorimetric method, Laborlab, São Paulo, SP, Brazil).

Detection of superoxide anions in aortic rings by lucigenin chemiluminescence

The lucigenin-derived chemiluminescence assay was used to determine superoxide levels in aortic rings homogenates 10% (wt/vol) prepared in phosphate buffer (20 mM of KH_2PO_4, 1 mM of EGTA, and 150 mM of sucrose). The reaction was started by the addition of NAD(P)H (0.1 mM) to the suspension (250 µL of final volume) containing sample (50 µL), lucigenin (5 µM), and phosphate buffer [pH 7.4]. Superoxide production was expressed as a relative light unit (RLU)/mg protein. Protein concentrations were determined with a protein assay reagent (Bio-Rad Laboratories)[21].

Measurement of tissue thiobarbituric acid-reacting substances (TBARS) and nitrite/nitrate (NOx)

The assays were performed following the manufacturer's instructions (TBARS assay kit, Cayman Chemical Company, USA, Cat. No. 10009055) and (Nitrite/Nitrate Colorimetric Assay Kit, Cayman Chemical Company - 780001). Thiobarbituric acid-reacting substances were determined using aortic rings which were homogenized in lysis buffer plus protease inhibitor and centrifuged (1600*g* for 10 min at 10°C). Subsequently, 25 µL of the supernatant or plasma were added to a 2 mL microtube to initiate the reaction with thiobarbituric acid (TBA). The malonaldehyde present in the sample reacts with the TBA to form a pink-colored product. After absorbance measurements (540−550 nm) the TBARS values were determined in mmol/mL. To measure the NO production, the nitrite (NO_2^-) and nitrate (NO_3^-) aortic rings were homogenized in 200 µL of PBS buffer (pH 7.4) and centrifuged (10000 g for 10 min at 24°C). Then, 200 µL of the supernatants obtained were centrifuged (14000*g* for 15 min at 24 °C) in 30 kDa ultracentrifugation devices. Centrifuged samples were used in a colorimetric assay based on the Nitrite/Nitrate reaction with the Griess reagent, which has a pink color diazo compound. After measuring the absorbances of the standards and samples (540-550 nm) the nitrate values expressed in nmoL/mg of protein were determined.

Statistical analysis

Data are given as the mean±standard error of the mean (SEM). The normality test (Kolmogorov-Smirnov test) was followed by the analysis of variance (one-way ANOVA) and Tukey posthoc test to identify differences between groups. Data analysis was performed using IBM SPSS v.21 software and a $p < 0.05$ was considered significant.

Result

Bodyweight gain and fat pad weight and serum parameters

Compared to the SD group, both trained groups had less body weight gain, −18% for CTR and −39% for the ITR group. However, only ITR results reach statistical significance. On the other hand, only CTR showed lower visceral fat as compared with the SD group (29%). In contrast, any differences were observed in glucose and triglycerides levels. Data are summarized in Table 1.

Oxidative stress biomarkers

Superoxide level, analyzed by lucigenin assay, was markedly reduced in both CTR (−28%) and ITR (−22%) compared with SD. Regarding lipid peroxidation (TBARS) and nitrate/nitrite levels, we did not observe differences (Table 2).

The endothelium-dependent response

Endothelium-dependent relaxation was significantly increased by both exercise regimens (CTR: $E_{max} = 85 \pm 6\%$ and ITR: $E_{max} = 84 \pm 1\%$) compared to sedentary rats (SD: $E_{max} = 62 \pm 5\%$). No changes were observed in agonist potency (Figure 1A). The maximal response to phenylephrine was not modified by exercise training. However, continuous exercise training increased aortic sensitivity to phenylephrine by 4-fold, on the other hand, interval training induced a 5-fold reduction in this agonist sensitivity (Figure 1).

Table 1 - Bodyweight gain, fat pad weight, and serum parameters after 7 weeks.

	SD	CTR	ITR	F	p-value
Body weight gain (g)	126.4 ± 8.7	103.6 ± 16.1	77 ± 9.9*	3.7	0.01
Visceral fat (g)	14.9 ± 1.2	10.6 ± 0.7*	13.7 ± 1.1	4.5	0.04
Glucose (mg/dL)	135.2 ± 12.4	121.8 ± 4.3	122.6 ± 8	0.7	0.51
Triglycerides (mg/dL)	85.5 ± 4.8	68.7 ± 9.3	68.5 ± 10.4	1.3	0.31

Data are given as the mean ± S.E.M. One-way ANOVA (Tukey posthoc, $p < 0.05$), n = 5 for each group.
*Different from SD.

Table 2 - Oxidative stress biomarkers after 7 weeks.

