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Exposure to high-fat diet since post-weaning induces cardiometabolic damage in adult rats

P. Fiorino [a,*], A.L.V. Américo [a,b], C.R. Muller [a,b], F.S. Evangelista [c], F. Santos [b], A.P.O. Leite [a,d], V. Farah [a,d]

[a] Renal, Cardiovascular and Metabolic Physiopharmacology Laboratory, Health and Biological Science Center, Mackenzie University, Sao Paulo, Brazil
[b] Experimental Pathophysiology Dept., Faculty of Medicine, University of Sao Paulo, Brazil
[c] School of Arts, Science and Humanities, University of Sao Paulo, Sao Paulo, Brazil
[d] Translational Medicine Division, Department of Medicine, Federal University of Sao Paulo, Sao Paulo, Brazil

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ABSTRACT

Aims: This study sought to investigate the metabolic, hemodynamic and autonomic responses in adult rats exposed to high-fat diet since post-weaning.
Main methods: Young male Wistar rats were assigned into groups fed with standard normal diet (3% lipids; ND, n = 8) or high-fat diet (30% lipids; HD, n = 8) during 8 weeks. Body composition, food intake, serum triglycerides, total cholesterol, insulin, leptin and adiponectin concentrations were determined. Hemodynamic and autonomic evaluations were performed. Renin angiotensin system and nitric oxide were also studied by pharmacological blockades.
Key findings: HD group showed no difference in body weight, total cholesterol, food intake in calories and insulin concentration, but visceral fat pads weight, triglycerides and leptin were higher in HD group. Moreover, HD group decreased adiponectin level, increased 12% of mean arterial pressure (MAP) and 6% of heart rate compared with ND group. Spectral analyses showed an increase in cardiovascular sympathetic modulation in HD compared with ND group. Depressor responses after losartan were higher in HD compared with ND group: -9 ± 0.7 vs. -3 ± 1.6 mmHg. Pressor responses after L-NAME were higher in HD compared with ND: 45 ± 8 vs. 32 ± 5 mmHg.
Significance: High-fat diet consumption during early period of life can increase WAT mass and MAP. These alterations may be mediated by an augment in sympathetic activity associated with higher leptin and lower adiponectin levels. These cardiometabolic damages can lead to the development of hypertension and increase cardiovascular risk in adulthood.

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1. Introduction

Hypertension is one of the main risk factors for development of cardiovascular diseases (CVD) and the prevalence in adults age 18 or more is around 22% [1], and in children and adolescents aged 3–18 years is 3.6% [2,3]. Risk factors for the development of hypertension include genetic and unhealthy lifestyle derived from the consumption of diets with high levels of salt and/or fat, physical inactivity, alcohol use and stress [1,4]. Clinical study demonstrated that overweight and obesity significantly increases the risk of hypertension [5] and type 2 diabetes [6], and that increases in arterial pressure (AP) at an early stage of life can lead to an adult hypertensive [3]. This has led to suggestions that interventions that prevent obesity in children may have beneficial effects on the cardiometabolic health in adulthood.

An excessive accumulation of white adipose tissue (WAT) has been strongly correlated with the development of hypertension since the WAT secrets vasoactive adipokines that will, directly or indirectly, control AP [2,7]. Leptin, which is one of the adipokines synthesized and secreted by white adipocytes, is increased in obese patients [8]. Higher leptin concentration can activate the sympathetic nervous system (SNS) through of sympathetic neurons stimuli in the hypothalamus and can also reduce the bioavailability of nitric oxide (NO) released by endothelium and adipocytes [9]. Thus, the development of hypertension in obese can be associated with an increase in peripheral vasoconstriction induced by SNS and a reduction in vasorelaxant effect of NO [9].

Adiponectin is another adipokine secreted by WAT which is associated with increases in glucose uptake in adipocytes and fatty acid oxidation in skeletal muscle and WAT [10]. Besides the metabolic control, the adiponectin has vasorelaxant effect on the small arteries and also reduces endothelium dysfunction [2]. It has been shown that adiponectin is reduced in obesity [11], which can also contribute to increase AP [2].

WAT can also modulate the vascular activity through the secretion of the components of renin angiotensin system (RAS) [2,4]. Angiotensin II

* Corresponding author at: Health and Biological Science Center, Mackenzie University, 896 Consolação St., São Paulo 01302-907, Brazil.
E-mail address: patriciafiorino@mackenzie.br (P. Fiorino).

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(Ang II) acting on AT1R (type 1 Ang II receptor) has a central role in mediating most of systemic and local actions of the RAS [12]. Ang II controls the AP by inducing vasoconstriction and increasing sodium reabsorption either via direct action on the kidneys or by the stimulation of aldosterone secretion [13]. The hyperactivity of systemic and WAT specific RAS has been associated with obesity [14,15], which is another mechanism that connects hypertension development with obesity. In fact, clinical trials have shown that AT1R blockers, renin inhibitors, or angiotensin converting enzyme (ACE) inhibitors reduce AP in obese hypertensive patients [16]. Moreover, the SNS hyperactivity also contributes to increase Ang II levels, which maximizes it actions [17].

Although the pathological consequence of high-fat diet and the association between obesity and hypertension are well documented in the literature [9,18], the effect of high-fat diet exposure during critical developmental periods such as post-weaning still needs investigation. Considering that cardiometabolic impairments that begin early in life are particularly critical, as they often predict cardiovascular dysfunction into adulthood, the aim of this study was to investigate the metabolic, hemodynamic and autonomic responses in adult rats exposed to high-fat diet since post-weaning. We hypothesized that fat mass accumulation damages the secretion of adipokines, which can increase the sympathetic activity and impair the vascular tonus. These responses raise the susceptibility to develop hypertension, leading to higher cardiovascular risk in adulthood.

