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High-intensity interval training has beneficial effects on cardiac remodeling through local renin-angiotensin system modulation in mice fed high-fat or high-fructose diets

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ABSTRACT

Aims: HIIT (high-intensity interval training) has the potential to reduce cardiometabolic risk factors, but the effects on cardiac remodeling and local RAS (renin-angiotensin system) in mice fed high-fat or high-fructose diets still need to be fully addressed.

Main methods: Sixty male C57BL/6 mice (12 weeks old) were randomly divided into three groups, control (C), High-fat (HF), or High-fructose diet (HRU) and were monitored for eight weeks before being submitted to the HIIT. Each group was randomly assigned to 2 subgroups, one subgroup was started on a 12-week HIIT protocol (T = trained group), while the other subgroup remained non-exercised (NT = not-trained group).

Key findings: HIIT reduced BM and systolic blood pressure in high-fat groups, while enhanced insulin sensitivity after high-fat or high-fructose intake. Moreover, HIIT reduced left ventricular hypertrophy in HF-T and HFRU-T. Notably, HIIT modulated key factors in the local left ventricular renin-angiotensin-system (RAS): reduced protein expression of renin, ACE (Angiotensin-converting enzyme), and (Angiotensin type 2 receptor) AT2R in HF-T and HFRU-T groups but reduced (Angiotensin type 1 receptor) AT1R protein expression only in the high-fat trained group. HIIT modulated ACE2/Ang (1–7)/Mas receptor axis. ACE2 mRNA gene expression was enhanced in HF-T and HFRU-T groups, complying with elevated Mas (Mas proto-oncogene, G protein-coupled receptor) receptor mRNA gene expression after HIIT.

Significance: This study shows the effectiveness of HIIT sessions in producing improvements in insulin sensitivity and mitigating LV hypertrophy, though hypertension was controlled only in the high-fat-fed submitted to HIIT protocol. Local RAS system in the heart mediates these findings and receptor MAS seems to play a pivotal role when it comes to the amelioration of cardiac structural and functional remodeling due to HIIT.

1. Introduction

The prevalence of obesity has increased worldwide and is associated with our current lifestyle, which promotes sedentary and bad eating habits as excessive intake of fructose, mainly found in industrialized beverages and food [1,2], or western diet, made up of excessive carbohydrate and fat. These conditions are collaborating to the currently increased incidence of cardiovascular diseases (CVD) [3,4].

The physical inactivity is harmful to cardiovascular function and has been associated with an increased risk of chronic diseases such as type 2 diabetes, and hypertension [5]. Moreover, nowadays the lack of time is the barrier to exercise adherence. In this context, high-intensity interval training (HIIT) is a mode of training that requires little time and can be described as 'brief intervals of vigorous activity interspersed with periods of low activity or rest,' which induces a strong acute physiological response [6]. Also, HIIT has demonstrated improvements in reducing cardiometabolic risk factors as the traditional moderate - intensity continuous training (MICT) [6,7].

In concerning of the diets, presently there is an increased interest in the potential role of the added sugars, mainly fructose as a contributing factor to CVD. When consumed in elevated concentrations, fructose can promote metabolic changes as hyperuricemia, inflammation [8], and hypertension [9].

It is important to note that the excessive dietary fat intake leads to increased lipid deposition in both adipose and non-adipose tissues. Also, dietary fat induces the oxidation of fatty acids and consequently increasing lipid peroxidation products promoting a chain of events that leads the development of CVD [10] like left ventricular hypertrophy

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(LVH) and diastolic dysfunction [11]. Likewise, a high-fructose diet negatively affects the cardiac structure and function [12].

On the other hand, exercise training is strongly associated with reduced chronic disease risk and has largely been employed to counter risk factors for obesity, hypertension, and CVD [13,14]. In this context, recent evidence indicates that HIIT provides a stronger stimulus than MICT for eliciting myocardial improvements [15].

However, while the relation between aerobic exercise and blood pressure and cardiovascular health has been extensively explored [16,17], little is known about the direct effects of HIIT on the molecular components of the renin-angiotensin system (RAS), especially in models of diet-induced obesity by fat or fructose.

It is well known that the RAS has widely cardiovascular regulatory effects and its abnormality participates the generation and development of hypertension [18]. In this way, the hyperactivation of the RAS contributes to structural and functional myocardial fibrosis and cardiac hypertrophy, and the local RAS in the heart may have a decisive role [15]. RAS deregulation also causes volume overload and peripheral vasoconstriction leading to increased LV diastolic filling pressures, LV hypertrophy (LVH) and alterations of cardiac geometry [19,20]. We know now that the classic ACE/Ang II/AT1 receptor axis is not the only signal pathway involved in the activation of RAS, but other pathways like the ACE2/Ang (1–7)/Mas receptor axis play a pivotal role counteracting many effects of Ang II on the cardiovascular and renal systems [21].