	SD	CTR	ITR	F	p-value
Lucigenin (RLU/mg protein)	59.1 ± 3.4	42.4 ± 2.3*	46.2 ± 3.5*	6.3	0.02
TBARS (mmol/mg protein)	10.7 ± 2.8	8.5 ± 3.2	7.6 ± 3.1	0.3	0.76
Nitrate/Nitrite (nmol/mg protein)	39.2 ± 5.4	45.1 ± 7.7	34.2 ± 4.5	0.9	0.44

Arterial production of superoxide by lucigenin-derived chemiluminescence assay. Lipidic peroxidation by thiobarbituric acid-reacting substances assay (TBARS). Nitrate/Nitrite production; Data are given as the mean ± S.E.M. One-way ANOVA (Tukey posthoc, $p < 0.05$), n = 5 for each group.
*Different from SD.

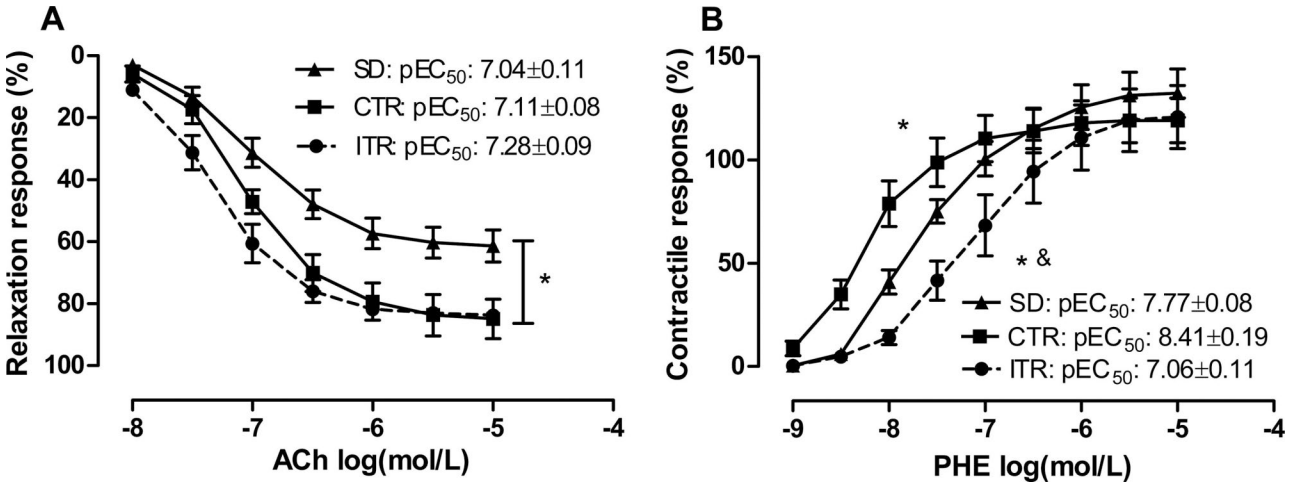

Figure 1 - Concentration-response curves to acetylcholine in aortic rings pre-contracted with phenylephrine (2 μM) (panel A) and concentration-response curve to phenylephrine in endothelium intact aortic rings (panel B) from sedentary (SD), aerobic continuous (CTR) and interval exercise training (ITR) rats. Data are means ± S.E.M. One-way ANOVA (Tukey post-test, $p < 0.05$), n = 5 in each group. *Different from SD; &different from CTR.

Discussion

To the best of our knowledge, our study is the first to show that continuous or interval exercise training, carried out 3 times a week for 7 weeks, improves endothelium-dependent vasodilatation response in the aortic artery from non-ovariectomized rats fed with fructose. Moreover, both exercise protocols reduced the superoxide level in the vasculature. We also observed that only interval exercise prevented excessive body weight gain and only continuous exercise prevented excessive visceral fat gain.

Previous research evaluating rats fed with a high caloric diet that performed continuous aerobic training reported similar effects on visceral fat after six or eight weeks of treadmill exercises[22,23]. We hypothesized that the protocol of interval exercise, carried out in this study, was not sufficient to decrease the visceral fat fructose-induced because it did not modify the *de novo* lipogenesis from fructose metabolism[24]. Fructose is a monosaccharide that is regulated by fructokinase in the liver and has no negative feedback system to control the entrance, which is favorable to fat synthesis[1]. In our study, female rats had free access to fructose in their drinking water during the entire intervention. Due to poor metabolic control of fructose entrance, expected to occur an accumulation of cellular energy and rapidly fat synthesis, which increases fat in visceral adipose tissue[1].