2. Materials and methods

2.1. Animals and diets

Experiments were performed in male Wistar rats post-weaned (21 days old), weighing between 50 and 60 g. The animals were randomly assigned to two groups and followed during eight weeks: standard normal diet (ND, n = 8) and high-fat diet (HD, n = 8). The ND (257 kcal/100 g) contained 3% of kilocalories from fat, 55% from carbohydrate and 22% from proteins (Nuvilab®, Paraná, Brazil). HD (381 kcal/100 g) was prepared mixing ND diet (400 g) with unsalted butter (200 g) (saturated fat), and contained 30% of kilocalories from fat, 23% from carbohydrates and 19% from proteins. Animals were maintained in the Central Animal Facility of University of Presbyterian Mackenzie (Sao Paulo) under the same housing conditions (12-h light/12-h dark cycle, temperature 23 ± 2 °C) with free access to tap water and food ad libitum. All procedures were performed in accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (n. 85–23, revised in 1996) and approved by the Ethics Committee of Mackenzie Presbyterian University (Protocol: 063/02/2010).

2.2. Body weight composition

Body weight was measured weekly at the same time of day using a digital balance (TOLEDO, model 9094c/4). Body weight gain was calculated as the difference between the body weight measured at the beginning and at the end of the PT protocol.

2.3. Food intake

The 24-h food intake was determined at the 7th week throughout the study in rats that were individually housed in the cage. Food consumption (Kcal/animal/24 h) was performed by multiplying food consumption (g/animal/24 h) by the amount of calories present in each diet.

2.4. Cardiovascular measurements

At the 8th week of the experimental protocol, the animals were anesthetized with Ketamine (Dopalen - 80 mg/kg, ip) and Xylazine (Anasedan - 12 mg/kg, ip) and submitted to surgery for catheterization of the femoral artery and vein. After 24 h of surgery, with the animals awake and moved freely during the experiments, arterial cannula was connected to a strain gauge transducer (Hewlett-Packard 1280, EUA), and AP signals were recorded during 30 min, starting just after the stabilization of the exploratory activity of the animal.

The overall variability of the pulse interval was assessed in the time and frequency domains by spectral analyses. Variance (VARPI) was analyzed in time-domain. The frequency-domain metrics included low frequency (LF: 0.2–0.75 Hz), which represented sympathetic modulation, and high frequency (HF: 0.75–4.0 Hz), which represented parasympathetic modulation. The LF and HF components are expressed in percentage and normalized units to represent total modulation, relative contribution of each power component and symphato-vagal balance, respectively. Moreover, the LF/HF power ratio was measured as the total variance of systolic arterial pressure (SAP) (VARSAP), peripheral sympathetic modulation (LF SAP) and alpha index, representing the ratio between cardiac and peripheral LF modulation.

2.5. Evaluation of baroreflex sensitivity

After recording the mean AP (MAP), the baroreflex sensitivity was evaluated after sequential injections of vasoactive drugs (0.1 mL), including phenylephrine (Fe, 0.5, 1, 2 and 4 μg/mL, Sigma Aldrich) and sodium nitroprusside (Np, 2.5, 5, 10 and 20 μg/mL, Sigma Aldrich), to produce pressure responses ranging from 5 to 30 mmHg. A 3- to 5-minute interval between doses was necessary for blood pressure to return to baseline [19]. The index of baroreflex sensitivity was calculated as the ratio between the HR responses to fluctuations in MAP (ΔHR/ΔMAP), representing the indices of bradycardia and tachycardia.

2.6. Pharmacological blockades

After recording baroreflex sensitivity and the MAP return to baseline value, we performed the blocked of AT1R using Losartan (10 mg/kg, Sigma Aldrich). After 24 h, the inhibition of NO was obtained with the administration of L-NAME (10 mg/kg, Sigma Aldrich). Then, after MAP return to baseline value, we inhibited the autonomic ganglion using Hexamethonium (20 mg/kg, Sigma). All drugs were administered in bolus and at the same order. The responses were expressed as delta MAP (ΔMAP) in mmHg [20].

2.7. Tissue and blood collection

To avoid residual effect of drugs, the animals were killed with an overload of anesthetic (Ketamine 160 mg/kg; Xylazine 24 mg/kg, ip) twenty-four hours after the last pharmacological blockade. Periepididymal and retroperitoneal fat pads were harvested and weighed. The cava venous blood was collected and centrifuged at 4 °C (10.000 g for 10 min) and serum was stored at −80 °C.

2.8. Serum analysis

Triglycerides and total cholesterol were evaluated by enzymatic colorimetric assays using commercial kits (Labtest®, Minas Gerais, Brazil), according to the manufacturer's guidelines. The determination of insulin, leptin and total adiponectin concentrations in the serum were performed using specific radioimmunoassay (RIA) kits (Linco Research Inc. ®). The insulin detection sensitivity was 0.02 ng/mL, the within-run variation was <5.8%, and the interassay CV was <10%. Assays were performed in duplicate using a sample volume of 50 μL. The leptin detection sensitivity was 0.2 ng/mL, the within-run variation was <4.6% and the interassay CV was <10%. Assays were performed in duplicate with a sample volume of 50 μL. Adiponectin detection sensitivity was 1 ng/mL, the within-run variation was <4.5% and the interassay CV

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