Considering that animals fed with high-fat or high-fructose diets are well-established mouse models used to study cardiac hypertrophy/cardiomyopathy [22,23], with insulin resistance, hypertension and overactivity of RAS and the pivotal role that RAS imbalance play on adverse cardiovascular remodeling, we hypothesized that HIIT alleviates the adverse cardiovascular remodeling and counter the metabolic impairments stemmed from excessive fat or fructose intake in mice by modulating the local RAS. For this, we evaluated the protein and gene expression of the RAS system in the LV, as well as the wall morphometry of the LV; Lipid profile, systolic blood pressure, and insulin sensitivity were also evaluated to determine how HIIT impacted cardiometabolic parameters after fructose or high-fat diet intake.

2. Material and methods

2.1. Animals and experimental design

The protocol and experiments were submitted and approved by the Ethics Committee on Animal Experiments of the State University of Rio de Janeiro (CEUA/013/2016), in accordance with the Guide for Care and Use of Laboratory Animals published by the U.S. National Institutes of Health (NIH Publication no. 85-23 revised in 1985). The environment was subjected to a 12 h light–dark cycles and air exchange (15 min/h), the animals were kept in a ventilated shelf system (EcoFlo system, Allentown, USA), under appropriate conditions of temperature (21 ± 2 °C) and humidity (60 ± 10%); with free access to specific experimental diets: Control, High-fat or High-fructose, and water ad libitum. The control and the high-fructose diets were isocaloric, differing in the amount of fructose (50% of the total energy as fructose in the high-fructose diet). The high-fat diet presented with 40% of the energy as lard, as seen in Table 1. The diets were prepared based on the American Institute of Nutrition standard rodent (AIN93-M) [24] and were produced by PragSolucoes (Jau, SP, Brazil).

Three-month-old male C57BL/6 mice were studied; each group was randomly assigned to one of the three groups (n = 20 per group), as follows: control, High-fat diet, or High-fructose diet and were monitored for eight weeks before the HIIT protocol. After eight weeks on the respective diets, each group was randomly subdivided into two subgroups (trained or non-trained), totalizing six groups (n = 10 each group) for a 12-week HIIT protocol, as follows:

Table 1
Dietary compositions. Protein, mineral and vitamin mixtures of all diets are in accordance with AIN-93 M. The experimental diets were modified in their respective nutrients: HFRU = 50% of fructose and HF = 40% lard + 10% soybean oil.

Nutrients	Diets		
	Control	HFRU	HF
Casein	140.0	140.0	175.0
Corn starch	620.7	146.4	347.7
Sucrose	100.0	100.0	100.0
Lard	–	–	**238.0**
Fructose	–	**474.3**	–
Soybean oil	40.0	40.0	40.0
Fiber	50.0	50.0	50.0
Vitamin mix	10.0	10.0	10.0
Mineral mix	35.0	35.0	35.0
Cystine	1.8	1.8	1.8
Choline	2.5	2.5	2.5
Antioxidant	0.008	0.008	0.008
Total (g)	**1000**	**1000**	**1000**
Energy	**3802.8**	**3802.8**	**5000**
Carbohydrate (%, energy)	**76**	**26**	**36**
Fructose (%, energy)		**50**	
Protein (%, energy)	**14**	**14**	**14**
Lipids (%, energy)	**10**	**10**	**50**

Abbreviations: control diet (C), high-fructose (HFRU), high-fat (HF).
Significance of bold means the quantity of major components in grams and energy.

a) C-NT: control diet during the experiment, non-trained;
b) C-T: control diet during the experiment, trained on an HIIT protocol for twelve weeks;
c) HF-NT: High-fat diet during the experiment, non-trained;
d) HF-T: High-fat diet during the experiment, trained on an HIIT protocol for twelve weeks;
e) HFRU-NT: High-fructose diet during the experiment, non-trained;
f) HFRU-T: High-fructose diet during the experiment, trained on an HIIT protocol for twelve weeks.

2.2. HIIT protocol

All mice assigned to the HIIT exercise training protocol were familiarized during five days with a rodent treadmill (LE 8710–Panlab Harvard Apparatus) before beginning the HIIT protocol (to 10 m/min 10–15 min). After this period, mice performed HIIT three days/week on alternating days over 12 weeks. HIIT consisted of 2 min of high-intensity 45 m/min (90% VO2) running and 1 min of low intensity at 15 m/min (30% VO2) running. VO2 peak was measured every fourth week to adjust exercise intensity. During the HIIT period, NT groups remained in their cages with water and ad libitum diets.

2.3. Quantitative insulin sensitivity check index - QUICKI

QUICKI was performed at the end of the experiment. Fasting blood glucose (FBG) and insulin (FINS) levels were measured after 20 weeks of diets exposure. The animal fasted for 6 h, and then blood samples were collected by cardiac puncture. Glucose measurements were obtained with a semiautomatic spectrophotometer and commercial kit (Bioclin, Quibasa, Belo Horizonte, MG, Brazil). Insulin levels were determined using the enzyme-linked immunosorbent assay kit (Rat/Mouse Insulin ELISA kit Cat. #EZRMI-13K, Millipore, Missouri, USA) and a TPREADER Thermoplate equipment (Bio Tek Instruments, Inc. Highland Park, USA).

The Quantitative insulin sensitivity check index (QUICKI) was calculated to address insulin sensitivity [25]. It was determined by the following mathematical equation: QUICKI = 1(logFINS [mU/L] + log [FBG(mmol/L)]).