Exercise training is considered a non-pharmacological approach to preventing cardiometabolic diseases. Trained subjects show a decrease in insulin resistance, systemic inflammation, improvement of lipid profile, and

cardiorespiratory fitness[25]. In the present study, neither of our exercise modes (CTR vs ITR) was effective in modifying plasma triglycerides. Similar results were observed in Sprague-Dawley rats submitted to 8 weeks of continuous and interval swimming exercise carried out 5 days a week[23]. Conversely, male Wistar rats fed with a high caloric diet had lower triglycerides when submitted to 5 days a week of treadmill running at moderate intensity for 4 or 12 weeks[13,26].

Several studies have demonstrated that the impairment of endothelium-dependent relaxation is a consequence of high-fat diet intake and obesity in both, human and animal models[27-29]. A multiplicity of mechanisms has been proposed to explain the impairment of endothelial function, which includes oxidative stress[30,31], a decrease in antioxidant capacity, and high plasma triglycerides[2,26]. In our study, aortas from SD animals showed endothelium-dependent relaxation of about 60%. This response is lower than that found in aortic rings from rats not exposed to fructose intake[26] and is like that observed in femoral rings from animals fed with a high-fat diet[29]. On the other hand, our continuous or interval exercise was effective to improve endothelium-dependent relaxation, even though the exercise sessions were carried out 3 times a week. This result is in agreement with previous findings showing improvement in relaxation response after exercise training sessions performed 5 times a week[9,29,32].

Our present findings showed that both continuous or interval training in female rats could be a non-pharmacological approach to preventing oxidative stress even in fructose-fed animals. These results are supported by tissue arterial production of superoxide levels, which were significantly decreased by approximately 26% and 22% in CTR and ITR respectively, as compared to the SD group. The pioneer studies showing the effect of physical exercise on endothelial cells were conducted in the 90s. It has been proposed that the increase of pulsatile blood flow on endothelial cells, promotes a potential mechanical stimulus for NO production[33] as was seen after 4 weeks of exercise training[34]. In addition, the bioavailability of NO could be increased either by the rise of antioxidant enzyme expression or reduction of reactive oxygen species (ROS)[9,11].

Previous studies have shown a significant increase in vascular expression and antioxidant activity of superoxide dismutase enzymes (SOD-1, SOD-2, and SOD-3) after training[26]. Moreover, trained animals show a rise in adaptative responses in catalase and glutathione peroxidase, reducing oxidative stress and the impairment in endothelium-dependent dilation[35,36]. Although we had not directly quantified the antioxidant production, we observed lower superoxide production in aortic tissue from trained rats. This result could be associated with the increased NO bioavailability which led to an improvement in endothelium-dependent relaxation. A previous study has shown that a lower generation of ROS in response to aerobic exercise training could prevent endothelial dysfunction[10].

Regarding contractile response, although the maximal response was unchanged, continuous and interval training exert different effects on an alpha-adrenergic sensitivity, probably related to the type of stimulus on the cardiovascular system. The phenylephrine sensitivity was reduced by 5-fold in the ITR group. A similar result was observed in intact or endothelium-denuded superior mesenteric artery from male Wistar submitted to swimming training[37] On the other hand, continuous training increased the alfa-adrenergic sensitivity by 4-fold and this result was similar to those observed in aortic rings from male Wistar rats that underwent physical exercise for four weeks[34]. An increase in male Sprague Dawley femoral artery vasoconstriction was seen after high-intensity treadmill exercise due to an augmented sympathetic stimulation[39]. This exercise intensity effect on aortic vasoconstriction was also demonstrated in male Wistar rats submitted to swimming exercise intensities with efforts at and above the lactate threshold eliciting an increase in contractility in an intensity-dependent manner[40]. The intensity-dependent response has been considered for the prescription of exercise for the control of hypertension, with greater amplitude of hypotensive response being observed after moderate-intensity exercise, below 70% of maximal oxygen consumption[41].

Conclusions

Continuous and interval aerobic training, carried out three days a week, were efficient to improve endothelium-dependent relaxation and reduce superoxide generation in the aorta from female rats fed with fructose. This effect was observed independent of body weight gain or fat pad amount. This result reinforces the importance of physical exercise as a protective factor against the development of cardiovascular diseases. Noteworthy this effect was observed even in the presence of daily consumption of large amounts of fructose, a nutrient that causes impairment in endothelium-dependent relaxation.

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Corresponding author

Camila de Moraes, Universidade de São Paulo, Escola de Educação Física e Esporte de Ribeirão Preto, Ribeirão Preto, SP, Brazil.
E-mail: camimoraes@usp.br.

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